BREAST

Tumour 18 F-FDG Uptake on preoperative PET/CT may predict axillary lymph node metastasis in ER-positive/HER2-negative and HER2-positive breast cancer subtypes

Jin You Kim · Suck Hong Lee · Suk Kim · Taewoo Kang · Young Tae Bae

Abstract

Objectives To evaluate the association between tumour FDG uptake on preoperative PET/CT and axillary lymph node metastasis (ALNM) according to breast cancer subtype.
Methods The records of 671 patients with invasive breast cancer who underwent ^{18}F-FDG PET/CT and surgery were reviewed. Using immunohistochemistry, tumours were divided into three subtypes: oestrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, and triple-negative. Tumour FDG uptake, expressed as maximum standardized uptake value (SUV_{max}), and clinicopathological variables were analysed.
Results ALNM was present in 187 of 461 ER-positive/HER2-negative, 54 of 97 HER2-positive, and 38 of 113 triple-negative tumours. On multivariate analysis, high tumour SUV_{max} (≥4.25) ($P<0.001$), large tumour size (>2 cm) ($P=0.003$) and presence of lymphovascular invasion ($P<0.001$) were independent variables associated with ALNM. On subset analyses, tumour SUV_{max} maintained independent significance for predicting ALNM in ER-positive/HER2-negative (adjusted odds ratio: 3.277, $P<0.001$) and HER2-positive tumours (adjusted odds ratio: 14.637, $P=0.004$). No association was found for triple-negative tumours ($P=0.161$).

Conclusions Tumour SUV_{max} may be an independent prognostic factor for ALNM in patients with invasive breast cancer, especially in ER-positive/HER2-negative and HER2-positive subtypes, but not in those with triple-negative subtype.
Key points
• Tumour SUV_{max} could be an imaging biomarker for predicting ALNM
• Tumour SUV_{max} predicting ALNM is effective in ER-positive/HER2-negative and HER2-positive subtypes
• Tumour SUV_{max} predicting ALNM is inaccurate in triple-negative subtypes
• Accurate prognostic prediction based on molecular subtype may facilitate individualized management

Keywords Breast neoplasms · Positron-emission tomography · Subtype · Lymph nodes · Metastasis

J. Y. Kim (✉) · S. H. Lee · S. Kim
Department of Radiology, Pusan National University Hospital, Pusan National University School of Medicine and Medical Research Institute, 1-10, Ami-Dong, Seo-gu, Busan 602-739, Korea
e-mail: youdosa@naver.com

T. Kang
Busan Cancer Center, Pusan National University Hospital, Busan, Republic of Korea

Y. T. Bae
Department of Surgery, Pusan National University Hospital, Busan, Republic of Korea

Introduction

The axillary lymph node (ALN) status is the most powerful prognostic factor and an important guide for treatment planning in patients with breast cancer [1, 2]. Although lymphovascular invasion, tumour size, and histological grade are well known for their association with ALN involvement [3–5], these established prognosticators are not always sufficient to justify omission of axillary dissection in patients at low risk of ALN metastasis. Efforts for preoperative risk assessment regarding ALN status are warranted and ongoing.

Breast cancer is a heterogeneous disease consisting of biologically distinct tumour subtypes. The breast molecular subtype has been correlated with tumour aggressiveness and identified as an independent prognostic factor for survival in patients with breast cancer [6, 7]. Immunohistochemical

(IHC) classification based on expression of the oestrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) is the most frequently used molecular marker in clinical practice and is valuable in predicting the clinical outcome as well as guiding targeted treatments [8]. IHC classification categorizes breast tumours into three major tumour subtypes: ER-positive (i.e., ER positive, HER2 negative, PR may be positive or negative), HER2-positive (i.e., HER2 positive; ER and PR may be positive or negative), and triple-negative (i.e., ER negative, PR negative and HER2 negative) [9, 10]; these correspond roughly to the intrinsic molecular subtypes of luminal, HER2-positive, and basal-like forms, respectively [11].

[18]F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is becoming increasingly important in the diagnosis and management of patients with breast cancer [12–14]. Recent studies found that ^{18}F-FDG uptake in breast cancer is associated with typical prognostic factors, including tumour size, lymph node status, and histological grade, as well as tumour subtype, which is also an independent predictor for prognosis [15–17]. However, controversy remains concerning the prognostic value of tumour ^{18}F-FDG uptake with regard to ALN metastasis, and little is known about potential differences in its value among molecular breast cancer subtypes.

Therefore, the purpose of the current study was to evaluate the association between tumour ^{18}F-FDG uptake on preoperative PET/CT and ALN metastasis in patients with various subtypes of invasive breast cancer.

