Molecular Breast Imaging New Modality for Diagnosing Breast Cancer

By Lillian H. Stern, M.D.

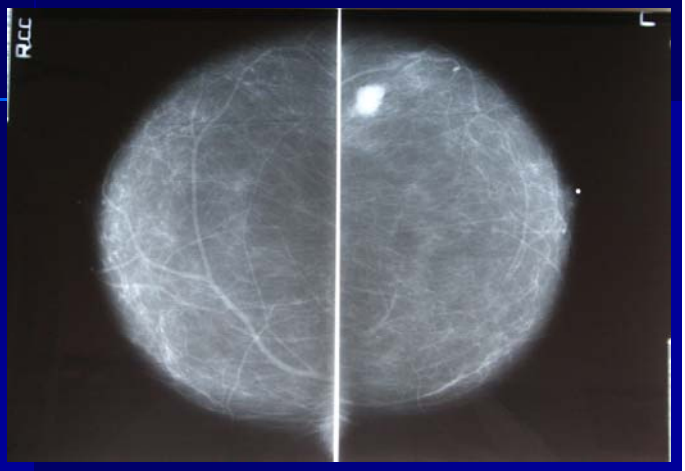
Don't we have enough tools for diagnosing Breast Cancer???

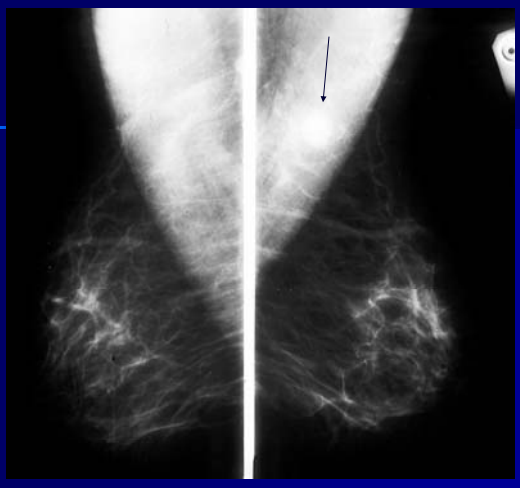
Current Modalities

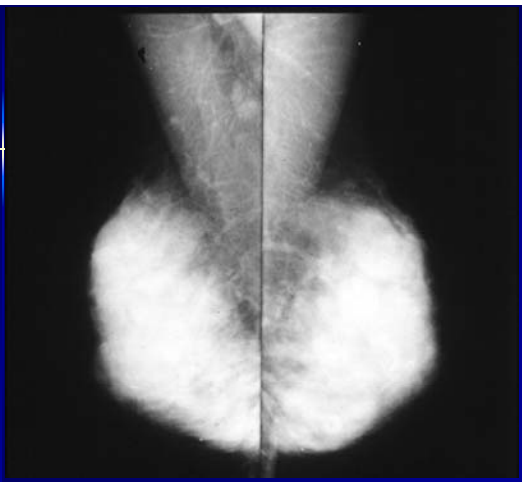
- Mammograms (analogue v. digital)
- Tomosynthesis
- Ultrasound
- MRI
- PET Scan
- Molecular Breast Imaging (BSGI. MBI, PEM)

Why do we need another tool?

- Many articles state that we miss 10% of breast cancer on mammography.
- It really is much higher especially in dense breasts!---It may be as high as 30%.
- Dense tissue camouflages cancers until they enlarge, become brighter than the surrounding tissue, or form discrete margins and/or calcifications.







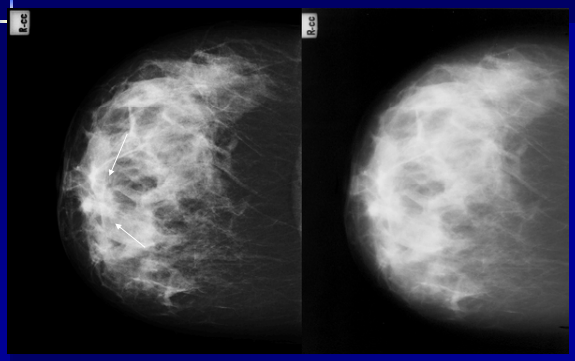
Old and new tools for detecting breast cancer.

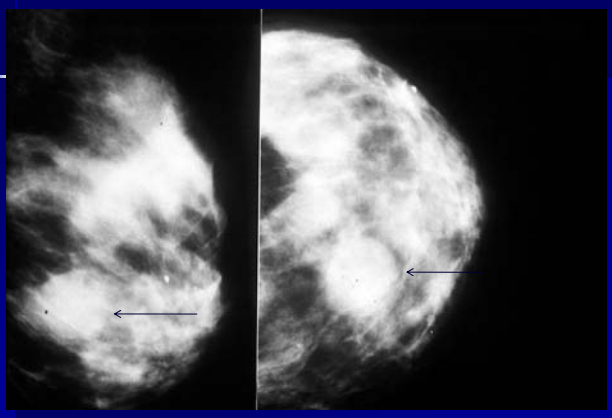
- Mammography is still the "Gold Standard."

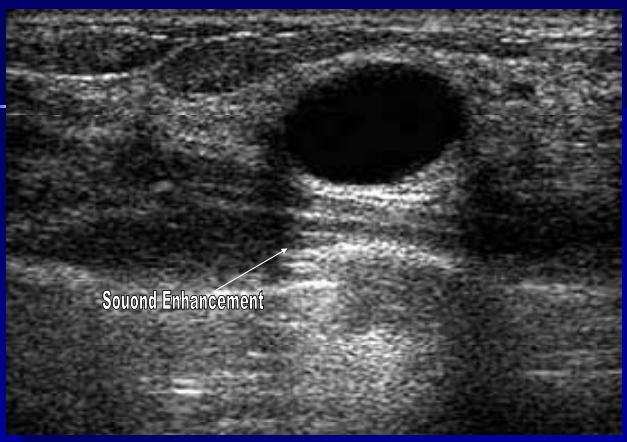
Digital Mammograms

- Performed just like a regular mammogram.
- Still need compression.
- Image is just recorded differently---- on a computer instead of x-ray film.
- Can see thru dense tissue better.

Digital Analogue







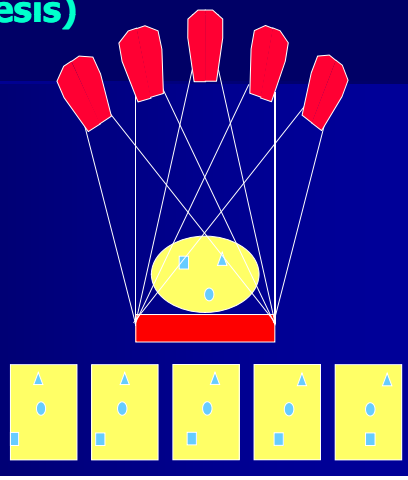
Solid Mass with Calcifications

Tomosynthesis

- 3-Dimensional picture using FFDM.
- Multiple X-ray pictures of the breast from many angles.
- Clears overlapping densities hiding an underlying abnormality.

3D Mammography (Tomosynthesis)

- Step, expose image
- 11 images, 5 degrees between images
- Total dose equal to single mammo
- Total imaging time about 7 seconds



Breast Tomosynthesis

When is overlapping ?

It is hard to interpret this

Courtesy of Dan Kopans, M.D.

