PET-imaging: when can it be used to direct lymphoma treatment?

Luca Ceriani

Nuclear Medicine and PET-CT centre
Oncology Institute of Southern Switzerland
Bellinzona
Disclosure slide

I declare no conflict of interest.
# PET-CT in Lymphoma

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Imaging Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial evaluation</td>
<td>Staging</td>
<td>Baseline PET</td>
</tr>
<tr>
<td>At the End of Treatment</td>
<td>Remission assessment</td>
<td>EoT PET</td>
</tr>
<tr>
<td>During treatment</td>
<td>Response assessment</td>
<td>Interim PET</td>
</tr>
<tr>
<td>After treatment</td>
<td>Surveillance</td>
<td>FU PET</td>
</tr>
</tbody>
</table>
PET-CT IN LYMPHOMA

From the Cheson’s criteria to the Lugano’s classification...

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Tromman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O’Doherty, Roland Hutschn, Alberto Biggi, and Bruce D. Cheson

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

**PET-CT IN LYMPHOMA**

- **Initial evaluation** → **Staging** → **Baseline PET**
- **At the End of Treatment** → **Remission assessment** → **EoT PET**
- **During treatment** → **Response assessment** → **Interim PET**
- **After treatment** → **Surveillance** → **FU PET**
PET-CT: the gold standard for routine staging of FDG avid lymphoma

Therefore, the consensus was that **PET-CT should be recommended for routine staging of FDG-avid, nodal lymphomas** (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma / Waldenström’s macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation) as the gold standard.

The following recommendations are intended for lymphomas with primarily nodal involvement, although they are also applicable to primary extranodal diffuse large B-cell lymphoma (DLBCL).

CT is indicated for staging non avid histologies.
In indolent lymphomas FDG PET-CT may be used to target biopsy in patients with suspected transformation.

Lugano classification – Cheson - JCO 2014
### PET-CT IN LYMPHOMA: staging

<table>
<thead>
<tr>
<th>Histology</th>
<th>Wellin Sagie JNM 2010</th>
<th></th>
<th>Barrington JCO 2014</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>No. of Pts.</td>
<td>FDG Avid %</td>
<td>No. of Pts.</td>
<td>FDG Avid %</td>
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<td>Mycosis fungoides</td>
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<td>Primary cutaneous anaplastic large T-cell L</td>
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<td>Plasmocitoma</td>
<td>3</td>
<td>100</td>
<td>-</td>
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</tbody>
</table>
PET-CT IN LYMPHOMA: staging

Extra nodal involvement

- **Focal FDG uptake** within the bone or bone marrow, liver, and spleen is highly sensitive for involvement in HL and aggressive NHL and may obviate the need for bone marrow biopsy.
- Diffuse increased uptake may occur with abnormal focal uptake, but in HL, diffuse uptake without focal activity often represents reactive hyperplasia and should not be confused with lymphomatous involvement.
- PET-CT can miss low-volume involvement, typically 20% of the marrow, and coexistent low-grade lymphoma in DLBCL, although this rarely affects management.
- The sensitivity of PET for diffuse marrow involvement is limited in FL, mantle-cell lymphoma, and most indolent lymphomas, where biopsy is required for staging.
- Magnetic resonance imaging (MRI) is preferred to assess suspected CNS involvement.
PET-CT IN LYMPHOMA: staging in HL

Focal BM uptake
Bone marrow involvement

Diffuse BM uptake

Unspecific (fever)

Corticosteroid therapy

BM rebound after CHT
The results of PET for nodal and extra-nodal staging of HD and high-intermediate grade NHL were clearly superior to conventional radiological imaging providing a stage modification in ~20 - 30% pts.
## PET-CT IN LYMPHOMA staging

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EORTC/GELA</th>
<th>GHSG</th>
<th>Hodgkin Lymphoma</th>
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<tbody>
<tr>
<td><strong>Limited stage patients</strong></td>
<td>CS I-II without risk factors (supradiaphragmatic)</td>
<td>CS I-II without risk factors</td>
<td>Early favorable HL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + IFRT 20Gy</td>
</tr>
<tr>
<td><strong>Intermediate stage patients</strong></td>
<td>CS I-II with ≥ 1 risk factor (supradiaphragmatic)</td>
<td>CS I, CS IIA with ≥ 1 risk factor; CS IIB with risk factors C/D, but not A/B</td>
<td>Early unfavorable HL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 ABVD + IFRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 BEACOPP esc + 2 ABVD + IFRT</td>
</tr>
<tr>
<td><strong>Advanced stage patients</strong></td>
<td>CS III-IV</td>
<td>CS IIB with risk factors A/B, CS III/IV</td>
<td>Advanced HL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6/8 ABVD ± IFRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 BEACOPP esc ± IFRT</td>
</tr>
</tbody>
</table>

