Potential and pitfalls in PET-imaging of lymphoma

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Disclosure slide

• I declare no conflict of interest.
Fields of further development

- PET Technology
- New techniques of hybrid imaging
- New metabolic biomarkers
- Radiotracers
- PET «culture»
Evolution of the PET technology

- CT attenuation correction
- Iterative protocols
- Lutetium oxyortho-silicate (LSO)
- Ultra-fast detector electronics (3D)
- Time-of-flight (TOF)
- Resolution recovery (PFS)
- Increase of axial FOV
- Continuous motion of the cradle

Sensitivity, Resolution, Image Quality
Technological developments improved the diagnostic accuracy

- **Sensitivity:**
  - Detection rate of lesions with low uptake
  - I.e. in FDG non-avid lymphoma
  - Radioactivity injected
  - Reduction of effective dose (~25%)

- **Resolution:**
  - Detection rate of smaller lesions (4-5 mm)
  - Time of PET images acquisition (15-20 min.)
  - Accuracy of measurement (quantification)
New techniques of hybrid imaging

- PET- CT (low dose)
- PET- CeCT (contrast enhanced – full dose)
- PET- MRI
New techniques of hybrid imaging: **PET-CeCT**

More anatomical details  
More precision in measurement  
No impact on PET findings.

Higher exposure to radiations  
PET-CT (low dose) 10-15 mSv  
PET-CeCT (full dose) 25-30 mSv
Clinical impact of CeCT combined with low-dose 18F-FDG PET-CT on routine lymphoma management.

N=237

- No CeCT impact 219 (92%)
- clear CeCT impact 7 (3%)
  (upstaging in 2, DVT detection in 5)
- debatable CeCT impact 11 (5%)
  (additional investigations with no treatment change in 10)

Chalave J et al. Leuk Lymphoma 2014
Can full-dose Contrast-enhanced CT be omitted from an FDG-PET/CT staging examination in newly FDG-avid lymphoma?

N=29
- No CeCT impact 27 (93%)
- upstaging 2 (7%)

Authors’ conclusions
unenhanced low-dose FDG-PET/CT should be the modality of choice at least in younger patients and in those at increased risk of CT contrast-induced allergic reactions or nephropathy

PET-imaging potential in lymphoma

Aggressive (FDG avid) lymphoma

PET-CT (low dose)  PET-CeCT (full dose)

PET-guided CeCT

Therapy

End – Therapy PET-CT (low dose)

Positive PET  Negative PET

PET-guided CeCT

STOP

Modified from Kostakoglu L. et al. EJNMMI 2014
End-Therapy PET-CT (low dose)

PET-guided CeCT

PET-imaging potential in lymphoma

Indolent (FDG non-avid) lymphoma

PET-CeCT (full dose)

Positive PET
Therapy

Negative PET
Therapy

End-Therapy PET-CT (low dose)

Positive PET

Negative PET

CeCT

STOP
New techniques of hybrid imaging: PET-MRI

Potential advantages:
- Reduction of Exposure to radiations
- Complementary/superior diagnostic value of MRI compared to CT
- Indications: bone marrow, soft tissues, spleen, liver.

Open problems:
- Attenuation correction
- MR-specific diagnostic limitations
- Workflow
- Design of suitable imaging protocols

Work in progress - No clinical role today. Complementary to PET-CT
New metabolic biomarkers

- **MTV**: metabolic tumor volume
  (Tumor burden)

- **TLG**: total lesion glycolysis
  (morpho-metabolic marker - MTV x Standard Uptake Value (SUV) mean)
  (metabolic burden)
Prognostic role of metabolic PET biomarkers in DLBCL

- Baseline MTV and TLG strongly predictive of prognosis, but on multivariate analysis only Deauville score after 2 cycles & baseline TLG were significant.

- A model combining these 2 parameters can predict a group with significantly low PFS.

N.G. Mikhaeel, Hematol Oncol 2013. 31(s 1):100.
Prognostic role of metabolic PET biomarkers in PMLBCL

Elevated vs. non-Elevated TLG

5-year PFS
- 64% vs. 97%
Logrank test, p < 0.0001

5-year OS
- 80% vs. 100%
Logrank test, p = 0.0001

PFS according to the combination of baseline TLG and post-treatment Deauville Score

TLGb < 5184 + DS 1-3
TLGb < 5184 + DS 4-5
TLGb > 5184 + DS 1-3

TLGb > 5184 + DS 4-5
Log-rank test p < 0.001

Ceriani L. et al. Hematol Oncol 2013. 31(s1):187-8
Zucca E. et al. Hematologica. 2014. 9(s1):524-525
Prognostic role of metabolic PET biomarkers in HD

Summary of Cox proportional hazards analysis of patient outcomes (in the context of early stage HD pts):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PFS p-value</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment PET Metrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUV max</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SUV mean</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MTV</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Interim PET Metrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUVmax</td>
<td>0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MTV</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>iSUV TLG</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SUV mean</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Calculated PET Metrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTV_{int/pre}</td>
<td>0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SUV_{mean/\text{int/pre}}</td>
<td>NS</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>SUV_{max/\text{int/pre}}</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>iSUV_{\text{int/pre}} TLG</td>
<td>0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>


