Disclosures

Gamma Medica employees:
   Brad Patt, PhD – CEO & founder
   James Hugg, PhD – CTO, VP-R&D
   Bryan Simrak, electronic engineer
   Peter Smith, field service engineer

Mayo Clinic:
   Exclusive license of MBI Intellectual Property & know-how to
   Gamma Medica; contract from Gamma Medica

Cleveland Clinic:
   Contract from Gamma Medica to develop breast lesion
   phantom

Grant funding from NIH National Cancer Institute (STTR, SBIR Bridge,
   & R01), Mayo Foundation, Susan G. Komen Foundation
Learning Objectives

• Understand the physics of MBI, BSGI, and PEM breast imaging.

• Understand how radiation dose can be lowered in MBI, BSGI, and PEM.

• Understand how to characterize the performance of MBI, BSGI, and PEM systems.
Outline

• Challenge of dense breasts
• Physics of MBI, BSGI, & PEM
• Radiation dose reduction
• Performance of MBI, BSGI, & PEM
Challenge of Dense Breasts
Dense Breast Tissue

- Breasts are composed of fatty (non-dense) tissue and connective (dense) tissue
  - X-rays do not penetrate dense connective tissue, so cancer is hidden and often can be missed

How other modalities work in dense breast:

- **Mammography**
  - Ineffective in dense breasts – very low sensitivity
  - Cancer is hidden until too late to treat effectively

- **Ultrasound**
  - Useful in dense breasts, but results depend on operator’s skill
  - Specificity is low

- **Breast MRI**
  - Useful in dense breasts, but costs 3x MBI
  - Too many false positives
  - Too many biopsies
Dense Breast Tissue – MBI provides a solution

- Cancer is often obscured by dense connective tissue that absorbs many X-rays.
- The sensitivity of screening mammography in dense breasts is below 30%.
- Gamma photons penetrate dense breast tissue with little absorption.

<table>
<thead>
<tr>
<th>Region</th>
<th>&gt; 50% Dense Breast Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>70%</td>
</tr>
<tr>
<td>Europe &amp; Americas</td>
<td>40-50%</td>
</tr>
</tbody>
</table>

Courtesy of Mayo Clinic
Dense Breast Increases Risk for Cancer

A 2002 study in *New England Journal of Medicine* (Boyd) found that:

women with significant dense breast tissue have a 4-6 times greater risk of developing breast cancer

## Breast Density – 3\textsuperscript{rd} Highest Relative Risk

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA mutation</td>
<td>20</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>8-10</td>
</tr>
<tr>
<td><strong>Dense breast parenchyma</strong></td>
<td>4-6</td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td>3-4</td>
</tr>
<tr>
<td>Family history (1\textdegree relative)</td>
<td>2.1</td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td>1.5</td>
</tr>
</tbody>
</table>

“Mammographic density is perhaps the most undervalued and underutilized risk in studies investigating the causes of BC.”
– Boyd, *NEJM*, 2002
Physics of MBI, BSGI, & PEM
Scintimammography

Original protocol
• Inject 20-30 mCi $^{99m}$Tc-sestamibi \textit{i.v.}
• Wait 5 minutes

Typical tumor/background uptake ratio: 5-10

Single-head gamma camera:
• 10 min lateral planar image of suspect breast
• 10 min lateral planar image of contralateral breast
• 10 min anterior planar image of both breasts

MBI evolved from scintimammography (SMM). Only lesions larger than 1 cm could be reliably detected by SMM because of the large distance from the collimator to the breast.
**$^{99m}$Tc-Sestamibi (MIBI)**  
(Cardiolite, Miraluma)

Half-life = 6 hours  
140 keV gamma emission

FDA clearance for breast 1997  
(20-30 mCi, 740-1110 MBq i.v.)

**Indicated for:**
- planar imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass

**Not indicated for:**
- breast cancer screening,
- to confirm the presence or absence of malignancy, and
- not an alternative to biopsy

Generic since Sept 2008

MIBI is 2-methoxy isobutyl isonitrile
Breast-Specific Gamma Imaging (BSGI)

- Single detector head
- NaI pixels (3.2 mm pitch, 6 mm thick)
- PS-PMT photodetectors
- 12% FWHM @140 keV

1st sale – 2005
~140 installations

Dilon 6800, 15 cm x 20 cm
15-30 mCi $^{99m}$Tc-sestamibi
Breast-Specific Gamma Imaging (BSGI)

Dilon Acella, 20 cm x 25 cm (uses DigiRad detector)
DigiRad Ergo with BSGI attachment, 31 cm x 40 cm

- Single detector head
- CsI pixels (3 mm pitch, 6 mm thick)
- Si photodiodes

1st offer – 2011
? installations
Molecular Breast Imaging (MBI)

