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Dedicated breast gamma camera imaging and breast positron emission tomography (breast PET): Current status and future directions

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Short Description:

Recent advances in nuclear medicine instrumentation have led to the emergence of improved molecular imaging techniques to image breast cancer: dedicated gamma cameras using γ -emitting ^{99m}Tc -sestamibi and breast-specific positron emission tomography (PET) cameras using ^{18}F -FDG. This review article focuses on the current role of such approaches in the clinical setting including diagnosis, assessing local extent of disease, monitoring response to therapy, and, for gamma camera imaging, possible supplemental screening in women with dense breasts. Barriers to clinical adoption and technologies and radiotracers under development will also be discussed.

Keywords

molecular breast imaging; positron emission mammography; breast PET; breast cancer; breast PET tracers

Anatomical imaging such as mammography and ultrasound are the mainstay of conventional breast imaging. Contrast-enhanced MRI, which is both anatomic and shows areas of increased vascularity and vascular permeability, is widely used for high-risk screening and assessing disease extent and response. Functional breast imaging techniques using dedicated gamma cameras or positron emission tomography (PET) scanners can complement conventional imaging by providing specific cellular information to aid in the diagnosis, staging, and treatment of breast cancer. The two most common radiotracers used for breast imaging are the gamma-emitting ^{99m}Tc -sestamibi (140 keV, half-life of 6 h) that measures mitochondrial activity and the positron emitting glucose analog ^{18}F -fluorodeoxyglucose (FDG, 511 keV, half-life of 110 min) that measures metabolic activity. Conventional whole-body gamma cameras and whole-body PET systems with large field of view have limited

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spatial resolution and low sensitivity for smaller tumors^{1,2}. The development of high resolution dedicated breast scanners has resulted in improved lesion detectability, particularly for sub-centimeter lesions, due to technical improvements in detector performance, the ability to position these compact cameras closer to the breast, and the availability of projections similar to those of mammography³. The goal of this article is to discuss existing clinical data for nuclear medicine imaging in breast cancer and review technologies in development.

DEDICATED SINGLE PHOTON GAMMA IMAGING

Dedicated breast gamma imaging utilizes semiconductor-based gamma cameras in a mammographic configuration to visualize the uptake of ^{99m}Tc-sestamibi. Sestamibi, originally developed as a cardiac tracer, is approved by the Food and Drug Administration for breast cancer imaging, accumulating selectively in breast tumors rather than surrounding normal breast tissue⁴. There are three different commercially available dedicated gamma camera systems. The breast specific gamma imaging (BSGI) detector system from Dilon Technologies (Newport News, VA) was the first dedicated breast gamma imaging system on the market. The original BSGI scanner consists of a single panel detector with NaI crystals and a field of view of 20 × 20 cm; a recent version uses cesium iodide (CsI) crystals with a larger field of view of 25 × 20 cm. Lumagem (previously Gamma Medica Inc., Salem, NH, recently acquired by CMR Naviscan Carlsbad, CA) and Discovery NM750b (GE Healthcare, Milwaukee, WI) systems are dual panel systems that use two cadmium zinc telluride (CZT) detector panels with a field of view of 20 × 16 cm and 24 × 16 cm respectively (see Table 1). Single panel detector systems are called breast specific gamma imaging systems and dual-panel systems are referred to as molecular breast imaging systems in much of the literature on this topic and will be so named in this paper. Dual-panel MBI systems show improved lesion detection sensitivity compared to single-panel systems, due to reduced lesion-to-detector distance, especially in women with large breasts and smaller lesions^{5,6}. Stereotactic biopsy capability is available for the Dilon and GE systems.

In all dedicated breast gamma camera imaging, patients are positioned similar to mammography to obtain craniocaudal (CC) and mediolateral oblique (MLO) views with only gentle compression applied to stabilize the breast. Patients are scheduled for imaging during days 7-14 of their menstrual cycle to decrease background tracer uptake. Early literature shows that patients were typically injected with 555-1100 MBq (15-30mCi) of ^{99m}Tc-sestamibi but lower doses of 370-444 MBq (10-12mCi) for BSGI and 148-296MBq (4-8 mCi) for MBI imaging are more common in current practice. Prior to injection, peripheral warming of the patient's upper torso is recommended to improve tracer uptake in the breast⁷. Patients are imaged five-minutes post injection. For Dilon and Lumagem systems, a single planar image is produced for each view. The GE system displays results from each of the upper and lower detectors and also creates an "average" CC and MLO view of each breast.

DEDICATED BREAST POSITRON EMITTING TOMOGRAPHY (PET)

Breast-specific PET uses detectors positioned close to the breast. Because most malignancies metabolize glucose at a faster rate than normal tissue, FDG uptake provides a functional map of tumor presence and activity. There are several breast-specific PET systems being developed and broadly they fall into two categories: positron emission mammography (PEM), where two planar detectors are placed on either side of the breast with the patient positioned analogous to mammography, and dedicated breast PET (dbPET) systems where the patient is prone and the breast imaged with a ring-shaped detector. Freifeder and Karp⁸ compared the designs of both ring and planar scanners and concluded there was no significant difference in lesion detection between PEM and dbPET scanners. While dbPET detectors had higher image contrast, better depth resolution and slightly better overall performance, PEM scanners had lower image noise, were more accommodating of different imaging configurations including different breast sizes, and potentially had lower cost.

The PEM Flex Solo II scanner from Naviscan (CMR Naviscan, Carlsbad, CA) is the most clinically validated breast-specific PET system available. The Solo II consists of two 6 cm × 16.4 cm opposing lutetium-yttrium oxyorthosilicate (LYSO) crystal-based PET detectors that move linearly within compression paddles placed on either side of a gently stabilized breast, covering a field of view 24 cm × 16.4 cm⁹. Patients are seated upright and positioned in either CC or MLO positions. Limited-angle reconstruction is performed to display 12 tomographic slices (slice thickness is total breast compressed thickness divided by 12) for each view. The in-plane resolution for PEM systems is 2.4 mm using the maximum likelihood estimation method (MLEM) reconstruction and 1.8 mm using the high-resolution reconstruction mode^{9,10}. The z-axis resolution is lower (4-6 mm) due to limited angle tomography (two parallel planar detectors are unable to provide 360 degree coverage for the breast). In addition, an FDA-approved PEM-guided biopsy system is available to sample suspicious breast lesions¹¹. Eo et al¹² found that PEM was more sensitive for smaller invasive tumors than PET-CT: 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 (with p-value for overall sensitivity difference of 0.004).

The MAMmography with Molecular Imaging (MAMMI) PET system (Oncovision, Valencia, Spain) is a commercially available true tomographic ring scanner using LYSO-based PET detectors, with an intrinsic spatial resolution of 1.6 mm¹³. Each breast is imaged separately, with the patient prone; the breast hangs pendulous (no compression) within a ring of detectors rotating around it. A prototype biopsy system is under development¹⁴. Shimadzu has developed the El Mammo dedicated breast PET systems and obtained clinical data with two different positioning configurations. The O-scanner is a tomographic ring system using a LGSO detector with 2.0 mm resolution in all three dimensions. Shimadzu's C-PEM consists of a C-shaped detector ring with the patient positioned semi-prone leaning into the scanner, offering better access to image the axillary nodes¹⁵.

For breast-specific PET imaging, patients are injected with approximately 185-370 MBq (5-10 mCi) of FDG after fasting for 4-6 hours. Blood glucose should be within normal limits

prior to FDG injection. Patients must wait for 60-90 minutes post injection to allow for optimal tracer uptake before imaging and should be resting quietly in a warm environment during the circulation time. PEM systems require that both breasts are imaged with standard mammographic CC and MLO views with scan time typically 10 minutes per breast per view (total of 40 minutes or more if additional views are needed). Positioning can be challenging for women with large breasts where tiling may be necessary, for those with very small breasts, and for lesions close to the chest wall. The most posterior tissues are difficult to fully image due to positioning the relatively bulky detectors (especially with dual-head MBI) and need for coincidence detection on PET. For these reasons, the use of trained technologists with experience in proper breast positioning as for mammography is recommended.

