Médecine nucléaire en évaluation thérapeutique

-

Exemple du lymphome

Pr Pierre-Yves SALAUN

Médecine Nucléaire et Biophysique

CHRU Brest - UBO

Contexte

Evaluation historique

- Ann Arbor pour le staging: clinique, BOM, CT
- Cheson pour l'évaluation thérapeutique

Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas

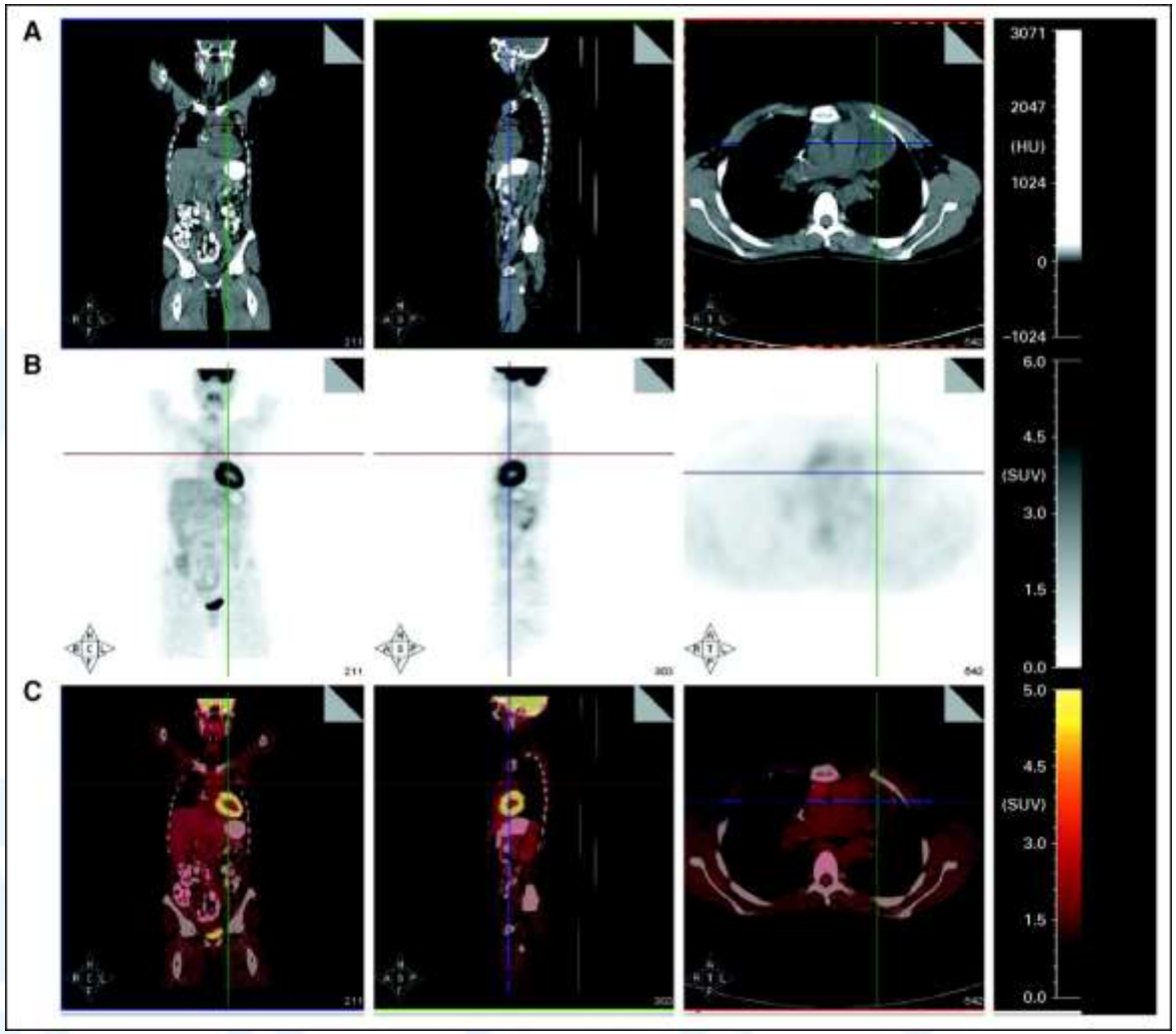
By Bruce D. Cheson, Sandra J. Horning, Bertrand Coiffier, Margaret A. Shipp, Richard I. Fisher, Joseph M. Connors, T. Andrew Lister, Julie Vose, Antonio Grillo-López, Anton Hagenbeek, Fernando Cabanillas, Donald Klippensten, Wolfgang Hiddemann, Ronald Castellino, Nancy L. Harris, James O. Armitage, William Carter, Richard Hoppe, and George P. Canellos

Abstract: Standardized guidelines for response assessment are needed to ensure comparability among clinical trials in non-Hodgkin's lymphomas (NHL). To achieve this, two meetings were convened among United States and international lymphoma experts representing medical hematology/oncology, radiology, radiation oncology, and pathology to review currently used response definitions and to develop a uniform set of criteria for assessing response in clinical trials. The criteria that were developed include anatomic definitions of response, with normal lymph node size after treatment of 1.5 cm in the longest transverse diameter by computer-assisted tomography scan. A designation of complete response/unconfirmed was adopted to include patients with a greater than 75% reduction in tumor size after therapy but with a residual mass, to include patients—especially those with large-cell NHL—who may not have residual 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 studies are not currently included in response definitions. Response rates may be the most important objective in phase II trials where the activity of a new agent is important and may provide support for approval by regulatory agencies. However, the goals of most phase III trials are to identify therapies that will prolong the progression-free survival, if not the overall survival, of the treated patients. We hope that these guidelines will serve to improve communication among investigators and comparability among clinical trials until clinically relevant laboratory and imaging studies are identified and become more widely available.

J Clin Oncol 17:1244-1253.

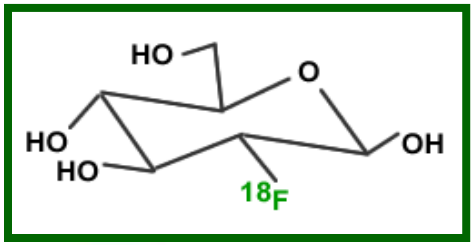
1999

Intérêt d'une imagerie moléculaire pour la caractérisation des masses résiduelles

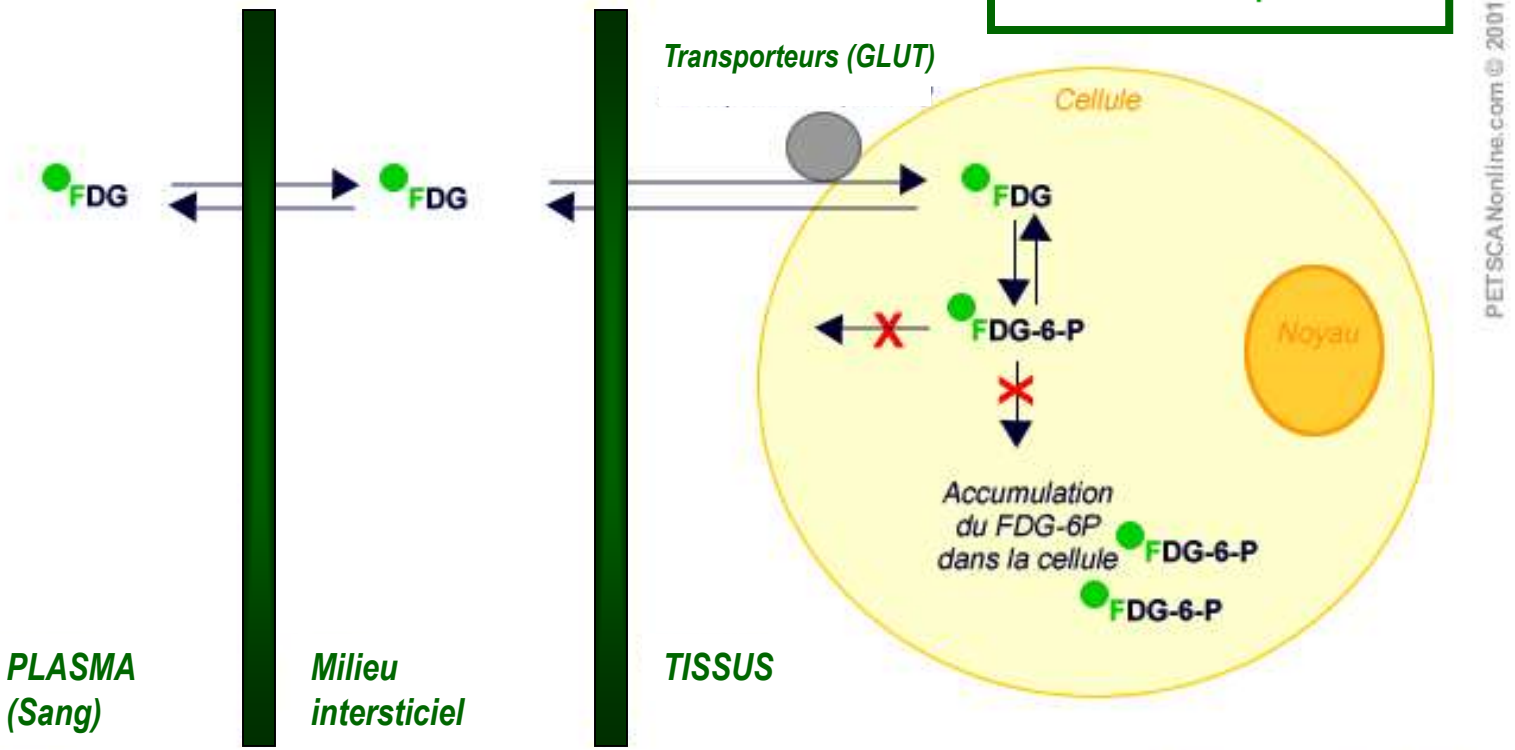


Juweid, M. E. et al. J Clin Oncol; 25:571-578 2007

^{18}Fluoro-Déoxy-Glucose



Métabolisme du FDG



Revised Response Criteria for Malignant Lymphoma

Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

A B S T R A C T

Purpose
Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods
The International Working Group response criteria (Cheson et al, J Clin Oncol 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of [^{18}F]fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results
New guidelines are presented incorporating PET, IHC, and flow cyto
response in non-Hodgkin's and Hodgkin's lymphoma. Standardized d
are provided.

Conclusion
We hope that these guidelines will be adopted widely by study grou
biotechnology companies, and regulatory agencies to facilitate the develo
effective therapies to improve the outcome of patients with lymphoma.

J Clin Oncol 25:579-586. © 2007 by American Society of Clinical Oncolo

2007

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidhauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

A B S T R A C T

Purpose
To develop guidelines for performing and interpreting positron emission tomography (PET) imaging for treatment assessment in patients with lymphoma both in clinical practice and in clinical trials.

Methods
An International Harmonization Project (IHP) was convened to discuss standardization of clinical trial parameters in lymphoma. An imaging subcommittee developed consensus recommendations based on published PET literature and the collective expertise of its members in the use of PET in lymphoma. Only recommendations subsequently endorsed by all IHP subcommittees were adopted.

Recommendations
PET after completion of therapy should be performed at least 3 weeks, and preferably at 6 to 8 weeks, after chemotherapy or chemoimmunotherapy, and 8 to 12 weeks after radiation or chemoradiotherapy. Visual assessment alone is adequate for interpreting PET findings as positive or negative when assessing response after completion of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define PET positivity for a residual mass $\geq$ 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node (ie, $\leq 1 \times 1$ cm in diameter) should be considered positive if its activity is above that of the surrounding background. Specific criteria for defining PET positivity in the liver, spleen, lung, and bone marrow are also proposed. Use of attenuation-corrected PET is strongly encouraged. Use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry.

J Clin Oncol 25:571-578. © 2007 by American Society of Clinical Oncology

Quand? Quels lymphomes?

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

Histology	Pretreatment	Mid-Treatment	Response Assessment	Post-Treatment Surveillance
Routinely FDG avid				
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	No†	Clinical trial	No†	No
MCL	No†	Clinical trial	No†	No
Variably FDG avid				
Other aggressive NHLs	No†	Clinical trial	No†‡	No
Other indolent NHLs	No†	Clinical trial	No†‡	No

Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.
*Recommended but not required pretreatment.
†Recommended only if ORR/CR is a primary study end point.
‡Recommended only if PET is positive pretreatment.

Cheson, J Clin Oncol, 2007

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

2014

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

See accompanying article on page 3048

A B S T R A C T

Abstract

The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

J Clin Oncol 32:3059-3067.

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

2014

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

See accompanying article doi: 10.1200/JCO.2013.54.8800

A B S T R A C T

Purpose
Recent advances in imaging, use of prognostic indices, and molecular profiling techniques have the potential to improve disease characterization and outcomes in lymphoma. International trials are under way to test image-based response–adapted treatment guided by early interim positron emission tomography (PET) –computed tomography (CT). Progress in imaging is influencing trial design and affecting clinical practice. In particular, a five-point scale to grade response using PET-CT, which can be adapted to suit requirements for early- and late-response assessment with good interobserver agreement, is becoming widely used both in practice- and response-adapted trials. A workshop held at the 11th International Conference on Malignant Lymphomas (ICML) in 2011 concluded that revision to current staging and response criteria was timely.

Methods
An imaging working group composed of representatives from major international cooperative groups was asked to review the literature, share knowledge about research in progress, and identify key areas for research pertaining to imaging and lymphoma.

Results
A working paper was circulated for comment and presented at the Fourth International Workshop on PET in Lymphoma in Menton, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidance regarding PET. Recommendations were made to optimize the use of PET-CT in staging and response assessment of lymphoma, including qualitative and quantitative methods.

Conclusion
This article comprises the consensus reached to update guidance on the use of PET-CT for staging and response assessment for [^{18}F]fluorodeoxyglucose-avid lymphomas in clinical practice and late-phase trials.

J Clin Oncol 32.

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See accompanying article doi: 10.1200/JCO.2013.54.8800

2014

Table 1. Summary of Recommendations

Recommendations
Section 1: Interpretation of PET-CT scans
1. Staging of FDG-avid lymphomas is recommended using visual assessment, with PET-CT images scaled to fixed SUV display and color table; focal uptake in HL and aggressive NHL is sensitive for bone marrow involvement and may obviate need for biopsy; MRI is modality of choice for suspected CNS lymphoma (type 1)
2. Five-point scale is recommended for reporting PET-CT; results should be interpreted in context of anticipated prognosis, clinical findings, and other markers of response; scores 1 and 2 represent CMR; score 3 also probably represents CMR in patients receiving standard treatment (type 1)
3. Score 4 or 5 with reduced uptake from baseline likely represents partial metabolic response, but at end of treatment represents residual metabolic disease; increase in FDG uptake to score 5, score 5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma represent treatment failure and/or progression (type 2)
Section 2: Role of PET-CT for staging
1. PET-CT should be used for staging in clinical practice and clinical trials but is not routinely recommended in lymphomas with low FDG avidity; PET-CT may be used to select best site to biopsy (type 1)
2. Contrast-enhanced CT when used at staging or restaging should ideally occur during single visit combined with PET-CT, if not already performed; baseline findings will determine whether contrast-enhanced PET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations (type 2)
3. Bulk remains an important prognostic factor in some lymphomas; volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomical size or volume, should be explored as potential prognosticators (type 3)
Section 3: Role of interim PET
1. If midtherapy imaging is performed, PET-CT is superior to CT alone to assess early response; trials are evaluating role of PET response–adapted therapy; currently, it is not recommended to change treatment solely on basis of interim PET-CT unless there is clear evidence of progression (type 1)
2. Standardization of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice (type 1)
3. Data suggest that quantitative measures (eg, δSUVmax) could be used to improve on visual analysis for response assessment in DLBCL, but this requires further validation in clinical trials (type 2)
Section 4: Role of PET at end of treatment
1. PET-CT is standard of care for remission assessment in FDG-avid lymphoma; in presence of residual metabolically active tissue, where salvage treatment is being considered, biopsy is recommended (type 1)
2. Investigation of significance of PET-negative residual masses should be collected prospectively in clinical trials; residual mass size and location should be recorded on end-of-treatment PET-CT reports where possible (type 3)
3. Emerging data support use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL; studies are warranted to confirm this finding in patients receiving maintenance therapy (type 2)
4. Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT, but additional studies are warranted (type 3)

Abbreviations: ASCT, autologous stem-cell transplantation; CMR, complete metabolic response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FDG, [^{18}F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PET, positron emission tomography; SUV, standardized uptake value; δSUVmax, change in maximum SUV.

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I. Interprétation

TEP-FDG recommandée dans les lymphomes avides de FDG

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See accompanying article doi: 10.1200/JCO.2013.54.8800

Table 2. FDG Avidity According to WHO Classification

Histology	No. of Patients	FDG Avid (%)
HL	489	97-100
DLBCL	446	97-100
FL	622	91-100
Mantle-cell lymphoma	83	100
Burkitt's lymphoma	24	100
Marginal zone lymphoma, nodal	14	100
Lymphoblastic lymphoma	6	100
Anaplastic large T-cell lymphoma	37	94-100*
NK/T-cell lymphoma	80	83-100
Angioimmunoblastic T-cell lymphoma	31	78-100
Peripheral T-cell lymphoma	93	86-98
MALT marginal zone lymphoma	227	54-81
Small lymphocytic lymphoma	49	47-83
Enteropathy-type T-cell lymphoma	20	67-100
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67
Mycosis fungoides	24	83-100
Sezary syndrome	8	100†
Primary cutaneous anaplastic large T-cell lymphoma	14	40-60
Lymphomatoid papulosis	2	50
Subcutaneous panniculitis-like T-cell lymphoma	7	71
Cutaneous B-cell lymphoma	2	0

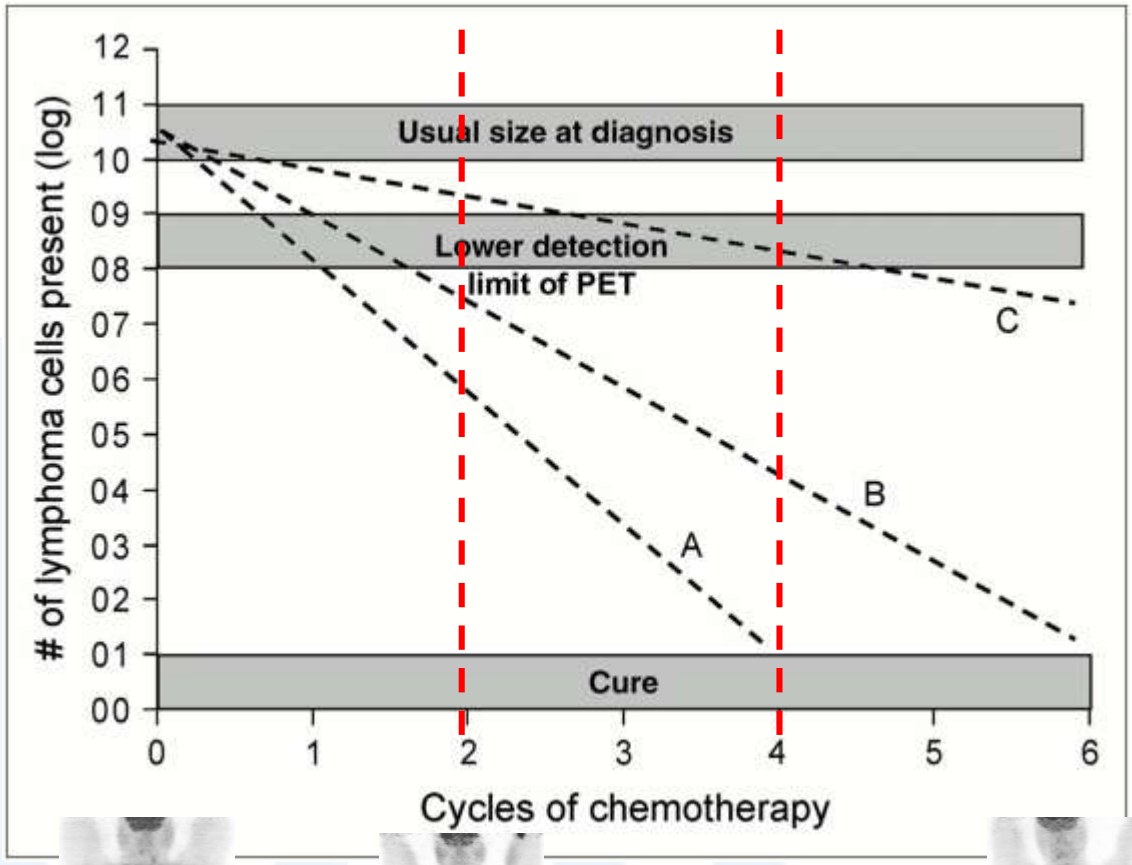
NOTE. Data adapted,[64] with additional updates.[18,33,34,65-67]

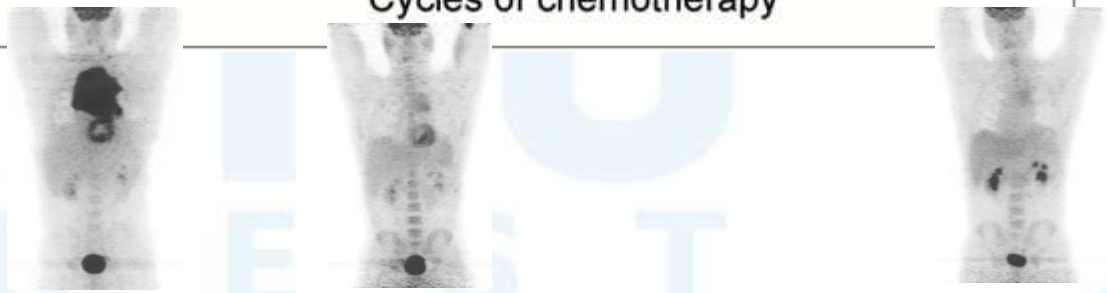
Abbreviations: DLBCL, diffuse large B-cell lymphoma; FDG, [^{18}F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*Only 27% of cutaneous sites.

