Role of PET in staging and treatment of lymphomas

ESMO preceptorship in lymphoma
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PET in lymphoma staging
PET/CT improves the accuracy of staging in aggressive lymphoma

- Clinical stage is the most important determinant for the choice of first line treatment strategy in lymphoma
- More individualized therapy increases demand for precise determination of initial disease extent
- PET/CT is more sensitive than conventional staging methods (incl. CT), with equal specificity\(^1,2\)
- In aggressive lymphomas PET/CT results in upstaging of 15-25% of patients, shift from early to advanced stage in 10-15% of patients\(^1,2\)

PET/CT: Handle with care

- Upstaging means further risk of overtreatment
- PET/CT staging should be accompanied by
- More refined and tailored treatment strategies to avoid overtreatment due to upstaging
- Relevant modifications to the staging system to enhance the benefits obtained from improved accuracy
- Radiotherapists have shown the way:
  - Smaller treatment volumes despite detection of more involved nodes (IFRT → INRT)\(^1\)

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\(1\) Girinsky et al. Radiother Oncol. 2007; 85: 178-86.
PET/CT obviates the need for routine BMB in HL

- Retrospective study of 454 Danish HL patients undergoing both PET/CT and BMB at staging\(^1\)
- 18% had focal skeletal FDG uptake, only 6% were BMB positive
- No patients with positive BMB were assessed as having stage I-II disease by PET/CT staging
- None of the 454 patients would have been allocated to another treatment on the basis of BMB results

Follicular lymphoma staging

- Multiple studies: 97-100% FDG-avidity in FL

Scott 2009:
76 low-grade NHL patients, 74% FL
PET/CT identified additional lesions in 50% of patients
Leading to a stage change in 32% and management change in 34%

Wirth 2008:
42 stage I-II FL patients
PET/CT meant upstaging to stage III-IV in 31%
Enlargement of involved fields in additional 14%

Janikova 2008:
82 FL patients
PET/CT showed more lesions in 50%
Upstaging in 18%

Le Dortz 2010:
45 FL patients
51% more nodal lesions and 89% more extranodal lesions than CT.
Upstaging in 18%, from stage I-II to stage III-IV in 11%

**Follicular lymphoma staging**

- 142 FL patients in the randomised Italian FOLL05 trial
  - Treatment: R-CHOP vs. R-CVP vs. R-FM
  - 32% of patients had more nodal areas on PET than on CT
  - 15 of 24 patients (62%) of patients with stage II on CT were upstaged by PET to stage III-IV

- **Conclusions:**
  - PET very sensitive in FL and has a profound impact on staging, treatment strategy and assessment of prognosis
  - Criteria for treatment vs. w&w should be revisited in large, PET/CT staged cohorts
  - PET/CT useful as a biopsy guide if suspected aggressive transformation / discordant

- **Upstaging**
  - 18-32%

- **Treatment change**
  - 11-28%

- **Stage I-II → stage III-IV**
  - 31-62%

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Early interim PET in lymphoma
Many studies show excellent outcomes for FDG-PET-negative HL patients compared with those showing persistent FDG uptake\textsuperscript{1–6}
Early interim PET in early stage HL

H10: 954 randomised to ABVD + Radiotherapy,
Early PET after 2 ABVD
No treatment modification according to early PET

Predictive role of early interim PET in DLBCL/aggressive B-NHL

1998

2002

2003

2005

2006

2007

2009

2009

2010

2011

2011

2011

+/- Rituximab

+ Rituximab
PET/CT for early treatment monitoring in HL and DLBCL

- PET-response to initial treatment is the most powerful prognostic indicator in lymphoma
- HL: NPV 90-95% PPV 60-80%
- DLBCL: NPV 80-85% PPV 50-70%
- In DLBCL, most failures occur in interim PET-negative patients
Interim PET in follicular lymphoma

- Prospective French study of 121 FL patients treated with R-CHOP
- PET/CT before treatment, after 4 cycles and after completion of treatment
- All PET/CT scans centrally reviewed and scored according to Deauville 5-point scale
- PET after 4 cycles predictive of PFS (p=0.0046)
  - Interim PET negative: 2-y PFS 86%
  - Interim PET positive: 2-y PFS 61%
- No significant prognostic value of CT response according to 1999 IWC criteria

