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

Michel Meignan
LYSA imaging
Hôpital Henri Mondor
University Paris Est, Créteil, France)

Lysa
THE LYMPHOMA STUDY ASSOCIATION

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

EANM European Association of Nuclear Medicine

&LI The European Lymphoma Institute

Lysa The Lymphoma Study Association

EORTC The future of cancer therapy

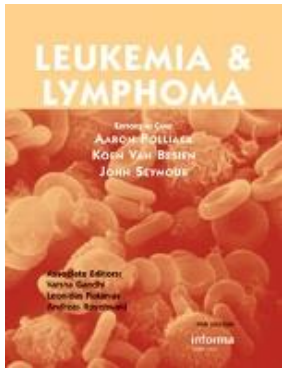
Fondazione Italiana Linfomi FIL

12-ICML 12th International Conference on Malignant Lymphoma Palazzo dei Congressi, Lugano (Switzerland), June 19-22, 2013

ESMO Good Science Better Medicine Best Practice European Society for Medical Oncology

EHA

Consensus: Imaging guidelines



Leukemia & Lymphoma, 2013; Early Online: 1–7

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.802784

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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 Meignan[1], Sally Barrington[2], Emmanuel Itti[1], Andrea Gallamini[3], Corinne Haioun[1] & Aaron Polliack[4]

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

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 Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

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

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

Based on Deauville criteria

First international workshop on PET in lymphoma (Deauville 2009)

Leukemia & Lymphoma, August 2009; 50(8): 1257–1260

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REVIEW

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

MICHEL MEIGNAN[1], ANDREA GALLAMINI[2], & CORINNE HAIOUN[3]

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

(Received 8 May 2009; accepted 12 May 2009)

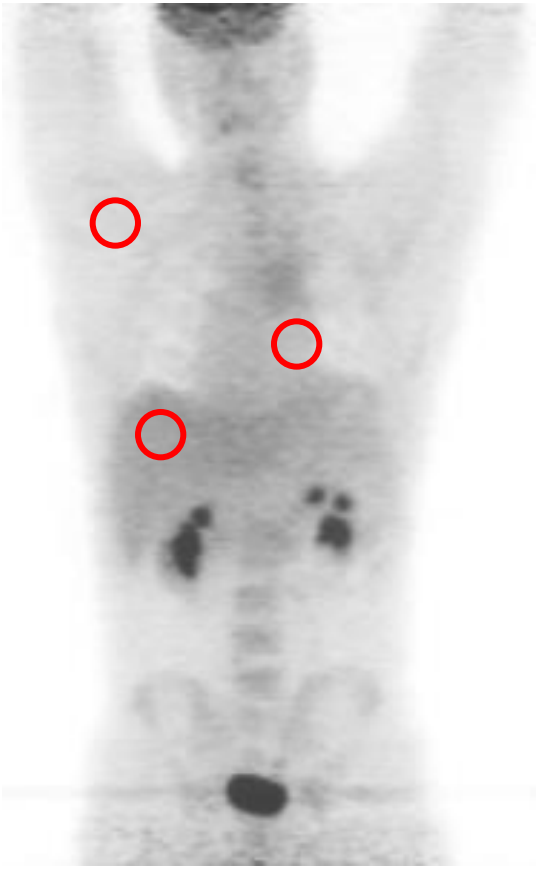
5th international workshop on PET in lymphoma (Menton 2014)

Deauville criteria developped for iPET
iPET + if residual uptake higher than a fixed reference background

Nearby background (NB)
SUVmax = 1

Mediastinal blood pool (MBP)
SUVmax = 1.6-1.8

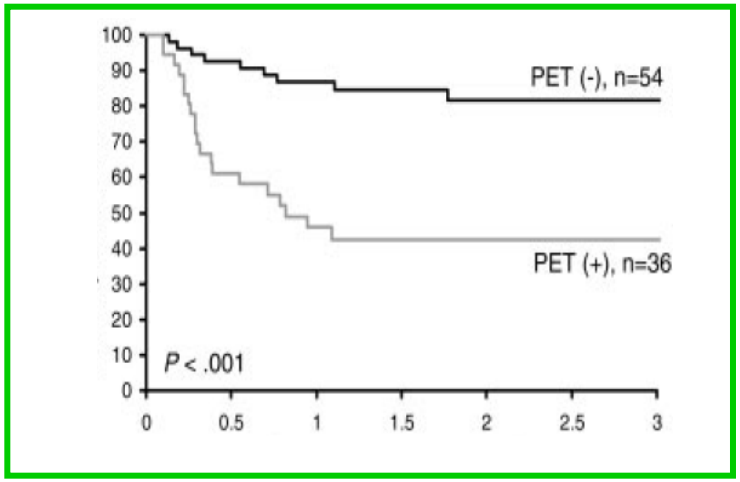
Liver (L)
SUVmax = 2.5



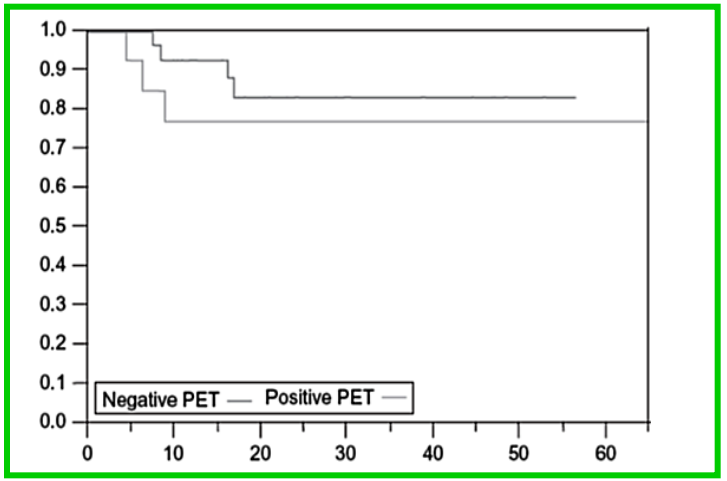
For the same residual uptake increasing the background turns a PET positive to a PET negative

Differences in Prognostic value of interim PET

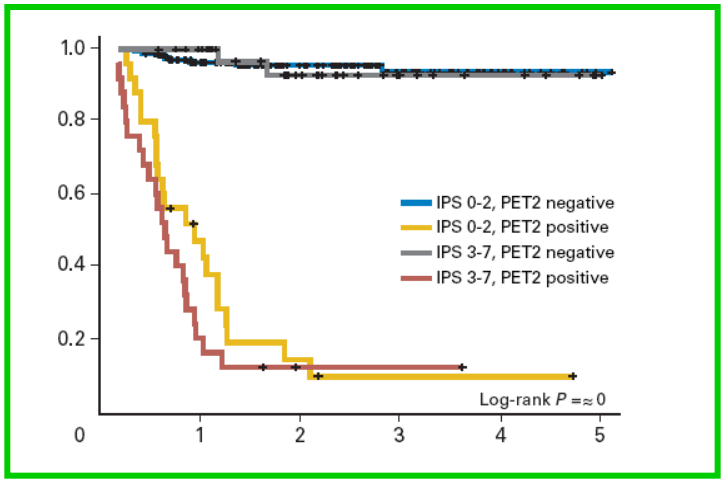
DLBCL — Haioun 2005



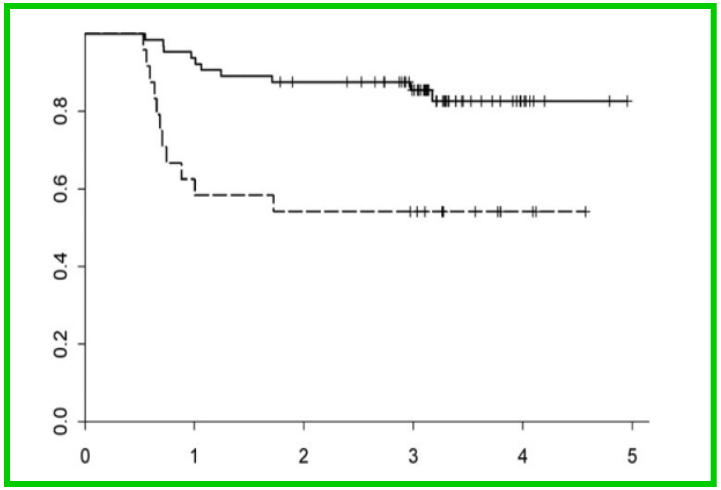
DLBCL — Han 2009



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

Meignan, *Leuk Lymphoma*, 2009; 50(8): 1257-60
Barrington, *EJNMMI*, 2010; 37(10):1824-33

