Initial experience of integrated PET/MR mammography in patients with invasive ductal carcinoma

Abstract
The purpose of this study was to evaluate the feasibility of integrated fluorine-18-fluorodeoxyglucose positron emission tomography/magnetic resonance ($^{18}$F-FDG PET/MR) mammography in invasive ductal carcinoma (IDC) patients. From August 2012 to March 2013, we enrolled 42 consecutive breast cancer patients who received whole-body PET/MR and subsequent PET/MR mammography by an integrated PET/MR scanner and were scheduled for surgery within 2 weeks after the scan. On the whole body PET/MR, 2-point Dixon VIBE, coronal T1w image, axial T2w image, and post-contrast T1 sequences were acquired with simultaneous PET acquisition. For PET/MR mammography, T1w, T2w, and dynamic contrast-enhancement (DCE) sequences were acquired using a breast coil during simultaneous PET acquisition. We compared the detectability of the lesions between whole-body PET/MR and PET/MR mammography. Forty-eight patients were diagnosed with IDC. Forty-eight patients were diagnosed with IDC. The SUV between whole-body PET/MR and PET/MR mammography showed strong and highly significant correlation ($r=0.987$, $P<0.001$). In conclusion, our results, although in a limited number of cases showed that integrated PET/MR mammography is feasible and has the advantage of combining high-resolution breast images with metabolic images. Furthermore, PET/MR mammography could provide an accurate diagnosis of IDC that are less than 1cm in size.

Introduction
The success of hybrid imaging using positron emission tomography (PET) and computed tomography (CT) has inspired physicians and medical physicists to develop a technically challenging but academically fascinating integrated imaging system involving PET and magnetic resonance (MR) imaging. This hybrid PET/MR imaging modality is of diagnostic value when the superior features of MR are desired (e.g., in cases of increased soft tissue contrast or reduced radiation dose and functional information). Recently, an integrated PET/MR scanner became available, and several reports involving PET and MR imaging have been published. According to these initial experiences, the image quality in integrated PET/MR is equivalent to that of PET/CT and meets oncologic diagnostic needs [1-3]. However, the ongoing challenge is to make optimum use of the integrated PET/MR scanner. Accordingly, it is necessary to identify the clinical indications that warrant its use and to establish a scanning protocol in clinical practice.

Fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) PET has been established as an important imaging modality for the diagnosis, staging, restaging, monitoring of the response to treatment, and estimation of the long-term prognosis in patients with breast cancer [4-7]. With both whole-body PET and PET/CT, however, the accuracy of detection and quantification of breast cancer is significantly reduced when the lesion is smaller than 1 cm or shows low $^{18}$F-FDG avidity [8, 9]. Computed tomography is beneficial in the diagnosis of such lesions; however, PET/CT does not provide an accurate depiction of the anatomy of the breast, primarily due to the weak soft-tissue contrast on CT. On the other hand, MR imaging (MRI) with a breast coil clearly depicts the anatomy of the breast. Therefore, for the evaluation of breast cancer, it might be worthwhile to integrate PET and MRI so that the anatomical, functional, and metabolic data are analyzed together, potentially...
producing synergistic effects. Thus far, an integrated PET/MR system has not been used for the evaluation of breast cancer. We believe that the field of oncology would benefit from whole-body staging of breast cancer together with high-spatial resolution imaging of the breast for surgical planning. Thus, the goal of this study was to evaluate, for the first time, the use of an integrated 18F-FDG PET/MR mammography system for the detection of primary lesions in patients with invasive ductal carcinoma (IDC).

Material and methods

The protocol of this study was approved by our institutional review board. In addition, informed consent was obtained from all the patients enrolled in this study.

Patients

From August 2012 to March 2013, PET/MR examinations were performed in 312 consecutive patients for the evaluation of breast cancer at our department. After reviewing their pathological results, we had identified 48 IDC in 42 women. These 42 women were enrolled in our study. They underwent a PET/MR examination for pre-operative evaluation and subsequently received surgery within 2 weeks of the scan. The exclusion criteria were: previous excisional biopsy, neoadjuvant chemotherapy, and known distant metastases. In addition, patients with IDC containing ductal carcinoma in situ (DCIS) were excluded from this study.

