Clinical Utility of Positron Emission Tomography Scanning in Breast Cancer Management

David Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging

In Memory: Edward V. Staab, M.D., co-author
You can find talk at...

radiology.emory.edu
MR/PET has completed its final design stage and is now operational. The PET/CT scanner is located in the Siemens factory in the Center for Nuclear Imaging (CNI) at the Wesley Wood Library. This unique arrangement is one of only two sites in the world where such a device is available. The unit has the capacity for simultaneous, simultaneous brain imaging. This device promises to allow the evaluation of human neural processing not previously possible.

Read more...

As a member of the Steering Committee for the Gently Campaign, Dr. Applegate has contributed to the awareness of reducing unnecessary radiation exposure to children. This campaign, led by the Alliance for Radiation Safety in Pediatric Imaging, is the leading national, weekly magazine for radiology professionals.

Read more...

**New Publication**


The research done in Dr. Hui Mao's lab collaborating with Dr. Lily Yang's lab in the Department of Surgery has lead to the development of a new biomarker targeted molecular imaging diagnostic of breast cancer.

Read more about the work in [MR Research](#).
Clinical Divisions - Nuclear Medicine & Molecular Imaging

The faculty of the Emory Division of Nuclear Medicine & Molecular Imaging offers the highest quality patient care, incorporating the latest knowledge, innovation and equipment. Nuclear Medicine not only uses the most advanced methods, but also helps set the bar for the field. All of the physicians are board-certified in nuclear medicine, and some are double-boarded in other fields, particularly Radiology, many have national and international reputations in their fields.

Equipment includes PET/CT and SPECT/CT scanners at Emory University Hospital (Dudley Hills campus) and Emory University Hospital Midtown. We offer a wide variety of specialized nuclear medicine therapies including those for thyroid cancer, bone cancer pain palliation, lymphoma, neuroendocrine tumors and Y-90 liver therapy in cooperation with Interventional Radiology. Research devices at our disposal include one of the few PET-MR units in the world, a high-resolution brain PET scanner, micro-PET for animal research, and a research cyclotron. A full range of nuclear medicine and PET/CT services are also provided at Grady Memorial Hospital and the Atlanta VA Medical Center.

The Division is integrally involved in research conducted by the Emory University School of Medicine faculty, including close collaboration with colleagues in radiology and cardiology and at the Emory Winship Cancer Institute. Our faculty are principal investigators and co-investigators on many research grants including those sponsored by the NIH.

- David M. Schuster, MD
  Director, Division of Nuclear Medicine and Molecular Imaging

Recent Accomplishments

Southeastern Chapter Society of Nuclear Medicine
Friday, Sept 25
David Schuster, MD

Practical PET-CT of the GI Tract
View Presentation

Montefiore Medical Center Visiting Professor
at the University Hospital for Albert Einstein College of Medicine
November 9 & 10
David Schuster, MD

PET-CT in Breast Cancer
View Presentation

Practical PET-CT of the GI Tract
View Presentation

Top Atlanta Doctors
Objectives

• Our shared objective is to decrease breast cancer morbidity and mortality

• Review current data supporting use of FDG PET in patients with breast cancer

• Understand the role of molecular imaging in diagnosis, staging, and therapy
Take Aways

• FDG PET:
  – Whole body imaging has limited value in detection and initial nodal staging
  – Useful for high risk, recurrence and restaging
  – Useful monitoring and predicting outcome
  – New devices and agents are promising
Good Review Papers

Also more recent


AND

$^{18}\text{F-FDG}$ Concentration in the Cell Is Proportional to Glucose Metabolism

GLUT

Glucose $\rightarrow$ Glucose $\rightarrow$ Glk-6-P $\rightarrow$ Glycogen $\uparrow$

Glycolysis

Pyruvate $\rightarrow$ Oxidation

$\uparrow$

Hexokinase II

FDG $\leftarrow$ FDG $\leftarrow$ FDG-6-P $\leftarrow$ FDG

Glucose

FDG
Malignant Versus Benign

• FDG is nonspecific

• Normal cells utilize glucose

• Malignant cells use more glucose than benign cells for energy
Biologic Correlates of FDG Uptake In Human Breast Cancer Measured by PET

- Glut-1 expression (FDG transportation)
- Hexokinase expression (enter metabolic pathway)
- Mitotic activity index
- Number of lymphocytes
- Tumor cells/volume
- Microvessel density
- Amount of necrosis

