PET IN LYMPHOMA

evidence based imaging?

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Evidence based imaging

No clear definition of evidence based imaging

No introduction of a single new imaging or other diagnostic modality has ever resulted in a proven survival benefit for lymphoma patients

Prior to PET and PET/CT, all imaging methods have been introduced into lymphoma management based on very little or no data

With PET, we are at least trying to provide such data
How do we measure PET in lymphoma?

1. Is the method accurate?
   - Yes

2. Does the method have an impact on patient management?
   - Sometimes

3. Does the method improve the outcome of patients?
   - We do not know
Outline

1) Staging
2) Treatment monitoring
3) Response evaluation
4) Follow-up
5) Recommendations
Patient-tailored therapy

High cure rates
Risk of overtreatment

Risk of relapse
Survivorship
1) Staging
Ideal

Accurate pre-treatment prognostic and predictive markers

Real world

Clinical staging

Prognostic scores


PET/CT improves the accuracy of lymphoma staging

Higher sensitivity than CT and other conventional staging methods, but not at the expense of the specificity

10-25% upstaging, many to a more advanced treatment

PET/CT affects the delineation of modern radiotherapy fields in roughly ¼-⅓ of patients

What is the consequence of improved staging accuracy?

“When the Okies left Oklahoma and moved to California, they raised the average intelligence in both states.”
- Will Rogers
What is the consequence of improved staging accuracy?

Better outcome for both early and advanced stages?
So why are we not happy?
Because we should be careful not to overtreat
What is the consequence of improved staging accuracy?

Better outcome for both early and advanced stages

So why are we not happy?

Because we should be careful not to overtreat

More accurate staging should be reflected by a corresponding change in treatment strategies and/or modifications of the staging system
2) Early treatment monitoring
PET for early treatment monitoring

Response to initial treatment is the most powerful prognostic indicator in lymphoma.

Responders and non-responders can be precisely identified by PET after a few chemotherapy cycles.

Early interim PET is the best tool for risk-adapted lymphoma therapy.
**TABLE 1.** Prognostic Value of $^{18}$F-FDG PET After 1–3 Cycles of Chemotherapy for Aggressive NHL and HL

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cycles of chemotherapy before PET</th>
<th>No. of patients</th>
<th>Type of lymphoma</th>
<th>No. (%) of patients whose PET results were:</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>total</td>
</tr>
<tr>
<td>Jerusalem et al. (13)</td>
<td>2000</td>
<td>2 or 3</td>
<td>28</td>
<td>NHL</td>
<td>5</td>
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<td>Mikhaeel et al. (14)</td>
<td>2000</td>
<td>2–4</td>
<td>23</td>
<td>NHL</td>
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<td>Spaepen et al. (15)</td>
<td>2002</td>
<td>3 or 4</td>
<td>70</td>
<td>NHL</td>
<td>33</td>
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<tr>
<td>Hoekstra et al. (16)</td>
<td>1993</td>
<td>1 or 2</td>
<td>13</td>
<td>HL</td>
<td>10</td>
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<tr>
<td>Kostakoglu et al. (17)</td>
<td>2002</td>
<td>1</td>
<td>13</td>
<td>HL</td>
<td>15</td>
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<tr>
<td>Torizuka et al. (18)</td>
<td>2004</td>
<td>1 or 2</td>
<td>3</td>
<td>NHL</td>
<td>16</td>
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<tr>
<td>Mikhaeel et al. (19)</td>
<td>2005</td>
<td>2 or 3</td>
<td>121</td>
<td>NHL</td>
<td>52</td>
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<tr>
<td>Haioun et al. (20)*</td>
<td>2005</td>
<td>2</td>
<td>90</td>
<td>NHL</td>
<td>36</td>
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<tr>
<td>Kostakoglu et al. (21)</td>
<td>2006</td>
<td>1</td>
<td>23</td>
<td>HL</td>
<td>16</td>
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<tr>
<td>Hutchings et al. (22)</td>
<td>2005</td>
<td>2 or 3</td>
<td>85</td>
<td>HL</td>
<td>13</td>
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<tr>
<td>Hutchings et al. (23)*</td>
<td>2006</td>
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<td>77</td>
<td>HL</td>
<td>16</td>
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<tr>
<td>Zinzani et al. (24)*</td>
<td>2006</td>
<td>2</td>
<td>40</td>
<td>HL</td>
<td>8</td>
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<tr>
<td>Gallamini et al. (25)*</td>
<td>2006</td>
<td>2</td>
<td>108</td>
<td>HL</td>
<td>20</td>
</tr>
<tr>
<td>Gallamini et al. (26)**</td>
<td>2007</td>
<td>2</td>
<td>260</td>
<td>HL</td>
<td>50</td>
</tr>
</tbody>
</table>

*Prospective study.