Imaging protocol

Patients fasted for at least 6h before the intravenous administration of 18F-FDG (mean, 270.5±65.9MBq; range, 176.1-490.6MBq). Before the injection of the radioisotope, the blood glucose concentration was confirmed below 150mg/dL. First, a supine whole-body PET/MR scan was performed 60-90min after the injection of 18F-FDG, covering a field of view from the skull base to the mid thighs. After whole-body PET/MR was completed, PET/MR mammography was performed with the patients in the prone position; the scan was started approximately 90-120min after the injection. The integrated PET/MR (BiographmMR; Siemens Healthcare, Erlangen, Germany) scanner consisted of a 3-T MR system and an inline PET system with an avalanche photodiodes (APD) detector. The APD are not only insensitive to a magnetic field but also have a small space to be cased within the MR gantry. The PET unit has an axial field of view of 25.8 cm and offers the advantage of fewer bed positions in a short time. The PET data were reconstructed using a 3-dimensional (3D) ordinary Poisson ordered-subsets expectation (OP-OSEM) algorithm with 2 iterations and 21 subsets (172×172 matrix, zoom 1, slice thickness 2mm). A post-reconstruction Gaussian filter with 6.0mm full-width at half-maximum was applied. An MRI-based attenuation correction of the PET data was accomplished according to the method described by Martinez-Möller et al [10].

The imaging protocol was designed with reference to the study by Martinez-Möller et al [11]. Whole-body PET/MR was performed in a caudocranial direction, with a total imaging matrix (TIM) coil. The TIM coil is an approved surface coil for PET/MR, which improves image quality and reduces imaging time with MRI, similar to that in standalone MRI. After acquisition of the initial T1-weighted two-point Dixon 3D volumetric interpolated breath-hold examination (VIBE) for attenuation correction, coronal T1-weighted turbo spin-echo (TSE) and axial T2-weighted fat saturated (fs) half-Fourier single-shot turbo spin-echo (HASTE) sequences were obtained during simultaneous PET acquisition. Four PET bed positions were usually required, and the emission time per bed was 3min.

The PET/MR mammography comprised a breast PET scan of 1 bed position and a simultaneous breast MRI using a standard 16-channel AI Breast Coil (RAPID Biomedical GmbH, Rimpar, Germany) device. The emission time of the PET scan was 8min. The breast MRI examination consisted of a localizer sequence, T1-weighted TSE, and T2-weighted fs TSE sequence, a single-shot spin-echo planar diffusion-weighted sequence, and 3D dynamic contrast-enhanced (DCE) sequence. DCE-MRI was performed with axial T1 3D VIBE imaging, with 1 pre-contrast and 5 post-contrast dynamic series performed within 5:18-8:22 depending on the breast thickness after bolus injection. Next, 3mL/s of gadopentetated-

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<td>Whole-body PET/MR</td>
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AC: attenuation correction; CM: contrast medium; DCE: dynamic contrast enhanced; DWI: diffusion weighted imaging; fs: fat saturated; GRAPPA: generalized autocalibrating partially-parallel acquisition; HASTE: half Fourier acquisition single shot turbo spin echo; TE: echo time; TR: repetition time; TSE: turbo spin echo; VIBE: 3-dimensional volumetric interpolated breath-hold examination.
imeglumine (0.1mmol/kg of body weight, MRbester, Taejoon Pharm, Seoul, Republic of Korea) was injected, followed by a 20mL saline flush. Finally, in the supine position, 3-axial T1-weighted fs VIBE sequences were obtained again for the whole lung, abdomen, and pelvis, during a single breath hold, respectively. The detailed protocol used for whole-body PET/MR and PET/MR mammography using the integrated PET/MR scanner is listed in Tables 1 and 2.

Image analysis
The analysis of whole-body PET/MR and PET/MR mammography images was performed by 2 nuclear medicine physicians. The PET and MR data sets were retrospectively analyzed on the PET/MR workstation (syngo.via; Siemens Medical Solutions) by using software (mMR general and MR BreVis; Siemens Medical Solutions).