| Risk factors          | (A) large mediastinal mass                      | (A) large mediastinal mass               |
|                       | (B) age ≥ 50 years                               | (B) extranodal disease                   |
|                       | (C) elevated ESR                                 | (C) elevated ESR                         |
|                       | (D) ≥ 4 nodal areas                              | (D) ≥ 3 nodal areas                      |
PET-CT IN LYMPHOMA
Prognostic value of functional baseline parameters

SUV = Standardized Uptake value = intensity of tracer uptake
MTV = Metabolic Tumor volume = tumoral mass metabolically active
TLG = Total Lesion Glycolysis [MTV x SUV mean] = metabolic tumor burden
Prognostic role of baseline PET biomarkers

Kanoun *EJNMMI 2014*
Prognostic role of baseline PET biomarkers

**DLBCL**

- **MTV**
  - BMTV < 379.16
  - BMTV ≥ 379.16
  - P = ns

- **TLG**
  - TIG < 704.77
  - TIG ≥ 704.77
  - P = .006

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**N.G. Mikhaeel, Hematol Oncol 2013. 31(s 1):100.**
IELSG 26 study: PET-CT in PMLBCL

SUV max, MTV and TLG showed significant prognostic impact at univariate analysis, only TLG retained statistical significance for both OS and PFS at multivariate analysis (Cox).

Prognostic role of baseline PET biomarkers

127 HL early stage pts.

The PFS in the high MTV group treated with combined modality therapy (CMT = ABVD +RT) was higher than that in the group treated with ABVD alone (P = 0.014).

Song MK et al. *Cancer Sci.* 2013
PET-CT IN LYMPHOMA : staging

Baseline PET, before treatment, provides:

- Accurate staging of disease
- Prognostic parameters

- the best benchmark to evaluate the degree of metabolic response during the therapy, increasing the accuracy of the subsequent response assessment
PET-CT IN LYMPHOMA

- Initial evaluation
- At the End of Treatment
- During treatment
- After treatment
- Staging
- Remission assessment
- Response assessment
- Surveillance
- Baseline PET
- EoT PET
- Interim PET
- FU PET
PET at end of treatment in lymphoma

PET-CT is standard of care for remission assessment in FDG-avid lymphoma.

Lugano classification – Barrington JCO 2014
EoT PET–CT in lymphoma

Visual assessment alone is adequate for interpreting PET findings. Deauville score for visual analysis: the 5-point scale.

1. No uptake.
2. Uptake ≤ mediastinum.
3. Uptake > mediastinum but ≤ liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new sites of disease.

X. New areas of uptake unlikely to be related to lymphoma
From the IHP (Cheson’s) criteria …..

The IHP criteria specified that uptake should be the mediastinal blood pool for lesions ≥ 2 cm or the adjacent background for smaller lesions to define metabolic response at the end of treatment.

….. to the Lugano classification

Five-point scale (Deauville scale) is recommended for reporting EoT PET-CT. Irrespective of the dimensions of the residual lesion
- scores 1 and 2 represent CMR;
- score 3 also represents CMR in patients receiving standard treatment *
- score 4 or 5 represents treatment failure
  • reduced FDG uptake from baseline (PMR)
  • no decrease in FDG uptake (MSD)
  • increased in FDG uptake to score 4 -5 and new FDG-avid foci (MPD)

* validated in HL, DLBCL, FL and PMBCL.
EoT PET-CT in lymphoma: timing

PET after completion of therapy should be performed:

• at least 3 weeks, and preferably at 6 to 8 weeks, after chT or immuno-chT
• 2 weeks after GCS-F treatment
• 3 months after RT or chemoradiotherapy.

