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REVIEW

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Potential Clinical Applications of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Magnetic Resonance Mammography in Breast Cancer

Ihn-Ho Cho[1] · **Eun-Jung Kong**[1]

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Abstract The whole-body positron emission tomography (PET)/magnetic resonance (MR) scan is a cutting edge technology providing comprehensive structural information from MR imaging and functional features from PET in a single session. Recent research findings and clinical experience have shown that ^{18}F-fluorodeoxyglucose (FDG) whole-body PET/MR imaging has a diagnostic performance comparable with or superior to that of PET/CT in the field of oncology, including for breast cancer. In particular, FDG PET/MR mammography in the prone position with the breast hanging in a pendant manner can provide more comprehensive information about the metabolism, anatomy, and functional features of a breast lesion than a whole-body PET/MR scan. This article reports on current state-of-the-art PET/MR mammography in patients with breast cancer and the prospects for potential application in the future.

Key words PET/MR · FDG · Breast cancer · Staging · Lymphatic metastasis · Attenuation correction

Introduction

Whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) has been established as an important imaging modality for the diagnosis, staging, restaging, monitoring of response to treatment, and estimation of the long-term prognosis in patients with breast cancer [1–4], but does not accurately show the anatomy of breast lesions because of the weak soft-tissue contrast in the CT component of this imaging technique. However, FDG PET/CT mammography acquired in the prone position with the breast hanging in a pendant manner, which is similar to the patient positioning used in magnetic resonance (MR) breast imaging, has been reported to have better diagnostic performance for local assessment and detection of regional lymph node metastasis in patients with breast cancer [5, 6].

Whole-body FDG PET/MR scanning was developed recently and has been shown to have diagnostic performance comparable with or superior to that of PET/CT for various types of cancer [7–9]. However, for breast cancer, whole-body FDG PET/MR imaging should be supplemented with PET/MR mammography when obtaining PET and MR breast images simultaneously in order to obtain comprehensive information on glucose metabolism, cross-sectional morphology, functional features such as tissue perfusion, enhancement kinetics, and diffusion weighted imaging (DWI) or spectroscopy of breast lesions (Fig. 1, Table 1) [10].

In this review of the early results published in the literature and our preliminary clinical experience, we discuss the potential role of FDG PET/MR mammography in the management of patients with breast cancer along with the relevant technical considerations.

Technical Aspects of Integrated PET/MR Mammography

For MR breast imaging, a multichannel radiofrequency (RF) breast coil is necessary for MR signal detection and to acquire high spatial resolution and high soft-tissue contrast MR images of the breast [11, 12]. However, a conventional radiofrequency

✉ Ihn-Ho Cho
Ihcho@med.yu.ac.kr

[1] Department of Nuclear Medicine, Yeugnam University Hospital, 317-1, Daemyung-dong,Nam-gu, Daegu 705-717, Republic of Korea

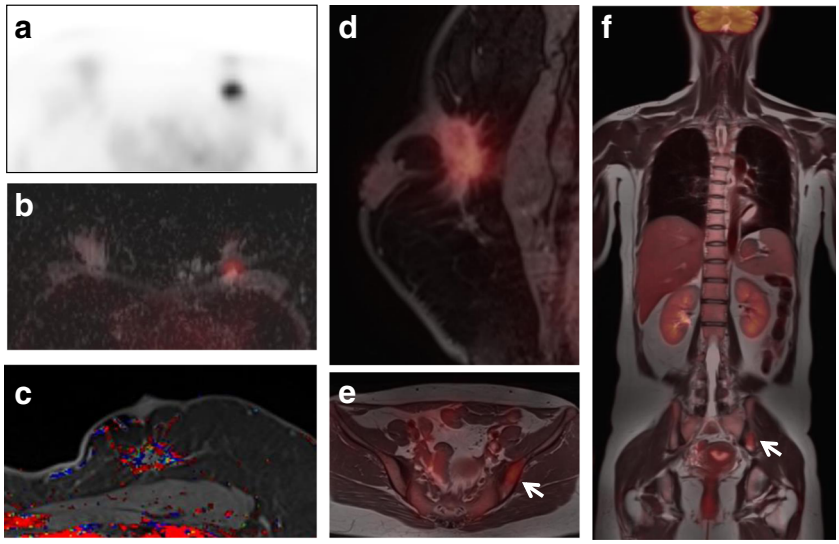

Fig. 1 Images of whole-body FDG PET/MR scan and PET/MR mammography obtained with a dedicated four-channel PET/MR breast coil in a 41-year-old woman with invasive ductal carcinoma. A spiculated enhancing mass with strong FDG uptake, a low apparent diffusion coefficient (ADC) value, and a washout enhancement pattern is seen at the 12 o'clock position in the left breast on FDG PET (**a**), FDG/ADC PET/ mammography (**b**), color-coded map of the maximum slope of enhancement (**c**), and FDG/T1 fat-saturated gradient-echo (fs GRE) PET/MR mammography (**d**). Pelvic FDG/T1 and whole body FDG/T2 PET/MR images (**e**, **f**) show moderate FDG uptake in the left iliac bone suspicious for bone metastasis (*arrows*)

