Prognostic Value of Primary Tumor Uptake on F-18 FDG PET/CT in Patients with Invasive Ductal Breast Cancer

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Abstract

Purpose To determine the prognostic implications of pretreatment F-18 FDG PET/CT in patients with invasive ductal breast cancer (IDC), we evaluated the relationship between FDG uptake of the primary tumor and known prognostic parameters of breast cancer. Prognostic significance of tumoral FDG uptake for the prediction of progression-free survival (PFS) was also assessed.

Materials and Methods Fifty-five female patients with IDC who underwent pretreatment F-18 FDG PET/CT were enrolled. The maximum standardized uptake value of the primary tumor (pSUVmax) was compared with clinico-pathological parameters including tumor size, grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor2 (HER2), axillary lymph node (LN) metastasis, and stage. The prognostic value of pSUVmax for PFS was assessed using the Kaplan-Meier method.

Results A high pSUVmax was significantly related to a higher stage of tumor size ($P<0.05$), grade ($P<0.001$), and stage ($P<0.001$). pSUVmax was significantly higher in ER-

negative tumors ($P<0.001$), PR-negative tumors ($P<0.001$), and positive LN metastasis ($P<0.01$), but not different according to HER2 status. pSUVmax was significantly higher in patients with progression compared to patients who were disease-free (10.6 ± 5.1 vs. 4.7 ± 3.5 , $P<0.001$). A receiver-operating characteristic curve demonstrated a pSUVmax of 6.6 to be the optimal cutoff for predicting PFS (sensitivity; 86.7%, specificity; 82.5%). The patients with a high pSUVmax (more than 6.6) had significantly shorter PFS compared to patients with a low pSUVmax ($P<0.0001$).

Conclusions pSUVmax on pretreatment F-18 FDG PET/CT could be used as a good surrogate marker for the prediction of progression in patients with IDC.

Keywords F-18 FDG PET/CT · Invasive ductal breast cancer · SUVmax · Prognosis

Introduction

According to an American Cancer Society investigation, breast cancer is the most common invasive cancer in women. In 2009, 192,370 new cases of invasive breast cancer were diagnosed among women, and approximately 40,170 women were expected to die from breast cancer [1]. Although it is curable when detected early, about one third of women with breast cancer eventually die of the disease. Therefore, choosing the optimal management starting from the accurate staging and prediction of the prognosis is very important.

Traditionally, pathological determination of the tumor size, histological tumor grade, axillary lymph node (LN) involvement, endocrine (hormonal) receptor status, and

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human epidermal growth factor receptor 2 (HER2) status have driven prognostic predictions for patients with breast cancer. However, most factors can be assessed only after surgery or invasive procedures for a definite tissue diagnosis.

Positron emission tomography (PET) with F-18 FDG has been widely used in clinical practice for the diagnosis, staging, treatment monitoring, and detection of disease recurrence in breast cancer patients [2]. F-18 FDG PET provides quantitative data on the level of metabolic activity by calculating the degree of F-18 FDG uptake, known as the standardized uptake value (SUV).

F-18 FDG PET/CT has been suggested to have a considerable prognostic utility in various cancers [3]. Recent studies on cancers of the head and neck, lung, and esophagus indicate that high FDG uptake on the primary tumor predicts worse outcome [4–8]. However, in breast cancer patients, the role of SUV in F-18 FDG PET/CT imaging has not been fully determined.

Therefore, we investigated the relationship between the maximum SUV of the primary tumor (pSUVmax) and

known prognostic parameters of breast cancer. Prognostic value of tumoral FDG uptake was evaluated for the prognosis of progression-free survival (PFS) in patients with newly diagnosed primary invasive ductal breast cancer (IDC).

Materials and Methods

Subjects

A total of 55 IDC female patients (age range; 34–75 years, mean age; 50.2±9.5 years) who underwent F-18 FDG PET/CT before any anticancer treatment from November 2005 to March 2008 were enrolled in this study. Primary breast cancer was diagnosed histopathologically with fine-needle aspiration cytology (FNAC) and/or core-needle biopsy (CNB). Patients with a history of insulin-dependent diabetes mellitus or who were diagnosed with excision biopsy were excluded. Primary tumor features included tumor size, tumor grade, estrogen receptor (ER) status,

