What Medical Physicists Need to Know About Breast Imaging with Nuclear Medicine Technology

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Conflict of Interest

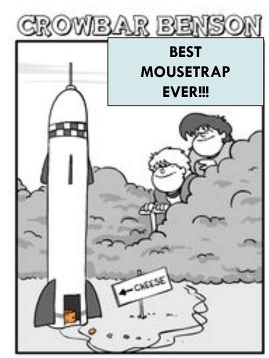
- Royalties for licensed technologies per agreement between Mayo Clinic and Gamma Medica

Clinical Practice

Dedicated CT
Automated US
Diffusion-weighted MR
Elastography
MR Spectroscopy
Contrast enhanced mammography
Vibro-acoustography
PET
SPECT
Microwave
PEM
Thermography
Optical
BSGI
MBI

Do we really need another breast imaging technology?

- Yes!
- If it can address limitations to standard imaging
  - Detection of mammographically-occult cancer in dense breasts
  - Alternative to MRI, when it is indicated but cannot be performed
- New technologies must offer substantial advantages over existing technologies to succeed



Nuclear Medicine in Breast Imaging

- The hope for functional imaging
  - Complement to anatomical imaging techniques
  - Offer earlier diagnosis

Nuclear Medicine in Breast Imaging

- Barriers
  - Nuclear medicine and breast imaging typically do not overlap
  - Poor reputation to overcome
    - Lacking high quality clinical studies in literature
    - Scintimammography did not work out
  - Radiation dose concerns

Learning Objectives

1. Give an overview of nuclear medicine technologies for breast imaging
2. Demonstrate how each technology is being used in clinical practice and research
3. Discuss radiation doses used in breast imaging and their associated risk

Nuclear imaging of the breast: Translating achievements in instrumentation into clinical use

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Approaches to imaging the breast with nuclear medicine and/or molecular imaging methods have been under investigation since the late 1980s when a technique called scintimammography was first introduced. This review charts the progress of nuclear imaging of the breast over the last 20 years, covering the development of newer techniques such as breast specific gamma imaging, molecular breast imaging, and positron emission mammography. Key issues critical to the adoption of these technologies in the clinical environment are discussed, including the current status of clinical studies, the efforts at reducing the radiation dose from procedures associated with these technologies, and the relevant radiopharmaceuticals that are available or under development. The necessary steps required to move these technologies from bench to bedside are also discussed. *© 2013 American Association of Physicists in Medicine.* [http://dx.doi.org/10.1118/1.4802733]

Hruska and O'Connor, Medical Physics, 40(5), May 2013

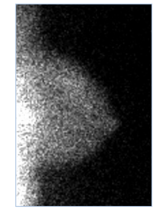
Commercially available systems

Scintimammography

- Conventional gamma camera with scintillating detector
- Bulky camera cannot be positioned close to the breast
- Interference from adjacent tissues (heart, liver)
- Poor sensitivity for small lesions
  - Non-palpable masses: 30-60%

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

Patient in prone position


Scintimammogram (lateral view)

Dedicated systems

- 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 systems: Name?

~~Scintimammography~~
~~Anything "nuclear"~~
Molecular breast imaging (MBI)

- Single-photon detectors
  - Single photon emission mammography
  - Breast Specific Gamma Imaging (BSGI) – Dilon Diagnostics term
  - Direct-conversion MBI
- Coincidence-detection systems
  - Positron Emission Mammography (PEM)
  - Dedicated Breast PET (DbPET)

Sestamibi vs. FDG

	Tc-99m sestamibi	F-18 FDG
Originally developed for	Myocardial perfusion imaging	Brain imaging
FDA approval	1997, for *diagnostic* breast imaging	2000, for *diagnostic* oncologic imaging
Production	Generator	Cyclotron
Photon energy	140 keV	511 keV
Mechanism of uptake in breast cancer	Uncertain • Passive diffusion • Proportional to blood flow and mitotic activity • >90% sequestered in mitochondria	Somewhat uncertain • Active transport • Marker for increased glucose metabolism

Sestamibi vs. FDG

Patient Preparation

	Tc-99m sestamibi	F-18 FDG
Fasting	Not required, may be beneficial	4-6 hour fast necessary
Testing	None	Glucose check
Wait time	Imaging begins ~ 5 min post-injection	Imaging begins ~45 min post injection

