The Potential of Dedicated Breast PET with a Ring-type Scanner —Basic Evaluation and Clinical Experience—


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Received December 8, 2017
Accepted March 4, 2018

In breast cancer, the survival rate is related to the size of the lesion. Since the spatial resolution of whole-body (WB)-PET is limited, it is difficult to evaluate small cancerous lesions. To improve resolution, high-resolution dedicated breast PET (db-PET) scanners have been developed. However, the potential of db-PET has not yet been established, and there has been no report of the application of db-PET on an Oncovision device (MAMMI) in breast cancer cases in Japan.

The purpose of this study was to evaluate the potential of db-PET for assessing breast cancer. The influence of image reconstruction parameters was verified in a phantom evaluation, while we quantitatively investigated the ability of db-PET to detect tumors, in comparison with WB-PET, with patients in the prone position, in a clinical evaluation. Despite a limited field of view in the vicinity of the chest wall, we show that db-PET has markedly better clinical value for diagnosing breast cancer as compared to WB-PET.

Key Words: positron-emission tomography, 18F-fluorodeoxyglucose, dedicated breast PET, breast cancer, reconstruction parameter

1. Introduction

Breast cancer is the most common cause of cancer-related death in women worldwide. Although the incidence and mortality rate varies worldwide, the breast cancer-related mortality rate has been increasing gradually in Japan.1 In patients with breast cancer, the survival rate is related to the size of the lesion, and early tumor detection has been identified as one of the most important factors related to the prognosis of breast cancer patients.2-4 In order to reduce the breast cancer-related mortality rate, it is crucial to identify small, early-stage breast cancer lesions, such as those with a diameter of 1 cm or less.
Positron-emission tomography (PET) with $^{18}$F-fluorodeoxyglucose (FDG) has been used for the diagnosis of breast cancer. There have been many reports of its clinical efficacy in the staging of breast cancer and prognosis prediction in patients with breast cancer.\textsuperscript{5–9) However, since the spatial resolution and sensitivity of whole-body (WB)-PET is limited, it is difficult to evaluate small cancerous lesions.\textsuperscript{2, 10) Furthermore, in patients with locally advanced cancer, biopsies are performed under imaging guidance to evaluate tumor subtypes and gene expression profiles in order to personalize treatment strategies.\textsuperscript{4) Therefore, when a biopsy is being considered, the reference image should provide more accurate detail.

To improve resolution, high-resolution dedicated breast PET (db-PET) scanners have been developed. The db-PET system can be classified into two types: the planar-type positron-emission mammography and tomographic exclusive PET-type, using a ring-type scanner.\textsuperscript{11, 12) The diagnostic capability of db-PET in breast cancer has been reported previously.\textsuperscript{13, 14) We introduced db-PET with a ring-type scanner for hanging breast imaging (MAMMI, Oncovision, Valencia, Spain) for the detection and diagnosis of breast cancer. However, the potential of db-PET has not yet been established, and there has been no report of the application of db-PET on an Oncovision device in Japan.

The purpose of this study was to evaluate the potential of db-PET for assessing breast cancer, based on both phantom and clinical evaluations. More specifically, the influence of image reconstruction parameters was verified in a phantom evaluation, while we quantitatively investigated the ability of dB-PET to detect tumors in comparison with WB-PET, with patients in the prone position, in a clinical evaluation.

2. Materials and methods

2.1 PET device

WB-PET-computed tomography (CT) was performed using a TruePoint Biograph16 PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). This provided 109 planes and a 22.1-cm axial field-of-view (FOV) with a system transaxial resolution of 5.9 mm at the center of the FOV, using 32,448 crystals of lutetium oxyorthosilicate (LSO). The db-PET device is based on monolithic lutetium-yttrium oxyorthosilicate (LYSO) crystals, a position-sensitive photomultiplier tube, and an electronic board including the high voltage power supply. It consists of 12 compact modules with a transaxial FOV of 170-mm diameter and a 40 mm axial FOV, which covers up to 170 mm, for longer breasts.\textsuperscript{11) The db-PET images are reconstructed with a three-dimensional (3D) standard maximum likelihood expectation maximization algorithm (3D-MLEM) with a voxel size of $1\times1\times1$ mm$^3$. The matrix size is $85\times85$, and the pixel size is 2.0 mm. The attenuation correction (AC) technique of db-PET is determined from AC factors (ACF) for each line of response (LOR). Linear attenuation coefficients at 511 keV for breast tissue ($\mu_{\text{breast}}$=0.098 cm$^{-1}$) and air ($\mu_{\text{air}}$=1.04 $10^{-4}$ cm$^{-1}$) are assigned to breast and air regions, respectively. The ACF for each LOR are then calculated as $\text{ACF-LOR}=\mu_{\text{breast}} \times L_{\text{breast}} \times \mu_{\text{air}} \times L_{\text{air}}$.