Table 1 Patient characteristics

	Variables	N (%) ^f	pSUVmax (mean ± SD)	P value
^a Clinical tumor size	Tumor size ^a			
	T1b; 0.5 cm<size≤1.0 cm	6 (10.9)	1.8±0.9	0.017†
	T1c; 1.0 cm<size≤2.0 cm	18 (32.7)	3.7±2.0	
	T2; 2.0 cm<size≤5.0 cm	22 (40)	7.2±4.1	
	T3; 5.0 cm<size	9 (16.4)	12.4±5.0	
^b Modified Scarff-Bloom-Richardson grading system	Histological grade ^b			
	Grade 1	10 (18.2)	2.1±0.6	<0.001†
	Grade 2	19 (34.5)	3.9±2.1	
	Grade 3	10 (18.2)	8.0±4.0	
	Not assessed	16 (29.1)		
^c According to immunohistochemical (IHC) staining for ER/PR/HER2 and FISH for HER2 gene amplification	Estrogen receptor (ER) ^c			
	Positive	38 (69.1)	4.5±3.4	<0.001*
^d IHC (3+) or in the case of IHC (2+), FISH positive	Negative	17 (30.9)	10.3±5.0	
	Progesterone receptor (PR) ^c			
^e AJCC staging system (7th edition)	Positive	37 (67.3)	4.3±2.7	<0.001*
	Negative	18 (32.7)	10.4±5.4	
^f Number of patients with percentage in parentheses	HER2 ^c			
	Positive ^d	18 (32.7)	7.8±5.9	0.212*
^g Maximum standardized uptake value	Negative	37 (67.3)	5.6±4.0	
	LN involvement, pathologic			
^h Mann-Whitney U-test	Negative	26 (47.3)	4.6±3.6	0.005*
	Positive	29 (52.7)	7.9±5.2	
ⁱ Kruskal-Wallis test	Stage, pathologic ^c			
	I	19 (34.5)	3.3±2.2	<0.001†
	II	15 (27.2)	5.7±3.9	
	III	14 (25.5)	8.9±5.9	
	IV	7 (12.8)	10.6±3.4	
	Disease group			
	Disease free	40 (72.8)	4.7±3.5	<0.001*
	Progression	15 (27.2)	10.6±5.1	

progesterone receptor (PR) status, and HER2 status (Table 1). To obtain the tumor size, the longest diameter of the tumor was carefully measured from the F-18 FDG PET/CT image. Mammography, breast USG, MRI, CT, whole body bone scan, and F-18 FDG PET/CT were used for the diagnosis of disease recurrence, metastasis, or progression, and all suspicious lesions were confirmed histologically by FNAC. Progression was defined as progression of disease to a more advanced TNM stage, a more advanced clinical stage, or relapse noted on images with histological confirmation.

F-18 FDG PET/CT

All patients fasted for at least 6 h before the administration of F-18 FDG, and blood glucose concentration was confirmed to be less than 150 mg/dl in all subjects. Approximately 8.1 MBq of F-18 FDG per kg of body weight was injected intravenously, and patients were advised to rest for an hour before acquisition of the PET/CT image. PET/CT scans were performed using Reveal HiRez (Siemens-CTI, Knoxville, TN; 6-slice CT) and Discovery STE (GE Healthcare, Milwaukee, WI; 16-slice CT). First, a low-dose CT scan was obtained for attenuation correction, and the PET scan was followed at 3 min per bed position. PET data were reconstructed iteratively using an ordered-subset expectation maximization algorithm with the low-dose CT data sets for attenuation correction. An SUV was measured for all primary breast cancer lesions and presented as the SUVmax.

The PET/CT images were interpreted by two experienced nuclear medicine physicians and a final consensus reached for

Fig. 1 pSUVmax differences according to disease group. Mann-Whitney U-test reveals a significant difference between the disease-free group and progression group ($P < 0.001$). Mean values of pSUVmax (4.7 in the disease-free group and 10.6 in the progression group) are indicated with purple boxes. The error bars represent the 95% confidence interval for mean

Fig. 2 Optimal cutoff of pSUVmax for predicting progression-free survival

all patients. Regions of interest (ROI) were placed manually over all breast tumors in attenuation corrected images, and the SUVmax within the ROIs was recorded.

