



Editorial Musings

Higher breast cancer conspicuity on dbPET compared to WB-PET/CT



Kayo Nishimatsu^a, Yuji Nakamoto^{a,*}, Kanae K. Miyake^a, Takayoshi Ishimori^a,
Shotaro Kanao^a, Masakazu Toi^b, Kaori Togashi^a

^a Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

^b Department of Breast Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

ARTICLE INFO

Article history:

Received 28 August 2016

Received in revised form 24 February 2017

Accepted 28 February 2017

Keywords:

Breast cancer

Positron-emission tomography (PET)

Dedicated breast PET scanner

PET/CT

ABSTRACT

Objectives: The purpose of this study was to evaluate lesion detectability of a dedicated breast positron-emission tomography (dbPET) scanner for breast cancers with an updated reconstruction mode, comparing it to whole-body positron-emission tomography/computed tomography (WB-PET/CT).

Materials and methods: A total of 179 histologically-proven breast cancer lesions in 150 females who underwent both WB-PET/CT and dbPET with ¹⁸F-fluorodeoxyglucose were retrospectively analyzed. The patient/breast/lesion-based sensitivities based on visual analysis were compared between dbPET and WB-PET/CT. For lesions visible on both PET images, SUVmax values of the tumors were measured, and tumor-to-background ratios (T/B ratios) of SUVmax were compared between the two scans. Subgroup analyses according to clinical tumor stage, histopathology and histological grade were also performed.

Results: Patient/breast/lesion-based sensitivities were 95%, 95%, and 92%, respectively, for dbPET, and 95%, 94%, and 88%, respectively, for WB-PET/CT. Mean $\pm$ standard deviation SUVmax values of FDG-avid tumors were 13.0 ± 9.7 on dbPET and 6.4 ± 4.8 on WB-PET. T/B ratios were also significantly higher in dbPET than in WB-PET/CT (8.1 ± 7.1 vs. 5.1 ± 4.5). In the subgroup analysis, no significant differences in sensitivities between dbPET and WB-PET/CT were found. However, T/B ratios of dbPET were significantly higher than those of WB-PET/CT in cT1c, cT2, cT3, invasive cancer, invasive carcinoma of no special type, mucinous carcinoma and Grades 1–3.

Conclusion: No significant differences in sensitivities were identified between dbPET using an updated reconstruction mode and WB-PET/CT; however, T/B ratios of dbPET were significantly higher than those of WB-PET/CT, indicating higher tumor conspicuity on dbPET.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Early tumor detection has been identified as one of the most important factors associated with the prognosis of breast cancer [1,2]. Several reports have been published about breast imaging with conventional whole body positron-emission tomography (WB-PET) using ¹⁸F-fluorodeoxyglucose (FDG) [1–6]. There have been many reports demonstrating clinical efficacy of FDG WB-PET or PET/computed tomography (CT) in staging or restaging, monitoring therapy response or predicting disease course in patients with breast cancer [3–6]. However, WB-PET is limited by its spatial resolution in the evaluation of small cancers [1,2].

Dedicated breast PET (dbPET) scanners have been developed to improve the ability to detect small breast tumors. The dbPET systems are classified into two types: a positron-emission mammography (PEM) type and a tomographic dedicated PET type using a ring-shaped scanner [7]. Several investigators have reported on PEM's diagnostic performance in breast cancer [8–16]. However, published clinical data on the tomographic dedicated PET system have been limited [17,18]. Previously, we have reported our preliminary results of diagnostic performance of full and partial ring-shaped scanners for detecting breast cancer in 69 patients, comparing with that of conventional WB-PET/CT [17]. Since then, software-based attenuation correction and optimized parameters for image reconstruction have become applicable in routine use.

The purpose of this retrospective study was therefore to re-evaluate the diagnostic performance of dbPET scanner with a ring shaped array of detectors in a larger population. We compared the detectability of dbPET using an updated reconstruction mode with

* Corresponding author.

E-mail address: ynakamoto1@kuhp.kyoto-u.ac.jp (Y. Nakamoto).

