PET/CT and Lymphoma: update with emphasis on new criteria

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U.T. M.D. Anderson Cancer Center
Disclosure

- No relevant conflict of interest
- No discussion of investigational drugs or technology
Lymphoma staging

- Lymphoma types
- Staging with PET
  - Bone marrow (BM) involvement
  - Information for radiation therapy
- Updated information

Response assessment

- PET response assessment
- 5-point scale (5-PS)

Surveillance imaging
Lymphoma - epidemiology

- Estimated 72,000 new cases in 2015
  - 7th most common cancer in USA
- Only about 20,000 deaths in 2015
  - Survival is 60-90%
    - HL > NHL
    - Localized > distant
- Most cases are in adults
- No strong association with race, gender, or socioeconomic background
Lymphoma classification

Hodgkin’s lymphoma
- Classical forms
  - Nodular Sclerosis (NS)
  - Mixed Cellularity (MC)
  - Lymphocyte Depletion (LD)
  - Lymphocyte Rich (LR)
- Nodular Lymphocyte Predominant (NLP)

Non-Hodgkin’s lymphoma
- Diffuse Large B Cell (DLBCL)
- Follicular (FL)
- Marginal Zone (MZL)
- Small Lymphocytic (SLL)
- Mantle cell (MCL)
- Burkitt’s
- T/NK cell
- Etc.
Hodgkin’s  DLBCL  Burkitt’s
FDG-avidity of lymphoma

- Weiler-Sagle et al., JNM 2010 51: 25-30
  - Activity above surrounding tissues

<table>
<thead>
<tr>
<th>Table 1. $^{18}$F-FDG Avidity of Lymphoma According to World Health Organization Histopathologic Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma</td>
</tr>
<tr>
<td>Marginal zone lymphoma, nodal</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Plasmacytoma</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Marginal zone lymphoma, splenic</td>
</tr>
<tr>
<td>MALT marginal zone lymphoma</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>
FDG-avidity of lymphoma

Highly FDG-avid
- Hodgkin’s lymphoma
- Diffuse large B cell (DLBCL)
- Burkitt’s

Variably FDG-avid
- Marginal zone lymphoma (MZL)
- Chronic / small lymphocytic (CLL/SLL)

Usually FDG-avid
- Follicular lymphoma (FL)
- Mantle cell lymphoma (MCL)

Rare lymphomas
- NK T cell
- Peripheral T cell (PTCL)
- Cutaneous lymphoma
- Angioimmunoblastic T cell
- Anaplastic large T cell (ALCL)
Ann Arbor system

(Carbone et al., Cancer Res 1971 31: 1860)

I Single LN region or extralymphatic site

II Two or more LN regions or with limited contiguous extralymphatic site on same side of the diaphragm

III LN regions on both sides of the diaphragm or with contiguous extralymphatic site

IV Disseminated involvement or multiple foci of one or more extralymphatic organs

A Asymptomatic (no B symptoms)

B Unexplained fever, night sweats or weight loss

X Bulky disease (Hodgkin's disease)
Revised Staging System
for primary nodal lymphomas

Limited

I  Single LN region or extralymphatic site

II  Two or more LN regions or with limited contiguous extra lymphatic site on same side of the diaphragm

II bulky  Stage II with “bulky” disease

Advanced

III  LN regions on both sides of the diaphragm or with contiguous extralymphatic site

IV  Disseminated involvement or multiple foci of one or more extralymphatic organs

A  HL only - Asymptomatic (no B symptoms)

B  HL only - Unexplained fever, night sweats or weight loss
MDACC algorithm for DLBCL

Stage I-II
- Non-bulky disease:
  - Complete response
  - Bulky disease:
    - Partial response

Stage III-IV
- Low clinical risk:
  - Refractory or progressive disease
- High clinical risk:
  - Refractory or progressive disease
  - Or clinical trial

Adapted from M.D. Anderson Manual of Medical Oncology, 2nd ed, 2011
PET/CT staging

- PET allows more accurate staging than CT alone in 10-40%.