Materials and methods

Patients

The Institutional Review Board of our hospital approved this study, and the requirement for informed consent was waived. Between January 2011 and December 2013, the medical records of 785 consecutive women diagnosed with invasive breast cancer who underwent whole-body ^{18}F-FDG PET/CT before breast surgery were evaluated retrospectively. Among these 785 patients, 114 were excluded: 39 who underwent surgical excision or vacuum-assisted breast biopsy for diagnosis prior to ^{18}F-FDG PET/CT, 42 with no focal uptake on ^{18}F-FDG PET/CT, 25 with an invasive tumour size <1 cm, and eight with no immunohistochemical data available. In women with bilateral cancer, only one tumour was included, and in women with multifocal or multicentric cancer, the largest tumour was included. After the exclusions, a total of 671 female patients with invasive breast tumours comprised our study population. The mean interval between the times of ^{18}F-FDG PET/CT and surgery was 13.5 days (range 1–34 days).

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT images were obtained using a Biograph instrument (Siemens Medical Solutions, Hoffman Estates, IL, USA) from the skull base to the upper thigh 1 h after intravenous administration of ^{18}F-FDG. All patients fasted for at least 8 h and had serum glucose levels <120 mg/dL at the time of ^{18}F-FDG injection (5.2 MBq/kg of body weight). First, a CT was acquired for attenuation correction (tube voltage 120 kVp, current intensity 80-170 mAs, and slice thickness 3 mm) without the use of a contrast agent, and a PET was then acquired in three-dimensional mode for 3 min per bed position. PET images were reconstructed to 168×168 image matrices using an iterative algorithm (two iterations, 21 subsets). The CT, PET, and fused PET/CT images were displayed in axial, coronal, and sagittal planes and were reviewed on a workstation.

The PET/CT images were interpreted by two experienced nuclear medicine physicians with consensus. Regions of interest were placed manually over the most intense areas on primary breast tumour slices on attenuation-corrected images. The SUV_{max} within the regions of interest was obtained and calculated as follows: SUV_{max}=maximum activity concentration in region of interest (MBq/g) / [injected dose (MBq)/body weight (g)].

Histological examination and immunohistochemistry

All patients underwent surgical resection for breast cancer with sentinel lymph node biopsy and/or axillary lymph node dissection. The histological type of invasive breast cancer, tumour size, histological grade, and lymphovascular invasion (LVI) status were determined from the surgically excised specimens. TNM staging was performed according to the American Joint Committee on Cancer (AJCC) sixth edition [18]. The tumours were graded histologically using the Nottingham combined histological grade system [19].

The formalin-fixed, paraffin-embedded tissue blocks were used for IHC. The expression status of ER, PR, HER2, p53, and Ki-67 was determined based on the surgical specimens by the avidin-biotin complex immunohistochemical technique. The ER and PR status was assessed using the Allred score, which was expressed as the sum of the proportion score and the intensity score of positively stained tumour cells [20]. Tumours with an Allred score of at least 3 were regarded as positive. The intensity of HER2 staining was scored as 0, 1+, 2+, or 3+ [21]. Tumours with a 3+ score were considered HER2-positive, and those with a 0 or 1+ score were considered HER2-negative. Tumours with a 2+ score were subjected to fluorescence *in situ* hybridization (FISH) analysis to determine the HER2 status. If the ratio of the HER2 gene signal to chromosome 17 probe signal was >2.2, the tumour was deemed HER2-positive. p53 was considered positive if there

was≥10 % positive nuclear staining regardless of the intensity [22]. For Ki-67, nuclear staining≥14 % was considered high-level expression [23].

In the present study, breast cancers were classified into three molecular subtypes based on IHC and FISH analyses of ER, PR, and HER2 statuses as follows: ER-positive/HER2-negative (ER-positive and/or PR-positive, HER2-negative), HER2-positive (ER-negative, PR-negative and HER2-positive), and triple-negative (ER-negative, PR-negative and HER2-negative).

Statistical analysis

The clinicopathological features were compared between patients with and without ALN metastasis using the chi-square test or Fisher's exact test for the categorical variables and the independent sample t-test for the continuous variables. The relationships between the tumour SUV_{max} and clinicopathological parameters were calculated using the Mann-Whitney U-test and the Kruskal-Wallis test. A receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the SUV_{max}. Multivariate logistic regression analysis was performed to determine the variables independently associated with ALN metastasis by including all of the significant factors ($P<0.05$) from univariate analysis.

SPSS software (version 18.0, SPSS, Chicago, IL, USA) was used for all data analyses except ROC curve analysis, which was performed using the MedCalc software program (version 10.3.0.0, MedCalc Software, Mariakerke, Belgium). A P value of less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

The median age of the 671 patients was 52 years (range, 23–88 years). Mastectomy ($n=227$) or breast-conserving surgery ($n=444$) was performed for all breast cancers. A complete axillary lymph node dissection was performed in 557 (83.0 %) patients, whereas an axillary sentinel lymph node biopsy without axillary dissection was performed in 114 (17.0 %) patients. Of 671 tumours, 279 (41.6 %) breast cancers were diagnosed as having ALN metastasis.

