TEP ET LYMPHOMES

mise au point - LES CRITERES DE LUGANO -

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

See accompanying article doi: 10.1200/JCO.2013.53.5229

Marie Luporsi IHN médecine nucléaire

ABSTRACT

Abstract

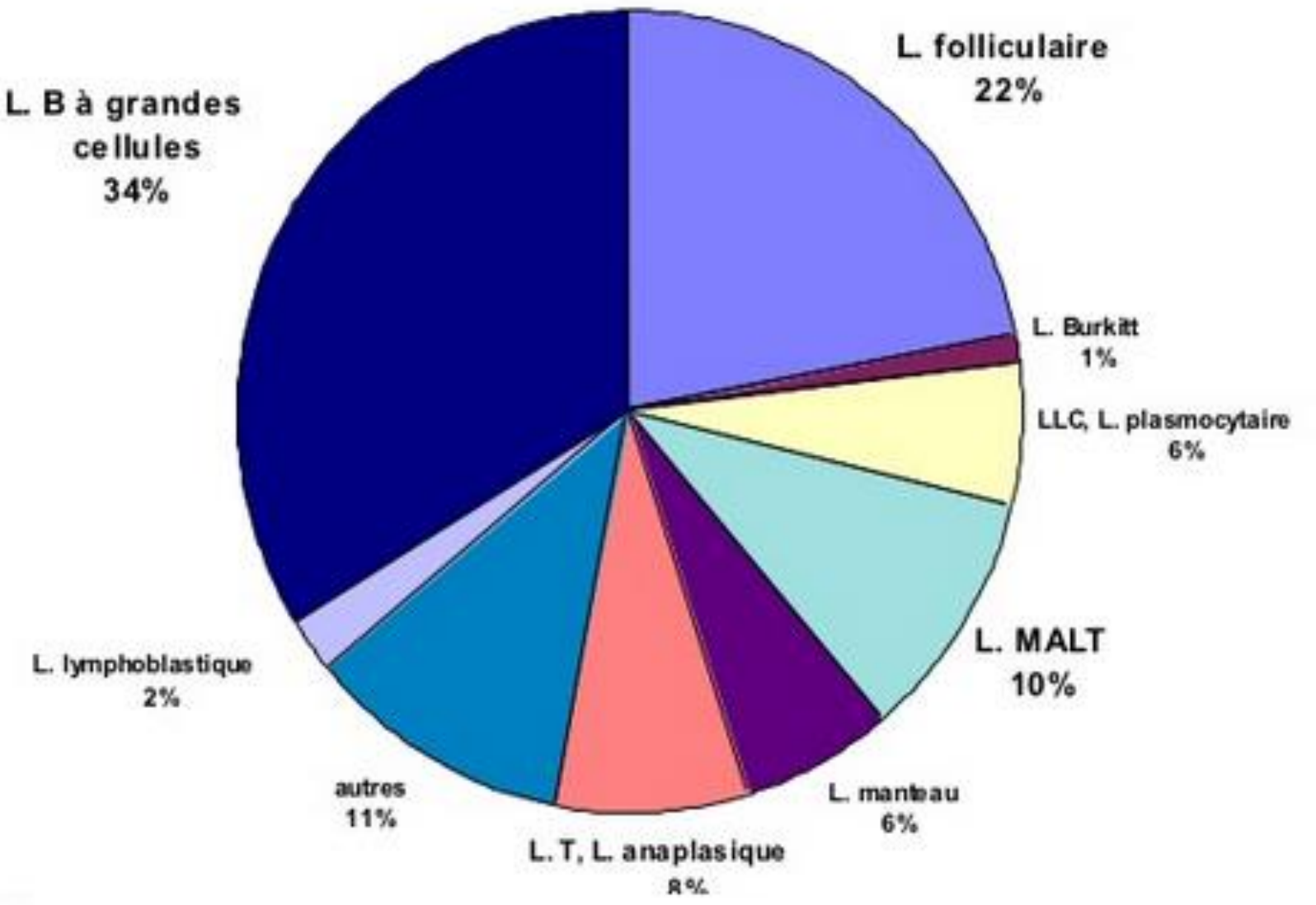
The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included 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.

GENERALITES

- Plus de 25 sous types de lymphomes:
  - 65% de lymphomes agressifs
  - 35% de lymphomes indolents
- Age moyen au diagnostic pour LMNH:
  - 65 ans
- Age moyen pour LH:
  - 20 à 30 ans et 70ans

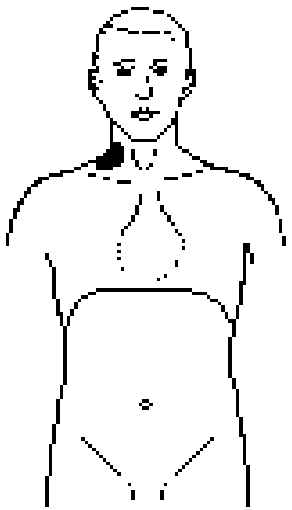
Fréquence des différents types histologiques de lymphome en Europe



TEP FDG et LYMPHOME

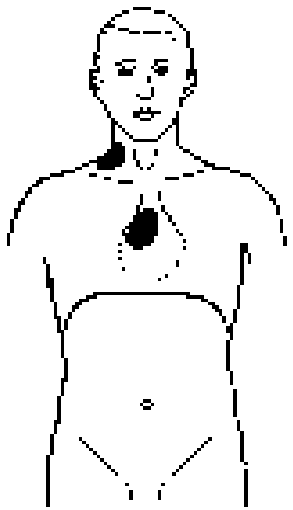
- 1971: Évaluation initiale ANN ARBOR (BOM/clinique)
- 1999: Évaluation thérapeutique Bruce Cheson reposant sur la TDM
- 2007: Juweid IWC introduisant la TEP au 18FDG

- 1971: Évaluation initiale **ANN ARBOR** (**BOM**/clinique)



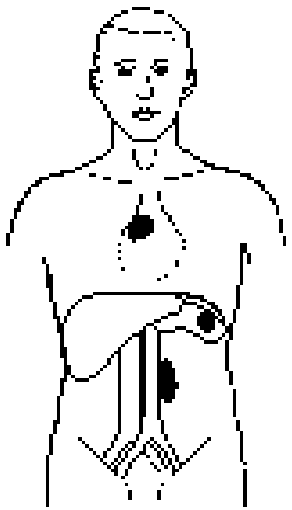
Stage I

single lymph node region or single extralymphatic site (Ie)



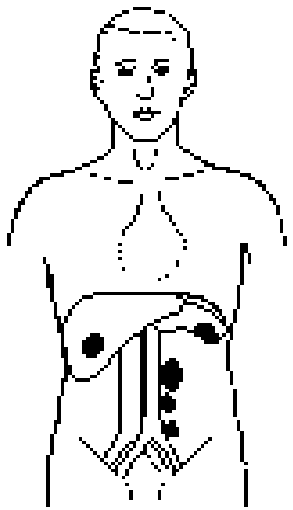
Stage II

two or more sites, same side of diaphragm or ō contiguous extralymphatic site (IIe)



Stage IIIs

both sides of diaphram or ō spleen (IIIs) or contiguous extralymphatic site (IIIe)



Stage IV

diffuse involvement of extralymphatic sites ± nodal disease

Stage subdivision: A-asymptomatic B-unexplained weight loss>10% in 6m and/or fever and/or night sweats

Extralymphatic = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches

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 Klippenstein, 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: Évaluation thérapeutique Bruce Cheson reposant sur la TDM**

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 ≥ 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node (ie, ≤ 1 × 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.

- **2007: Juweid IWC introduisant la TEP au 18FDG**

Nouvelles recommandations - LUGANO -

- TEP recommandée uniquement pour les lymphomes avides de FDG *(LH, LBDGC, folliculaire, manteau, …)*.

- Intérêt pour:

  le staging initial,

  l' évaluation intermédiaire et

  l' évaluation de fin de traitement.

- Non recommandée pour la surveillance.

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,[84] with additional updates.[18,33,34,65-87]

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.

