Molecular Breast Imaging

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- Mayo Foundation
- Friends for an Earlier Breast Cancer Test

Mammography: The Problem

Breast cancer and tumors appear white on mammogram

Cancer clearly visible in non-dense breast

Sensitivity 80%-90%

Cancer would be occult in dense breast

Sensitivity 40%-70%

Breast Cancer

Comparative Relative Risks

<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 (1st 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>

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>
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<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>
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<tr>
<td>Leach, 2005</td>
<td>U.K.</td>
<td>649</td>
<td>40</td>
<td>NA</td>
<td>77</td>
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<tr>
<td>Sardanelli, 2006</td>
<td>Italy</td>
<td>3571</td>
<td>40</td>
<td>43</td>
<td>81</td>
</tr>
</tbody>
</table>
American Cancer Society
New guidelines issued on March 28th, 2007
Recommemad 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 over 1500 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%

Nuclear Medicine / Molecular Imaging
Scintimammography
• Tc-99m sestamibi approved by the FDA for breast imaging in 1997
• Several large multicenter studies undertaken in late 1990s
  (2000 patients)
  Sensitivity = 85%, specificity = 89%

  Sensitivity 35-64% for lesions <1 cm
  Sensitivity ~55% for masses <1.5 cm

Impact of Tumor Size on Metastatic Disease

<10 mm: 5-year survival = 98%
30 mm: 5-year survival = 75%
Conventional Scintimammography

Small Field of View Gamma Cameras

Digirad
Multicrystal
Cesium Iodide
+ Photodiodes

Dilon Inc.
Multicrystal
Sodium Iodide
+ PMTs

CZT Technology
Cadmium Zinc Telluride (CZT) Semiconductor

Breast Phantom: Comparison between Systems*


<table>
<thead>
<tr>
<th>Tumor Depth</th>
<th>MC-Nal</th>
<th>NaI</th>
<th>CZT</th>
<th>MC-CsI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 cm</td>
<td></td>
<td></td>
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Cadmium Zinc Telluride (CZT) Detector

- Excellent Intrinsic Resolution = 1.6 mm
- Excellent Energy Resolution 4.0%
- 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 developed for nuclear cardiology
How does Molecular Breast Imaging Work?

- Patient receives an IV injection of a radiotracer (Tc-99m sestamibi)
- The tracer preferentially accumulates in cancer cells and is not influenced by breast density
- The breast is lightly compressed between the 2 MBI gamma cameras, only light pain-free compression is necessary
- Imaging starts ~5 minutes post injection. Acquire CC and MLO views of each breast for 10 minutes each.
- Procedure performed by nuclear medicine technologist trained in mammographic positioning techniques

Can MBI find small breast tumors?

- MBI Prototypes developed at Mayo over last 6 yrs using detectors from Gamma Medica and GE Healthcare
- Cadmium Zinc Telluride (CZT) gamma camera technology
  - Expensive – currently limited to small field of view detectors
  - Dual-detector design optimized for breast imaging
  - Anticipated cost ~$400 / study
Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera for Detection of Small Breast Tumors


Comparison of Screening MBI and Mammography

- 1000 patient screening study
- Funded by Susan G. Komen Foundation
- Compare MBI and mammography in patients with dense breasts at high risk of breast cancer
  - Prior history of breast cancer
  - Family history in one FDR or two SDR
  - Gail lifetime risk > 20%
  - Prior atypia or LCIS

Question – is MBI a viable screening adjunct to mammography in patients with dense breasts?

Results

- In 958 patients studied, a total of 14 cancers in 12 patients were diagnosed.
  - 8 cancers detected by MBI alone
  - 1 cancer detected by mammography alone
  - 2 cancers detected by both MBI and mammography

Comparison of Imaging Modalities

- MBI
- Mammography
- Combination

Screening Patient Examples (1)

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

9 mm Ductal Carcinoma In Situ

MBI vs. SPECT

Parathyroid scan with Tc-99m sestamibi performed 4 weeks prior to MBI study in Screening Patient Example #3

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

9 mm Invasive Ductal Carcinoma

Screening Patient Examples (3)

Screening Patient Examples (4)

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

7 mm Tubulolobular Carcinoma
Results in 958 Patients with 12-month Follow-up

Sensitivity: All cancers detected by any means in the 12-month period since the MBI study.

- 10 / 14 cancers detected by MBI (sensitivity = 71%)
- 3 / 14 cancers detected by mammography (sensitivity = 21%)

Specificity: Patients with a negative follow-up mammogram at 1 year and no clinical symptoms at 12-months were assumed to be disease free.

- Specificity - MBI: 93% Recall Rate – 7.5%
- Specificity - mammography: 90% Recall Rate – 9.2%

Molecular Breast Imaging in Patients undergoing Myocardial Perfusion Imaging

- MBIs performed in women presented for myocardial perfusion studies, no additional dose needed
- Of 158 patients
  - 3 cancers detected, 1 only detected by MBI
  - 1 patient with uptake in papilloma and atypia
  - 154 patients with negative findings
- Negative screening mammogram
- Myocardial perfusion scan and MBI 1 week later
- Follow-up Dx mmg/US positive, 8 mm IDC/DCIS
- Breast MRI correlated with MBI

MBI - Potential Screening Application

- MBI has 2-3 times sensitivity of mammography in the high-risk and dense breast populations
- MBI appears to have comparable sensitivity (80%) to that reported for MRI in women at increased risk of breast cancer
- American Cancer Society guidelines recommend annual MRI if lifetime risk exceeds 20%; would impact up to 1.5 million women annually in the U.S.
- Cost of MBI estimated at ~1/5th cost of Breast MRI
- Currently no clinical systems available
  - First clinical systems in late 2009?

MBI - Limitations and Disadvantages

- False positive findings in some cases of fibroadenomas, papillomas, fat necrosis
- Uptake of Sestamibi is influenced by hormonal changes
- MBI - high radiation dose relative to mammography
Cumulative Cancer Incidence per 100,000 women from annual screening with Mammography or Tc-99m sestamibi starting at age 40

- 2 - 4 mCi Sestamibi
- Mammogram is < 1.0 mSv
- MBI with 20 mCi Tc-99m sestamibi = 6.5 mSv
- Dose reduction techniques have been developed to reduce administered dose of Tc-99m sestamibi to 2-4 mCi
  - collimator optimization
  - energy window optimization
  - noise reduction algorithms
  - composite image from opposing detectors
MBI - Future Directions

- 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

Molecular Breast Imaging

Future Developments – New Radiopharmaceuticals

- Tc-99m Sestamibi
- Tc-99m Bombesin
- Tc-99m δV-3 Integrin
- Tc-99m Annexin V
- Tc-99m Glucarate
- Tc-99m EC-glucosamine
- Tc-99m (V)-DMSA
- Tc-99m Vitamin B12
- I-123 Iodo-estradiol
- I-123 Methoxy-vinylestradiol
- I-123 Dimethyl-Tamoxifen
- I-123 Iodo-methoxybenzamide