Molecular Breast Imaging

Development of a Low-Dose Screening Test for Dense Breasts

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Conflict of Interest
• Royalties for technologies licensed to Gamma Medica Ideas

Overview
• Current methods for screening in dense breasts
• Nuclear Medicine’s role in breast imaging
• Low-Dose Molecular Breast Imaging (MBI)
  • Screening in dense breasts
  • Other applications
  • Limitations and advantages
  • Future developments

Mayo’s MBI Team
Breast Cancer Screening Guidelines

In US, women are urged to get annual screening mammograms starting at age 40
- Long debate about use in women ages 40-49
- USPSTF has recommended against use of routine mammography in women under 50 twice since 1997

Breast exam guidelines now call for less testing
Change debated
Potential harm of frequent mammograms outweighs benefit, task force says

By Rob Stein, Washington Post Staff Writer
Tuesday, November 17, 2009

“Tens of thousands of lives are being saved by mammography screening, and these idiots want to do away with it,” said Daniel B. Kopans, a radiology professor at Harvard Medical School. “It’s crazy -- unethical, really.”
Support of continued annual screening starting at age 40

- American Cancer Society
- American College of Radiology
- American College of Obstetrics and Gynecology
- Susan G Komen for the Cure
- Radiologic Society of North America
- Medical Centers

17 days later, Congress banned the use of these new guidelines in determining insurance coverage

Breast Cancer Screening Guidelines
Should women be screened?

yes, mortality benefit has been shown

Breast Cancer Screening Guidelines
Should women be screened?

yes, mortality benefit has been shown

Only mammography has demonstrated mortality benefit

As much as two-thirds of the decline in breast cancer mortality can be attributed to screening mammography

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

When to start?
How often?

Why is benefit of mammography less in younger women?
**Why is benefit less for younger women?**

**Breast Density**
- Most important factor in failure of mammography to detect cancer
- Explains 68% of decreased sensitivity in younger women

Buist et al: JNCI, 2004

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**Breast Density Classification**

- **Fatty**
- **Scattered**
- **Heterogeneously dense**
- **Extremely dense**

< 25% dense
25-50% dense
51-75% dense
>75% dense

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**Breast Density by Age**

80% have dense breasts at age 40
40% have dense breasts at age 80

Kopans: Breast Imaging, 2nd ed, 1998

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**Performance of mammography in dense breasts**

- Report sensitivity of mammography in extremely dense breasts ranges from 30-63%
  - Using follow-up mammogram findings as reference standard probably results in overestimate of true sensitivity

Camey PA et al, Ann Intern Med 2003;138:168-75
Digital Mammography

- ACRIN DMIST trial
  - 50,000 women screening with both film and digital mammography
  - Single subgroup in whom digital was significantly better than film: pre- or peri-menopausal women <50 years with dense breasts
    - Sensitivity: 59% digital, 27% film

Pisano et al. NEJM 2005; 353:17

Density is an independent risk factor

- Density strongly associated with risk of developing breast cancer (4-6 x that of fatty replaced breasts)
- Greater likelihood of cancer recurrence in dense breasts


Breast Density
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 (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>

Population Attributable Risk

- Breast density: 33%
- Family history: 9%
- BRCA 1, 2 mutations: 5%

Cuzick J. The Breast 2003; 12: 405-411
What are the current screening alternatives for women with dense breasts?

- Tomosynthesis
- Ultrasound
- MRI

**Tomosynthesis**
- (See previous lecture for expert review)
- Recently FDA-approved
- Multiple studies ongoing
- ACRIN is likely to fund clinical trial

**Ultrasound**
- ACRIN 6666 trial (high risk and dense breasts)
  - physician-performed WBU
  - Increased diagnostic yield from 7.6/1,000 with mammography alone to 11.8/1,000 by adding WBU
  - Substantial number of false positives, PPV = 9%
  - Berg et al, JAMA

- Automated Whole Breast Ultrasound
  - Increased diagnostic yield from 3.6/1,000 with mammography alone to 7.2/1,000 by adding AWBU
  - PPV = 38%
  - Many images to review
  - Kelly et al, Eur Radiol 2010; 20:734-742
**Magnetic Resonance Imaging**

