Clinical Utility of PET 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…
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)

- Glucose
- FDG

GLUT

Hexokinase II

Glycolysis

Glycogen

Pyruvate

Oxidation

Glucose → Glk-6-P → Glycogen

Pyruvate → Oxidation

Glucose → Hexokinase II → Glk-6-P

FDG → Hexokinase II → FDG-6-P

FDG Concentration in the Cell Is Proportional to Glucose Metabolism (GLUT 1 and 5)
Biologic Correlates of FDG Uptake in Human Breast Cancer on PET

- Glut-1/hexokinase expression
- Mitotic activity index
- Histology grade
- P53 mutation
- Tumor cells/volume
- Microvessel density
- Amount of necrosis

- ER, PR status
  - High with triple negative and HER2
  - Lower with Luminal A
- Uptake inversely correlates with prognosis (DFS and OS)
- Uptake positively correlates with pCR after neoadjuvant chemo
  - High proliferation increases likelihood of pCR, but survival advantage mitigated by tumor biology

PET-CT

• Fasting: at least 4-6 hours except water
• Check glucose (<150-200)
  – Increased insulin, decreased sensitivity
  – Differences in BGL will affect comparability of SUV
    • Many research studies exclude BGL>130-160
• 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 $\approx 10\text{-}20\%$
  - Uptake time, body habitus, BGL/insulin
  - Lesion size
    - Partial volume
  - Not just $\text{SUV}_{\text{max}}$ but extent of uptake
- GCSF within 3 weeks and chemotherapy within 1 month may alter FDG 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
    - usually mild
  - Ductal ectasia
  - Complex cysts
  - Fibrocystic change
  - Inflammation/infection
  - Post-surgical/hematoma
  - 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

*Benveniste et al. Eur J Rad 2014;83:919*
FDG Uptake in Breast – Benign Variants

Post-surgical inflammatory changes
Mastitis in a Male with Hot Axillary Node
Lobular Carcinoma Causing Gastric Outlet Obstruction

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

• **NCCN 2014**
  - 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
    • (may obviate need for other studies)
  - “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**
  - Initial and 3 post-treatment
    • Staging of patients with distant metastasis
    • Restaging of patients with locoregional recurrence or metastasis
    • Monitoring response to therapy
Payers Selective and Misleading Use of Literature

- Push back from payers e.g. insisting on a bone scan and full body CT scans before PET, and then only if “equivocal or suspicious” (not defined as negative)

- Guideline of one payer says:
  - *Bone scan should be the initial study for bone pain or suspicion of skeletal disease, unless neurologic compromise is evident. Bone scan has similar concordance with PET scan for detecting bone metastasis (J Clin Oncol 2010;28: 3154-3159).*

- **Title of paper:** *Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer*
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/MBI subjects of a separate talk.

Evidence that FDG adds specificity to MR:

Bitencourt et al. Eur J Rad 2014;83:1381
Babe et al. JNM 2014;55:736
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 for breast cancer management
  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 Excellent for Mediastinal or IM Metastases

- **Eubank et al; J Clin Oncol 2001;19:3516-3523**
  - PET: 85% sens; 90% spec; 88% accuracy
  - CT: 50% sens; 83% spec; 70% accuracy
  - Upstaged 10/33

- **Seo et al. EJNM 2014;41:438**
  - Used any minimal IM uptake as positive; PPV 87.1%

- **Guide decision and field for radiation therapy in high risk disease by detecting level 3, supraclavicular and IM nodes**
  - **Koolen et al. Br Ca Res Tr 2012;135:231**
  - **Choi et al. J Breast Ca 2013;16:202**
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?