To reduce the risk of false positive findings
EoT PET-CT in lymphoma: timing

Intra-lesional inflammation

Neoplastic cells

Inflammatory cells

Immuno-CHT

Re-growth

2 weeks

4 weeks

Time

Intra-lesional FDG uptake

CHT

PET

Nuclear Medicine and PET/CT centre
## EoT PET-CT IN LYMPHOMA

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangerter$^{20}$</td>
<td>89</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>Jerusalem$^{42}$</td>
<td>35</td>
<td>42.9</td>
<td>100</td>
</tr>
<tr>
<td>Zinzani$^{47}$</td>
<td>31</td>
<td>92.9</td>
<td>100</td>
</tr>
<tr>
<td>Mikhaeel$^{44}$</td>
<td>45</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Naumann$^{48}$</td>
<td>15</td>
<td>85.7</td>
<td>88.2</td>
</tr>
<tr>
<td>Spaepen$^{45}$</td>
<td>93</td>
<td>70.3</td>
<td>100</td>
</tr>
<tr>
<td>Cashen$^{50}$</td>
<td>50</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Gigli$^{49}$</td>
<td>42</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td><strong>HL</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spaepen$^{46}$</td>
<td>60</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Engert$^{51}$</td>
<td>728</td>
<td>NA</td>
<td>94.6</td>
</tr>
<tr>
<td>Cerchi$^{52}$</td>
<td>130</td>
<td>92.3</td>
<td>100</td>
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</tbody>
</table>

Cheson  JCO 2011
### PET-CT in Lymphoma: EOT PET

#### Table A3: Studies, Including ≥50 With Homogenous Patient Populations With HL or Aggressive NHL or FL, Reporting Outcomes According to Visual Assessment With End-of-Treatment PET

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Disease and Stage</th>
<th>No. PET Negative</th>
<th>NPV</th>
<th>PPV</th>
<th>FTF/PEFS at (years)</th>
<th>PFS/EFS</th>
<th>PET Negative (%)</th>
<th>PET Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaepen K et al; Br J Haematol 115:272-278, 2001</td>
<td>2001</td>
<td>60</td>
<td>IIA-IVB HL</td>
<td>55</td>
<td>100</td>
<td>91</td>
<td>2</td>
<td>91</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>Cerri et al²⁶*</td>
<td>2010</td>
<td>50</td>
<td>IV HL (patients in CRu/PR on CT)</td>
<td>23</td>
<td>100</td>
<td>92</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td>Engert et al²⁷†</td>
<td>2012</td>
<td>739</td>
<td>IIB-IV HL</td>
<td>548</td>
<td>96</td>
<td>NA</td>
<td>5</td>
<td>92</td>
<td>86†</td>
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<tr>
<td>Barnes et al⁰⁰</td>
<td>2011</td>
<td>96</td>
<td>I-II nonbulky HL</td>
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<td>94</td>
<td>46</td>
<td>4</td>
<td>94</td>
<td>64</td>
<td></td>
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<tr>
<td>Spaepen et al⁶¹</td>
<td>2001</td>
<td>93</td>
<td>Aggressive NHL</td>
<td>50</td>
<td>100</td>
<td>70</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td>Micallef et al⁲²*</td>
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<td>69</td>
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<td>50</td>
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<td>Trotman et al⁹³</td>
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<td>High-tumor burden FL</td>
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<tr>
<td>Dupuis et al⁵⁴*</td>
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<td>106</td>
<td>High-tumor burden FL</td>
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<td>NS</td>
<td>NS</td>
<td>2</td>
<td>87</td>
<td>51</td>
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**Abbreviations:** CRu, unconfirmed complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; FTF, freedom from treatment failure; HL, Hodgkin lymphoma; NA, not applicable; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NS, not stated; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PR, partial response.

*Prospective study.
†Treatment guided by end-of-treatment PET.

Barrington JCO 2014
PET-CT IN LYMPHOMA

- **Initial evaluation**
  - Staging
  - Baseline PET

- **At the End of Treatment**
  - Remission assessment
  - EoT PET

- **During treatment**
  - Response assessment
  - Interim PET

- **After treatment**
  - Surveillance
  - FU PET
INTERIM PET-CT

Definition
PET scan performed early after few cycles of chemotherapy (2 to 4 cycles)

Aim
- to assess early the efficacy of the treatment

Clinical meaning
- chemosensitivity
INTERIM PET-CT IN LYMPHOMA: when positive, when negative?