(RF) coil for MR signal reception in integrated PET/MR breast imaging causes significant attenuation and scattering of 511-keV positron annihilation photons before they reach the PET detector, resulting in poor PET image quality and image artifacts because the coil lies within the PET field of view during acquisition of PET data [13, 14]. Some studies have reported that use of a conventional RF coil, which contains a substantial amount of plastic and metal material, results in an 11–20 % underestimation of PET activity, causing substantial regional bias in PET quantification [13, 15].

Attenuation correction of PET data obtained by integrated PET/MR breast imaging using a four-channel or 16-channel RF coil was recently developed and evaluated by a CT-based, three-dimensional hardware attenuation map of an RF coil fused with a patient's MR-based attenuation correction map [16, 17]. When this method is used, small misalignments

Table 1 Acquisition protocols of clinical torso PET/MR imaging and PET/MR mammography (used at Yeungnam University Hospital)

	TE/TR(ms)	FOV(mm)	Matrix	Resolution	Acquisition time (min)
Torso PET/MR					
PET (5 bed × 3 min/bed)		594		4.2 × 4.2	
Dixon VIBE for AC	1.23/3.60	400	172 × 172	1.6 × 1.2	00:32 × 5
Axial fs T2 HASTE	67/1,000	400	180 × 320	1.7 × 1.3	00:54 × 5
Coronal T2 HASTE	76/1,000	450	232 × 256	1.8 × 1.8	00:59 × 5
PET/MR mammography					
PET (1 bed for 25 min)		594		4.2 × 4.2	
Dixon VIBE for AC	1.23/306	400	172 × 172	1.6 × 1.2	00:32
Axial T1	9.6/683	340	250 × 384	1.4 × 0.9	01:32
Axial fs T2	72/5,200	340	269 × 384	1.3 × 0.9	00:18
DWI	86/10,300	340	77 × 192	2.5 × 2.0	03:36
DCE	1.43/4.02	340	276*384	1.2 × 0.9	08:28
Sagittal fs T2	3.68/8.29	340	256 × 320	0.8 × 0.6	03:16
Axial VIBE	1.43/4.02	340	296 × 384	1.1 × 0.9	02:50

AC attenuation correction, *DCE* dynamic contrast-enhanced imaging, *DWI* diffusion-weighted imaging, *fs* fat-saturated, *HASTE* half-Fourier acquisition single-shot turbo spin echo, *VIBE* volume-interpolated breath-hold examination

could create image artifacts and result in incorrect quantification, so the coil needs to be placed as accurately as possible. In addition, the CT scan of the coil, which contains metal components, may produce artifacts that affect the quality of the PET image [16]. In addition, as with the integrated whole-body PET/MR scan [18–21], variable attenuation map artifacts have been observed using the CT-based template attenuation map in PET/MR breast imaging with a four-channel RF coil (Fig. 2).

Further development and validation of a dedicated PET/MR breast coil for MR signal detection without significant attenuation and scattering of photons and including the CT-based template map for PET/MR mammography is required.

The SIGNA PET/MR system (GE Healthcare, Little Chalfont, UK) with a silicon photomultiplier PET detector and time-of-flight PET capability has recently been developed in order to achieve higher sensitivity and spatial resolution of PET imaging, and could be better for detecting malignant breast lesions than the Biograph mMR (Siemens, Munich, Germany), which uses avalanche photodiodes in the PET detector [22]. If the sensitivity of the PET detector used in the PET/MR scanner to or better than that of positron emission mammography (PEM), PET/MR mammography could be used to detect smaller malignant lesions with low FDG avidity and provide more detailed molecular information on small-sized breast cancers.

