PET/CT in Lymphoma

FDG-avidity
Staging (nodal & extra nodal)
Response evaluation
  Early assessment during treatment / interim (iPET)
  Remission assessment at the end of treatment
The Deauville 5 point scale (5PS)

Helle W Hendel
Lymphoma

Subtypes differ in molecular characteristics biologic behavior aggressive indolent

The WHO histologic classification morphologic immunohistochemical genetic features

The most important factors for therapy and prognosis histologic subtype extent of disease

Coloured scanning electron micrograph of dividing Hodgkin's cells taken from the pleural effusions of a 55 year old, male patient with "mixed cellularity Hodgkin disease"
Conventional imaging is based on extent and size

Limitations
Benign lymph node enlargement
Malignant small lymph nodes

Limited detection extra nodal disease in spleen, liver, and bone marrow

Equivocal lesions require additional imaging or biopsy
FDG-avidity (WHO classification)

METHODS:
The reports from FDG PET/CT studies performed in a single center for staging of 1,093 patients with newly diagnosed Hodgkin disease and non-Hodgkin lymphoma were reviewed for the presence of FDG avidity.

766 patients with a histopathologic diagnosis verified according to the WHO classification were included in the final analysis.

Weiler-Sagie M et al
FDG Avidity in Lymphoma Readdressed: A Study of 766 Patients JNM 2010
FDG-avidity

METHODS (cont):
FDG avidity was defined as the presence of at least 1 focus of FDG uptake reported as a disease site.

Non avidity was defined as disease proven by clinical examination, conventional imaging modalities, and histopathology with no F-FDG uptake in any of the involved sites.

Weiler-Sagie M et al
FDG Avidity in Lymphoma Readdressed: A Study of 766 Patients JNM 2010
FDG-avidity is lower in indolent disease (83%) than in aggressive disease (97%).

Indolent subtypes (eg. plasmacytoma, follicular lymphoma) are FDG-avid
Aggressive (enteropathy-type T-cell lymphoma) has low FDG-uptake

**TABLE 1**

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>H_{18F}-FDG-avid</th>
<th>Negative</th>
<th>% H_{18F}-FDG avidity</th>
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<tbody>
<tr>
<td>Hodgkin disease</td>
<td>233</td>
<td>233</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Burkitt lymphoma</td>
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<td>18</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Mantle cell lymphoma</td>
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<td>14</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Anaplastic large T-cell lymphoma</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Marginal zone lymphoma, nodal</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>100</td>
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<td>Lymphoblastic lymphoma</td>
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<td>4</td>
<td>4</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Plasmacytoma</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Natural killer/T-cell lymphoma</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100</td>
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<td>Diffuse large B-cell lymphoma</td>
<td>222</td>
<td>216</td>
<td>6</td>
<td>97</td>
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<tr>
<td>Follicular lymphoma</td>
<td>140</td>
<td>133</td>
<td>7</td>
<td>95</td>
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<td>Peripheral T-cell lymphoma</td>
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<td>9</td>
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<td>90</td>
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<td>29</td>
<td>24</td>
<td>5</td>
<td>83</td>
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<td>Enteropathy-type T-cell lymphoma</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
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<tr>
<td>Marginal zone lymphoma, splenic</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
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<tr>
<td>MALT marginal zone lymphoma</td>
<td>50</td>
<td>27</td>
<td>23</td>
<td>54</td>
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<td>Lymphomatoid papulosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>40</td>
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</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Clinical subtype</th>
<th>n</th>
<th>H_{18F}-FDG-avid</th>
<th>Negative</th>
<th>% H_{18F}-FDG avidity</th>
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<tbody>
<tr>
<td>Aggressive*</td>
<td>293</td>
<td>285</td>
<td>8</td>
<td>97</td>
</tr>
<tr>
<td>Indolent†</td>
<td>240</td>
<td>200</td>
<td>40</td>
<td>83</td>
</tr>
</tbody>
</table>

† Follicular lymphoma (all grades), marginal zone lymphoma (nodal and extranodal), small lymphocytic lymphoma, plasmacytoma, primary cutaneous anaplastic large cell lymphoma, and lymphomatoid papulosis.
Lymphoma

Common radiographic features of lymphoma

Homogeneous lymph node lesions
Continuous or scattered whole body distribution of nodal lesions.
Splenomegaly and intra spleen lesions,
Non-destructive expansion of extranodal lesions,
invasive progression without occlusion of the adjacent gastrointestinal tract or vessels
Renal cortical lesions (rare in other malignancies)

