The Future of Breast Imaging in Nuclear Medicine

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Primary Breast Imaging Modalities
Strengths and Weaknesses

- Screening mammography
- Digital mammography
- Ultrasound
- MRI
- Scintimammography
- Molecular Imaging of the Breast
28-65% of decline in breast cancer mortality can be attributed to use of screening mammography in women older than 40.

Cancer Intervention and Surveillance Network, NEJM 2005;353:1784-1792
Mammography and Breast Density

- Relative amount of fat vs. connective and epithelial tissues
- Different proportions account for variation in density on x-ray
- Fat is radiolucent, appears dark
- Connective and epithelial tissues are radiologically dense, appear white
Breast Density Classification

- <25%: Sensitivity 70%-90%
- 25-49%: Sensitivity 40%-70%
- 50-74%: Sensitivity 40%-70%
- ≥75%: Sensitivity 40%-70%

Breast cancer and tumors appear white on mammogram and may be indistinguishable from dense breast tissue.
<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>Dense breast parenchyma</td>
<td>4-6</td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td>3-4</td>
</tr>
<tr>
<td>Family history (1° relative)</td>
<td>2.1</td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td>1.5</td>
</tr>
<tr>
<td>Prempro (WHI)</td>
<td>1.26</td>
</tr>
</tbody>
</table>
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Digital Mammography

- Analogous to film vs digital camera
- Images stored digitally; easy to retrieve & compare
- Enables contrast enhancement and magnification
- Resolution inferior to film screen
- Easier implementation of CAD

Digital image
Screen-film image
DMIST Trial
Pisano et al, NEJM 2005

- Multicenter trial (33 sites)
- Comparison of digital and film mammography in 49,528 asymptomatic women presenting for screening mammography
- Follow-up at 1 yr and 1 yr+3 months
Conclusion: The big print (widely reported in the media)

“Digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women.”

Conclusion – 1 year later: The fine print (presented RSNA 2006)

“Pre or Peri-menopausal women under the age of 50 who had dense breasts comprised the ONLY group for which digital mammography was significantly better than film.”
### DMIST Trial – Table 3 (465 day follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Digital</th>
<th>Film</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.41±0.03</td>
<td>0.41±0.03</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.98±0.001</td>
<td>0.98±0.001</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>0.12±0.01</td>
<td>0.13±0.01</td>
</tr>
<tr>
<td><strong>Women &lt;50 yr old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.49±0.06</td>
<td>0.35±0.06</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.97±0.001</td>
<td>0.98±0.001</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.08±0.01</td>
<td>0.07±0.01</td>
</tr>
<tr>
<td><strong>Premenopausal and perimenopausal women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.47±0.05</td>
<td>0.38±0.05</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.97±0.001</td>
<td>0.98±0.001</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.10±0.01</td>
<td>0.09±0.01</td>
</tr>
<tr>
<td><strong>Women with heterogeneously dense or extremely dense breasts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.38±0.04</td>
<td>0.36±0.04</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.97±0.001</td>
<td>0.97±0.001</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.10±0.01</td>
<td>0.10±0.01</td>
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Pisano et al, NEJM 2005
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ACRIN 6666
Screening Breast Ultrasound in High-Risk Women

Multicenter trial (22 sites) with 2637 women enrolled
Annual ultrasound and mammography for 3 years

**JAMA 2008; 299: 2151-2163.**

- 41 cancers detected
  - 20 by mammography (sens 50%)
  - 20 by ultrasound (sens 50%)
  - 12 additional by ultrasound
  - 9 by neither modality

**Mammography:**
- 2.6% biopsy, 29% positive

**Ultrasound:**
- 5.2% biopsy, 8.8% positive

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Study PI – Wendie Berg: "Women contemplating breast ultrasound screening must be aware of the substantial risk of false positives"

Study Co-I – Etta Pisano: “based on the study results, it is difficult to determine whether screening ultrasound is worthwhile”
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## Sensitivity of MMG, US, and MRI in Women at Increased Risk