Biologic Correlates of FDG Uptake In Human Breast Cancer Measured by PET

- Most significantly related to SUV:
  - Tumor size
  - Histological grade and type
  - Ki-67
  - Estrogen receptor (negative)

*Gil-Rendo et al. Br J Surg 2009;96:166*
NCCN 2009

• PET/CT noted only for:
  – Invasive stage 3
  – Recurrent
  – Stage 4

• Generally discouraged
  – except when other studies equivocal or suspicious; biopsy more useful

• Not our experience
  – And what do others say….?
CMS

**Approved**

- Staging of patients with distant metastasis
- Restaging of patients with locoregional recurrence or metastasis
- For monitoring response to therapy
  - When a change in therapy is contemplated

**Not Approved**

- Initial diagnosis of breast cancer
- Axillary lymph node staging and surgical planning
PET/CT
Patient Preparation

- Fasting: at least 4-6 hours
- Make sure no IV dextrose is being given
- Check glucose (<150-200)
  - Increased insulin, decreased sensitivity
- Full history
  - Last surgery, chemo, radiation
  - Old or correlative studies
Protocol

- 10-15 mCi of FDG IV
  - Contralateral to breast lesion
- Wait quietly in a room for 60-90 min
- Image after emptying bladder
- Most image supine with arms up
- Typical skull base to mid-thigh
- PET-CT imaging: 20-30 minutes
Novel PET-CT Techniques

• Dual time point imaging
  • Mavi et al. J Nucl Med 2006;47:1440
  • Cancer: slightly increased uptake with time
  • Normal and inflammation: no change to slightly decreased
  • Change is $\leq 10\%$

• Whole body PET/CT Mammography
  • Prone imaging in special cradle after WB PET
Interpretation

• Non-physiologic uptake over background
• The hotter it is, the more likely cancer
  – Beware false pos/neg
• Must integrate all data
  – Cannot just look at images for what is hot

• SUV Variability
  – Time from injection to image
  – Body composition weight/Fat
  – Blood glucose/Insulin
  – Lesion size
    • Partial volume
  – Technical factors
  – Not just $\text{SUV}_{\text{max}}$ but extent of uptake
FDG Uptake in Breast – Variants

• False positives:
  – Dysplasia
  – 10% fibroadenomas
  – Ductal ectasia
  – Inflammation/infection
  – Post-surgical
  – Silicon leak
  – Fat necrosis
  – Even a bee sting

• False negatives:
  – Lesions < 1 cm
  – Tubular carcinoma
  – Lobular carcinoma
  – Carcinoma in-situ

• Diffuse Uptake
  – Dense breasts
  – Menstrual cycle
  – Lactating breasts
FDG Uptake in Breast – Benign Variants

Normal Breasts

Breast tissue uptake – young adult
FDG Uptake in Breast – Benign Variants

Inflammation – Breast Implants
FDG Uptake in Breast – Benign Variants

Post-surgical inflammatory changes
FDG Uptake in Breast CA– Benign Variants

Benign “brown” fat uptake
FDG Uptake in Breast CA – Benign Variants

Lymph node uptake from dose infiltration
Breast Cancer – Initial Assessment

1) Clinical examination

2) Imaging
   - Mammography
   - Ultrasound
   - MRI

3) Needle biopsy

4) Staging

PET plays biggest role in staging and restaging
## Staging

### American Joint Committee on Cancer (AJCC) TNM Staging System For Breast Cancer

#### Primary Tumor (T)
Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by the physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **Tis (DCIS)**: Ductal carcinoma in situ
- **Tis (LCIS)**: Lobular carcinoma in situ
- **Tis (Paget’s)**: Paget’s disease of the nipple with no tumor

Note: Paget’s disease associated with a tumor is classified according to the size of the tumor.

