Advanced Imaging for Breast Cancer:
Screening, Diagnosis, and Assessing Response to Therapy

Nuclear Emission Imaging: Single Photon & PET

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Nuclear Medicine and PET

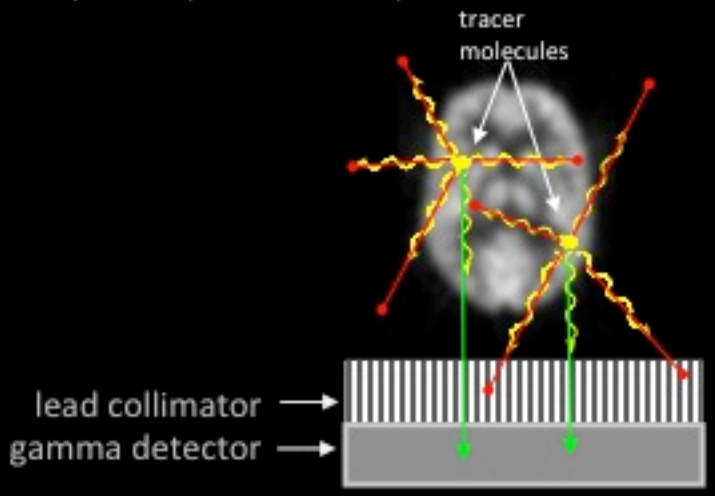
Emission imaging using internally administered physiological tracers tagged with radio-isotopes

'**Functional**' imaging: observe biochemistry in action; molecular pathways illuminated

- complementary to other imaging techniques
- extremely high sensitivity to low levels of radiotracer (pico-molar)
- tends to lack anatomical detail
- final spatial resolution ~ cm range

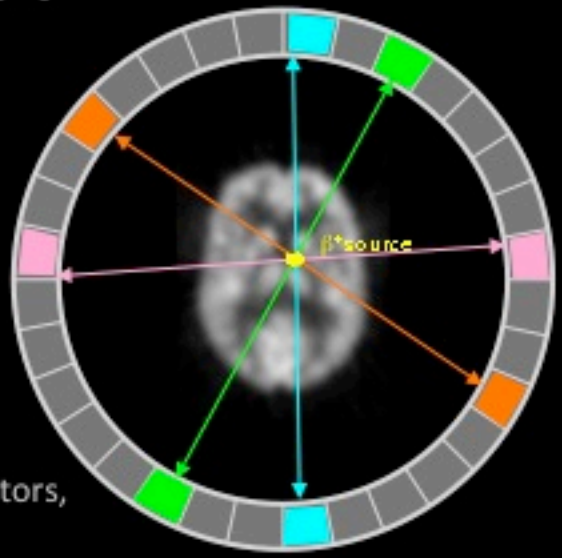
Single photon (planar, SPECT)

- Lead collimators form image
  - reduce photon sensitivity
  - restrict spatial resolution
- Quantification is very challenging
- Dual-tracer imaging possible (distinct gamma energies)
- Dynamic possible with planar, not SPECT



PET

- No lead collimator
  - anti-parallel photons → 'electronic' collimation
- Quantitative
- Unique gamma energy (511keV) makes dual-isotope all but impossible
- Dynamic imaging



full ring of detectors,
no collimator

Radionuclide Labeled Tracers

Tracers are key to success of nuclear emission imaging

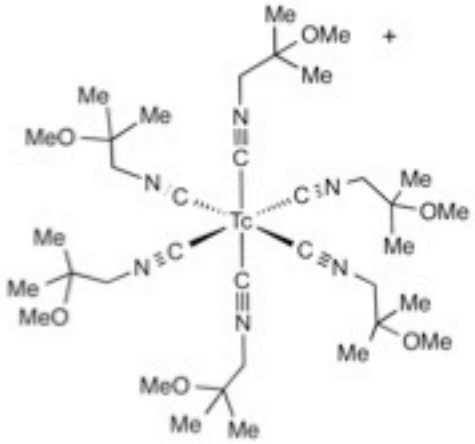
- PET isotopes more favorable for radiochemistry (isotopes found in organic chemistry, ^{11}C, ^{13}N, ^{15}O)
- Larger variety of PET tracers have been used for breast cancer imaging
- PET isotopes in general more difficult (expensive) to produce
- PET isotopes have shorter half-lives; good for dosimetry but difficult to transport

Nuclear breast imaging workhorse tracers:

Single-photon:

^{99m}Tc-Sestamibi

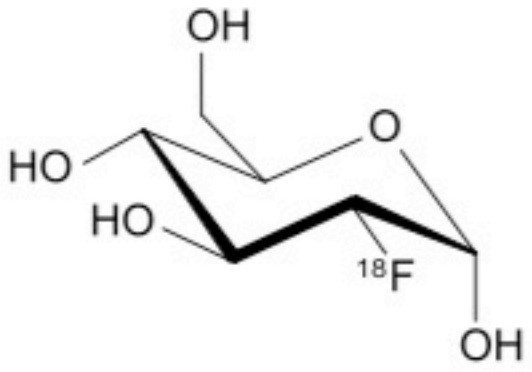
Hexakis(2-methoxy-2-methylpropylisonitrile) technetium (^{99m}Tc)



PET:

^{18}F-Fluorodeoxyglucose (FDG)

2-Deoxy-2-[^{18}F]fluoroglucose



Aims & Requirements of Breast Cancer Imaging

Detection vs. Assessment:

Detection: is something there? (Yes/No, qualitative imaging)

Assessment: reveal molecular signatures & longitudinal changes in molecular pathway activity (quantitative imaging)

PRE-diagnosis:

Large number of scans on asymptomatic population put restrictions on cost, risk (e.g. radiation)

➔ mammo, US are preferred

POST-diagnosis:

Risk from disease and cost of treatments changes tolerance for cost and risk

➔ MRI, PET more acceptable

Note: lesion location usually known, altering the goal of imaging

Treatment: high per-patient cost ➔great value in optimizing

Challenges for Detection/Diagnosis

Screening requirements:

- low risk
- low cost
- rapid
- advantages over existing screening methods
  - challenges: dense breasts, invasive lobular carcinoma
- qualitative imaging may suffice (detection task)

PET relies on efficacy of radiotracer

^{18}F-FDG:
- -uptake in fibroglandular tissue (dense breasts)
- -low uptake in lobular, DCIS is common [1], [2]
- -high uptake in inflammatory processes

other tracers may better meet challenges

[1] Buck et al., *Eur. J. Nucl. Med. Mol. Imaging* 2002

[2] Bos et al., *J. Clin. Oncol.* 2002

Current Use and Developing Potential

Diagnosis & Staging – Currently the primary application of PEM

- resolving cases equivocal by other modalities
- extent of disease within breast (multi-focal, multi-centric)

➔ surgery planning

Predicting & Monitoring Therapy

- use of NM/PET as an *in-situ* prognostic biomarker

- Assessing target status ("comprehensive immunohistochemistry in vivo")
- Assessing pharmacokinetics and biodistribution
- Confirming selective targeting and predicting toxicity
- Optimizing dose scheduling
- Identifying indications and patients groups
- Therapy planning and individualization