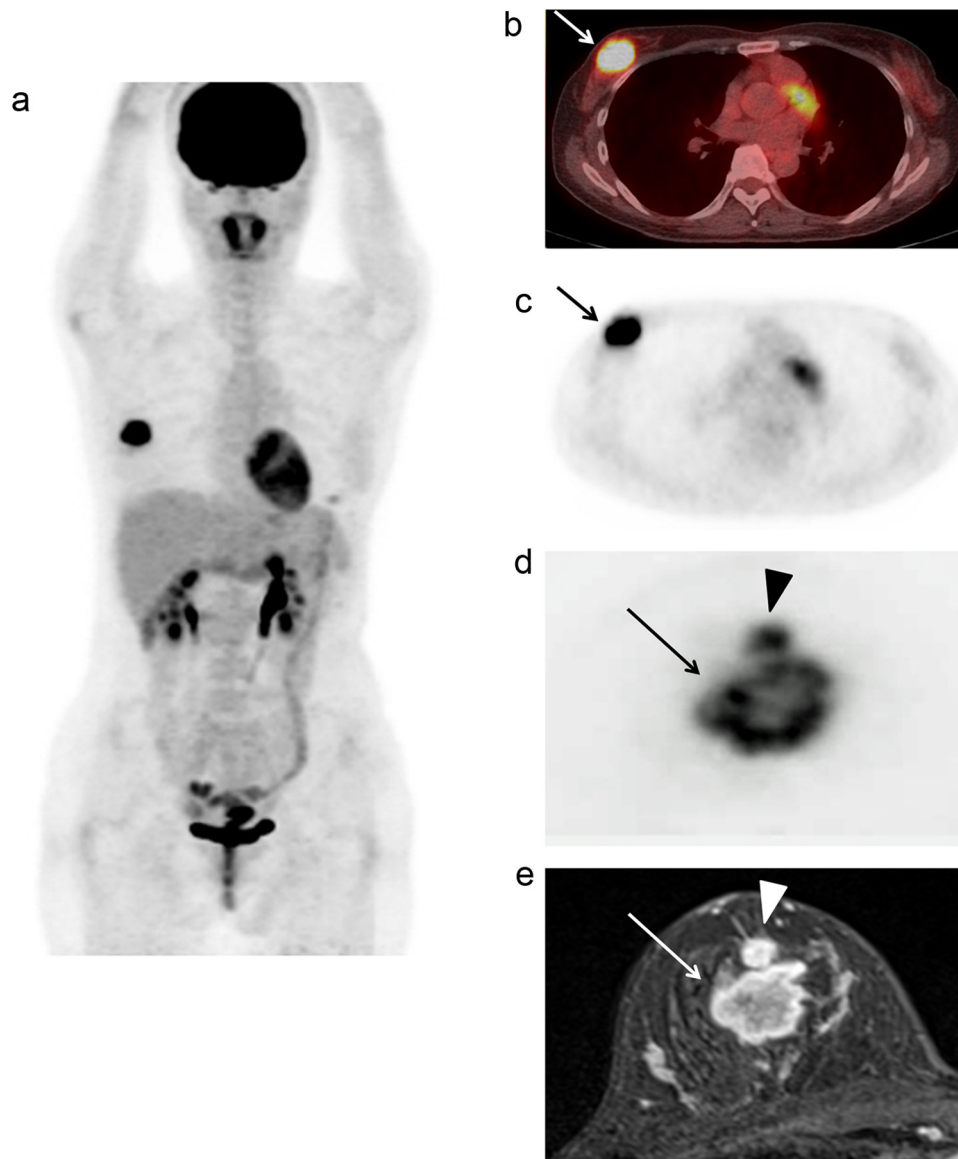


Fig. 1. A 41-year-old woman with invasive ductal carcinoma (Grade 2) in both breasts. A maximum intensity projection image of WB-PET (a), axial images of WB-PET/CT fusion (b) and WB-PET (c) show massive FDG uptake in right breast (arrow). An axial image of dbPET (d) shows ring-like uptake, resembling the contrast enhancement pattern in MRI (e). A small nodule is separately depicted from a main tumor (arrowhead). (dbPET SUVmax = 17.1, WB-PET/CT SUVmax = 10.3, T/B ratio is not available because of bilateral cancers).

that of conventional WB-PET/CT. In addition, we performed quantitative analysis on breast cancers visualized on PET, and investigated differences in quantitative values of breast cancers between dbPET and WB-PET/CT.

2. Material and methods

2.1. Patients

A total of 163 consecutive chemotherapy- and hormonal therapy-naïve women who were suspected of having or were known to have breast cancer by physical examination or imaging modalities, such as mammography, ultrasound, CT or MRI, and who underwent both dbPET and WB-PET/CT scans from June 2010 through February 2014, were included in this study. There were no patients with plasma glucose levels >200 mg/dl at administration of FDG.

This study was approved by the institutional review board and ethics committee of our institute in accordance with the Declaration of Helsinki; written informed consent was obtained from each patient for access to their data.

2.2. Imaging protocol

Patients fasted for at least four hours before the administration of FDG (approximately 3.7 MBq/kg of weight). Approximately 60 min later, a WB-PET/CT scan, which integrates a bismuth germinate crystal detector array with a 16-slice multidetector CT scanner, was first performed with spine position (Discovery ST Elite; GE Healthcare, Waukesha WI, USA).

For attenuation correction and anatomic localization, CT scanning (120 kVp tube voltages, 20–100 mA tube current (automatic setting) with 0.6 s per tube rotation, pitch 1.75 and 3.75 mm section thickness) was performed. Then, PET emission scanning was performed with an acquisition time of 2–3 min per bed posi-

Table 1
Baseline characteristics of the 179 lesions in 150 patients.

Characteristic		Value %	
Age (year)	Range	26–89	
	Mean $\pm$ SD	55.7 $\pm$ 12.9	
Histopathology	Invasive cancer of no special type (NST)	148	83%
	Invasive lobular carcinoma (ILC)	12	7%
	Mucinous carcinoma	8	4%
	Other invasive carcinoma	6	3%
	Ductal carcinoma <i>in situ</i> (DCIS)	5	3%
Histological grade	Grade 1	42	23%
	Grade 2	94	53%
	Grade 3	38	21%
	Non-invasive carcinoma	5	3%
Clinical tumor size (mm)	Range	3–91	
	Mean $\pm$ SD	25.9 $\pm$ 18.0	
Non-invasive carcinoma	Range	5–45	
	Mean $\pm$ SD	19.8 $\pm$ 18.5	

SD; standard deviation.

tion. The images were reconstructed using a three-dimensional iterative reconstruction algorithm (VUE Point Plus) with two iterations of three-dimensional ordered-subset expectation maximum (3D-OSEM) with 14 subsets, matrix 128×128 , voxel size; $4.7 \times 4.7 \times 3.8$ mm.

Approximately 90 min after FDG injection, breast scanning with the dbPET was performed for 5 min for each breast with prone position. The involved breast was scanned first, followed by the contralateral breast. A time interval between the first scans of involved breasts and the second scans of contralateral breasts was about 6.9 min.

The dbPET scanner (a prototype of Elmammo, Shimadzu, Kyoto, Japan) consists of 36 detector modules arranged in three contiguous rings, with a 195 mm diameter and axial length of 155.5 mm. The transaxial effective field-of-view (FOV) is 180 mm. Each detector block consists of a four-layer 32×32 array of lutetium oxyorthosilicate (LGSO) crystals coupled to a 64-channel position-sensitive photomultiplier tube via a light guide.

In this study, we applied more optimized parameters for image reconstruction from the raw data; one iteration of a three-dimensional list mode dynamic row-action maximum-likelihood algorithm (DRAMA), which is a modified version of the row-action maximum likelihood algorithm (RAMLA) [19], with 128 subsets, relaxation control parameter $\beta = 5$, matrix size 236×236 with a post reconstruction smoothing Gaussian filter (1.5 mm full width at half maximum) and scatter correction. Also, attenuation correction was applied by extracting image contour with level set methods [20]. In our previous report demonstrating preliminary results [17], we had adopted the same algorithm, but a different relaxation control parameter ($\beta = 100$) was used for image reconstruction, and scatter and attenuation correction had not been applied. Recovery coefficient with this optimized reconstruction mode was demonstrated by Miyake et al. [21]. Voxel size was $0.78 \times 0.78 \times 0.78$ mm. The spatial resolution was estimated to be <1.5 mm at the centre of the FOV. We performed cross-calibrations between the dbPET scanner and well-counter/well-counter and curie-meter with a phantom. Then, we calculated calibration coefficients of dbPET and converted pixel values to SUV values.

