Jpn J Clin Oncol 2008;38(4)250–258
doi:10.1093/jjco/hyn019

Clinicopathological and Prognostic Relevance of Uptake Level using ^{18}F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Fusion Imaging (^{18}F-FDG PET/CT) in Primary Breast Cancer

Shigeto Ueda[1], Hitoshi Tsuda[2], Hideki Asakawa[1], Takashi Shigekawa[3], Kazuhiko Fukatsu[4], Nobuo Kondo[5], Mikio Yamamoto[5], Yukihiro Hama[6], Katsumi Tamura[6], Jiro Ishida[6], Yoshiyuki Abe[6] and Hidetaka Mochizuki[1]

[1]Department of Surgery, National Defense Medical College, Tokorozawa, Saitama, [2]Department of Basic Pathology, National Defense Medical College, Tokorozawa, Saitama, [3]Department of Breast Oncology, International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan, [4]Department of Basic Traumatology, National Defense Medical College, Tokorozawa, Saitama, [5]Department of Biochemistry, National Defense Medical College, Tokorozawa, Saitama and [6]Tokorozawa PET diagnostic Imaging clinic, Tokorozawa, Saitama

Received January 13, 2008; accepted February 21, 2008

Objective: Using integrated ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (^{18}F-FDG PET/CT), the clinical significance of ^{18}F-FDG uptake was evaluated in patients with primary breast cancer.
Methods: Clinicopathological correlation with the level of maximum standardized uptake values (SUV) 60 min obtained from preoperative ^{18}F-FDG PET/CT were examined in 152 patients with primary breast cancer. The prognostic impact of the level of SUV was explored using simulated prognosis derived from computed program Adjuvant! in 136 (89%) patients with invasive ductal carcinoma (IDC).
Results: High SUV level was significantly correlated with tumor invasive size ($\leq$2 cm) ($P < 0.0001$), higher score of nuclear grade ($P < 0.0001$), nuclear atypia ($P < 0.0001$) and mitosis counts ($P < 0.0001$), negative hormone receptor status ($P = 0.001$), high score of c-erbB-2 expression ($P = 0.006$), lymph node metastasis ($P = 0.002$), and IDC in comparison with invasive lobular carcinoma ($P = 0.004$). Multivariate analyses showed tumor invasive size, nuclear grade and estrogen receptor negativity were significantly correlated with SUV in primary breast cancer ($P < 0.0001, < 0.0001$, and < 0.012, respectively), and nuclear grade was significantly correlated with SUV in tumors of invasive size 2 cm or less ($P < 0.0001$). Tumors with high SUV (cutoff value 4.0) showed higher relapse and mortality rate compared to those with low SUV ($P < 0.0001$).
Conclusions: High uptake of ^{18}F-FDG would be predictive of poor prognosis in patients with primary breast cancer, and aggressive features of cancer cells in patients with early breast cancer. ^{18}F-FDG PET/CT could be a useful tool to pretherapeutically predict biological characteristics and baseline risk of breast cancer.

Key words: breast cancer – ^{18}F-FDG – PET/CT – SUV – prognosis

INTRODUCTION

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), a modality of imaging glucose metabolism in cancer cells, is a new approach for staging of primary cancer and detection of distant metastasis (1–3).

For reprints and all correspondence: Hitoshi Tsuda, Department of Basic Pathology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan. E-mail: htsuda@ndmc.ac.jp

Breast cancer cells overexpress glucose transporter at the membrane and the level of active hexokinase in their cytoplasm is increased compared with adjacent normal tissues. The uptake of ^{18}F-FDG by breast cancer cells is reported biologically to reflect their glucose hypermetabolism (4,5). Some studies suggested that the level of ^{18}F-FDG uptake in breast cancers is significantly correlated with tumor size, higher histological grade, Ki-67 labeling index, the number of mitotic figures and abrogation of the p53. Therefore,

primary breast cancers with higher levels of ^{18}F-FDG uptake are considered to have more aggressive potential than those with low ^{18}F-FDG uptake (6,7).

Recently, the integrated ^{18}F-FDG PET/Computed tomography fusion imaging (^{18}F-FDG PET/CT) has been shown to be able to visualize anatomical localization of the hypermetabolic cancer lesions more accurately than ^{18}F-FDG PET only. Therefore, the ^{18}F-FDG PET/CT would be more informative for pre-therapeutic staging of the entire body and for the evaluation of proliferation activity of the tumors than a single examination of ^{18}F-FDG PET (8).

To date, the most significant prognostic parameters of breast cancer are axillary nodal status, size of the primary tumor, c-erbB-2 (HER2/neu), estrogen receptor (ER) and progesterone receptor (PgR). On the other hand, a definite conclusion remains to be reached concerning the prognostic relevance of the level of ^{18}F-FDG uptake in breast cancer.