➔ **these applications require or benefit from quantitative imaging**

Whole-Body Gamma Camera

Scintimammography

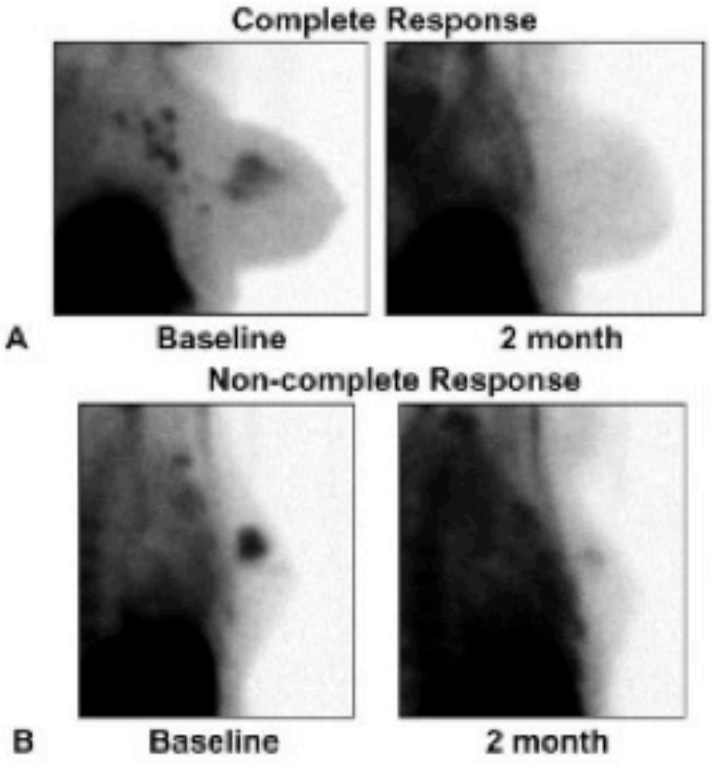
Tracer:
^{99m}**Tc-Sestamibi**

- Cardiac perfusion agent
- Correlates with blood flow
- Characterize P-glycoprotein expression; multi-drug resistance -- predict and reflect response to chemotherapy.

✓ **Locally advanced breast cancer**

✗ **Small lesions not visualized using common clinical gamma camera equipment.**

Residual Tumor Uptake of [99mTc]-Sestamibi after Neoadjuvant Chemotherapy for Locally Advanced Breast Carcinoma Predicts Survival



Dunnwald et al, CANCER 103(4), 2005
Conclutions: High MIBI uptake after neoadj. predicted poor survival - serial MIBI imaging may provide useful surrogate endpoint for neoadj. chemo. therapy trials

PET Imaging of Breast Cancer

Somewhat random selection of breast PET literature over the years.

Whole-Body PET Scanners

- Wahl, et al., Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology*. **1991**;179:765–770.
- Adler, et al., Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-D-glucose PET. *Radiology*.**1993**;187:743–750.
- Dehdashti, et al., Positron tomographic assessment of estrogen receptors in breast cancer : a comparison with FDG-PET and in vitro receptor assays. J Nucl Med **1995**;36:1766
- Avril, el al., Glucose Metabolism of Breast Cancer Assessed by 18F-FDG PET: Histologic and Immunohistochemical Tissue Analysis, J Nucl Med **2001**; 42:9–16
- Pio, et al., PET with fluoro-L-thymidine allows early prediction of breast cancer response to chemo- therapy. J Nucl Med **2003**;44:76P.
- Eubank WB, Mankoff DA: Current and future uses of positron emission tomography in breast cancer imaging. Semin Nucl Med, 34:224-240, **2004**.
- Kenny, et al. Quantification of cellular proliferation in tumour and normal tissues of patients with breast cancer by [18F]fluorothymidine-positron emission tomography imaging: evaluation of analytical methods. Cancer Res, **2005**;65:10104–12.
- Linden, et al.: Quantitative Fluoroestradiol Positron Emission Tomography Imaging Predicts Response to Endocrine Treatment. J Clin Oncol 24(18):10.1200/JCO.2005.04.3810 (publ online ahead of print), **2006**.
- Dunnwald, et al., Tumor Metabolism and Blood Flow Changes by Positron Emission Tomography: Relation to Survival in Patients Treated With Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer, JCO 26(27), **2008**.
- …. literature continues to present day

PET Imaging of Breast Cancer

Avril, et al. *JCO* 2000

"Partial volume effects and varying metabolic activity (dependent on tumor type) seem to represent the most significant limitations for the routine diagnostic application of PET. The number of invasive procedures is

Whole-body PET

- spatial resolution is not sufficient for imaging early-stage breast cancer
- potential for detection of recurrence
- potential for selection/monitoring therapy

restricted to relatively advanced disease

biology and help tailor therapy to individual patient by improving our ability to quantify the therapeutic target, identify drug resistance factors, and measure and predict early response.

Dedicated Single-Photon Breast Imagers

Commercial Single-Photon Dedicated Breast Imaging

Terminology:
- Breast-specific gamma imaging (BSGI)
- Molecular breast imaging (MBI)

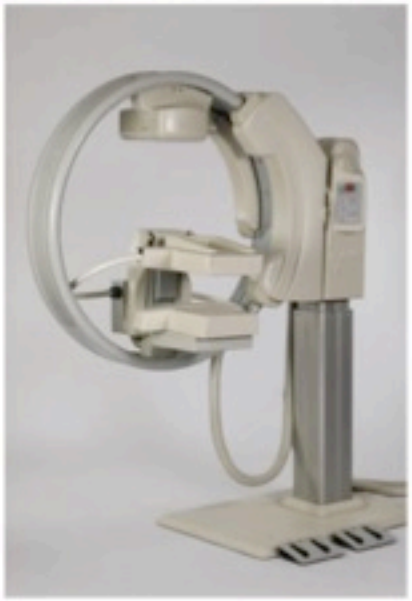
Scintillation crystals

- photomultiplier tubes (PMT)
- Si-PiN diodes

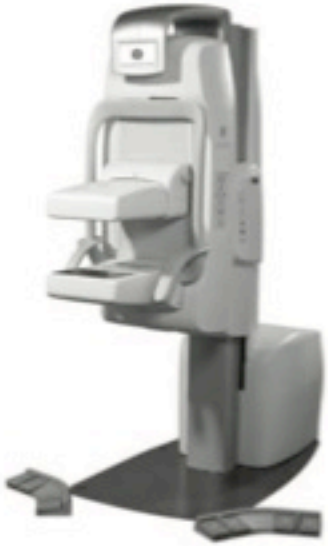
Dilon 6800: NaI(Tl)-PSPMT 15x20cm, 3.0x3.0mm pixels
Acella: CsI(Tl)-SiPiN 20x25cm, 3.2x3.2mm pixels
each are single-head
~15-20% energy FWHM (140keV)

Cadmium Zinc Telluride (CZT)

direct gamma ray conversion



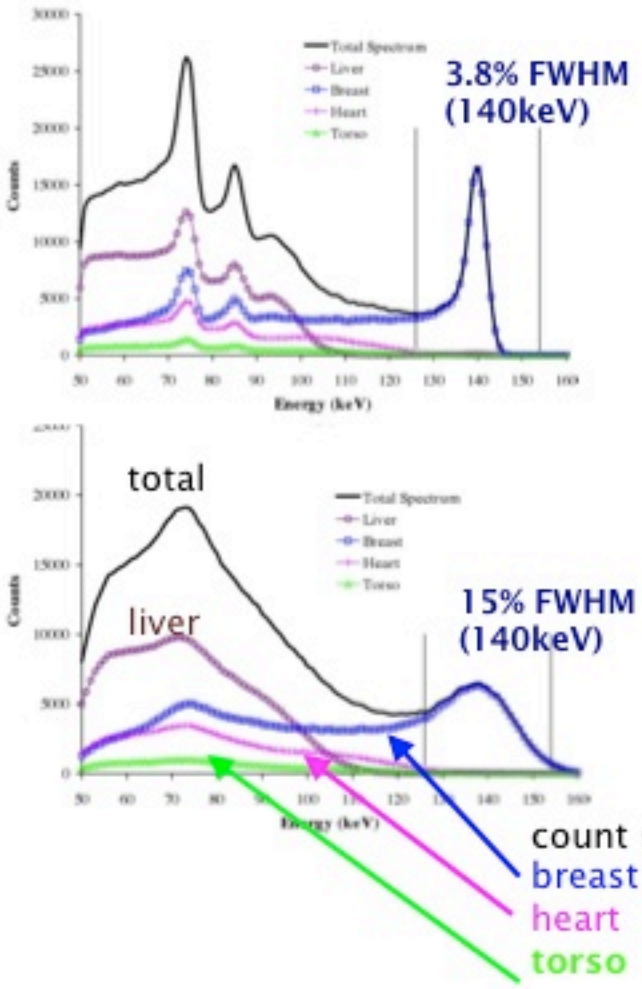
LumaGEM (Gamma Medica):
dual-head
20cm X 16cm
1.6 mm pixels – 5 mm thick
~4% energy FWHM (140keV)