Patients' characteristics and the association with axillary nodal status are presented in Table 1. The mean tumour size was 2.5±1.5 cm (range, 1.0–11.7 cm). The tumour subtype in most cases was ER-positive/HER2-negative ($n=461$, 68.7 %) followed by triple-negative ($n=113$, 16.8 %) and HER2-positive ($n=97$, 14.5 %) tumours. The histological types of invasive cancer included the following: invasive ductal

carcinoma ($n=610$, 90.9 %), invasive lobular carcinoma ($n=23$, 3.4 %), and other specified cancers ($n=38$, 5.7 %; 17 mucinous carcinomas, ten metaplastic carcinomas, seven papillary carcinomas, three tubular carcinomas, and one medullary carcinoma). ALN status correlated with the mean tumour size, pathological tumour stage, histological grade, Ki-67 status, LVI, type of surgery, and tumour subtype (Table 1).

FDG PET/CT and clinicopathologic parameters of the primary tumour

Table 2 shows the tumour SUV_{max} in relation to clinicopathologic parameters. The primary tumour SUV_{max} was significantly higher in patients with ALN metastasis than without ALN metastasis (8.6±4.9 vs. 6.2±4.9, $P<0.001$). With regard to tumour subtypes, the mean SUV_{max} of the triple-negative and HER2-positive tumours was 9.6±6.0 and 8.9±4.6, respectively, which was higher than that of ER-positive/HER2-negative tumours (6.7±4.6) ($P<0.001$ and $P<0.001$, respectively). The primary tumour SUV_{max} was also significantly higher in the tumours of younger patients (<45 years), those of a larger size (>2 cm) or higher histological grade (grade 3), those that were ER-negative, PR-negative, HER2-positive, or p53-positive, and those with higher expression of Ki 67, lymphovascular invasion, or ductal histology (Table 2).

Table 3 shows the tumour SUV_{max} values according to nodal status and tumour subtype. ALN positivity was present in 40.6 % (187 of 461) of ER-positive/HER2-negative tumours, 55.7 % (54 of 97) of HER2-positive tumours, and 33.6 % (38 of 113) of triple-negative tumours. In the triple-negative phenotype, there was no significant difference between the tumour SUV_{max} with and without ALN metastasis (9.4±7.5 vs. 10.6±5.3, $P=0.092$) (Table 3) (Fig. 1).

Univariate and multivariate analysis

Based on ROC curve analysis, the SUV_{max} of the primary tumours significantly discriminated the ALN involvement in breast cancer (area under the curve=0.704, $P<0.001$). In addition, the optimal cut-off value of the tumour SUV_{max} was identified as 4.25. On univariate analysis, a high SUV_{max} (≥4.25) was associated significantly with ALN metastasis ($P<0.001$). Large tumour size (>2 cm) ($P<0.001$), higher histological grade (grade 3) ($P=0.001$), higher expression of Ki 67 (≥14 %) ($P=0.005$), and presence of LVI ($P<0.001$) were also associated with a higher probability of ALN metastasis. Those variables that showed statistical significance ($P<0.05$) on univariate analysis were included in the multivariate analysis. In the multivariate analysis, a high SUV_{max} (≥4.25) (adjusted odds ratio (OR): 3.497, 95 % CI: 2.245, 5.446, $P<0.001$), large tumour size (>2 cm) (adjusted OR: 1.794, 95 % CI: 1.223, 2.632, $P=0.003$), and presence of LVI

