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Molecular Imaging of the Breast

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Conflict of Interest

Dr. M.K. O'Connor — Royalties - Gamma Medica; Research funding – GE Healthcare

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National Institute of Health
Dept. of Defense
Susan G Komen Foundation
Mayo Foundation
Friends for an Earlier Breast Cancer Test

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Molecular Imaging of the Breast Instrumentation

- PEM (Positron Emission Mammography)
  - Clinical unit developed by Naviscan
  - Numerous prototype PEM and PEM/CT units under development
- BSGI (Breast Specific Gamma Imaging)
  - Single detector, multicrystal NaI based gamma camera
  - Developed by Dilon Technologies
- MBI (Molecular Breast Imaging)
  - Dual detector Cadmium Zinc Telluride based gamma cameras
  - Clinical units developed by Gamma Medica and GE Healthcare

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PEM Flex II (Naviscan)	• 2 opposing detectors – limited angle tomography • Numerous clinical studies reported
Mammi-PEM (Oncovision)	• Ring detector – full 3-D images • In early clinical trials in Europe
Clear-PEM (Consortium of 7 European Institutions)	• 2 opposing rotating detectors (LYSO) – full 3-D images • In testing at Hospital of the Portuguese Institute of Oncology
C-PEM (Shimadzu Corporation)	• Unique C-shaped detector ring (LGSO) – full 3-D images • In testing at Kyoto University
MDA-PEM (M.D. Anderson)	• 2 opposing rotating detectors (LYSO) – full 3-D images • In development at M.D. Anderson Cancer Center – low cost
PEM-CT (University California - Davis)	• 2 opposing rotating detectors (LYSO) – full 3-D images • Cone beam CT

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PEM (Positron Emission Mammography)

2 scanning arrays (~5 x 16 cm) of LYSO crystals

- Original design proposed by Weinberg in 1995
- Only system that is FDA approved
- Clinical studies: 10 mCi F-18 FDG
- FOV: 16 cm x 24 cm
- Limited angle tomography
  2.4 mm resolution (in plane)
  8.0 mm resolution (cross-plane)
  (JNM 2009;50:1666-1675)

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The Breast Journal
ORIGINAL ARTICLE
PET-Guided Breast Biopsy

Kalinyak et al, Breast J 2011; 17: 143-151.

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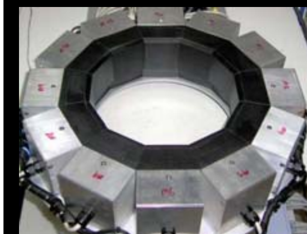
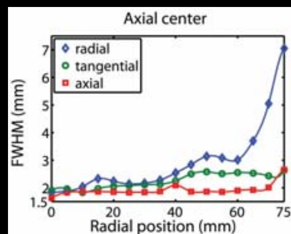
Mammi-PEM

LYSO Block Crystal: 40 x 40 mm coupled to a PSPMT
Axial FOV = 4 cm
Spatial resolution = 1.6 – 1.9 mm



LYSO modules



Spatial Resolution

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Mammi-PEM

12 modules of 4 cm x 4 cm LYSO crystals + PSPMT

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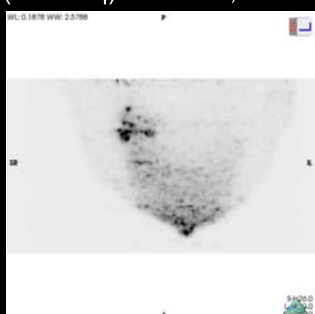
Mammi-PEM

2.8 mCi (100 MBq) F-18 FDG, 12 minute acq.