2.2 Phantom study

2.2.1 NU 4-2008 phantom

The NU 4-2008 phantom is a cylindrical container with internal dimensions of 50mm in length and 15 mm in radius and comprises three regions. The central part (15-mm length) is free of any object and serves as a uniform region.\textsuperscript{15–17) At the end of the phantom, two fillable cylindrical chambers (15-mm length, 8-mm inner diameter, and 10-mm outer diameter) are attached to the cover. Contrast evaluation
was performed in this region: we examined the effect of changing the iteration number of the image reconstruction parameter on the imaging, and optimized the db-PET image. The end of the opposite phantom was occupied by a cylindrical block of 20 mm in length and 15 mm in radius. Five fillable rods with diameters of 1–5 mm were drilled parallel to, and with their center at 7 mm from the cylinder axis. The recovery coefficient of db-PET was measured in this region.

2.2.2 Phantom evaluation in db-PET

The NEAM NU 4-2008 phantom, with a capacity of approximately 20 mL, was placed on the center in db-PET. The NU 4-2008 phantom was then filled with $^{18}$F-FDG, with the radioactivity concentration set at 4 kBq/mL. The phantom radioactivity concentration was set according to clinical conditions. The radioactivity concentrations in the two fillable cylindrical chambers were set at 8 kBq/mL and 16 kBq/mL. PET data were collected for 5 min, based on clinical conditions, and we performed both contrast evaluation and recovery coefficient measurement. The phantom experiment was conducted three times in each verification. The db-PET image was analyzed using OsiriX version 3.2 imaging software (Apple Technology Co, Cupertino, CA, USA.).

2.2.3 Contrast evaluation

A phantom study was performed to assess the value of db-PET for improving the signal-to-noise ratio (SNR) and to estimate the optimal iteration number of PET reconstruction parameters required for this algorithm. The iteration number of 3D-MLEM algorithms was changed from 1 to 50. The parameter that can be changed in db-PET is only the iteration number.

2.2.4 Noise evaluation of reconstructed PET images

For the assessment of background uptake, regions of interest (ROIs) with a diameter of 22.5 mm were placed at the center of the uniform region. The ROI was placed on a total of five slices, including two slices prior to and two slices following the center slice in the uniform region. Coefficient of variation (CV) (%) was evaluated by averaging the five ROIs. The CV was determined using the following formula [Eq. 1].

$$CV(\%) = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{SD_i}{Background} \right) \times 100$$

where "Background" was defined as the mean radioactivity in the ROI of the uniform region, and SD was defined as the standard deviation (SD) in the background ROI. Both background and SD values were calculated for all five ROIs.

2.2.5 Contrast ratio and SNR in reconstructed PET images

We performed two model phantom studies: one was performed with the phantom filled with $^{18}$F-FDG with a concentration of twice the background radioactivity, and the other was filled with $^{18}$F-FDG with a concentration of four times the background level. The total activity in the FOV was about 8 or 16 kBq/mL, while the background was 4 kBq/mL. The contrast ratios and SNRs between the two fillable cylindrical chambers, with an 8-mm diameter, and the background on the reconstructed NEMA NU 4-2008 phantom images were calculated using the following formulas [Eqs. 2, 3].

$$\text{Contrast ratio} = \frac{\text{Signal}}{\text{Background}}$$

$$\text{SNR} = \frac{\text{Signal}-\text{Background}}{\text{SD}}$$

where "Signal" is the maximum radioactivity of each of the two fillable cylindrical chambers and "Background" is the mean radioactivity in the ROI of the uniform region. SD was defined as the standard deviation in the background ROI.

