Molecular Breast Imaging: Rogue Technology to Mainstream Practice
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Disclosure
• Royalties for MBI technologies licensed to CMR Naviscan

A Serendipitous Discovery
Campeau et al, Clin Nucl Med 1992
Myocardial perfusion scan
Breast cancer
Parathyroid adenoma
Lung cancer
Scintimammography

- Scintillating gamma cameras
- FDA-approved for diagnostic breast imaging
  - 1996: Tc-99m tetrofosmin
  - 1997: Tc-99m sestamibi
- Positioning limitations
  - Spatial resolution falls off with distance
  - Uptake in adjacent organs
- Poor sensitivity for small non-palpable masses: 30-60%

Dedicated Systems

- Allows positioning in standard mammographic views

Advantage of Dedicated Systems
Commercial Systems

- 2011: FDA-approval of 2 CZT-based dual-head units
- 2016: Dilon became distributor of GE system
- 2017: CMR Naviscan acquired Gamma Medica

Dilon' GE
Discovery NM 750b
2.5 mm pixels
24 cm x 16 cm FOV

CMR Naviscan
LumaGem
1.6 mm pixels
20 cm x 16 cm FOV

MBI Exam Protocol

- CNMTs, trained in mammographic positioning perform exam
- IV injection Tc-99m sestamibi (8 mCi)
- Imaging can begin right after injection
- CC / MLO views (< 10 min per view)
- Patient comfort measures
  - Seated w/ pillows
  - Gentle breast compression
  - Breath normally
  - Watch TV, listen to music, read

Uptake of Sestamibi in the Breast

- Rapid blood clearance, immediate breast uptake
- Tc-99m sestamibi uptake in cancer - not well-understood
  - Sequestered in mitochondria
  - Influenced by blood flow and angiogenesis
  - Some association with tumor size, receptor status and proliferation
  - Multidrug resistance proteins (Pgp) can limit retention
- Slow washout
  - Not rapid washout like iodine or gadolinium contrast
  - Tumor washout associated with blood flow (mean half-life ~4 hr)

Early Results with Dedicated Cameras

- Tumor extending to nipple
- Extensive tumor
- 3 tumors 17, 6, 3 mm
- Additional disease occult on mammography

Let's Call it "Molecular Breast Imaging"

Molecular Imaging is ...broadly defined as the in vivo characterization and measurement of biologic processes at the cellular and molecular levels.

In contradistinction to "conventional" diagnostic imaging, it sets forth to probe the specific molecular abnormalities that are the basis of disease, rather than imaging the end effects of these molecular alterations.


The Hope for Molecular Breast Imaging

- With radiopharmaceuticals targeted to breast disease:
  - Detect cancer earlier than it appears on anatomic techniques
  - Provide prognostic information
  - Provide risk information
Diffusion of Innovations Theory  
Everett Rogers, 1962  
Crossing the Chasm  
Geoffrey Moore, 1991

Key Ideas to Cross the Chasm:
- Choosing a Target Market
- Positioning Relative to Other Products
- Understanding the Whole Product

Target Market:
Which patients benefit from MBI?

- Preoperative Staging
- Evaluation of Neoadjuvant Therapy
- Detection of Recurrence
- Evaluation for Unknown Primary
- Problem Solving
- Breast Cancer Screening

Consider MBI when:
- Conventional imaging with mammography / ultrasound is not sufficient (dense breast, post-surgery, etc)
- When MRI would be preferred but not feasible
Performance of Mammography is Variable

Breast composition categories, ACR BI-RADS 5th ed.

Breast composition categories, ACR BI-RADS 5th ed.

