PET-based response criteria in lymphoma: Current status and future directions

Michel Meignan
LYSA imaging
Hôpital Henri Mondor
University Paris Est, Créteil, France
Conclusions of the ICML imaging group

4th International Workshop on PET in Lymphoma
Menton, October 4-5, 2012

12th International Conference on Malignant Lymphoma
Lugano 12-22 June, 2013
Consensus: Imaging guidelines

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REVIEW

Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3–5 October 2012

Michel Meignan1, Sally Barrington2, Emmanuel Itti, Andrea Gallamini, Corinne Haioun1 & Aaron Polliack4

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group


Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard J. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zuccon, and T. Andrew Lister
Based on Deauville criteria

First international workshop on PET in lymphoma (Deauville 2009)

Report on the First International Workshop on interim-PET scan in lymphoma

MICHIEL MEIGNAN¹, ANDREA GALLAMINI², & CORINNE HAIOUN³

¹Nuclear Medicine Department, H. Mondor Hospital, AP-HP/Paris 12 University, Creteil, France, ²Hematology Department and BMT Unit, Az. Ospedaliera S. Croce e Carle, Cuneo, Italy, and ³Hematology Department, H. Mondor Hospital, AP-HP/Paris 12 University, Creteil, France

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5th international workshop on PET in lymphoma (Menton 2014)
Deauville criteria developed for iPET

iPET + if residual uptake higher than a fixed reference background

Nearby background (NB)
SUV\text{max} = 1

Mediastinal blood pool (MBP)
SUV\text{max} = 1.6-1.8

Liver (L)
SUV\text{max} = 2.5

For the same residual uptake increasing the background turns a PET positive to a PET negative.
Differences in Prognostic value of interim PET

DLBCL

Haioun 2005

DLBCL

Han 2009

HL

Gallamini 2007

HL

Straus 2011
Differences in Prognostic value of interim PET

- timing of interim PET (1-4 cycles)
- histotypes of lymphoma
- Residual tumour, inflammatory or environmental cells
- treatment regimens

- criteria of interpretation +++ Minimal residual uptake tolerate /reference background to declare a patient responder or non responder.
- Complicated by the interobserver variability for PET visual reporting
Deauville criteria/ 5 Point Scale

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**

Scale scoring the level of residual uptake
Score 4 gives the best interobserver reproducibility

International Validation Study of iPET after 2 cycles reported with DC in advanced stage HL

n = 260 PET at cycle 2

3y FFS: 95% v 28%

Biggi, Gallamini et al. JNM 2013, 54 :1-
International Validation Study of iPET after 2 cycles reported with DC in DLBCL

n = 114 PET2

3y PFS: 81% v 59%

3y PFS: 80% v 40%

Swiss Observational study: Prospective evaluation of the predictive value of PET in 141 patients with DLBCL under R-CHOP-14 (SAKK 38/07) for iPET and end treatment PET.
High tumour burden Follicular Lymphoma
Pooled analysis in 246 patients with centrally reviewed postinduction PET-CT

MFU=54.8 months
Cut-off ≥ 4 predictive of PFS & OS (Kappa 0.61-0.7),

Trotman, Lancet Haematol 2014 1; 1-
For FDG-avid lymphomas:

• PET-CT is standard of care for remission assessment

• The Five Point Scale (5-PS, DC) is recommended for reporting interim and end-of-treatment PET scans
  – One method is preferable for PET visual assessment at both time points
  – DC validated for each step of response assessment
Recommendations of ICML 2014

• Baseline PET-CT improves the accuracy of subsequent response assessment

• Interim PET
  – If mid therapy imaging is performed, PET-CT is superior to CT
  – Trials are currently evaluating the role of PET response adapted therapy
  – Meantime it is not recommended to change treatment based solely on PET-CT unless there is clear evidence of progression
Response classification according to 5-PS (Lugano classification)

Score 1, 2 is Complete Metabolic Response (CMR)
Score 3 is probably also CMR with standard treatment
But in response-adapted trials exploring de-escalation, score 3 may be deemed inadequate response to avoid under-treatment
Interpretation of score 3 depends on timing of assessment, clinical context & treatment.
Response classification according to 5-PS (Lugano classification)

Score 4, 5 with reduced uptake from baseline is partial metabolic response (PMR)
- At interim this suggests responding disease
- At end of treatment this indicates residual disease
Bone marrow: Residual marrow uptake > 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.