2.2.6 Recovery coefficient measurement

The db-PET images were reconstructed with a 3D-MLEM (12 iterations) algorithm. The radioac-
tivity concentration was measured using an ROI of 5 mm with each rod in the central slice, and we set an ROI of 22.5 mm in the uniform area.\textsuperscript{15–17} The recovery coefficient was calculated using the following formula [Eq. 4].

\[
\text{Recovery coefficient} = \frac{\text{Signal}}{\text{Background}}
\]  

(4)

where “Signal” is the maximum radioactivity of each rod and “Background” is the mean radioactivity in the ROI of the uniform region.

Furthermore, in order to simulate the upper outer quadrant of the breast, which is the site typically affected by breast cancer, the phantom was moved 4 cm off-center in the x direction and 4 cm off-center in the y direction to estimate the recovery coefficient.

2·3 Clinical evaluation

This retrospective cohort study in a single center was approved by the institutional review board, and informed consent was obtained from each patient. A total of 75 Japanese women (mean age: 52.3±12.3 years) with histologically proven breast lesions, and who underwent both db-PET and WB-PET/CT scans, were retrospectively enrolled for the clinical evaluation in this study. Sixty-six cases had invasive ductal carcinoma, eight had ductal carcinoma \textit{in situ}, and one had lobular carcinoma \textit{in situ} (tumor size: 20.9±13.2 mm, range: 4–61 mm). There were no patients with plasma glucose levels $>$200 mg/dL at administration of FDG.

Patients were administered 3.5–4.0 MBq/kg of \textsuperscript{18}F-FDG intravenously, and WB-PET/CT and db-PET images were acquired with the patients in the prone position, with breasts hanging pendant, at 60 min (range: 45–70 min) and 90 min (range: 80–110 min) after injection, respectively.

2·3·1 PET scan

WB-PET data were reconstructed using a 5.0-mm resolution with a full-width half-maximum Gaussian filter with a 3D-ordered subset expectation maximization algorithm (two iterations, 24 subsets), and an image matrix size of $128 \times 128$ pixels. For AC and anatomical localization, CT scanning (120 kVp tube voltages, 100 mA tube current with 0.5 s per tube rotation, pitch 1.75 and 3.75 mm section thickness) was performed. The WB-PET scanned from the vertex to the upper thigh using 3-min scans and six to seven bed positions. The db-PET images were reconstructed with a 3D-MLEM (12 iterations) algorithm. Dead time, scatter, and random events corrections were considered in the reconstruction process.

2·3·2 Image analysis

Both db-PET and WB-PET images were analyzed using OsiriX imaging software. Primary tumor detection was assessed and FDG uptake was calculated as the maximum standardized uptake value (SUV\text{max}) by using volumes-of-interest (VOIs). The db-PET and WB-PET images were visually evaluated by nuclear medicine physicians, and the sensitivities for breast cancer detection were calculated. The SUV\text{max} of breast cancer on both images were compared. Furthermore, we compared the ability of WB-PET and db-PET to detect the tumor lesions. We calculated the tumor-to-normal tissue ratio (T/N ratio), where tumor is the SUV\text{max} of the lesion, and the SUVmean of the contralateral breast tissue is defined as normal tissue.

2·4 Statistical analysis

Data are presented as the mean±S.D. The correlation between db-PET SUV\text{max} and WB-PET SUV\text{max} was evaluated using Pearson’s correlation coefficient, using IBM SPSS 21.0 for Windows (IBM COMPANY, Chicago, IL, USA). For comparison of the SUV\text{max} and T/N ratio of db-PET and WB-PET, Paired \textit{t}-test was used. A \textit{p} value $<$0.05 was considered statistically significant.
3. Results

3.1 Phantom evaluation

Fig. 1 shows the reconstructed images of the NEMA NU-4 2008 phantom with a 3D-MLEM (12 iterations) algorithm. (a) is the uniform region, (b) shows two fillable cylindrical chambers of 8 mm in diameter, (c) represents five fillable rods with diameters of 1–5 mm. (d) simulates the upper outer quadrant of the breast which moved (c) 4 cm off-center in the x direction and 4 cm off-center in the y direction (Color online).