Whole-body PET/MR
The PET images were evaluated visually and quantitatively. During visual analysis, the images were classified as follows: no distinguishable uptake (G0), suspicious increased uptake (G1), mild uptake (G2), and obvious uptake (G3). The SUVmax was measured for each individual tumor. In addition, the intratumoral signal intensity (SI) of the tumor was visually evaluated on T1-weighted TSE, T2-weighted HASTE, and post-contrast VIBE images.

PET/MR mammography
The PET image of the breast was analyzed by using the same method as that of whole-body PET analysis. The findings of DCE-MRI were analyzed with MR BreVis software. For the DCE-MRI analysis, subtraction images were generated by subtracting the pre-contrast images from all contrast-enhanced images. Subsequently, the tumor size, morphologic pattern (shape, margin, and internal enhancement of the mass lesion) during the early phase, and kinetics (percentage SI increase during the early phase and kinetic curve type during the delayed phase) were evaluated for each lesion according to the Breast Imaging Reporting and Data System MRI guidelines [12]. After detection of the enhanced lesions on subtraction images, the region of interest (ROI)-based time–SI curves were plotted at the enhancing tumor to depict enhancement kinetics during the dynamic study. To assess the early-phase SI increase, we calculated the enhancement for the first post-contrast image: percentage enhancement at early phase (%)=[(first post-contrast SI-pre-contrast SI)/pre-contrast SI]×100% [13]. The type of kinetic curve characterized the relative SI change: 3 types of delayed curves were defined: type 1 curve=persistent (continuous increase in SI after peak enhancement >10%); type 2 curve=plateau (steady SI after peak enhancement +/-10%); and type 3 curve=wash out (SI decrease after peak enhancement>10%) [13].

Statistical analysis
The statistical analyses were performed with IBM SPSS statistical software, version 19 (IBM SPSS North America, Chicago, IL, USA). A P value of <0.05 was considered statistically significant. The correlation between SUV_{whole-body} and SUV_{mammography} was examined using Pearson’s correlation and linear regression analysis. We also evaluated the correlation between histologic tumor size and measured tumor size using Pearson’s correlation.

Results
Forty-two women, aged 51.8±10.8 years, range, 29-76 years, with 48 IDC (right 23 and left 25) were enrolled in the study. Three patients had multiple IDC. The number of IDC in these 3 patients was 2, 3, and 4, respectively. The average size of the 48 tumors was 1.89±1.19cm (0.2-5.8cm); 10 IDC were ≤1.0cm wide, 24 IDC were 1.1-2.0cm, 13 IDC were 2.1-5.0cm, and 1 IDC was >5.1cm. Furthermore, axillary lymph node metastases were detected in 12 patients.

All patients received surgical treatment within 2 weeks (1-14 days) of the integrated PET/MR examination. Breast-conserving surgery, modified radical mastectomy, and skin-sparing mastectomy were performed in 26, 13, and 3 patients, respectively. Eleven patients received axillary dissection, and 31 patients underwent sentinel lymph node biopsy.

Analysis of whole-body PET/MR
The ^{18}F-FDG avidity of tumors was evaluated by visual analysis
More than half: 25/48 of IDC showed low SI by T1-weighted TSE, and more than two thirds, 33/48 showed high SI by T2-weighted fs HASTE. In the post-contrast VIBE images, even more, 40/48 IDC showed enhancement. In Group A, the T1-weighted TSE image did not show any lesion with low SI; there was 1 (10%) high SI mass observed by T2-weighted fs HASTE and 4 enhancing masses (40%) observed by VIBE. In Group B, two thirds, 25/48 IDC showed low SI lesions on T1-weighted TSE images, more, 32/48 showed high SI lesions on T2-weighted fs HASTE images, and even more, (94.7%) 36/48 showed enhancing masses on VIBE images (Table 3).

Analysis of PET/MR mammography

No difference in 18F-FDG uptake was observed between whole-body PET/MR and subsequent PET/MR mammography. Excluding G0, the mean SUV was 0.7±0.7 in Group A, 3.9±3.9 in Group B, and 3.5±3.8 overall. A strong and highly significant correlation was found between SUVwhole body and SUVmammography (r=0.987, P<0.001; Fig. 2).

