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

Nuclear Emission Imaging: Single Photon & PET

Lawrence MacDonald, PhD
University of Washington
Department of Radiology
Seattle, WA

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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

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![Diagram of emission and PET imaging](image-url)
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

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
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 $[99m$Tc]-Sestamibi after Neoadjuvant Chemotherapy for Locally Advanced Breast Carcinoma Predicts Survival

Dunnwald et al, CANCER 103(4), 2005
Conclusions: 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**

- 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

... 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 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 make PET useful for determining the extent of disease or to assess therapy response.

Bubank & Mankoff, Sem Nucl Med 2003

PET is a noninvasive imaging method that is useful for lesion 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 unsuspected micrometastases. PET has been shown to be superior 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 mechanisms remain unclear. FDG uptake in the lesion may represent increased glucose metabolism or may be specifically altered. 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.
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

Cadmium Zinc Telluride (CZT)
direct gamma ray conversion

Dillon 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)

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)
Simulated energy spectra:

- 3.8% FWHM (140 keV)
- 15% FWHM (140 keV)

Simulation:

**EFFECT OF ENERGY RESOLUTION ON SCATTER FRACTION AND TUMOR CONTRAST**

LumaGEM standard collimator

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

tumor location: chest wall/middle/nipple

Hruska IEEE TNS 2008
Gamma Camera Collimator Optimization

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

<table>
<thead>
<tr>
<th>Detector</th>
<th>CZT pixel size (mm)</th>
<th>Collimator</th>
<th>Hole shape</th>
<th>Material</th>
<th>Hole length (cm)</th>
<th>Hole diameter (mm)</th>
<th>Septal thickness (mm)</th>
<th>Theoretical geometric efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMI LumaGem</td>
<td>1.6</td>
<td>GMI Standard</td>
<td>Hexagonal</td>
<td>Lead</td>
<td>2.50</td>
<td>2.54</td>
<td>0.30</td>
<td>$6.1 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GMI Optimized</td>
<td>Square, registered</td>
<td>Tungsten</td>
<td>0.94</td>
<td>1.225</td>
<td>0.375</td>
<td>$9.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>GE Discovery NM 750b</td>
<td>2.5</td>
<td>GE Standard</td>
<td>Square, registered</td>
<td>Lead</td>
<td>3.47</td>
<td>2.26</td>
<td>0.24</td>
<td>$2.9 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GE Optimized</td>
<td>Square, registered</td>
<td>Lead</td>
<td>2.10</td>
<td>2.10</td>
<td>0.40</td>
<td>$6.0 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

Resolution @ 3cm + increase per cm distance from collimator:

- 4.8mm + 1.26 mm/cm
- 5.6mm + 1.26 mm/cm
- 4.5mm + 0.95 mm/cm

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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

**dual 20° angle collimator:**

- first view
- move collimator
- second view

Separately: slanted collimator (15°) available for imaging closer to the chest wall
Planar single-photon + planar mammography
University of Virginia

SPECT + CT
Duke University


<table>
<thead>
<tr>
<th>Target</th>
<th>Tracer</th>
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<tbody>
<tr>
<td>Perfusion</td>
<td>TI-201 Thallous Chloride</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Sestamibi</td>
</tr>
<tr>
<td></td>
<td>Tc-99m tetrofosmin</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>Tc-99m EC-glucosamine</td>
</tr>
<tr>
<td>Hormone receptor</td>
<td>I-123 estradiol</td>
</tr>
<tr>
<td>HER2</td>
<td>In-111 trastuzumab</td>
</tr>
<tr>
<td>Cell proliferation/angiogenesis</td>
<td>Tc-99m maraciclatide</td>
</tr>
<tr>
<td></td>
<td>In-111 bevacizumab</td>
</tr>
<tr>
<td>Amino acid transporters &amp; protein synthesis</td>
<td>Tc-99m methionine</td>
</tr>
<tr>
<td></td>
<td>I-123 methyltyrosine</td>
</tr>
<tr>
<td>Cell surface receptor (VPAC1)</td>
<td>Tc-99m VPAC1</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Tc-99m EC-annexin V</td>
</tr>
<tr>
<td>Somatostatin receptors</td>
<td>In-111 octreotide</td>
</tr>
</tbody>
</table>
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 cm² detectors
- limited-angle (tomosynthesis)

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

- 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

lima et al., JNM 2012
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

<table>
<thead>
<tr>
<th>Institute</th>
<th>Detector Technology</th>
<th>Citation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke</td>
<td>PMT</td>
<td>Turkington <em>IEEE NSS/MIC Conf. Record</em>, pgs. 1883-86</td>
<td>2002</td>
</tr>
<tr>
<td>BNL</td>
<td>APD</td>
<td>Ravindranath <em>IEEE NSS/MIC Conf. Record</em>, pages 3315–17</td>
<td>2009</td>
</tr>
<tr>
<td>Shimadzu</td>
<td>PMT</td>
<td>Furuta <em>IEEE NSS/MIC Conf. Record</em>, pages 2548-52</td>
<td>2009</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>PMT</td>
<td>Zhang <em>IEEE TNS</em> 57(1):104-110</td>
<td>2010</td>
</tr>
<tr>
<td>UW</td>
<td>GM-SiPM</td>
<td>MacDonald <em>IEEE NSS/MIC Conference</em></td>
<td>2011</td>
</tr>
</tbody>
</table>

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

Patient study:
- O-Shape: 9/76 lesions outside FOV
- C-Shape: 6/76 lesions outside FOV

Furuta et al., 2009 IEEE NSS/MIC Conference Record
lima et al., JNM 2012
Limited-Angle vs. Full Tomography

Simulation

Reconstruction

O-Shape

C-Shape

Standard MAP

UBT-enhanced MAP

Measured

C-shaped

Full-ring

(a) hot rod in the air

(b) hot rod in the background

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

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
2. Protein Metabolism
3. Proliferation
4. Hypoxia
5. Receptor
6. Blood Flow
7. Membrane biosynthesis
8. Vascularity

- $^{18}$F-FDG
- $^{11}$C-Methionine
- $^{11}$C-Thymidine
- $^{18}$F-Fluorothymidine
- $^{18}$F-FMISO
- $^{18}$F-Estradiol
- $^{64}$Cu-VPAC1
- $^{15}$O-H$_2$O
- $^{11}$C-Choline
- $^{11}$C-acetate
- $^{18}$F Integrins

This list focuses on oncology and is not exhaustive
**PEM-PET Scanner: West Virginia University**

**Fully Tomographic (360°)**

- Detectors:
  - $2 \times 2 \times 15 \text{ mm}^3 \text{LYSO + PS-PMT}$
  - $15 \times 20 \text{ cm}^2$ 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.
UC Davis Dedicated Breast PET/CT

Detectors:
- 3 mm x 3 mm x 20 mm LYSO + PS-PMT
- 11.9 x 11.9 cm² rotating detectors (2)
- 3D MAP tomography
- 2.5 mm FWHM resolution average
- CT – cone beam
- prone patient

Breast PET/CT

DCE-MRI

correlated results

Histology

Bowen et al., JNM 2009

Slides courtesy of Ramsey Badawi, UC Davis
- ‘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 

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 

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