Ann Nucl Med
DOI 10.1007/s12149-016-1127-2

ORIGINAL ARTICLE

Prognostic value of primary tumor SUV_{max} on F-18 FDG PET/CT compared with semi-quantitative tumor uptake on Tc-99m sestamibi breast-specific gamma imaging in invasive ductal breast cancer

Jang Yoo[1] · Hai-Jeon Yoon[1] · Bom Sahn Kim[1]

Received: 12 July 2016 / Accepted: 11 September 2016

Abstract
Objective This study aimed to evaluate the prognostic value of F-18 FDG PET/CT in comparison with Tc-99m sestamibi breast-specific gamma imaging (BSGI) and previously established clinical prognostic parameters of invasive ductal breast carcinoma (IDC).
Methods We retrospectively included 157 female IDC patients (mean age 49.2 years, range 29.9–78.9) who underwent PET/CT and BSGI. The maximum standardized uptake value (SUV_{max}) and tumor to normal background ratios (TNRs) of their primary tumors were measured on PET/CT and BSGI, respectively. Univariate and multivariate survival analyses were performed to evaluate the prognostic value of the measured parameters and other clinical prognostic factors: age, menopausal status, breast density, pathologic tumor size (pTS), axillary nodal status (ANS), nuclear grade, histologic grade, hormone receptor status of estrogen (ER) and progesterone receptors (PR) and HER-2 expression.
Results Among 157 patients, recurrences occurred in 22 patients (14.0 %). In univariate analyses, pTS ($p < 0.0001$), ANS ($p < 0.0001$), nuclear grade ($p = 0.0046$), histologic grade ($p = 0.0001$), ER status ($p < 0.0001$), PR status ($p = 0.0037$), HER-2 status ($p = 0.0007$), primary tumor SUV_{max} ($p < 0.0001$) and TNR ($p = 0.0001$) were significant predictors of recurrence. Among them, pTS ($p = 0.0172$), ANS ($p = 0.0416$), ER status ($p = 0.0375$) and primary tumor SUV_{max} ($p = 0.0239$) were independent prognostic factors in multivariate regression analysis.
Conclusions High primary tumor SUV_{max} of PET/CT and high TNR of BSGI were poor prognostic factors in IDC patients; in addition, primary tumor SUV_{max} was an independent prognostic factor along with pTS, ANS and ER status.

Keywords F-18 FDG PET/CT · Tc-99m sestamibi breast-specific gamma imaging · Invasive ductal breast carcinoma · Prognostic factor · Recurrence-free survival

Introduction

Breast cancer has been known to be a significant worldwide public health problem and progressive disease, which is the second leading cause of female cancer deaths [1, 2]. It is assumed that breast cancer is a heterogeneous tumor that exhibits various patterns of progression, different prognoses, and varying therapeutic outcomes.

Invasive ductal carcinoma (IDC) is well established as the most common histologic subtype of breast cancer, and is characterized by malignant ductal proliferation along with stromal invasion. The clinical management of IDC is assessed by TNM classification, histological grade and the expression of specific hormonal receptors and molecular characteristics in tissue specimens [3, 4]. Furthermore, up-to-date guidelines for breast cancer management have considered these factors to identify individualized treatment plans. After proper treatment, however, 10–20 % of the patients with early stages of breast cancer will relapse with locoregional recurrences or metastatic disease in their future life [5]. Therefore, determining the prognostic significance of IDC is very important, not only for discovering

✉ Bom Sahn Kim
kbomsahn@ewha.ac.kr

[1] Department of Nuclear Medicine, Ewha Womans University School of Medicine, Seoul, South Korea

Published online: 19 September 2016

the treatment strategies and patient stratification, but also for improving patients' survival rates.

In prior reports, the prognostic significance of IDC was affected by diverse clinic pathological characteristics, such as tumor size, axillary lymph node involvement, and histologic status [6, 7]. Furthermore, preoperative molecular imaging modalities have been established to identify the malignancy of primary breast cancer lesions and provide prognostic information.

F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is becoming a beneficial and approved imaging modality for assessing breast cancer recurrences and distant metastases [8]. Previous studies [9–11] have investigated the standardized uptake value (SUV) of primary breast cancer as an estimate of glucose metabolism that reflects the cancer cell glycolysis and metabolic activity of malignant tumors, which is significantly correlated with the disease prognosis.

Tc-99m sestamibi, a lipophilic cation, used in breast-specific gamma imaging (BSGI), a molecular breast imaging technique, has been proposed to become a valuable modality for detecting breast cancer as well as predicting its prognosis. The Tc-99m sestamibi uptake of BSGI represents mitochondria metabolic activity, and it is sequestered in response to mitochondrial transmembrane potentials and accumulates primarily within mitochondria [12, 13]. According to a previous study [14], Tc-99m sestamibi has been shown to correlate with histological, molecular and biochemical features of various cellular pathways, such as apoptosis, proliferation, P-glycoprotein expression and neoangiogenesis.

