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Use of Breast-Specific PET Scanners and Comparison to MRI

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Introduction

Positron-emission tomography-computed tomography (PET-CT) is widely used for breast cancer staging when metastatic disease is suspected, as it provides both functional and anatomic information. Breast-specific PET has been developed to provide functional information on breast lesions with the hope of improving detection of clinically important disease and reducing false positives. A variety of positron-emitting radiotracers have been developed and others are in validation, with the most widely utilized being the glucose analog 18F-2-deoxy-2-fluoro-D-glucose (FDG) with a 110-minute half-life. FDG is taken up by metabolically active cells including tumor cells, inflammatory cells, brain, kidney, and brown adipocytes, and is phosphorylated, preventing its release from the cell. Breast PET has high sensitivity for invasive breast cancer and has been validated in women with newly diagnosed breast cancer as an alternative to breast MRI to depict disease extent^{1,2}. We will review those data and describe preliminary results for other indications for the use of breast PET.

Breast-Specific PET Devices

Whole body PET (WBPET) and PET-CT are not optimal for evaluation of the breasts due to supine positioning and low resolution (5–6 mm) which limits detection of sub-centimeter cancers³. Breast PET uses detectors positioned close to the breasts either similar to mammography with gentle stabilization or in the prone or semi-prone position. PET requires coincidence detection of the pair of 511 KeV gamma rays emitted in opposite directions at the time of annihilation of the positron. This requirement for coincidence detection has

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implications near the chest wall where it may be difficult to position detectors on opposing sides without noisy background from the heart or liver.

The first commercially available breast PET system, a Positron Emission Mammography (PEM) system from Naviscan PET Systems (currently CMR Naviscan, Carlsbad, CA), now modified as the PEM Flex Solo II (Figure 1, 2), uses limited angle tomography. Patients are seated upright and the breast is gently stabilized between clear compression paddles with positioning as for mammography. There are two opposing PET detectors that move in a linear manner within the compression paddles to scan the breast for approximately 10 minutes per image. The PEM Flex Solo II is the most widely used breast PET system to date and has been installed in over 50 sites across the United States, Latin American and Asia. Importantly, direct PEM-guided biopsy has been developed, validated, and FDA-approved for sampling breast lesions⁴. Unlike MRI, specimens obtained during PEM-guided biopsy can be imaged to confirm adequate sampling and direct the pathologist's attention to the samples of interest.

The MAMmography with Molecular Imaging (MAMMI) PET system from Oncovision (Valencia, Spain) is an FDA-approved true tomographic ring scanner where patients are scanned in the prone position. The breast hangs pendulous without compression within a ring of detectors that rotate around the breast. The EI Mammo dedicated breast scanner (Shimadzu Corporation, Kyoto, Japan) has two different positioning configurations: an O-scanner where the positioning is prone, similar to MAMMI PET, and C-PEM, consisting of a C-shaped detector ring with the patient positioned semi-prone leaning into the scanner. The C-shaped detector ring rotates to accommodate the arm for both right and left breast imaging. Other breast - specific PET systems are in development⁵. While both ring and planar scanners have their own strengths and drawbacks, no differences in lesion sensitivity were noted between them⁶.

Imaging Protocol and Radiation Exposure

In clinical studies using breast-specific PET systems, patients are injected with approximately 185–370 MBq (5–10 mCi) FDG after fasting for 4–6 hours. Blood glucose is tested prior to injection and should be in the normal range. Patients must rest quietly for 60–90 minutes following injection prior to commencing imaging. For PEM systems, typically both craniocaudal and mediolateral oblique views are obtained for 5–10 minutes of scan time per breast per view. For other systems, the scan time varies from 5–30 minutes per breast depending on the size of the breast.

PEM images are displayed as a 12-slice tomographic view with slice thickness equal to the compressed breast thickness divided by 12. A standardized PEM⁷ interpretation lexicon which uses terminology similar to BI-RADS MRI⁸ has been developed. Importantly, with only two hours' training, 36 observers showed excellent sensitivity for cancer at 96% (range 75–100%) and specificity at 84% (range 66–97%) in an interpretive skills task of 49 breasts including 20 (41%) cancers⁹. The same 36 observers also reviewed MRI images from 32 breasts in 30 patients with sensitivity of 82% (range 45–100%) and specificity of 67% (range 38–91%). Inter-observer agreement in description of PEM findings was moderate to

substantial with kappa of 0.57 for lesion type (mass or nonmass uptake) and 0.63 for final assessment⁷.