Discovery NM 750b (General Electric):
dual-head
24cm X 16cm
2.5 mm pixels – 5 mm thick
~6.5% energy FWHM (140keV)

Gamma Camera Energy Resolution

Simulated energy spectra:



Simulation:
EFFECT OF ENERGY RESOLUTION ON SCATTER FRACTION AND TUMOR CONTRAST
LumaGEM standard collimator

Energy Resolution (FWHM at 140 keV)	Energy Window	Relative Sensitivity	Scatter Fraction*	Torso Fraction*	Tumor: Breast = 5:1 Depth = 1 cm
3.8%	-5/ +10%	76%	6.6%	1.3%	0.96/ 0.97/ 1.22
3.8%	± 10%	100%	13.9%	2.5%	0.86/ 1.04/ 1.16
7.0%	± 10%	100%	14.2%	2.7%	0.84/ 0.93/ 1.14
10%	± 10%	99%	14.2%	2.9%	0.83/ 1.03/ 1.15
15%	± 10%	97%	15.9%	3.3%	0.76/ 0.93/ 1.17
20%	± 10%	93%	19.2%	4.0%	0.77/ 0.88/ 1.11

tumor location:
chest wall/middle/nipple

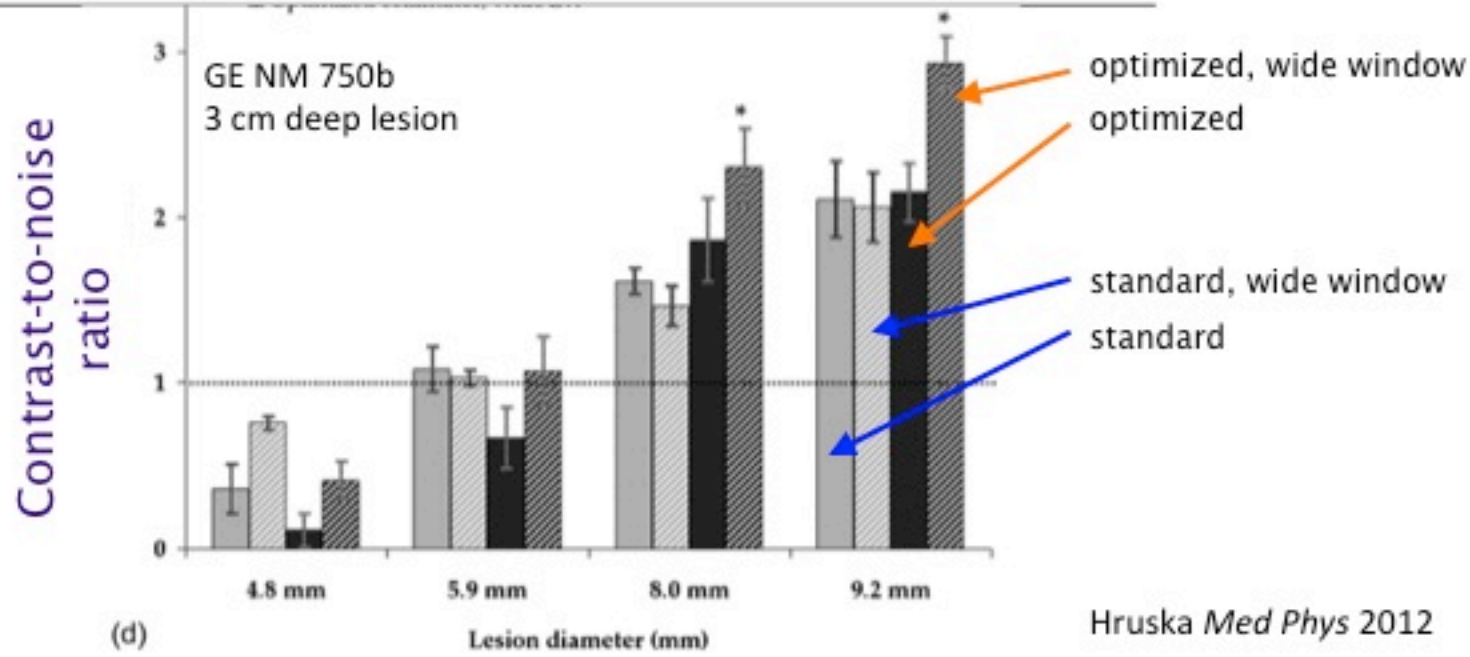
Hruska *IEEE TNS* 2008

Gamma Camera Collimator Optimization

Optimize collimator to allow lower injected activity
maintain spatial resolution at a level suggested by typical clinical findings

TABLE I. Specifications of standard collimators and optimized low-dose collimators for each CZT detector.

Detector	CZT pixel size (mm)	Collimator	Hole shape	Material	Hole length (cm)	Hole diameter[a] (mm)	Septal thickness (mm)	Theoretical geometric efficiency[b]	resolution @ 3cm + increase per cm distance from collimator
GMI LumaGem	1.6	GMI Standard	Hexagonal	Lead	2.50	2.54	0.30	6.1×10^{-4}	4.8mm + 1.26 mm/cm
		GMI Optimized	Square, registered	Tungsten	0.94	1.225	0.375	9.0×10^{-4}	5.6mm + 1.26 mm/cm
GE Discovery NM 750b	2.5	GE Standard	Square, registered	Lead	3.47	2.26	0.24	2.9×10^{-4}	
		GE Optimized	Square, registered	Lead	2.10	2.10	0.40	6.0×10^{-4}	4.5mm + 0.95 mm/cm



Hruska *Med Phys* 2012

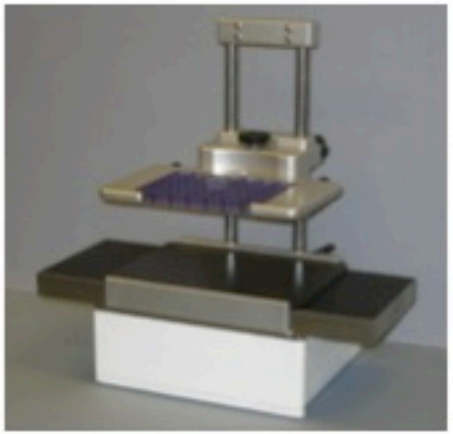
Gamma Camera Guided Biopsy

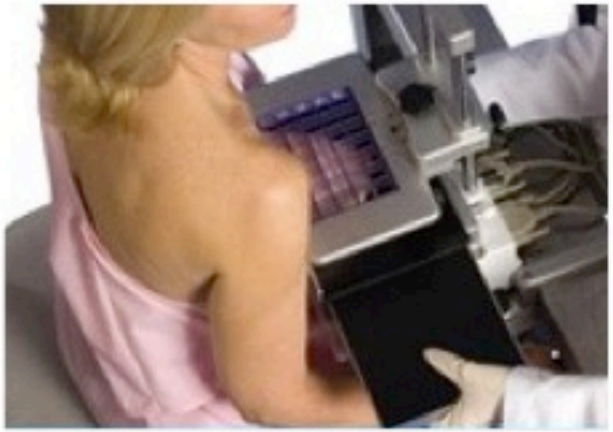
- **Dilon system GammaLoc**
  Similar approach to two-view stereotactic x-ray biopsy guidance
  FDA cleared