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

n = 260 PET at cycle 2

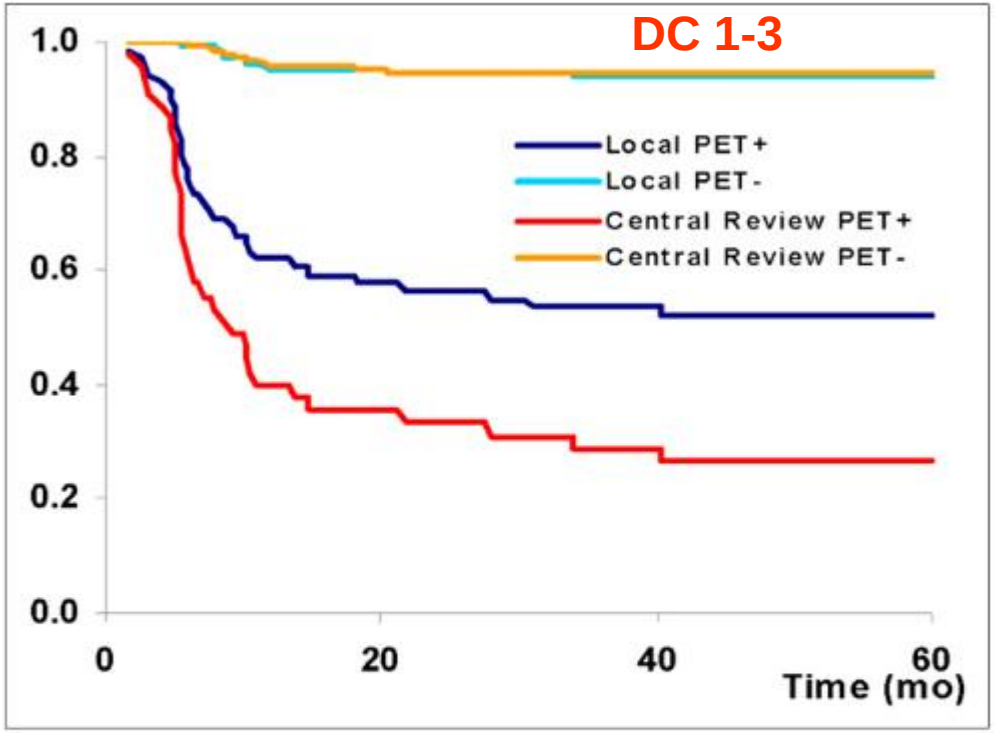


FIGURE 1. Three-year FFS of interim PET–positive and interim PET–negative patients according to review panel using 5-PS and according to local review.

PET-ve DS 1-3
PET+ve DS 4-5

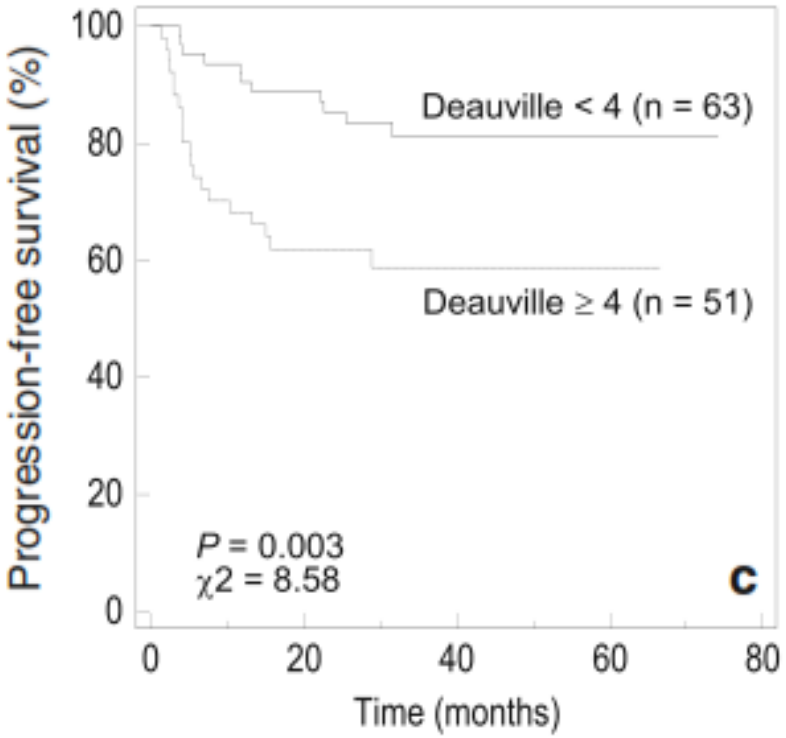
DC 4-5

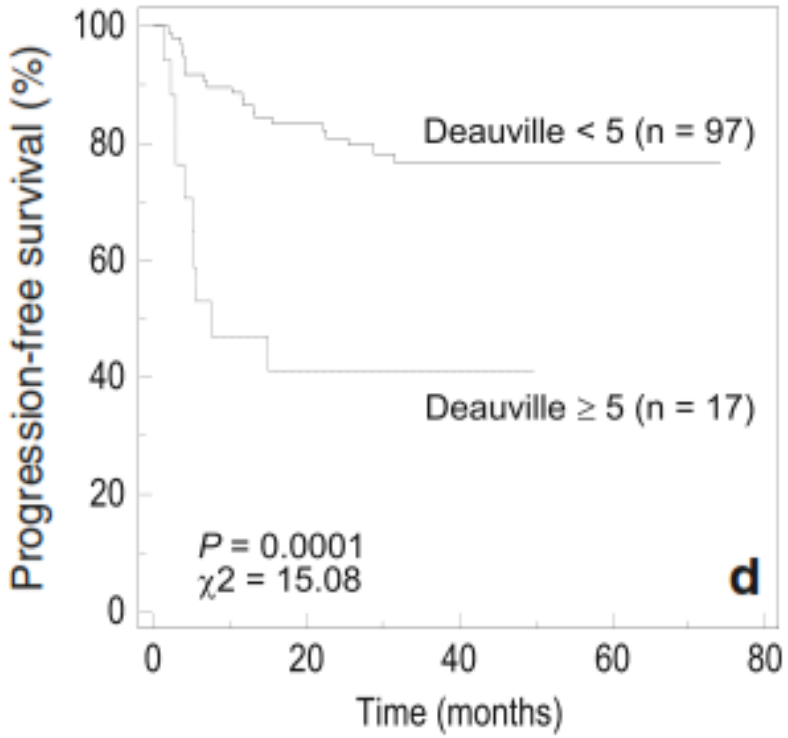
3y FFS : 95% v 28%

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%

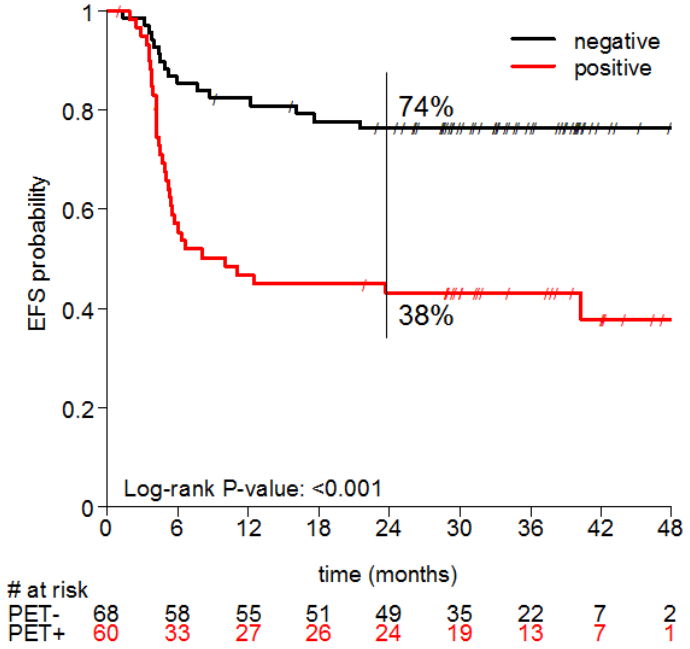
3y PFS : 80% v 40%

Itti et al. EJNMMI 2013, DOI 10.1007/s00259-013-2435-6

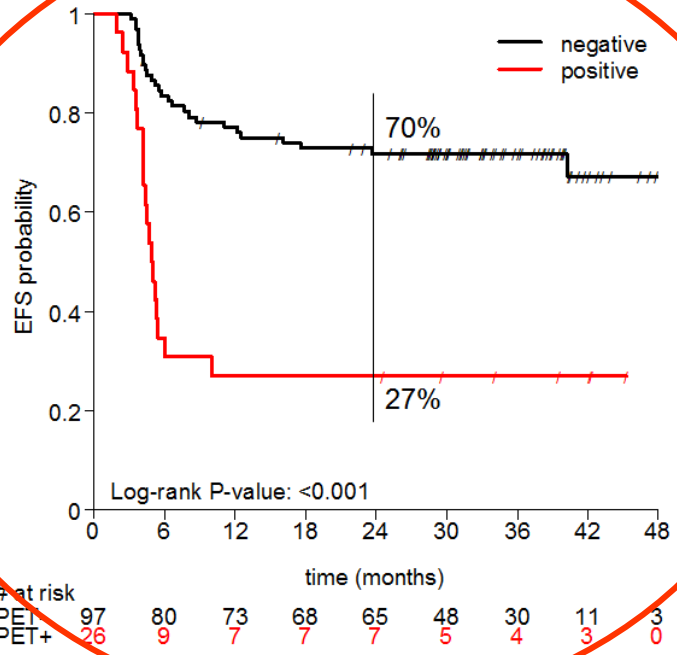
Swiss Observational study: Prospective evaluation of the predictive value of PET in 141 patients with DLBCL under R-CHOP-14 (SAKK 38/07) for iPET and end treatment PET