IMAGING TECHNIQUES AND INTERPRETATION

Interpretive Criteria

Standardized terminology to characterize and interpret findings has been developed for both MBI¹⁶ and PEM images¹⁷, similar to the Breast Imaging and Reporting and Data System (BI-RADS) lexicon for MRI¹⁸. Experienced breast imagers have achieved high diagnostic accuracy and inter-observer agreement after minimal (approximately 2 hour) training on either MBI or PEM. For six observers interpreting MBI, the median sensitivity was 100% (range, 90-100%), specificity 88% (range, 83-97%), and area under the ROC curve (AUC) 0.94 (range, 0.93-0.98)¹⁹. Inter-observer agreement was substantial for lesion type ($\kappa = 0.79$) and non-mass distribution ($\kappa = 0.63$), and excellent for final assessment ($\kappa = 0.84$)¹⁹. Across 36 observers from 15 sites interpreting PEM images, mean sensitivity, specificity, and AUC for PEM were 96% (range, 75-100%), 84% (range, 66-97%), and 0.95 (range, 0.82-1.0)²⁰. Inter-observer agreement in description of PEM findings was moderate to substantial with kappa of 0.57 for lesion type (focus, mass or non-mass uptake) and 0.63 for final assessment. Because fat necrosis, fibroadenomas, and other benign and atypical lesions can show radiotracer accumulation, both modalities must be interpreted together with mammography and other current or prior breast imaging and appropriate patient history. The use of BI-RADS final assessment category 3, probably benign, is not recommended for either PEM or MBI as lesions designated as probably benign had a malignancy rate of 9.4% (3/32)¹⁷ and 8% (4/50)¹⁹ respectively, greater than the expected 2% rate for lesions assessed as BI-RADS 3 and recommended for surveillance with other breast imaging modalities²¹.

Quantitative Imaging

For breast gamma imaging, quantification of uptake is not routinely available¹⁹. However, PEM interpretation is usually based on both visual and semi-quantitative uptake¹⁷. Regions of interest (ROIs) are drawn around the lesion and around an area of normal breast representative of mixed glandular and fatty background tissue to obtain a semi-quantitative lesion-to-background (LTB) ratio, also known as a PEM uptake value (PUV). The PUV lacks attenuation and scatter correction and thereby differs from the standardized uptake value (SUV) used in whole-body PET or PET/CT, although maximum PUV and maximum SUV were highly correlated ($r = 0.79$) in a study by Wang et al²². For dedicated breast PET detectors, the maximum uptake value for lesions on dbPET was found to be higher than

WBPET SUV for corresponding lesions^{23,24}. Narayanan et al¹⁷ showed that both LTB and PUV_{max} were significantly greater ($p < 0.001$) across all malignant lesions compared to all benign lesions. In two separate series^{22,25}, invasive ductal cancers (IDC) had higher PUV_{max} than invasive lobular cancers (ILC). PUV_{max} values for high grade carcinomas were greater than those of lower grade cancers and were higher for triple negative breast cancers than for HER2/Neu-receptor positive or estrogen-receptor positive cancers. No specified threshold for malignancy exists, although a recent study comparing LTB and PUV_{max} recommended the use of PUV_{max} due to its simplicity and reproducibility²⁶. Another study²⁷ evaluated PUV_{max} and LTB using healthy tissue in the contralateral breast as background and found that both PUV_{max} and LTB were significantly higher for tumors compared to benign lesions. In that study, Muller et al suggested a threshold value of PUV_{max} > 1.9 and found that among 151 pathologically proven lesions, PEM had 100% sensitivity (26/26 lesions) and 96% specificity (120/125 lesions). This requires further validation; at present, it is recommended that any abnormal uptake be viewed as suspicious unless correlated with a known benign finding on mammography, other breast imaging, or clinical examination (e.g. sebaceous cyst).

Radiation Dose

One of the biggest concerns with radionuclide breast imaging is the radiation exposure of the whole body associated with systemic radiotracer injection. All efforts must be made to reduce radiation dose while maintaining diagnostic image quality. The typical dose of ^{99m}Tc-sestamibi for BSGI has been between 555–1,110 MBq (15–30 mCi), with a 1110 MBq dose, resulting in an estimated whole-body dose of 8.9 to 9.4 mSv. This is comparable to the effective estimated dose of 6.2–7.1 mSv for a 370MBq (10mCi) injection of FDG, although is more than 10 times greater than that from two-view mammography (0.3–0.6 mSv)²⁸. The radiation dose to the breast itself from these injections is 2 mGy for ^{99m}Tc-sestamibi and 2.5mGy for FDG, slightly less than the mean glandular dose (3.7mGy) from digital mammography. The radiation dose and resulting estimated risks are higher to other organs such as large intestine (40–55.5mSv) for ^{99m}Tc -sestamibi and bladder (59mSv) for FDG examinations²⁸. For a 40 year old women, the estimated whole-body radiation-induced cancer incidence from a single examination using conventional doses of FDG and ^{99m}Tc -sestamibi for breast imaging are 5–7 times higher than from mammography, while the radiation-induced mortality is estimated to be 20 times higher than mammography as many of the cancers potentially induced would be less treatable than breast cancer²⁹. In fact, with a low dose of 300 MBq (8mCi), the estimated benefit to risk ratio for dedicated breast gamma imaging for 40–49 year old women (performed annually over the 10 year range) was 5 compared to 13 for mammography alone³⁰. The benefit to risk ratio increased with screening age for both mammography and gamma imaging. To utilize MBI or PEM for breast cancer screening for women ages 40–49 with dense breasts with predicted risk-benefit ratios comparable to mammography, the administered radiotracer injections would have to be reduced to less than 150MBq (5 mCi) for ^{99m}Tc-sestamibi and to 70MBq (1 mCi) for FDG.

Optimization of collimators and widened energy windows coupled with improved noise reduction algorithms have allowed dose reduction of ^{99m}Tc-sestamibi to 150–300MBq

(5-8mCi) in dual-panel systems while maintaining equivalent image quality^{31,32}. Adjustments to patient preparation by ensuring that the patient is fasting and kept warm can improve ^{99m}Tc-sestamibi uptake by breast cancer and can allow further decrease in injected dose to approximately 156 MBq (4mCi)³³. The effective whole-body radiation dose from 150MBq is 1.1 mSv with an effective breast dose of 0.25 mGy, making it feasible to be considered for screening. Studies with low dose (7-10 mCi) BSGI are also underway³⁴. There have been similar efforts to halve the radiation dose for PEM with a corresponding increase in scan duration to maintain the total image counts³⁵; lower image counts increase noise and reduce lesion detection but more efforts are needed to arrive at a reduced dose producing optimal images within a clinically feasible scan time.

CLINICAL EVIDENCE

The American College of Radiology (ACR) recently released clinical practice parameters for the use of dedicated breast gamma imaging (both BSGI and MBI) using a gamma camera³⁶ and outlined potential clinical indications particularly in cases where breast MRI is not feasible. The clinical indications include (a) extent of disease/preoperative staging in newly diagnosed breast cancer (b) evaluation of response to neoadjuvant chemotherapy (c) detection of local breast cancer recurrence (d) evaluation for primary breast cancer in women with unknown primary and (e) breast cancer screening for high risk women for those who cannot undergo MRI and (f) MBI as adjunct to conventional breast imaging for problem solving in indeterminate cases.

A meta-analysis of BSGI showed a pooled diagnostic sensitivity of 95% [95% CI: 93 to 96%] and specificity of 80% [95% CI: 78 to 82%] in detecting breast cancers³⁷. The pooled sensitivity of BSGI in detecting sub-centimeter cancers was 84% (95% CI 80 to 88%) and that of detecting ductal carcinoma in situ (DCIS) was 88% (95% CI 81 to 92%). The pooled rate of detecting additional multifocal, multicentric or bilateral cancers in patients with known current malignancy was 6% [95% CI: 5 to 8]. Hruska et al³⁸ also compared the performance of dual-panel CZT MBI systems and showed higher sensitivity (90%, 115/128) compared to a single-panel CZT camera (80%, 102/128). In the same study, dual-panel cameras had 82% (50/61) sensitivity for sub-centimeter lesions compared to 68% (41/61) for single-panel cameras. Conners et al³⁹ retrospectively reviewed 390 invasive tumors (mean size 1.5 cm) in 286 women injected with 8-33mCi of ^{99m}Tc sestamibi who underwent MBI; invasive disease was correctly identified in 341/390 lesions (87.4%). MBI was better in depicting IDC (211/245, 86.1% sensitivity) than ILC (38/67, 56.7%) ($p < 0.0001$).

A recent meta-analysis of 8 prospective PEM studies in 873 women⁴⁰ with newly diagnosed breast cancer showed pooled sensitivity and specificity estimates of 85% (95% CI: 83-88%) and 79% (95% CI: 74-83%), respectively, and AUC of 0.88. Cancers missed were usually small or outside the field of view.

