The role of PET in haematological malignancies

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EORTC Lymphoma Group
PET in haematology

- **Lymphoma:**
  - Widespread use in staging, treatment monitoring, radiotherapy planning, etc. Several thousand studies.

- **Myeloma:**
  - Emerging role. A number of reports suggest a role in staging and treatment monitoring.

- **Leukemia:**
  - Not used. Sporadic case reports suggest a possible role in the diagnosis of extramedullar AML.
  - Potential role in the diagnosis of Richter transformation
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 over-treatment 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)²

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

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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%\(^1\)

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%\(^3\)

Janikova 2008:
82 FL patients
PET/CT showed more lesions in 50%
Upstaging in 18%\(^2\)

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%\(^5\)

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%

Mantle cell lymphoma staging

- MCL highly FDG-avid\(^1\)
- PET/CT alters staging in more than half of patients, mostly upstaging\(^1,2\)
- Patients with truly localized MCL are more accurately identified with PET/CT\(^1,2\)
- High FDG uptake predicts a worse outcome than low-grade uptake, suggesting that metabolic activity correlate to tumor aggressiveness\(^2\)

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Staging of other indolent lymphomas

- SLL has variable FDG avidity\(^1\)
- In FDG-avid cases the uptake is usually discrete, and, as for CLL, PET/CT is useful for selecting biopsy site in suspected Richter’s transformation\(^2,3\)
- The value of PET/CT staging in MALT lymphoma/MZL is controversial and the reported FDG-avidity in is inconsistent\(^1,4\)
- Nodal MZL are usually FDG-avid, while this is rarely the case for extranodal MZL\(^1,4\)

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}

Predictive role of early interim PET in DLBCL/aggressive B-NHL
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\(^1\)
- 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\(^3\)

Early PET-response adapted therapy – Hodgkin lymphoma
Early stage HL: Can a negative early PET/CT select patients who do not need radiotherapy?

<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>GHSG HD16 1</td>
<td>Early stage HL no risk factors</td>
<td>No radiotherapy in experimental arm if PET-negative after 2xABVD</td>
<td>I</td>
</tr>
<tr>
<td>EORTC/GELA/FIL H10 (Completed)</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>UK NCRI RAPID (Completed)</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>CALGB 50604</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>CALGB 50801</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</td>
<td>Early stage HL bulky</td>
<td>4xBEACOPPesc + RT if PET-positive after 2xABVD</td>
<td>II</td>
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</table>
UK/NCRI RAPID final analysis

- 602 patients included
- 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
  - 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

EORTC/LYSA/FIL H10 interim analysis

- 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; advised to stop randomisation of PET2 negative patients

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

Should treatment be escalated in early PET-positive patients?

- 1950 patients randomised
  - 754 favourable
  - 1196 unfavourable
- Median follow-up 4.5 years
- PET2 positive:
  - F: 54 patients (14%)
  - U: 138 patients (23%)

**Progression-Free Survival**

- HR (95% CI) = 0.42 (0.23, 0.74)
- p=0.002 *
- 5-yr PFS: 91% vs. 77%

**Overall Survival**

- HR (95% CI) = 0.45 (0.19, 1.07)
- p=0.062
- 5 yr OS: 96% vs. 89%

1. Raemaekers JM, et al. ICML Lugano 2015,
PET response adapted treatment of advanced HL

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<td>Intensification to BEACOPPesc if PET-positive after 2xABVD</td>
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<td>Stage IIB-IV</td>
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2 cycles ABVD

**PET negative**

4 cycles ABVD

**PET positive**

- BEACOPP 4+4
- R-BEACOPP 4+4

Randomize

NFT

RT to sites of initial bulky disease

PI: Andrea Gallamini, Cuneo IT
GITIL HD 0607 interim analysis

- 773 patients included
- 151 PET2 post (19.5%) and 622 PET2 neg (80.5%)
- 500 patients evaluable for treatment response with min 2y follow-up:
  - PET2 positive: CR rate 74%
  - PET2 negative: CR rate 95%
- Long-term outcome
  - PET2 positive: 4-y FFS 62% and 4-y OS 86%
  - PET2 negative: 4-y FFS 85% and 4-y OS 95%
  - Entire cohort: 4-y FFS 81% and 4-y OS 93%

## PET response adapted treatment of advanced HL

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2 cycles ABVD

PET negative

- 4 cycles AVD
- 4 cycles ABVD

Follow-up (no radiation)

PET positive

- 4 cycles BEACOPP
- PET -ve
- 2 cycles BEACOPP

PET +ve
- Follow-up (no radiation)

RT: PET+ Residual on CT >2.5cm (INRT)

Salvage

PI: Prof. Peter Johnson, Southampton
RATHL results:

- Omitting bleomycin significantly reduced the rate of infections and pulmonary toxicity.
- Omitting bleomycin did not affect the 3-year progression-free survival (84-85% in both arms).
- Omitting bleomycin did not affect the 3-year overall survival (97% in both arms).