SAKK

Interim PET, central review, 5-point scale

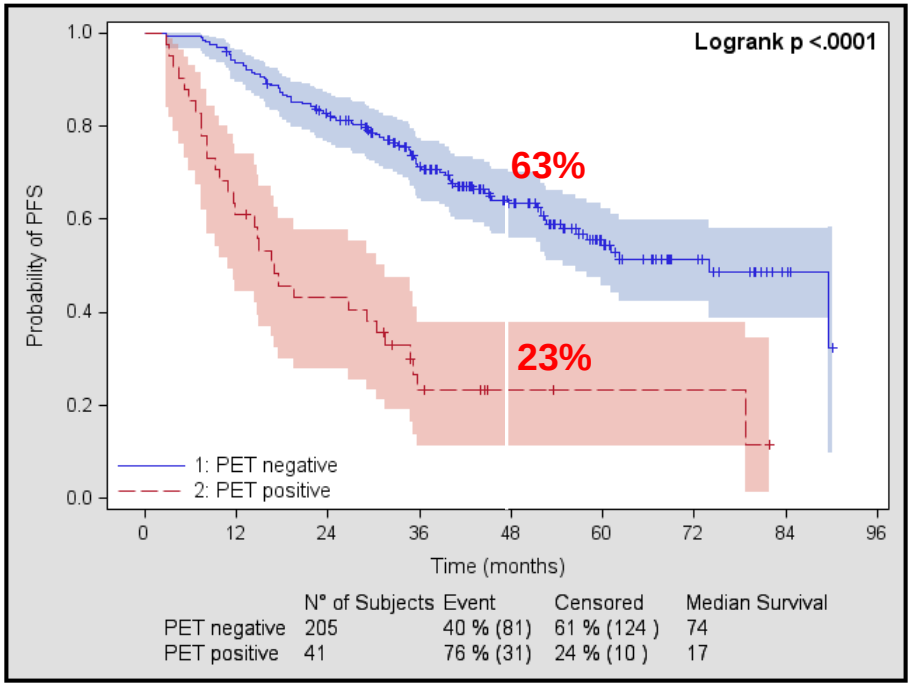


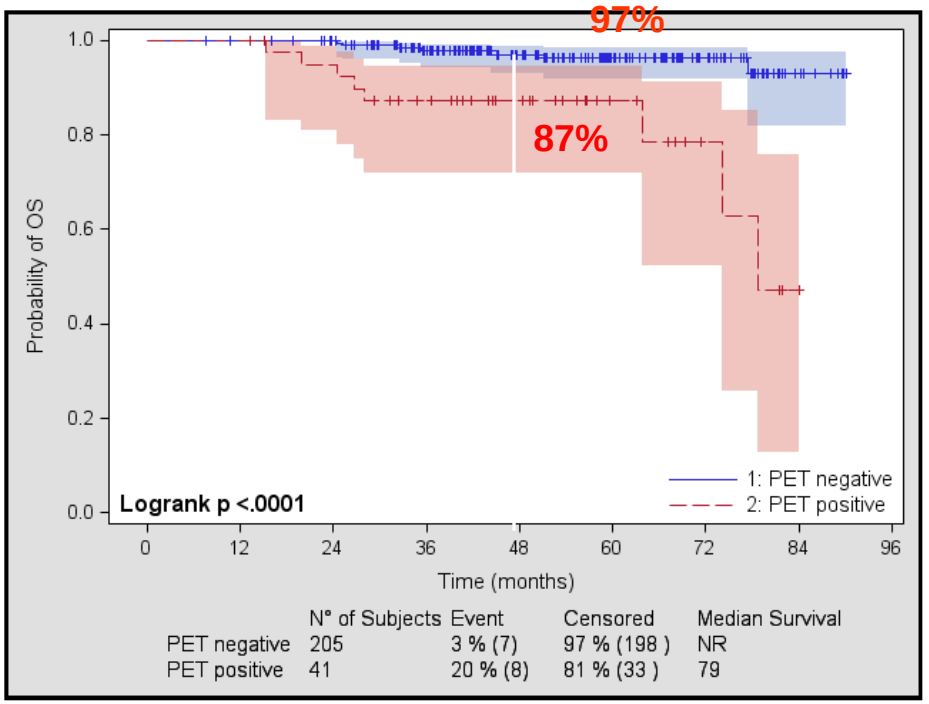
End of treatment, central review, 5-point scale, liver cut-point



C. Mamot, *Hematol Oncol* 2013. 31(suppl 1):100-1. Abs 15

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-*

Recommendations of ICML 2014

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

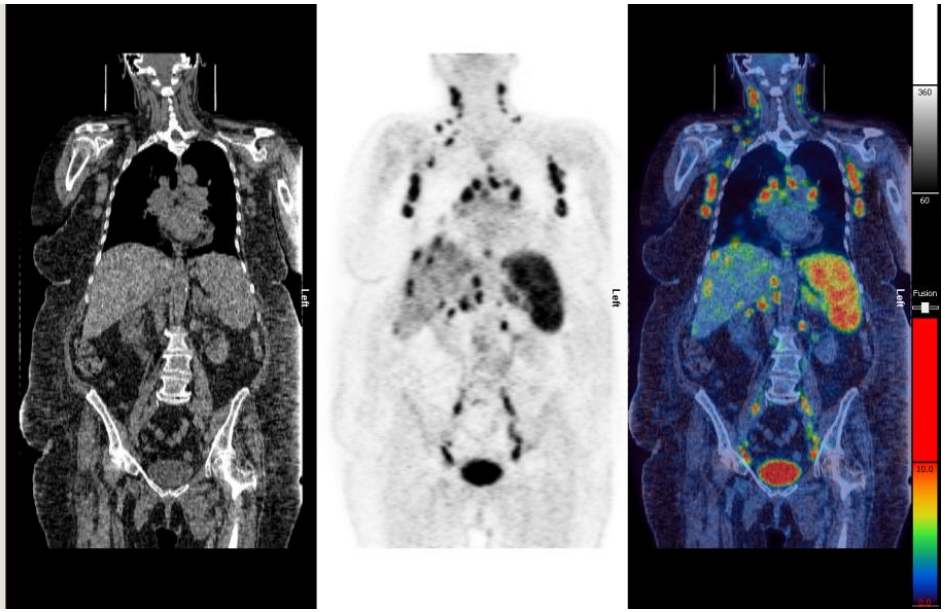
Timing of PET-CT scans

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

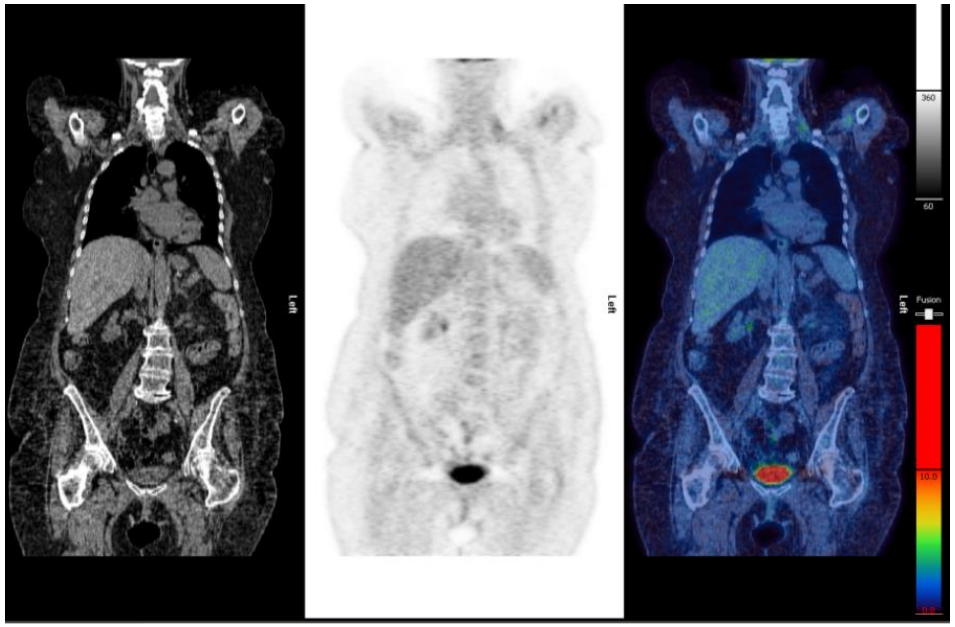
End of treatment scans : should be performed 6-8 weeks post chemotherapy ideally (but a minimum of 3 weeks)