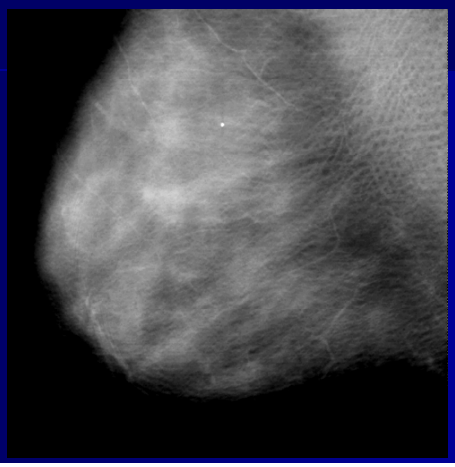
Breast Tomosynthesis

It is hard to interpret this

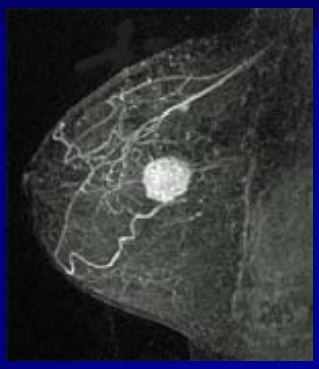
When is overlapping ?

Examples of Tomosynthesis

Tomosynthesis Mammography Reconstruction



MRI (Angiogenesis)



MRI is an excellent tool!

- When it is very positive-it is dramatic.
- But frequently it has several questionable areas which require a 6 month follow-up or a repeat study at a different time in the menstrual cycle.
- Sometimes when patient comes for MRI biopsy, abnormal area no longer visible.

MRI is expensive!

- Some patients can't have test because of metal or pacemakers.
- Some patients can't lay on stomach.
- Some patients are claustrophobic.

Radiologist has to scroll thru 700 images!

- Patient usually has to wait several weeks to get on the MRI schedule and may have to come back for the opposite breast.
- Patient may not get the results for several days.
- MRI usually requires precertification.

Anxiety!!!!

- Patient!!!
- Clinicians!!
- Radiologists! Will I miss a cancer? Will I be sued?

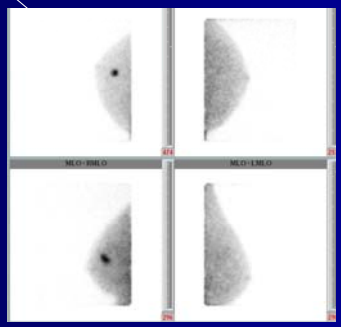
Goals for decreasing everyone's anxiety!

- Decrease number of indeterminate Studies
- Decrease number of BIRADS 3 = 6 month follow-up.
- Decrease number of benign biopsies.

Molecular Imaging

- Instead of looking at structures (anatomy) or angiogenesis, these tests analyze **cellular activity**.
- Cancer cells are more active than normal cells and the mitochondria will therefore absorb more of the injected radioactive isotope.

Molecular Breast Imaging Positive Cancer on Right



Molecular Breast Imaging

- Involves an injection into a vein of a tracer dose of radioactive material.
- Images of only the breast are obtained using the same views as a mammogram. Direct comparison with the mammogram is therefore possible!
- Active cells produce a black spot similar to a PET scan.

BSGI (Dilon) or MBI (Mayo Clinic) Tc99 Sestamibi

- Readily available (Can borrow a dose from cardiac stress test.)
- Can quickly add on a patient already in department.
- No fasting. No delay after injection.
- No contraindications

Isotope for PEM (Positron Emission Mammography)

- Use FDG similar to a PET scan.
- Patients must fast.
- One hour delay between injection and imaging.
- Concern in Diabetics

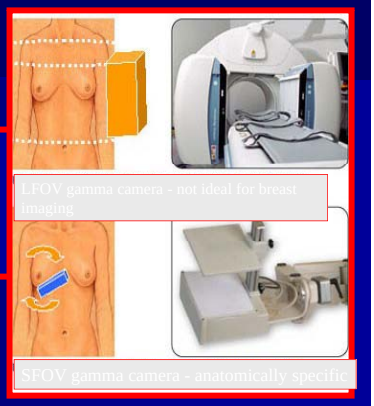
Scintimammography

- This is the old name—developed in the 1990's
- Failed to demonstrate small cancers

Scintimammography

- Patient laid prone on a regular nuclear medicine table.
- Detail was not good enough to pick up small cancers

The weakness of conventional breast scintigraphy is the low resolution of the standard gamma camera



The Dilon 6800 Gamma Camera

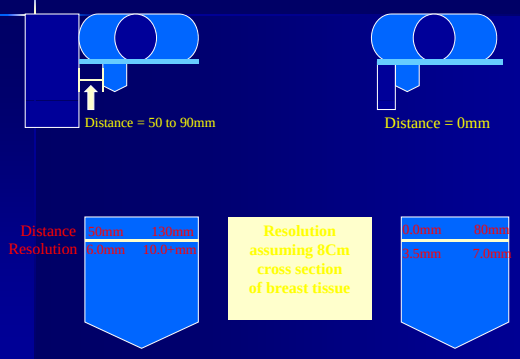
The Dilon 6800 Gamma Camera *can replicate any mammographic view.*

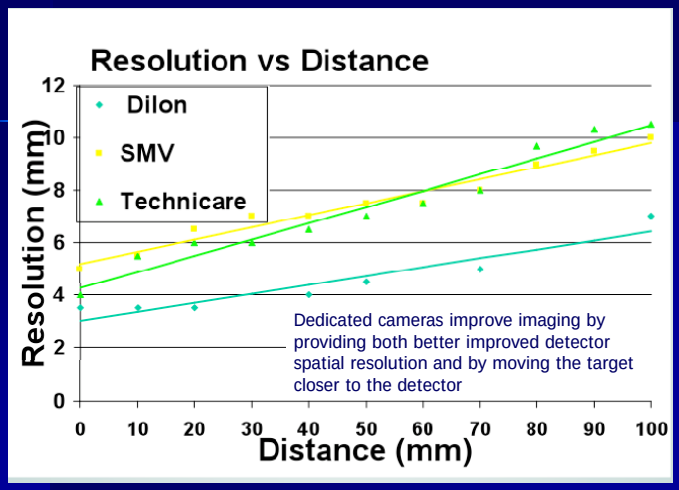
Cranial Caudal

Oblique

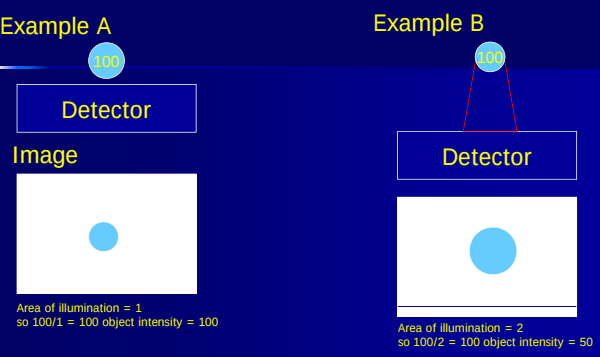
Medial

Comparative Resolution Based on Geometric Factors



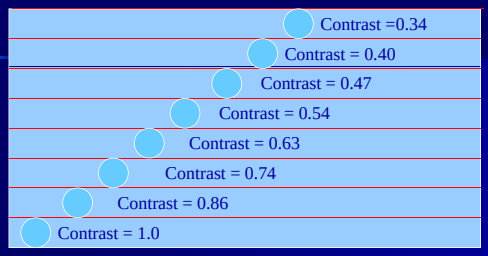


Partial Volume effect



The area of the object in both cameras contains the same number of counts so the counts/area of example A is higher than example B. This results in better contrast for the image in example B.

