MAYO CLINIC

Molecular Breast Imaging: Rogue Technology to Mainstream Practice

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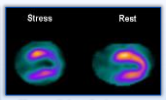
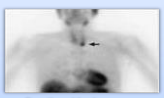
Disclosure

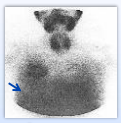
- Royalties for MBI technologies licensed to CMR Naviscan

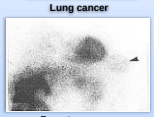
A Serendipitous Discovery



Myocardial perfusion scan


Parathyroid adenoma

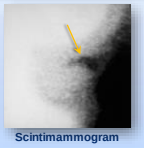

Lung cancer


Breast cancer

Aktolun et al, *Clin Nucl Med* 1992
Campeau et al, *Clin Nucl Med* 1992

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%

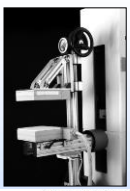


Scintimammogram

Khalkhali et al, JNM 2000
Palmedo et al, EJNM 1998

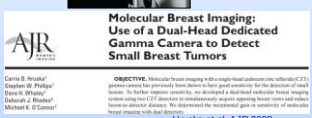
Dedicated Systems

Dilon BSGI system



Prototype dual-head CZT system

Brem et al, JNM 2002

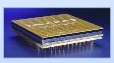


Hruska et al, AJR 2008

Advantage of Dedicated Systems

- Allows positioning in standard mammographic views

Conventional NaI detector



CZT module and detector

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
~~Gamma Medica~~
LumaGem
1.6 mm pixels
20 cm x 16 cm FOV

MBI Exam Protocol

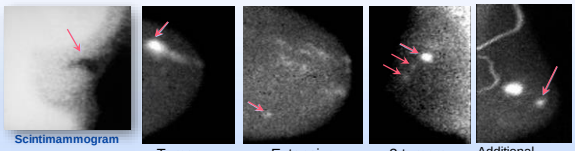
- CNMTs, trained in mammographic positioning perform exam
- IV injection Tc-99m sestamibi (8 mCi)
- Imaging can begin right after injection
- CC / MLO views (< 10 min per view)
- Patient comfort measures
  - Seated w/ pillows
  - Gentle breast compression
  - Breath normally
  - Watch TV, listen to music,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

Arbab et al. *J Nucl Med* 1996; Mankoff et al, *Nucl Med Biol* 2002; Moretti et al, *Eur J Nucl Med Mol Imaging* 2005

Early Results with Dedicated Cameras



Scintimammogram

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.

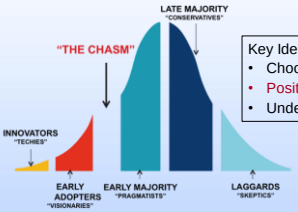
In contradistinction to "conventional" diagnostic imaging, it sets forth to probe the specific molecular abnormalities that are the basis of disease, rather than imaging the end effects of these molecular alterations.

- Wagenaar D.J., Weissleder R., and Hengerer A.: Glossary of molecular imaging terminology. Acad Radiol 2001

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?

ACR PRACTICE PARAMETER FOR THE PERFORMANCE OF MOLECULAR BREAST IMAGING (MBI) USING A DEDICATED GAMMA CAMERA

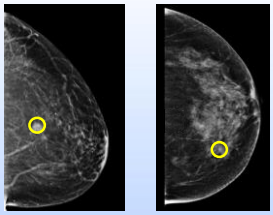
II. INDICATIONS

The clinical indications for MBI are becoming better defined as more research data have become available. Particularly applicable when MRI is not feasible, potential indications currently include, but are not limited to:

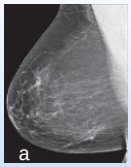
- Preoperative Staging
- Evaluation of Neoadjuvant Therapy
- Detection of Recurrence
- Evaluation for Unknown Primary
- Problem Solving
- Breast Cancer Screening

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

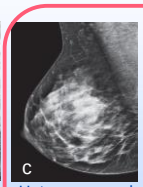


Breast composition categories, ACR BI-RADS 5th ed.

