Advances and Future Directions of Molecular Breast Imaging

Running title: Molecular Breast Imaging

Matthew F. Covington, MD¹, Ephraim E. Parent, MD, PhD², Elizabeth H. Dibble, MD³, Gaiane M. Rauch, MD, PhD⁴, Amy M. Fowler, MD, PhD⁵.

¹Center for Quantitative Cancer Imaging, Huntsman Cancer Institute and University of Utah Department of Radiology and Imaging Sciences, Salt Lake City, UT. matthew.covington@hsc.utah.edu.

²Mayo Clinic Department of Radiology, Jacksonville, FL. Parent.Ephraim@mayo.edu.

³Warren Alpert Medical School of Brown University/Rhode Island Hospital Department of Diagnostic Imaging, Providence, RI. edibble@lifespan.org.

⁴MD Anderson Cancer Center, Departments of Abdominal and Breast Imaging, Houston, TX. gmrauch@mdanderson.org.

⁵University of Wisconsin School of Medicine and Public Health, Departments of Radiology and Medical Physics and the University of Wisconsin Carbone Cancer Center, Madison WI. afowler@uwhealth.org.

Corresponding Author:
Matthew F. Covington, MD
Huntsman Cancer Institute
2000 Circle of Hope
Salt Lake City, UT 84112
801-213-8438
matthew.covington@hsc.utah.edu

Financial support: None.

Word count: 3993 words
Abstract

Molecular breast imaging (MBI) using $^{99m}$Tc-sestamibi has advanced rapidly over the past decade. Technical advances allow lower dose, higher resolution imaging, and biopsy capability. MBI can be used for supplemental breast cancer screening with mammography for women with dense breasts, neoadjuvant therapy response assessment, extent of disease evaluation, and breast cancer risk prediction. This article highlights the current state-of-the-art and future directions of MBI.

Keywords: molecular breast imaging; MBI; breast specific gamma imaging; nuclear breast imaging; sestamibi
**Introduction**

“Molecular breast imaging” may broadly refer to all nuclear medicine and advanced MRI techniques for breast imaging. However, the term molecular breast imaging (MBI) usually refers to dedicated breast imaging systems using $^{99m}$Tc-sestamibi with dual-head solid-state cadmium-zinc-telluride (CZT) detectors. Compared to breast specific gamma imaging (BSGI) that uses single-head scintillation detectors, MBI uses dual-head CZT detectors and advanced collimator designs to improve spatial resolution, shorten imaging times, and facilitate lower-dose imaging. This article summarizes the current state-of-the-art and future uses of MBI.

**Current State-of-the-Art**

There are two commercially available MBI systems: LumaGem (CMR Naviscan, Carlsbad, CA) and Eve Clear Scan (SmartBreast Corp, Pittsburgh, PA). Both use CZT semiconductor detectors that directly convert gamma photons into electrons. Dual-head CZT detectors improve small lesion detection compared to single-head BSGI systems (1).

The primary radiopharmaceutical used for MBI is $^{99m}$Tc-sestamibi. $^{99m}$Tc-sestamibi uptake in breast tumors results from increased mitochondrial density, increased blood flow, and negative membrane potentials of tumor cells (2). $^{99m}$Tc-sestamibi has been used in hundreds of thousands of patients with a favorable safety profile and few contraindications, namely pregnancy and prior allergic reaction to $^{99m}$Tc-sestamibi (2). Patients who are breast feeding may continue, unless otherwise specified by institutional guidelines. $^{99m}$Tc-sestamibi clears from the bloodstream rapidly within 2–3 min, thus, image acquisition can begin within 5 minutes after injection (3). Fasting, warming with a blanket and keeping the patient still may reduce background breast uptake (4).

Standard craniocaudal and mediolateral oblique projections of each breast are acquired using gentle compression, with 7-10 minutes per view (4). Breast positioning is comparable to mammography
aiding correlation of findings between mammography and MBI. MBI detector size is 20×16 cm or 24×16 cm, compared with 24×29 cm for mammography. Tiled acquisitions may be required with MBI if breast size exceeds the field-of-view. Lesions near the chest wall and axillary lymph nodes may be difficult to visualize with MBI, due to increased dead space at the edge of the field-of-view (8 mm) compared to mammography (4 mm) (4). Furthermore, MBI detectors are opaque, making maximal posterior positioning difficult to confirm (4). The patient can breathe normally during imaging with instructions to otherwise remain still to reduce motion blur. Performing screening MBI during the follicular phase may minimize background parenchymal uptake (BPU) and menstrual cycle phase may be included in the report (5). However, no studies have examined menstrual cycle timing and MBI diagnostic performance and recent data from screening breast MRI outcomes indicate that scheduling based on menstrual cycle phase is not necessary (6). MBI should not be scheduled within 4 half-lives of other 99mTc-based studies, PET/CT, and targeted radionuclide therapies due to photon energy window overlap.