All IDC showed contrast enhancement in DCE-MRI findings. The size of the tumor measured by PET/MR mammography was 2.0±1.2cm, which was closely related to the size measured by histological analysis (r=0.925, P<0.001).

Furthermore, the IDC were observed to have the following morphologies: 4 IDC, round; 6, oval; 18, lobular; 20, irregular; 22, spiculated; 10, smooth margin; 22, irregular margin; and 16, spiculated margin. Analysis of the internal enhancement and semiquantitative analysis with SUV. There were 10 IDC with no or very weak uptake (G0 or G1), 5 G2, and 33 G3. According to the size of the tumor, we classified IDC into 2 groups: 1.0cm or smaller, Group A and larger than 1.0cm, Group B. Group A tumors were further classified as follows: G0, 5; G1, 4; and G3, 1. Group B tumors were classified as follows: G1, 1; G2, 5; and G3, 32. Excluding G0, the mean SUV was 1.2±0.9 in Group A, 4.9±4.8 in Group B, and 4.5±4.7 overall.

More than half: 25/48 of IDC showed low SI by T1-weighted TSE, and more than two thirds, 33/48 showed high SI by T2-weighted fs HASTE. In the post-contrast VIBE images, even more, 40/48 IDC showed enhancement. In Group A, the T1-weighted TSE image did not show any lesion with low SI; there was 1 (10%) high SI mass observed by T2-weighted fs HASTE and 4 enhancing masses (40%) observed by VIBE. In Group B, two thirds, 25/48 IDC showed low SI lesions on T1-weighted TSE images, more, 32/48 showed high SI lesions on T2-weighted fs HASTE images, and even more, (94.7%) 36/48 showed enhancing masses on VIBE images (Table 3).
The average size of the tumors included in this study was 18.2±6.2 cm, including 1 tumor showing slow increase during the early phase. During the delayed phase, 43 IDC showed washout kinetics, 3 showed a plateau, and only 1 showed a persistent type.

Discussion

In this study, we investigated the use of hybrid imaging in patients with IDC and found that PET/MR mammography was feasible and more useful than whole-body PET/MR imaging for the diagnosis of IDC.

Only one of the ten ≤1 cm wide tumors showed increased 18F-FDG uptake. We could detect 2/10 tumors by whole-body PET/MR images, considering both 18F-FDG PET and anatomical changes revealed by MRI. However, PET/MR mammography showed all 10 tumors with contrast enhancement. Thus, whole-body PET/MR was not sufficient for the diagnosis of breast malignancy, whereas PET/MR mammography could detect small lesions in addition to possible multiple tumors [14] (Fig. 3).

The average size of the tumors included in this study was <2 cm; therefore, conventional whole-body PET/MR could not detect these tumors during the diagnosis of breast cancer. On the other hand, PET/MR mammography could depict the shape, margin, and internal enhancement pattern of these tumors; it could also show the enhancement pattern over time as well as the 18F-FDG avidity. Therefore, PET/MR mammography is more suitable than whole-body PET/MR imaging for the morphologic evaluation of tumors larger than 1 cm in size as well as for the detection of small lesions. Features such as the shape, margin, and internal enhancement patterns are also useful tools for distinguishing malignant from benign lesions [15]. We did not include benign disease in this study, and therefore, we could not evaluate the differential diagnosis of malignant and benign lesions by PET/MR mammography. However, it is likely that the metabolic and morphologic information obtained by PET/MR mammography can increase the diagnostic accuracy of malignant tumors. Moy et al [16] reported that fused PET/MR mammography could increase the positive predictive value and specificity compared to MR imaging alone and the sensitivity and negative predictive value compared to 18F-FDG PET alone.

No difference in 18F-FDG uptake between whole-body PET/MR and PET/MR mammography was observed. The correlation between SUV whole body and SUV mammography was strong and highly significant. However, a steady percentage of radioactivity attenuation was observed due to radiofrequency of the breast coil. In the near future, commercialization of the radiofrequency breast coil may result in the development of breast coils with no global attenuation on the PET emission data; in addition, further improvement of the resolution of the PET detector is expected.

