Positron Emission Mammography

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AAPM 2010

21 July 2010

Overview

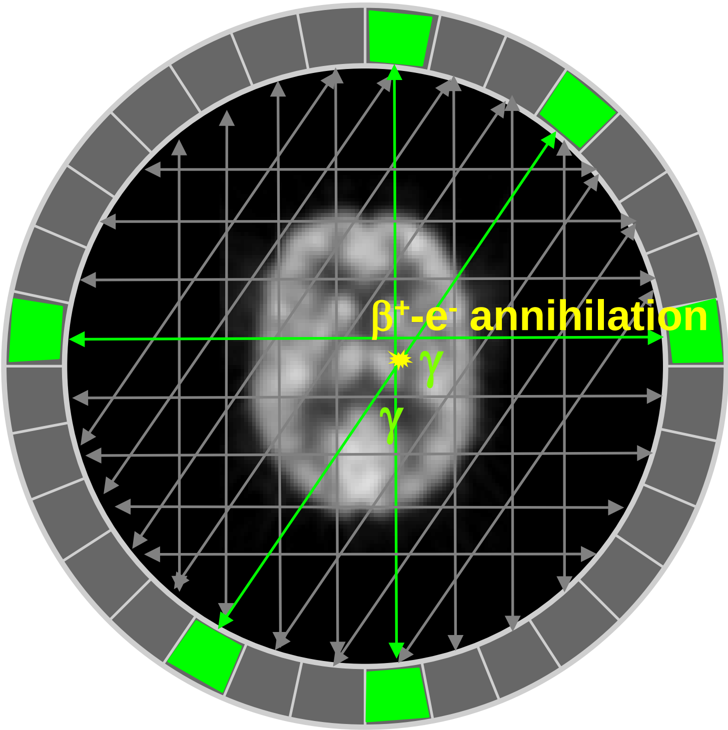
- PET imaging of breast cancer
- PEM development
- Planar vs. volumetric imaging
- PEM characterization and examples
- Review learning objectives

Learning Objectives

- Understand the differences between whole-body PET and PEM
- Understand the differences between mammography and PEM
- List possible clinical applications/indications for PEM
- Describe clinical operation and requirements of PEM scanning

Positron

- Uses **positron** (β^+) emitting radio-isotopes to label physiologic tracers (e.g. radiopharmaceuticals)
- Positrons are unstable in that they annihilate with electrons, resulting in two anti-parallel photons each with energy 511 keV
- PET scanners measure coincident annihilation photons and collimate the source of the decay via coincidence detection



Emission

- The source of the signal is **emission** of photons from within the patient, as opposed to photons transmitted through the patient in x-ray imaging (mammography)

Functional Imaging

(molecular imaging)

Tomography

- Three-dimensional volume image reconstruction through collection of projection data from all angles around the patient

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**.

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 therefore unlikely to be significantly reduced by PET imaging in patients presenting with abnormal mammography.

However, the high positive-predictive value, resulting from the increased metabolic activity of malignant tissue, may be used with carefully selected subsets of patients as well as to determine the extent of disease and to assess therapy response.

Eubank & Mankoff, *Semi Nucl Med* 2003

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used for detection, staging, and response monitoring in breast cancer patients. Although studies have proven its accuracy in detection of the primary tumor and axillary staging, its most important current clinical application is in detection and defining the extent of recurrent or metastatic breast cancer and for monitoring response to therapy. PET is complementary to conventional methods of staging in that it provides better sensitivity in detecting nodal and lytic bone metastases; however, it should not be considered a substitute for conventional staging studies, including computed tomography and bone scintigraphy. FDG uptake in the primary tumor carries prognostic information, but the underlying biochemical mechanisms responsible for enhanced glucose metabolism have not been completely elucidated. Future work using other PET tracers besides FDG will undoubtedly help our understanding of tumor 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.

Whole-body PET

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

Dedicated Breast PET / PEM
History

Concept

Functional imaging is conceptually complementary to the anatomical info. of mammography, US, MRI.
→ moderate specificity of anatomical imaging leads to high number of negative biopsies

Development

PEM has been proposed for ~ 15 years

(Thompson et al. 1994 *Med Phys*)

Dedicated breast PET scanner allows improved :
spatial resolution and
photon-detection sensitivity
relative to whole-body PET
→ **earlier intervention**

Dedicated Breast Positron Emission Imaging Applications

Diagnosis/ screening	What role? early stage triple-negative? DCIS?
Characterization	Disease extent (multi-focal/centric) Surgical planning Therapy selection & monitoring
Physiologic Tracers	^{18}F-fluoro -deoxyglucose (FDG) -estradiol (FES) -thymidine (FLT), -misonidazole (FMISO)

Best application will be evaluated in the context of other imaging methods

Mammography
X-ray tomosynthesis
Ultrasound
Magnetic Resonance Imaging
Dedicated gamma cameras (single-photon imaging)
Optical techniques

PEM Detector Development

- Montreal Neurological Institute: Thompson, Murthy, et al.
- Th. Jefferson Natl. Lab: Majewski, et al.
- LBNL: Huber, Wang, Moses, et al.
- Naviscan PEM Flex™: commercial system.
- West Virginia University : Raylman, Smith, et al.
- Clear-PEM Collaboration: Varela, Abreu, et al.
- UC-Davis: Bowen, Badawi, et al.
- Stanford University: Levin, et al.
- Others

Clinical PEM Tests

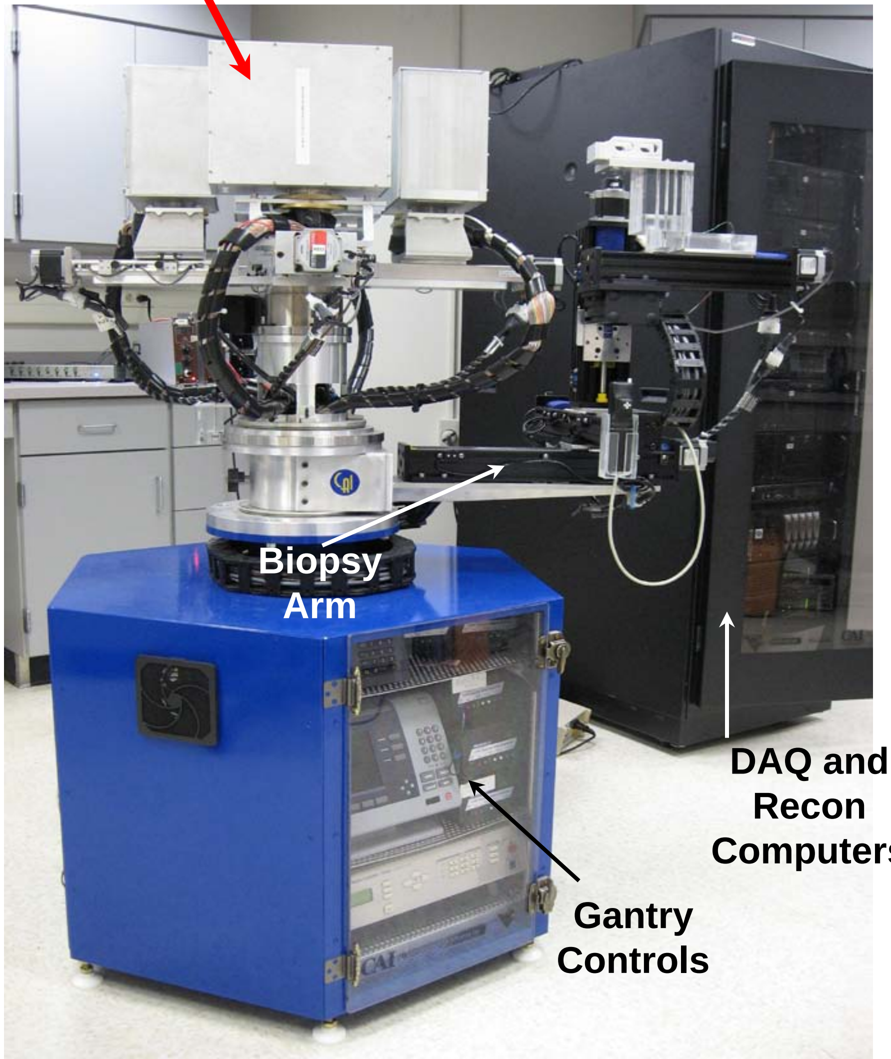
Citation (camera)	No. Patients (eval.)	Results sens./specificity/accur.
• Murthy, et al. *J Nucl Med* 2000.	16 (14)	80% /100% / 86%
• Levine, et al. *Ann* Surg Oncol 2002.	16	86% / 91% / 89%
• Rosen, et al., *Radiol* 2005.	23	86% / 33%* / PPV=90% NPV=25%*
• Tafra, et al. *Am J Surg* 2005.	44	3 ca. by PEM only/75%+ &100%- marg.
• Berg, et al. *Breast J* 2006.	94 (77)	90% / 86% / 88%
• 2003 WB-PET Meta-analysis	13 studies	89% / 80% (2-4cm lesn)

* 95%CI: 2%-79%; lack of TN

These preliminary studies:

- used different prototype PEM cameras with a range of performance capabilities
- used different patient inclusion criteria
- mostly small patient numbers

PEM-PET Scanner Geometry (WVU)



Raylman, Majewski, Smith, et al.
Phys. Med. Biol. 2008
West Virginia Univ.

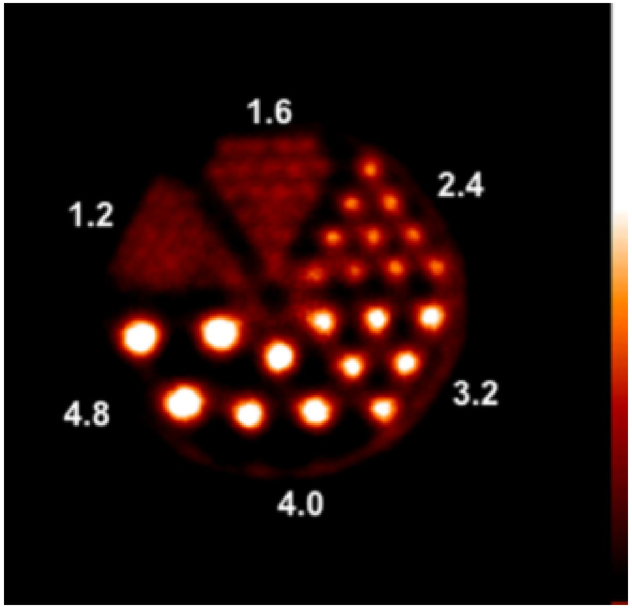


Figure 6. PEM/PET image of the micro-Derenzo phantom reconstructed with the 3D-OSEM algorithm. The diameters of the rods (in millimeters) are shown. A maximum acceptance angle of 20° was used to create this image.