Local Assessment of Breast Lesions

Dynamic contrast-enhanced MR breast imaging providing information on cross-sectional morphology and the functional features of lesions, including tissue perfusion and enhancement kinetics, plays an important role in characterization of breast lesions and differentiating malignant from benign lesions [11, 12]. These findings can be important for preoperative planning in certain circumstances, such as in young women, women with dense breasts, and where there is a high risk of multifocal/multicentric lesions [23]. However, the specificity of MR imaging for characterization of breast cancer varies widely because of normal enhancing breast tissue and the biological heterogeneity of breast cancer [24–29].

FDG PET has shown high sensitivity and specificity for detection of primary large and palpable breast tumors [30, 31]. However, the sensitivity decreases when the lesions are small and non-palpable, low-grade, or non-invasive neoplasms [31]. In addition, because the CT component of PET/CT is of limited value for characterization of breast lesions, FDG PET/CT is generally not recommended for local assessment of breast cancers [32].

However, there have been some studies of dedicated breast PET devices and use of a breast-positioning device for PET to detect breast cancer and to reduce the risk of false-negative results. Kaida et al. [33] reported that prone breast imaging using a positioning device may help to improve the detection rate of breast cancer in screening. Heusner et al. [6] reported that FDG PET/CT mammography may be more accurate than MR breast imaging in the pretherapeutic differentiation of breast lesions as solitary, multifocal, or multicentric tumors. Further, Koolen et al. [34] reported that response monitoring with FDG PET/CT mammography was possible in 95 % of all tumors in patients scheduled to receive neoadjuvant chemotherapy. Finally, Moon et al. [35] reported that FDG PET/CT mammography provided more correct classification of the focality of lesions than MR breast imaging (95 % vs 90 %).

Positron emission mammography (PEM) has been developed and applied in clinical practice [36]. For detection of breast cancer, PEM uses a dedicated scanner with two parallel photon detectors similar to mammography compressors [37]. PEM has been reported to be more sensitive than whole-body PET/CT in evaluation of breast cancer, with a high sensitivity for tumors smaller than 1 cm and proved to be complementary to MR breast imaging for defining the extent of preoperative mass in the ipsilateral breasts of women with newly diagnosed breast cancer [37, 38]. PEM was more specific than MR breast imaging and less likely to prompt unnecessary biopsies [39].

A study by Moy et al. [40] showed the potential benefit of combining both FDG PET mammography and MR breast

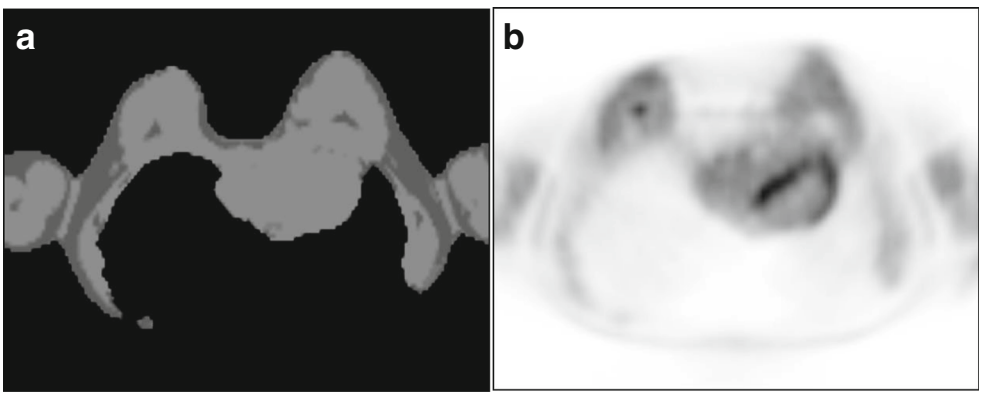

Fig. 2 A 46-year-old woman with breast cancer. A μ-map of FDG PET/MR mammography (**a**) show body contour artifact with missing dorsal body contour including both lungs causing failure of attenuation correction on an axial PET image (**b**)

imaging acquired separately and later fused with a semiautomatic landmark-based, non-rigid fusion program. In 90 breast lesions, combining both techniques increased the positive predictive value (PPV) and specificity in patients for whom the MR breast-imaging outcome alone would have been nonspecific. The increase in PPV from 77 % in MR breast imaging to 98 % in fused PET/MR breast imaging and the increase in specificity from 53 to 97 % were statistically significant. However, the sensitivity of MR breast imaging was 95 %, that of PET breast imaging was 57 %, and that of fused PET/MR breast imaging was 83 %. The false-negative rate on PET breast imaging was 26.7 %, and after fusion this number was reduced to 9 %.