Both FDG-PET/CT and BSGI have been suggested as valuable molecular imaging tools that indicate the biological features of cancer and predict the future disease prognosis [9, 12]. FDG-PET/CT is necessary for the evaluation of nodal status and distant metastasis at initial work-up and BSGI is an effective complementary modality to discriminate multifocal or multicentric breast lesions, especially in dense breasts. There are some reports to demonstrate that BSGI is more sensitive in detection of ductal carcinoma in situ (DCIS) than FDG-PET/CT. On FDG-PET/CT, sensitivity was 75 % for DCIS, however, sensitivity was 83 % for DCIS on BSGI [15, 16]. For these reasons, several clinical institutions use those imaging modalities together and the clinical comparison of them would be important. To the best of our knowledge, there have not been any analyses comparing the value of prognostic factors between F-18 FDG and Tc-99m sestamibi uptake in patients with breast cancer.

The aim of this study is to investigate the prognostic significance of nuclear imaging parameters by FDG PET/CT and BSGI for predicting disease recurrence in breast cancer.

Materials and methods

Patients

A retrospective review of our database between November 2010 and August 2013 included 157 patients who were newly diagnosed with breast cancer and who underwent preoperative F-18 FDG-PET/CT and Tc-99m BSGI as well as mammography (MMG), ultrasonography (US) and/or magnetic resonance imaging (MRI). All patients underwent surgery: 116 had breast conserving surgeries and subsequent radiotherapy, 33 had modified radical mastectomies and eight had skin-sparing mastectomies with breast reconstruction; in all patients, IDC was histologically confirmed. Among them, 104 patients were treated with adjuvant chemotherapy in accordance with standard guidelines of National Comprehensive Cancer Network (NCCN). We excluded women who had bilateral breast cancer, a distant metastasis or a previous history of another malignancy and the patients who had neoadjuvant chemotherapy or radiotherapy before PET/CT or BSGI.

During the follow-up period after surgery, the follow-up protocol was based on regular visits every 3 months, and the final update to the clinical application was made in April 2016. The retrospective chart review was approved by our institutional review board, and all of the clinical information was obtained from medical records.

F-18 FDG-PET/CT and image analysis

All patients fasted for at least 6 h before the F-18 FDG-PET/CT scans. Blood glucose levels were measured and were required to be less than 140 mg/dl before an intravenous injection of 5.18 MBq/kg of F-18 FDG. A CT scan without contrast agent was performed first, and then a PET scan was obtained from the base of the skull to the thigh, using a Siemens Biograph mCT with 128-slice CT (Siemens Medical Solutions, Erlangen, Germany) at 1 h after an injection of radiopharmaceutical isotope. The spatial resolution at the center of the PET was 2.0 mm full width at half maximum (FWHM) in the transaxial direction and 2.0 mm FWHM in the axial direction. Three-dimensional emission was used for the acquisition parameters for PET images, and it required a 2 min scan per bed position for 5–7 positions. PET images were reconstructed to 200 × 200 matrices and 3.4 mm × 3.4 mm pixel sizes with a 3.0-mm slice thickness using a three-dimensional OSEM iterative algorithm (two iterations and 21 subsets) with time of flight and point spread functions. The patients were supine position and were allowed to breathe normally during PET/CT image acquisition.

Two experienced nuclear medicine physicians (J.Y. and B.S.K with 5- and 10-year experiences in nuclear medicine

imaging, respectively) who were strictly blinded to the patient's clinical information, reviewed the PET/CT images, and a final consensus was reached for each patient. Image interpretation was performed in terms of the identification of FDG uptake regions and the anatomic delineation of all FDG-avid lesions on the co-registered PET/CT images. Quantitative analyses of primary breast tumors were measured using commercial software (Siemens Medical Solutions, Erlangen, Germany), which produces a convenient and automatic way to delineate a three-dimensional volume of interest (VOI) of a primary tumor using an isocontour threshold method. For quantitative analysis, images of each breast tumor were evaluated by calculating the SUV_{max} normalized to the patient's body weight. Then, the SUV_{max} was compared between patient groups with reference to each clinicopathological variable, such as the tumor size, axillary lymph node status (ANS), histologic grade, nuclear grade, hormone receptor status of estrogen (ER) and progesterone (PR) and human epidermal growth factor receptor-2 (HER-2) expression.

BSGI and image analysis

Each patient was intravenously injected with 555–925 MBq of Tc-99m sestamibi via an upper extremity on the opposite side to the primary breast cancer. After 10 min, patients were placed in the seated position and craniocaudal (CC) and mediolateral oblique (MLO) images of bilateral breasts were acquired by a high-resolution breast-specific gamma camera (Dilon 6800 gamma camera; Dilon Technologies, Newport News, VA, USA) with a systemic energy window centered over the 140-keV photopeak. For each planar image, more than 100,000 counts were obtained for the CC imaging and more than 120,000 counts for the MLO imaging using a low-energy general-purpose collimator.

All images were interpreted by the same physicians who reviewed the PET/CT images and were analyzed in consensus. The tumor to normal background ratio (TNR) was obtained by measuring the number of uptake counts of the primary tumor and normal background breast tissue, respectively. In this study, the primary tumor and normal background uptake counts were used as a circular region of interest (ROI) covering the tumor lesion and background breast tissue of each patient; this was previously used as the semiquantitative method in BSGI [12]. Maximal pixel counts of the primary tumor were measured on each planar image. Three circular ROIs with 1 cm in diameter were placed on normal background breast tissue, and the average of the mean pixel counts of these three ROIs were considered as a single value. The TNR was then estimated by dividing the maximal pixel count of the primary tumor by the mean value of normal background breast tissue uptake. The higher TNR was determined for further analysis between CC and MLO images. Likewise, the TNR was compared between patient groups according to each clinicopathological factor.