†Only 62% of cutaneous sites.

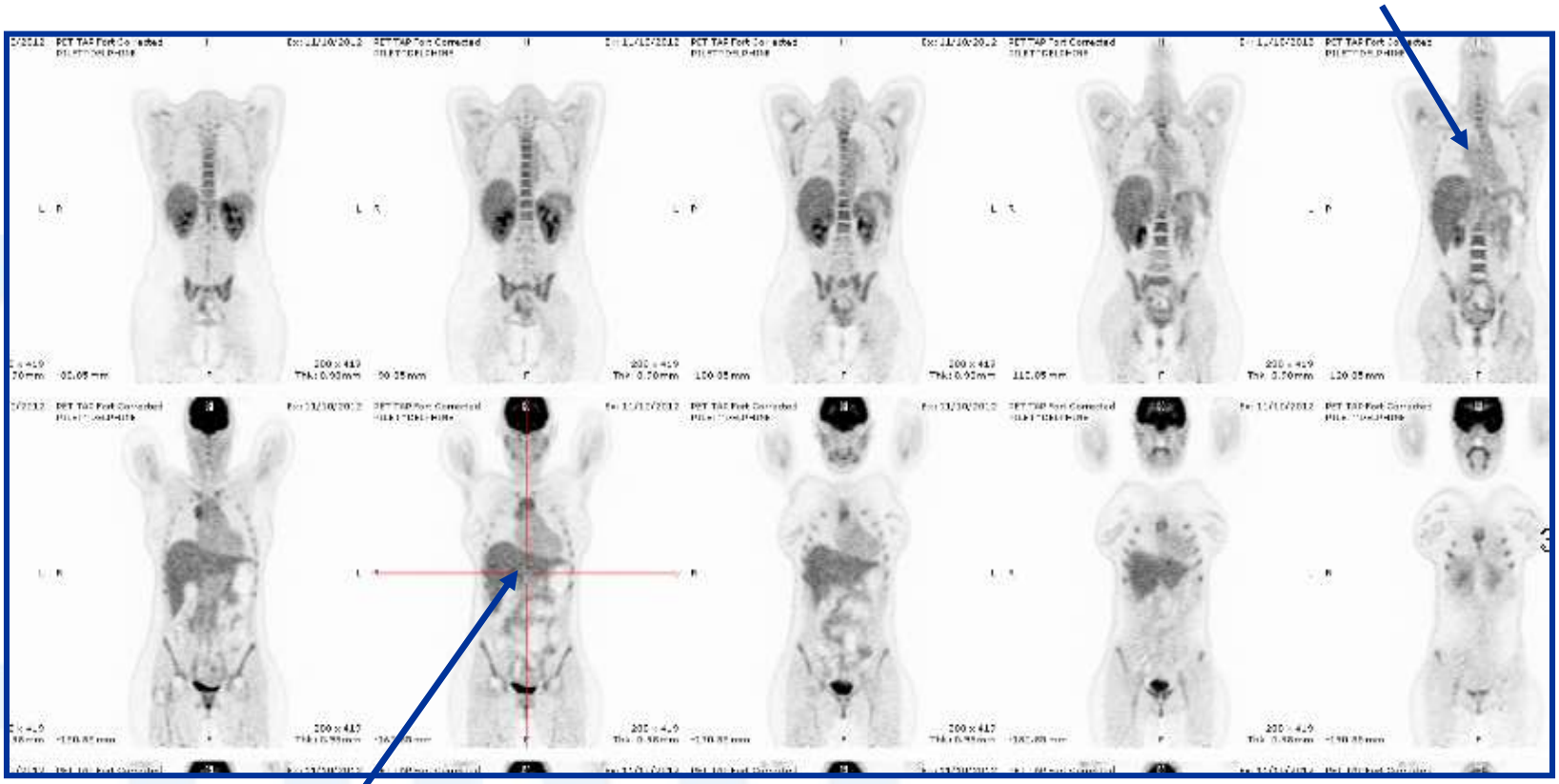
3 étapes dans l'évaluation: initial, intermédiaire (iTEP), fin de traitement





Échelle de Deauville
(5-point scale: 5-PS)
Recommandée pour l'évaluation thérapeutique

Bruit de fond médiastinal



Bruit de fond hépatique

Échelle de Deauville
(5-point scale: 5-PS)
Recommandée pour l'évaluation thérapeutique
Fixation la plus intense sur un site initialement envahi

score 1 : pas d'hyperfixation

score 2 : fixation ≤ médiastin

score 3 : fixation > médiastin mais ≤ foie

score 4 : fixation > foie

score 5 : fixation >> foie et/ou progression

score 1: pas d'hyperfixation

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

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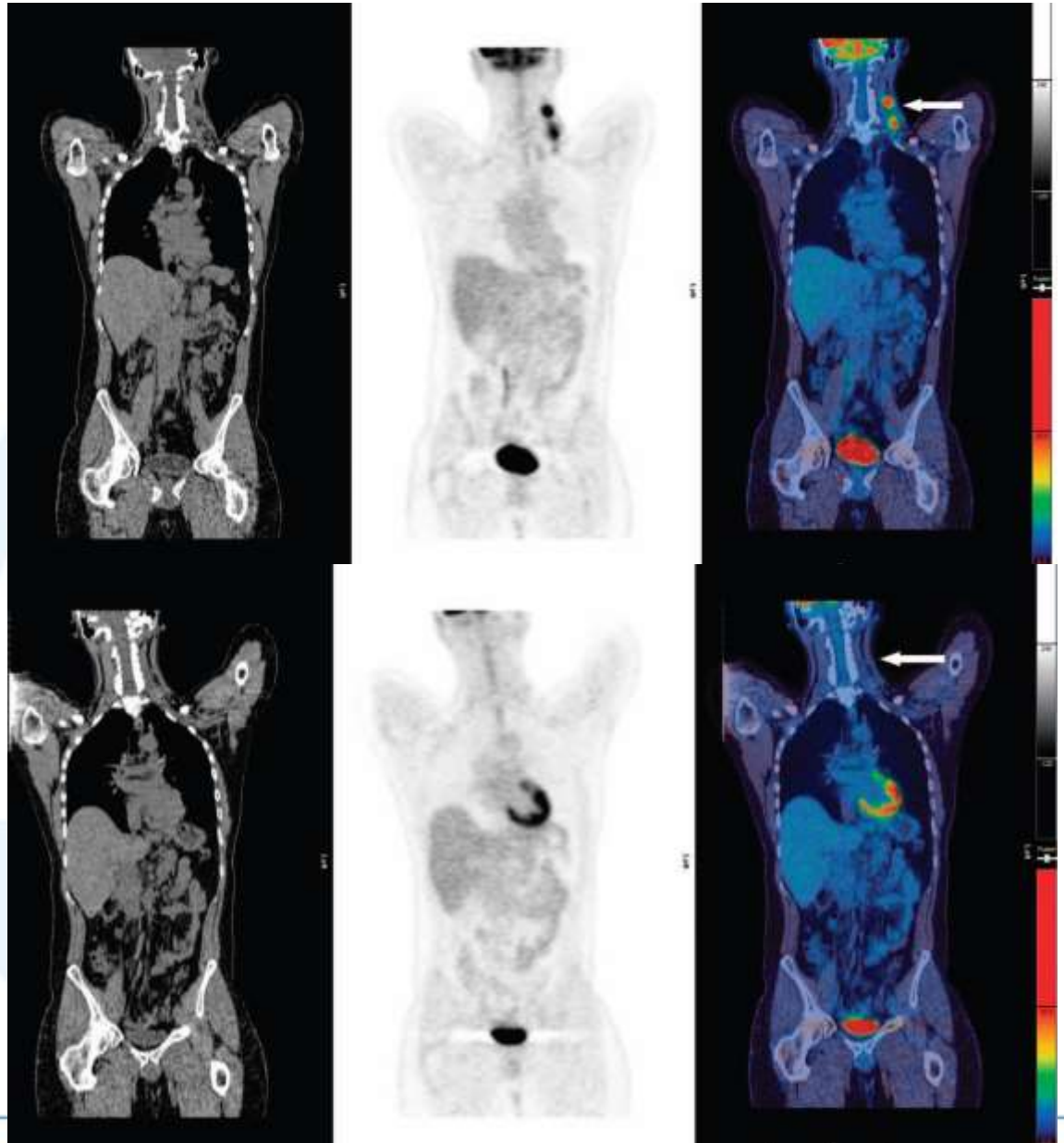
See accompanying article doi: 10.1200/JCO.2013.54.8800



score 2: fixation ≤ médiastin

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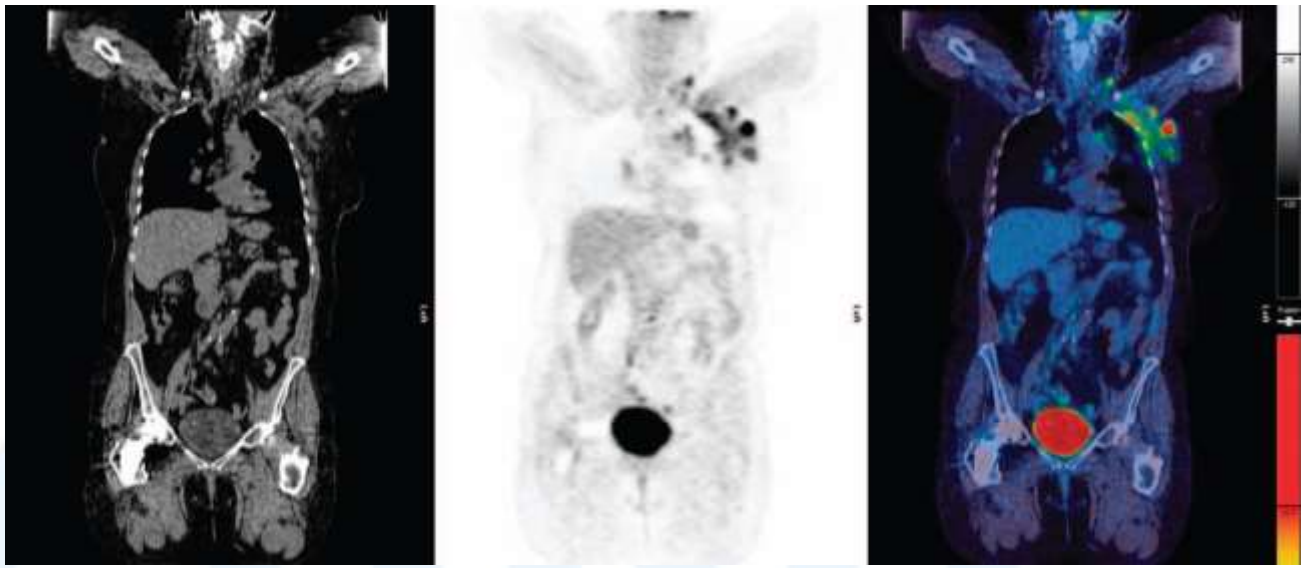

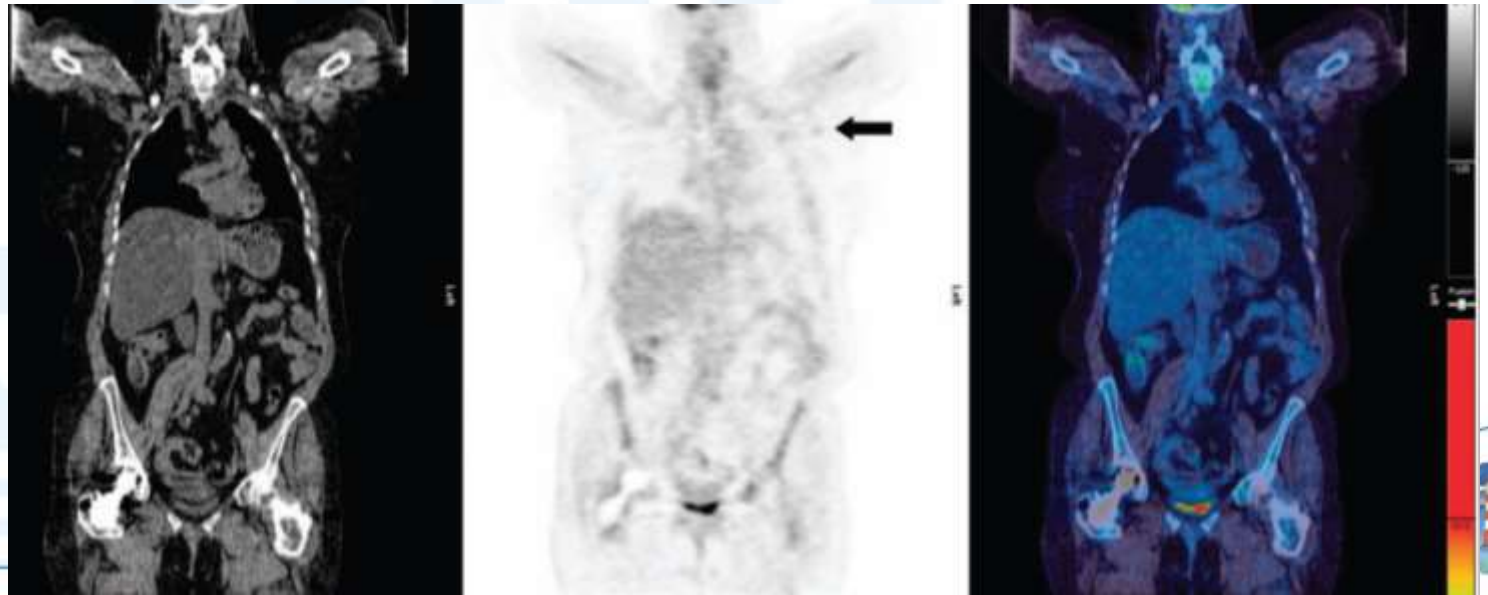

score 3: fixation > médiastin mais ≤ foie

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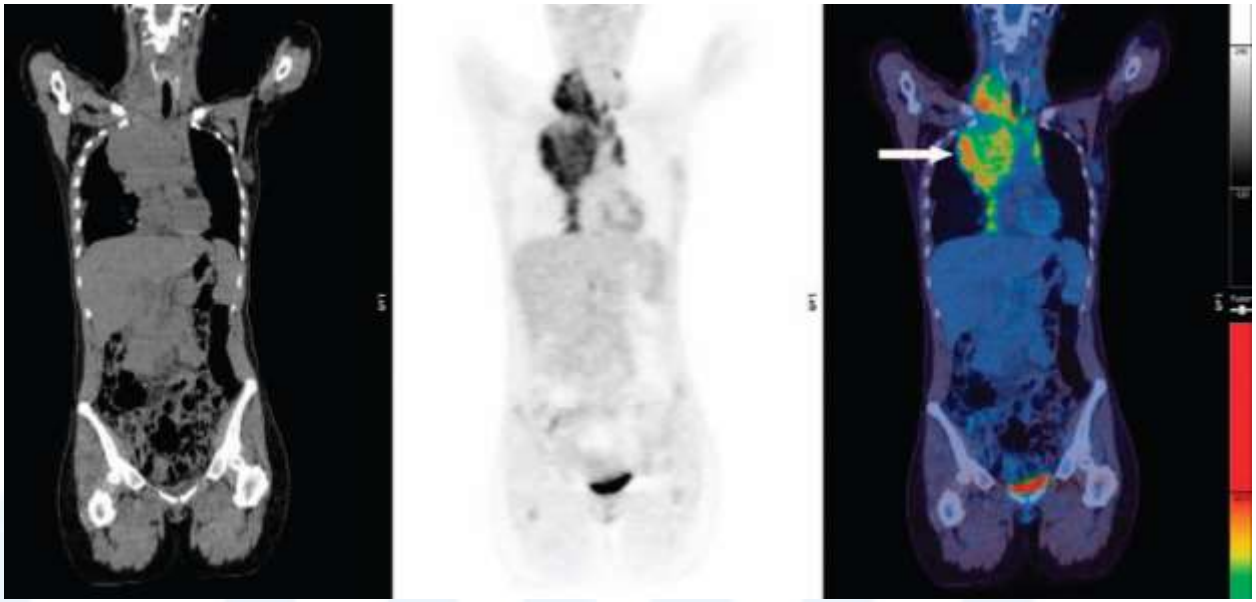

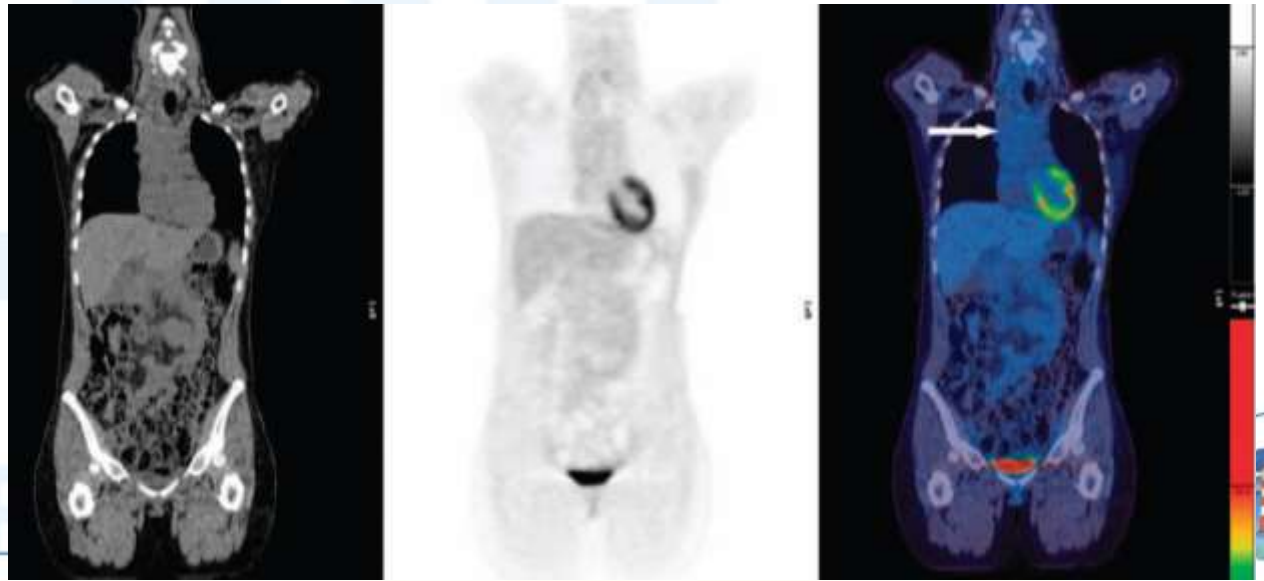

score 4: fixation > foie

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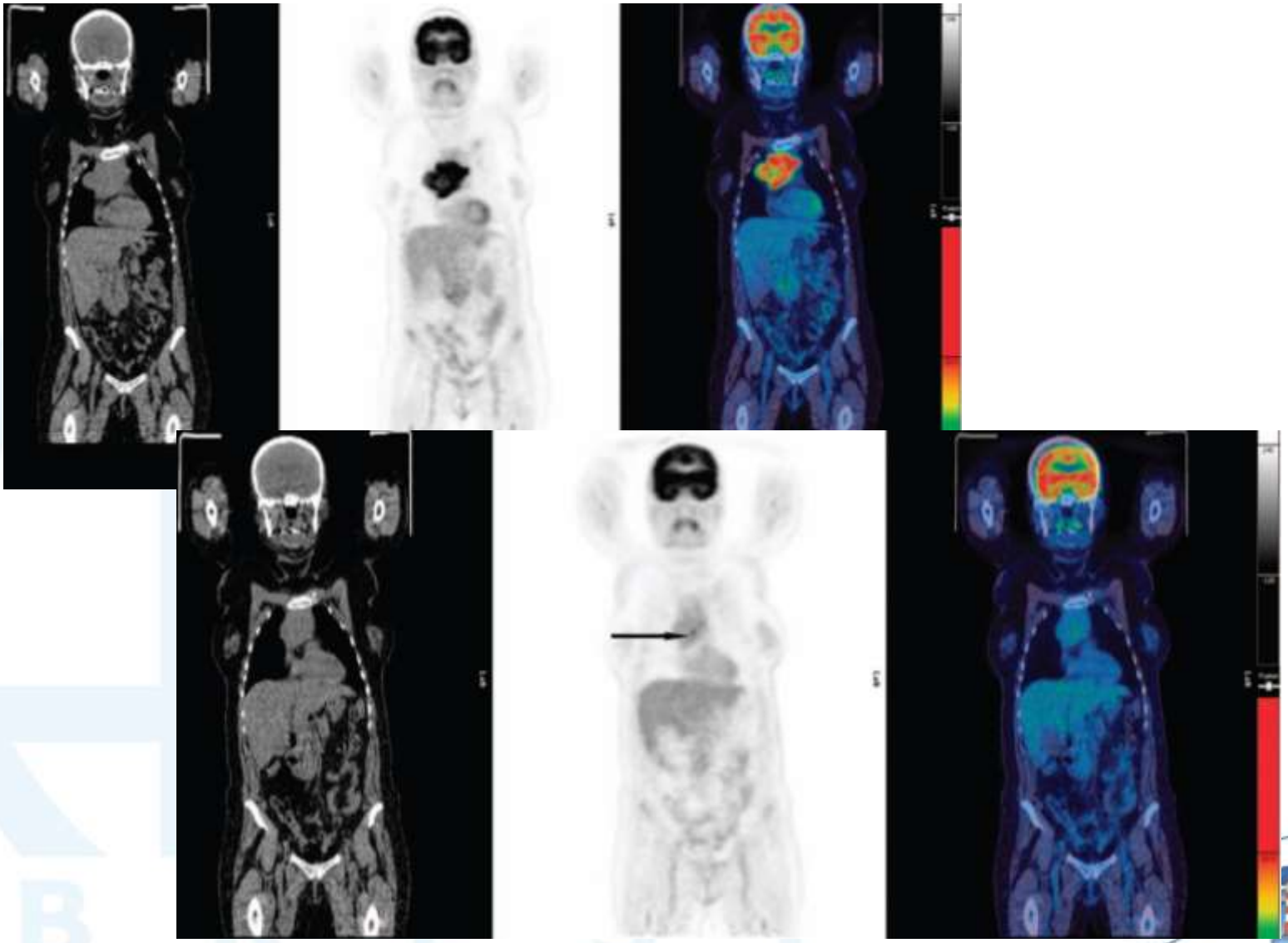

score 5: fixation >> foie et/ou progression

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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