Table 1 Patient characteristics and axillary lymph node status

Variable	Total	Node negative	Node positive	P value
No. of patients	671	392	279	
Median age (range), years	52 (23, 88)	52 (23, 84)	53 (29, 88)	0.457
Mean tumour size (range), cm	2.5±1.5 (1.0, 11.7)	2.1±1.1 (1.0, 9.5)	3.1±1.9 (1.0, 11.7)	< 0.001
Pathological tumour stage				
T1	319 (47.5)	234 (59.7)	85 (30.5)	< 0.001
T2	307 (45.8)	147 (37.5)	160 (57.3)	
T3	45 (6.7)	11 (2.8)	34 (12.2)	
Histological grade				
Grade 1	116 (17.3)	91 (23.2)	25 (9.0)	< 0.001
Grade 2	278 (41.4)	161 (41.1)	117 (41.9)	
Grade 3	277 (41.3)	140 (35.7)	137 (49.1)	
ER status				
Negative	228 (34.0)	129 (32.9)	99 (35.5)	0.509
Positive	443 (66.0)	263 (67.1)	180 (64.5)	
PR status				
Negative	279 (41.6)	163 (41.6)	116 (41.6)	1.000
Positive	392 (58.4)	229 (58.4)	163 (58.4)	
HER2 status				
Negative	460 (68.6)	274 (69.9)	186 (66.7)	0.399
Positive	211 (31.4)	118 (30.1)	93 (33.3)	
P53 status				
Negative	501 (74.7)	290 (74.0)	211 (75.6)	0.653
Positive	170 (25.3)	102 (26.2)	68 (24.4)	
Ki-67 status				
<14 %	325 (48.4)	208 (53.1)	117 (41.9)	0.005
≥14 %	346 (51.6)	184 (46.9)	162 (58.1)	
Lymphovascular invasion				
Negative	424 (63.2)	316 (80.6)	108 (38.7)	< 0.001
Positive	247 (36.8)	76 (19.4)	171 (61.3)	
Type of surgery				
Breast-conserving surgery	444 (66.2)	305 (77.8)	139 (49.8)	< 0.001
Mastectomy	227 (33.8)	87 (22.2)	140 (50.2)	
Histology				0.80
Ductal	610 (90.9)	354 (90.3)	256 (91.8)	
Lobular	23 (3.4)	14 (3.6)	9 (3.2)	
Others	38 (5.7)	24 (6.1)	14 (5.0)	
Tumour subtype				
ER-positive/HER2-negative	461 (68.7)	274 (69.9)	187 (67.0)	0.004
HER2-positive	97 (14.5)	43 (11.0)	54 (19.4)	
Triple-negative	113 (16.8)	75 (19.1)	38 (13.6)	

Unless otherwise noted, numbers in parentheses are percentages. *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

(adjusted OR: 5.301, 95 % CI: 3.670, 7.657, $P<0.001$) were associated independently with ALN metastasis (Table 4).

Considering the correlation of the tumour SUV_{max} with the tumour subtype (Table 2), a sub-analysis was performed to investigate potential differences in the results obtained among the various tumour molecular subtypes. In the ER-positive/HER2-negative and the HER2-positive tumours, the tumour SUV_{max} maintained independent significance on multivariate analysis for predicting ALN involvement, after controlling for tumour size, LVI, histological grade and Ki-67 status (adjusted OR: 3.277, 95 % CI: 1.980, 5.421, $P<0.001$ and adjusted OR:14.637, 95 % CI: 2.386, 89.784, $P=0.004$, respectively) (Figs. 2 and 3). In the triple-negative tumours, the SUV_{max}

was not associated with ALN metastasis ($P=0.161$) (Table 5) (Fig. 4).

Discussion

Consistent with the results of previous studies, we found that ALN metastasis was associated with LVI [5, 24]. In the present study, the presence of LVI was the strongest predictor of ALN metastasis (adjusted OR: 5.301, 95 % CI: 3.670, 7.657, $P<0.001$) regardless of the tumour subtype. In particular, for triple-negative tumours, LVI was the only variable

Table 2 Relationship between the tumour SUV_{max} and clinicopathological parameters

Variables	N (%)	Mean SUV_{max}	Range	P value
Age (years)				
< 45	161 (24.0)	8.1±5.4	1.4, 28.0	0.007
≥ 45	510 (76.0)	6.9±4.9	1.1, 28.5	
Lymph node status				
Negative	392 (58.4)	6.2±4.9	1.2, 28.5	< 0.001
Positive	279 (41.6)	8.6±4.9	1.1, 28.4	
Tumour size (cm)				
≤ 2	319 (47.5)	5.3±4.0	1.2, 28.0	< 0.001
> 2	352 (52.5)	9.0±5.3	1.1, 28.5	
Histological grade				
Grade 1, 2	394 (58.7)	5.3±3.8	1.2, 24.7	< 0.001
Grade 3	277 (41.3)	9.9±5.5	1.1, 28.5	
ER status				
Negative	228 (34.0)	9.4±5.6	1.6, 28.5	< 0.001
Positive	443 (66.0)	6.1±4.3	1.1, 28.4	
PR status				
Negative	279 (41.6)	8.6±5.4	1.2, 28.5	< 0.001
Positive	392 (58.4)	6.2±4.6	1.1, 28.4	
HER2 status				
Negative	460 (68.6)	6.7±5.0	1.1, 28.5	< 0.001
Positive	211 (31.4)	8.3±5.2	1.5, 25.9	
P53 status				
Positive	170 (25.3)	8.9±5.5	1.1, 28.0	< 0.001
Negative	501 (74.7)	6.6±4.8	1.2, 28.5	
Ki 67 status				
<14 %	325 (48.4)	5.4±4.2	1.2, 28.4	< 0.001
≥14 %	346 (51.6)	8.9±5.3	1.1, 28.5	
Lymphovascular invasion				
Negative	424 (63.2)	6.6±5.1	1.1, 28.5	< 0.001
Positive	247 (36.8)	8.3±4.9	1.3, 26.5	
Histology				
Ductal	610 (90.9)	7.4±5.1	1.1, 28.5	0.001
Lobular	23 (3.4)	4.0±2.2	1.3, 10.2	
Other	38 (5.7)	6.5±4.8	1.2, 22.6	
Tumour subtype				
ER-positive/HER2-negative	461 (68.7)	6.7±4.6	1.1, 28.4	< 0.001
HER2-positive	97 (14.5)	8.9±4.6	1.9. 20.7	
Triple-negative	113 (16.8)	9.6±6.0	1.6, 28.5	

