Clinical Utility of Positron Emission Tomography Scanning in Breast Cancer Management

David Schuster, MD
Director, Division of Nuclear Medicine and Molecular Imaging
Department of Radiology and Imaging Sciences
Emory University

In Memory: Edward V. Staab, M.D., co-author
COI

- No specific COI
- Dr. Schuster involved in Emory University commercial grants
Take Aways

• FDG PET:
  – Indicates level of glycolysis in normal and abnormal tissues
  – Whole body imaging has limited value in detection and initial axillary nodal staging
  – Useful for high risk, recurrence and restaging
  – Useful for monitoring treatment response and predicting outcome
Let’s Start With a Patient…

- 50 year old woman, right breast mass
- Grade 2 infiltrating lobular carcinoma
- ER positive, PR positive, HER-2/neu negative
- Palpable right axillary nodes, but moveable
  - no other suspicious findings
- Clinical stage IIIA – T2, N2, M0
- PET-CT performed to assess treatment options
Clinically LABC

Uptake in breast, axilla, IM, supraclavicular, mediastinum, liver, and also…
Clinically LABC

...spine

This is an example of how PET-CT can provide one stop shopping in the right patient population...
What is PET?

Not This…
PET/CT
Positron Imaging

- Inject patient with a radiotracer with an unstable nucleus – positrons emitted
- Positrons are anti-matter to electrons
- Positron meets electron – Gets annihilated – Two 511 KeV photons imaged
  - (not positron)
$^{18}$F-FDG Concentration in the Cell Is Proportional to Glucose Metabolism (GLUT 1 and 5)
Malignant Versus Benign

- Malignant cells use more glucose than benign cells for energy
- FDG is nonspecific
  - Normal cells utilize glucose too
Biologic Correlates of FDG Uptake In Human Breast Cancer on PET

- Glut-1 expression (FDG transportation)
- Hexokinase expression (enter metabolic pathway)
- Mitotic activity index
- Histology grade
- P53 mutation
- Tumor cells/volume
- Microvessel density
- Amount of necrosis
- ER, PR status
  - High with triple negative
- Uptake inversely correlates with prognosis (DFS and OS)

Wang et al. AJR 2011;197:W247; Morris et al. Cancer 2012 [EPUB]
PET-CT

- Fasting: at least 4-6 hours
- Bring any prior outside studies
- Check glucose (<150-200)
  - Increased insulin, decreased sensitivity
- FDG IV
  - Contralateral side of primary breast lesion
- Image supine with arms up
- 10-30 minutes
Platform Table

Patient in position #1 – CT plane.

Patient in position #2 – PET plane
SUV

• SUV variability even ideally ≈ 10-20%
  – Time from injection to image
  – Body composition weight/Fat
  – Blood glucose/Insulin
  – Lesion size
    » Partial volume
  – Technical factors
  – Not just SUV$_{\text{max}}$ but extent of uptake

• Must integrate all data
  – Cannot just look at images for what is hot
  – Do not base treatment decisions on small changes in SUV alone
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

Post-surgical inflammatory changes
Lobular Carcinoma Causing Gastric Outlet Obstruction

Subtle non-avid infiltrative much better seen with contrast CT
When Should PET Be Used?

- **NCCN 2012**
  - Not indicated for stage 1, 2 or operable 3
  - Optional for T3, N1, M0
  - Discouraged for routine evaluation of recurrent or metastatic disease
  - Most helpful when other studies are equivocal/suspicious especially with LABC

- **ASCO**
  - Routinely in metastatic and recurrent breast carcinoma in patients with clinical suspicion

- **CMS**
  - Staging of patients with distant metastasis
  - Restaging of patients with locoregional recurrence or metastasis
  - Monitoring response to therapy
Let’s Break it Down
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 with Whole Body PET

  - 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
But may be good for problem cases such as implants and dense breasts
Incidental Cancers

- Any incidental FDG avid breast lesion merits evaluation
  - Cancer in 37.5-56% incidental breast uptake on PET
    - Kang et al. AJR 2011;197:341

- Also, incidental other primary cancers found on PET

Incidental bilateral ovarian cancer found during staging for breast cancer
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?

