Molecular Breast Imaging
New Modality for Diagnosing Breast Cancer

By Lillian H. Stern, M.D.

Don’t we have enough tools for diagnosing Breast Cancer???

Current Modalities

- Mammograms (analogue v. digital)
- Tomosynthesis
- Ultrasound
- MRI
- PET Scan
- Molecular Breast Imaging (BSGI, MBI, PEM)

Why do we need another tool?

- Many articles state that we miss 10% of breast cancer on mammography.
- It really is much higher especially in dense breasts!—It may be as high as 30%.
- Dense tissue camouflages cancers until they enlarge, become brighter than the surrounding tissue, or form discrete margins and/or calcifications.
Old and new tools for detecting breast cancer.

- Mammography is still the “Gold Standard.”

Digital Mammograms
- Performed just like a regular mammogram.
- Still need compression.
- Image is just recorded differently----on a computer instead of x-ray film.
- Can see thru dense tissue better.
Tomosynthesis
- 3-Dimensional picture using FFDM.
- Multiple X-ray pictures of the breast from many angles.
- Clears overlapping densities hiding an underlying abnormality.

3D Mammography (Tomosynthesis)
- Step, expose image
- 11 images, 5 degrees between images
- Total dose equal to single mammo
- Total imaging time about 7 seconds

Breast Tomosynthesis
It is hard to interpret this when everything is overlapping...

Breast Tomosynthesis
It is hard to interpret this...
**Examples of Tomosynthesis**

**Tomosynthesis Mammography Reconstruction**

**MRI (Angiogenesis)**

**MRI is an excellent tool!**
- When it is very positive—it is dramatic.
- But frequently it has several questionable areas which require a 6 month follow-up or a repeat study at a different time in the menstrual cycle.
- Sometimes when patient comes for MRI biopsy, abnormal area no longer visible.

**MRI is expensive!**
- Some patients can’t have test because of metal or pacemakers.
- Some patients can’t lay on stomach.
- Some patients are claustrophobic.

**Radiologist has to scroll thru 700 images!**
- Patient usually has to wait several weeks to get on the MRI schedule and may have to come back for the opposite breast.
- Patient may not get the results for several days.
- MRI usually requires precertification.
Anxiety!!!!

- Patient!!!
- Clinicians!!
- Radiologists! Will I miss a cancer? Will I be sued?

Goals for decreasing everyone’s anxiety!

- Decrease number of indeterminate Studies
- Decrease number of BI RADS 3 = 6 month follow-up.
- Decrease number of benign biopsies.

Molecular Imaging

- Instead of looking at structures (anatomy) or angiogenesis, these tests analyze cellular activity.
- Cancer cells are more active than normal cells and the mitochondria will therefore absorb more of the injected radioactive isotope.

Molecular Breast Imaging Positive Cancer on Right

- Involves an injection into a vein of a tracer dose of radioactive material.
- Images of only the breast are obtained using the same views as a mammogram. Direct comparison with the mammogram is therefore possible!
- Active cells produce a black spot similar to a PET scan.

Molecular Breast Imaging

- BSGI (Dilon) or MBI (Mayo Clinic) Tc99 Sestamibi
  - Readily available (Can borrow a dose from cardiac stress test.)
  - Can quickly add on a patient already in department.
  - No fasting. No delay after injection.
  - No contraindications
Isotope for PEM (Positron Emission Mammography)

- Use FDG similar to a PET scan.
- Patients must fast.
- One hour delay between injection and imaging.
- Concern in Diabetics

Scintimammography

- This is the old name—developed in the 1990’s
- Failed to demonstrate small cancers

Scintimammography

- Patient laid prone on a regular nuclear medicine table.
- Detail was not good enough to pick up small cancers

The Dilon 6800 Gamma Camera can replicate any mammographic view.
Comparative Resolution Based on Geometric Factors

Resolution vs Distance

- Dilon
- SMV
- Technicare

Dedicated cameras improve imaging by providing both better improved detector spatial resolution and by moving the target closer to the detector.

Partial Volume effect

Example A
Example B

Detector
Detector

Image

Area of illumination = 1
as 100 x 100 object intensity = 100

Area of illumination = 2
as 100 x 2 = 100 object intensity = 50

The area of the object in both cameras contains the same number of counts so the counts/area of example A is higher than example B. This results in better contrast for the image in example B.

