PET and PET/CT in Lymphoma and Monitoring Therapy

Dominique Delbeke, MD, PhD

VUMC PET/CT Conference 2009
Classification of Lymphomas

- Working Formulation = outdated
- **REAL Classification** (Revised European American Lymphoma)
- **WHO Classification** (World Health Organization) = updated REAL

- Three major categories
  - Hodgkin’s Lymphoma
  - B-cell Neoplasms
  - T-cell/natural killer (NK)-cell neoplasms

REAL/WHO Classification of Lymphomas
Hodgkin’s Lymphomas (HL)

- Nodular lymphocyte-predominant Hodgkin’s lymphoma (NLP).
  - Best prognosis: $\text{SUV max} = 9.3$ (n=7)

- Classical Hodgkin’s lymphoma.
  - Nodular sclerosis Hodgkin’s lymphoma (NS).
    - Most common: $\text{SUV max} = 16.3$ (n=36)
  - Lymphocyte-rich classical Hodgkin’s lymphoma.
    - Good prognosis
    - Worse prognosis than NS: $\text{SUV max} = 20.8$ (n=11)
  - Lymphocyte-depleted Hodgkin’s lymphoma
    - Worse prognosis.

Hutchings M et al. Hematol Oncol 2006;24:146-150.
Distribution of Types of NHL and FDG Uptake

Aggressive Types and HL: Intense FDG uptake
- Diffuse Large B-cell lymphoma 30%
- Mantle cell lymphoma 6%
- Peripheral T-cell lymphoma 7%
- Small lymphocytic lymphoma 7%
- Marginal zone B-cell lymphoma, MALT 8%

Indolent Types: Low to Moderate FDG uptake
- Follicular lymphoma 22%

Adapted from the NHL Classification Project: Blood 1997;89:3909.
FDG Uptake versus WHO Classification (n = 172)

- Two studies of 172 and 255 patients

- Sensitivity according to histology:
  - Hodgkin’s lymphoma (HL):
  - Diffuse large B-cell (LBCL):
  - Mantle cell lymphoma (MCL):
  - Follicular lymphoma (FL):
  - Marginal zone lymphoma:
  - Peripheral T-cell lymphoma:
  - Small lymphocytic lymphoma:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity Elstrom R et al.</th>
<th>Sensitivity Tsukamoto N et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma (HL)</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Diffuse large B-cell (LBCL)</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Mantle cell lymphoma (MCL)</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Follicular lymphoma (FL)</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>
49 year-old male with suspicion of recurrent mantle cell lymphoma
**FDG Uptake versus WHO Classification (n = 255)**

**TABLE 1**

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of patients</th>
<th>SUV max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDG</td>
<td>FDG and Ga-67</td>
</tr>
<tr>
<td>ALC1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>AITL</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>NK/T-nasal</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PTCL</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Burkitt</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>DLBCL</td>
<td>81</td>
<td>62</td>
</tr>
<tr>
<td>FL</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>MZLs</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>MALT</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>SMZL</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>MCL</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>SLL</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>HL</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
FDG PET for Low-grade Lymphoma

- Study of 42 patients comparing CM (PE, ENT, CT, gastroscopy, BM biopsy) and PET:
  - LN:
    - Follicular lymphoma: PET detected 40% > LN than CM.
    - Small lymphocytic lymphoma/CLL: PET sensitivity = 58%
  - Extranodal sites: PET = CM but are complimentary
  - BM: Low sensitivity for PET.

- 37 patients with CLL
  - Richter transformation into diffuse large cell lymphoma: n=11
    - FDG PET Sensitivity: 91% (SUV > 5)
    - False +: n=9 but 3 had incidental other malignancies
    - FDG PET Specificity: 80%

68-year-old male with low-grade lymphoma with multiple LN in the neck and abdomen

Diagnosis:
1) False – low grade lymphoma
2) Fem-Fem graft
FDG PET and T-cell Lymphoma


