Molecular Imaging of the Breast

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Conflict of Interest
Dr. M.K. O’Connor
Royalties - Gamma Medica
Research funding – GE Healthcare

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- Susan G. Komen Foundation
- Mayo Foundation
- Friends for an Earlier Breast Cancer Test

Molecular Imaging of the Breast Instrumentation

- PEM (Positron Emission Mammography)
  * Clinical unit developed by Naviscan
  * Numerous prototype PEM and PEM/CT units under development

- BSGI (Breast Specific Gamma Imaging)
  * Single detector, multicrystal NaI based gamma camera
  * Developed by Dilon Technologies

- MBI (Molecular Breast Imaging)
  * Dual detector Cadmium Zinc Telluride based gamma cameras
  * Clinical units developed by Gamma Medica and GE Healthcare

PEM (Positron Emission Mammography)

- Original design proposed by Weinberg in 1995
- Only system that is FDA approved
- Clinical studies: 10 mCi F-18 FDG
- FOV: 16 cm x 24 cm
- Limited angle tomography
  2.4 mm resolution (in plane)
  8.0 mm resolution (cross-plane)
  (JNM 2009;50:1666-1675)

PET-Guided Breast Biopsy

**Mammi-PEM**

LYSO Block Crystal: 40 x 40 mm coupled to a PSPMT
Axial FOV = 4 cm
Spatial resolution = 1.6 – 1.9 mm

**Clear-PEM**

2 detector arrays of LYSO crystals (6144 crystals)
18 x 16 cm FOV
Spatial resolution (x, y, z): 2.4 x 1.8 x 2.7 mm

**C-PEM (Shimadzu Corporation)**

Detector ring: 78 cm diameter
Axial FOV: 4.8 cm per ring.
System can be expanded up to 3 rings.
C-PEM (Shimadzu Corporation)

Ring comprises 48 detector modules
4098 LGSO crystals
1.5 x 1.5 mm crystals
Measured resolution (x, y, z):
1 mm x 1.3 mm x 1 mm
Yamada et al, IEEE NSS 2007

MDA - PEM (M.D. Anderson)

2 detector arrays of LYSO crystals coupled to PMTs
1.54 x 1.54 mm crystals
In-plane resolution: 1.5-2.5 mm
Cross-plane resolution: ~4.5 mm

PEM / CT (UCD)

2 detector arrays of LYSO crystals coupled to PSPMTs
768 Slice Cone Beam CT

Crystal size (mm) 3 x 3 x 20
Crystal array 81 (9 x 9)
No. of detector blocks 16 (4 x 4)
FOV (cm) 11.9 (axial + transaxial)

PEM / CT (UCD)

Axial (A) and coronal (B) PEM/CT images in a patient with IDC and DCIS
Bowen et al, JNM 2000;50: 1401-1408

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Instrumentation

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BSGI (Breast Specific Gamma Imaging) developed by Dilon Technologies

Developed by Majewski et al, 1998

FOV: 15 cm x 20 cm
Single detector with array of 3 mm x 3 mm NaI crystals

3.3 mm intrinsic resolution
~14% energy resolution

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Cadmium Zinc Telluride (CZT) Detector

- Intrinsic Resolution = 1.6 mm / 2.5 mm
- Energy Resolution 4.0% / 6.5%
- Can be operated at room temp
- Dead space ~8 mm – ideal for breast imaging
- Expensive – currently limited to small field of view detectors

Technology

<table>
<thead>
<tr>
<th>Technology</th>
<th>Tumors 5-10 mm in size</th>
<th>Tumors &lt; 5 mm in size</th>
<th>All Tumors (128 in 88 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard γ-Camera*</td>
<td>55%</td>
<td>No data</td>
<td>82%</td>
</tr>
<tr>
<td>Single-head MBI</td>
<td>76%</td>
<td>44%</td>
<td>90%</td>
</tr>
<tr>
<td>Dual-head MBI</td>
<td>87%</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

**Multi-modality MBI/CT and BSGI/DBT**

Combined BSGI/Tomosynthesis system (University of Virginia)

Combined MBI/CT system (Duke University Medical Center)

**Molecular Imaging of the Breast Imaging Procedure**

**PEM**
- IV injection of F-18 FDG
  - 10 mCi (PEM-Flex system)
  - 2.8 mCi (Mammi-PEM)

- Fasting and monitoring of blood glucose
- Imaging starts 45-60 minutes post injection.
- Naviscan system: Mammographic orientation with light breast compression.
- Newer PEM systems: Breast is pendulous
- FDG preferentially accumulates in cancer cells and is not influenced by breast density or hormonal status