- $8^* \text{ mCi } ^{99m}\text{Tc-sestamibi } i.v.$
- mild stabilization (~1/3 MMG force)
- scan within 5 minutes
- 4 views: LCC, LMLO, RCC, RMLO
- 5-10 min/view

* 8 mCi is current Mayo Clinic protocol; 2-4 mCi goal (2013)
Molecular Breast Imaging (MBI) Protocol

- The patient is injected with Tc-99m Sestamibi
- The injection is in the contra-lateral arm
- If there are suspicious areas in both breasts an injection in the foot is preferred
- The patient is imaged about 5 minutes after injection
  - 8 mCi – 5 minutes/view
  - 4 mCi – 10 minutes/view
Easily able to do both CC and MLO views

• LumaGEM™ uses light compression (15 lbs of force as compared to 40-45 lbs used in mammography)
• Breast tissue simply needs to be immobilized / stabilized
2 Commercial MBI Systems

Gamma Medica LumaGEM
1st sale – 2009
20 installations

Both are FDA 510(k) cleared

Both are dual head & use CZT detectors

GE Healthcare Discovery NM750b
1st sale – 2012
4 installations
Positron Emission Mammography (PFM)

Naviscan PEM
16 cm x 24 cm
1st Sale – 2005
50 installations

- $^{18}$F-FDG (2 hour half-life) and coincidence detection using small scintillator/PMT detectors that physically scan side-to-side to form a limited-angle PET scan.

- Patient preparation: 12-24 hour fast, 1-2 hour quiet uptake delay after injection of 10 mCi $^{18}$F-FDG.

14% FWHM @ 511 keV
MBI, BSGI, & PEM Instruments

Gamma Medica
LumaGEM MBI

GEHC
MBI

Dilon, Digirad
Single Head BSGI

Naviscan
PEM

MBI, BSGI, & PEM

– Significantly improves specificity versus other secondary screening modalities (similar sensitivity to MRI)

– Cost of both capital equipment to providers and scan to payers is approx. one-third of MRI
Q1: What is the radiopharmaceutical (and its half-life) most commonly used for MBI or BSGI?

0% a) $^{18}$F-FDG (2 hr)

0% b) $^{123}$I-MIBG (13 hr)

0% c) $^{99m}$Tc-Tetrofosmin (4 hr)

0% d) $^{99m}$Tc-Sestamibi (13 hr)

0% e) $^{99m}$Tc-Sestamibi (6 hr)
Q1: What is the radiopharmaceutical (and its half-life) most commonly used for MBI or BSGI?

a) $^{18}$F-FDG (2 hr)
b) $^{123}$I-MIBG (13 hr)
c) $^{99m}$Tc-Tetrofosmin (4 hr)
d) $^{99m}$Tc-Sestamibi (13 hr)
e) $^{99m}$Tc-Sestamibi (6 hr)

Key Technology: solid state gamma sensor (CZT) with custom ASICs

Gamma ray detector CZT module used in *LumaGEM*

ASIC technology developed from space and high-energy physics applications.

Below: NASA SWIFT satellite
New Crystal and Solid State Technology

- Cadmium-Zinc-Telluride ($\text{Cd}_{0.9}\text{Zn}_{0.1}\text{Te}$) Crystals (CZT)
- Detector has 8 by 6 module configuration
- Each crystal unit is 1” X 1”
- Field of View is 16 cm X 20 cm (wide FOV available: 16 cm x 24 cm)
Cadmium Zinc Telluride (CZT)

Three major commercial sources of CZT

- Endicott Interconnect (former eV Products) [Pennsylvania]
- GE Healthcare (former Orbotec / Imarad) [Israel]
- Redlen [British Columbia, Canada]

Two dominant detector module configurations:

- Both - 5 mm thick, 16 x 16 = 256 pixels/module
- Gamma Medica (optimized for breast):
  - 2.5 cm x 2.5 cm, 1.6 mm pixel pitch, 4.7% FWHM @140 keV
- GE Healthcare (optimized for heart):
  - 4 cm x 4 cm, 2.5 mm pixel pitch, 6% FWHM @140 keV
Q2: Compare BSGI and MBI: how many detector heads are used and what type of detectors?