Figure 1. SUV max according to histological subtypes. Scattergram of the maximum standard uptake value (SUV max) according to histological subtypes. SUV max varied widely within the same histological subtype. Abbreviations: PTCLu, peripheral T-cell lymphoma, unspecified; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; C-ALCL, primary cutaneous anaplastic large cell lymphoma; AILT, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; MF/SS, mycosis fungoides and Sézary syndrome.
62 year old female with peripheral T-cell lymphoma

Before therapy: Left lung and numerous cutaneous lesions

After therapy
FDG Uptake to Differentiate Indolent vs Aggressive

- 97 patients with NHL untreated for 6 months
  - Indolent: SUV = 7.0 +/- 3.1
  - Aggressive: SUV = 19.6 +/- 9.3

- Despite overlap:
  - Indolent: SUV all < 13
    - SUV > 10 exclude indolent with spec 81%
  - Aggressive: SUV all > 13

- FDG uptake can be heterogeneous in the same patient:
  - Presumably representing different clones of cells
  - With different glucose metabolism
  - And different biologic behaviour

Patient with lymphoma
FDG PET guide biopsy to the lesion with most uptake

Pre-therapy

Post-therapy
FDG PET for Lymphoma: Prognostic Value

- Study of 34 patients with untreated lymphoma:
- Follow-up 15-50 months after starting therapy:
  Patients with recurrence had higher SUV pre-therapy than patients in remission.
  - Patients (n=22) in complete remission and no recurrence:
    - SUV 6.4 +/- 3.0
  - Patients (n = 6) in complete remission, then recurrence:
    - SUV 7.0 +/- 2.9
  - Patients (n=6) with no remission:
    - SUV 14.4 +/- 5.5.
- Survival was longer for patients with SUV <8.0

Current Clinical Applications for PET in Oncology

- PET with FDG = imaging modality allowing direct evaluation of the cellular glucose metabolism
- Most malignant tumors:
  - Increased number of glucose transporter proteins
  - Increased glycolytic enzyme levels
    - Increased FDG uptake compared to normal cells
- FDG PET became an established imaging modality for:
  - Diagnosing malignancies (differentiate benign from malignant lesions)
  - Staging and restaging malignancies
  - Monitor therapy: Early and after completion
  - Assess recurrence
FDG PET for the Diagnosis of Lymphoma

- Non specific lymphadenopathy
- HIV+ patients with cerebral lesions:
  - Toxoplasmosis: 60%
    - Low FDG uptake
  - High grade lymphoma: 30%
    - High FDG uptake
    - Poor prognosis
  - Another etiology: 10%
    - PML

Menendez JA et al. Neurosurg focus 2000;8:e2.
FDG PET for Initial Staging of Lymphoma

Importance for prognosis
- Stage I/II: 70 - 80% cure rate
- Stage III/IV: 40% cure rate

Implications for treatment
- Stage I/II: XRT alone or in combination with chemotherapy
- Stage III/IV: chemotherapy

Change from stage I/II to III/IV has major implications:
- FDG PET upstage ~ 10% of patients from I/II to III/IV
Comparison FDG PET and $^{67}$Ga for staging Lymphoma

- Study of 51 patients (38 NHL and 13 HD)
  - Target/bg ratio: FDG > $^{67}$Ga
  - Sensitivity:
    
    |            | FDG PET | $^{67}$Ga |
    |------------|---------|-----------|
    | patient    | 100%    | 80%       |
    | lesions    | 100%    | 71%       |

  Staging: FDG PET upstaged 25% (13/51) patients

- Study of 84 patients comparing $^{67}$Ga and camera-based FDG:
  - Accuracy:
    
    |            | FDG PET | $^{67}$Ga |
    |------------|---------|-----------|
    | patient    | 83%     | 63%       |
    | lesions    | 87%     | 33%       |

FDG PET for Staging Lymphoma

- Study of 52 patients: PET was compared to CT using ROC analysis.

