ORIGINAL ARTICLE

Factors Associated with ^{18}F-Fluorodeoxyglucose Uptake in T1 and T2 Invasive Ductal Carcinoma of the Breast

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Abstract

Purpose The objective of this study was to investigate the relationship between diversity of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake of primary tumor in positron emission tomography (PET) and various clinicopathologic factors in breast cancer of same pathologic T1, T2 stage.

Methods A total of 258 patients with invasive ductal breast cancer were enrolled in this study. All patients underwent ^{18}F-FDG PET-CT before surgery. Patients were divided into two groups according to tumor size based on the pathologic T stage, and maximum standardized uptake value (SUVmax) of 2.5, respectively.

Results On the univariate analysis, estrogen receptor (ER), tumor size, lymphovascular invasion, p53, pathologic N status (pN) and Nottingham tumor grade (NG) were associated with high SUVmax in T1 and T2 breast cancer. On the multivariate logistic regression, tumor size and NG remained significant variables dividing high and low SUVmax. In the T1 group, ER, p53 and NG were significantly associated with high SUVmax on the univariate analysis. In this group, p53 and NG remained significant variables for dividing high and low SUVmax on the multivariate logistic regression. In the T2 group, only NG was associated with high SUVmax on the univariate analysis.

Conclusions NG showed an association with ^{18}F-FDG uptake in both T1 and T2 breast cancer independently; however, p53 in T1 breast cancer.

Keywords F-18 Fluorodeoxyglucose · Positron emission tomography · Breast neoplasms · TNM staging

Introduction

Breast cancer is the most common malignancy among women, and the second most frequent cancer overall [1]. In patients with breast cancer, staging of locally advanced cancer allows appropriate treatment options and offers prognostic information. For this purpose, preoperative ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) is recommended in patients with breast cancer [2, 3]. Although ^{18}F-FDG PET-CT has proved to be valuable for deciding appropriate treatment options, the degree of ^{18}F-FDG uptake, measured as maximum standardized uptake value (SUVmax), is diverse and highly versatile for evaluating the therapeutic effect and prognosis [4–6].

Hormone receptor, including estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), p53, Ki67 expression, lymphovascular invasion, surgical margin involvement, tumor size, pathologic N status (pN) and Nottingham tumor grade (NG) are well known clinicopathologic factors that influence the prognosis of breast cancer [3, 7, 8]. Several studies have investigated the associating factors that affect the intensity of ^{18}F-FDG uptake in breast cancer, and have focused on these clinicopathologic factors of breast cancer [9–11]. The relationship between clinicopathologic factors of breast cancer and the intensity of ^{18}F-FDG uptake is not completely consensual; nevertheless, most of previous studies have shown that there is a strong

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relationship between the tumor size and SUVmax; thus, PET imaging has been reported for hard to detect small breast cancers [9, 12, 13].

In the clinical setting, the intensity of ^{18}F-FDG uptake of breast cancer with similar tumor size was diverse [4, 14–18], and there were some cases of small-sized breast cancer with relatively intense ^{18}F-FDG uptake. For this reason, this study was designed to investigate the relationship between clinicopathologic factors for prediction of the aggressiveness of the primary tumor and the intensity of ^{18}F-FDG in the relatively early T stage of breast cancer. In addition, we also investigated how these prognostic factors influence ^{18}F-FDG uptake in each T1 and T2 stage of breast cancer.

Materials and Methods

Patients

We reviewed the medical records of 327 patients with breast cancer, evaluated at Pusan National University Hospital, who had undergone curative surgery and been confirmed as having invasive ductal carcinoma (IDC) between Jan 2012 and May 2013. Of the 327 potentially eligible patients (51 years; 22–88 years), there were 42 patients with tumors less than 10 mm, 6 patients with pathologic T3 (pT3) tumor, and 16 patients with pT4 tumor; 21 patients who did not have complete postoperative histopathologic data were excluded from the study. Finally, 258 patients were enrolled in this study. Patients were divided into two groups according to the tumor size based on the pathologic T stage. Tumor sizes of 10 mm or less were excluded because of partial volume effect. In T1 the group, patients whose tumors were larger than 10 mm, and 20 mm or less were included; in T2 group patients, whose tumors were larger than 20 mm, and 50 mm or less were included. All patients underwent ^{18}F-FDG PET-CT before surgery. Patients were also divided into low and high SUV groups according to an SUVmax of 2.5 [4]. This retrospective study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital.