2.3. Image interpretation

DbPET and WB-PET/CT images were visually evaluated by consensus by two readers, who were board-certified radiologists and

nuclear medicine physicians, and the sensitivities for breast cancer detection were calculated. The observers were blind to all clinical information and findings of other imaging modalities. In addition, quantitative values of breast cancer on both images were compared.

Focal increased uptake that was fully or partially included within the FOV of the PET images was regarded as positive. Lesions that were completely outside the FOV on dbPET were excluded from analysis, for precise comparison of depiction by dbPET and WB-PET/CT. No or faint uptake was regarded as negative. Equivocal uptake located close to the boundary of the FOV on dbPET and difficult to distinguish from image noise was also judged as negative. If multiple lesions were observed in a single breast, two representative lesions (usually, the largest and the second-largest ones) were analyzed for a more reliable correlation between radiologic and pathologic findings as in the previous study [17]. The detection rate of dbPET and WB-PET/CT was evaluated on a patient-basis, breast-basis and lesion-basis, based on pathological findings. Breast-based specificity was also calculated. The sensitivity and specificity were calculated as follows: Sensitivity = the number of true positive patients/breasts/lesions divided by the number of total patients/affected breasts/breast cancer foci; Specificity = the number of true negative breasts divided by the number of total non-affected breasts.

In cases with true-positive uptake on both PET systems, the maximum standardized uptake value (SUVmax) of tumors and normal contralateral breast tissue were measured using volumes of interest on dbPET and WB-PET/CT. Tumor-to-background ratio (T/B ratio), defined as the SUVmax of tumor divided by the SUVmax of contralateral normal breast tissue, was calculated, based on a previous report [22].

In addition, the peak standardized uptake value (SUVpeak) of tumors were measured for lesions greater than 2 cm, according to a recommendation by Wahl et al. for accurate measurement [23], and metabolic tumor volume (MTV) with the threshold of 50% SUVmax and total lesion glycolysis (TLG) were also calculated. Then, we compared them between the two scans.

Clinical T tumor size (cT) staging was assessed on the basis of an image with the best definition of the lesion. T4 tumors were classified by size, as in the study by Avril et al. [2]. Subgroup analyses according to tumor size, histopathological subtype and histological grade were also performed.

2.4. Standard of reference

Diagnosis of breast cancers was histopathologically determined after biopsy ($n = 89$) or surgery ($n = 90$). All pathologic results were confirmed according to the classification of breast tumors by the World Health Organization 2012.

2.5. Statistical analysis

McNemar's test was used to examine differences between dbPET and WB-PET/CT in patient-based, breast-based and lesion-based sensitivities. The correlation between tumor SUVmax, SUVpeak, MTV and TLG on dbPET and that on WB-PET/CT were evaluated using the Pearson correlation coefficient. A paired *t*-test was used to compare tumor SUVmax, SUVpeak, MTV, TLG and T/B ratios between dbPET and WB-PET/CT. A *p* value <0.05 was considered statistically significant. Quantitative data are presented as mean $\pm$ standard deviations (SD) unless otherwise specified.

3. Results

After excluding 16 lesions outside the FOV on dbPET for comparison net sensitivities with dbPET and WB-PET/CT, a total of 150

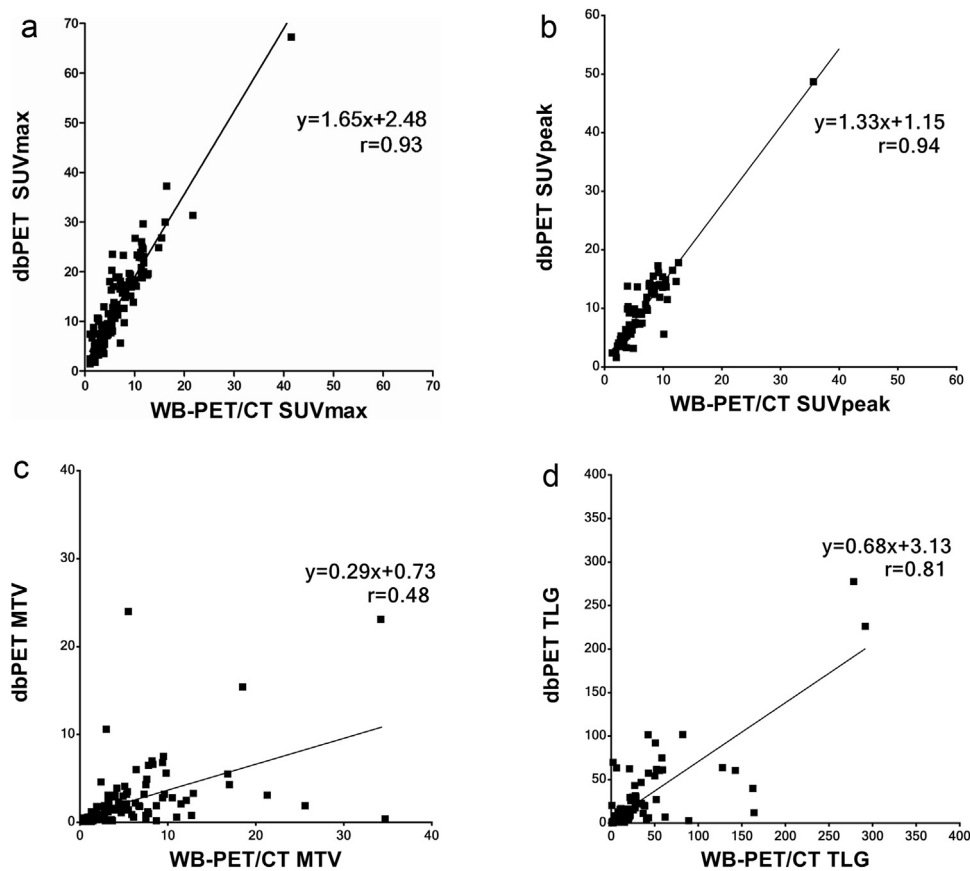


Fig. 2. Correlation of quantitative parameters between dbPET and WB-PET/CT are demonstrated. The graph (a) shows the correlation of SUVmax on dbPET with that of WB-PET/CT in 117 cancer foci. The SUVmax of dbPET is approximately 1.7 times higher than that of WB-PET/CT ($r=0.93$, $p<0.0001$). The graph (b) shows the correlation of SUVpeak on dbPET with that of WB-PET/CT in 71 cancer foci. The SUVpeak of dbPET is approximately 1.3 times higher than that of WB-PET/CT ($r=0.94$, $p<0.0001$). The graph (c) shows the correlation of MTV on dbPET with that of WB-PET/CT in 117 cancer foci. A weak correlation is observed between them ($r=0.48$, $p<0.0001$). The graph (d) shows the correlation of TLG on dbPET with that of WB-PET/CT in 117 cancer foci. A positive and linear correlation was observed, but it was weak, compared to SUVmax and SUVpeak ($r=0.81$, $p<0.0001$).