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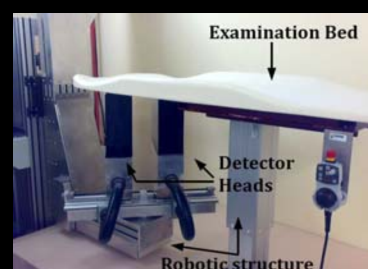
Clear-PEM

2 detector arrays of LYSO crystals (6144 crystals)
18 x 16 cm FOV
Spatial resolution (x, y, z): 2.4 x 1.8 x 2.7 mm



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Clear-PEM

1st installation @
Hospital of the Portuguese Institute of Oncology

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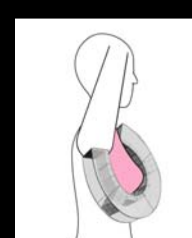
C-PEM (Shimadzu Corporation)

Detector ring: 78 cm diameter
Axial FOV: 4.8 cm per ring.
System can be expanded up to 3 rings.



C-PEM (Shimadzu Corporation)

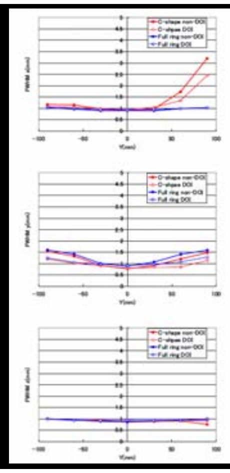
Ring comprises 48 detector modules

4098 LGSO crystals

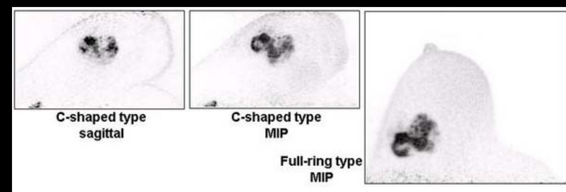
1.5 x 1.5 mm crystals

Measured resolution (x, y, z): 1 mm x 1.3 mm x 1 mm

Yamada et al, IEEE NSS 2007



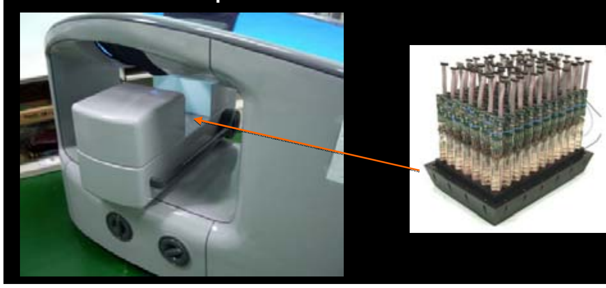
C-PEM (Shimadzu Corporation)



Kitamura et al, Proceedings WMIC 2010

MDA - PEM (M.D. Anderson)

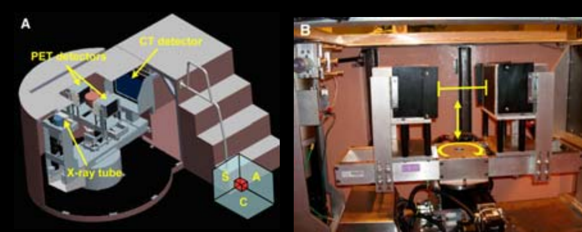
2 detector arrays of LYSO crystals coupled to PMTs
1.54 x 1.54 mm crystals
In-plane resolution: 1.5-2.5 mm
Cross-plane resolution: ~4.5 mm



PEM / CT (UCD)

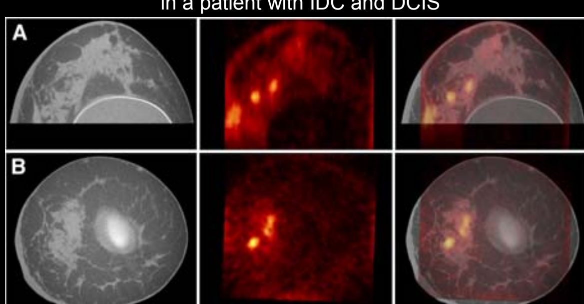
2 detector arrays of LYSO crystals coupled to PSPMTs
768 Slice Cone Beam CT

Crystal size (mm)	3 × 3 × 20
Crystal array	81 (9 × 9)
No. of detector blocks	16 (4 × 4)
FOV (cm)	11.9 (axial + transaxial)



PEM / CT (UCD)