Sestamibi vs. FDG

Dosimetry

	Tc-99m sestamibi	F-18 FDG
Target organs	colon, kidneys, bladder, gallbladder	bladder, heart, brain
Physical half-life	6 hours	110 min
Biological half-life	6 hours	10 hours
Effective half-life	3 hours	104 min
Effective dose	0.333 mSv/mCi	0.703 mSv/mCi

Dedicated systems: Single photon

Breast Specific Gamma Imaging (BSGI)
Dilon Diagnostics

Dilon 6800:
Multicrystal Sodium Iodide (NaI) scintillator + PSPMTs
Pixel size: 3.0 mm
FOV: 20 x 16 cm

New generation, Acella:
Multicrystal CsI crystals + solid-state photodiodes
Pixel size: 3.2 mm
Larger FOV: **25 x 20 cm**

FDA-approved, BSGI-guided biopsy system available

Image courtesy of Dilon Diagnostics

Dedicated systems: Single photon

Direct Conversion MBI (DC-MBI)
GE Healthcare
Discovery NM 750

Semiconductor Cadmium Zinc Telluride (CZT)

- Improved energy resolution
- Pixel size: 2.5 mm
- FOV: 20 x 20 cm
- Dual-head configuration
- Registered collimators
- Spatial resolution best at collimator face (~pixel size), degrades to ~5 mm at center of 6 cm-thick breast

Image courtesy of GE Healthcare

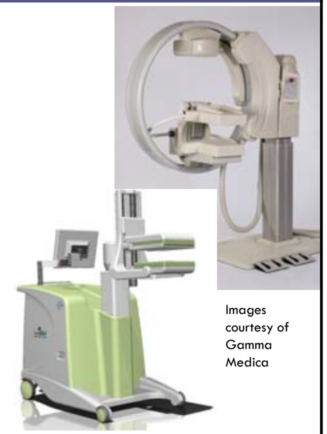
Dedicated systems: Single photon

Direct Conversion MBI (DC-MBI)
Gamma Medica
LumaGem

Semiconductor Cadmium Zinc Telluride (CZT)

- Improved energy resolution
- Pixel size: 1.6 mm
- FOV: 20 x 16 cm
- Dual-head configuration
- Registered collimators
- Spatial resolution best at collimator face (~pixel size), degrades to ~5 mm at center of 6 cm-thick breast

Biopsy capability in development

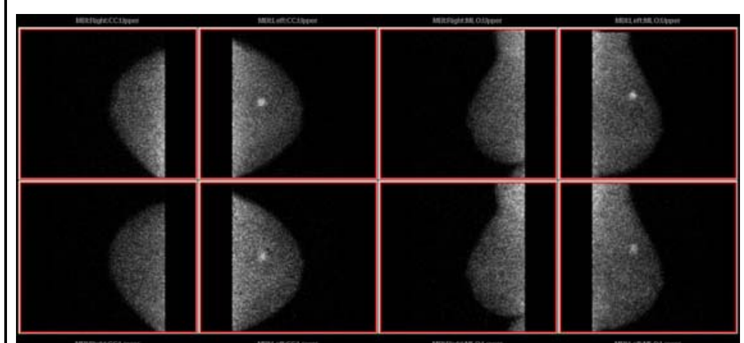


Images courtesy of Gamma Medica

Dedicated systems: Single photon

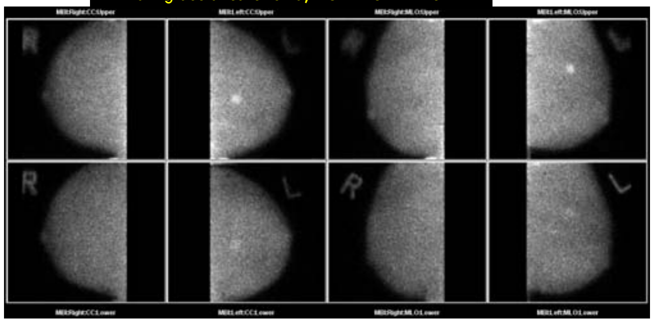
- Imaging procedure
  - Tc-99m sestamibi injected IV
  - Patient positioned by specially trained technologist
  - Imaging begins immediately after injection
  - Two views of each breast acquired (CC and MLO)
  - Light, pain-free compression