- Naviscan PEM Flex biopsy guidance also FDA approved

Other manufacturers adding biopsy guidance capability

www.dilon.com





radioisotope rod for needle placement verification

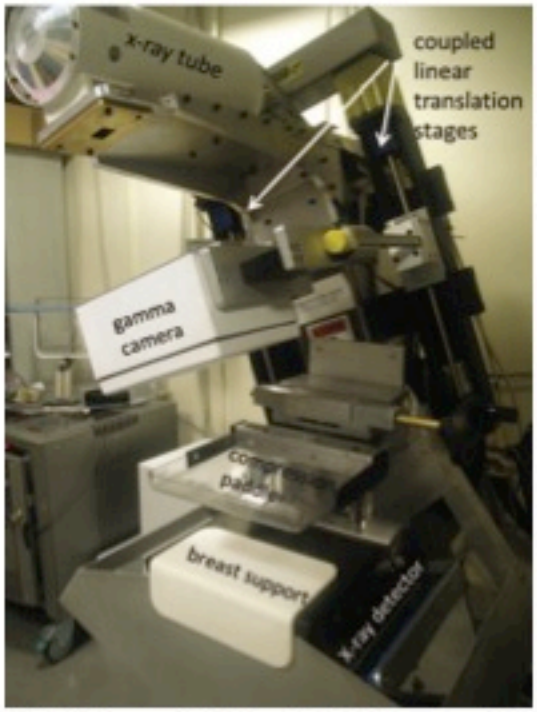
dual 20° angle collimator:

first view ⇢ move collimator second view

Separately: slanted collimator (15°) available for imaging closer to the chest wall

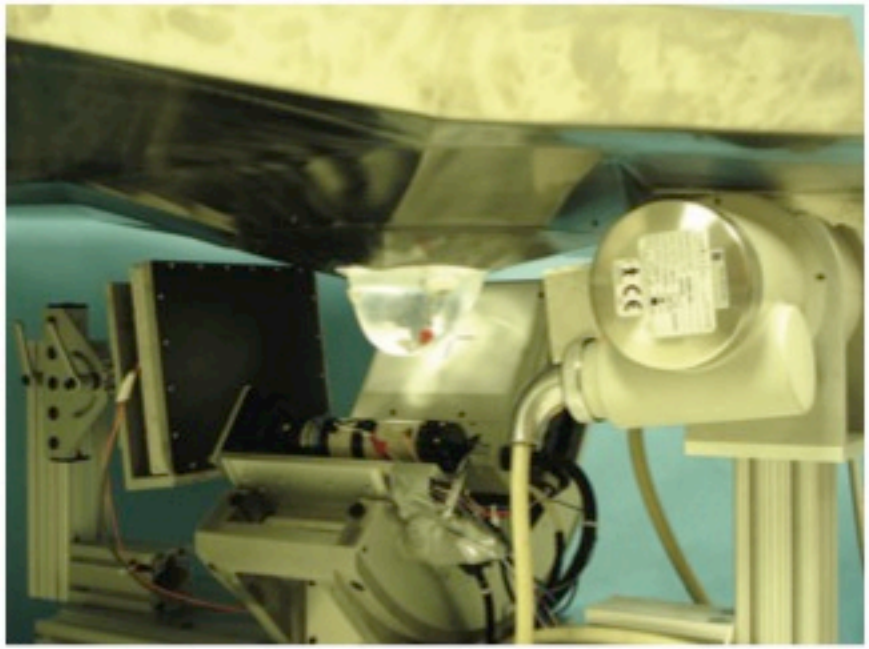
Dual Nuclear Medicine / X-Ray Systems

Planar single-photon + planar mammography
University of Virginia



M. B. Williams, P. G. Judy, S. Gunn, and S. Majewski, "Dual-modality breast tomosynthesis," Radiology **255**, 191–198 (2010).

SPECT + CT
Duke University



C. N. Brzymialkiewicz, M. P. Tornai, R. L. McKinley, S. J. Cutler, and J. E. Bowsher, "Performance of dedicated emission mammotomography for various breast shapes and sizes," Phys. Med. Biol. **51**, 5051–5064 (2006).

Beyond ^{99m}Tc-Sestamibi

Other single-photon tracers under investigation for breast imaging

Target	Tracer
Perfusion	Tl-201 Thallous Chloride Tc-99m Sestamibi Tc-99m tetrofosmin
Glucose metabolism	Tc-99m EC-glucosamine
Hormone receptor	I-123 estradiol
HER2	In-111 trastuzumab
Cell proliferation/angiogenesis	Tc-99m maraciclatide In-111 bevacizumab
Amino acid transporters & protein synthesis	Tc-99m methionine I-123 methyltyrosine
Cell surface receptor (VPAC1)	Tc-99m VPAC1
Apoptosis	Tc-99m EC-annexin V
Somatostatin receptors	In-111 octreotide

Dedicated PET Breast Imagers

Terminology: **Positron Emission Mammography (PEM)**

As with single-photon cameras,
focus began with the qualitative detection task

- high spatial resolution
- high photon sensitivity

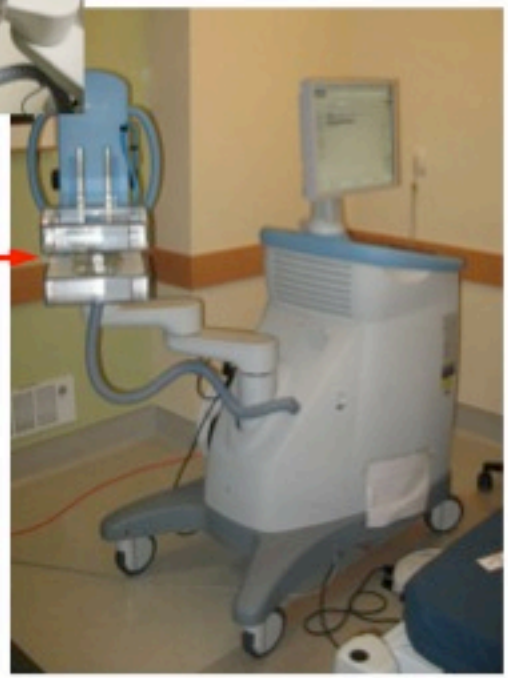
Recognition of biomarker applications

- quantitative accuracy becomes important

Commercial Dedicated Breast PET

Detectors close to the breast increases sensitivity to 511 keV photons
➔ this is strongly dependent on the size/extent of the detectors

Naviscan PEM Flex Solo II:
two 5x16 cm^2 detectors
limited-angle (tomosynthesis)

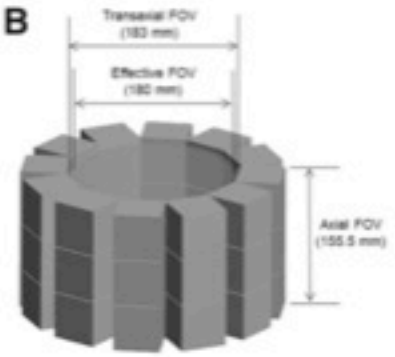


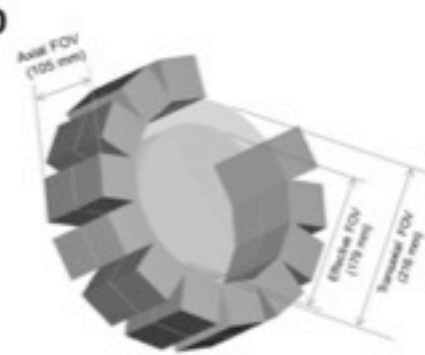
detectors
scan FOV:
24 x 16 cm

- LYSO crystals
- 2.2 x 2.2 x 13 mm
- spatial resolution:
~ 2.4 mm in-plane
(~ 8.0 mm cross-plane not displayed)
- **no quantitative corrections**