0%  a) BSGI: 2 CZT; MBI: 1 scintillator
0%  b) BSGI: 1 CZT; MBI: 2 scintillator
0%  c) BSGI: 1 scintillator; MBI 2 CZT
0%  d) BSGI: 2 scintillator; MBI 1 CZT
0%  e) BSGI: 1 scintillator; MBI 2 scintillator
Q2: Compare BSGI and MBI: how many detector heads are used and what type of detectors?

a) BSGI: 2 CZT; MBI: 1 scintillator
b) BSGI: 1 CZT; MBI: 2 scintillator
c) BSGI: 1 scintillator; MBI 2 CZT
d) BSGI: 2 scintillator; MBI 1 CZT
e) BSGI: 1 scintillator; MBI 2 scintillator

## Comparison of Breast Imaging Modalities

<table>
<thead>
<tr>
<th></th>
<th>MBI</th>
<th>Digital Mammography</th>
<th>Tomosynthesis</th>
<th>MRI</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probe</strong></td>
<td>Gamma emission</td>
<td>X-ray transmission</td>
<td>X-ray transmission</td>
<td>RF excitation / emission</td>
<td>Sound-wave transmission</td>
</tr>
<tr>
<td><strong>Imaging Type</strong></td>
<td>Molecular</td>
<td>Anatomic</td>
<td>3D Anatomic</td>
<td>3D Anatomic / Physiologic</td>
<td>Anatomic</td>
</tr>
<tr>
<td><strong>Clinical Indications</strong></td>
<td>Secondary Dx / dense-breast screening</td>
<td>Screening</td>
<td>Secondary Dx / dense-breast screening (TBD)</td>
<td>Secondary Dx</td>
<td>Secondary Dx</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>80-95%</td>
<td>30% Dense breast</td>
<td>60%? Dense breast (TBD)</td>
<td>80-91%</td>
<td>50% dense breast with Mammography</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>76-94%</td>
<td>70-80%</td>
<td>80-90% (TBD)</td>
<td>20-90%</td>
<td>50-60%</td>
</tr>
<tr>
<td><strong>Reimbursement</strong></td>
<td>$300-$600</td>
<td>$85-$140</td>
<td>$85-$140 (TBD)</td>
<td>$535-$1,200</td>
<td>$90-$150</td>
</tr>
<tr>
<td><strong>Whole-Body Radiation Dose</strong></td>
<td>1.2 mSv</td>
<td>0.5 mSv</td>
<td>1.0 mSv</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Patient Tolerance</strong></td>
<td>~100% (mild immobilization)</td>
<td>~80% (painful compression)</td>
<td>~80% (painful compression)</td>
<td>~60% (prone)</td>
<td>~100%</td>
</tr>
<tr>
<td><strong>Interpretation Difficulty</strong></td>
<td>Easy hot spot images</td>
<td>More difficult</td>
<td>More difficult</td>
<td>Most difficult &amp; most images</td>
<td>More difficult - operator dependent</td>
</tr>
<tr>
<td><strong>Exam Time</strong></td>
<td>40 minutes or *20 minutes</td>
<td>15 to 20 minutes</td>
<td>15 to 20 minutes</td>
<td>60 to 90 minutes</td>
<td>45 to 60 minutes</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Highest sensitivity and specificity; Low dose; Mild immobilization</td>
<td>Lowest cost; Low dose; High accessibility</td>
<td>Better dense-breast sensitivity than mammography</td>
<td>High sensitivity; No radiation</td>
<td>Low cost; No radiation; High accessibility</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>*Currently: long exam</td>
<td>Low dense breast sensitivity; Painful compression</td>
<td>Double MMG dose; Painful compression</td>
<td>Lower specificity; False positives; Difficult to read; Low patient tolerance; Many contraindications; Highest cost; Slow</td>
<td>Low sensitivity; Low specificity; False positives; Operator dependent; Slow</td>
</tr>
</tbody>
</table>

* Improvements in progress will result in 20 minute exam and dense-breast screening PMA (c. 2013).
## Comparison of Molecular Imaging Products