Example Direct-Conversion MBI



Better detection with dual-head MBI

Infiltrating ductal carcinoma, 1.5 x 1.3 x 1.2 cm



Sensitivity for small cancers improved from 68% with single head to 82% (p=0.004) with dual-head

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

Dedicated systems: Coincidence

Positron Emission Mammography (PEM)

Naviscan

PEM-Flex

- Two opposing detectors within transparent compression plates
- Scanning arrays of LYSO crystals
- 24 x 16 cm FOV
- Limited angle tomo – 3D slices
- Resolution best in middle of breast ~2 mm, degrades to 6-9 mm for slices closest to detector

FDA-approved, PEM-guided biopsy system available

Image courtesy of Naviscan

Dedicated systems: Coincidence

Dedicated Breast PET

Oncovision

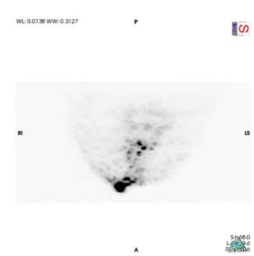
Mammi Breast PET

Ring of 12 LYSO scintillating crystals

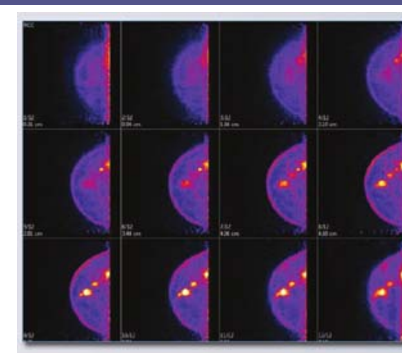
- Reported using <2 mCi FDG
- 3D tomographic dataset collected in 5 min
- Resolution 2 mm, isotropic

Images courtesy of Oncovision

Examples: Coincidence Systems



Mammi-PET example



Naviscan PEM 3D slices

Clinical Evaluations

Clinical evaluations

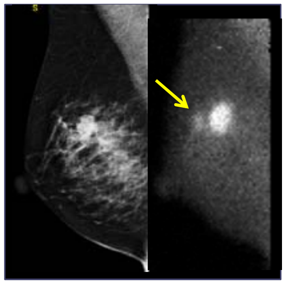
- Pre-operative evaluation

Pre-operative evaluation

- MRI now often used in pre-operative evaluation
  - Detects additional sites of mammographically-occult cancer
    - Ipsilateral breast: 7-12% of women
    - Contralateral breast: 3-4% of women
  - High sensitivity: approaching 100%
  - Variable specificity: 26-90%
    - (= false positives in 10 to 74% of patients)

Pre-operative evaluation

- Single photon system studies
  - Additional sites of malignancy in 9-11% of patients with newly diagnosed cancer
  - False positives in 7-20% of patients



Direction-conversion MBI detects additional site of disease occult on mammography

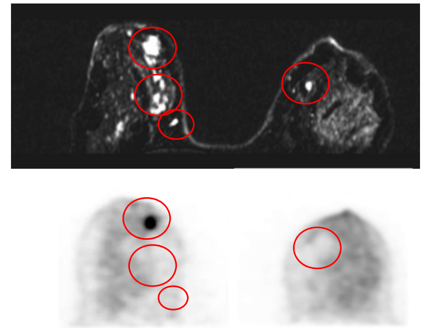
Brem et al. Academic Radiology 2010
Killelea et al. Am J Surgery 2009
Zhou et al. Am J Surgery 2009
O'Connor et al. J Nuclear Medicine (abstract) 2011

Pre-operative evaluation

- Multicenter trial of PEM vs. MRI in pre-op setting
- Ipsilateral evaluation in 388 patients
  - Additional disease detected beyond mammography and ultrasound
    - MRI: 13% of patients
    - PEM: 11 % of patients
    - Both MRI and PEM: 18% of patients
- PEM and MRI were complementary
- MRI was more sensitive, PEM had better specificity

Berg et al. Radiology 2011
Berg et al. AJR 2012

Pre-operative evaluation: Mammi PET



False positive ipsilateral and contralateral lesions on MR were correctly negative on PET

Courtesy of Dr. José Ferrer . ERESA. Hospital General Universitario of Valencia. Spain