Taneja et al. [41], who assessed the utility of whole-body FDG PET/MR scanning including PET/MR mammography and MR breast imaging in the initial staging of patients with breast cancer, reported a higher diagnostic confidence for detection of breast cancer using PET/MR mammography than using PET breast imaging or MR breast imaging.

Botsikas et al. [42], who evaluated primary lesions in 58 patients with breast cancer using a sequential whole-body FDG PET/MR scanner (Philips Ingenuity TF PET/MR; Philips Healthcare, Best, The Netherlands), reported that sensitivity for primary cancers with MR breast imaging and fused PET/MR breast imaging was 100 and 77 %, respectively, and specificity for MR breast imaging and fused PET/MR breast imaging was 67 and 100 %.

Grueneisen et al. [43] reported that 47 (96 %) of 49 patients with breast cancer were identified using FDG PET/MR mammography and MR breast imaging, whereas PET/CT detected 46 (94 %) and missed a synchronous carcinoma in the contralateral breast in one patient. PET/MR mammography and MR breast imaging enabled correct identification of multifocal/multicentric disease in three further patients if compared with PET/CT. For the correct T stage, PET/MR mammography and MR breast imaging showed identical results and were correct in significantly more cases than PET/CT. PET/MR mammography could provide more sensitive detection of breast lesions than PET/CT (true positive rate 68.7 % vs 62.7 %, respectively).

Kong et al. [10] compared whole-body FDG PET/MR scan and PET/MR mammography with regard to their ability to detect breast lesions. The overall sensitivity was 79.2 % (38/48) on PET, 87.5 % (42/48) on whole-body PET/MR scan, and 100 % on PET/MR mammography. PET/MR mammography detected small lesions in addition to possible multiple tumors.

FDG PET/MR mammography has been shown to depict the shape, margin, and internal enhancement pattern of breast cancer and show the enhancement pattern over time, and FDG avidity to provide structural and functional information with better soft-tissue contrast and high spatial resolution by MR imaging complementary to the metabolic data obtained from FDG PET (Figs. 3 and 4) [10]. However, more extensive clinical studies are needed to determine the added value of FDG PET/MR mammography when these two modalities are combined.

Regional Lymph Node Assessment

The status of the axillary lymph nodes is one of the most important prognostic factors in breast cancer. FDG PET/CT could be used for prediction of lymph node metastasis from breast cancer due to its ability to detect malignant pathology by an abnormal increase in glucose metabolism even in non-pathologically enlarged lymph nodes not captured by CT. Several authors have reported that FDG PET and PET/CT have high specificity for evaluation of axillary lymph nodes, but are of limited value because of low sensitivity and high false-negative rates [44, 45].

However, FDG PET/CT could detect previously unsuspected locoregional extra-axillary lymph node metastases and was useful as an additional imaging tool for assessment of extra-axillary lymph node metastases, with a significant impact on patient management [46]. PET/CT has a potential advantage in evaluation of regional lymph nodes in particular locations, such as the internal mammary and infraclavicular lymph nodes [47].

FDG PET/CT mammography reportedly images a wider area of the axillary fossa so that the anatomic structures of the axilla can be more easily differentiated from one another than is possible using whole-body PET/CT, even though there were no significant differences in the number of metastatic axillary lymph nodes that could be detected between these two types of study [5, 35, 48]. Koolen et al. [49] reported that combining prone and standard supine FDG PET/CT detected locoregional lymph node metastases with a sensitivity of 82 % and a specificity of 92 %, which changed the indication for radiotherapy in a substantial proportion of patients based on detection of occult N3 nodes.

MR breast imaging is not considered effective for lymph node staging in the preoperative breast cancer setting, and is not recommended for that purpose. However, careful reading and variable MR imaging parameters, such as morphologic characteristics, and functional parameters, such as patterns of dynamic enhancement and restriction of diffusion, have been proposed for evaluation of metastatic lymph nodes because the axillary and internal mammary lymph nodes are usually included in the field of view when imaging the breast by MR [50].

