Potential applications of PET/CT in MALT and PMLBC lymphoma

Luca Ceriani, Gaetano Paone and Emanuele Zucca

Nuclear Medicine PET-CT Centre and Research Division
Oncology Institute of Southern Switzerland
Ospedale San Giovanni Bellinzona
The value of positron emission tomography (PET) scan is controversial and has little clinical utility [IV, D]∗.

* IV Retrospective cohort studies or case-control studies
  D Moderate evidence against efficacy or for adverse outcome, generally not recommended
PET-CT in MALT lymphoma


• Staging and risk assessment of marginal zone lymphoma:

“...The value of positron emission tomography (PET) scan is controversial, has uncertain clinical utility and is not recommended...”
A sword of Damocles

Potential applications of PET-CT in MALT lymphoma?!!
PET-CT in MALT lymphoma

### Table 1. Recommended Timing of PET (PET/CT) Scans in Lymphoma Clinical Trial

<table>
<thead>
<tr>
<th>Histology</th>
<th>Pretreatment</th>
<th>Mid-Treatment</th>
<th>Response Assessment</th>
<th>Post-Treatment Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely FDG avid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Follicular NHL</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
<tr>
<td>MCL</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
<tr>
<td>Variably FDG avid</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Other aggressive NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not††</td>
<td>No</td>
</tr>
<tr>
<td>Other indolent NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not††</td>
<td>No</td>
</tr>
</tbody>
</table>

†Recommended only if ORR/CR is a primary study end point.
‡Recommended only if PET is positive pretreatment.

Cheson B. et al. JCO 2007
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</tr>
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</table>

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Cheson B. et al. JCO 2007
# PET-CT sensitivity in MALT lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Primary site</th>
<th>No of cases</th>
<th>Sensitivity (95% C.I.)</th>
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<tbody>
<tr>
<td>Beal</td>
<td>2005</td>
<td>gastric</td>
<td>10</td>
<td>60% (26-88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>extragastric</td>
<td>32</td>
<td>88% (71-96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all sites</td>
<td>42</td>
<td>81% (66-91%)</td>
</tr>
<tr>
<td>Alinari</td>
<td>2006</td>
<td>gastric</td>
<td>7</td>
<td>100% (59-100%, one-sided)</td>
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<tr>
<td></td>
<td></td>
<td>extragastric</td>
<td>19</td>
<td>73% (49-91%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all sites</td>
<td>26</td>
<td>81% (61-93%)</td>
</tr>
<tr>
<td>Hoffman</td>
<td>2006</td>
<td>gastric</td>
<td>9</td>
<td>44% (14-79%)</td>
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<tr>
<td></td>
<td></td>
<td>extragastric</td>
<td>26</td>
<td>58% (37-77%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all sites</td>
<td>35</td>
<td>54% (37-71%)</td>
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<tr>
<td>Ambrosini</td>
<td>2006</td>
<td>gastric</td>
<td>9</td>
<td>100% (66-100%, one-sided)</td>
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<td>Karam</td>
<td>2006</td>
<td>all sites</td>
<td>12</td>
<td>75% (43-94%)</td>
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<tr>
<td>Radan</td>
<td>2008</td>
<td>gastric</td>
<td>24</td>
<td>71% (49.87%)</td>
</tr>
<tr>
<td>Perry</td>
<td>2007</td>
<td>gastric</td>
<td>18</td>
<td>39% (17-64%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>extragastric</td>
<td>15</td>
<td>73% (45-92%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all sites</td>
<td>33</td>
<td>54% (36-72%)</td>
</tr>
<tr>
<td>Tsukamoto</td>
<td>2007</td>
<td>all sites</td>
<td>52</td>
<td>82% (73-88%)</td>
</tr>
<tr>
<td>Economoto</td>
<td>2008</td>
<td>gastric</td>
<td>5</td>
<td>0% (0-52%, one-sided)</td>
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<tr>
<td></td>
<td></td>
<td>extragastric</td>
<td>8</td>
<td>100% (66-100%, one-sided)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all sites</td>
<td>13</td>
<td>62% (32-86%)</td>
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<tr>
<td>Weiler-Seige</td>
<td>2010</td>
<td>all sites</td>
<td>50</td>
<td>54% (39-68%)</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>296</td>
<td>70% (64-75%)</td>
</tr>
</tbody>
</table>
PET-CT in MALT lymphoma
PET-CT in MALT lymphoma

MALT originating from the left lacrimal gland
Factors affecting PET-CT sensitivity in MALT: thickness of the lesion

- 13 untreated MALT lymphoma
  - 5 gastric
  - 8 nongastric
- 8 of 8 non-gastric lymphoma were FDG-PET positive
- no abnormal FDG accumulation was observed in all gastric cases
- Non-gastric lymphoma lesions could be confirmed on CT
- Mucosal lesions of gastric lymphoma detected only by EGD

FDG-PET detects MALT lymphoma when it forms gross lesions, whereas it is difficult to detect gastrointestinal mucosa infiltrates
Factors affecting PET-CT sensitivity in MALT: FDG avidity of the lesion

FDG avidity and PET/CT patterns in primary gastric lymphoma
Radan et al. EJNMMI 2008

• In primary gastric lymphoma, FDG uptake can be differentiated from physiologic tracer activity by intensity but not by pattern...