In the present study, we investigate the clinicopathological implications of the level of standardized uptake values (SUV) obtained from preoperative ^{18}F-FDG-PET/CT imaging in 152 patients with newly diagnosed primary breast cancer in our institute. We assessed levels of ^{18}F-FDG uptake to breast cancer using maximum SUV obtained 60 min later after injection of ^{18}F-FDG. In addition, we examined the prognostic relevance of the level of ^{18}F-FDG uptake using computed program Adjuvant!.

PATIENTS AND METHODS

Eligible Patients

Between April 2005 and March 2007, ^{18}F-FDG PET/CT scans were performed for 152 patients to determine clinical staging of breast cancer before initial therapy. Primary breast cancer was histopathologically diagnosed with fine needle aspiration cytology and/or core needle biopsy (CNB). Patients who did not have the evidence of distant metastatic spread using X-ray, ultrasonography, or ^{18}F-FDG PET/CT were eligible for operable candidates of primary breast cancer. Patients who were pregnant, who were taken history of insulin-depended diabetes mellitus from clinical notes, or who had previously received treatment to breast cancer were excluded from indication for ^{18}F-FDG PET/CT. All patients underwent surgery within 4 weeks after ^{18}F-FDG PET/CT examination.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board in our medical school. Informed consent was obtained from all patients with regard to ^{18}F-FDG PET/CT examination.

^{18}F-FDG PET/CT and Quantification of ^{18}F-FDG uptake in Primary Breast Cancer

All patients received ^{18}F-FDG PET/CT scans (Biograph LSO Emotion, Siemens) at Tokorozawa PET Diagnostic Imaging Clinic (Tokorozawa, Japan).

Patients were fasted at least 4 h before ^{18}F-FDG PET study. One hour after intravenous administration of 3.7 Mbq/kg ^{18}F-FDG, a transmission scan using CT for attenuation correction and anatomical imaging was acquired for 90 s. IV contrast was not administered to patients for the CT portion of the ^{18}F-FDG PET/CT.

Back projection image was obtained after Gaussian filter was applied. The spatial resolution of the reconstructed images was 6.0–7.0 mm in cranio-caudal, 6.3–7.1 mm in right–left and 6.3–7.1 mm in anterior–posterior directions.

A regions of interest (ROI) was placed in the primary lesion (Fig. 1), including the highest uptake area (circle ROI, 2 cm in diameter) and SUV maximum in the ROI was calculated. The SUV was calculated using the following formula: SUV = activity in region of interest (MBq/ml)/injected dose (MBq/kg body weight).

SUV is decay-corrected tissue activity divided by the injected dose per patient body.

Surgery

A total of 152 patients received mastectomy or breast conserving surgery with sentinel node biopsy or axillary dissection. In all patients, primary systemic therapy was not performed before surgery. Sentinel node biopsy was performed by the procedure written previously (9).

Patient Characteristics

This study consisted of 152 female patients (age range 34–81 years, mean 54 years). Patients included 3 (2%) patients with Stage 0, 46 (30%) patients with Stage I, 98 (64%) patients with Stage II, 5 (4%) patients with Stage III (Table 1). Averaged SUV stratified by pathological stages consisted 3.1 ($\pm$2.1 SD) in Stage 0, 3.3 ($\pm$2.5 SD) in Stage I, 5.6 ($\pm$3.7 SD) in Stage II and 5.7 ($\pm$4.3 SD) in Stage III (Table 2). For the purposes of this study, the following characteristics were recorded from patients' clinical charts. Primary tumor features included age, sizes of tumor invasive size (cm), histological types (invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), ductal carcinoma *in situ* (DCIS), mucinous carcinoma, and apocrine carcinoma), nuclear grade with nuclear atypia score and mitotic count score, axillary lymph node involvement, ER status, PgR status and c-erbB-2 status (Table 1). Tumor invasive size was estimated by measuring a maximum diameter of tumor invasive component (cm).

Immunohistochemistry

Formalin-fixed tumor samples obtained from surgery were routinely fixed with formalin, embedded in paraffin, cut into 4 μm-thick sections and subjected to immunohistochemistry. The expressions of ER and PgR, and c-erbB-2 were analysed immunohistochemically using specific primary antibody (Dako, Grostrup, Denmark) as previously written in our reports (10).