Brookhaven Breast PET/MRI

A Simultaneous PET/MRI Breast Scanner based on the RatCAP

B. Ravindranath[1], S. H. Maramraju[1], S. S. Junnarkar[2], S. S. Southekal[1], S. P. Stoll[2], J.-F. Pratte[2], M. L. Purschke[2], X. Hong[3], D. Bennett[3], K. Cheng[3], D. Tomasi[2], D. S. Smith[2], S. Krishnamoorthy[1] ,P. Vaska[2], C. L. Woody[2], D. J. Schlyer[2]

[1]Biomedical Engineering, Stony Brook University, Stony Brook, NY, USA
[2]Brookhaven National Laboratory, Upton, NY, USA
[3]Aurora Imaging Technology Inc, North Andover, MA, USA

IEEE NSS Conf. Proceedings 2008

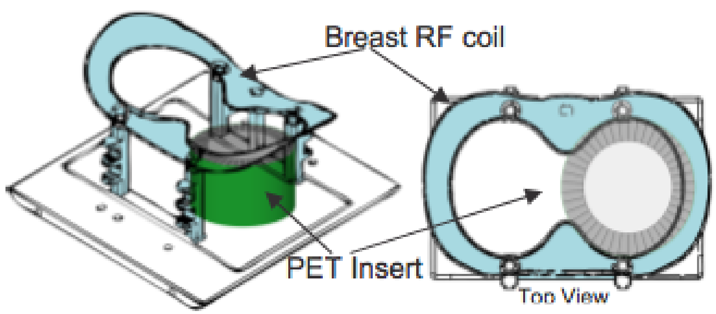


Fig. 2: Schematic diagram of the PET insert and MR coil.

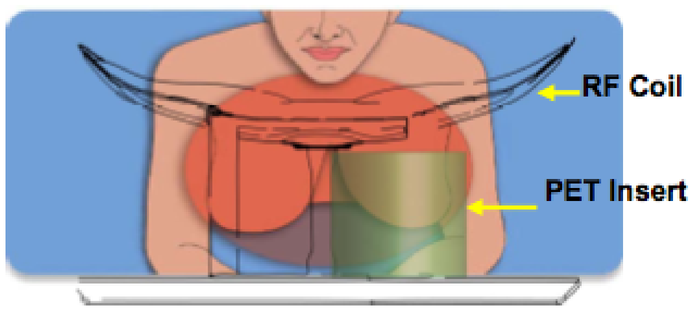
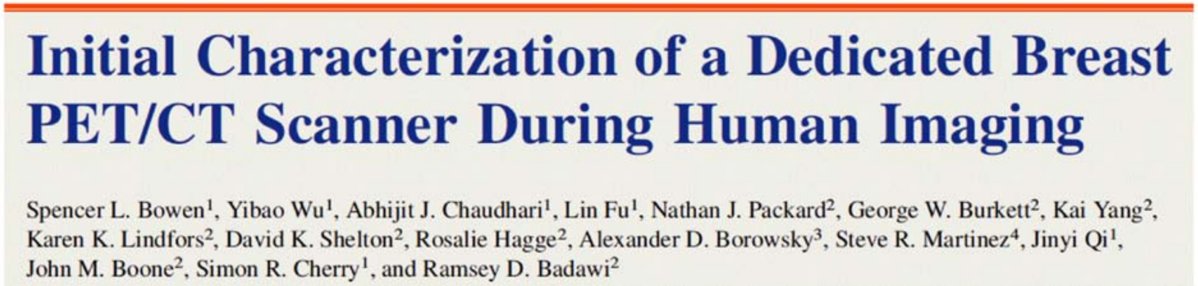


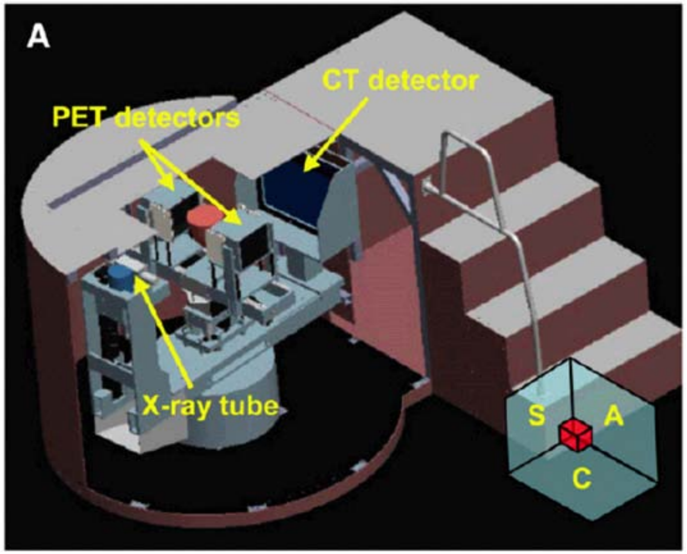
Fig. 3: Patient positioned with Breast PET insert inside Aurora Breast RF Coil

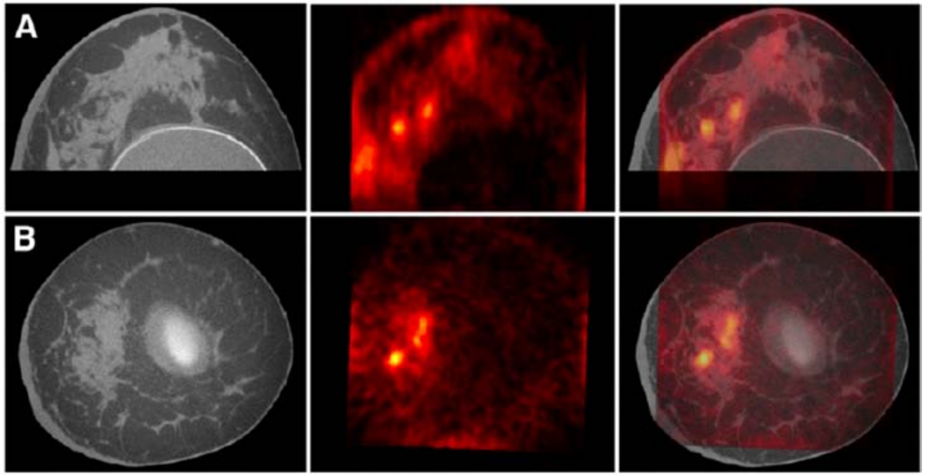
UC Davis Breast PET/CT


Initial Characterization of a Dedicated Breast PET/CT Scanner During Human Imaging

Spencer L. Bowen[1], Yibao Wu[1], Abhijit J. Chaudhari[1], Lin Fu[1], Nathan J. Packard[2], George W. Burkett[2], Kai Yang[2], Karen K. Lindfors[2], David K. Shelton[2], Rosalie Hagge[2], Alexander D. Borowsky[3], Steve R. Martinez[4], Jinyi Qi[1], John M. Boone[2], Simon R. Cherry[1], and Ramsey D. Badawi[2]

Journal of Nuclear Medicine 50(9):1401-1408, 2009



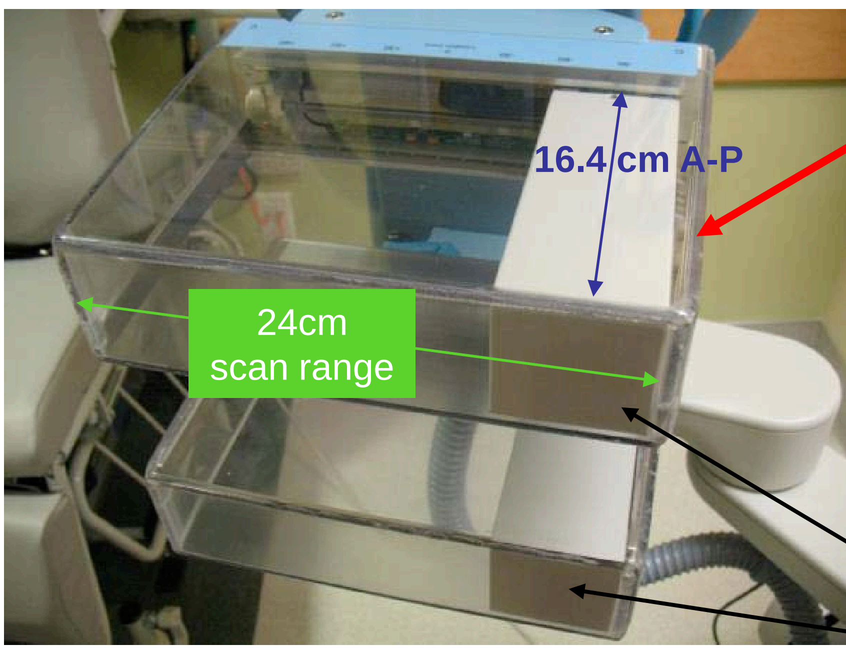


CT PET Fused

PEM Flex Solo II (Naviscan, Inc.)