Significance of Breast Density

- **Prevalent:** 48% of US women have dense breasts
- **Masks BC:** Mammography misses 75% of cancers in dense breasts
- **Poor outcomes:** Higher rate of advanced cancers, interval cancers, and BC mortality
- **Independently associated with BC risk**
- **Density Inform Legislation:** Women are seeking solution

Screening MBI Evidence: Prospective Clinical Trials

- 2 single institution trials (Mayo)
  - Trial 1: 20 mCi Tc-99m sestamibi, N = 936
  - Trial 2: 8 mCi Tc-99m sestamibi, N = 1585

- Enrolled
  - Asymptomatic women presenting for screening
  - Dense breasts on last mammogram
- Mammography and MBI performed in all subjects
- Tests read independently

Screening Evidence: Retrospective Reviews

- Community-based clinical practice (ProMedica Breast Care)
  - 8 mCi MBI offered after negative mammogram
  - Women with dense breasts who did not meet risk criteria for MR

- Academic medical center (George Washington University)
  - Most recent mammogram benign (included BIRADS 1, 2 and 3)
  - 60% w/ personal hx, 30% w/ family history
  - 60% with dense breasts
  - Administered activities from 7 – 32 mCi

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<table>
<thead>
<tr>
<th>Study</th>
<th>Tc-99m sestamibi administered</th>
<th>N</th>
<th>IDCIR, relative to 2D mammography</th>
<th>Size of cancers detected only by MBI (95% CI)</th>
<th>Add. Recall Rate</th>
<th>PPV of MBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodes, 2011</td>
<td>Dense breasts + additional risk factor</td>
<td>20 mCi</td>
<td>936</td>
<td>7.5</td>
<td>5.3</td>
<td>1.1 (0.4 – 5.1)</td>
</tr>
<tr>
<td>Rhodes, 2015</td>
<td>Dense breasts</td>
<td>8 mCi</td>
<td>1585</td>
<td>8.8</td>
<td>6.9</td>
<td>0.9 (0.5 – 1.1)</td>
</tr>
<tr>
<td>Shermis, 2016</td>
<td>Negative mammography, dense breasts, &lt;20% risk</td>
<td>8 mCi</td>
<td>1696</td>
<td>7.7</td>
<td>6.5</td>
<td>1.0 (0.6 – 2.4)</td>
</tr>
<tr>
<td>Brem, 2016, BSGI</td>
<td>Dense mammography + additional risk factor</td>
<td>7.7–10 mCi</td>
<td>196–653</td>
<td>16.5</td>
<td>7.1</td>
<td>2.5 (0.3 – 4.0)</td>
</tr>
</tbody>
</table>

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Hruska, AJR 2017; 208
2D screening mammogram: BI-RADS 1 - Negative
Scattered fibroglandular densities (BI-RADS 3rd edition.)

Left CC  
Left MLO
Right CC  
Right MLO

Example MBI exam:
45 year-old premenopausal woman presenting for screening

Surgical pathology:
Invasive lobular carcinoma  
Node positive

MBI: Spatial Resolution Limits

Mammogram 2 years prior  
Grade II Invasive Ductal Carcinoma, 3 mm

MBI in the Era of Digital Breast Tomosynthesis

55 year-old woman with self-reported "thickening", Negative 2D mammogram, DBT and US

MBI with 20 mCi Tc-99m sestamibi  
1.3 cm mass with high intensity uptake

MBI with 20 mCi Tc-99m sestamibi  
1.3 cm mass with high intensity uptake
November 2014

August 2013

April 2012

May 2011

Incidental 11-cm Grade I, Invasive Lobular Carcinoma with micromets found on MBI “normal volunteer” study

2D mammogram

DBT

MBI

Density MATTERS

(MBI And Tomosynthesis To Eliminate the Reservoir of Undetected Cancer$)

Pis: Deb Rhodes, MD & Carrie Hruska, PhD; Lead Radiologist: Katie Hunt, MD

• First multicenter, prospective clinical trial of MBI screening
• First comparison of MBI vs. Digital Breast Tomosynthesis (DBT)
• Primary objective: Compare rates of invasive cancer detection
• Enrolling 3000 women
  • Presenting for screening DBT
  • Dense breasts on last mammogram
• 2 rounds of annual DBT and MBI to evaluate change in rate of advanced cancer presentation