- **T1**: Tumor 2 cm or less in greatest dimension
  - **T1mic**: Microinvasion 0.1 cm or less in greatest dimension
  - **T1a**: Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
  - **T1b**: Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
  - **T1c**: Tumor more than 1 cm but not more than 2 cm in greatest dimension

- **T2**: Tumor more than 2 cm but not more than 5 cm in greatest dimension

- **T3**: Tumor more than 5 cm in greatest dimension

- **T4**: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
  - **T4a**: Extension to chest wall, not including pectoralis muscle
  - **T4b**: Edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
  - **T4c**: Both T4a and T4b
  - **T4d**: Inflammatory carcinoma

#### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to movable ipsilateral axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in ipsilateral infracavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supracavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in ipsilateral infracavicular lymph node(s)</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)</td>
</tr>
<tr>
<td>N3c</td>
<td>Metastasis in ipsilateral supracavicular lymph node(s)</td>
</tr>
</tbody>
</table>

*Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Staging continued on next page (ST-2)
Table 1 (continued)

Pathologic (pN)*

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)</td>
</tr>
</tbody>
</table>

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

<table>
<thead>
<tr>
<th>pN0(i-)</th>
<th>No regional lymph node metastasis histologically, negative IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0(i+)</td>
<td>No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)*</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)*</td>
</tr>
</tbody>
</table>

*Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

RT-PCR: reverse transcriptase/polymerase chain reaction.

<table>
<thead>
<tr>
<th>pN1</th>
<th>Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent***</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1mi</td>
<td>Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastasis in 1 to 3 axillary lymph nodes</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*</td>
</tr>
</tbody>
</table>

| pN1c      | Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden) |

<table>
<thead>
<tr>
<th>pN2</th>
<th>Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN2a</td>
<td>Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN2b</td>
<td>Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pN3</th>
<th>Metastasis in 10 or more axillary lymph nodes, or in infracavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN3a</td>
<td>Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infracavicular lymph nodes</td>
</tr>
<tr>
<td>pN3b</td>
<td>Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*</td>
</tr>
<tr>
<td>pN3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

** Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Staging continued on next page (ST-3)
**Table 1 (continued)**

**Distant Metastasis (M)**
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TIS</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
</tbody>
</table>

* T1 includes T1mic

**HISTOPATHOLOGIC GRADE (G)**
All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended.

The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3-5 points is grade 1; a combined score of 6-7 points is grade 2; a combined score of 8-9 points is grade 3.


**HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Low combined histologic grade (favorable)</td>
</tr>
<tr>
<td>G2</td>
<td>Intermediate combined histologic grade (moderately favorable)</td>
</tr>
<tr>
<td>G3</td>
<td>High combined histologic grade (unfavorable)</td>
</tr>
</tbody>
</table>

**HISTOPATHOLOGIC TYPE**

The histopathologic types are the following:

- **In situ Carcinomas**
  - NOS (not otherwise specified)
  - Intraductal
  - Paget's disease and intraductal

- **Invasive Carcinomas**
  - NOS
  - Ductal
  - Inflammatory
  - Medullary, NOS

Medullary with lymphoid stroma
Mucinous
Papillary (predominantly micropapillary pattern)
Tubular
Lobular
Paget's disease and infiltrating
Undifferentiated
Squamous cell
Adenoid cystic
Secretory
Cribriform

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit [www.cancerstaging.net](http://www.cancerstaging.net).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.
FDG PET in Breast Cancer
Clinical Applications

Detection of the Primary Lesion
Initial Lymph Node Assessment
Evaluation of Distant Metastasis / Bony Metastasis
Monitoring Response to Chemotherapy
Monitoring Response to Hormonal Therapy
Recurrence
50 y/o woman, recently diagnosed right breast ductal carcinoma.

No adenopathy or distant metastasis
Primary Lesion

  - 144 patients with 185 breast tumors
  - pT1, only 30/44 (68%) breast carcinomas were detected, compared with 57/62 (92%) at stage pT2
  - 65% lobular carcinomas false-negative (65%) compared with ductal carcinomas (24%)
  - PET scans: high PPV (97%) for breast cancer

• **Scheidhauer et al. EJNM 2004;31:S70**
  - Overall PET for primary lesion
    • 64-96% sensitivity
    • 73-100% specificity
Detection of Primary Breast Cancer

- Most false negatives
  - Small size (<1cm)
  - Low-grade malignancies (tubular or lobular Ca)
  - Diffuse growth pattern

Avril, et al. JNM 2001;42:9
But may be good for problem cases such as implants and dense breasts
Diagnosis: Summary

• Initial promise in the primary diagnosis of breast cancer
  – Later studies pointed out limitations
  – Lack of sensitivity with small lesions