^{18}F-FDG PET-CT Imaging and Analysis

All patients fasted for at least 8 h before undergoing ^{18}F-FDG PET-CT. Their median blood glucose level was 93 mg/dl (64-167 mg/dl) before ^{18}F-FDG administration. ^{18}F-FDG PET-CT imaging studies were conducted 60 min after intravenous injection of ^{18}F-FDG. Patients were hydrated with 500 ml of water taken orally before PET-CT imaging. Low-dose CT from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization. Patients were examined using two types of PET-CT

scanner. The first was Gemini TF (Philips, Milpitas, CA, USA), which consists of a germanium oxyorthosilicate full-ring PET scanner and a dual-slice helical CT scanner. Thereafter, an emission scan was conducted in the three-dimensional mode. PET data were obtained using a high-resolution whole-body scanner with an axial field of view of 18 cm. The average axial resolution varied between 4.2 mm full-width at half-maximum in the center and 5.6 mm at 10 cm. The average total PET-CT examination time was 30 min. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and were reoriented in axial, sagittal, and coronal slices. The row action maximum likelihood algorithm was used for three-dimensional reconstruction. The other PET-CT scanner used was Biograph40 (Siemens, Knoxville, TN, USA). PET data were obtained using a high-resolution whole-body scanner with an axial field of view of 21.6 cm. The average axial resolution varied between 2.0 mm full-width a half-maximum in the center and 2.4 mm at 28 cm. The average total PET-CT examination time was 20 min. Attenuation correction was performed for all patients with iterative reconstruction. PET-CT images were analyzed at three different planes: transverse, coronal, and sagittal.

All PET-CT images were evaluated by two nuclear physicians, blinded to all imaging studies, clinical and pathological results. A volume of interest (VOI) was drawn over each breast cancer. SUVmax of each lesion was measured automatically and semiquantitatively on the workstation.

Clinicopathologic Factors

ER, PR, HER2, p53, Ki67 expression, lymphovascular invasion, surgical margin, tumor size, pN and NG were selected as clinicopathologic factors. Patients were pathologically staged according to American Joint Committee on Cancer 7th edition [19]. Tumor size was estimated by measuring the maximum diameter of the tumor invasive component (millimeters). Pathologic N status was categorized as nodal metastasis positive or negative. NG was determined on the basis of tubular formation, nuclear pleomorphism, and mitotic count. Each of these features was scored from 1 to 3, and then each score was added to give a final total score range from 3 to 9. Lymphovascular invasion or surgical margin involvement was determined on the histopathologic findings of hematoxylin and eosin staining under a high-power-field. ER, PR, HER2, p53 and Ki-67 expression were analyzed immunohistochemically using antibodies prepared against these proteins. Immunohistochemistry staining with the antibody was carried out with suitable positive and negative controls. The results were semi-quantitatively scored on a scale of 0, 1+, 2+ and 3+. The 0 and 1+ were considered negative, and 2+ and 3+ were considered as positive.

Statistical Analysis

The Mann–Whitney test was used to investigate the association between tumor size, Ki67 or NG and SUVmax. Associations between other clinicopathologic factors and SUVmax were examined using the chi-squared test. Logistic regression was performed to examine which clinicopathologic factors can reflect intensity of ^{18}F-FDG uptake. The statistical analyses were performed using MedCalc® (Ostend, Belgium) for windows version 12.7.0.0 and a p value of less than 0.05 was regarded as significant.

Results

The characteristics of patients are shown in Table 1. SUVmax and tumor size ranged from 1.00 to 47.90 and 11 to 48 mm, respectively. Of the 258 patients, 216 patients (83.7 %) were included in the high SUVmax group. ER, PR, HER2 and p53 were found positive in 176 (68.2 %), 162 (62.8 %), 90 (34.9 %) and 76 (29.5 %) of the patients (Table 1).

