Role of PET in staging and treatment of lymphoma

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The hallmarks of cancer
Hanahan & Weinberg, Cell 2000 + 2011
Cancer cells can limit their energy metabolism largely to glycolysis, even in the presence of oxygen ("aerobic glycolysis")

- Rapidly growing tumours have glycolytic rates up to 200 x that of the normal tissues
- Lower efficiency of energy production, but upregulation of glucose transporters (GLUT1)
- Visualized by FDG-PET
Tumour microenvironment

The "reverse Warburg effect": Induced by the cancer cells by oxidative stress in adjacent stromal cells, promoting aerobic glycolysis under normoxic conditions.
FDG-PET for staging of lymphomas
FDG-PET/CT should be used for staging in clinical practice and clinical trials, but it is not routinely recommended in lymphomas with low FDG avidity

Barrington S et al. JCO 2014; 32: 3048-58

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
<th>FDG Avid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>489</td>
<td>97-100</td>
</tr>
<tr>
<td>DLBCL</td>
<td>446</td>
<td>97-100</td>
</tr>
<tr>
<td>FL</td>
<td>622</td>
<td>91-100</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, nodal</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma</td>
<td>37</td>
<td>94-100*</td>
</tr>
<tr>
<td>NK/T-cell lymphoma</td>
<td>80</td>
<td>83-100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>31</td>
<td>78-100</td>
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<tr>
<td>Peripheral T-cell lymphoma</td>
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<td>86-98</td>
</tr>
<tr>
<td>MALT marginal zone lymphoma</td>
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<td>54-81</td>
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<tr>
<td>Small lymphocytic lymphoma</td>
<td>49</td>
<td>47-83</td>
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<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>20</td>
<td>67-100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, splenic</td>
<td>13</td>
<td>53-67</td>
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<tr>
<td>Marginal zone lymphoma, unspecified</td>
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<td>67</td>
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<tr>
<td>Mycosis fungoides</td>
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<td>83-100</td>
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<tr>
<td>Sezary syndrome</td>
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<td>100†</td>
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<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
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<td>40-60</td>
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<tr>
<td>Lymphomatoid papulosis</td>
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<td>50</td>
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<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>Cutaneous B-cell lymphoma</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Different extranodal sites may show more or less "avidity", caused primarily by diffuse and low volume disease

- Cutaneous lymphomas often do not show up in cutaneous sites
• Indolent lymphomas in the wall of hollow organs often do not show up
Bone marrow involvement

- PET is highly sensitive for focal involvement, and obviates the need for biopsy in HL (El-Galaly T. JCO 2012; 30: 4508-14)

- PET is less sensitive for diffuse involvement (typically in indolent lymphomas)
FDG-PET improves the accuracy of staging (i.e. anatomic definition of extent and location)

• Change in stage in 10-30 % of patients, most often upstaging, and may lead to changes in management strategy

• Ensures that fewer patients are undertreated or overtreated

• Particularly important if radiotherapy is an option (localized vs. disseminated disease)

• Ensures inclusion of all involved sites if radiotherapy is given

• May identify optimal biopsy site if discordant histology or transformation is suspected

• Facilitates response evaluation with PET after therapy
FDG-PET for early prediction and treatment modification
Mantle field (EFRT) or involved field (IFRT)

Based on:
• 2 D planning
• Regions
• Bony landmarks defining fields
• ”Fixed” margins

Involved site (ISRT) or involved node (INRT)

Based on:
• 3 D planning
• Actual lymphoma involvement
• Contouring of volumes (GTV, CTV, PTV)
• Margins (GTV → CTV) based on clinical judgement and (CTV → PTV) based on internal and setup uncertainties
Highly conformal radiotherapy
(3D conformal, intensity modulated radiotherapy IMRT, volumetric arc therapy VMAT)

• High dose volume conforms almost precisely to the target we contour
• Very steep dose gradients around the target
• Precise target definition is crucial
• If we contour too small we will miss lymphoma and jeopardize the patient’s chance of cure
• If we contour too large unnecessary radiation will be given to normal structures
PET/CT improves accuracy of staging and target volume definition in FDG-avid lymphomas