Image quality depends on the total PEM image counts and therefore lesion detection sensitivity and diagnostic accuracy reduces with lower dose or image time¹⁰. Image counts can be increased by increasing either the injected activity or scan duration or both, but these cannot be boosted arbitrarily due to concerns for higher radiation exposure and/or procedure time.

Radiation dose to the patient is a significant concern for breast-specific PET imaging. A typical dose of 10 mCi (370 MBq) results in an estimated effective dose of 6.2–7.1 mSv, more than 10 times that associated with two-view screen film mammography¹¹. The whole body effective dose is the sum of individual organ doses weighted by pre-defined tissue weighting factors. Unlike mammography, radiation exposure is to the whole body due to the systemic injection of FDG. The bladder receives the highest dose at 59mSv with dose to the other organs ranging from 2.5mSv to 8mSv¹². The radiation dose to the breast itself, at 2.5 mGy, is comparable to the mean glandular dose from digital mammography at 4 mGy. Considering the whole-body radiation exposure, patient preparation, and scan time, breast PET is unlikely to be used in the screening setting. Because of the high-energy emissions, shielding requirements for installing the breast PET scanner can be challenging and may require shielding of offices above and below the device.

Local Extent of Disease

There is a lack of consensus about the use of pre-operative MRI to assess local extent and select patients for breast conserving treatment¹³. A large prospective multicenter trial of PEM and MRI in 388 women with newly diagnosed biopsy-proven cancer, where breast-conserving therapy was planned, was led and reported by Berg et al¹. Of 388 index breasts with cancer, 75 (19%) ultimately were pure ductal carcinoma in situ (DCIS). For the 386 index malignancies that had surgery, with a median invasive tumor size of 1.5 cm (range 0.4–6.9), PEM depicted 357 (92.5%) versus MRI at 344 (89.1%, $p=0.079$). Among 19 sites of biopsy-proven malignancy that were falsely negative on PEM were 11 cancers with no radiotracer uptake and 6 where the cancer could not be included in the field of view. Of 388 ipsilateral breasts, 82 (21%) had an additional 116 tumor foci not known at study entry, with a median invasive tumor size of 0.7 cm, and PEM depicted 42 (51%) with MRI showing 49 (60%, $p=0.24$). PEM and MRI were complementary with 61/82 (74%) of additional foci identified by the combination ($p<0.001$ vs. MRI alone). Importantly, review of conventional imaging showed 7 foci of malignancy (8.5% of additional foci) not seen on PEM or MRI, emphasizing the need for breast imaging radiologists to interpret PEM together with the patient's other breast imaging and history.

Sensitivity by tumor type was explored for the 116 malignant lesions identified after study entry¹. DCIS was poorly detected by either PEM (23/56, 41% lesions) or MRI (22/56, 39% lesions, $p=0.83$). The 59 foci of invasive cancer were less well identified using PEM at 24/59 (41%) sensitivity compared to MRI at 38 (64%, $p=0.004$). Unlike studies with WBPET³,

PEM detection of invasive lobular cancer was not worse than invasive ductal cancer. Fewer atypical hyperplasias or lobular carcinoma in situ lesions were seen on PEM than MRI.

The sensitivity of PEM and MRI improved with increasing tumor size ($p=0.021$), as analyzed for the 40 additional foci that were $>90\%$ invasive: 4/16 (25%) T1a lesions were seen; as were 6/13 (46%) of T1b and 3/5 (60%) T1c¹. Comparable results for MRI were 5/16 (31%) T1a, 12/13 (92%) T1b, and 5/5 (100%) T1c lesions. Eo et al¹⁴ compared PEM tumor detection with PET-CT as a function of tumor size and showed that PEM was more sensitive for small invasive tumors (with p -value for overall sensitivity difference of 0.004): 11/15 (73%) T1a or T1b; 42/44 (95%) T1c; and 44/44 (100%) T2 tumors were seen on PEM compared to 9/15 (60%) T1a or T1b; 37/44 (84%) T1c; and 42/44 (95%) T2 tumors on PET-CT.