≥ 3 months after radiotherapy

Baseline

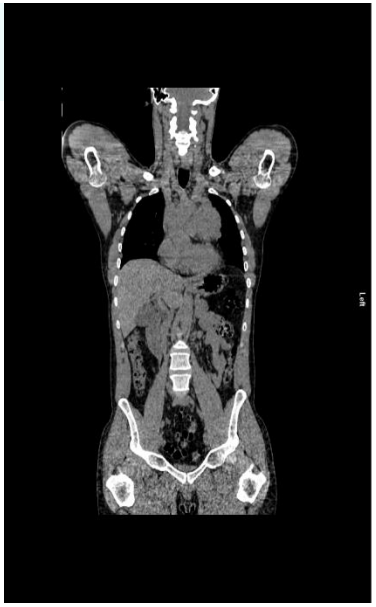


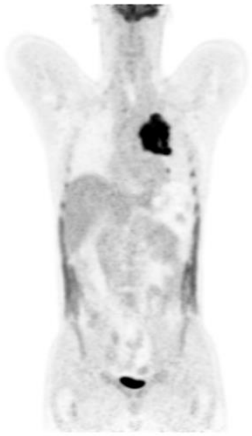
Response



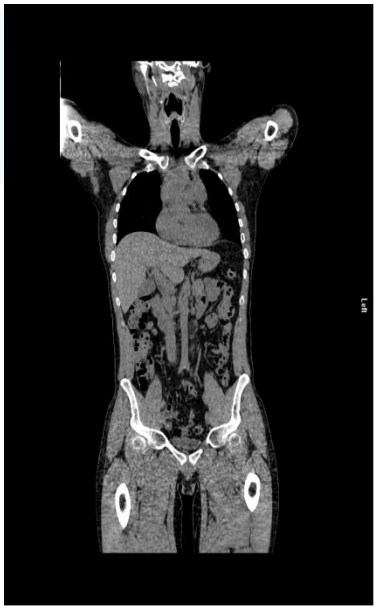
CMR

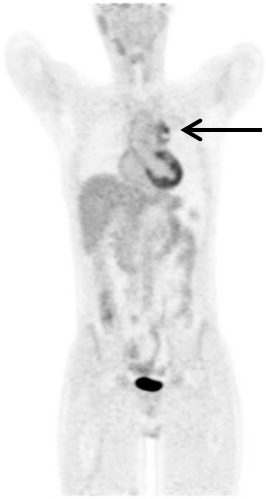
Baseline

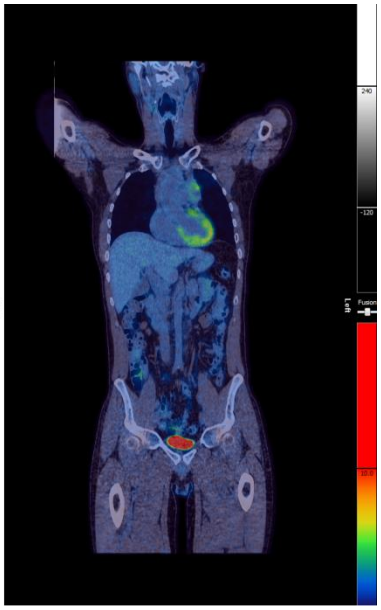




Response interim

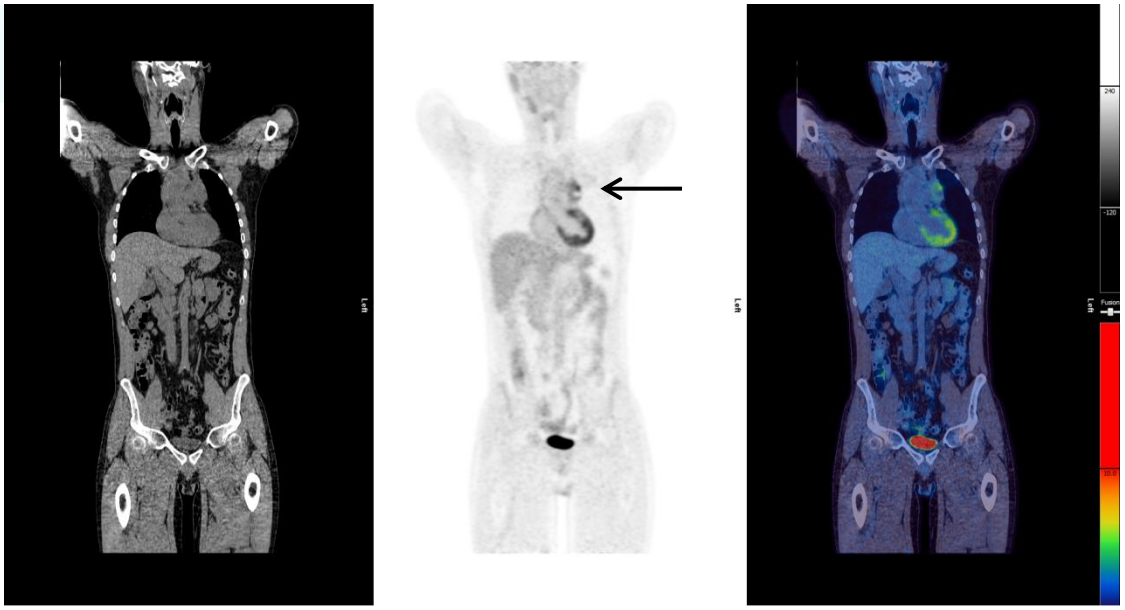




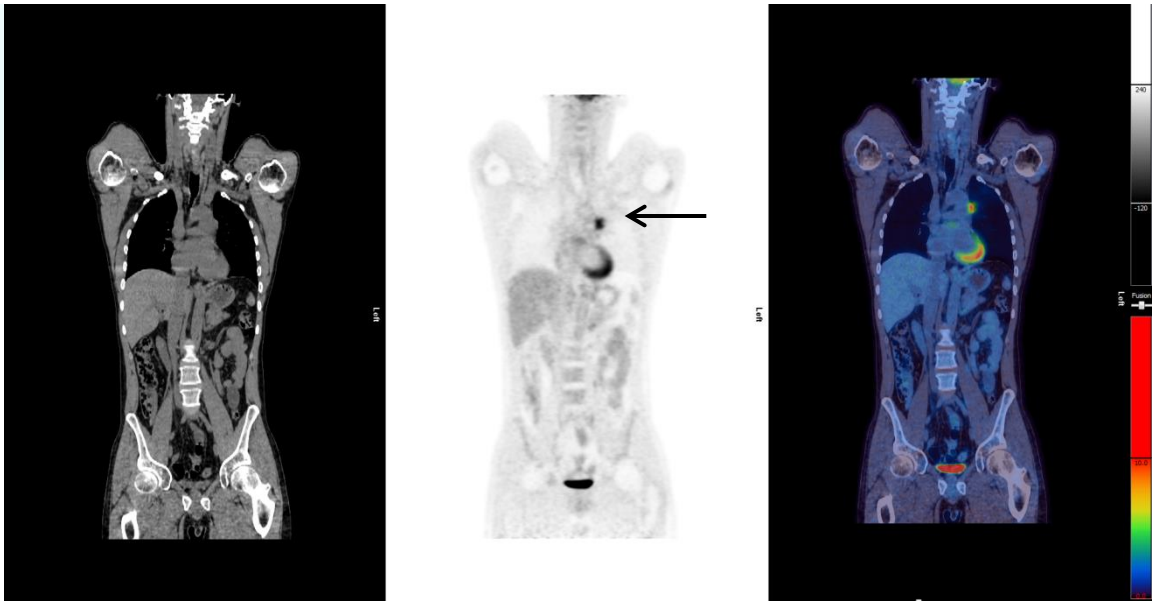


PMR

Interim



Response End

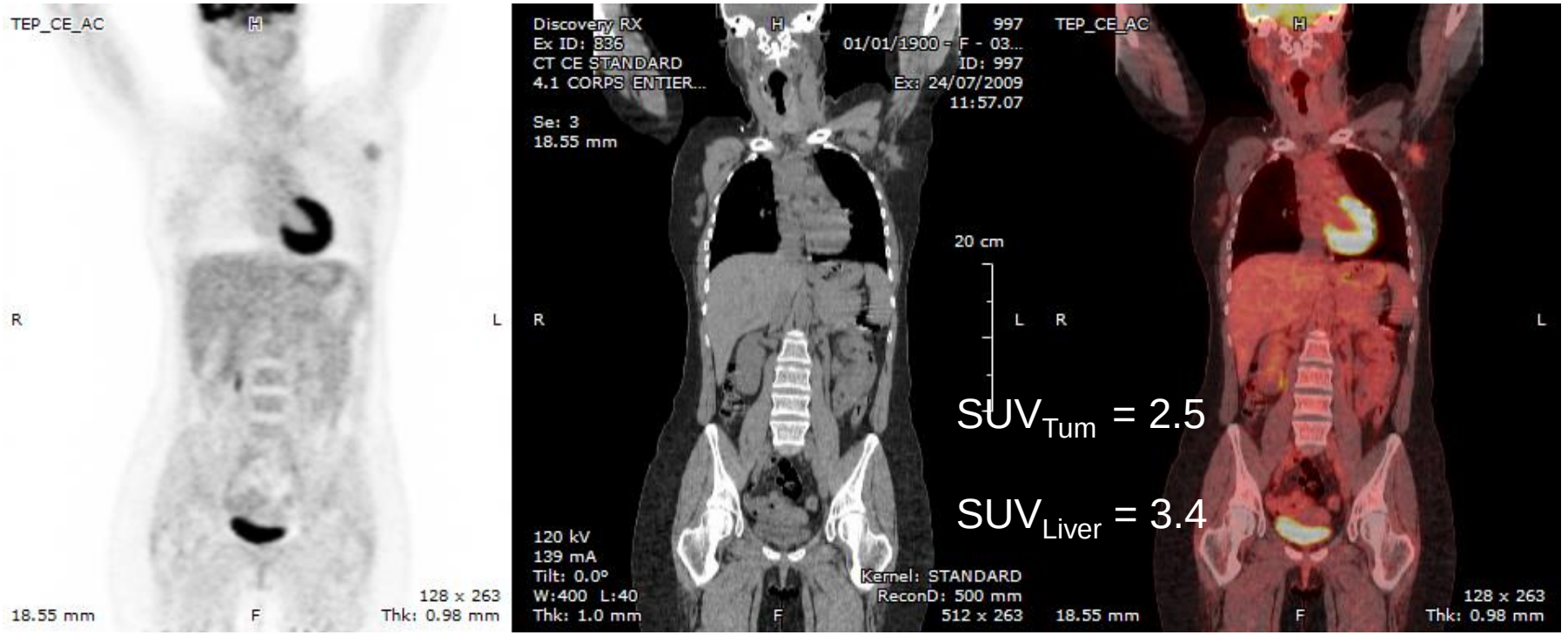


PMR= residual metabolic disease

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

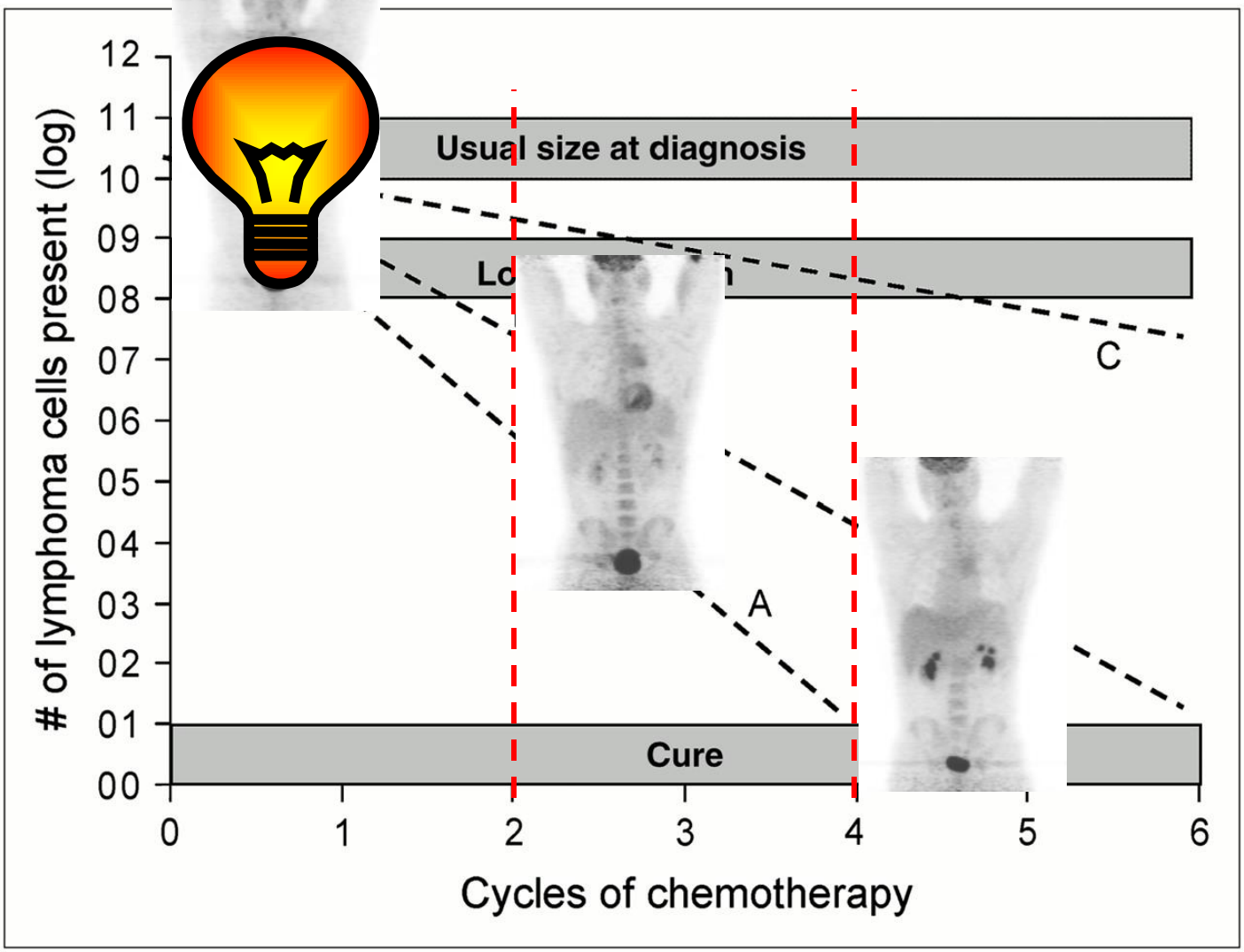
Difficulty in visual reporting



Argument for quantitative PET

Kinetics of tumour destruction (DLBCL)