Extent of disease/surgical management

In a retrospective study⁴¹ of 82 patients who underwent BSGI for newly diagnosed breast cancer, 18 (22%) were found to have additional suspicious findings based on BSGI including 7/82 (8.5%) with additional malignancy. Kim et al⁴² evaluated the adjunctive

benefits of BSGI compared to MRI in 97 lesions in 66 breast cancer patients with dense breasts and showed comparable sensitivity for BSGI and MRI at 88.8% (23/26, 95% CI: 69.8 to 97.6%) and 92.3% (24/26, 95% CI: 74.9 to 99.1%) respectively. Specificity was lower for MRI at 39.4% (28/71, 95% CI: 28.0 to 51.7%) vs 90.1% (64/71, 95% CI: 80.7 to 95.9%) for BSGI ($p < 0.0001$). Similar results were found in a meta-analysis comparing BSGI to MRI in detecting breast cancer⁴³. Ten studies with 517 patients were included and the pooled sensitivities of BSGI and MRI were: 84% (95% CI: 79 to 88%) and 89% (95% CI: 84 to 92%) respectively, and the pooled specificities of BSGI and MRI were: 82% (95% CI: 74 to 88%) and 39% (95% CI: 30 to 49%) respectively. Edwards et al⁴⁴ retrospectively analyzed 163 women who were candidates for breast conserving surgery and later underwent mastectomy, 118 of whom had BSGI and 45 of whom had MRI. Management was changed to mastectomy in 11.9% (14/118) of those who had BSGI and 28.9% (13/45) of those who had MRI; in all cases, change to mastectomy was confirmed as appropriate. Percutaneous biopsy is recommended prior to conversion to mastectomy as some benign lesions will appear suspicious. Both BSGI and MRI tended to underestimate disease extent: 15.4% (16/104) of patients who underwent breast-conserving therapy based on BSGI findings required a single re-excision due to positive surgical margins and another 15/104 (14.4%) required mastectomy. In the MRI group, 6/32 (18.8%) required a single reexcision, and 2/32 (6.3%) required mastectomy.

Berg et al⁴⁵ compared the performance characteristics of PEM and MRI in a prospective multi-institutional randomized study of 388 women with newly diagnosed cancer (median invasive tumor size of 1.5 cm, range 0.4-6.9 cm) and found that PEM and MRI had comparable sensitivity with PEM having greater specificity. PEM depicted 357 of 386 (92.5%) index malignancies with surgical pathology, while MRI depicted 344/386 (89.1%, $p = .079$). Of 388 ipsilateral breasts, 82 (21%) had additional disease (116 malignant foci) not known at study entry, with a median size of additional invasive disease of 0.7 cm; and PEM depicted cancer in 42/82 (51%) with MRI showing additional disease in 49 (60%, $p = 0.24$). PEM and MRI were complementary, with 61/82 (74%) of breasts with additional malignancy identified by the combination ($p < .001$ vs. MRI alone). In another series⁴⁶ of 208 women with biopsy proven primary breast cancer, PEM and MRI had equivalent sensitivity in depicting index lesions (155/167, 92.4%) compared to WBPET (117/173, 67.9%, $p < 0.001$). There were 67 additional unsuspected ipsilateral lesions of which 40 were proven to be cancer. PEM had sensitivity of 85% (34/40) and specificity of 74% (20/27) compared to MRI sensitivity of 98% (39/40) and specificity of 48% (13/27) [$p = 0.074$, for sensitivity; $p = 0.096$ for specificity]

The detection sensitivity of PEM for identifying previously unsuspected DCIS was 41% (23/56)⁴⁵ in one multicenter series and 28/62 (45%) if another series by Schilling et al is included. In three separate series⁴⁷⁻⁴⁹, patients with newly diagnosed DCIS were imaged with BSGI & MRI respectively; BSGI had a pooled sensitivity of 80% (60/75, range 68.6% - 91%) for DCIS while pooled MRI sensitivity was 91.8% (56/61, range: 88-94%).

In the prospective multicenter study by Berg et al⁴⁵ comparing PEM and MRI for surgical planning, MRI was better at predicting extent of disease than PEM. Eighty-nine of 388 (23%) participants required more extensive surgery: 61 (69%) of these women were

identified with MR imaging, and 41 (46%) were identified with PEM ($p = .003$); 14 (3.6%) women had malignancies seen only on PEM. MRI led to more unnecessary mastectomies ($n=10$) than PEM ($n=6$), though this difference was not significant. In the same series, reported separately⁵⁰, 15 women had contralateral cancer (median size 10 mm, range 1-22 mm) identified after study entry and only three (20%) were prospectively identified on PEM compared to 14 (93%) by MRI though 11/15 (73%) were visible on PEM in a retrospective blind independent review. One contralateral cancer was missed on both modalities.

In this same study⁵⁰, the addition of conventional imaging (mammography and/or ultrasound) improved the sensitivity of PEM imaging from 51% (42/82) to 65% (53/82), $p<0.001$. Importantly there were seven DCIS (7/82, 9%) cases only on conventional imaging.

Similar results were observed in a retrospective study⁵¹, where 1024 patients who had ultrasound and BSGI were retrospectively analyzed. Of the 117 cases with positive mammogram, there were nine cases (9/117, 8%) missed by BSGI, leading to the recommendation that BSGI cannot obviate biopsies recommended by mammogram. For both breast PET and breast gamma imaging, it is critical to review the images together with conventional imaging, biopsy history and any other imaging. Benign findings such as fibroadenomas, fibrocystic change, fat necrosis, papillomas, atypical hyperplasia, and lobular carcinoma in situ can all show radiotracer accumulation and review of concomitant conventional imaging can improve the performance of the nuclear modalities and reduce false positives.

Monitoring Response to Treatment

Guo et al⁵² performed a meta-analysis to study the effectiveness of ^{99m}Tc-sestamibi in predicting the response to neoadjuvant chemotherapy (NAC) in 503 patients with breast cancer. The pooled sensitivity across 14 studies was 86% [95% CI: 78 to 92%], specificity was 69% [95% CI: 64 to 74%] and AUC was 0.86. Most studies used whole body SPECT; only three used dedicated breast-specific systems. In one study⁵³, 19 patients completed MBI imaging and neoadjuvant chemotherapy prior to surgery and lesion-to-background ratio was compared with extent of residual disease at surgery using the residual cancer burden. Reduction in LTB ratios in MBI images performed 3-5 weeks after starting NAC was an accurate predictor of residual disease at completion of chemotherapy. Using a threshold of 50% reduction in LTB ratio as a predictor for response, the sensitivity, specificity and AUC in predicting residual disease was 92.3% (95% CI: 0.74 to 0.99%), 83.3% (95% CI: 0.44 to 0.99%) and 0.92 respectively. In another study⁵⁴, 18 invasive breast cancer lesions in 17 patients undergoing NAC were imaged using MBI prior to final surgery with strong correlation ($r=0.681$, $p=0.002$) between measured size on MBI and residual tumor size at histopathology; although there was a decrease in LTB, that was not found to be predictive of residual disease. Menes et al⁵⁵ correlated the accuracy of MBI in detecting residual disease after NAC with molecular subtypes and found stronger correlation with triple negative and HER2/neu positive subtypes ($r=0.92$ and 0.62 , respectively). Sensitivity and specificity for all 51 women (of whom 16 had pathologic complete response) was 83% (29/35, 95% CI: 66 to 93%) and 69% (11/16, 95% CI: 42 to 88%) compared to 88% (15/17, 95% CI: 62 to 98%)

and 75% (9/12, 95% CI: 43 to 93%) for the subset with triple negative or HER2/neu positive tumors. The largest of these studies was done by Lee et al⁵⁶, who compared the performance of BSGI and MRI in predicting residual tumor after NAC in a series of 122 women, of whom 104 had residual tumor at pathology. BSGI identified 77/104 (74.0%) with residual tumor, not statistically different from the 85/104 (81.7%) shown on MRI ($p=0.134$). Interestingly, in this group, both MRI and BSGI underestimated residual tumor size in HER2-positive tumors.