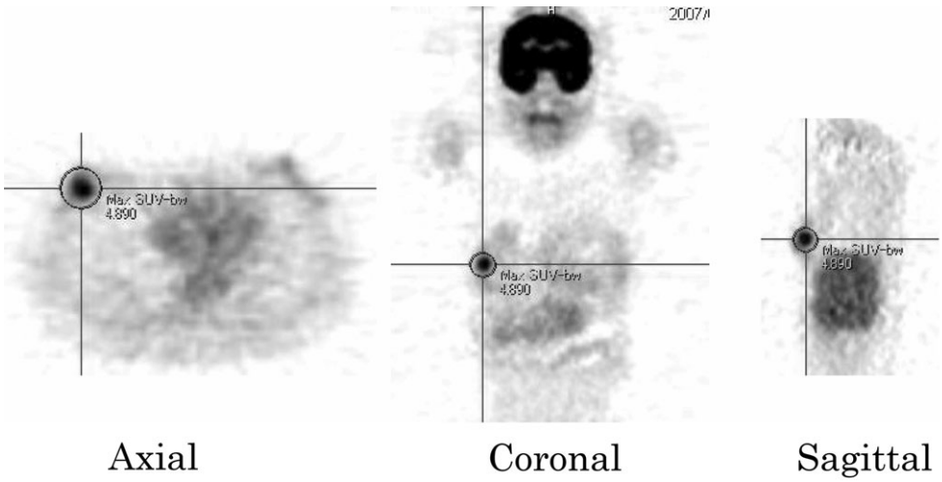

Figure 1. For semiquantitative of ^{18}F-FDG uptake, the region of interest (ROI) was placed in the primary lesion, including the highest uptake area (circular ROI, 2 cm in diameter), and maximum standardized update values (SUV) in the ROI was calculated. SUV is decay-corrected tissue activity divided by the injected dose per patient body. Representative axial, coronal and sagittal ROIs were shown in this figure. The spatial resolution of the reconstructed images was 6.0–7.0 mm in cranio-caudal, 6.3–7.1 mm in right-left and 6.3–7.1 mm in anterior-posterior directions.

Scoring System of Nuclear Grade

Nuclear grade of IDC was given according to General Rules for Clinical and Pathological Recording of Breast Cancer, 15th edition by two pathologists always including one who is experienced in breast pathology (HT) (11). Nuclear grade was given by the sum of the nuclear atypia score and the mitosis counts score. Nuclear atypia score was defined as following; Score 1: Nuclei were relatively uniform in size and shape, and chromatin was inconspicuous. Score 2: Intermediate between 1 and 3. Score 3: There were considerable variations in size and shape of nuclei and the increase and unevenness of chromatin, sometimes having giant nucleoli. After selecting the area in which mitoses were the most abundant on low to intermediate magnifications, the mitotic figures were counted on a high magnification. Mitotic count score was defined as following; Score 1: 0–4 mitoses, Score 2: 5–10 mitoses, Score 3: more than 10 mitoses per 10 high power fields using eyepieces of 20 mm field of view (40× Objective).

Simulated Prognosis Derived from Ajuvant! And SUV in Breast Cancer

The computed program Adjuvant! is an assistant tool for making decisions of adjuvant therapies for women with breast cancer (http://www.adjuvantonline.com). We used the computed program Adjuvant! to simulate the prognostic significance of the level of SUV in tumor. For the entries of information including age, menopausal status, tumor size, number of positive axillary nodes and ER status, baseline prognostic estimates are given by each patient. Physical conditions of all patients were in good health. Estimated incidences of recurrence and mortality 10 years after surgical therapy was computed by this program (12). And we compared estimated prognosis in baseline risk between high and low SUV groups by showing bow and whisker plot.

Univariate Analyses According to Clinicopathological Parameters and Prognosis

The correlations between levels of SUV and clinicopathological parameters were evaluated using the Mann–Whitney *U*-test and the Kruskal–Wallis test. A value of $P < 0.05$ was defined to be statistically significant. All statistic analyses were performed using Statview5.0 software (SAS Institute Inc.). The *t*-value is calculated by the formula: $t\text{-value} = (Y_A - Y_B)/s\sqrt{1/NA + 1/NB}$, where Y_A, the mean percentage of prognosis in low SUV group; Y_B, the mean percentage of prognosis in high SUV group; s, standard deviation; NA, sample size of low SUV group; NB, sample size of high SUV group. *T*-statistics determine whether prognosis rates of the low SUV group and the high SUV group differ significantly. According to the analysis, an explanatory factor showing an absolute *t*-value, which is more than 2, is significantly correlated with dependent variables.

Multivariate Analysis

Multiple regression analysis was performed to select independent clinicopathological variables associated with SUV for all 152 patients with primary breast cancer and for 78 patients having primary breast cancer with tumor invasive size 2 cm or less. Multivariate models were correlated using variables with a $P < 0.05$ in the univariate analyses. Variables in these models were included tumor invasive size, nuclear grade, ER, HER2 and nodal status. Histology was not entered in the models because a majority of cases were IDC. SUV and tumor invasive size was analysed as continuous variables, nuclear grade was categorized as grade 1 or 2

