Positron Emission Tomography Clinical Applications
Homer A. Macapinlac, MD

Major research advances in cancer treatment, prevention, and screening
- 1.4 million Americans will be diagnosed
- 570,000 will die of the disease
- Survival rates for cancer are increasing from 50% to 64% over the last 30 years
- New chemotherapy regimens
- Targeted Therapies
- Prevention


WHO Tobacco Free Initiative
- Tobacco is the second major cause of death in the world.
- 5 million deaths each year
- If current smoking patterns continue, it will cause 10 million deaths/year by 2020.
- Half the people that smoke today –
- 650 million people will eventually be killed by tobacco.


Role of FDG PET in Oncology
Synergy of Anatomy & Function
- FDG PET - excellent tumor detection
  - distinguish benign from malignant
  - identify nodal and distant metastases
- CT - excellent resolution
  - T stage and localization
- PET AND CT Improve accuracy of staging
  - extent of disease
Positron Emitters (Cyclotron)

- F-18 (108 min)
  - FDG (glycolysis/ cardiac viability), ion (bone)
- C-11 (20 Min)
  - methionine (amino acid metabolism)
- N-13 (10 min)
  - ammonia (myocardial perfusion)
- O-15 (2 min)
  - water (cerebral perfusion)
- Cu, Zn, K, Br, I, P, Fe, Ga

FDG PET

Patient Preparation

- Fasting - 6 hours/overnight ("south beach prep")
  - Encourage water intake
  - Last meal – high protein low carbohydrate
  - Medications - o.k.
- Head Neck, Breast Ca, Thyroid Ca
  - Xanax 0.5 mg p.o. 5-10 min pre-inj
- Diabetic patients
  - Well controlled
**PET-CT Scanning Technique**

- FDG 15-20 mCi IV bolus
- 60-90 minute uptake phase
- Arms up except - melanoma, head neck
- CT - 120Kvp 120 mA (can go lower)
  - Breath hold with CT over chest (8 slices)
  - Free breathing with CT (16 of > slices)
  - Soft tissue, lung/bone CT recon
- PET – 1.5-3.0 min 2D emission scan/FOV

**CMS Coverage for PET in Oncology**

- Diagnosis, Staging, Restaging of Cancer
  - Lung (NSCLC), Esophageal Ca, Lymphoma, Melanoma, Colorectal, Head/Neck, Cervical Ca
- Breast Ca
  - Re-staging - locoregional recurrence/metastasis
  - Monitoring tumor response
- Thyroid CA (-) I-131, > TGB
- National Oncologic PET Registry
**Staging**

International System for Staging Lung Cancer

TNM Descriptors:

- T - primary tumor
- N - lymph nodes
- M - metastases

Mountain. Chest 1997; 111:1710-1717

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**Lung Cancer Staging**

- Treatment based on stage
- Survival correlates with stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-Year Survival</th>
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<tbody>
<tr>
<td>I</td>
<td>60-80%</td>
</tr>
<tr>
<td>II</td>
<td>5-50%</td>
</tr>
<tr>
<td>IIIa</td>
<td>10-40%</td>
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<tr>
<td>IIIb, IV</td>
<td>&lt;5%</td>
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**Computed Tomography (CT)**

- Excellent for Extent of Disease Evaluation
- Limited in distinguishing benign from malignant lesions
- Limited for Chest Wall and Mediastinal invasion
- Sensitivity/Specificity: 50-70%

Vansteenkiste Lancet Oncology Vol 5; 531-540, 2004

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**T3**
Staging the Mediastinum

• CT - 1 cm short-axis diameter has the best trade-off between sensitivity and specificity

• Malignant lymph nodes may be < 1 cm and this explains the limited sensitivity of CT, estimated to be 57%, specificity of 82%
  – Toloza EM. Noninvasive staging of non-small cell lung.

PET/CT
The “N” Factor

FDG PET Improves Staging

• PET potentially avoided unnecessary thoracotomy in 1 out of 5 patients

• Nodal Stage: Sensitivity/Specificity 85/91%
  – High NPV

• M1 detection – mean 13%
  – Stage I - 7.5%, Stage II - 18%, Stage III – 24%

Lymph Nodes - PET/CT

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
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<tbody>
<tr>
<td>Sens</td>
<td>70</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Spec</td>
<td>59</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Accu</td>
<td>63</td>
<td>89</td>
<td>93</td>
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</table>

Antoch. Radiology, 2003
Staging – PET/CT

ASCO NSCLC Dx Guideline 2003
Staging Distant Metastases

- General – FDG PET recommended when there is no evidence of distant metastatic disease on CT scan chest
- Bone – bone scan optional, Bx/MR/CT
- Brain – CT/MRI
- Adrenal – FDG PET/US/CT - Bx
- Liver - FDG PET/US/CT - Bx