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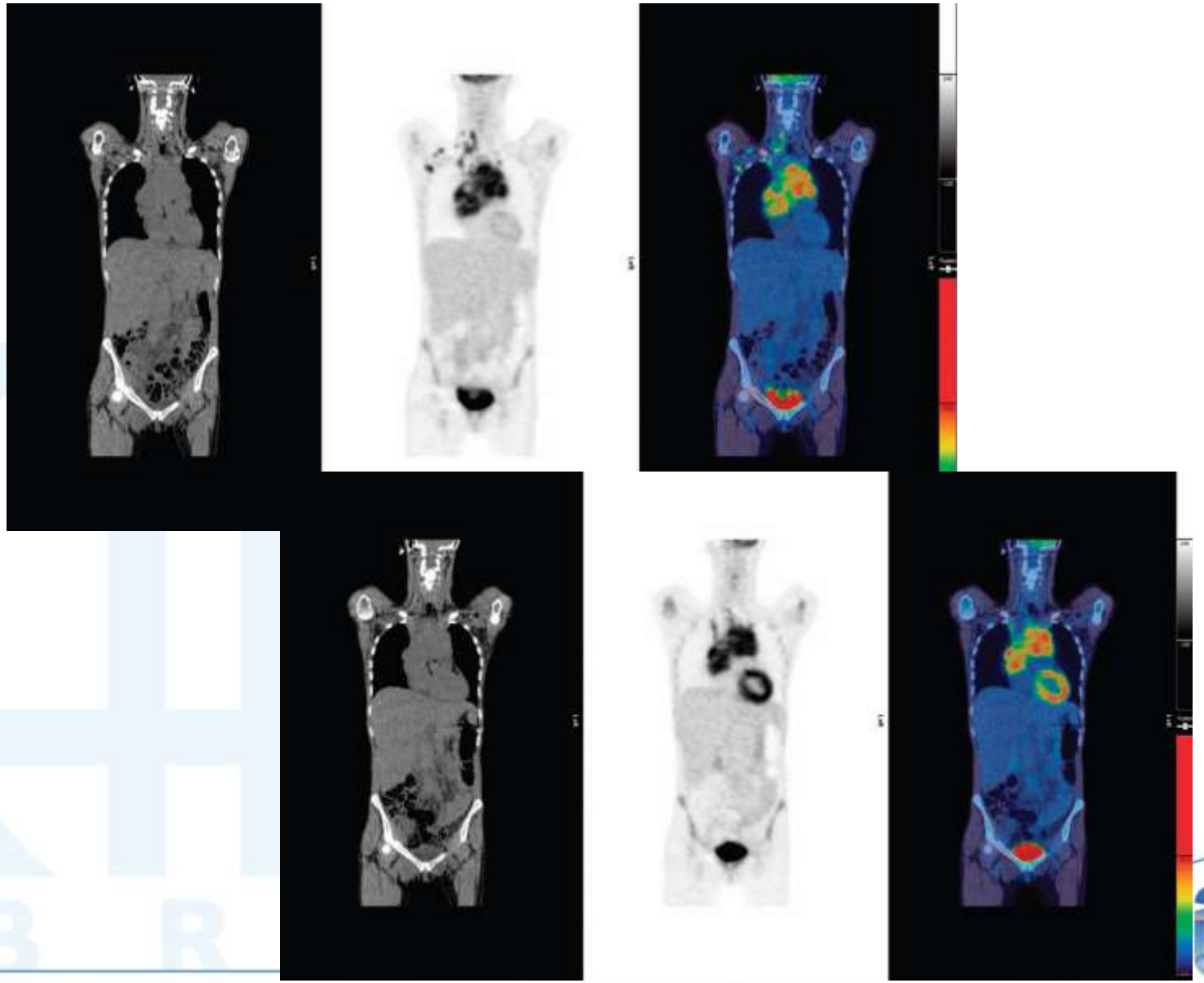


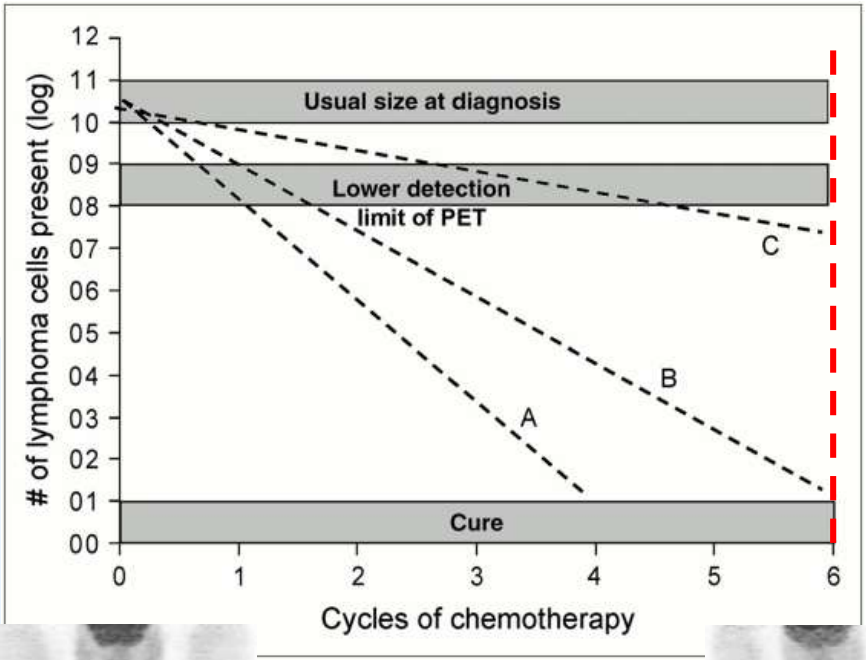
II. Bilan initial

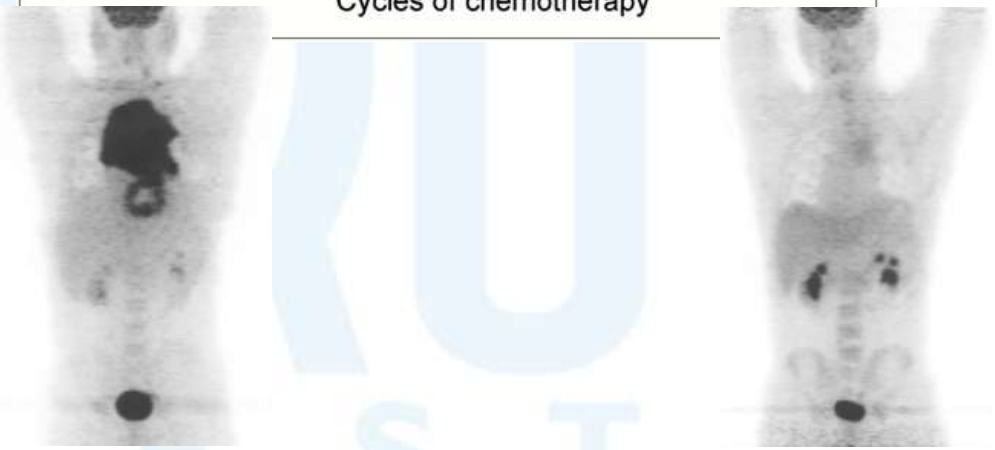
TEP recommandée pour les lymphomes avides de FDG

- Bilan d'extension des lymphomes avides de FDG
- Analyse visuelle
- Sensibilité et Spécificité de la TEP FDG > CT (gg < 1 cm, foie, rate)
- Lésions focales dans le foie, la rate et le squelette fortement suspectes
- IRM recommandée pour les atteintes du SNC (fixation cérébrale du FDG)
- Biopsie guidée par la TEP

III. Evaluation en fin de traitement

Concept de l'évaluation de fin de traitement





Problématique : la malade est il guéri ?

- Masses résiduelles: Tumeur viable ou nécrose/fibrose? (2/3 des MDH)
- **Exactitude 80% à 90%, >> CT (40%)**
- VPN 80% à 90%
- 85% de VPP pour les LNH agressifs et 65% pour les MDH (20% pour le CT pour les MDH)

LBDGC

- 54 patients, LNH agressifs
- CT + TEP, 1 à 16 semaines après 4 à 8 cures de chimiothérapie
- Survie sans progression selon la classification IWC / IWC-PET

Table 1. IWC+PET-Based Response Designations Based on the IWC Designations and PET Findings

IWC+PET-Based Response Designations	Description
CR	CR by IWC with a completely negative PET
	CRu, PR, or SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy
	PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) ≥ 1.5 cm (≥ 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass
	CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass
	SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	SD by IWC with a positive PET at the site of a previously involved node/nodal mass (ie, residual mass)
PD	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion)
	PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of < 1.5 cm (< 1.0 cm in the lungs)

Abbreviations: IWC+PET, International Workshop Criteria plus positron emission tomography; CR, complete response; BMB, bone marrow biopsy; CT, computed tomography; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

(1) Juweid ME, J Clin Oncol, 2005;23:4652-

LBDGC

		IWC-PET					
	Réponse	RC	RC nc	RP	SD	PD	Total
IWC	RC	17	0	0	0	0	**17**
	RC nc	5	0	2	0	0	**7**
	RP	10	0	9	0	0	**19**
	SD	2	0	1	6	0	**9**
	PD	1	0	0	0	1	**2**
	Total	**35**	**0**	**12**	**6**	**1**	**54**

nc, non confirmée; SD, stable disease; PD, progressive disease
IWC, International Workshop Criteria; PET, positron emission tomography

(1) Juweid ME, J Clin Oncol, 2005;23:4652-61

IWC / IWC + PET: *PFS*

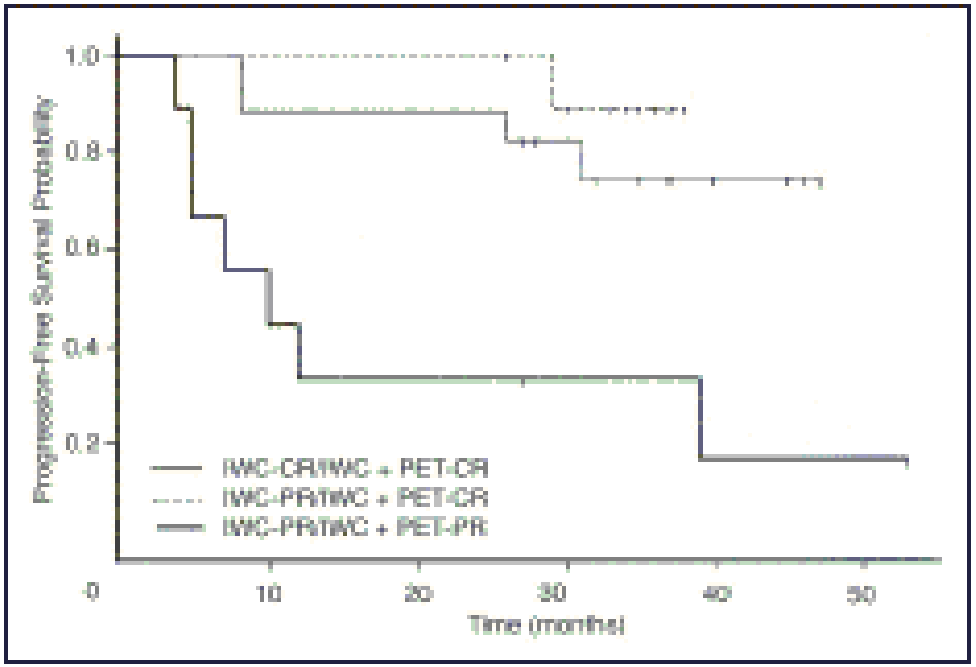
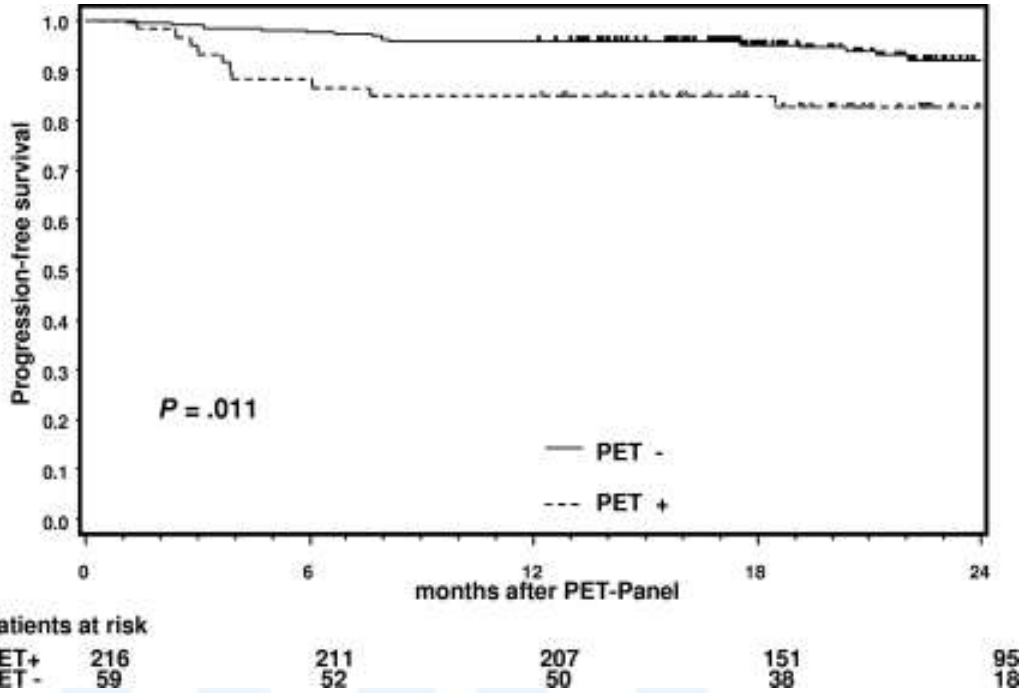


Fig 5. Progression-free survival by the International Workshop Criteria (IWC) and IWC plus positron emission tomography (PET) based on the Kaplan-Meier method. (——) Patients with complete response (CR) by IWC and CR by IWC+PET (n = 17); (– – –) patients with partial response (PR) by IWC and CR by IWC+PET (n = 10); (——) patients with PR by IWC and PR by IWC+PET (n = 9); (|) censored observations.

Juweid ME, J Clin Oncol, 2005;23:4652-61

Hodgkin



PFS for patients with PET^{+} and PET^{-} residual tissues.
***Kobe et al, Blood.* 2008 November 15; 112(10): 3989–3994.**

Folliculaire

Clinical Cancer Research

End-therapy positron emission tomography for treatment response assessment in follicular lymphoma: A systematic review and meta-analysis

Junhee Pyo, Kyung Won Kim, Heather A. Jacene, et al.

Clin Cancer Res Published OnlineFirst September 19, 2013.

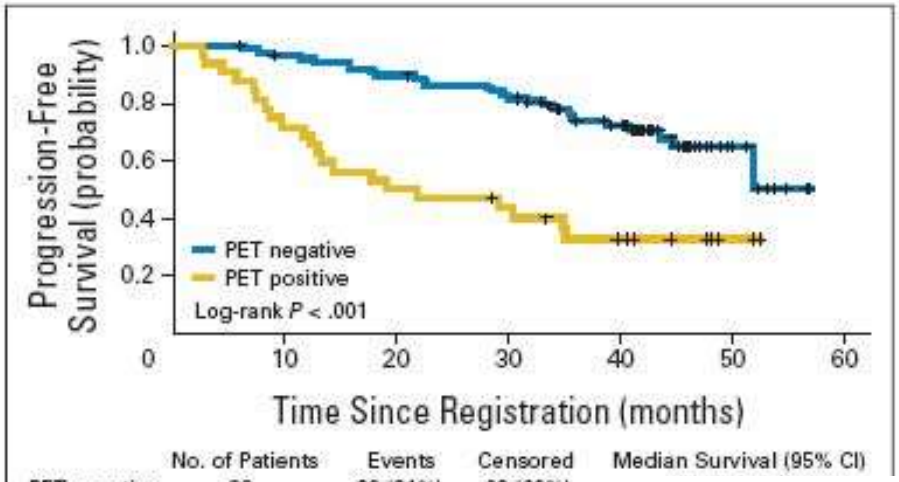
First author (year of publication)	Location (study period)	No. of analyzed patients	Study design	Clinical setting	Histologic grade	Chemotherapy regimen	Type of PET scanner	PET response criteria	CT response criteria
Bishu et al (2007) (14)	Nebraska, USA (1999-2006)	16	Retrospective	Untreated FL	1, 2	Conventional CTx or CIT	PET or PET/CT	Qualitative assessment	1999-IWG criteria
Dupuis et al (2012) (15)	Multicenters in Italy and France (2007-2009)	104	Prospective	Untreated FL	1, 2, and 3A	CIT	PET/CT*	Deauville 5-point scale	1999-IWG criteria
Janikova et al (2008) (16)	Brno, Czech Republic (2002-2007)	93	Retrospective						
Le Dortz et al (2010) (17)	Rennes, France (NA)	45	Retrospective						
Lopci et al (2010) (18)	Multicenters in Italy (NA)	59	Retrospective						
Lopci et al (2012) (19)	Bologna, Italy (NA)	91	Retrospective						
Trotman et al (2011) (20)	Multicenters in 25 countries (2004-2007)	122	Prospective						
Zinzani et al (2007) (21)	Bologna, Italy (2002-2004)	45	Retrospective	Untreated FL	1, 2	CIT	PET	Qualitative assessment	1999-IWG criteria

Abbreviations: FL = follicular lymphoma; CTx = chemotherapy; CIT = chemoimmunotherapy; RIT = radioimmunotherapy; IWG = international working group; NA, not available.

* Information obtained by communication with authors of the original literature.

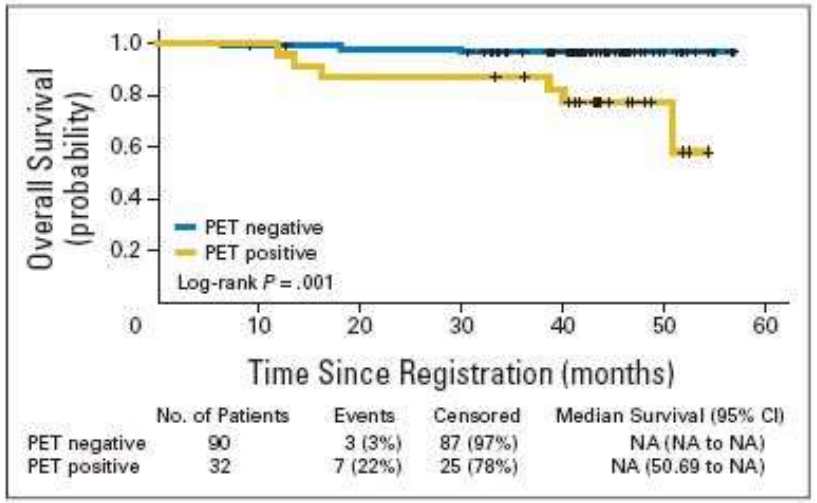
In conclusion, the current evidence in the literature consistently shows that PET-based response criteria are more predictive of PFS than CT-based criteria and more efficient in determining CR and detecting residual

Folliculaire



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	
PET positive	32	21 (66%)	11 (34%)	

Fig 2. Prognostic impact of postinduction positron
computed tomography (PET-CT) on progression-free s
tients. PET negative designates patients (n = 90) with
induction therapy, and PET positive designates those (
PET-CT. Log-rank $P < .001$. N/A, not applicable.