Clinical evaluations

- Pre-operative evaluation
- Monitoring neoadjuvant therapy

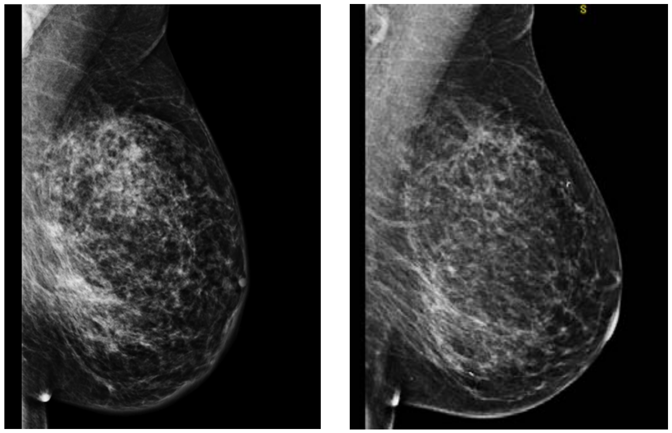
Monitoring neoadjuvant therapy

- Direct conversion MBI – Mayo Clinic
  - Change in uptake of Tc-99m sestamibi performed at 3 to 5 weeks following initiation of NAC were accurate at predicting the presence or absence of residual disease at NAC completion Mitchell et al. Clin Nuc Med 2013
- PEM study – MD Anderson
  - Both higher baseline FDG uptake and a decrease in uptake from baseline to 14 days into chemotherapy were significantly associated with pCR

Yang et al. Presented at RSNA 2011

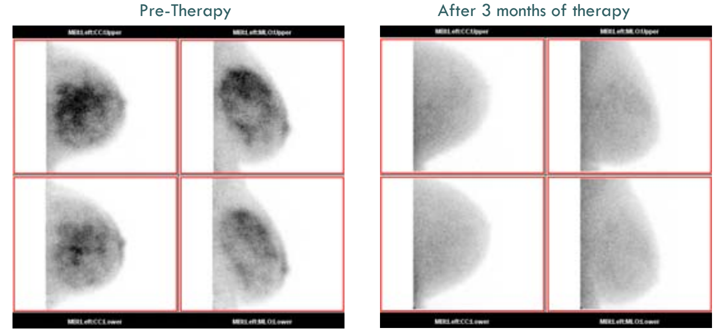
Neoadjuvant Therapy Case #1
Mammogram shows no change

Pre-Therapy | After 3 months of therapy



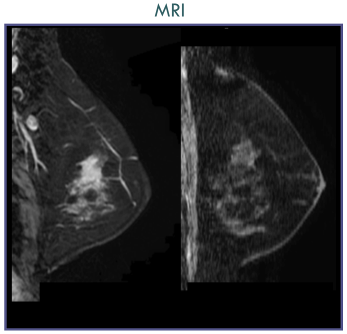
Neoadjuvant Therapy Case #1
MBI demonstrates pathologic complete response

Pre-Therapy | After 3 months of therapy



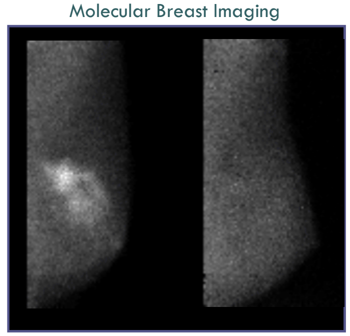
Neoadjuvant Therapy Case #2
MRI vs. MBI

MRI



Pre-therapy | Post-therapy

Molecular Breast Imaging



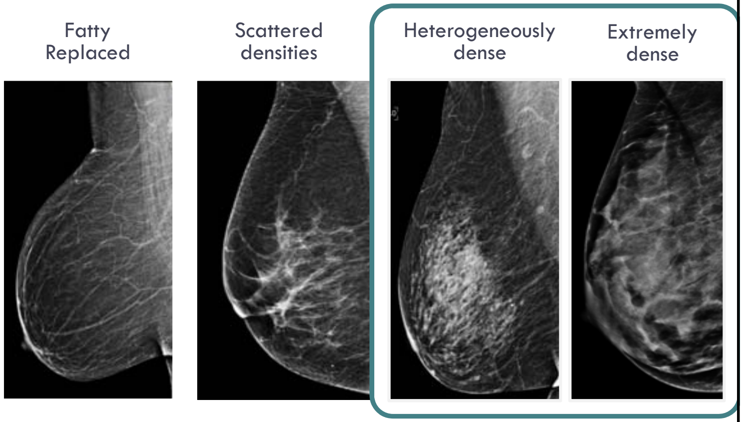
Pre-therapy | Post-therapy

Initial diagnosis: IDC with large Area of DCIS
MRI: indicated residual disease
Left Mastectomy: Surgical Pathology indicated no residual viable cancer