Table 1. Patient characteristics

Variables	Number =152	(%)
Age		
[range]	[34–81]	
<45	29	(19)
45≤	123	(81)
Tumor invasive size (cm)		
≤2	78	(51)
2<	74	(49)
Histology		
DCIS	3	(2)
IDC	136	(89)
ILC	9	(6)
Apocrine	2	(1)
Mucinous	2	(1)
Nuclear grade		
1	43	(28)
2	36	(24)
3	60	(39)
Not graded	13	(9)
Nuclear atypia score		
1	32	(21)
2	71	(47)
3	36	(24)
Not graded	13	(9)
Mitotic count score		
<5	61	(40)
5 to 10	33	(22)
≥11	58	(38)
Nodal metastasis		
negative	99	(65)
positive	53	(35)
Estrogen receptor (ER)		
10%>	33	(22)
10%≤	119	(78)
Progesterone receptor (PgR)		
10%>	50	(33)
10%≤	102	(67)
c-erbB-2 (HER2)		
0	40	(26)
1+	74	(49)
2+	17	(11)
3+	14	(9)
unknown	7	(5)
Approach to primary tumor		
Lunpectomy	62	(41)
Mastectomy	90	(59)
Primary axillary approach		
Ax dissection	75	(49)
SLNB	77	(51)
Pathological stage		
0	3	(2)
I	46	(30)
II	98	(65)
III	5	(3)
Standardized update value (SUV)		
[range]	[0.94–17.8]	
≤4.0	83	(55)
4.0<	69	(45)

DCIS, ductal carcinoma *in situ*; IDC, invasive ducta carcinoma; ILC, invasive lobular carcinoma; Ax, axillary; SLNB, sentinel node biopsy.

versus grade 3, ER was categorized as negative versus positive, HER2 was categorized as scores 0 or 1+ versus score 2+ or 3+, and nodal status was categorized as nodal metastasis positive versus negative. All statistic analyses were performed using Statview5.0 software (SAS Institute Inc.).

RESULTS

Patient Characteristics

The clinicopathological features of the 152 patients are listed in Table 1. One hundred and thirty-six tumors (89%) were IDC, nine tumors (6%) were ILC and three tumors (2%) were DCIS. Other special subtypes included 2 (1%) apocrine carcinoma and 2 (1%) mucinous carcinoma.

Comparison Between SUV and Clinicopathological Parameters

In 152 primary breast cancers, the average level of SUV was 5.0 (Standard deviation, SD, 3.5). The correlations of the level of SUV with clinicopathological parameters were presented in Table 2.

The levels of SUV were significantly different between the patients tumor groups of 2 cm or less and greater than 2 cm, respectively ($P < 0.0001$).

The mean level of SUV was significantly lower in ILC than IDC ($P = 0.004$). Differences in the uptake level were not significantly between IDC and DCIS and between IDC

Table 2. Correlations between clinicopathological parameters and the levels of SUV

Variables	Comparision	SUV (Mean ± SD)	*P* value
Age (year)	<45	5.0 ± 3.3	0.45*
	45≤	4.4 ± 3.4	
Tumor invasive size (cm)	≤2	3.3 ± 2.7	<0.0001*
	2<	5.8 ± 3.6	
Histology	DCIS	3.1 ± 2.1	
	IDC	4.8 ± 3.5	0.004*
	ILC	1.4 ± 1.5	
	Apocrine	4.3 ± 3.2	
	Mucinous	3.0 ± 0.1	
Nuclear Grade	Grade 1	3.4 ± 3.4	<0.0001†
	Grade 2	4.0 ± 2.3	
	Grade 3	6.3 ± 3.5	
Nuclear atypia score	1	2.9 ± 3.0	<0.0001†
	2	4.8 ± 2.4	
	3	6.2 ± 3.5	
Mitotic counts score	0–4	2.7 ± 2.2	<0.0001†
	5–10	4.8 ± 3.2	
	11≤	5.9 ± 3.7	
Estrogen receptor (ER)	ER+	4.0 ± 3.0	0.001*
	ER−	6.4 ± 4.1	
Progesterone receptor (PgR)	PgR+	4.1 ± 2.9	0.04*
	PgR−	5.4 ± 4.2	
Combined hormone receptors	ER+ and/or PgR+	4.0 ± 3.0	0.001*
	ER− and PgR−	6.4 ± 4.1	
c-erbB-2 (HER2)	0 and 1+	4.0 ± 3.1	0.006*
	2+ and 3+	6.2 ± 4.2	
Nodal metastasis	Negative	3.9 ± 3.1	0.002*
	Positive	5.7 ± 3.7	
Pathological stage	0	3.1 ± 2.1	0.006†
	I	3.3 ± 2.5	
	II	5.6 ± 3.7	
	III	5.7 ± 4.3	

*Mann-Whitney *U*-test, †Kruskal-Wallis test.
Abbreviations used are same as those used in Table 1.

and other special subtypes, although the mean SUV level in DCIS was relatively low.

With regard to tumor nuclear grade and its components, the mean level of SUV was significantly different among the tumor groups of Grade 1, Grade 2 and Grade 3 ($P < 0.0001$). The mean level of SUV elevated on stepwise manner in accordance with increase in nuclear atypia score and mitotic count (each, $P < 0.0001$).