patients (age range: 26–89 y, mean: 55.7 y) with 179 breast cancer foci in 154 breasts were analyzed in this study (Table 1). Of the 150 women, 24 patients (25 breasts) had multiple lesions in one breast and four patients had bilateral breast cancers. The mean clinical tumor size of invasive carcinomas was 25.9 mm and that of non-invasive cancers was 19.8 mm. Of the 179 breast cancer foci, 174 were invasive carcinomas and five were non-invasive cancers.

Patient-based and breast-based sensitivities were almost equivalent between dbPET and WB-PET/CT (patient-based, 95% vs. 95%, $p=1.00$; breast-based, 95% vs. 94%, $p=0.72$) (Table 2). Lesion-based sensitivities of dbPET were slightly higher than WB-PET/CT (92% vs. 88%), but not to a significant extent ($p=0.06$).

PET images of contralateral breasts that were considered as normal were available for the quantitative analysis in 140 patients excluding 10 patients (four patients with bilateral breast cancers, three patients with contralateral post-mastectomy state, two patients who denied dbPET scanning for the contralateral breast, and one patient who was lactating).

False positive uptakes in the contralateral breasts were identified in eight breasts on dbPET and in three breasts on WB-PET/CT. Thus, breast-based specificity was 94% (132/140) on dbPET and 98% (139/142) on WB-PET/CT.

The SUVmax of dbPET and WB-PET/CT were 13.0 ± 9.7 (range: 0.9–67.3) and 6.4 ± 4.8 (range: 1.0–41.5), respectively ($p<0.0001$) (Table 3). One of the representative cases is shown in Fig. 1.

There were 117 breast cancers which were visually positive on both dbPET and WB-PET/CT systems and fully included within

the FOV of dbPET images. There was a strong linear correlation between SUVmax on dbPET and that of WB-PET/CT (SUVmax; $r=0.93$, $p<0.0001$) (Fig. 2a). Of the 117 breast cancers, 71 lesions were equal to or larger than 2 cm in size and available for SUVpeak measurement. There was also a strong linear correlation between SUVpeak on dbPET and that of WB-PET/CT (SUVpeak; $r=0.94$, $p<0.0001$) (Fig. 2b). The tumor SUVmax and SUVpeak on dbPET were approximately 1.7 and 1.3 times higher than those of WB-PET/CT, respectively. A weak correlation was observed between MTV on dbPET and that of WB-PET/CT (MTV; $r=0.48$, $p<0.0001$) (Fig. 2c). Also, a positive and linear correlation was observed between TLG on dbPET and that of WB-PET/CT (TLG; $r=0.81$, $p<0.0001$), but correlation was weak, compared to SUVmax and SUVpeak (Fig. 2d). The SUVpeak, MTV and TLG of dbPET and WB-PET/CT were 9.5 ± 6.4 vs. 6.3 ± 4.5 (range: 1.6–48.7 vs. 1.3–35.6), 2.3 ± 3.6 vs. 5.3 ± 5.9 (range: 0.1–24.0 vs. 0.4–34.7) and 20.9 ± 38.1 vs. 26.3 ± 45.5 (range: 0.6–277.6 vs. 0.8–278.4), respectively (SUVpeak and MTV: $p<0.0001$, TLG: $p<0.05$).

Mean SUVmax of the contralateral breasts was 1.8 ± 0.6 (range: 0.7–3.7) on dbPET and 1.4 ± 0.4 (range: 0.6–2.6) on WB-PET/CT. T/B ratios of dbPET and WB-PET/CT were 8.1 ± 7.1 (range: 0.8–47.1) and 5.1 ± 4.5 (range: 0.8–40.3), respectively, (Table 3). T/B ratios on dbPET were significantly higher than those of WB-PET/CT ($p<0.0001$) (Fig. 3).

When invasive cancers were analyzed according to tumor size (Table 4), sensitivities were 0% for cT1a, and 100% for cT2 and cT3, with either dbPET or WB-PET/CT. In cT1b, cT1c and cTis, sensitiv-

Table 2
Sensitivities of dbPET and WB-PET/CT on patient, breast and lesion based analysis.

	n	dbPET	WB-PET/CT	p
Patient-based sensitivity	150	95% (143/150)	95% (142/150)	1.00
Breast-based sensitivity	154	95% (147/154)	94% (145/154)	0.72
Lesion-based sensitivity	179	92% (165/179)	88% (157/179)	0.06

Table 3
SUVmax and T/B ratio of PET positive lesions.

	dbPET	WB-PET/CT	p
SUVmax	13.0 ± 9.7 range: 0.9–67.3	6.4 ± 4.8 range: 1.0–41.5	<0.0001 [n = 154]
T/B ratio	8.1 ± 7.1 range: 0.8–47.1	5.1 ± 4.5 range: 0.8–40.3	<0.0001 [n = 142]

Data are shown as mean ± standard deviation with range. Number of available lesions in comparison between both PET systems is shown in brackets.

Table 4
Sensitivities, SUVmax and T/B ratio of PET positive lesions according to clinical-T stages of invasive cancers.

clinical-T stage	Lesion-based sensitivity				SUVmax			T/B ratio		
	n	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p
cT1	88	85% (75/88)	78% (69/88)	0.11	10.2 ± 9.7	4.4 ± 3.3	<0.0001 [n = 67]	6.1 ± 6.3	3.4 ± 2.5	<0.0001 [n = 62]
cT1a	3	0% (0/3)	0% (0/3)	NA	–	–	NA	–	–	NA
cT1b	20	65% (13/20)	50% (10/20)	0.45	5.1 ± 4.0	2.0 ± 1.0	<0.05 [n = 8]	1.8 ± 1.2	1.5 ± 0.7	0.36 [n = 7]
cT1c	65	95% (62/65)	91% (59/65)	0.25	11.3 ± 10.2	4.8 ± 3.3	<0.0001 [n = 59]	6.9 ± 6.6	3.7 ± 2.6	<0.0001 [n = 55]
cT2	65	100% (65/65)	100% (65/65)	NA	15.8 ± 10.0	8.3 ± 5.7	<0.0001 [n = 65]	10.4 ± 7.8	6.6 ± 1.8	<0.0001 [n = 60]
cT3	21	100% (21/21)	100% (21/21)	NA	15.2 ± 6.3	7.8 ± 3.3	<0.0001 [n = 21]	8.7 ± 5.4	5.9 ± 3.2	<0.05 [n = 19]
cTis	5	80% (4/5)	40% (2/5)	0.62	7.3 ± 4.4	3.6, 2.4	NA [n = 1]	3.0	2.0, 1.6	NA [n = 1]

T4 tumors are classified into their tumor size.