The relationships between various clinicopathologic factors and ^{18}F-FDG uptake were summarized in Table 2. On the univariate analysis, ER ($p = 0.0045$), tumor size ($p < 0.0001$), lymphovascular invasion ($p = 0.0382$), p53 ($p = 0.0110$), NG ($p < 0.0001$) and pN ($p = 0.0470$) were significantly associated with high SUVmax in T1 and T2 breast cancer (Table 2, Fig. 1). ER ($p = 0.0045$), p53 ($p = 0.0025$) and NG ($p = 0.0004$) were significantly associated with high SUVmax in the T1 group on the univariate analysis (Table 2, Figs. 1 and 2). In the T2 group, only NG ($p = 0.0279$) was associated with high SUVmax on the univariate analysis (Table 2, Fig. 1). On the multivariate analysis, tumor size (OR 5.1925, 95 % CI 2.2384-12.0453; $p = 0.0001$) and NG (OR 1.5695, 95 % CI 1.2011-2.0508; $p = 0.0010$) remained statistically significant variables for determining high and low SUVmax. In the T1 group, p53 (OR 10.0595, 95 % CI 1.2775-79.2110; $p = 0.0283$) and NG (OR 1.5365, 95 % CI 1.1093-2.1281; $p = 0.0098$) were independent factors to determine high and low SUVmax on the multivariate analysis.

Discussion

Breast cancer appears to display considerably variable ^{18}F-FDG uptake, so several studies have examined the correlation between ^{18}F-FDG uptake and various prognostic factors [3, 9–13, 18]. Buck et al. [10] and Crippa et al. [18] examined the possible association between ^{18}F-FDG uptake in breast cancer and several clinicopathologic factors. Both studies, and our study, indicated that there was no significant correlation between ^{18}F-FDG uptake and the hormone receptor status. In

Table 1 Patients' characteristics

Variables		n (%)	SUVmax (mean ± SD)
Age (years)	51 (22–84)		6.88 ± 5.15
SUVmax	High (≥2.5)	216 (83.7)	7.85 ± 5.09
	Low (<2.5)	42 (16.3)	1.90 ± 0.41
Estrogen receptor	+	176 (68.2)	5.53 ± 3.67
	-	82 (31.8)	9.79 ± 6.53
Progesterone receptor	+	162 (62.8)	5.72 ± 4.78
	-	96 (37.2)	8.85 ± 5.20
HER2	+	90 (34.9)	7.76 ± 6.10
	-	168 (65.1)	6.41 ± 4.52
Tumor size (mm)	21 (11–48)		
Surgical margin	+	9 (3.5)	9.55 ± 5.35
	-	249 (96.5)	6.80 ± 5.14
Lymphovascular invasion	+	88 (34.1)	7.39 ± 4.37
	-	170 (65.9)	6.62 ± 5.51
p53	+	76 (29.5)	8.55 ± 5.94
	-	182 (70.5)	6.19 ± 4.63
Nottingham tumor grade	3-5	47 (18.2)	3.37 ± 2.02
	6-7	104 (40.3)	5.62 ± 3.34
	8-9	107 (41.5)	9.64 ± 6.09
Ki-67 (%)	20 (0–95)		
T stage	1	126 (48.8)	5.38 ± 5.31
	2	132 (51.2)	8.32 ± 4.57
N stage	1, 2, 3	119 (46.1)	7.26 ± 4.37
	0	139 (53.9)	6.56 ± 5.74

HER2 human epidermal growth factor receptor 2, *SUVmax* maximum standardized uptake value

addition, Buck et al. [10] demonstrated that there was no significant correlation between ^{18}F-FDG uptake and HER2 over-expression, and this was consistent with our results.

In the present study, we showed that tumor size and NG could influence the intensity of ^{18}F-FDG uptake in breast cancer. We thought that SUV values greater than 2.5 might represent relatively intense ^{18}F-FDG uptake, so we regarded SUVmax greater than 2.5 as high SUVmax [4]. The positive relationship between SUVmax and tumor size in the present study was in accordance with previous studies. PET imaging has been reported to provide a low sensitivity to detect small breast cancers, but an increase in metabolic activity with tumor growth [9, 12, 13]. However, SUVmax of breast cancer with similar small size was also variable [4, 14–18], and small sized breast cancer might have high SUVmax. Similarly, Ueda et al. [9] reported no significant relationship between tumor size and SUVmax, especially in lesions of 2 cm or less. Also, Avril et al. [20] reported that there was no significant relationship between tumor size and ^{18}F-FDG uptake. This discrepancy in the

Table 2 Univariate and multivariate analysis of clinicopathologic factors influencing ^{18}F-FDG uptake in breast cancer