Fig. 2 The relationship between the coefficient of variation (CV) and iteration number (Color online).

Fig. 3 The relationship between the contrast ratio and iteration number (Color online).

contrast ratio increased with the iteration number, and the concentration model using four times the background radioactivity converged faster than that using twice the background level. In Fig. 4, the relationship between SNR and iteration number is shown: the SNR peaked at an iteration number of 12 in the concentration model using four times the background level, and gradually decreased thereafter. The
optimum image reconstruction condition of db-PET was determined to be 12 iterations, based on this result. The SNR of the concentration model with twice the background was almost the same at an iteration number of 18 or more. When the number of iterations was four or less, the value fluctuated and was unstable. The relationship between recovery coefficient and rod size is shown in Fig. 5. The recovery coefficient depended on rod size, and decreased as the rod size became smaller. As shown in the phantom image in Fig. 1, when the recovery coefficient was 0.2 or more, the rod could be distinguished, up to a rod size of 2 mm. Moreover, when simulating the upper outer quadrant of the breast, the recovery coefficient decreased by about 20% on average for each rod.

3.2 Clinical evaluation

Fig. 6 shows the positive correlation of SUV values between db-PET and WB-PET/CT ($r = 0.79$, $p < 0.01$). The SUVmax of db-PET was about 2.2 (2.17 ± 0.89) times higher than that of WB-PET, representing a statistically significant increase. Table 1 show the comparison of each index between db-PET and WB-PET. The SUVmax, normal tissue, and T/N ratio values of db-PET were 14.9 ± 8.8,
1.48±0.4, and 10.7±6.6, respectively, while those of WB-PET were 7.8±5.5, 1.21±1.08, and 7.3±5.3, respectively. The SUVmax and T/N ratio of db-PET were statistically significantly better than those of WB-PET (p<0.01). The T/N ratio of db-PET was about 1.8 (1.77±1.26) times higher than that of WB-PET (p<0.01).

The sensitivity of db-PET was 80.0% [60/75]. FDG accumulation patterns were classified into four categories by visual evaluation. Fig. 7 shows FDG accumulation pattern of WB-PET and db-PET. The result of FDG accumulation pattern shows in Table 2. Fifty-one cases (Pattern 1: 68.0% [51/75]) were similarly evaluated by db-PET and WB-PET. Three cases (Pattern 2: 4.0% [3/75]) had positive findings with db-PET, but lesions could not be detected with WB-PET. In six cases (Pattern 3 8.0% [6/75]), db-PET imaging could visualize the tumor shape in greater detail and allowed examination of daughter nodules. Sixteen cases (Pattern 4: 20.0% [15/75]) had positive findings on WB-PET, but no abnormality could be detected in db-PET, because it was outside the imaging FOV of db-PET. Fig. 8 shows comparative images of a case of ductal carcinoma; db-PET allowed more detailed investigation of tumor shape than WB-PET.

4. Discussion

In this study, db-PET was applied to Japanese breast cancer patients, which has not been reported previously, and the characteristics of db-PET were clarified. Imaging using db-PET improved quantitative evaluation and detectability as compared to WB-PET and was effective for the diagnosis of breast cancer.

Table 2 The details of the FDG accumulation patterns of db-PET compared to WB-PET

<table>
<thead>
<tr>
<th>Pattern*</th>
<th>n =75</th>
<th>Value (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>68.0% [51/75]</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4.0% [3/75]</td>
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<tr>
<td>3</td>
<td>6</td>
<td>8.0% [6/75]</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>20.0% [15/75]</td>
</tr>
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* Pattern 1: db-PET = WB-PET.
Pattern 2: db-PET: positive, WB-PET: negative.
Pattern 3: db-PET clearer than WB-PET.
Pattern 4: db-PET negative.
We first optimized the image reconstruction parameters of db-PET using a phantom study. Since the MLEM method employs successive approximation, more accurate reconstructed images can theoretically be obtained by using increased numbers of iterations. However, when processing data obtained in clinical situations, an increase in the iteration number results in the enhancement of noise, as well as reconstruction of the true signal. When striving to increase the capability of detecting lesions, consideration of the relationship between contrast and noise is important. Therefore, it was necessary to evaluate the influence of iteration number accurately to determine optimal parameters for image reconstruction. For the reasons, in this study, the iteration number was determined based on the radioactivity concentration 1:4 model which is generally used for phantom evaluation.