Impact of Attenuation

<table>
<thead>
<tr>
<th>Lesion Depth</th>
<th>% of photons</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>85.8</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>73.6</td>
<td>0.74</td>
</tr>
<tr>
<td>3</td>
<td>63.1</td>
<td>0.63</td>
</tr>
<tr>
<td>4</td>
<td>54.2</td>
<td>0.54</td>
</tr>
<tr>
<td>5</td>
<td>46.5</td>
<td>0.47</td>
</tr>
<tr>
<td>6</td>
<td>44.9</td>
<td>0.43</td>
</tr>
<tr>
<td>7</td>
<td>34.2</td>
<td>0.34</td>
</tr>
<tr>
<td>8</td>
<td>29.3</td>
<td>0.29</td>
</tr>
</tbody>
</table>

What does all this mean?

The dedicated breast gamma camera designs greatly improve the sensitivity for small lesions through a combination of:
- improved extrinsic spatial resolution
- Imaging the breast directly against the detector
- Applying mild compression

The Clinical Evidence


As in all imaging, there is a desire to lower the dose as much as possible. According to the National Institutes of Health (NIH), the risks from the radiation dose associated with both mammography and BSGI procedures at 20 – 30 mCi are considered to be "minimal".

The radiation dose from the BSGI at 20 – 30 mCi is equivalent to living in Denver, Colorado for one year and is acceptable for the diagnostic population.

According to the drug data sheet for Cardiolite, the prescription range is from 10 to 30 mCi. Therefore, if a center wishes to minimize radiation dose from this procedure, lower doses and longer imaging times can be utilized.

It is important to note that this pharmaceutical has been used in cardiac imaging for nearly 20 years without a single reported adverse reaction to the radiation dose.

### Radiation Dosimetry

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Administered Dose</th>
<th>Effective Dose Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening MMG - 4 view only</td>
<td>N/A</td>
<td>0.7 mSv</td>
</tr>
<tr>
<td>Does not include diagnostic MMG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSGI (Sestamibi)</td>
<td>20 mCi</td>
<td>6.7 mSv</td>
</tr>
<tr>
<td>CT chest</td>
<td>N/A</td>
<td>7.8 mSv</td>
</tr>
<tr>
<td>Coronary CT (Women)</td>
<td>N/A</td>
<td>10.2 mSv</td>
</tr>
<tr>
<td>PET (F-18 FDG)</td>
<td>10 mCi</td>
<td>11.1 mSv</td>
</tr>
<tr>
<td>CT abdomen and pelvis</td>
<td>N/A</td>
<td>14.7 mSv</td>
</tr>
<tr>
<td>PET/CT</td>
<td>10 mCi</td>
<td>23.0 mSv</td>
</tr>
</tbody>
</table>

### The Impact of Dedicated Detectors on Dose

Dedicated detectors are up to 4 times more sensitive than the standard cameras. This indicates that it should be possible to use a lower dose.

Anecdotally, some centers have used doses around 12 - 15 mCi. BUT remember that all of studies to date to establish efficacy have been conducted at 20 – 30 mCi AND a lesser dose is an off label use.


### Dose Reduction Study

As in all imaging, there is a desire to lower the dose as much as possible.

Obviously, the risk of a missed cancer is a far greater risk to the patient than the risk of the radiation dose.

Therefore lowering the dose to a level that decreases the sensitivity of the examination is not beneficial to the patient.

**Question:** How far can the dose be lowered without negatively impacting the efficacy of this imaging procedure?

**Answer:** No one knows, but a multi-center prospective trial is under way to answer this question.

### Risk vs. Benefit

As with all medical procedures, we must evaluate the procedure risk against the benefit to the patient.

Radiation risk is just one form of risk.

We use BSGI selectively in three primary populations.

- Patients who have a negative or indeterminate mammogram/ultrasound and a remaining clinical concern
- Patients at high risk for breast cancer if MMG is not sufficient for screening (dense, complex, or difficult interpret)
- Patients with positive mammograms or known breast cancer diagnosis to improve treatment planning.
Risk vs. Benefit Cont.

- In the retrospective analysis of BSGI patients presented at RSNA in 2009, we established that BSGI detected 30 malignant and 7 high-risk lesions in 240 patients (15.4%) with negative or indeterminate mammograms (15.4%) with negative or indeterminate mammograms.
- The overall sensitivity of MMG and BSGI was 71% and 93% respectively.
- It is clear that this imaging procedure is beneficial in detecting cancers occult to mammography and that it improves the management of properly selected cases.
- The radiation risk is far outweighed by the benefit to properly selected patients.
- Work is underway to lower the dose.