**Radiation Exposure**

The radiation absorbed dose during MBI is proportional to the administered activity of 99mTc-sestamibi. Optimizations in detector design, patient preparation, and tracer delivery have reduced the administered activity from 740–1100 MBq (20–30 mCi) to the current off-label standard of 240-300 MBq (6.5–8 mCi) (7,8). Weight-based adjustments for injected activity are not necessary for MBI (9). The average radiation absorbed dose to the breast from 300 MBq (8 mCi) of 99mTc-sestamibi is estimated to be 1.1 mGy compared to 3.0-4.5 mGy with mammography and tomosynthesis.

Since 99mTc-sestamibi is systemically distributed, tissues outside of the breast receive the largest radiation dose. The estimated effective (whole-body) dose for 300 MBq (8 mCi) 99mTc-sestamibi is 2.1-2.6 mSv, which is at, or lower than, annual natural background levels (~3 mSv) (10). For reference, the effective dose of chest CT can approach 6 mSv (11). Tissues with highest exposures include colon (7.1
mGy), urinary bladder (3.2 mGy), and gallbladder (11.5 mGy) (12). Various organizations assessing radiation risk and radiation protection (Health Physics Society, American Association of Physicists in Medicine, International Organization for Medical Physics, and United Nations Scientific Committee on the Effects of Atomic Radiation) state that risks from radiation doses less than 100 mSv are not significantly different from zero (10). Thus, current MBI radiation exposure is deemed to pose negligible risk to the patient with minimal theoretical risk of inducing cancer in any of these organs (10).

The administered activity of $^{99m}$Tc-sestamibi for MBI continues to decrease with technologic advancement. Tao et al. showed that new image processing algorithms maintain lesion conspicuity with a simulated half-dose, 150 MBq (4 mCi) injection (13). Continued advances in CZT module design will improve sensitivity and should allow further dose reduction.

**Indications/Clinical Applications**

**Supplemental Screening**

Approximately 43% of the 40 million individuals in the U.S. screening population have dense breast tissue (14-16). Screening mammography has relatively reduced sensitivity for breast cancer detection in individuals with dense breasts (15). Furthermore, breast cancer risk is higher for individuals with dense breasts (15,17). Supplemental screening may therefore benefit 16-20 million U.S. individuals with dense breasts who are at risk for a false-negative screening mammogram. Breast cancer detection with supplemental screening methods such as whole-breast ultrasound, breast MRI, contrast-enhanced mammography, and MBI is not limited by dense breast tissue (15).

The ideal supplemental screening modality would have a high breast cancer detection rate and a high negative predictive value while maintaining safety, affordability, ease of access, quick imaging acquisition and interpretation times, and acceptable rates of false-positive findings. While MBI addresses some of these issues, it also has some limitations as a screening test. MBI excels with high lesion-to-background contrast in individuals with dense breasts or breast implants (18), with an
incremental cancer detection rate of 8.8 per 1000 exams upon first MBI screening \((8)\). For comparison, the baseline detection rate of screening mammography is approximately 3.2 cancers per 1000 individuals screened \((19)\). Incremental cancer detection rate per 1000 exams in individuals with dense breasts is approximately 1.7 for tomosynthesis, 2.7 for ultrasound, 15 for full-protocol MRI, and 10 for abbreviated MRI \((15)\). MBI also provides favorable false-positive rates \((20)\), recall rates \((8)\), rapid interpretation times \((18)\), low cost \((15)\), few contraindications \((21)\) and a high negative predictive value \((22)\). Disadvantages of MBI for supplemental screening include an imaging exam time of 28 to 40 minutes \((15)\), need for nuclear medicine licensing and coordination between nuclear medicine and breast imaging sections, lack of widespread availability, variable insurance coverage, and a higher whole-body radiation exposure compared to other supplemental screening options \((10,13,15)\).