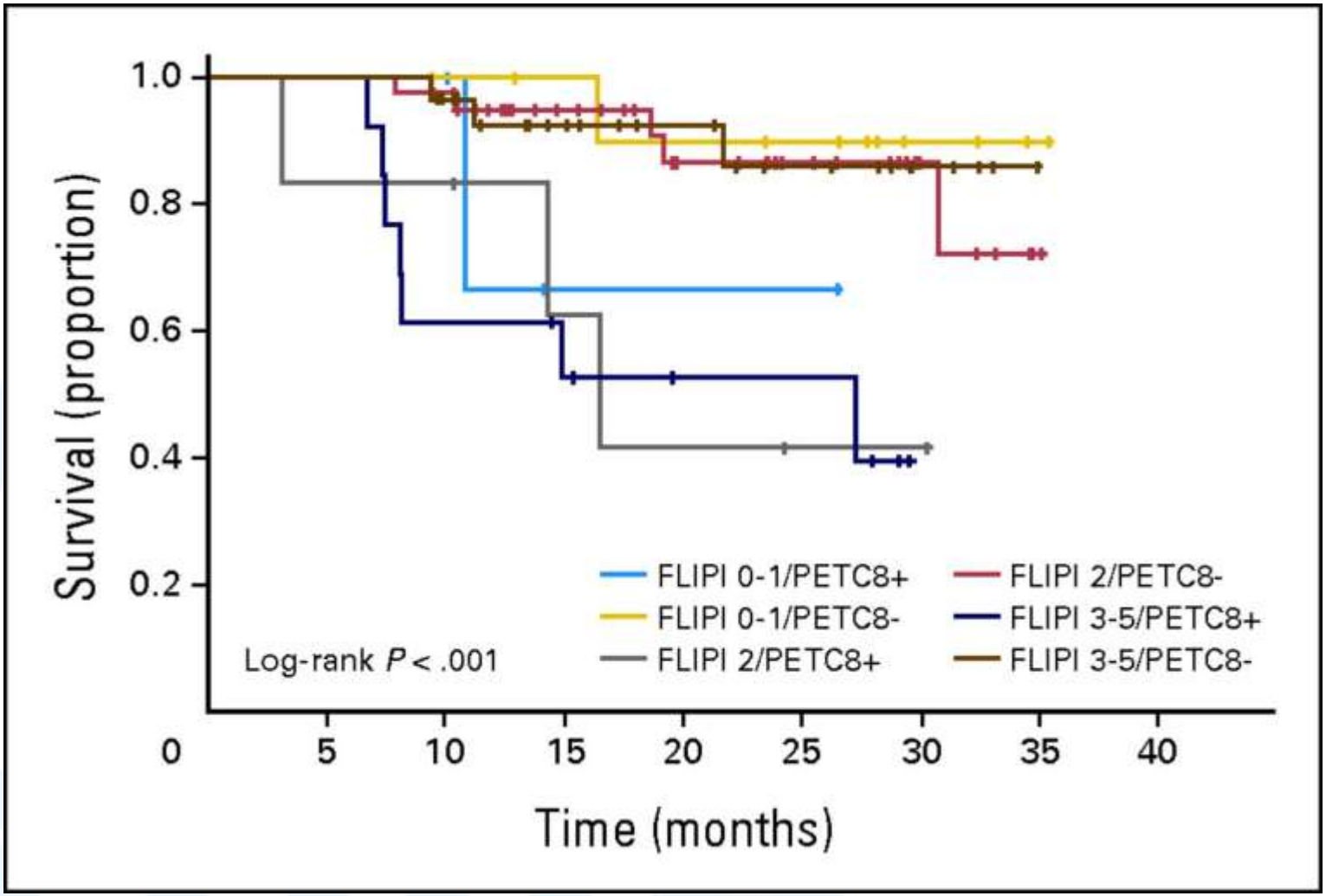
	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	3 (3%)	87 (97%)	NA (NA to NA)
PET positive	32	7 (22%)	25 (78%)	NA (50.69 to NA)

Fig 4. Prognostic impact of postinduction positron emission tomography–computed tomography (PET-CT) on overall survival (OS) in 122 patients. PET negative designates patients (n = 90) with a negative PET-CT after induction therapy, and PET positive designates those (n = 32) with a positive PET-CT. Log-rank $P = .001$. N/A, not applicable.

Traitement par 6R-CHOP ou 8R-CVP puis randomisation pour traitement d'entretien

Trotman et al, JCO, 2011

Progression-free survival according to Follicular Lymphoma International Prognostic Index (FLIPI) score and final positron emission tomography (PET) review.



Dupuis J et al. JCO 2012;30:4317-4322

Intérêt de la TEP-FDG en fin de traitement

- TEP-FDG > CT pour confirmer la rémission
- Recommandée pour les lymphomes avides de FDG
- Valeurs pronostiques démontrées pour
  - LBDGC
  - Hodgkin
  - Lymphome folliculaire ±

- Masses positives dans le LBDGC et le hodgkin à biopsier avant de décider d'un rattrapage

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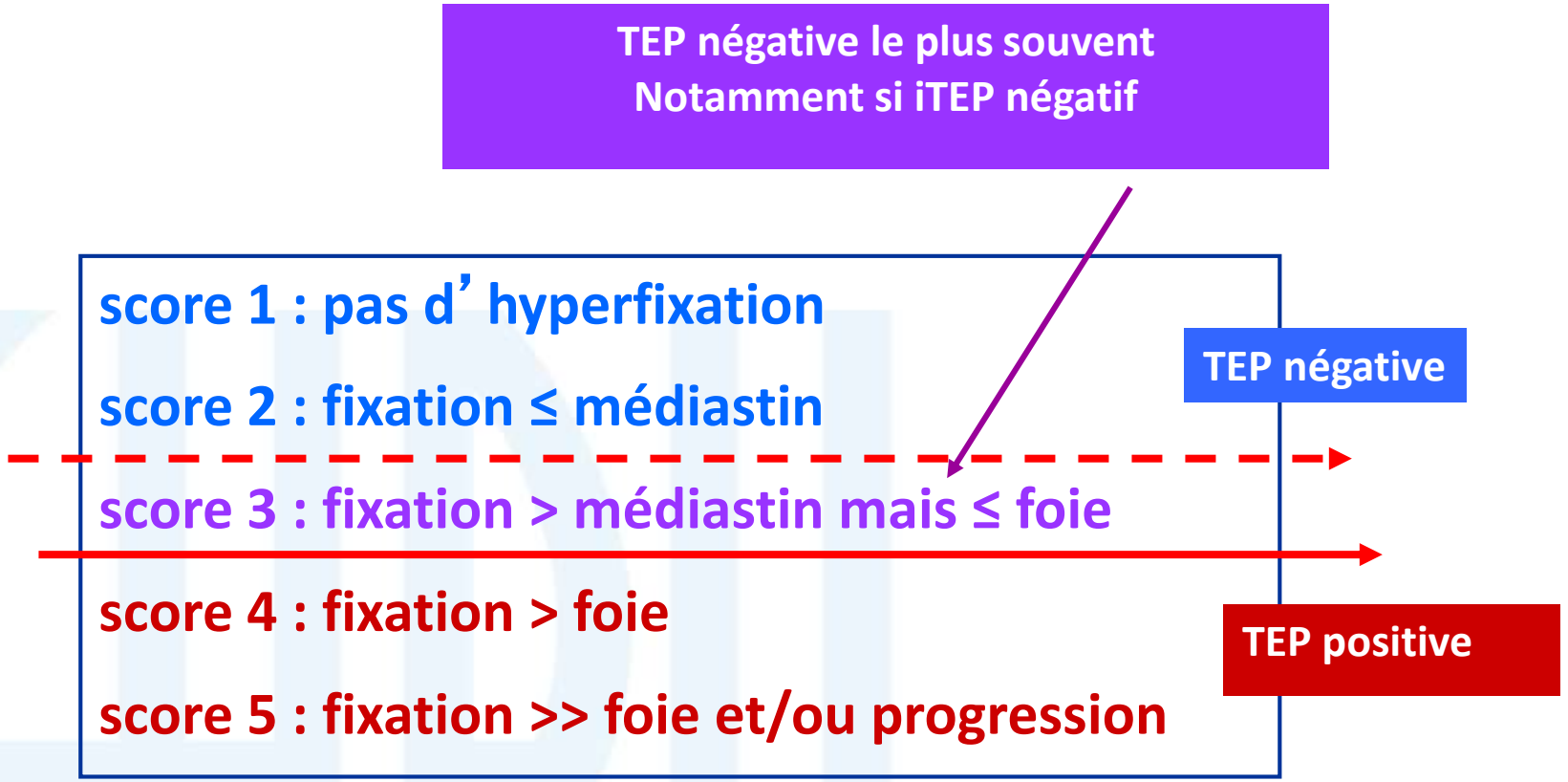
interprétation

- **Echelle 5-PS recommandée pour l'évaluation de fin de traitement**

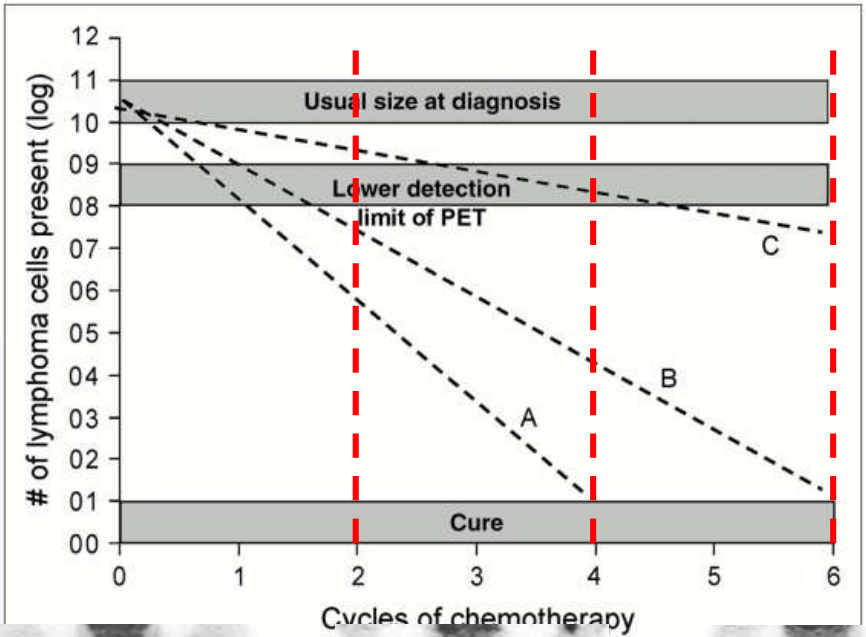
Scores 1 and 2 are therefore considered to represent CMR. Score 3 also likely represents CMR at interim[25] and good prognosis at completion of standard treatment.[34,94,99] However, in trials where de-escalation is based on PET response, it may be preferable to consider score 3 as inadequate response to avoid undertreatment.[42]

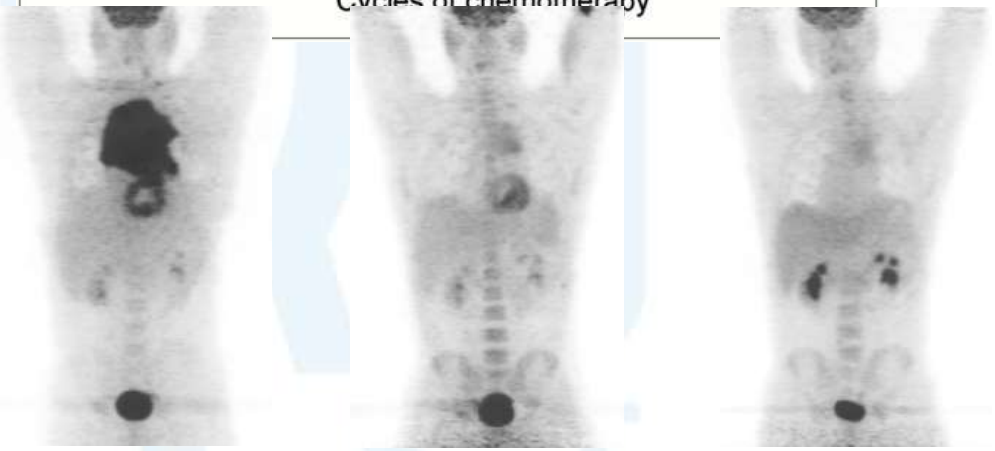
Recommendation. The 5-PS is recommended for reporting PET-CT. Results should be interpreted in the context of the anticipated prognosis, clinical findings, and other markers of response. Scores 1 and 2 represent CMR. Score 3 also probably represents CMR in patients receiving standard treatment (type 1).


TEP négative le plus souvent
Notamment si iTEP négatif
score 1 : pas d'hyperfixation
score 2 : fixation ≤ médiastin
score 3 : fixation > médiastin mais ≤ foie
score 4 : fixation > foie
score 5 : fixation >> foie et/ou progression
TEP négative
TEP positive

IV. TEP intermédiaire

Concept de l'évaluation intermédiaire





TEP et évaluations précoces ou, le concept de la chimiothérapie “sur mesure”

- Plus la réponse est rapide plus la rémission est durable
- TEP précoce: marqueur de substitution de chimiosensibilité
- Stratégies adaptées au risque : allègement/intensification
- Rationnel: Il faut “taper juste” dès la 1ère ligne de chimio

Concerne les lymphomes présentant les + forts taux de prolifération :

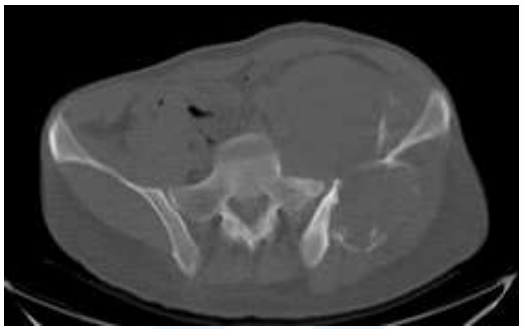
→ LDGCB et Hodgkin

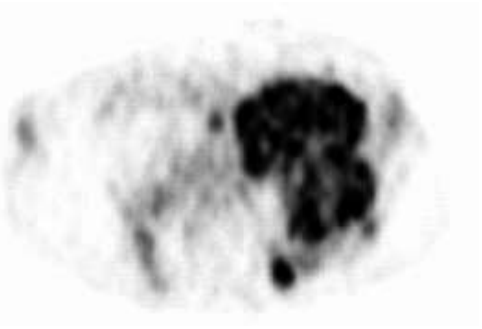
Armitage et al. *J Clin Oncol* 1986;4:160-4

Interim PET (Hodgkin)

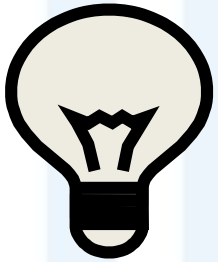
RSC = 1% de la population ¢^{aire}

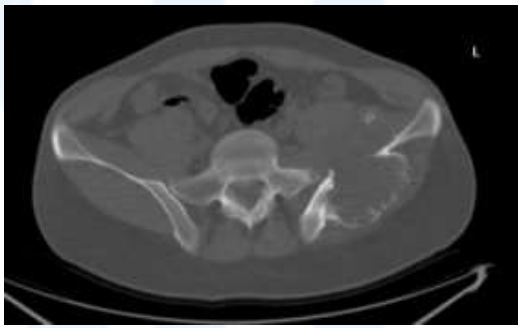
PET 0





PET 2



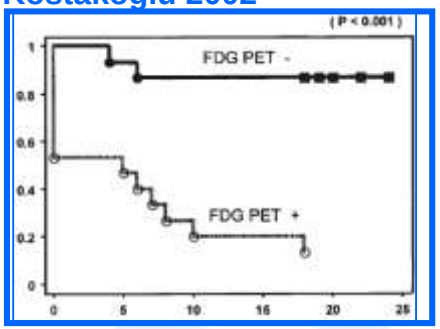


- Le µenvironnement ¢^{aire} augmente le signal métabolique
- Réponse de type tout ou rien (on/off)
- Persistance d'une fixation minime (BEACOPP)

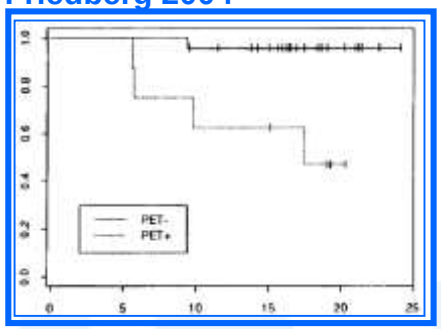
TEP précoce (Hodgkin)

Valeur prédictive, pas de changement thérapeutique

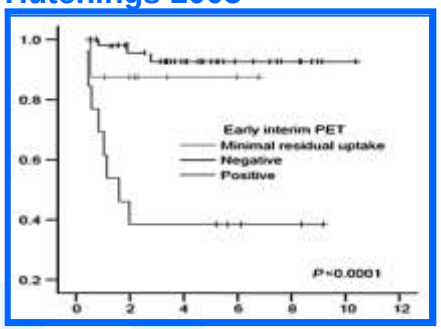
Kostakoglu 2002



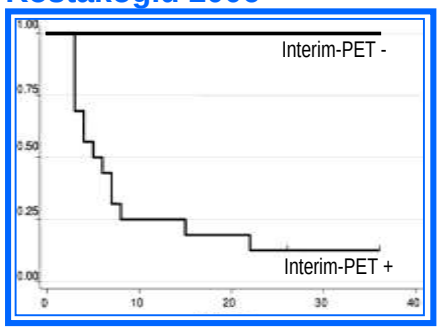
Friedberg 2004



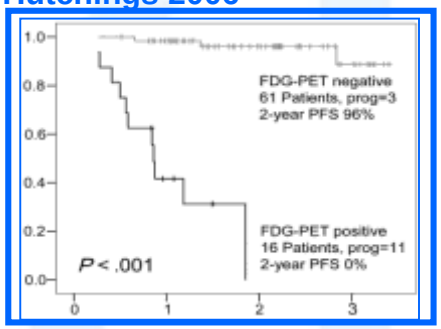
Hutchings 2005



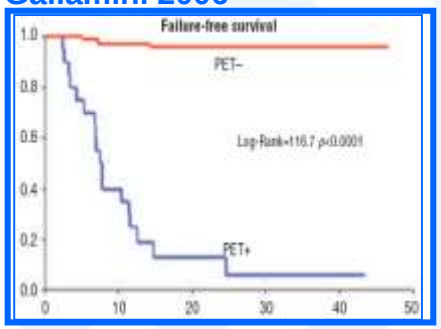
Kostakoglu 2006



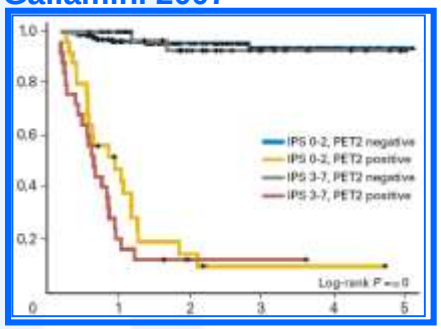
Hutchings 2006



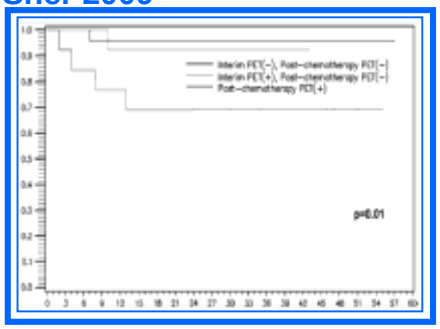
Gallamini 2006



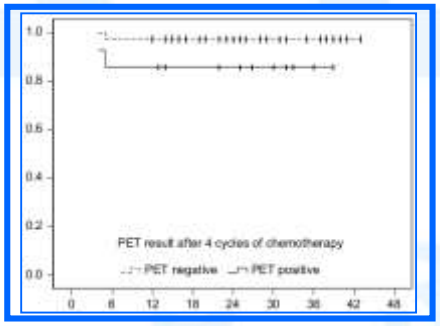
Gallamini 2007



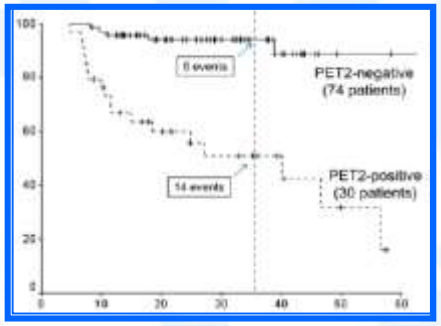
Sher 2009



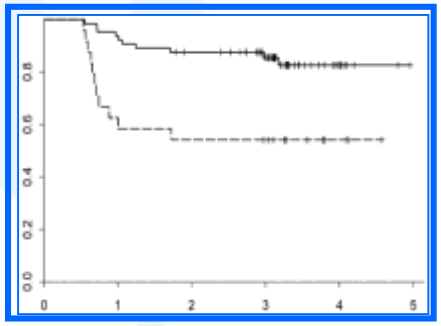
Markova 2009



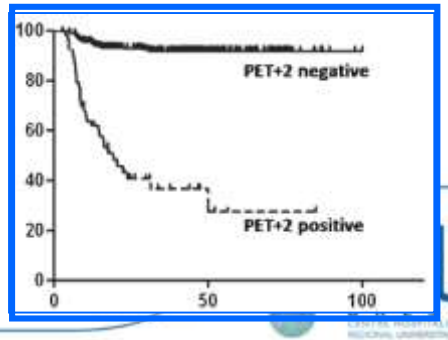
Cerci 2010



Straus 2011



Zinzani 2011



Hétérogénéité des séries (Hodgkin)