Clinicopathological characteristics and treatment

Clinicopathological characteristics analyses included age, menopausal status, breast density, pathologic tumor size, axillary lymph node involvement and nuclear and histologic grades, which were scored by the modified Bloom-Richardson grading system. Immunohistochemistry (IHC) was assessed by an indirect immunoperoxidase protocol using antibodies directed against ER, PR and HER-2. ER and PR positivity were determined as the presence of 10 % or more positively stained nuclei in ten high power fields, according to the Allred system. Staining results of HER-2 were classified according to the American Society of Clinical Oncology/College of American Pathologists guidelines [17]. HER-2 positivity was defined as 3+ in IHC or 2+ in gene amplification using fluorescence in situ hybridization of greater than 2.2-fold. Triple negativity denoted all negative findings for ER, PR, and HER-2.

During follow-up, when patients were suspected to have a recurrence, imaging studies including US, MMG, chest CT, whole body bone scan, PET/CT or histologic diagnosis were ordered depending on the corresponding physician's discretion. Time to recurrence was calculated as the time interval from the date of the initial diagnosis to the date of the first finding that suggested recurrence on any images and that led to further studies (e.g., pathologic confirmation or additional imaging studies).

Statistical analysis

Data are listed as the mean value ± the standard deviation and the 95 % confidence interval (CI). The correlation between the levels of primary tumor SUV_{max}, TNR and clinicopathological characteristics were investigated using the independent *t* test for bimodal variables and the analysis of variance test for trimodal variables as calculated by the MedCalc software package (Ver. 9.5, MedCalc Software, Mariakerke, Belgium). To evaluate the optimal cut-off values of SUV_{max} and TNR for the prediction of disease recurrence, receiver-operating characteristic (ROC) analysis was performed. For survival analysis, Kaplan–Meier analysis and Cox proportional regression analysis were used regarding disease recurrence. The log-rank test was used for the univariate analysis of the prognostic factors. All prognostic variables with statistical significance in univariate analysis were included in the multivariate regression analysis to investigate independent significant factors. Variables were entered into the multivariate

regression model in a stepwise method if $p < 0.05$ and were removed if $p > 0.1$. A p value of less than 0.05 was considered statistically significant.

Results

Patients' characteristics

Patient characteristics are detailed in Table 1. The mean age of the subjects was 49.2 ± 10.2 years (range 29.9–78.9 years), and the mean clinical follow-up period was 35.1 ± 14.4 months (range 6.8–62.8 months). Disease recurrence occurred in 22 patients (14.0 %). Pathologic tumor size (pTS) was estimated at its greatest diameter confirmed by pathologic report, and the cutoff point was ≤20 mm. Axillary lymph node status was divided into two categories, negative and positive, according to pathologic report.

Table 1 Characteristics of patients

Variable	Status	Number	%
Age (years)	≤50	99	63.1
	>50	58	36.9
Menopausal status	Pre	98	62.4
	Post	59	37.6
Breast density	Non-dense	31	19.7
	Dense	126	80.3
Tumor size (mm)	≤20	92	58.6
	>20	65	41.4
ANS	Negative	99	63.1
	Positive	58	36.9
Nuclear grade	G1	7	4.5
	G2	90	57.3
	G3	60	38.2
Histologic grade	G1	33	21.0
	G2	69	43.9
	G3	55	35.1
ER	Negative	33	21.0
	Positive	124	79.0
PR	Negative	33	21.0
	Positive	124	79.0
HER-2	Negative	121	77.1
	Positive	36	22.9
TN	TN	10	6.4
	Non-TN	147	96.7
SUV_{max}	>8.7	35	22.3
	≤8.7	122	77.7
TNR	>4.01	51	32.5
	≤4.01	106	67.5

ANS axillary lymph node status, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor 2, *TN* triple negative, SUV_{max} maximum standardized uptake value, *TNR* tumor to normal background ratio

Correlation between nuclear medicine imaging parameters and clinicopathologic factors

Table 2 shows the SUV_{max} differences with respect to the clinicopathologic factors and TNR. The mean SUV_{max} value of the 157 patients was 6.4 ± 4.5 (range 1.2–26.5). Among the clinicopathologic factors, the pTS, ANS, nuclear grade, histologic grade, ER and PR had significant correlation with SUV_{max}, which increased with increasing tumor size and tumor grade ($p < 0.001$). SUV_{max} was significantly higher in ER-negative ($p = 0.0019$), PR-negative ($p = 0.0067$) and positive ANS ($p = 0.0195$) groups. SUV_{max} was significantly different between the TNR subgroups (cutoff value: 4.01, $p < 0.0001$). However, there was no significant correlation between SUV_{max} and age, menopausal status, breast density, HER-2 status or triple negative status. In the multivariate analysis, pTS ($p = 0.0023$), histologic grade ($p < 0.0001$) and TNR ($p < 0.0001$) were determined to be independent factors.