- In hands of expert readers:
  - Very high sensitivity (approaching 100%)
  - Acceptable specificity
- ACS issued 2007 recommendations
  - Annual screening MRI in women with risk >20%
  - Not enough evidence to recommend for screening in dense breasts
  - ACS recognized that specificity in community practice setting can be ~50%


**Nuclear Medicine Imaging of the Breast**

- Scintimammography / Breast Scintigraphy
- Breast-Specific Gamma Imaging (BSGI)
- Positron Emission Mammography (PEM)
- Molecular Breast Imaging (MBI)

**Scintimammography**

- Refers to conventional “scintillating” gamma camera – technology of 1990’s
- Bulky camera cannot be positioned close to the breast
- Interference from adjacent tissues (heart, liver)
- Poor sensitivity for lesions < 1 cm

*Patient in prone position*  
*Scintimammogram (lateral view)*  
*www.imagis.com*

**Scintimammography**

*Effect of Breast Thickness on Lesion Detection*  
*Tumor Depth = 3 cm*  
*Tumor Depth = 7 cm*  
*6–8 cm*  
*2–3 cm*
Dedicated Nuclear Medicine Detectors

- Allow positioning in standard mammographic views
- Minimal interference from adjacent tissues
- Better spatial resolution due to:
  - Close contact of breast with detector
  - Pixilated detectors

Dedicated Nuclear Medicine Detectors

BSGI
Dilon Diagnostics
Single Photon Detection
Multi-crystal Sodium Iodide (NaI) + PMTs

PEM
Naviscan
Coincidence Detection
Scanning arrays of LYSO crystals

www.dilon.com
www.naviscan.com

Semiconductor Detector
Cadmium Zinc Telluride

4 cm x 4 cm
Cadmium zinc telluride (CZT) module
Pixel size: 1.6 mm or 2.5 mm

Scintillating vs. Semiconductor Detectors

Scintillator (NaI)
- Converts gamma ray photons to light
- Photomultiplier tubes (PMT) converts light to electrons

Semiconductor (CZT)
- Direct conversion: gamma rays to electrons
- Improved energy and spatial resolution over NaI
Our first prototype: Molecular Breast Imaging CZT gamma camera

Molecular Breast Imaging Systems
FDA-approved, clinically available
Dual-head CZT detectors

Gamma Medica
LumaGen
GE Healthcare
Discovery NM 750

MBI Procedure
- Tc-99m sestamibi injected IV
- Patient positioned by specially trained technologist
- Imaging begins immediately after injection
- Two views of each breast acquired (CC and MLO)
- Light, pain-free compression

Tc-99m sestamibi
- Developed for cardiac imaging
- FDA-approved for diagnostic breast imaging in 1997
- Exact mechanism of uptake in cancer uncertain
  Proportional to blood flow and mitotic activity
- Imaging can commence minutes after injection
- Effective half-life = 3 hours
- Uptake not influenced by breast density
Could MBI Find Small Breast Tumors?

Detection of cancer in 88 patients with 128 tumors

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th># of tumors</th>
<th>Single head MBI</th>
<th>Dual head MBI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 mm</td>
<td>61</td>
<td>68%</td>
<td>82%</td>
<td>0.004</td>
</tr>
<tr>
<td>All</td>
<td>88</td>
<td>80%</td>
<td>90%</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Hruska et al, AJR 2008; 191: 1808-1815

Two Heads are Better than One...