Detectors:

- 2 mm x 2 mm x 13 mm LYSO + PS-PMT
- 5.0 x 16.4 cm^2 detectors scan together
- 3D LM ML-EM Tomosynthesis
- No attn. or scatter correction
- Rotating arm accommodates conventional mammography imaging views
- Variable compression & scan distance



Detectors

compression detector
support detector

Planar vs. Volumetric Imaging

Planar imaging

- No image reconstruction required
- Projection in single direction
  - entire object volume is projected onto single plane resulting in considerable overlap

Examples: Mammography, plain-film x-rays

Tomosynthesis (Limited-angle) Imaging

- Requires image reconstruction
- Projection images at several angles, but not full 360º coverage
  - multiple slices of the object volume are separable, overlap or blurring remains

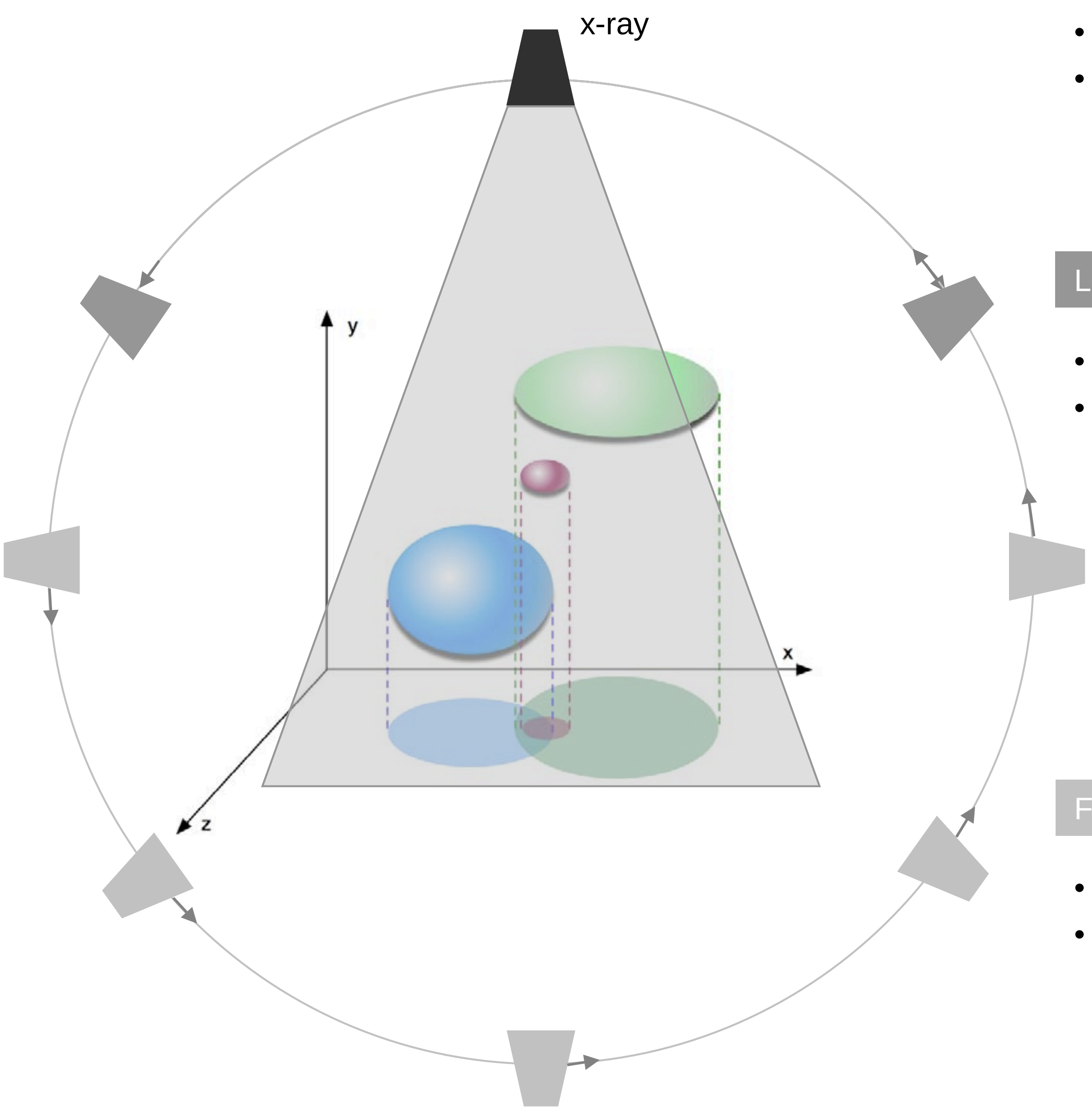
Examples: breast, thorax, orthopedic, angiography (emerging uses)

Tomography (full 360º angular sampling)

- Requires image reconstruction
- Projections around the entire object at all angles
  - fully 3-dimensional **isotropic** reconstruction possible

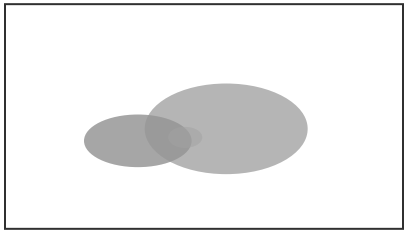
Examples: X-ray CT, SPECT, PET, MRI

Planar vs. Volumetric Imaging



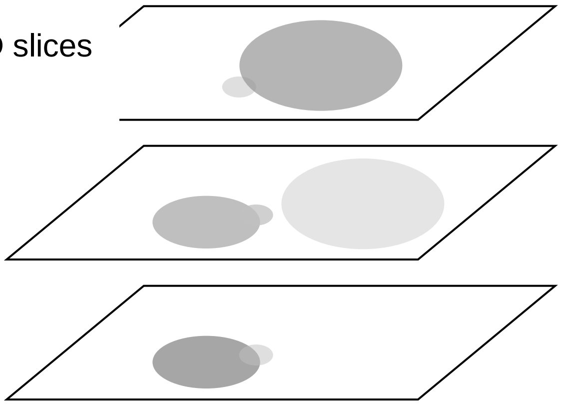
Planar

- Single 2-D image
- All objects overlap



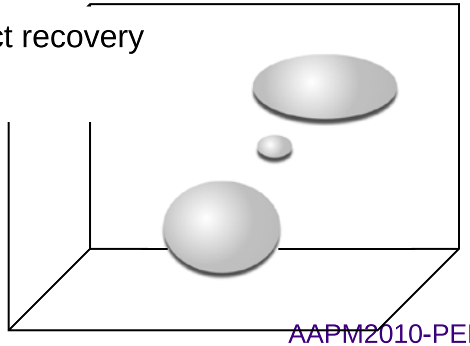
Limited Angle (Tomosynthesis)

- Multiple 2-D slices
- Anisotropic



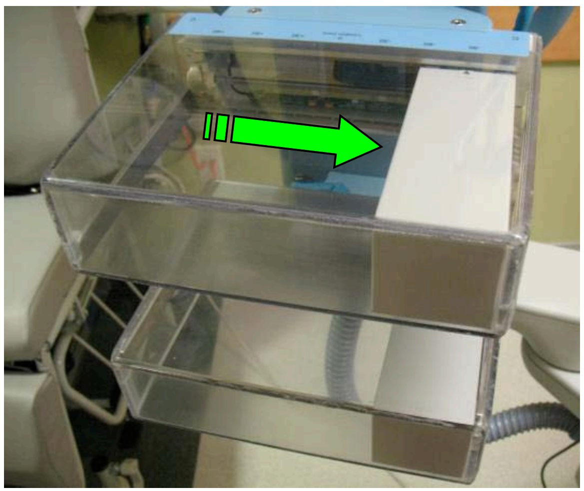
Fully Tomographic (360º)

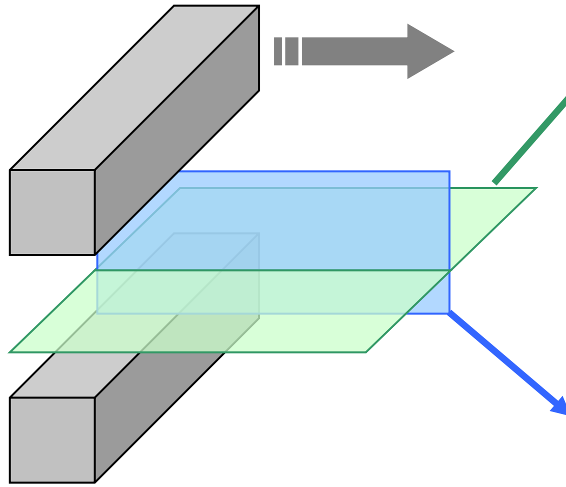
- Full 3-D object recovery
- Isotropic



PEM Flex Tomosynthesis

'In-plane' image slices vs. 'cross-plane' image slices





In-plane:
slices parallel to detector faces

in-plane images are viewed clinically

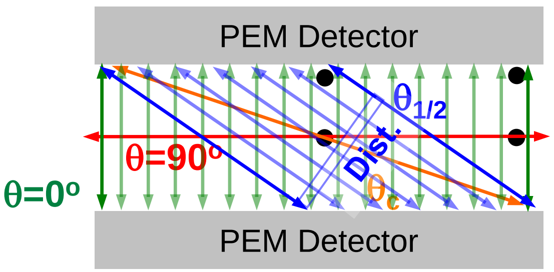
Cross-plane:
slices perpendicular to detector faces

cross-planes <u>not</u> intended for viewing; two views needed (e.g. MLO & CC)