Song MK et al. *Cancer Sci.* 2013
New metabolic biomarkers

- **MTV**: metabolic tumor volume  
  (Tumor burden)

- **TLG**: total lesion glycolysis  
  (morpho-metabolic marker - MTV x Standard Uptake Value (SUV) mean)  
  (metabolic burden)

**Open problems:**
- Lack of standardization
- Time expensive procedure
New radiotracers

3’-deoxi-3’-18F-fluoro-thymidine (FLT): marker of proliferative activity.

\[ ^{18} \text{FLT uptake} < ^{18} \text{FDG} \text{ in tumor lesions} \]

- Promising probe to determine therapy response and to distinguish between tumors and inflammatory masses
  - FLT uptake not affected by the temporary intralesional rise in the inflammatory cells (lower false positive rate).

- Predictive marker of response, early during the treatment
- Prognostic marker baseline
New « cultural» approaches

- Common language and standard criteria
- Collect data (metanalysis and multicentre trials)
- Share experiences

*J Clin Oncol* 32. © 2014

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

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

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 Mikhael, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Miteller, Lawrence H. Schwartz, Emanuele Zucca, Richard L. Fisher, Judith Treiman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O’Doherty, Roland Hustin, Alberto Biggi, and Bruce D. Cheson
PET-imaging pitfalls in lymphoma

Common causes of false-positive FDG PET findings

- Inflammation
- Infections

Specificity
Inflammation:
- related to the therapy
  - intra-lesional (Immuno- /chemo- therapy)
  - intra and peri-lesional (radiotherapy)
  - organs (side effects /drug toxicity/ reaction)

- due to cronic inflammatory diseases
  i.e. sarcoidosis, tuberculosis..

Infections:
- secondary to leucopenia
  (pneumonia, enterocolitis, urinary infections ..)
- relapse of known diseases (HIV+ pts.)
Common causes of false-positive FDG PET findings

Intra-lesional inflammation

- Neoplastic cells
- Inflammatory cells
- Immuno-CHT
- Re-growth

CHT
PET

2 weeks
4 weeks

Time
High incidence of false-positive PET scans in patients with aggressive non-Hodgkin’s lymphoma treated with rituximab-containing regimens. 

Han H. S. et al.  *Annals of Oncology* 2009

Authors’ conclusions
Compared with previous reports in pre-rituximab era, addition of rituximab resulted in reduced PPV and sensitivity of mid- and post-therapy PET in pts with aggressive B-cell NHL.

Change of the definition of the metabolic CR:
Deauville Score 3: residual uptake $\leq$ liver uptake
Cronic inflammatory diseases

Basal staging
Follicular lymphoma

End-treatment
Biopsy: sarcoidosis
PET-imaging pitfalls in lymphoma

11/2007
HD
HIV +

05/2008
CR

02/2010

Biopsy: follicular hyperplasia
Reactive adenopathy
Differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy using quantitative FDG PET and symmetry.

<table>
<thead>
<tr>
<th>Metric</th>
<th>HIV-associated lymphoma (N=19)</th>
<th>HIV-associated reactive adenopathy (N=22)</th>
<th>P value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single SUL-Max</td>
<td>15.9±6.8</td>
<td>2.9±2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TLG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2,146.5±2,778.5</td>
<td>30.6±53.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1,766 (1.97 – 12,660)</td>
<td>1.0 (1.0 – 153.3)</td>
<td></td>
</tr>
<tr>
<td>Single SUL-Peak</td>
<td>12.6±5.7</td>
<td>2.0±2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycolytic volume/MTV</td>
<td>409.8±611.5</td>
<td>9.6±14.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sum SUL-Peak</td>
<td>69.3±54.5</td>
<td>7.2±9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sum SUL-Max</td>
<td>104.3±88.9</td>
<td>16.3±20.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Summed CT nodal size</td>
<td>104.5±73.5</td>
<td>61.8±48.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Single nodal visual score b, reader 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4 (0 – 4)</td>
<td>4 (0 – 4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sum nodal visual score, reader 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>24 (0 – 60)</td>
<td>11.5 (0 – 66)</td>
<td>0.41</td>
</tr>
<tr>
<td>Nasopharyngeal region SUL-Max</td>
<td>3.5±3.2</td>
<td>3.7±2.9</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Gold standard : Biopsy or cytologic assessment

Mhlanga JC et al. EJNMMI 2014
PET-imaging pitfalls in lymphoma

**DLBCL**

Bone marrow reaction

![Images showing PET scans at different time points: basal staging, after 2nd cycle CHT and G-CSF, after 3rd cycle CHT, and a final image.]

- **07/08**: Basal staging
- **09/08**: After 2nd cycle CHT and G-CSF
- **10/08**: After 3rd cycle CHT
- **01/09**
- **04/09**
PET-imaging pitfalls in lymphoma

BM lesions: the flip-flop phenomenon

BM reaction after ChT

Multi focal BM lesions
The interpretation of the PET-CT findings can be further optimized by a bidirectional communication between oncologist and nuclear physician.
Thank you for attention!