Impact of Attenuation



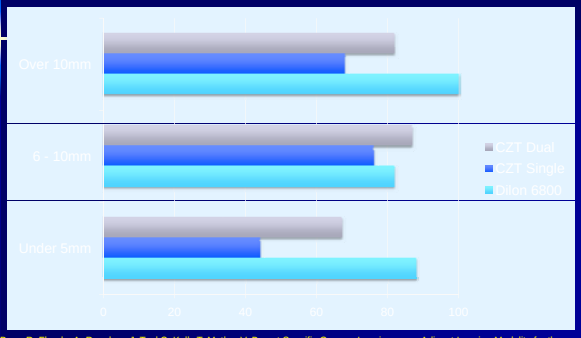
Lesion Depth	% of photons	Contrast
0	100	1.0
1	85.8	0.86
2	73.6	0.74
3	63.1	0.63
4	54.2	0.54
5	46.5	0.47
6	49.9	0.5
7	34.2	0.34
8	29.3	0.29

What does all this mean?

The dedicated breast gamma camera designs greatly improve the sensitivity for small lesions through a combination of:

- improved extrinsic spatial resolution
- Imaging the breast directly against the detector
- Applying mild compression

The Clinical Evidence



Brem R, Floerke A, Rapelyea J, Teal C, Kelly T, Mathur V. Breast Specific Gamma Imaging as an Adjunct Imaging Modality for the Diagnosis of Breast Cancer. Radiology, 2008; 247(3):651-57.
Hruska C, Phillips SW Whaley DH, Rhodes DJ, O'Connor MK. Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera to Detect Small Breast Tumors. AJR:191, December 2008

Tc99m-Sestamibi History

- Originally developed as a cardiac imaging agent - FDA approved in 1991
  - Same day imaging limited to 40 mCi for stress and rest
  - Two day imaging limited to 60 mCi for stress and rest
- Breast imaging was added to the drug data sheet in 1996
  - Based on imaging conducted with standard gamma cameras, the recommended dose was 20 – 30 mCi.
  - The SNM adopted this recommendation in their Breast Scintigraphy protocol
  - All of the studies published since then have utilized a 20 – 30 mCi

www.cardoilite.com
www.snm.org

BSGI Radiation Dosimetry

- According to the National Institutes of Health (NIH), the risks from the radiation dose associated with both mammography and BSGI procedures at 20 – 30 mCi are considered to be "minimal".
- The radiation dose from the BSGI at 20 – 30 mCi is equivalent to living in Denver, Colorado for one year and is acceptable for the diagnostic population.
- According to the drug data sheet for Cardiolite, the prescription range is from 10 to 30 mCi. Therefore, if a center wishes to minimize radiation dose from this procedure, lower doses and longer imaging times can be utilized.
- It is important to note that this pharmaceutical has been used in cardiac imaging for nearly 20 years without a single reported adverse reaction to the radiation dose.

Radiation Dosimetry

	Administered Dose	Effective Dose Equivalent
Screening MMG - 4 view only Does not include diagnostic MMG	n/a	0.7 mSv
BSGI (Sestamibi)	20 mCi	6.7 mSv
CT chest	N/A	7.8 mSv
Coronary CT (Women)	N/A	10.2 mSv
PET (F-18 FDG)	10 mCi	11.1 mSv
CT abdomen and pelvis	N/A	14.7 mSv
PET/CT	10 mCi	23.0 mSv

Mammography Dosimetry: American College of Radiology, www.acr.org. Sestamibidosimetry for BSGI: International Commission on Radiologic Protection. Radiation Dose to Patients from Radiopharmaceuticals. New York, NY: Permamon Press; 1988. ICRP Publication 53. Cardiolite Drug Data Sheet. Bristol Myers Squibb. May 2003. FDG Dosimetry for PEM Dosimetry - F-18-Fluorodeoxyglucose. NUREG/CR-6345, page 9, September 18, 1992. J.E. Kalinyak, MD, PhD. "Comparison of Radiopharmaceuticals Used in Positron Emission Mammography (PEM) and Breast Specific Gamma Imaging (BSGI). White paper. Naviscan PET Systems, Inc., March 2007. CT of chest abdomen and pelvis: Bushberg et al. The essential physics of Medical Imaging. 2nd ed. Philadelphia PA. Lippincott Williams and Wilkens; 2002 795-812. Coronary CT: Ropers et al. Usefulness of multidetector row spiral CT for the noninvasive detection of coronary artery stenosis. PET/CT: Annals of the International Commission on Radiation Protection. Dose to patients from radiopharmaceuticals. Publication 80. Tarrytown NY. Elesevier Science Inc. 1999.

The Impact of Dedicated Detectors on Dose

Table 1 System sensitivity (counts · min^{-1} · kBq^{-1}) comparison using the appropriate collimator and energy window for each system

System	Collimator	Energy window	Sensitivity	Relative sensitivity*
CZT	GE LEHR	20%	3.46	34.2%
Cal SS	Digirad LEHR	20%	3.27	27.2%
NaI PSPMT	Dilon LEHS	−5%/+15%	8.07	100%
Anger camera	Elscint LEUHR	20%	2.89	20.4%

Dedicated detectors are up to 4 times more sensitive than the standard cameras

This indicates that it should be possible to use a lower dose.

Anecdotally, some centers have used doses around 12 - 15 mCi

BUT remember that all of studies to date to establish effiicacy have been conducted at 20 – 30 mCi AND a lesser dose is an off label use

Carrie B. Hruska, Michael K. O'Connor and Douglas A. Collins. Comparison of small field of view gamma camera systems for scintimammography. Nucl Med Commun 26:441–445.

Dose Reduction Study

- As in all imaging, there is a desire to lower the dose as much as possible.
- Obviously, the risk of a missed cancer is a far greater risk to the patient than the risk of the radiation dose
- Therefore lowering the dose to a level that decreases the sensitivity of the examination is not beneficial to the patient

Question: How far can the dose be lowered without negatively impacting the efficacy of this Imaging procedure?

Answer: No one knows, but a multi-center prospective trial is under way to answer this question

Risk vs. Benefit

- As with all medical procedures, we must evaluate the procedure risk against the benefit to the patient
- Radiation risk is just one form of risk
- We use BSGI selectively in three primary populations
  - Patients who have a negative or indeterminate mammogram/ultrasound and a remaining clinical concern
  - Patients at high risk for breast cancer if MMG is not sufficient for screening (dense, complex, or difficult interpret)
  - Patients with positive mammograms or known breast cancer diagnosis to improve treatment planning.

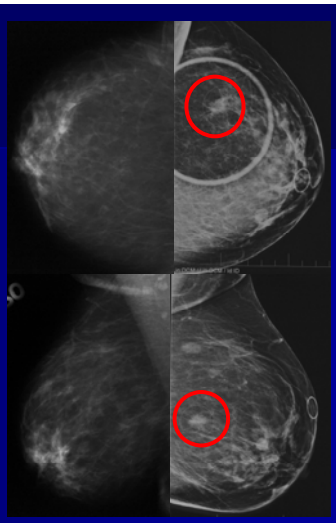
Risk vs. Benefit Cont.

- In the retrospective analysis of BSGI patients presented at RSNA in 2009, we established that BSGI
  - BSGI detected 30 malignant and 7 high-risk lesions in 240 patients (15.4%) with **negative or indeterminate mammograms**
  - The overall sensitivity of MMG and BSGI was 71% and 93% respectively.
- It is clear that this imaging procedure is beneficial in detecting cancers occult to mammography and that it improves the management of properly selected cases
- The radiation risk is far outweighed by the benefit to properly selected patients
- Work is underway to lower the dose

Newly diagnosed breast cancer requiring preoperative work-up.