• Role to play in a select group of patients
  – Dense breasts or with implants and other surgery
  – Localizing primary tumor in patients with metastases of breast origin when mammography/MRI is indeterminate
  – Patients in which biopsy is not a desirable option

• Any incidental FDG avid breast lesion merits evaluation

• *Discussion so far is for whole body scanners…*
But Now on the Horizon... PEM

Detection of Primary Breast Carcinoma with a Dedicated, Large-Field-of-View FDG PET Mammography Device: Initial Experience

Eric L. Rosen, MD
Timothy G. Turkington, PhD
Mary Scott Soo, MD
Jay A. Baker, MD
R. Edward Coleman, MD

Published online 10.1148/radiol.2342040654
Radiology 2005; 234:527-534
Duke PEM Device

  - 23 patients, 24 lesions
  - 18 TP
  - 1 TN
  - 2 FP (fat necrosis)
  - 3 FN (1 DCIS, 2 IDC)
Malignant:
Invasive ductal Ca, Grade 3
Apocrine features
Focal mucinous differentiation
1.0 X .8 X .7cm
Guiding Surgery: Multifocality

Courtesy Mary Beth Lobrano M.D., East Jefferson General Hospital, Metairie LA
PEM Multicenter Trial

  - 94 patients w/ known or suspected lesions
  - 90% sens, 86% spec, 88% accuracy
  - 1/2 T1a, 4/6 T1b, 7/7 T1c
  - 3/4 invasive lobular
  - But had mammos, knew index lesion
  - 9/15 non-index positive were benign
  - Partially funded by Naviscan which makes FDA approved PEM device
PEM

- Higher resolution, less attenuation
- Shorter imaging time
- Can correlate with mammography
- Biopsy guiding device now available
  - *Phys Med Biol* 2008;53;637
- FDG still issues with nonspecificity
- More work and multi-center trials required
Scintimammography

- Single photon radiotracer
  - Tc99m Sestamibi
    - Localizes to cancer through various mechanisms
- Whole body scanner limited resolution
- False positive:
  - Benign lesions
  - Inflammation
  - Fat necrosis
Scintimammography

- Now like PEM, high resolution small FOV gamma cameras
- Early results promising
  - *Bern et al. Radiology 2008;247:651*
- Large comparative trials needed
- New device from Duke combines SPECT and CT for 3D volumetric imaging of the breast
FDG PET in Breast Cancer
Clinical Applications

Detection of the Primary Lesion
Initial Lymph Node Assessment
Evaluation of Distant Metastasis / Bony Metastasis
Monitoring Response to Chemotherapy
Monitoring Response to Hormonal Therapy
Recurrence
Can PET take Place of Axillary Nodal Dissection/SLN?

- Early studies weighted to advanced breast cancer
- Sensitivity depends on axillary tumor burden and uptake in primary tumor

- Prospective multicenter, 360 patients (not PET/CT)
  - 61% sensitivity; 80% specificity
  - Small and fewer axillary nodes, more false negative
51 y/o Woman, Ductal Adenocarcinoma
Baseline FDG PET: Initial Staging
PET Versus SLN?

- Consensus is NO

  - 236 patients; PET-CT
  - Interpretation geared for highest sensitivity
  - All SLN; full ALND if PET or SLN positive
  - 37% sensitivity; 96% specificity
Staging – Lymph Nodes

- Sentinel lymph node dissection
  - High sensitivity and specificity to avoid unnecessary full axillary dissections

- FDG PET is not of sufficient sensitivity
  - To take the place of fine sectioning and immunohistochemical lymph node evaluation

- Because of high positive predictive value, PET can obviate a sentinel lymph node procedure
  - Backed up by US or image guided sampling
Staging – Lymph Nodes

• Suspected high-risk disease (e.g. LABC)
  – PET can detect IM and supraclavicular nodes as well as distant metastases

  – May be especially useful for inner quadrant lesions
    • *J Nucl Med.* 2005 Sep;46(9):1455
      – 6 x incidence on PET of isolated extra-axillary mets
      – Triple risk for disease progression

  – *Nason et al, Cancer* 2000;89:2187
    • Increased false negative SLN rate after neoadjuvant chemotherapy for LABC
FDG to Detect Mediastinal or Internal Mammary Metastases

- **Eubank et al; J Clin Oncol 2001;19:3516**
  - Retrospective 92 patients
    - High frequency advanced disease
  - PET: 85% sens; 90% spec; 88% accuracy
  - CT: 50% sens; 83% spec; 70% accuracy
  - Upstaged 10/33