**MBI / BSGI**
- IV injection of Tc-99m sestamibi
  - 20-30 mCi (BSGI)
  - 4-8 mCi (MBI)

- No patient preparation required
- Imaging starts ~5 minutes post injection.
- Mammographic orientation with tight breast compression.
- Sestamibi preferentially accumulates in cancer cells and is influenced by breast density
- Uptake of sestamibi is influenced by hormonal effects

**Molecular Imaging of the Breast Clinical Indications**

**BSGI (Breast Specific Gamma Imaging)**

Administered doses
- 20 – 37 mCi Tc-99m sestamibi
  (Brem et al, Academic Radiol 2010; 17: 735-743)

Applications:
- Problem solving in indeterminate cases (BIRAD 3)
- Pre-operative evaluation of disease extent

Retrospective reviews
- 68 patients: Sensitivity 89%, specificity 90%
  (Kim BS, Ann Nucl Med 2012; 26: 131-137)

Limited prospective studies performed to date

**Molecular Imaging of the Breast BSGI Clinical Results**

Pre-operative evaluation
- 82 patients – 18 additional abnormality on BSGI, 7 cancers
- 138 patients – 25 additional abnormality on BSGI, 15 cancers

Adjunct Diagnostic Tool
- 146 patients – 167 lesions underwent biopsy
  BSGI detected 80/83 malignant lesions (96% sensitivity)
  identified 50/84 benign lesions (60% specificity)

**BSGI as an adjunct diagnostic tool – results from a multi-institution registry of 1024 patients**

<table>
<thead>
<tr>
<th>Performance Parameter</th>
<th>Mamrogram</th>
<th>Ultrasound</th>
<th>Breast Specific Gamma Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>74</td>
<td>84</td>
<td>70</td>
</tr>
<tr>
<td>Specificity</td>
<td>79</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>71</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>82</td>
<td>15</td>
<td>83</td>
</tr>
</tbody>
</table>

Note: Data are percentages.
Positive Mammogram

1.1 cm nodular density in upper inner right breast 9.5 cm from the nipple

Positive Mammogram

2 x 1 cm IDC with multiple satellite lesions confirmed as DCIS on MRI

MBI Procedure

- Complementary opposing views of the breast
- Image interpretation: 8 images
- Time to interpret: ~1-2 minutes

Molecular Imaging of the Breast

Clinical Indications

Mammogram

Patient pre and post neoadjuvant therapy

Pre-Therapy

After 3 months of therapy

Molecular Breast Imaging

Patient pre and post neoadjuvant therapy

Molecular Breast Imaging

Patient pre and post neoadjuvant therapy
PEM Imaging in patients undergoing neoadjuvant therapy

Patient with multifocal breast cancer before and after neoadjuvant chemotherapy

(Koolen et al, Ann Oncology 2012; Article ID 438647)

Molecular Imaging of the Breast

Clinical Indications

Shilling et al, EJNMMI 2011;38:23-26

Sensitivity: PEM vs MRI

<table>
<thead>
<tr>
<th>Breast Cancer</th>
<th>PEM</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>90%</td>
<td>83%</td>
</tr>
<tr>
<td>Invasive DC</td>
<td>93%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Nuclear Imaging vs MRI

- PEM (Berg et al, Radiol 2012;198:219-232)
  - Comparable estimate of disease extent

<table>
<thead>
<tr>
<th>Modality</th>
<th>Accurate</th>
<th>Underestimated</th>
<th>Overestimated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEM</td>
<td>68%</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>MRI</td>
<td>75%</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>
• Dense breast tissue decreases sensitivity/specificity of mammography
• Density, itself, significantly increases risk of breast cancer

Goal - Compare MBI and mammography in asymptomatic patients with dense breasts and increased risk of breast cancer (~1000 patients)
• MBI performed using 20 mCi Tc-99m sestamibi per study
• Question – is MBI a viable screening adjunct to mammography in patients with dense breasts?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mammography</th>
<th>MBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>3/11</td>
<td>9/11</td>
</tr>
<tr>
<td>No.</td>
<td>% 27</td>
<td>82</td>
</tr>
<tr>
<td>Specificity</td>
<td>840/925</td>
<td>861/925</td>
</tr>
<tr>
<td>No.</td>
<td>% 91</td>
<td>93</td>
</tr>
<tr>
<td>Recall rate</td>
<td>88/936</td>
<td>71/936</td>
</tr>
<tr>
<td>No.</td>
<td>% 9</td>
<td>8</td>
</tr>
</tbody>
</table>

Rhodes, Radiology, 2011

8 mammographically occult cancers detected on MBI
• 313 patients enrolled Oct 2008 – June 2010
• 284 / 306 patients negative or benign findings on MBI
• 22 (7.2%) patients with positive MBI findings
• 4 cases confirmed as breast cancer (all negative on mammogram)
Patients with Positive MBI findings

- 4 new cancers detected by MBI
  - 12 mm IDC/ILC
  - 9 mm IDC
  - 2 mm IDC + 6 mm DCIS
  - 3 mm DCIS

Supplemental diagnostic yield of 13.1 per 1000 women screened.