Shimadzu: two models:18 cm diam.
O-shape: 15.5 cm axial
C-shape: 10.5 cm axial

- LGSO crystals, 1.44 x 1.44 x 18 mm
- 4 layers to measure depth-of-interaction 4.5mm/layer
- spatial resolution ~ 1.0 mm FWHM



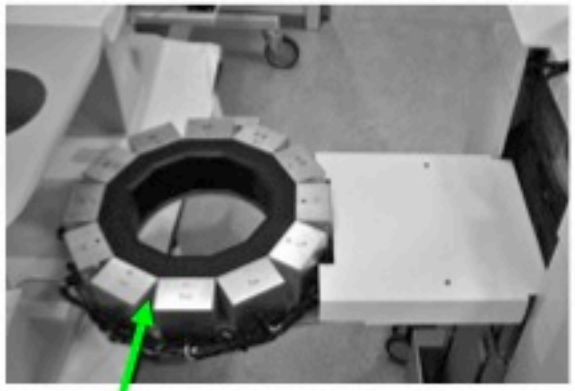


Iima et al., *JNM* 2012

Commercial System Developed Under EU-037555

Oncovision MAMMI:
17 cm imaging diameter monolithic scintillation crystals

- 3.5-4.0 cm axial detector size, scans to cover 17 cm axial
- LYSO
- ~1.5 mm spatial resolution
- depth-of-interaction capable via monolithic crystal



40 x 40 x 10 mm³ tapered monolithic scintillation crystals:

- ➢ no cutting into tiny pixels
  → saves labor & waste
- ➢ no inter-crystal dead space
  → improves sensitivity

Requires more complex calibration than pixilated detector

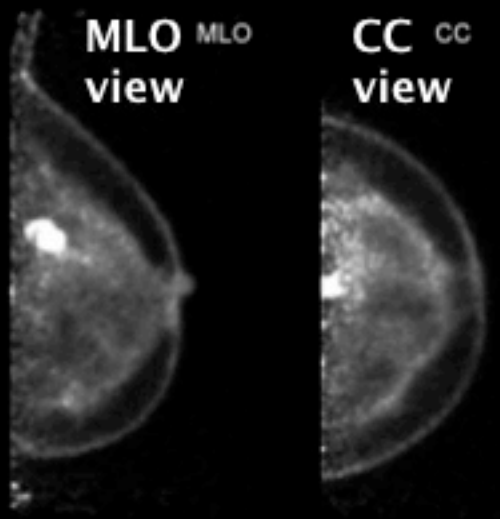
Dedicated Breast PET Development

Institute	Detector Technology	Citation	Year
McGill	PMT	Thompson *Med Phys* 21:529-538	1994
Naviscan	PMT	Weinberg *Eur J Nucl Med* 23:804-806	1996
Duke	PMT	Turkington *IEEE NSS/MIC Conf. Record, pgs. 1883-86*	2002
LBNL	PMT/PIN-diode	Wang *IEEE TNS* 53(3):1129-1135	2006
Clear-PEM	APD	Abreu *Nucl Instr Meth A* 571:81-84	2007
WVU	PMT	Raylman, *Phys Med Biol* 53(3):637-653	2008
PENN	PMT	Surti *Phys. Med. Biol.* 53 2911-2921	2008
UCD	PMT	Bowen *J. Nucl. Med.* 50:1401-08	2009
BNL	APD	Ravindranath *IEEE NSS/MIC Conf. Record*, pages 3315–17	2009
Shimadzu	PMT	Furuta *IEEE NSS/MIC Conf. Record*, pages 2548-52	2009
MD Anderson	PMT	Zhang *IEEE TNS* 57(1):104-110	2010
Stanford	APD/CZT	Peng *Phys Med Biol*, 55:2761-2788	2010
UW	GM-SiPM	MacDonald *IEEE NSS/MIC Conference*	2011
OncoVision	PMT	Moliner Med Phys 39(9):5393-5404	2012

List is not exhaustive

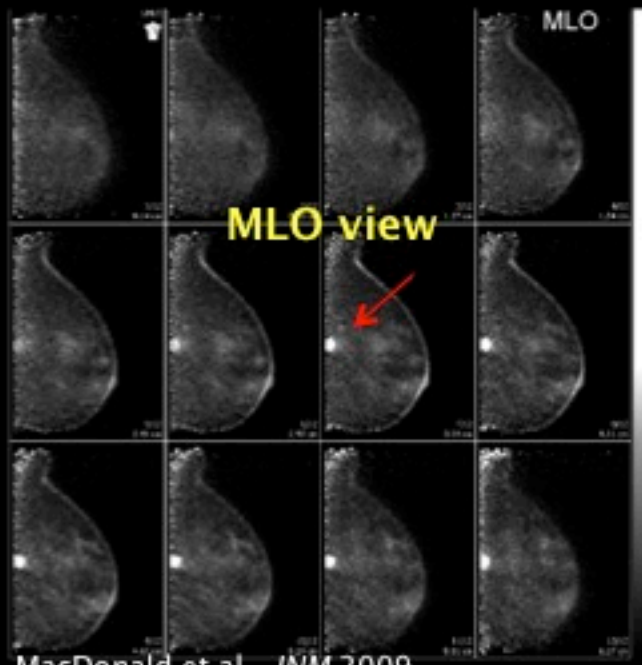
Currently scanning patients

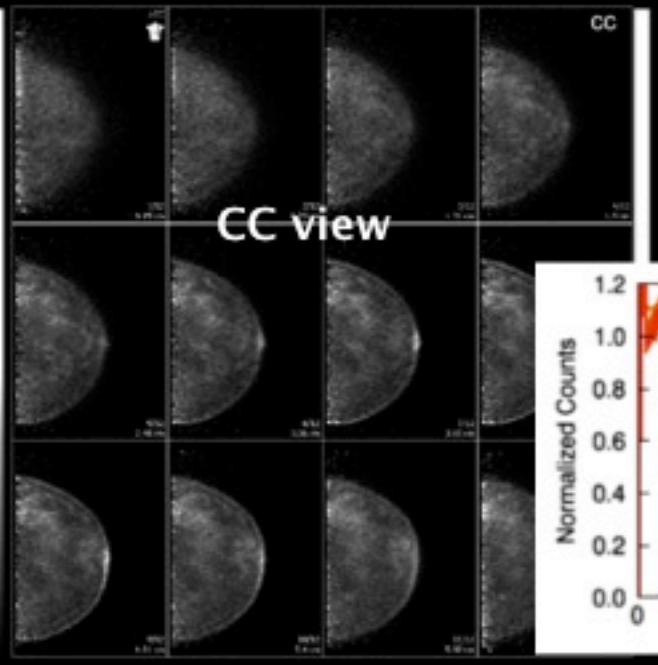
PEM Imaging at Chest Wall

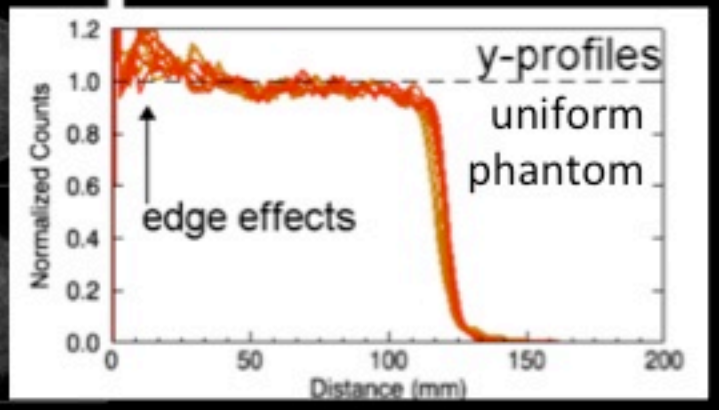


PEM Flex Solo II examples

- Physical geometry limits PET imaging at the chest wall
- PET scanners have lower sensitivity at the edge of the field of view