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

independently associated with ALN status (adjusted OR: 10.423, 95 % CI: 3.761, 28.889, P<0.001). Despite its strong predictive value, LVI can be assessed histologically only after surgery using haematoxylin and eosin staining. On the other hand, a great advantage of the tumour SUV_{max} as a biomarker for predicting ALN metastasis is that it can be easily assessed preoperatively. In the present study, the tumour SUV_{max} was the second strongest prognostic factor in 671 patients with

Table 3 Tumour SUV_{max} values according to nodal status and tumor subtype

Nodal status	ER-positive/HER2-negative		HER2-positive		Triple-negative	
	N (%)	Mean SUV_{max} (range)	N (%)	Mean SUV_{max} (range)	N (%)	Mean SUV_{max} (range)
Node negative	274 (59.4)	5.2±4.2 (1.2, 28.5)	43 (44.3)	7.5±4.4 (1.9, 16.9)	75 (66.4)	9.4±7.5 (1.6, 28.5)
Node positive	187 (40.6)	7.8±5.0 (1.1, 28.4)	54 (55.7)	10.2±4.4 (2.9, 20.7)	38 (33.6)	10.6±5.3 (2.6, 22.8)
1–3	119 (25.8)	7.2±4.8 (1.1, 28.4)	29 (29.9)	9.8±4.7 (3.2, 20.7)	22 (19.5)	9.6±5.6 (2.6, 21.5)
4 or more	42 (9.1)	8.2±4.3 (2.5, 23.1)	11 (11.3)	10.4±3.9 (3.9, 16.1)	9 (8.0)	11.7±4.5 (3.0, 18.6)
9–10 or more	26 (5.6)	9.7±5.0 (4.4, 22.4)	14 (14.4)	10.6±4.2 (2.9, 17.9)	7 (6.2)	12.1±5.7 (4.4, 22.8)

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Fig. 1 Box plots of tumour SUV_max in breast cancer patients with and without axillary lymph node metastasis according to molecular subtype. Open circles represent outlier and asterisks represent extreme values
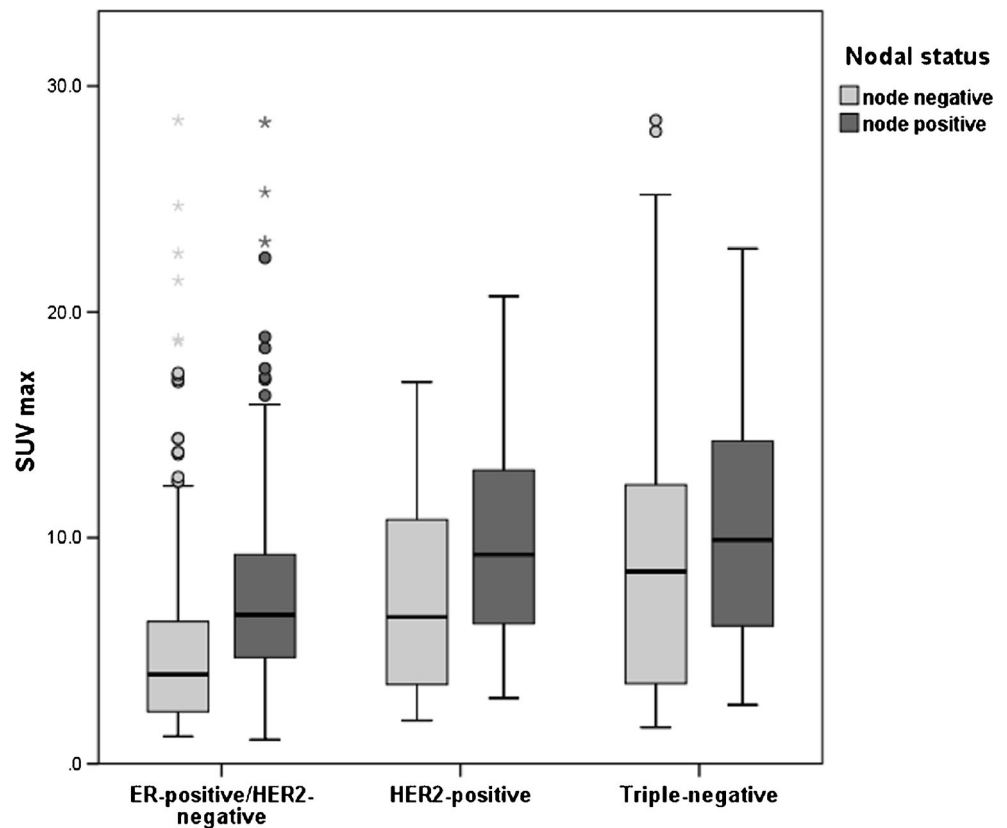
invasive breast cancer (adjusted OR: 3.497, 95 % CI: 2.245, 5.446, $P<0.001$).