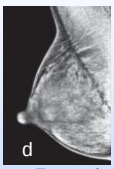


Fatty Replaced

Scattered areas of fibroglandular density



Heterogeneously dense



Extremely dense

% of women:	10%	40%	40%	10%

Significance of Breast Density

- Prevalent: 48% of US women have dense breasts[1]
- Masks BC: Mammography misses 75% of cancers in dense breasts[2]
- Poor outcomes: Higher rate of advanced cancers, interval cancers, and BC mor
- Independen
- Density Info solution

Target Market: Women with Dense Breasts Need a Better Screening Solution

1. Breast Cancer Surveillance Consortium Data Explorer. Accessed 2/20/2019.
2. Berg et al. JAMA 2012; Rhodes et al. AJR Am J Roentgenol 2015; Rhodes et al. Radiology. 2011;258(1):106-18.
3. Aiello et al. Cancer Epidemiol Biomarkers Prev 2005; Bertrand et al. Breast Cancer Res 2013;Kerlikowske et al. Ann Intern Med 2015; Chiu et al. Cancer Epidemiol Biomarkers Prev 2010.; Olsen et al. Journal of Cancer. 2009.
4. Boyd et al. N Engl J Med 2007

Screening MBI Evidence: Prospective Clinical Trials

- 2 single institution trials (Mayo)
  - Trial 1: 20 mCi Tc-99m sestamibi, N = 936 Rhodes et al, Radiology 2011
  - Trial 2: 8 mCi Tc-99m sestamibi, N=1585 Rhodes et al, AJR 2015
- 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

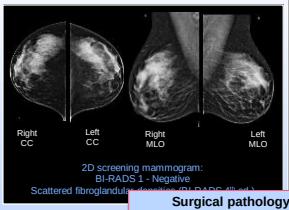
    Shermis et al, AJR 2016
- Academic medical center (George Washington University)
  - Most recent mammogram benign (included BIRADS 1, 2 and 3)
  - 60% w/ personal hx, 30% with family history
  - 60% with dense breasts
  - Administered activities from 7 – 32 mCi

    Brem et al, JNM 2016

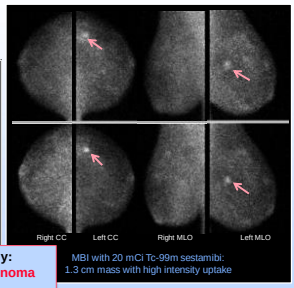
Study	Tc-99m sestamibi admin. activity	N	ICDR, relative to 2D mammography		Size of cancers detected only by MBI Median (Range)	Addl. Recall Rate	PPV3 of MBI
			Invasive + DCIS	Invasive only			
Rhodes, 2011 Dense breasts + additional risk factor	20 mCi	936	**7.5**	**5.3**	1.1 (0.4 – 5.1)	5.9%	28%
Rhodes 2015 Dense breasts	8 mCi	1585	**8.8**	**6.9**	0.9 (0.5 – 4.1)	6.6%	33%
Shermis 2016 Negative mammogram, dense breasts, <20% risk	8 mCi	1696	**7.7**	**6.5**	1.0 (0.6 – 2.4)	8.4%	19%
Brem 2016, BSGI Benign mammogram + additional risk factor	7–10 mCi 16–32 mCi	196 653	**16.5**	**7.1**	2.5 (0.3 – 4.0)	25%	14%

Hruska, AJR 2017; 208

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



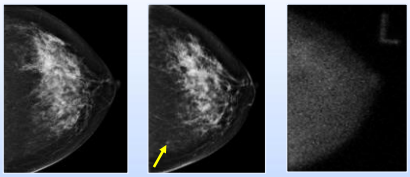
2D screening mammogram:
BI-RADS 1 - Negative
Scattered fibroglandular