There has been only one study⁵⁷ to date evaluating the performance of PEM in predicting residual tumor post NAC. In a study comparing the performance of PEM to whole body PET (WBPET) in 20 patients imaged pre, during, and post NAC, there was no difference in performance in predicting complete response between WBPET and PEM at the completion of NAC. At the interim point, the SUV_{max} of WBPET (AUC= 0.761) was superior to the PUV_{max} (AUC, 0.648) for predicting non-pathologic complete response (pCR). After NAC, the PUV_{max} (AUC, 0.796) was superior to the SUV_{max} of WBPET (AUC, 0.671) in predicting residual disease. After all treatment, the PUV_{max} and lesion to background ratio (LTB) was significantly lower in the pCR group than in the non-PCR group PUV_{max} , 1.0 ± 0.2 vs 2.5 ± 2.7 [$p = 0.0351$].

Breast Density

The BI-RADS system identifies four categories of breast density based on the level of fibroglandular tissue present in the breast: A) predominantly fatty, B) scattered fibroglandular density, C) heterogeneously dense and D) extremely dense. Dense breast tissue has been found to be an independent predictor of breast cancer risk^{58,59}. As more and more states require that a patient's mammography results letter include information about breast density⁶⁰, there has been increased awareness of the masking effect of dense tissue on mammography, potentially delaying cancer diagnosis and resulting in worse outcomes. Supplemental screening using ultrasound, MRI, or other methods is being considered in women with dense breasts. Background parenchymal enhancement on MRI and background uptake of radiotracers may correlate with subsequent cancer risk^{61,62} and may help identify women who should have regular supplemental screening. Increased background uptake is correlated with increase in breast density for BSGI and MBI⁶³, though some extremely dense breasts appear photopenic; cancer detection is not impaired⁶⁴.

Increased FDG uptake is seen with greater breast density and may impair cancer detection on PEM. Koo et al⁶⁵ reported data from a study comparing 52 women who had both PEM and MRI. Increased FDG uptake correlated with increased breast density with mean $\pm$ SD background ^{18}F -FDG uptake on PEM of 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 ($n=16$). In the multicenter study of Berg et al⁴⁵, MRI was more sensitive than PEM in heterogeneously dense or extremely dense breasts: 34/60, 57%, vs. 22/60, 37%, $p=.031$. Hormonal or menopausal status did not affect the performance of PEM.

Positioning Issues

Visualizing posterior lesions remains a challenge for dedicated breast imaging. In the multicenter series by Berg et al⁴⁵, in six of the 388 (1.5%) breasts, the index malignancy was outside the field of view. Shimadzu tested both the O-PEM and C-PEM configurations and found that both scanners had similar sensitivity: 82% (62/76) and 83% (63/76) respectively⁶⁶. However, nine lesions with the O-scanner and 6 lesions with the C-scanner were outside the field of view, thereby reducing the sensitivity of dedicated breast PET. In a MAMMI-PET study by Teixeira et al⁶⁷, 23/234 (9.8%) of the lesions not visualized because they were too close to the pectoral muscle and out of the field of view of MAMMI-PET. Similarly for an MBI study by Connors⁶⁸, 8/360 (2.2%) tumor foci were thought to have been missed because they were outside the field of view.

Screening

Due to proven reduction in mortality from breast cancer⁶⁹, mammography remains the primary method for breast cancer screening. The Mayo group has studied MBI for supplemental screening in women with dense breasts, using a reduced dose of 300 MBq (8 mCi) ^{99m}Tc-sestamibi⁷⁰. In 1651 asymptomatic women with dense breasts who underwent adjunct MBI imaging, along with mammographic screening, 14 additional cancers were detected by MBI: overall cancer detection increased from 3.2 to 12.0 per 1000 ($p < 0.001$) (supplemental yield of MBI of 8.8 per 1000, 95% CI: 4.3 to 13.3). In another supplemental screening study of 1696 women⁷¹, 13 mammographically occult malignancies were detected by MBI for a supplemental cancer detection rate of 7.7 per 1000 (13/1696) (Table 3).

Yamamoto et al⁷² injected 265 women (165 of whom were asymptomatic and 100 with breast symptoms) with a reduced FDG dose of 4.6 mCi and imaged them using PEM. Six additional cancers were found on PEM alone with average patient recall rate, positive predictive value, and cancer detection rate of PEM 8.3, 27.3, and 2.3% respectively. Of the six cancers found on PEM, two were found in patients with no breast symptoms, two were found in breasts that were previously followed for benign findings and two had suspicious lesions associated with breast cancer. However even with reduced radiation dose, it is unlikely that PEM would be used for routine screening. The requirement for fasting and study time of around 100 minutes per patient (FDG uptake time and scan time) is not conducive to patient throughput in a screening setting. Further, there are shielding requirements for a PEM scanner due to the high-energy photons from FDG that make it challenging to install in most breast centers.

FUTURE DEVELOPMENTS

Instrumentation

At present, breast PET is limited to locoregional staging and monitoring response to treatment. However, there is potential for improvement in the breast-PET performance with new scanners that have optimized type of detectors, detector configurations, photomultipliers and electronics. A dual-head PEM scanner with both detector modules rotating around a prone breast is being developed by a Portuguese Crystal Clear collaboration based at CERN⁷³. In addition, there are several dedicated breast PET scanners that are still in

development phase at various academic research laboratories including PEM/PET at West Virginia University⁷⁴, and portable dual panel PET at Stanford University⁷⁵. The development of integrated multi-modality imaging systems combining functional imaging and anatomic imaging modalities is gaining momentum in research laboratories around the world. Several researchers are working on hybrid systems such dedicated simultaneous PET-MRI system developed at the Brookhaven National Laboratory⁷⁶, where a PET ring detector has been integrated with a 1.5T dedicated breast MRI scanner. Other multimodality systems under development include Clear PEM-Sonic, developed by CERN that has a ring type breast PET scanner integrated with an ultrasound system developed by Supersonic Imagine⁷⁷ (Aix-en-Provence, France). The group at University of California Davis is developing a dedicated breast PET/CT scanner consisting of a dual-head PET camera and cone-beam CT integrated into a single gantry and have performed early clinical feasibility studies⁷⁸. A group at University of Washington, Seattle⁷⁹, is developing a PET /X scanner integrating dedicated breast PET with X-ray mammography to use the metabolic information from the hybrid image to assess and select effective targeted breast cancer therapies for each patient.

Dedicated multimodality gamma systems that combine CT imaging with gamma images are in development at Duke University⁸⁰ and University of Naples⁸¹ and a dedicated gamma tomosynthesis system is being developed at the University of Virginia⁸². Initial evaluation of dual-modality tomosynthesis in 21 lesions in 17 women injected with ^{99m}Tc-sestamibi showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 86%, 100%, 100%, 93%, and 95%, respectively⁸³. An integrated ultrasound, single head CZT scanner system is being developed to enable real-time registration of US to MBI for diagnostic evaluation of breast lesions detected on MBI⁸⁴.

Radiotracers

While FDG and ^{99m}Tc-sestamibi remain the primary radiotracers used in dedicated breast molecular imaging, new radiotracers⁸⁵ are likely to play a larger role in imaging and clinical evaluation of breast tumors, though none are currently approved for clinical use in the United States. 3-Deoxy-3-18F-fluorothymidine (FLT) is a cell proliferative agent believed to be more specific for breast tumors than FDG PET. In several WB-PET/CT studies to monitor response to treatment⁸⁶, FLT appeared to be a good predictor of early response to chemotherapy, despite concerns regarding its surrogate proliferative status. McKinley⁸⁷ at al reported that as FLT PET reflects the tumor proliferative indices indirectly as a function for the thymidine salvage pathway, it creates challenges in estimating the extent of proliferation and using the magnitude of FLT uptake to quantify proliferative index.

Clinical studies evaluating 18F-fluoroestradiol (18F-FES), an estrogen receptor (ER) expression biomarker, show benefit in metastatic breast cancer patients and in treatment monitoring in patients undergoing endocrine therapy⁸⁸. Building on the clinical success of HER2 targeted therapy using monoclonal antibody to the HER2 receptor (trastuzumab), there are several imaging agents being developed for both PET (e.g., 68Ga, 124I and 89Zr) and SPECT (ndium-111, Iodine-131, technetium-99m) imaging⁸⁹ using radiolabeled trastuzumab. Feasibility studies with 89Zr-trastuzumab for HER2 PET imaging in 14

patients with Her2 positive metastatic breast cancer showed the ability to visualize and quantify uptake in HER-2 positive lesions⁹⁰. Another study using ⁸⁹Zr-trastuzumab PET/CT to image metastatic breast cancer patients with Her2-negative primary cancer, showed that it could detect unsuspected HER2-positive metastases in these patients⁹¹. Distant metastasis may lose or gain receptor expression leading to incorrect choice of treatment based on primary tumor characteristics alone⁹². The ability to visualize or detect receptor status by trastuzumab or 18F-FES support the idea that functional imaging of distant receptors can help determine the appropriate treatment option for metastatic cancer.

