Role of PET in staging and treatment of lymphomas
Disclosures

- Roche: Consultant
- Takeda: Consultant
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

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
- 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

- 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%

Early interim PET in lymphoma
Many studies show excellent outcomes for FDG-PET-negative HL patients compared with those showing persistent FDG uptake.1–6

Early interim PET in early stage HL

HI0 : 954 randomised to ABVD + Radiotherapy,
Early PET after 2 ABVD
No treatment modification according to early PET

A. Progression-Free Survival

HR=5.70 (95%CI= 3.59 to 9.06)
P<.001

B. Overall Survival

HR=6.68 (95%CI= 3.14 to 14.4)
P<.001

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

- 1998
- 2002
- 2003
- 2005
- 2006
- 2007
- 2009
- 2010
- 2011
- 2011

Graphs and images showing statistical analyses and survival rates with and without Rituximab treatment.
PET/CT for early treatment monitoring in DLBCL

- Relatively high predictive values:
  - NPV 80-85%
  - PPV 50-70%
- Nevertheless, most failures still occur in interim PET-negative patients
Interim PET in follicular lymphoma

- Prospective French study of 121 FL patients treated with R-CHOP\(^1\)
- 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\(^2\)
- 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\(^3\)

International validation study of the Deauville 5-point scale for interim PET in HL\textsuperscript{1,2}

- 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
### Early stage HL: Can a negative early PET/CT select patients who do not need radiotherapy?

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<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>
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<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>
UK/NCRI RAPID final analysis

- 602 patients included
- **No stratification by risk factors**
- 420 patients PET-negative after 3 x ABVD randomised to IFRT or NFT
- Non-inferiority margin = 7%
- Median follow-up 60 months

3-year PFS (ITT)
- 3 x ABVD + IFRT = 94.6%
- 3 x ABVD + NFT = 90.8%
- Difference = -3.8% (95% CI: -8.8 to 1.3%)

3-year OS
- 97.1% vs 99.0% (NS)

**Conclusions:**
- Study did not show non-inferiority
- PET3 negative patients have a very good prognosis, regardless of consolidation radiotherapy

---

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**

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<th>C-Std</th>
<th>C-Exp</th>
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<tbody>
<tr>
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<td>192</td>
<td>169</td>
</tr>
<tr>
<td>1</td>
<td>157</td>
<td>152</td>
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<td>81</td>
<td>63</td>
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<tr>
<td>8</td>
<td>81</td>
<td>14</td>
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**HR (95% CI) = 0.42 (0.23, 0.74) p=0.002**
5-yr PFS: 90.6% vs. 77.4%

**Overall Survival**

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<td>15</td>
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<td>8</td>
<td>2</td>
<td>1</td>
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**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 (Completed)</td>
<td>Stage IIB-IV + stage II A with RF</td>
<td>Intensification to BEACOPPesc if PET-positive after 2xABVD</td>
<td>II</td>
</tr>
<tr>
<td>RATHL (Completed)</td>
<td>Stage IIB-IV</td>
<td>Intensification to BEACOPP if PET-positive after 2xABVD Randomisation between ABVD and AVD if PET-negative</td>
<td>III</td>
</tr>
<tr>
<td>Israel/Rambam (Completed)</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 (Completed)</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>
</tr>
<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 – DLBCL
## PET-response adapted therapy for DLBCL

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High risk DLBCL: $aalPI > 1$ or $aalPI = 1$ with high beta 2-microglobulin (>30 mg/l) + eligible for high-dose therapy
**GELTAMO phase II study**

- Patients in complete remission after interim PET (N = 36) had significantly better 3-year PFS than those with partial response (N = 30)
  - CR: 3-year PFS 81%
  - PR: 3-year PFS 57%

## PET-response adapted therapy for DLBCL

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BCCA phase II study

- DLBCL and PMBCL, all stages and risk groups
- 155 patients
- After 4 cycles of standard R-CHOP21 therapy:
  - 59% PET-negative, 33% PET-positive and 8% PET-indeterminate
- PET-positive patients continued with 4 x R-ICE

## PET-response adapted therapy for DLBCL

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ECOG/ACRIN E3404

DLBCL stages 3-4 and 2 bulky

Total enrollment N=100

Path ineligible N=19
Never started treatment N=1

Eligible and started initial R-CHOP N=80

Adverse events N=1
Patient withdrawal N=1
Other complicating disease N=1
Lost to follow-up after cycle 1 N=1

Completed 4 cycles of R-CHOP N=76

Mid-treatment PET + N=13

Adverse events N=1
Patient withdrawal N=1
Other complicating disease N=1

Eligible for subsequent treatment N=13

Completed 4 cycles of R-ICE N=10

Mid-treatment PET – N=63

Patient withdrawal N=1
Ineligible (no CT scan after cycle 3) N=1

Eligible for subsequent treatment N=61

Completed 2 more cycles of R-CHOP N=58

Death N=1
Progressive Disease N=1
Alternative therapy N=1

ECOG/ACRIN E3404

- 2-year PFS for PET-positive patients = 42%
- Not regarded as encouraging

## PET-response adapted therapy for DLBCL

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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