<table>
<thead>
<tr>
<th></th>
<th>Gamma Medica</th>
<th>GE Healthcare</th>
<th>Dilon</th>
<th>Naviscan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modality</strong></td>
<td>MBI</td>
<td>MBI</td>
<td>Breast Specific Gamma Imaging</td>
<td>Positron Emission Mammography (PEM)</td>
</tr>
<tr>
<td><strong>Detector Configuration</strong></td>
<td>2 heads only</td>
<td>1 or 2 heads</td>
<td>1 head only</td>
<td>2 heads only</td>
</tr>
<tr>
<td><strong>Detectors</strong></td>
<td>CZT</td>
<td>CZT</td>
<td>Nal+PS-PMTs (6800) or CsI+APDs (Acella)</td>
<td>LSO/LYSO + PS-PMTs</td>
</tr>
<tr>
<td><strong>Energy Resolution</strong></td>
<td>4.7% FWHM @140 keV</td>
<td>6.0% FWHM @140 keV</td>
<td>12.0% FWHM @140 keV</td>
<td>14.0% FWHM @ 511keV</td>
</tr>
<tr>
<td><strong>Pixel Pitch</strong> (Intrinsic Resolution)</td>
<td>1.6 mm</td>
<td>2.5 mm</td>
<td>3.2 mm</td>
<td>2.0 mm</td>
</tr>
<tr>
<td><strong># Pixels / System</strong></td>
<td>24,576</td>
<td>12,288 or 6,144 (single)</td>
<td>3,072 (6800) or 5,248 (Acella)</td>
<td>4,056</td>
</tr>
<tr>
<td><strong>Collimator</strong></td>
<td>Registered tungsten low-dose</td>
<td>Registered lead</td>
<td>LEGP lead</td>
<td>Coincidence for PET</td>
</tr>
<tr>
<td><strong>Geometric Efficiency (System Sensitivity)</strong></td>
<td>1,600 cps/MBq</td>
<td>550 (single) or 1,100 cps/MBq</td>
<td>400 cps/MBq (single head)</td>
<td>unpublished</td>
</tr>
<tr>
<td><strong>Clinical Dose</strong></td>
<td>*4 mCi 99mTc-Sestamibi</td>
<td>8 mCi 99mTc-Sestamibi</td>
<td>15 mCi 99mTc-Sestamibi</td>
<td>10 mCi 18F-FDG</td>
</tr>
<tr>
<td><strong>Whole-Body Dose</strong></td>
<td>*1.2 mSv</td>
<td>2.4 mSv</td>
<td>4.5 mSv</td>
<td>7 mSv</td>
</tr>
<tr>
<td><strong>Biopsy Guidance</strong></td>
<td>Yes: mid-2012</td>
<td>Under development</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Useful Field of View</strong></td>
<td>15.4 x 20.5 cm² or 15.4 x 24.0 cm²</td>
<td>15.7 x 23.6 cm²</td>
<td>15.0 x 20.0 cm² or 20.0 x 25.0 cm²</td>
<td>16.3 x 24.0 cm²</td>
</tr>
<tr>
<td><strong>Integral Uniformity</strong></td>
<td>1.1%</td>
<td>1.2%</td>
<td>10%</td>
<td>unpublished</td>
</tr>
</tbody>
</table>

* Improvements in progress will result in 2 mCi (0.6 mSv) in early 2013.
# Published Clinical Studies: Sassari, Italy 1635 patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Pt. #</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanu</td>
<td>Compare w/SPECT, $^{99m}$Tc-tetrofosmin (TF)</td>
<td>29</td>
<td>93</td>
<td>100</td>
<td>EANM 2006 P211</td>
</tr>
<tr>
<td>Spanu</td>
<td>BrCa detection, TF</td>
<td>85</td>
<td>90.3-100%</td>
<td>91.7</td>
<td>Int J Onc 31: 369-377 (2007)</td>
</tr>
<tr>
<td>Spanu</td>
<td>BrCa detection, TF</td>
<td>129</td>
<td>92.5-100%</td>
<td>88.2</td>
<td>EANM 2007 P198</td>
</tr>
<tr>
<td>Spanu</td>
<td>Neoadjuvant, TF</td>
<td>32</td>
<td>92.5-100%</td>
<td>88.2</td>
<td>EANM 2007 P201</td>
</tr>
<tr>
<td>Spanu</td>
<td>Neoadjuvant, TF</td>
<td>38</td>
<td></td>
<td></td>
<td>SNM 2008 1445</td>
</tr>
<tr>
<td>Spanu</td>
<td>BrCa detection, TF</td>
<td>242</td>
<td>95.4%</td>
<td></td>
<td>SNM 2008 1447</td>
</tr>
<tr>
<td>Spanu</td>
<td>BrCa detection, TF</td>
<td>145</td>
<td>97.2%</td>
<td>86.4</td>
<td>Clin Nuc Med 33(11) (2008):739-742</td>
</tr>
<tr>
<td>Spanu</td>
<td>Compare w/mammo, TF</td>
<td>232</td>
<td>93.2 (90.1 mammo)</td>
<td>88.2 (52.9 mammo)</td>
<td>QJ Nuc Med 53(2) (2009): 133-143</td>
</tr>
<tr>
<td>Spanu</td>
<td>BrCa detection, TF</td>
<td>321</td>
<td>88.9-100</td>
<td>86.4</td>
<td>SNM 2009 1696</td>
</tr>
<tr>
<td>Spanu</td>
<td>Compare w/mammo, TF Concl: 30% can avoid Bx</td>
<td>353</td>
<td>87.5</td>
<td>88.6</td>
<td>SNM 2010 1623</td>
</tr>
<tr>
<td>Spanu</td>
<td>Compare w/DCE MRI, TF Concl: MRI overstages</td>
<td>29</td>
<td>96.5 (96.5 MRI)</td>
<td></td>
<td>SNM 2010 1205</td>
</tr>
</tbody>
</table>
# Published Clinical Studies: Mayo Clinic 2747 patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Pt. #</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor</td>
<td>MBI for small tumor detection</td>
<td>100</td>
<td>85% (overall)</td>
<td></td>
<td>Int J Onc 31: 369-377 (2007)</td>
</tr>
<tr>
<td>O’Connor</td>
<td>MBI as adjunct to mammo</td>
<td>800</td>
<td>85.7 (28.6 mammo)</td>
<td>93.9 (91.2 mammo)</td>
<td>SNM 2008 Abst 159</td>
</tr>
<tr>
<td>Hruska</td>
<td>Compare dual camera versus single; BI-RADS 4 or 5</td>
<td>150</td>
<td>90 (80 single) all 82 (68 single) &lt;10 mm</td>
<td></td>
<td>Amer J Roent 191 (2008) 1805-1815</td>
</tr>
<tr>
<td>Rhodes</td>
<td>Compare w/mammo, Screening of dense breasts</td>
<td>1007</td>
<td>50 (25 mammo) DCIS 100 (29 mammo) Invasive 82 (27 mammo) All Ca 91 All Ca MBI/Mammo</td>
<td>93 (91 mammo)</td>
<td>Radiol 258 (2011): 106-118.</td>
</tr>
</tbody>
</table>
Molecular Breast Imaging (MBI)