Table 3. Multiple regression analysis for 152 patients with primary breast cancer

Variables	*t* value	*P* value	*R*, Adjusted R^2
Tumr invasive size	4.52	<0.0001	0.85
Grade	4.91	<0.0001	0.72
ER	2.55	0.012	
HER2	0.93	0.36	
Nodal metastasis	0.67	0.5	

Between ER-positive group (10%≤) and ER-negative group (10%>), the mean levels of SUV of ER-negative group was significantly higher than that of ER-positive group ($P = 0.001$). Between PgR-positive (10%≤) and PgR-negative groups (10%>), the mean SUV of the PgR-negative groups was significantly higher than that of PgR-positive groups ($P = 0.04$).

With regard to combined hormone receptors status, between the tumor group of ER-positive and/or PgR-positive and of ER-negative and PgR-negative in combined receptors, the mean levels of SUV of the latter were also higher than that of the former ($P = 0.001$).

With regard to c-erbB-2 status, the mean level of SUV was higher in the tumor groups of scores 2+ and 3+ than in the tumor groups of scores 0 and 1+ ($P = 0.006$).

With regard to lymph nodal status, the mean level of SUV was higher in the tumor group with metastatic lymph nodes than in the group without metastatic lymph nodes (3.9 ± 3.1 SD) ($P = 0.002$).

Tumor invasive size ($P < 0.0001$), nuclear grade ($P < 0.0001$) and ER status ($P = 0.012$) independently influenced on the stats of SUV (4.0 or higher versus <4.0) in a multiple regression model for 152 patients (Table 3). The correlation coefficient (R^2) of combination of three parameters with SUV was 0.72. In a multiple regression model for 78 patients having primary breast cancer with tumor invasive size 2 cm or less, nuclear grade only was the independent factor that influenced on the status of SUV ($P < 0.0001$). The correlation coefficient (R^2) of nuclear grade with SUV was 0.7 (Table 4).

Patients' Prognosis and Cutoff Value of SUV

We performed a simulation of prognostic baseline risk according to 136 patients with IDC. Sixteen patients with tumors of special types including ILC, mucinous carcinoma and apocrine carcinoma were excluded from the evaluation.

The prognostic impact of the level of SUV in tumors was explored for various cutoff values in 136 IDCs. Cases were defined into two groups by six tentative thresholds (2.0, 3.0, 3.5, 4.0, 4.5 and 5.0) of SUV. Table 5 shows the number of patients who exceeded the threshold (high SUV group) and whose SUVs were the value of threshold or less (low SUV

Table 4. Multiple regression analysis for 78 patients with tumor size of 2.0 cm or less

Variables	*t* value	*P* value	*R*, adjasted R^2
Tumr invasive size	1.66	0.1	0.84
Grade	3.84	0.003	0.7
ER	0.49	0.63	
HER2	0.76	0.45	
Nodal metastasis	0.45	0.65	

group), estimated incidence of relapse and mortality after 10 years, *t*-value and *P* value were compared.

The *P* value between tentative low and high SUV groups increased in accordance with elevation of cutoff SUV up to the value of 3.0. However, the *P* values between the low and high SUV groups did not differ ($P < 0.0001$) when a cutoff value between the two SUV groups exceeded 3.0. All of absolute *t*-values between tentative low and high SUV groups were more than 2.0 and when the cutoff SUV was 4.0, the absolute *t*-value was maximal. Therefore, we defined cutoff value between the low SUV group and the high SUV group as 4.0.

On a prognostic evaluations by computed program Adjuvant!, patients with the low SUV group (4.0 or less) had tendency of lower 10-year relapse rate and 10-year mortality than the high SUV group (more than 4.0).

Sixty-five patients with low SUV tumors were estimated to show a 29.5% (±18.2 SD) and a 13.4% (±17.1 SD) of 10-year recurrence rate and mortality, respectively, whereas 71 patients with high SUV tumors were estimated to show a 51.0% (±23.2 SD) and a 33.3% (±23.4 SD) of 10-year recurrence rate and mortality, respectively. Both of estimated relapse rate and mortality differed significantly between the high SUV group and the low SUV group ($P < 0.0001$, each).

Tumor Characteristics in the Cases that Showed Discrepancy Between SUV and Prognosis Simulated by Computed Program Adjuvant!

Table 6 shows clinicopathological characteristics of 12 patients with discrepancy between their estimated prognosis and SUV uptake values of primary tumors. Four cases (L1–L4) were estimated to be poor prognosis despite being categorized in the low SUV group (SUV 4.0 or less). In the four patients in the low SUV group, the SUV averaged 2.6 (2.14–2.82) and size of tumor invasion averaged 5.3 cm. All of the four patients had lymph node involvement in their axilla.

Other eight cases (H1–H8) were estimated to be better prognosis despite being categorized in the high SUV group (SUV higher than 4.0). In the eight patients in the high SUV group, the SUV averaged 6.8 (4.42–14.7) and size of tumor invasion averaged 1.3 cm. All patients had no metastastic foci in their axillary lymph nodes.