Botsikas et al. [42], who evaluated 198 lymph node groups (34 malignant, 164 benign) in 58 patients with breast cancer using a sequential whole-body FDG PET/MR scanner (Philips Ingenuity TF PET/MR), reported that sensitivity with MR breast imaging and fused PET/MR breast imaging was 88 and 79 %, respectively, and specificity for MR breast imaging

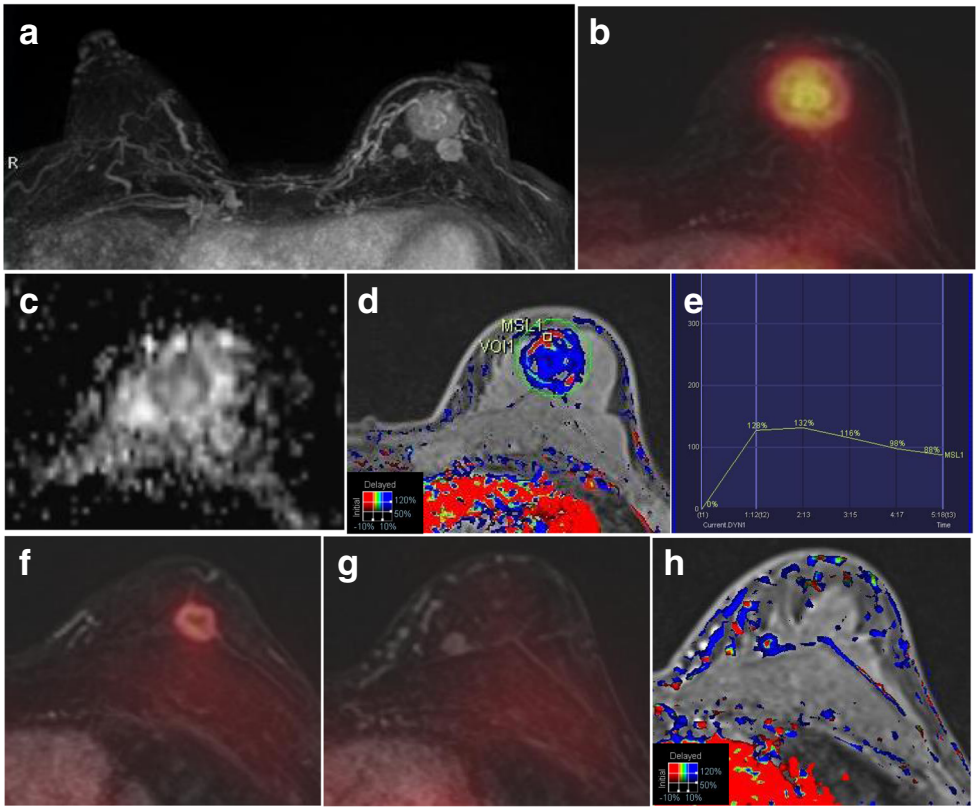

Fig. 3 A 52-year-old woman with three invasive ductal carcinomas in the left breast. **a** The MIP of a contrast-enhanced T1 fs GRE subtraction image shows three enhancing masses in the left breast. **b** FDG/T1 fs GRE PET/MR mammography shows the largest hypermetabolic mass with a low ADC value (0.962×10^{-3} mm^2/s) (**c**) and a washout enhancement (**d**, **e**). **f**, **g** FDG/T1 fs GRE PET/MR mammography shows two enhancing masses, one with moderate FDG uptake and one with no FDG uptake. **h** The smallest enhancing mass without FDG uptake is shown as a washout enhancement pattern on the color-coded map

and fused PET/MR breast imaging was 98 and 100 %. However, others reported no significant differences between PET/CT, MR breast imaging, and PET/MR mammography for detection of axillary node-positive patients when a dedicated PET/MR breast-imaging coil was not used. The diagnostic confidence score was higher for PET/MR mammography than for PET or MR breast imaging alone [41, 43].

FDG PET/MR mammography may be useful for axillary, internal mammary, and supraclavicular lymph nodes because the combination of advanced MR imaging sequences for tissue characterization with FDG PET metabolic data could result in more accurate identification of metastatic invasion of lymph nodes (Fig. 5). However, additional FDG PET/MR mammography using an additional volume-interpolated breath-hold examination including the axillary and supraclavicular area might be needed because the field of view of the integrated PET/MR scanner is too small to include both the breast and supraclavicular areas (Fig. 6).

Evaluation of Response to Therapy

Neoadjuvant chemotherapy (NAC) has been established as the standard treatment for locally advanced breast cancer. Patients who achieve a pathologic complete response after NAC have longer disease-free and overall survival rates than non-responders [51–53]. For assessment of