• Defining FDG avidity and PET/CT patterns in Ag-NHL and a subgroup of MALT before treatment may be important for response monitoring.
MALT lymphoma
(Extranodal Marginal Zone B-Cell Lymphoma of MALT)

HISTOLOGICAL FEATURES

- centrocyte-like cells (usually)
- lymphoepithelial lesions
- plasma cell differentiation
- scattered transformed blasts
- admixed non-neoplastic T-cell
- follicular colonisation

http://www.ncl.ac.uk/pathology/teaching/
Factors affecting PET-CT sensitivity in MALT: histology of the lesion

original article

18F-Fluoro-deoxy-glucose positron emission tomography in lymphoma of mucosa-associated lymphoid tissue: histology makes the difference

M. Hoffmann¹, S. Wöhrer³, A. Becherer¹, A. Chott², B. Streubel², K. Kletter¹ & M. Raderer³
Departments of ¹Nuclear Medicine, ²Pathology and ³Internal Medicine I, Medical University Vienna, Vienna, Austria

<table>
<thead>
<tr>
<th>FDG–PET scan findings</th>
<th>True positive</th>
<th>False positive</th>
<th>True negative</th>
<th>False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (35)</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>pMALT (19)</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MALT (16)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>13</td>
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MALT, mucosa-associated lymphoid tissue; pMALT, MALT lymphoma with plasmacytic differentiation.
Factors affecting PET-CT sensitivity in MALT: histology of the lesion

18F-Fluoro-deoxy-glucose positron emission tomography in lymphoma of mucosa-associated lymphoid tissue: histology makes the difference

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PET-CT in MALT lymphoma – any predictive value?

Role of $^{18}$F-FDG PET Scans in Patients with *Helicobacter pylori*-Infected Gastric Low-Grade MALT Lymphoma

Kyung Ho Song¹, Mijin Yun¹, Jie-Hyun Kim¹, Woo Ick Yang¹, Dae Ryong Kang¹, Jae Bock Chung¹, and Yong Chan Lee¹

*Gut and Liver, Vol. 5, No. 3, September 2011, pp. 308-314*

**Fig. 2.** Baseline standardized uptake values (SUVs) and changes in the SUV according to clinical outcome. The boxes represent the 25th and 75th percentile, the thick horizontal bars represent the median, and the upper and lower horizontal bars represent the maximum and minimum data. CR, complete remission.
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Fig. 2. Baseline standardized uptake values (SUVs) and changes in the SUV according to clinical outcome. The boxes represent the interquartile range, the thick horizontal bars represent the median, and the upper and lower horizontal bars represent the maximum and minimum values. CR, complete remission.

**Treatment failures:**
- 1 case needed RT
- 1 case with Transformation to DLBCL
PET-CT in MALT lymphoma – any clinical value?

K. P. Beal, H. W. Yeung & J. Yahalom

FDG-PET scanning for detection and staging of extranodal marginal zone lymphomas of the MALT type: a report of 42 cases

Annals of Oncology 16: 473–480, 2005

- 4 of 42 (10%) patients upstaged due to FDG-PET findings
- 8 pts with post-treatment PET:
  - 5/8 CR
  - 3/8 indeterminate or mixed response
- The 6 patients with negative initial FDG-PET scans were NED at a median follow-up of 12.5 months.
Clinical relevance of 18F-FDG uptake in staging and follow-up of primary gastric lymphoma


42 primary gastric lymphoma:
32 DLBCL
10 extranodal MZL (MALT lymphomas)

9 (7 DLBCL, 2 MALT) up-staged based on the PET/CT results compared to CT
6 down-staged after PET/CT

high SUVmax significantly associated with advanced Lugano stage (p < 0.001).

24 with follow-up PET/CT scan and endoscopy:
11 ulcerative or mucosal lesions with residual uptake (all these lesions pathologically benign without evidence of lymphoma)

PET/CT can be used for primary gastric lymphoma staging but...
the residual uptake observed during follow-up should be interpreted cautiously and should be combined with endoscopy and multiple biopsies of the stomach.
PET-CT in MALT lymphoma staging

Relevant issues in staging MALT lymphoma:

• asymptomatic dissemination in patients with apparently localized disease
• high proportion (up to one third) of patients with early dissemination at multiple extranodal sites

Hence, extensive staging has been recommended

Thieblemont et al. Blood 2000
Zucca et al. Blood 2003
de Boer et al. Haematologica 2008
PET-CT in MALT lymphoma staging

