FDG PET for therapy response assessment in lymphoma: Beyond Lugano Classification

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Assess lymphoma response to therapy: Pre-PET era


Bruce D. Cheson, Sandra J. Horning, Bertr Coiffier, Margaret A. Shipp,

Abstract

ABSTRACT: Standardized guidelines for response assessment are needed to ensure disease. Single-photon emission computed tomography gallium scans are encouraged as a valuable adjunct to assessment of patients with large-cell NHL, but such scans require appropriate expertise. Flow cytometric, cytogenetic, and molecular
FDG avidity according to WHO classification

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
<th>FDG Avid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>489</td>
<td>97-100</td>
</tr>
<tr>
<td>DLBCL</td>
<td>445</td>
<td>97-100</td>
</tr>
<tr>
<td>FL</td>
<td>622</td>
<td>91-100</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, nodal</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma</td>
<td>37</td>
<td>94-100*</td>
</tr>
<tr>
<td>NK/T-cell lymphoma</td>
<td>80</td>
<td>89-100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>31</td>
<td>78-100</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>73</td>
<td>56-89</td>
</tr>
<tr>
<td>MALT marginal zone lymphoma</td>
<td>227</td>
<td>54-81</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>49</td>
<td>47-83</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>20</td>
<td>67-100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, splenic</td>
<td>13</td>
<td>83-67</td>
</tr>
<tr>
<td>Marginal zone lymphoma, unspecified</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>24</td>
<td>83-100</td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td>2</td>
<td>100+</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
<td>14</td>
<td>40-60</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>Cutaneous B-cell lymphoma</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Data adapted with additional updates. DLBCL, diffuse large B-cell lymphoma; FDG, [18F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.
*Only 27% of cutaneous sites.
†Only 62% of cutaneous sites.


and

Numerous validation studies to define the prognostic value of PET/CT at baseline, interim or EOT

Some published validation study series demonstrated good performance


90 patients with newly diagnosed aggressive lymphoma

At mid-induction, "early PET" was considered negative in 54 patients and positive in 36. After completion of induction, 83% of PET-negative patients achieved complete remission compared with only 58% of PET-positive patients. The 2-year estimates of EFS reached 82% and 43%, respectively (P < .001), and the 2-year estimates of OS reached 90% and 61%, respectively (P = .006).

Therefore……
PET/CT scan—modality of choice in staging and restaging lymphoma
International Harmonization Project Criteria

Revised Response Criteria for Malignant Lymphoma
Bruce D. Cheson, Beatrice Pfisterer, Malik E. Jiwad, Randy D. Gascoyne, Lea Specht, Sandra J. Horning

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma
Malik E. Jiwad, Sigrid Stoeckert, Otto S. Hoeksstra, Felix M. Mollophy, Markus Dietlein, Ali Guermazi,
Key points in IHP criteria

- EOT PET.

- Mediastinal blood pool is the reference:
  - For residual mass > 2 cm: positive if >
  - For lesions < 2 cm: positive if any uptake > background

- Category of CRu (unconfirmed) by CT is eliminated.
IHP criteria: Far from perfect

Using these criteria (MBP is really a quite low threshold in some patients) some studies have reported very high rates of false positivity of EOT PET in NHL with a PPV as low as 26%

Where is Lugano classification from?

5 points scale using mediastinum and liver as reference proposed—London Criteria.

Relatively less variation of mediastinal and liver FDG uptake during course of treatment, therefore ideal as reference organs.

Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma

Sally F. Barrington · Wendi Qian · Edward J. Somer · Antonella Franceschetto ·

Conclusion: In NKT cell lymphoma nasal type, the FDG avidity of mediastinum and liver on sequential PET/CT scans over the treatment course is relatively stable and comparable.