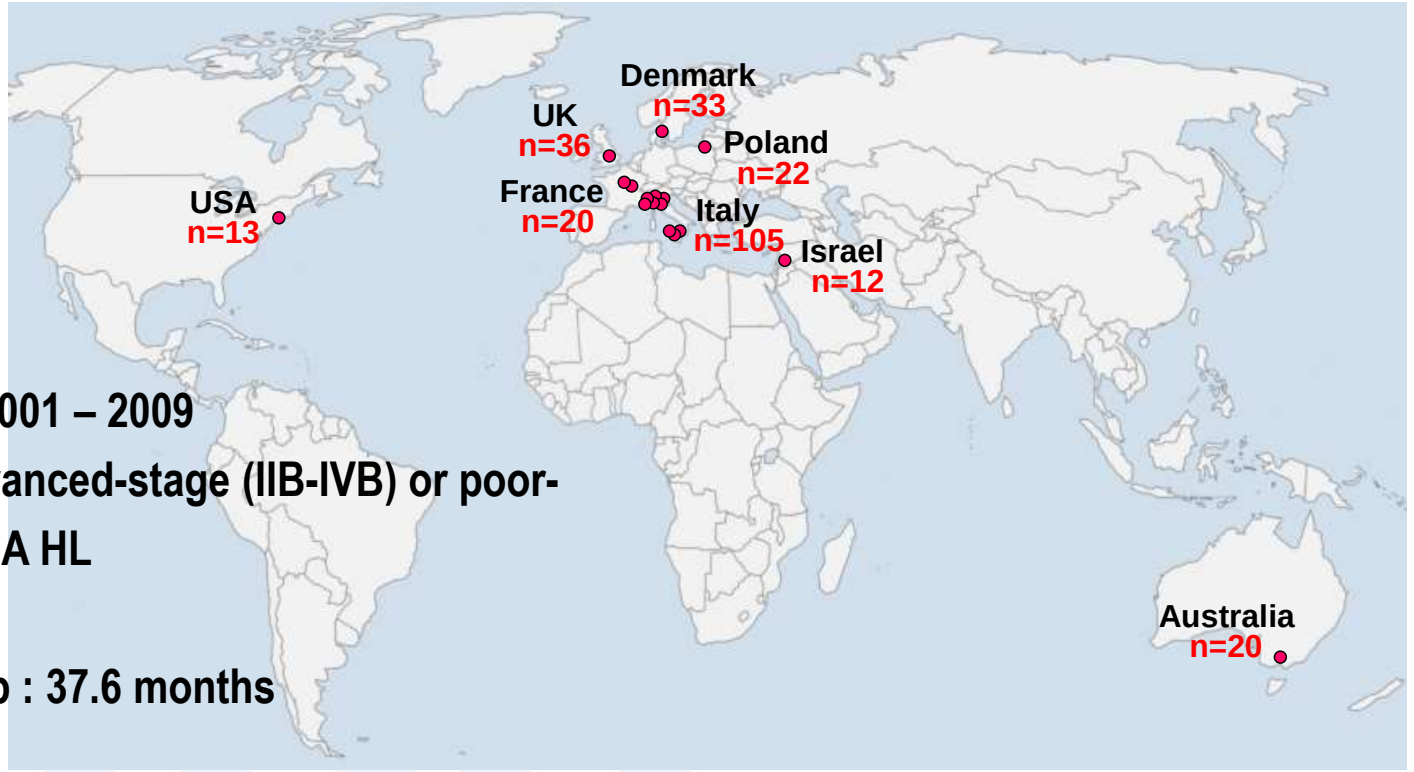
Study	N	Interim PET after…	Median follow-up	PET neg	PET pos	BEACOPP$_{ESC}$
Kostakoglu J Nucl Med 2002	all stages	1 cycle	19 mo	2-y PFS=85%	2-y PFS<15%	no
Friedberg Leuk Lymphoma 2004	advanced	3 cycles	24 mo	2-y PFS=95%	2-y PFS=48%	no
Hutchings Ann Oncol	all stages	2-3 cycles	40.2 mo	5-y PFS=92%	5-y PFS=39%	no
Kostakogl Cancer 20				2-y PFS=100%	2-y PFS 13%	no
Hutchings Blood 200				2-y PFS=96% 2-y PFS=96%	2-y PFS=0% 2-y PFS=19%	3%
Gallamini Haematolo				2-y FFS=96%	2-y FFS=6%	no
Gallamini J Clin Oncol 2007	advanced	2 cycles	26.3 mo	2-y PFS=96%	2-y PFS=13%	no
Sher Ann Oncol 2009	early stage	??	40.8 mo	2-y FFS=95%	2-y FFS=69%	no
Markova Ann Oncol 2009	advanced	4 cycles	12 mo	2-y PFS=97%	2-y PFS=86%	100%
Cerci J Nucl Med 2010	all stages	2 cycles	36 mo	3-y EFS=91%	3-y EFS=53%	no
Straus Blood 2011	early stage	2 cycles	39.6 mo	2-y PFS=88%	2-y PFS=54%	no*
Zinzani Eur J Nucl Med 2011	all stages	2 cycles	31 mo	9-y PFS=92%	9-y PFS=27%	no

Pas de changement thérapeutique

*AVG

Etude de validation de l'échelle de Deauville: IVS HL

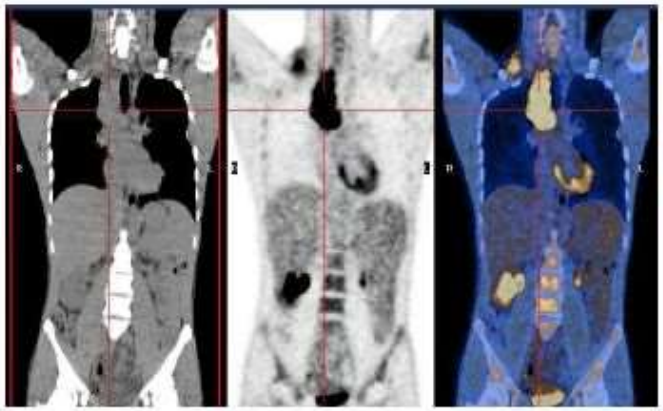
Gallamini A, Barrington S, Biggi A, Gregianin M, Hutchings M, Kostakoglu L, Meignan M, Chauvie S



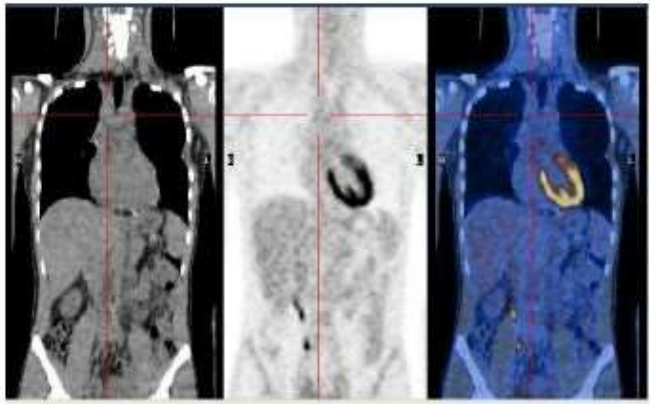
- Study period : 2001 – 2009
- 260 patients Advanced-stage (IIB-IVB) or poor-prognosis stage IIA HL
- 17 centers
- Median follow-up : 37.6 months
- 6 reviewers
- Therapy: ABVD x 6 cycles plus or minus consolidation radiotherapy.
- Staging at baseline and after 2 ABVD with PET-CT(PET-0 and PET-2)
- No treatment change depending on interim-PET results

Gallamini A et al. Haematologica 2014;99:1107-1113

Baseline PET-0



Interim (after 2 ABVD cycle) PET-2



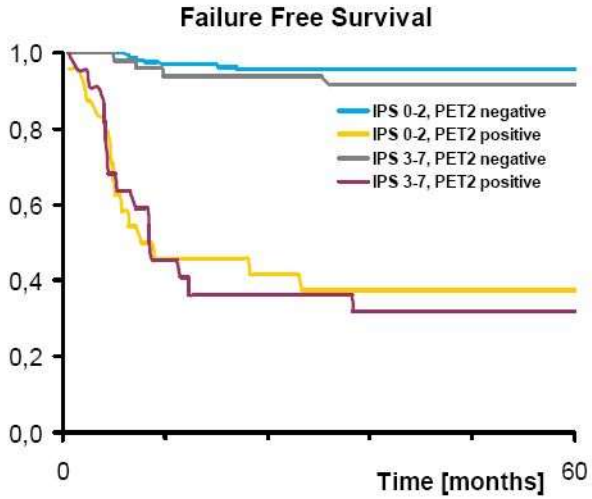
DEAUVILLE 5-point scale

- *no uptake*
- *uptake ≤ mediastinum*
- *uptake > mediastinum but ≤ liver*

PET negative

- *moderately increased uptake compared to liver*
- *markedly increased uptake compared to liver*

PET positive



Gallamini A et al. Haematologica 2014;99:1107-1113

Hodgkin « localisé »

VOLUME 32 · NUMBER 12 · APRIL 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

score 1 : pas d'hyperfixation

score 2 : fixation ≤ médiastin

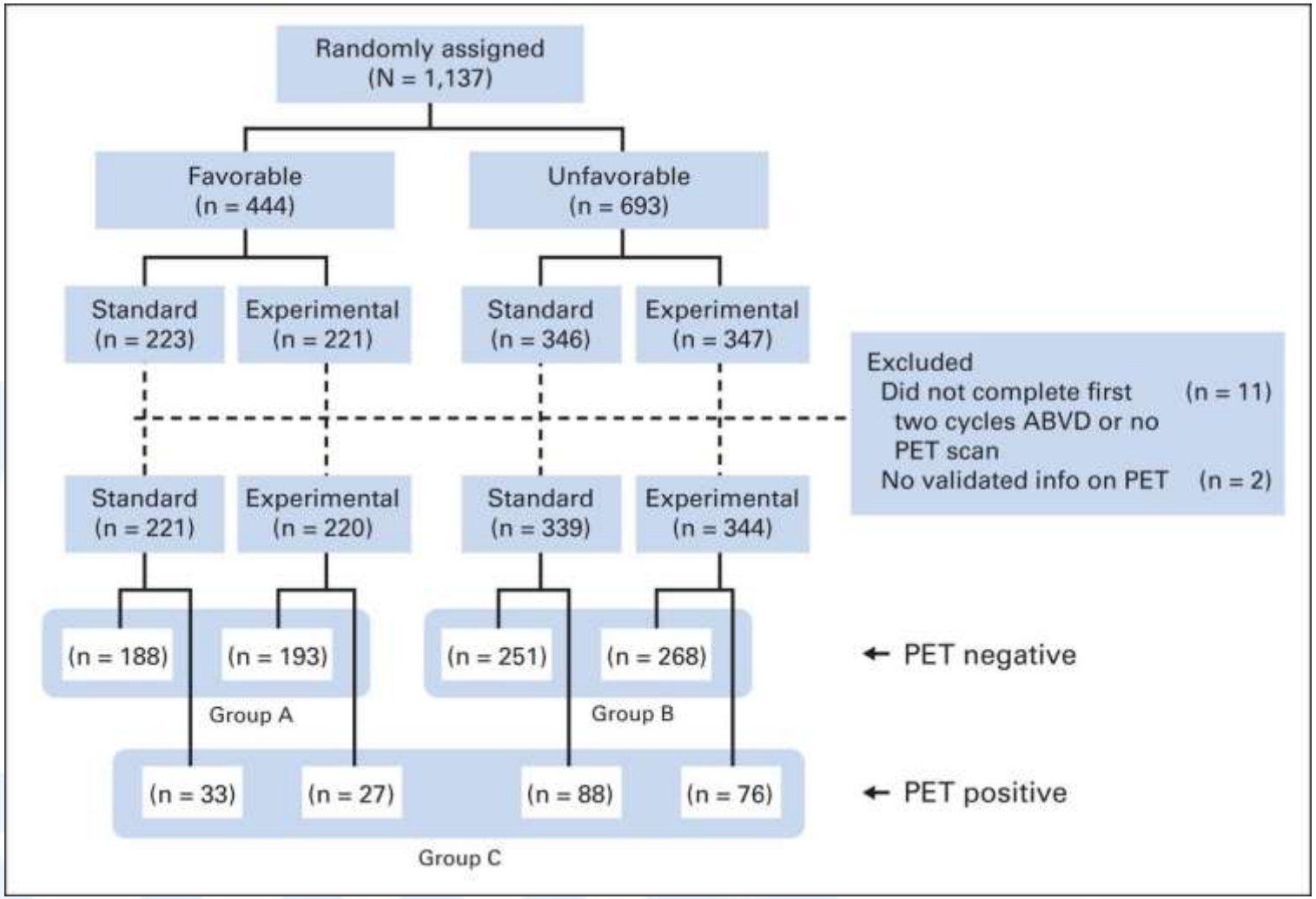
score 3 : fixation > médiastin mais ≤ foie

score 4 : fixation > foie

score 5 : fixation >> foie et/ou progression

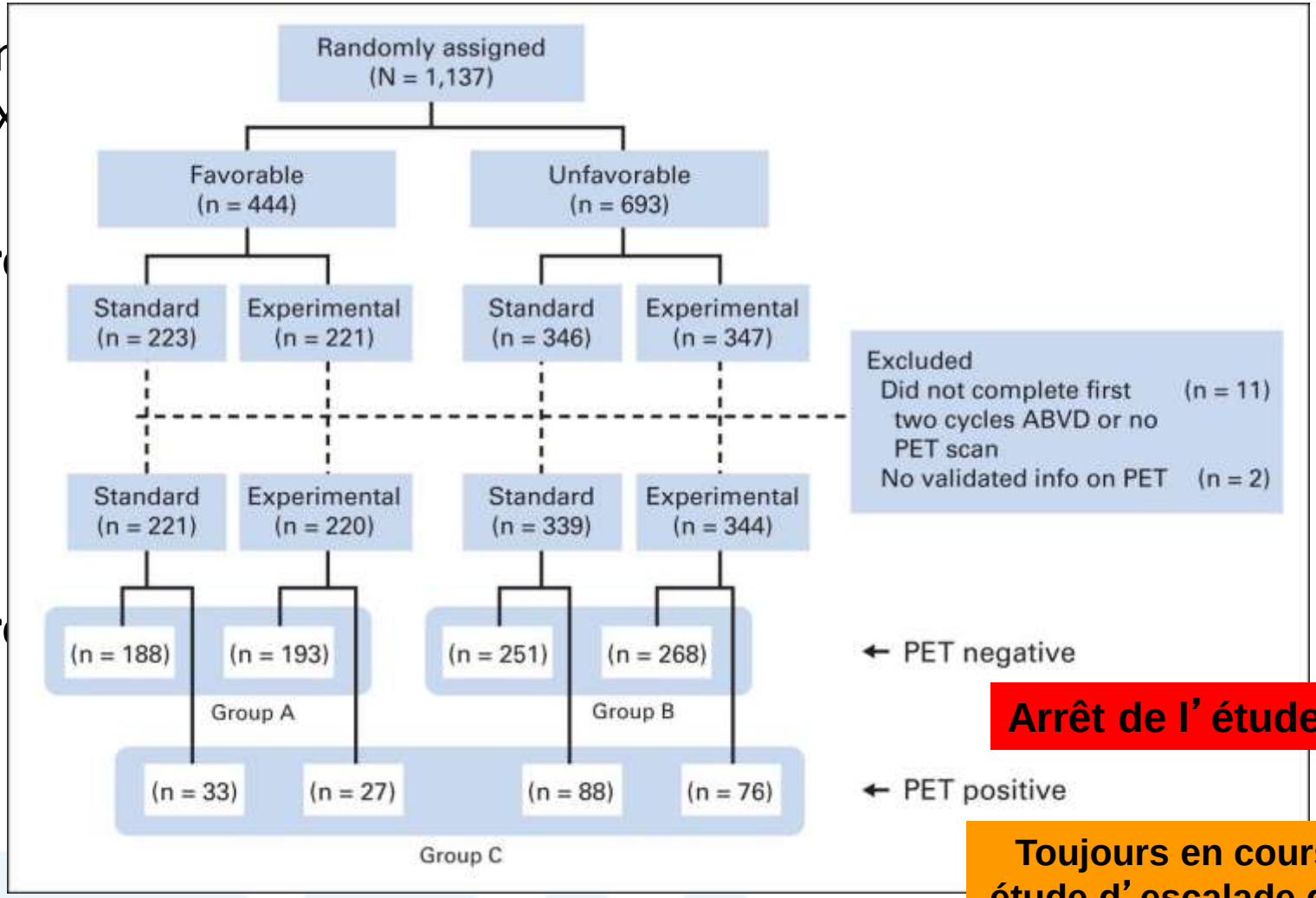
Objectif principal: Mettre en évidence la non-infériorité, en terme de PFS, du traitement expérimental par rapport au traitement validé associant chimio-radiothérapie

Flowchart of patients included in interim analysis.



Raemaekers J M et al. JCO 2014;32:1188-1194

- Ar… la tox…
- **Gr…**
  - …
  - …
- **Gr…**
  - …
  - …



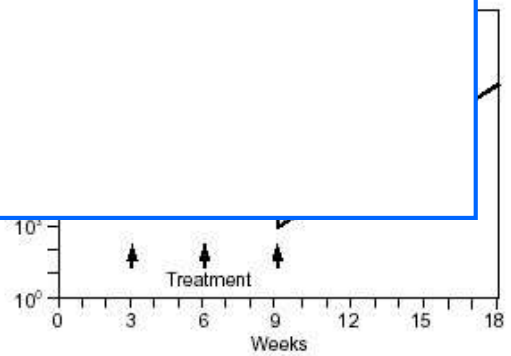
Arrêt de l'étude

Toujours en cours, étude d'escalade des mauvais répondeurs.

Timing de la TEP précoce

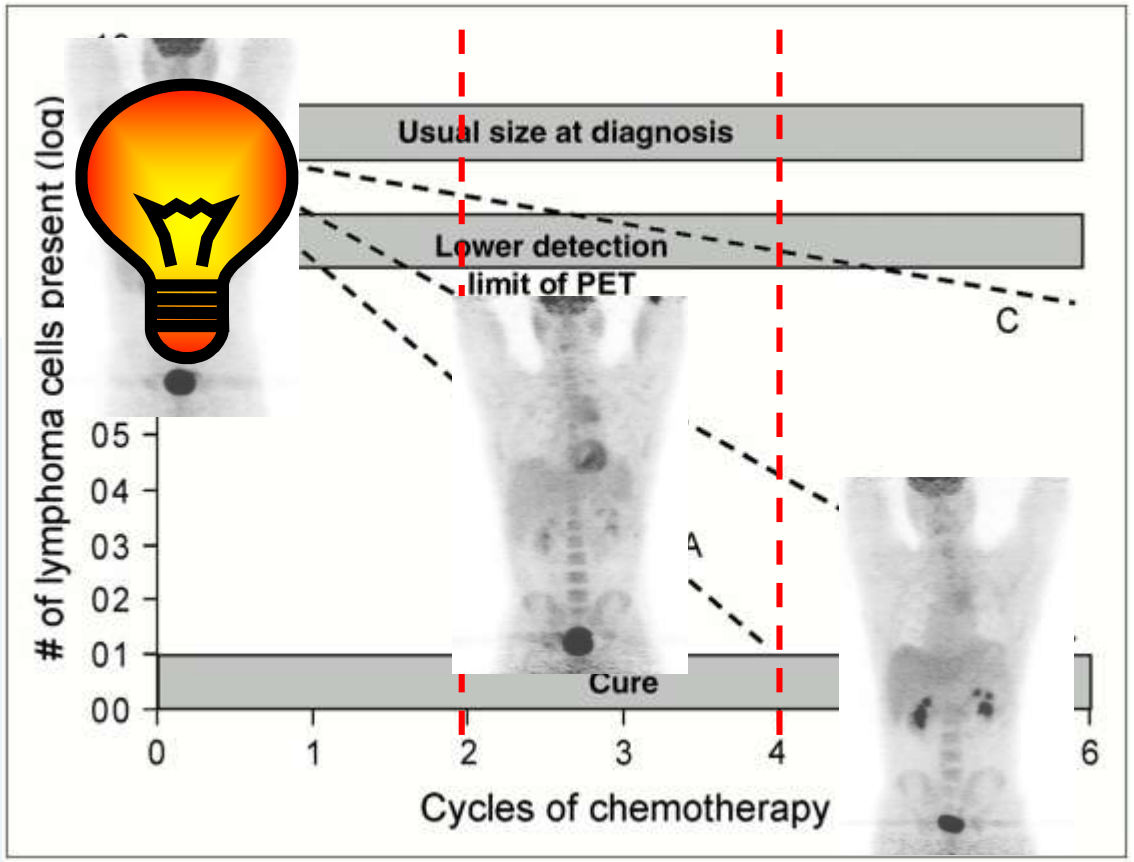
- **La TEP précoce a plusieurs significations**
- **<u>Après 1 à 2 cycles</u> :**
  - **Réponse des ¢ ayant le tps de doublement le + rapide**
  - **Chimiosensibilité (répondeurs vs. non répondeurs)**

→ Ne pas mélanger les résultats PET2 et PET4
→ Pas indispensable d'obtenir une négativité du PET
→ Les critères d'interprétation doivent être différents



Interim PET (LDGCB)

LBC = 90% de la population ¢aire

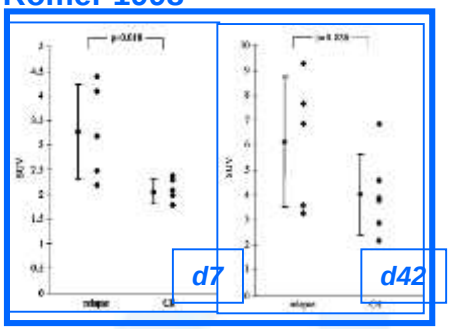


- **Réponse graduelle (continue) +/- rapide**
- **Persistance d'une fixation résiduelle +/- importante**

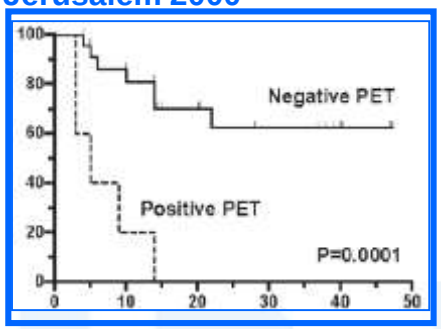
TEP précoce (LDGCB)