Correlations between TNR and the clinicopathologic factors are listed in Table 3. The pTS ($p < 0.0001$), ANS ($p = 0.0466$), histologic grade ($p = 0.004$), ER ($p = 0.0049$) and PR ($p = 0.0006$) showed significant correlations with TNR. TNR was also significantly different between SUV_{max} subgroups (cutoff value: 8.7, $p = 0.0027$). However, there was no significant correlation between TNR and age, menopausal status, breast density, nuclear grade, HER-2 status or triple negative tumors. Only pTS ($p = 0.0001$) and PR ($p = 0.0017$) were identified as independent variables in the multivariate analysis.

Recurrence-free survival

An ROC curve suggested a SUV_{max} of 8.7 to be the proper cutoff value to predict recurrence-free survival (RFS); the area under the curve (AUC) was 0.773, and the standard error was 0.0631. An SUV_{max} of 8.7 presented 72.7 % sensitivity and 82.2 % specificity for predicting the disease recurrence. The optimal cutoff value of TNR by ROC curve analysis was 4.01 (AUC: 0.716, standard error 0.0522). The sensitivity and specificity of TNR in the prediction of recurrence were 72.7 and 70.4 %, respectively.

The results of the univariate analyses are listed in Table 4. The RFS of the high SUV_{max} and TNR groups were significantly lower than those of the opposite groups were ($p < 0.0001$ and $p = 0.0001$, respectively). The survival curves of each group are shown in Fig. 1. In univariate analyses, large pTS ($p < 0.0001$), positive ANS ($p < 0.0001$), high nuclear grade ($p = 0.0046$), high

Table 2 Correlation between SUV_{max} and clinicohistopathologic features of IDC

Variable	SUV_{max}	*p* value	
		Univariate	Multivariate
Age (years)		0.1406	
≤50	6.81 ± 4.92		
>50	5.70 ± 3.60		
Menopausal status		0.2985	
Pre	6.69 ± 4.97		
Post	5.91 ± 3.64		
Breast density		0.4918	
Non-dense	6.90 ± 5.18		
Dense	6.27 ± 4.31		
Tumor size (mm)		<0.0001*	0.0023*
≤20	4.56 ± 3.47		
>20	8.45 ± 4.50		
ANS		0.0195*	
Negative	5.75 ± 4.17		
Positive	7.50 ± 4.84		
Nuclear grade		<0.001*	
G1	2.68 ± 0.72		
G2	5.16 ± 3.17		
G3	8.69 ± 5.37		
Histologic grade		<0.001*	<0.0001*
G1	3.38 ± 1.72		
G2	5.54 ± 3.23		
G3	9.29 ± 5.31		
ER		0.0019*	
Negative	8.56 ± 5.34		
Positive	5.82 ± 4.06		
PR		0.0067*	
Negative	8.29 ± 4.62		
Positive	5.89 ± 4.34		
HER-2		0.1032	
Negative	6.08 ± 4.64		
Positive	7.48 ± 3.86		
Triple negative		0.0793	
TN	8.84 ± 5.87		
Non-TN	6.23 ± 4.34		
TNR		<0.0001*	<0.0001*
>4.01	9.27 ± 4.89		
≤4.01	4.81 ± 3.36		

ANS axillary lymph node status, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor 2, *TN* triple negative, SUV_{max} maximum standardized uptake value, *TNR* tumor to normal background ratio

* $p < 0.05$

Table 3 Correlation between TNR and clinicohistopathologic features of IDC

Variable	TNR	*p* value	
		Univariate	Multivariate
Age (years)		0.4537	
≤50	3.60 ± 1.50		
>50	3.81 ± 1.91		
Menopausal status		0.1715	
Pre	3.54 ± 1.45		
Post	3.92 ± 1.95		
Breast density		0.5250	
Non-dense	3.51 ± 1.31		
Dense	3.72 ± 1.74		
Tumor size (mm)		<0.0001*	0.0001*
≤20	3.16 ± 1.28		
>20	4.34 ± 1.78		
ANS		0.0466*	
Negative	3.48 ± 1.57		
Positive	4.03 ± 1.78		
Nuclear grade		0.076	
G1	2.69 ± 0.71		
G2	3.55 ± 1.46		
G3	4.00 ± 1.93		
Histologic grade		0.004*	
G1	2.99 ± 1.00		
G2	3.60 ± 1.49		
G3	4.20 ± 2.00		
ER		0.0049*	
Negative	4.41 ± 2.25		
Positive	3.49 ± 1.41		
PR		0.0006*	0.0017*
Negative	4.56 ± 2.17		
Positive	3.45 ± 1.41		
HER-2		0.0679	
Negative	3.55 ± 1.51		
Positive	4.13 ± 2.05		
Triple negative		0.4006	
TN	4.11 ± 1.87		
Non-TN	3.65 ± 1.64		
SUV_{max}		0.0027*	
>8.7	4.36 ± 1.33		
≤8.7	3.45 ± 1.70		

ANS axillary lymph node status, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor 2, *TN* triple negative, SUV_{max} maximum standardized uptake value, *TNR* tumor to normal background ratio