- Pre-chemo PET/CT acquired with the patient in treatment position on a flat table top and with involvement of radiation oncology
- Post-chemo planning CT
- Diagnostic i.v. contrast enhanced CT is essential (PET/CT can be done with contrast with no interference with the attenuation correction)
- Oral contrast for abdominal and pelvic involvement
- 4D-CT imaging helpful for determining ITV
PET changes target volume in 30-60 % of patients compared to CT

- Terezakis et al. IJROBP 2014; 89: 376-83
- 89 pts. With PET+ lymphoma
- Treatment volume was contoured on CT and on PET/CT by 3 radiation oncologists and 3 nuclear medicine physicians

<table>
<thead>
<tr>
<th>Table 2</th>
<th>PET/CT GTV alteration relative to CT-based treatment planning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GTV-RO</td>
</tr>
<tr>
<td></td>
<td>Change</td>
</tr>
<tr>
<td>Increase in GTV</td>
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</tr>
<tr>
<td>&gt;5%-10%</td>
<td>5</td>
</tr>
<tr>
<td>&gt;10%-20%</td>
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<tr>
<td>&gt;20%-50%</td>
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<tr>
<td>&gt;50%</td>
<td>4</td>
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<tr>
<td>Total increase</td>
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<tr>
<td>Decrease in GTV</td>
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</tr>
<tr>
<td>&gt;5%-10%</td>
<td>6</td>
</tr>
<tr>
<td>&gt;10%-20%</td>
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<tr>
<td>&gt;20%-50%</td>
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<tr>
<td>&gt;50%</td>
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<tr>
<td>Total decrease</td>
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<tr>
<td>Change in GTV</td>
<td></td>
</tr>
<tr>
<td>±5%</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography; GTV = gross tumor volume; NMP = nuclear medicine physicians; PET = positron emission tomography; RO = radiation oncologists.
PET is prognostic

- An early interim PET-scan (typically after 2 cycles of chemotherapy) is highly predictive of outcome in most lymphoma types.
- Prognostication up front before any therapy would be even better.
- It has been demonstrated that the total tumour burden is the most important prognostic factor in HL in the pre-PET era (Specht L, Gobbi PG).
- Total tumour burden on CT is highly correlated with metabolic tumour volume (MTV) on PET/CT, which could be generated semi-automatically from PET images (Meignan, Berkowitz).
- MTV is prognostic in several lymphoma types (Song M-K. Cancer Sci 2013; 104: 1656-61).
- ΔSUV is being explored.
Is PET predictive?
Should treatment be modified according to iPET?

- Up till now no randomized evidence to support it
- Should not be done outside clinical trials
- In the EORTC H10 trial the final analysis of the patients who were PET+ after 2 cycles of ABVD has shown improved outcome with switch to BEACOPPesc (Raemaekers J, presented in Lugano 2013)
PET is prognostic pre-HDT-ASCT (left) but not pre-NMA-allo-SCT (right)

Sauter CS et al. Blood 2015; 125: 2579-81

Sauter CS et al. Biol Blood Marrow Transplant 2014; 20: 881-4
FDG-PET for response evaluation
Response evaluation

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

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

JCO 2014; 32: 3059-67

- PET/CT should be used in FDG-avid histologies
- Deauville criteria:
  - 1. No uptake
  - 2. Uptake ≤ mediastinum
  - 3. Uptake > mediastinum but ≤ liver
  - 4. Uptake moderately higher than liver
  - 5. Uptake markedly higher than liver and/or new lesions
  - X. New areas of uptake unlikely to be related to lymphoma
- A complete metabolic response even with persistent mass is considered CR
Lymphoma patient, FDG-PET/CT before and after 4 cycles of chemotherapy
What does it mean to be PET+/- after chemotherapy?

HD15, BEACOPPesc

Picardi, VEBEP

Advani, Stanford V

Sher, ABVD

p<0.01
What is the negative predictive value of FDG-PET?

**DLBCL**

- FDG-PET did not predict outcome in high risk pts after 4 x R-CHOP14
- PET+ were biopsied, 33/38 were negative, all showed inflammation, no correlation with SUV

Moskowitz CH et al. JCO 2010; 28: 1896-1903
No indication for PET in routine follow-up
Thank you for your attention