  
  – 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
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 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)

- **Yeh et al.** Radiographics 2013;33:2003
  - Nice review on inflammatory breast cancer
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
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

65 year old asymptomatic IDC clinical stage IIA, T2 N0 grade 2, status post lumpectomy with sentinel 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

  - 89 patients both FDG and MDP (Planar + SPECT)

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<th>Type</th>
<th>FDG</th>
<th>MDP</th>
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<tr>
<td>Osteoblastic</td>
<td>55.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>100%</td>
<td>70%</td>
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<tr>
<td>Mixed</td>
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<tr>
<td>Invisible</td>
<td>87.5%</td>
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- Most authors 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 manubrium hot on bone scan, but not hot on PET

Right sacral non-sclerotic lesion, not hot on bone scan but hot on PET
FDG PET in Breast Cancer
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Recurrence
FDG PET to Monitor Breast Cancer Response to Therapy: Mid-Therapy

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

  - 50 patients all triple negative; 30.3 month mean followup
  - Epirubicin + cyclophosphamide +/- docetaxel
    - 20 EC-D; 30 SIM (nonuniform therapy regimes)
  - PET after 2 cycles; 126 mg/dl cutoff for blood glucose
  - >42% decline SUVmax; pCR 59%; 3 yr EFS 77.5%
  - <42% decline in SUV; 0% pCR; 3 yr EFS 47.1%

- Other well designed studies by others with different tumor biology and NAC regimens similar findings but varying cut points (e.g. NEO-ALTTO used Δ15%)
  - Gebhart et al. JNM 2013;54:1862
  - Humbert et al EJNM 2014;41:416
FDG PET for Neoadjuvant Chemotherapy Response

• Problem: Studies have heterogenous tumor phenotypes/methodology, uptake parameters (SUV vs TLG), definition of histopathologic response, overlap of FDG response on ultimate responders vs NR

• Yet, initial FDG uptake and response is predicated on histology, type and even sequence of chemotherapy
PET with NAC to Monitor 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

- But despite low sensitivity for pCR, molecular imaging helpful for assessing overall biologic behavior
  - Sampling error
  - FDG PET response has prognostic significance
  - Support use of alternative therapy with lack of PET response
    - Encourage increased post-therapy surveillance
PET and MRI for NAC
Complementary or Superfluous?

- MR volumes correlate better with Miller-Payne grading than PET SUV and complete MRI response correlates well with macroscopic pathologic complete response.
- PET more accurate in predicting pathologic NR
- Will PEM or other tracers make a difference?
Monitoring Therapy for Metastatic Disease

• **Question:** Outside clinical trial, when is PET-CT adequate in deciding when to change therapy for metastatic breast cancer and when is a diagnostic CT needed with reference to RECIST for progressive disease?

• **Answer:** Traditional approach is certainly RECIST but anatomic imaging inadequate since metabolic response can be uncoupled from morphologic
  – Use at least 20-30% change in SUV
  – Appearance of new lesions
  – PERCIST if available
Monitoring Therapy for Metastatic Disease

- **Kostakoglu D. Sem Nucl Med 2013;43:229**
  - Mounting evidence that FDG PET is most accurate technique to assess response at end of therapy
- Also early identification non-responders useful
  - Chemotherapy may have modest survival advantage
  - Patient offered palliative therapy
Monitoring Therapy for Metastatic Disease

- Bone disease is nonmeasurable on CT
  - FDG PET-CT especially useful
    - As lesion treated, uptake decrease and increased sclerosis
    - Can find new activation in prior dormant disease

- New CMS guidelines limits 3 post-therapy PETs
  - Use wisely
    - If easily measurable on CT, use CT most often
    - Baseline PET-CT, then mid-therapy and then at end
      - Add PET for equivocal CT
      - And clinical progression despite negative CT
Extensive breast cancer pleural implants in the left chest, and after one dose of kinase inhibitor after which the implants resolved.
FDG PET in Breast Cancer

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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)

  - Trial of Letrozole and Bevacizumab; 20% decrease SUVmax
  - Strong association between improved PET and cCR and pCR
FDG PET in Breast Cancer

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Recurrence
PET Excellent for Recurrence

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

- \textit{Manohar, et al. Nucl Med Comm 2012;33:591}
  - Sensitivity 98.7%; Specificity 85.3%

  - Sensitivity 93%; Specificity 100%

  - Changed management in 51%

  - Accurate on or off HT
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*
    - *More study is needed*

- **Multiple other studies similar results**
  - Aukema, et al. EJSO 2010;36:387
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
  – Useful as a problem solving tool
  – **Does not take place of SLN**
  – 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
  – Histology 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
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

• 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)
• 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