Axial (A) and coronal (B) PEM/CT images in a patient with IDC and DCIS



Bowen et al, JNM 2000;50: 1401-1408

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BSGI (Breast Specific Gamma Imaging)
developed by Dilon Technologies

Developed by Majewski et al, 1998

FOV: 15 cm x 20 cm
Single detector with array of 3 mm x 3 mm NaI crystals

3.3 mm intrinsic resolution
~14% energy resolution

BSGI (Breast Specific Gamma Imaging)

- Large number of clinical studies reported
- Tc-99m sestamibi 20-30 mCi
- CC and MLO views acquired
- Primary application as adjunct diagnostic technique
- Biopsy scheme recently developed (employs slant-hole collimation)

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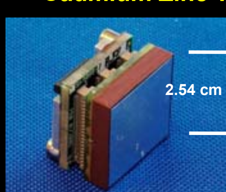
Molecular Breast Imaging

- Cadmium Zinc Telluride (CZT) gamma camera technology
- Dual-detector design optimized for breast imaging →
- 2 Clinical units available
  - 16 x 20 cm FOV (GM)
  - 20 x 24 cm FOV (GE)


GM - LumaGem


GE – NM750b

Cadmium Zinc Telluride (CZT) Detector



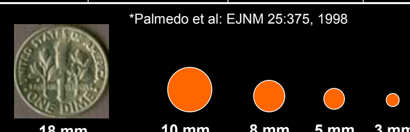
- Intrinsic Resolution = 1.6 mm / 2.5 mm
- Energy Resolution 4.0% / 6.5%
- Can be operated at room temp
- Dead space ~8 mm – ideal for breast imaging
- Expensive – currently limited to small field of view detectors

AJR

Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera to Detect Small Breast Tumors

Technology	Tumors 5-10 mm in size	Tumors < 5 mm in size	All Tumors (128 in 88 patients)
Standard γ-Camera*	55%	No data	
Single-head MBI	76%	44%	82%
Dual-head MBI	87%	67%	90%

*Palmedo et al: EJNM 25:375, 1998



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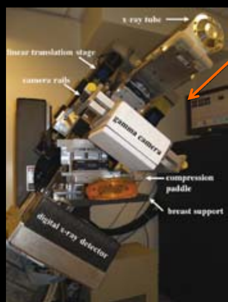
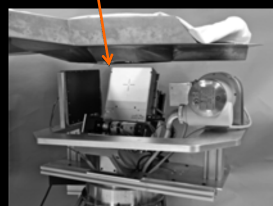
Multi-modality
MBI/CT and BSGI/DBT



Combined BSGI/Tomosysthesis system (University Virginia)

Combined MBI/CT system (Duke University Medical Center)



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Molecular Imaging of the Breast
Imaging Procedure

PEM	MBI / BSGI
• IV injection of F-18 FDG. 10 mCi (PEM-Flex system) 2.8 mCi (Mammi-PEM) • Fasting and monitoring of blood glucose • Imaging starts 45-60 minutes post injection. • Naviscan system: Mammographic orientation with light breast compression. • Newer PEM systems: Breast is pendulant • FDG preferentially accumulates in cancer cells and is *not influenced by breast density or hormonal status*	• IV injection of Tc-99m sestamibi. 20-30 mCi (BSGI) 4-8 mCi (MBI) • No patient preparation required • Imaging starts ~5 minutes post injection. • Mammographic orientation with light breast compression. • Sestamibi preferentially accumulates in cancer cells and is *not influenced by breast density* • Uptake of sestamibi *is influenced by hormonal effects*

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Molecular Imaging of the Breast
Clinical Indications

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BSGI (Breast Specific Gamma Imaging)

Administered doses
- 20 – 37 mCi Tc-99m sestamibi
- (Brem et al, Academic Radiol 2010; 17: 735-743)

Applications:
- Problem solving in indeterminate cases (BIRAD 3)
- Pre-operative evaluation of disease extent

Retrospective reviews
- 66 patients: Sensitivity 89%, specificity 90%
- (Kim BS, Ann Nucl Med 2012; 26: 131-137)

Limited prospective studies performed to date

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Molecular Imaging of the Breast
BSGI Clinical Results

Pre-operative evaluation

82 patients – 18 additional abnormality on BSGI, 7 cancers
Am J Surg. 2009;198:470-4. Killelea et al.