- In another study, PET led to:
  - Change in stage: 44%
  - Change in management: >60%
Updated recommendations – staging assessment

- PET/CT is the gold standard for staging of all FDG-avid nodal lymphomas
  - Everything except
    - CLL/SLL
    - Lymphoplasmacytic/Waldenstrom’s macroglobulinemia
    - Mycosis fungoides
    - Marginal zone lymphoma*
  - Unless there is suspected aggressive transformation
FDG-avidity of lymphoma

- Weiler-Sagle et al., JNM 2010 51: 25-30
  - Activity above surrounding tissues

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>(^{18}\text{F-FDG-avid})</th>
<th>Negative</th>
<th>% (^{18}\text{F-FDG avidity})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin disease</td>
<td>233</td>
<td>233</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>18</td>
<td>18</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, nodal</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>222</td>
<td>216</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>140</td>
<td>133</td>
<td>7</td>
<td>95</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>29</td>
<td>24</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>Marginal zone lymphoma, splenic</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>MALT marginal zone lymphoma</td>
<td>50</td>
<td>27</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>All</td>
<td>766</td>
<td>718</td>
<td>48</td>
<td>94</td>
</tr>
</tbody>
</table>
Updated recommendations – staging assessment

- PET/CT is the gold standard for staging of all FDG-avid nodal lymphomas
  - Everything except
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Improved detection with PET

Lymphoma in muscle

Marrow involvement by lymphoma
Diffuse bone marrow activity

Multiple causes

- Activation after therapy
  - Chemotherapy
  - Growth factor administration
- Cytopenia
  - Anemia
  - Thrombocytopenia
- Infection
  - Leukocyte stimulation
  - Infection of marrow
- *Diffuse tumor infiltration
Heterogenous tumor in marrow
Focal bone involvement

Limited causes

- Tumor involvement
- Fracture / trauma
- Inflammation / DJD
PET and BM biopsy (BM Bx)

BM Bx negative
PET + vs -

BM Bx positive
PET + vs -

FIGURE 6. PFS of patients with negative BMB (A) or positive BMB (B) considering their $^{18}$F-FDG PET/CT status.
False neg PET for BM in DLBCL

- PET is more sensitive than BM Bx
- Misses “low volume disease” in 10-20%

Kahn Blood 2013
Updated recommendations – bone marrow involvement

- **PET/CT replaces BM Bx in HL**
  - “if a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL”

- **Positive PET/CT obviates the need in DLBCL**
  - BM Bx may be obtained with negative PET/CT
  - “a PET-CT scan indicating bone or marrow involvement is usually sufficient to designate advanced-stage disease, and a BMB [bone marrow biopsy] is not required . . . If the scan is negative, a BMB is indicated to identify involvement by discordant histology if relevant for a clinical trial or patient management.”

- **Unilateral BM Bx in other types**
  - Insufficient data
When is XRT used?

- **Limited stage disease**
  - Stage I or stage II

- **Adjuvant for bulky disease**
  - For HL
    - > 10 cm mass of > 1/3 transthoracic diameter, traditional definition
  - For NHL
    - 6-10 cm proposed but not validated
    - Report longest measurement

- **Palliative therapy**
Lymphoma and XRT
(the past)

- EFRT - Extended field radiation therapy
  - “traditional” method to XRT
  - Covers large region
    - e.g. mantle field or inverted-Y
  - High cure rates, but associated toxicity
    - Acute radiation toxicity
    - Long-term risk of associated malignancies
Lymphoma and XRT (the present)

- IFRT – involved field radiation therapy
  - “modern” method for XRT
    - Reduced toxicity while maintaining high cure rates
  - XRT to region defined by anatomic landmarks
  - For example, mediastinal field
    - Covers supraclavicular, mediastinal, and hilar LNs
    - Superior border: C5-6
      - Top of larynx if supraclavicular LN involved
    - Inferior border: 2cm below lowest LN or 5 cm below the carina
    - Lateral border: 1.5 cm beyond post-chemo volume
Mantle field | IFRT

![Images of Mantle field and IFRT]

<table>
<thead>
<tr>
<th></th>
<th>Mantle 20 y/o</th>
<th>Mantle 30 y/o</th>
<th>IFRT 20 y/o</th>
<th>IFRT 30 y/o</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast CA</td>
<td>4.8</td>
<td>2.1</td>
<td>1.8 (62%)</td>
<td>0.8 (62%)</td>
</tr>
<tr>
<td>Lung CA</td>
<td>18.0</td>
<td>7.4</td>
<td>14.2 (21%)</td>
<td>5.8 (21%)</td>
</tr>
</tbody>
</table>

20-year Excess Relative Risk (ERR) with 35 Gy
Lymphoma and XRT (the future)

- ISRT – involved site radiation therapy
  - Newest approach
  - XRT to only LNs involved
    - Based on pre-therapy imaging
    - Precise boundary limit to be defined (eg <5 cm)

Courtesy Dr. Leslie Ballas
What does the radiation oncologist need to know?