Nouvelles recommandations - LUGANO -

- **Échelle de DEAUVILLE** pour tous:
  - 2 BDF visuels : médiastin et foie
  - 5 scores:

score 1 : pas d'hyperfixation

score 2 : fixation ≤ médiastin

score 3 : fixation > médiastin mais ≤ foie

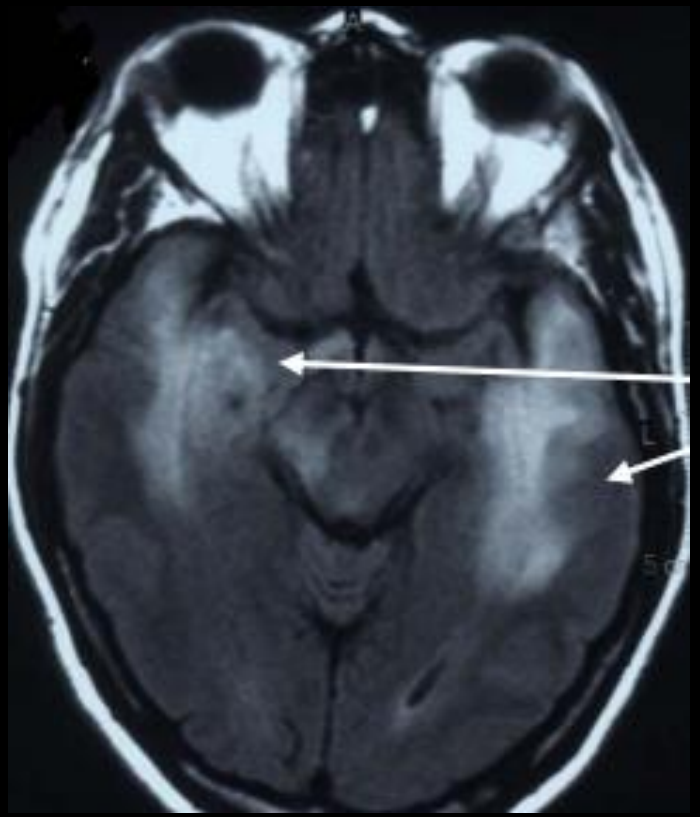
score 4 : fixation > foie

score 5 : fixation >> foie et/ou progression

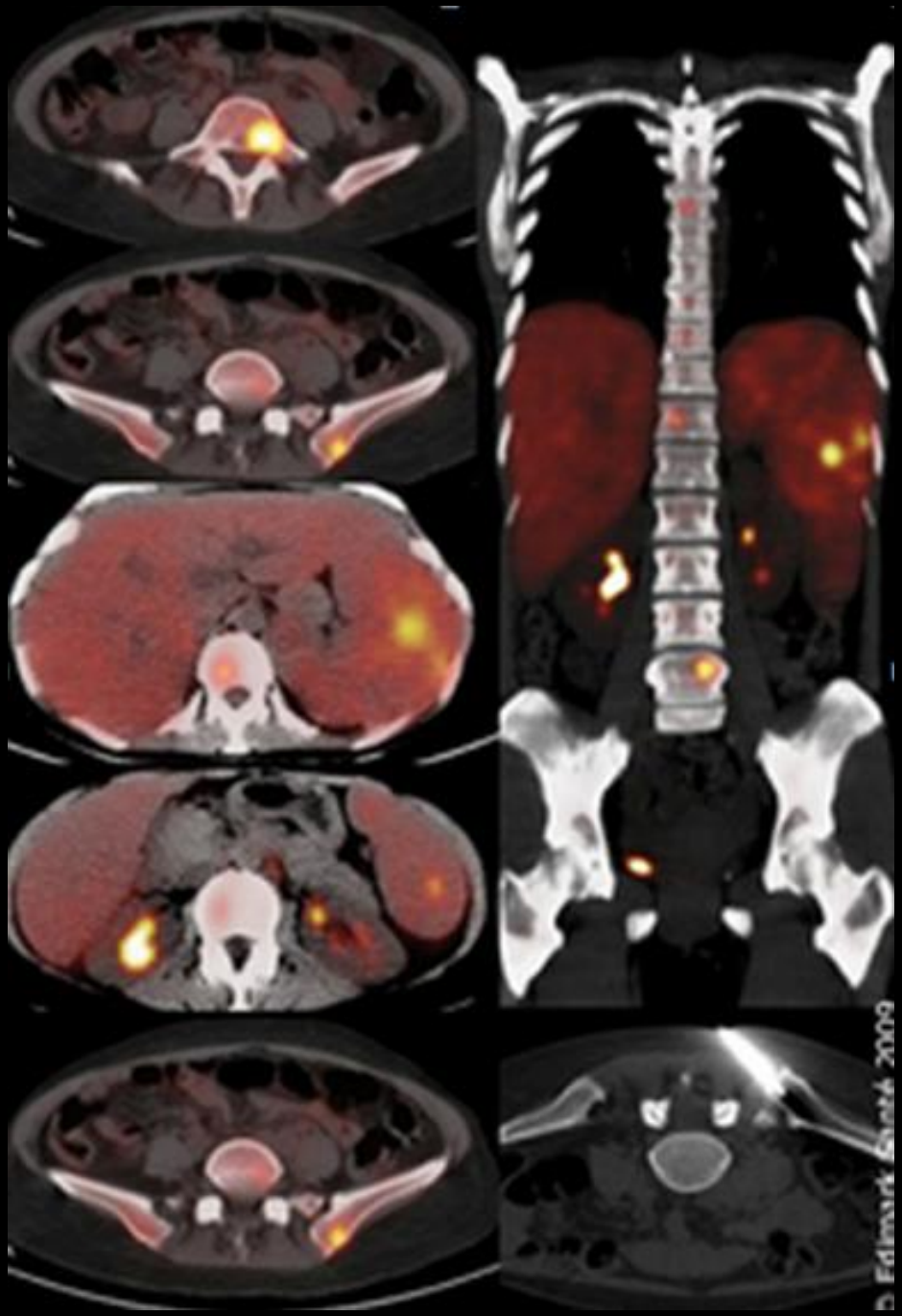
Fixation la plus intense sur un site initialement envahi

TEP et évaluation Initiale

- Analyse visuelle.
- Se et Sp de la TEP > TDM.
- IRM reste recommandée pour les atteintes du SNC.
- Biopsies guidées par la TEP.