- May help guide decision and field for radiation therapy in high risk disease
Breast Cancer with IM Node on PET (also axillary nodes)

Correlated with MR as well
Mediastinal and Liver Metastases
FDG PET in Breast Cancer
Clinical Applications

Detection of the Primary Lesion
Lymph Node Assessment
Evaluation of Distant Metastasis / Bony Metastasis
Monitoring Response to Chemotherapy
Monitoring Response to Hormonal Therapy
Recurrence
Distant Disease

• Systemic staging not useful with early stage breast cancer (unless suspicion)
  – Low incidence metastases
  – Possibility false positives

• But with high risk such as LABC and IBC and Stage 2 and 3, evidence for use
  • Chia et al. J Clin Onc 2008;26:786
PET Excellent for WB Staging

  - 117 pre-op patients: PET more accurate for LN and distant

  - 69 patients with new LABC
  - Sens 93%; Spec 85%
  - Contrast CT better than PET for liver
  - PET better for other organs, regions

- Above for PET alone
PET-CT for Distant Staging

- **Carkaci et al. JNM 2009;50:231**
  - 41 patients with inflammatory breast cancer
  - PET-CT found 20 patients with distant disease (7 unsuspected)

- **Alberini et al. Cancer 2009 30;115:5038**
  - 59 patients with inflammatory breast cancer
  - PET-CT useful for nodes and distant disease
  - 31% distant lesions
  - Prognostic information
PET-CT for Distant Staging

- *Dirisamer et al. Eur J Rad 2009 Jan 30*
  - PET/CT +c in 52 patients with suspected recurrence
  - 42/52 had metastases
  - CT: 28/42; PET:34/42; PET/CT: 40/42
    - most improvement of PET/CT over PET due to lung
FDG PET-CT Staging

70 y/o woman, infiltrating ductal carcinoma grade III (7x6x5 cm), s/p recent mastectomy and axillary dissection (+2/14 nodes)
Multifocal Breast Carcinoma with Axillary Nodes

Unexpected sternal met and IM node
33 y/o woman, infiltrating ductal carcinoma, s/p partial right mastectomy, axillary dissection, chemotherapy and radiation therapy
FDG PET
Unsuspected Disease

Extensive malignant lymphadenopathy

Skeletal metastasis unsuspected on CT
Controversy: Detection of Bone Metastases in Breast Cancer

- “FDG PET has superior accuracy in detecting bone metastases (in comparison to Tc99m MDP)”

- “---PET is superior to bone scan in detecting bone metastases” American Society of Clinical Oncology

- Tc99m MDP bone scan is much more sensitive than FDG PET in breast cancer patients.
  Uematsu AJR 2005;184:1266
Bone Metastases in Breast Cancer

Nakai et al, EJNM 2005;32:1253

- 89 patients both FDG and MDP (Planar + SPECT)
- 55 with bone metastases
- Relative visualization rate

<table>
<thead>
<tr>
<th>Type</th>
<th>FDG</th>
<th>MDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblastic</td>
<td>55.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Mixed</td>
<td>94.7%</td>
<td>84.2%</td>
</tr>
<tr>
<td>Invisible</td>
<td>87.5%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Overall: PET 83.1% accuracy MDP 79.8%
18F PET

- 18F Fluoride PET and PET-CT more accurate than bone scanning
  - Even-Sapir et al. JNM 2004;45:272

- Iaguru et al. JNM 2009;50:501
  - Cocktail of 18F-FDG and 18F
  - One session PET-CT
  - Good pilot data
  - (But response criteria may be confusing)
Natural History of Treated Bone Metastases in Breast Cancer

- *Tateishi et al. Radiology 2008;247:189*
  - Increased density on CT and decreased SUV
  - Predictors of response duration

  - FDG PET/CT better reflects true tumor activity
  - FDG avidity predicts survival difference
Incidental Cancers

Incidental bilateral ovarian cancer found during staging for breast cancer
Staging - Metastases

- PET is superlative in this group of patients to detect distant disease

- Bone scan is sensitive for purely blastic lesion, while PET more sensitive for lytic

- PET/CT may be optimal since sclerotic lesions will be seen on CT portion
  - More studies