- 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
PET Excellent to Detect Mediastinal or IM Metastases

- *Eubank et al; J Clin Oncol 2001; 19: 3516-3523*
  - 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
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

- **Niikura et al. Oncologist 2011;16:1111**
  - 225 retrospective study from MD Anderson
  - For distant metastases:
    - PET/CT 97.4% sensitivity; 91.2% specificity
    - CI 85.9% sensitivity; 67.3% specificity
      » CT, ultrasound, bone scan, plain film
Bone Scan

33 y/o woman, infiltrating ductal carcinoma, s/p partial right mastectomy, axillary dissection, chemotherapy and radiation therapy
Unsuspected Disease

Extensive malignant lymphadenopathy

Skeletal metastasis unsuspected on CT
Controversy: PET in Early Stage Breast Carcinoma

- Why the fuss?
  - Rapid growth in all advanced imaging including PET in stage 1-2 breast carcinoma

![Graph showing % Having Modality over time with markers for FDA Approval and CMS Approval]
What’s the Fuss?

  - 375 patients prospective multicenter stage 1 and 2
    - T1=207, T2=110, T3=8
    - For ALN PET specificity 99.6%, sensitivity 23.7% (not news)
    - PET positive 15 for distant mets: TP=5, FP=10

- **Editorial by David Mankoff et al J Clin Onc 2012;30:1252**
  - Do the math…
    - At low disease prevalence even a highly accurate test will have far more FP vs TP and result in low yield
    - But in advanced and recurrent disease prevalence rises and also more aggressive disease so greater FDG uptake
Mirrored in Other Studies…

- **Groves at al. The Oncologist 2012;17:613**
  - Stage 1-2 (not clear how distributed)
    - 5/70 PET positive but 2/5=TP, 3/5=FP

  - 256 patient retrospective with N2 (62%) and N3 (38%)
    - Stage 4 (not just by PET) in 16%
    - T0/T1=0%; T2=6%; T3=22%; T4=36%

- **ACR Appropriateness Criteria for Stage 1 Breast Carcinoma**
  - Any advanced imaging including PET = 2/10
  - No survival difference or QOL intense surveillance vs symptomatic imaging
Key Papers Push Back

  – 131 patient prospective: 2A=36, 2B=48, 3A=47
    • PET and conventional imaging including CT
    • Staging modified 5.6% 2A, 14.6% 2B, 27.6% 3A, 56% 3A (N2)
    • 2B and operable 3A (similar) 13% change stage
    • PET better than CI, fewer FP than bone scan (1 vs 4)

• Bernsdorf et al. Annals Oncology 2012;23:2277
  – 103 patients with tumors ≥ 2cm
    • PET 12 extraAx LN; 2 new primary; 6 distant
    • PET change management N(-)=6%; N(+)=18%
    • They recommend using for T2 lesions or above
PET Useful for IBC Distant Staging

- **Carkaci et al. JNM 2009;50:231**
  - PET-CT found 20/41 IBC patients with distant disease
    - 7 unsuspected

- **Alberini et al. Cancer 2009;115:5038**
  - For IBC, PET added nodal and distant disease detection
    - Prognosis (SUV >5 and distant disease worse)
Show Me the Cutoff!

- Certainly not stage 1 and probably not 2A
- Good case can be made for 2B, especially bad actors histologically and node positive and/or IBC
- Reasonable to do systemic staging with stage 3
  - PET done well and backed up by biopsy
- If clinical suspicion use even for early stage

- Chia et al. J Clin Onc 2008;26:786
What to Use?

- Best to know your population and how well PET is performed and read at your facility
- In general FDG PET-CT much more accurate than conventional imaging for distant disease
  - *Nikura et al. The Oncologist 2011;16:1111*
65 year old asymptomatic IDC clinical stage IIA, T2 N0 grade 2, status post lumpectomy with sentinel lymph node biopsy: now pT2 N1a.

Post op changes right breast.
Uptake left 3rd rib, right ilium, proximal right femur.
MR guided biopsy ilium positive for metastasis.