Not available; NA.

The number of available lesions in comparison between both PET systems is shown in brackets.

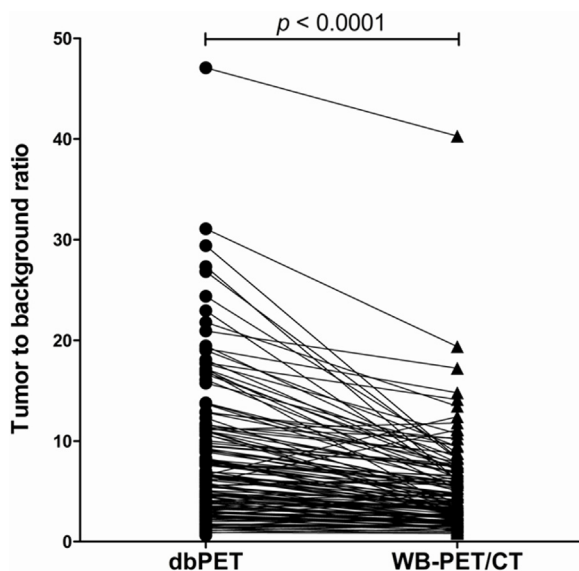


Fig. 3. The graph shows tumor to background ratios calculated by the dbPET and WB-PET/CT scanners. Significant differences are found between the ratios obtained with each scanner ($p < 0.0001$).

ities of dbPET were slightly higher than those of WB-PET/CT (65% vs. 50% in cT1b, 95% vs. 91% in cT1c, and 80% vs. 40% in cTis); however, the differences did not reach statistical significance. SUVmax of dbPET were significantly higher than those of WB-PET/CT in all T stages except for cT1a and cTis. T/B ratios of dbPET were significantly higher than those of WB-PET/CT in cT1c (6.9 ± 6.6 vs. 3.7 ± 2.6 , $p < 0.0001$, $n = 55$), cT2 (10.4 ± 7.8 vs. 6.6 ± 1.8 , $p < 0.0001$, $n = 60$) and cT3 (8.7 ± 5.4 vs. 5.9 ± 3.2 , $p < 0.05$, $n = 19$).

In the subgroup analysis according to the histopathological subtypes (Table 5), the sensitivities of dbPET and WB-PET/CT were high $\geq 90\%$, and almost equivalent between the two systems in invasive

cancer of no special type (NST) or mucinous cancers, but dbPET tended to have higher sensitivities, compared with WB-PET/CT for invasive lobular carcinoma (ILC) (83% vs. 67%, $p = 0.48$, $n = 12$) and for ductal carcinoma *in situ* (DCIS) (80% vs. 40%, $p = 0.62$, $n = 5$) without statistical significance (Fig. 4). SUVmax in dbPET was consistently higher than that in WB-PET/CT in all histopathological types. T/B ratios of dbPET were significantly higher than those of WB-PET/CT in NST (8.5 ± 7.2 vs. 5.3 ± 4.7 , $p < 0.0001$, $n = 119$) and mucinous carcinoma (3.4 ± 2.1 vs. 1.9 ± 0.8 , $p < 0.05$, $n = 8$).

Although there was no significant difference in sensitivities between the two scanners in any histological grades of invasive cancers (Table 6), SUVmax and T/B ratios of dbPET were significantly higher than those of WB-PET/CT (T/B ratios: Grade 1; 4.8 ± 4.2 vs. 3.1 ± 2.0 , $p < 0.0001$, $n = 29$, Grade 2; 7.2 ± 6.5 vs. 5.2 ± 5.0 , $p < 0.0001$, $n = 78$, Grade 3; 13.7 ± 7.9 vs. 6.6 ± 4.3 , $p < 0.0001$, $n = 34$).

4. Discussion

We re-evaluated the breast cancer sensitivity of full-ring dbPET using optimized reconstruction methods in a total 150 patients, and additionally investigated quantitative features of breast cancers. Our results showed that lesion-based sensitivity excluding lesions completely outside the FOV was slightly higher with dbPET (92%) than with WB-PET/CT (88%), although there was no statistical significance ($p = 0.06$). In the subgroup analyses in terms of tumor size, histology and grade, no significant differences were identified between dbPET and WB-PET/CT in the sensitivity in any subgroups. However, T/B ratios on dbPET were significantly higher than those on WB-PET/CT, suggesting dbPET improves tumor conspicuity. Higher T/B ratios may indicate an advantage of dbPET over WB-PET/CT that facilitates tumor recognition and increases confidence in the diagnosis.

According to studies on PEM, the reported lesion-based sensitivities and specificities ranged from 79% to 96% and from 33% to 100%, respectively [9–16]. A meta-analysis of eight published stud-

Table 5
Sensitivities, SUVmax and T/B ratio of PET positive lesions according to histopathological subtypes.

	Lesion-based sensitivity				SUVmax			T/B ratio		
	n	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p
Invasive	174	93% (161/174)	89% (155/174)	0.11	13.1 ± 9.8	6.4 ± 4.8	<0.0001 [n = 153]	8.1 ± 7.1	5.1 ± 4.5	<0.0001 [n = 141]
NST	148	93% (137/148)	90% (133/148)	0.29	12.9 ± 9.7	6.7 ± 5.0	<0.0001 [n = 131]	8.5 ± 7.2	5.3 ± 4.7	<0.0001 [n = 119]
ILC	12	83% (10/12)	67% (8/12)	0.48	7.9 ± 4.6	5.8 ± 2.3	<0.01 [n = 8]	5.4 ± 4.9	5.2 ± 3.5	0.47 [n = 8]
Mucinous	8	100% (8/8)	100% (8/8)	NA	6.0 ± 4.1	2.6 ± 1.6	<0.05 [n = 8]	3.4 ± 2.1	1.9 ± 0.8	<0.05 [n = 8]
Others	6	100% (6/6)	100% (6/6)	NA	15.3 ± 9.2	6.8 ± 3.6	<0.05 [n = 6]	13.0 ± 9.8	5.9 ± 3.1	0.07 [n = 6]
DCIS	5	80% (4/5)	40% (2/5)	0.62	7.3 ± 4.4	3.6, 2.4	NA [n = 1]	3.0	2.0, 1.6	NA [n = 1]

Invasive cancer of no special type; NST, Invasive lobular carcinoma; ILC, Ductal carcinoma *in situ*; DCIS, Not available; NA.