Secondary Diagnosis

Mammogram

20 mm cancer seen on MMG & MBI

Additional 10 mm cancer seen only on MBI

Molecular Breast Imaging

Courtesy of Mayo Clinic.
Patient Example: IDC with DCIS extension

Digital Screening Mammography (Negative)
Molecular Breast Imaging (Positive)
17 mm IDC with DCIS extension

Courtesy of Mayo Clinic.
Patient Example: Ductal Carcinoma In Situ

Digital Screening Mammography (Negative)

Molecular Breast Imaging (Positive)

9 mm Ductal Carcinoma In Situ

 Courtesy of Mayo Clinic.
Patient Example: Tubulolobular Carcinoma

Digital Screening Mammography (Negative)
Molecular Breast Imaging (Positive)

7 mm Tubulolobular Carcinoma

Courtesy of Mayo Clinic.
Patient Example: MBI versus MRI

Infiltrating Lobular Carcinoma

- Index lesion detected on mammography (blue arrows)
- Multifocal cancer detected by MBI and MRI only (yellow arrows)

Screen Mammogram  MBI  Breast MRI

Courtesy of Mayo Clinic.
Patient Example: MBI versus MRI

Pre and Post Neoadjuvant Chemotherapy

MRI

Pre-therapy
Initial diagnosis: IDC with large Area of DCIS
MRI: indicated residual disease
Left Mastectomy: Surgical Pathology indicated no residual viable cancer

Post-therapy

False Positive from MRI ➔ Unnecessary Mastectomy

MBI

Pre-therapy

4.5 x 4.5 x 4.5 cm mass

2.0 x 1.1 x 2.0 cm mass

Post-therapy

Molecular Breast Imaging

Pre-therapy

Post-therapy

Courtesy of Mayo Clinic
The same Mayo Clinic authors have compiled teaching files and recorded a video CME course on “Molecular Breast Imaging Interpretation” – soon to be released.
Published MBI Screening Clinical Data

High-Risk Screening Study

Inclusion Criteria: Dense Breast + another high risk factor

1,007 patient study shows:

- 91% Sensitivity (MMG+MBI)
- 93% Specificity (MBI alone)

Includes one year follow up

Jan. 2011 Radiology
Low-Dose Dense-Breast MBI Screening

Funded by Susan G. Komen Foundation

Inclusion Criterion: > 50% Dense Breast on prior year’s MMG

8 mCi $^{99m}$Tc-sestamibi (analyzed as 4 mCi – half acquisition time)

1,700 patient study ended cohort enrollment in February 2012 with one year follow up

Interim results (reported RSNA 2011):

Diagnostic performance characteristics at participant level:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident MMG</th>
<th>Prevalent MBI</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>3/15 (30%)</td>
<td>13/15 (87%)</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td>Recall Rate</td>
<td>137/1252 (11%)</td>
<td>128/1252 (10%)</td>
<td>221/1252 (18%)</td>
</tr>
<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>
</table>

Full report at RSNA 2012

Courtesy Deborah J. Rhodes, MD, Mayo Clinic
Q3: The SNM recommends for BSGI a 925 MBq (25 mCi) $^{99m}$Tc-Sestamibi dose; what is the dose currently used by the Mayo Clinic for MBI?