260 patients with advanced HL

All baseline and interim (PET2) PET/CT scans were independently scored by six blinded reviewers

According to the Deauville 5-point scale

3-year failure free survival:
- 95% for PET negative
- 28% for PET positive

5 Point Scale (Deauville criteria)

1. no uptake
2. uptake ≤ mediastinum
3. uptake > mediastinum but ≤ liver
4. moderately increased uptake compared to liver
5. markedly increased uptake compared to liver and/or new lesions

**markedly** increased uptake is taken to be uptake > 2-3 times the SUV max in normal liver
Early PET-response adapted therapy – Hodgkin lymphoma
# PET-response adapted treatment of early stage Hodgkin lymphoma

<table>
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<th>Study</th>
<th>Patients</th>
<th>Main PET-driven intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>UK NCRI RAPID (Published)</td>
<td>Early stage HL</td>
<td>If PET-negative after 3xABVD randomization to RT vs. no RT</td>
<td>III</td>
</tr>
<tr>
<td>EORTC/GELA/FIL H10 (Published)</td>
<td>Early stage HL</td>
<td>Experimental arm: No radiotherapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD</td>
<td>III</td>
</tr>
<tr>
<td>CALGB 50604 (Published)</td>
<td>Early stage HL non-bulky</td>
<td>Additional ABVDx2 and no radiotherapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD</td>
<td>II</td>
</tr>
<tr>
<td>GATLA HL05 (Published)</td>
<td>All stages HL</td>
<td>No further treatment if PET-negative after 3 x ABVD</td>
<td>II</td>
</tr>
<tr>
<td>GHSG HD16 (Completed accrual)</td>
<td>Early stage HL no risk factors</td>
<td>No radiotherapy in experimental arm if PET-negative after 2xABVD</td>
<td>III</td>
</tr>
<tr>
<td>CALGB 50801 (Recruiting)</td>
<td>Early stage HL bulky</td>
<td>Additional ABVDx4 and no radiotherapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD</td>
<td>II</td>
</tr>
<tr>
<td>ECOG 2410 (Recruiting)</td>
<td>Early stage HL bulky</td>
<td>4xBEACOPPesc + RT if PET-positive after 2xABVD</td>
<td>II</td>
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</tbody>
</table>
H10 interim analysis – PET2 negative

- 1950 patients randomised
- 1137 patients available for interim analysis
- Non-inferiority margin 10%
- Median follow-up 13 months
- PET2 negative, favourable:
  - 1-y PFS 94.9% if no RT
  - 1-y PFS 100% if INRT
- PET2 negative, unfavourable:
  - 1-y PFS 94.7% if no RT
  - 1-y PFS 97.3% if INRT

IDMC conclusion: Unlikely to show non-inferiority
→ stop treatment stratification of PET2 negative patients

Authors’ conclusion: Cannot exclude non-inferiority of chemo only arm, but early outcome is excellent in both arms

H10 final analysis of PET2 negative favourable patients

- 465 patients with **favourable** disease had treatment stratified according to a negative PET2:
- Median follow-up 5.0 years
- ITT analysis:
  - 31 PFS events in no RT arm
  - 2 PFS events in INRT arm
  - 5-y PFS **87.1** if no RT
  - 5-y PFS **99.0%** if INRT
  - 5-y OS **99.6%** if no RT
  - 5-y OS **100%** if INRT

H10 final analysis of PET2 negative unfavourable patients

- 594 patients with **unfavourable** disease had treatment stratified according to a negative PET2:
  - Median follow-up 5.1 years
  - ITT analysis:
    - 32 PFS events in no RT arm
    - 22 PFS events in INRT arm
    - 5-y PFS **89.6%** if no RT
    - 5-y PFS **92.1%** if INRT
    - 5-y OS **98.1%** if no RT
    - 5-y OS **96.2%** if INRT

Authors’ conclusion: Cannot exclude non-inferiority of chemo only arm, but early outcome is excellent in both arms (unchanged)

Does escalation in early PET-positive patients improve outcomes? Final results of the H10 study