<table>
<thead>
<tr>
<th>Location</th>
<th>PET</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN</td>
<td>0.996</td>
<td>0.916</td>
</tr>
<tr>
<td>Extranodal</td>
<td>0.990</td>
<td>0.916</td>
</tr>
<tr>
<td>Subdiaphragmatic</td>
<td>0.996</td>
<td>0.905</td>
</tr>
<tr>
<td>Infradiaphragmatic</td>
<td>0.999</td>
<td>0.952</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>BM biopsy = PET, both &gt;CT</td>
<td></td>
</tr>
</tbody>
</table>

PET changed stage and management in 8% of patients

Lymphoma originate from extralymphatic organs in up to 30% of patients

HD: 35%
- Frequency of spleen involvement: 23%
- Frequency of hepatic involvement: 3%
- Frequency bone marrow involvement: 10%

NHL: 60%
- Frequency of spleen involvement: 22%
- Frequency of hepatic involvement: 15%
- Frequency bone marrow involvement: 25%
FDG PET versus Bone Scintigraphy (BS) for Lymphoma

Study of 56 patients: 34 HD, 22 NHL

- Concordant bone marrow involvement in 12/56 patients was found by both PET and BS
  - PET detected 30 regions, BS 20 regions
- PET+, BS-: 5 patients (12 regions) (3 T+, 2 unresolved)
- BS+, PET-: 5 patients (3 F+, 3 unresolved)

FDG PET has a high PPV, and higher sensitivity and specificity than bone scintigraphy.

FDG PET for Staging Lymphoma: Bone Marrow
A meta-analysis

13 studies with 587 patients comparing FDG PET to BM bx:
- Sensitivity: 51%
- Specificity: 91%
- 6/12 patients with FDG PET + and BM – became BM + when rebx at FDG + sites
- Analysis of subgroups of patients:
  - FDG PET more sensitive for HD and aggressive lymphomas

FDG PET for Staging Lymphoma: Bone Marrow

- FDG uptake in the bone marrow
  - mild uptake is physiologic.
  - uptake greater than that of the liver is abnormal.

- Prospective evaluation of 78 untreated patients (39 HD, 39 NHL) compared PET and posterior iliac crest biopsy (70 bilateral).
  - PET / Bx concordant: 64 patients (57 -, 7 +)
  - Bx +/- PET -: 4 patients
  - PET+, Bx-: 10 patients (8 T+, 2?)

- False positives: reactive bone marrow hyperplasia

- False negatives: low grade lymphomas

- PET changed staging in 10% (8/78)

41-year-old male diagnosed with Stage 1A NHL (bx R inguinal LN) 1 year ago and treated with XRT. Current CT shows mediastinal LN

Diagnosis: Widespread lymphoma with BM involvement
# FDG PET for Staging Lymphoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients (#)</th>
<th>Sites (location)</th>
<th>Sites (#)</th>
<th>PET&gt;CS (% sites)</th>
<th>CS&gt;PET (% sites)</th>
<th>Stage* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moog</td>
<td>97</td>
<td>60</td>
<td>Nodal</td>
<td>191</td>
<td>13</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hoh</td>
<td>97</td>
<td>18</td>
<td>All</td>
<td>37</td>
<td>8</td>
<td>8</td>
<td>22%</td>
</tr>
<tr>
<td>Moog</td>
<td>98</td>
<td>81</td>
<td>Extranodal</td>
<td>73</td>
<td>33</td>
<td>10</td>
<td>16%</td>
</tr>
<tr>
<td>Carr</td>
<td>98</td>
<td>50</td>
<td>BM</td>
<td>50</td>
<td>16</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Moog</td>
<td>98</td>
<td>78</td>
<td>BM</td>
<td>78</td>
<td>13</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>Bangerter</td>
<td>98</td>
<td>44</td>
<td>All</td>
<td>155</td>
<td>11</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LN</td>
<td>141</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extranodal</td>
<td>6</td>
<td>33</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BM</td>
<td>8</td>
<td>50</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Delbeke</td>
<td>00</td>
<td>45</td>
<td>All</td>
<td>129</td>
<td>19</td>
<td>13</td>
<td>16%</td>
</tr>
<tr>
<td>Huentenschmidt</td>
<td>01</td>
<td>45</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Buchmann</td>
<td>01</td>
<td>52</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Jerusalem</td>
<td>01</td>
<td>33</td>
<td>LN HD</td>
<td>20</td>
<td>6</td>
<td>7 (1F+)</td>
<td>18%</td>
</tr>
<tr>
<td>Schoder</td>
<td>01</td>
<td>52</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td>44%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>506</strong></td>
<td></td>
<td><strong>713</strong></td>
<td><strong>8-50%</strong></td>
<td><strong>1-17%</strong></td>
<td><strong>7-44%</strong></td>
</tr>
</tbody>
</table>
Pediatric Lymphomas