DISCUSSION

In the univariate analyses, we clearly demonstrated high SUV level detected with ^{18}F-FDG PET/CT was correlated with bigger invasion size of tumor, higher nuclear grade, higher scores of nuclear atypia and mitosis counts, negative hormone receptor status, high score of c-erbB-2 expression, lymph node metastasis and IDC in comparison with ILC.

Above all, mean level of SUV was lower than 4.0 in the groups of diameter of tumor invasion with 2.0 cm or less, DCIS, ILC, mucinous carcinoma, nuclear atypia score 1,

Table 5. SUV cutoff and 10-year prognosis simulated by the software program Adjuvant!

Cutoff SUV	Category	Number of patients with IDC (136)	10-year prognisis by Adjuvant! (% ± SD)					
			Recurrence	*t* value	*P* value	Mortality	*t* value	*P* value
2	Low SUV group	37	27.6 ± 18.6	−3.88	0.0002	11.9 ± 18.1	−3.59	0.0005
	High SUV group	99	44.2 ± 23.3			26.9 ± 22.9		
3	Low SUV group	54	29.4 ± 20.3	−4.48	<0.0001	13.3 ± 19.4	−4.2	<0.0001
	High SUV group	82	46.5 ± 22.7			29.1 ± 22.7		
3.5	Low SUV group	62	29.4 ± 19.2	−5.14	<0.0001	13.3 ± 18.3	−4.85	<0.0001
	High SUV group	74	48.4 ± 23.1			30.9 ± 23.0		
4	Low SUV group	65	29.5 ± 18.2	−5.99	<0.0001	13.4 ± 17.4	−5.67	<0.0001
	High SUV group	71	51.0 ± 23.2			33.3 ± 23.4		
4.5	Low SUV group	63	29.1 ± 17.8	−5.56	<0.0001	13.0 ± 17.1	−5.14	<0.0001
	High SUV group	73	52.1 ± 22.9			34.4 ± 23.2		
5	Low SUV group	56	32.2 ± 20.0	−4.9	<0.0001	15.5 ± 18.6	−4.88	<0.0001
	High SUV group	80	50.6 ± 23.4			33.5 ± 24.1		

Table 6. Tumor characteristics in the cases that showed discrepancy between SUV and prognosis simulated by the software program Adjuvant!

No.	Age	SUV	Tumor size (cm)	Tumor invasive size (cm)	Grade	ER/PgR	HER2	Axillary FDG uptake	Number of axillary involvement	Relapse (%)	Mortality (%)
L1	40	2.14	1.6	1.6	3	+/+	1+	+	15	89	70
L2	54	2.82	5	5	2	+/−	1+	+	1	68	45
L3	48	2.6	4.5	2.5	3	+/+	2+	−	1(micro)	58	35
L4	41	2.73	12	12	2	+/+	0	+	18	93	77
H1	47	4.42	1.7	1.7	1	+/+	1+	−	0	18	3
H2	67	5.29	3.5	1.1	1	+/−	1+	−	0	18	3
H3	42	5.49	1.5	1.5	2	+/+	1+	−	0	25	8
H4	47	5.56	1	1	1	+/+	1+	−	0	18	3
H5	80	5.89	1.9	1.4	2	+/+	1+	−	0	25	8
H6	62	6.48	2	0.2	1	+/+	1+	−	0	18	3
H7	39	6.92	9.2	0.2	1	+/+	2+	−	0	15	1
H8	71	14.7	2.9	2.9	1	+/−	1+	−	0	26	9

micro, mircometastasis; FDG, fluorodeoxyglucose.

mitotic count score 1 and no nodal metastasis. Although other groups stratified by ER, PgR or c-erbB-2 might show significant differences, the mean levels of SUV in all groups were higher than 4.0.

Using a multivariate analysis, we showed bigger tumor invasive size, higher nuclear grade and ER negativity were independent variables correlated with high SUV in patients having primary breast cancer. The correlation coefficient of $R^2 = 0.72$ indicated 72% of tumoral SUV was explained by bigger tumor invasive size, higher nuclear grade and ER negativity. Likewise, in 78 patients having tumors 2 cm or less in size, 70% of tumoral SUV was explained by nuclear grade of primary breast cancer.

Some data of correlation between the level of SUV and clinicopathological parameters were published with regard to ^{18}F-FDG PET (5,6,13,14). In the present study, with regard to ^{18}F-FDG PET/CT, the results were similar, and the parameters for proliferative activities and aggressiveness of cancer cells were strongly correlated with high levels of SUV in cancer cells. We suppose that the levels of the SUV from ^{18}F-FDG uptake might be useful to predict biologically aggressive carcinoma cells.

The levels of SUV in IDC were significantly higher than that in ILC, as previously reported by other authors (5). And tumor grade was also a significant factor with a major influence on the level of SUV in breast cancer (14). Bos *et al.* described a significant correlation between ^{18}F-FDG uptake and mitotic activity of tumor cells (13). In contrast, Andreas *et al.* found there were no correlation of the level of ^{18}F-FDG uptake in primary breast cancers with tumor size, hormone receptors status, c-erbB-2 status or axillary lymph node involvement (6). Some parameters in the present report were inconsistent with the results described in the previous reports. Differences in criteria for judgment of positive and negative groups for c-erbB-2, hormone receptors, or those for categorization of nodal status and tumor size might have given rise to such inconsistency.