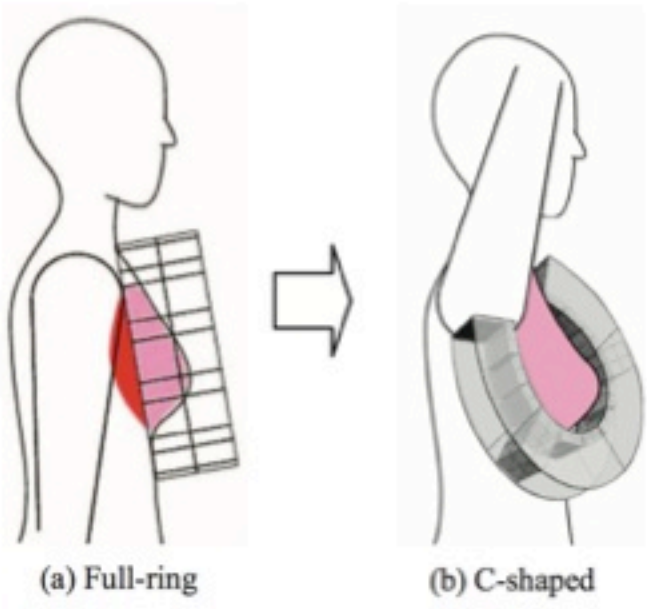
MacDonald et al., *JNM* 2009

PEM Design Strategies

Shimadzu

C-Shaped Scanner: limited-angle but better access to chest wall and axilla

O-Shaped Scanner: full-angle tomography but limited access to chest wall and axilla



Furuta et al., 2009 *IEEE NSS/MIC Conference Record*

photograph

imaging position

Patient study:

O-Shape: **9**/76 lesions outside FOV

C-Shape: **6**/76 lesions outside FOV

Iima et al., *JNM* 2012

Limited-Angle vs. Full Tomography

Simulation

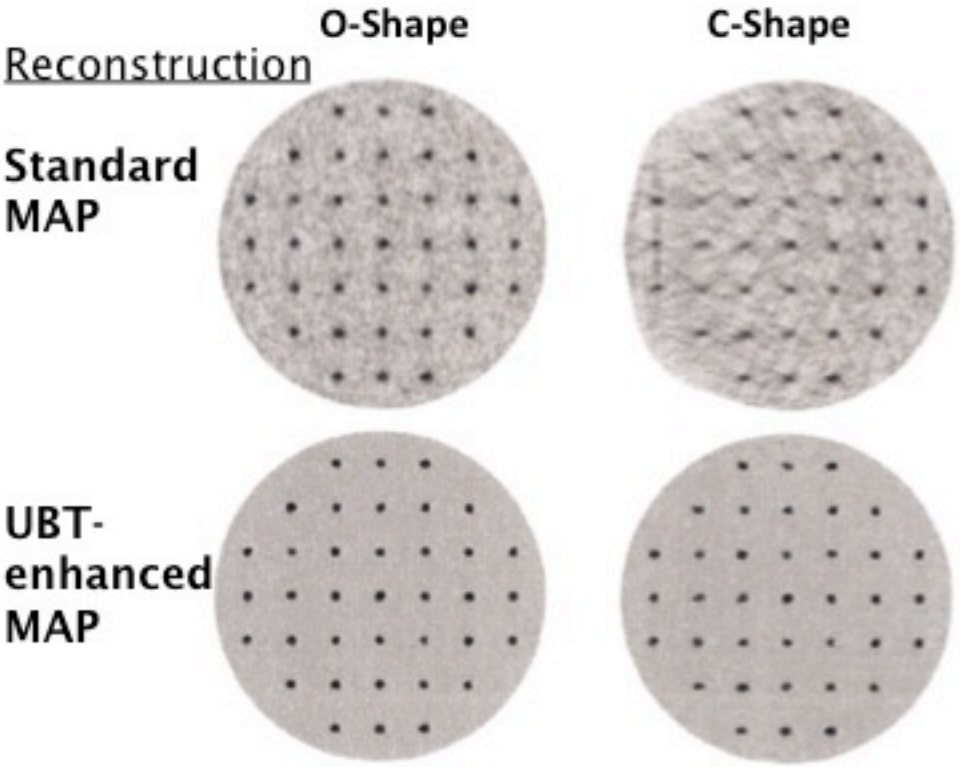
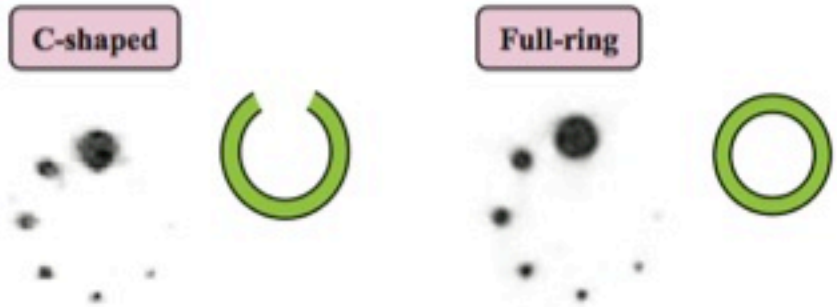


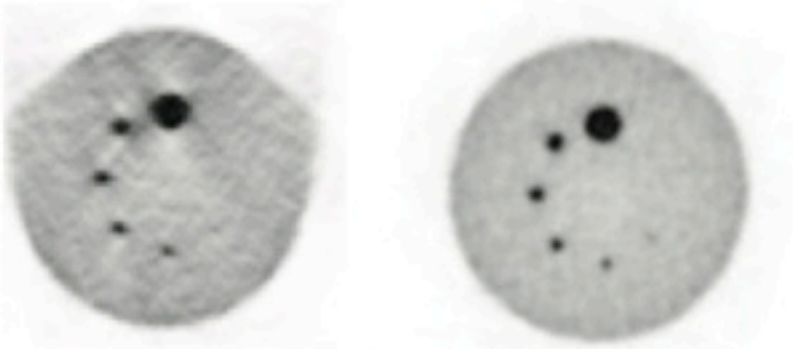
Fig. 5. Reconstructed images for the full-ring scanner (left) and the C-shaped scanner (right) with the ordinary MAP-EM (top) and the UBT-MAP-EM using uniform background template (bottom).

Kitamura et al., 2008 *IEEE NSS/MIC Conference Record*

Measured



(a) hot rod in the air



(b) hot rod in the background

FIG. 13. Reconstructed images of the rod-source phantom.