In the contrast evaluation, the radioactivity value increased due to an increase in the number of iterations used for image reconstruction, and quantitativeness improved by converging to a true value. When using a high radioactivity concentration to background ratio, convergence occurred more rapidly, but in cases with low radioactivity concentrations, such as with small lesions, sufficient repetitive calculations were necessary.

In the recovery coefficient analysis, it was possible to detect a rod size of up to 2 mm. MAMMI db-PET spatial resolutions are 1.6, 1.8, and 1.9 mm in the axial, radial, and tangential directions, respectively. This result was a reasonable value, corresponding to the spatial resolution of MAMMI db-PET. However, the resolution was markedly reduced in the area that simulated the upper outer quadrant of a breast. With increased distance from the central position of the FOV in db-PET, the recovery coefficient deteriorated. Techniques for correcting the resolution, such as the depth-of-interaction (DOI) technique may resolve this problem, but even without use of the DOI technique, sufficiently detectability were obtained for rod size of 5 mm.

In the clinical evaluation, the parameters of db-PET image reconstruction were optimized and clinical evaluation was performed. Comparison between db-PET and WB-PET imaging in clinical cases, revealed that the SUV obtained was about 2.2 times higher due to the high resolution of db-PET and the quantitativeness was improved in db-PET, demonstrating the effectiveness of db-PET. The results of
this study were similar to or better than those of previous reports.\textsuperscript{12, 22} Breast cancer is a heterogeneous disease consisting of distinct histopathological subtypes with different clinical outcomes. This classification of subtypes has been refined considering molecular classification, which enables combination with biological features. Moscoso et al. reported the possibility that the biological characteristics of breast tumors could be revealed by texture analysis of db-PET images,\textsuperscript{21} which were presumably obtained at high resolution. However, the db-PET acquisitions commenced about 30 min after WB-PET/CT acquisitions. Tumor uptake has been reported to increase from the early phase to the delayed phase and this may have affected the accumulation of FDG in db-PET.\textsuperscript{7}

In terms of the ability to detect breast cancer, the T/N ratio of db-PET was significantly higher than that of WB-PET, and 10\% of lesions that could not be detected or could not be clearly visualized by WB-PET were detected by db-PET imaging. These results suggest that db-PET is useful for detailed analysis of breast cancer lesions, and contribute to breast cancer diagnosis.

4.1 Study Limitation

However, db-PET was limited in demonstrating primary tumors in the vicinity of the thoracic wall. When the lesion was included in the FOV of db-PET, it could be clearly visualized, but when located outside the FOV, it was difficult to detect 20\% of lesions, which was somewhat higher than previously reported.\textsuperscript{13} This may be due to racial differences, as a previous study had reported that Japanese women have breast that are characteristically denser and smaller than those of Caucasian women.\textsuperscript{23, 24} This issue of falling outside the scan range of db-PET should be addressed to allow visualization of the most dorsal breast lesions. Also, in this study no investigation was done on breast cancer subtypes. Further studies should be investigated to the association between db-PET and breast cancer subtypes.

5. Conclusion

In this study, image reconstruction parameters of db-PET were optimized based on a NEMA NU 4-2008 phantom, and db-PET was compared to WB-PET in a clinical evaluation, clarifying the capability of db-PET. Despite a limited FOV in the vicinity of the chest wall, db-PET has markedly better clinical value for diagnosing breast cancer than WB-PET. In future, it will be necessary to improve detectability of lesions outside the current FOV of db-PET.

References


要旨

リング型乳房専用 PET 装置の基礎評価と臨床経験

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2017年12月8日 受付
2018年3月4日 受理

本研究の目的は、dedicated breast PET (db-PET) が乳がんの診断に有効であるか検討することである。NEMA NU-4 2008 ファントムを使用して db-PET の画像再構成パラメータを最適化した。75名の乳がん症例において、全身用 PET/CT 装置によって得られた WB-PET 画像と db-PET 画像を比較検討した。
db-PET の定量性および検出能は、WB-PET と比較して統計学的に有意に改善し、乳がんの診断能向上に有効であることが明らかとなった。