Immunohistochemistry

Immunohistochemical (IHC) staining was performed on tissue slices from formalin-fixed, paraffin-embedded representative breast tumors. ER, PR, and HER2 expression was assessed by IHC using commercial monoclonal antibodies for ER (Neomarker, 1:200, Fremont, CA), PR (Neomarker, 1:400, Fremont, CA), and HER2 (DakoCytomation, 1:300, Glostrup, Denmark); the iView DAB Detection kit (Ventana Medical Systems, Inc., AZ) was used as a secondary antibody. The results were recorded according to the American Society of Clinical Oncology/College of Amer-

Fig. 3 Progression-free survival according to the pSUVmax

ican Pathologists (ASCO/CAP) guidelines [9]. Cases with an HER2 IHC staining score of more than 2 were tested by HER2 gene amplification using the fluorescence in situ hybridization (FISH) method. HER2 positive was defined as an IHC staining score of 3+ or, in the case of an IHC staining score of 2+, FISH positive.

Statistical Analysis

Data are expressed as the mean $\pm$ SDs. The relationship between levels of primary tumor SUVmax (pSUVmax) and clinicopathological parameters was evaluated using the Mann-Whitney U-test and the Kruskal-Wallis test using MedCalc software, version 11.3.3 (MedCalc, Mariakerke, Belgium). To identify an optimal cutoff value of pSUVmax for the prediction of progression, receiver-operating characteristic (ROC) analysis was performed. Moreover, we used the log rank test according to the all patient's pSUVmax. Cutoff value was established by the maximum log rank statistical value. A pSUVmax higher than the cutoff value was defined as a "high SUVmax," and a pSUVmax below the cutoff value was defined as a "low SUVmax" for FDG-positive tumors. Kaplan-Meier curves for high vs. low pSUVmax were calculated for PFS by log-rank test. A P value of less than 0.05 was considered to be statistically significant.

Results

Patients' Characteristics

Pertinent characteristics of the patients are summarized in Table 1. The mean age was 50.2 ± 9.5 years, ranging from 34 to 75. The median follow-up period was 30 months (mean $\pm$ SD = 32.1 ± 6.6 , range: 26–54 months). Tumor stage was categorized by the size of primary tumor (T): 24

(43.6%) in T stage 1, 22 in T stage 2, and 9 (16.4%) patients in T stage 3. Axillary LN involvement at pathology was observed in 29 patients (52.7%).

There were 19 (34.5%) patients in stage I, 15 (27.2%) in stage II, 14 (25.5%) in stage III, and 7 (12.8%) in stage IV IDC (Table 1). Among 55 patients, 50 underwent surgery, but 5 received radiotherapy and/or chemotherapy without surgery. While 46 patients received chemotherapy, 36 received radiotherapy, and 36 received hormonal therapy, according to clinical status. No patients died during the follow-up period, 40 (72.8%) patients were in a disease-free status, and 15 (27.2%) patients presented a progression during follow-up. Eight of these 15 patients showed remission after first-line treatment, but experienced a recurrence during follow-up. Another seven patients showed progression despite various treatment strategies.

Relationship Between pSUVmax and Clinicopathological Parameters

Table 1 shows pSUVmax differences according to the clinicopathological parameters. Mean pSUVmax of the 55 patients was 6.3 ± 4.8 (range, 1.0–21.5). The mean pSUVmax was significantly different among the T-stage groups ($P=0.017$) and was increased by increases in the tumor size. Mean pSUVmax was also significantly different among different tumor grade groups ($P<0.001$) and was increased by increases in the tumor grade. pSUVmax was significantly higher in ER-negative tumors ($P<0.001$), PR-negative tumors ($P<0.001$), and tumors with positive LN metastasis ($P=0.005$) compared to ER-positive tumors, PR-positive tumors, and tumors without LN metastasis, respectively. However, there was no significant difference in pSUVmax according to HER2 status ($P=0.212$). The mean pSUVmax was 3.3 ± 2.2 in stage I, 5.7 ± 3.9 in stage II, 8.9 ± 5.9 in stage III, and 10.6 ± 3.4 in stage IV, respectively, which are significantly different between each group ($P<0.001$).

Table 2 Tumor characteristics in the cases with discrepancy between pSUVmax and prognosis

Disease group	pSUVmax	Age	Tumor size	Grade	ER	PR	HER2	N	M	Stage	PFS (months)
Progression	2.8	52	4.4 cm	N/A	+	+	-	2	0	IIIA	15
Progression	3.5	53	1.6 cm	2	+	+	+	3	0	IIIC	10
Disease free	7.2	56	3.0 cm	3	-	-	-	0	0	IIA	31
Disease free	9	45	2.7 cm	3	-	+	-	0	0	IIA	27
Disease free	9.1	41	1.6 cm	2	+	+	-	0	0	I	30
Disease free	11.6	37	3.0 cm	3	-	-	-	0	0	IIA	26
Disease free	12.3	40	5.7 cm	N/A	-	-	-	2	0	IIIA	24
Disease free	12.3	41	2.8 cm	3	+	-	+	3	0	IIIC	47
Disease free	15.7	34	7.5 cm	3	+	-	-	0	0	IIA	31