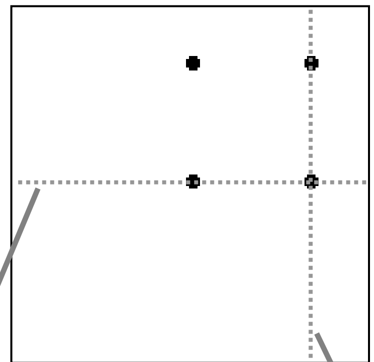
Tomosynthesis Limitations

Incomplete angular sampling - Simulation

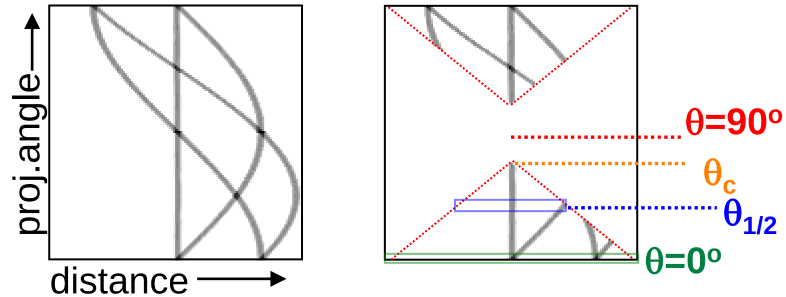
Angular Sampling; coincidence lines

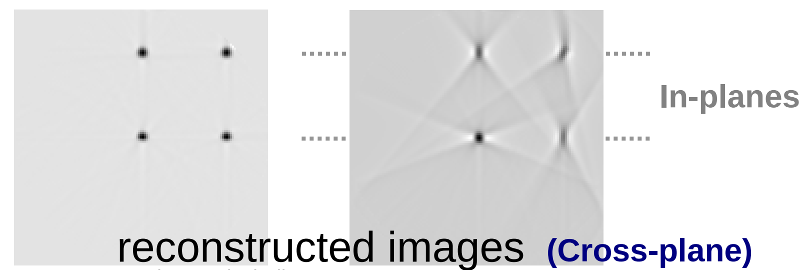


Object

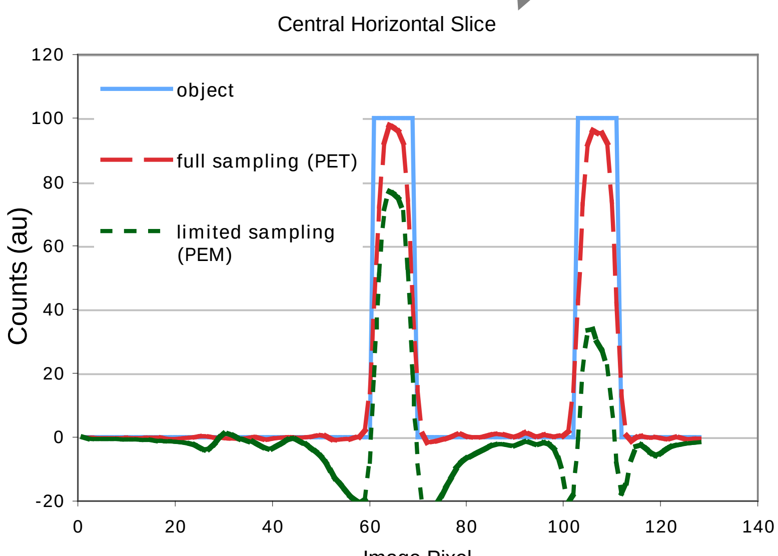


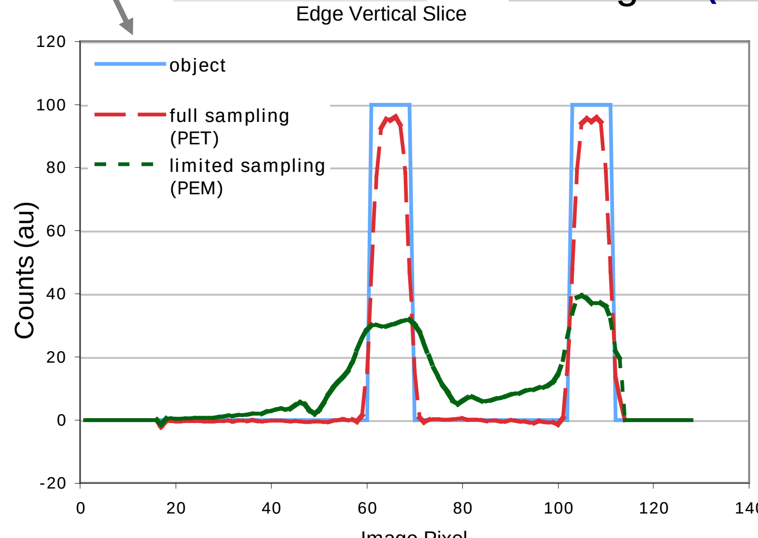
Sinograms





reconstructed images **(Cross-plane)**

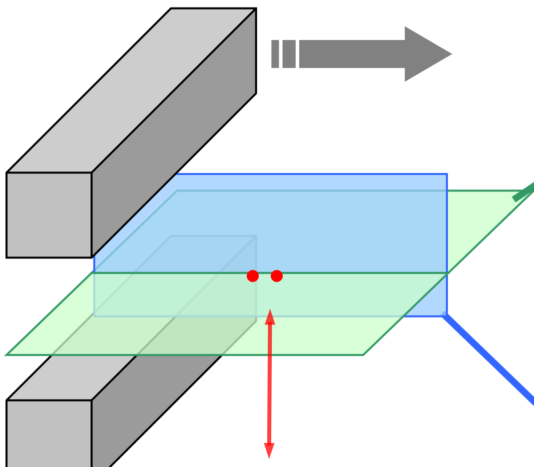


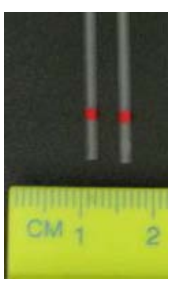


Tomosynthesis: Spatial Anisotropy

PEM Flex
Max. Likelihood-Expectation Maximization
(statistical, iterative)
image reconstruction

detectors scan in unison

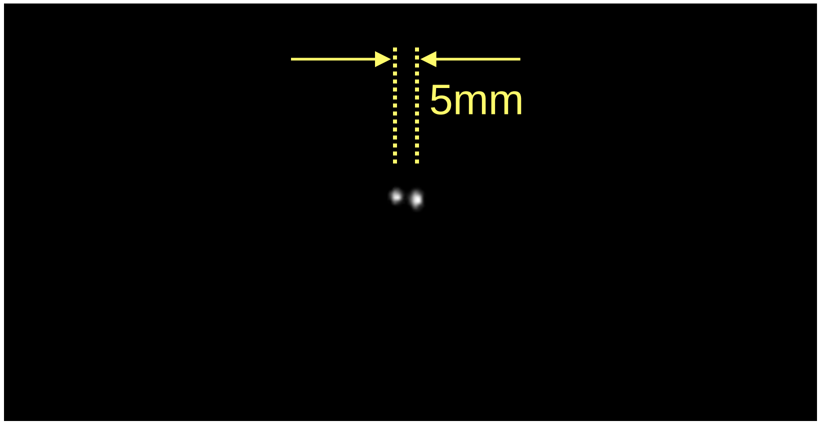




1-mm point sources in air

In-plane (parallel to detector faces)

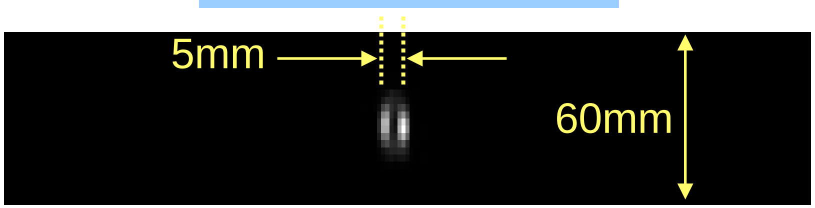
viewed clinically



In-plane FWHM = 2.4 ± 0.3 mm

Cross-pl FWHM = 8.0 ± 1.0 mm

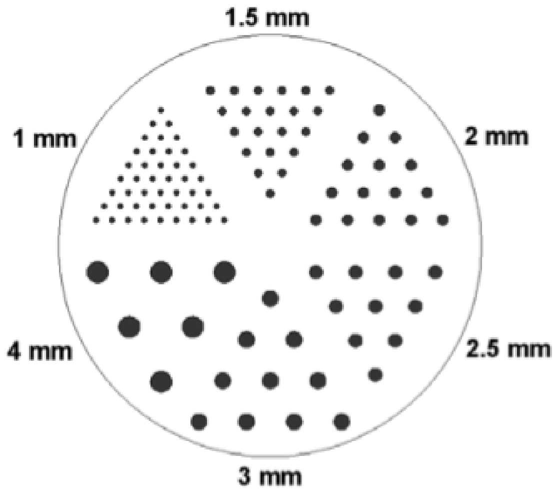
Cross-plane



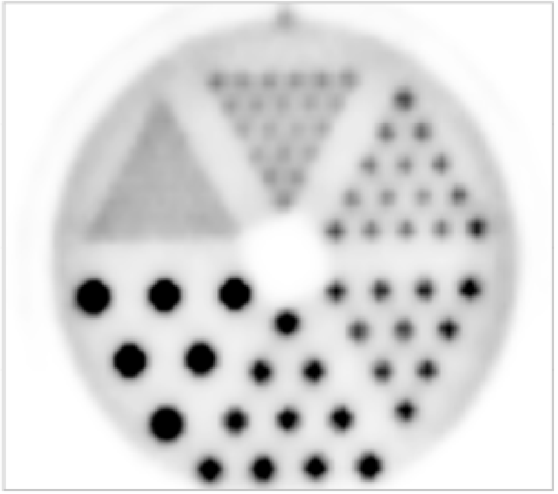
(not for viewing)

PEM Flex vs. Whole-Body PET

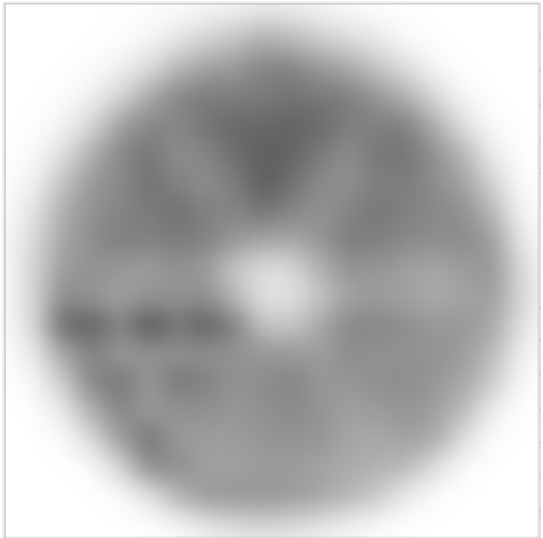
Hot-Rod Phantom



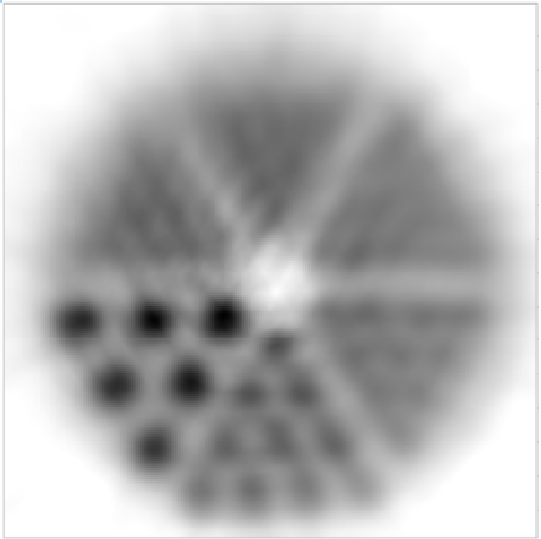
PEM Flex Image



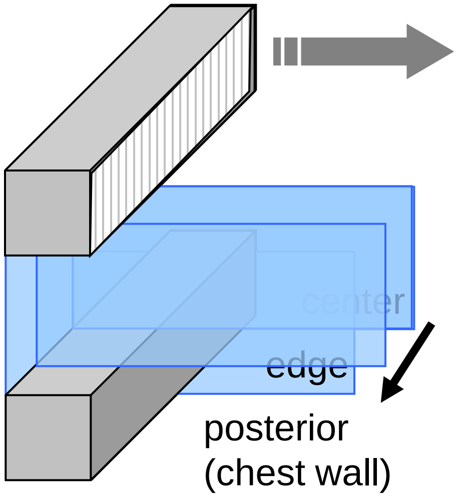
Whole-body PET (GE DST)
Typical clinical settings