The oncologists need a dichotomous response (black or white; positive or negative; prognostically favourable or unfavourable)

<table>
<thead>
<tr>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
</table>

No FDG uptake | High FDG uptake

The grey zone

MRU

Interim PET describes a dynamic and continuous biological process
**INTERIM PET-CT IN LYMPHOMA**

**Rationale:** Relationship of residual tumor FDG Uptake to Clinical Outcome

Significant residual activity may be present even in patients with good prognosis.
INTERIM PET-CT IN LYMPHOMA

NHL

- baseline
- interim after 2 courses
- after the end of CHT

minimal residual uptake

positive
equivocal
negative
INTERIM PET-CT

The Lugano classification

Five-point scale (Deauville scale) is recommended for reporting iPET-CT

- scores 1 and 2 represent CMR;

- score 3 also probably represents CMR in patients receiving standard treatment *

- score 4 or 5 represents residual metabolic disease
  - reduced FDG uptake from baseline likely represents chemotherapy-sensitive disease with partial metabolic response
  - increase in FDG uptake to score 4-5, score 4-5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma represent treatment failure and/or progression

*The interpretation of a score of 3 can be different in response adapted trials.
Interim PET (2 cycles) in advanced HL

Clinical outcome for patients according to International Prognostic Score (IPS) group and positron emission tomography (PET) results after two cycles of ABVD

PET negative < Liver SUVmax
MRU - SUVmax between 2 and 3.5

Gallamini A et al. JCO 2007
Interim PET (4 cycles R-CHOP) in Follicular lymphoma

Impact of $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High–Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d’Etudes des Lymphomes de l’Adulte and GOELAMS


With a median follow-up of 23 months, 2-year PFS rates were

86% for interim PET–negative vs
61% for interim PET–positive pts
Interim PET (2 cycles) in aggressive DLBCL

Early $^{18}$F-FDG PET for Prediction of Prognosis in Patients with Diffuse Large B-Cell Lymphoma: SUV-Based Assessment Versus Visual Analysis

Lin, *JNM 2007*

Graph showing the probability of EFS (%) over months after randomization.

- PET (-): 79%
- PET (+): 51%

PET neg: DS ≤ 3
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients With HL</th>
<th>No. of Patients With NHL</th>
<th>PET Negative (%)</th>
<th>PFS/EFS (%)</th>
<th>PET Positive (%)</th>
<th>PFS/EFS (%)</th>
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<tr>
<td>Jerusalem</td>
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<td></td>
<td>82</td>
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<td>47</td>
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<td>84</td>
<td>53</td>
<td>0</td>
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<tr>
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<td></td>
<td>60</td>
<td>82</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Mikhaeel</td>
<td>121</td>
<td></td>
<td>41.3</td>
<td>93</td>
<td>43</td>
<td>30</td>
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<td>Kostakoglu</td>
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<td>74</td>
<td>100</td>
<td>26</td>
<td>12.5</td>
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<tr>
<td>Zinzani</td>
<td>24</td>
<td></td>
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<td>100</td>
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<td>Safar</td>
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<td></td>
<td>61.5</td>
<td>89</td>
<td>38.5</td>
<td>17</td>
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<tr>
<td>Cashen</td>
<td>50</td>
<td></td>
<td>63</td>
<td>81</td>
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</tr>
<tr>
<td>Gigli</td>
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<td></td>
<td>30</td>
<td>85</td>
<td>33</td>
<td>55</td>
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<td>67</td>
<td>90</td>
<td>21</td>
<td>60</td>
</tr>
<tr>
<td>Pregno</td>
<td>82</td>
<td></td>
<td>67</td>
<td>84</td>
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<td>74</td>
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<tr>
<td>Hutchings</td>
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<td>13</td>
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<tr>
<td>Hutchings</td>
<td>77</td>
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<td>79</td>
<td>95</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Zinzani</td>
<td>40</td>
<td></td>
<td>80</td>
<td>97</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Gallamini</td>
<td>260</td>
<td></td>
<td>81</td>
<td>95</td>
<td>19</td>
<td>14</td>
</tr>
</tbody>
</table>

Cheson JCO 2011
PET-CT IN LYMPHOMA: interim evaluation

Table A2. Studies Including ≥ 50 Patients With Aggressive NHL Reporting Outcomes According to Visual Assessment With Interim PET