1. Johnson PW, et al. ICML 2015, plenary session, abstract #008
PET response adapted treatment of advanced HL

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GHSG HD18 trial for advanced stages (ongoing)

2 x BEACOPP escalated (esc)

PET +
- 4xBEACOPPesc
- 4xR-BEACOPPesc

PET -
- 4xBEACOPPesc
- 2xBEACOPPesc

After chemo: PET; RX to PET+ res nodes >2.5 cm
PET-: Follow up

Courtesy of Andreas Engert
Upcoming EORTC advanced HL study

1 x Br-AVD

PET+

6 x BrECADD

PET-

5 x Br-AVD

Br-AVD: Brentuximab vedotin, adriamycin, vinblastine, dacarbazine
BrECADD: Brentuximab vedotin, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone
Early PET-response adapted therapy – NHL
**PET-response adapted therapy for DLBCL**

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<td>BCCA PET in DLBCL</td>
<td>DLBCL</td>
<td>4 cycles R-ICE if PET-positive after 4 x R-CHOP</td>
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<td>NCI/Johns Hopkins <em>(Completed)</em></td>
<td>aNHL</td>
<td>Salvage with HD+ASCT if PET-positive after 2-3 x (R-)CHOP</td>
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<td>PETAL</td>
<td>aNHL</td>
<td>Randomisation between R-CHOP and Burkitt regimen if PET-positive after 2 x R-CHOP</td>
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Prospective, biopsy controlled determination of “positive PET”

- Therapy interval 2 weeks
- PET 10-14 days post cycle 4
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM

MSKCC 01-142: DLBCL: Risk Adapted Therapy
CS II/IX, III or IV disease, age-adjusted IPI 1-3, transplant eligible

## German PETAL trial

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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

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\(^3\)

- PET can be used to determine the need for additional radiotherapy in advanced HL\(^4,5\)

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

GHSG HD 15 experience

- 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

- 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

Follicular lymphoma – post treatment

- Analysis of PRIMA sub-study:
- 122 patients with post-treatment PET/CT
- PET/CT superior to CT for post-treatment response evaluation

Conventional restaging with CT

PET/CT restaging

1. Trotman et al. JCO 2011;29:3194-3200
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, )
  - Interim PET negative: 2-y PFS 87% and 2-y OS 100%
  - Interim 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 aggressive lymphoma routine follow-up

- At first remission, PET/CT sensitivity and negative predictive value (NPV) are close to 100%, 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
- 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 do better after salvage therapy than patients with low tumour burden and discrete symptoms

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

Post-induction PET/CT before HD+ASCT predicts outcome in relapsed DLBCL patients

Post-induction PET and radiotherapy in relapsed DLBCL

- MSKCC retrospective experience in 189 pt.

- PFS for PET-positive patients who receive RT before HD+ASCT is equal to

- PFS for patients who are PET-negative before HD+ASCT
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 Zucchi, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O’Doherty, Roland Rustinx, 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 Zucchi, and T. Andrew Lister

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
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<th>PET – CT based metabolic response</th>
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<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>
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<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>
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* 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
PET in myeloma
Myeloma is an FDG-avid disease

- Identification of truly solitary plasmacytoma
- Distinction of MGUS or SMM from active MM
- Assessment of risk by measuring disease extent
  - PET/CT is incorporated into the new Durie-Salmon staging system (DSS PLUS)
- Detection of extraosseous myeloma
- Response assessment
Identification of truly solitary plasmacytoma

- MRI detects evidence of MM in app. 25% of patients with SP on radiographic bone survey\(^1\)
- PET/CT detects additional lesions in 33-47% of cases\(^2\)
- In one study, the combination of normal PET/CT and normal bone marrow (incl. flow) identifies a group with 100% disease-free survival after local radiotherapy\(^3\)

Distinction of MGUS or SMM from active MM

- Due to a higher sensitivity than radiography and MRI, PET/CT may help establishing the MM diagnosis in patients with monoclonal gammopathy

Detection of extraosseous myeloma

- Extramedullary disease is seen in 10-15% of MM patients
- This incidence is increasing
- Extramedullary disease is a marker for
  - more aggressive disease
  - poorer survival

Response assessment with PET

PET in myeloma - conclusions

- MRI and PET/CT are equal for the staging assessment of bone and marrow involvement.
- PET/CT is superior to MRI for detection of extramedullary disease.
- PET/CT is particularly useful for differentiation between solitary plasmocytoma and multiple myeloma.
- PET/CT can help differentiate between MGUS/SMM and MM.
- PET/CT assessment of disease extent can enhance the risk assessment of MM patients.
- A number of studies show that PET before and after transplant are predictive of disease-free survival.
Thank you!