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Breast PET/MR Imaging

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INTRODUCTION

New hybrid imaging technology brings together the molecular sensitivity of PET, the high-contrast anatomic imaging of MR imaging, and depending on the pulse sequences used, the functional imaging capabilities of MR imaging, in a single PET/MR exam. PET and MR imaging each already play central roles in breast cancer imaging, MR imaging predominantly as a focused examination, screening for and evaluating the extent of disease pretherapy and posttherapy,¹ and PET predominantly as a whole-body examination, assessing for distant metastases during initial staging and later surveillance.^{2,3} However, PET, specifically positron emission mammography, is also used in focused breast examinations⁴ and whole-body MR imaging has also been used in imaging metastatic spread.^{5,6} PET and MR images of the breast have been fused^{7–10} to investigate potential benefits of combining these modalities. Now, PET/MR imaging hybrid scanners, depending on the model, simultaneously or sequentially acquire and coregister PET and MR imaging data. These simultaneous scans are being put to use in patients with breast cancer not only for disease detection, but also elucidating imaging biomarkers, which may eventually guide treatments and predict prognoses. This article provides an overview of breast and whole-body examination feasibility and techniques, summarizes PET and MR imaging of the breast for lesion detection, outlines current investigations into multiparametric PET/MR imaging of the breast, looks at PET/MR imaging in the setting of neoadjuvant chemotherapy (NAC), and reviews the pros and cons of PET/MR whole-body imaging in the setting of metastatic or suspected metastatic breast cancer.

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PET/MR IMAGING FEASIBILITY AND PROTOCOLS

Technical Feasibility

Accurate quantitation of radiotracer activity via standardized uptake values (SUVs) in PET imaging is highly important, especially for comparing between examinations, and requires reliable attenuation correction. Computed tomography (CT) attenuation correction is based on tissue density information (Hounsfield units) provided by CT.¹¹ MR imaging, however, does not rely on tissue density in generating signal and therefore PET/MR imaging required a new method for attenuation correction, one that addressed the patient's attenuation map and attenuation maps for MR imaging hardware, such as coils. Techniques for MR imaging-based attenuation correction include the Dixon sequence-derived segmentation method, which assigns attenuation coefficients after tissue identification using standard reference values,^{12,13} and an atlas-based method, which corrects images using a template data set.¹³ The segmentation method is currently in use by commercial scanners.

For breast examinations, generating attenuation correction maps for breast coils was an early issue. Fortunately, feasibility studies integrating 4- and now 16-channel breast coils into a simultaneous PET/MR imaging system (Biograph mMR, Siemens Healthcare, Erlangen, Germany) have shown technical success with accurate SUV quantification and high MR image quality.^{14,15} Successful prone hybrid breast imaging has also been demonstrated with sequential PET/MR imaging (Philips Ingenuity, Philips Healthcare, Cleveland, OH).¹⁶

SUV values derived from PET/MR imaging via MR imaging-based attenuation correction and from PET/CT via CT-based attenuation correction have shown strong correlations in breast cancer metastases^{17,18} and mostly moderate correlations in normal tissues,^{17–22} validating the use of PET/MR imaging-derived SUV values in breast cancer imaging. The stronger correlations in metastases may relate, at least in part, to lesser washout in metastases compared with normal tissues because PET/MR imaging was performed after PET/CT in these studies. Finally, although correlations between PET/MR imaging and PET/CT-derived SUV values are high in breast cancer metastases, SUV values should not be compared between longitudinal PET/CT and PET/MR imaging examinations in the same patient because they are similar but not identical examinations.

Tracers

In breast cancer imaging, fluorine-18 fluorodeoxyglucose (¹⁸F-FDG), which images cellular glucose uptake,²³ is the tracer most commonly used for localized and whole-body examinations. Typically, breast cancer cells are more metabolically active and demonstrate higher glucose uptake than their background organs, thus allowing for lesion detection.