IRM FLAIR retrouvant des lésions bitemporales en hypersignal d'un LBDGC

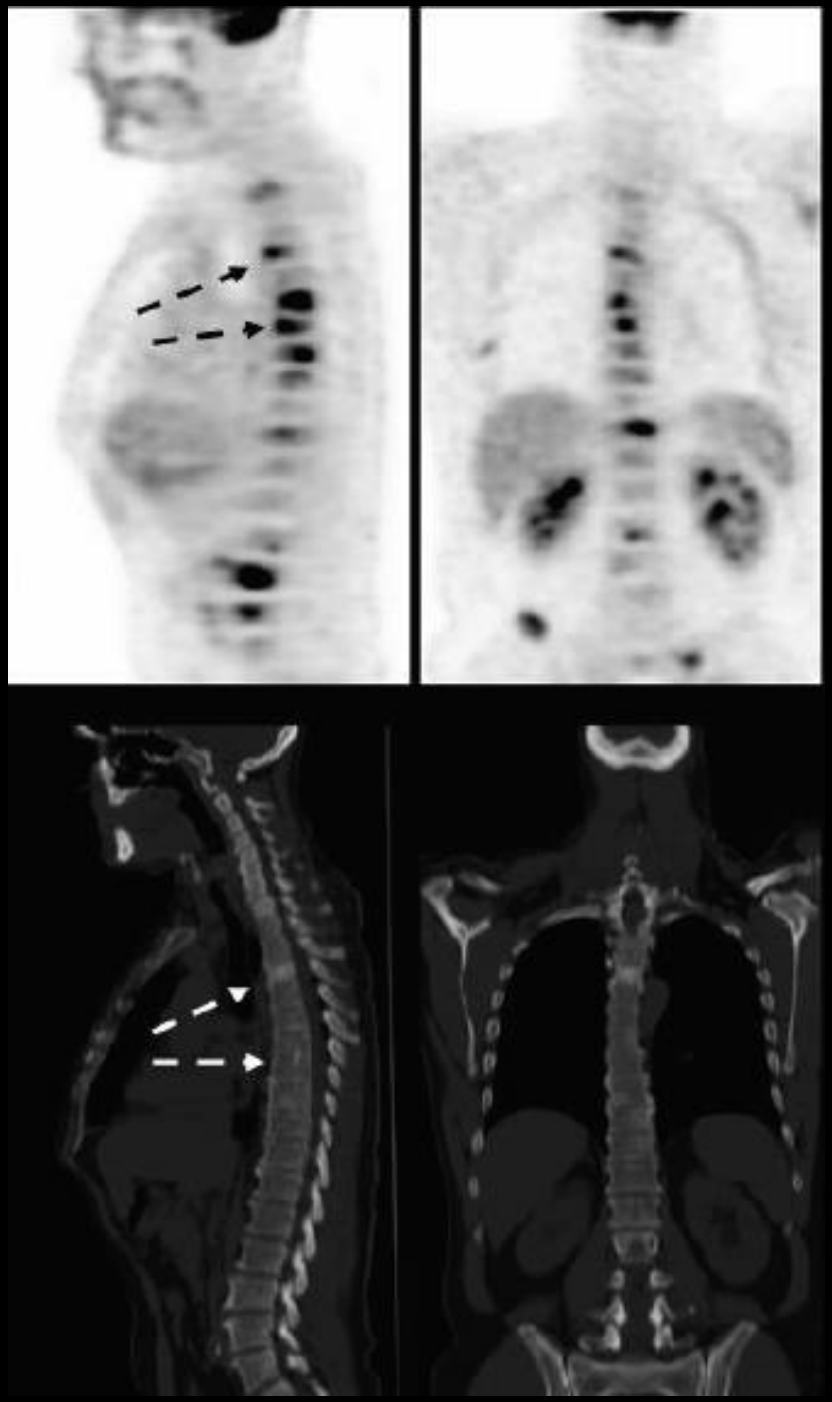


Femme 37 ans présentant des douleurs osseuses : première biopsie ostéo-médullaire à l'aveugle suspecte de lymphome, mais sans typage possible. La TEP confirme les lésions spléniques et met en évidence plusieurs lésions osseuses. La biopsie guidée par la TEP au niveau d'une lésion osseuse iliaque met en évidence un lymphome B riche en cellules T.

E de Kerviler et al, 2009

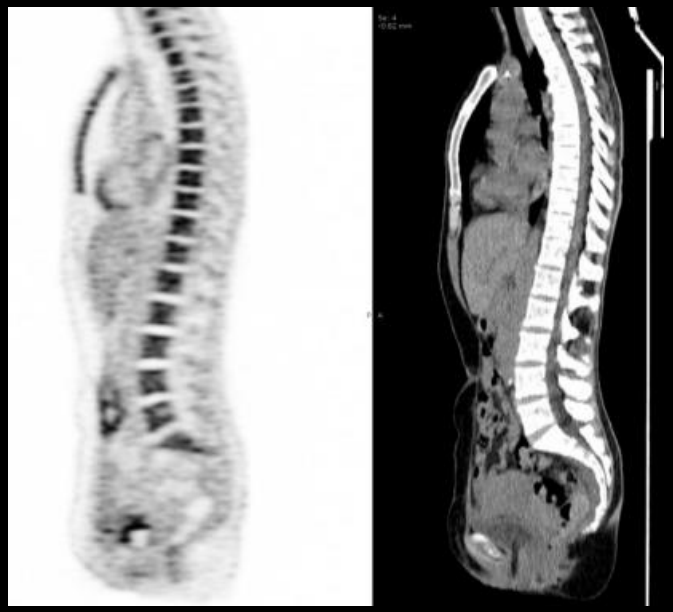
TEP et évaluation Initiale

- Des **fixations focales** de la moelle osseuse pour les **LH et LNH agressifs** sont hautement suspectes et permettent de se soustraire à la BOM.



atteinte ostéo-médullaire multifocale d'un L.H.

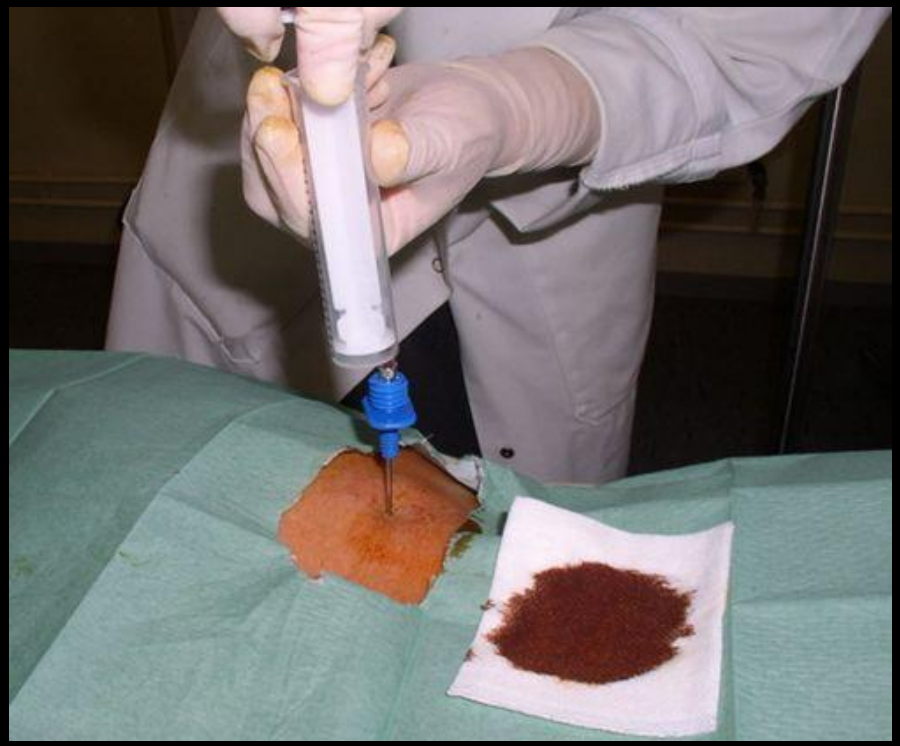
- Une fixation osteo-médullaire diffuse sans lésion focale fait évoquer une hyperplasie réactionnelle dans le LH (ou le LBDGC avec un syndrome inflammatoire important…) dans tout autre cas il faut suspecter un envahissement tumoral.



A gauche : stimulation médullaire diffuse réactionnelle dans un L.H.

TEP et évaluation Initiale

- **La BOM reste indispensable pour les lymphomes folliculaires,du manteau, et autres lymphomes indolents car Se de la TEP-FDG reste très modérée.**