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Chemotherapy</th>
<th>No. of Cycles of Therapy</th>
<th>No. PET Negative</th>
<th>At (years)</th>
<th>PET Negative (%)</th>
<th>PET Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaepen et al58</td>
<td>2002</td>
<td>70</td>
<td>Mostly CHOP (n = 56)</td>
<td>3-4</td>
<td>37</td>
<td>2</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>Haïoun et al55</td>
<td>2005</td>
<td>90</td>
<td>CHOP or ACVB/ACE (n = 53) plus rituximab (n = 37)</td>
<td>2</td>
<td>54</td>
<td>2</td>
<td>82</td>
<td>43</td>
</tr>
<tr>
<td>Mikhaeel et al57</td>
<td>2005</td>
<td>121</td>
<td>Mostly CHOP (n = 97)</td>
<td>2-3</td>
<td>69</td>
<td>5</td>
<td>89</td>
<td>16</td>
</tr>
<tr>
<td>Cashen et al136*</td>
<td>2011</td>
<td>50</td>
<td>R-CHOP</td>
<td>2-3</td>
<td>26</td>
<td>2</td>
<td>85</td>
<td>63</td>
</tr>
<tr>
<td>Micallef et al52*</td>
<td>2011</td>
<td>76</td>
<td>ER-CHOP</td>
<td>2</td>
<td>60</td>
<td>2</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>Yang et al28*</td>
<td>2011</td>
<td>159</td>
<td>R-CHOP</td>
<td>3-4</td>
<td>116</td>
<td>3</td>
<td>86</td>
<td>29</td>
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<tr>
<td>Yoo et al136</td>
<td>2011</td>
<td>156</td>
<td>R-CHOP</td>
<td>2-4</td>
<td>100</td>
<td>3</td>
<td>84</td>
<td>66</td>
</tr>
<tr>
<td>Zinzani et al29</td>
<td>2011</td>
<td>91</td>
<td>Mostly R-CHOP (n = 66), rituximab (n = 91)</td>
<td>Midtreatment</td>
<td>58</td>
<td>5</td>
<td>75</td>
<td>18</td>
</tr>
<tr>
<td>Safar et al31</td>
<td>2012</td>
<td>112</td>
<td>R-CHOP (n = 81), R-ACVB (n = 31)</td>
<td>2</td>
<td>70</td>
<td>3</td>
<td>84</td>
<td>47</td>
</tr>
<tr>
<td>Pregno et al30</td>
<td>2012</td>
<td>88</td>
<td>R-CHOP</td>
<td>2-4</td>
<td>66</td>
<td>2</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>Nols et al58</td>
<td>2013</td>
<td>73</td>
<td>R-CHOP (n = 48), R-miniCHOP (n = 8), ACVB (n = 17), CHOP (n = 1)</td>
<td>3-4</td>
<td>53</td>
<td>2</td>
<td>84</td>
<td>47</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, doxorubicin, cyclophosphamide, and etoposide; ACVB, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; E, etoposide; EFS, event-free survival; NHL, non-Hodgkin lymphoma; PET, positron emission tomography; PFS, progression-free survival; R, rituximab.  
*Prospective study.
INTERIM PET IN LYMPHOMA

**DLBCL**

Quantitative analysis: $\Delta$ SUV max

$\Delta$ SUV max (PET 0 –PET 2)

- $> 65.7\%$ 2-ys EFS 79%
- $< 65.7\%$ 2-ys EFS 21%

15% pts with visual interim PET + were reclassified for $> 65.7\%$

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative</td>
<td>76%</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>Visual analysis</td>
<td>65%</td>
<td>74%</td>
<td>50%</td>
</tr>
<tr>
<td>(liver uptake)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INTERIM PET: how to use it?

Response assessment: to investigate early the efficacy of the treatment

• Interim PET widely used in clinical practice to monitor therapy (but not necessarily to change standard therapy)

• Role of interim PET in response adapted therapy (under investigation in trials)
INTERIM PET: how to use it?

PET guided response adapted therapy: the paradigm

interim-PET negative: good response; effective treatment

downward arrow

de-escalation of the therapy to spare over-treatment

interim-PET positive: poor response; ineffective treatment

downward arrow

change or escalation of the therapy to avoid under-treatment
INTERIM PET IN LYMPHOMA

GOOD Response

POOR Response

Deauville score

1 2 3 4 5

overlap between the two different populations
iPET-CT: treatment concepts in response adapted clinical trials

**GOOD Response**

- **Strategy 1**
  - More intensive 1st line
  - Interim PET-
  - De-escalate
  - Risk: overtreatment
- **iPET neg**
  - DS 1-2
- **Lower rate of iPET -**
  - NPV
  - PPV

**POOR Response**

- **Strategy 2**
  - Less intensive 1st line
  - Interim PET+
  - Escalate
  - Risk: undertreatment
- **iPET pos**
  - DS 4-5
- **Lower rate of iPET+**
  - NPV
  - PPV
The Lugano classification

Five-point scale (Deauville scale) is recommended for reporting iPET-CT

- scores 1 and 2 represent CMR;

- score 3 also probably represents CMR in patients receiving standard treatment.
  In response-adapted trials exploring treatment de-escalation, a more cautious approach may be preferred, judging a score of 3 to be an inadequate response to avoid under treatment.

