Biopsy guided by molecular breast imaging (MBI)

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Molecular Breast Imaging (MBI) uses single gamma photon emission to visualize breast tumors that are often occult on mammography (Fig. 1 on page 3), especially in the 40-50% of European and American women with radiographically dense breasts (Fig. 2 on page 3). MBI is emerging as a promising adjunct diagnostic modality [1-4]. Further, MBI has recently demonstrated a strong potential for use as an adjunct screening tool for women with radiographically dense breasts [5]. Two technical prerequisites for potential MBI screening are 1) a reduced radiation dose comparable with screening mammography [6] and 2) MBI-guided biopsy capability for the ~15% of cases when an MBI detected lesion is occult on ultrasound and mammography. After achieving these technical prerequisites, of course, multiple site clinical trials will be required to prove efficacy and to gain regulatory approval. Our purpose was to enable low-dose MBI screening and MBI guidance for biopsy.
**Fig. 1:** Figure 1. Example of dense mammogram (MMG) read as normal and corresponding MBI revealing malignant lesion. Courtesy of Mayo Clinic.

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**Fig. 2:** Figure 2. Not only do dense breasts obscure the presence of cancer, they also significantly increase the risk of cancer.

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Methods and Materials

MBI was developed over the past 15 years as a technical improvement over prone scintimammography using either $^{99m}$Tc-sestamibi or $^{99m}$Tc-tetrofosmin for planar gamma photon emission imaging. Three commercial MBI systems are available, all with FDA 510(k) clearance: Dilon Technologies offers a single-head gamma camera system using a NaI scintillator and photomultiplier tubes with a pixel size of 3.2 mm; Gamma Medica offers a dual-head system using solid-state CZT direct conversion detectors with 1.6 mm pixels; and GE Healthcare offers a dual-head CZT system with 2.5 mm pixels. The patient is injected intravenously with the radiotracer and is immediately positioned sitting (or standing) with one breast mildly immobilized (~1/3 the compression force of mammography) between the two gamma cameras (Fig. 3 on page 7) (or one camera and a compression paddle for Dilon). Images are acquired for 5-10 minutes each in standard mammographic views (CC and MLO) for each breast. The images (Fig. 4 on page 7) are generally straightforward to interpret and report with the guidance of a recently published lexicon [7,8].

Dose reduction: An MBI screening pilot study was conducted in 2010 at Mayo Clinic in 936 patients at a dose of 20 mCi (740 MBq) sestamibi, as indicated by the radiotracer label [5]. In parallel, we developed several technical improvements to lower the required dose (currently off-label use). First, we optimized the pixel size and design of the registered collimator (one hole aligned with each pixel). As Fig. 5 on page 8 shows, the optimal pixel size is 1.2-1.6 mm. The Gamma Medica MBI system (LumaGEM®), at 1.6 mm, is about 40% more efficient than the 2.5 mm GE system, and twice as efficient as the Dilon 3.2 mm system. Higher efficiency corresponds with lower dose capability. In addition, the better spatial resolution results in higher contrast recovery for smaller lesions, which again can be traded for reduced dose.

With this improvement, a second MBI dense-breast (50% or greater, no other risk factors considered for inclusion) screening study was conducted at a dose of 8 mCi (296 MBq) in 2011 - February 2012 at Mayo Clinic. Furthermore, the 8 mCi studies were acquired as two summed 5 minute acquisitions, so that additional analysis could be performed at an equivalent count density to a 10 minute 4 mCi study. A subsequent study is testing the efficacy of 4 mCi injected dose and results indicate that this dose level is adequate. Additional technical improvements are being developed to further lower administered radiopharmaceutical dose to a goal of 2 mCi (74 MBq) corresponding to a whole-body exposure dose of 0.6 mSv. Fig. 6 on page 9 shows one of several works in progress: fusion of the two planar images using signal preserving, noise-cancellation filters. The potential dose reduction is 5X, bringing the 2 mCi dose goal within striking distance. Fig. 7 on page 10 shows a comparison of whole-body exposure doses for various imaging modalities, including the three commercial MBI systems. The Gamma Medica
(LumaGEM®) system is shown at the current clinically proven injected dose of 4 mCi. When the dose is soon lowered to 2 mCi, MBI whole-body dose will be equivalent to screening mammography.