138 patients – 25 additional abnormality on BSGI, 15 cancers
Am J Surg. 2009;197:159-63. Zhou et al.

Adjunct Diagnostic Tool

146 patients – 167 lesions underwent biopsy

BSGI detected 80/83 malignant lesions (96% sensitivity)
identified 50/84 benign lesions (60% specificity)

Radiology. 2008;251:651-7. Brem et al.

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Jean M. Weigert, Margaret L. Bertrand, Leora Lanzkowsky, Lillian H. Stern, Douglas A. Kieper

Results of a Multicenter Patient Registry to Determine the Clinical Impact of Breast-Specific Gamma Imaging, a Molecular Breast Imaging Technique

BSGI as an adjunct diagnostic tool – results from a multi-institution registry of 1024 patients

TABLE 1: Overall Performance of Each Imaging Modality for 329 Patients

Performance Parameter	Imaging Modality: Mammogram	Ultrasound	Breast-Specific Gamma Imaging
Sensitivity	74	84	92
Specificity	79	62	70
Positive predictive value	71	60	68
Negative predictive value	82	85	93

Note—Data are percentages.

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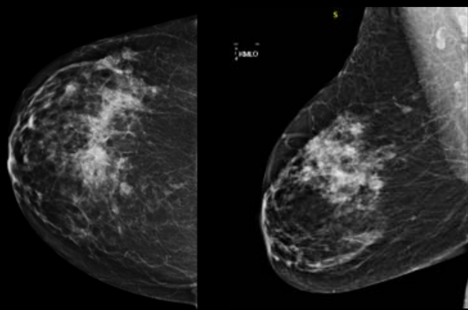
Positive Mammogram



1.1cm nodular density in upper inner right breast 9.5cm from the nipple

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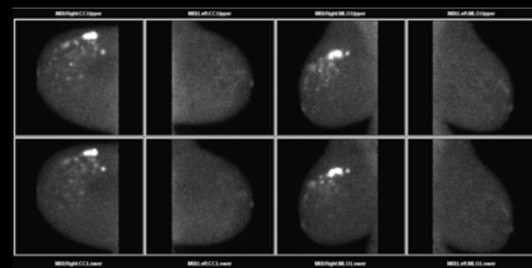
MBI Procedure

- Complementary opposing views of the breast
- Image interpretation: 8 images
- Time to interpret: ~1-2 minutes



2 x 1 cm IDC with multiple satellite lesions confirmed as DCIS on MRI

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Molecular Imaging of the Breast Clinical Indications

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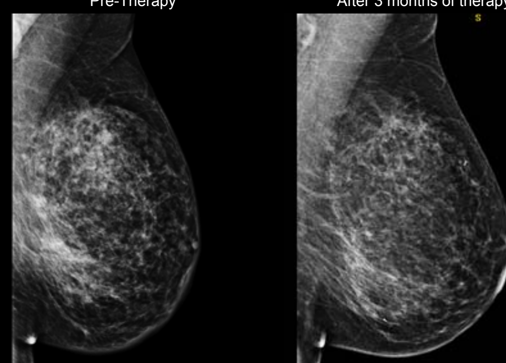
Mammogram Patient pre and post neoadjuvant therapy

Pre-Therapy / After 3 months of therapy



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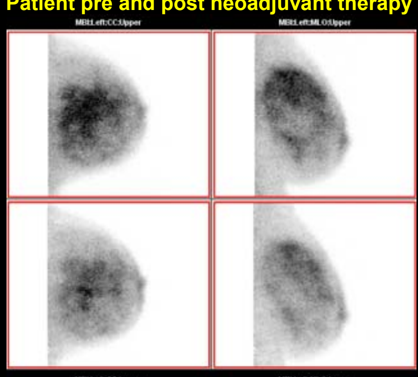
Molecular Breast Imaging Patient pre and post neoadjuvant therapy