The multicenter PEM study showed that for the 306 breasts without additional cancer, PEM was more specific than MRI, with 279 (91.2%) negative on PEM compared to 264 (86.3%) on MRI ($p=0.032$), though overall accuracy was not different: AUC of PEM was 0.72 compared to 0.76 for MRI ($p=0.37$). Sensitivity could have been artificially reduced and specificity could have been artificially inflated for PEM as direct PEM-guided biopsy only became available midway through the study, which would have discouraged biopsy of lesions seen only on PEM. Similar results were observed in the non-overlapping single-center series of Schilling et al comparing PEM and MRI², and both Schilling et al and a subset analysis by Kalinyak et al from the multicenter trial¹⁵ showed improved diagnostic performance of PEM compared to WBPET.

Data from the multicenter study showed that MRI imaging was more accurate in surgical planning than PEM with an accurate estimate of disease extent in 292/388 (75%) breasts as compared to 262/388 (67%) for PEM. Both modalities were equally likely to overestimate the extent of disease, though PEM tended to underestimate more than MRI. In a recent study of 619 patients diagnosed with breast cancer, Kuhl et al¹⁶ showed that MRI is sensitive in depicting DCIS components associated with invasive cancer and when used with MRI-guided biopsy, MRI improved surgical treatment. In separate studies, PEM¹⁷ and MRI^{18,19} were found to be particularly valuable in selecting patients for possible accelerated partial breast irradiation (APBI).

In the multicenter PEM study, 15 women were found to have contralateral cancer (median size 10 mm, range 1–22 mm) and, prospectively, only 3 (20%) were identified as suspicious by PEM compared to 14 (93%) by MRI ($p<.001$) with one missed on both²⁰. Another three contralateral cancers were considered probably benign, BI-RADS 3, on PEM. On later radiologist review, blinded to results, 11 (73%) were recognized as suspicious on PEM. Lesions seen on PEM should be viewed as suspicious unless known benign by prior biopsy. A probably benign assessment, BI-RADS 3, with short-term interval follow-up (usually in six months) is not appropriate for lesions seen on PEM, with 3/32 (9.4%) such lesions malignant in a non-overlapping training set of cases⁷.

Visualizing tissues close to the chest wall has been a challenge for both PEM and other breast-specific PET systems. In a prospective multicenter study, 206 patients were imaged

using both PET-CT and MAMMI-PET²¹. MAMMI-PET had a sensitivity of 88.9% (depicting 183/206 lesions) while PET-CT had a sensitivity of 91% (depicting 186/206 lesions, $p=0.61$). Of the 23 index lesions missed by MAMMI-PET, 20 were located close to the pectoral muscle. In another single site study²², Shimadzu's O-Scanner and C-scanner were evaluated and their performance compared with PET-CT and MRI in 69 women with 76 known or suspected breast lesions. Both O-scanner and C-scanner had similar sensitivity: 82% (62/76) and 83% (63/76) respectively. In comparison, the lesion-based sensitivity of MRI was 100% (76/76) and that of PET-CT was 92% (70/76). Nine lesions with the O-scanner and 6 lesions with the C-scanner were outside the field of view, thereby reducing the sensitivity of the dedicated breast PET. Like the MAMMI-PET study, all lesions that were outside the field of view were close to the chest wall and could not be imaged even with special attention to patient positioning.

Axilla

Often it is difficult to include the axillae with breast-specific PET due to positioning similar to mammography or even on a prone table. In the prospective multicenter trial described¹, the false positive and false negative rates for axillary nodal metastases were high for both PEM and MRI. Of 19 axillae suspicious on PEM, only 10 (53%) actually had nodal metastatic disease; of 27 axillae suspicious on MRI, only 13 (48%) had metastatic nodes. Of 326 axillae negative on PEM, 68 (20.9%) had metastases and of 318 negative on MRI, 65 (20.4%) had metastases, for overall sensitivity of 10/78 (13%) for PEM and 13/78 (17%) for MRI, not significantly different. Dedicated views of the axillae with the detectors in front and behind the patient's elevated arm can be obtained with PEM, but are not standard, and results with WBPET and PET-CT have not been encouraging for assessment of the axilla²³. In a recent meta-analysis of 21 studies, MRI has shown to be more sensitive for diagnosing axillary lymph node metastasis compared to PET-CT with comparable specificities²⁴. In a subset of patients in the PEM multicenter trial who had PET-CT, only 8 (33%) of 24 women with nodal metastases were identified on PET-CT and 7/80 (8.8%) axillae without metastatic disease were falsely suspicious.