¹⁸F sodium fluoride (Na-F), a bone-specific radiotracer, has also been administered in patients with breast cancer^{24,25} to look for bony metastatic disease. In a recent study by Piccardo and colleagues,²⁴ ¹⁸F-NaF PET/CT demonstrated higher sensitivity (100%) for osseous lesions than ¹⁸F-FDG PET/CT (72%). However, none of the ¹⁸F-FDG PET/CT-negative patients went on to have disease progression during the follow-up period. Moreover, ¹⁸F-FDG SUV mean and whole-body bone metabolic burden were independently and significantly associated with overall survival, whereas none of the ¹⁸F-NaF PET/CT

parameters were associated with overall survival. This study suggests ^{18}F -FDG has a closer relationship with biologically active breast cancer than does ^{18}F -NaF, likely because ^{18}F -FDG uptake into skeletal metastases is thought to be predominantly within breast cancer tumor cells, whereas ^{18}F -NaF uptake reflects osseous blood flow and bone remodeling²⁶ and may provide positive results in the setting of osseous remodeling following chemotherapy.

Breast cancer can be homogenous or change gene expression patterns over time. This could be because of a variety of reasons including a response to therapy, or have metastases with biologies that differ from the index lesion. Therefore, several additional tracers in development are particularly exciting for their potential to noninvasively assess therapeutic targets, such as hormone receptors^{27,28} and human epidermal growth factor receptor 2 (HER2).^{29–31} This in turn helps improve individualized treatments. Additional tracers that may become useful in breast cancer imaging target gastrin-releasing peptide receptors, cellular proliferation, membrane lipid synthesis, and amino acid transport and are well reviewed by Tabouret-Viaud and coworkers.³²

Suggested Protocols

Following a pre-examination fast of at least 4 hours, an ^{18}F -FDG injection of approximately 555 MBq is performed followed by a rest for 45 minutes in a darkened, quiet room before beginning imaging. For localized breast PET/MR imaging, the patient is then placed in prone position in a dedicated breast coil. PET acquisition can either begin after the 45-minute resting period or, if dynamic PET data are desired, the injection can occur on the scanner and imaging can begin at the time of injection. For simultaneous PET/MR imaging, PET data acquisition can be performed throughout the entire examination and therefore is not the rate-limiting factor. MR imaging sequences run during PET/MR imaging vary according to desired information. Typically, routine dynamic contrast-enhanced (DCE) MR imaging sequences including a T2-weighted fat-suppressed, T1-weighted non-fat-suppressed, a precontrast fat-suppressed T1-weighted radial three-dimensional (3D) gradient echo sequence, and up to four postcontrast fat-saturated T1-weighted radial 3D gradient echo sequences are run. Diffusion-weighted imaging (DWI) sequences and modified postcontrast sequences can also be run and processed to assess additional parameters, such as diffusion and perfusion, and are described later. Three-dimensional proton MR spectroscopic imaging (3D ^1H -MRSI) has also been performed in the setting of breast PET/MR imaging.³³

For whole-body breast MR imaging in the setting of breast cancer, fasting time, injection dose, and resting time is similar to a focused breast examination. The examination is performed in supine position with dedicated PET/MR imaging head and flexible body matrix coils and most often consists of six to seven stations from thighs to vertex, depending on the height of the patient. PET data are acquired for at least 2 minutes per station (or for the duration of the station) when the examination is begun around 45 minutes postinjection and as such, the MR imaging sequences are usually the rate-limiting factor for whole-body examinations. If PET/MR imaging is performed after PET/CT or after a local breast PET/MR imaging (without an additional FDG injection), PET data can be acquired for longer time periods, up to about 7 minutes per station, to mitigate signal loss caused by

tracer clearance. The MR imaging sequences run at each station can vary. The authors find it useful to image from the thighs to the vertex to allow for MR imaging contrast injection during the liver station, which allows for noncontrast T1-weighted images of the bony pelvis and contrast-enhanced T1-weighted liver and brain images. More detailed potential whole-body PET/MR imaging structures are presented in Table 1.