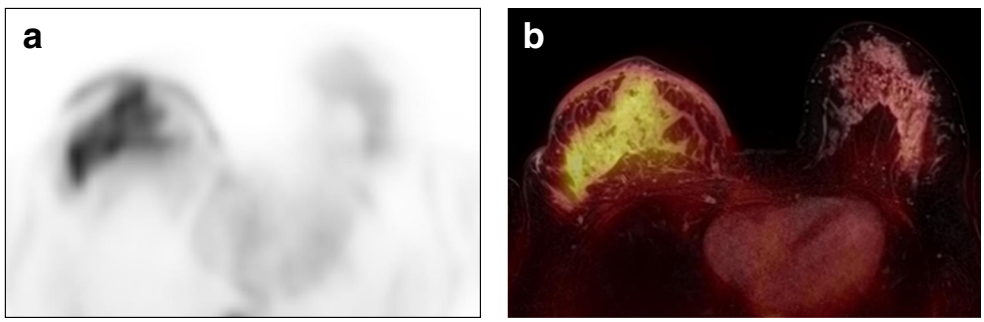

Fig. 4 A 31-year-old woman with an inflammatory breast cancer in the left breast. The diffuse, infiltrative, non-mass enhancement involving the entire right breast with increased FDG uptake and diffuse FDG uptake overlying thickened skin is shown in the FDG PET image (**a**) and on FDG/T1 fs GRE PET/MR mammography (**b**)

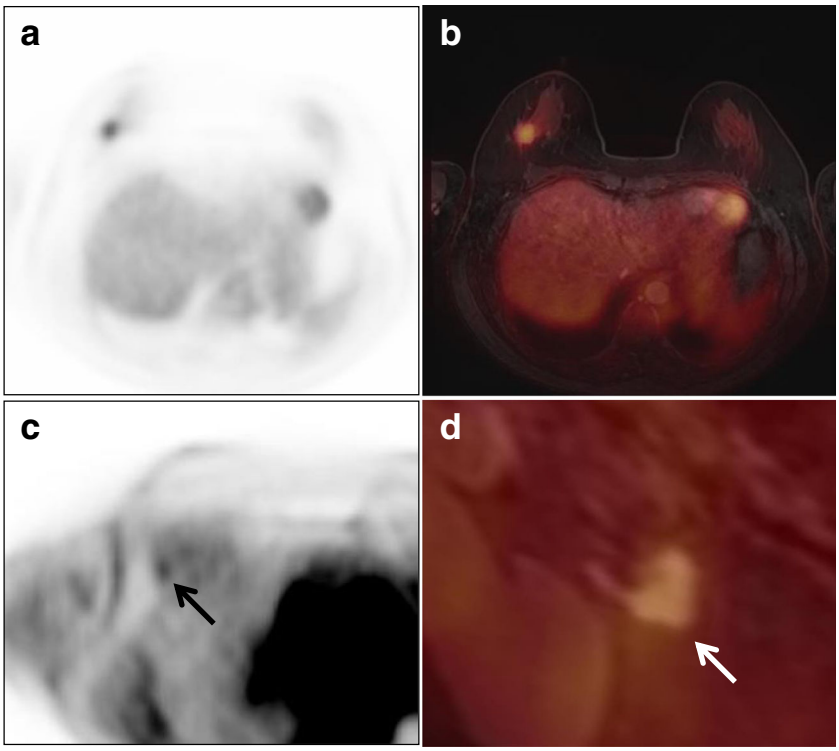

Fig. 5 A 49-year-old woman with an invasive carcinoma and one axillary lymph node metastasis. Increased FDG uptake is shown in the upper outer quadrant of the right breast on FDG PET (**a**) and FDG/T1 fs GRE PET/MR mammography (**b**). Axillary lymph node (*arrow*) with faint FDG uptake and focal cortical thickening is seen in the right axilla on FDG PET (**c**) and FDG/T1 fs GRE PET/MR mammography (**d**)

tumor response after NAC, FDG PET, or PET/CT, DWI, and dynamic contrast-enhanced MR breast imaging is known to provide an accurate assessment [54, 55].

In a recent study by Park et al. [56] comparing DWI with PET/CT for predicting a complete response to NAC in patients with breast cancer, combined use of DWI and PET/CT showed higher diagnostic performance (area under the curve [AUC], 0.94) than PET/CT (AUC, 0.87) or DWI (AUC, 0.91), and could potentially improve the specificity of this prediction. In addition, An et al. [57] showed that combined use of PET/CT with dynamic contrast-enhanced MR breast imaging or DWI could improve the specificity for predicting a pathologic response after NAC.

Therefore, FDG PET/MR mammography could be a useful tool in evaluation of response to NAC (Fig. 7).