Quantification

Using WBPET, quantitative, and, for PEM, semi-quantitative uptake of FDG have been shown to correlate with known histopathologic and immunohistochemical prognostic factors including risk of nodal metastases and greater uptake predicts response to chemotherapy^{25,26}. Increasing uptake has been shown with increasing tumor grade and with triple receptor negative tumor type^{15,25}. Lower uptake has been observed in invasive lobular carcinoma¹⁵. Like the Standardized Uptake Value (SUV) used in whole body PET studies, the PEM Uptake Value (PUV) is a quantitative measure of the FDG uptake in the image. Although Wang et al²⁵ have reported a high to moderate correlation between SUV and PUV in breast tissue, the PUV value differs from SUV in absolute value because PEM images do not have corrections for attenuation or scatter. The maximum PUV for a region of interest (PUVmax) has been shown to be superior to other quantitative measures such as lesion to background (LTB) ratio for differentiating between benign and malignant tissue due to the simplicity and reproducibility of PUVmax²⁷. Muller²⁸ suggested a threshold value of

PUVmax >1.9 as predictive of malignancy based on an analysis of 108 patients. Other studies^{1,27} have found it difficult to use a discriminatory threshold for predicting malignancy, although median PUVmax for malignancies was significantly greater than that for benign lesions. In the results reported by Narayanan et al⁷, the median PUVmax for benign lesions was 1.0 (SD, 0.4); for high-risk lesions, 1.3 (SD, 0.4); for DCIS, 1.1 (SD, 0.9); and for invasive malignancies with or without DCIS, 1.4 (SD, 0.6); $p = 0.001$ for differences among groups, but there was substantial overlap with some fibroadenomas, fat necrosis, and atypical hyperplasias showing intense FDG uptake.

Background FDG Uptake and Breast Density

Uptake of FDG in normal breast tissue increases with visual mammographic BI-RADS breast density and decreases with patient age/postmenopausal status. An early retrospective study of 94 women with suspicious breast lesions²⁹ looking at a region of interest in the normal contralateral breast showed average mean (and maximum) background glandular PUV of 0.33(0.60) in fatty breasts, 0.41(0.72) in breasts with scattered fibroglandular density, 0.65(1.05) in heterogeneously dense breasts, and 0.85(1.30) in extremely dense breasts; increasing background FDG uptake (PUVmax) was highly correlated with increasing breast density (Spearman's correlation coefficient = 0.76, $p < 0.0001$). In a more recent study of 52 women who had both PEM and MRI³⁰, the mean $\pm$ SD background 18F-FDG uptake on PEM was 0.25 ± 0.13 in almost entirely fatty breasts ($n=5$), 0.46 ± 0.21 in breasts with scattered fibroglandular density ($n=12$), 0.62 ± 0.20 in heterogeneously dense breasts ($n=19$), and 0.76 ± 0.23 in extremely dense breasts ($n=16$). Koo et al³⁰ showed an inverse relationship of FDG uptake to patient age and menopausal status independent of breast density; background parenchymal enhancement on MRI slightly increased with increasing background FDG uptake but was not an independent predictor of FDG uptake in regression analysis. Such differences in background FDG uptake may slightly affect interpretive performance: in the multicenter study of Berg et al¹, MRI was more sensitive than PEM in heterogeneously dense or extremely dense breasts: 34/60, 57%, vs. 22/60, 37%, $p=.031$. While background parenchymal enhancement on MRI has been shown to predict risk of developing cancer³¹, background FDG uptake has not been studied in this regard.

Response to Primary Chemotherapy

Noritake et al³² compared the performance of PEM with that of WBPET in assessing the therapeutic response to neoadjuvant chemotherapy in 20 patients. Patients were imaged at three time points: before, during (interim), and after neoadjuvant chemotherapy. PEM PUVmax was highly correlated with SUVmax on WBPET (Pearson correlation coefficient $r = 0.78$). At the interim time point, when therapy could be changed based on imaging findings, reduction in PUVmax did not distinguish patients who ultimately had pathologic complete response (pCR) from those who did not whereas SUVmax on WBET did. At completion of chemotherapy, further reduction in PUVmax did distinguish the 9 patients with pCR from 11 without ($p=0.035$) though there was overlap in the groups. With increasing interest in nonsurgical approaches to women with pCR, functional imaging is of increasing potential importance to distinguish scar from residual viable tumor. Direct comparison of PEM and MRI has not been performed for this indication.