Some authors indicated that high levels of ^{18}F-FDG uptake are a prognostic factor for recurrence in patients having primary cancer (1,15,16). In the present study, we suggested the patients' group with a high SUV level might predict poor outcome in relapse and mortality by simulation using computed program Adjuvant! (Fig. 2). We considered that the SUV of 4.0 might be one of the optimal ones to predict prognosis. Ohtsuka *et al.* studied the prognostic significance of SUV on ^{18}F-FDG PET in patients with lung adenocarcinoma at pathological Stage I. They described that patients with tumor with 3.3 or higher of SUV showed higher rate of recurrence compared with patients with tumor with lower than 3.3 of SUV (17). The cutoff value of SUV 3.3 was similar with the value set in the present study.

As shown in Table 6, there were 12 patients with tumors with substantial discrepancy between the level of SUV in primary cancer and estimated prognosis. In four patients categorized as the low SUV group, the combination of other clinicopathological parameters by the computed program Adjuvant! indicated poor prognosis. In tumors of these four cases, three patients of the low SUV group, high level of SUV in axilla was detected by ^{18}F-FDG PET/CT and these findings could predict axillary lymph node metastasis. One remaining patient had solitary micrometastasis in an axillary sentinel node, but we could not pre-surgically detect a high level of SUV in axilla. Micrometastasis in the sentinel node was intraoperatively identified by frozen sectioning procedure. From the present results, we suppose that it might be difficult to predict metastatic potential to axillary lymph nodes by the level of SUV in primary cancer.

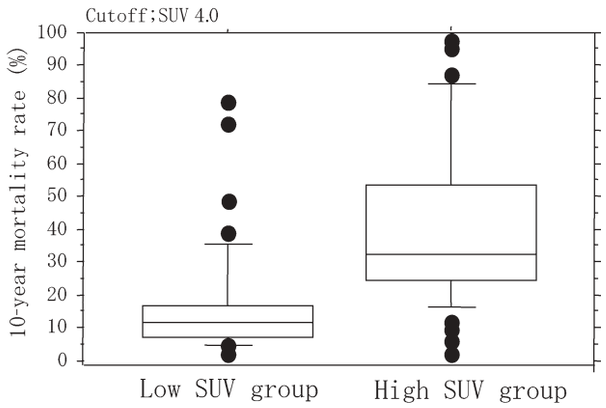

Figure 2. Prognostic significance of SUV simulated by the data published on computed program Adjuvant! (http://www.adjuvantonline.com). Mann–Whitney *U*-test reveals significant higher incidence of mortality after 10 years in high SUV (higher than 4.0) group compared to in low SUV (4.0 or less) group. Mean mortality rate (13.4% in low SUV group and 33.3% in high SUV group) are indicated with horizontal bars. The vertical bars indicate the range and the horizontal boundaries of the boxes represent 10 and 90% confidential indexes. Round plots represent outliers.

On the other hand, in eight patients with tumors categorized as the high SUV group, the combination of other clinicopathological parameters indicated better prognosis. All these eight patients were negative of axillary lymph node metastasis and had comparatively small sizes of tumor invasion (averaged 1.3 cm). One of the eight patients had a large sized tumor (9.2 cm in diameter), but the tumor was predominantly composed of an intraductal component, and the size of tumor invasion was only 0.2 cm in diameter. The histological types of these eight primary tumors were confirmed to be solid-tubular or papillotubular carcinoma, which were characterized by large nest, expansive growth of cancer cells and a smaller amount of stromal tissue component (data not presented).

From these results, it appeared that high density of viable cancer cells, regardless of invasive type or intraductal type, might contribute to high SUV levels of primary cancer.

Recently, primary systemic therapy has come to be widely performed for patients with early-stage breast cancer. CNB of tumor tissue becomes more important to know tumor characteristics before surgery. Many authors reported increased tumoral uptake of ^{18}F-FDG in breast cancer is closely correlated with the density of viable carcinoma cells, microvessel density and proliferative activity (4,5,18). These reports suggest that glucose hypermetabolism detected by ^{18}F-FDG using PET would reflect the dense proliferation of highly malignant breast cancer cells. Recently, ^{18}F-FDG PET/CT is more widely used than ^{18}F-FDG PET alone. The diagnostic accuracy of ^{18}F-FDG PET/CT is superior to that of CT or ^{18}F-FDG PET alone in the staging of patients with various cancers (19,20). Before primary systemic therapy, it might be possible to predict more precisely biological characteristics of primary breast cancer as well as the staging by the combination of ^{18}F-FDG PET/CT and CNB.