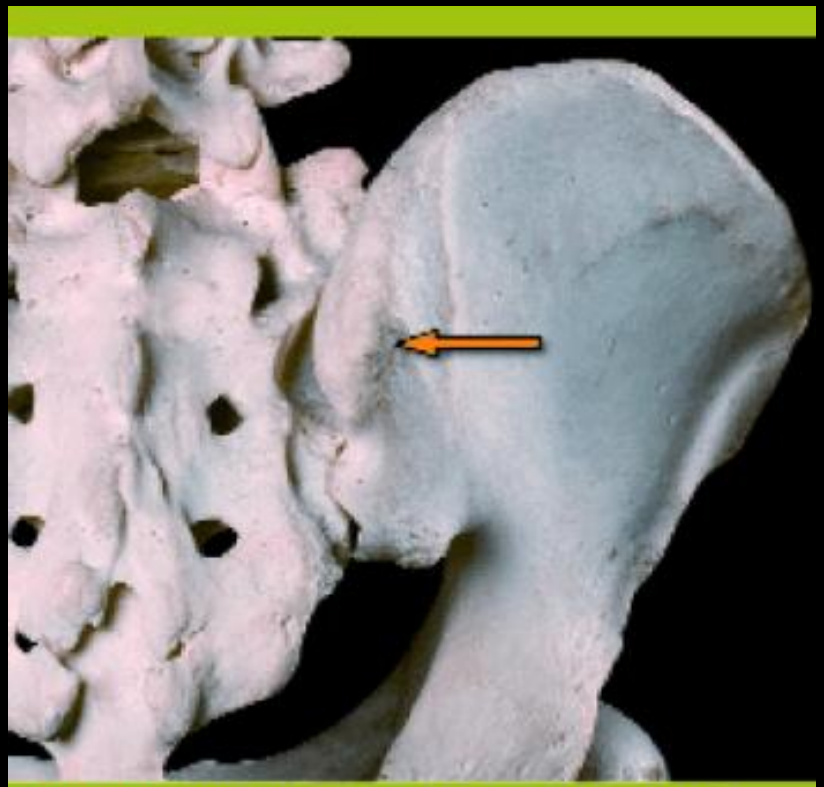


Figure 2. Epine iliaque postéro-supérieure : site de premier choix

TEP et évaluation Initiale

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

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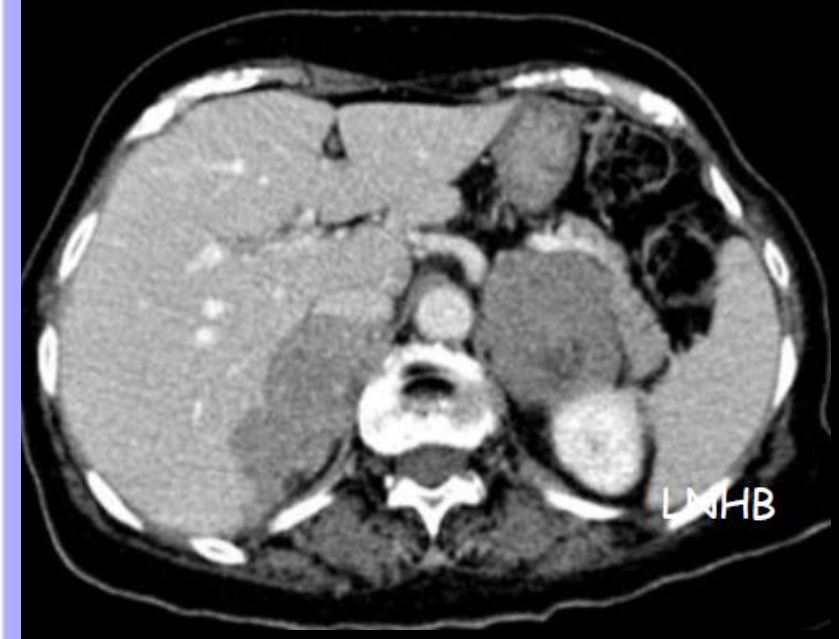
Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

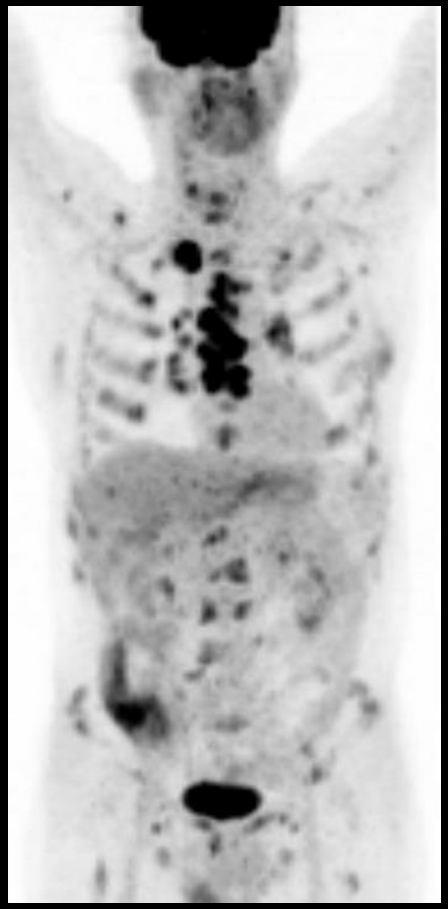
*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.



LMNH B avec atteinte surrénalienne

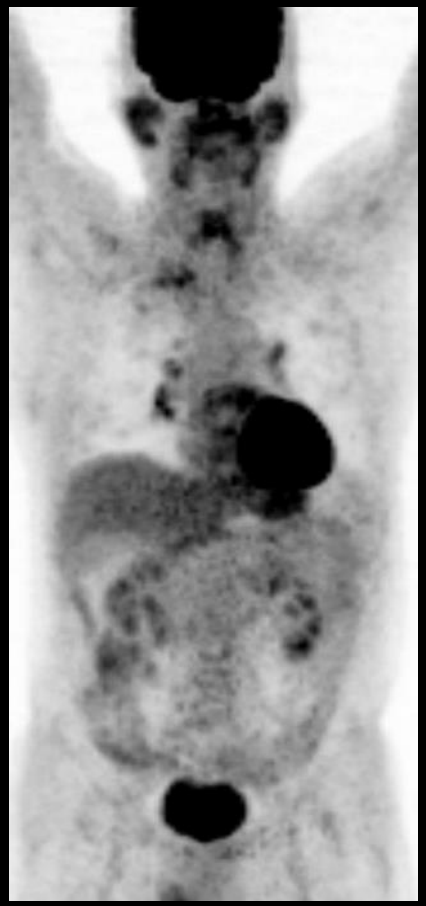
TEP et évaluation intermédiaire

- Idéalement après 2 cures de chimiothérapie.
- Intérêt : déterminer différents profils répondeurs (lent vs rapide).
- TEP = marqueur de substitution de chimio-sensibilité



A gauche: Lymphome T réfractaire à une première ligne de chimiothérapie

A droite: réponse partielle après 4 cycles de Brentuximad (stade IV Deauville)

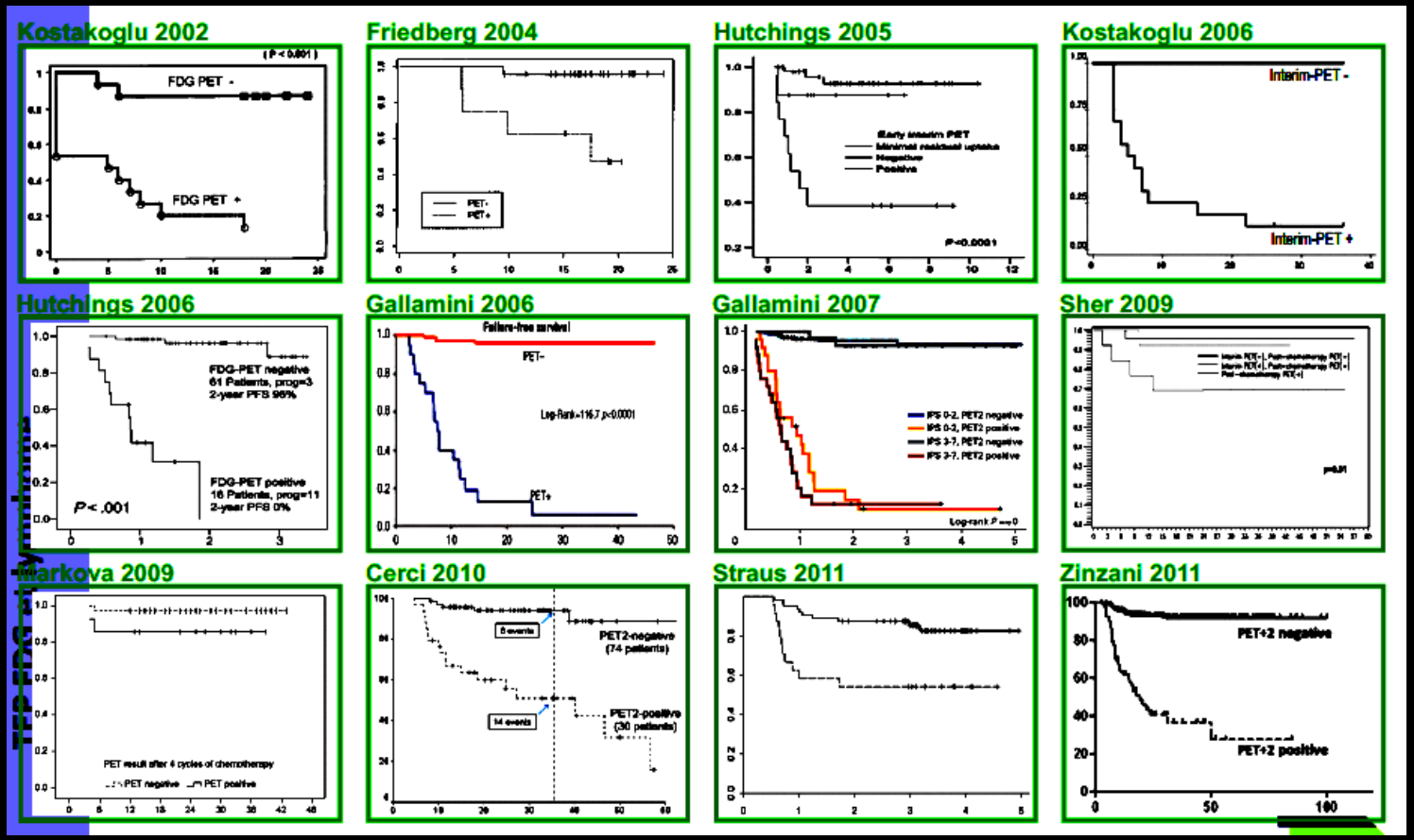


TEP et évaluation intermédiaire

- La valeur pronostique de la TEP intermédiaire a été prouvée.
- Mais l'intérêt de modifier l'attitude thérapeutique en fonction des données de la TEP n'a pas encore été démontré (essais nombreux en cours).