- Upper and lower extent of lymphoma
  - Based on pre-therapy scans

- Lateral extent of lymphoma
  - Based on post-therapy scans
Reporting for lymphoma staging (suggested)

1. Nodal involvement
   - Extent of nodal involvement
     - Limited vs extensive (both sides of diaphragm)
     - Bulky tumor
   - For early stage disease (XRT candidate)
     - Upper and lower extent of disease

2. Extranodal involvement
   - “extranodal involvement of ________ ”
     - Number of extranodal sites may matter
Updated recommendations – staging assessment

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- Unilateral BM Bx in other types
  - Insufficient data
Updated recommendations – measurable lesions

- **Lymph nodes**
  - Longest diameter (LDi) > 1.5 cm

- **Extranodal disease**
  - Longest diameter (LDi) > 1.0 cm

- **Bulky disease**
  - “X” designation no longer necessary
  - HL: single LN ≥ 10cm or > 1/3 thoracic diameter
  - NHL: 6-10 cm

- **Splenic involvement**
  - Solitary mass
  - Focal nodular lesions
  - Diffuse miliary lesions
  - Homogenous splenomegaly
    - > 13 cm vertical length

- **Liver involvement**
  - Focal or diffuse
  - Size is not a reliable criteria

- **6 target lesions**
  - LDi and short diameter
outline

- Lymphoma staging
  - Lymphoma types
  - Staging with PET
    - Bone marrow (BM) involvement
    - Information for radiation therapy
  - Updated information

- Response assessment
  - PET response assessment
  - 5-point scale (5-PS)

- Surveillance imaging
PET Response Assessment – who is responding to therapy?
## PET – response assessment

<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</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>Hodgkin’s</strong></td>
<td>80% (52/65)</td>
<td>91% (174/92)</td>
<td>74% (52/70)</td>
<td>93% (174/187)</td>
<td>88% (226/257)</td>
</tr>
<tr>
<td><strong>NHL</strong></td>
<td>67% (35/52)</td>
<td>100% (86/86)</td>
<td>100% (35/35)</td>
<td>83% (86/103)</td>
<td>88% (121/138)</td>
</tr>
</tbody>
</table>
Prediction of response: PET vs CT

Hutchins et al., Blood 2006 107: 52
PET improves prediction of therapy response

Table 4. Two- and 3-Year PFS in the Various Response Designations by IWC and IWC+PET

<table>
<thead>
<tr>
<th>Response Designation</th>
<th>2-Year PFS Rate (%)</th>
<th>95% CI</th>
<th>3-Year PFS Rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IWC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (n = 17)</td>
<td>88.2</td>
<td>72.9 to 100</td>
<td>74.1</td>
<td>51.7 to 96.5</td>
</tr>
<tr>
<td>CRu (n = 7)</td>
<td>85.7</td>
<td>59.8 to 100</td>
<td>85.7</td>
<td>59.8 to 100</td>
</tr>
<tr>
<td>PR (n = 19)</td>
<td>68.4</td>
<td>47.5 to 89.3</td>
<td>62.2</td>
<td>39.9 to 64.1</td>
</tr>
<tr>
<td>SD (n = 9)</td>
<td>33.3</td>
<td>2.5 to 64.1</td>
<td>33.3</td>
<td>2.5 to 64.1</td>
</tr>
<tr>
<td>PD (n = 2)</td>
<td>50.0</td>
<td>0.0 to 100.0</td>
<td>50.0</td>
<td>0.0 to 100.0</td>
</tr>
<tr>
<td>IWC+PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (n = 35)</td>
<td>91.4</td>
<td>82.2 to 100.0</td>
<td>79.9</td>
<td>65.1 to 94.7</td>
</tr>
<tr>
<td>CRu (n = 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR (n = 12)</td>
<td>41.7</td>
<td>13.8 to 69.6</td>
<td>41.7</td>
<td>13.8 to 69.6</td>
</tr>
<tr>
<td>SD (n = 6)</td>
<td>16.7</td>
<td>0.0 to 46.5</td>
<td>16.7</td>
<td>0.0 to 46.5</td>
</tr>
<tr>
<td>PD (n = 1)</td>
<td>0.0</td>
<td>0.0 to 97.5</td>
<td>0.0</td>
<td>0.0 to 97.5</td>
</tr>
</tbody>
</table>