Whole-body PET (GE DST)
Highest possible resolution settings



Limited Coincidence Sampling at Edge



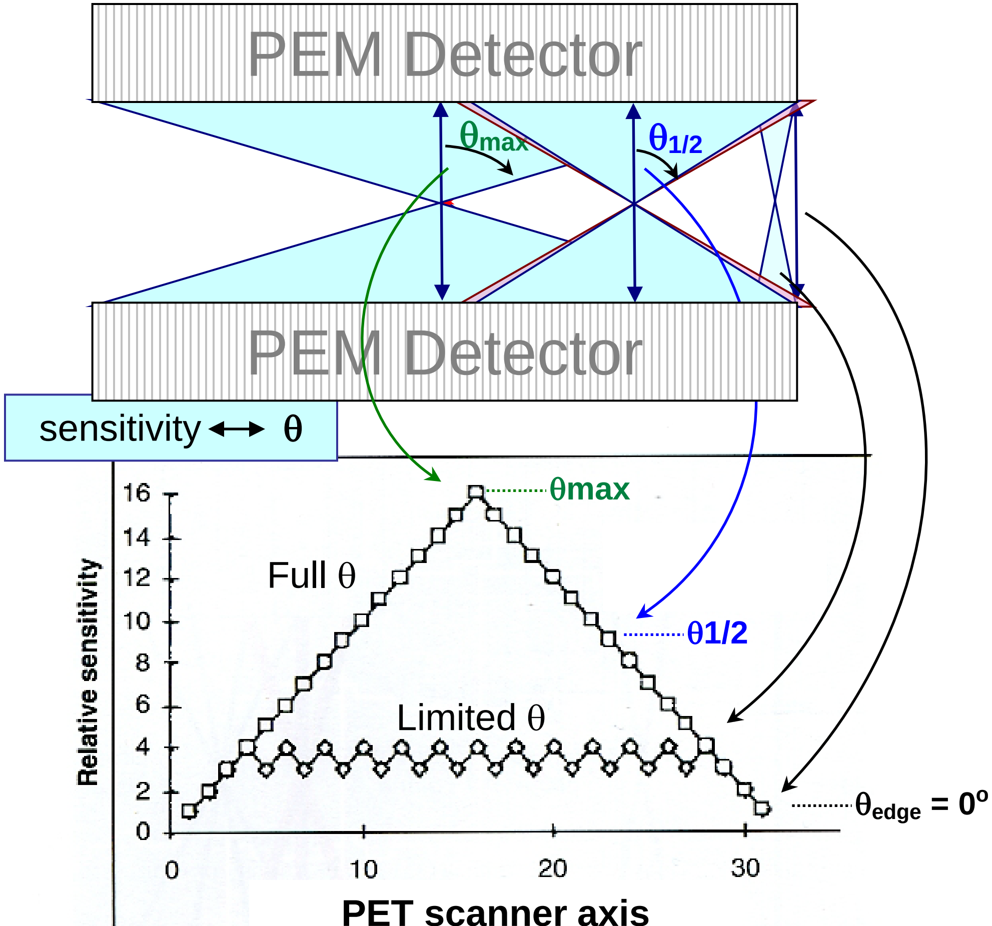
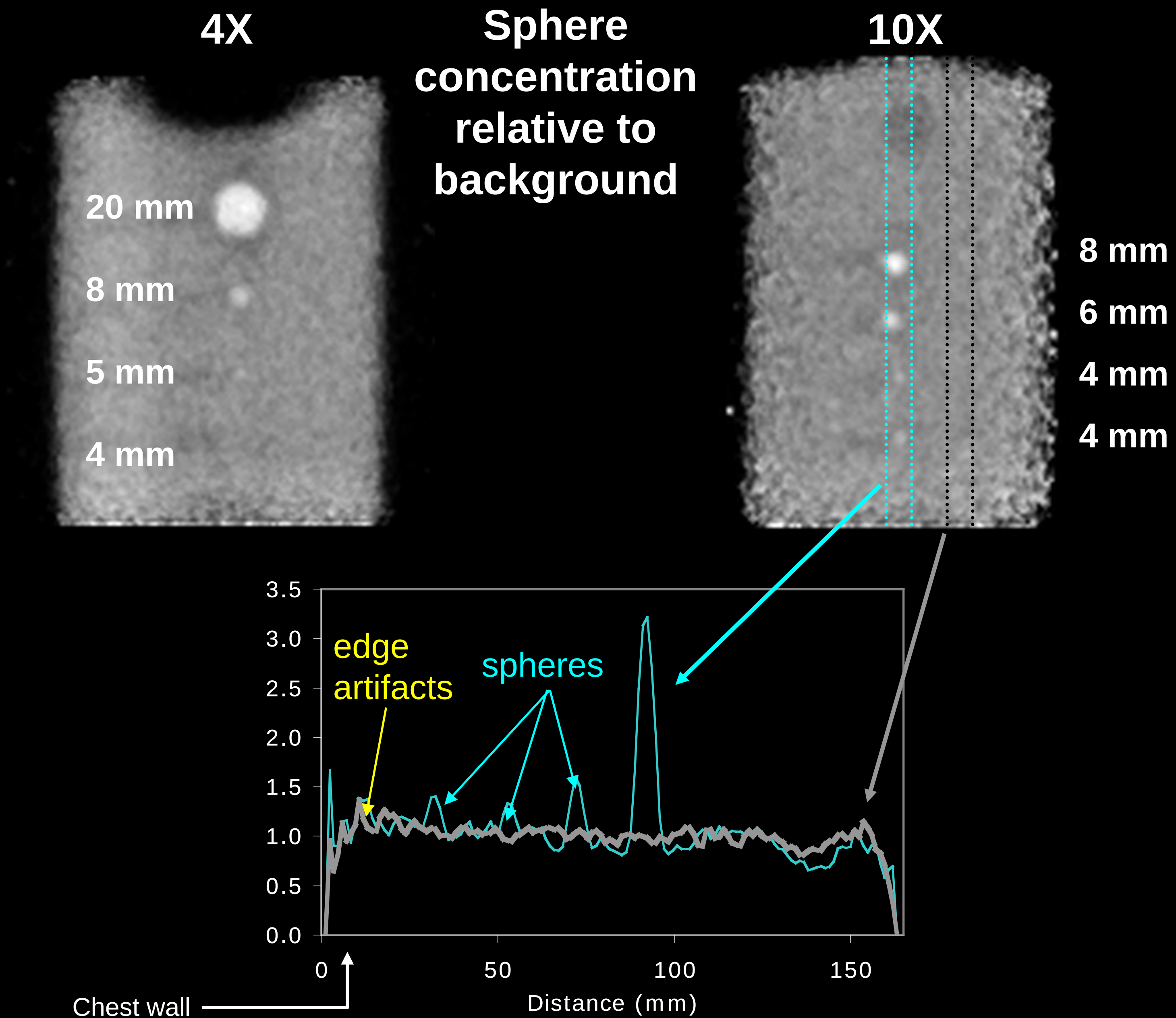


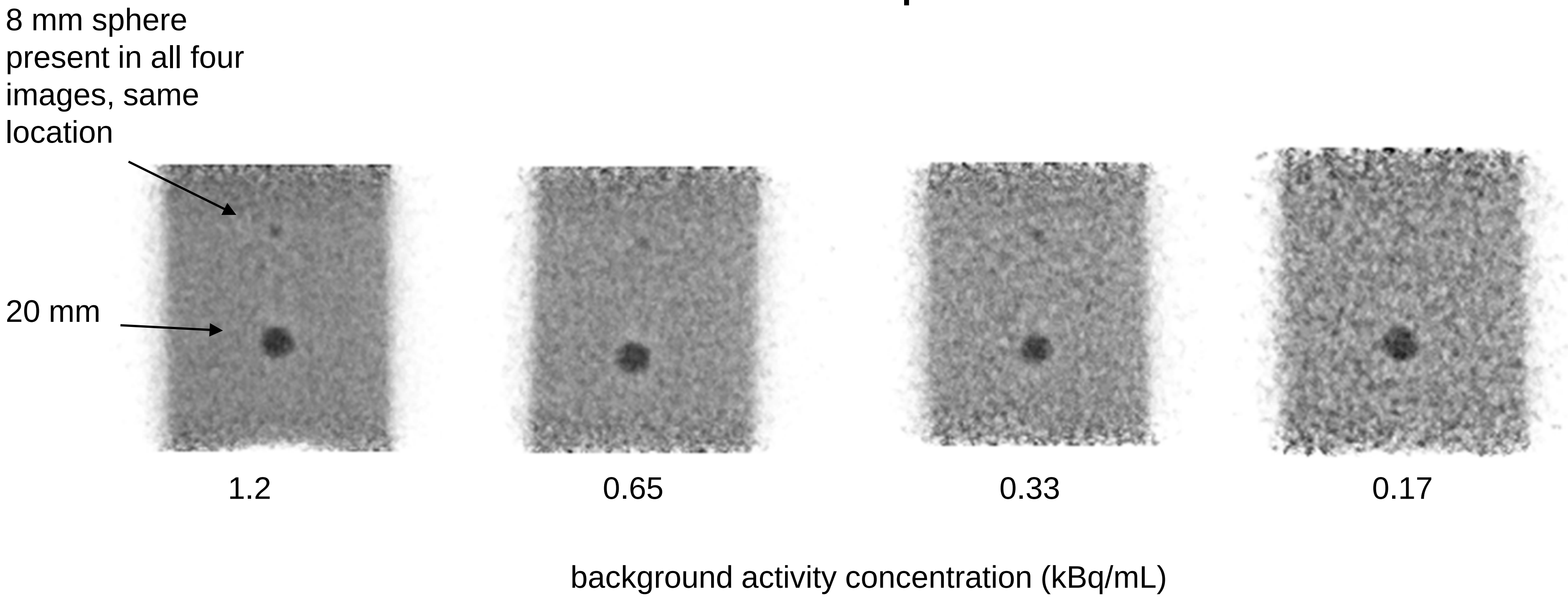
FIGURE 10 Comparison between 2D (axial collimation in place) and 3D (axial collimation removed) sensitivity.

from “Emission Tomography”, Eds. Wernick, Aarsvold, pg.186

Detection Limits



4X sphere-to-background activity concentration ratio
85 mm detector separation



PET and PEM Dosimetry

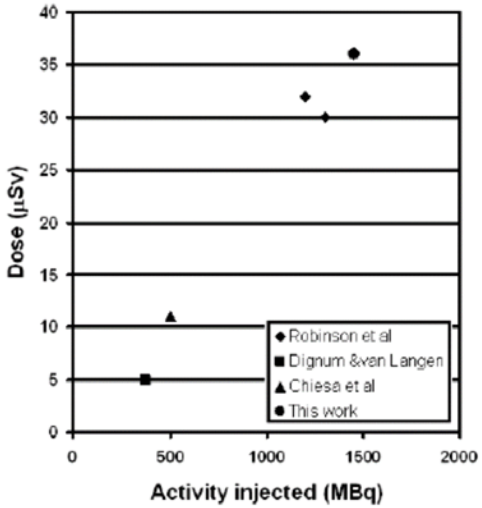
Dosimetry per unit injected activity should be similar for whole-body PET and PEM

Estimated average effective dose (μSv)

Procedure	**to patient[3]**	**to technologist[1]**
Mammography	400 (100-600)*^	
Chest CT	7,000 (4,000-18,000)*	
PET inj. activity = 10 mCi (370MBq)	7,000	1.7 - 3.2+

* range found in literature
^ patient mammo. dose will increase 2.4X based on new 2007 ICRP tissue-weighting factors
+ depending on amount of shielding used

citation[2]



Dose to technicians vs. injected activity of ^{18}F

Citations estimate dose for different tasks
(dose preparation, injection, patient handling, etc.)