Other invasive cancers included carcinoma with apocrine differentiation (n = 3), adenoid-cystic carcinoma (n = 1), solid papillary carcinoma with invasive lesion (n = 1), and adenosquamous carcinoma (n = 1).

The number of available lesions in comparison between both PET systems is shown in brackets.

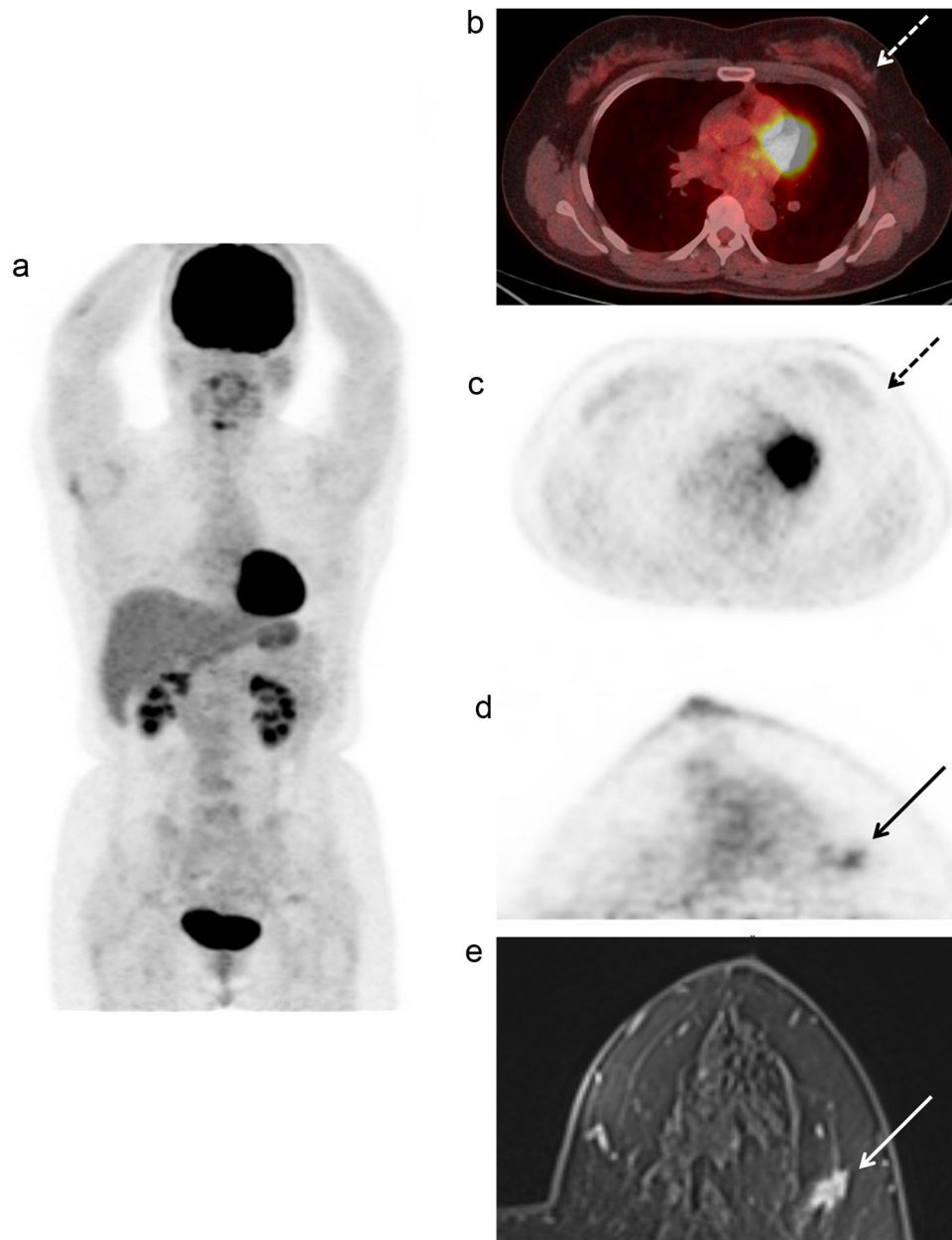


Fig. 4. A 49-year-old woman with invasive lobular carcinoma (Grade 1) in the left breast. A MIP image of WB-PET (a), axial images of WB-PET/CT fusion (b) and WB-PET (c) do not show focal FDG uptake in the left breast. An axial image of dbPET (d) depicts a focus of accumulation (dbPET SUVmax = 1.6, T/B ratio = 1.1), corresponding to a small nodule with contrast enhancement on MRI (e) (arrow).

Table 6

Sensitivities, SUVmax and T/B ratio of PET positive lesions according to histological grades of invasive cancers.

	Lesion-based sensitivity				SUVmax			T/B ratio		
	n	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p	dbPET	WB-PET/CT	p
Grade 1	42	88% (37/42)	79% (33/42)	0.22	8.6 ± 6.8	4.2 ± 3.1	<0.0001 [n = 32]	4.8 ± 4.2	3.1 ± 2.0	<0.0001 [n = 29]
Grade 2	94	93% (87/94)	90% (85/94)	0.62	12.6 ± 9.4	6.5 ± 5.1	<0.0001 [n = 84]	7.2 ± 6.5	5.2 ± 5.0	<0.0001 [n = 78]
Grade 3	38	97% (37/38)	97% (37/38)	NA	18.9 ± 10.5	8.5 ± 4.6	<0.0001 [n = 37]	13.7 ± 7.9	6.6 ± 4.3	<0.0001 [n = 34]

Not available; NA.