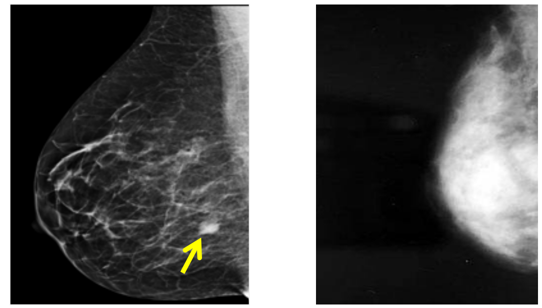
Clinical evaluations

- Pre-operative evaluation
- Monitoring neoadjuvant therapy
- Screening
  - Yes, I said screening

ACR BI-RADS Classification of Breast Density



More difficult to detect cancer in a dense breast



> 80% likelihood of finding a tumor in non-dense breast

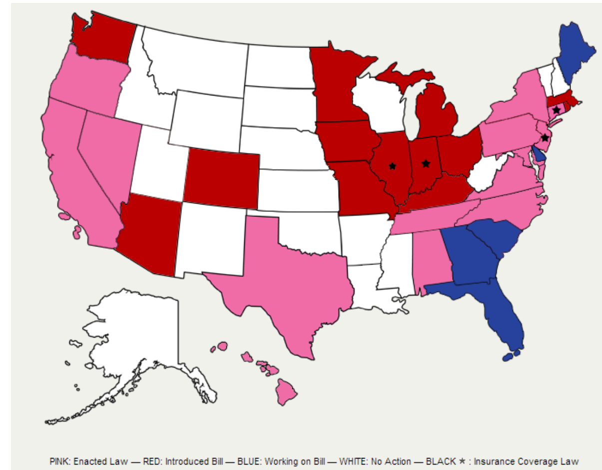
< 40% likelihood of finding a tumor in extremely dense breast

Motivation: Breast Density and its Risks

- Breast density is the most important factor in failure of mammography to detect cancer
  - Among women age 40-49 years, there is 15-fold increased risk of missed breast cancer in those with extremely dense vs fatty breasts (Kerlikowske, N Engl J Med 2007)
  - Increases false-positive mammograms 3-fold (Carney et al, Ann Int Med 2003)
  - Increases biopsies (Yankaskas et al, AJR 2002)
- Independent risk factor for development of breast cancer, RR = 4-6 (extremely dense vs. fatty replaced) (Boyd et al, NEJM 2007)

Breast Density Notification Laws

- Communication of mammogram result to patient by letter is mandated by federal law (Mammography Quality Standards Act, 1992)
- Communication of information about breast density to the patient is not a U.S. federal law….yet
- 14 states to date have passed mandatory breast density notification laws



State of Connecticut letter to patients: What does it say?

"If your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplementary screening tests... A report of your mammography results, which contains information about your breast density, has been sent to your physician's office and you should contact your physician if you have any questions or concerns about this report."

What supplemental test?

- Not enough evidence to recommend any particular modality for supplemental screening
- Contenders
  - Tomosynthesis
  - Whole-breast ultrasound (Automated or hand-held)
  - MRI
  - MBI?

Mayo MBI Screening Studies

- Dual-head direct conversion MBI systems
- 20 mCi (740 MBq) Tc-99m sestamibi
  - Designed as proof of principle to determine if increased diagnostic yield could be achieved
    Rhodes et al. Radiology 2010
- 8 mCi (300 MBq) Tc-99m sestamibi
  - After dose-reduction techniques were implemented
    Manuscript under review