* $p < 0.05$

Table 4 Significance of variables in univariate survival analyses

Variable	No. of recurrences	Mean survival (months)	*p* value
Age (years)			0.9352
≤50	14	36.0 ± 13.6	
>50	8	33.5 ± 15.2	
Menopausal status			0.1795
Pre	11	36.2 ± 13.3	
Post	11	33.3 ± 15.5	
Breast density			0.3189
Non-dense	6	33.1 ± 16.4	
Dense	16	35.6 ± 13.7	
Tumor size (mm)			<0.0001*
≤20	2	38.0 ± 13.6	
>20	20	31.0 ± 14.5	
ANS			<0.0001*
Negative	5	36.0 ± 14.6	
Positive	17	33.5 ± 13.6	
Nuclear grade			0.0046*
G1	0	40.8 ± 11.1	
G2	7	36.3 ± 13.9	
G3	15	32.6 ± 14.6	
Histologic grade			0.0001*
G1	0	37.9 ± 14.5	
G2	6	36.5 ± 13.5	
G3	16	32.1 ± 14.6	
ER			<0.0001*
Negative	12	28.8 ± 12.7	
Positive	10	36.8 ± 14.2	
PR			0.0037*
Negative	9	29.3 ± 14.3	
Positive	13	36.6 ± 13.9	
HER-2			0.0007*
Negative	11	36.0 ± 13.5	
Positive	11	32.0 ± 16.2	
Triple negative			0.5530
TN	2	33.9 ± 10.2	
Non-TN	20	35.2 ± 14.3	
SUV_{max}			<0.0001*
>8.7	16	36.6 ± 14.1	
≤8.7	6	30.7 ± 13.8	
TNR			0.0001*
>4.01	16	31.9 ± 14.9	
≤4.01	6	36.9 ± 13.6	

ANS axillary lymph node status, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor receptor 2, *TN* triple negative, SUV_{max} maximum standardized uptake value, *TNR* tumor to normal background ratio

* $p < 0.05$

histologic grade ($p = 0.0001$), negative ER ($p < 0.0001$), negative PR ($p = 0.0037$) and positive HER-2 ($p = 0.0007$) were statistically significant as poor prognostic factors for RFS. After multivariate analysis, only ER status ($p = 0.0375$), ANS ($p = 0.0416$), pTS ($p = 0.0172$) and SUV_{max} ($p = 0.0239$) were evaluated as

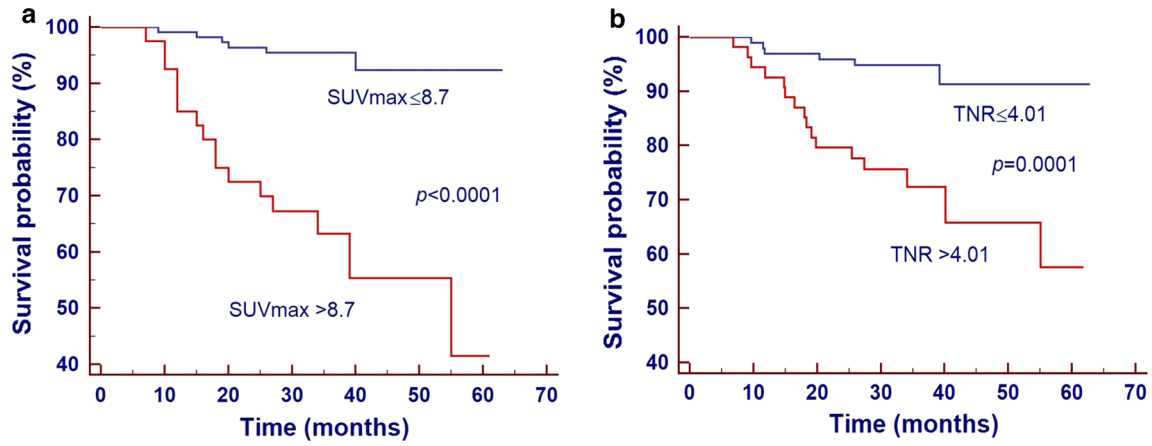

Fig. 1 Kaplan–Meier survival curves of nuclear imaging parameters in invasive ductal breast cancer: **a** SUV_{max} and **b** TNR

Table 5 Results of multivariate analysis for predicting recurrence-free survival

Variable	HR	95 % CI	*p* value
ER status			
Negative	2.7501	1.0657–7.0972	0.0375
ANS			
Positive	2.9968	1.0482–8.5676	0.0416
SUV_{max}			
>8.7	3.4430	1.1843–10.0096	0.0239
Tumor size (mm)			
>20	6.6699	1.4103–31.5459	0.0172

ER estrogen receptor, *ANS* axillary lymph node status, SUV_{max} maximum standardized uptake value, *HR* hazard ratio, *CI* confidence interval

independent significant prognostic factors for predicting RFS (Table 5). Representative cases with different prognostic factors are illustrated in Figs. 2 and 3.