Funded by...
Density MATTERS case example 1:
62-year-old woman presenting for screening

Biopsied by ultrasound guidance
0.9 cm Grade II, Invasive ductal carcinoma
Triple Negative, Node negative

Density MATTERS case example 2:
71-year-old woman presenting for screening

Biopsied by ultrasound guidance
1.0 cm Grade I, Invasive ductal carcinoma
ER+, PR+, HER2- Node negative

Density MATTERS case example 3:
57-year-old woman presenting for screening

Ultrasound-guided biopsy: Grade II Invasive ductal carcinoma,
ER+, PR+, HER2+
After neoadjuvant therapy: 0.5 cm residual disease, Node negative
Density MATTERS case example 4:
51 year old woman presenting for screening

1.4 cm Grade II Invasive lobular carcinoma, ER+ PR+ HER2-
Node negative

Density MATTERS Multicenter Preliminary Results
In first 1200 women...

<table>
<thead>
<tr>
<th>Modality</th>
<th>Invasive Cancer Sensitivity</th>
<th>All Cancer Detection Rate</th>
<th>Invasive Cancer Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBT alone</td>
<td>4 / 15 (27%)</td>
<td>5.0 per 1000</td>
<td>3.5 per 1000</td>
</tr>
<tr>
<td>DBT + MBI</td>
<td>14 / 15 (93%)</td>
<td>14.2 per 1000</td>
<td>11.7 per 1000</td>
</tr>
</tbody>
</table>

Incremental cancer detection from MBI: 9.2 per 1000, 8.4 per 1000

• 11 additional cancers detected with MBI
  - 9 invasive ductal, 1 invasive lobular, 1 DCIS
  - Median size 1.2 cm, range 0.5 – 2.6 cm
  - Range of grades (I-III) and biologies: 1 triple negative, 2 HER2+

Positioning MBI
How does MBI fit in with other breast modalities?
Comparison of Supplemental Screening Modalities
(Adapted from Berg, JNM 2016; Costs updated)

<table>
<thead>
<tr>
<th>Modalities</th>
<th># of women with dense breasts</th>
<th># of women found to have cancer</th>
<th># of women recalled for additional testing</th>
<th>Exam reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis</td>
<td>1 – 2</td>
<td>18 to 30 fewer</td>
<td></td>
<td>$134*</td>
</tr>
<tr>
<td>Whole-breast ultrasound</td>
<td>2 – 4</td>
<td>Another 130</td>
<td></td>
<td>$165**</td>
</tr>
<tr>
<td>MBI</td>
<td>8</td>
<td>Another 65</td>
<td></td>
<td>$296*</td>
</tr>
<tr>
<td>MR Imaging</td>
<td>10</td>
<td>Another 90</td>
<td></td>
<td>$1,197*</td>
</tr>
</tbody>
</table>

*Mean reimbursement from actual claims (Vlahiotis et al, Clinicoecon Outcomes Res 2018); MBI reimbursed with codes 78800 – Tumor imaging, limited area, A9500 – Tc-99m-labeled sestamibi
**Only national average Medicare reimbursement available for whole-breast ultrasound

MBI Cost-Effectiveness

<table>
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<tr>
<th>Screening approach</th>
<th>Cost per patient screened</th>
<th>Cost per cancer detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D mammography alone</td>
<td>$176</td>
<td>$55,851</td>
</tr>
<tr>
<td>2D mammography + single supplemental MBI</td>
<td>$571</td>
<td>$47,597</td>
</tr>
</tbody>
</table>

Costs obtained from national average Medicare reimbursement rates, 2014

Total costs include:
Screening tests, diagnostic imaging workup, biopsy costs, and pathology charges up to point of pathology proven breast cancer diagnosis