MR IMAGING AND PET IN LOCALIZED BREAST EXAMINATIONS

As our most sensitive examination,^{34,35} breast MR imaging is commonly used to screen women at high risk, to assess disease extent, to evaluate response to chemotherapy, to assess for occult breast cancers in the setting of axillary metastases, and to problem solve difficult cases.¹ Like all breast imaging modalities, MR imaging yields false-positive results, which require expensive, invasive, and ultimately unnecessary biopsies. On its own, PET/CT is not adequately sensitive for breast cancers, in one study detecting only 30 of 44 invasive cancers 2 cm or less.³⁶ This low sensitivity is in keeping with the low spatial resolution of PET/CT, which varies according to device, but is approximately 5 to 6 mm full width at half maximum.³²

Comparison and Fusion

When comparing ¹⁸FDG-PET/CT with breast MR imaging for the identification of breast cancers, MR imaging demonstrates increased sensitivity,^{7,37,38} especially in subcentimeter lesions,^{10,39,40} nonmass lesions,¹⁰ and lobular cancers.³⁷ Moreover, DCE-MR imaging has been shown to be more sensitive alone than when combined with PET.^{7,10,41}

However, Pinker and coworkers³³ further explored PET and MR imaging fusion, using simultaneously acquired PET and multiparametric MR imaging including DCE, DWI, and 3D 1H-MRSI data in 53 malignant and 23 benign breast lesions categorized as BI-RADS 0, 4, or 5 on initial mammographic or sonographic imaging. In contrast to studies using only DCE-MR imaging and PET data, the authors found that all four PET and MR imaging parameters together provided the highest area under the curve (AUC) of 0.935 (0.835–1), and that this AUC was significantly higher than AUCs for DCE–MR imaging or PET alone and for DCE–MR imaging combined with DWI, 3D 1H-MRSI, or PET. The authors' criteria for a positive examination were clear: with three parameters, two or more positive sequences; with four parameters, three or more positive sequences; or, in the case of two positive parameters, a positive DCE-MR imaging sequence. Had this categorization been applied to the tumors in the previously described series, unnecessary biopsies would have been reduced by 50% as compared with DCE–MR imaging alone (three of six biopsies) and by up to 38% as compared with DCE–MR imaging and one additional parameter (3 of 8–10 biopsies).

PET and MR Imaging in Local Staging

When performing examinations for extent of disease, detecting multifocality and nodal disease becomes important. MR imaging has been shown to be more sensitive but less specific than PET/CT^{37,38,42} or PET alone for multifocality,⁴³ whereas PET/CT has generally been shown to have a higher sensitivity for axillary nodal metastases.^{38,42,43} PET

and MR imaging have demonstrated similar performance for the detection of internal mammary adenopathy.⁴⁴ MR imaging and PET/MR imaging have been shown to be more likely than PET/CT to determine the correct maximum diameter of the tumor (T stage), which may be useful in surgical and oncologic planning.³⁸ Hybrid PET/MR imaging may be of particular use in this extent-of-disease setting, where the increased sensitivity of MR imaging for multifocal disease and the increased sensitivity of PET for axillary nodal disease could come together in a single examination.

Correlating PET and MR Imaging Parameters and Prognostic Factors

PET/dynamic contrast enhancement—A couple of groups have explored relationships between metabolism and perfusion, looking at SUVmax, metabolic tumor volume, total lesion glycolysis, and a PET-derived heterogeneity factor and K trans, a volume transfer coefficient reflecting vascular permeability, Kep, a flux rate constant, and Ve, an extracellular volume ratio reflecting vascular permeability; and the relationships between these parameters and prognostic factors (Fig. 1).

Kim and colleagues⁴⁵ found an inverse correlation between SUVmax and Ve, where increased glucose metabolism was seen in higher cellularity tumors. On further review of that same group of patients, An and colleagues⁴⁶ found that the inverse correlation between SUVmax and Ve held in nontriple negative breast cancers (TNBC), as did a positive correlation between SUVmax and Kep, whereas in TNBC, no correlations between perfusion and metabolic parameters were seen, possibly because of the smaller sample size (n = 17). This group also looked at recurrence-free survival and found that patients with more heterogeneous FDG uptake had worse recurrence-free survival than patients with less heterogeneous tumors.⁴⁵ In a smaller study, Margolis and colleagues⁴⁷ found that metabolic tumor volume inversely correlated with Kep and K trans and that metastatic burden correlated positively with K trans and SUVmax and negatively with Kep.