Abbreviations: PFS, progression-free survival; IWC, International Workshop Criteria; IWC+PET, IWC plus positron emission tomography; CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Juweid et al., JCO 2005
Residual mass vs residual disease or recurrence

- 40-60% have radiographic abnormality after treatment
- only 10-20% of those have residual disease/relapse

Radford J Clin Onc 1988; 6: 940
Cannellos J Clin Onc 1988; 6: 931
Revised IWC response criteria for malignant lymphoma

<table>
<thead>
<tr>
<th>Designation</th>
<th>Definition</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No evidence of disease</td>
<td>If PET +, now PET negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If PET -, normal size on CT</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of disease</td>
<td>50% decrease in area on CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If PET + may remain PET positive but no new sites</td>
</tr>
<tr>
<td>SD</td>
<td>Not CR/PR or PD</td>
<td>If PET +, no new sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If PET -, no change in CT size</td>
</tr>
<tr>
<td>PD or relapse</td>
<td>New lesion or &gt;50% growth</td>
<td>If PET +, new PET positive lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If PET -, new &gt;1.5cm CT lesion or &gt;50% increase on CT</td>
</tr>
</tbody>
</table>
Tumor cell killing vs PET detection

Kasamon et al., JNM 2007 48: 19S
Deauville criteria for interim PET

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No UPTAKE</td>
</tr>
<tr>
<td>2</td>
<td>UPTAKE ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Mediastinum &lt; UPTAKE ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>UPTAKE moderately &gt; liver</td>
</tr>
<tr>
<td>5</td>
<td>UPTAKE marked &gt; liver&lt;br&gt;Or new site of likely lymphoma</td>
</tr>
</tbody>
</table>

- Doesn’t define positive vs negative
- What is “moderate” vs “marked” increase
- For use with interim PET, not end-of-therapy
# 5-point scale for lymphoma response assessment

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No UPTAKE above background</td>
</tr>
<tr>
<td>2</td>
<td>UPTAKE ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Mediastinum &lt; UPTAKE ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>UPTAKE moderately &gt; liver</td>
</tr>
<tr>
<td>5</td>
<td>UPTAKE marked &gt; liver</td>
</tr>
<tr>
<td></td>
<td>Or new site of likely lymphoma</td>
</tr>
<tr>
<td>X</td>
<td>New uptake unrelated to lymphoma</td>
</tr>
</tbody>
</table>

- **Visual analysis**
- **Uptake marked greater than liver is 2-3x**
# Lugano Classification

<table>
<thead>
<tr>
<th>Designation</th>
<th>PET/CT response</th>
<th>CT response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Score 1-3</td>
<td>With or without residual mass</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>Score 4-5 reduced vs baseline</td>
<td>≥ 50% decrease in SPD</td>
</tr>
<tr>
<td></td>
<td>- Responding at interim</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Residual at end of therapy</td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>Score 4-5 no change vs baseline</td>
<td>&lt; 50% decrease in SPD</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>Score 4-5 increased vs baseline</td>
<td>≥ 50% increase in SPD</td>
</tr>
<tr>
<td></td>
<td>New site of lymphoma</td>
<td>Regrowth of resolved lesion</td>
</tr>
<tr>
<td></td>
<td>New node or extranodal site</td>
<td></td>
</tr>
</tbody>
</table>

Cheson J Clin Onc 2014
A positive score (4 or 5) does not distinguish between PR, SD, or PD

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheson 2007</td>
<td>Equal to or below regional background</td>
<td>Above regional background</td>
</tr>
<tr>
<td>(old criteria)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheson 2014</td>
<td>Equal to or below liver activity (score 1-3)</td>
<td>Above liver activity (score 4-5)</td>
</tr>
<tr>
<td>(5-PS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Updated recommendations – response assessment