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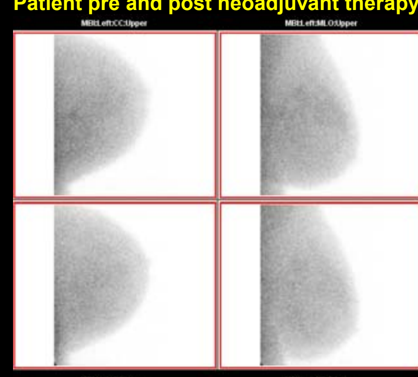
Molecular Breast Imaging Patient pre and post neoadjuvant therapy



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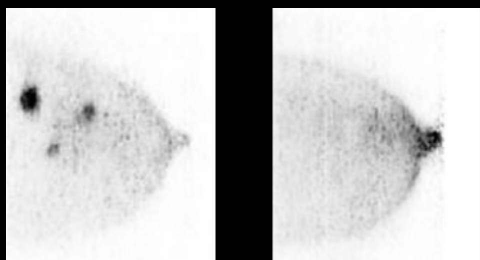
PEM Imaging in patients undergoing neoadjuvant therapy

Patient with multifocal breast cancer before and after neoadjuvant chemotherapy



(Koolen et al, Ann Oncology 2012; Article ID 438647)

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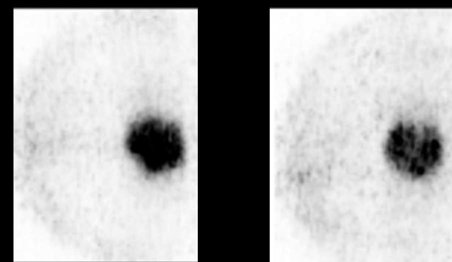
PEM Imaging in patients undergoing neoadjuvant therapy

Patient with multifocal breast cancer before and after neoadjuvant chemotherapy



(Koolen et al, Ann Oncology 2012; Article ID 438647)

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Molecular Imaging of the Breast Clinical Indications

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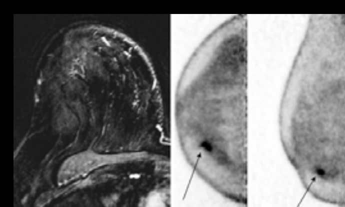
Sensitivity: PEM vs MRI

Breast Cancer	PEM	MRI
DCIS	90	83
Invasive BC	93	95



Shilling et al, EJNMMI 2011;38:23-26

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Nuclear Imaging vs MRI

- **PEM (Berg et al, Radiol 2012;198:219-232)**
  - **Comparable estimate of disease extent**

	Estimate of Disease Extent		
Modality	Accurate	Underestimated	overestimated
PEM	68%	22%	11%
MRI	75%	12%	13%

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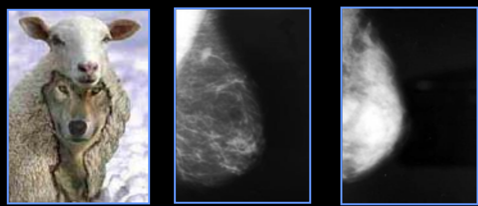
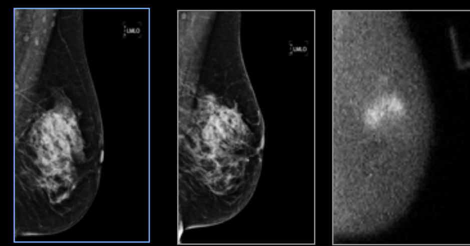
Molecular Imaging of the Breast Clinical Indications

MBI as a Screening Tool ?