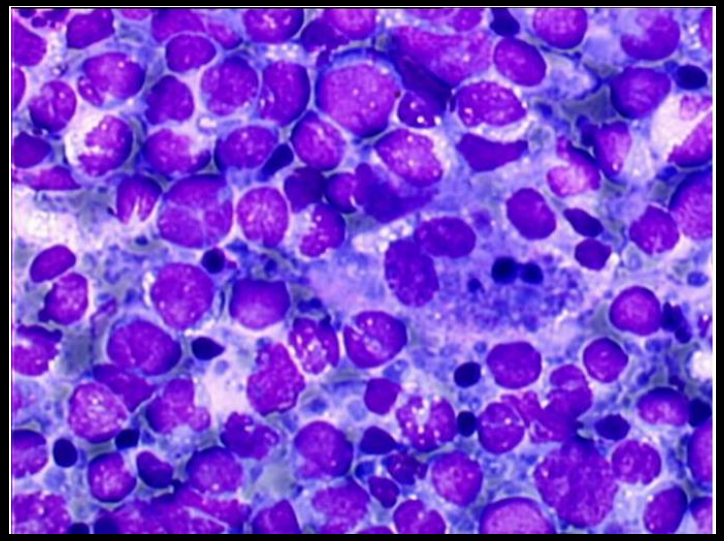
Valeur pronostique de la TEP intermédiaire dans la Maladie de Hodgkin

E. ITTI, Montpellier 2012



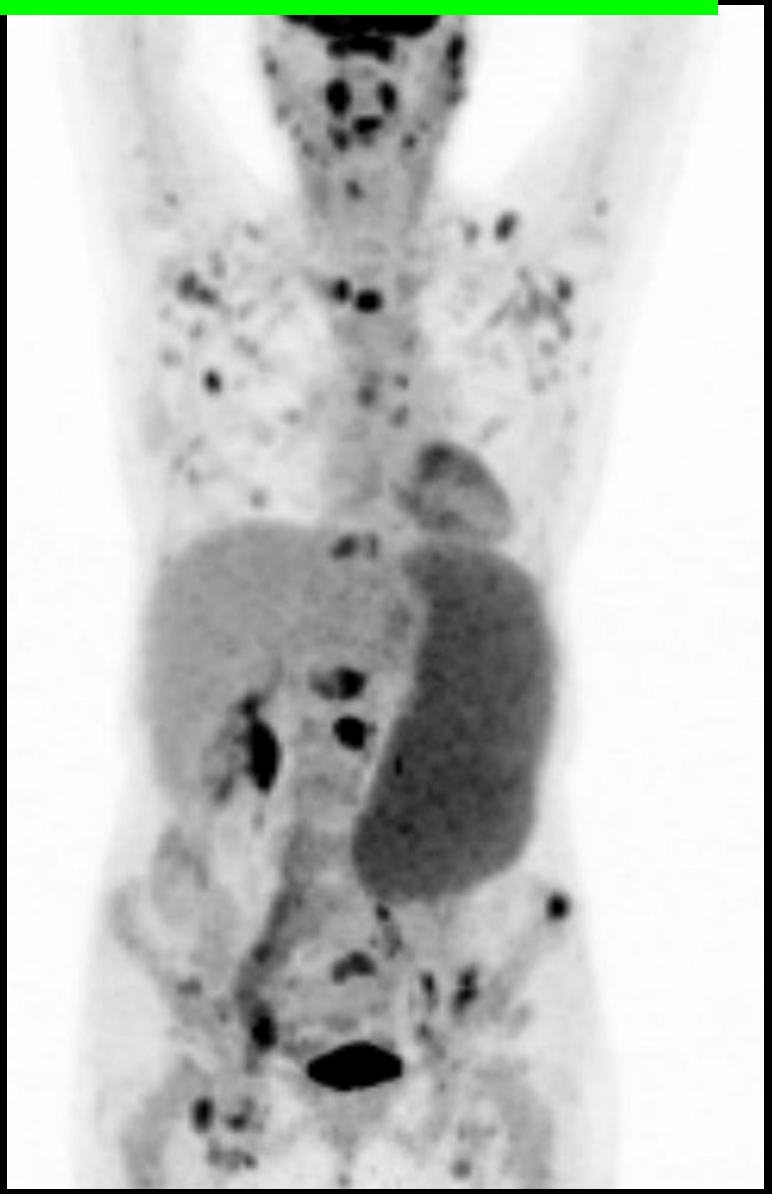
traitements actuels des lymphomes

- **Lymphomes agressifs**:
  - **Autogreffe possible en 1re ligne**
  - **RCHOP Haute DOSE**
  - **Radiothérapie**



Histologie LBDGC

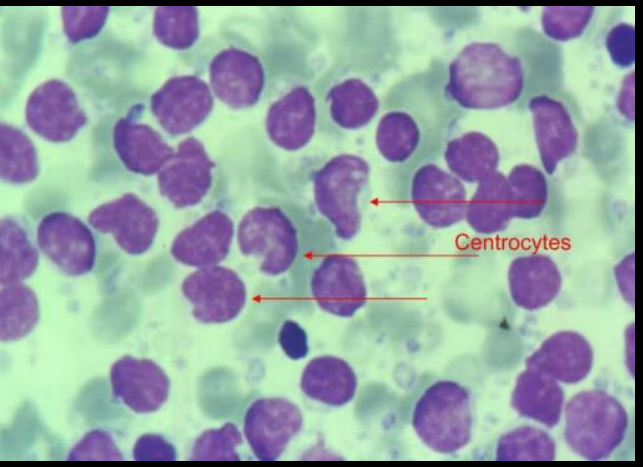
A droite : lymphome agressif avec atteinte osseuse, ORL et ganglionnaire sus et sous diaphragmatique



traitements actuels des lymphomes

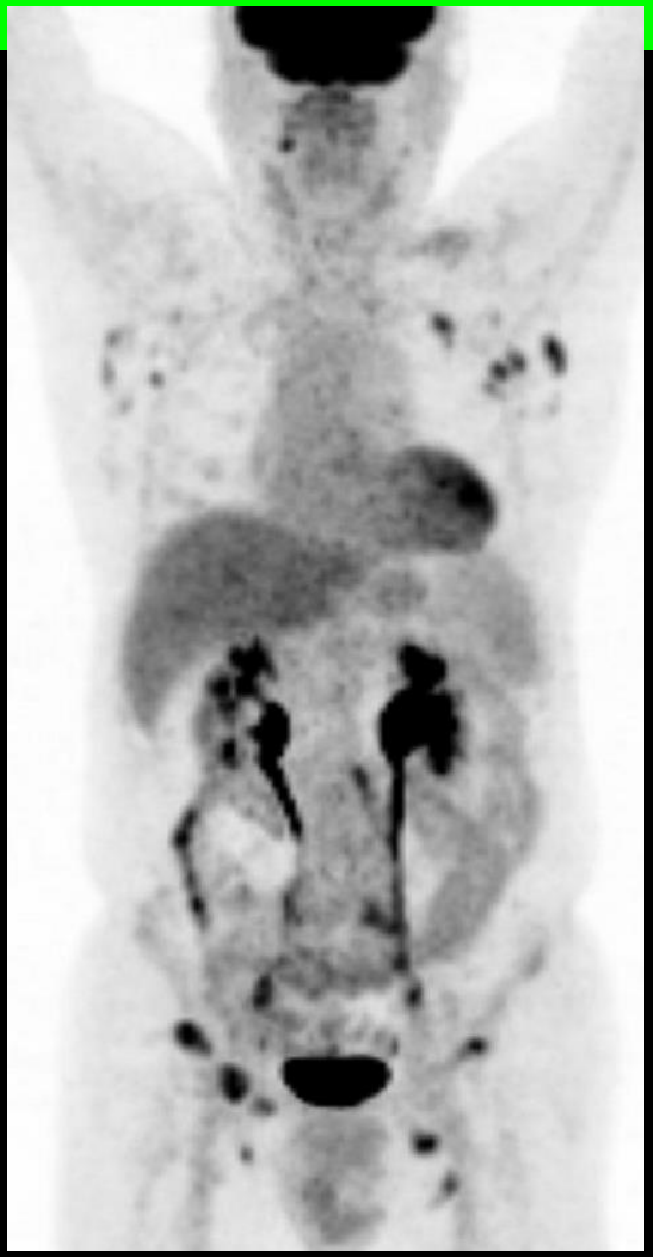
- **Lymphomes indolents:**
  - En première intention:

    Surveillance /R-CHOP/ RITUXIMAB
  - Ou TTT d' Entretien
  - Ou Zevalin
  - Autogreffe en deuxième intention



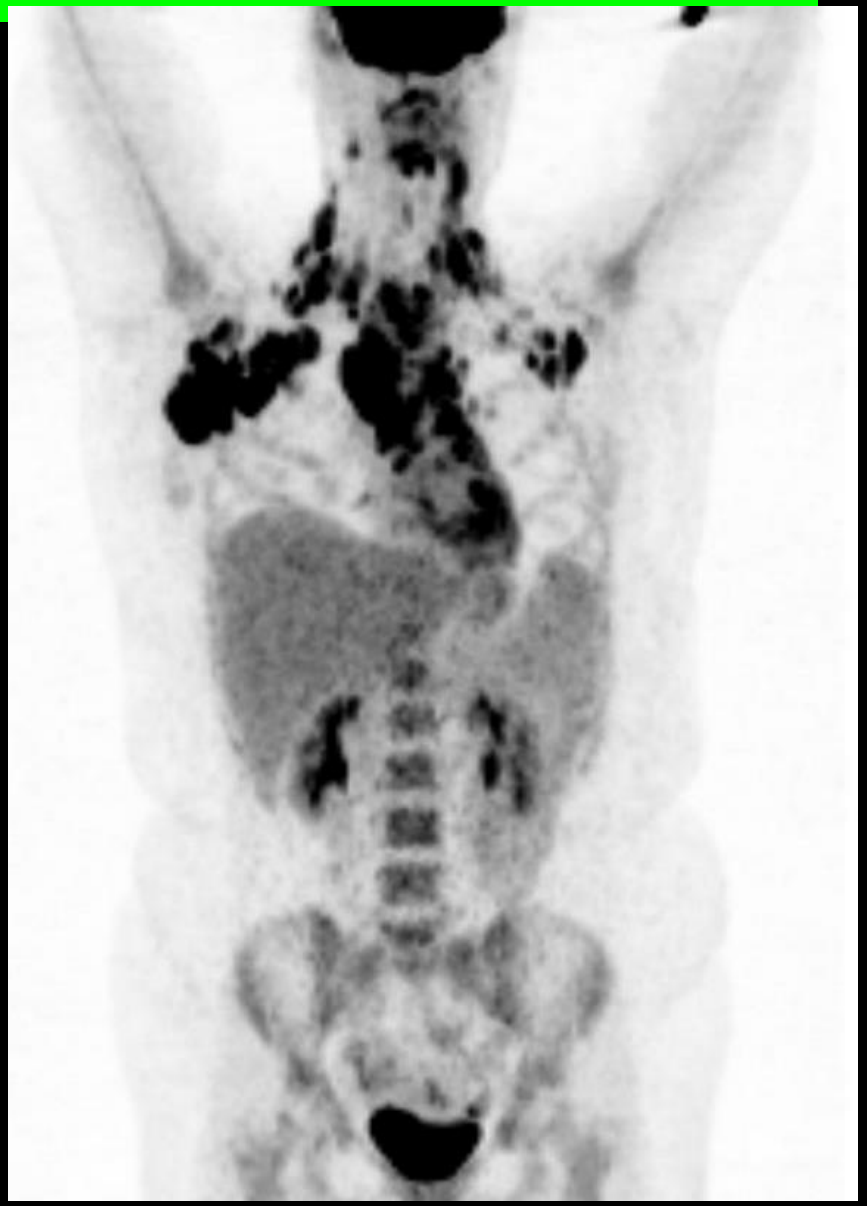
A gauche : Histologie lymphome folliculaire

A droite : lymphome folliculaire en rechute ganglionnaire sus et sous diaphragmatique

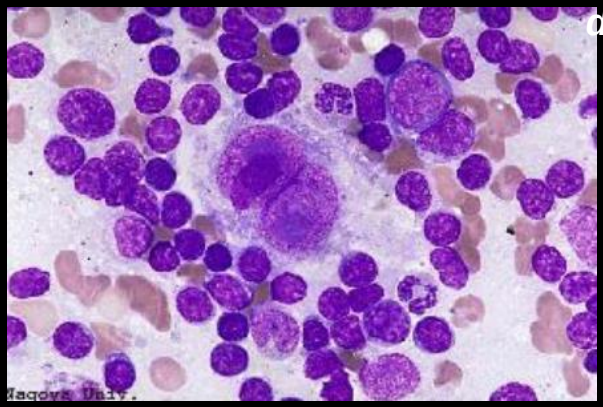


traitements actuels des lymphomes

- **Maladies de Hodgkin:**
  - **BECOOP, ABVD**
  - **Autogreffe si réfractaire ou rechute**
  - **RTE**



A droite : lymphome de Hodgkin avec atteinte pulmonaire et ganglionnaire sus et sous diaphragmatique