- Staging (n=25): PET change stage in 23% compared to CT
- Staging (n=113): PET changed stage and treatment in 10% of patients compared to CM
- Staging (n=55 HD): Accuracy: FDG PET 96%, CM 85%

**Prediction of relapse:** 23 patients
- Sensitivity: 100%, Specificity 57%
- NPV: 100%, PPV: 18% because of F+

**Prediction of relapse:** 41 patients
- FDG PET/CT +: 32% but only 15% had recurrence
  - Sensitivity 95%, PPV 53%
- CT persistent anomalies: 51%
  - Sensitivity 79%, PPV 52%

Meany HJ et al. Pediatr Blood Cancer 2006;
17 year old with recurrent NHL on chemotherapy

June 2004

August 2004
CMV infection
PET/CT in NCCN Practice Guidelines

Summary of Recommendations: Lymphoma

Recommendation:

- Baseline for lymphoma that are potentially curative (HD, DLBCL)
- Baseline to exclude systemic disease in clinically localized lymphoma:
  - HD, DLBCL, FL, Mantle cell,, AIDS related B-cell,
  - Nodal and splenic marginal zone, peripheral T-cell, MALT
- To evaluate residual masses
- To monitor therapy of aggressive lymphoma (HD, DLBCL)

Not indicated:

- To monitor therapy if CT is normal
- Surveillance

Hodgkin Disease/Lymphoma

**CLINICAL PRESENTATION:**
Classical Hodgkin lymphoma

**PRIMARY TREATMENT**

- **Chemotherapy** + involved-field RT

  - Stage IA-IIB Nonbulky
    - **ABVD** x 6 cycles (category 2B)
      - Restage after chemotherapy with PET/CT
    - Stable or progressive disease
      - Observe → See Follow-up HODG-7
  - **Complete response (CR)**
    - Complete IFRT → Observe → See Follow-up HODG-7

  - **Partial response (PR)**
    - Positive → See Progressive Disease or Relapse HODG-8
      - Negative → IFRT
  - **Biopsy**
    - Positive → See Progressive Disease or Relapse HODG-8
      - Negative → IFRT

  - **PET positive** → See HODG-8
  - **PET negative** → See Follow-up HODG-7

  - **Restage with PET/CT**

- **Restaging PET/CT**

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Recommendations on the Use of $^{18}$F-FDG PET in Oncology

Panel Composition

The panel comprised experts in clinical oncology or hematology, radiology or nuclear medicine (specializing in PET), and outcomes or health services researchers with expertise in evidence-based medicine. Both academic and community practitioners were included. A patient representative was also included on the panel.
Restaging Lymphoma: PET/CT versus PET or CT

- Study of 27 patients using 12 months follow-up as standard of reference
- Sensitivity on patient- and lesion-based evaluation: PET/CT the best!
  - PET/CT: 93% (patient) and 96% (lesion)
  - PET and CT side by side: 93% (patient) and 91% (lesion)
  - PET alone: 86% (patient) and 78% (lesion)
  - CT alone: 78% (patient) and 61% (lesion)

15-year old female with a history of HD and a new palpable lesion in the right neck

From Delbeke D. Cancer J 2003.
PET/CT in Lymphoma:
Enhanced Full-dose PET/CT vs Low-dose PET/CT

47 patients with lymphoma

- 2 pairs of interpreters: 1 radiologist/1 nuclear physician
  blind interpretation of either Full-dose PET/CT or Low-dose PET/CT
- Region-based analysis: no significant difference
  - Full-dose CT:
    - less equivocal (n=2/188 sites) and
    - more extranodal sites (n=4/188 sites)
- Staging: Almost perfect agreement (46/47 patients)
- Conclusions:
  - Low-dose PET/CT may suffice
  - Full-dose CT for selected cases