- Dense breast tissue decreases sensitivity/ specificity of mammography
- Density, itself, significantly increases risk of breast cancer

MBI as a Screening Tool



MMG November 2008 | MMG October 2010 | MBI October 2010

Grade III Invasive Lobular Carcinoma, 3.6 cm; node positive

ORIGINAL RESEARCH ▪ BREAST IMAGING

Deborah J. Rhodes, MD
Carrie B. Hruska, PhD
Stephen W. Phillips, MD[2]
Dana H. Whaley, MD
Michael K. O'Connor, PhD

Dedicated Dual-Head Gamma Imaging for Breast Cancer Screening in Women with Mammographically Dense Breasts[1]

▪ *Radiology*: Volume 258: Number 1—January 2011

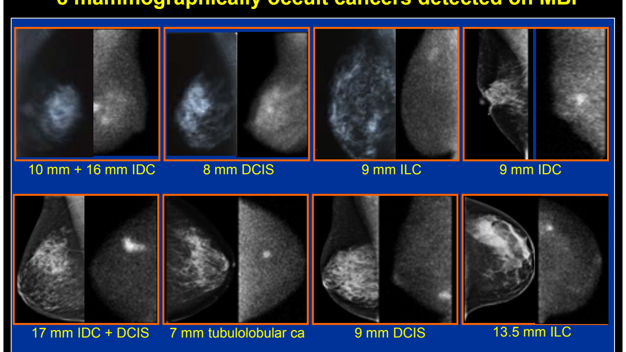
- Goal - Compare MBI and mammography in asymptomatic patients with dense breasts and increased risk of breast cancer (~1000 patients)
  - MBI performed using 20 mCi Tc-99m sestamibi per study
- Question – is MBI a viable screening adjunct to mammography in patients with dense breasts?

Diagnostic accuracy of screening mammography and MBI

Characteristic	Mammography No.	Mammography %	MBI No.	MBI %
Sensitivity	3/11	27	9/11	82
Specificity	840/925	91	861/925	93
Recall rate	88/936	9	71/936	8

Rhodes, Radiology, 2011

8 mammographically occult cancers detected on MBI



JOURNAL OF **Women's Health**

March 2012, epub, ahead of print

Evaluation of Molecular Breast Imaging in Women Undergoing Myocardial Perfusion Imaging with Tc-99m Sestamibi

- 313 patients enrolled Oct 2008 – June 2010
- 284 / 306 patients negative or benign findings on MBI
- 22 (7.2%) patients with positive MBI findings
- 4 cases confirmed as breast cancer (all negative on mammogram)

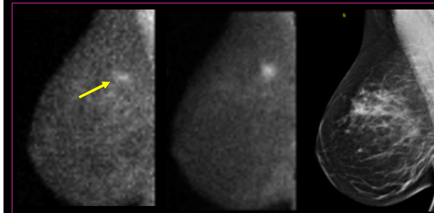
Patients with Positive MBI findings

- 4 new cancers detected by MBI
  - 12 mm IDC/ILC
  - 9 mm IDC
  - 2 mm IDC + 6 mm DCIS
  - 3 mm DCIS

supplemental diagnostic yield of 13.1 per 1000 women screened

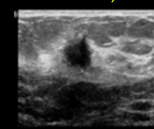
MBI Detected Cancer

- Screening mammography in June 2008 noted stable nodule, unchanged from previous annual mammogram
- Patient presented for myocardial perfusion scan in Feb 2009
- Enrolled in MBI study - positive
- Patient returned March 2010 for evaluation – palpable, mammographically occult breast cancer



MBI - 2009 MBI - 2010 Mammogram - 2010

12 mm invasive cancer (mixed lobular and ductal features)



MBI for Breast Cancer screening in women with mammographically dense breasts

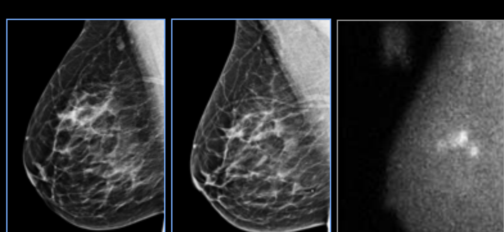
- Goal – Comparison of MBI and mammography in asymptomatic patients with dense breasts (~1600 patients or 20 cancers)
- Evaluation of low-dose MBI as a viable screening adjunct to mammography in patients with dense breasts?
  - MBI performed using 8 mCi Tc-99m sestamibi per study