0%  a) 148 MBq (4 mCi)
0%  b) 296 MBq (8 mCi)
0%  c) 370 MBq (10 mCi)
0%  d) 555 MBq (15 mCi)
0%  e) 740 MBq (20 mCi)
Q3: The SNM recommends for BSGI a 925 MBq (25 mCi) $^{99m}$Tc-Sestamibi dose; what is the dose currently used by the Mayo Clinic for MBI?

a) 148 MBq (4 mCi)

b) 296 MBq (8 mCi)

c) 370 MBq (10 mCi)

d) 555 MBq (15 mCi)

e) 740 MBq (20 mCi)

Breast Cancer Imaging Market Segments

1. General Screening
   - Recommended for women over 40 (or 50?)
   - Biggest player: Digital Mammography
   - Future players: TomoSynthesis, Counting mode MMG (MicroDose), Color CT

2. Secondary Diagnostic
   - MMG equivocal; for surgical staging & treatment monitoring
   - Emerging, growing market beginning ~2005
   - Biggest player: MRI
   - Other players: Ultrasound, MBI

3. High-Risk Screening
   - Brand-new field
   - Dense breasts, family history, BRCA genes, Ashkenazi
   - Biggest players: Ultrasound, MRI
   - Future players: MBI
Clinical Flowchart: MBI Screening & Diagnosis

High Risk (Dense Breast) Screening: MBI becomes standard

Secondary Diagnosis: MBI with MBI-guided Biopsy competes with MRI, US
Radiation dose reduction
Radiation Dose Reduction

Consider the exam-time/dose tradeoff yield from improving technology:

- detector & collimator optimization
- energy window optimization
- noise reduction algorithms
- fusion image from two detectors

Initial dose for BSGI and MBI was 20-30 mCi $^{99m}$Tc-sestamibi. MBI dose has been lowered to 8 mCi and ongoing development promises to lower it further to 2-4 mCi.
### Typical Radiation Doses (From Various Sources)*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watching television</td>
<td>0.01 mSv/year</td>
</tr>
<tr>
<td>Air travel (roundtrip from Washington, D.C., to Los Angeles, Calif.)</td>
<td>0.05 mSv</td>
</tr>
<tr>
<td>Medical chest X-ray (one film)</td>
<td>0.1 mSv</td>
</tr>
<tr>
<td>Nuclear medicine thyroid scan</td>
<td>0.14 mSv</td>
</tr>
<tr>
<td>Full set of dental X-rays</td>
<td>0.4 mSv/year</td>
</tr>
<tr>
<td>Mammogram (four views)</td>
<td>0.7 mSv</td>
</tr>
<tr>
<td>Average annual exposure living in the United States</td>
<td>3 mSv/year</td>
</tr>
<tr>
<td>Average annual exposure from breathing radon gas</td>
<td>2 mSv</td>
</tr>
<tr>
<td>Nuclear medicine lung scan</td>
<td>2 mSv</td>
</tr>
<tr>
<td>Nuclear medicine bone scan</td>
<td>4.2 mSv</td>
</tr>
<tr>
<td>Nuclear cardiac diagnostic test (technetium or Tc-99m)</td>
<td>10 mSv</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>10 mSv</td>
</tr>
<tr>
<td>Various PET studies (¹⁸F FDG)</td>
<td>14 mSv</td>
</tr>
<tr>
<td>Tobacco products (amount for a smoker’s lungs from 20 cigarettes a day)</td>
<td>53 mSv/year</td>
</tr>
<tr>
<td>Cancer treatment (tumor receives)</td>
<td>50,000 mSv</td>
</tr>
</tbody>
</table>

*Radiation doses are estimated; obtained from various sources.*
Radiation Dose Reduction

• Consider the time-dose tradeoff yield from improving technology:
  - detector / collimator optimization
  - energy window optimization
  - noise reduction algorithms
  - composite image from two detectors

![Image of Tungsten square holes registered to detector pixels]

*Courtesy of Mayo Clinic*
## System sensitivity – effect of collimation and energy window

Study performed by Mayo Clinic on LumaGEM & GE MBI system

<table>
<thead>
<tr>
<th>Detector</th>
<th>Collimator</th>
<th>Energy Window</th>
<th>counts/min/μCi</th>
<th>Relative gain in counts/pixel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CZT 1.6 mm Pixel (GMI)</strong></td>
<td>Standard</td>
<td>Standard, 140 ± 10%</td>
<td>312</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>Wide, 112 – 154 keV</td>
<td>391</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Tungsten design</td>
<td>Standard 140 ± 10%</td>
<td>905</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Tungsten design</td>
<td>Wide, 112 – 154 keV</td>
<td>1132</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>CZT 2.5 mm Pixel (GE)</strong></td>
<td>Standard</td>
<td>Standard, 140 ± 10%</td>
<td>254</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>Wide, 112 – 154 keV</td>
<td>331</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>optimized design</td>
<td>Standard 140 ± 10%</td>
<td>534</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>optimized design</td>
<td>Wide, 112 – 154 keV</td>
<td>705</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Study performed by Mayo Clinic on LumaGEM & GE MBI system