Valeur prédictive, pas de changement thérapeutique

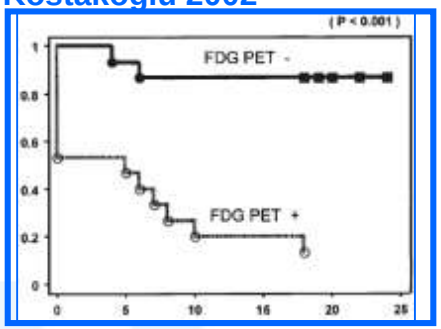
Römer 1998



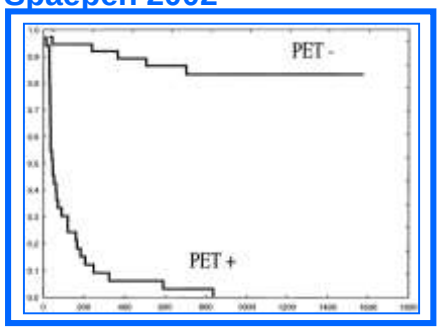
Jerusalem 2000



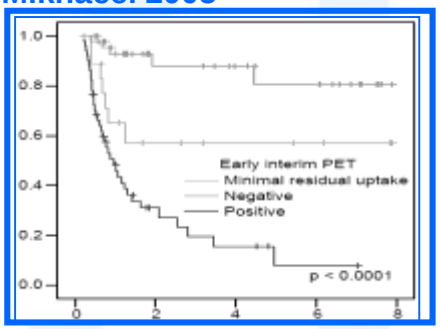
Kostakoglu 2002



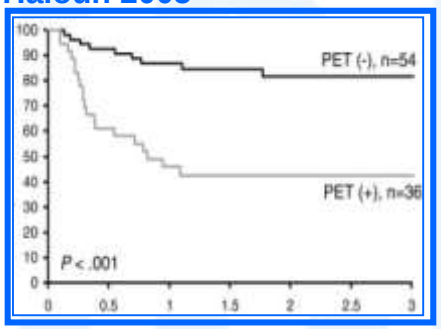
Spaepen 2002



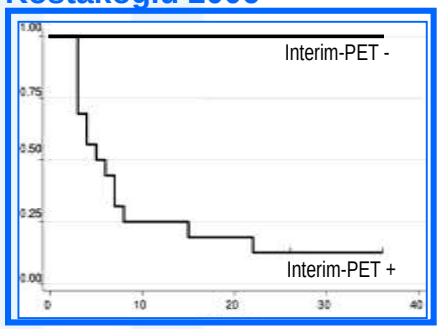
Mikhaeel 2005



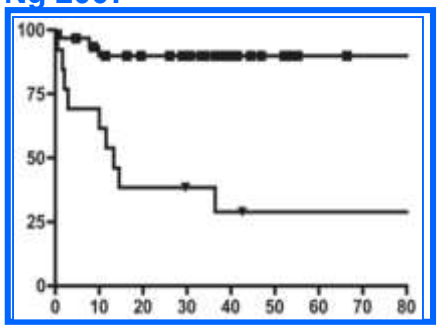
Haioun 2005



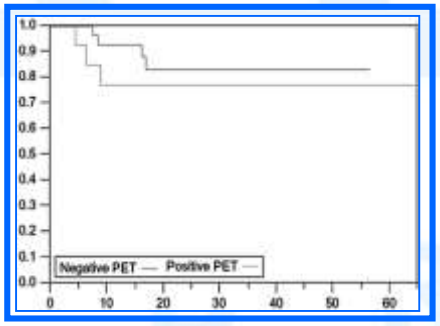
Kostakoglu 2006



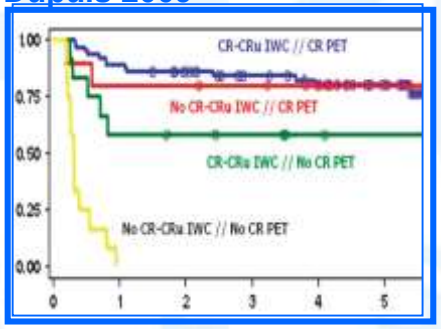
Ng 2007



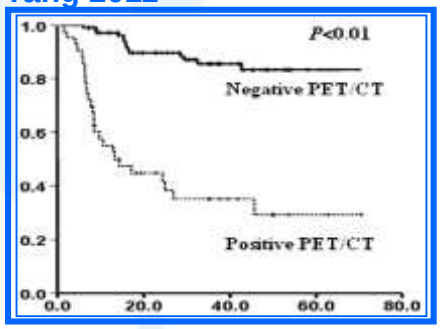
Han 2009



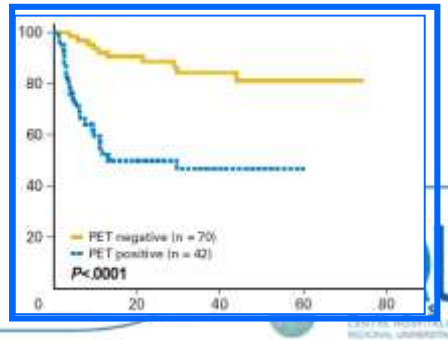
Dupuis 2009



Yang 2011



Safar 2012



Hétérogénéité des séries (LDGCB)

Study	N	Interim PET after…	Median follow-up	PET neg	PET pos	Rituximab
Römer Blood 1998	11 (mixed NHL)	7d-42d	??			no
Jerusalem Haematologica 2000	28 (16 DLBCL)	2-5 cycles	17.5 mo	2-y PFS=62%	2-y PFS=0%	no
Kostakoglu J Nucl Me	30	1 cycle	19 mo	2-y PFS=85%	2-y PFS<15%	no
Spaepen Ann Oncol				2-y PFS=85%	2-y PFS=4%	no
Mikhaeel Ann Oncol				5-y PFS=87%	5-y PFS=34%	~20%
Haioun Blood 200				2-y EFS=82%	2-y EFS=43%	41%
Kostakoglu Cancer 2006	47 (24 DLCL)	1 cycle	28 mo	2-y PFS=100%	2-y PFS 13%	100%
Ng Leuk Lymphoma 2007	45	2-4 cycles	28 mo	2-y PFS=88%	2-y PFS=38%	40%
Han Ann Oncol 2009	40 (29 DLBCL)	2-4 cycles	24 mo	2-y PFS 83%	2-y PFS 77%	100%
Dupuis Ann Oncol 2009	103	4 cycles	53 mo	5-y EFS=80%	5-y EFS=36%	49%
Yang Eur J Cancer 2011	161	3-4 cycles	30.8 mo	3-y PFS=86%	3-y PFS=29%	100%
Safar J Clin Oncol 2012	112	2 cycles	38 mo	3-y PFS=84%	3-y PFS=47%	100%

Pas de changement thérapeutique

Échelle de Deauville
(5-point scale: 5-PS)
Recommandée pour l'évaluation thérapeutique

Protocole de recherche

score 1 : pas d'hyperfixation

score 2 : fixation ≤ médiastin

Des-escalade

score 3 : fixation > médiastin mais ≤ foie

Escalade

score 4 : fixation > foie

score 5 : fixation >> foie et/ou progression

Variabilité des cut-offs en fonction de la question clinique (escalade-des-escalade)

Échelle de Deauville
(5-point scale: 5-PS)
Recommandée pour l'évaluation thérapeutique

En routine, question de l'escalade

score 1 : pas d'hyperfixation

score 2 : fixation ≤ médiastin

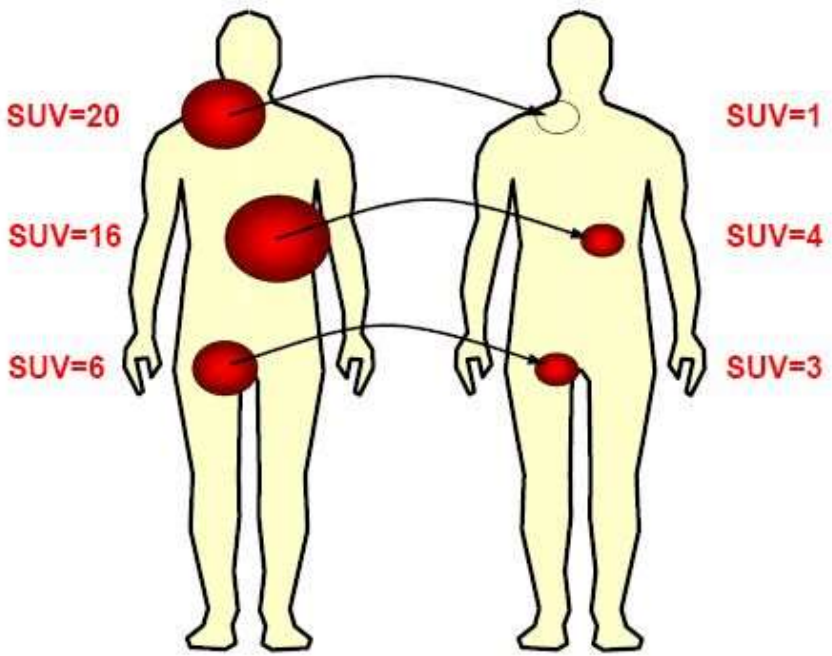
score 3 : fixation > médiastin mais ≤ foie

score 4 : fixation > foie

score 5 : fixation >> foie et/ou progression

Approche semi quantitative DLBCL ?

DeltaSUV: (SUVmax1 – SUVmax2)/SUVmax1
Prendre la lésion la plus fixante sur chaque examen



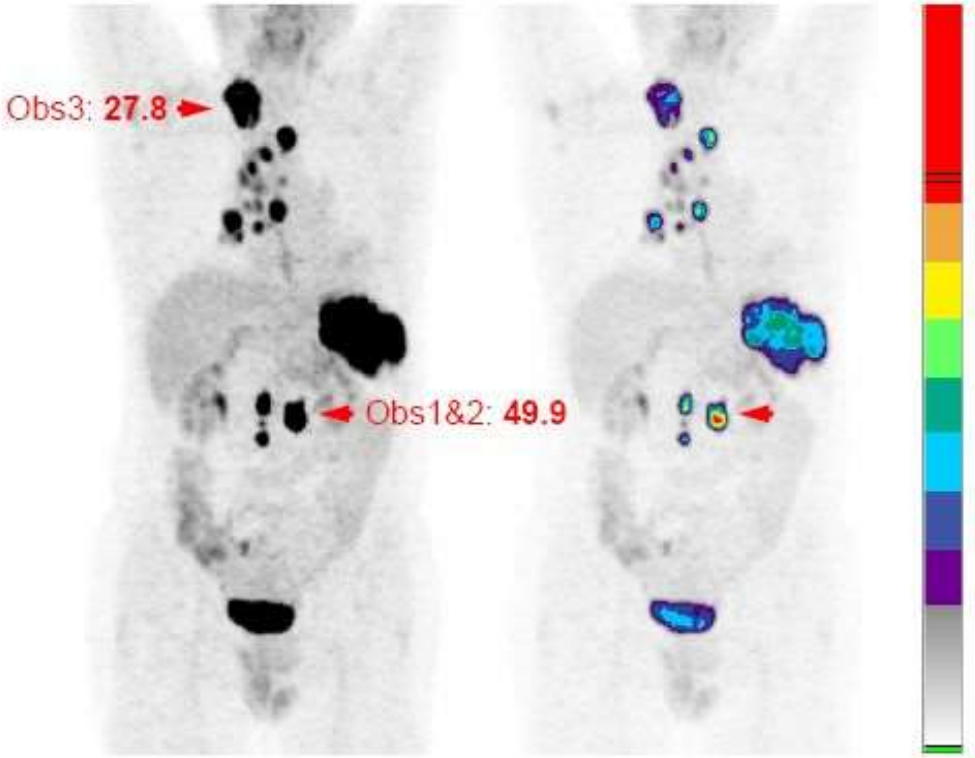
Whichever the location:
SUV_0=20, SUV_2=4
ΔSUV=80%→CR

Follow-up of a target:
ΔSUV_{t1}=95% →CR
ΔSUV_{t2}=75% →CR
ΔSUV_{t3}=50% →PR

Retrospective target:
ΔSUV_{t2}=75% →CR
ΔSUV_{t3}=50% →PR

Itti E, Menton 2011

- MIP
- color scale

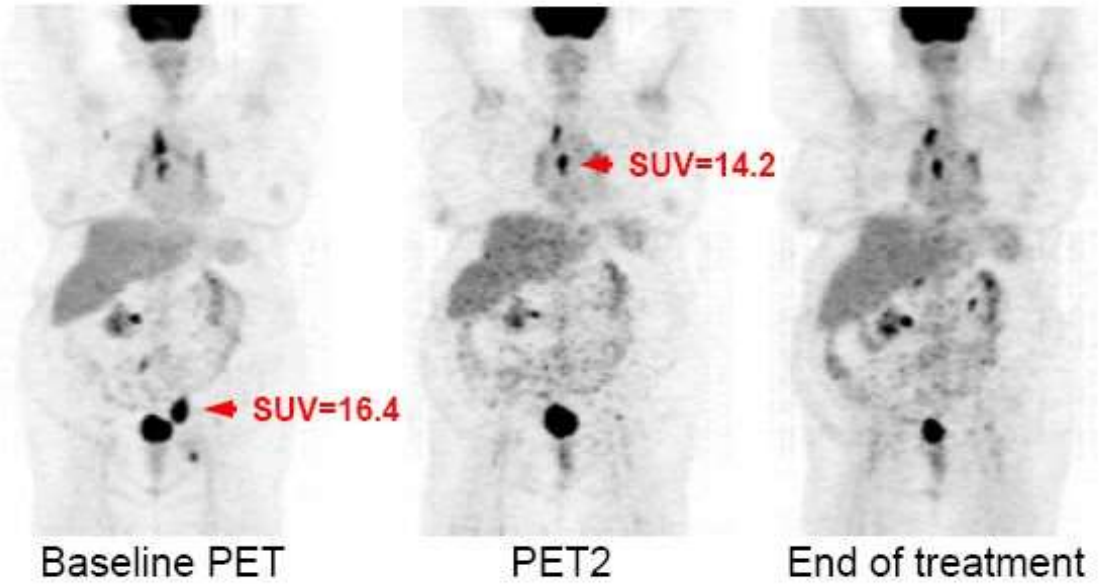


→ uretera?

Lin et al. *J Nucl Med* 2007;48:1626-32

Itti E, Menton 2011

Limits of this approach



→ ΔSUV=13%, no event after 43 mo f-u

→ Sarcoidosis activation?

Itti E, Menton 2011

Eur J Nucl Med Mol Imaging (2013) 40:1312–1320
DOI 10.1007/s00259-013-2435-6

LBDGC

ORIGINAL ARTICLE

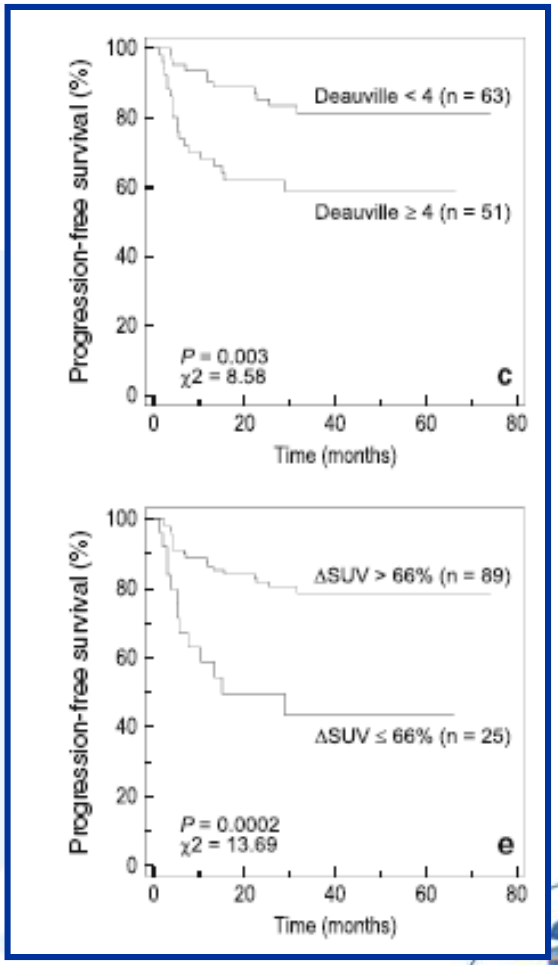
An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUVmax

Emmanuel Itti · Michel Meignan · Alina Berriolo-Riedinger · Alberto Biggi · Amanda F. Cashen · Pierre Véra · Hervé Tilly · Barry A. Siegel · Andrea Gallamini · René-Olivier Casasnovas · Corinne Haioun

Table 2 Interobserver agreement for interim PET positivity for different cut-off scores of the Deauville five-point scale and ΔSUVmax ≤66 %

PET2 positivity cut-off	Cohen's κ		
	Observers 1 and 2	Observers 1 and 3	Observers 2 and 3
Deauville score ≥2	0.33	0.36	0.56
Deauville score ≥3	0.65	0.52	0.49
Deauville score ≥4	0.80	0.65	0.53
Deauville score ≥5	0.71	0.39	0.43
ΔSUVmax ≤66 %	0.92	0.82	0.74

Landis and Koch scale for κ interpretation: 0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, 0.81–1.00 almost perfect agreement



Limites de la méthodes

ISSUES REGARDING BASELINE SUV < 10 AND INTERIM SUV > 5.0

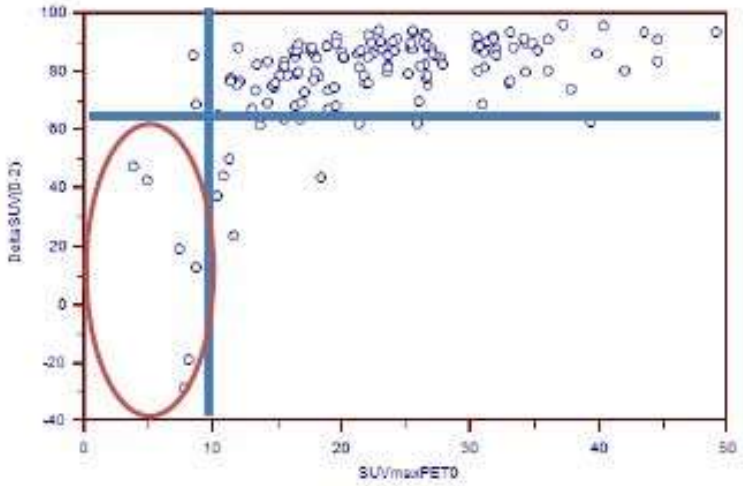
Casasnovas, Menton 2011

Tumors with baseline uptake < 10

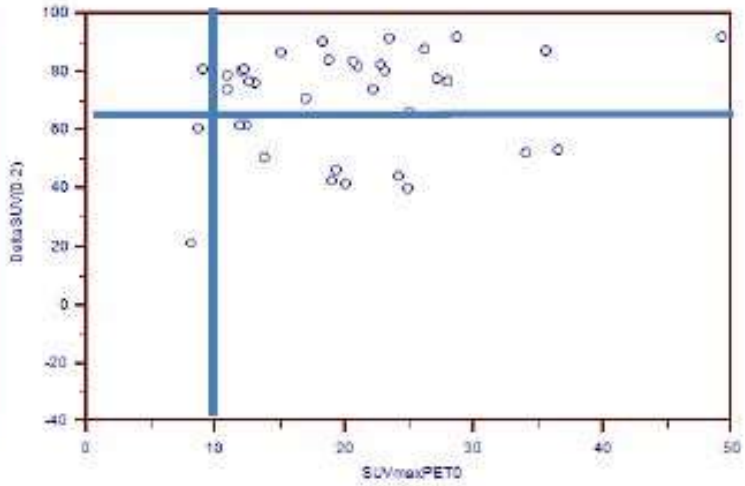
LNH 2007-3B

N = 179; Median Fu =15 months

No Event



Event

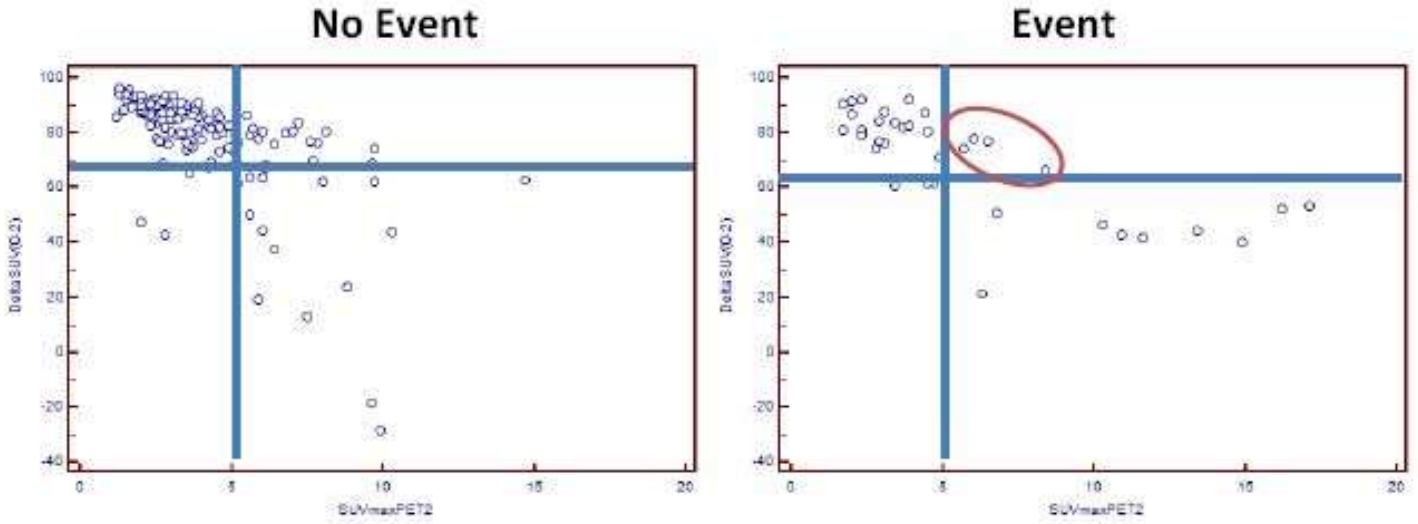


False positive rate	6/8 (75%) cases with **baseline SUV<10**, ΔSUVmax<66%, have no event
	12/22 (54%) cases with **baseline SUV>10**, ΔSUVmax<66%, have no event

Casasnovas, Menton 2011

Tumors PET2 uptake > 5
LNH2007-3B

N = 179; Median Fu = 15 months



False negative rate	4/26 (15%) cases with **PET2 SUVmax >5**, ΔSUVmax>66%, have event 20/123 (16%) cases with **PET2 SUVmax <5**, ΔSUVmax>66%, have event

Casasnovas, Menton 2011

Approche semi quantitative DLBCL ?