Additional MR Sequences for FDG PET/MR Mammography

Diffusion-Weighted Imaging

DWI is a quantitative MR imaging technique that provides information on water diffusion in tissues in the form of apparent diffusion coefficient (ADC) values, which in turn provide information about the tissue microstructure. Restricted diffusion is observed in tissues with high cellularity, e.g., tumors, abscess, fibrosis, and cytotoxic edema. Relative free diffusion is observed in tissues with low cellularity or tissues with disrupted cell membranes, e.g., cysts and necrotic tissue [58, 59]. DWI has been reported to reveal information about tumor cellularity and thus to provide prognostic information on

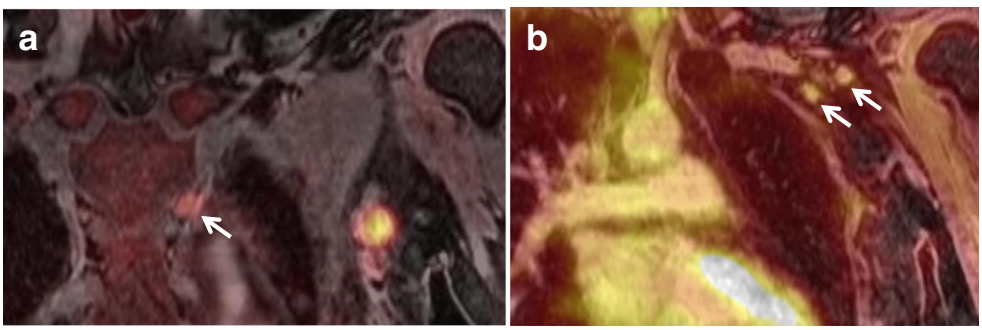

Fig. 6 A 29-year-old woman with an invasive carcinoma and axillary and internal mammary lymph node metastasis. FDG/VIBE PET/MR mammography showed multiple hypermetabolic lymph nodes in the left first and second intercostal space (**a**) and left axilla (level I and II) (**b**)

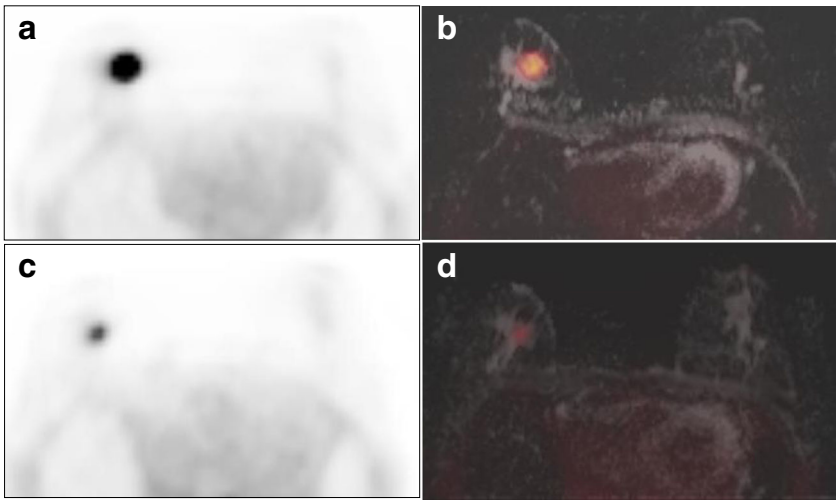

Fig. 7 A 72-year-old woman with an invasive carcinoma. Baseline FDG PET (**a**) and FDG/ADC PET/MR mammography (**b**). After the first cycle of neoadjuvant chemotherapy, a significant reduction in tumor FDG uptake from an SUV_{max} of 13.8 to an SUV_{max} of 6.4 without a change in the ADC is seen on FDG PET (**c**) and FDG/ADC PET/MR mammography (**d**). Histopathology at completion of chemotherapy showed no residual disease in the tumor bed

breast cancer [60, 61]. However, the clinical value of DWI remains limited, because the frequent pathologic heterogeneity of breast cancers and the necrotic tissues commonly found with aggressive tumors contribute to high ADC values [62–65].

FDG uptake and ADC represent different aspects of the biological features of tumor cells and have not shown a good correlation in breast cancer. However, both types of study may have a role for predicting the prognosis of breast cancer [66–68] (Fig. 8). FDG PET/MR mammography using integrated PET/MR scanning for glucose metabolism and DWI need to be studied more detail.

MR Spectroscopy

MR spectroscopy noninvasively measures not only metabolites in a selected region, such as choline, reflecting cellular proliferation, but also *N*-acetyl aspartate, creatine, and lactate, which can be helpful in characterization of some suspicious lesions, although only total choline has been used for breast cancer [69].