Methods: Study Design

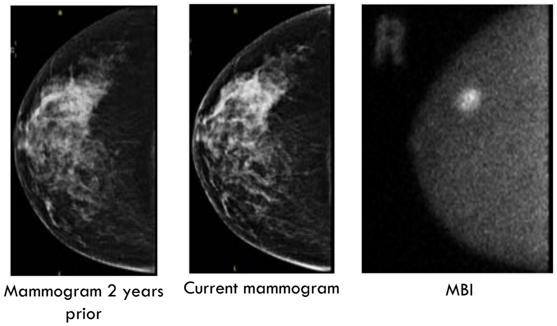
- Asymptomatic patients presenting for screening mammogram who had dense breasts on prior mammogram
- All participants had both mammogram and MBI (performed within 21 days of each other)
- Mammogram and MBI interpreted independently
- Cancer status established by
  - Any histopathologic diagnosis within 1 year
  - Conclusive negative imaging at > 1 year

Results: Cancer Detection

- 2548 analyzable participants in two screening trials
- 32 patients diagnosed with breast cancer
  - 8 detected by mammography alone
  - 29 detected when MBI was added to mammography

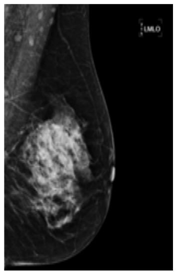
	Mammography alone	**Mammography + Adjunct MBI**	**p-value**
Cancer detection rate (Yield)	3.1 per 1000 (8/2548)	11.4 per 1000 (29/2548)	<0.001
Supplemental yield		**8.3 per 1000**	

Case 1: Mammographically Occult Invasive Ductal Carcinoma

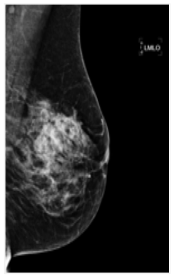


Grade II Invasive Ductal Carcinoma, 1.9 cm

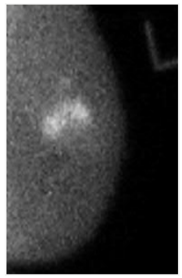
Case 2: Mammographically Occult Invasive Lobular Carcinoma



Mammogram 2 years prior



Current mammogram


MBI

Grade III Invasive Lobular Carcinoma, 3.6 cm

Results: Tumor Characteristics

21 patients with cancer detected only by MBI

- 17 of 21 invasive cancer
- Median size 0.95 cm (range 0.4 – 5.1 cm)
- 2 patients had bilateral breast cancer detected only by MBI

6 patients with cancer not detected on MBI

- 3 of 6 invasive cancer
- Smaller: Median size 0.6 cm (range 0.3-0.7cm)

Adjunct Screening Modality	Yield/1000 Mammography alone	Yield/1000 Mammography + Adjunct	Supplemental yield	% increase in cancers detected
Tomosynthesis (Skaane) All densities	6.1	8.0	1.9	31%
Tomosynthesis (Ciatto) Dense subset	4.1	6.6	2.5	61%
Ultrasound (Berg) ACRIN 6666 Year 1 DB + additional risk	7.5	12.8	5.3	71%
Ultrasound (Berg) ACRIN 6666 Year 2,3 DB + additional risk	8.1	11.8	3.7	46%
MRI (Berg) ACRIN 6666 Year 3 DB + additional risk	8.2	26.1	17.9	220%
MBI (Rhodes) Intermediate risk Dense breasts	3.1	11.4	8.3	270%

Effect on PPV (malignancies per biopsy performed)

Adjunct Screening Modality	Mammography alone	Mammography + adjunct screening	P-value
Ultrasound (Berg) ACRIN 6666 Year 1	29%	11%	<0.001 ↓
Ultrasound (Berg) ACRIN 6666 Year 2,3	38%	16%	<0.001 ↓
MRI (Berg) ACRIN 6666 Year 3	50%	25%	0.08 ↓
MBI (Rhodes) Dense breasts	21%	27%	0.64 ↑

Berg et al. JAMA 2012
Rhodes et al. Radiology 2011

MBI Screening Conclusions

- Compared to other modalities, adjunct MBI in dense breasts gave
  - Higher supplemental yield than tomosynthesis or ultrasound, not as high as MRI
  - No reduction in PPV as observed with ultrasound (and likely MRI)
- Radiation dose reduction successfully implemented
  - Results between 20 mCi and 8 mCi studies nearly identical