Studied 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
Δ SUVmax

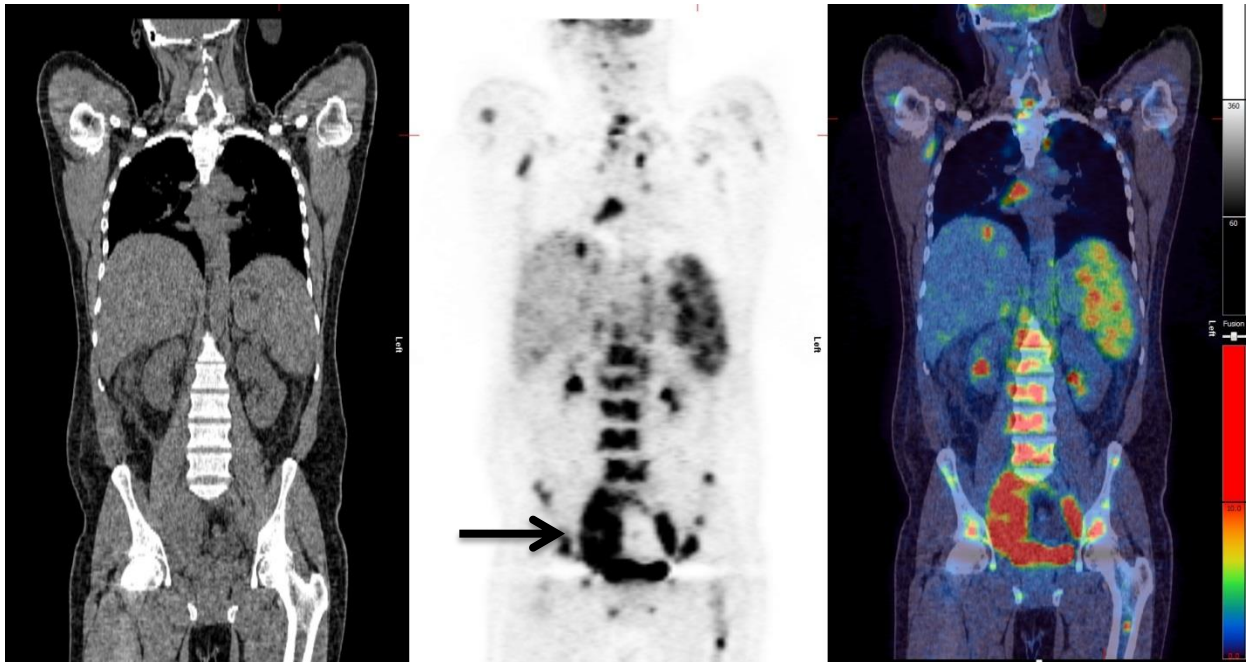
Maximum SUV

Hottest lesion on baseline

Hottest lesion at response

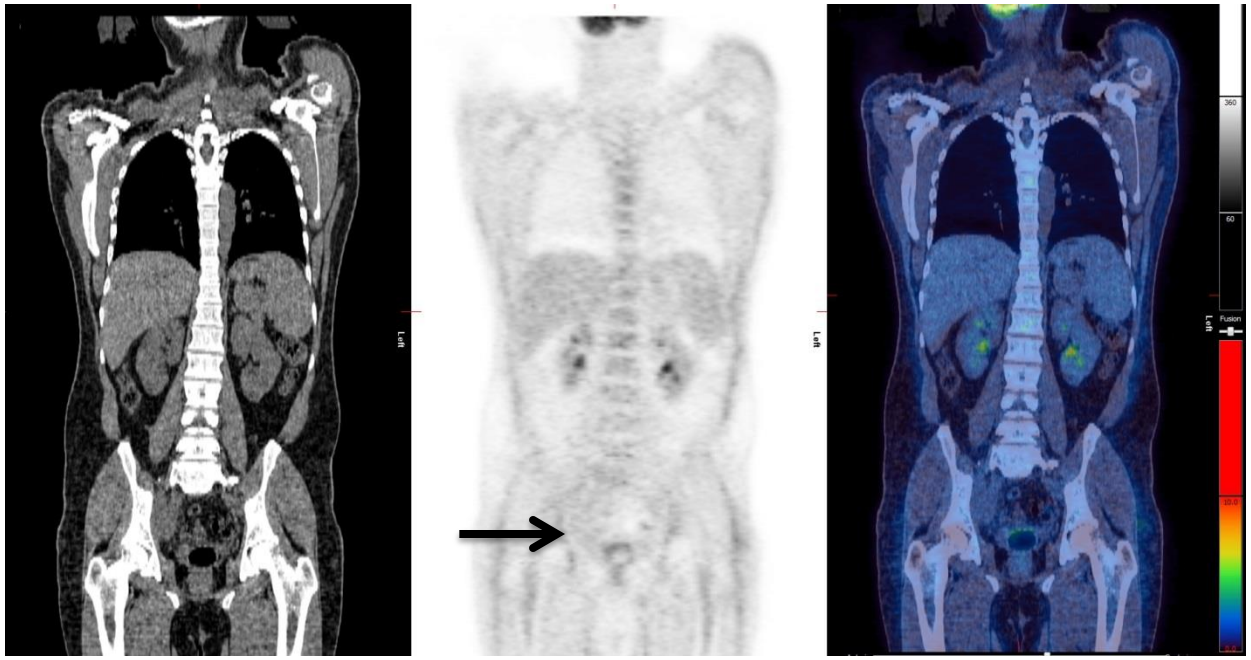
Δ SUV is % change between these Maximum SUV

Staging



SUV = 25.0

Interim



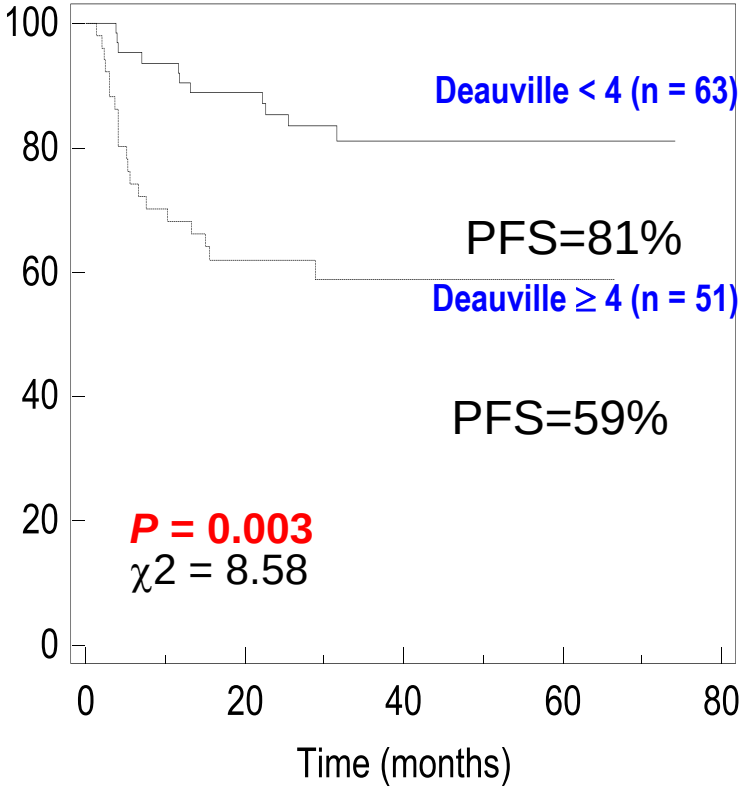
SUV = 2.6

ΔSUV 90%

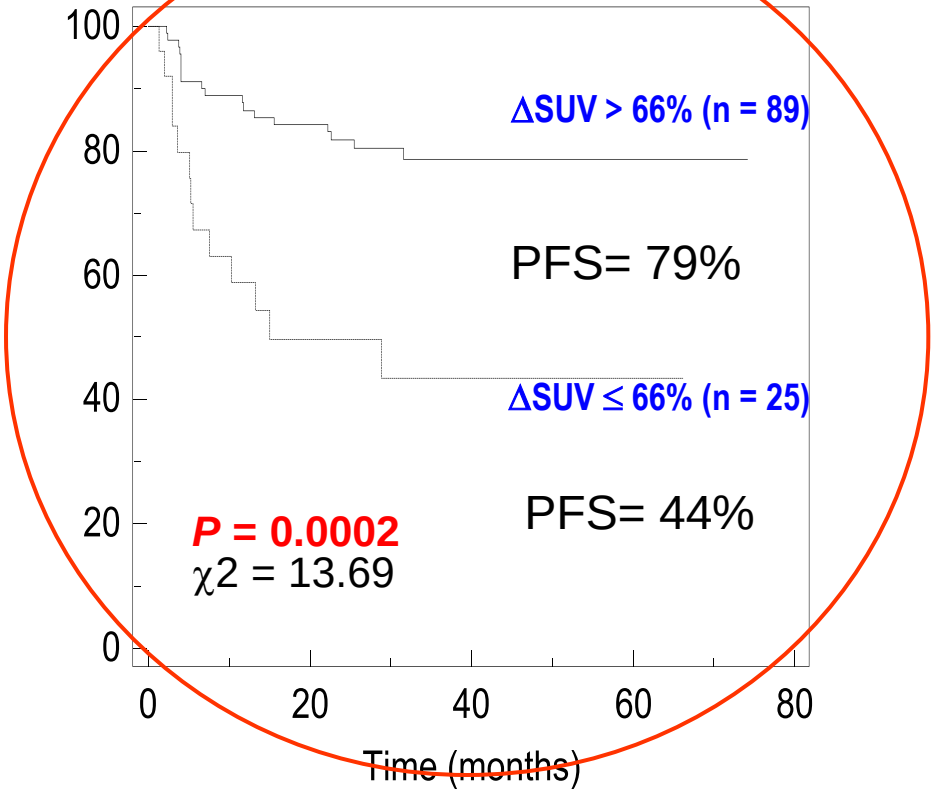
Reporting interim PET by Integrative ΔSUVmax more predictive of outcome than scoring residual activity at one step of the kinetics (DS)

DLBCL

Interobserver κ= **0.668**



Interobserver κ= **0.83**



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

Itti , 2013, Eur J Nucl Med Mol Imaging

Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26–27 September 2011 and Menton 2011 consensus

Michel Meignan[1], Andrea Gallamini[2], Emmanuel Itti[1], Sally Barrington[3], Corinne Haioun[1] & Aaron Polliack[4]