N/A, not assessed; PFS, progression-free survival

Progression-Free Survival

Fifteen (27.2%) of the 55 patients experienced progression, and the median follow-up time to progression was 31 months (range: 26–49 months). pSUVmax was significantly higher in patients with progression than in those who were disease free. The mean pSUVmax of the disease-free group was 4.7 ± 3.5 and that of the progression group was 10.6 ± 5.1 ($P < 0.001$, Fig. 1).

A ROC curve demonstrated a pSUVmax of 6.6 to be the optimal cutoff for predicting PFS (area under the curve: 0.848; standard error: 0.0668) (Fig. 2). A pSUVmax of 6.6 yielded a sensitivity of 86.7% and a specificity of 82.5% for prediction the PFS. Also, the result of the log-rank test according to the all patient's pSUVmax showed a cutoff value of 6.6, representing maximum log rank statistical value.

In the survival analysis using the Kaplan-Meier method, patients with a pSUVmax of more than 6.6 had a significantly shorter PFS than patients with one less than 6.6 ($P < 0.0001$, Fig. 3).

Meanwhile, nine patients showed a discrepancy between the pSUVmax and prognosis (Table 2). Two patients categorized in the low pSUVmax group experienced a recurrence, and both of these patients had axillary lymph node metastases.

Discussion

Various prognostic factors have been proposed for the risk stratification of patients with breast cancer, such as involvement of axillary LNs, presence of distant metastases, endocrine (hormonal) receptor status, and HER2 status. However, these pathological predictors can only be obtained after surgery, which is frequently associated with significant morbidity and mortality. Also tissue samples sometimes cannot be obtained even with invasive diagnostic procedures. On the other hand, F-18 FDG PET can provide quantitative information about tumor glucose metabolism, which represents the aggressiveness of the malignant lesion. FDG uptake can be evaluated non-invasively and be measured with good inter-test reproducibility [10]. Therefore, quantitative FDG-PET can be a valuable adjunct to conventional preoperative clinical assessment (Fig. 4).

In our study, the pSUVmax level was significantly higher in larger tumors, higher grade tumors, ER-negative tumors, PR-negative tumors, and tumors with axillary LN involvement. This tendency has also been reported previously [11–16]. Kawamura et al. demonstrated that FDG uptake was affected by the number of metabolically active tumor cells [17]. Consequently, as the cancer stage becomes higher, increased glucose uptake is represented as increased

Fig. 4 A 71-year-old female patient diagnosed with invasive ductal breast cancer (pSUVmax 7.0, tumor size 3.6 cm, ER-, PR-, HER2+). **a** F-18 FDG PET/CT before cancer treatment. In the pre-treatment, a focal hypermetabolic lesion in the left breast and enlarged LNs with focal FDG uptake in the left axillary area were shown, which were histologically confirmed as malignancy in both lesions (long arrow). **b** In the follow-up F-18 FDG PET/CT taken after neoadjuvant chemotherapy and operation, there was no evidence of residual malignancy. **c** But 6 months later, a newly found hypermetabolic lesion in the right breast on the 2nd follow-up F-18 FDG PET/CT was shown and histologically confirmed as metastasis (short arrow). In addition, FDG uptake in the left internal mammary LN was shown (long dotted arrow)

SUV. In this study, the pSUVmax was significantly correlated with the pathological stage, similar to the results of various malignancies in other organs [6, 14, 18–20]. Cancer progression means that the tumor grows larger,

invades deeper, and metastasizes to other organs. Therefore, primary breast cancers with higher levels of F-18 FDG uptake are considered to have more aggressive characteristics than those with a low F-18 FDG uptake (Fig. 5).