1. **Radiation Dose to PET Technologists and Strategies to Lower Occupational Exposure, F. Roberts et al., *J Nucl Med Technol 2005; 33:44–47***
2. **Doses to Nuclear Technicians in a Dedicated PET/CT Center Utilising 18F Fluorodeoxyglucose (FDG), T. Seierstad, et al., *Radiation Protection Dosimetry (2007), Vol. 123, No. 2, pp. 246–249***
3. **Effective Doses in Radiology and Diagnostic Nuclear Medicine: A Catalog, Mettler, et al., *Radiology: Volume 248: Number 1—July 2008***
4. **Personal Radiation Doses in PET/CT Facility: Measurements vs. Calculations, E. Hippeläinen, et al., *Radiation Protection Dosimetry (2008), Vol*. 132, No. 1, pp. 57–63**
5. **Positron Emission Mammography (PEM) Imaging: Radiation Exposure to Technologist, W. Luo, et al. Presented at SNM Annual Meeting 2010**

PEM Protocol; Swedish Cancer Institute

PET-CT

Pre-scan fast (reduce blood glucose (FDG))
Inject 600 MBq (16 mCi) FDG
60 min. uptake
~30 min. PET-CT exam

PEM Flex

Follows Whole-Body PET/CT exam
7 min. each view

- 1st contralateral craniocaudal (CC)
- 2nd ipsilateral CC
- 3rd ipsilateral medio-lateral-oblique (MLO)
- 4th contralateral MLO

PEM-only

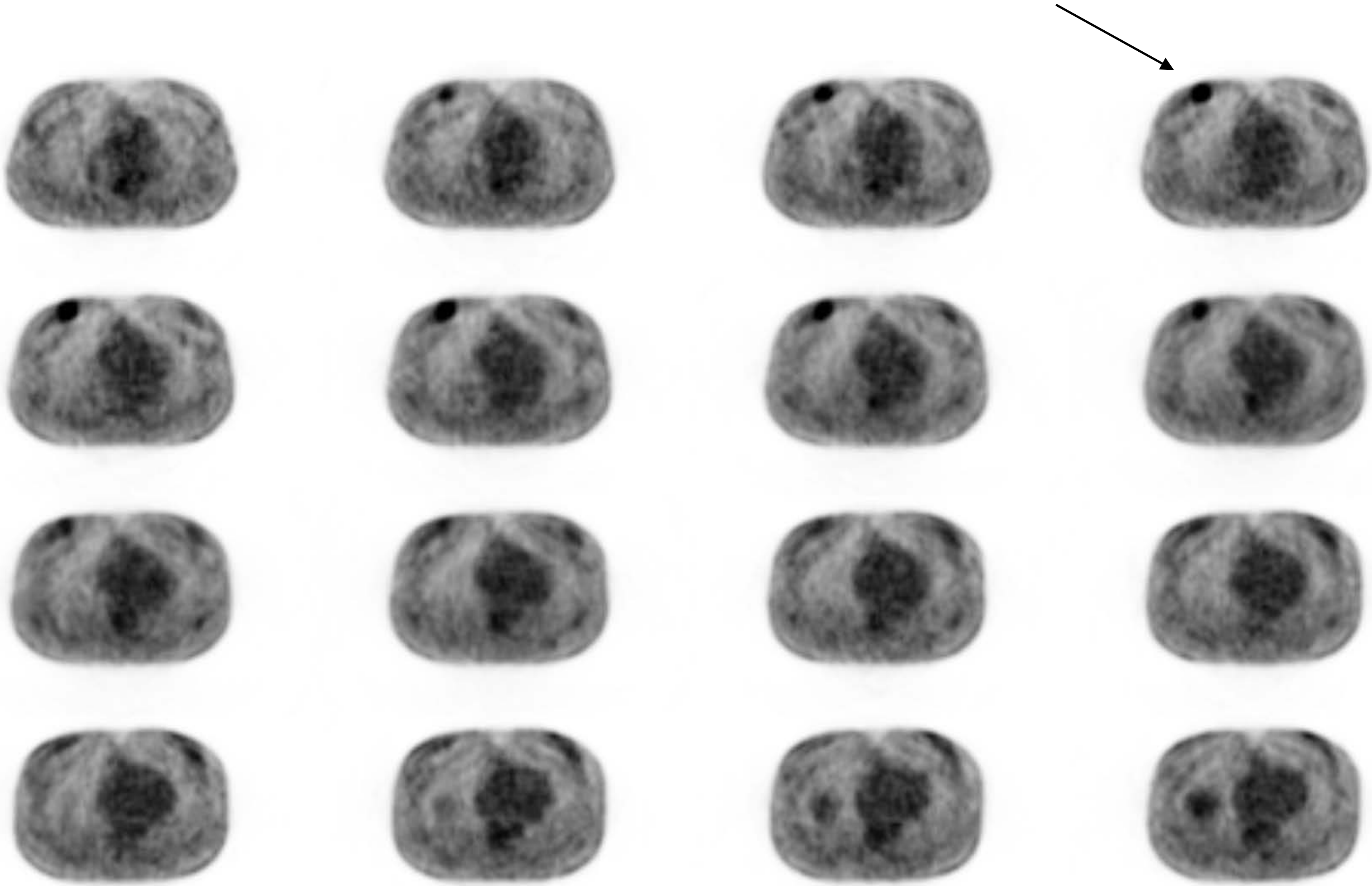
Inject 370 MBq (10 mCi)

Follow same protocol, 60 min. post-injection

NEW PEM study beginning using 185 MBq (5 mCi) injection, and scanning 60, 90, and 120-min. post-injection