It is especially noteworthy that nuclear grade alone accounted for level of SUV for patients having tumor size 2 cm or less in a multiple regression analysis. This finding might prompt us to do further research for applying ^{18}F-FDG uptake in regarding an indication of primary systemic therapy of patients having early breast cancer treatment.

In conclusion, we showed significant correlation of the level of SUV in breast cancer with clinicopathological parameters and suggested its prognostic implications. It could be a useful tool to pretherapeutically predict biological characteristics and baseline risk of breast cancer.

Funding

This work was supported by a Grant-in-Aid for Promotion of Defense Medicine from the Ministry of Defense of Japan.

Conflict of interest statement

None declared.

References

1. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: An analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;17(10):3201–6.
2. Santiago JF, Gonen M, Yeung H, Macapinlac H, Larson S. A retrospective analysis of the impact of 18F-FDG PET scans on clinical management of 133 breast cancer patients. *Q J Nucl Med Mol Imaging* 2006;50(1):61–7.
3. Port ER, Yeung H, Gonen M, Liberman L, Caravelli J, Borgen P, et al. 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography scanning affects surgical management in selected patients with high-risk, operable breast carcinoma. *Ann Surg Oncol* 2006;13(5):677–84.
4. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. *N Engl J Med* 2006;354(5):496–507.
5. Buck AK, Schirrmeister H, Mattfeldt T, Reske SN. Biological characterisation of breast cancer by means of PET. *Eur J Nucl Med Mol Imaging* 2004;31(Suppl 1):S80–7.
6. Buck A, Schirrmeister H, Kuhn T, Shen C, Kalker T, Kotzerke J, et al. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. *Eur J Nucl Med Mol Imaging* 2002;29(10):1317–23.
7. Smith TA, Sharma RI, Thompson AM, Paulin FE. Tumor 18F-FDG incorporation is enhanced by attenuation of P53 function in breast cancer cells in vitro. *J Nucl Med* 2006;47(9):1525–30.
8. Tatsumi M, Cohade C, Mourtzikos KA, Fishman EK, Wahl RL. Initial experience with FDG-PET/CT in the evaluation of breast cancer. *Eur J Nucl Med Mol Imaging* 2006;33(3):254–62.
9. Sato K, Tamaki K, Shigekawa T, Tsuda H, Kosuda S, Kusano S, et al. Clinically useful detection criteria for sentinel nodes in patients with breast cancer using a radioisotope technique. *Jpn J Clin Oncol* 2002;32(10):403–6.
10. Tsuda H, Tani Y, Weisenberger J, Kitada S, Hasegawa T, Murata T, et al. Frequent KIT and epidermal growth factor receptor overexpressions in undifferentiated-type breast carcinomas with 'stem-cell-like' features. *Cancer Sci* 2005;96(6):333–9.
11. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403–10; *Histopathology* 2002;41(3A):151.
12. Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, et al. Computer program to assist in making decisions about adjuvant

therapy for women with early breast cancer. *J Clin Oncol* 2001;19(4):980–91.
13. Bos R, van Der Hoeven JJ, van Der Wall E, van Der Groep P, van Diest PJ, Comans EF, et al. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. *J Clin Oncol* 2002;20(2):379–87.
14. Crippa F, Seregni E, Agresti R, Chiesa C, Pascali C, Bogni A, et al. Association between [18F]fluorodeoxyglucose uptake and postoperative histopathology, hormone receptor status, thymidine labelling index and p53 in primary breast cancer: a preliminary observation. *Eur J Nucl Med* 1998;25(10):1429–34.
15. Oshida M, Uno K, Suzuki M, Nagashima T, Hashimoto H, Yagata H, et al. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro[18F]-D-glucose. *Cancer* 1998;82(11):2227–34.
16. Higashi K, Ueda Y, Arisaka Y, Sakuma T, Nambu Y, Oguchi M, et al. 18F-FDG uptake as a biologic prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. *J Nucl Med* 2002;43(1):39–45.
17. Ohtsuka T, Nomori H, Watanabe K, Kaji M, Naruke T, Suemasu K, et al. Prognostic significance of [(18)F]fluorodeoxyglucose uptake on positron emission tomography in patients with pathologic stage I lung adenocarcinoma. *Cancer* 2006;107(10):2468–73.
18. Guo J, Higashi K, Ueda Y, Oguchi M, Takegami T, Toga H, et al. Microvessel density: correlation with 18F-FDG uptake and prognostic impact in lung adenocarcinomas. *J Nucl Med* 2006;47(3):419–25.
19. Chen YK, Su CT, Ding HJ, Chi KH, Liang JA, Shen YY, et al. Clinical usefulness of fused PET/CT compared with PET alone or CT alone in nasopharyngeal carcinoma patients. *Anticancer Res* 2006;26(2B): 1471–7.
20. Antoch G, Saoudi N, Kuehl H, Dahmen G, Mueller SP, Beyer T, et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J Clin Oncol* 2004;22(21):4357–68.