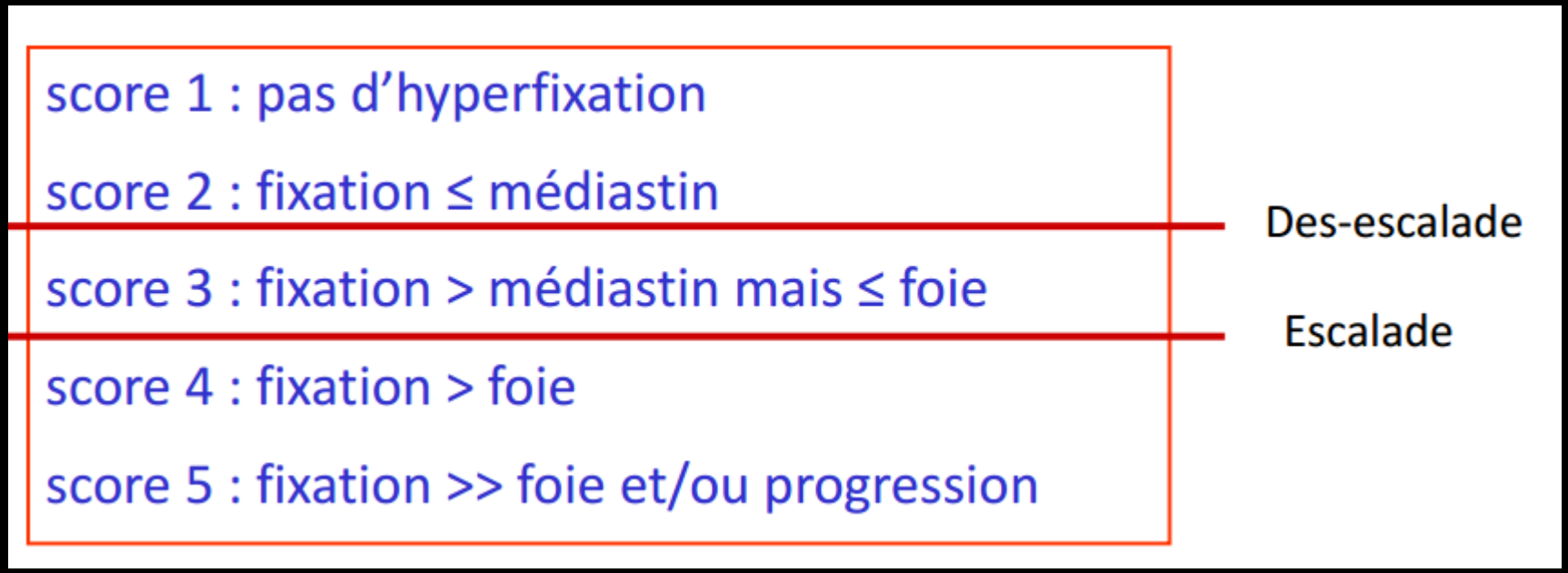


histologie Lymphome de Hodgkin

TEP et évaluation intermédiaire

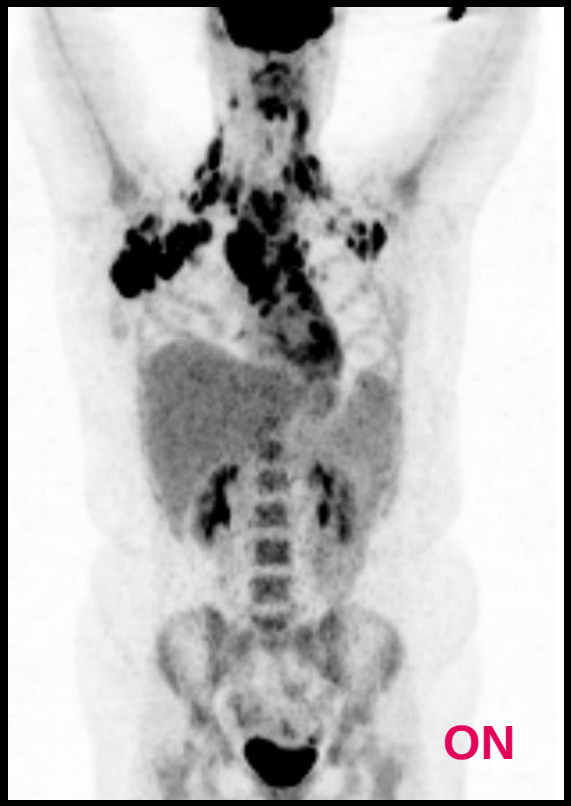
- **DEAUVILLE pour tous:**

  Echelle 5-PS recommandée

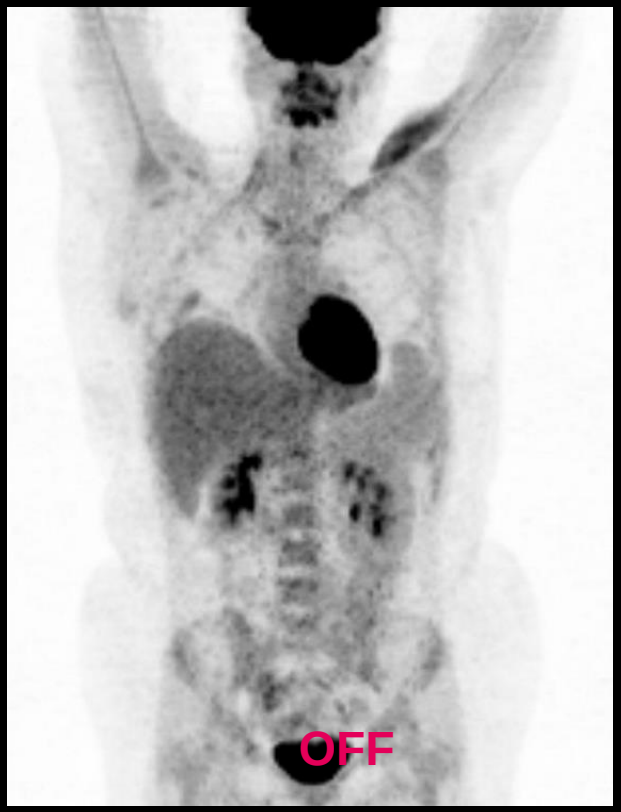


TEP et évaluation intermédiaire

- **La Maladie de HODGKIN:**
  - Se comporte **comme une maladie ON/OFF inflammatoire**.
  - **80% de bons répondeurs** (DEAUVILLE I et II).
  - Études en cours pour désescalade thérapeutique (AHL_2011).



Réponse complète après 2 cures de BEACOPP d'une Maladie de Hodgkin initialement stade IV Ab pulmonaire



TEP et évaluation intermédiaire

- **Le Lymphome B diffus à grandes cellules:**

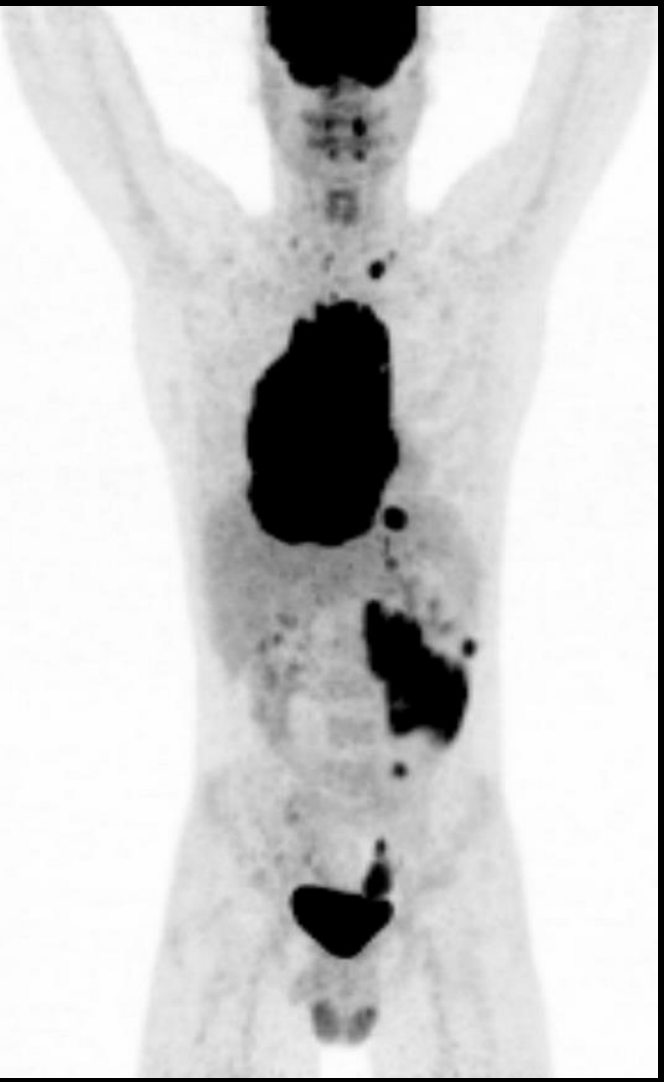
  - Ne se comporte pas en maladie ON/OFF.
  - Plutôt une réponse graduelle plus ou moins rapide à la chimiothérapie.

Un outil supplémentaire pour l'évaluation en TEP 18-FDG:

- DELTA SUV = (SUVmax1 – SUVmax2) / SUVmax1

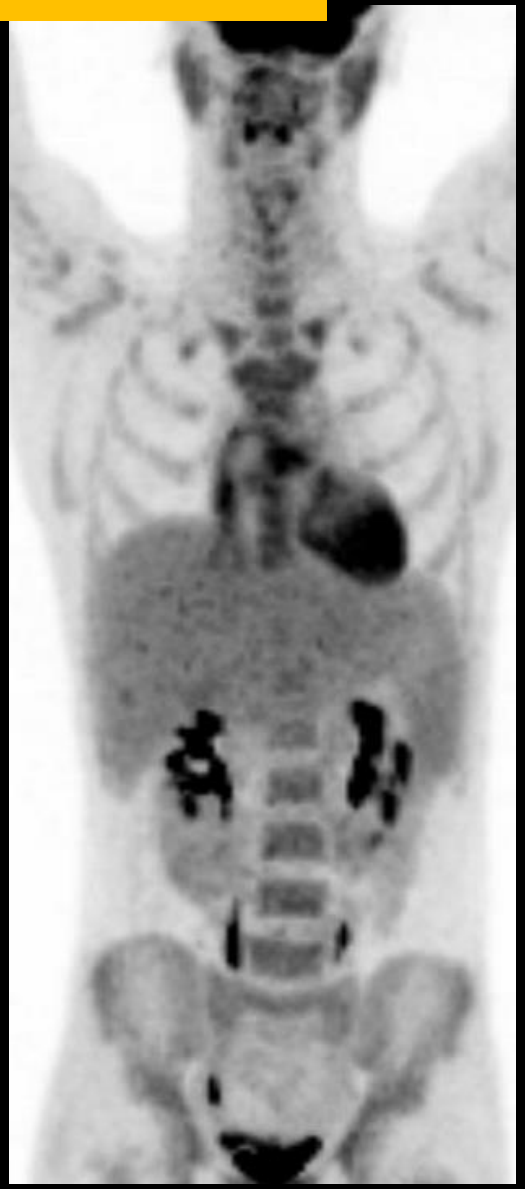
- CUT OFF DELTA SUV:
  - TEP négative si ΔSUVmax > 66% à 2 cures
  - TEP négative si ΔSUVmax >70% à 4 cures