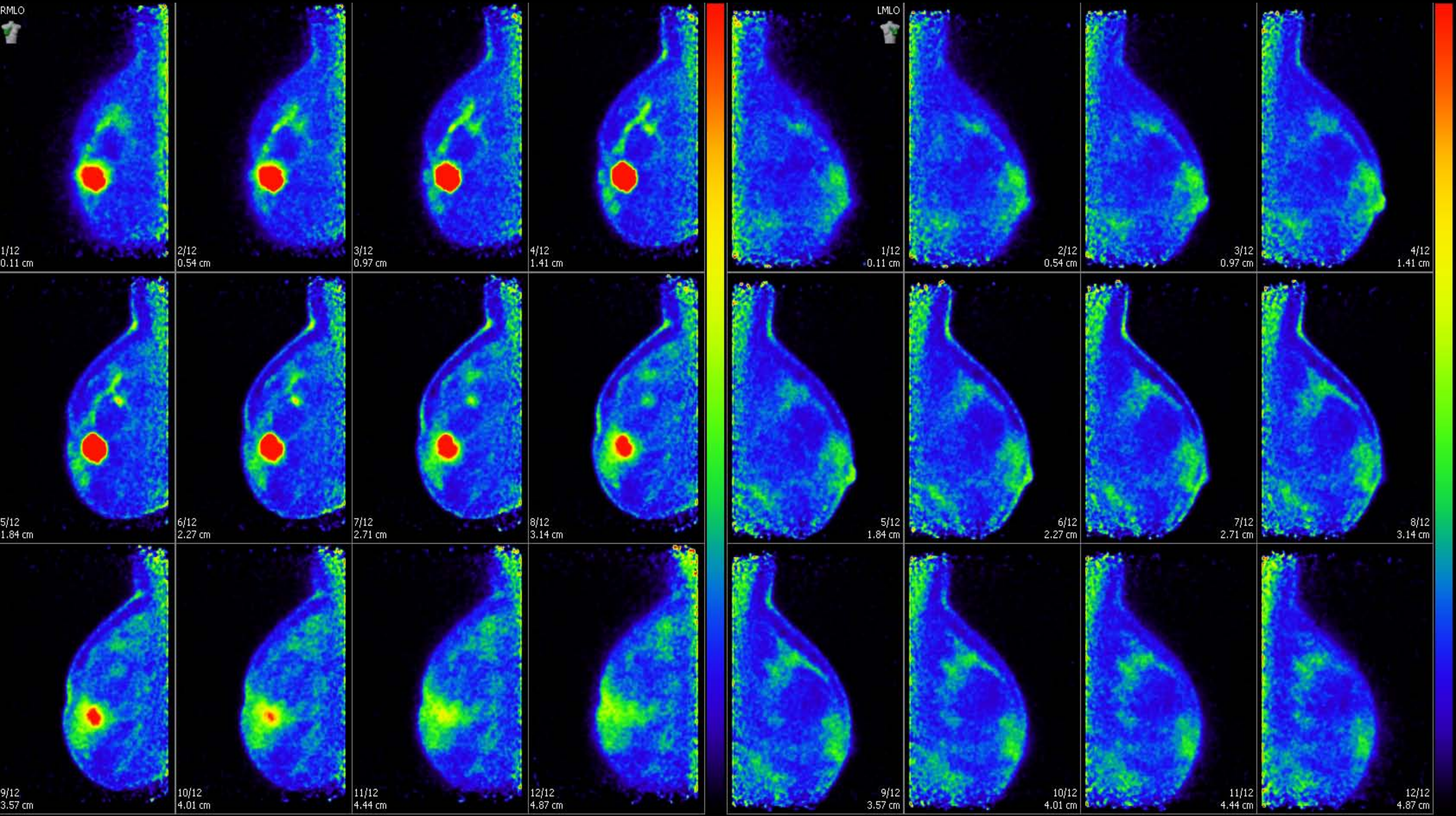
Case 1: Whole-body PET

Max SUV = 5.4 g/ml



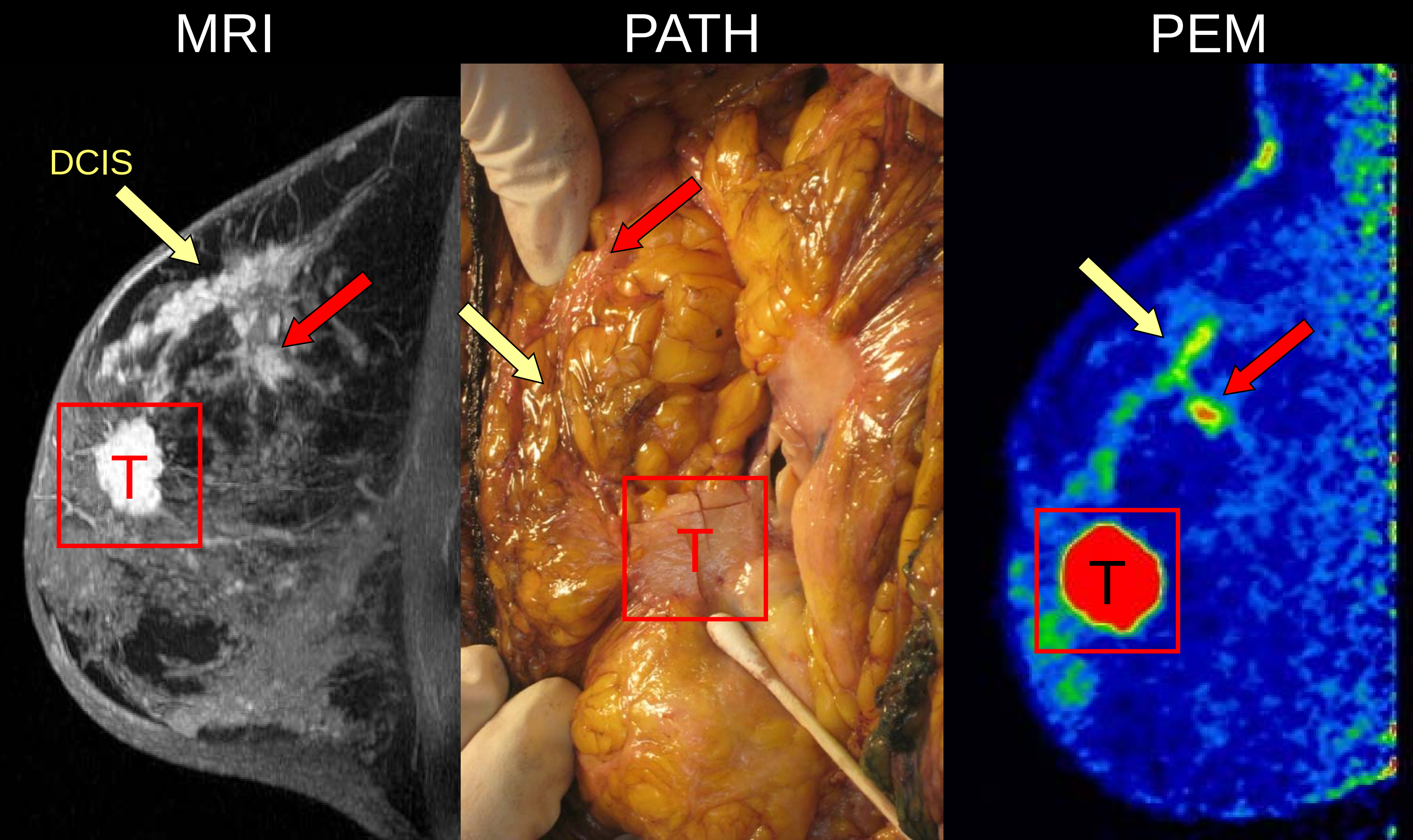
Case 1 PEM: Multicentric with DCIS

Infiltrating ductal ca. (IDC)
Ductal carcinoma in situ (DCIS)
and 2ND small tumor