	Univariate			Multivariate	
All (n = 258)	SUVmax ≥ 2.5	SUVmax < 2.5	*p* value	OR (95 % CI)	*p* value
Estrogen receptor (positive)	139	37	0.0045		
Progesterone receptor (positive)	130	32	0.0736		
HER2 (positive)	79	11	0.2649		
Tumor size (mm)	2.35 ± 0.83	1.63 ± 0.48	<0.0001	5.1925 (2.2384-12.0453)	0.0001
Surgical margin (positive)	9	0	0.3730		
Lymphovascular invasion (positive)	80	8	0.0382		
p53 (positive)	71	5	0.0110		
Nottingham tumor grade	7.17 ± 1.39	5.83 ± 1.32	<0.0001	1.5695 (1.2011-2.0508)	0.0010
Ki67 (%)	25.02 ± 23.49	23.54 ± 26.72	0.2818		
Pathologic N status (positive)	106	13	0.0470		
1 cm < T1 ≤ 2 cm (n = 126)	SUVmax ≥ 2.5	SUVmax < 2.5	*p* value	OR (95 % CI)	*p* value
Estrogen receptor (positive)	66	32	0.0045		
Progesterone receptor (positive)	66	27	0.3234		
HER2 (positive)	26	7	0.5984		
Surgical margin (positive)	3	0	0.6987		
Lymphovascular invasion (positive)	24	6	0.5185		
p53 (positive)	29	1	0.0025	10.0595 (1.2775-79.2110)	0.0283
Nottingham tumor grade	6.63 ± 1.44	5.61 ± 1.30	0.0004	1.5365 (1.1093-2.1281)	0.0098
Ki67 (%)	25.27 ± 23.81	20.98 ± 24.80	0.1946		
Pathologic N status (positive)	33	8	0.3331		
2 cm < T2 ≤ 5 cm (n = 132)	SUVmax ≥ 2.5	SUVmax < 2.5	*p* value	OR (95 % CI)	*p* value
Estrogen receptor (positive)	73	5	0.8984		
Progesterone receptor (positive)	64	5	0.8875		
HER2 (positive)	53	4	0.7877		
Surgical margin (positive)	6	0	0.8802		
Lymphovascular invasion (positive)	56	2	0.3115		
p53 (positive)	42	4	0.7921		
Nottingham tumor grade	7.57 ± 1.21	6.67 ± 1.12	0.0279		
Ki67 (%)	24.84 ± 23.34	32.89 ± 32.77	0.5710		
Pathologic N status (positive)	73	5	0.8984		

SUVmax maximum standardized uptake value, *HER2* human epidermal growth factor receptor 2, *OR* odds ratio

existing literature may be explained by immunohistochemical and histologic differences. As breast cancer is a very heterogenous disease with variable phenotypes, different histological and immunohistochemical characteristics can influence the glycolytic pathway and the variability in the glycolytic phenotype [21, 22].
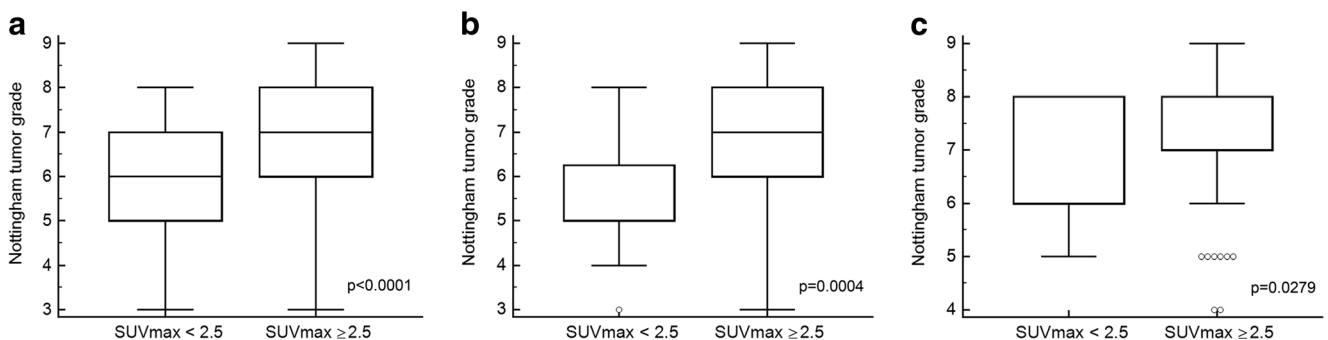
Fig. 1 Comparison of Nottingham tumor grade between the high SUVmax group and low SUVmax group. Nottingham tumor grade was significantly higher in the high SUVmax group than in low SUVmax group. **a** All-size group; **b** T1 group; **c** T2 group