Excellent reproducibility of scoring tested in 50 patients -- 47 patient complete consensus over 4 centers
London Criteria -- 5PS
Adopted in Deauville, France, 2009 -- Deauville criteria

<table>
<thead>
<tr>
<th>Score</th>
<th>PET/CT scan result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake above background</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum but ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately increased compared to the liver at any site</td>
</tr>
<tr>
<td>5</td>
<td>Uptake markedly increased compared to the liver at any site</td>
</tr>
<tr>
<td>X</td>
<td>New areas of uptake unlikely to be related to lymphoma</td>
</tr>
</tbody>
</table>

Leukemia & Lymphoma, Aug 2009; 50(8): 1257–1260
Leukemia & Lymphoma, Dec 2010; 51(12): 2171–2180
Leukemia & Lymphoma, Oct 2012; 53(10): 1876–1881
Leukemia & Lymphoma, Jan 2014; 55(1): 31-37
Leukemia & Lymphoma, May 2015; 56(5): 1229-1232
Leukemia & Lymphoma, Oct 2016; 58(10): 2298-2303
Examples

Score 4
Uptake > Liver

Positive by Deauville 5PS

Score 3
Uptake ≤ Liver

Negative by Deauville 5PS

Kostakoglu, Gallamini, JNM 2013; 54: 1082-93
Uptake ≤ Liver and > MBP

Negative result by Deauville 5PS
Positive result by IHP criteria

Kostakoglu, Gallamini, JNM 2013; 54: 1082-93
Prognostic value of interim FDG PET/CT in Hodgkin’s lymphoma patients treated with interim response-adapted strategy: comparison of International Harmonization Project (IHP), Gallamini and London criteria

Pierre-Yves Le Roux • Thomas Gastinne • Steven Le Gouill • Emmanuel Nowak


90 patients

Initial interpretation

PPD or relapse
7 (12%)

59 negative interim PET

31 positive interim PET

PPD or relapse
5 (19%)

IHP criteria

PPD or relapse
7 (11%)

59 + 5 = 64 negative interim PET
(0/5 PPD or relapses)

5

31-5 = 20 positive interim PET

PPD or relapse
5 (23%)

Gallamini criteria

PPD or relapse
7 (10%)

59 + 11 = 70 negative interim PET
(0/11 PPD or relapses)

11

31-11 = 20 positive interim PET

PPD or relapse
5 (30%)

5-point scale

PPD or relapse
7 (9%)

59 + 20 = 79 interim PET = 1, 2, 3 or 4
(0/20 PPD or relapses)

20

31-20 = 11 interim PET = 5

PPD or relapse
6 (55%)

PPD: Primary progressive disease.
Fig. 4 Kaplan-Meier survival curves showing the PFS according to interim PET/CT results using initial criteria (a), IHP criteria (b), Gallamini criteria (c) and the 5-point scale (d)
Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification


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 Mikhail, Lale Kestakoglu, Michel Meignan, Martin Hutchings.
Summary

q Deauville 5PS applicable to FDG-avid nodal lymphomas essentially all histologic types, both iPET and EOT.

q iPET is less predictive for response with immunochemotherapy. It is not recommended to change treatment solely on basis of interim PET-CT.

q EOT PET-CT is standard of care and a much better predictor, especially for HD, NHL, and FL; (-) with high NPP, (+) needs biopsy if salvage considered.
**OBJECTIVE:** To evaluate the PFS at 36 months for patients who are PET-negative after 2 courses of chemotherapy, and receive 4 additional courses of ABVD followed by involved-nodal radiotherapy (INRT) of 30-30.6 Gy.

*Courtesy: Prof. Terry Wong, NUC*
Things not mentioned in Lugano classification

q Deauville 5 PS is not applicable to the following histology types:

β The following FDG variable subtypes:
• Chronic lymphocytic leukemia (CLL)
• Small lymphocytic lymphoma
• Lymphoplasmocytic lymphoma
• Waldenstrom macroglobulinemia
• Marginal zone lymphoma

β Cutaneous/subcutaneous lymphoma including mycosis fungoides/Sezary syndrome.

β Primary extranodal lymphoma which have separate criteria.

q Score 5 = more than 2-3 times higher than liver by SUVmax

q What’s special for response assessment in patients with immunochemotherapy??
Era of immunomodulatory therapy

- Immunomodulatory monoclonal antibodies that are directed against CTLA-4, the programmed death protein 1 (PD-1)/programmed death receptor ligand 1 (PD-L1) of T-cells

- Ipilimumab, tremelimumab, nivolumab, Pembrolizumab

- FDA approval of nivolumab, Pembrolizumab for patients with relapsed and refractory Hodgkin lymphoma
New patterns of treatment response of immunotherapy