**MBI-guided Biopsy:** Fig. 8 on page 11 shows a potential clinical workflow chart in which screening MBI would be used as an adjunct to mammography in women with dense breasts. If a lesion is found on MBI, second-look ultrasound will be used to guide biopsy in the ~85% of cases where the lesion will also be visible on ultrasound. In the ~15% of cases where MBI lesions are occult on both MMG and ultrasound, MBI-guided biopsy will be used. We have now developed an MBI-guided biopsy accessory that is easy and efficient to use and provides 3D lesion targeting, stereotactic needle guidance, needle location confirmation, and post-biopsy confirmation of specimens and lesion volume reduction. The vacuum-assisted needle biopsy (or wire localization for excisional biopsy) is performed by lateral approach between the two cameras.

Fig. 9 on page 12 shows a prototype of the MBI-guided biopsy accessory (patent pending). Several following figures will illustrate the operation of the device. Fig. 10 on page 13 shows the accessory deployed in a patient biopsy procedure. The small CZT gamma camera is pointed toward the lesion visualized on the two main CZT gamma cameras of the MBI system. Together the three cameras determine the 3D xyz lesion position. The needle guide holder on the right in Fig. 10 is positioned so that the biopsy gun can be placed hub-to-hub to place the sampling region of the core needle either in or near the lesion, as desired. Fig. 11 on page 14 illustrates the software display of the 3D xyz coordinates of the desired needle tip placement. The software will also display the proper position for the needle guide holder for the specific core biopsy needle being used.

Fig. 12 on page 15 shows verification of the needle track with respect to the lesion. After the trocar cuts the needle track, it is removed, leaving a sleeve in place. A radioactive line source (typically $^{57}$Co) is introduced and imaged by the MBI cameras to verify that the lesion has not moved and that the needle track is in the intended position. Fig. 13 on page 15 illustrates the hub-to-hub placement of a biopsy gun. The lesion is sampled multiple times. Repeat MBI imaging will show a diminished count density in the lesion because it has been partially removed. Fig. 14 on page 16 shows a biopsy sample tray and an MBI image of the samples. Regions with higher count density correspond to the lesion tissue with high radiotracer uptake (typically 20:1 lesion : background uptake). The sample image can be sent along with the samples to guide histopathology analysis.
**Fig. 3:** Figure 3. Position for MBI: patient sitting, imaging begins within less than 5 minutes after intravenous injection of radiotracer (99mTc-sestamibi or 99mTc-tetrofosmin), breast mildly stabilized between two small field-of-view gamma cameras. LCC (left cranial-caudal) view is illustrated. Example comparison images show radiographically dense mammogram and corresponding MBI showing occult lesion. Breast images courtesy of Mayo Clinic.

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**Fig. 4:** Figure 4. Comparisons of normal dense mammograms and MBI: in each pair, the digital mammogram is on the left and the MBI on the right; four patients are shown. Courtesy of Mayo Clinic.

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Fig. 5: Figure 5. Registered collimator and pixel size optimization for MBI. The collimator spatial resolution was set to 5 mm at a depth of 3 cm, which is halfway through an average mildly compressed breast. Septal penetration was constrained to less than 2%. The septal thickness and length were varied to optimize the geometric efficiency (sensitivity). For pixel pitch of 2.5 mm or greater, there is no difference between lead or tungsten collimators. However, for smaller pixel pitches, tungsten has an advantage. The optimal pixel size is 1.2-1.6 mm.

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**Fig. 6:** Figure 6. Work-in-progress to further reduce MBI dose. On left are the MBI images from the top and bottom detectors in RMLO (right medial-lateral-oblique) view. The images can be fused using a noise-cancelling, signal-preserving filter to yield equivalent image quality with only 20% of the data, equivalent to a 5X dose reduction. Courtesy of Michael O'Connor, PhD, Mayo Clinic.

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**Fig. 7:** Figure 7. Comparison of whole-body ionizing radiation doses for various imaging methods and non-imaging activities (annual airline crew exposure, annual background radiation).