However, in the subgroup analysis, the tumour SUV_max was found to have prognostic value for predicting ALN metastasis that differed depending on the breast cancer subtype. The tumour SUV_max on preoperative PET/CT correlated well with ALN metastasis for ER-positive/HER-negative and HER2-positive tumours ($P<0.001$, $P=0.004$, respectively),

but not for triple-negative tumours ($P=0.161$). This observation may be due to the aggressive biology of triple-negative breast cancers. The majority of triple-negative tumours had high histological grade (grade 3, 73.5 %) and higher expression of Ki 67 ($\geq$14 %, 82.3 %), so that they were more likely to show a higher SUV_max (mean, 9.6) regardless of axillary nodal status, which could explain the lack of prognostic significance of SUV_max in this group of breast cancers. In

Table 4 Univariate and multivariate logistic regression analysis for axillary lymph node metastasis

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	P Value	Odds ratio (95 % CI)	P Value
Age ($\geq$45 versus<45 years)	0.933 (0.652, 1.336)	0.706		
Tumour SUV_max ($\geq$4.25 versus<4.25)	4.956 (3.387, 7.251)	< 0.001	3.497 (2.245, 5.446)	< 0.001
Tumour size (>2 cm versus$\leq$2 cm)	3.380 (2.442, 4.679)	< 0.001	1.794 (1.223, 2.632)	0.003
Histological grade (grade 3 versus grade1/2)	1.737 (1.270, 2.374)	0.001	0.935 (0.619, 1.412)	0.748
ER status (negative versus positive)	1.121 (0.812, 1.549)	0.488		
PR negativity (negative versus positive)	1.000 (0.732, 1.365)	0.999		
HER2 positivity (positive versus negative)	1.161(0.835, 1.614)	0.374		
P53 status (positive versus negative)	0.916 (0.643, 1.306)	0.629		
Ki 67 status ($\geq$14 % versus<14 %)	1.565 (1.148, 2.133)	0.005	1.057 (0.707, 1.579)	0.788
LVI (presence versus absent)	6.583 (4.651, 9.319)	< 0.001	5.301 (3.670, 7.657)	< 0.001
Histology (ductal versus other)	1.195 (0.695, 2.055)	0.520		