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

Surgical pathology:
Invasive lobular carcinoma
Node positive

MBI: Spatial Resolution Limits



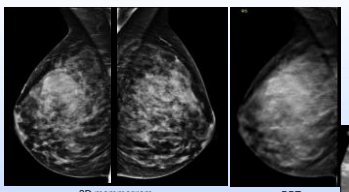
Mammogram 2 years prior

Current mammogram

MBI

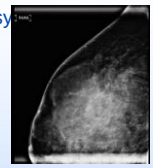
Grade II Invasive Ductal Carcinoma, 3 mm

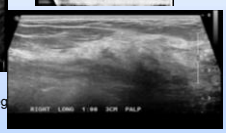
MBI in the Era of Digital Breast Tomosy



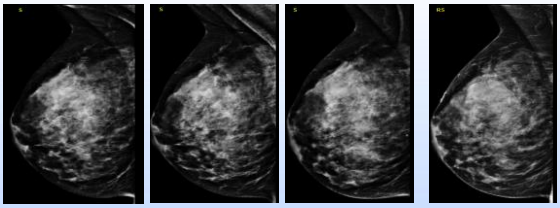
2D mammogram

DBT



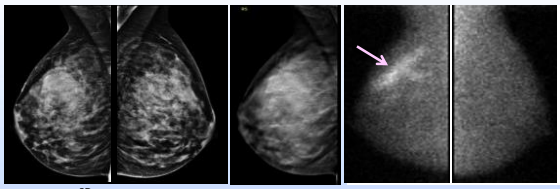


55-year-old woman with self-reported “thickening”, Neg



May 2011 | April 2012 | August 2013 | November 2014

MBI in the Era of Digital Breast Tomosynthesis



2D mammogram | DBT | MBI

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

Density MATTERS

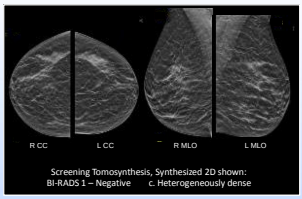
Funded by susan g. komen.

(MBI And Tomosynthesis To Eliminate the Reservoir of Undetected CancerS)

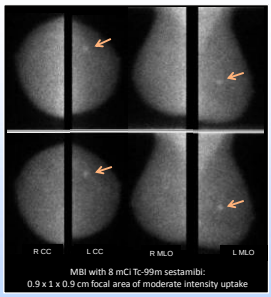
PIs: Deb Rhodes, MD & Carrie Hruska, PhD; Lead Radiologist: Katie Hunt, MD

- 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*

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



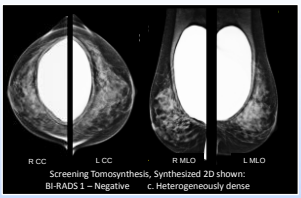
Screening Tomosynthesis, Synthesized 2D shown:
BI-RADS 1 – Negative c. Heterogeneously dense



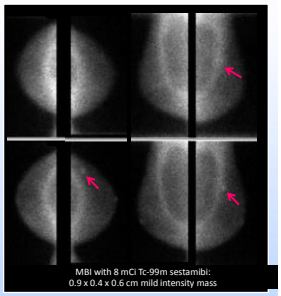
MBI with 8 mCi Tc-99m sestamibi:
0.9 x 1 x 0.9 cm focal area of moderate intensity uptake

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



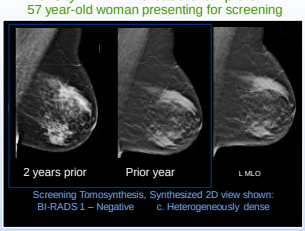
Screening Tomosynthesis, Synthesized 2D shown:
BI-RADS 1 – Negative c. Heterogeneously dense



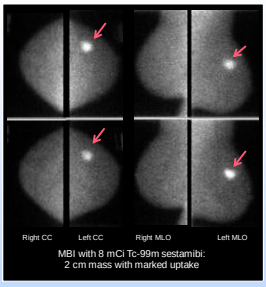
MBI with 8 mCi Tc-99m sestamibi:
0.9 x 0.4 x 0.6 cm mild intensity mass