- 2 Cures:
  - négatif: **ΔSUVmaxPET0-2 > 66%**
  - Positif**: ΔSUVmaxPET0-2 ≤ 66%**
- 4 Cures:
  - Négatif**: ΔSUVmaxPET0-4 >70%**
  - Positif**: ΔSUVmaxPET0-4 ≤ 70%**

Exceptions:

Si SUVmax baseline **< 10 et/ou** SUVmax **PET2/4 ≥ 5, on utilise l'échelle de Deauville…**

Intérêt de la TEP-FDG

- TEP-FDG > CT pour évaluer la réponse
- Valeurs pronostiques démontrées dans le LH
- Valeurs pronostiques démontrées dans le LBDGC
  - *!Peut-être moins prédictif dans le contexte de l'immuno-chimiothérapie*
- Intérêt d'un changement thérapeutique induit par la TEP non démontré:

Beaucoup d'essais cliniques en cours

Intérêt de la TEP-FDG

- **Echelle 5-PS recommandée pour l'évaluation intermédiaire en routine et dans beaucoup d'essais cliniques**

- **DeltaSUV prometteur pour les LBDGC**

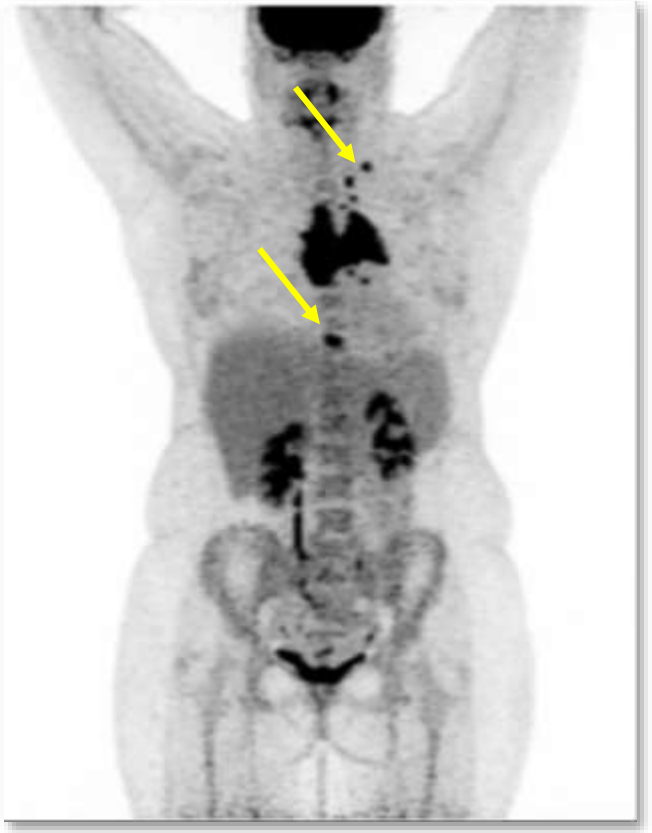
V. Quelques exemples

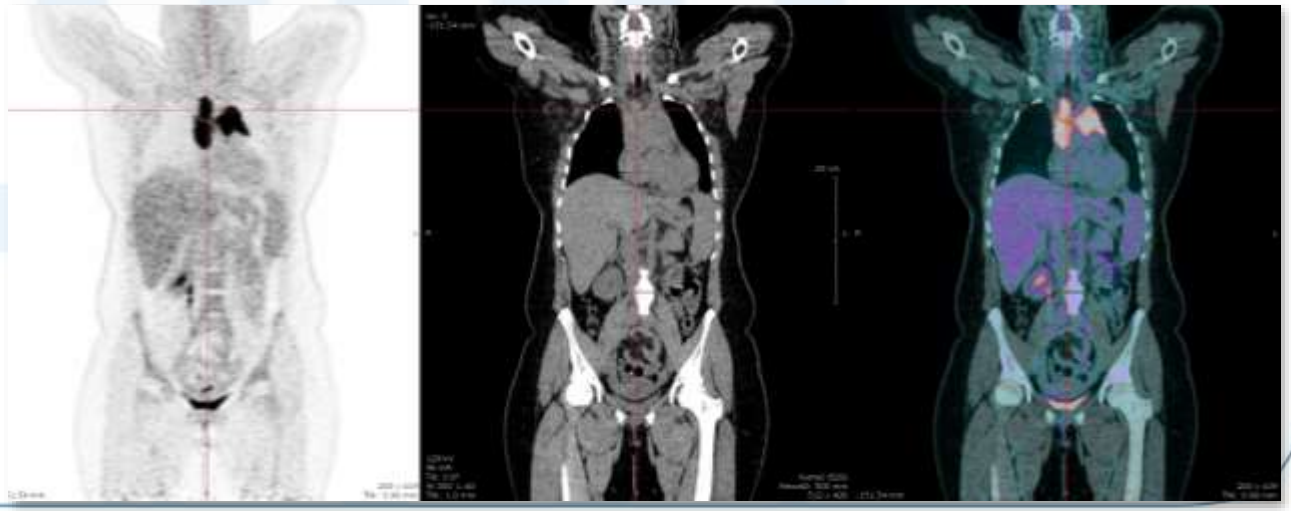
Melle G. C.

- Née le 22/09/1982
- Masse médiastinale responsable d'un syndrome cave
- CT: « *masse médiastinale isolée de 77 x 71 x 64 mm* »
- Ana-path: « *localisation médiastinale d'un LBGC s'accordant avec un lymphome B primitif du médiastin* »
- BOM: « *moelle hématopoïétique riche et bien différenciée, INDEMNE d'infiltration lymphomateuse* »
- Score IPI : I

Melle G. C., TEP

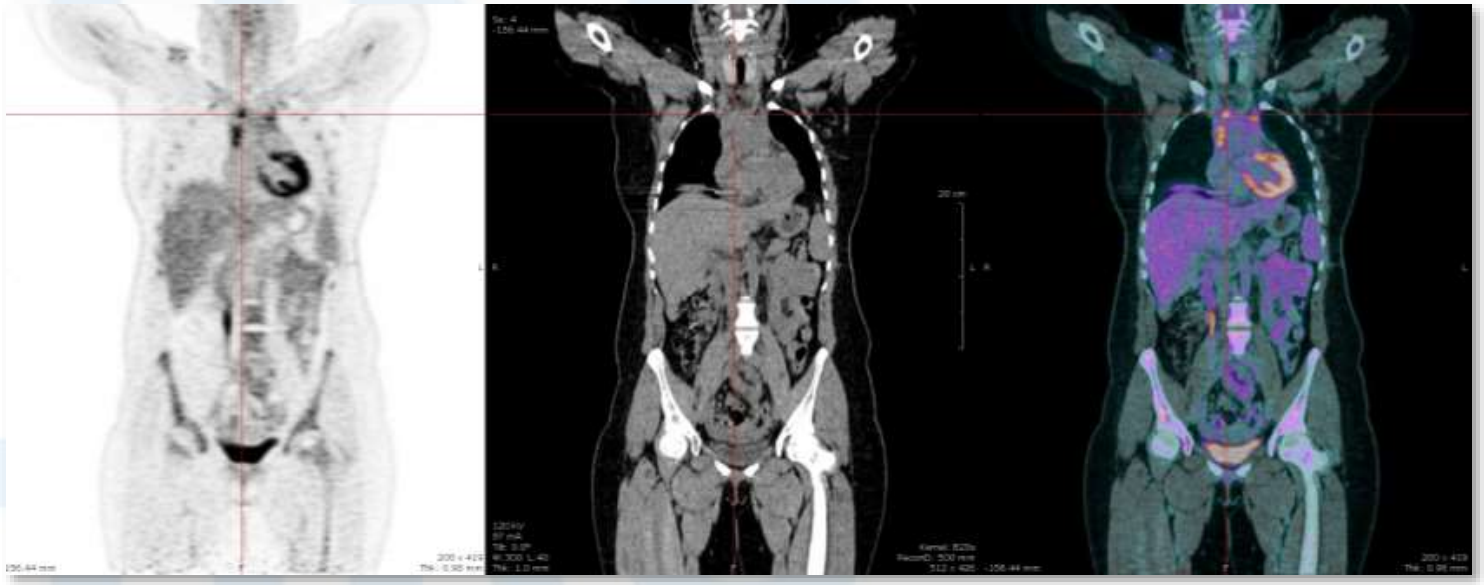
- Masse médiastinale + ADP sus-diaphragmatiques hyper-métaboliques
- HAOM diffuse sans anomalie focalisée : non spécifique
- Masse médiastinale : SUV max à 33,7





Melle G. C., TEP à C2

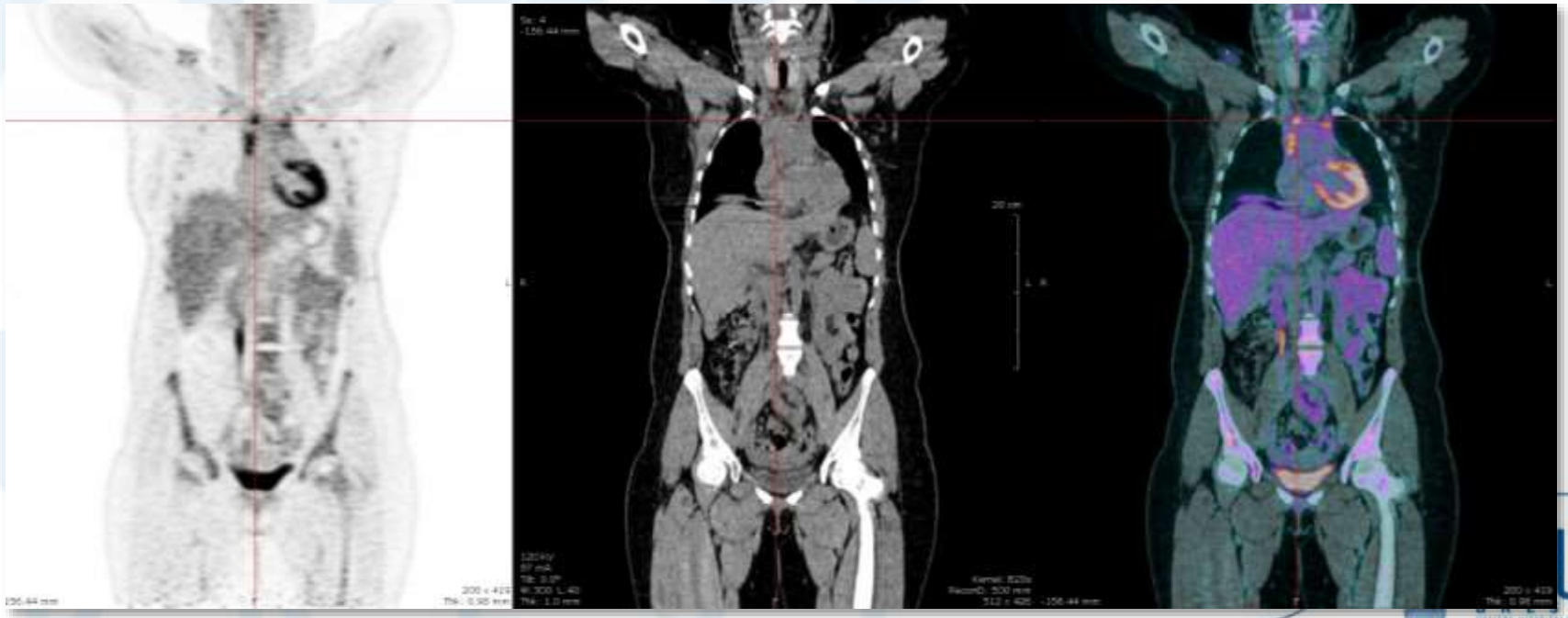
- Bonne ou mauvaise réponse à c2 ?



Melle G. C., TEP à

!!! Le calcul du ΔSUVmax Sans analyse visuelle n'est pas suffisant

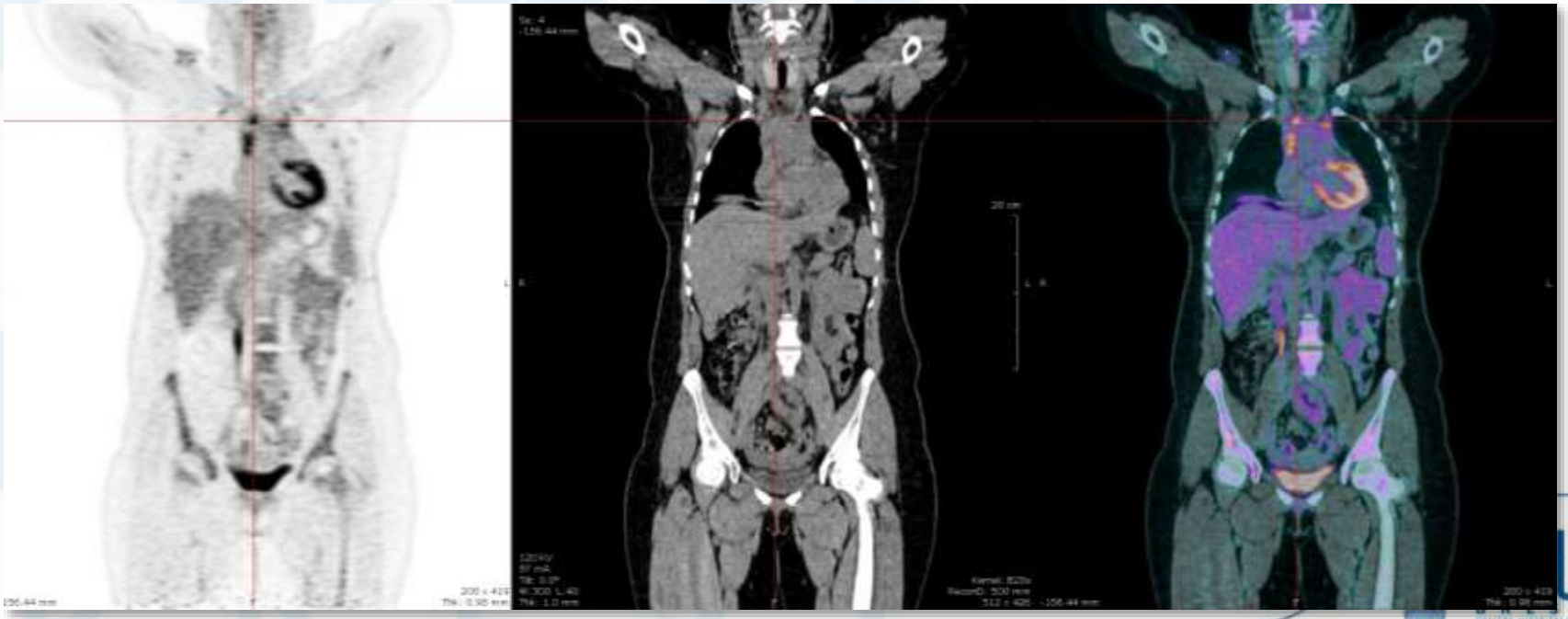
- Masse résiduelle médiastinale Deauville 5
- ΔSUVmax à 78,28%
- Mais SUVmax à 7,3



Melle G. C., TEP a

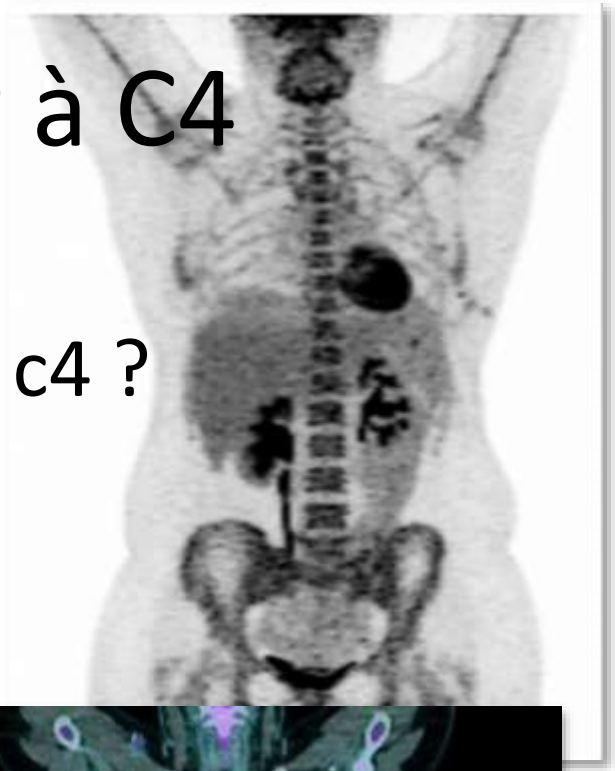
!!! Le calcul du ΔSUVmax Sans analyse visuelle n'est pas suffisant

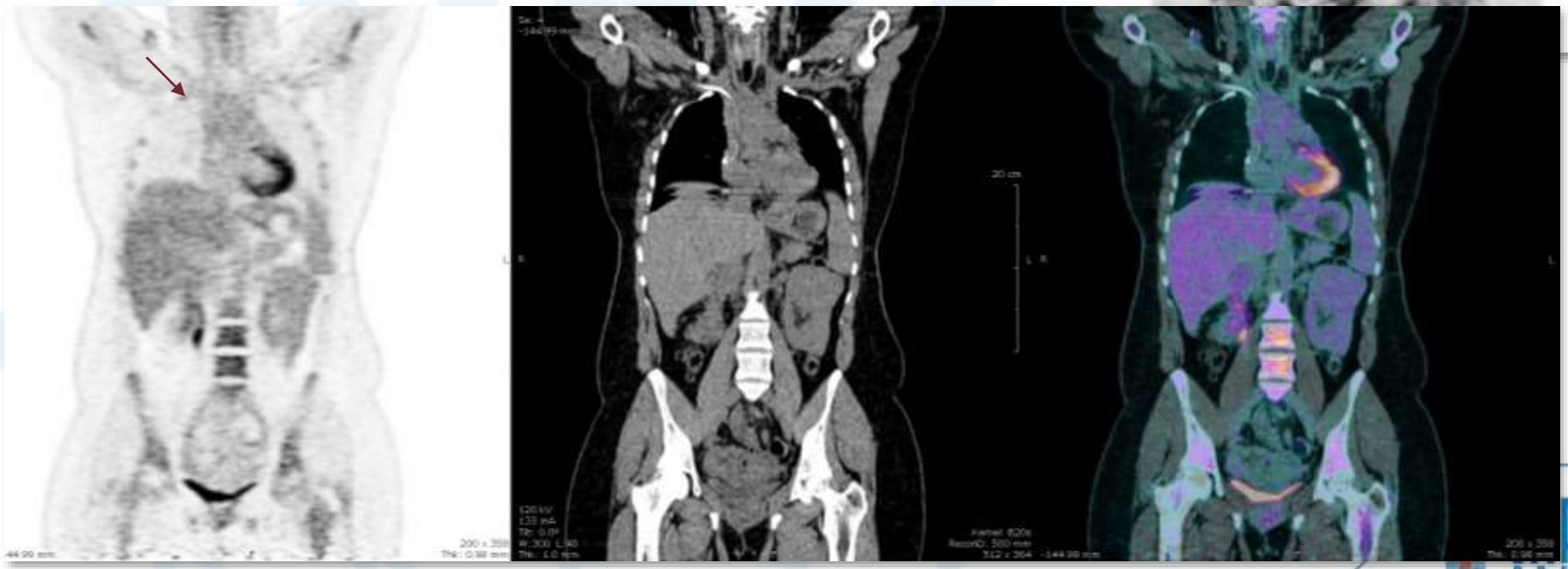
- Masse résiduelle médiastinale Deauville 5
- ΔSUVmax à 78,28%
- Mais SUVmax à 7,3
- TEP + à c2



Melle G. C.,TEP à C4

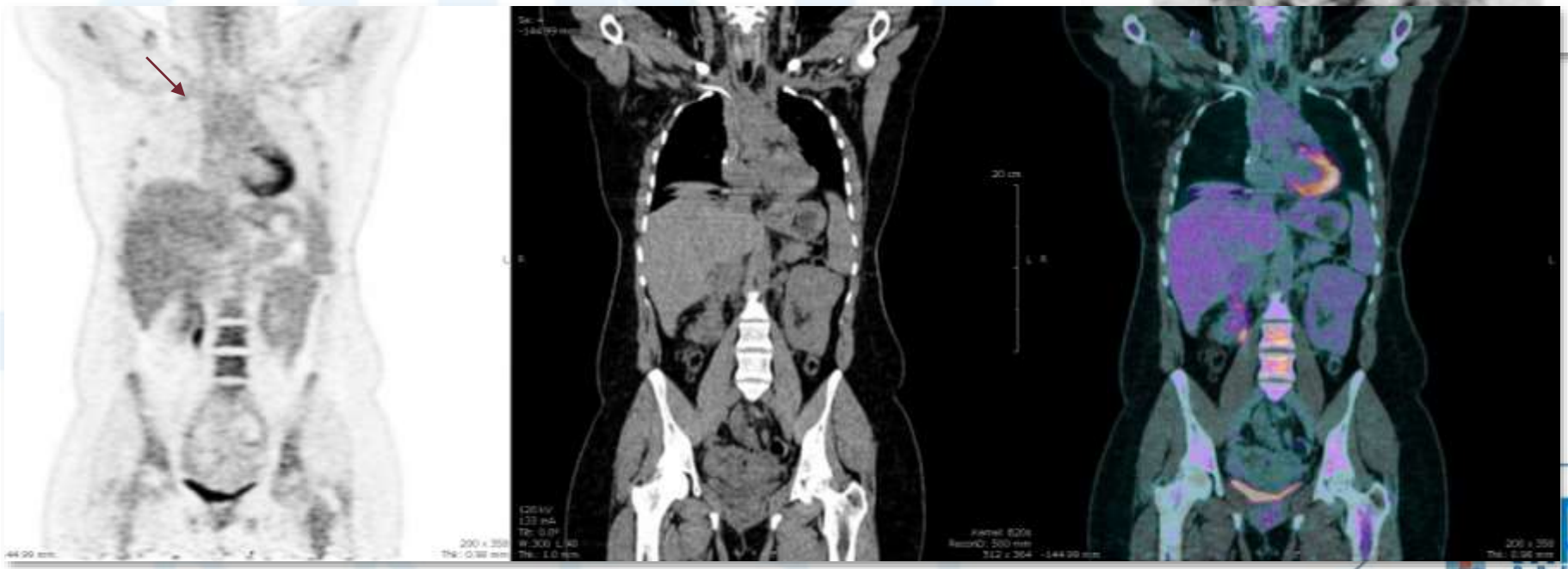
- Bonne ou mauvaise réponse à c4 ?