Other PET agents that are being developed include ¹⁸F-misonidazole (¹⁸F-FMISO, a hypoxia imaging agent)⁹³, ¹⁸F-Fluciclovine⁹⁴ (amino acid transport agent), and ¹⁸F-FENP⁹⁵ (a progesterone receptor targeted agent). SPECT and PET radiotracers targeted to breast cancer angiogenesis makers such as vascular endothelial growth factor (VEGF) and integrins are also being evaluated. One such angiogenesis marker, ^{99m}Tc-NC100692⁹⁶ (Maraciclalide, GE Healthcare, Milwaukee, WI) was compared to ^{99m}Tc-sestamibi in 30 patients with suspected breast cancer and showed comparable diagnostic performance for both radiopharmaceuticals⁹⁶ AUC from ROC analysis was 0.83 for ^{99m}Tc-sestamibi and 0.87 for ^{99m}Tc maraciclalide (p = 0.64). Yet another technetium-based gamma imaging agent being studied is ^{99m}Tc -tetrofosmin MBI - a cardiac imaging agent that has a similar method of localization as sestamibi but with improved liver clearance. In one series⁹⁷, 321 patients with suspicious breast lesions were imaged with MBI after being injected with ^{99m}Tc - tetrofosmin with sensitivity of 96.4% (267/277) and specificity of 86.4% (38/44).

SUMMARY

Nuclear medicine modalities have been used for staging and additional diagnostic evaluation, and show particular promise in predicting treatment response and monitoring. Studies with PEM and BSGI/MBI have shown sensitivity comparable to breast MRI with better specificity. The development of standardized interpretation lexicon, breast biopsy and efforts to reduce radiation dose are critical to the further evolution of these new modalities. The ACR practice guidelines suggests that MBI could be used for breast screening in women identified as high risk and for those with dense breasts who cannot undergo MRI, but the overall radiation dose must be reduced to make this a clinically feasible alternative. While Naviscan's PEM scanner and GE's MBI system have developed biopsy-guidance, it is important for other nuclear breast imaging modalities to have similar tools. New breast imaging specific radiotracers are expected to help in molecular characterization of breast tumors to facilitate appropriate personalized treatment.

References

1. Khalkhali I, Iraniha S, Diggles LE, Cutrone JA, Mishkin FS. Scintimammography: the new role of technetium-99m Sestamibi imaging for the diagnosis of breast carcinoma. Q J Nucl Med. 1997;41(3):231–238. [PubMed: 9274131]
2. Avril N, Rose CA, Schelling M, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. J Clin Oncol. 2000;18(20):3495–3502. [PubMed: 11032590]

3. Hruska CB, O'Connor MK. Nuclear imaging of the breast: translating achievements in instrumentation into clinical use. *Med Phys*. 2013;40(5):050901. [PubMed: 23635248]
4. Taillefer R The role of 99mTc-sestamibi and other conventional radiopharmaceuticals in breast cancer diagnosis. *Semin Nucl Med*. 1999;29(1):16–40. [PubMed: 9990681]
5. Hruska CB, Boughey JC, Phillips SW, et al. Scientific Impact Recognition Award: Molecular breast imaging: a review of the Mayo Clinic experience. *Am J Surg*. 2008;196(4):470–476. [PubMed: 18723155]
6. Long Z, Hruska C, O'Connor M. Low dose breast imaging-comparative performance of MBI and BSGI systems. *Journal of Nuclear Medicine*. 2015;56(supplement 3):1863.
7. Swanson T, Tran T, Ellingson L, Solberg C, O'Connor M, Hruska C. High-quality molecular breast imaging: A guide for technologists from the Mayo Clinic experience. *Journal of Nuclear Medicine*. 2017;58(supplement 1):1157.
8. Freifelder R, Karp JS. Dedicated PET scanners for breast imaging. *Phys Med Biol*. 1997;42(12):2463–2480. [PubMed: 9434301]
9. Macdonald L, Edwards J, Lewellen T, Rogers J, Kinahan P. Clinical Imaging Characteristics of the Positron Emission Mammography PEM Flex Solo II. *IEEE Nucl Sci Symp Conf Rec* (1997). 2008;11(2008):4494–4501. [PubMed: 20502537]
10. Luo W AE, Matthews CG. Performance evaluation of a PEM scanner using the NEMA NU 4–2008 small animal PET standards. *IEEE Trans Nucl Sci*. 2010;57:9.
11. Kalinyak JE, Schilling K, Berg WA, et al. PET-guided breast biopsy. *Breast J*. 2011;17(2):143–151. [PubMed: 21276128]
12. Eo JS, Chun IK, Paeng JC, et al. Imaging sensitivity of dedicated positron emission mammography in relation to tumor size. *Breast*. 2012;21(1):66–71. [PubMed: 21871801]
13. Koolen BB, Aukema TS, Gonzalez Martinez AJ, et al. First clinical experience with a dedicated PET for hanging breast molecular imaging. *Q J Nucl Med Mol Imaging*. 2013;57(1):92–100. [PubMed: 23474637]
14. Collarino A FV, Pereira Arias-Bouda LM, Sánchez AM, de Geus-Oei LF, Masetti R, Valdés Olmos RA. Novel frontiers of dedicated molecular imaging in breast cancer diagnosis. *Transl Cancer Res*. 2017;2017.
15. Miyake KK, Nakamoto Y, Togashi K. Current Status of Dedicated Breast PET Imaging. *Current Radiology Reports*. 2016;4(4):16.
16. Conners AL, Maxwell RW, Tortorelli CL, et al. Gamma camera breast imaging lexicon. *AJR Am J Roentgenol*. 2012;199(6):W767–774. [PubMed: 23169751]
17. Narayanan D, Madsen KS, Kalinyak JE, Berg WA. Interpretation of positron emission mammography: feature analysis and rates of malignancy. *AJR Am J Roentgenol*. 2011;196(4):956–970. [PubMed: 21427350]
18. Morris EA CC, Lee CH, et al. ACR BI-RADS® Magnetic Resonance Imaging In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. In: Radiology ACo, ed. Reston, VA2013.
19. Conners AL, Hruska CB, Tortorelli CL, et al. Lexicon for standardized interpretation of gamma camera molecular breast imaging: observer agreement and diagnostic accuracy. *Eur J Nucl Med Mol Imaging*. 2012;39(6):971–982. [PubMed: 22289959]
20. Narayanan D, Madsen KS, Kalinyak JE, Berg WA. Interpretation of positron emission mammography and MRI by experienced breast imaging radiologists: performance and observer reproducibility. *AJR Am J Roentgenol*. 2011;196(4):971–981. [PubMed: 21427351]
21. Sickles E, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS® Mammography In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. In: Radiology ACo, ed. Reston, VA2013.
22. Wang CL, MacDonald LR, Rogers JV, Aravkin A, Haseley DR, Beatty JD. Positron emission mammography: correlation of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status and 18F-FDG. *AJR Am J Roentgenol*. 2011;197(2):W247–255. [PubMed: 21785049]
23. Nakamoto R, Nakamoto Y, Ishimori T, et al. Diagnostic performance of a novel dedicated breast PET scanner with C-shaped ring detectors. *Nuclear Medicine Communications*. 2017;38(5):388–395. [PubMed: 28306620]