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2
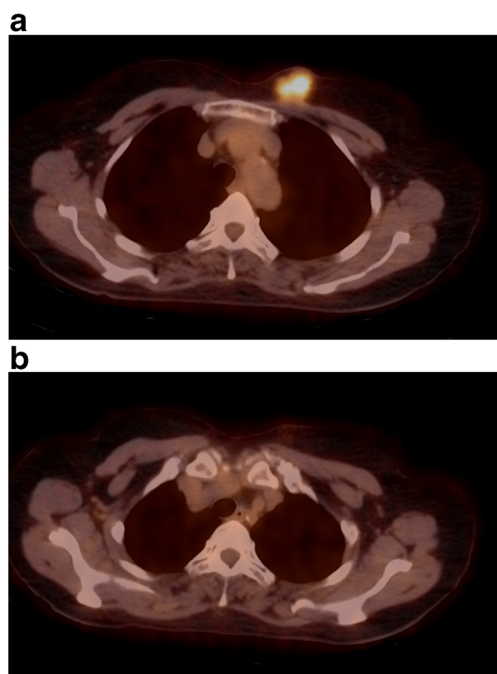
Fig. 2 ER-positive/HER2-negaitve breast cancer in a 46-year-old woman. ^{18}F-FDG PET/CT showed a hypermetabolic mass in the upper inner quadrant of the left breast with a SUV_{max} of 7.8 (**a**). There was no abnormal metabolism in the left axillary area (**b**). Surgical histopathology revealed a 3.0-cm invasive ductal carcinoma with a histological grade of 2 that was ER-positive, PR-positive, and HER2-negative. The Ki 67 index was 50 % and p53 was negative. Axillary lymph node metastasis was found in one out of 4 resected nodes
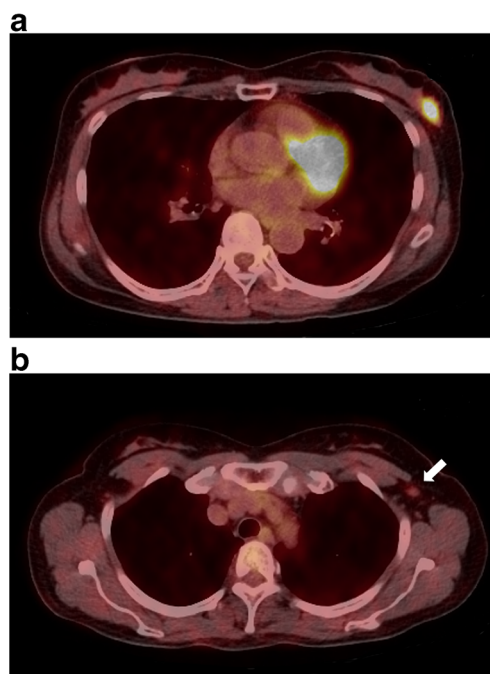
Fig. 3 HER2-positive breast cancer in a 57-year-old woman. ^{18}F-FDG PET/CT showed a hypermetabolic mass in the lower outer quadrant of the left breast with a SUV_{max} of 9.5 (**a**), and one enlarged lymph node with focal FDG uptake (SUV_{max} 3.9) in the left axillary area (*arrow*) (**b**). Surgical histopathology revealed a 2.1-cm invasive ductal carcinoma with a histological grade of 3 that was ER-negative, PR-negative, and HER2-positive. The Ki 67 index was 20 % and p53 was negative. Axillary lymph node metastasis was found in one out of 13 resected nodes

addition, for triple-negative tumours, the earlier reported correlation between tumour size and node positivity was not observed. Although the reason is not clear, one possible explanation is that the mechanism of spread of tumour may differ between triple-negative and other subtypes. It has been suggested that triple-negative breast cancers tend to spread haematogenously rather than via lymphatics [25]. We consider that the triple-negative subtype is a separate biological phenotype that necessitates preoperative prognostication to tailor individual treatment plans.

Knowledge of axillary nodal status before surgery is important because it influences the decision making of clinicians regarding the management of patients with breast cancer. Although sentinel lymph node biopsy is considered an alternative to ALN dissection in clinically node-negative patients due to its high sensitivity and accuracy [26, 27], this procedure is still invasive and carries a risk of surgical complications such as lymphoedema, axillary paraesthesia, seroma, and wound infection [28]. Additionally, sentinel lymph node biopsy is performed at the time of primary tumour excision, resulting in a longer surgical duration. Multiple non-invasive imaging methods such as mammography, ultrasound, and magnetic resonance imaging have been used for preoperative axillary staging, but accurate prediction remains a challenge. In a recent study, 14 % of the patients who had no suspicious

lymph node findings on physical examination, mammography, ultrasound, and magnetic resonance imaging were found to have positive lymph nodes confirmed histologically following surgery [29]. Furthermore, in breast cancer patients, ^{18}F-FDG PET/CT is effective for detection of distant metastasis, but its value for axillary staging is not established. In the previous studies, the diagnostic accuracy of ^{18}F-FDG PET/CT for ALN metastasis showed a low sensitivity, ranging from 37 % to 84.5 %, whereas the specificity was higher than 96 % [12, 30–32]. Therefore, it is suggested that ^{18}F-FDG PET/CT could play a possible role in preselecting candidate for axillary dissection for patients with positive axillary nodes on PET/CT, which could reduce unnecessary sentinel lymph node biopsy [30]. New techniques for improving spatial resolution of PET/CT are needed to increase detectability of small lymph nodes.

^{18}F-FDG PET is not currently recommended for routine use in breast cancer patients [33], but it has been used increasingly in many hospitals not only for staging work-up, but also for predicting the therapeutic response to neoadjuvant chemotherapy [14]. A significant correlation was found among 18 F-FDG uptake in breast cancer, histobiological factors, and tumour angiogenesis [15, 16, 34]. Ueda et al. [16] demonstrated that tumours with a high SUVmax were associated with