Patient is claustrophobic and refused MRI leading to a recommendation for BSGI.

Courtesy of Dr. Mike Linver, X-ray Associates of New Mexico, Albuquerque, NM



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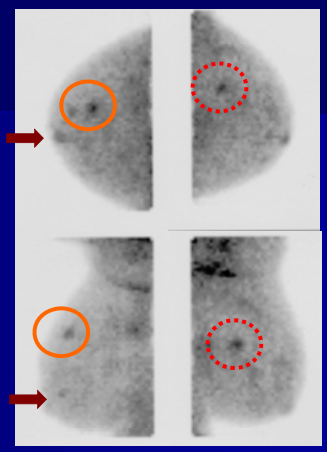
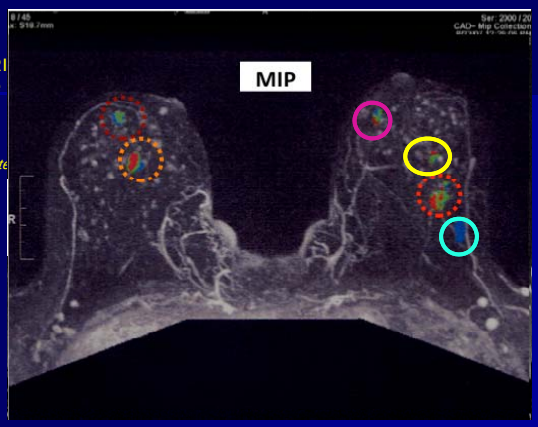
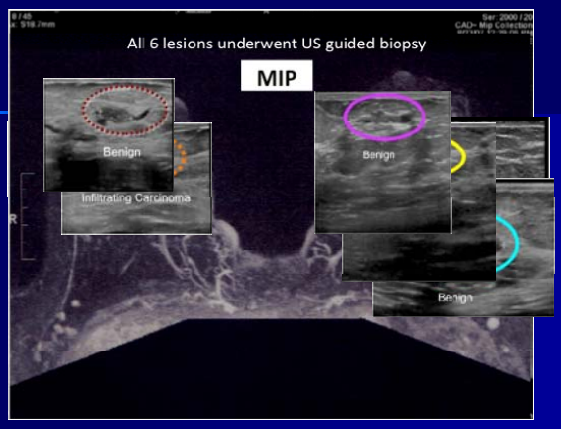


Now the patient agrees to an MRI yielding multiple enhancing sites

Courtesy of Dr. Mike Linver, X-ray Associates of New Mexico, Albuquerque, NM





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

- Evaluation of equivocal mammography and/or Ultrasound.
- Cancer surveillance in patients with a personal history of breast cancer.
- Positive mammogram prior to biopsy to aid in biopsy target selection, particularly in patients with multiple suspicious areas
- Palpable mass not demonstrated in mammogram or ultrasound.
- Radiodense breast tissue difficult to image mammographically
- Screening in high-risk patient populations

Bertrand M, Lanzkowsky L, Stern L, Weigert J. Podium Presentation Radiologic Society of North America Annual Meeting. November 29th – December 4th 2009.

Clinical Utility of Breast Specific Gamma Imaging For Evaluating Disease Extent in the Newly Diagnosed Breast Cancer Patient

- 138 newly diagnosed cancers
- Found additional disease in 11% of cases
- Sensitivity = 91.4%
- Specificity = 94.2%

Zhou M, Johnson N, Gruner S, Ecklund GW, Muenier P, Bryn S, Green G, et al. Clinical Utility of Breast Specific Gamma Imaging For Evaluating Disease Extent in the Newly Diagnosed Breast Cancer Patient. The American Journal of Surgery, Vol 197, No 2, February 2009.

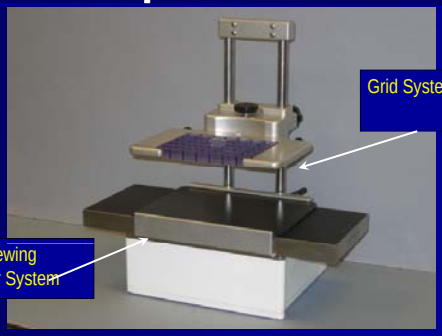
Clinical Data Summary

Of 16 papers and presentations

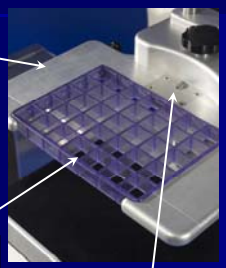
Total Number of patients	3494
Overall Sensitivity	92.1%
Overall Specificity	78.1%
Overall PPV	57.7%
Overall NPV	97.3%

GammaLōc® System

Stereotactic System Components



Grid System Fiducial & Collimator References



Grid Support

Needle Positioning Block

Grid (disposable)

Fiducial Marker Source

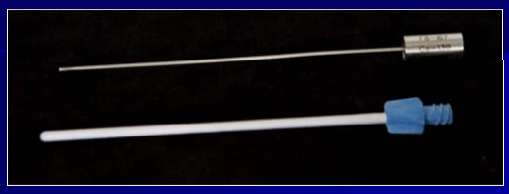
Column and Hole Reference

Column and Hole Reference

Gamma Emitting Marker

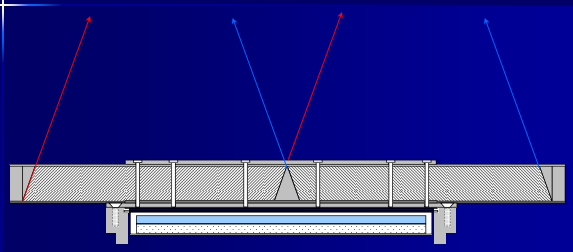
Radioactive Source (Reusable)

Sterile Sleeve (Single Use)



Assembled

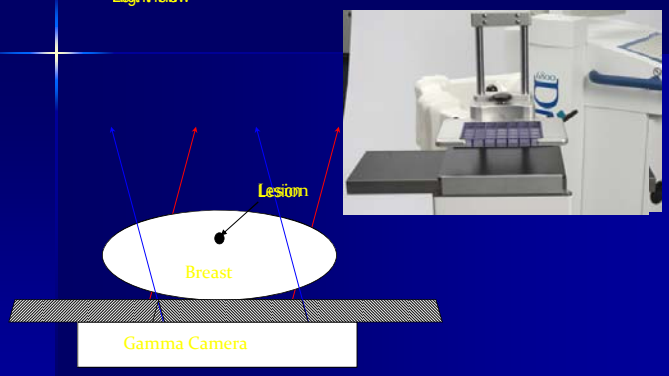
Compatible with Existing Dilon 6800



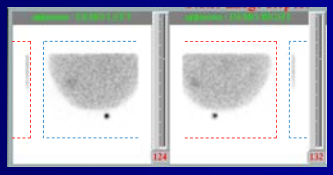
Front View

Slant-hole Collimator Concept

Left View

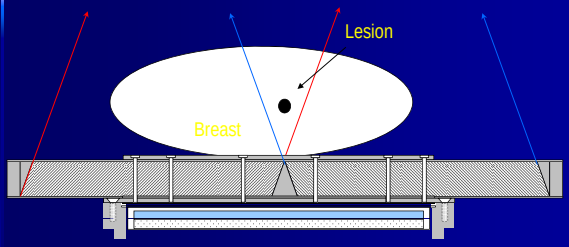


Localization



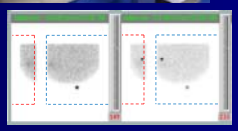
Slant-hole Collimator Concept

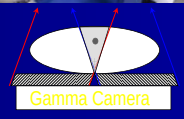
Centered View - for validation and biopsy