24. Nishimatsu K, Nakamoto Y, Miyake KK, et al. Higher breast cancer conspicuity on dbPET compared to WB-PET/CT. *European Journal of Radiology*. 2017;90(Supplement C):138–145. [PubMed: 28583624]
25. Kalinyak JE, Berg WA, Schilling K, Madsen KS, Narayanan D, Tartar M. Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT. *Eur J Nucl Med Mol Imaging*. 2014;41(2):260–275. [PubMed: 24085500]
26. Yamamoto Y, Tasaki Y, Kuwada Y, et al. Positron emission mammography (PEM): reviewing standardized semiquantitative method. *Ann Nucl Med*. 2013;27(9):795–801. [PubMed: 23818008]
27. Muller FH, Farahati J, Muller AG, Gillman E, Hentschel M. Positron emission mammography in the diagnosis of breast cancer. Is maximum PEM uptake value a valuable threshold for malignant breast cancer detection? *Nuklearmedizin*. 2016;55(1):15–20. [PubMed: 26627876]
28. Hendrick RE. Radiation doses and cancer risks from breast imaging studies. *Radiology*. 2010;257(1):246–253. [PubMed: 20736332]
29. O'Connor MK, Li H, Rhodes DJ, Hruska CB, Clancy CB, Vetter RJ. Comparison of radiation exposure and associated radiation-induced cancer risks from mammography and molecular imaging of the breast. *Med Phys*. 2010;37(12):6187–6198. [PubMed: 21302775]
30. Hendrick RE, Tredennick T. Benefit to Radiation Risk of Breast-specific Gamma Imaging Compared with Mammography in Screening Asymptomatic Women with Dense Breasts. *Radiology*. 2016;281(2):583–588. [PubMed: 27257949]
31. Hruska CB, Weinmann AL, O'Connor MK. Proof of concept for low-dose molecular breast imaging with a dual-head CZT gamma camera. Part I. Evaluation in phantoms. *Med Phys*. 2012;39(6):3466–3475. [PubMed: 22755726]
32. Long Z, Connors AL, Hunt KN, Hruska CB, O'Connor MK. Performance characteristics of dedicated molecular breast imaging systems at low doses. *Med Phys*. 2016;43(6):3062–3070. [PubMed: 27277053]
33. O'Connor MK, Hruska CB, Tran TD, et al. Factors influencing the uptake of ^{99m}Tc-sestamibi in breast tissue on molecular breast imaging. *J Nucl Med Technol*. 2015;43(1):13–20. [PubMed: 25613340]
34. Kuhn KJ, Rapelyea JA, Torrente J, Teal CB, Brem RF. Comparative Diagnostic Utility of Low-Dose Breast-Specific Gamma Imaging to Current Clinical Standard. *Breast J*. 2016;22(2):180–188. [PubMed: 26662297]
35. MacDonald LR, Hippe DS, Bender LC, et al. Positron Emission Mammography Image Interpretation for Reduced Image Count Levels. *J Nucl Med*. 2016;57(3):348–354. [PubMed: 26635337]
36. Radiology ACo. ACR Practice parameter for the performance of molecular breast imaging (MBI) using a dedicated gamma camera. <https://www.acr.org/~media/ACR/Documents/PGTS/guidelines/MBI.pdf> Accessed October 26, 2017.
37. Sun Y, Wei W, Yang HW, Liu JL. Clinical usefulness of breast-specific gamma imaging as an adjunct modality to mammography for diagnosis of breast cancer: a systemic review and metaanalysis. *Eur J Nucl Med Mol Imaging*. 2013;40(3):450–463. [PubMed: 23151912]
38. Hruska CB, Phillips SW, Whaley DH, Rhodes DJ, O'Connor MK. Molecular breast imaging: use of a dual-head dedicated gamma camera to detect small breast tumors. *AJR Am J Roentgenol*. 2008;191(6):1805–1815. [PubMed: 19020253]
39. Connors AL, Jones KN, Hruska CB, Geske JR, Boughey JC, Rhodes DJ. Direct-Conversion Molecular Breast Imaging of Invasive Breast Cancer: Imaging Features, Extent of Invasive Disease, and Comparison Between Invasive Ductal and Lobular Histology. *AJR Am J Roentgenol*. 2015;205(3):W374–381. [PubMed: 26295674]
40. Caldarella C, Treglia G, Giordano A. Diagnostic performance of dedicated positron emission mammography using fluorine-18-fluorodeoxyglucose in women with suspicious breast lesions: a meta-analysis. *Clin Breast Cancer*. 2014;14(4):241–248. [PubMed: 24472718]
41. Killelea BK, Gillego A, Kirstein LJ, et al. George Peters Award: How does breast-specific gamma imaging affect the management of patients with newly diagnosed breast cancer? *Am J Surg*. 2009;198(4):470–474. [PubMed: 19800450]

42. Kim BS. Usefulness of breast-specific gamma imaging as an adjunct modality in breast cancer patients with dense breast: a comparative study with MRI. *Ann Nucl Med*. 2012;26(2):131–137. [PubMed: 22006539]
43. Zhang A, Li P, Liu Q, Song S Breast-specific gamma camera imaging with 99mTc-MIBI has better diagnostic performance than magnetic resonance imaging in breast cancer patients: A metaanalysis. *Hell J Nucl Med*. 2017;20(1):26–35. [PubMed: 28315905]
44. Edwards C, Williams S, McSwain AP, et al. Breast-specific gamma imaging influences surgical management in patients with breast cancer. *Breast J*. 2013;19(5):512–519. [PubMed: 23848225]
45. Berg WA, Madsen KS, Schilling K, et al. Breast cancer: comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast. *Radiology*. 2011;258(1):59–72. [PubMed: 21076089]
46. Schilling K, Narayanan D, Kalinyak JE, et al. Positron emission mammography in breast cancer presurgical planning: comparisons with magnetic resonance imaging. *Eur J Nucl Med Mol Imaging*. 2011;38(1):23–36. [PubMed: 20871992]
47. Keto JL, Kirstein L, Sanchez DP, et al. MRI versus breast-specific gamma imaging (BSGI) in newly diagnosed ductal cell carcinoma-in-situ: a prospective head-to-head trial. *Ann Surg Oncol*. 2012;19(1):249–252. [PubMed: 21739318]
48. Kim JS, Lee SM, Cha ES. The diagnostic sensitivity of dynamic contrast-enhanced magnetic resonance imaging and breast-specific gamma imaging in women with calcified and non-calcified DCIS. *Acta Radiol*. 2014;55(6):668–675. [PubMed: 24043881]
49. Brem RF, Fishman M, Rapelyea JA. Detection of ductal carcinoma in situ with mammography, breast specific gamma imaging, and magnetic resonance imaging: a comparative study. *Acad Radiol*. 2007;14(8):945–950. [PubMed: 17659240]
50. Berg WA, Madsen KS, Schilling K, et al. Comparative effectiveness of positron emission mammography and MRI in the contralateral breast of women with newly diagnosed breast cancer. *AJR Am J Roentgenol*. 2012;198(1):219–232. [PubMed: 22194501]
51. Weigert JM, Bertrand ML, Lankowsky L, Stern LH, Kieper DA. Results of a multicenter patient registry to determine the clinical impact of breast-specific gamma imaging, a molecular breast imaging technique. *AJR Am J Roentgenol*. 2012;198(1):W69–75. [PubMed: 22194518]
52. Guo C, Zhang C, Liu J, Tong L, Huang G. Is Tc-99m sestamibi scintimammography useful in the prediction of neoadjuvant chemotherapy responses in breast cancer? A systematic review and meta-analysis. *Nucl Med Commun*. 2016;37(7):675–688. [PubMed: 26974314]
53. Mitchell D, Hruska CB, Boughey JC, et al. 99mTc-sestamibi using a direct conversion molecular breast imaging system to assess tumor response to neoadjuvant chemotherapy in women with locally advanced breast cancer. *Clin Nucl Med*. 2013;38(12):949–956. [PubMed: 24152645]
54. Wahner-Roedler DL, Boughey JC, Hruska CB, et al. The use of molecular breast imaging to assess response in women undergoing neoadjuvant therapy for breast cancer: a pilot study. *Clin Nucl Med*. 2012;37(4):344–350. [PubMed: 22391702]
55. Menes TS, Golan O, Vainer G, et al. Assessment of Residual Disease With Molecular Breast Imaging in Patients Undergoing Neoadjuvant Therapy: Association With Molecular Subtypes. *Clin Breast Cancer*. 2016;16(5):389–395. [PubMed: 27282845]
56. Lee HS, Ko BS, Ahn SH, et al. Diagnostic performance of breast-specific gamma imaging in the assessment of residual tumor after neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer Res Treat*. 2014;145(1):91–100. [PubMed: 24671359]
57. Noritake M, Narui K, Kaneta T, et al. Evaluation of the Response to Breast Cancer Neoadjuvant Chemotherapy Using 18F-FDG Positron Emission Mammography Compared With Whole-Body 18F-FDG PET: A Prospective Observational Study. *Clin Nucl Med*. 2017;42(3):169–175. [PubMed: 28072617]
58. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology*. 2004;230(1):29–41. [PubMed: 14617762]
59. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159–1169. [PubMed: 16775176]
60. Weblink. <http://densebreast-info.org/legislation.aspx>. [Webiste].