Other Applications

While one study of 265 women, including 165 who were asymptomatic, used PEM to “screen” for breast cancer³³, this will not be discussed further due to the substantial whole body radiation exposure and patient preparation that render breast PET impractical for screening. One study³⁴ evaluated PEM in women with suspicious calcifications going to biopsy; among 40 patients with 15 malignancies, PEM identified 14 (93.3%) cancers with one false negative intermediate grade DCIS and one false positive fibroadenoma (accuracy 95%). Further study of PEM for problem solving is warranted, but may not be competitive against the much lower cost contrast-enhanced mammography. Dedicated breast PET-MRI systems are in early development phase at various academic research laboratories^{35,36} but it is premature to comment on the clinical utility. Early results with integrated whole body-PET/MRI have not shown superior performance in detecting breast lesions compared to MRI alone³⁷, but technical improvements in dedicated breast PET devices may improve PET performance (Table 1).

Summary

Breast-specific PET imaging demonstrates high sensitivity for breast lesions and has shown promise for evaluating extent of disease in patients diagnosed with breast cancer. While PEM and MRI are complementary and the use of both improves overall performance, it is not recommended to use both because of the substantial cost and minimal added benefit in such an approach. Breast MRI is widely used in breast imaging clinics. While the lack of specificity is a known disadvantage of MRI, there are several other factors that preclude the use of MRI for patients. These include contraindications to gadolinium-based contrast agents, claustrophobia, obesity, and having metal implants such as pacemakers³⁸. As most of these MRI contraindications do not affect PEM imaging, PEM is an excellent alternative for those patients who need but cannot or will not undergo diagnostic breast MRI. Breast imagers should interpret breast PET to assure full correlation with prior breast imaging, history, and appropriate management in conjunction with a multidisciplinary specialty team.

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Key Points

- PEM shows sensitivity similar to MRI in detecting malignant breast lesions with better specificity than MRI.
- Breast PET can be used in women where breast MRI is contraindicated.
- Breast imagers should interpret breast PET to assure full correlation with prior breast imaging, history, and appropriate management in conjunction with a multidisciplinary specialty team.

Synopsis

The goals of this article are to discuss the role of breast-specific PET imaging of women with breast cancer, compare the clinical performance of PEM and MRI for current indications, and provide recommendations for when women should undergo PEM instead of breast MRI.

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Figure 1.
CMRNaviscan's PEM Flex Solo II PEM scanner. Courtesy of CMR Naviscan, with permission.

Figure 2.

45 year-old woman with invasive lobular carcinoma. (A) 12-slice PEM mediolateral oblique view shows multi-lobulated irregular mass or group of masses spanning 3.2 cm (straight arrows) and scattered foci closer to the nipple (circle). (B) Sagittal T1-weighted contrast-enhanced subtraction MR image shows 3.2-cm irregular mass (arrow) with small enhancing foci more anteriorly (circle). At mastectomy, 3.0 cm of grade 1 invasive lobular carcinoma was found with lobular carcinoma in situ. More anterior foci of radiotracer uptake/MRI

enhancement were due to sclerosing adenosis and fibroadenomas. One axillary node was metastatic.

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Table 1

Comparison of Breast PET and Diagnostic MRI

Issue	Breast PET	MRI
Patient Characteristic		
Weight > 300 lbs, pacemaker (most), claustrophobia, allergy to gadolinium contrast	Acceptable	Contraindicated
Fasting 4–6 hr	Required	N/A
Blood glucose <140 mg/dl	Required	N/A
GFR < 60	Acceptable	Reduce dose of contrast if GFR 30–60; avoid if <30
Pregnancy	Contraindicated	Contraindicated
Breast Implants	Acceptable	Acceptable
Examination Time	40 min	40 min
Ionizing Radiation	6.23 mSv ^b	None
Standardized Interpretive Criteria ^c	Yes	Yes
Image-guided Core Biopsy	Yes	Yes
Specimen Imaging at Time of Biopsy	Yes	No
Cost	800–2000 USD	700–2000 USD

USD = United States dollars.

^b Effective whole body radiation dose after a single 370 MBq (10 mCi) injected dose, compared to mammography at 0.5 mSv and background radiation at 2.5–10 mSv per year^{12,40}.

^c Standardized Interpretive Criteria^{8,9}

Adapted from Kalles V, Zografos GC, Provatopoulou X, Koulocheri D, Gounaris A. The current status of positron emission mammography in breast cancer diagnosis. *Breast Cancer*. 2013;20(2):123–130, with permission.