PET/diffusion-weighted imaging—The relationships between SUV uptake, apparent diffusion coefficient (ADC) values, and histologic and prognostic factors have been investigated by several groups, with mixed results. Some studies have shown an inverse correlation between SUV and ADC in cancers,^{40,48} whereas others have not.^{49–51} SUVmax has been shown to positively correlate with many prognostic factors including tumor size,^{48–51} nuclear/histologic grade,^{48–51} higher Ki67,^{40,48,52} TNM staging,⁴⁸ TNBC tumor type,^{40,51} lymph node positivity,^{48,49,51} ER–,^{48,49,51} PR–,^{48,51} and HER2+ status.^{48,49} ADC shows fewer relationships, but has been correlated with PR+,⁵⁰ ER+,⁵¹ and HER2– cancers,^{50,51} and with tumor size, Ki67 expression, histologic subtype, the presence of axillary metastases, and TNM staging.⁴⁸ Karan and colleagues,⁴⁹ however, saw no correlations between ADC median and many of these metrics. Low ADC and high SUVmax have been associated with vascular invasion.^{40,49} SUVmax correlated inversely with progression-free survival and overall survival.⁵⁰ The stronger and more numerous correlations between SUVmax and prognostic factors and survival suggest PET may be of particular interest in predicting clinical outcomes.

PET and MR Imaging and Neoadjuvant Chemotherapy

During therapy—PET/CT and MR imaging have also been investigated in the setting of NAC. Of particular focus has been whether PET or MR imaging during NAC is more useful in predicting pathologic complete response (pCR) and outcome. Now, however, how PET and MR imaging metrics can be used together is of increasing interest (Fig. 2).

Most studies comparing PET and MR imaging aimed at predicting pCR (performed during NAC) show changes in PET and MR metrics, but slightly improved performance with SUVmax in predicting response. Pahk and colleagues⁵² looked at patients specifically with luminal B-type breast cancer and found PET imaging outperformed MR imaging because a change in SUV of 69% provided a sensitivity of 86% and a specificity of 100% whereas an MR imaging–based change in size of 38% provided sensitivity of 64% and specificity of 71%. Similarly, Tateishi and colleagues⁵³ found that PET (% of original SUVmax) and MR imaging metrics (% of original K_{ep} and % of original area under the time intensity curve at 90 seconds) predicted response to therapy, but that change in SUVmax was the most accurate. Combining modalities and clinical factors, Pengel and colleagues⁵⁴ found that age, breast cancer subtype, % change in SUVmax, and % change in largest tumor diameter on MR imaging predicted near pCR. This group then combined metrics and found that changes in SUVmax and tumor diameter together with breast cancer subtype yielded the highest AUC. Looking at outcomes, Lim and colleagues⁵⁵ found that lesser declines in SUV (41% threshold), MR slope (−6% threshold), lesser increases in ADC (11% threshold), and ER negativity were associated with poorer disease-free survival. Patients meeting thresholds for lesser declines in SUV and MR slope had a much higher recurrence rate (78%) than those that did not (13%).

In less conventional imaging, Jacobs and colleagues⁵⁶ compared sodium (^{23}Na) MR imaging with PET/CT and DCE–MR imaging and found that tissue sodium concentrations increased in all partial responders and decreased in the single nonresponder, thereby providing better differentiation between partial and nonresponders than MR imaging tumor volumes or SUV max, which decreased similarly in partial responders and nonresponders. Cho and colleagues⁵⁷ compared ^1H -MRSI with PET and found mean % reductions for total choline, SUV max, SUV peak, and total lesion glycolysis were greater in the pCR group than in non-pCR group, but no cutoff values were identified. Here, AUC was similar between reduction in MR imaging and PET-related variables.

After therapy—When assessing residual disease after NAC and before surgery, PET and MR imaging metrics seem to be complimentary, with PET generally providing greater sensitivity and MR imaging generally providing greater specificity. In a 2016 meta-analysis performed by Liu and colleagues,⁵⁸ data from 382 patients in six studies demonstrated sensitivity and specificity of 65% and 88% and 86% and 72% for MR imaging and PET, respectively, for pCR. Park and colleagues,⁵⁹ whose patient population was included in the analysis, also found that DWI had 100% sensitivity for pCR when a 55% increase in ADC was used at a cutoff. In an effort toward multiparametric analysis, An and colleagues⁶⁰ looked at DCE–MR imaging, DWI–MR imaging, and PET/CT and found increased specificity and negative predictive value when either DCE–MR imaging or DWI was

combined with PET as compared with PET alone. More information is needed in terms of how the two modalities are optimally combined to understand and to assess response to NAC.