†This publication reported updated results for cohorts for which some data were previously reported elsewhere.

**Positive predictive value** 60-100%

**Negative predictive value** 80-100%

<table>
<thead>
<tr>
<th>Study title/description</th>
<th>Study group (reference)</th>
<th>Form of lymphoma</th>
<th>Main PET-driven intervention</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{18})F-FDG PET–stratified R-DICEP and R-TEAM/ASCT for diffuse large B-cell lymphoma (PET CHOP)</td>
<td>Alberta Cancer Board (30)</td>
<td>DLBCL</td>
<td>Salvage with HD + ASCT if PET results are positive after 2× R-CHOP</td>
<td>Phase II</td>
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<tr>
<td>Associations of rituximab and chemotherapy with PET-driven strategy for lymphoma (LNB1007-3B)</td>
<td>GELA (37)</td>
<td>DLBCL</td>
<td>Salvage with HD + ASCT if PET results are positive after 2× R-CHOP</td>
<td>Phase III*</td>
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<tr>
<td>Tailoring treatment for B-cell NHL on basis of PET results midtreatment</td>
<td>British Columbia Cancer Agency (32)</td>
<td>Advanced DLBCL</td>
<td>4 cycles of R-ICE if PET results are positive after 4× R-CHOP</td>
<td>Phase II</td>
</tr>
<tr>
<td>(^{18})F-FDG PET for predicting relapse in NHL patients undergoing chemotherapy with or without ASCT</td>
<td>Johns Hopkins University (33)</td>
<td>Aggressive NHL</td>
<td>Salvage with HD + ASCT if PET results are positive after 2× or 3× CHOP or R-CHOP</td>
<td>Phase II</td>
</tr>
<tr>
<td>PET-guided therapy of aggressive NHL</td>
<td>University Hospital, Essen, Germany (34)</td>
<td>Aggressive NHL</td>
<td>CHOP or R-CHOP vs. Burkitt lymphoma regimen if PET results are positive after 2× CHOP or R-CHOP</td>
<td>Phase III</td>
</tr>
<tr>
<td>RAPID trial</td>
<td>U.K. NCRI Lymphoma Group (91)</td>
<td>Early-stage HL</td>
<td>Randomization to RT vs. no RT if PET results are negative after 3× ABVD</td>
<td>Phase III</td>
</tr>
<tr>
<td>HD16 protocol for early-stage HL</td>
<td>German Hodgkin Study Group (35)</td>
<td>Early-stage HL</td>
<td>No radiotherapy in experimental arm if PET results are negative after 2× ABVD</td>
<td>Phase III</td>
</tr>
<tr>
<td>(^{18})F-FDG PET–guided therapy or standard therapy for stage I or II HL (H10 protocol)</td>
<td>EORTC–GELA–III (36)</td>
<td>Early-stage HL</td>
<td>No radiotherapy in experimental arm if PET results are negative after 2× ABVD</td>
<td>Phase III</td>
</tr>
<tr>
<td>PET-adapted chemotherapy for advanced HL</td>
<td>GITIL (39)</td>
<td>Advanced HL</td>
<td>Intensification to BEACOPPesc if PET results are positive after 2× ABVD</td>
<td>Phase II</td>
</tr>
<tr>
<td>(^{18})F-FDG PET response–adapted therapy for advanced-stage HL (RATHL)</td>
<td>U.K. NCRI Lymphoma Group (40)</td>
<td>Advanced HL</td>
<td>Intensification to BEACOP if PET results are positive after 2× ABVD</td>
<td>Phase III*</td>
</tr>
<tr>
<td>HD + ASCT in patients with positive results of PET after 2× ABVD and RT vs. no RT in patients with negative results of PET (HD0801)</td>
<td>IIL (41)</td>
<td>Advanced HL</td>
<td>Salvage regimen if PET results are positive after 2× ABVD</td>
<td>Phase III*</td>
</tr>
<tr>
<td>HD18 protocol for advanced-stage HL</td>
<td>German Hodgkin Study Group (42)</td>
<td>Advanced HL</td>
<td>4× vs. 8× BEACOPPesc in experimental arm if PET results are negative after 2 cycles</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
3) Post-treatment evaluation
Post-treatment evaluation