## PET-response adapted therapy for DLBCL

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<th>Main PET-driven intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI/Johns Hopkins</td>
<td>aNHL</td>
<td>HD+ASCT if PET-positive after 2-3 x (R-)CHOP</td>
<td>II</td>
</tr>
<tr>
<td>MSKCC 01-142</td>
<td>DLBCL</td>
<td>HD+ASCT if PET-positive and Bx-positive after 2 x R-(maxi)CHOP14</td>
<td>II</td>
</tr>
<tr>
<td>LYSA (GELA) LNH2007-3B</td>
<td>DLBCL</td>
<td>HD+ASCT if PET-positive after 2 x R-CHOP</td>
<td>II</td>
</tr>
<tr>
<td>GELTAMO</td>
<td>DLBCL</td>
<td>HD+ASCT if PET-positive after 3 x R-megaCHOP</td>
<td>II</td>
</tr>
<tr>
<td>BCCA PET in DLBCL</td>
<td>DLBCL</td>
<td>4 x R-ICE if PET-positive after 4 x R-CHOP</td>
<td>II</td>
</tr>
<tr>
<td>ECOG/ACRIN E3404</td>
<td>DLBCL</td>
<td>4 x R-ICE if PET-positive after 4 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>
<tr>
<td>GAINED (ongoing)</td>
<td>DLBCL</td>
<td>Randomisation between R-chemo and G-chemo. HD+ASCT if PET-positive after 2 cycles</td>
<td>II</td>
</tr>
</tbody>
</table>
LNH 2009-1B

DLBCL: 18-80 y, aalPI=0

Planned accrual = 650 pts: 566 patients enrolled

Non inferiority of the experimental arm
Standard arm: 80% 3y-PFS ; Experimental arm: 3y-PFS >70% (HR=1.6)
Post-treatment PET guided selection of patients for consolidation and maintenance
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\(^4,5\)

PET/CT determines the need for consolidation radiotherapy in advanced HL

GHSG HD15 experience\(^1,2\)

- BEACOPP chemotherapy
  - Only patients with a PET-positive residual mass > 2.5 cm received RT
  - 4-year PFS 91.5% in post-treatment PET-negative patients

BCCA experience\(^3\)

- ABVD chemotherapy
  - Only patients with a PET-positive residual mass > 2.0 cm received RT
  - 3-year PFS 89% in post-treatment PET-negative patients

Bulky disease has no impact on PFS in post-treatment PET-negative patients despite omission of radiotherapy

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)

FOLL12 TRIAL DESIGN
I° line, stage II–IV, FL

(P.I. M. Federico)

FOLLICULAR NHL
Grade I–II–IIIa
Age 18–75
Stage II–IV
Active disease
FLIPI2≥1

INDUCTION therapy
R-CHOP/R-B

Experiment al arm

Standard arm

PET/MRD

CR, PR

R-maintenance every 2 months x 2 yr

<PR

Salvage

Patients with no molecular markers

PET–

MRD

Neg

Observation

Pos

Rituximab weekly x 4

PET+

(90)Y ibritumomab tiuxetan + R-maintenance every 2 months x 2 yr

<PR

Salvage

Courtesy of Stefano Luminari
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%\textsuperscript{1}

46 patients, 3-y EFS 82% vs. 41%\textsuperscript{2}

\textsuperscript{1}Mocikova H, et al. Leuk Lymphoma 2011;52:1668–74.
PET/CT may help tailor salvage treatment for relapsed HL


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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

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

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
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PET – CT based metabolic response</th>
</tr>
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<tbody>
<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>
<tr>
<td>PMR</td>
<td>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 &gt; 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.</td>
</tr>
<tr>
<td>NMR</td>
<td>Score 4 or 5 with no significant change in uptake from baseline. At interim or end of treatment</td>
</tr>
<tr>
<td>PMD</td>
<td>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</td>
</tr>
</tbody>
</table>

* 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.
Patient case - staging

- 19 year old male college student
- Presents mid 2014 with enlarged lymph nodes on both sides of the neck
  - Prior to this, enlarged lymph node on the right side for 6 months and three times seen by GP who suspected viral infection
- Fever and night sweats
  - → finally referred to a diagnostic unit
- Biopsy from the right cervical region showed mixed cellularity HL
- PET/CT: Supradiaphragmatic disease only, but severe extranodal spread to both lungs and the thoracic wall
- No severe anaemia, but lymphocytopenia and marginal hypoalbuminaemia
Patient case – early response

- After 2 x ABVD a PET/CT showed residual activity in the mediastinum (> liver background)
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**
After 2 x ABVD a PET/CT shows residual activity in the mediastinum.

The patient was offered intensification with BEACOPPesc.

Based on GITIL0607 and RATHL.

Continues with ABVD and completes 6 cycles.

Post-treatment PET/CT shows ?
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
After 2 x ABVD a PET/CT shows residual activity in the mediastinum. The patient was offered intensification with BEACOPPesc. Based on GITIL0607 and RATHL. Continues with ABVD and completes 6 cycles. Post-treatment PET/CT shows progressive metabolic disease. **Biopsy-proven failure**. Still only supradiaphragmatic disease. Starts DHAP salvage chemotherapy.
Patient case – relapse treatment

- After 2 x DHAP
- Goes on with SC harvest and 3\textsuperscript{rd} DHAP, BEAM is planned
- After 3 x DHAP
- GVD + IFRT is offered as salvage and accepted by the patient
- After GVD + IFRT, CT shows structural regression and HD BEAM is given in Sept. 2015
- Post-treatment PET/CT Oct. 2015
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 improves outcomes and reduces over-treatment in HL

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

- **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