Pros and Cons:
Interim PET in DLBCL

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Pros
Is there any evidence that early PET (after 1 or 2 cycles) has a prognostic role in DLBCL?

Should we report early PET qualitatively or quantitatively?
Interim PET

Predictive value in aggressive lymphomas

Interim PET

Predictive value in aggressive non-Hodgkin’s lymphomas
Interim PET

Predictive value in aggressive non-Hodgkin’s lymphomas
Interim PET

What is a negative PET scan?

What is a negative PET scan?

(R-)CHOP-1 2 3 4 5 6

Negative ? Positive ?
Interim PET

Method of PET evaluation

- True negative
- False positive

Threshold of detectability by PET

Tumor metabolism vs Treatment cycles
Interim PET

Method of PET evaluation

Visual assessment

SUV-based assessment

92 DLBCL patients, PET after cycle 2

Interim PET

SUV-based PET evaluation: confirmatory studies

Visual assessment

SUV-based assessment

Casasnovas et al, Blood 118: 37, 2011; IVS DLBCL, Menton 2011
Is histological confirmation the „gold standard“ reference for patients with mid-treatment positive PET?
Interim PET

**Histological confirmation in interim PET positive patients**

![Diagram of clinical workflow]

- **R-CHOP-14 x 4** (n=97)
  - 38 positive (PET+)
  - 59 negative (PET-)
  - 33 repeat biopsy (Bx+)
  - 5 biopsy negative (Bx-)
  - Consolidation B: ICE x 2
    - RICE x 1 followed by HDT/ASCT
  - Consolidation A: ICE x 3 followed by observation

Interim biopsy

*Predictive of treatment failure?*

<table>
<thead>
<tr>
<th>Method of tissue sampling</th>
<th>(47%)</th>
<th>(29%)</th>
<th>(21%)</th>
<th>(3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core needle biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Endoscopy</strong></td>
<td></td>
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<tr>
<td><strong>Open surgery</strong></td>
<td></td>
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<tr>
<td><strong>Fine needle aspiration</strong></td>
<td></td>
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</table>

**Prediction of outcome?**

<table>
<thead>
<tr>
<th></th>
<th><strong>Biopsy</strong></th>
<th>(\text{neg.})</th>
<th>(\text{pos.})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment failure</strong></td>
<td></td>
<td>(\text{no})</td>
<td>(\text{yes})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>2</td>
</tr>
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</table>

Fisher's Exact Test: \(p = 0.338\)

**Success rate of core needle biopsy**

**Aggressive NHL** (Pappa et al. 1996)
- Posttreatment evaluation \(60\%\)
- Suspected progression \(83\%\)

**All lymphomas** (de Kerviler et al. 2000)
- Suspected progression or recurrence \(89\%\)

**All lymphomas** (Goldschmidt et al. 2003)
- Suspected progression \(75\%\)

**Average success rate** \(77\%\)

1 Pappa et al, J Clin Oncol 14: 2427, 1996
2 De Kerviler et al, Cancer 89: 647, 2000

Is interim PET feasible in multicenter clinical trials?
Interim PET

Requirements in multicenter clinical trials

Standardization of the procedure
- timing in relation to chemotherapy
- control of comedication
- preparation of the patient
- scanning conditions

Standardized, reproducible, easy-to-use method of evaluation
Interim PET

Interval between chemotherapy and PET

Day 10

1. Macrophages
2. Lymphoma cells
3. Necrosis

Day 15

Viable tumor cells

Inflammatory cells

Interim PET

*Interval between chemotherapy and PET*

<table>
<thead>
<tr>
<th>Pretreatment PET</th>
<th>Interim PET day 13</th>
<th>Interim PET day 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction $SUV_{max}$:</td>
<td><strong>56%</strong></td>
<td><strong>83%</strong></td>
</tr>
</tbody>
</table>

Hüttmann et al, J Clin Oncol 28: e488, 2010
Interim PET

Requirements in multicenter clinical trials

Standardization of the procedure

- interval from last chemotherapy: as long as possible
- control of comedication: no G-CSF
- preparation of the patient: fasting conditions, glucose level
- scanning conditions: type of scanner, interval injection-scanning

Standardized, reproducible, easy-to-use method of evaluation

- quantitative assessment
Interim PET

False positive PET scans – positive predictive value ↓


False positive PET results

Visual assessment: normal

Interval: 10 – 14 days

G-CSF
Can we change treatment on interim PET results?
Interim CT

Role in treatment decisions

Therapy cycles
1 - 3

Interim CT

SD
PD

Refractory

CR PR

Therapy cycles
4 - 6
Interim CT

Arbitrary borders between treatment success and failure
Interim CT

Role in treatment decisions in DLBCL?

CT-response-adapted therapy:
8 x CHOP versus 4 x CHOP + HDT

No improvement despite intensification

Interim PET

Role in treatment decisions in DLBCL?

SUV-based assessment

< 2/3 reduction → poor outcome

Interim PET

PETAL Trial

Standard R-CHOP

Interim PET

Standard R-CHOP

Standard R-CHOP

Burkitt Protocol

Prediction of outcome?

Interim PET

neg.

pos.

Treatment failure

no

242

30

yes

27

11

310 patients

Risk ratio: 2.673

Fisher's Exact Test: \( p = 0.008 \)
Interim PET

**PETAL trial – standardization of scanning conditions**

Interval chemotherapy – PET2

- Patients
- Days after first day of last chemotherapy
- Responders
- Non-responders
- Median = 19 days
- n = 406

**Interval injection – scanning**

-Responders = 332
-Non-responders = 54
Cons ?
Interim PET

Proportion of treatment failures correctly predicted

SUV-based assessment

## Interim PET

*Proportion of treatment failures correctly predicted*

<table>
<thead>
<tr>
<th>Study</th>
<th>No. pts.</th>
<th>Treatment failures</th>
<th>% iPET- TF</th>
<th>% iPET+ TF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2007</td>
<td>92</td>
<td>34 (37%) at 3 yrs.</td>
<td>53 %</td>
<td>47 %</td>
</tr>
<tr>
<td>IVS 2011</td>
<td>120</td>
<td>38 (32%) at 3 yrs.</td>
<td>58 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Casasnovas 2011</td>
<td>85</td>
<td>21 (23%) at 2 yrs.</td>
<td>71 %</td>
<td>29 %</td>
</tr>
<tr>
<td>PETAL 2010</td>
<td>310</td>
<td>38 (12%) at 10 mo.</td>
<td>71 %</td>
<td>29 %</td>
</tr>
</tbody>
</table>

Only 13% – 22% of patients are interim PET positive.

Only 29% – 47% of treatment failures occur in the interim PET positive group.

→ **The majority of treatment failures are not predicted by interim PET!**
1. Is there any evidence that early PET (after 1 or 2 cycles) has a prognostic role in DLBCL?
   
   *Yes!*

2. Should we report early PET qualitatively or quantitatively in DLBCL?

   *Quantitatively!*

3. Is histological confirmation the „gold standard“ reference for patients with mid-treatment positive PET?

   *No!*

4. Is interim PET feasible in multicenter clinical trials?

   *Yes!*

5. Can we change treatment on interim PET results?

   *This needs to be tested in prospective clinical trials!*