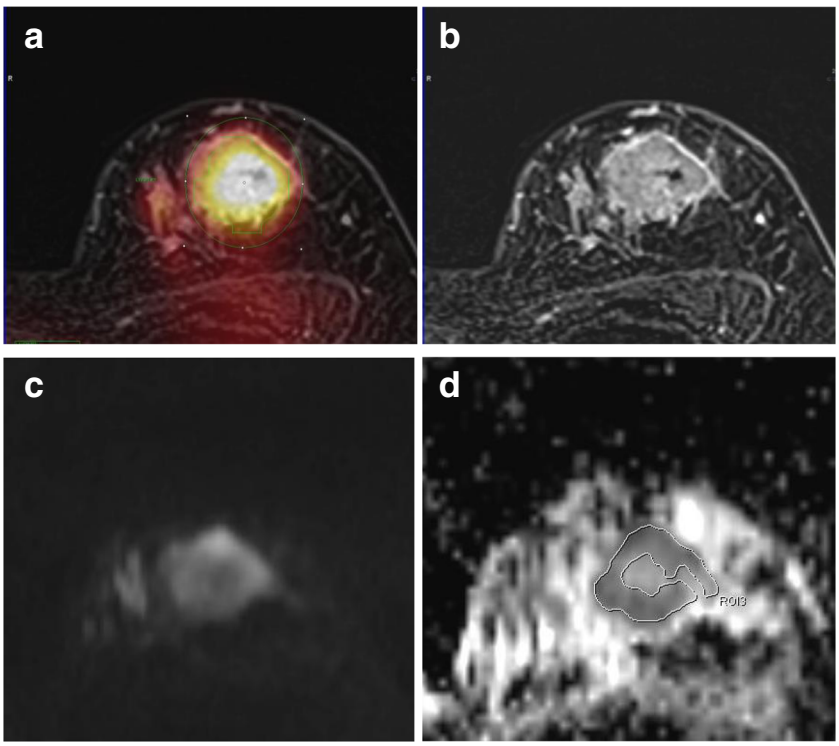

Fig. 8 Comparison between FDG uptake and the ADC in a 52-year-old woman with a 3.5-cm invasive ductal carcinoma. **a** Region of interest for measuring SUV_{max} is drawn on the axial PET/MR mammography (SUV_{max}, 8.63). **b** Contrast-enhanced T1 fs GRE subtraction image showed a heterogeneous enhancing mass. **c** DWI (*b* value, 800 mm^2/s) shows high signal intensity within the tumor. **d** For measurement of the mean ADC, a region of interest is manually drawn within a mass lesion on an ADC map (mean ADC, 0.825×10^{-3} mm^2/s)

Combining this molecular information with glucose metabolism obtained from PET will likely benefit oncologic care. Cho et al. [70] reported good diagnostic performance of MR spectroscopy and FDG PET in the early prediction of the pathologic response to NAC in patients with breast cancer.

Breast MR spectroscopy performed by integrated PET/MR scanner is not acquired with FDG PET data simultaneously yet and takes additional time. However, breast MR spectroscopy during the PET/MR mammography examination using an integrated PET/MR scanner seems promising due to more accurate co-registration between FDG avidity and spectroscopy.

Summary and Conclusion

Unlike FDG PET/CT mammography, FDG PET/MR mammography could be done a breast imaging study additional to a whole-body PET/MR scan in the supine position for patients with breast cancer without adding radiation. It is worthwhile performing FDG PET/MR mammography simultaneously as a preoperative imaging tool to obtain functional and morphologic data as a "one stop shop," even though it adds a further 30 min to the examination.

FDG PET/MR mammography affords higher diagnostic performance and confidence than whole-body PET/MR imaging and PET/CT mammography for determining the local extent of malignant breast lesions and for planning surgery, and is comparable with MR breast imaging alone [41–43]. The diagnostic performance for detection of axillary lymph node metastasis is similar to that of PET/CT and MR breast imaging [43]. Whole-body FDG PET/MR imaging combined with PET/MR mammography in a single session to stage local breast cancer and detect distant metastasis simultaneously could be a very effective imaging technique in patients with breast cancer. Further, the comprehensive information on glucose metabolism, cross-sectional morphology, functional features such as tissue perfusion, enhancement kinetics, and DWI or spectroscopy of breast lesions obtained by FDG PET/MR mammography would also be useful in the future for individualized treatment strategies in patients with breast cancer according to their tumor biology.

Compliance with Ethical Standards

Conflict of Interest Ihn-ho Cho and Eung-Jung Kong declare that they have no conflict of interest.

Ethical Statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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