PET and Monitoring Response to Therapy

- Limitations of conventional imaging:
  - Residual mass due to fibrosis
  - Therapy-related new findings
  - Anatomical regression of tumor takes time:
    - Cytotoxic versus cytostatic therapy
    - WHO = World Health Organization (two dimensional, partial = >50% decrease)
    - RECIST = Response Evaluation Criteria in Solid Tumors (tumor max axial diameter, >30% decrease)

- Role of PET (metabolic evaluation)
  - Metabolic changes occur before anatomical changes
  - For example: FDG PET can characterize residual masses as metabolically active or not
Lymphoma: Restaging and Monitoring Therapy

- Early assessment of response to therapy
  - Early-stages: 75-90% patients respond to therapy
  - Advanced stages or relapse: < 50% are curable
  - Early assessment of response to therapy is critical

- Prediction of response to therapy after completion
  - Residual mass in 2/3 patients but only ~ 20% residual masses have residual tumor

- Prediction of relapse before high-dose therapy with stem cell transplantation
### Predictive Value of WB FDG PET for Post-Treatment Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Mixed Population</strong></td>
<td>79% 67/85</td>
<td>94% 257/272</td>
<td>82% 67/82</td>
<td>93% 257/275</td>
<td>91% 324/357</td>
</tr>
<tr>
<td><strong>HD</strong></td>
<td>80% 52/65</td>
<td>91% 174/192</td>
<td>74% 52/70</td>
<td>93% 174/192</td>
<td>88% 226/257</td>
</tr>
<tr>
<td><strong>NHL</strong></td>
<td>67% 35/62</td>
<td>100% 86/86</td>
<td>100% 35/35</td>
<td>83% 86/103</td>
<td>88% 121/138</td>
</tr>
<tr>
<td><em><em>NHL</em> Meta-analysis</em>*</td>
<td>72% ~400 patients</td>
<td>100% ~400 patients</td>
<td>97% ~400 patients</td>
<td>78% ~400 patients</td>
<td></td>
</tr>
</tbody>
</table>

Predictive Value of WB FDG PET in Early Response Assessment

<table>
<thead>
<tr>
<th>Authors</th>
<th># Cycles</th>
<th>Median FU (Months)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikhaeel 2000</td>
<td>2-4</td>
<td>30</td>
<td>100</td>
<td>94</td>
<td>87</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Jerusalem 2000</td>
<td>2-5</td>
<td>17</td>
<td>42</td>
<td>100</td>
<td>100</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>Kostakoglu 2002</td>
<td>1</td>
<td>19</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Spaepen 2002</td>
<td>3-4</td>
<td>36</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>84</td>
<td>91</td>
</tr>
<tr>
<td>Zijlstra 2003</td>
<td>2</td>
<td>25</td>
<td>64</td>
<td>75</td>
<td>75</td>
<td>64</td>
<td>69</td>
</tr>
<tr>
<td>Torizuka 2004</td>
<td>1-2</td>
<td>24</td>
<td>87</td>
<td>50</td>
<td>87</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>Friedberg 2004</td>
<td>3</td>
<td>24</td>
<td>80</td>
<td>94</td>
<td>80</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>Overall (217 patients)</td>
<td></td>
<td></td>
<td>79%</td>
<td>92%</td>
<td>90%</td>
<td>81%</td>
<td>85%</td>
</tr>
</tbody>
</table>

## Generalized Relapse at 2 years - Consider SCT

Is pre-transplant PET useful?