Furuta et al., 2009 *IEEE NSS/MIC Conference Record*

Beyond ^{18}F-FDG

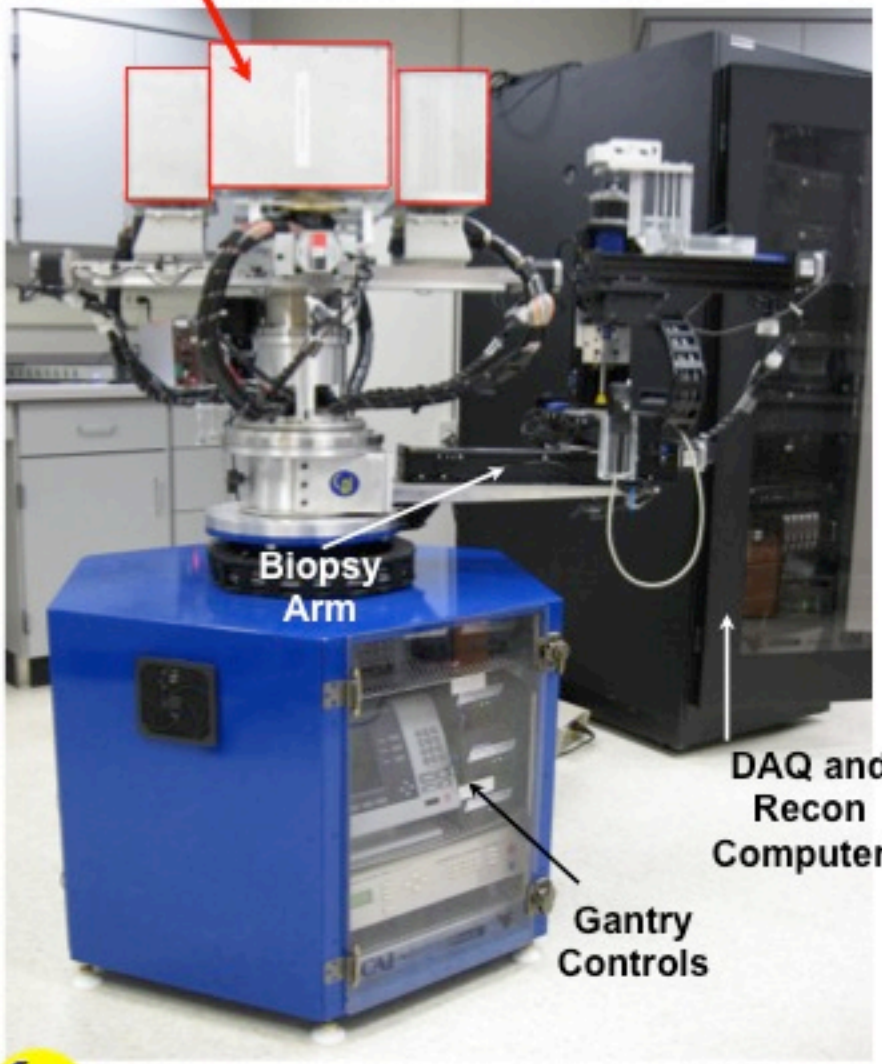
Many other tracers have been developed and used
➔ still quite limited availability

Tracers used in breast PET (research)

1. Glucose Metabolism	^{18}F-FDG
2. Protein Metabolism	^{11}C-Methionine
3. Proliferation	^{11}C-Thymidine ^{18}F-Fluorothymidine
4. Hypoxia	^{18}F-FMISO
5. Receptor	^{18}F-Estradiol ^{64}Cu-VPAC1
6. Blood Flow	^{15}O-H_2O
7. Membrane biosynthesis	^{11}C-Choline ^{11}C-acetate
8. Vascularity	^{18}F Integrins

this list focuses on oncology and is not exhaustive

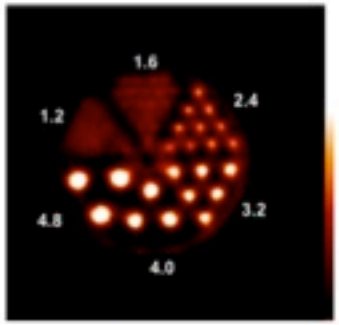
PEM-PET Scanner: West Virginia University



Fully Tomographic (360°)

Detectors:

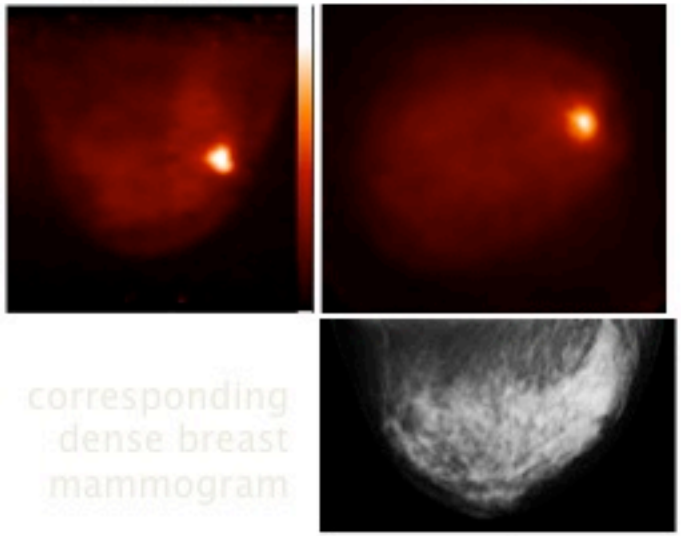
- 2 x 2 x 15 mm³ LYSO + PS-PMT
- 15 x 20 cm² rotating detectors
- 3D OSEM tomography
- 2.0 mm FWHM resolution average
- CT being added
- prone patient
- biopsy guidance