Predictive values of PET/CT and BSGI according to the breast density

For further evaluation, the patients were categorized into two groups according to mammography categories as defined by the Breast Imaging Reporting and Data System as follows: BI-RADS type I: glandular tissue is less than 25 %, type 2: ranging from 25 to 50 % of breast, type 3: ranging from 51 to 75 % of the breast tissue, type 4: greater than 75 % glandular and fibrous tissue. 31 were in the non-dense breast patients group (BI-RADS type 1 and 2) and 126 were in the dense breast patients group (BI-RADS type 3 and 4). Then, we analyzed and compared the SUV_{max} and TNR of each group to determine the prognostic values and the significant differences between patients with non-dense and dense breasts. There were no significant correlations with the SUV_{max} and TNR of the primary tumors between those groups. In multivariate analysis, only SUV_{max} was a significant independent prognostic factor in both the non-dense breast group and the dense breast group ($p = 0.0100$, HR 26.9498, CI 2.2245–326.4966, and $p = 0.0020$, HR 5.3673, CI 1.8627–15.4652, respectively).

Discussion

The use of nuclear molecular imaging modalities such as PET/CT and BSGI for breast cancer can improve primary tumor detection and predict the prognosis after treatment. In this study, we demonstrated the prognostic values of nuclear molecular parameters determined by PET/CT and BSGI compared with previously well-known prognostic parameters in patients with breast cancer. Our study indicated that SUV_{max}, which represents the aggressiveness of the malignant lesion, is an independent prognostic parameter for RFS as important as larger tumor size, axillary lymph node involvement and ER negativity, which have been established as clinicopathological prognostic factors [18, 19]. Therefore, primary breast cancers with higher levels of SUV_{max} indicate more aggressive features than those with a low SUV_{max}. These results correspond with those of previous studies [20, 21]. In our current study, univariate survival analyses showed that TNR was statistically significant ($p = 0.0001$); however, in multivariate analysis, TNR was not a statistically significant prognostic factor. These results differ from those of Yoon et al. [12], who studied 162 patients with invasive ductal breast cancer for prognostic value using semi-quantitative tumor uptake on Tc-99m sestamibi BSGI, suggesting TNR was the independent prognostic factor in IDC. This difference might be because Yoon et al. analyzed the significance of BSGI

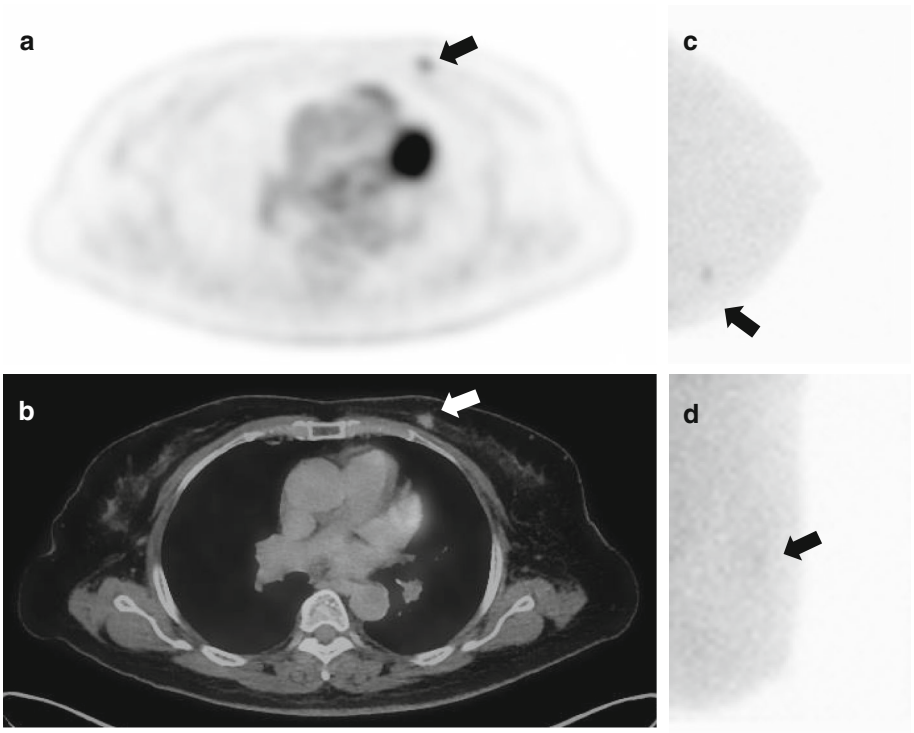

Fig. 2 A 40-year-old patient diagnosed with invasive ductal breast cancer (SUV_{max} 1.7, TNR 2.1, negative ANS, pTS 11 mm, positive ER). **a** PET and **b** transaxial fusion view of ^{18}F FDG PET/CT and **c** CC view and **d** MLO view of BSGI demonstrate faint uptake in the upper inner quadrant of left breast (*arrows*). This patient had no recurrence during the follow-up period of 31.2 months