PET has very high NPV and variable PPV for post-treatment evaluation with conventional treatment

New response criteria: If PET-negative = CR
Hodgkin lymphoma

A

IWC

IWC + PET

Time to next treatment (years)

CR
CRu
PR
SD

0.0
0.2
0.4
0.6
0.8
1.0

0
2
4
6
8
10
12

B

IWC

IWC + PET

Overall survival (years)

CR
CRu
PR
SD
PD

0.0
0.2
0.4
0.6
0.8
1.0

0
2
4
6
8
10
12

Brepoels et al. Leuk Lymphoma 2007;48:1539–47
Aggressive NHL

4) Follow-up
Routine surveillance after therapy
What is the point?

Patient reassurance

Detection of second tumours

Monitoring late effects of chemo- and radiotherapy
gonadal, cardiac, pulmonary, musculoskeletal, endocrine etc.

Most importantly: *early diagnosis of relapse*
Early diagnosis of relapse

We like to identify a relapse as early as possible

We know that tumour burden is a prognostic factor

But do patients with minimal, asymptomatic disease do better after salvage therapy than patients with low tumour burden and discrete symptoms?

**We do not know!**

This should be kept in mind when considering different surveillance strategies
Routine CT surveillance came in through the back door

210 HL patients. 37 relapses – only 4 patients asymptomatic at the time of diagnosis of relapse
Radford et al. BMJ 1997

The increased value of routine CT is limited
PET in follow-up
Zinzani JCO 2009

Large, prospective study of 421 lymphoma patients (160 HL, 183 aggressive NHL, 78 FL)

Patients PET/CT scanned after 6, 12, 18, 24 months, and annually thereafter

Large, prospective study of 421 lymphoma patients (160 HL, 183 aggressive NHL, 78 FL)

Patients PET/CT scanned after 6, 12, 18, 24 months, and annually thereafter

Same relapse pattern as reported by Radford et al.
Zinzani et al. – conclusions

PET/CT detects a number of unexpected relapses before CT and prior to symptoms

Most relapses are detected 1) during the first year, and 2) in early interim PET-positive patients

It took 1,789 PET/CT scans to detect 14 relapses earlier than CT and other methods would have done

- Crocchiolo et al. Ann Hematol 2009
- Maeda et al. ASH 2009
- Lee et al. Cancer 2010
- El-Galaly et al. Leuk Lymphoma 2011

Retrospective studies showing a high false-positive rate of follow-up PET/CT
Conclusions on PET in follow-up

Sensitivity and NPV close to 100% - higher than CT

PPV 23-100% (different pre-test likelihood, reading criteria)

It takes 50-100 PET/CT scans to detect one relapse earlier than conventional methods, including CT (Zinzani et al., Lee et al.)

The benefit of routine PET/CT surveillance is highest during the first 1-2 years in patients with a residual mass (Petrausch)

in patients with a positive early interim PET (Zinzani)
5) Recommendations
Staging – *standard of care*

- Increased staging accuracy – better basis for risk stratified treatment
- More refined definition of radiotherapy volumes – less irradiation to normal tissues

**Early response monitoring – clinical trial settings**

- Early PET/CT may help tailor therapy to the individual patient and thus improve outcomes while still reduce unnecessary over-treatment

**Posttreatment evaluation – standard of care**

- High NPV – suited for characterisation of a residual mass
- Moderate PPV – treatment failure can only be safely determined with biopsy

**Radiotherapy planning – standard of care**

- PET/CT is needed to further refine radiotherapy volumes and help reduce irradiation to normal tissues

**Follow-up – when clinically indicated**

- Not indicated for routine surveillance
Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography for Interim Response Assessment of Advanced-Stage Hodgkin’s Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review
Teruhiko Terasawa, Joseph Lau, Stéphane Bargar, Olivier Couturier, Tomomitsu Hotta, Martin Huchings, Takashi Nihashi, and Hirokazu Nagai

Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography in Response Assessment Before High-Dose Chemotherapy for Lymphoma: A Systematic Review and Meta-Analysis
Teruhiko Terasawa, Issa J. Dahanber, Takashi Nihashi

18F-FDG PET for Posttherapy Assessment of Hodgkin’s Disease and Aggressive Non-Hodgkin’s Lymphoma: A Systematic Review
Teruhiko Terasawa, Takashi Nihashi, Tomomitsu Hotta, and Hirokazu Nagai

DOI: 10.2967/jnumed.107.039867