The estimated benefit of MBI in terms of deaths averted is 5-9 times greater than the estimated risk of lives lost when used for supplemental screening \((23)\) and estimated benefit-to-radiation risks now approach that of mammography \((23)\). However, concerns regarding MBI radiation risks, though disputed, have delayed widespread use for supplemental screening \((10,21,23)\). The American College of Radiology Appropriateness Criteria for Supplemental Breast Cancer Screening Based on Breast Density currently do not recommend MBI \((24)\).

The prospective multicenter Density MATTERS trial compares MBI with tomosynthesis for supplemental screening in women with dense breasts. This is the first trial to examine incidence screening MBI in which performance is evaluated not only for the initial scan but also at a subsequent screening round. Preliminary results show an incremental cancer detection rate for MBI beyond tomosynthesis of 9.3 per 1000 screened, with six invasive cancers seen only on MBI (median size 1 cm, 5 of 6 lymph node negative) among 537 of the planned 3000 participants \((25)\). By comparison, results of the ECOG/ACRIN EA1141 trial of abbreviated breast MRI for screening women with dense breasts reported an incremental invasive cancer detection rate of abbreviated breast MRI after tomosynthesis of 7 per 1000
screened (26). Thus, MBI may detect invasive breast cancers occult on tomosynthesis in women with dense breasts at a similar rate as abbreviated breast MRI. Studies of women invited to undergo screening breast MRI showed that 41-42% declined participation for reasons including lower socioeconomic status, self-reported contraindications to MRI (27), claustrophobia, and financial concerns (28). MBI may be considered as an alternative for such individuals.

Local Tumor Extent

For newly diagnosed breast cancer, accurate determination of disease extent is important for defining clinical stage and for preoperative therapy and surgical planning. MBI can be used for local tumor staging to detect multifocal, multicentric, or contralateral malignancy, especially for patients who cannot obtain preoperative breast MRI (Figure 1). A study comparing extent of disease using MBI, contrast-enhanced mammography, and MRI found that MBI and contrast-enhanced mammography were effective for local staging with similar visualization of the index cancers and higher specificity for additional cancers compared with MRI (20). However, unlike MRI, MBI is limited for evaluation of axillary and chest wall disease. In a study of 90 patients with breast cancer prior to starting neoadjuvant chemotherapy, MBI detected 16/20 tumors smaller than 1 cm compared to 17/20 tumors for MRI (29).

An additional limitation of MBI for surgical planning regards invasive lobular carcinomas, which have less intense sestamibi uptake compared to invasive ductal carcinomas, resulting in lower detection (30).

Neoadjuvant Therapy Response

Neoadjuvant chemotherapy (NAT) is often standard-of-care for locally advanced breast cancer. NAT can reduce tumor burden allowing less extensive surgery. MBI is relatively accurate for prediction of pathological response and evaluation of residual disease after NAT (Figure 2). A meta-analysis of 14 studies with 529 breast cancer patients found that MBI had a sensitivity of 70.3% (95%CI: 56.5-81.3%) and a specificity of 90.1% (95% CI: 77.5-96.0%) for residual disease (31). A retrospective report of 114 patients who underwent NAT found slightly lower sensitivity for MBI versus MRI (70% vs 83%) but higher
specificity (90% vs 60%) for residual disease, with similar overall performance (respective kappa values 0.47 vs 0.41 (p<0.001)) (32). A prospective study of 104 patients undergoing NAT found that MBI had lower sensitivity than MRI (58.9% vs 82.8%) but improved specificity (82.4% vs 69.4%) in evaluating residual disease (29). Accuracy of MBI for residual disease assessment depends on tumor molecular subtype, with highest accuracy for triple negative and human epidermal growth factor receptor 2 (HER2) -positive subtypes, and lowest for luminal subtypes (33). However, no imaging technique is currently able to definitively determine complete pathologic response to therapy without surgical confirmation, in part due to inherent resolution limitations.

Present and Future Developments:

MBI-Guided Biopsy

For suspicious MBI findings, biopsy is necessary to confirm malignancy. For MBI-detected masses, targeted ultrasound and ultrasound-guided biopsy is performed, paralleling MRI workflows. In a study of 1585 examinations performed before availability of MBI-biopsy, 115 MBI-positive findings were detected, resulting in 50 biopsy recommendations. Of these 50 lesions recommended for biopsy based on MBI, 38 (76%) were visible sonographically, but 12 (24%) required MBI biopsy (34). The billed expense of MRI-guided biopsy is estimated at $3500, while MBI-guided biopsy is roughly half this amount (35).