In that direction, Partridge and colleagues⁶¹ looked at dynamic PET measures including 18F FDG transport rate (K1) and metabolism flux constant (ki) and DCE-MR imaging measures including peak enhancement (PE), signal enhancement ratio (SER), and tumor volume. They found that changes in glucose delivery were correlated with changes in vascularity (SER) and that ki correlated with SER, PE, and tumor volume. Decreases in K1, ki, PE, and SER were greater for patients with pCR as compared with those with residual disease. In the future, studies like this may help clinicians better understand therapeutic processes, such as drug delivery and uptake, and it is hoped propel clinicians toward the goal of increasingly personalized medicine.

WHOLE-BODY PET/MR IMAGING

PET/MR imaging is particularly interesting as a possible improvement over PET/CT oncologic whole-body imaging because MR imaging provides improved lesion detection in the brain, breast, liver, kidneys, and bones as compared with CT. CT detects more pulmonary lesions, especially less than 1 cm,^{62,63} although the clinical importance of pulmonary lesions missed on PET/MR imaging is still unclear.⁶³

In whole-body imaging for breast cancer, PET/MR imaging has been shown to provide improved sensitivity over PET/CT^{6,64,65} or PET alone,⁴³ particularly for breast cancers,⁶⁴ liver metastases,⁶⁴ and bone metastases^{6,64,65} (Figs. 3 and 4). PET/MR imaging has also been shown to detect brain metastases.⁶⁴ Despite outperforming PET/CT, whole-body PET/MR imaging still lags behind prone positioned dedicated breast PET/MR imaging for breast cancer detection, in one study seeing only 40% (4 of 10) of subcentimeter breast cancers seen on the dedicated breast examination.⁴⁰

When separated out by sequence, DCE-MR imaging has been shown to be most useful for breast and brain lesions, DWI has been shown to be most useful for liver and bone metastases, and PET has been shown to be most useful for lymph node metastases.⁶⁴ These variable strengths highlight the advantage of multimodality imaging. In particular, combining PET and DWI may be important because PET has been shown to greatly improve the specificity of DWI in whole-body imaging.⁶⁶ In addition, omitting the whole-body CT from the PET examination can decrease the radiation dose by half.⁶⁴ These data suggest a wider role for PET/MR imaging in breast cancer staging and surveillance, particularly in young patients and in patients undergoing serial examinations.

SUMMARY

In focused breast and whole-body settings, PET/MR imaging can bring metabolic, anatomic, spectroscopic, and diffusion- and perfusion-based data together in a single examination that is directed at detecting and/or further understanding breast cancer. In local staging, PET and MR imaging seem to be complimentary with MR imaging providing greater accuracy for satellite lesions and PET providing greater sensitivity for axillary nodes. In imaging

metastatic disease, PET and MR imaging are again complimentary, with MR imaging providing high sensitivity and PET tempering the relatively low specificity of DWI. Looking ahead, the multiparametric imaging possible with PET/MR imaging may provide new biomarkers, which it is hoped will help to personalize treatments and to provide more prognostic information. Additionally, as MR imaging techniques and radiotracers continue to be developed, the possibilities will continue to expand, granting a very bright future.

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KEY POINTS

- PET/MR imaging is a flexible hybrid technology that can be customized with any PET tracer or MR imaging sequence. For localized breast PET/MR imaging examinations, 18F-FDG-PET and DCE-MR imaging data sets are typically acquired, often also with DWI.
- For whole-body PET/MR imaging examinations in the setting of breast cancer, 18F-FDG-PET data are acquired with contrast-enhanced MR imaging, DWI, and additional T2-weighted sequences.
- In breast PET/MR imaging examinations, PET and MR imaging provide complimentary information that can yield increased sensitivity for satellite lesions and axillary lymph node metastases over either examination alone.
- In breast PET/MR imaging examinations, multiple PET- and MR imaging–derived parameters are being investigated for their abilities to predict and assess response to treatments.
- In whole-body imaging, PET/MR imaging is more sensitive than PET/CT for lesion detection, especially for lesions in the bone, liver, and breast, and requires approximately half of the radiation required for PET/CT.