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>F/U</th>
<th>FDG PET</th>
<th>PFS</th>
<th>Median PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svoboda</td>
<td>50</td>
<td>Median 19 months</td>
<td>Neg n=64% Pos n=36%</td>
<td>19 months</td>
<td>5 months</td>
<td>Not reached 19 months</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schot</td>
<td>39 NHL 28</td>
<td>Median 22 months</td>
<td>Neg n=43% Pos n=41%</td>
<td>71%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filmont</td>
<td>20 preBMT</td>
<td>Median 13.3 months</td>
<td>Neg n=8 Pos n=12</td>
<td>87%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filmont</td>
<td>23 postBMT</td>
<td>Median 13.3 months</td>
<td>Neg n=9 Pos n=14</td>
<td>89%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kassim</td>
<td>39 NHL preBMT</td>
<td>Median 428 days. For CR &gt;180 days</td>
<td>Neg 22 Pos 17</td>
<td>20%</td>
<td>17.5 months</td>
<td>4.2 months</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kassim</td>
<td>50 NHL post BMT</td>
<td>Neg 31 Pos 19</td>
<td>10%</td>
<td>17.5 months</td>
<td>3.2 months</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monitoring radioimmunotherapy therapy of lymphoma

65 year-old male with follicular lymphoma

\(^{131}\text{I}-\text{Bexxar}\)

April 05  July 05  Nov 05
15 year-old male with lymphoma

Pre-Therapy

After 2 cycles

After completion

6 months F/U
Sources of False +/- Interpretations

- **F+: Physiologic FDG uptake**
  - Lymphoid tissue
  - Brown adipose tissue
  - Glandular tissue
  - Muscular system
  - GI tract
  - GU tract

- **F+: Inflammation**
  - Therapy-related
    - Therapy-related: Ostomies, drainage tubes, stents (percutaneous more common), radiation therapy, chemotherapy
  - Trauma
  - Infection
    - Abscesses, Acute cholecystitis, Acute cholangitis, Acute pancreatitis (chronic pancreatitis but uncommon), Inflammatory bowel disease, Diverticulitis
  - Granulomatous disease: TB, fungi
62 year-old male s/p resection of recurrent lymphoma of the small bowel 2 weeks earlier.

Diagnosis: post-operative changes
Bone marrow biopsy L iliac crest
57 year-old male diagnosed with esophageal cancer in July underwent a follow-up to assess response to therapy.

Initial staging: July

Post-therapy: October
48 year-old man with HD diagnosed in 2003 who presented with suspected recurrence in April 2004

4/04

10/04: Post-therapy
Sources of False +/- Interpretations

- False negative include:
  - Small lesions (<5-10 mm, i.e. ampullary carcinomas, miliary carcinomatosis; for accurate SUV > 2 cm)
  - Low cellular density
    - Tumors of the infiltrating type (cholangiocarcinomas)
    - Tumors with large mucinous components
    - Tumor necrosis
  - Some low grade tumors: Lymphoma, sarcoma,…
  - Low sensitivity: ~ 50-80%
    - GU: Prostate, Renal cell
    - GYN: Ovarian (mucinous, miliary spread)
    - Hepatocellular
    - Differentiated neuroendocrine
    - Bronchioalveolar
  - Hyperglycemia and/or insulin less than 3 H prior to FDG
Pretreatment FDG PET:
- Aggressive lymphoma (HD, DBCL, FL, MCL): recommended
- Indolent lymphoma (T-cell, MALT, SLL): mandatory
CT and PET or PET/CT

- Initial staging:
  - Contrast-enhanced CT (CECT) + FDG PET
  - or PET/CECT

- After therapy
  - CT should be complemented with PET
  - PET/CT if no liver/spleen involvement
  - PET/CECT if liver/spleen involvement
  - Size and FDG-avidity need to be reported

Protocols:

Monitoring Response to Therapy with FDG PET

**Timing in Relation to Therapy**

- **Surgery:**
  - ~ 2 months for surgical site
  - Anytime for staging elsewhere.

- **Radiation**
  - Wait as long as possible after radiation
  - Comparison to baseline PET is helpful
  - Knowledge of radiation ports is helpful.