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



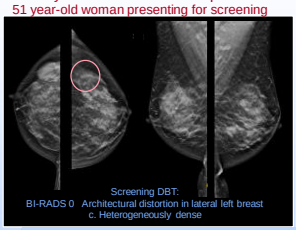
Screening Tomosynthesis, Synthesized 2D view shown:
BI-RADS 1 – Negative c. Heterogeneously dense

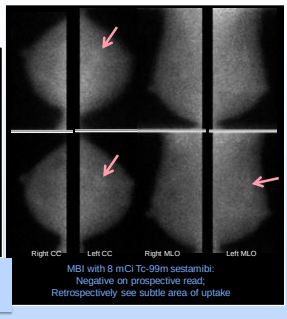


MBI with 8 mCi Tc-99m sestamibi:
2 cm mass with marked uptake

US-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

MBI with 8 mCi Tc-99m sestamibi:
Negative on prospective read;
Retrospectively see subtle area of uptake

Density MATTERS Multicenter *Preliminary* Results

- In first 1200 women…

Modality	Invasive Cancer Sensitivity	All Cancer Detection Rate	Invasive Cancer Detection Rate
DBT alone	4 / 15 (27%)	5.0 per 1000	3.3 per 1000
DBT + MBI	14 / 15 (93%)	14.2 per 1000	11.7 per 1000
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)

If 1000 women with dense breasts have supplemental screening after 2D digital mammography with…	# of additional women found to have cancer	# of women recalled for additional testing	Exam reimbursement
Tomosynthesis	1 – 2	18 to 30 fewer	$134*
Whole-breast ultrasound	2 – 4	Another 130	$165**
MBI	8	Another 65	$296*
MR Imaging	10	Another 90	$1,197*

*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

Screening approach	Cost per patient screened	Cost per cancer detected
2D mammography alone	**$176**	**$55,851**
2D mammography + single supplemental MBI	**$571**	**$47,597**

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

Berg et al, Reasons women at elevated risk of breast cancer refuse MR…, Radiology 2009
Sohn et al, Poor compliance in screening breast MRI in high risk women… J Am Coll Surg 2017
deLange et al, Reasons for (non)participation in supplemental population-based MRI… Clin Rad 2018

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

American College of Radiology Manual on Contrast Media, 2018
Silberstein et al, Prevalence of adverse reactions in nuclear medicine. J Nucl Med 1996
Nyakale et al, Nuclear medicine-induced allergic reactions. Curr Allergy Clin Immunol 2015
Kim et al, Anaphylaxis to iodinated contrast media: clinical characteristics related with development of anaphylactic shock. PlosOne 2014

That's great, but… "it's a whole body dose"

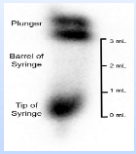
MBI and FDG-PEM

Supplementing mammography with MBI in women with dense breasts increases the cancer detection rate [44,45]. However, there have been no large population studies of MBI for screening and whole body radiation dose with this technique is concerning [46]. FDG-PEM is similarly limited by radiation dose and lack of evidence in large screening populations.

ACR Appropriateness Criteria® Breast Cancer Screening. 2017

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



Weinmann et al. *Medical Physics* 2009; Hruska et al. *Medical Physics* 2012; Swanson et al. JNMT 2013

Radiation from Mammography

- X-rays only to the breast
- Absorbed dose in fibroglandular tissue (Mean glandular dose):
  - 1.9 mGy per view[1]
  - 4.15 mGy per patient[1]

- **Effective dose ~ 0.5 mSv**

Radiation from MBI

- Systemic radiotracer uptake

Absorbed dose = Energy deposited per unit mass of tissue

- 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: 2.1 mSv** [2]

[1]ACRIN DMIST data, Hendrick et al, AJR 2010; [2]Andersson et al. EJNMMI Physics 2014,

How much dose reduction is necessary?

AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

…epidemiological evidence supporting increased cancer incidence or mortality from radiation doses below 100 mSv is inconclusive

HPS Specialists in Radiation Protection

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

International Organization for Medical Physics IOMP

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

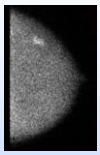
UNSCEAR

… doubling the dose doesn't double the cancers **below 100 mSv per year**

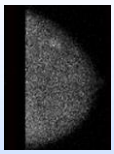
MAYO CLINIC PET

Further Cuts in Dose

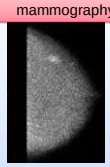
MBI dose equivalent to mammography



Standard MBI
8 mCi Tc-99m sestamibi
(2 mSv)



¼ counts
2 mCi Tc-99m sestamibi
(0.5 mSv)



¼ counts
with Denoising Algorithm
(0.5 mSv)

MAYO CLINIC PET

Tao et al. "Dose Reduction in Molecular Breast Imaging using ClearMBI - a New Image Processing Framework", in press, AJR

The Whole Product

What else is needed besides the detector?

MAYO CLINIC PET

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

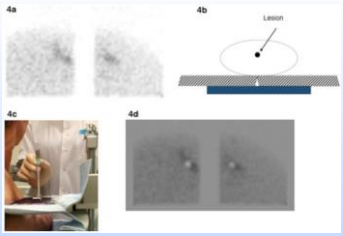


Figure from Collarino et al. *Clin Transl Imaging* 2016

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

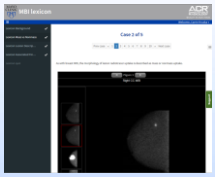
MBI System Redesign with Biopsy Capability
Under Evaluation at Mayo Clinic Rochester- installed May 2019

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



Conners et al, AJR 2012
Conners et al, Eur J Nucl Med Mol Imaging. 2012
ACR MBI Training Module, Lead contributor Dr. Katie Hunt, FSBI

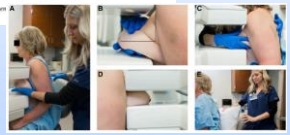
MBI Technologist Training

CONTINUING EDUCATION

Best Practices in Molecular Breast Imaging: A Guide for Technologists

Tiffinee N. Swanson, CNMT[1], Thuy D. Tran, CNMT[1], Lacey R. Ellingson, CNMT[1], Michael K. O'Connor[2], Deborah J. Rhodes[2], Katie N. Hunt[2], Amy Lynn Conners[1], and Carrie B. Hruska[1]

[1]Department of Radiology, Mayo Clinic, Rochester, Minnesota; and [2]Departmen
Rochester, Minnesota



Swanson et al, JNMT 2018

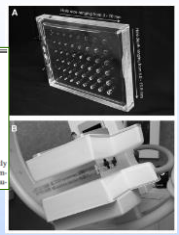
MBI Quality Control (Physicist Guide)

Guidelines for Quality Control Testing of Molecular Breast Imaging Systems

Sara M. Nardinger, CNMT, Thuy D. Tran, CNMT, Tiffinee N. Swanson, CNMT, Lacey R. Ellingson, CNMT, Courtney M. Solberg, CNMT, Michael K. O'Connor, PhD, and Carrie B. Hruska, PhD

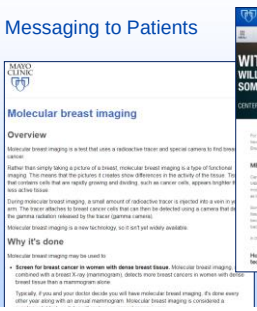
Department of Radiology, Mayo Clinic, Rochester, Minnesota

Molecular breast imaging (MBI) is a nuclear medicine test that uses dedicated γ-cameras designed for imaging of the breast. Several types of dedicated MBI cameras are currently available (*1*). Here, we refer to MBI as imaging systems comprising detectors designed for single-photon–emitting radiotra-