61. Hruska CB, Scott CG, Conners AL, et al. Background parenchymal uptake on molecular breast imaging as a breast cancer risk factor: a case-control study. *Breast Cancer Res.* 2016;18(1):42. [PubMed: 27113363]
62. King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA. Background parenchymal enhancement at breast MR imaging and breast cancer risk. *Radiology.* 2011;260(1):50–60. [PubMed: 21493794]
63. Hruska CB, Rhodes DJ, Conners AL, et al. Background parenchymal uptake during molecular breast imaging and associated clinical factors. *AIR Am J Roentgenol.* 2015;204(3):W363–370.
64. Rechtman LR, Lenihan MJ, Lieberman JH, et al. Breast-specific gamma imaging for the detection of breast cancer in dense versus nondense breasts. *AJR Am J Roentgenol.* 2014;202(2):293–298. [PubMed: 24450668]
65. Koo HR, Moon WK, Chun IK, et al. Background (1)(8)F-FDG uptake in positron emission mammography (PEM): correlation with mammographic density and background parenchymal enhancement in breast MRI. *Eur J Radiol.* 2013;82(10):1738–1742. [PubMed: 23806533]
66. Iima M, Nakamoto Y, Kanao S, et al. Clinical performance of 2 dedicated PET scanners for breast imaging: initial evaluation. *J Nucl Med.* 2012;53(10):1534–1542. [PubMed: 22933819]
67. Teixeira SC, Rebolledo JF, Koolen BB, et al. Evaluation of a Hanging-Breast PET System for Primary Tumor Visualization in Patients With Stage I-III Breast Cancer: Comparison With Standard PET/CT. *AJR Am J Roentgenol.* 2016;206(6):1307–1314. [PubMed: 27058014]
68. Berg WA. Nuclear Breast Imaging: Clinical Results and Future Directions. *J Nucl Med.* 2016;57 Suppl 1:46S–52S. [PubMed: 26834102]
69. Siu AL, Force USPST. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2016;164(4):279–296. [PubMed: 26757170]
70. Rhodes DJ, Hruska CB, Conners AL, et al. Journal club: molecular breast imaging at reduced radiation dose for supplemental screening in mammographically dense breasts. *AJR Am J Roentgenol.* 2015;204(2):241–251. [PubMed: 25615744]
71. Shermis RB, Wilson KD, Doyle MT, et al. Supplemental Breast Cancer Screening With Molecular Breast Imaging for Women With Dense Breast Tissue. *AJR Am J Roentgenol.* 2016;207(2):450–457. [PubMed: 27186635]
72. Yamamoto Y, Tasaki Y, Kuwada Y, Ozawa Y, Inoue T. A preliminary report of breast cancer screening by positron emission mammography. *Ann Nucl Med.* 2016;30(2):130–137. [PubMed: 26586370]
73. Abreu MC, Almeida P, Balau F, et al. Clear-PEM: a dedicated PET camera for improved breast cancer detection. *Radiat Prot Dosimetry.* 2005;116(1-4 Pt 2):208–210. [PubMed: 16604628]
74. Raylman RR, Abraham J, Hazard H, et al. Initial clinical test of a breast-PET scanner. *J Med Imaging Radiat Oncol.* 2011;55(1):58–64. [PubMed: 21382190]
75. Peng H, Levin CS. Design study of a high-resolution breast-dedicated PET system built from cadmium zinc telluride detectors. *Phys Med Biol.* 2010;55(9):2761–2788. [PubMed: 20400807]
76. Ravindranath B, Junnarkar S, Purschke M, et al. Results from a simultaneous PET-MRI breast scanner. *Journal of Nuclear Medicine.* 2011;52(supplement 1):432.
77. Cucciati G AE, Bugalho R, Cao L Development of ClearPEM-Sonic, a multimodal mammography system for PET and Ultrasound. *Journal of Instrumentation.* 2014;9(CD3008).
78. Bowen SL, Wu Y, Chaudhari AJ, et al. Initial characterization of a dedicated breast PET/CT scanner during human imaging. *J Nucl Med.* 2009;50(9):1401–1408. [PubMed: 19690029]
79. MacDonald LR, Hunter WC, Kinahan PE, Miyaoka RS. Effects of Detector Thickness on Geometric Sensitivity and Event Positioning Errors in the Rectangular PET/X Scanner. *IEEE Trans Nucl Sci.* 2013;60(5):3242–3252. [PubMed: 26160982]
80. Tornai MPSJP, Mann SD, McKinley RL Development of Fully-3D CT in a Hybrid SPECT-CT Breast Imaging System In: *Imagin B, ed. Lecture Notes in Computer Science* 2016.
81. Mettivier G, Bliznakova K, Sechopoulos I, et al. Evaluation of the BreastSimulator software platform for breast tomography. *Phys Med Biol.* 2017;62(16):6446–6466. [PubMed: 28398906]
82. Williams MB, Judy PG, Gunn S, Majewski S. Dual-modality breast tomosynthesis. *Radiology.* 2010;255(1):191–198. [PubMed: 20308457]

83. Gong Z, Williams MB. Comparison of breast specific gamma imaging and molecular breast tomosynthesis in breast cancer detection: Evaluation in phantoms. *Med Phys*. 2015;42(7):4250–4259. [PubMed: 26133623]
84. O'Connor MK, Morrow MM, Tran T, Hruska CB, Connors AL, Hunt KN. Technical Note: Development of a combined molecular breast imaging/ultrasound system for diagnostic evaluation of MBI-detected lesions. *Med Phys*. 2017;44(2):451–459. [PubMed: 28133745]
85. Meng Q, Li Z. Molecular Imaging Probes for Diagnosis and Therapy Evaluation of Breast Cancer. *International Journal of Biomedical Imaging*. 2013;2013:14.
86. Bollineni VR, Kramer GM, Jansma EP, Liu Y, Oyen WJ. A systematic review on [(18)F]FLT-PET uptake as a measure of treatment response in cancer patients. *Eur J Cancer*. 2016;55:81–97. [PubMed: 26820682]
87. McKinley ET, Ayers GD, Smith RA, et al. Limits of [18F]-FLT PET as a biomarker of proliferation in oncology. *PLoS One*. 2013;8(3):e58938. [PubMed: 23554961]
88. Currin E, Linden HM, Mankoff DA. Predicting Breast Cancer Endocrine Responsiveness Using Molecular Imaging. *Curr Breast Cancer Rep*. 2011;3(4):205–211. [PubMed: 23105956]
89. Capala J, Bouchelouche K. Molecular imaging of HER2-positive breast cancer: a step toward an individualized 'image and treat' strategy. *Curr Opin Oncol*. 2010;22(6):559–566. [PubMed: 20842031]
90. Dijkers EC, Oude Munnink TH, Kosterink JG, et al. Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther*. 2010;87(5):586–592. [PubMed: 20357763]
91. Ulaner GA, Hyman DM, Ross DS, et al. Detection of HER2-Positive Metastases in Patients with HER2-Negative Primary Breast Cancer Using 89Zr-Trastuzumab PET/CT. *J Nucl Med*. 2016;57(10):1523–1528. [PubMed: 27151988]
92. Hoefnagel LD, van de Vijver MJ, van Slooten HJ, et al. Receptor conversion in distant breast cancer metastases. *Breast Cancer Res*. 2010;12(5):R75. [PubMed: 20863372]
93. Valk PE, Mathis CA, Prados MD, Gilbert JC, Budinger TF. Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole. *J Nucl Med*. 1992;33(12):2133–2137. [PubMed: 1334136]
94. Ulaner GA, Goldman DA, Gonen M, et al. Initial Results of a Prospective Clinical Trial of 18F-Fluciclovine PET/CT in Newly Diagnosed Invasive Ductal and Invasive Lobular Breast Cancers. *J Nucl Med*. 2016;57(9):1350–1356. [PubMed: 26940766]
95. Dehdashti F, McGuire AH, Van Brocklin HF, et al. Assessment of 21-[18F]fluoro-16 alpha-ethyl-19-norprogesterone as a positron-emitting radiopharmaceutical for the detection of progesterin receptors in human breast carcinomas. *J Nucl Med*. 1991;32(8):1532–1537. [PubMed: 1869974]
96. O'Connor MK, Morrow MMB, Hunt KN, et al. Comparison of Tc-99m maraciclalide and Tc-99m sestamibi molecular breast imaging in patients with suspected breast cancer. *EJNMMI Res*. 2017;7(1):5. [PubMed: 28091980]
97. Spanu A, Chessa F, Sanna D, Marongiu P, Nuvoli S, Madeddu G. The role of 99mTc-tetrofosmin molecular breast imaging (MBI) in patients with breast lesions. *Journal of Nuclear Medicine*. 2009;50(supplement 2):1696.
98. Hsu DF, Freese DL, Levin CS. Breast-Dedicated Radionuclide Imaging Systems. *J Nucl Med*. 2016;57 Suppl 1:40S–45S. [PubMed: 26834101]
99. Hruska CB. Molecular Breast Imaging for Screening in Dense Breasts: State of the Art and Future Directions. *AJR Am J Roentgenol*. 2017;208(2):275–283. [PubMed: 27762607]

Key Points

1. Dedicated breast imaging using gamma and PET scanners provide similar high sensitivity and specificity and can be used as an adjunct to mammography in women with breast cancer.
2. Both dedicated breast PET and dedicated gamma camera images must be interpreted together with mammography and other prior breast imaging, biopsy history, and patient risk factors.
3. Dose reduction strategies are critical to allowing greater use of nuclear medicine modalities, especially in the screening setting.
4. Newer technologies and tracers are under development to improve the performance of nuclear breast imaging.