Radiation Dose

Radiation Risks of Breast Imaging

Modality	Dose to Breast (mGy)	Effective Dose (mSv)	Single exam, age 40: LAR of Fatal Cancer
Mammography (2-view bilateral screen)	3.7 (digital)	0.44 (digital)	1.3 – 1.7
PEM (10 mCi F-18 FDG)	2.5	6.2 – 7.1	31
BSGI/ MBI (20-30 mCi Tc-99m sestamibi)	1.3 – 2	5.9 – 9.4	26 – 39

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

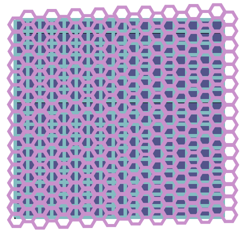
Hendrick RE, Radiology 2010; 257:246-253

AAPM Policy Statement

- Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged.

Dose reduction for Direct Conversion MBI

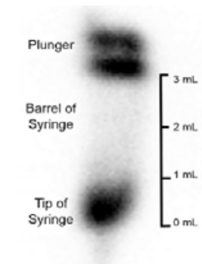
- New collimator
  - Registered
  - Optimized for dual-head imaging
- Widened energy window
  - Incomplete charge collection in CZT
  - Capture photons mis-registered at lower energies
- **These 2 strategies allowed reduction from 20 mCi to 8 mCi Tc-99m sestamibi**



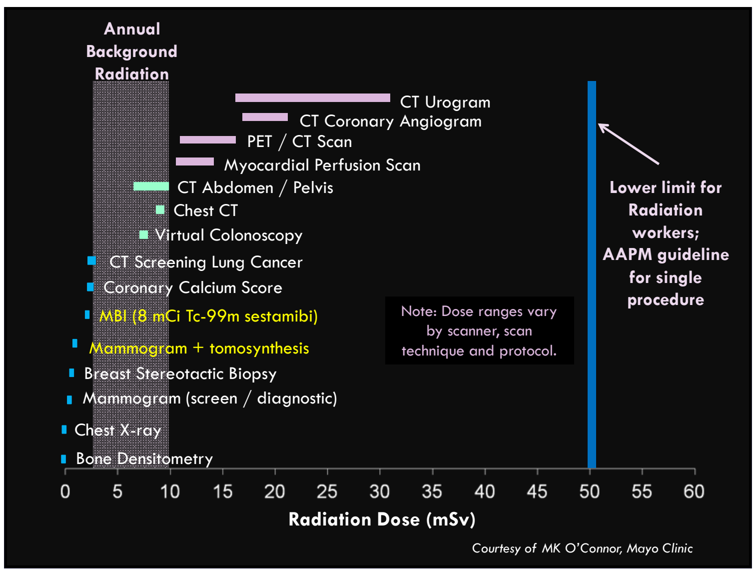
Weinmann et al. Medical Physics 2009; 36: 845-856 *Hruska et al. Medical Physics 2012*

Dose reduction for Direct Conversion MBI

- Injection procedure, account for adhesion to syringes
  - What we thought was 8 mCi injection actually ~6.5 mCi
- Patient prep?
  - Fasting and Warming appear to improve breast uptake
- **With all strategies combined, 4 mCi Tc-99m sestamibi doses appear feasible**



Swanson et al. J Nuclear Medicine Technology 2013.



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BSGI/ MBI (20-30 mCi Tc-99m sestamibi)	1.3 – 2	5.9 – 9.4	26 – 39
MBI (4-8 mCi Tc-99m sestamibi)	0.25 – 0.5	1.2 – 2.4	5.2 – 10

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

Hendrick RE, Radiology 2010; 257:246-253

Perspective

Doubling a very small amount is still inconsequential. It is like saying: “Yesterday there was a matchstick on the football field; today there are two matchsticks on the football field. Matchstick pollution has increased by a massive 100% in only 24 hours.” The statement is mathematically correct but silly and misleading.

Kelvin Kemm

www.cfact.org/2013/10/12/physicist-there-was-no-fukushima-nuclear-disaster/

Moving into Clinical Practice

- Radiation risk education, dose reduction efforts
- Industry involvement
- Radiologist involvement:
  - Familiar format, correlation with other imaging
  - Standardized interpretation and reporting
  - Direct-biopsy capability
- Rigorous patient studies
  - Published outside of technical journals
  - Multicenter trials

Conners et al, EJNMMI 2012
Conners et al, AJR 2012
Narayanan et al, AJR 2011