- Start with PET/CT
  - If negative, and suspect bone, obtain bone scan
PET/CT and Whole-Body MRI Complementary

- **Antoch et al. JAMA 2003;290:3199**
  - PET correct TNM 75/98; WBMRI correct 53/98
  - MRI more sensitive for bone and liver
  - PET/CT more sensitive for lung and nodes

- **Schmidt et al. Eur J Rad 2008;65:47**
  - WBMRI: 93% sens, 86% spec, 91% accuracy
  - PET-CT: 91% sens, 90% spec, 91% accuracy
  - PET-CT superior for nodal disease
  - Another study with bone metastases by the same group showed higher sensitivity for WBMRI but specificity for PET-CT
FDG PET in Breast Cancer
Clinical Applications

Detection of the Primary Lesion
Lymph Node Assessment
Evaluation of Distant Metastasis / Bony Metastasis
Monitoring Response to Chemotherapy
Monitoring Response to Hormonal Therapy
Recurrence
Prognostic Significance of FDG-PET in Breast Cancer

• *Oshida et al. Cancer 1998;82:2227*
  – 70 women with primary breast cancer
  – Multivariate analysis:
  – SUV is an independent predictor of disease-free survival (inversely)
  – Correlation between SUV and microvessel density
Clinical Need: Determine the Response to Therapy

- Histopathologic response – gold standard
- Anatomic criteria (WHO, RECIST) inadequate
- Questions:
  - Is the tumor responding?
  - Can one provide an early assessment of response?
  - Can one determine residual disease post-therapy?
FDG PET for Evaluating Chemotherapy Response

- Most PET series with neoadjuvant therapy
- Most studies at mid-therapy
  - Primary tumor decline of $\leq 50\%$ baseline SUV predicts good response
- Some studies with early PET (1-2 cycles) predict better discrimination
- Presence of uptake on PET after chemotherapy predictive of relapse
  - But absence of uptake is not sensitive for pCr
FDG PET to Monitor Breast Cancer Response to Therapy: Mid-Therapy

(Wahl, J Clin Oncol 11:2101, 1993)
Early PET to Monitor Response


- PET after first and second course chemotherapy
  - Compared with baseline scan in 22 patients

- Histopathology gold standard

- After the first course of chemotherapy
  - All responders correctly identified (SUV ≤ 55% baseline)
  - Sensitivity 100%, specificity 85%
Early PET to Monitor Response

- *Rousseau et al. J Clin Onc 2006;24:5366*
- 64 patients stage 2 and 3
- 60% decrease SUV predicts responders
  - One course: 61% sens, 96% spec
  - Two courses: 89% sens, 95% spec

- Studies depend on how close one looks
  - Combined total and near total in pCR group
  - But are a few cells important?
Metastases: Response to Therapy

  - After chemotherapy, 17 metastatic lesions responded.
  - In those lesions
    - SUV decreased to 72% +/- 21% after the first cycle
    - 54% +/- 16% after the second cycle.
  - Uptake in lesions not responding (n = 9)
    - Declined only to 94% +/- 19% after first cycle
    - 79% +/- 9% after the second cycle.
  - Differences between responding and nonresponding lesions statistically significant after the first (P = 0.02) and second (P = 0.003) cycles.
Extensive breast cancer pleural implants in the left chest, and after one dose of kinase inhibitor after which the implants resolved.
PET and MRI are Complementary

  - 16 lesions in 15 women LABC before and after neoadjuvant chemotherapy
  - PET correctly predicted lack of response (5/6)
  - MRI predicted non response correctly (0/6)
  - MRI predicted complete response 100%
  - PET more accurate in predicting pathologic NR
  - Complete response by MRI correlated well with macroscopic pathologic complete response
FDG PET in Breast Cancer
Clinical Applications

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Recurrence
Metabolic Flare: Indicator of Hormone Responsiveness in Advanced Breast Cancer


- 40 women with advanced ER-positive (ER+) breast cancer
- PET before and 7 to 10 days after tamoxifen therapy
- Responders:
  - Tumor FDG uptake increased (28.4% +/- 23.3%)
- Nonresponders:
  - No significant change (10.1% +/- 16.2%)
- Conclusion: Results of PET are predictive of responsiveness to tamoxifen therapy in patients with advanced ER+ breast cancer.
Summary: Monitoring Tumor Response with FDG/PET