Hruska et al, “Diagnostic workup….” AJR 2015

MBI Reimbursement

- National average charge for MBI / BSGI: $450
- Mean reimbursement of MBI / BSGI claims: $296*
  - 78800 (Tumor imaging, limited area)
  - A9500 (Tc-99m-labeled sestamibi)
- MBI coverage for indication of breast density (R92.2) at Mayo
  - Medicare and Medicaid cover
- 2019 review: 93% of commercial insurers processed and paid correctly

*Mean reimbursement from 2011-2015 claims data (Vlahiotis et al, Clinicoecon Outcomes Res 2018)
Patient Tolerability

- ~40% of women refuse free MRI
  - Claustrophobia, prone positioning
  - Injection also a barrier
- MBI
  - Anecdotally, patients report an easy test
  - Also requires injection
  - 40 minutes of imaging time (for now)
- Survey will evaluate patient tolerability and acceptance of MBI

Implementing MBI: Tc-99m Sestamibi

- Tc-99m is a gamma-emitting radionuclide
  - 140 keV gamma rays, 6 hour half-life
  - Can be obtained in pre-dispensed unit doses from commercial vendors; Central nuclear medicine pharmacy not required
  - No special room shielding required
  - Facility will need
    - Radionuclide license
    - Physician Authorized User
    - RSO oversight

Tc-99m Sestamibi: Safety Profile

- Radio tracer: monitors physiologic process, but at low concentration; no pharmacologic effect
- Long history of safe use – since 1990
- No contraindications (except pregnancy)
- Adverse reactions to sestamibi
  - 1 to 6 events per 100,000 injections (~0.006%); Mild (e.g. metallic taste)
  - Compare to
    - Iodinated contrast: reactions in 0.6%; severe / life-threatening 0.04%
    - Gadolinium-based: reactions in 0.2%; severe in 0.008%; long-term retention
That's great, but… “it's a whole body dose”

**Dose Reduction Strategies**

- 20 – 30 mCi to 8 mCi Tc-99m sestamibi
  - Registered collimator optimized for dual-head system
  - Widened energy window optimized for CZT detectors

- Potential to drop below 8 mCi
  - Account for residual activity in syringe (avg ~1.5 mCi)
  - Patient warming
  - Patient fasting

**Radiation from Mammography**

- X-rays only to the breast
- Absorbed dose = Energy deposited per unit mass of tissue
- Absorbed dose in fibroglandular tissue (Mean glandular dose):
  - 1.9 mGy per view
  - 4.15 mGy per patient

**Radiation from MBI**

- Systemic radiotracer uptake
- Absorbed doses vary in organs
- For 8 mCi Tc-99m sestamibi:
  - Large intestine 11-15 mGy
  - Small intestine 8 mGy
  - Breast 0.5 mGy

**Effective dose applies weighting factors that account for**

- Type of radiation
- All organs irradiated AND the radiosensitivity of these organs

- Effective dose ~ 0.5 mSv
- Effective dose: 2.1 mSv

Footnotes:

1. ACRIN DMIST data, Hendrick et al. 2010
2. Andersson et al., EJNMMI Physics 2014
...epidemiological evidence supporting increased cancer incidence or mortality from radiation doses below 100 mSv is inconclusive...

...below levels of about 100 mSv above background from all sources combined, the observed radiation effects in people are not statistically different from zero.

...patients exposed to low doses (< 100 mSv)... the estimates are highly speculative because of various random and systematic uncertainties embedded in them.