- score 4 or 5 represents residual metabolic disease
  - reduced FDG uptake from baseline likely represents chemotherapy-sensitive disease with partial metabolic response
  - increase in FDG uptake to score 4-5, score 4-5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma represent treatment failure and/or progression
Early Treatment Intensification in Advanced-Stage High-Risk Hodgkin Lymphoma (HL) Patients, with a Positive FDG-PET Scan After Two ABVD Courses – First Interim Analysis of the GITIL/FIL HD0607 Clinical Trial

Gallamini Abs. 550 ASH 2012

1-y PFS

PET (+) 80.5% vs PET (-) 97.3%

Strategy 2

Less intensive 1st line
Interim PET+
Escalate
Risk: undertreatment

iPET pos
DS 4-5
GHSG - HD 18

Nuclear Medicine and PET/CT centre

Strategy 1

More intensive 1st line
↓
Interim PET-
↓
De-escalate

Risk: overtreatment

iPET neg
DS 1-2

DS 2,3,4,5

standard
6x BEACOPP esc

PET positive
Arm A
1 x BEACOPP esc

3 x BEACOPP esc
closed
3 x BEACOPP esc

RT on PETpos. rests ≥ 2.5cm

Follow up

PET negative
Arm B
1 x BEACOPP esc

1 x BEACOPP esc

Arm C
Arm D

de-escalation
4x BEACOPP esc

2 x BEACOPP esc

CT-0 (Staging)

CT-2 + PET-2

CT-6/CT-4
+ PET-6/PET-4
Involved Field Radiotherapy Versus No Further Treatment in Patients with Clinical Stages IA and IIA Hodgkin Lymphoma and a ‘Negative’ PET Scan After 3 Cycles ABVD. Results of the UK NCRI RAPID Trial

Previously untreated stages I and II HL, no B symptoms or mediastinal bulk

<table>
<thead>
<tr>
<th>Progression</th>
<th>9</th>
<th>20</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>6</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>PFS at 3 yrs</td>
<td>93.8%</td>
<td>90.7%</td>
<td>85.9%</td>
</tr>
<tr>
<td>OS at 3 yrs</td>
<td>97.0%</td>
<td>99.5%</td>
<td>93.9%</td>
</tr>
</tbody>
</table>

Strategy 1

More intensive 1st line
↓
Interim PET-
↓
De-escalate

Risk: overtreatment

iPET neg
DS 1-2
PET-CT IN LYMPHOMA: interim PET

Recommendations

• If midtherapy imaging is performed, PET-CT is superior to CT alone to assess early response;

• trials are evaluating role of PET response–adapted therapy;

• currently, it is not recommended to change treatment solely on basis of interim PET-CT unless there is clear evidence of progression.

Barrington  JCO 2014
PET-CT IN LYMPHOMA

- **Initial evaluation** → **Staging** → **Baseline PET**
- **At the End of Treatment** → **Remission assessment** → **EoT PET**
- **During treatment** → **Response assessment** → **Interim PET**
- **After treatment** → **Surveillance** → **FU PET**
PET-CT IN LYMPHOMA: surveillance

Surveillance scans after remission are discouraged, especially for DLBCL and HL (false positive rate ~ 20%), although a repeat study may be considered after an equivocal finding after treatment.

Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.

Cheson JCO 2014
When can we use the PET-imaging to direct lymphoma treatment?

- **Baseline** to better stage the disease and to re-address it toward a more appropriate therapy (10-20%) *(gold standard in FDG avid Lymphoma)*

- **During treatment** to explore chemosensitivity and predict response to the therapy
  - The PET guided response-adapted therapy may be considered a reality in HL.
  - For aggressive NHL (DLBCL, PMLBCL, FL) the role of iPET to guide therapy is still under investigation in clinical trials.

- **After the treatment** to assess the efficacy of the therapy and to establish remission status *(standard of care in FDG avid Lymphoma)*