Update on PET Imaging in Breast Cancer

Surgical Oncology Network
Breast Cancer Conference

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Medical Director, BCCA Centre of Excellence for Functional Cancer Imaging

Why PET?

- Isotopes of naturally occurring elements
- High sensitivity
- Accurate quantification
- Whole body scan capability
- High clinical sensitivity & specificity
Advantages of PET over Anatomical Imaging

- Functional change often precedes anatomical change
- Benign vs malignant
- Post-treatment change vs recurrence
- Ideally suited for pre-clinical and clinical imaging of cancer biology

Potential Role for PET

- Characterization of breast lesions
- Axillary lymph node staging
- *Restaging/detection of recurrent disease
- *Evaluation of response to treatment

*Medicare approved for reimbursement in USA
Normal Variants and Biologic Correlates

- $^{18}$F-FDG uptake in breast cancer correlates with:
  - Microvasculature
  - Glucose transporter expression
  - Tumor volume
  - Proliferation rate

- FDG localization higher in:
  - Ductal vs lobular carcinoma
  - Grade 3 vs grade 1-2 carcinomas

Normal Variants and Biologic Correlates

- Increased FDG uptake may be seen in:
  - Dense breasts/young patients
  - Lactating breasts
  - Mastitis
  - Recent incisions/hematomas
  - Some fibroadenomas
  - Muscle and brown fat
Characterization of Primary Breast Cancer

- No role in detection/diagnosis of non-invasive breast cancer
- Invasive disease sensitivity 83 – 93%
- Results of FDG-PET vary as a result of the heterogeneity of breast cancers
  - False negatives: <1cm, well differentiated (tubular, lobular histologies)


<table>
<thead>
<tr>
<th>Size</th>
<th>Patients</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>12</td>
<td>42%</td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>44</td>
<td>68%</td>
</tr>
<tr>
<td>2 – 5 cm</td>
<td>62</td>
<td>92%</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>14</td>
<td>100%</td>
</tr>
<tr>
<td>Invas. Ductal</td>
<td>97</td>
<td>76%</td>
</tr>
<tr>
<td>Invas. Lobular</td>
<td>23</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Characterization of Primary Breast Cancer**

- Recent metaanalysis* showed a NPV of 88% (diagnosis missed in 12%)
- FDG-PET not suitable for breast cancer screening
- Development of dedicated PET instrumentation may increase role of PET in diagnosis of breast cancer


**Initial Staging of the Axilla**

Effectiveness for occult axillary disease

Centers for Medicare and Medicaid services (CMS)

- Metaanalysis 203 pts (4 studies) 2002
  - confirmed breast cancer
  - no palpable axillary nodes
  - no distant mets
  - PET before node dissection
Initial Staging of the Axilla

- Pooled sensitivity 81% (40-93%)
- Specificity 95% (87-100%)

Conclusions:
False negative rate for PET too high (19%)
- Axillary node sampling should remain the standard of care.

Prospective, multicenter trial 360 pts with newly diagnosed invasive breast cancer
- Mean sensitivity 61% (54-67%)
- Mean specificity 80% (79-81%)
- Nodal SUV >1.8 PPV 90% but sensitivity of 32%
**Initial Staging of the Axilla**


**Conclusion:**

- FDG-PET often fails to detect axillae with few and small nodal mets.
- Not routinely recommended for axillary staging in newly diagnosed breast cancer pts.

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**Internal Mammary/Mediastinal Lymph Node Metastases**

Eubank et al., J Clin Onc 2001; 19: 3519 – 3523

73 consecutive pts with recurrent or metastatic dx

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>54%</td>
<td>85%</td>
</tr>
<tr>
<td>Specificity</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>73%</td>
<td>88%</td>
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</table>
Left breast cancer with internal mammary lymph node metastasis

Delineating Recurrent and Metastatic Disease

Hubner et al., Clin Posit Imag. 2000; 3: 197-205

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>PET</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71%</td>
<td>85%</td>
</tr>
<tr>
<td>Specificity</td>
<td>54%</td>
<td>73%</td>
</tr>
</tbody>
</table>
76 yo woman. Tc-99 MDP bone scan shows increased uptake in lumbar spine due to degenerative change (false positive) whereas FDG-PET is normal (true neg finding).