TEP et évaluation intermédiaire



A gauche: LBDGC stade III

A droite : bonne réponse métabolique après 4 cures (ΔSUV max>70%)



TEP et évaluation intermédiaire

- **Mais l'usage du DELTA SUV est limité pour :**
  - **Une mesure de SUVmax <10 sur la TEP 1**
  - **Ou une mesure de SUVmax ≥ 5 sur la TEP 2**
- **Dans ces cas de figure : on revient à DEAUVILLE**

TEP et évaluation intermédiaire

- **Synthèse pour le LBDGC:**
  - **2 Cures:**
    - **TEP négatif: ΔSUVmaxPET0-2 > 66%**
    - **TEP Positif: ΔSUVmaxPET0-2 ≤ 66%**
  - **4 Cures:**
    - **TEP Négatif: ΔSUVmaxPET0-4 >70%**
    - **TEP Positif: ΔSUVmaxPET0-4 ≤ 70%**
  - **Exceptions:**
    - **Si SUVmax initiale < 10 et/ou SUVmax intermédiaire ≥ 5 alors on utilise l' échelle de DEAUVILLE**

TEP et évaluation de fin de traitement

- **TEP-FDG > CT pour confirmer la rémission**
- **Valeurs pronostiques démontrées pour:**
  - **LBDGC**
  - **Hodgkin**
  - **Lymphome folliculaire ±**
- **Masses résiduelles positives dans le LBDGC et le Hodgkin : à biopsier avant de décider d'un rattrapage**

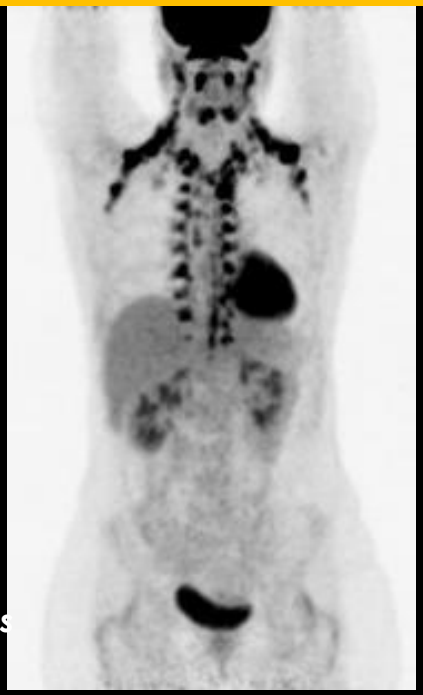
TEP et évaluation de fin de traitement

- **FAUX POSITIFS:**

  hyperplasie thymique, graisse brune,

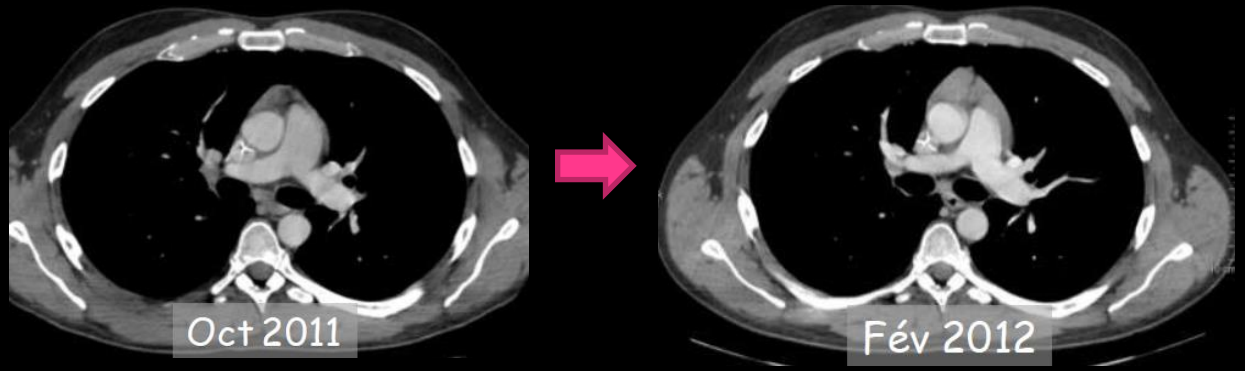
  réaction médullaire et splénique,

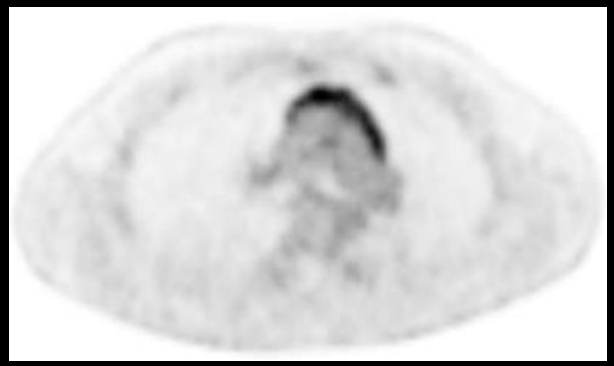
  infection.



Ci-contre: lipolyse de stress

- **FAUX NEGATIFS: EVP**

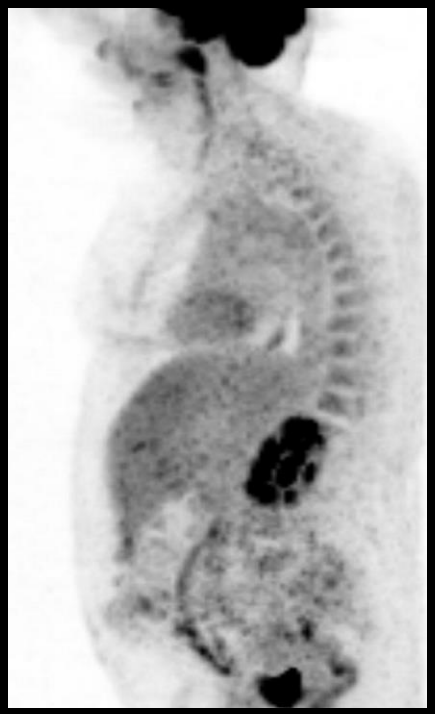




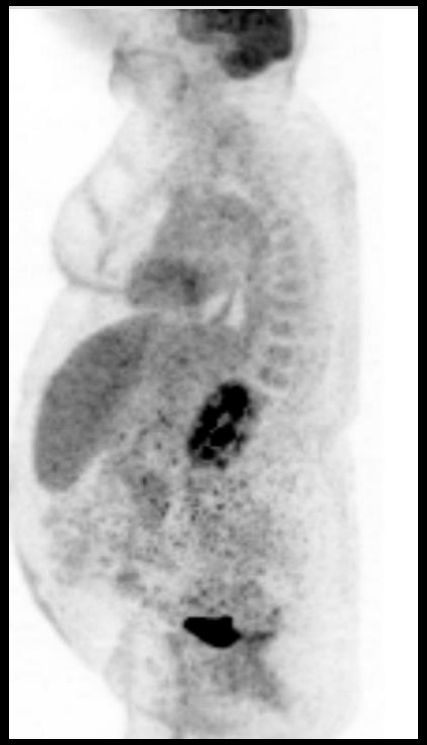
Rebond thymique

TEP et évaluation de fin de traitement

- **Échelle de DEAUVILLE:**
- **Score I et II: TEP négative**
- **Score III et IV: TEP positive**
- **Score III : TEP négative (mais nuancer le compte rendu si patient mauvais répondeur sur la TEP intermédiaire en rappelant le statut III ou IV)**



Lymphome B diffus du cavum en réponse métabolique complète en fin de traitement.



Mise au point basée sur le cours de DES de Médecine Nucléaire du docteur Françoise KRAEBER-BODÉRÉ 2014