Advances and Future Directions in Molecular Breast Imaging
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The authors have no disclosures.
Breast Cancer Facts

+250,000
New cases of breast cancer each year

+42,000
Female breast cancer deaths each year

28%
5-year survival rate for metastatic BC

Top 10 Cancers by Rates of Cancer Deaths
All Types of Cancer, United States, 2018

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Rate per 100,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and Bronchus</td>
<td>34.8</td>
</tr>
<tr>
<td>Female Breast</td>
<td>19.8</td>
</tr>
<tr>
<td>Prostate</td>
<td>18.9</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>13.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11.1</td>
</tr>
<tr>
<td>Liver and Intrahepatic Bile Duct</td>
<td>6.6</td>
</tr>
<tr>
<td>Ovary</td>
<td>6.3</td>
</tr>
<tr>
<td>Leukemias</td>
<td>6.0</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>5.1</td>
</tr>
<tr>
<td>Corpus and Uterus, NOS</td>
<td>5.0</td>
</tr>
</tbody>
</table>

What is Molecular Breast Imaging?

Conventional systems
Scintimammography

Breast-specific
gamma imaging

CZT-based
gamma camera

PEM/PET

NM Breast-dedicated Modalities
Molecular Breast Imaging

Protocol

Patient preparation:
• Follicular phase of the menstrual cycle preferred, between days 2 and 12
• Fast for 3 hours prior to the study
• Warming blanket on arrival

Exam protocol:
• 6–8 mCi (222–296 MBq) of 99mTc-sestamibi intravenously
• Light breast compression (about 5 lbs [2.3 kg])
• 7 minutes per view, total of 28 minutes
• Eight images in the craniocaudal (CC) and mediolateral oblique (MLO) views

Indications

• Preoperative Staging in Newly Diagnosed Breast Cancer
• Evaluation of Response to Neoadjuvant Chemotherapy
• Detection of Local Breast Cancer Recurrence
• Breast Cancer Screening
• MBI as Adjunct to Conventional Breast Imaging for Problem Solving in Indeterminate Cases
Molecular Breast Imaging

Findings and Reporting

Reference to screening mammogram

Background uptake intensity
- Mild, moderate, severe

Lesion Uptake intensity
- Compared to subcutaneous fat
- Mild, moderate, severe

Mass uptake

Nonmass uptake
- Distribution
- Symmetry

Associated findings
- Nipple, axilla, vessel uptake


Mass like uptake

Non mass like uptake
Molecular Breast Imaging

Summary

**Advantages**
- Well-tolerated by patients
- Increased breast cancer detection rate in women with dense breast tissue
- Safe radiation level
- Inexpensive
- Guided tissue biopsy available for suspicious lesions identified on MBI

**Limitations**
- Requires injection
- Long scanning time
- May need cross-over expertise in nuclear medicine and breast imaging

**Future**
- Providing prognostic information
- Theranostics
What is PEM/dedicated breast PET?

Whole body PET CT limitations in breast cancer:
- Limited assessment of primary lesions
- Low nuclear grade
- Invasive lobular carcinoma
- Ductal carcinoma in situ
- Small tumors (<1cm)

- PEM and dbPET to increase sensitivity for small lesions
- dbPET provide substantial gain in spatial resolution (from 5-6mm to 1-2mm)
- First PEM system comprised two planar bismuth germanate detectors (20-mm thick) coupled to position-sensitive photomultiplier tubes
- The system co-registered with mammograms

Figure 1. PEM instrument (PEM-I). Left: Photograph in the mammographic clinic shows the instrument attached to the cassette holder of the x-ray mammographic system. Right: Cross-sectional diagram shows the layout of the detectors and the details of patient positioning during clinical scanning.