Ohta, Nuc Med Commun 2001; 22(8): 875-879

Delineating Recurrent and Metastatic Disease


- 57 pts suspected disease recurrence
- Sensitivity 93%
- Specificity 79%

- Nonosseous mets only – Sensitivity 96%
Recurrent Breast cancer involving left axillary and supraclavicular lymph nodes. MRI interpreted as post-radiotherapy fibrosis

UCLA School of Medicine

Delineating Recurrent and Metastatic Disease

Limitations of PET:

- Lower sensitivity than bone scan for osseous mets
  - PET better than bone scan for osteolytic lesions
- Not sensitive for detecting brain mets
- Resolution

BCCA
Delineating Recurrent and Metastatic Disease

Vranjesevic et al., J Nuc Med., 2002, 43; 325-329

Prediction of Outcome by PET

61 women  Reason of PET Evaluation:
69% evaluation for residual/recurrent dx
16% evaluation of increasing tumor markers
15% suspicious findings on CT

PET done within 3 mos of CI and correlated with clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>CI*</th>
<th>PET</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>79%</td>
<td>93%</td>
</tr>
<tr>
<td>Specificity</td>
<td>68%</td>
<td>84%</td>
</tr>
<tr>
<td>NPV</td>
<td>59%</td>
<td>80%</td>
</tr>
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*Conventional imaging (X-ray, bone scan, CT, MRI, US)

PET significantly better in predicting DFS
Delineating Recurrent and Metastatic Disease

Vranjesvic et al., J Nuc Med., 2002, 43; 325-329

Kaplan-Meier estimates of disease free survival

Delineating Recurrent and Metastatic Disease

Impact on Patient Management

Yap et al., J Nuc Med, 2001; 42: 1334-1337

- Prospective survey 160 breast cancer patients
- PET changed the clinical stage in 36%
  - 28% upstaged
  - 8% downstaged
- Resulted in:
  - intermodality changes in 28%
  - intramodality changes in 30%
Evaluating Treatment Response

- Earlier recognition of ineffective therapy
  - allow change to an alternative, more effective regimen
  - avoid morbidity and costs
- Potential roles:
  - neoadjuvant (locally advanced)
  - distant metastatic disease

Metabolic change precedes anatomic change

Evaluating Treatment Response

- Rapid decrease in glucose metabolism in responders can be detected as early as after the first cycle of CTX
- Serial measurements of SUV
**Financial Considerations**

**FDG-PET is expensive**
- PET scanner ~2–5 million $CAD
- Cost per scan ~$2000
- FDG-PET can be cost-effective
  - Demonstrated in lung, colon, melanoma etc
  - PET potentially reduces ineffective/unnecessary treatment and morbidity

**Conclusions**
- Role of FDG-PET in characterizing breast cancers remains to be defined.
- PET cannot detect micrometastases and should not replace surgical staging of axillary nodes.
- PET is not indicated in the routine assessment of primary breast cancer.
Conclusions

- PET can detect metastatic disease missed by CI and may be considered when staging or restaging patients with known or suspected distant mets.
  - CI is equivocal or confusing
    - eg. liver lesions, brachial plexopathy, equivocal bone scan
  - Restaging prior to aggressive local therapy
  - Rising tumor markers

- PET may be useful for early therapy evaluation in pts with locally advanced and/or metastatic disease.
**Future Prospects**

- New technologies will increase the role of PET in breast cancer:
  - Higher resolution scanners
  - PET/CT
  - PET/stereotactic mammography units
  - Gamma probes for PET isotopes

**Molecular Imaging with PET in Breast Cancer**

<table>
<thead>
<tr>
<th>PET Tracer</th>
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<tbody>
<tr>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>18F-FDG</td>
</tr>
<tr>
<td>Cell proliferation</td>
</tr>
<tr>
<td>18F-thymidine</td>
</tr>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>18F-FMISO</td>
</tr>
<tr>
<td>Protein synthesis</td>
</tr>
<tr>
<td>11C-methionine</td>
</tr>
<tr>
<td>Receptors</td>
</tr>
<tr>
<td>18F-estradiol, HER2/neu minibody</td>
</tr>
<tr>
<td>Gene expression</td>
</tr>
<tr>
<td>18F-antisense oligonucleotides</td>
</tr>
</tbody>
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PET/CT Design

Somatom AR.SP

PET/CT scanner

ECAT ART

CT

Fused image viewer

PET
**PET/CT scanners:**

Renal Cancer
46 year old male with renal cancer, status post nephrectomy and chemotherapy. Biograph identified mediastinal lymph node metastasis.