Newly diagnosed breast cancer requiring preoperative work-up.

Patient is claustrophobic and refused MRI leading to a recommendation for BSGI.

Courtesy of Dr. Mike Linver, X-ray Associates of New Mexico, Albuquerque, NM

Now the patient agrees to an MRI yielding multiple enhancing sites.

Courtesy of Dr. Mike Linver, X-ray Associates of New Mexico, Albuquerque, NM

Results of a Multi-Center Patient Registry to Determine the Clinical Impact of Breast-Specific Gamma Imaging, a Molecular Breast Imaging Technique

- Evaluation of equivocal mammography and/or ultrasound.
- Cancer surveillance in patients with a personal history of breast cancer.
- Positive mammogram prior to biopsy to aid in biopsy target selection, particularly in patients with multiple suspicious areas.
- Palpable mass not demonstrated in mammogram or ultrasound.
- Radiodense breast tissue difficult to image mammographically.
- Screening in high-risk patient populations.

Clinical Utility of Breast Specific Gamma Imaging For Evaluating Disease Extent in the Newly Diagnosed Breast Cancer Patient

- 138 newly diagnosed cancers
- Found additional disease in 11% of cases
- Sensitivity = 91.4%
- Specificity = 94.2%


Clinical Data Summary
Of 16 papers and presentations

<table>
<thead>
<tr>
<th>Total Number of patients</th>
<th>3494</th>
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<tbody>
<tr>
<td>Overall Sensitivity</td>
<td>92.1%</td>
</tr>
<tr>
<td>Overall Specificity</td>
<td>78.1%</td>
</tr>
<tr>
<td>Overall PPV</td>
<td>57.7%</td>
</tr>
<tr>
<td>Overall NPV</td>
<td>97.3%</td>
</tr>
</tbody>
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GammaLoc® System

Stereotactic System Components

Gamma Emitting Marker

Grid System Fiducial & Collimator

References

Gamma Emitting Marker

Radioactive Source (Reusable)

Sterile Sleeve (Single Use)

Assembled
Compatible with Existing Dilon 6800

Front View

Slant-hole Collimator Concept

Rignt View

Left View

Lesion

Breast

Gamma Camera

Localization

Slant-hole Collimator Concept

Centered View - for validation and biopsy

Gamma Camera

Clinical Considerations

<table>
<thead>
<tr>
<th>Radioactive Marker</th>
<th>Energy of emission photon</th>
<th>Half Life (minutes)</th>
<th>Pre-study fasting</th>
<th>Time from injection to imaging (minutes)</th>
<th>Recommended pre-procedural testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG</td>
<td>111 KeV</td>
<td>110</td>
<td>4 - 6 hours</td>
<td>90 - 90 minutes</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>sestamibi</td>
<td>140 KeV</td>
<td>360</td>
<td>None</td>
<td>5 minutes</td>
<td>None</td>
</tr>
</tbody>
</table>

One Image is used to monitor the X, Y, Z location of a Marker Source
Energy Resolution

"Neither qualitative nor quantitative assessment of tumor contrast in breast phantom images provided a strong relationship between energy resolution and tumor contrast."


Spatial Resolution

- An examination of the effect of pixel size on breast lesion contrast.
- Detectors with pixel sizes of 1.4, 2.2 and 3.2mm were tested
- Conclusion, "The camera with the largest (3.2mm) crystal pitch performed better than the others tested..."


Dual Head Detector

- "The use of a dual-head system is not absolutely necessary for acquiring opposing views of the breast because it is possible to obtain the superior and inferior views of the CC position and medial and lateral views of the MLO position with separate acquisitions performed using only one single-head detector."

- "We realize that the cost of the molecular breast imaging system would be increased by adding a second detector head, however, because this study was a preliminary study with a prototype system, a true cost–benefit ratio of commercial dual-head molecular breast imaging compared with single-head molecular breast imaging is yet to be determined."


BSGI and PEM

- Each view takes 8 - 10 minutes.
- Usually image both breasts.
- Add axillary view if suspect a cancer to look for positive lymph nodes.
**Molecular Breast Imaging**

- If it is positive—usually very discrete hot spot or spots.
- If it is negative—the chances of missing something is extremely small.