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Subjects (no.)</th>
<th>Sensitivity MMG (%)</th>
<th>Sensitivity US (%)</th>
<th>Sensitivity MRI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl, 2000</td>
<td>Germany</td>
<td>192</td>
<td>33</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Warner, 2004</td>
<td>Canada</td>
<td>236</td>
<td>36</td>
<td>33</td>
<td>77</td>
</tr>
<tr>
<td>Kriege, 2004</td>
<td>Netherlands</td>
<td>1,909</td>
<td>40</td>
<td>NA</td>
<td>71</td>
</tr>
<tr>
<td>Kuhl, 2005</td>
<td>Germany</td>
<td>529</td>
<td>33</td>
<td>40</td>
<td>91</td>
</tr>
<tr>
<td>Leach 2005</td>
<td>U.K.</td>
<td>649</td>
<td>40</td>
<td>NA</td>
<td>77</td>
</tr>
<tr>
<td>Sardanelli, 2006</td>
<td>Italy</td>
<td>3571</td>
<td>40</td>
<td>43</td>
<td>81</td>
</tr>
</tbody>
</table>
Recommend annual MRI screening for women with a high lifetime risk of breast cancer – defined as 20% or more.
MRI: Main Disadvantages

Complexity
- Typical contrast enhanced breast MRI may contain 900-1000 images

Cost (Medicare reimbursement rate)
- Analog Mammogram ~ $90
- Digital Mammogram ~ $140
- Bilateral breast ultrasound ~ $200
- Bilateral MRI > $1,000

Specificity
- (tertiary centers) ~ 90%
- (community centers) ~ 50%
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Scintimammography

- Tc-99m sestamibi approved by the FDA for breast imaging in 1997
- Several large multicenter studies undertaken in late 1990s
    Sensitivity = 85%, specificity = 89%
    Sensitivity 35-64% for lesions <1 cm
    Sensitivity ~55% for masses <15 mm
Impact of Tumor Size on Metastatic Disease

- <10 mm: 5-year survival = 98%
- 30 mm: 5-year survival = 70%


Node negative (%)

- <10 mm: 5-year survival = 98%
- 30 mm: 5-year survival = 70%

Conventional Scintimammography
Anatomic vs Molecular Imaging

Mammography

Compression Paddle

X-ray Film Cassette

Nuclear Medicine

Compression Paddle

Gamma Camera
Anatomic vs Molecular Imaging

Mammography
Compression Paddle
X-ray Film Cassette

Nuclear Medicine
Compression Paddle
Gamma Camera

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Effect of Breast Thickness on Lesion Detection

Tumor Depth = 7 cm
Tumor Depth = 3 cm
Primary Breast Imaging Modalities
Strengths and Weaknesses

• Screening mammography
• Digital mammography
• Digital Breast Tomosynthesis
• Ultrasound
• MRI
• Scintimammography

Molecular Imaging of the Breast
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**Positron Emission Mammography**

- **F-18 FDG, 8-20 mCi**
- **High spatial resolution**
  - 1.5 - 2.0 mm in-plane resolution
- **4-10 minute scan time**
- **3-D tomographic PET images**
- **Variable uptake in some breast cancers**
- **Very early stages of this technology**
  - Anticipate improvement in radiopharmaceuticals / technology

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2008 Annual Meeting of the Society of Nuclear Medicine (SNM)
PEM in Pre-surgical Evaluation

- Approximately 10% of B.C. patients will have additional lesions undetected by mammography
- Accurate identification of additional ipsi-lateral or contra-lateral disease – comparable sensitivity to MRI
- Discrimination of malignant from benign lesions within the same breast
- Significantly better resolution than conventional PET

Same phantom filled with FDG imaged on PEM and WBPET
Multi-center study of 92 malignant breast lesions in 77 women

PEM overall sensitivity for detecting cancer was 90%, specificity 86%

Sensitivity 63% for cancers < 1 cm

Sensitivity 91% for DCIS

Possible reduced sensitivity for lobular / tubular carcinomas due to decreased metabolic activity
Single-Photon Imaging Technology

Small Field of View Gamma Cameras

Digirad
Multicrystal
Cesium Iodide
+ Photodiodes

Dilon Inc.
Multicrystal
Sodium Iodide
+ PMTs

Gamma Medica
Cadmium Zinc Telluride (CZT)
Semiconductor

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Detection of Ductal Carcinoma in Situ with Mammography, Breast Specific Gamma Imaging, and Magnetic Resonance Imaging: A Comparative Study

Technologies

3000 3 x 3 mm NaI crystals
Energy resolution 15-20%

Procedure

25-30 mCi Tc-99m Sestamibi
4 x 10 minute views (CC & MLO)

Results

22 cases of biopsy-proven DCIS in 20 women
91% detected with BSGI
82% detected with mammo
88% detected with MRI

Pathology

Pathologic tumor size of the DCIS ranged from 2 to 21 mm (mean 9.9 mm).
Semiconductor Detector
Direct conversion of Gamma Ray – Electrical Current

Electron Energy

Conduction Band

Band Gap ~ 1 eV

Valence Band

Semiconducting Material

Electrode

V-

Semiconductor Detector

V+

γ-ray

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Cadmium Zinc Telluride (CZT) Detector