In particular, the formation of multiple lymph node lesions in distant sites is one of the characteristics differentiating lymphoma from lymph node metastasis of common cancer,
FDG-PET allows whole-body scanning which is a strong point in its favour.
Example of renal cortical lesion
Staging HL and aggressive NHL

In both HL and aggressive NHL, FDG-PET detects more disease sites (nodal and especially extranodal), than conventional imaging, resulting in a higher sensitivity, leading to significant upward stage migration.
## FDG PET for staging of lymphoma

<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>No. of patients</th>
<th>Upstage (%)</th>
<th>Downstage (%)</th>
<th>Change in therapy (%)</th>
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<tr>
<td><strong>HL</strong></td>
<td></td>
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<td>Buchman et al. [22]</td>
<td>25</td>
<td>8</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Wirth et al. [32]</td>
<td>31</td>
<td>14</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Pelosi et al. [33]</td>
<td>35</td>
<td>11.4</td>
<td>8</td>
<td>9</td>
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<tr>
<td>Naumann et al. [29]</td>
<td>88</td>
<td>14.7</td>
<td>8</td>
<td>18</td>
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<tr>
<td><strong>NHL</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Bangerter et al. [23]</td>
<td>44</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Partridge et al. [26]</td>
<td>44</td>
<td>40.9</td>
<td>&lt;10</td>
<td>25</td>
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<tr>
<td>Jerusalem et al. [25]</td>
<td>33</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weiharauch et al. [27]</td>
<td>22</td>
<td>18</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Munker et al. [34]</td>
<td>73</td>
<td>29</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hutchings et al. [30]</td>
<td>99</td>
<td>17</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Rigacci et al. [35]</td>
<td>186</td>
<td>14</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

In the past, most clinical studies on PET have focused on diagnostic accuracy or changes in management, without bridging the gap to patient-relevant outcomes.
PET seems to be at least as sensitive as blind bone marrow biopsy in HL and aggressive NHL and may eliminate the need for bone marrow biopsy in the primary staging.
Bone marrow involvement in HL

5 BMB positive; advanced stage, abnormal PET
12 cases missed by BMB

PET-CT upstaged 9.7% of patients

BMB upstaged one patient (stage IV PET-CT)
BMB did not alter clinical management

*93 HL – 5 year retrospective data

<table>
<thead>
<tr>
<th>PET-CT pattern</th>
<th>Number (positive BMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>48 (0)</td>
</tr>
<tr>
<td>Reactive</td>
<td>28 (0)</td>
</tr>
<tr>
<td>Positive</td>
<td>17 (5) *</td>
</tr>
</tbody>
</table>

Reactive = diffuse symmetrical uptake
Positive = Patchy focal uptake

Conclusion: BMB has little or nothing to offer staging HL in the PET-CT era

Consider whether FDG-positive truly represents bone/bone marrow involvement:
- FDG avid disease
- Correlation with advanced stage (CT, anemia, raised LDH, B-symptoms)

El-Galaby TC et al. routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naïve patients with Hodgkin lymphoma. J Clin Oncol 2012;30:4508-14
Bone marrow involvement DLBCL

In Newly Diagnosed Diffuse Large B-Cell Lymphoma, Determination of Bone Marrow Involvement with $^{18}$F-FDG PET/CT Provides Better Diagnostic Performance and Prognostic Stratification Than Does Biopsy

Louis Berthet$^1$, Alexandre Cochet$^{1,2}$, Salim Kanoun$^1$, Alina Berriolo-Riedinger$^1$, Olivier Humbert$^{1,2}$, Michel Toubeau$^1$, Inna Dygai-Cochet$^1$, Caroline Legouge$^3$, Olivier Casasnovas$^3$, and François Brunotte$^{1,2}$

**DEFINITION OF NEGATIVE PET**

![DEFINITION OF NEGATIVE PET](image)

**INITIAL FALSE NEGATIVE BMB**

![INITIAL FALSE NEGATIVE BMB](image)

**TARGETED MR**

![TARGETED MR](image)

**RESPONSE TO TREATMENT**

![RESPONSE TO TREATMENT](image)

**FIGURE 1.** Diffuse bone marrow uptake pattern in $^{18}$F-FDG PET/CT. (A and B) Uptake lower than (A) or similar to (B) that in liver was considered negative for BMB. (C) Uptake higher than that in liver was always linked to anemia or inflammatory processes and also considered negative for BMB.

