Clinical Utility of Positron Emission Tomography Scanning in Breast Cancer Management

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

• No specific COI

• Dr. Schuster involved in Emory University commercial grants
  – Blind reader Amyvid Post-Market Study

• American Imaging Management Specialty Physician Advisory Panel
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)
- Uptake positively correlates with pCR after neoadjuvant chemo

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 2013**
  - Better than earlier versions
  - Not indicated for stage 1, 2 or operable 3
  - Optional for locally advanced or higher (Stage 3a and above) including IV/recurrent
  - “Encouraged” for IBC
  - 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

PEM and BSGI subject of a separate talk
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

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Recurrence
Can PET take Place of Axillary Nodal Dissection/SLN?

- Consensus is NO

- **Veronesi et al. Annals Onc 2007;18:473**
  - 236 patients; PET-CT
  - Interpretation geared for highest sensitivity
  - All SLN; full ALND if PET or SLN positive
  - 37% sensitivity; 96% specificity

- PET-CT more accurate than ultrasound
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

- Guide decision and field for radiation therapy in high risk disease by detecting level 3, supraclavicular and IM nodes
Breast Cancer with IM Node on PET (also axillary nodes)

Correlated with MR as well
FDG PET in Breast Cancer

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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
FDG PET
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
What’s the Fuss?

• *Pritchard et al. J Clin Onc 2012;30:1274*
  
  – 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

  
  • 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

• **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

- **Groheux, et al. JNCI 2012;104:1879**
  - 254 patient prospective: 2A=44, 2B=56, 3A=63, 3B=74, 3C=17
    - PET-CT changed stage in 30.3%
    - Staging modified 4.5% 2A, 16.1% 2B, 31.7% 3A, 51.4% 3B, 47.1% 3C
    - PET better than CI, fewer FP than bone scan (3 vs 7)

- **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

  - 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
  - Groheux et al. Radiology 2013;266:388
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
  – Chest CT better for small lung nodules
• 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)

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<th>FDG</th>
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<tr>
<td>Osteoblastic</td>
<td>55.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Osteolytic</td>
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<td>70%</td>
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<tr>
<td>Invisible</td>
<td>87.5%</td>
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- 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
Breast CA Mixed Bone Lesions

- Sclerotic sternum hot on bone scan, but not hot on PET

- Right sacrum non-sclerotic lesion not hot on bone scan but hot on PET

Actually very mild diffuse uptake on bone scan post MR guided biopsy
FDG PET in Breast Cancer
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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 heterogeneous tumor phenotypes/methodology uptake parameters (SUV vs TLG) and definition of histopathologic response
  - Yet, initial FDG uptake and response is predicated on histology, type and even sequence of chemotherapy
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

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

- Pretreatment SUV should be high enough to detect meaningful change; low SUV may indicate chemotherapy resistance
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*
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Recurrence
Response to Hormonal Therapy

  - 40 women with advanced ER-positive (ER+)
  - PET metabolic flare 7 to 10 days after tamoxifen
  - Greater flare correlates with response
    - *Initial agonist effect before antagonist predominate*

  - 22 patients ER+ Her-, PET baseline and 10 weeks
  - PET response correlated with PFS (but not OS)
FDG PET in Breast Cancer

Clinical Applications

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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%
Not Recommended for Asymptomatic Surveillance

  - Breast Cancer Follow-Up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update
  - Use of CBCs, chemistry panels, bone scans, chest radiographs, liver ultrasounds, computed tomography scans, positron emission tomography, magnetic resonance imaging, or tumor markers (carcinoembryonic antigen, CA 15-3, and CA 27.29) is not recommended for routine breast cancer follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination
Recurrence and Metastases

  - 89 patients with elevated Ca 15-3 and negative exam
  - Negative conventional imaging
  - 40/89 disease detected; 23/40 solitary; 7/23 CR
  - Recommend do not wait for clinical symptoms
    - *Lucky for patients ASCO was not strictly followed*
    - *Perhaps more study is needed*

- Multiple other studies similar results
  - Aukema et al. EJSO 2010;36:387
  - Champion et al. Cancer 2011;117:1621
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

- 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

• Do not routinely use advanced imaging for asymptomatic surveillance (more than 6 months-1 year after CR)
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