### How to reduce NTCP?

3DCRT/IMRT/Proton

### Effect of FDG-PET on Radiation Treatment Volumes in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients w/ change in RTP</th>
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<tbody>
<tr>
<td>Hiffer</td>
<td>1998</td>
<td>7/15 (46%)</td>
</tr>
<tr>
<td>Nestle</td>
<td>1999</td>
<td>12/34 (35%)</td>
</tr>
<tr>
<td>Munley</td>
<td>1999</td>
<td>12/35 (34%)</td>
</tr>
<tr>
<td>Vanuystel</td>
<td>2000</td>
<td>45/73 (62%)</td>
</tr>
<tr>
<td>Giraud</td>
<td>2001</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>McManus</td>
<td>2001</td>
<td>38/102 (37%)</td>
</tr>
<tr>
<td>Erdi</td>
<td>2002</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Ciernik</td>
<td>2003</td>
<td>18/39 (56%)*</td>
</tr>
<tr>
<td>Brianzoni</td>
<td>2005</td>
<td>11/25 (44%)*PET/CT</td>
</tr>
</tbody>
</table>

Delineation of GTV & Normal Organs in the Thorax

![Image of thorax with labeled organs](image)
**MELANOMA**

**PET Imaging Summary**

- Thin melanomas (T1 ≤ 1.0 mm) radiologic, FDG-PET imaging not cost-effective
- Stage II (T2-4, N0 clinically), Sentinel Node Biopsy, CXR and LDH
- Stage III (N1-3) and IV (M1), CT/MR/PET to detect occult metastases if resection a therapeutic consideration

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**Sentinel Lymph Node Biopsy**

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**FDG PET**

**High risk Melanoma**

- Prospective 100 pts (>1.5mm)
- Accuracy -
  - FDG PET -92%, Conventional - 77%
- CT - better in lung (87% vs 69%)
- PET - better in abdomen (100% vs 27%)
  - Cervical metastasis (100% vs 66%)
- FDG PET sensitive and specific for staging

Rinne et al. Cancer; 82(9):1664-71 1998

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**67 year old patient, melanoma right foot**

- Clark level IV, Breslow thickness 4.5 mm.
- Right groin lymph node dissection, 2 of 4 nodes containing microscopic metastases.
- Referred for assessment of extent of systemic metastases.
Role of FDG PET Head and Neck Ca

- T staging
  - unknown primary
- N Staging
- Post treatment setting
- Monitoring of Response to Therapy

Case of Unknown Primary

- 68 year old man
- Presents with left neck mass
- Biopsy – keratinizing squamous cell ca
- MDACC physical exam – no mucosal lesions, fiber optic exam of the upper aerodigestive tract negative.
- Workup – PET/CT and Diagnostic CT
FDG PET in Thyroid CA

- Negative whole body I-131 scans
  - 37 pts post thyroidectomy and I-131 Rx
- Elevated thyroglobulin
  - PET localized disease in 71%
  - 1 FP, 5 FN (small cervical nodes)
  - PPV - 92%
- Low thyroglobulin - NPV - 93%
- 19/37 - PET changed clinical management

J Clin Endocrinol Metab; 84(7):2291-302 1999
COLORECTAL CANCER
Role of PET

- Rectal CA pre-op: nodal and distant mets
- Liver resection - R/O extra-hepatic mets
- Rising CEA, negative CT
- Pelvic abnormalities post surgery or RT
- Monitoring of Response

Utility of FDG PET prior to resection of liver metastases

- 40 pts evaluated prior to resection
- PET influenced clinical management in 40% and directly altered management in 23%
  - 6 patients spared laparotomy
  - 3 patients had extrahepatic mets
  - *PET missed peritoneal mets in 3 pts
  - *PET missed sub-centimeter liver lesions


Overall Survival of Patients Undergoing Hepatic Resection for Metastatic Colorectal Ca

FDG PET in Cervical Ca

- Nodal Staging – FDG PET is better
  - PET>CT sensitivity 86-100% >25-67%
  - (Rose 1999, Grigsby 1999, Sugawara 1999)
  - PET>MRI sensitivity 83-91% > 50-73%
  - (Vogelsang 1999, Reinhardt/Narayan 2001)

Monitoring Anti-Cancer Rx

  - False (+) rate acceptable if 50% decrease in size
- WHO – 2 perpendicular diameters
  - 50% or > Reduction product – partial response
- RECIST – Response Evaluation Criteria in Solid Tumors – 30% decrease in longest dia