Murthy K et al. 2000
PEM/dedicated breast PET

Indications

• Currently, no ACR or SNMI clinical practice parameters

Initial staging

PEM vs MRI:

**Berg et al. N=388:**
- PEM comparable sensitivity, greater specificity, and similar additional disease detection (51% for PEM and 60% for MRI)

**Schilling et al. N=208:**
- PEM and MRI comparable sensitivity and specificity

Patient with biopsy proven invasive mammary carcinoma in which MRI failed to demonstrate index lesion. On PEM the focal uptake corresponding to the lesion is demonstrated. Schilling K et al. Eur J Nucl Med Mol Imaging. 2011.

Monitoring response to neoadjuvant chemotherapy

• Identify non responders, surgical planning
• Distinguishing recurrent carcinoma from scar

F18 estradiol Whole Body PET-CT

**Indications**
- Critical role in tumor heterogeneity
- Defining etiology of endocrine resistance
- Problem-solving
- Staging or restaging low metabolic rate breast cancer

**Interfering medications**
- ER modulator
- ER down regulator—may reduce detection of ER+

**Protocol**
- 3-6 mCi FES injection
- 45-60 min uptake time
- Injection away from site of known primary breast cancer
- Include all known lesions in the FOV

**Limitations**
- High liver uptake interfere with hepatic metastases assessment
- Bowel excretion
- Less brain uptake

**Improved depiction of low metabolic breast tumor subtypes. Ulaner et al: Comparison between F18 estradiol and F18 FDG for lobular carcinoma showing improved depiction of metastatic disease with F18 estradiol.**

**Possible benefit of combined FDG and F18 estradiol (FES): Bottoni et al:**
- Single assessment could not predict overall disease-free survival
- Only FDG correlated with progression free survival (lower receptor expression, higher metabolic rate = lower degree of cellular differentiation)
- FES/FDG ratio correlated with overall survival
Radioimmunotherapy

Principles

- Isotopes conjugated to mAb
- Target cancerous cells
- Protect healthy cells
- Minimally invasive
- Short treatment

D’Huyvetter M et al. 2021: Phase 1 clinical trial of $^{131}$I-GMIB-anti-HER2-VHH1

- Safe and stable after administration, with rapid clearance in healthy volunteers
- Tracer accumulated in metastatic sites of patients with stage IV HER2-positive breast cancer
- Patients who have progressed on trastuzumab, pertuzumab, or trastuzumab emtansine, given its different mode of action
AI in Molecular Breast Imaging – Classifying BPU

- Artificial intelligence based techniques such as machine learning and convolutional neural networks, have made headway into different subtypes of breast imaging, most notably in mammography, and CT.
- The applications to molecular breast imaging are relatively understudied but show great promise.
- One study completed in 2021 showed that CNN's could be applied to automatically and accurately characterize the background parenchymal uptake (BPU) of breast tissue, an independent marker for malignancy risk. This correlates with tissue density seen on mammograph.
- This objectivizes BPU to minimize inter-observer and intra-observer variability. It also provides objective characterization of BPU in patients undergoing tamoxifen or aromatase inhibitors.
- Further investigations will look into how marked BPU uptake differs from radiotracer uptake as in a tumor.

Radiomics based on $^{18}$F-FDG PET/CT to differentiate breast carcinoma from lymphoma

- In one study published in 2021, standardized uptake values were combined with radiomic features obtained from $^{18}$F-FDG PET/CT to accurately classify breast tumors into carcinoma or lymphoma.
- When combined with clinical information, the model was able to accurately characterize with AUC of 0.867 and 0.806.

Summary

- Breast dedicated molecular imaging provides safe, inexpensive breast cancer detection rate in women with dense breast tissue
- Guided tissue biopsy available or under development for suspicious lesions identified on MBI, PEM, and db-PET systems
- Breast dedicated modalities may require cross over expertise or nuclear medicine and breast imager radiologists
- Continued research looking at noninvasive prognostic tools that are well-tolerated by patients and account for tumor heterogeneity
- Great potential of radionuclides and radiopharmaceuticals for breast cancer treatment with promising alternative for HER2 positive patients with progression after trastuzumab treatment
References