Must be willing to biopsy for proper use of PET.
Bone Metastases in Breast Cancer

- Nakai et al, EJNM 2005;32:1253
  - 89 patients both FDG and MDP (Planar + SPECT)

<table>
<thead>
<tr>
<th></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>

- Most papers strongly supports PET-CT over bone scan
  - Han et al. Acta Radiol 2011;52:1009

- PET better for treatment response; no chemo flare
- Start with PET/CT
  - If negative, and suspect bone, obtain bone scan
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
FDG PET for Evaluating Chemotherapy Response

- Overall consensus is early or mid-therapy PET better predictor of ultimate response
  - Poor response on PET predictive of treatment failure
  - Absence of uptake is not sensitive for pCr

- Studies have heterogenous tumor phenotypes/methodology
  - Yet, initial FDG uptake and response is predicated on histology, type and even sequence of chemotherapy
    - Scheider-Kolsky et al. Br Ca Res 2010;12:R37
    - Humbert et al. Annals Onc 2012 [EPUB]
Early PET to Monitor Response

  - 20 patients all triple negative
  - Epirubicin + cyclophosphamide +/- docetaxel
  - PET after 2 cycles
  - Evaluated surgically and 20 month followup
  - <42% decline in SUV, 100% predictive non-pCR
  - 44% early relapse PET NR; 0% for PET responders

  - < Δ 15% PET response 100% predictive non-pCR
  - PET response correlated with RFS (85% vs 44%), not OS
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

- PET more accurate in predicting pathologic NR
- Complete response by MRI correlated well with macroscopic pathologic complete response

- **Dose-Schwarz et al. Br J Cancer 2010;102:35**
- **Park et al. Acta Radiol 2011;52:21**
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
Response to Hormonal Therapy

  - 40 women with advanced ER-positive (ER+) tumors
  - PET metabolic flare 7 to 10 days after tamoxifen treatment
  - Greater flare correlates with response

  - 22 patients ER+ Her-, PET baseline and 10 weeks follow-up
  - PET response correlated with PFS (but not OS)
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
PET Excellent for Recurrence

- Detection of early recurrence may have important survival benefit
  - With CI, difficult to differentiate true recurrence from postsurgical and radiation sequelae, but PET-CT performs well

- **Manohar et al. Nucl Med Comm 2012;33:591**
  - Sensitivity 98.7%; Specificity 85.3%

- **Dirisamer et al. Eur J Rad 2010;73:294**
  - Sensitivity 93%; Specificity 100%

- **Radan et al. Cancer 2006;107:2545**
  - Changed management in 51%
Recurrence and Metastases

- **Grasetto et al. Eur J Rad 2010**
  - 89 patients with elevated Ca 15-3
  - negative conventional imaging
  - 40/89 disease detected; 23/40 solitary; 7/23 CR
  - Recommend do not wait for clinical symptoms
    - *Lucky for patients NCCN was not strictly followed*

- Multiple other studies similar results
  - **Aukema et al. EJSO 2010;36:387**
  - **Champion et al. Cancer April 15, 2011 [EPUB]**
Patient with cancer recurrence in the right breast and skin implants

and an unexpected vertebral body metastasis…
Summary

• WB PET does not have sufficient sensitivity as a primary screening or initial axillary staging modality
  – May be useful as a problem solving tool
  – **Does not take the place of SLN to detect minimal disease**
  – But high PPV, can obviate SLN
    • Backed up by US or image guided sampling

• Radiation Oncologist may want to know how many nodes positive but hard to tell after neoadjuvant response
  – Pathology may not be reliable to evaluate by treatment effect
    • PET high PPV to count nodes on pre-therapy scan if one had been performed for LABC
Summary

• PET has utility in patients with:
  – Suspected distant metastases
  – Evaluate locoregional extent in the high-risk patient
  – Detect recurrence and monitor response to therapy
  – Change management in up to 50%

• FDG PET more accurate for lymph node and distant metastasis compared to conventional imaging
  – Not worthwhile routinely for stage 1 and 2A
  – My breakpoint somewhere in 2B - 3 territory
  – More sensitive than bone scan for most lesions
    • Start with PET, then go to bone scan if still suspicion
    • In general as bone lesion responds, becomes sclerotic on CT and FDG uptake decreases.
      » Unlike bone scan flare.
Summary

• Prognostic information and following response to therapy
  – Early or mid-therapy PET better predictors than post-therapy
  – Lack of PET response highly predictive for residual disease
    • minimal residual tumor cannot be reliably detected
  – No well defined universal criteria for PET response
    • multi-center trials needed with individual phenotypes and standardized PET methodology

• Great efficacy with suspected recurrence
  – Surpasses conventional imaging for whole body evaluation
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