**Progression-Free Survival**

HR (95% CI) = 0.42 (0.23, 0.74) p=0.002 *
5-yr PFS: 90.6% vs. 77.4%

**Overall Survival**

HR (95% CI) = 0.45 (0.19, 1.07) p=0.062
5 yr OS: 96.0% vs. 89.3%


- ITT: 361 PET2 positive patients
- Median follow-up 4.5 years
- 97 patients with favourable disease:
  - Std. arm: PFS event in 5/54 = 9.2%
  - Exp. arm: PFS event in 3/43 = 6.9%
- 264 patients with unfavourable disease:
  - Std. arm: PFS event in 36/138 = 26.0%
  - Exp. arm: PFS event in 13/126 = 10.3%
# PET response adapted treatment of advanced Hodgkin lymphoma

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<tr>
<td>GITIL HD0607</td>
<td>Stage IIB-IV + stage IIA with RF</td>
<td>Intensification to BEACOPPesc if PET-positive after 2xABVD</td>
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<tr>
<td>RATHL</td>
<td>Stage IIB-IV</td>
<td>Intensification to BEACOPP if PET-positive after 2xABVD</td>
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<tr>
<td></td>
<td></td>
<td>Randomisation between ABVD and AVD if PET-negative</td>
<td></td>
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<tr>
<td>Israel/Rambam</td>
<td>Early stage + RF/bulk or advanced stage</td>
<td>PET after 2xBEACOPPbaseline or BEACOPPesc: Proceed to 4xBEACOPPesc If PET-positive or 4xBEACOPPbaseline if PET-negative</td>
<td>II</td>
</tr>
<tr>
<td>IIL HD0801</td>
<td>Stage IIB-IV</td>
<td>Salvage regimen if PET-positive after 2xABVD. Randomisation between radiotherapy and no further treatment after completion of 6xABVD if PET-negative after 2xABVD</td>
<td>III</td>
</tr>
<tr>
<td>GHSG HD18</td>
<td>Stage IIB-IV</td>
<td>4 vs. 6 x BEACOPPesc in experimental arm if PET-negative after 2 cycles. Standard arm: 6 x BEACOPPesc.</td>
<td>III</td>
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<tr>
<td>LYSA AHL2011</td>
<td>Early stage HL bulky</td>
<td>De-escalation from BEACOPPesc to ABVD in exper. arm in case of a negative PET after 2 and 4 cycles. Standard arm: 6 x BEACOPPesc.</td>
<td>III</td>
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<tr>
<td>SWOG S0816</td>
<td>Stage III-IV</td>
<td>Intensification to BEACOPPesc if PET-positive after 2xABVD</td>
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Early PET-response adapted therapy – NHL
## German PETAL trial

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<th>Study title/Group</th>
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<tr>
<td>MSKCC 01-142</td>
<td>DLBCL</td>
<td>Salvage with HD+ASCT if PET-positive and Bx-positive after 2 x R-(maxi)CHOP14</td>
<td>II</td>
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<tr>
<td>LYSA (GELA) LNH2007-3B</td>
<td>DLBCL</td>
<td>Salvage with HD+ASCT if PET-positive after 2 x R-CHOP</td>
<td>II</td>
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<tr>
<td>BCCA PET in DLBCL</td>
<td>DLBCL</td>
<td>4 cycles R-ICE if PET-positive after 4 x R-CHOP</td>
<td>II</td>
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<tr>
<td>NCI/Johns Hopkins  (Completed)</td>
<td>aNHL</td>
<td>Salvage with HD+ASCT if PET-positive after 2-3 x (R-)CHOP</td>
<td>II</td>
</tr>
<tr>
<td>PETAL</td>
<td>aNHL</td>
<td>Randomisation between R-CHOP and Burkitt regimen if PET-positive after 2 x R-CHOP</td>
<td>III</td>
</tr>
</tbody>
</table>
German PETAL trial

Standard R-CHOP → Interim PET → Standard R-CHOP, Standard R-CHOP, Burkitt Protocol

Courtesy of Prof. U Dührsen, Essen
German PETAL trial

- 959 patients recruited 2007-2012
- 853 patients evaluable for the ITT analysis
- 746 pts. (87 %) interim PET negative and 107 (13 %) interim PET positive
- In interim PET positive patients, a switch to the Burkitt-type regimen showed no beneficial effect on
  - TF (HR 1.6, CI 0.9 – 2.7)
  - CR rate (50 % vs. 31 %, p=0.10)
  - OS (HR 1.0, CI 0.5 – 2.1).
- Similar results were obtained, when the analysis was restricted to DLBCL