Score 4, 5 with no change in uptake from baseline means no metabolic response (NMR)
Response classification according to 5-PS (Lugano classification)

Score 4, 5 with an increase in uptake from baseline &/or new lesions (new avid –foci consistent with lymphoma) is progressive metabolic disease (PMD)
- At interim and end of treatment NMR and PMD indicates treatment failure

Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered or an interval scan where clinical likelihood of disease is low to decide on treatment (or not)

Residual size mass and location should be recorded in PET-CT reports where possible
Timing of PET-CT scans

**Interim scans**: should be performed as long as possible after the last chemotherapy administration

**End of treatment scans**: should be performed 6-8 weeks post chemotherapy ideally (but a minimum of 3 weeks)

≥ 3 months after radiotherapy
PMR = residual metabolic disease
Future directions for response assessment

• Quantitative PET-CT for response assessment: 2 arguments to use it
  – Need to decrease interobserver variability due to visual reporting
  – Need to integrate the kinetics of tumour destruction

• Integrative PET combining baseline data (PET, Clinical, Biology, Imaging) with response data (PET, Imaging)
  – For better risk stratification
Difficulty in visual reporting

Argument for quantitative PET
Kinetics of tumour destruction (DLBCL) Stuudied by PET during induction chemotherapy
Reporting interim PET in Diffuse Large B Cell Lymphoma: the Zeno’s paradox

The “freezing” evaluation of the residual tracer uptake by visual scoring (DS) at one moment of this kinetics miss the entire phenomenon and remind us of the paradox of the Greek philosopher Zeno of Elea. At any instant of time the arrow has no motion, since time is composed of multiple freezing instances in succession.

Zeno’s arrow

By contrast the quantitative approach combining SUVmax baseline and after treatment to obtain Δ SUVmax between base line and either of the chemotherapy cycles integrates this kinetic information.
Quantitative approaches

$\Delta$ SUVmax

Maximum SUV

Hottest lesion on baseline

Hottest lesion at response

$\Delta$ SUV is % change between these

Maximum SUV
Delta SUV (ΔSUV)

Staging

Interim

SUV = 25.0

SUV = 2.6

ΔSUV 90%
Reporting interim PET by Integrative $\Delta$SUVmax more predictive of outcome than scoring residual activity at one step of the kinetics (DS).

**DLBCL**

Interobserver $\kappa = 0.668$

IVS: 114 pts, 5 centers, 3 observers, PET 2 cycles; med FU 39 months

Initial SUVmax<10
Interim SUVmax>5
Implement ΔSUV analysis with 5 point scale with the liver cut-off
Combining analysis of residual uptake (DS) with $\Delta$SUV kinetic approach at 3-4 cycles in DLBCL (74 patients)

71% patients
Double negative excellent outcome
Double positive poor outcome

Nols et al. Leuk Lymphoma 2013
PETAL

DLBCL: 18-60y

Δ SUVmax: cut-off 66%
GAINED
DLBCL, 18-60y, aalPI = 1-3: Phase III – 2 arms

CHEMO14 according to center decision:
- ACVBP14
- CHOP14

Induction

PET results

consolidation

According to randomization arm and CHEMO14 regimen

GA101: 1000mg by injection
D1-D8 cycles 1 -2
Combining in HL base line data, TMTV and response data, $\Delta$SUVmax (PET2)

Combining BCL2 protein expression and BCL2 gene alteration with early PET response at 2 cycles in DLBCL allows improved stratification.

**BCL2 prot 50%+DS (n=86)**
3-y PFS: 83.8% vs. 71.1% vs. 43.1%

**BCL2-FISH+DS (n=83)**
3-y PFS: 85.7% vs. 55.0% vs. 28.6%

6th International Workshop on PET in Lymphoma
Menton (France), September 19-20, 2016

Organizing committee: M Meignan (France), A Gallamini (Italy), C Haioun (France), S Barrington (UK), E Itti (France), S Luminari (Italy), A Versari (Italy), E Zucca (Switzerland).