- **Guidelines for PET Interpretation (Juweid ME et al. JCO 2007):** Timing
  - During therapy: At least 2 weeks after last chemotherapy or just before next cycle to avoid stunning*
  - After completion of therapy: at least 3 weeks, preferably 2-months
Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Monaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidlauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

Visual assessment alone is adequate for pos or neg:
- For residual mass > 2 cm: pos if > mediastinal blood pool (BP)
- For lesions < 2 cm: pos if any uptake > background

FDG PET for Monitoring Response in Lymphoma

Specific criteria:

- **Liver or spleen:**
  - > or < 1.5 cm with uptake > liver/spleen: positive
  - > 1.5 cm with uptake < liver/spleen: negative
  - Spleen diffuse uptake > liver: positive if no cytokine administration past 10 days

- **Lung:**
  - New nodule > 1.5 cm with uptake > BP is suggestive if lung involvement at baseline
  - New nodule < 1.5 cm FDG-: indeterminate
  - New nodule FDG + with otherwise complete response: infection

- **Bone marrow:**
  - Multifocal: positive
  - Diffuse even > liver: Hyperplasia

Procedure Guideline for Tumor Imaging with $^{18}$F-FDG PET/CT 1.0*

Dominique Delbeke1, R. Edward Coleman2, Milton J. Guiberteau3, Manuel L. Brown4, Henry D. Royal5, Barry A. Siegel6, David W. Townsend6, Lincoln L. Berland7, J. Anthony Parker8, Karl Hubner9, Michael G. Stabin10, George Zubal11, Marc Kachelriess12, Valerie Cronin13, and Scott Hollbrook14

1Vanderbilt University Medical Center, Nashville, Tennessee; 2Duke University Medical Center, Durham, North Carolina; 3Christus St. Joseph Hospital, Houston, Texas; 4Henry Ford Hospital, Detroit, Michigan; 5Mallinckrodt Institute of Radiology, St. Louis, Missouri; 6University of Tennessee, Knoxville, Tennessee; 7University of Alabama Hospital, Birmingham, Alabama; 8Beth Israel Deaconess Hospital, Boston, Massachusetts; 9University of Tennessee Medical Center, Knoxville, Tennessee; 10Vanderbilt University, Nashville, Tennessee; 11Yale University, New Haven, Connecticut; 12Institute of Medical Physics, University of Erlangen-Nurnberg, Erlangen, Germany; 13Mercy Hospital, Buffalo, New York; and 14Cumberland Isotopes, Coeburn, Virginia

I. PURPOSE

The purpose of these guidelines is to assist physicians in recommending, performing, interpreting, and reporting the results of $^{18}$F-FDG PET/CT for oncologic imaging of adult and pediatric patients.

II. BACKGROUND INFORMATION AND DEFINITIONS

PET is a tomographic scintigraphic technique in which a $^{18}$F-FDG PET and CT are proven diagnostic procedures. Although techniques for registration and fusion of images obtained from separate PET and CT scanners have been available for several years, the readily apparent and documented advantages of having PET and CT in a single device have resulted in the rapid dissemination of this technology in the United States. This Procedure Guideline pertains only to combined PET/CT devices.
SNM Procedure Guidelines for FDG PET/CT

- Purpose
- Background Information and Definitions
- Procedure
  - Patient Preparation
  - Information Pertinent to Performing the Procedure (focused history)
  - Radiopharmaceutical
  - Image Acquisition
- Intervention
- Processing
- Interpretation Criteria
- Reporting
- Quality Control
- Sources of Error
- Qualification of Personnel

SNM Guideline J Nucl Med 2006;47:1227
SNM PET/CT Guidelines: Reporting

Description of findings

- Quality of the study
- By body region:
  - Describe location, extent and intensity of abnormal FDG uptake and describe the relevant morphologic findings related to PET abnormalities on the CT.
  - An estimate of the intensity of uptake may be described as mild, moderate or intense or in relation to a reference standard (e.g. normal liver SUVweight ~ 2.0).
  - The integrated PETT/CT report should include any detected incidental findings on the CT scan that are relevant to patient care.
  - If the CT scan was requested and performed as a diagnostic examination, the CT component of the study may be reported separately, if necessary, to satisfy regulatory, administrative or reimbursement requirements. In that case, the PET/CT report can refer to the diagnostic CT scan report for findings not related to the PET/CT combined findings.