- PET-CT should be used for most lymphomas
  - CT for low or variable FDG avid lymphomas
- Use 5-point scale
  - 1-2 is complete metabolic response/CR
  - 3 depends upon timing, clinical context, and Rx
    - Good prognosis with 3 at end of therapy
    - But may be inadequate for interim response
  - 4-5 at end of therapy indicates treatment failure
- Inadequate data for quantitative cutoff
Lymphoma staging
- Lymphoma types
- Staging with PET
  - Bone marrow (BM) involvement
  - Information for radiation therapy
- Updated information

Response assessment
- PET response assessment
- 5-point scale (5-PS)

Surveillance imaging
Lymphoma relapse rate

- 421 pts with lymphoma
  - Followed with exam, labs, and PET
- 118 relapses
  - 3-6 FP PET per time pt

A. Hodgkin’s lymphoma

B. Aggressive NHL

C. Indolent NHL
Surveillance imaging does not affect clinical outcome

- 1200 pts with DLBCL after initial therapy
  - Danish pts had routine imaging, Swedish did not

El-Galaly JCO 2015
Utility of routine post-therapy imaging in DLBCL

- 552 patients after treatment (surveillance)
  - Every 6 mths x 3 yrs, then annual
  - Relapse in 112 (20%) – 104 evaluable

67 pts identified before scheduled visit

24 of the other 37 pts had suspicious clinical features (labs, symptoms, or exam)

Only 13 pts asymptomatic and identified by imaging (CT or PET)

Thompson JCO 2014
Updated recommendations – surveillance imaging

- Surveillance scans after remission are discouraged for DLBCL and HL
  - Re-evaluation of an equivocal finding
  - High false positive PET findings
  - Routine imaging may not affect outcome
- “Judicious use of follow-up scans” in indolent lymphomas with asymptomatic abdominal or retroperitoneal disease
- Follow-up scans should be prompted by clinical indications
<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Clinical followup</th>
<th>Imaging followup</th>
</tr>
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<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Q3-6 mths x 3 yrs Annual up to 5 yrs</td>
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<td>DLBCL stage I-II</td>
<td>Q3-6 mths x 5 yrs</td>
<td>As clinically indicated</td>
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<td>Q2-3 mths x 1st yr Q3 mths during 2nd yr Q6 mths thereafter</td>
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<td>MCL, MZL</td>
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SUMMARY: use PET/CT for staging of most lymphomas
SUMMARY: PET can replace BM Bx
SUMMARY: use PET/CT for response assessment
### SUMMARY: 5-point scale for lymphoma response assessment

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>No UPTAKE above background</td>
</tr>
<tr>
<td>2</td>
<td>UPTAKE ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Mediastinum &lt; UPTAKE ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>UPTAKE moderately &gt; liver</td>
</tr>
</tbody>
</table>
| 5     | UPTAKE marked > liver  
Or new site of likely lymphoma |
| X     | New uptake unrelated to lymphoma |

- **Visual analysis**
- **Uptake marked greater than liver is 2-3x**

Cheson J Clin Onc 2014  
Barrington J Clin Onc 2014
### SUMMARY: PET response assessment

<table>
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<tr>
<th></th>
<th>CR</th>
<th>PR/SD/PD</th>
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<tr>
<td>Cheson 2007 (old criteria)</td>
<td>Equal to or below <strong>regional</strong> background</td>
<td>Above <strong>regional</strong> background</td>
</tr>
<tr>
<td>Cheson 2014 (5-PS)</td>
<td>Equal to or below <strong>liver</strong> activity (score 1-3)</td>
<td>Above <strong>liver</strong> activity (score 4-5)</td>
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- PR/SD/PD depends upon less/similar/more activity *(consider using CT changes also)*
### SUMMARY: less is more???