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Fig. 8: Figure 8. Potential screening flow with screening MBI used as an adjunct to mammography in dense breast. When a lesion is visualized by MBI, second-look ultrasound will be used to guide biopsy in ~85% of cases. In the ~15% of cases where the lesion is occult on both MMG and ultrasound, MBI-guided biopsy will be used.

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**Fig. 9:** Figure 9. Prototype MBI-guided biopsy accessory. On the left is a small CZT camera with registered collimator that is used to determine the height of the lesion above the lower camera (cover shown sitting atop a box for display). On the right is a needle-guide holder that can be positioned to guide a biopsy gun to the determined 3D stereotactic position of the MBI visualized lesion.

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**Fig. 10:** Figure 10. Illustration of MBI-guided biopsy device positioning. The small CZT gamma camera on the left is pointed toward the lesion to determine, along with the two main MBI gamma cameras the 3D xyz lesion location. The needle guide on the right is positioned to guide the biopsy needle hub-to-hub to the appropriate location in or near the lesion.

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**Fig. 11:** Figure 11. Example of software display of lesion location in 3D xyz coordinates which are used to position the needle guide.

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**Fig. 12:** Figure 12. Verification of the needle track placement and non-movement of the lesion using a radioactive line source (typically 57Co).

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**Fig. 13:** Figure 13. Biopsy gun is in place; samples are taken from the lesion. Repeat MBI imaging will show reduced count density in the partially removed lesion.

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**Fig. 14:** Figure 14. Biopsy tissue samples are placed in a tray (right) and then imaged by the MBI cameras. The image (left) will show hotter (higher count density) regions representing the sampled lesion. This image can be sent to pathology along with the samples to guide analysis.
Results

The second dense-breast MBI screening study (8 mCi) at Mayo Clinic concluded enrollment with 1649 patients when 21 cancers had been detected. After one year of follow up, full results will be published. Fig. 15 on page 19 shows intermediate analysis of diagnostic performance metrics at the participant level in the first 1252 patients. Sensitivity and PPV of dense-breast screening MBI was much higher than mammography. Fig. 16 on page 19 shows example patient images from the study. In each case shown, the dense breast mammogram was normal but the MBI revealed an occult lesion.

The LumaGEM® MBI system is now being used for additional screening clinical trials because a low dose of radiopharmaceutical has been demonstrated to be efficacious and MBI-guided biopsy has been developed and has begun clinical evaluation. Setup, operation, and clinical workflow have been optimized through interaction between physicists and clinical radiologists.
Fig. 15: Figure 15. Intermediate analysis of diagnostic performance metrics at the participant level in the first 1252 patients of an 8 mCi MBI screening trial at Mayo Clinic in women with 50% or greater dense breast (no other risk factors used for selection). Courtesy of Deborah Rhodes, MD, Mayo Clinic. (Reported at RSNA 2011)

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<table>
<thead>
<tr>
<th>Metric</th>
<th>Incident MMG</th>
<th>Prevalent MBI</th>
<th>Combination</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>3/15 (20%)</td>
<td>13/15 (87%)</td>
<td>14/15 (93%)</td>
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<tr>
<td>Recall Rate</td>
<td>137/1252 (11%)</td>
<td>128/1252 (10%)</td>
<td>221/1252 (18%)</td>
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<tr>
<td>Biopsies</td>
<td>13/1252 (1%)</td>
<td>38/1252 (3%)</td>
<td>48/1252 (4%)</td>
</tr>
<tr>
<td>PPV</td>
<td>3/137 (2%)</td>
<td>13/128 (10%)</td>
<td>14/221 (6%)</td>
</tr>
</tbody>
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Fig. 16: Figure 16. Example patients from 8 mCi dense breast screening study. In each case the lesion was occult on mammography, but well visualized on MBI. Courtesy of Deborah Rhodes, MD, Mayo Clinic. (Reported at RSNA 2011)

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Conclusion

The LumaGEM® MBI system is being used for confirmatory multi-site low-dose dense-breast screening trials following the highly successful initial trials at the Mayo Clinic. Early results of MBI-guided biopsies are expected mid-2013 when FDA 510(k) clearance will be sought.
References

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LumaGEM® is FDA 510(k) cleared

LumaGUIDE™ is a work-in-progress

Low-dose MBI (diagnostic or screening) is an off-label use of Tc99m-Sestamibi (Cardiolite®)

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