Nardinger et al, JNMT 2018

Messaging to Patients



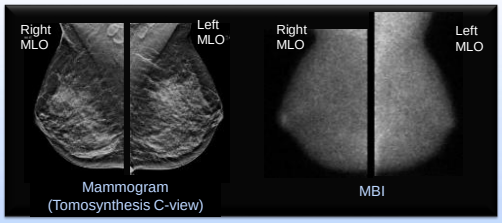
Molecular breast imaging

Overview

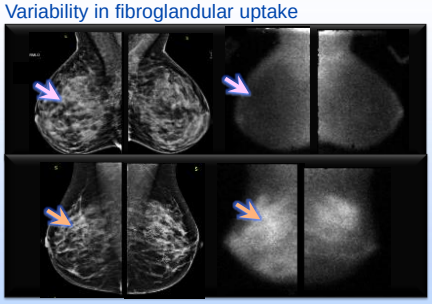
Why it's done

MBI and Breast Cancer Risk

Typical Negative MBI Screening Exam



Variability in fibroglandular uptake



Lack of uptake: Photopenia

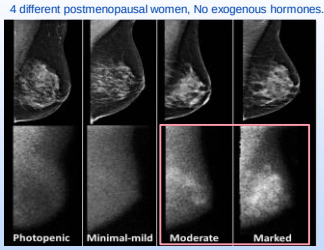
Marked uptake

Background Parenchymal Uptake (BPU) on MBI

4 different postmenopausal women, No exogenous hormones.

Mammograms
Similar density

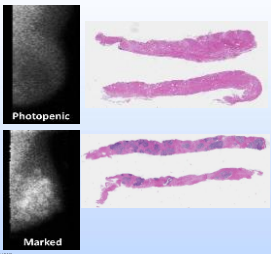
MBI Exams
Variable BPU



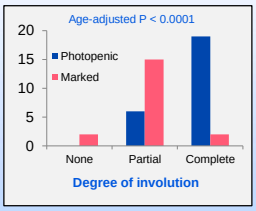
OR: 3-5, after adjustment for density and hormonal factors

Hruska et al, Breast Cancer Research 2016

Histologic Correlates of BPU: Lobular involution

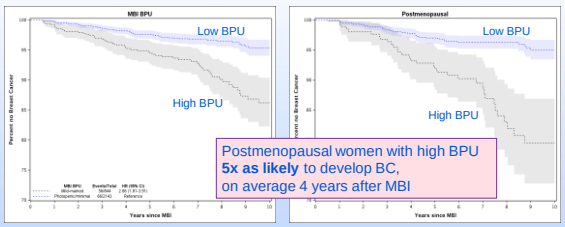


Photopenic tissue more likely to be completely involuted



BPU and Risk of Future Breast Cancer

- Cohort of 3000 women followed for 10 years

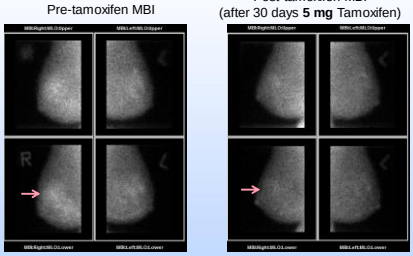


Postmenopausal women with high BPU **5x as likely** to develop BC, on average 4 years after MBI

Pilot Study of Low-dose Tamoxifen

Pre-tamoxifen MBI

Post-tamoxifen MBI (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

Michael O'Connor, PhD; Deborah Rhodes, MD; Katie Hunt, MD; Amy Conners, MD; Dana Whaley, MD; Shannon Zingula, MD; Doug Collins, MD; Stephen Phillips, MD; Rickey Carter, PhD

Thuy Tran, Tiffinee Swanson, Lacey Ellingson, Ashlee Stanke, Courtney Solberg, Jackie Moehring, Erika Olson, Carley Pletta, Karlie Gottwald, Torey Alabin, Michelle Bartel, Kathy Stern, Chelsie VanOort, Bill Rossini, Peggy Nordine, Tammy Evans, Linda Miller, MD; Ramila Mehta, Jennifer Geske

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