- Excellent Intrinsic Resolution = 1.6 – 2.5 mm
- Excellent Energy Resolution 3.5 – 6.5%
- Can be operated at room temp
- No dead space – ideal for breast imaging
- Expensive – currently limited to small field of view detectors
- First commercial gamma cameras using CZT available 2008
Molecular Breast Imaging

- CZT Gamma Camera Technology (GE Healthcare and Gamma Medica-Ideas)
- 2 Opposing CZT Detectors
- High Intrinsic Spatial Resolution (1.6-2.5 mm)
- Optimal configuration for breast imaging
- Dual-detector configuration permits quantification of tumor uptake
Can MBI find small breast tumors?

- 8.1, 10mm IDC
- 17, 5.7, 3.3 mm ILC
- 4.7 mm IDC
- 12.7, 5.0 mm IDC
- 5.5 mm ILC
- 13.7, 11.7 mm ILC
- 8.0 mm IDC with Extensive DCIS
- 2.5 mm IDC
- ~9 mm DCIS
- 7.0, 6.0 IDC
Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera for Detection of Small Breast Tumors

AJR 2008; submitted

Carrie B. Hruska, Ph.D., Stephen W. Phillips, M.D., Dana H. Whaley, M.D., Deborah J. Rhodes, M.D., Michael K. O‘Connor, Ph.D.

<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></td>
</tr>
<tr>
<td>Single-head MBI</td>
<td>76%</td>
<td>44%</td>
<td>82%</td>
</tr>
<tr>
<td>Dual-head MBI</td>
<td>87%</td>
<td>67%</td>
<td>90%</td>
</tr>
</tbody>
</table>


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Objective: Evaluation of MBI as a Screening Technique in Women at Increased Risk of Breast Cancer

Study Design:
- Compare MBI and mammography in asymptomatic patients with dense breast pattern on mammogram and who were at high risk of breast cancer
  - Prior history of BC, not on Tam or AI
  - Family history in one FDR or two SDR
  - Gail 5-year risk > 1.66 %
  - Gail lifetime risk > 20%
  - Prior atypia or LCIS
  - > 50% of breast considered dense tissue on a prior mammogram
Screening Study: Interim Results*
950 screening patients studied as of April 2008

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Cancers Detected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>MBI</td>
<td>77% (10/13)</td>
</tr>
<tr>
<td>Combination</td>
<td>85% (11/13)</td>
</tr>
</tbody>
</table>

Specificity: Mammography: 91.2%, MBI: 93.9%
Screening Patient Examples

Digital Screening Mammography (Negative)

Molecular Breast Imaging (Positive)
26x10x16 mm IDC with DCIS
Digital Screening Mammography (Negative)

Molecular Breast Imaging (Positive)

9 mm Ductal Carcinoma In Situ
Screening Patient Examples

Digital Screening Mammography (Negative)

Molecular Breast Imaging (Positive)

7 mm Tubulolobular Carcinoma
Parathyroid scan with sestamibi

MBI vs. SPECT
Screening Patient Examples

Digital Screening Mammography (Negative)

Molecular Breast Imaging (Positive)

9 mm Invasive Ductal Carcinoma
Limitations of Molecular Imaging of the Breast

- Radiation dose to the body
  - MBI Study ~ 7 mSv for 740 MBq
  - PEM Study ~7 mSv for 370 MBq
  - Mammogram < 1 mSv

- Dose becomes a significant issue for any screening study performed annually!
Molecular Imaging of the Breast
Future Developments – New Radiopharmaceuticals

- Tc-99m Sestamibi
- Tc-99m Alpha5-Beta3 Peptide
- Tc-99m Thio-glucose
- Tc-99m EC-glucosamine
- Tc-99m (V)-DMSA
- Tc-99m Vitamin B12
- I-123 Methoxy-vinylestradiol
- I-123 Dimethyl-Tamoxifen

- F-18 FDG
- F-18 Fluoro-L-thymidine (FLT)
- F-18 Vitamin B12
Molecular Imaging of the Breast

- Clinical applications
  - Screening in high-risk women
  - Pre-operative staging to exclude multifocal/contralateral cancers
  - Neo-adjuvant chemotherapy evaluation

- Alternative radiotracers
  - Improved detection of lesions < 5 mm
  - Improved detection of DCIS and atypia
  - Improved determination of tumor grade

- Dual-detector configurations (PEM, MBI) permit quantitation of tumor uptake
  - Better distinguish benign from malignant lesions
  - Monitor tumor uptake and size

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