System sensitivity – effect of collimation and energy window

62%
Radiation Dose Reduction

- Consider the time-dose tradeoff yield from improving technology:
  - detector / collimator optimization
  - energy window optimization
  - noise reduction algorithms
  - composite image from two detectors

Wide energy window (20%) (110-154 keV)

CZT spectral tail: charge-sharing (10%) & hole-trapping

~1.4 gain in sensitivity

Very little scatter in breast

Courtesy of Mayo Clinic
Dual-Image Fusion & Noise Reduction - WIP

20 mCi (old protocol)

Top R MLO

Bottom R MLO

4 mCi (new WIP protocol)

Fused MLO

• noise reduction algorithms
• fusion image from two detectors

The top and bottom planar images are fused with use of an adaptive, edge-preserving, noise-reduction filter

Mayo Clinic is validating use of 4 mCi $^{99m}$Tc-sestamibi protocol in clinical studies
This low dose is equivalent to screening MMG

Courtesy of Mayo Clinic
Radiation Dose Comparisons

MBI at 2-4 mCi essentially equivalent to screening MMG
# Breast Imaging Radiation Dose

*Assumes annual breast screening for ages 40-80

~ Calculated capability – no clinical trial evidence

<table>
<thead>
<tr>
<th>Modality</th>
<th>Radiation</th>
<th>Dose / year</th>
<th>Risk*: Attributable Deaths / 100,000</th>
<th>Benefit*: Lives Saved / 100,000</th>
<th>Benefit / Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBI – Gamma Medica LumaGEM</td>
<td>2-4 mCi $^{99}$Tc-MIBI</td>
<td>~0.6 - 1.2 mSv</td>
<td>36-72</td>
<td>2408</td>
<td>34-67:1</td>
</tr>
<tr>
<td>Digital Mammography</td>
<td>X-rays</td>
<td>~0.5 mSv</td>
<td>15</td>
<td>845</td>
<td>56:1</td>
</tr>
<tr>
<td>Tomosynthesis</td>
<td>X-rays</td>
<td>~1 mSv</td>
<td>40</td>
<td>~1600</td>
<td>~40:1</td>
</tr>
<tr>
<td>PEM - Naviscan</td>
<td>10 mCi $^{18}$FDG</td>
<td>~7 mSv</td>
<td>408</td>
<td>~2000</td>
<td>~5:1</td>
</tr>
<tr>
<td>BSGI – Dilon 6800 &amp; Digirad Ergo</td>
<td>15 mCi $^{99}$Tc-MIBI</td>
<td>~4.5 mSv</td>
<td>270</td>
<td>~1800</td>
<td>~7:1</td>
</tr>
<tr>
<td>MBI - GE Discovery 750b</td>
<td>8 mCi $^{99}$Tc-MIBI</td>
<td>~2.4 mSv</td>
<td>140</td>
<td>~2200</td>
<td>~16:1</td>
</tr>
</tbody>
</table>

* Dense-breast

Shorter Exam Times

After dose reduction to MMG level:

GMI & Mayo Clinic are developing new technology (electronics and software algorithms) to achieve by mid-2013:

- 3 - 5 min/view @ 4mCi  or
- 6 - 8 min/view @ 2 mCi

Result: 15 – 35 min total screening exam time
Mammographically Occult Cancers Detected on MBI

10 mm + 16 mm IDC
8 mm DCIS
9 mm ILC
9 mm IDC

17 mm IDC + DCIS
7 mm tubulolobular ca
9 mm DCIS
13.5 mm ILC (total extent 5.1 cm)

Courtesy of Mayo Clinic.
Q4: What are the most important factors leading to a dose reduction in MBI?