Positron emission mammography imaging with the patient in the prone position is more useful than that in the supine position for detecting lesions and understanding anatomical locations because it is more representative of the original anatomy that relies on gravity. Besides, it is favorable for the co-registration of PET data and MR anatomical information.

Recently, positron emission mammography (PEM) was developed and applied in clinical practice. Positron emission mammography uses a dedicated scanner for breast cancer detection with 2 parallel photon detectors similar to mammography compressors [17]. Positron emission mammography was more sensitive than whole-body PET/CT in evaluating breast cancer, with a high sensitivity for tumors smaller than 1 cm [18]. Moreover, the sensitivity, specificity, and diagnostic capability of PEM were higher than those of MRI [19]. If the sensitivity of the PET detector in the PET/MR scanner could be similar to that of PEM, PET/MR mammography could be used to detect smaller lesions with low 18F-FDG avidity and provide more detailed molecular information in small-sized breast cancer.

To take advantage of the unique features of the integrated PET/MR scanner, it is important to use MRI not only for anatomical reference using PET images but also for assessing the detailed architecture and obtaining functional information by using novel MRI techniques. The aforementioned uses of PET/MR differentiate it from PET/CT, in which low-dose CT data are used for anatomical reference and attenuation correction. Although diffusion-weighted imaging (DWI) was not performed in this study, a recent study showed a significant negative correlation between standardized uptake value (SUV) and the apparent diffusion coeffi-
cient (ADC) [20]. In addition, the SUV and ADC values were correlated to several histopathological prognostic factors, which contribute to the prognosis of breast cancer [20-22]. The information provided by both PET and DWI can be complementary because the 2 modalities provide different biochemical information. It is expected to be useful in predicting the prognosis and evaluating the therapeutic effect in multi-parametric quantitative analysis using $^{18}$F-FDG avidity, DWI, and DCE, etc.

Our study has several limitations. First, the number of subjects was small. Second, we did not include patients with benign disease because the PET/MR study was performed for staging of breast cancer before the operation. If PET/MR mammography were used for the differential diagnosis of malignant and benign masses, it would increase the specificity, similar to that of PEM. Third, the breast coil used in this study was not an approved surface coil; therefore, it resulted in global attenuation on the PET emission data. However, the correlation between SUV of whole-body PET/MR and that of PET/MR mammography was very good. Therefore, attenuation induced by the radiofrequency of the breast coil may not be an obstacle in the clinical use of PET/MR mammography. Moreover, in the near future, the following technological developments will further improve this technique—software for high resolution reconstruction, an advanced detector such as Silicon Photomultiplier (SiPM), and approved surface coils for PET/MR mammography that consider attenuation. These developments could make PET/MR mammography more useful in diagnosis and prognostic estimation by improving the signal-to-noise ratio [23].

The small number of subjects in this study was not enough to show the additional advantages of integrated PET/MR mammography because both PET and MRI are good individual diagnostic modalities for breast cancer. Nevertheless, PET/MR mammography was shown to be useful for the diagnosis of small lesions; it revealed metabolic characteristics that make it an excellent imaging technique. Importantly, this integrated PET/MR study for the diagnosis of breast cancer is the first of its kind. This is the first study in integrated PET/MR system with simultaneous PET and MR acquisition. Previous studies [20-22] were not performed in the integrated system. They were performed in separated PET/CT and MRI at different times. Further investigations, which involve diverse histologic types of breast cancer and predict prognosis and therapeutic responses by using PET/MR mammography, must be performed to establish the use of this hybrid technique for the diagnosis of breast cancer.

In conclusion, the combined use of whole-body PET/MR and PET/MR mammography demonstrated the potential of a “one-stop shop” modality for the preoperative evaluation of breast cancer. PET/MR mammography might especially be useful in the detection of small lesions with no $^{18}$F-FDG uptake, may provide more detailed anatomic information and help in tumor characterization of $^{18}$F-FDG-avid lesions.

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The authors declare that they have no conflicts of interest.

Bibliography