Courtesy of Prof. U Dührsen, Essen
Post-treatment PET in lymphoma
FDG-PET for post-treatment evaluation

- In HL and DLBCL, PET has very high negative predictive value (NPV) and variable positive predictive value (PPV) for post-treatment evaluation with conventional treatment.\(^1\)
- The international response criteria for lymphoma are PET/CT based.\(^2\)
- If PET-negative, the patient is in complete remission.
- The new criteria more predictive than previous CT-based criteria.\(^3\)
- EOT PET can be used to select patients for consolidation radiotherapy in advanced HL.\(^4,5\)

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Follicular lymphoma – post treatment

- Prospective French study of 121 FL patients treated with R-CHOP
- PET/CT before treatment, after 4 cycles and after completion of treatment
- All PET/CT scans centrally reviewed and scored according to Deauville 5-point scale
- End-of-treatment PET predictive of PFS and OS (p=0.0046)
  - EOT PET negative: 2-y PFS 87% and 2-y OS 100%
  - EOT PET positive: 2-y PFS 51% and 2-y OS 88%
- No significant prognostic value of CT response according to 1999 IWC criteria (or FLIPI)

Follow-up PET imaging in lymphoma
PET/CT in routine follow-up of lymphomas

- At first remission, PET/CT sensitivity and negative predictive value (NPV) are very high, however:¹,²
  - Higher rates of false-positives than CT
  - PET/CT and CT have similarly (low) positive predictive value (PPV) for detection of recurrent lymphoma/secondary malignancies

- In HL it takes 50–100 FDG-PET scans to detect one relapse earlier than conventional methods (including CT)³,⁴

- Currently, no available evidence to show that patients with minimal, asymptomatic disease respond better to 2\textsuperscript{nd} line therapy than patients with low tumour burden and discrete symptoms

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PET in salvage treatment for relapsed/refractory lymphoma
Post-induction PET/CT before HD+ASCT predicts outcome in relapsed HL patients

PFS/EFS for relapsed HL patients according to pre-transplant PET/CT

76 patients, 2-y PFS 73% vs. 36%\(^1\)  
46 patients, 3-y EFS 82% vs. 41%\(^2\)

PET/CT may help tailor salvage treatment for relapsed HL

New imaging recommendations and response criteria
Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group


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

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PET – CT based metabolic response</th>
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<tr>
<td>CMR</td>
<td>Score 1, 2, 3* in nodal or extranodal sites with or without a residual mass using 5-PS</td>
</tr>
</tbody>
</table>
| PMR       | Score 4 or 5, with reduced uptake compared with baseline and residual mass(es) of any size. 
  *At interim*, these findings suggest responding disease 
  *At end of treatment* these findings indicate residual disease 
  Bone marrow: Residual marrow uptake > normal marrow but reduced compared with baseline (diffuse changes from chemotherapy allowed). If there are persistent focal changes in marrow with a nodal response, consideration should be given to MRI, biopsy or interval scan. |
| NMR       | Score 4 or 5 with no significant change in uptake from baseline *At interim or end of treatment* |
| PMD       | Score 4 or 5 with an increase in uptake from baseline and/or New FDG-avid foci consistent with lymphoma *At interim or end of treatment* |

*Score 3 in many patients indicates a good prognosis with standard treatment. However in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as inadequate response to avoid under-treatment*
PET in lymphoma - summary
PET in lymphoma: summary

- **Staging PET/CT** *(standard of care)*
  - Increased staging accuracy – better basis for risk-stratified treatment
  - More refined definition of radiotherapy volumes – less irradiation to normal tissues
  - Baseline scan essential for subsequent PET/CT monitoring

- **Early response monitoring** *(standard of care)*
  - PET/CT is highly prognostic and superior to mid-treatment CT
  - PET-response adapted tailored treatment may improve outcomes and reduce over-treatment

- **Post-treatment evaluation** *(standard of care)*
  - Cornerstone in current response criteria (Lugano)
  - Offers improved selection of patients for consolidation radiotherapy in HL

- **Follow-up** *(no indication for routine use)*
  - PET/CT not indicated for routine surveillance but useful if relapse is suspected

- **R/R disease** *(standard of care)*
  - Pre-transplant PET/CT – good predictor of outcome after HD-ASCT
  - Limited data on the value of PET/CT guided therapy