Figure 1:
MAMMI-PET Image of a 60 year-old woman with a 7-mm invasive ductal carcinoma (arrow). (Courtesy of Dr. R.A. Valdés Olmos, Amsterdam/Leiden, The Netherlands)

Figure 2:

74-year-old woman with mass in her right breast detected by screening mammography and ultrasound. The tumor is well visualized by both contrast-enhanced-MRI (A, arrow) and Elmammo PET scanner. Patient was imaged for 5 min/breast and images are obtained in both standard (B) and enhanced resolution reconstruction mode (C). Pathology showed 7-mm mucinous carcinoma with negative sentinel nodes. (Courtesy of Kanae Miyake and Yuji Nakamoto)

Figure 3:

BSGI showed two areas of focal uptake in a 82-year-old woman with dense breasts. The first (B, arrow) is consistent with the irregular mass noted on the mammogram (A, arrow). The second (B, arrowhead) is within an area of stable dense breast parenchyma. Pathology showed infiltrating ductal carcinoma at both sites. (*Courtesy of, Dilon, Courtesy of West Valley Imaging*)

Figure 4:

81-year-old high-risk (based on lifetime risk assessment models) female with dense breasts had a negative mammogram but underwent additional screening with MBI (8mCi injected dose). MBI showed intense uptake in an irregular mass (arrow). Biopsy showed invasive ductal carcinoma. (*Courtesy of Robin Shermis, MD ProMedica Toledo Hospital, Toledo, OH*)

Figure 5:
55F with extensive high nuclear grade DCIS in right breast. 12 slice PEM image showed increased FDG uptake in the area of DCIS segmental distribution (circle) (*Courtesy Dr. Wendie Berg*)

Figure 6:

66 y/o woman with bilateral cancer seen on PEM. Right breast has previously known high grade DCIS. Pathology after bilateral mastectomy showed 3.1 cm high grade DCIS (A, arrows), ER/PR negative and node negative for the right breast and 2.2 cm IDC-ILC with DCIS and LCIS involving three quadrants in the left breast (B, circle). ER/PR positive, HER2 negative with 1/14 nodes positive.

Figure 7:

51-year-old female with known left breast invasive ductal carcinoma was imaged with both MBI and MRI. MIP of MRI showed enhancement at site of benign right breast stereotactic biopsy for calcifications. On the left side, an irregular heterogeneously enhancing left breast mass in the 10 o'clock (A, arrow) position with predominantly washout kinetics measuring 3 cm in greatest dimension was observed, corresponding to the known cancer. MBI was performed on the GE dual head MBI system with the injection of 7.3mCi of ^{99m}Tc -sestamibi. MLO views showed mild patchy background parenchymal uptake with no

suspicious areas of radiotracer uptake on the right. The known cancer was visualized on the left breast as an irregular mass measuring 2.7cm (B, arrow). As the mass is close to the chest wall, the full posterior aspect of the mass is not included in the images.

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Gamma Camera Breast Imaging

Table 1.

Dilon Diagnostics, Newport News, VA				Gamma Medica Inc., Salem, NH	(GE Healthcare, Milwaukee, WI)

SYSTEM	Dilon Diagnostics 6800	Gamma Medica LumaGEM 3200S	GE Healthcare Discovery NM750b		
Detector	NaI	Cadmium Zinc Telluride (CZT)	Cadmium Zinc Telluride (CZT)		
Detector Geometry	Single Panel Detector	Dual Panel Detectors	Dual Panel Detectors		
FOV (cm)	20 × 20	20 × 16	24 × 16		
Biopsy	Available	In Development	Available		
Spatial Resolution	4-4.2 mm	4.8-5.6 mm	4.4-4.6 mm		
Injected dose	10-12mCi	4-8mCi	4-8mCi		
Pixel Size	3 mm	1.6 mm	2.5 mm		

Adapted from Hsu⁹⁸ et al

Table 2.

Dedicated PET Breast Imaging

CMR Naviscan, Carlsbad, CA					Oncovision, Valencia, Spain	Shimadzu Corporation, Kyoto, Japan	Shimadzu Corporation Kyoto, Japan

System	PEM Flex Solo II	MAMMI PET	EL mammo-O-Scanner	C-PEM			
Detector Configuration	Planar Detector	Ring Detector	Ring Detector	C-shaped detector			
Detector	LYSO	LYSO	LGSO	LGSO			
Patient Position	Upright, like mammography	Prone	Prone	Semi prone			
FOV	24 × 16.4cm	Transaxial FOV is 170mm	Transaxial FOV is 183mm	Transaxial FOV is 216mm			
Biopsy	Yes	Under Development	No	No			
Spatial Resolution *	1.8-2.4mm (Z axis = 6-8.5mm)	1.8×1.9×1.6 (x,y,z)	<2mm	<2mm			
Compression	Gentle compression	No	No	No			
Images	Tomographic 3D	3D	3D	Tomographic 3D			

* Resolution changes based on reconstruction algorithms.
.Adapted from Hsu⁹⁸ et al and Kanae et al¹⁵

BSGI/MBI Screening Studies

Table 3:

	Study Population	N	Device	DOSE	Number of cancers detected	Cancer Detection Rate ^a	Recall Rate ^b	PPV ₁ ^c	PPV ₃ ^d	Scan Time
Rhodes et al (2010)	Women with heterogeneously or extremely dense breasts + 1 additional risk factor	936	MBI	740 MBq (20 mCi)	11	7.5/1000	8% (71/936)	2% (9/73)	8% (10/36)	10 minutes per view
Hruska et al (2012)	women undergoing a nuclear cardiology stress	306	MBI	666 to 2035 MBq (18 to 55 mCi)	4	13.1/1000	7% (22/306)	18% (4/22)	44% (4/9)	3-5 minutes per view
Rhodes et al (2015)	asymptomatic women with mammographically dense breasts	1585	MBI	300 MBq (8mCi)	21	8.8/1000	6.6% (119/1585)	14% (17/119)	33% (17/51)	10 minutes per view (total 40 minutes)
Brem et al (2016)	Women with no mammographic symptoms	653	BSGI	High Dose: 781 MBq (21.1 mCi)	12	18.4/1000	25.5% (161/653)	7.4% (12/161)	15.4% (12/78)	6-10 min per view, total 40 minutes
Brem et al (2016)^e	Women with no mammographic symptoms	196	BSGI	Low dose: 296 MBq (8.0 mCi)	2	10.2/1000	26% (51/196)	3.9% (2/51)	10.5 (2/9)	6-10 min per view, total 40 minutes
Shermis et al (2017)	Women with negative mammography study.	1696	MBI	300 MBq (8 mCi)	13	7.7/1000	8.4 (143/1696)	9.1 (13/143)	19 (12/62)	7-10 minutes per view

^aDetection rate: cancer detection rate of MBI or BSGI in number of women diagnosed with cancer per 1000 women screened

^bRecall rate: number of positive exams per total number of patients

^cPPV1 = number of malignancies per all abnormal BSGI examinations

^dPPV3 = number of malignancies per all biopsies performed

^eBoth low dose & high dose BSGI data are reported in the same paper: Cancer detection rate was not statistically different between the two groups $\chi^2 = 0.62$, (95%CI: 0.12 to 2.48, p=0.44)

Adapted from Hruska et al⁹⁹.