Diagnostic Performance Characteristics of Screening MMG and MBI at Participant Level (interim results)

Study was closed to enrollment at end of February 2012 – 12 month follow-up in progress
Interim report to be presented at RSNA 2012

Characteristic	Incident MMG No.	Incident MMG %	Prevalance MBI No.	Prevalance MBI %
Sensitivity	3/15	30	13/15	87

Mammographically Occult Invasive Ductal Carcinoma Nondense Breast



MMG March 2009 MMG March 2011 MBI March 2011

Grade II Invasive Ductal Carcinoma, 4.1 cm

Summary findings – 3 MBI screening trials

Trial	# Patients	Recall Rate (%) MBI	Recall Rate (%) Mammo	Diagnostic Yield / 1000 MBI	Diagnostic Yield / 1000 Mammo
Dense Breast, increased risk	936	7.6	9.4	9.6	3.2
Cardiac Patients	303	7.2	N/A	13.1	N/A
Dense Breast (low dose MBI)	1649	7.6	10.9	10.3	3.0

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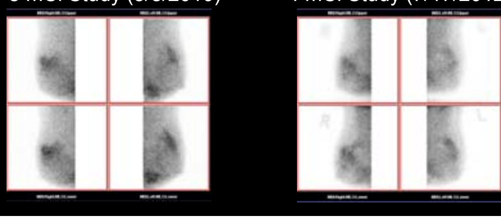
Interval Screening

MBI vs Mammography in women with dense breasts

- Compare interval screen detected breast cancer with MBI and mammography (~2000 patients or 20 cancers)
  - MBI performed using 4 mCi Tc-99m sestamibi per study

8 mCi Study (3/8/2010) | 4 mCi Study (7/17/2012)



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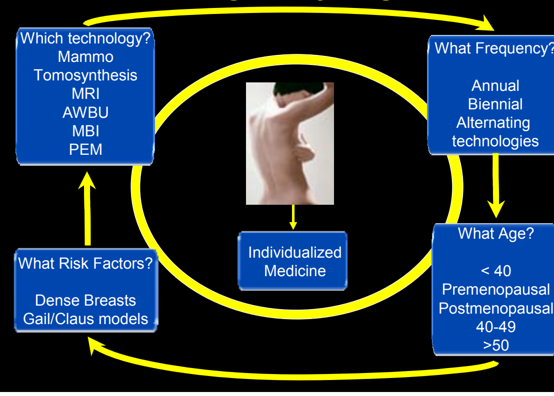
Which Technology for Screening& Early Diagnosis?



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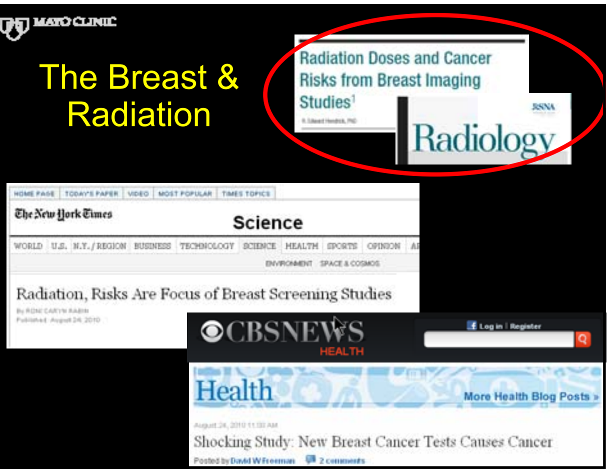
The Breast & Radiation



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Relative Radiation Risks

(assuming validity of LNT hypothesis / BEIR VII Report)

Radiation dose to patients

Mammogram	~ 0.7 mSv
PEM-Flex (10 mCi F-18 FDG)	~ 7 mSv
Mammi-PEM (2.8 mCi F-18 FDG)	~ 2 mSv
BSGI (25-30 mCi Tc-99m mibi)	~ 9 mSv
MBI (4 mCi Tc-99m mibi)	~ 1.2 mSv