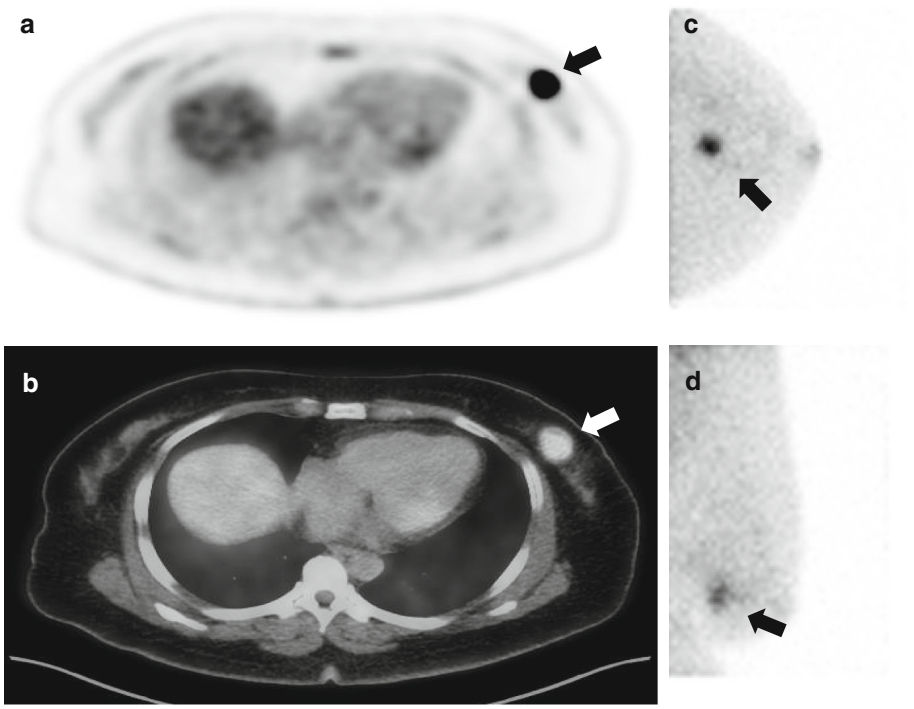

Fig. 3 A 47-year-old patient diagnosed with invasive ductal breast cancer (SUV_{max} 22.3, TNR 5.73, positive ANS, pTS 21 mm, negative ER). In **a** PET and **b** transaxial fusion view of ^{18}F FDG PET/CT, a hypermetabolic lesion in the lower outer quadrant of left breast and a lymph node with focal FDG uptake in the left axillary area were shown. **c** CC view and **d** MLO view of BSGI demonstrate focal uptake in the lower outer quadrant of left breast (*arrows*). This patient had a recurrence in the left cervical lymph node after 18.3 months

only to predict the prognoses in patients with breast cancer. Other possibilities may include the fact that in PET/CT with automatic delineation, the interobserver variability of the three-dimensional VOI would be decreased, and therefore this could emphasize the detection of breast cancer using higher contrast between primary tumor and background breast tissue than that of BSGI. Additionally, it is presumed that the factors affecting SUV_{max} value, such as glucose transporter expression and hexokinase activity in tumor cells, could be more valuable prognostic indicators than the mitochondrial metabolic activity represented by BSGI.

Although TNR is a convenient semiquantitative measure, as it is a measurement of the radiotracer accumulation within the ROI, it may depend not only on abundant mitochondrial activity within tumor cells, but also on breast fibroglandular density [22–24]. These previous reports have noted that the background uptake of BSGI could be affected by breast density and could influence the value of TNR due to the limitations of accurate ROI delineation on BSGI images. In addition, there have been several published reports evaluating factors that affect F-18 FDG uptake in normal breast tissue, such as breast density, and controversy regarding this issue remains [25–27]. Therefore, we speculated that there might be a relationship between normal background uptake on PET/CT and BSGI according to the breast density in respect of this limitation. We demonstrated that the SUV_{max} of the primary tumor may be less affected by breast density and can be assessed as an independent prognostic factor in patients with invasive ductal carcinoma regardless of their breast density.

In this study, nuclear molecular imaging parameters such as SUV_{max} and TNR were significantly correlated with the clinicopathologic features. As established by previous studies, this study verifies that PET/CT and BSGI parameters have potential prognostic importance and may be valuable imaging modalities for predicting the molecular characteristics of the breast cancer and the disease prognosis. The highlight of our study results in evaluating breast cancer patients for RFS is that SUV_{max} is expected to provide superior prognostic implications compared to TNR, and we also demonstrated that SUV_{max} is an independent prognostic factor in patients with both non-dense and dense breasts. This is the first study that statistically investigated the differences in the prognostic values of PET/CT and BSGI parameters for predicting the disease recurrence.

There were some limitations to this study. First, it is a retrospective study that may include variations in menstrual cycles, and hormone replacement therapy or hormonal stimuli have been suggested to affect the F-18 FDG and Tc-99m sestamibi uptake. Second, because these results were conducted in patients with IDC only, the findings cannot be generalized to other subtypes of breast cancer, even though the majority of breast cancers consist of the IDC subtype. Therefore, we suggest that further prospective studies are necessary to design and evaluate the prognostic factors in patients with breast cancer according to whole histologic subtype. Despite these limitations, this study provides strong evidence to demonstrate the clinical value of PET/CT, which should be considered an important factor to determine the patient's treatment strategy and predict the prognosis.

Acknowledgments This research was supported by Grants (2015R1C1A1A02037051, 2012M3A9B6055379) from the National Research Foundation of South Korea.