0%  a) Quantum efficiency of the detector, LEHS collimator
0%  b) Patient prep (fasting, delay for background washout), LEHS collimator
0%  c) LEHS collimator, noise reduction filter, CZT detectors
0%  d) Optimal pixel size, registered collimator, two detector heads, noise reduction filter
0%  e) Registered tungsten collimator, CZT detectors
Q4: What are the most important factors leading to a dose reduction in MBI?

a) Quantum efficiency of the detector, LEHS collimator
b) Patient prep (fasting, delay for background washout), LEHS collimator
c) LEHS collimator, noise reduction filter, CZT detectors
d) Optimal pixel size, registered collimator, two detector heads, noise reduction filter
e) Registered tungsten collimator, CZT detectors

Pre-requisite to screening: MBI-guided Biopsy

MBI-guided biopsy on LumaGEM® is being developed

- Clinical trials at beta sites mid-2012
- Stereotactic targeting
- Lateral access to breast between detectors
- Specimen verification

Screening MMG → Screening MBI → Bx? (No → Home)

Yes → 2nd-Look US

US-guided Bx

Yes: ~85% Visible? No: ~15%

MBI-guided Bx

Breast Quadrants and Breast Cancers

Visualize occult lesions with higher specificity
BSGI- & PEM-guided Biopsy

Dilon – top approach

Naviscan – lateral approach

PEM limited angle tomography produces 12 slices (5 mm thick for average mildly compressed breast): inherent 3D lesion location

Sliding slant-hole collimator for stereo 3D lesion location
Blevis, US2010/0329419
Q5: What advantages does MBI-guided biopsy (MBI-Bx) have over mammography-guided biopsy in women with dense breast tissue?

MBI-Bx has:

- a) higher resolution, higher reimbursement, and is faster
- b) higher specificity, instant specimen verification, and visualizes occult lesions
- c) higher photon energy, lower radiation dose, and higher reimbursement
- d) higher sensitivity, specificity, and resolution
- e) lower radiation dose, instant specimen verification, and higher reimbursement
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MBI-Bx has:

a) higher resolution, higher reimbursement, and is faster

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c) higher photon energy, lower radiation dose, and higher reimbursement

d) higher sensitivity, specificity, and resolution

e) lower radiation dose, instant specimen verification, and higher reimbursement

Performance of MBI, BSGI, & PEM
Performance tests

Several NEMA NU1 tests can be adapted to characterize the performance of the small-FOV planar gamma cameras of MBI and BSGI.

Collimators in place (extrinsic) for all:

- Energy Resolution
- Uniformity
- Spatial Resolution
- Sensitivity (Geometric Efficiency)
Energy Resolution

Planar $^{57}\text{Co}$ or Flood $^{99m}\text{Tc}$ source placed between two detector heads

Individual CZT pixel energy calibrations (linear) applied

Summation of energy spectrum of all pixels

Fit Gaussian to photopeak
Energy Resolution - Example

4.0% FWHM
140.5 keV

Typical: 4.7 ± 0.4%
Uniformity

Planar $^{57}$Co or Flood $^{99m}$Tc source placed between two detector heads

Uniformity map measured (1 wk – 1 mo)

Uniformity corrections applied

Calculate NEMA integral & differential uniformity for entire FOV
Uniformity - Example

Typical:
1.1 ± 0.2% integral
0.9 ± 0.1% differential

Displayed to show very small differences
Spatial Resolution (No scatter)

Thin tubing filled with $^{99m}$Tc
Offset 3 cm from detector cover
Detector separation 6 cm
Measure in x&y orientations
Measure profiles, deconvolve ID of tubing

Typical:
5.0 ± 0.9 mm FWHM
9.1 ± 1.6 mm FWTM
Sensitivity (Geometric Efficiency)

Tubing filled with 99mTc, coiled to fit dose calibrator
Place between detector heads
Count 10 minutes
Calculate

Typical:
667 ± 56 cps/MBq/head = 1482 ± 124 cpm/mCi/head
NEMA 2 measurements can be adapted to characterize PEM performance.

I have had no access to a PEM, so I have no examples.
Breast Lesion Phantom - WIP

GMI is developing a breast lesion phantom with Frank DiFilippo (Cleveland Clinic) & Michael O’Connor (Mayo Clinic), to measure:
  • Lesion detectability
  • Contrast recovery

Validation on multiple vendor systems (MBI & PEM)

Goal: to specify phantom and procedure for ACR accreditation

Conclusions

• Every MBI, BSGI, or PEM system is more sensitive than screening MMG in dense breasts

• **Dose** must be reduced to match screening MMG (LumaGEM has demonstrated this low-dose capability)

• **MBI-guided biopsy** must be demonstrated (LumaGEM will provide biopsy guidance in mid-2012)

• **Exam time** must be reduced to under 30 minutes (LumaGEM will achieve this by mid-2013)

• **Clinical trials** must demonstrate value of dense-breast MBI screening (Mayo Clinic / LumaGEM trial will be published mid-2013)
Learning Objectives

• Understand the physics of MBI, BSGI, and PEM breast imaging.

• Understand how radiation dose can be lowered in MBI, BSGI, and PEM.

• Understand how to characterize the performance of MBI, BSGI, and PEM systems.