Spatial resolution phantom

FDG-PEM/PET Image

Coronal Transaxial



corresponding dense breast mammogram

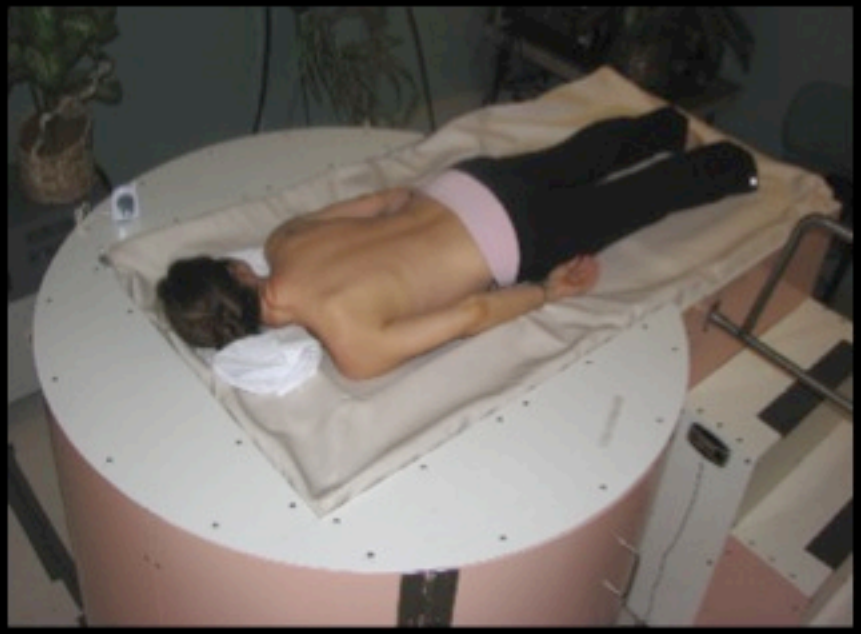
Slides courtesy of Raymond Raylman, WVU

Raylman, Majewski, Smith, et al.
Phys. Med. Biol. 2008

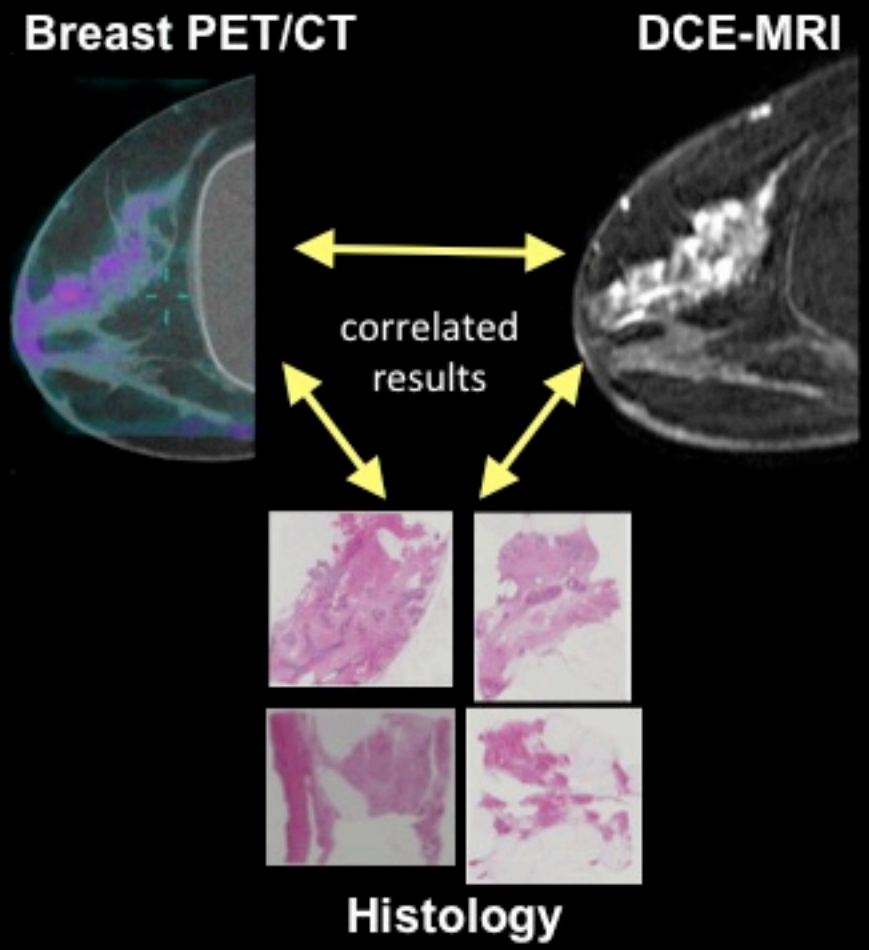
UC Davis Dedicated Breast PET/CT

Detectors:

- 3 mm x 3 mm x 20 mm LYSO + PS-PMT
- 11.9 x 11.9 cm^2 rotating detectors (2)
- 3D MAP tomography
- 2.5 mm FWHM resolution average
- CT – cone beam
- prone patient



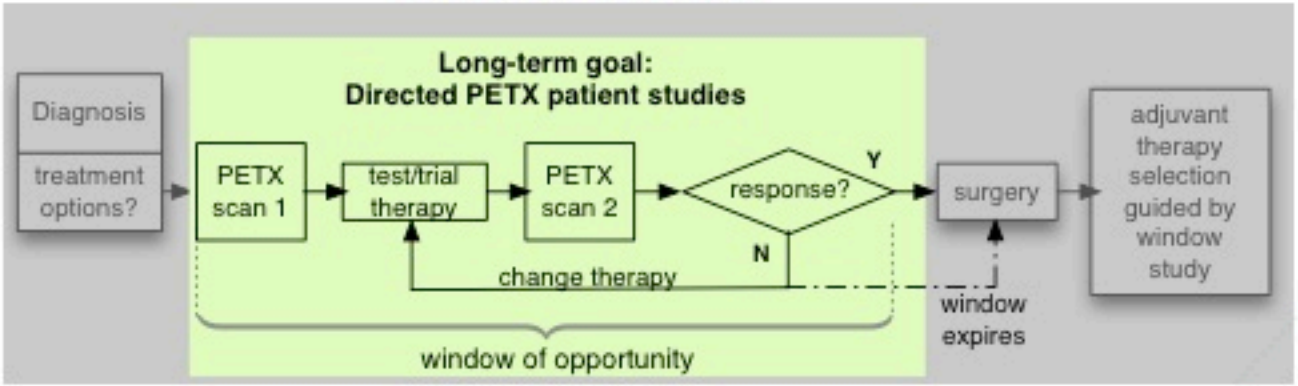
Slides courtesy of Ramsey Badawi, UC Davis



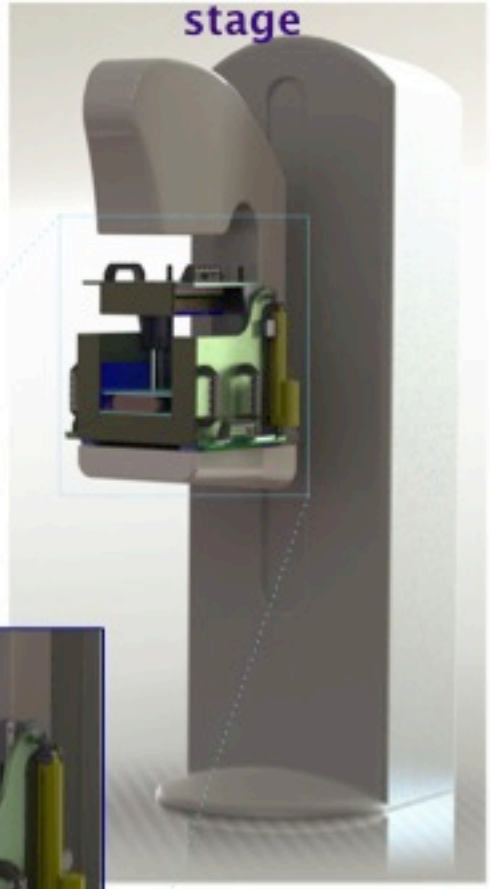
Bowen et al., *JNM* 2009

University of Washington Breast PET/X

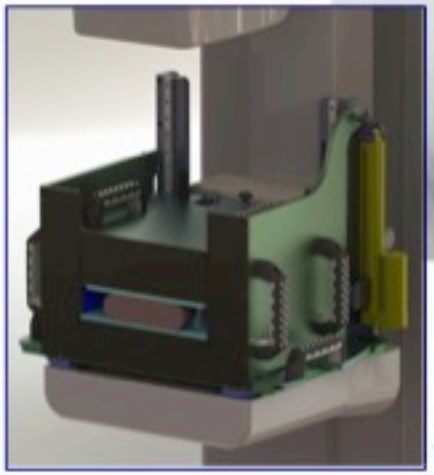
Directed PET/X 'window' studies



Design of PET/X detector mounting stage



- 'Window' studies currently under investigation at the UW in locally-advanced breast cancer using WB-PET [1,2,3] ➔ use PET/X to study early-stage disease
- PET/X detector mounting stage recently built (based on design schematic at right)



[1] "Early Assessment of Response to Aromatase Inhibitor (AI) Therapy" Linden, et al., *ASCO* 2009

[2] "Fluoroestradiol (FES) Positron Emission Tomography (PET) Reveals Differences In Pharmacodynamics Of Aromatase Inhibitors, Tamoxifen, And Fulvestrant In Patients With Metastatic Breast Cancer" Linden et al., *Clin Cancer Res* 17(14):4799-4805, 2011

[3] "Quantitative Fluoroestradiol Positron Emission Tomography Imaging Predicts Response to Endocrine Treatment in Breast Cancer" Linden et al., *JCO* 24(18):2793-2799, 2006

Review & Summary

- Dedicated breast vs. Whole-body cameras
  - Improved spatial resolution is primary goal; for imaging earlier-stage lesions
  - Active research into reducing dose on dedicated systems
  - Imaging at chest wall is challenging; physical access, higher statistical noise (PET)
- Planar vs. limited-angle vs. fully tomographic imaging
  - Limited-angle → susceptible to spatial and quantitative distortions
  - requirements depend on clinical task/application
- Clinical uses and challenges
  - Screening requires low cost, low risk, rapid scanning → FDG has challenges
  - Diagnosing equivocal cases, local staging are currently the primary applications
  - Selecting (individualization), monitoring, and developing new therapies are promising areas – quantitative PEM best for assessment task
- Several systems available commercially, others under development
  - Combination of commercial and research systems currently gaining utilization, also still defining best uses
- Single-photon designs: dual-head CZT vs. single-head scint.-based
  - Benefits of improved energy resolution? Cost of dual-head CZT
- Several distinct PEM designs
  - makes for difficult performance comparison and testing standardization