Front View

Verification with Radioactive Marker





One Image is used to monitor the X, Y, Z location of a Marker Source

Clinical Considerations

	Energy of emission photon	Half Life (minutes)	Pre-study fasting	Time from injection to Imaging	Recommended pre-procedural testing
FDG	511 KeV	110	4 - 6 hours	60 – 90 minutes	Blood glucose
sestamibi	140 KeV	360	None	5 minutes	None

Sensitivity by Subgroup
** Differences are not statistically significant

BSGI		PEM	
Overall	96%	Overall	90%
DCIS	94%	DCIS	91%
ILC	93%	ILC	75%
Sub-centimeter	89%	Sub-centimeter	63%

BSGI - Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V. Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. Radiology. 247(3):651-7, 2008 June.
Brem R, et al. Breast Specific Gamma Imaging in Women with One

Suspicious or Cancerous Breast Lesion. Invasive Lobular Carcinoma: Detection with Mammography, Ultrasound, Magnetic Resonance Imaging, and Breast-specific Gamma Imaging (BSGI). 2008 Radiological Society of North America Annual Meeting.

PEM - Berg WA, Weinberg IN, Narayanan D, Lobrano ME, Ross E, Arnodei L, Tafra L, Adler LP, Uddo J, Stein W 3rd, Levine EA. High-resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. Breast J. 2006 Jul-Aug;12(4):309-23.

Energy Resolution

"Neither qualitative nor quantitative assessment of tumor contrast in breast phantom images provided a strong relationship between energy resolution and tumor contrast."

Carrie B. Hruska, Michael K. O'Connor. CZT detectors: How important is energy resolution for nuclear breast imaging? PhysicaMedica. Vol 21, Sup 1: 72-75. 2006

Spatial Resolution

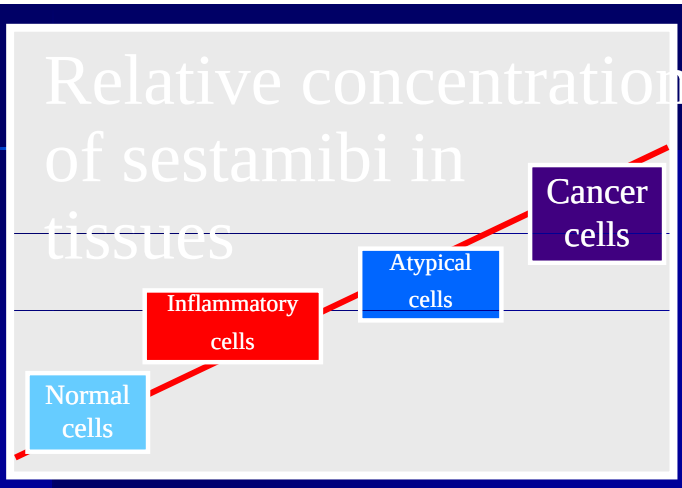
- An examination of the effect of pixel size on breast lesion contrast.
- Detectors with pixel sizes of 1.4, 2.2 and 3.2mm were tested
- Conclusion, "The camera with the largest (3.2mm) crystal pitch performed better than the others tested…"

Mitali J. Moré, *Patricia J. Goodale, Stan Majewski, and Mark B. Williams.* Evaluation of Gamma Cameras for Use in Dedicated Breast Imaging. IEEE Trans NuclSci, 53:5; 2675-9. 2006

Dual Head Detector

- "The use of a dual-head system is not absolutely necessary for acquiring opposing views of the breast because it is possible to obtain the superior and inferior views of the CC position and medial and lateral views of the MLO position with separate acquisitions performed using only a single-head detector."
- "We realize that the cost of the molecular breast imaging system would be increased by adding a second detector head; however, because this study was a preliminary study with a prototype system, a true cost–benefit ratio of commercial dual-head molecular breast imaging compared with single-head molecular breast imaging is yet to be determined."

Hruska C, Phillips SW Whaley DH, Rhodes DJ, O'Connor MK. Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera to Detect Small Breast Tumors. AJR:191, December 2008



BSGI and PEM

- Each view takes 8 – 10 minutes.
- Usually image both breasts.
- Add axillary view if suspect a cancer to look for positive lymph nodes.

Molecular Breast Imaging

- If it is positive—usually very discrete hot spot or spots.
- If it is negative—the chances of missing something is extremely small.

Who should perform BSGI?

- Breast Center
- Nuclear Medicine Department

Requirements

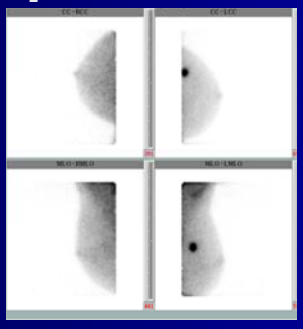
- Small room. Machine is very mobile.
- Hot Lab
- License to inject isotope.
- Tech excellent at BREAST POSITIONING!
- Radiologist adept at correlating Mammogram, Ultrasound, MRI, and BSGI.

How is test received by patients?

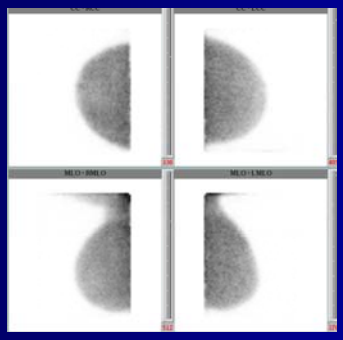
- 1. Test is relatively comfortable.
- 2. No compression.
- 3. No claustrophobia.
- 4. Can watch TV.
- 5. Get results immediately!!!!

Correlation with other studies is essential!

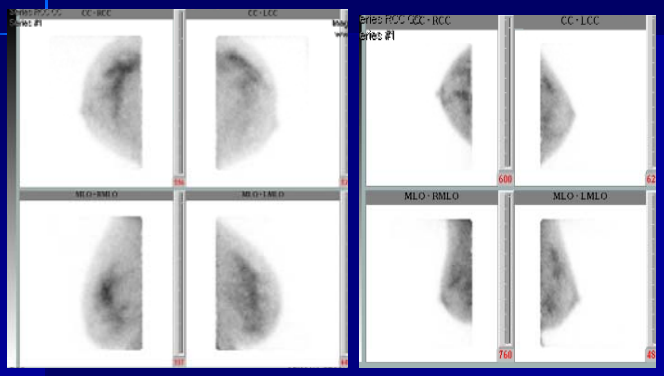
Typical positive BSGI study left breast upper-outer quadrant



Typical Normal Study

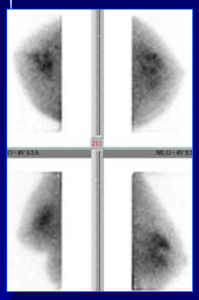


Vague Bilateral Uptake



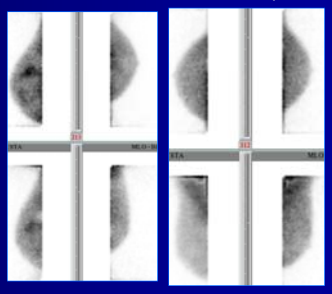
Hormonal Activity

Just as in MRI, hormone influence may interfere with imaging--day 2 - 12 of cycle optimal