Oncology Biomarker Qualification Initiative
FDA, NCI, part of the NIH and CMS

- First project to be implemented will serve to validate and standardize the use of FDG-PET
- Trials of patients being treated for non-Hodgkin's lymphoma, to determine if FDG-PET is a predictor of tumor response.
- Data resulting from this type of evidence-based study will help both FDA and CMS work with drug developers based on a common understanding of the roles of these types of assessments.

http://www.cancer.gov/newscenter/pressreleases/OBQI

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
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<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>FDG-avid or PET (+) prior to therapy; mass of any size permitted if PET negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>FDG-avid or PET (+) prior to therapy, one or more PET positive at previously involved site</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>FDG-avid or PET (+) prior to therapy; PET (+) at prior sites of disease and no new sites on CT or PET</td>
</tr>
<tr>
<td>PD</td>
<td>Any new lesion or increase by 50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, 50% increase in SPD of more than one node, or 50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis</td>
</tr>
</tbody>
</table>


Large B-cell Diffuse Lymphoma Response to R-CHOP

Baseline
SUV<sub>cor</sub> = 7.7

1 Day
SUV<sub>cor</sub> = 1.2

20 Days
SUV<sub>cor</sub> = 0.0

End
SUV<sub>cor</sub> = 0.0

**Follicular Lymphoma**

- 4 cycles R-CHOP
- 2 cycles R-ESHAP
- 2 cycles R-hyperCVAD

**FDG PET**

**Breast Cancer**

- Diagnosis – limitations, size/type
- Axillary Staging – limitations, SLN
- Evaluation of Recurrent disease
- Evaluation of Locally Advanced Cancer
- Evaluation of Response
  - Define criteria for different types
  - Improvement of outcomes

**Inflammatory Breast Cancer**

- Rare, aggressive, young, poor prognosis
- MRI was the most accurate imaging technique in detecting a primary breast parenchymal lesion
- Sonography can be useful in diagnosing regional nodal disease.
- PET/CT provides additional information on distant metastasis, and it should be considered in the initial staging of IBC.

By using a threshold of 55% decrease below the baseline FDG PET predicted histological response with an accuracy of 88% (after 1. CTx) and 91% (after the 2. CTx).

Conclusion:
Prediction of histological response by PET helpful in management by avoiding ineffective CTx or continue dose intense CTx.
FDG PET-Guided Chemotherapy:

Sample Trial

1. Baseline FDG-PET
2. Standard Rx Cycle 1
3. FDG-PET
   - Metabolic Response
   - Metabolic Non-response
   - Randomize
     Continue Std Rx
     Alternative Rx
   - Follow: overall survival, progression-free survival

CMS Coverage for PET

- Epilepsy - Localize the seizure foci in patients with intractable seizures that are being worked up for surgery (FDG)
- Alzheimer’s Disease (FDG)
- Myocardial Perfusion Imaging
  - Rb82 (Generator)
  - N-13 Ammonia (NH3)
- Myocardial Viability
  - F-18 FDG

Dementia

- Affects 8% of persons > 65 years
- Affects 47% of persons > 85 years
- Alzheimer’s disease accounts for 70%

I have a photographic memory, but once in a while I forget to take off the lens cap
-Milton Berle

Proposed criteria for the diagnosis of Alzheimer's disease

- Early and significant episodic memory impairment
- One or more abnormal biomarkers:
  - MRI – atrophy: medial temporal lobe, hippocampi, entorhinal cortex, amygdala
  - PET - FDG, FDDNP, PiB (Pittsburgh cpd)
  - CSF analysis of amyloid beta or tau proteins

Normal Aging

Conclusions

- Memory loss is part of aging process
- Alzheimer’s disease is most common cause of dementia
- FDG-PET is accurate in the early diagnosis of Alzheimer’s disease
- Molecular imaging agents are being developed that will be more accurate than FDG
FDG-PET in a 17-year-old patient with intractable partial epilepsy not localized by EEG or MRI (normal).


**Perfusion and Metabolism Patterns**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Irreversible Dysfunction</th>
<th>Reversible Dysfunction</th>
</tr>
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**Diagnostic accuracy of Rb-82 myocardial perfusion PET: comparison with Tc-99m MIBI SPECT.**

- 112 SPECT Tc-99m sestamibi and 112 PET rubidium-82 MPI— in patient populations matched by sex, BMI, and presence/extent CAD.
- Diagnostic accuracy was higher for PET for both stenosis severity thresholds of 70% (89% vs 79%, \( p = .03 \)) and 50% (87% vs 71%, \( p = .003 \)) and was higher in men and women, in obese and nonobese patients, and multivessel CAD.
- Myocardial perfusion PET was superior to SPECT in image quality, interpretive certainty, and diagnostic accuracy.