**Who should perform BSGI?**

- Breast Center
- Nuclear Medicine Department

**Requirements**

- Small room. Machine is very mobile.
- Hot Lab
- License to inject isotope.
- Tech excellent at BREAST POSITIONING!
- Radiologist adept at correlating Mammogram, Ultrasound, MRI, and BSGI.

**How is test received by patients?**

- 1. Test is relatively comfortable.
- 2. No compression.
- 3. No claustrophobia.
- 4. Can watch TV.
- 5. Get results immediately!!!!

**Correlation with other studies is essential!**

**Typical positive BSGI study left breast upper-outer quadrant**
Typical Normal Study

Vague Bilateral Uptake

Hormonal Activity

Just as in MRI, hormone influence may interfere with imaging—day 2 - 12 of cycle optimal

6 months later, off HRT

Typical pattern

Asymmetrical pattern

Focal abnormal: Can be malignancy, inflammation, atypia, or some benign processes

Invasive ductal carcinoma

Breast Abscess

What size lesion can Molecular Imaging find?

- Many 3 -5 mm lesions have been found.
- Occasionally see a 1.5 mm lesion.
- Most infiltrating lobular cancers (Frequently missed on Mammography until 5-6 cm.)
Clinical Indications

- Probable Breast Malignancy
- 1. Evaluate extent of cancer
- 2. Evaluate for synchronous disease in same or opposite breast
- (Multifocal or Multicentric Disease)

Unifocal invasive ductal carcinoma

Multifocal cancer extending to nipple

Multifocal Cancer
**Positive Core Biopsy**

- Should all patients recently diagnosed with breast cancer have an MRI or BSGI before deciding on a definite surgical plan?
- BSGI or MRI changes management in 10-20% of selected cases!

**Personal History of Breast Cancer**

- 1. Suspected Recurrence
- 2. Monitoring Response to Therapy

**76 year old**

- Had benign biopsy right breast in 2002. Now area of scar has changed slightly.

**Scar vs. Recurrence**

2002 vs. 2006 images show slight changes in the area of the scar.
Suspicious calcifications BSGI indicates recurrence at lumpectomy site

lumpectomy scar vs. recurrence- Normal BSGI - no recurrence

Response to Neoadjuvant Chemotherapy

Is this the right treatment?

PEM v BSGI

- PEM or BSGI can be used to assess breast in patient diagnosed with breast cancer.
- At this time PEM can not be reimbursed for work-up of a patient with abnormal mammogram, ultrasound, or unexplained symptoms, but with no personal history of breast cancer.
Daily Uses in patients with no Breast Cancer

- 1. Bloody Nipple Discharge
- 2. Unexplained Palpable Mass
- 3. Bilateral Masses-Which should be biopsied?
- 4. Calcifications- Which should be biopsied?
- 5. Cysts Obscuring Underlying Tissue.

- 6. Extremely Dense Breasts plus Breast Cancer Gene or Strong Family History.
- 7. Free Silicone Injections
- 8. Breast Implants

Bloody Nipple Discharge

55 year old patient with persistent palpable abnormality upper outer quadrant right breast
Mammography, ultrasound, and BSGI normal
Biopsy concordant - no atypia or malignancy

Bilateral Masses

Which ones need biopsy

Bilateral multifocal phyllodes tumors
Multiple Fibroadenomas

Which calcifications should we worry about?

Microcalcifications of extensive in-situ malignancy

Technically difficult mammogram
- 1. Radiodense breasts
- 2. Implants
- 3. Free Silicone

Dense breasts
Positive family history

3 mm IDCa
**Limitations of BSGI**

- Cases with vague patchy uptake bilaterally.
- Immediately following surgery, area will be positive and may stay positive for up to a year.
- Can not assess for clear margins.
- Can not assess for posterior chest wall or pectoral muscle involvement.
- Even with excellent positioning may miss cancers close to chest wall or deep in axilla.
Things BSGI cannot do.

- 100% sensitivity and specificity
- Resolve lesions under 2mm.
- Image close to chest wall

It Let’s You Sleep At Night

- We would like to make the diagnosis as quickly and as accurately as possible.
- We need to decrease patient’s anxiety as quickly and accurately as possible.
- We need to decrease the number of BIRADS 3 (indeterminate) studies and number of biopsies.

Bringing New Excitement into Breast Imaging

- Multimodality!
- Back to patient contact!
- Being a detective.
- Following trail all the way to a conclusion!
- Giving good advice to patients and other physicians.