Relevant issues in MALT lymphoma staging:

• asymptomatic dissemination in patients with apparently localized disease
• high proportion (up to one third) of patients with early dissemination at multiple extranodal sites

Hence, extensive staging has been recommended

FDG-PET/CT results in upstage in approx. 10-20% of cases

Thieblemont et al. Blood 2000
Zucca et al. Blood 2003
de Boer et al. Haematologica 2008
Potential applications of PET-CT in MALT lymphoma

- significant PET-positive rate (< in superficial gastric lesions)
- the degree of FDG uptake may have prognostic/predictive value
- high uptake may identify aggressive subtypes or transformation
- PET-CT may provide more accurate staging than CE-CT (upstaging in 10-20% of FDG-positive cases)
- Potential value for response assessment in non-gastric disease?
Potential applications of PET-CT in MALT lymphoma

- significant PET-positive rate (< in superficial gastric lesions)
- the degree of FDG uptake may have prognostic/predictive value
- high uptake may identify aggressive subtypes or transformation
- PET-CT may provide more accurate staging than CE-CT (upstaging in 10-20% of FDG-positive cases)
- Potential value for response assessment in non-gastric disease?

These hypotheses need to be tested in large prospective studies
Open questions in primary mediastinal large B-cell lymphoma (PMLBCL)

- Are third-generation chemotherapy regimens still superior in the era of rituximab?
- **What is the role of PET scanning in determining cure after chemotherapy?**
- Can consolidative radiotherapy be omitted in selected individuals?
- **Can the PET scanning drive this selection?**
IELSG-26 study on the PET/CT response after R-chemotherapy in primary mediastinal (thymic) large B-cell lymphoma (PMLBCL)

125 PMLBCL enrolled

Baseline PET
(within 14 days before R-Chemo)

Full course of chemotherapy:
R-CHOP 21 or R-CHOP 14 or
R-MACOP-B or R-VACOP-B

Final PET
(3-4 weeks after R-Chemo)

Consolidation RT
(according to local policy)

Post-RT PET
at least 2 months after RT

Interim PET suggested, not mandatory after half of planned R-Chemo

Actually given to 92% of patients

Follow-up
IELSG-26 study: PET/CT response Criteria for final PET (at 3-4 weeks after R-Chemotherapy)

* IHP criteria (Juweid et al. JCO 2007)

Negative final PET: no residual uptake or minimal residual uptake ≤ MBP

* Deauville criteria [5-point visual analysis scale] (Leuk Lymphoma 2009)

1. No uptake.
2. Uptake ≤ mediastinum.
3. Uptake > mediastinum but ≤ liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new disease sites

1 2 3 4 5
negative positive

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP
**IELSG-26 study: Preliminary results**

Post R-chemo PET interpretation - **blind central review**
115 /125 studies reviewed

<table>
<thead>
<tr>
<th>Deauville score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nr. of patients</strong></td>
<td>12</td>
<td>42</td>
<td>27</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>PD or relapse</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

- **47% (54 PET -)** (95% CI 36-58)
- **53% (61 PET +)** (95% CI 42-64)

(95% CI 36-58) (95% CI 42-64)
IELSG-26 study: Preliminary results

<table>
<thead>
<tr>
<th>Deauville score</th>
<th>Nr. of patients</th>
<th>NPV = 98%</th>
<th>MBP cut off</th>
<th>PPV = 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>54 PET -</td>
<td></td>
<td>61 PET +</td>
</tr>
<tr>
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<td>42</td>
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<td>3</td>
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<tr>
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NPV = 99%

IELSG - 26 study: Preliminary results

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP
IELSG-26 study: Preliminary results

IELSG-26 study: Kaplan-Meier estimates of progression-free survival in PMLBCL, according to the PET response defined using the liver uptake cut-off, at 3-4 weeks after immunochemotherapy.

Logrank test, P<0.001

Number at risk

<table>
<thead>
<tr>
<th>Deauville score 1-3</th>
<th>81</th>
<th>79</th>
<th>65</th>
<th>37</th>
<th>16</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deauville score &gt;3</td>
<td>34</td>
<td>25</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

percent progress-free
IELSG-26 study: preliminary conclusions

1. with the MBP cut-point, the PET+ rate (Deauville score>2) after R-Chemo in PMLBCL was higher (53%) than in DLBCL or HL

2. >90% of pts are projected to be alive and progression-free at 5 years post treatment and a negative PET/CT after R-Chemo is significantly associated with a longer PFS.

3. pts with Deauville score 3 had a clinical outcome identical to those with score 1-2, suggesting that the liver uptake may represent a more appropriate cut-point for the definition of CR.

4. Pts with score 4 and 5 had a significantly worse PFS and OS

5. a negative PET after R-CHT may select a subgroup of patients who may not need consolidation RT (IELSG 37 study is ongoing)
Thank you for your attention!