Scan protocol: 
- **CT** 100 mAs, 130 kV, pitch 1.5, 5 mm slice width
- **PET** 555 MBq FDG, 180 min p.i., 5 min/bed, 6 beds, 30 min scan time

Data Courtesy of Indiana University PET Imaging Center

BCCA
Hepatocellular Cancer
42 year old female referred with stomach pain. Ultrasound showed multiple liver lesions. PET/CT to evaluate partial liver resection and partial living donor transplantation. Biograph identified no distant metastases; liver tumor penetration of diaphragm. Transplantation cancelled.

Scan protocol:
- CT: 125 mAs, 130 kV, pitch 1.5, 5 mm slice width
- PET: 388 MBq FDG, 60 min p.i., 5 min/bed, 6 beds

Data Courtesy of University Hospital Essen

Lung Cancer
Case: 63 year old male with a mass in the right lung. Biograph LSO identified peripheral lesion activity.

Scan protocol:
- CT: i.v. and oral contrast, 100 mAs, 130 kVp, 5 mm slices
- PET: 500 MBq FDG, 60 min p.i., 2 min/bed, 6 beds, 12 min scan time

Data Courtesy of Hong Kong Baptist Hospital
Commercial PET/CT Scanners

Siemens/CTI  Phillips/ADAC  GE Medical Systems

Monitoring Response to Treatment

In NSCLC, a single, early post-treatment PET scan is a better predictor of response than:
- CT response
- stage
- pre-treatment performance status

*Mach Manus: J Clin Oncol, Volume 21(7). April 1, 2003.1285-1292*
### Limitations of FDG-PET

- Resolution
- Sensitivity may be less for low grade tumors
- Patient may move during scan
- Brown fat, sarcoidosis, benign inflammation – false positives

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### Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Patient Studies</th>
<th>Sensitivity PET</th>
<th>Sensitivity CT</th>
<th>Specificity PET</th>
<th>Specificity CT</th>
<th>Accuracy PET</th>
<th>Accuracy CT</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>318</td>
<td>91</td>
<td>93</td>
<td>93</td>
<td></td>
<td>95</td>
<td></td>
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<tr>
<td>Staging</td>
<td>2034</td>
<td>91</td>
<td>63</td>
<td>88</td>
<td>96</td>
<td>90</td>
<td>0</td>
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<tr>
<td>Dx/Staging</td>
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<td>75</td>
<td>83</td>
<td></td>
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<td>Recurrence</td>
<td>977</td>
<td>80</td>
<td>90</td>
<td>85</td>
<td>96</td>
<td>82</td>
<td>89</td>
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<tr>
<td>Monitoring Response</td>
<td>269</td>
<td>81</td>
<td>96</td>
<td></td>
<td></td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

A tabulated Summary of the FDG PET Literature. J of Nucl Med. 2001 May; 42 (5 Suppl)
Trends in FDG-PET Oncology

- Identify functional change
- Diagnose disease
- Stage disease
- Plan patient specific treatment
- Monitor disease response

Why PET?

- Isotopes of naturally occurring elements
- High sensitivity
- Accurate quantification
- Whole body scan capability
- High clinical sensitivity & specificity
The Role of FDG-PET in Breast Cancer

- Indications for FDG-PET Imaging
  - Staging after tissue diagnosis if suspicion of distant metastases is high
  - Restaging after treatment or recurrence
  - Evaluation of response to therapy

68 yo patient with breast cancer and chest wall pain
Limitations of Conventional Imaging in Oncology

- Functional change often precedes anatomical change
  - Diagnosis and staging
  - Residual mass
  - Anatomical regression takes time
- Treatment related new findings

50 yo woman. FDG-PET (A,B) shows met in spine which is not seen in Tc-99m MDP bone scan (C) (false neg).

Yang, J Cancer Res Clin Onc 2002; 128(6): 325-328
Internal Mammary/Mediastinal Lymph Node Metastases

Multicentre Study to Assess the Positive Predictive Value of PET in the Preoperative Evaluation on Internal Mammary Lymph Nodes in Breast Cancer Subjects

Status: ongoing

Anatomical versus Functional Imaging

CT

FDG-PET