Missed cancers occurred more often in women with large compressed breast thickness

Better detection with Dual-head MBI, example 1
Better detection with Dual-head MBI, example 1

Images courtesy of Dr. Judy Boughey, Mayo Clinic

MBI for Screening in Dense Breasts
Funded by Komen for the Cure

- Eligible women:
  - Asymptomatic
  - Presenting for routine screening mammography
  - Heterogeneously or extremely dense breasts based on past prior mammogram

Rhodes et al. Radiology, Jan 2011

Results
- 1007 patients enrolled, 936 with known cancer status
- Mean age of patients: 55.7
- 12 cancers diagnosed
  - 1 by mammography only
  - 8 by MBI only
  - 2 by both
  - 1 by neither (detected at next annual mammogram)

Examples of Mammographically Occult Cancers Detected on MBI

Proof of Concept: MBI in Screening Setting

- Diagnostic yield increased detection from 3.2/1,000 for mammography alone to 10.7/1,000 by adding MBI (p=0.016)
- Sensitivity: 3/11 for mammography, 9/11 for MBI
- Specificity: 91% for mammography, 93% for MBI
- PPV of MBI = 12%, four times higher than mammography (3%) (P=0.01)
- Proof of concept: Need to verify findings using low dose (4 mCi) MBI

Radiation Risks of MBI

<table>
<thead>
<tr>
<th>Modality</th>
<th>Dose to Breast (mGy)</th>
<th>Effective Dose (mSv)</th>
<th>Single exam, age 40: LAR of Fatal Cancer</th>
<th>Annual exams, ages 40-80: LAR of Fatal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography (2-view bilateral screen)</td>
<td>3.7 (digital) 4.7 (film)</td>
<td>0.44 (digital) 0.56 (film)</td>
<td>1.3 – 1.7</td>
<td>20 – 25</td>
</tr>
<tr>
<td>PEM (10 mCi F-18 FDG)</td>
<td>2.5</td>
<td>6.2 – 7.1</td>
<td>31</td>
<td>400†</td>
</tr>
<tr>
<td>BSGI MBI (20-30 mCi Tc-99m sestamibi)</td>
<td>1.3 – 2</td>
<td>5.9 – 9.4</td>
<td>26 – 39</td>
<td>360 – 540†</td>
</tr>
</tbody>
</table>

Effective Dose accounts for organ-specific doses and weighting factors, and represents the dose to the entire body; LAR = Lifetime Attributable Risk per 100,000 women

†Data from: O'Connor et al. Medical Physics 2010; 37 (12).

Comparison with Background Radiation

LAR of Fatal Cancer due to Annual Background Radiation per 100,000 women
(birth to 80 years)

- U.S. Average (3.1 mSv/year) – 1010
- Colorado (~4.5 mSv/year) – 1460
- Florida (~2.5 mSv/year) – 810

25 mCi MBI screening, age 40-80 (~7.6 mSv/year) – 450
Low dose MBI screening, age 40-80 (~1.2 mSv/year) – 108

Data from: O'Connor et al. Medical Physics 2010; 37 (12).
**MBI Dose Reduction**

- For annual breast screening, target dose for MBI is 4 mCi Tc-99m sestamibi
  - 1.2 mSv effective dose
  - Equivalent to ~2 screening mammograms
  - Intended screening interval would be 2 years

- MBI dose reduction schemes
  - Optimization of collimator
  - Use of widened energy window
  - Post-acquisition image processing

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**Collimator Optimization**

- Hexagonal holes changed to square registered holes
  - Improves active area, count sensitivity
  - Holes closer together, switched from lead to tungsten
  - Shorten bore, more count sensitive but give up resolution
  - Dual-detector design means only ½ of breast needs adequate resolution for each detector

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**Collimator Optimization**

- MBI performed with conventional and optimized collimators
  - ~3 gain in counts

MBI: detected multifocal invasive lobular carcinoma and nipple adenoma.
Digital Mammography: benign stable findings

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**MBI Dose Reduction: Wide Energy Acceptance Window**

- Tailing Effect in CZT:
  - “Good” photopeak events mis-registered at lower energies
  - Due to incomplete charge trapping in semiconductor

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MBI Dose Reduction: Wide Energy Acceptance Window

- MBI performed with conventional and widened energy window
- 1.4 – 3.3x gain in counts
- Tradeoff: more counts but some scatter at chest wall

Low-Dose MBI: New Collimation and Wider Energy Window

- Target recruitment: 2400
- Accrual to date: 600
- 8 mCi dose
  - Can simulate images at 2, 4, and 6 mCi doses
- 9 cancers diagnosed
  - 8 detected by MBI
  - 0 detected by mammography
  - 1 found on prophylactic mastectomy
- PPV = 35%