Typical pattern

6 months later, off HRT

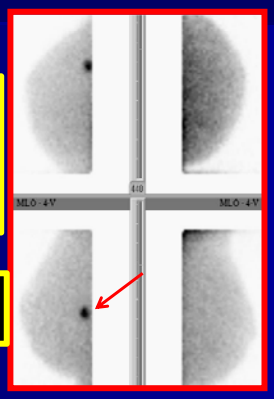


Asymmetrical pattern

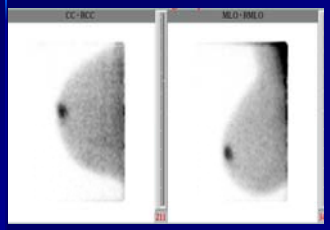
Biopsy

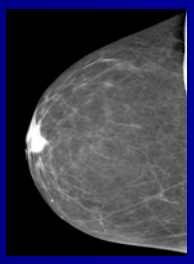
Focal abnormal:
Can be malignancy
inflammation, atypia
or some benign processes

Invasive ductal carcinoma



Breast Abscess

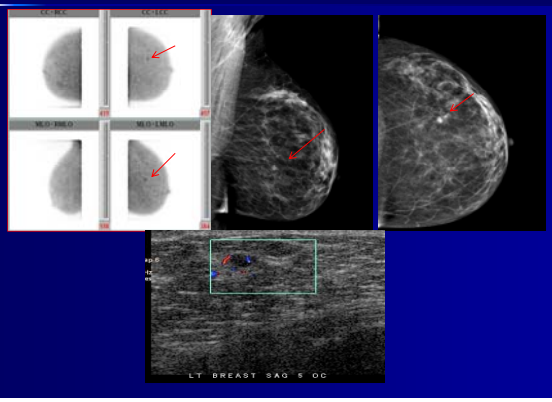




What size lesion can Molecular Imaging find?

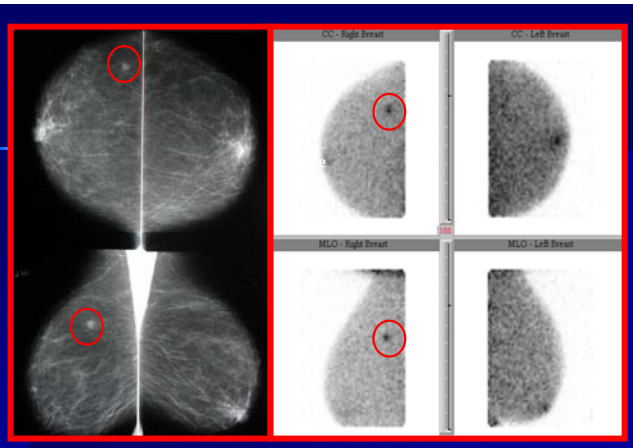
- Many 3 -5 mm lesions have been found.
- Occasionally see a 1.5 mm lesion.
- Most infiltrating lobular cancers (Frequently missed on Mammography until 5-6 cm.)

5 mm lesion Papilloma

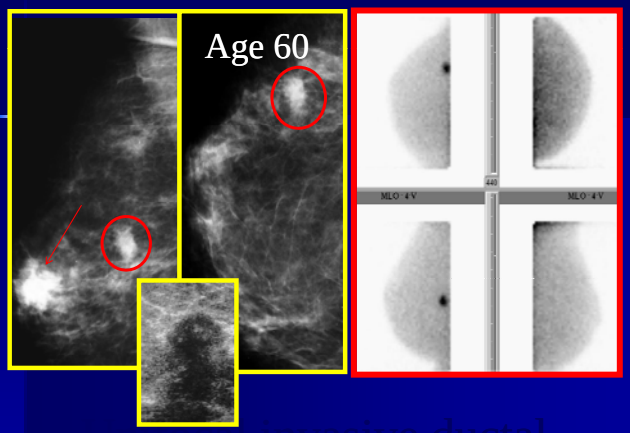


Clinical Indications

- Probable Breast Malignancy
- 1. Evaluate extent of cancer
- 2. Evaluate for synchronous disease in same or opposite breast
- (Multifocal or Multicentric Disease)

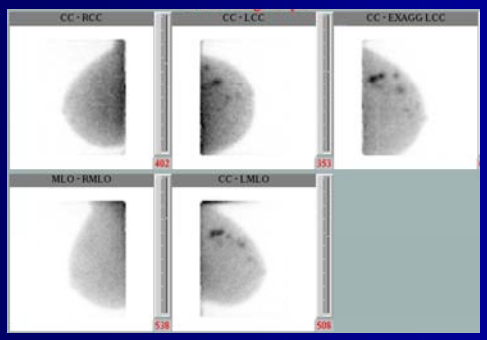


Unifocal invasive ductal carcinoma

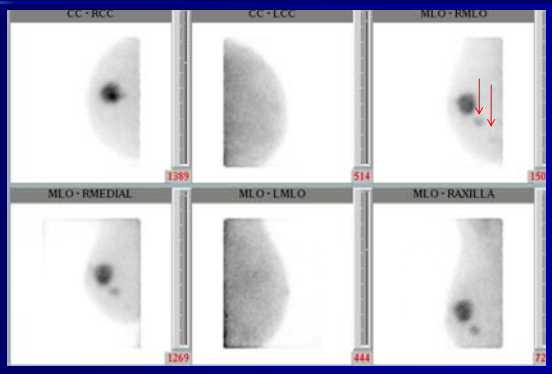


Unifocal invasive ductal carcinoma

Multifocal cancer extending to nipple



Multifocal Cancer



Positive Core Biopsy

- Should all patients recently diagnosed with breast cancer have an MRI or BSGI before deciding on a definite surgical plan?
- BSGI or MRI changes management in 10-20% of selected cases!

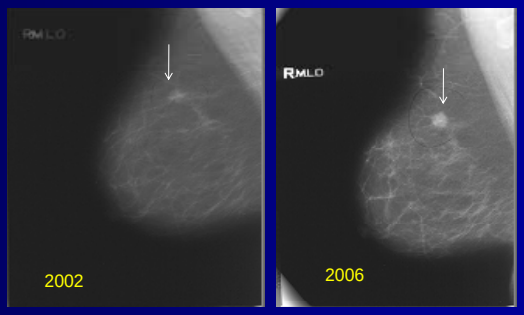
Personal History of Breast Cancer

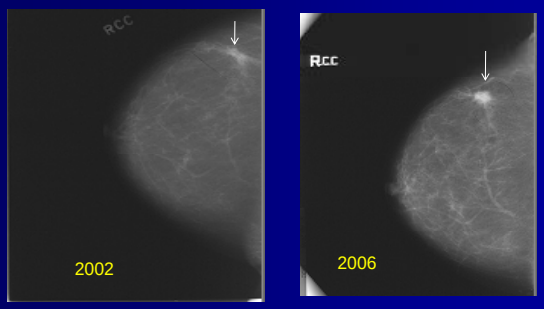
- 1. Suspected Recurrence
- 2. Monitoring Response to Therapy