Fig. 2 Comparison of p53 between the high SUVmax group and low SUVmax group. Tumor protein p53 was a significant variable for determining high and low SUVmax groups in the T1 group. **a** All-size group; **b** T1 group; **c** T2 group
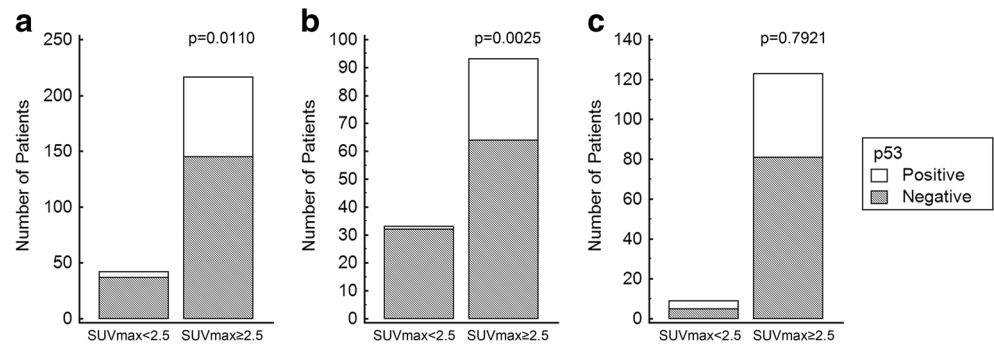
In the subgroup analysis, we divided patients into two groups by tumor size, according to the pathologic T stage given by the American Joint Committee on Cancer, 7th edition [19], and presumed to have similar treatment plan and prognosis, to find additional prognostic factors in the same T stage. Tumor protein p53 and NG in the T1 group, and NG in the T2 group could make a difference of ^{18}F-FDG uptake. These data mean that regardless of tumor size, NG was an independent factor influencing ^{18}F-FDG uptake. A significant relationship between SUVmax and pathologic grade represented by NG has been reported, and which is due to the finding that less differentiated tumors with higher tumor growth rates exhibit higher ^{18}F-FDG uptake [13, 20]. These results may be due to high levels of glucose transporter 1 at the membrane and increased level of hexokinase in the cytoplasm, encountered in high-grade human cancers including breast cancer [9, 23, 24]. NG is determined by evaluating morphologic features including tubule formation, nuclear pleomorphism and mitotic count [7, 25, 26]. The lowest score is given to well-differentiated tumors that all form tubules and have a low mitotic rate. Hence, the data presented here signify that a more differentiated tumor may have a lower ^{18}F-FDG uptake in breast cancer.

In the present study, we found the relationship between p53 and SUVmax in the T1 group, but not in the T2 group. In agreement with our study, Crippa et al. [18] reported a positive correlation between ^{18}F-FDG uptake and p53 overexpression. The p53 gene functions as a tumor suppressor, preventing cancer [27, 28]. The capability that p53 status affects biological behavior was raised in a previous study in which the presence of p53 mutations in aggressive breast cancer was demonstrated [29, 30]. Hence, the data presented here signify that T1 breast cancer, at a relatively early stage, with high ^{18}F-FDG, may be related to aggressive breast cancer, and careful monitoring may be necessary. Also, there is evidence linking the development and progression of cancer with an accumulation of mutations at the genomic level [27, 28]. These mutations are thought to result either in the activation of proto-oncogenes or in the loss of tumor suppressor gene potential. So, their accumulation will eventually drive cancer cells further into anaplasia [29]. Compared with other clinicopathologic factors, p53 is related to the development of cancer, and it may influence the aggressive nature of tumor only in a relatively early stage.

Our study had several limitations. First, this study was a retrospective one with a relatively small number of patients. Second, we simplified the degree of ^{18}F-FDG uptake and categorized groups according to SUVmax of 2.5. Consequently SUVmax was regarded as a discrete variable, and it led to loss of some information. Third, we did not assess the association between prognosis and clinicopathologic factors used as variables in this study. Fourth, it might have been a limitation to use two different scanners.

Conclusion

NG showed an association with ^{18}F-FDG uptake in both T1 and T2 breast cancer independently; however, p53 in T1 breast cancer.

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