Low-dose screening Funded by Komen for the Cure

September 2007 – 20 mCi Tc-99m sestamibi

Same patient in December 2010 – 4 mCi Tc-99m sestamibi
Non-screening applications of MBI

Mammogram 2010
Read as extremely dense; Negative

Mammogram 2011
Read as extremely dense; Negative

MBI 2011
Final path
Right Mastectomy: DCIS
Patient unable to have MRI due to implanted device

Mammogram: irregular nodule in UOQ at site of palpable abnormality
Ultrasound: 2.3 cm irregular hypoechoic mass

MRI: index carcinoma - 1.6 x 2.4 cm irregular enhancing mass; satellite lesion - 0.9 x 1.4 cm

Final Pathology: Infiltrating ductal carcinoma, grade III, forming 2 masses: 2.2 cm, and 0.9 cm

Tubular Carcinoma 0.5 cm
ILC 3.6 cm; LN+
DCIS 0.6 cm

DCIS - final path pending
1.9 cm IDC

MBI in preoperative evaluation

MBI: Uptake in 2 foc; 2.5 cm and 0.9 cm

MRI index carcinoma - 1.6 x 2.4 cm irregular enhancing mass; satellite lesion - 0.9 x 1.4 cm
**Good correlation between MBI and MRI**

9 mm cancer (Ductal Carcinoma In Situ)

Screen Mammogram  MBI  Breast MRI

**Neoadjuvant Therapy Case #1**
Mammogram shows no change

Pre-Therapy  After 3 months of therapy

**Neoadjuvant Therapy Case #1**
MBI demonstrates pathologic complete response

**Neoadjuvant Therapy Case #2**
MRI and MBI

Initial diagnosis: IDC with large Area of DCIS
MRI indicated residual disease
Left Mastectomy. Surgical Pathology indicated no residual viable cancer
**MBI - Limitations and Disadvantages**

False positive findings in some cases of fibroadenomas, papillomas, fat necrosis.

- Biopsies with benign findings:
  - ~3% of screening cases

**Fibroadenoma**

**Benign Papilloma**

**MBI - Limitations and Disadvantages**

False positive findings in some cases of fibroadenomas, papillomas, fat necrosis.

Uptake of Sestamibi is influenced by hormonal changes – benign parenchymal uptake
**Effect of Menstrual Cycle**

- **Follicular Phase**
- **Luteal Phase**

**MBI - Limitations and Disadvantages**

False positive findings in some cases of fibroadenomas, papillomas, fat necrosis.

Uptake of Sestamibi is influenced by hormonal changes – benign parenchymal uptake

Injection

Radiation

Time to perform
**MBI - Limitations and Disadvantages**

False positive findings in some cases of fibroadenomas, papillomas, fat necrosis.

Uptake of Sestamibi is influenced by hormonal changes – benign parenchymal uptake

Injection

Radiation

Time to perform

Biopsy capability – in development

**Advantages of MBI**

- Compared to mammography:
  - Higher sensitivity in dense breasts
  - Less compression; patient comfort

- Compared to MRI:
  - Option if contraindication to MRI (claustrophobia, pacemaker, clips, impaired renal function)
  - Generalizability
    - Interpretation easy to learn
    - Rapid interpretation
    - Highly reproducible between readers, even those newly trained
  - 5-fold less expensive than MRI, $600 vs $3000 at Mayo

**Future Developments in MBI**

- Combined MBI / Ultrasound system with real-time MBI-guided biopsy in development

- Investigation of other radiopharmaceuticals
  - Improved lesion detection / characterization

- Standardized reporting, terminology, and training course for MBI interpretation

  - Collaboration with Dr. Wendie Berg (UPMC)

- Development of standardized QC tests and phantom for dedicated pixilated gamma cameras
Thank you!

This work has been funded in part by the following:
Mayo Foundation
National Institute of Health
Dept. of Defense
Susan G Komen For the Cure Foundation
Friends for an Earlier Breast Cancer Test