References

1. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomark Prev. 2010;19:1893–907.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58:71–96.
3. Choi BB, Kim SH, Kang BJ, Lee JH, Song BJ, Jeong SH, et al. Diffusion-weighted imaging and FDG PET/CT: predicting the prognoses with apparent diffusion coefficient values and maximum standardized uptake values in patients with invasive ductal carcinoma. World J Surg Oncol. 2012;10:126.
4. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract. 2010;6:195–7.
5. Freedman GM, Fowble BL. Local recurrence after mastectomy or breast-conserving surgery and radiation. Oncology (Williston Park, NY). 2000;14:1561–81 **(discussion 1581–2, 1582–4)**.
6. Biglia N, Maggiorotto F, Liberale V, Bounous VE, Sgro LG, Pecchio S, et al. Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). Eur J Surg Oncol. 2013;39:455–60.
7. Lim ST, Choi JE, Kim SJ, Kim HA, Kim JY, Park HK, et al. Prognostic implication of the tumor location according to molecular subtypes in axillary lymph node-positive invasive ductal cancer in a Korean population. Breast Cancer Res Treat. 2016;156:473–83.
8. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat. 2005;90:105–12.
9. Song BI, Hong CM, Lee HJ, Kang S, Jeong SY, Kim HW, et al. Prognostic value of primary tumor uptake on F-18 FDG PET/CT in patients with invasive ductal breast cancer. Nucl Med Mol Imaging. 2011;45:117–24.
10. Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. 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. 2008;38:250–8.
11. Nakajo M, Kajiya Y, Kaneko T, Kaneko Y, Takasaki T, Tani A, et al. FDG PET/CT and diffusion-weighted imaging for breast cancer: prognostic value of maximum standardized uptake values and apparent diffusion coefficient values of the primary lesion. Eur J Nucl Med Mol Imaging. 2010;37:2011–20.
12. Yoon HJ, Kim Y, Chang KT, Kim BS. Prognostic value of semiquantitative tumor uptake on Tc-99m sestamibi breast-specific gamma imaging in invasive ductal breast cancer. Ann Nucl Med. 2015;29:553–60.
13. Del Vecchio S, Zannetti A, Aloj L, Salvatore M. MIBI as prognostic factor in breast cancer. Q J Nucl Med. 2003;47:46–50.
14. Del Vecchio S, Salvatore M. 99mTc-MIBI in the evaluation of breast cancer biology. Eur J Nucl Med Mol Imaging. 2004;31(Suppl 1):S88–96.
15. Span A, Chessa F, Meloni GB, Sanna D, Cottu P, Manca A, et al. The role of planar scintimammography with high-resolution dedicated breast camera in the diagnosis of primary breast cancer. Clin Nucl Med. 2008;33:739–42.

16. Yoon HJ, Kim YM, Kim BS. Intratumoral metabolic heterogeneity predicts invasive components in breast ductal carcinoma in situ. Eur Radiol. 2015;25:3648–58.
17. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25:118–45.
18. 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. C. W. Elston & I. O. Ellis. Histopathology 1991; 19; 403–10. Histopathology. 2002;41:151–2.
19. Garne JP, Aspegren K, Linell F, Rank F, Ranstam J. Primary prognostic factors in invasive breast cancer with special reference to ductal carcinoma and histologic malignancy grade. Cancer. 1994;73:1438–48.
20. Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-deoxy-2-fluoro-D-glucose-positron emission tomography. J Cancer Res Clin Oncol. 2004;130:273–8.
21. Ikenaga N, Otomo N, Toyofuku A, Ueda Y, Toyoda K, Hayashi T, et al. Standardized uptake values for breast carcinomas assessed by fluorodeoxyglucose-positron emission tomography correlate with prognostic factors. Am Surg. 2007;73:1151–7.
22. Wei J, Chan HP, Helvie MA, Roubidoux MA, Sahiner B, Hadjiiski LM, et al. Correlation between mammographic density and volumetric fibroglandular tissue estimated on breast MR images. Med Phys. 2004;31:933–42.
23. Kim BS. Usefulness of breast-specific gamma imaging as an adjunct modality in breast cancer patients with dense breast: a comparative study with MRI. Ann Nucl Med. 2012;26:131–7.
24. Yoon HJ, Kim Y, Lee JE, Kim BS. Background 99mTc-methoxyisobutylisonitrile uptake of breast-specific gamma imaging in relation to background parenchymal enhancement in magnetic resonance imaging. Eur Radiol. 2015;25:32–40.
25. Vranjesevic D, Schiepers C, Silverman DH, Quon A, Villalpando J, Dahlbom M, et al. Relationship between 18F-FDG uptake and breast density in women with normal breast tissue. J Nucl Med. 2003;44:1238–42.
26. Kumar R, Chauhan A, Zhuang H, Chandra P, Schnall M, Alavi A. Standardized uptake values of normal breast tissue with 2-deoxy-2-[F-18]fluoro-D:glucose positron emission tomography: variations with age, breast density, and menopausal status. Mol Imaging Biol. 2006;8:355–62.
27. Mavi A, Cermik TF, Urhan M, Puskulcu H, Basu S, Cucchiara AJ, et al. The effect of age, menopausal state, and breast density on (18)F-FDG uptake in normal glandular breast tissue. J Nucl Med. 2010;51:347–52.