- The first new pattern of response is clinically stable disease after completion of treatment followed by an eventual decline in tumor burden.
The 2\textsuperscript{nd} new pattern is a delayed tumor response to treatment after an initial increase in tumor burden that manifests as an increase in tumor size.
The 3rd new pattern of response is the appearance of new lesions after the completion of treatment that precede a decrease in tumor burden at subsequent follow-up examinations. The appearance of new lesions may represent an interval increase in the size of micrometastases.
Patterns of an irR on FDG PET

- Reactive nodal uptake in drainage basin of metastases
- For mediastinal / hilar nodes: symmetry
- Reactive diffuse splenic uptake
- High tonsilar +/- para-appendiceal uptake (lymphoid hyperplasia)

Courtesy: Prof. M Hofman, Peter Mac
Imaging Findings of Immune-related Adverse Events

It is important for the imager to recognize the unique adverse events associated with immunotherapy to guide appropriate treatment and avoid potential imaging pitfalls that could be mistaken for metastatic progression of disease.
Key points of the immune-related response criteria are as follows:

- Because of a potentially delayed response to immunotherapy treatment, imaging assessment of treatment response or disease progression after completion of treatment should be made with two consecutive follow-up imaging studies performed at least 4 weeks apart.

- New or enlarging lesions do not necessarily represent progression of disease immediately after completion of treatment. Because of this, follow-up imaging should be performed at least 4 weeks later to assess for further changes in tumor burden.

Evolution still continuing……
LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC)

β Tumor flare or pseudo-progression has been well described with checkpoint blockade therapy in lymphoma.

β **Provisional** “Indeterminate Response” (IR) was introduced in order to identify such lesions until confirmed as flare/pseudoprogression or true PD.

β “Tumor flare” occurs, generally during the first two to three weeks of treatment – acute inflammatory reaction.

β These criteria were proposed to **overcome the limitations of the Lugano classification**.
IR(1): Increase in overall tumor burden (as assessed by SPD) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration repeat imaging in 4-8 weeks of the original IR(1) time point.
IR(2): Appearance of new lesions; or growth of one or more existing lesion(s) $\geq 50\%$; at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment a biopsy is strongly encouraged in such cases.
IR(3): Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number an increase in FDG avidity of one or more lesions suggestive of lymphoma, without a concomitant increase in size of those lesions meeting PD criteria does not constitute PD.
In summary

<table>
<thead>
<tr>
<th>IR1:</th>
<th>≥50% increase in SPD in first 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR2a:</td>
<td>&lt;50% increase in SPD with new lesion(s)</td>
</tr>
<tr>
<td>IR2b:</td>
<td>&lt;50% increase in SPD with ≥50% increase in PPD of a lesion or set of lesions at any time during treatment</td>
</tr>
<tr>
<td>IR3:</td>
<td>Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD</td>
</tr>
</tbody>
</table>
Follow-up of IR

- Repeat scan in 12 wks (earlier if indicated)
- PD if:
  - IR1 – further increase in SPD
  - IR2 – new lesion added to SPD (unless benign) and, if ≥50% increase – PD
  - IR3 – PD if increase in size or new lesions

Courtesy: Prof. Terry Wong, NUC
q 26 yom, HL, s/p ABVD and ICE, Kaytruda 03/16-05/16

02/2016

05/2016

09/2016
5/16 patients (31%) displayed new imaging patterns related to antiPD1; we observed two transient progressions consistent with indeterminate response according to the LYRIC 2016 criteria (IR2b at 14 months and IR3 at 18 months), and three patients with new lesions associated with immune-related adverse events.

Indeed, the persistence of 18F-FDG PET positive lesions at 3-month does not preclude a prolonged clinical benefit.
Interestingly, healthy spleen tissue 18F-FDG uptake appears significantly increase in responders suggesting a favorable immunological reconstitution.
Take home message

q Assessing treatment response in lymphoma with FDG PET has been a concerted effort for decades.

q Lugano classification applies to most subtypes under traditional or salvage therapy but does not work well for patients on novel immunomodulatory therapy, particularly for iPET.

q Lyric is proposed for assessment of PD in lymphoma patients on immunomodulatory therapy with three ‘IR’ categories described.

q The key to deal with ‘IR’ is repeated scan in 3 months.
Thank you!

I love Nanjing!