Clinical Utility of PET in Breast Cancer Management

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In Memory: Edward V. Staab, M.D., co-author
No COI
Talk can be found at radiology.emory.edu
Emory Department of Radiology and Imaging Sciences

Mission Statement

Emory Department of Radiology and Imaging Sciences serves the community through advanced innovation, translational research and clinical application of imaging sciences. The department is committed to excellence in scholarship and to the training of the next generation of radiologists, technologists, and imaging scientists. The department's goal is to provide the highest quality patient care with predictive, diagnostic, and therapeutic imaging-based approaches.

Recent Accomplishments

3 Distinguished Investigator Award

Baowei Fei was one of 43 researchers that were selected as recipients of the Academy of Radiology Research (ARR) 2013 Distinguished Investigator Award. The Distinguished Investigator Award recognizes individuals for their accomplishments in the field of imaging research and significant contributions to the record of scientific progress and innovation. The ARR held an induction ceremony for members of its Council of Distinguished Investigators on Monday, December 2 at RSNA 2013.
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 our 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 (Clifton campus) and Emory University Hospital Midtown. We offer a wide variety of specialized nuclear medicine therapies including that 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 a high-resolution brain PET scanner, micro-PET/CT for animal research, and a research cyclotron. A full range of nuclear medicine and PET/CT services are also provided at Grady Memorial Hospital, Emory Johns Creek Hospital, and the Atlanta VA Medical Center. The Division is integrally involved in research as well as close collaboration with colleagues in Radiology, Cardiology and 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
  Associate Professor of Radiology and Imaging Sciences
  Director, Division of Nuclear Medicine and Molecular Imaging

Recent Conferences

Lecture: Molecular Imaging of Prostate Cancer: Beyond the Bone Scan
Lecturer: David Schuster, MD

35th Annual High Country Nuclear Medicine Conference in Vail
Feb 28-Mar 5

Lecture:
Robert Lull Memorial Lecture: Growing into Mentorship
Lecturer: David Schuster, MD
Society of Nuclear Medicine 2013 Annual Meeting June 8-12th
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)
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 and HER2
- 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
- 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 $\approx 10\text{-}20\%$
  - 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

- 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 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
Payers Selective and Misleading Use of Literature

• Review of literature suggests that while PET alone may have similar per patient sensitivity, PET-CT clearly superior to CI
  – Specificity higher in any case
  – It’s all about proper staging for proper therapy

• *Cochet et al. EJNM Oct 2013 [EPUB]*
  – Prospective 142 patient ≥ T2, CI followed by PET-CT
  – 21% upstaged, 16% downstaged by PET-CT
  – PET-CT stronger prognostic stratification than CI on multivariate analysis
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
FDG PET

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
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
    – Dunne et al. Br J Rad 2013;86:[EPUB]

• 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
Clinical Applications
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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

• 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 and may obviate SLN in locally advanced disease
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 Nov 2013 [EPUB]**
  - 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 [EPUB]**
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
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

![Chart showing trend in % Having Modality with FDA and CMS Approval dates](chart.png)
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
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 = 2/9
  - 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 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)

- **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)

<table>
<thead>
<tr>
<th>Type</th>
<th>FDG</th>
<th>MDP</th>
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<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>
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<tr>
<td>Invisible</td>
<td>87.5%</td>
<td>25%</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

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 to Monitor Breast Cancer Response to Therapy: Mid-Therapy

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

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

- **Hirakata et al. Anticancer Res 2014;34:221**
  - 37 patients NAC docetaxel followed by FEC
  - PET after 1st course docetaxel
  - 0/8 patients with < $\Delta$ 18% had cCR or cPR
  - 16/16 patients with $\geq \Delta$SUV 45% had cPR or cCR
  - Others in between
Neoadjuvant Therapy

- PET in multicenter Neo-ALTTO trial
  - **Gebhart et al. JNM 2013;54:1862**
  - 66 patients Her2 pos, mixed HR
  - Neoadjuvant lapatinib and/or trastuzumab
  - PET-CT baseline, 2 and 6 weeks then paclitaxel
    - Response change defined as SUV 15% decrease
  - Overall pCR 42% for PET responders; 21% for nonresponders
    - Less overlap with HR pos but also less pCR overall
  - May be too heterogenous population and perhaps imaging target (GLUT) not optimized for biologic target (HER2)
FDG PET for Neoadjuvant Chemotherapy Response

• Problem: Studies have heterogeneous 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

  – 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

– Other well designed studies by Groheux with different tumor biology and NAC regimens similar findings but varying cut points
  • Groheux et al. Cancer 2103 [EPUB]
  • Groheux et al. Br J Ca 2013;109:1157
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 with NAC: More Data and Longer Followup

  - Meta-analysis NAC 15 studies, 745 patients
  - Overall sensitivity 80.5%; specificity 78.8%; PPV 79.8%, NPV 79.5%
  - FP rate 11.2% PET after 1st course vs 19.3% 2nd course

- **Humbert et al EJNM Nov 2013 [EPUB]**
  - 61 patient Her2 pos, mixed NAC
  - PET after 1st course (tumor>liver uptake high metabolic at baseline)
  - ΔSUV ≤ 16% had 49.2% 5 year survival
  - Low metabolic or ≥ ΔSUV 16% had 96.2-100% survival
PET and MRI for NAC
Complementary or Superfluous?

- MR volumes correlate better with Miller-Payne grading than PET SUV
- PET more accurate in predicting pathologic NR
- Complete response by MRI correlated well with macroscopic pathologic complete response
- Will PEM or other tracers make a difference?
Response to Therapy for Metastatic Breast Cancer

  - Multivariate analysis 47 patients post-chemo PET
  - Response on PET most powerful and independent predictor of survival

- Pretreatment SUV should be high enough to detect meaningful change
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

  - 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

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+)
    - 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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Monitoring Response to Hormonal Therapy

Recurrence
PET Prognostic Biomarker

• Relationship between uptake and recurrence
    • Odds ratio 6.98 for recurrence with SUVmax>3

• SUVmax only part of story
  – MTV, TLG, others being investigated
    • Ulaner et al. Cancer Medicine 2013;2:725

• Nakajima et al. Int J Rad Onc Biol Phys 2013;87:738
  • Multivariate analysis of 1-3 node positive
  • MTV only independent prognostic factor for locoregional DFS at 3 years compared with SUV, ER status, number nodes, etc.
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

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

  - Sensitivity 93%; Specificity 100%

  - 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*
    - *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)
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