...doubling the dose doesn’t double the cancers below 100 mSv per year

Further Cuts in Dose

- Standard MBI: 8 mCi Tc-99m sestamibi (2 mSv)
- 1/4 counts: 2 mCi Tc-99m sestamibi (0.5 mSv)
- 1/4 counts with Denoising Algorithm (0.5 mSv)


The Whole Product

What else is needed besides the detector?
Biopsy Capability

- MBI finds lesions that are occult on mammography / DBT
- Lesions are typically biopsied with ultrasound guidance
  - Some lesions have no correlate on mammo or ultrasound

In 1585 women screened with 8 mCi MBI:
  19 (1.2%) required MRI
  11 (0.7%) required MRI-guided biopsy

Rhodes et al, AJR 2015; Hruska et al, AJR 2015

Dilon Gamma Loc System for BSGI

- FDA-approval since 2009
- Upright position
- Vacuum-assisted bx device
- Sliding slant-hole collimator to obtain stereo pair
- Ce-139 source for verification
- Report of 104 successful biopsies in 99 women
  - 15 cancers, 0.2 to 1.9 cm

Brem et al, AJR 2018

GE MBI-Guided Biopsy Accessory

FDA-approved 2017

First MBI-guided Biopsy at MD Anderson

Courtesy of Gaiane Rauch, MD, PhD; Beatriz Adrada, MD; Tanya Moseley, MD; Cheenu Kappadath, PhD; Jennifer McClung, RT

creativecommons.org/licenses/by/4.0/; No changes made
MBI System Redesign with Biopsy Capability
Under Evaluation at Mayo Clinic Rochester - installed May 2019

Upper head retracts
Compression paddle interchangeable with biopsy grid

MBI Training for Radiologists

- MBI Lexicon for Interpretation
  - Validated in breast radiologists newly trained in MBI
  - High diagnostic accuracy and observer agreement (κ = 0.84) after 2-hour training session
- MBI training module through ACR
- Mayo MBI Workshop, Dec 2019

MBI Technologist Training


Swanson et al., JNMT 2018

Conners et al., AJR 2012
ACR MBI Training Module, Lead contributor Dr. Katie Hunt, FSBI

Conners et al., AJR 2012
ACR MBI Training Module, Lead contributor Dr. Katie Hunt, FSBI
MBI Quality Control (Physicist Guide)

Guidelines for Quality Control Testing of Molecular Breast Imaging Systems

Nerdinger et al., JNM'T 2018

Messaging to Patients

Molecular breast imaging

Overview

Molecular breast imaging is a novel form of breast imaging. MBI is a non-invasive imaging tool that helps detect breast cancer using imaging agents that accumulate in malignant tissue.

Why MBI is unique

MBI can detect cancer before clinical symptoms appear, making it a valuable tool in personalized medicine. MBI is non-invasive and can be performed on an outpatient basis, providing early detection and improved patient outcomes.

MBI and Breast Cancer Risk

MBI helps to identify which women may benefit from more aggressive treatment strategies, such as chemotherapy, and can help personalize patient care. By detecting cancer early, MBI has the potential to save lives and improve outcomes for women with breast cancer.
Typical Negative MBI Screening Exam

Variability in fibroglandular uptake

Background Parenchymal Uptake (BPU) on MBI
Histologic Correlates of BPU: Lobular involution

Photopenic tissue more likely to be completely involuted

Degree of involution

None     Partial       Complete

Age-adjusted P < 0.0001

BPU and Risk of Future Breast Cancer

- Cohort of 3000 women followed for 10 years

Low BPU

High BPU

Postmenopausal women with high BPU 5x as likely to develop BC, on average 4 years after MBI

Pilot Study of Low-dose Tamoxifen

Pre-tamoxifen MBT

(Post-tamoxifen MBT

after 30 days 5 mg Tamoxifen)

Hruska et al, Breast Cancer Research 2019
Conclusions

• MBI Works … it reveals clinically-important cancers occult on mammography/DBT due to high breast density

• Adoption will depend on
  - Target Market (Clear Indications for MBI)
  - Positioning (Cost, safety, patient tolerance)
  - Whole product (Biopsy, Training resources)

• BPU on MBI is an imaging marker of breast cancer risk

• Future investigation of targeted tracers and theranostic tracers in the breast

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