Case 1

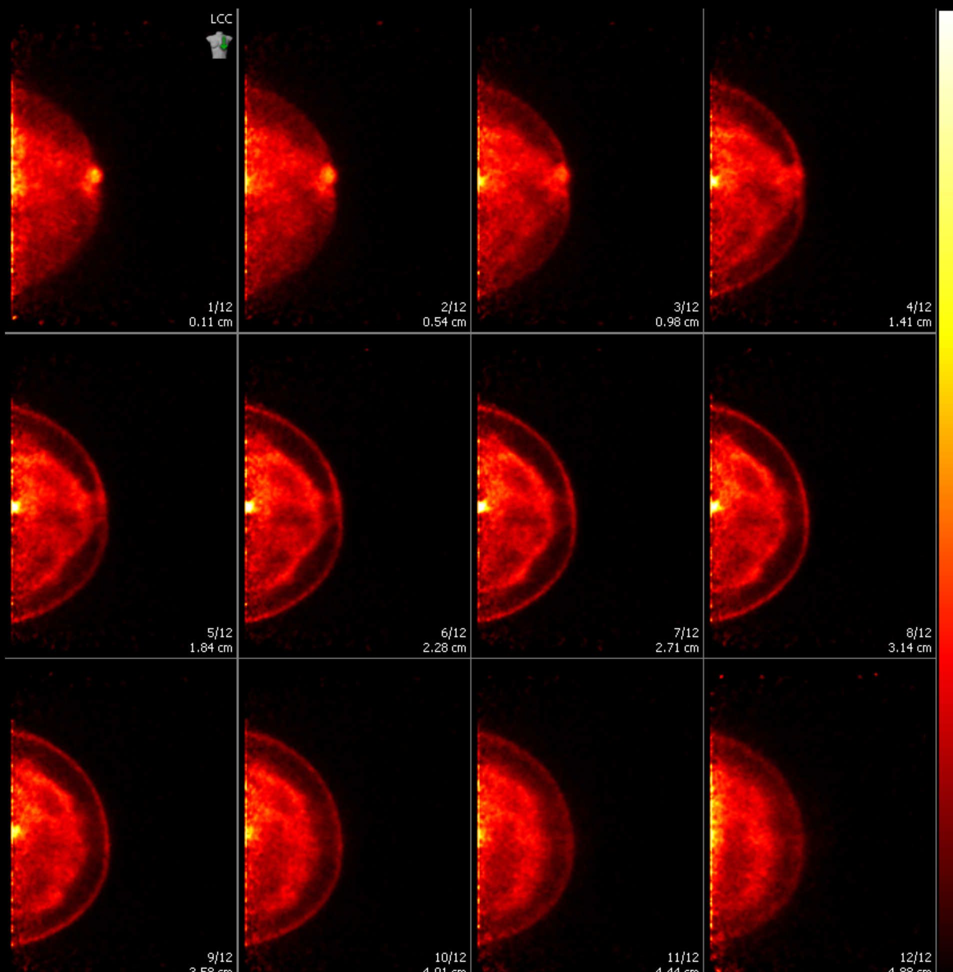
Correlation with MRI and pathology



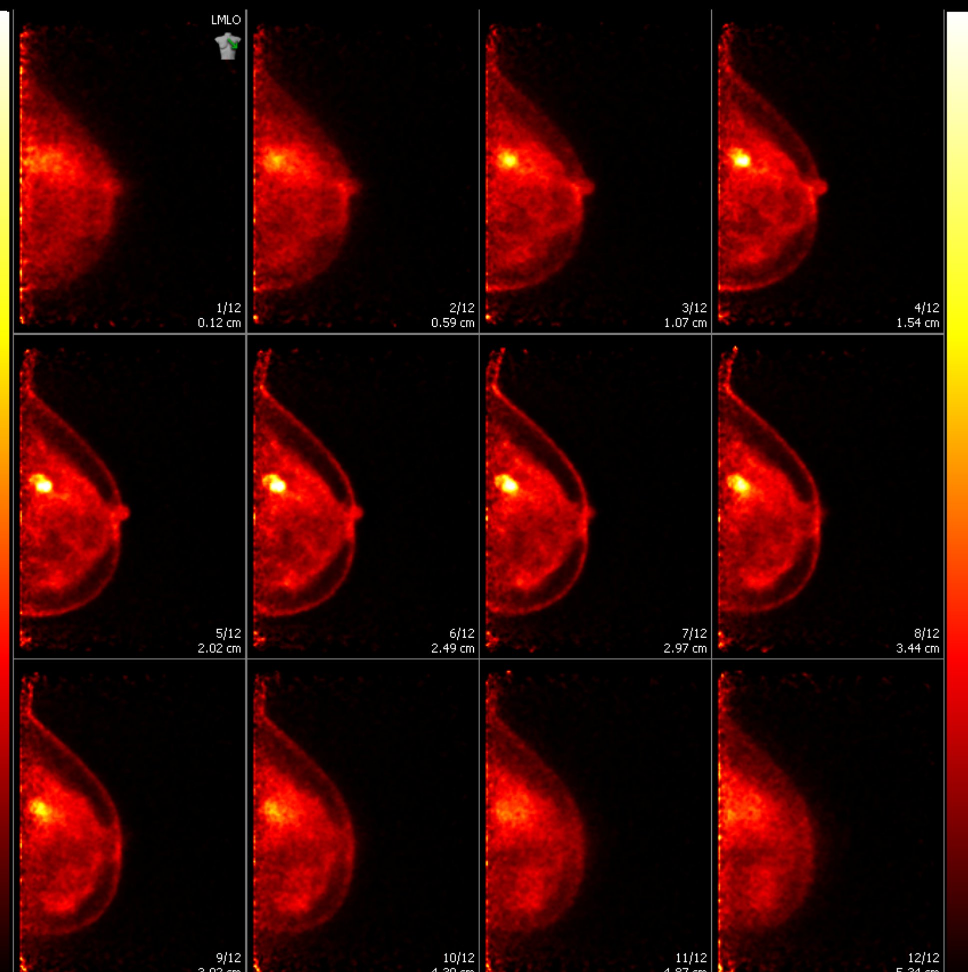
Case 2: Posterior Lesion

Lesion is seen on both views

CC



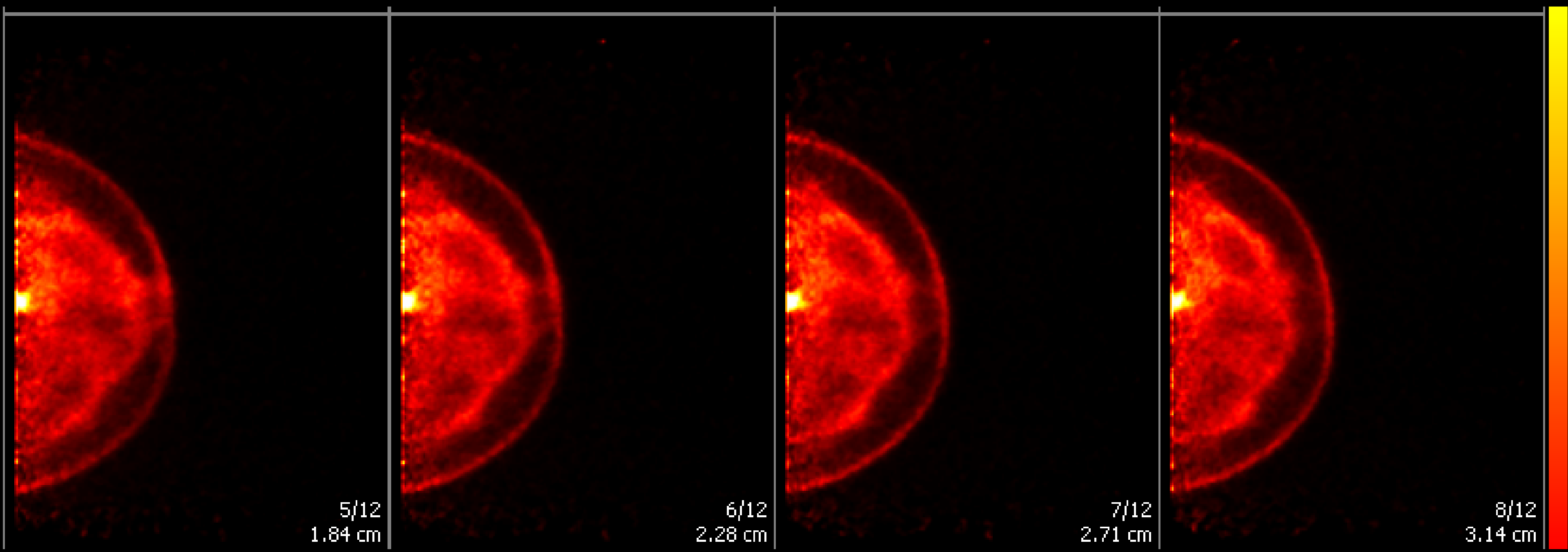
MLO



Case 2: Posterior Lesion

Lesion easily distinguished from edge noise artifacts

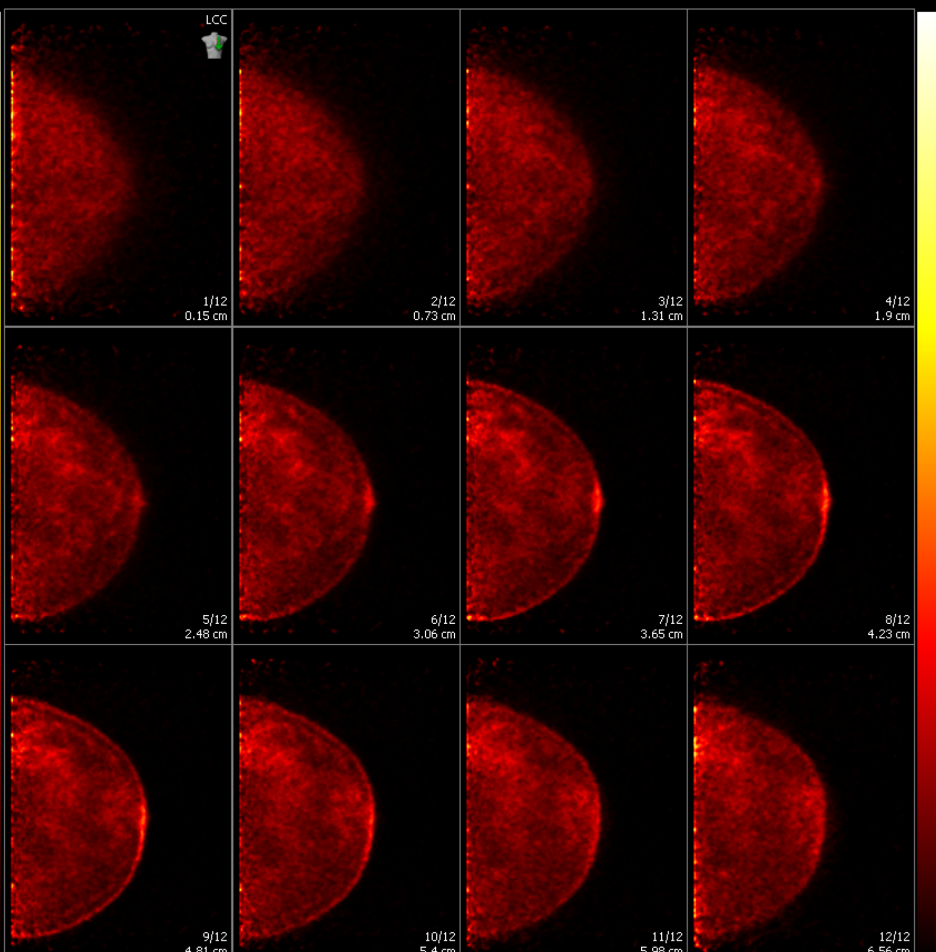
CC



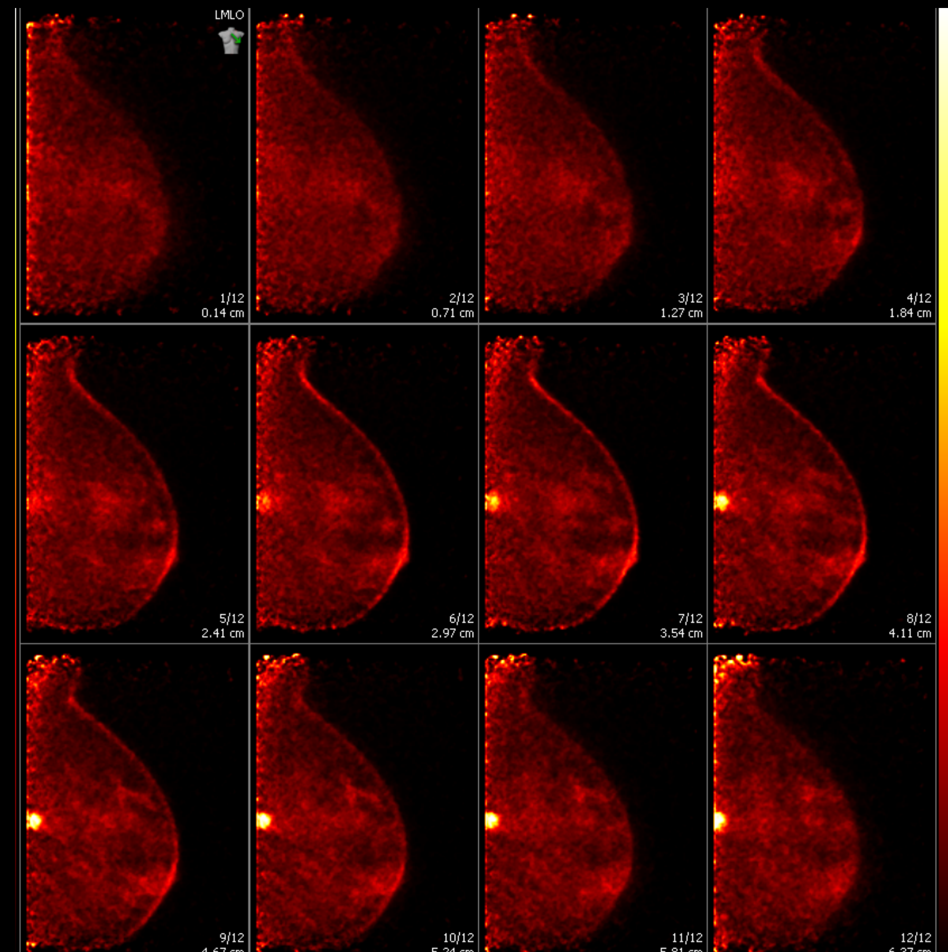
Case 3: Posterior Lesion

Lesion seen on only one view

Missed on CC view



Seen on MLO view



Learning Objectives

1. Understand the differences between whole-body PET and PEM

- Spatial Resolution
  - PEM systems designed to have better spatial resolution (1-2 mm vs. 5-10 mm)
  - This comes at the cost of field-of-view
- Photon-Detection Sensitivity
  - Closer proximity of PEM detectors increases geometric sensitivity
  - Allows lower dose/faster imaging/longer uptake time
- Tomography vs. Tomosynthesis
  - Isotropic vs. anisotropic spatial resolution
  - Some PEM systems are tomographic

Learning Objectives

2. Understand the differences between mammography and PEM

- Transmission vs. Emission Imaging
  - Transmission: known x-rays shot through subject, measure number emerging
  - Emission: radio-tracer administered internally, measure number emerging
- Anatomical vs. Functional Imaging
  - Anatomical: tissue density in mammo., little or no info. about biological activity
  - Functional: accumulation of injected physiological molecule; little anatomical info.
- Planar vs. Tomosynthesis (or Tomographic)
  - Planar is single projection view with considerable tissue overlap
  - Tomosynth./tomographic is 3-dimensional volumetric image
- Utilities, cost, dose, …
  - PEM is an emerging technology still undergoing clinical development
  - PEM provides complementary info. to mammo., and will likely be used after mammo.
  - PEM will likely be more costly, and have higher dose than mammo.

Learning Objectives

3. Possible Clinical Applications/Indications for PEM

- Screening Level ????
  - Not likely for general purpose screening (cost, dose)
  - Perhaps for certain high-risk groups for which mammo. in known to be less effective
- DCIS Characterization ????
  - High resolution and diverse tracers (FDG, FES, FLT, FMISO) could elucidate DCIS
- Disease Extent for Surgical Planning
  - Identify multi-centric/multi-focal/bi-lateral disease for surgical treatment planning
- Therapy Selection and Monitoring
  - Use early response scans to determine if therapy is having an effect
  - Periodic scan to follow therapy efficacy

Learning Objectives

4. Clinical Operation & Requirements of PEM Scanning

- Patient Handling
  - Fast prior to scan (lower blood glucose (FDG))
  - 60+ min. between injection and scanning
  - Potentially lower dose than whole-body PET
  - Patient positioning
    - similar to mammography (Naviscan PEM Flex)
    - prone on other PEM systems

- Facilities Needs
  - Hot lab, uptake room
  - Depends on particular PEM scanner
    - Mammography-size suite (PEM Flex)
    - Larger room required for other prototypes

Acknowledgements

James Rogers, M.D., John Edwards, M.D.

Jennifer Coburn, Kris Kohn, Joiem Kawas

Swedish Cancer Institute

Paul Kinahan, Tom Lewellen

UW Radiology