For pop. of 100,000 women undergoing above procedures at age 40, estimated cancer mortality (based on BEIR VII)

Mammogram	~ 2
PEM-Flex (10 mCi F-18 FDG)	~ 30
BSGI (25-30 mCi Tc-99m mibi)	~ 35
Mammi-PEM (2.8 mCi F-18 FDG)	~ 8
MBI (4 mCi Tc-99m mibi)	~ 4

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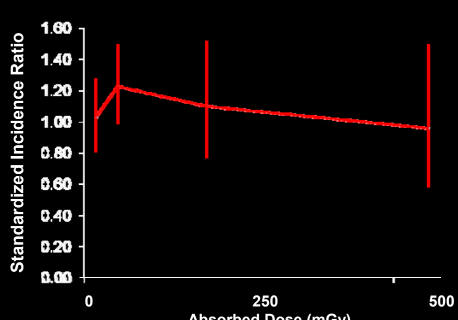
Breast Cancer Risk after Radiotherapy in Infancy

Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years



Lundell et al, Radiation Research 1999; 151: 626-632

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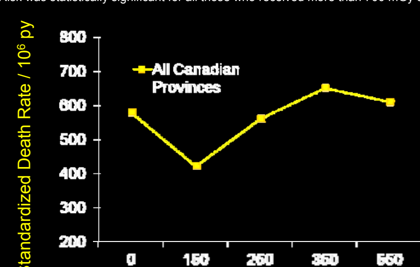
Mortality from Breast Cancer after Irradiation during Fluoroscopic Examinations in Patients being treated for Tuberculosis

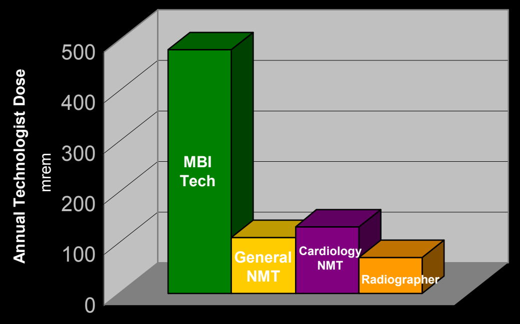
Miller AB et al, NEJM 1989; 321: 1285-1289.

31,710 women treated between 1930 - 1952

"Risk was statistically significant for all those who received more than 700 mGy of radiation"



MBI: Implications for Radiation Exposure to the Technologist from 8 patients / day, 20 mCi / patient

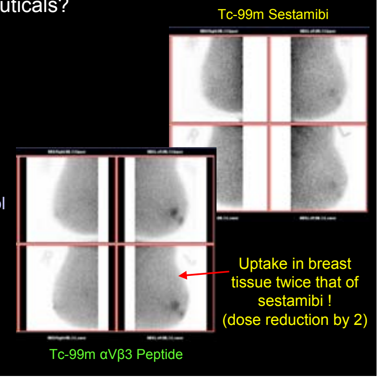


Pletta CK, et al. J Nucl Med 2009; 50 (Suppl 2): 428P.

Radiopharmaceuticals

- New radiopharmaceuticals?

- Tc-99m Sestamibi
- Tc-99m Tetrofosmin
- F-18 FDG
- Tc-99m αV-β3 Integrin
- F-18 αV-β3 Integrin
- Tc-99m Annexin V
- I-123 Iodo-estradiol
- I-123 Methoxy-vinylestradiol
- I-123 Dimethyl-Tamoxifen
- F-18 estradiol



Conclusions

Significant developments in both PET and SPECT instrumentation dedicated to breast imaging

Radiation doses are or will be at comparable levels to mammography for both PEM and MBI

Barriers to clinical use?
- Lack of multi-center trials
- Few prospective clinical trials to date
- Lack of reimbursement for clinical studies
- Difficulty in integrating nuclear medicine procedures into a breast imaging practice