The number of available lesions in comparison between both PET systems is shown in brackets.

ies demonstrated the pooled sensitivity and specificity of PEM to be 85% (95% CI, 83%–88%) and 79% (95% CI, 74%–83%), respectively [8]. In our study, the lesion-based sensitivity of dbPET was 92%, suggesting dbPET has comparable photon sensitivity to PEM even for tumors in uncompressed breasts.

Several groups have shown that PEM improved the sensitivity for breast cancers compared to WB-PET or WB-PET/CT [11,12]. Kalinyak et al. showed that PEM was significantly more sensitive (92%) than WB-PET (56%) in 69 patients and than WB-PET/CT (87%) in 109 patients [12]. In our study with 179 breast cancers in 150 patients, the sensitivity of dbPET (92%) was not significantly different from that of WB-PET/CT (88%); however the difference was marginally insignificant ($p = 0.06$). We suspect that this was partly because our study population consisted of a lower proportion of small cancers (subcentimeter cancer/all subjects = 13% [23/179]) compared with Kalinyak's study (31% [54/175]).

For cT2–3 tumors (>2.0 cm, $n = 86$), both WB-PET/CT and dbPET achieved sensitivities of 100%. For cT1c tumors (>1.0 to ≤ 2.0 cm), both dbPET (95%) and WB-PET/CT (91%) still had relatively high sensitivity. However, for subcentimeter tumors (≤ 1.0 cm, cT1a–b, $n = 23$), the sensitivity of WB-PET/CT was limited, being only 43% (10/23), comparable with previous studies that showed conventional WB-PET or WB-PET/CT have low sensitivity for tumors <1 cm [1]. Detection of subcentimeter tumors is one of the biggest interests in the clinical application of high-resolution PET systems. According to previous studies of PEM, the sensitivity for T1a ($n = 2$ –16) and T1b ($n = 6$ –40) widely ranged from 25% to 100% and from 46% to 95%, respectively [10,12,15,16]. In our study with dbPET, we failed to detect all three cT1a tumors with both dbPET and WB-PET/CT. The spatial resolution of our full-ring type scanner was <1.5 mm at centre of FOV [20], which was higher than PEM type scanners, but it did not contribute to improve higher detectability. However, the number of subjects in cT1a was too small to analyze the merits of dbPET compared to WB-PET/CT or PEM scanner. For cT1b tumors ($n = 20$), the sensitivity of dbPET was slightly higher than those of WB-PET/CT, which was considered comparable with previous reports by a PEM type scanner [10,12,15,16]. Further examinations with more cases of small lesions are necessary to discuss the diagnostic performance of dbPET.

In terms of histological types and grades, the sensitivity of ILC, DCIS and Grade 1 tended to be higher in dbPET than in WB-PET/CT. ILC are known to show low FDG accumulation and low detection rate with WB-PET/CT [2]. Lower grade tumors have been reported to be associated with lower SUVmax on WB-PET/CT [24]. Our observation may indicate that dbPET might have a potential utility to improve the visualization of tumors which tend to accumulate less FDG and could be false negative on WB-PET/CT, such as ILC, DCIS and low grade tumors in addition to subcentimeter cancers. Further studies with larger study population would be warranted.

In terms of quantitative analysis, there was a strong linear correlation of SUVmax between dbPET and WB-PET/CT, indicating that quantitative data from dbPET may be acceptable to use. SUVmax in breast cancers on dbPET was constantly higher than that on WB-PET/CT, except for some subgroups with limited number of subjects, as well as in normal breast tissue. We suppose this ten-

dency of increasing SUVmax was mainly because of the small voxel size ($0.78 \times 0.78 \times 0.78$ mm) of dbPET compared with that of WB-PET/CT ($4.7 \times 4.7 \times 3.8$ mm), which makes SUVmax on dbPET less susceptible to partial volume artifact. Moreover, dbPET acquisitions commenced about 30 min after WB-PET/CT acquisitions. It may have affected FDG accumulation. It has been reported that tumor uptake increases from early to delayed phase (time interval; about 40 min) with change of SUVmax by $8.3 \pm 11.5\%$ [22]. Thus, the different period after injection may have also caused relatively higher uptake in dbPET.

In contrast to SUVmax, T/B ratio is considered not to be affected by the scanner used. Significantly higher T/B ratios on dbPET than on WB-PET/CT were thought to indicate higher tumor conspicuity against the background physiological uptake, which may be an advantage in dbPET over WB-PET/CT. It should be noted that T/B ratios were calculated using contralateral normal breasts as background in this study, because it was sometimes difficult to distinguish breast tissue uptake from tumor uptake in an involved breast, especially when a tumor or tumors spread into the breast tissue without forming clear margins. Thus, there could be a possible difference between our T/B ratios and common T/B ratios that use ipsilateral breast uptake as background due to different uptake period. However, our additional analysis showed there was no significant difference in SUVmax on dbPET between contralateral and ipsilateral breasts (data not shown).

The dbPET scanner could be advantageous to detect small tumors due to its higher conspicuity; however, clinical superiority to conventional WB-PET/CT for detection of small lesions has not been apparent in this investigation. Therefore, it may not be a cost-effective tool at this time. If it is confirmed that a dbPET scanner is a useful tool for detection of small lesions, resulting in reduction of medical costs as well as improvement of prognosis, the scanner could be recognized as a cost-effective modality.

This study had several limitations. First, we excluded 16 lesions (8%) located outside the FOV of dbPET in this analysis for reliable comparison of depiction by both scanners, resulting in over-estimation of dbPET. In addition, we evaluated only up to two lesions in each breast, even if there were multiple lesions, for reliable comparison with pathological findings, which might have also yielded over-estimation of both scanners. Second, histopathological results were obtained by biopsy in 89 of 179 cases. Therefore, the entire tumor might not have been evaluated in these cases, resulting in degradation of reliable histopathological results. Finally, it is known that physiological uptake in normal breast tissue depends on estrous cycle [25]. In this investigation, we did not take patients' estrous cycle into account, which might have affected T/B ratios.

5. Conclusions

Attenuation-corrected dbPET images reconstructed using optimized parameters with a larger population demonstrated that lesion-based sensitivity was slightly higher on dbPET than on WB-PET/CT. In addition, T/B ratios on dbPET were significantly higher than those on WB-PET/CT, indicating higher tumor conspicuity on dbPET. In the subgroup analysis, dbPET tended to reserve higher

sensitivities for tumors compared with limited sensitivities on WB-PET/CT, such as subcentimeter tumors, Grade 1, ILC and DCIS, although there were no significant differences.