Leuk Lymphoma, 2012

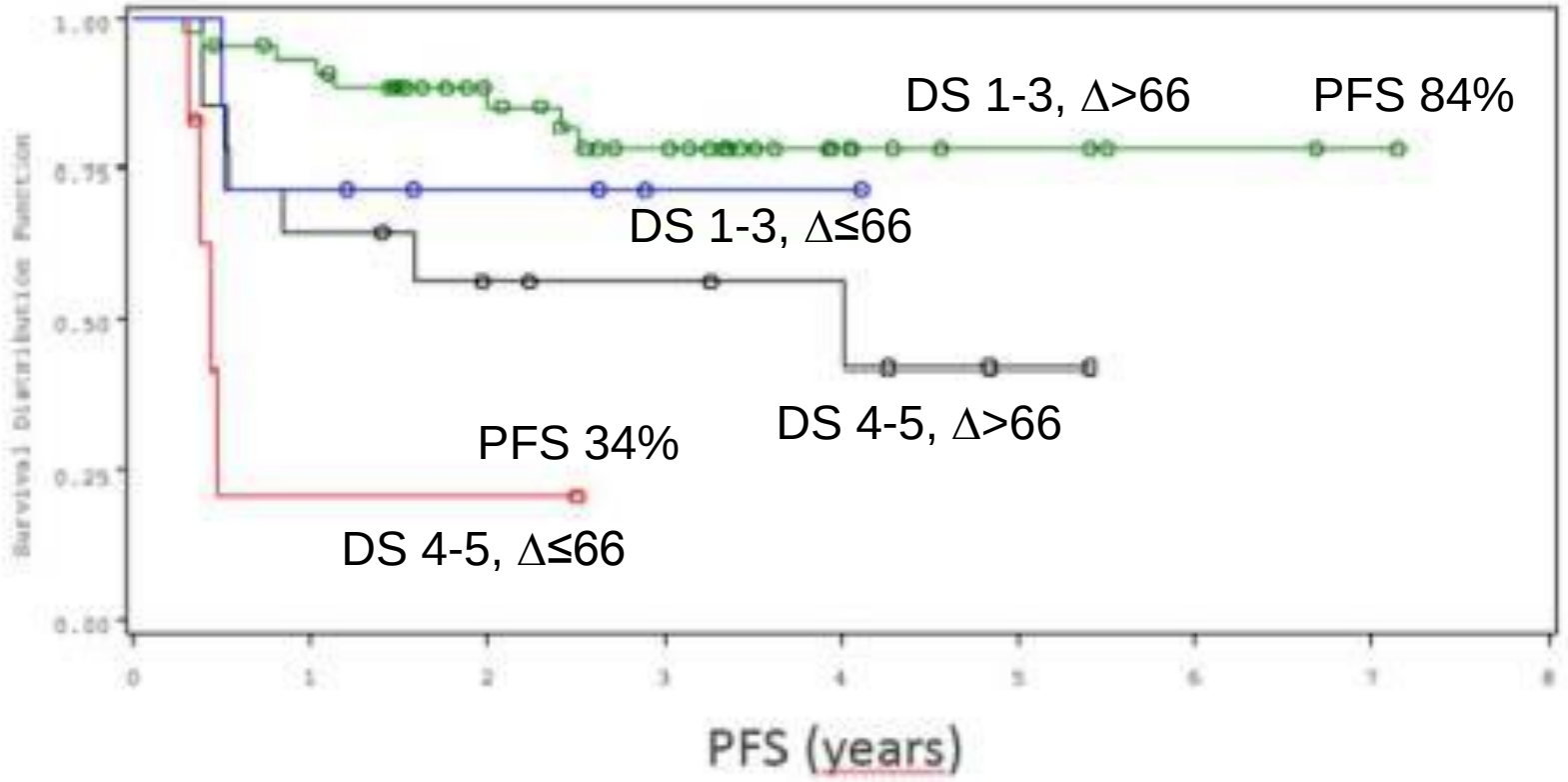
Initial SUVmax<10

Interim SUVmax>5

Implement ΔSUV analysis with 5 point scale with the liver cut-off

Combining analysis of residual uptake (DS) with ΔSUV kinetic approach

at 3-4 cycles in DLBCL (74 patients)