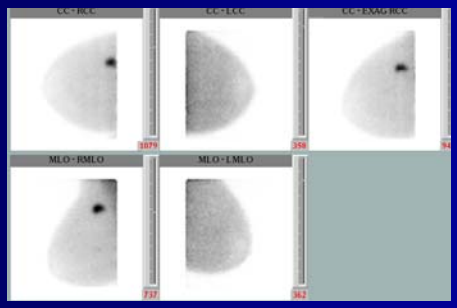
76 year old

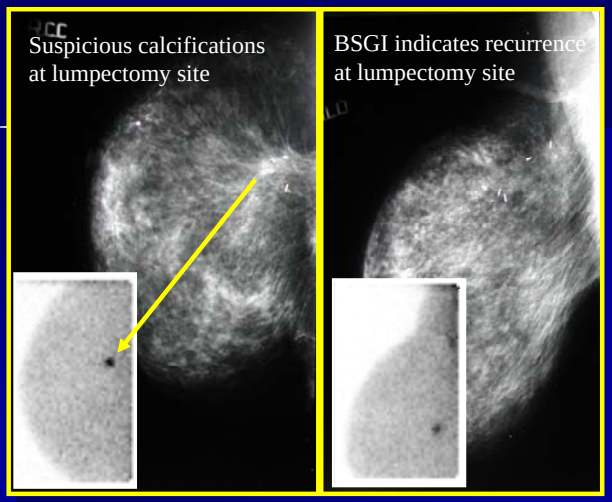
- Had benign biopsy right breast in 2002. Now area of scar has changed slightly.

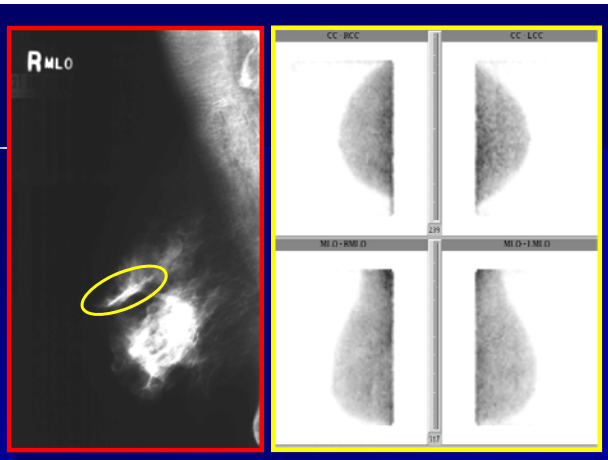
Scar vs. Recurrence







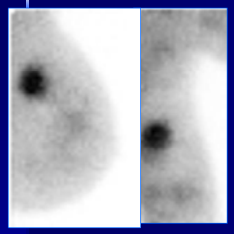




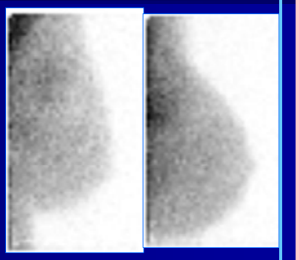
lumpectomy scar vs. recurrence- Normal BSGI - no recurrence

Response to Neoadjuvant Chemotherapy

Preoperative Chemotherapy
Is this the right treatment?



Initial study 12-07

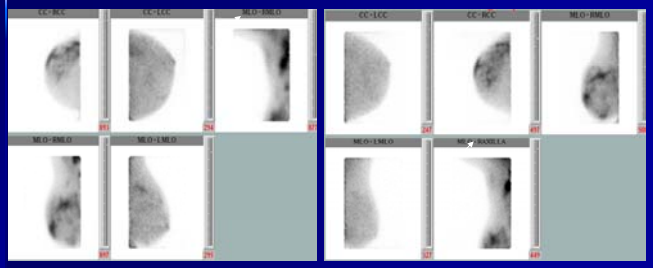


Halfway point of chemo 3-08

Triple Negative Receptors

Before Chemo

After 5 months



PEM v BSGI

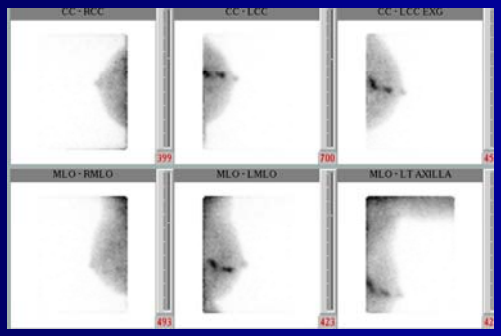
- PEM or BSGI can be used to assess breast in patient diagnosed with breast cancer.
- At this time PEM can not be reimbursed for work-up of a patient with abnormal mammogram, ultrasound, or unexplained symptoms, but with no personal history of breast cancer.

Daily Uses in patients with no Breast Cancer

- 1. Bloody Nipple Discharge
- 2. Unexplained Palpable Mass
- 3. Bilateral Masses-Which should be biopsied?
- 4. Calcifications- Which should be biopsied?
- 5. Cysts Obscuring Underlying Tissue.

- 6. Extremely Dense Breasts plus Breast Cancer Gene or Strong Family History.
- 7. Free Silicone Injections
- 8. Breast Implants
- 9. Asymmetric Density esp. if no older Mammogram.

Bloody Nipple Discharge



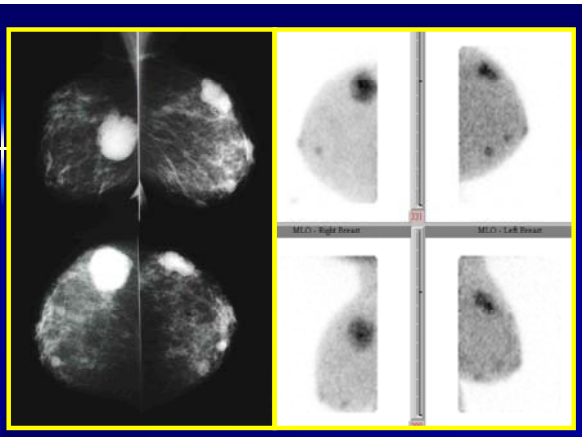
55 year old patient with persistent palpable abnormality upper outer quadrant right breast

Mammography, ultrasound, and BSGI normal

Biopsy concordant - no atypia or malignancy

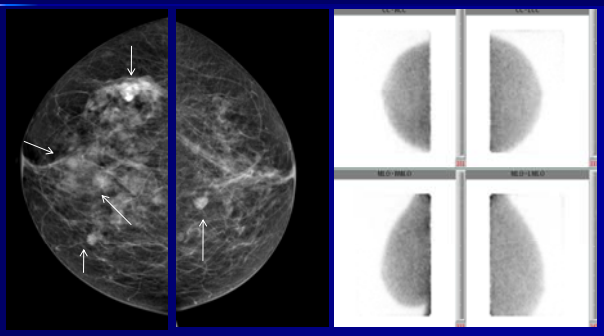
Bilateral Masses

Which ones need biopsy

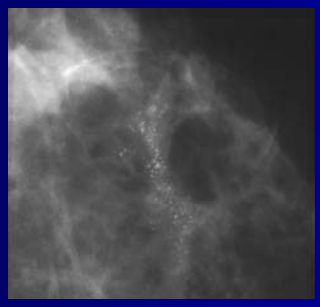


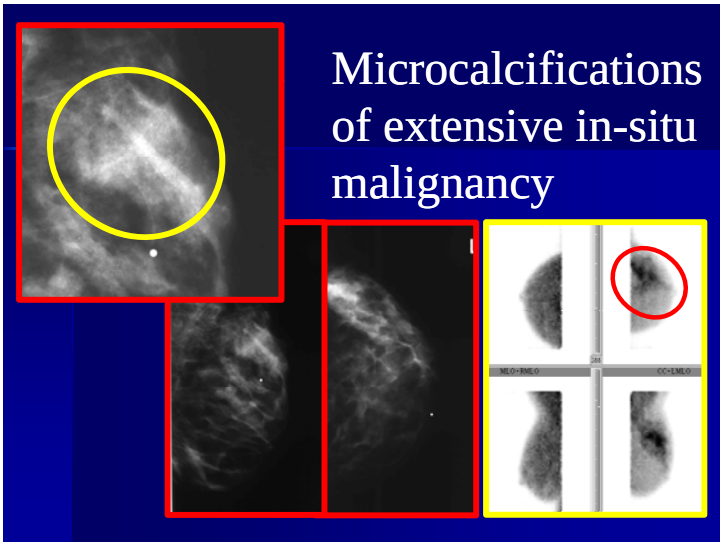
Bilateral multifocal phyllodes tumors

Multiple Fibroadenomas



Which calcifications should we worry about?