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NCCN guidelines HL 02.2015
NCCN guidelines NHL 02.2016
1. Which statement best reflects the relationship between PET/CT and bone marrow (BM) status in lymphoma patients?
   A. PET/CT alone accurately predicts bone marrow status
   B. PET/CT used to direct BM biopsy is most accurate
   C. Diffuse marrow uptake on PET indicates diffuse tumor involvement
   D. Either a focal PET/CT positive bone marrow lesion or positive bone marrow biopsy predicts poor prognosis (KEY)

Correct answer is D
Berthet et al., JNM 2015 (and others) showed that patients with either PET positive marrow lesions or positive bone marrow biopsy have a similar poor survival. Although the Cheson JCO 2014 criteria note that HL or DLBCL patients may not need a staging BM biopsy, they note that low volume diffuse disease is missed in 10-20% of DLBCL patients by PET; so PET alone does not accurately predict BM status. Pakos et al., JNM 2005 did a meta-analysis and found that 6/12 (50%) of patients with negative iliac BM biopsy had a positive repeat/directed biopsy; so even directed biopsy is likely inaccurate. Diffuse marrow activity is commonly associated with growth factor administration, especially in the post-therapy state; so may not indicate diffuse tumor involvement.

2. According to the 2014 lymphoma response criteria (Cheson et al., JCO 2014)
   A. Mediastinal blood pool activity is the reference organ for determining complete response (CR) or residual disease (PR, SD, or PD)
   B. Any new sites of activity should be given a 5-PS of “5” and considered positive for lymphoma
   C. FDG PET/CT should be used to determine response in all types of lymphoma
   D. The 5-point score does not distinguish between a partial response (PR), stable disease (SD), or progressive disease (PD) (KEY)

Correct answer is D
A score of 1-3 is considered a complete response, whereas a score of 4-5 can represent either PR, SD, or PD, depending upon whether the residual uptake is considered decreased (PR), unchanged (SD) or increased (PD) compared to baseline. Liver activity, not mediastinal blood pool activity, is the reference organ for determining CR vs residual disease. If a new site of activity is thought to be unrelated to lymphoma, it should be noted as an “X” rather than as a “5.” CT, rather than PET/CT should be used to determine responses for lymphomas with low or variable avidity.

3. Which is true about residual masses in lymphoma?
   A. They are common after therapy and accurately predict treatment failure
   B. They are considered indeterminate, but if decreasing in size can qualify as Complete Response unconfirmed (CRu)
C. If PET negative, are considered unlikely to contain residual lymphoma (KEY)
D. Remain stable anatomically (same size) and persist for the lifetime of the patient

Correct answer is C
Cheson JCO 2007 criteria eliminated the CRu classification, in part based on Juweid et al JCO 2005 data showing that inclusion of PET information into existing criteria resulted in better prediction of response. Residual masses are common after therapy but rarely contain viable tumor, Radford JCO 1988 and Cannellos JCO 1988, and they may continue to regress even after completion of therapy.

4. For which type of lymphoma would PET/CT be unlikely to provide useful information for staging and response assessment?
   A. Nodular Lymphocyte Predominant Hodgkin Lymphoma
   B. Lymphoplasmacytic lymphoma (aka Waldenstrom’s macroglobulinemia) (KEY)
   C. Follicular Lymphoma, grade 2
   D. Chronic Lymphocytic Leukemia with suspected Richter’s transformation

Correct answer is B
Cheson JCO 2014 the consensus recommendation is to use PET/CT for routine staging of all lymphoma except for chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom’s macroglobulinemia, mycosis fungoides, and marginal zone NHL, unless there is a suspicion of aggressive transformation.

5. Which statement is true regarding post-therapy imaging for lymphoma patients?
   A. PET/CT is more likely to be a false positive in an asymptomatic patient seen 6 years after completion of therapy for HL (KEY)
   B. In DLBCL, PET/CT should be obtained every 3-6 months after completion of therapy as it will often detect asymptomatic relapses
   C. Circulating tumor DNA and whole body MRI should be obtained instead of PET/CT during the first 2 years of followup for MZL patients
   D. A positive PET/CT in a FL patient within the first year after completing therapy is more likely to be a true positive for relapse than a positive scan obtained more than a year of followup

Correct answer is A
Zinzani JCO 2009, DLBCL and HL are more likely to relapse within the first 12-18 mths after completing therapy. This study also showed that indolent lymphomas, such as FL, have a similar rate of recurrence during the 4 years followup. Thompson et al., showed that most of the DLBCL relapses will be clinically evident, with few detected only by imaging. Although circulating tumor DNA and whole body diffusion weighted MRI are potential promising methods for detecting lymphoma, they are not clinically indicated at this time.