MBI-directed biopsy is currently available for one system (Eve Clear Scan). This unit is a self-contained accessory, mounted on the dual-head system that includes an angled pair of CZT detectors for obtaining stereotactic views and allows specimen imaging to confirm adequate sampling. A BSGI-guided biopsy system has also been described (36). MRI-guided biopsy can be used if an MRI correlate is identified, but it does not allow specimen imaging.
Breast Cancer Risk Assessment

Numerous models exist for predicting an individual’s breast cancer risk (37). These models inform whether and when individuals should undergo high-risk screening and potentially benefit from risk-reducing endocrine therapy or prophylactic mastectomy.

Imaging biomarkers are increasingly used for risk stratification (38). Breast density is an anatomic imaging biomarker associated with increased breast cancer risk (15,39). Growing evidence suggests that functional imaging modalities, like MBI and MRI, can predict breast cancer risk (40-42), perhaps more accurately than risk models alone (42). BPU on MBI is a reliable quantitative and qualitative biomarker (41,43) that describes the amount of radiotracer uptake in normal breast tissue relative to subcutaneous fat. BPU is assessed qualitatively as photopenic, minimal-mild, moderate, and marked (44) (Figure 3). BPU is analogous to background parenchymal enhancement (BPE) on MRI, which describes the amount of normal breast tissue enhancement, and is similarly assessed qualitatively as minimal, mild, moderate, or marked (45). Beyond predicting breast cancer risk, BPU varies with menopausal status and dose of risk-reduction endocrine therapy (46). A large single-center study found that BPU is an independent risk factor for breast cancer with postmenopausal women with elevated BPU and dense breasts at highest risk, well-above the threshold for considering use of risk-reducing therapy (47). Future studies incorporating functional imaging biomarkers into breast cancer risk models may facilitate personalized screening and risk management.

Novel Radiotracers

MBI systems can also be used for research using gamma-emitting radionuclides targeting more specific aspects of tumor biology beyond 99mTc-sestamibi uptake. Radiolabeled antibodies, peptides, and receptor ligands may broaden future applications of MBI for tumor phenotyping, neoadjuvant treatment selection, and therapy response prediction. Use of MBI for αvβ3 integrin-targeted imaging of tumor
angiogenesis has been explored in two small studies (48,49). Other $^{99m}$Tc-labelled radiotracers targeting specific receptors such as estrogen receptor and HER2 have been developed and could utilize MBI technology, although not yet evaluated.

**Conclusion:**

MBI is an important emerging breast imaging technology for supplemental screening, local tumor staging, neoadjuvant therapy response assessment, and breast cancer risk assessment.

Disclosures:
Covington-Consultant for Invicro, LLC for medical imaging review.
Parent-Research funding from Blue Earth Diagnostics.
Dibble-None.
Rauch-Research funding from GE Healthcare.
Fowler-UW-Madison Department of Radiology receives research support from GE Healthcare and book chapter royalty from Elsevier, Inc.
All disclosures are outside of the scope of this project.
References:


Figure 1. MBI with 300 MBq (8 mCi) $^{99m}$Tc-sestamibi for extent of disease evaluation. 59-year-old woman with a palpable irregular mass in the right upper central breast measuring 3.3 cm on craniocaudal (CC) (a) and mediolateral oblique (MLO) (b) mammograms (arrows). MBI showed 10 cm of uptake on CC (c) and MLO (d) views (arrows). Post-contrast axial (e) and sagittal (f) MRI confirmed 10.2 cm of abnormal enhancement (arrows). Following neoadjuvant chemotherapy and mastectomy, surgical pathology showed 8 cm treated tumor bed with 0.2 cm of residual invasive carcinoma.
Figure 2. 38-year-old woman with right breast triple negative and node negative invasive ductal carcinoma. Pretreatment MRI (a) and MBI with 300 MBq (8 mCi) $^{99m}$Tc-sestamibi (b). Postcontrast sagittal fat-suppressed T1-weighted MRI shows an irregular mass in the right breast (arrow). Intense uptake is seen on the mediolateral oblique MBI view (arrow). On post-treatment imaging, there is no residual enhancement on MRI (c), and no residual uptake on MBI (d). Surgical pathology showed pathologic complete response.
Figure 3. Photopenic (fibroglandular uptake less intense than fat) (a), minimal-mild (fibroglandular uptake is equal to just noticeably more intense than fat) (b), moderate (fibroglandular uptake more intense than mild, but less than twice as intense compared to fat) (c), and marked (fibroglandular uptake at least twice as intense as fat) (d) background parenchymal uptake on MBI (8 mCi $^{99m}$Tc-sestamibi).