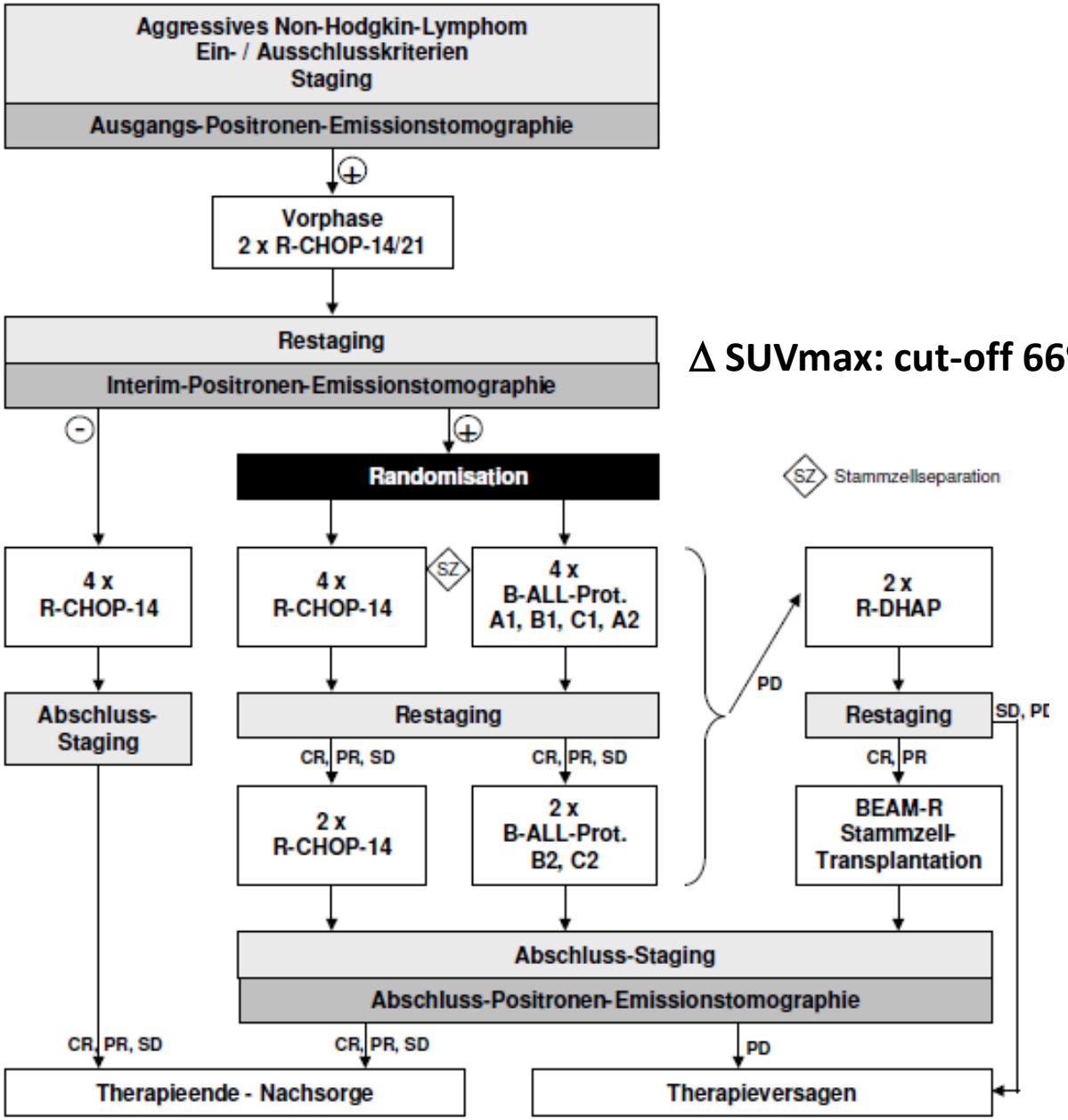


71% patients
Double negative excellent outcome
Double positive poor outcome

Nols et al. Leuk Lymphoma 2013

PETAL

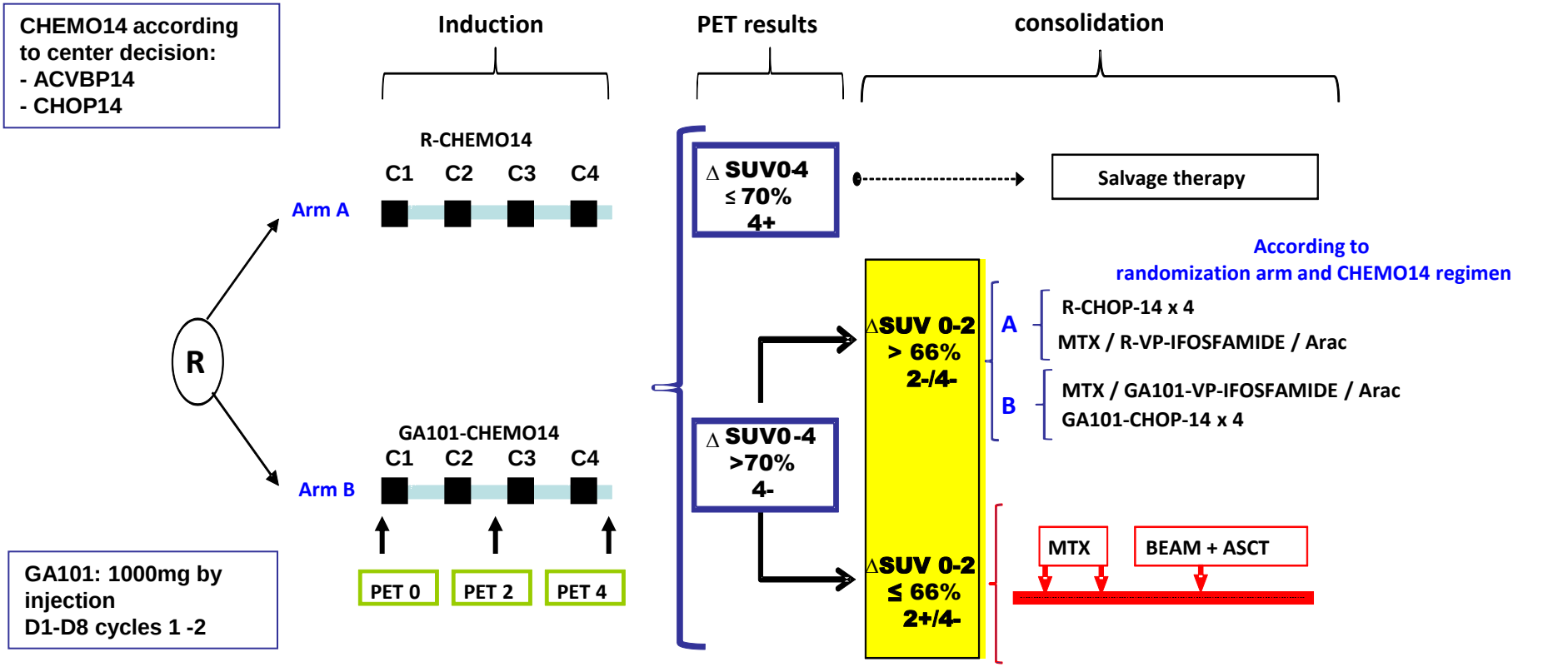
DLBCL: 18-60y



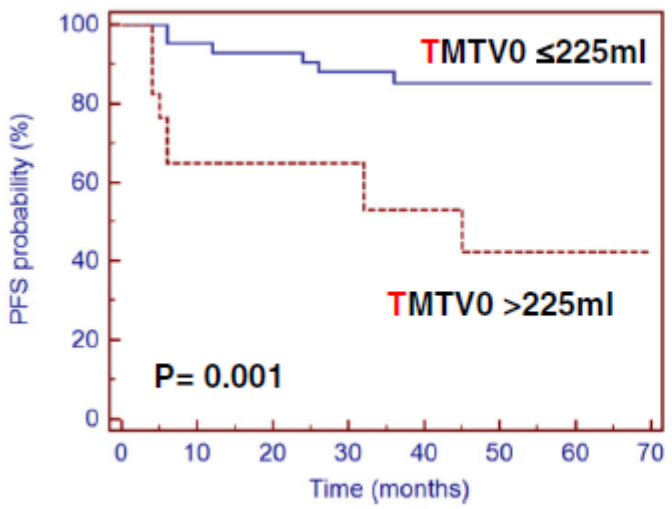
Δ SUVmax: cut-off 66%

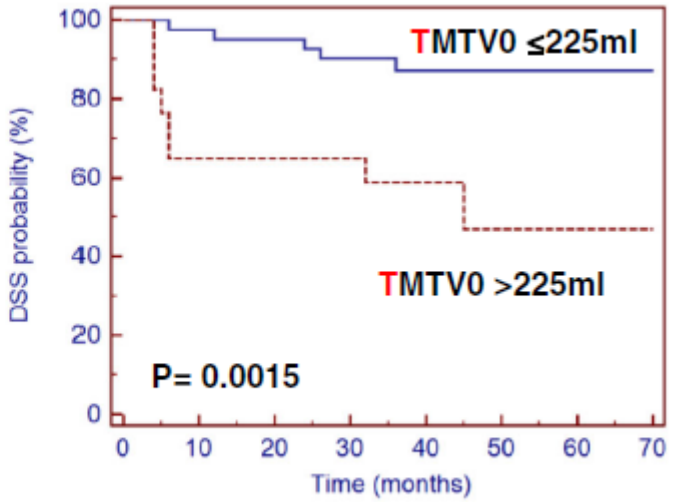
GAINED

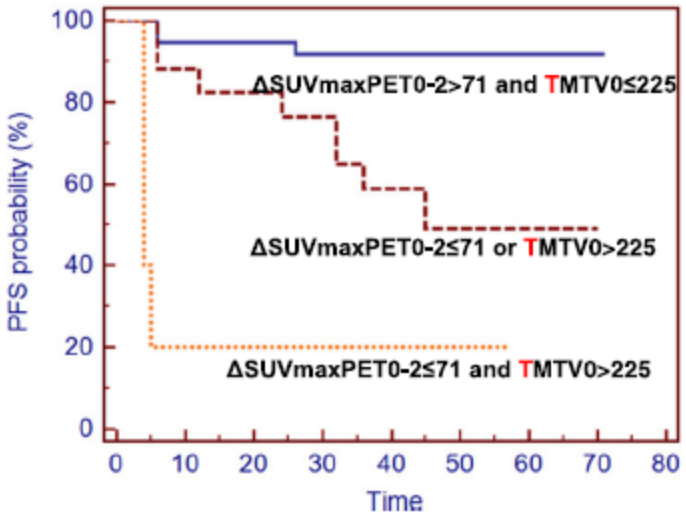
DLBCL, 18-60y, aaIPI = 1-3: Phase III – 2 arms