Conflict of interest

Authors have no conflict of interest.

Acknowledgements

We thank Tae Oishi for her excellent clinical assistance and Yoshiyuki Yamakawa, Masafumi Furuta, Junichi Ohi and Keishi Kitamura for their technical advice.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] N. Avril, J. Dose, F. Jänicke, et al., Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose, *J. Clin. Oncol.* 14 (1996) 1848–1857.
- [2] N. Avril, C.A. Rosé, M. Schelling, et al., Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations, *J. Clin. Oncol.* 18 (2000) 3495–3502.
- [3] K. Scheidhauer, C. Walter, M.D. Seemann, FDG PET and other imaging modalities in the primary diagnosis of suspicious breast lesions, *Eur. J. Nucl. Med. Mol. Imaging* 31 (Suppl. 1) (2004) S70–9.
- [4] S. Escalona, J.A. Blasco, M.M. Reza, E. Andradás, N. Gómez, A systematic review of FDG-PET in breast cancer, *Med. Oncol.* 27 (2010) 114–129.
- [5] B.B. Koolen, K.E. Pengel, J. Wesseling, et al., FDG PET/CT during neoadjuvant chemotherapy may predict response in ER-positive/HER2-negative and triple negative: but not in HER2-positive breast cancer, *Breast* 22 (2013) 691–697.
- [6] S.M. Lee, S.K. Bae, T.H. Kim, et al., Value of 18F-FDG PET/CT for early prediction of pathologic response (by residual cancer burden criteria) of locally advanced breast cancer to neoadjuvant chemotherapy, *Clin. Nucl. Med.* 39 (2014) 882–886.
- [7] S.L. Bowen, Y. Wu, A.J. Chaudhari, et al., Initial characterization of a dedicated breast PET/CT scanner during human imaging, *J. Nucl. Med.* 50 (2009) 1401–1408.
- [8] C. Caldarella, G. Treglia, A. Giordano, Diagnostic performance of dedicated positron emission mammography using fluorine-18-fluorodeoxyglucose in women with suspicious breast lesions: a meta-analysis, *Clin. Breast Cancer* 14 (2014) 241–248.
- [9] D. Narayanan, K.S. Madsen, J.E. Kalinyak, W.A. Berg, Interpretation of positron emission mammography and MRI by experienced breast imaging radiologists: performance and observer reproducibility, *AJR Am. J. Roentgenol.* 196 (2011) 971–981.
- [10] W.A. Berg, K.S. Madsen, K. Schilling, et al., Breast cancer: comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast, *Radiology* 258 (2011) 59–72.
- [11] Y. Yamamoto, Y. Ozawa, K. Kubouchi, S. Nakamura, Y. Nakajima, T. Inoue, Comparative analysis of imaging sensitivity of positron emission mammography and whole-body PET in relation to tumor size, *Clin. Nucl. Med.* 40 (2015) 21–25.
- [12] J.E. Kalinyak, W.A. Berg, K. Schilling, K.S. Madsen, D. Narayanan, M. Tartar, Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT, *Eur. J. Nucl. Med. Mol. Imaging* 41 (2014) 260–275.
- [13] K. Murthy, M. Aznar, C.J. Thompson, A. Loutfi, R. Lisbona, J.H. Gagnon, Results of preliminary clinical trials of the positron emission mammography system PEM-I: a dedicated breast imaging system producing glucose metabolic images using FDG, *J. Nucl. Med.* 41 (2000) 1851–1858.
- [14] E.L. Rosen, T.G. Turkington, M.S. Soo, J.A. Baker, R.E. Coleman, Detection of primary breast carcinoma with a dedicated: large-field-of-view FDG PET mammography device: initial experience, *Radiology* 234 (2005) 527–534.
- [15] W.A. Berg, I.N. Weinberg, D. Narayanan, et al., High-resolution fluorodeoxyglucose positron emission tomography with compression (positron emission mammography) is highly accurate in depicting primary breast cancer, *Breast J.* 12 (2006) 309–323.
- [16] K. Schilling, D. Narayanan, J.E. Kalinyak, et al., Positron emission mammography in breast cancer presurgical planning: comparisons with magnetic resonance imaging, *Eur. J. Nucl. Med. Mol. Imaging* 38 (2011) 23–36.
- [17] M. Iima, Y. Nakamoto, S. Kanao, et al., Performance of 2 dedicated PET scanners for breast imaging: initial evaluation, *J. Nucl. Med.* 53 (2012) 1534–1542.
- [18] B.B. Koolen, S. Vidal-Sicart, J.M. Benlloch Baviera, R.A. Valdes Olmos, Evaluating heterogeneity of primary tumor 18F-FDG uptake in breast cancer with a dedicated breast PET (MAMMI): a feasibility study based on correlation with PET/CT, *Nucl. Med. Commun.* 35 (2014) 446–452.
- [19] E. Tanaka, H. Kudo, Optimal relaxation parameters of DRAMA (dynamic RAMLA) aiming at one-pass image reconstruction for 3D-PET, *Phys. Med. Biol.* 55 (2010) 2917–2939.
- [20] Y. Yamakawa, K. Kitamura, Attenuation correction using level set method for application specific PET scanners, *IEEE Sci Symp Conf Rec* (2011) 3130–3132.
- [21] K.K. Miyake, K. Matsumoto, M. Inoue, et al., Performance evaluation of a new dedicated breast pet scanner using NEMA NU4-2008 standards, *J. Nucl. Med.* 55 (2014) 1198–1203.
- [22] A. Mavi, M. Urhan, J.Q. Yu, et al., Dual time point 18F-FDG PET imaging detects breast cancer with high sensitivity and correlates well with histologic subtypes, *J. Nucl. Med.* 47 (2006) 1440–1446.
- [23] R.L. Wahl, H. Jacene, Y. Kasamon, M.A. Lodge, From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors, *J. Nucl. Med.* 50 (Suppl) (2009) 122S–150S.
- [24] M. Nakajo, Y. Kajiya, T. Kaneko, 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* 37 (2010) 2011–2020.
- [25] D. Vranjesevic, C. Schiepers, D.H. Silverman, et al., Relationship between 18F-FDG uptake and breast density in women with normal breast tissue, *J. Nucl. Med.* 44 (2003) 1238–1242.