• Valuable for prognostic information and following response to therapy
  – Minimal residual tumor cannot be reliably detected

• Residual disease present if focal uptake after therapy

• Responding tumors show greater decrease in relative uptake to baseline
  – Identify nonresponders earlier

• Use a combination of $\geq 50\%$ SUV decline and visual analysis, but no well defined universal criteria
Summary: Monitoring Tumor Response with FDG/PET

- Timing of scan relative to treatment is important
  - Early versus midpoint versus completion

- Careful attention to detail of PET scans is needed
  - Same scanner, same uptake time, partial volume

- Standardized multi-center trials needed

- Other PET probes?
FDG PET in Breast Cancer

Clinical Applications

Detection of the Primary Lesion
Lymph Node Assessment
Evaluation of Distant Metastasis / Bony Metastasis
Monitoring Response to Chemotherapy
Monitoring Response to Hormonal Therapy
Recurrence
Recurrence

• Detection of early recurrence may have important survival benefit
• Increase in serum tumor markers
• Signs and symptoms suggesting recurrence, but negative or equivocal conventional studies
• Difficult to differentiate true recurrence from post-surgical and radiation sequelae
Useful to Detect Metastases

• *Radan et al. Cancer* 2006;107:2545
  – 47 patients with increased tumor markers
  – Sens 90%; Spec 71%; Accuracy 83%
  – Performed significantly better than CT
  – Changed management in 51%

  – 60 patients with suspected recurrence
  – Locoregional: Sens 89%; Spec 84%; Accuracy 87%
  – Distant: Sens 100%; Spec 97%; Accuracy 98%
Meta-analysis of FDG-PET for Breast Cancer Recurrence and Metastases

- 808 patients
- 1013 lesions
- Results
  - Sensitivity 92.7%
  - Specificity 81.6%
  - False positive 11%
Patient with cancer recurrence in the right breast and skin implants

and an unexpected vertebral body metastasis…
Summary: Recurrence and PET

- Great efficacy with suspected recurrence
- Surpasses utility of conventional imaging modalities for whole body evaluation
  - Complementary to MR
- False positives can be problematic
  - Experience and PET(CT) help
    - *Fueger et al. Mol Imaging Biol 2005;7:369*
      - PET-CT restaged 89.7% correctly
On the Horizon

• How can PET and other imaging correlate and integrate with novel biomarkers such as circulating tumor cells for therapy response

• *De Giorgi et al. J Clin Onc 2009;27:3303*
  – Mid-therapy CTC counts and PET predicted overall survival
  – CTC better in multivariate analysis

• More research needed
Other New (and Old) Agents

• Tumor perfusion and angiogenesis
  – $^{15}$O H$_2$O
  – Dynamic FDG PET

  – High metabolism relative to perfusion associated with poor response

    • Combined PET/dynamic contrast CT
    • Metabolism and perfusion
Other New (and Old) Agents

- Receptor Imaging
  - $^{18}$F FES (Fluoroestradiol)
    - ER expression, predicts response to therapy
  - Radiolabelled trastuzumab (HER2)

- Tumor biosynthesis
  - Lipid: $^{18}$F FCH, $^{11}$C Choline, $^{11}$C-Actetate

- Cellular proliferation
  - $^{18}$F FLT (fluorothymididine)

- Cell death (apoptosis)
  - $^{99m}$Tc-Annexin
In Conclusion…

- PET has utility in patients with:
  - Suspected distant metastases
  - Evaluate locoregional extent in the high-risk patient
  - Detect recurrence and monitor response to therapy
  - Changed management in 10-50% of selected patients

- WB PET does not have sufficient sensitivity as a primary screening or initial staging modality
  - Useful as a problem solving tool
  - Initial staging in high-risk disease due to its high positive predictive value
In Conclusion…

- FDG PET more accurate for lymph node and distant metastasis compared to conventional imaging
  - Does not take the place of SLN
- Differentiates responders from non-responders early in the course of chemotherapy
- Prognostic accuracy superior to conventional imaging studies
- More sensitive than bone scan for lytic bone marrow metastases (bone scan is more sensitive for sclerotic lesions)
  - PET/CT may make this point moot
And .....

- Don’t forget, breast cancer in men
  - 60 year old veteran with right lumpectomy positive for cancer
  - Negative mammo left
  - PET performed
  - Unsuspected contralateral cancer