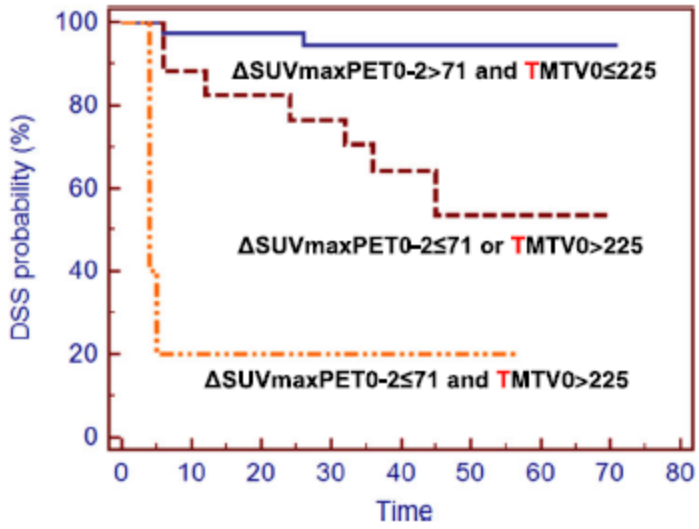


Combining in HL base line data,TMTV and response data, ΔSUVmax (PET2)



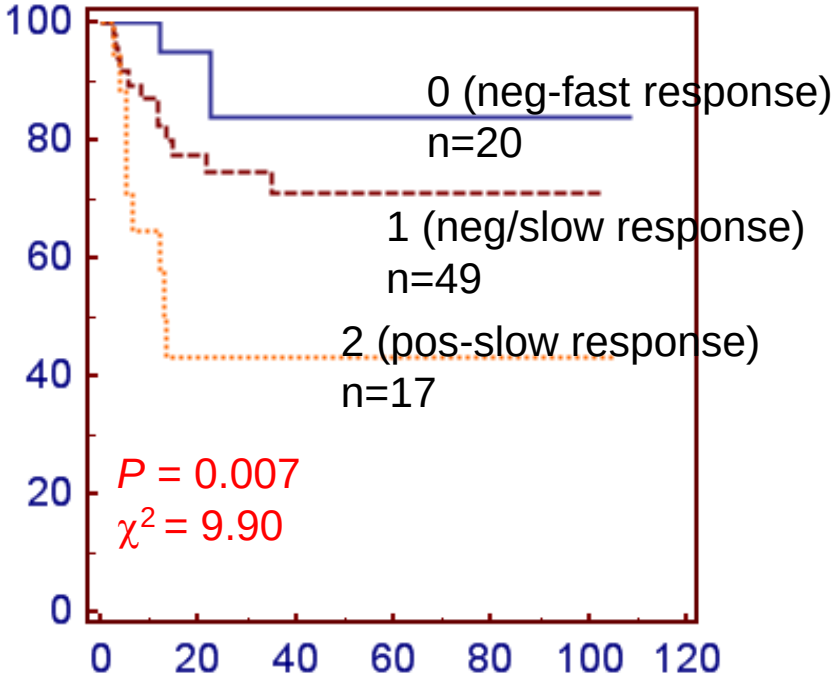






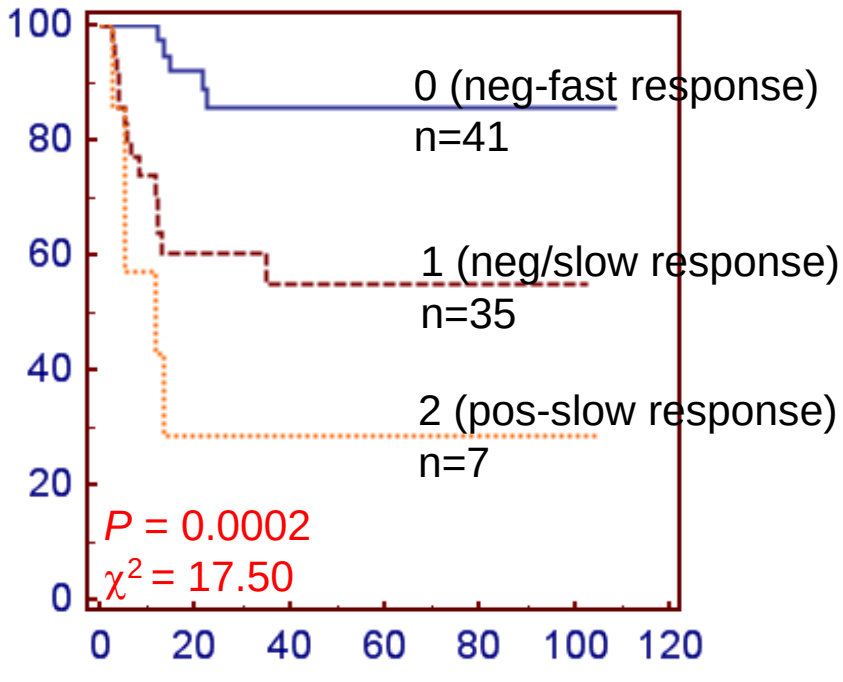
Kanoun et al. Eur J Nucl Med Mol Imaging, 2014

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%

Copie-Bergman. *Hematol Oncol* 2013: 31;151-200. Abs 210

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).