Fig. 1.

A 39-year-old woman with ER, PR, and HER2 positive right breast invasive ductal carcinoma. ER, estrogen receptor; PR, progesterone receptor. (A) Axial postcontrast MR imaging shows a 2.5-cm enhancing mass consistent with the known carcinoma. (B) PET axial images demonstrate a corresponding FDG-avid mass. (C) PET/MR imaging fused images. (D–F) Ktrans, kep, and Vp color maps superimposed on axial postcontrast images. Color bar ranges are represented as follows: Ktrans, -0.09 to 0.25 min $^{-1}$; kep, 0.06 to 2.61 min $^{-1}$; and Vp, 0% to 1.24% . These values are consistent with a malignant lesion.

Fig. 2.

Preneoadjuvant and postneoadjuvant chemotherapy on PET/MR imaging. A 53-year-old woman with a 3.5-cm invasive ductal carcinoma. (A) Axial postcontrast MR imaging shows a 3.8-cm enhancing mass consistent with the known carcinoma. (B) Diffusion image (B value 800) demonstrates a hyperintense mass. (C) PET/MR imaging fused images. Posttreatment images demonstrate the cancer has decreased in size. (D) Axial postcontrast MR imaging shows a 1.6-cm enhancing mass consistent with the known carcinoma. (E) Diffusion image (B value 800) demonstrates a hyperintense mass. (F) PET/MR imaging fused images.

Fig. 3.

Liver metastases seen best on PET/MR imaging: 56-year-old patient with a history of right breast invasive ductal cancer and known liver metastases. (A) Contrast-enhanced T1-weighted image demonstrates multiple metastases (*arrows*) with increased FDG uptake also readily visible on the (B) fused T1-weighted and PET image (*arrows*). (C) Contrast-enhanced CT image only clearly shows a single metastasis (*arrow*). (D) Although the fused PET/CT image shows additional hypermetabolic lesions (*arrows*), high background hepatic FDG uptake makes detection more difficult than on PET/MR imaging (B). (E, F) Corresponding DWI image and ADC map from the PET/MR image demonstrate even more metastases (*arrows*) with restricted diffusion (high signal on DWI and low signal on the corresponding ADC map) than seen on the (A) T1-weighted or (B) T1/PET images.

Fig. 4.

A single osseous metastasis, the only evidence of metastatic disease, seen only on PET/MR imaging. A 75-year-old woman with a history of left invasive ductal cancer, status postmastectomy, imaged for surveillance. (A) Diffusion-weighted imaging shows this metastasis as a focus of restricted diffusion in the right ilium (*circle*), which demonstrates mild FDG uptake on the (B) fused T1-weighted/PET image (*circle*). (C) CT and (D) fused PET/CT images show no evidence of disease at the same location.

Table 1

Suggested MR imaging sequences by station for whole-body PET/MR imaging in the setting of breast cancer

Station	T1-Weighted Sequences	T2-Weighted Sequences
All	Coronal 3D gradient echo for creation of DIXON-based μ -map	Coronal high-speed turbo spin echo T2
Bone/pelvis	Radial 3D gradient echo, noncontrast preferred, or T1 DIXON (fat-containing lesions)	Axial high-speed turbo spin echo, or Axial 3 b-value DWI
Liver/abdomen	Radial 3D fat-suppressed gradient echo with or without contrast	Axial high-speed turbo spin echo, axial 3 B-value DWI, possible axial fat-saturated T2 (fat-containing lesions)
Lung/thorax	Radial 3D fat-suppressed gradient echo with or without contrast	
Brain/head	Postcontrast magnetization prepared rapid gradient echo Precontrast 3D gradient echo useful for hemorrhage	T2 postcontrast FLAIR (leptomeningeal disease)