Limitations

Clinical relevance

Comparative data

SNM Guideline J Nucl Med 2006;47:1227
Image Interpretation and Analysis
Do We Need Quantification?

- Visual analysis
- Semi-quantitative analysis using ratio of activity in two ROI: Lesion/background or right/left
- Semi-quantitative analysis: Standard uptake value

\[
\text{Activity in ROI (microcuries/ml)}
\]
\[
\text{SUV} = \frac{\text{Activity in ROI (microcuries/ml)}}{\text{Dose (mCi)} / \text{Weight (kg)}}
\]
Standard Uptake Value

 Depend on patient characteristics:
  - Dose infiltration
  - Plasma glucose levels/metabolic state of the patient
  - Body weight
  - Body surface area
  - Body composition: lean body mass

 Affected by tumor size because of partial volume effects.

 Depends on imaging protocol:
  - Time of imaging after FDG administration
  - ROI size: SUV max vs SUV avg vs SUV peak

 Depends on operator to draw ROI:

Thie JA. J Nucl Med 2004;45(9):1431-1434
SUV: Requires measurements of absolute concentration of positron emitter (in microCi/cc) in region of interest (ROI).

- **Depends on system characteristics:**
  - Detector normalization and calibration
  - Resolution of the PET system (partial volume effects)
  - Correction for artifacts related to the scanner:
    - Deadtime/Random/Scatter correction
  - Image reconstruction: FBP vs Iterative
  - Attenuation correction:
    - CT versus radioactive source
    - Patient motion
Reproducibility of the SUV depends on:
- Patient characteristics
- Tumor size
- Imaging protocol
- Operator and SUVavg vs SUVmax vs SUV peak
- System characteristics
- Rigorous quality control of the PET system

May not be comparable from one facility to another or in the same facility

Alternative: ratio to internal reference standard

Percent change is more reliable
<table>
<thead>
<tr>
<th></th>
<th>SUV</th>
<th>T/L</th>
<th>SUV</th>
<th>T/L</th>
<th>SUV</th>
<th>T/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal liver</td>
<td>2.4</td>
<td></td>
<td>1.3</td>
<td></td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Liver mets</td>
<td>16.2</td>
<td>6.7</td>
<td>9.2</td>
<td>4.8</td>
<td>15.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Periportal</td>
<td>12.8</td>
<td>5.3</td>
<td>8.1</td>
<td>6.2</td>
<td>12.2</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Baseline

Day 10: Muscular uptake

Day 38: Progression

118-001-011 MIP images: Colon cancer
Visual versus SUV Interpretation

Guidelines for PET Interpretation (Juweid ME et al. JCO 2007)
- After completion of therapy:
  - Visual assessment alone is adequate for pos or neg
  - For residual mass > 2 cm: pos if > mediastinal blood pool
  - For lesions < 2 cm: pos if any uptake > background
- During treatment:
  - In clinical trials only
  - Semi-quantitation may be helpful (e.g. SUV)

Recommendations for the Use of FDG PET in NCI Clinical Trials (Shankar LK et al. JNM 2006)
- SUV_{BSA or LBM}
- SUV of reference organ
- SUV max or peak
- Consistency in ROI

Lymphoma
Revised Response Criteria (adopted by NCCN)

Revised Response Criteria for Malignant Lymphoma

ABSTRACT

Purpose
Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods
The International Working Group response criteria (Cheson et al, J Clin Oncol 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of [18F]fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results
New guidelines are presented incorporating PET, IHC, and flow cytometry for definitions of response in non-Hodgkin’s and Hodgkin’s lymphoma. Standardized definitions of end points are provided.

Conclusion
We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new agents.
CRuncomfirmed category is eliminated because of FDG PET (adopted by NCCN)

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Varibly FDG-avid or PET negative; regression to normal size on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes</td>
<td>≥ 50% decrease in SPD of nodules for single nodule in greatest transverse diameter; no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Varibly FDG-avid or PET negative; regression on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Varibly FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed disease</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>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
<tr>
<td>or PD</td>
<td></td>
<td>Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Thank you!

Grand Bahama 2004