MBI Detected Cancer

- Screening mammography in June 2008 noted stable nodule, unchanged from previous annual mammogram.
- Patient presented for myocardial perfusion scan in Feb 2009.
- Enrolled in MBI study - positive.
- Patient returned March 2010 for evaluation – palpable, mammographically occult breast cancer.

MBI for Breast Cancer screening in women with mammographically dense breasts

- Goal – Comparison of MBI and mammography in asymptomatic patients with dense breasts (~1600 patients or 20 cancers).
- Evaluation of low-dose MBI as a viable screening adjunct to mammography in patients with dense breasts?
  - MBI performed using 8 mCi Tc-99m sestamibi per study.

Diagnostic Performance Characteristics of Screening MMG and MBI at Participant Level (interim results)

Study was closed to enrollment at end of February 2012 – 12 month follow-up in progress.
Interim report to be presented at RSNA 2012.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident MMG</th>
<th>Prevalance MBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>3/15</td>
<td>13/15</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Summary findings – 3 MBI screening trials

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Recall Rate (%)</th>
<th>Diagnostic Yield / 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense Breast, increased risk</td>
<td>936</td>
<td>7.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Cardiac Patients</td>
<td>303</td>
<td>7.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Dense Breast (low dose MBI)</td>
<td>1649</td>
<td>7.6</td>
<td>10.9</td>
</tr>
</tbody>
</table>
Interval Screening
MBI vs Mammography in women with dense breasts

- Compare interval screen detected breast cancer with MBI and mammography (~2000 patients or 20 cancers)
- MBI performed using 4 mCi Tc-99m sestamibi per study

8 mCi Study (3/8/2010) 4 mCi Study (7/17/2012)

Which Technology for Screening & Early Diagnosis?

- Mammo
- Tomosynthesis
- MRI
- AWBU
- MBI
- PEM

What Frequency?
- Annual
- Biennial
- Alternating

What Risk Factors?
- Dense Breasts
- Gail/Claus models

Individualized Medicine

Which technology?

- MBI
- PEM

What Age?
- < 40 Premenopausal
- Postmenopausal
- 40-49
- > 50

What Risk Factors?

- Dense Breasts
- Gail/Claus models

Relative Radiation Risks
(assuming validity of LNT hypothesis / BEIR VII Report)

Radiation dose to patients
- Mammmogram ~ 0.7 mSv
- PEM-Flex (10 mCi F-18 FDG) ~ 7 mSv
- Mammi-PEM (2.8 mCi F-18 FDG) ~ 2 mSv
- BSGI (25-30 mCi Tc-99m mibi) ~ 9 mSv
- MBI (4 mCi Tc-99m mibi) ~ 1.2 mSv

For pop. of 100,000 women undergoing above procedures at age 40, estimated cancer mortality (based on BEIR VII)
- Mammmogram ~ 2
- PEM-Flex (10 mCi F-18 FDG) ~ 30
- BSGI (25-30 mCi Tc-99m mibi) ~ 35
- Mammi-PEM (2.8 mCi F-18 FDG) ~ 8
- MBI (4 mCi Tc-99m mibi) ~ 4

Breast Cancer Risk after Radiotherapy in Infancy
Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years

Lundell et al, Radiation Research 1999; 151: 626-632
Conclusions

Significant developments in both PET and SPECT instrumentation dedicated to breast imaging

Radiation doses are or will be at comparable levels to mammography for both PEM and MBI

Barriers to clinical use?
• Lack of multi-center trials
• Few prospective clinical trials to date
• Lack of reimbursement for clinical studies
• Difficulty in integrating nuclear medicine procedures into a breast imaging practice

Radiopharmaceuticals

• New radiopharmaceuticals?

- Tc-99m Sestamibi
- Tc-99m Tetrofosmin
- F-18 FDG
- Tc-99m αV-β3 Integrin
- F-18 αV-β3 Integrin
- Tc-99m Annexin V
- I-123 Iodo-estradiol
- I-123 Methoxy-vinylestradiol
- I-123 Dimethyl-Tamoxifen
- F-18 estradiol

Uptake in breast tissue twice that of sestamibi (dose reduction by 2)