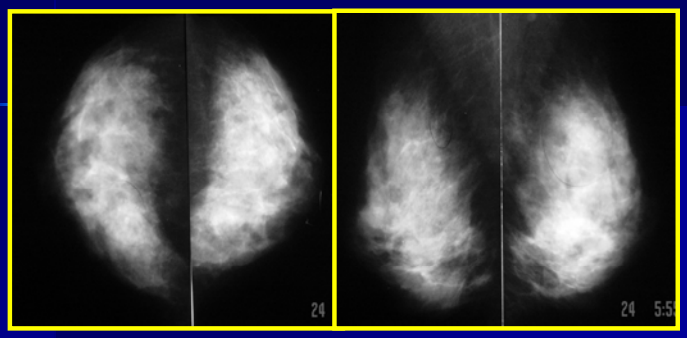




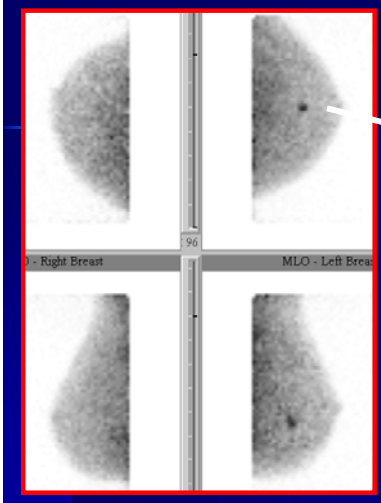
Microcalcifications of extensive in-situ malignancy

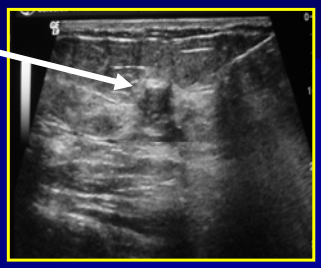
Technically difficult mammogram

- 1. Radiodense breasts
- 2. Implants
- 3. Free Silicone



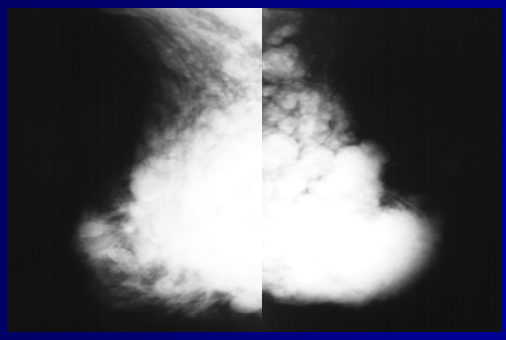
Dense breasts
Positive family history

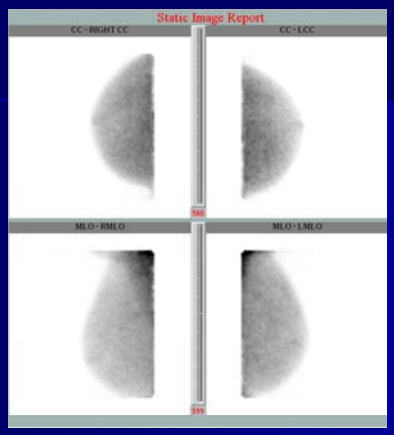




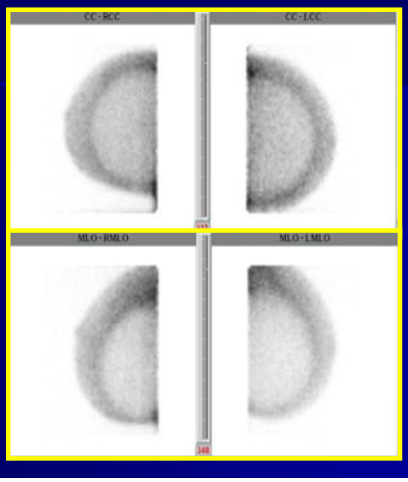
3 mm
IDCa

Free Silicone

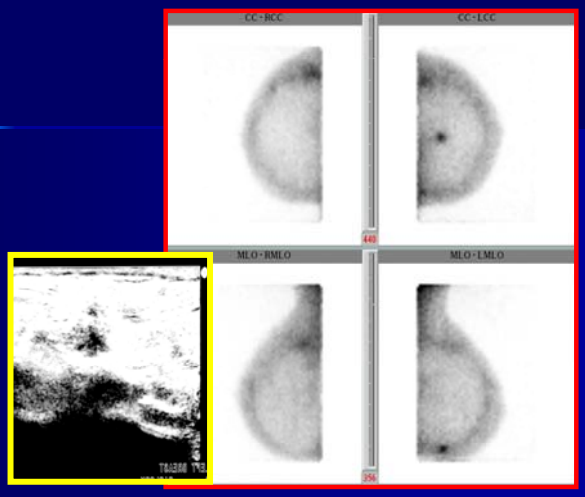




Normal



Invasiv



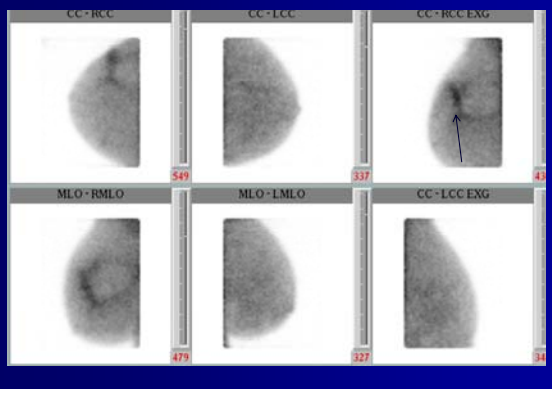
Limitations of BSGI

- Cases with vague patchy uptake bilaterally.

Limitations of BSGI

- Immediately following surgery, area will be positive and may stay positive for up to a year.
- Can not assess for clear margins.
- Can not assess for posterior chest wall or pectoral muscle involvement.
- Even with excellent positioning may miss cancers close to chest wall or deep in axilla.

Uptake along surgical margin



Things BSGI cannot do.

- 100% sensitivity and specificity
- Resolve lesions under 2mm.
- Image close to chest wall

It Let's You Sleep At Night

- We would like to make the diagnosis as quickly and as accurately as possible.
- We need to decrease **patient's anxiety** as quickly and accurately as possible.
- We need to decrease the number of BIRADS 3 (indeterminate) studies and number of biopsies.

Bringing New Excitement into Breast Imaging

- Multimodality!
- Back to patient contact!
- Being a detective.
- Following trail all the way to a conclusion!
- Giving good advice to patients and other physicians.