Table 5 Multivariate analysis according to tumour subtype

Variable	ER-positive/HER2-negative (n=461)		HER2-postivie (n=97)		Triple-negative (n=113)	
	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value
SUV$_{max}$ (≥4.25)	3.277 (1.980, 5.421)	< 0.001	14.637 (2.386, 89.784)	0.004	2.454 (0.698, 8.622)	0.161
Tumour size (>2 cm)	2.107 (1.327, 3.345)	0.002	1.595 (0.510, 4.993)	0.042	0.909 (0.358, 2.308)	0.841
LVI (presence)	3.997 (2.562, 6.237)	< 0.001	9.906 (3.412, 28.755)	< 0.001	10.423 (3.761, 28.889)	< 0.001
Histological grade (grade 3)	1.273 (0.757, 2.141)	0.362	0.286 (0.084, 0.971)	0.055	0.871 (0.265, 2.859)	0.820
Ki 67 status (≥14 %)	0.973 (0.602, 1.573)	0.912	1.252 (0.373, 4.198)	0.716	2.169 (0.514, 9.151)	0.292

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *LVI* lymphovascular invasion
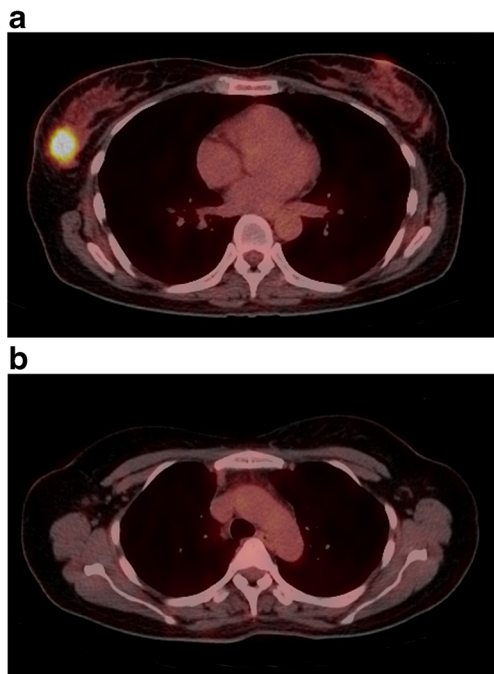
increased 10-year relapse and 10-year mortality rates in patients with breast cancer. Furthermore, Song et al. [35] found that the SUV$_{max}$ of metastatic ALN was predictive of disease recurrence. Therefore, we believe that tumour 18 F-FDG uptake on preoperative PET/CT could be an emerging prognostic biomarker for breast cancer that may improve preoperative prediction of ALN status in breast cancer patients with particular tumour subtypes.

Histologically similar tumour phenotypes may behave differently clinically, which is believed to be due to molecular differences in these tumours. Previous studies have shown that different molecular types of breast cancers have different treatment response and survival outcomes [9, 36]. Triple-

Fig. 4 Triple-negative breast cancer in a 43-year-old woman. ^{18}F-FDG PET/CT showed a hypermetabolic mass in the upper outer quadrant of the right breast with a SUV$_{max}$ of 10.4 (**a**). There was no abnormal metabolism in the right axillary area (**b**). Surgical histopathology revealed a 3.5-cm invasive ductal carcinoma with a histological grade of 3 that was ER-negative, PR-negative, and HER2-negative. The Ki 67 and p53 indices were 40 % and 85 %, respectively. No axillary lymph node metastasis was found

negative breast cancers have more aggressive biological features and are associated with poorer clinical outcomes compared with other subtypes [37, 38]. Recently, the association of gene expression with tumour metabolism was investigated by ^{18}F-FDG PET/CT. As expected, clinically aggressive tumours such as triple-negative and HER2-positive tumours showed greater FDG uptake than did luminal tumours [17, 39]. We also confirmed metabolic differences, represented by the SUV$_{max}$ on ^{18}F-FDG PET/CT, in tumours by molecular subtype. A better understanding of molecular biology could improve our understanding of breast cancer biology, and accurate prognostic prediction based on molecular biomarkers may facilitate improved prevention and individualized management of breast cancer patients.

Our study had several limitations. First, this was a retrospective study from a single centre, which inevitably introduces considerable selection bias. Second, we categorized breast cancer subtypes by IHC instead of gene expression profiles, which could have affected our results. However, previous studies suggested that the IHC profile can be a useful surrogate for microarray-based gene expression profiling [23, 40]. Finally, we did not evaluate the correlation between tumour FDG uptake and long-term clinical outcomes because the follow-up duration was short. ALN status has been shown to be associated with mortality in breast cancer patients [41]. Further prospective studies are needed to validate our results.

In conclusion, the results of the present study suggest that tumour FDG uptake may be associated independently with ALN metastasis among patients with certain tumour subtypes, particularly ER-positive/HER-negative and HER2-positive tumours. The triple-negative tumours, however, failed to demonstrate this association. Further research is warranted to investigate tumour subtype-specific prognostic markers that enable individualized treatment plans for patients with invasive breast cancer.

consent was waived by the Institutional Review Board. No study subjects or cohorts have been previously reported. Methodology: retrospective, observational, performed at one institution.

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