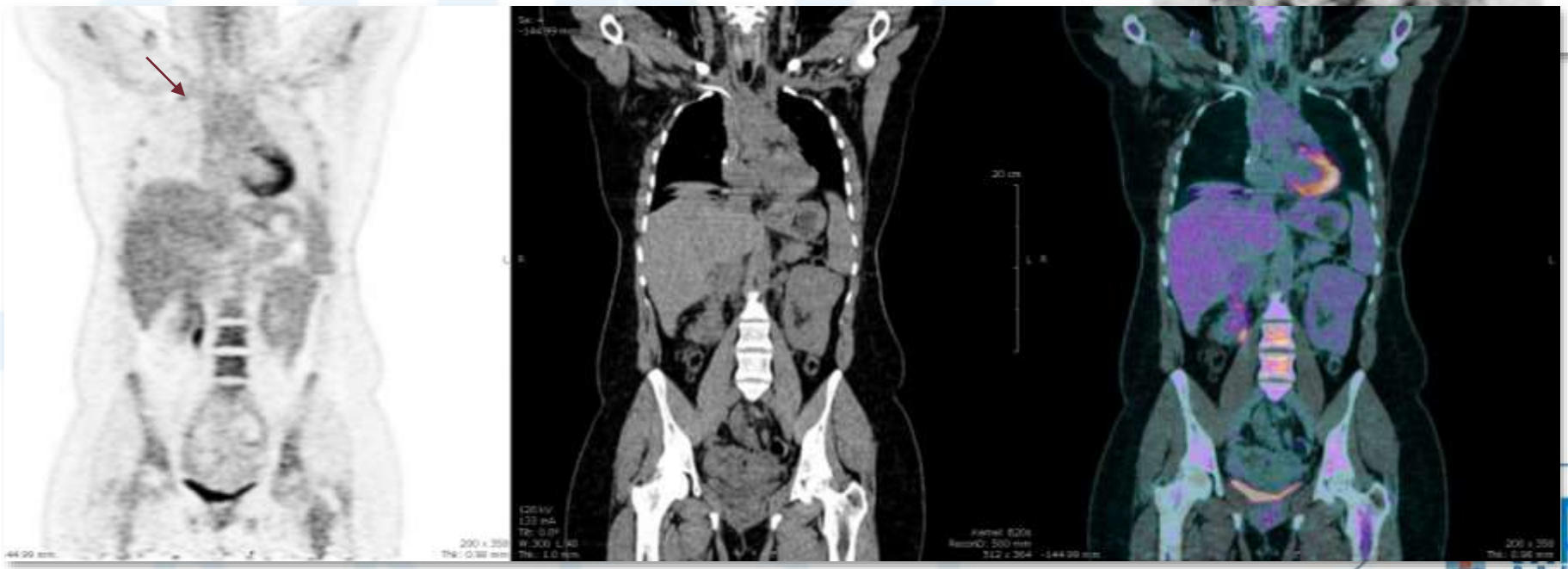
Melle G. C., TEP à C4

- Masse résiduelle médiastinale Deauville 3
- SUVmax à 3,93 et ΔSUVmax à 88%



Melle G. C., TEP à C4

- Masse résiduelle médiastinale Deauville 3
- SUVmax à 3,93 et ΔSUVmax à 88%
- TEP – à C4

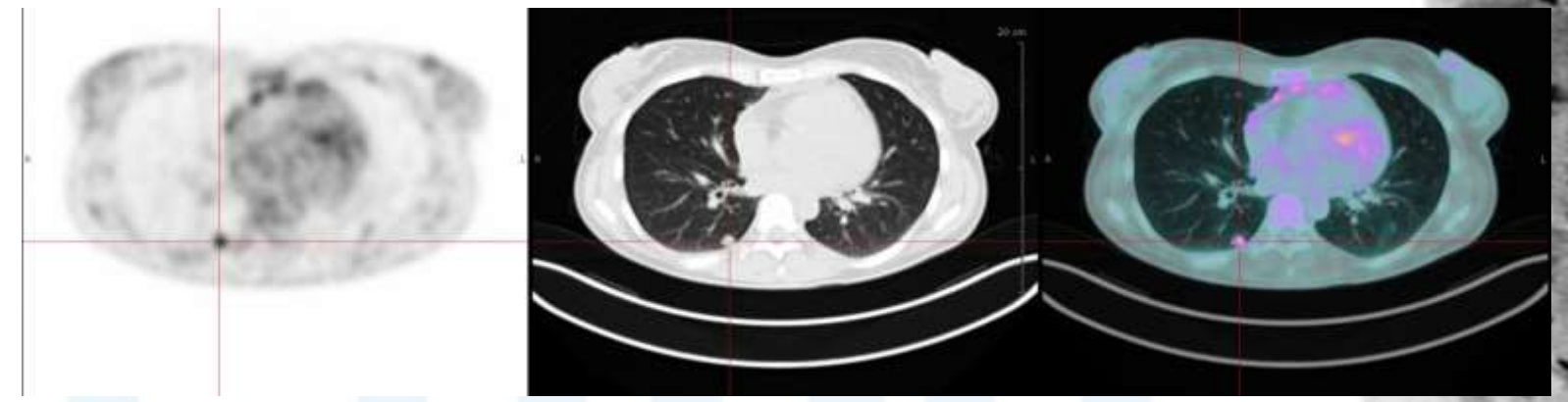


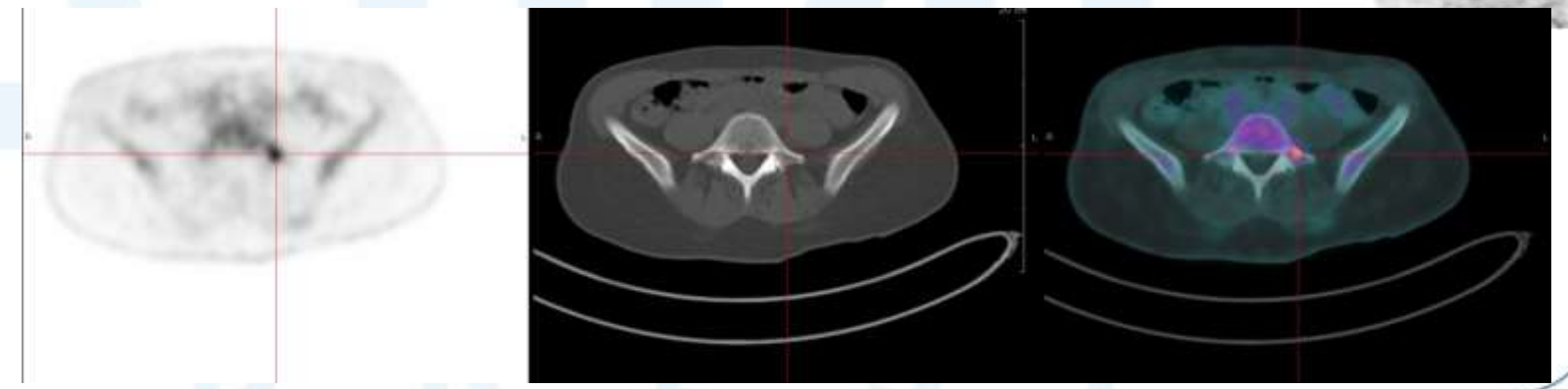
Mme C. S.

- Née le 13/12/197
- Masse médiastinale : DLBCL CD 20+
- CT : Masse médiastinale, ADP sus-diaph et nodules pulmonaires
- Biopsie ostéo-médullaire : « *moelle hématopoïétique de richesse normale, bien différenciée, dépourvue d'infiltrat lymphomateux*»
- Stade IV, IPI 2

Mme C. S., TEP initiale

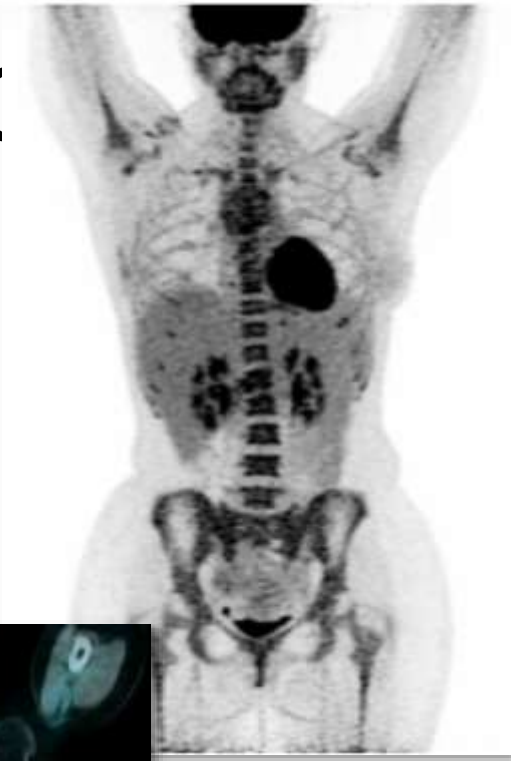
- Masse médiastinale :
- SUVmax à 32,97

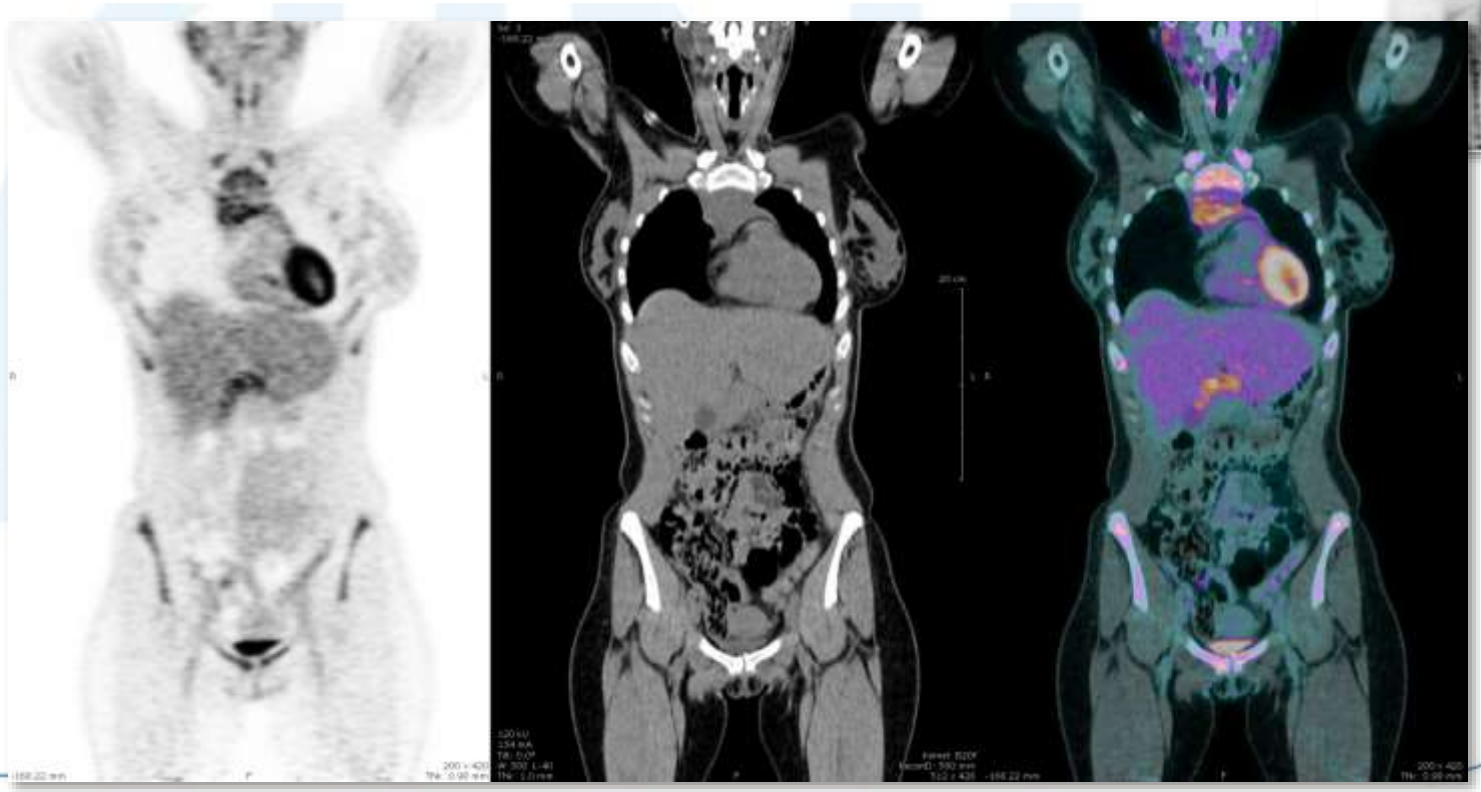




Mme C. S., TEP à C

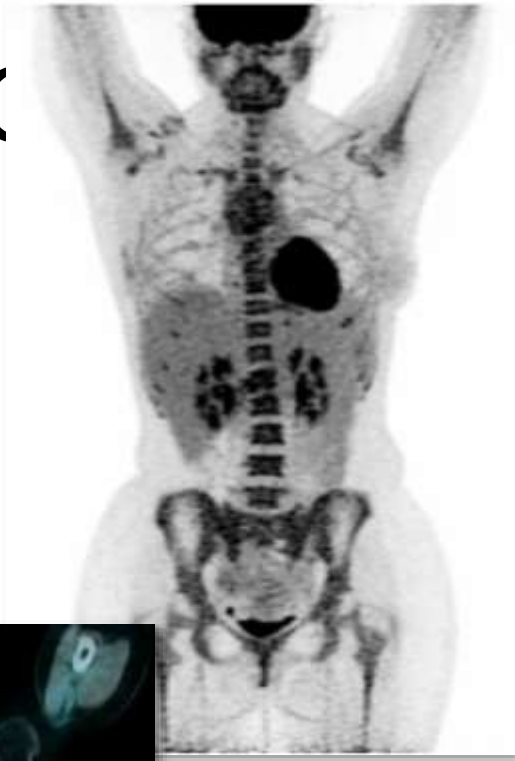
- Masse résiduelle médiastinale : SUVmax à 6,5
- Deauville 5
- ΔSUVmax > 80% mais Deauville 5 sur la masse médiastinale

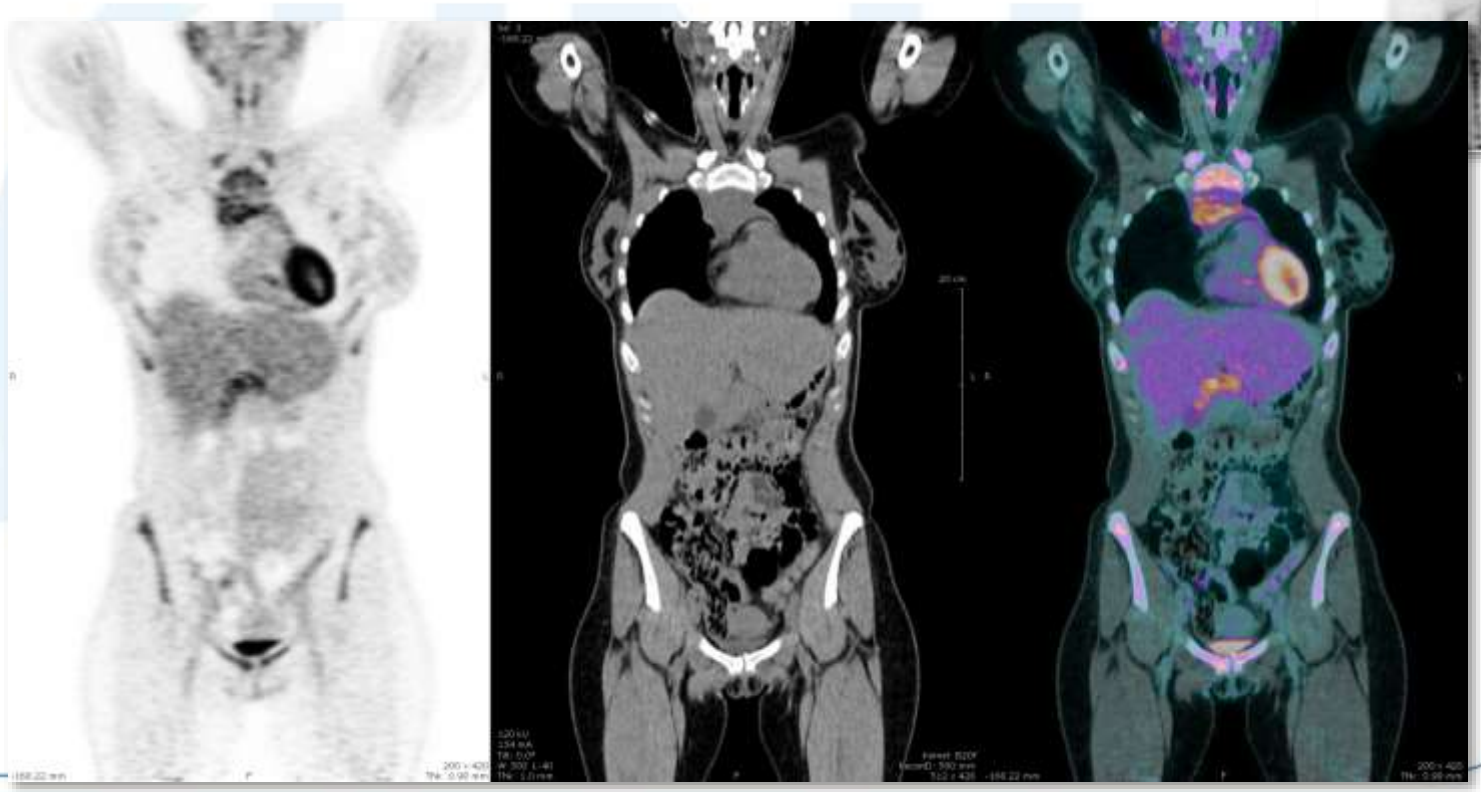




Mme C. S., TEP à C

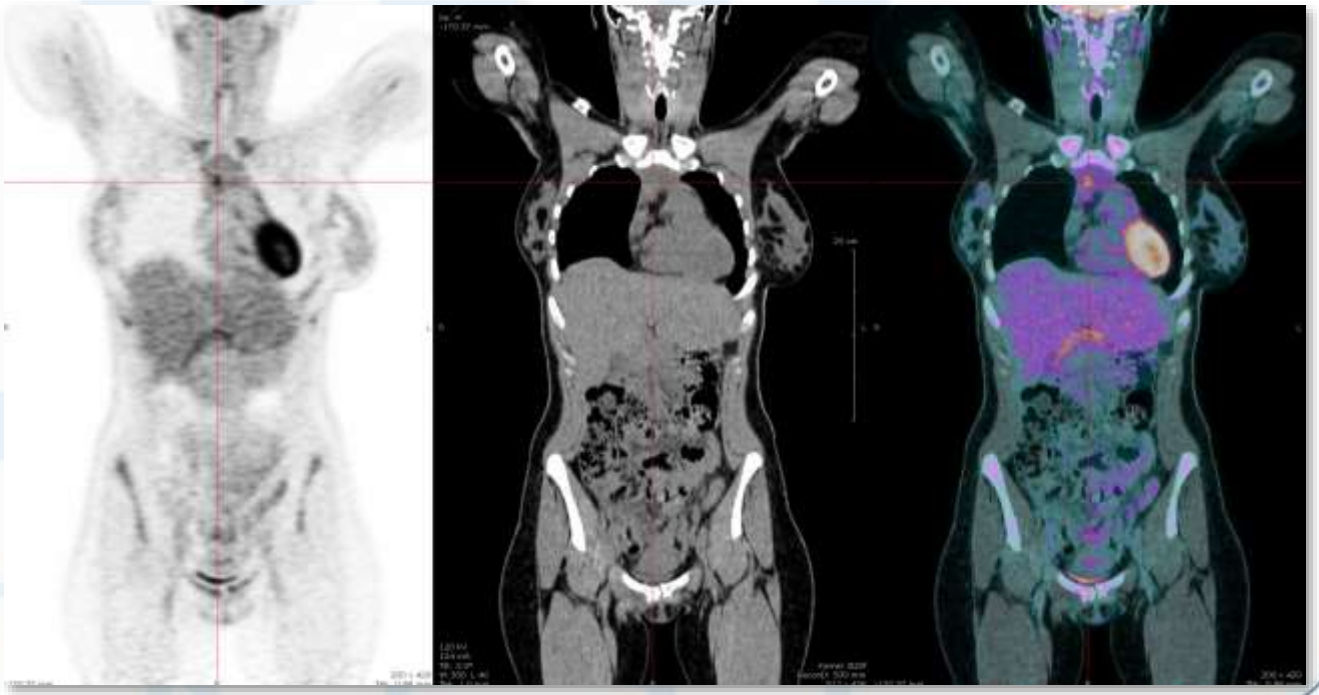
- Masse résiduelle médiastinale : SUVmax à 6,5
- Deauville 5
- ΔSUVmax > 80% mais Deauville 5 sur la masse médiastinale
- TEP+ C2





Mme C. S., TEP à C4

- Masse résiduelle médiastinale : SUVmax à 5,06
- ΔSUVmax supérieur à 80% mais Deauville 4 en médiastinal



Mme C. S., TEP à C4

- Masse résiduelle médiastinale : SUVmax à 5,06
- ΔSUVmax supérieur à 80% mais Deauville 4 en médiastinal
- TEP + à c2 et c4