On the other hand, pSUVmax according to HER2 status showed no significant difference in our study. Our result is different from that of Ueda et al., who studied 152 patients with primary breast cancer for the clinicopathological and prognostic relevance of FDG uptake level. In the Ueda et al. study, the tumor groups were categorized into scores of 0 or 1+ versus scores of 2+ or 3+; the mean level of SUV was higher in the tumor groups with scores of 2+ and 3+ than in those with scores of 0 and 1+ [15]. However, in our study, HER2 positive was defined as a score of 3+ or, in the case of a score of 2+, FISH positive. Meanwhile, in a study by Gil-Rendo et al., there was no significant correlation between HER2 and FDG uptake, and HER2 positive was defined as a cutoff of over 10% membrane staining [13]. We postulate that discrepancy criteria of HER2 positive led to different results. Other possibilities may include a triple-negative breast tumor. Basu et al. observed that triple-negative breast tumors (ER negative, PR negative, and HER 2 negative) were associated with enhanced FDG uptake commensurate with their aggressive biology [21]. Among 37 patients with HER2-negative tumors, 8 (21.6%) patients had triple-negative breast tumors. Furthermore, the mean pSUVmax of these 8 patients was 9.0 ± 4.2 , and the mean pSUVmax of the other 29 patients was 4.7 ± 3.5 in our study.

The present study showed that pSUVmax was significantly higher in patients with progression compared to disease-free patients (Fig. 1). There have been several reports suggesting that breast cancers with a high FDG uptake showed higher relapse and mortality rates compared to those with a low FDG uptake [14–16]. In these reports,

histological subtypes of the enrolled patients were consistent with invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, mucinous carcinoma, and apocrine carcinoma. However, breast cancer is a remarkably heterogeneous disease, and prognosis of the breast cancer is also dependent upon histological subtypes [22]. Therefore, their results cannot be generalized to every patient.

In a study by Ueda et al., the mean level of SUV was significantly lower in invasive lobular carcinoma than in IDC, and the mean SUV level in ductal carcinoma in situ was relatively low compared to IDC [15]. A pSUVmax of 4.0 was suggested to be the optimal cutoff for risk stratification in their study. In addition, Inoue et al. also demonstrated the standard cutoff for the pSUVmax to be 4.0 [16]. However, a detailed study in the same histological subtypes is necessary for the determination of the accurate value for risk stratification since not only pSUVmax, but also prognosis is different according to the histological subtypes. Only invasive ductal carcinoma was included in our study population to eliminate these errors.

The optimal cutoff for the pSUVmax to differentiate the progression was 6.6 in our study. Twenty patients with a pSUVmax greater than 6.6 had a 1-year overall PFS rate of 40.0%, which was significantly lower than that of 97.1% in 35 patients with a pSUVmax 6.6 or less. As shown in Table 2, even though there were nine patients with a discrepancy between the level of pSUVmax and prognosis, these findings proved the eligibility of pSUVmax as a prognostic parameter for IDC.

Multivariable analysis study in a large series of patients previously showed that the SUV was an independent predictor of relapse-free survival in women with breast cancer [14]. Inoue et al. demonstrated longer survival in patients with a lower SUV and higher SUVs in

Fig. 5 A 43-year-old female patient diagnosed with invasive ductal breast cancer (pSUVmax 2.9, tumor size 2.2 cm, ER+, PR+, HER2+). In initial F-18 FDG PET/CT, a mildly hypermetabolic lesion was shown (pSUVmax is lesser than 6.6) and histologically confirmed as

malignancy in the right breast (long arrow). In the follow-up F-18 FDG PET/CT taken after the operation, chemotherapy, and hormonal therapy, there was no evidence of residual or recurrent malignancy

recurrent tumors in a study of 81 patients with 61 months' follow-up [16]. In that study, the combination of SUV and positive PET axillary status was found to be a significant prognostic factor, being independent of clinical tumor and LN factors in multivariable analysis. However, in our study, multivariable analysis regarding LN metastasis status was not possible, because there were no patients with progression among the patients with LN-negative metastasis.

This study has limitations that possibly influence the results. First, all the patients had prior diagnostic fine-needle aspiration and/or core-needle biopsy. Consequently, the overall amount of F-18 FDG uptake of the primary breast tumor might have been affected. It is possible that an inflammatory reaction after biopsy could have contributed to the amount of FDG uptake, although this may not have been significant. Considering the design of the study, this type of effect was unavoidable and likely did not substantially alter the results described. Second, the small number of enrolled patients and the shorter time of follow-up periods could be another limitation of this study. Since all patients were alive, survival analysis was not computed in this study. Additional larger and prospective studies are required to elucidate the clinical significance of pSUVmax on F-18 FDG PET for predicting progression in patients with IDC.

In conclusion, pSUVmax has a strong relationship with known prognostic parameters of breast cancer and could be useful to predict the prognosis in patients with IDC.

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