**FIGURE 2.** Unifocal bone marrow uptake pattern in $^{18}$F-FDG PET/CT. Focal lesion on right pelvic bone (A) was shown to be located on right part of sacrum (B), with no underlying anomaly on CT (C). Usual BMB in left posterior iliac crest was negative. Targeted MR imaging confirmed BMB. According to our criteria, patient was considered to have BMB.

**FIGURE 3.** Patient with negative initial BMB of left posterior iliac crest. (A) Initial $^{18}$F-FDG PET/CT highlighted multifocal uptake in bone marrow. Guided biopsy of right iliac crest came back positive. (B) $^{18}$F-FDG PET/CT monitoring revealed excellent metabolic response. According to our criteria, this patient was considered to have BMB.

Bone marrow involvement DLBCL

Criteria for BMI in the study:
Targeted MR imaging
Guided biopsy
Disappearance of bone marrow uptake concomitant with reduced uptake in other 18F-FDG–avid lymphoma lesions on PET/CT monitoring

<table>
<thead>
<tr>
<th>N = 133</th>
<th>BMB+ (8)</th>
<th>BMB- (125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT+ (32)</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>PET/CT- (101)</td>
<td>2</td>
<td>99</td>
</tr>
</tbody>
</table>

PET/CT vs BMB
Sensitivity : 93.9 vs 24.2
NPV: 89% vs 80%
Specificity and PPV: ns

Among 26 patients with positive FDG PET/CT and negative BMB 11 were upstaged
Bone marrow involvement DLBCL

**FIGURE 5.** PFS according to BMB (A) or $^{18}$F-FDG PET/CT status (B).

PFS was higher for patients with
- negative BMB (A)
- Same pattern seen with negative FDG PET/CT (B)
Bone marrow involvement DLBCL

NEGATIVE BMB

PET negative
N = 99

PET positive
N = 26

POSITIVE BMB

PET negative
N = 2

PET positive
N = 6
Currently, only BMB is recommended for the evaluation of BMI in HL and Non HL

BMI is usually focal

The diagnostic performance of 18F-FDG PET/CT is better than BMB

Bone marrow status with 18F-FDG PET/CT appears to be a better independent prognostic factor than bone marrow status with BMB in non HL
PET-CT can miss low volume BM involvement (< 20% of the marrow) and co-existent low grade lymphoma in DLCBCL although this rarely affects management.

The sensitivity of PET for diffuse marrow involvement is limited in FL and mantle cell and most indolent lymphomas where biopsy is required for stating.
Intracerebral lymphoma often shows intense uptake, leptomeningeal disease which may be diffuse and low volume may be missed.

MRI is preferred to assess suspected CNS involvement.
Staging of FDG-avid lymphoma

FDG PET/CT is recommended in staging and at baseline for comparison in (early and) end of treatment response evaluation preferably in clinical trials.

May be used to select the best site to biopsy

Focal uptake in HL and aggressive NHL is sensitive for BM involvement.

MRI is the modality of choice for suspected CNS lymphoma.
Surrogate endpoint and decision guide

- Tumor response serves as an important surrogate for other measures of clinical benefit such as progression-free and overall survival.
- Tumor response also serves as an important guide in decisions regarding continuation or change of therapy.
- In the (near) past response was based mainly on morphological criteria with a reduction in tumor size on CT as the most important factor.
• Resolution of uptake at sites of initial disease indicates metabolic response.
• Reduction of uptake may also indicate satisfactory response but the degree of uptake that is indicative of response is dependent on
  - the timing of the scan during treatment
  - the clinical context  
    (prognosis, lymphoma subtype, treatment regimen)
• A baseline scan is considered optimal for the accuracy of subsequent response assessment
Early response evaluation/interim (iPET): Prediction of response to therapy

End of treatment evaluation
Prognostication (PFS, OS)
Residual masses

- After completion of therapy CT will often reveal residual masses. It is very difficult to assess whether this represents viable lymphoma, fibrotic scar tissue or necrosis in patients with otherwise clinical complete response. To perform a biopsy on all these lesions would be impractical, and even if it were done it would be too inaccurate.

- CRu – complete remission unconfirmed
The International Harmonization Project (IHP) incorporated FDG-PET findings into the definitions of end-of-treatment response in FDG-avid lymphomas in 2007. CRu* was eliminated:

**CR is FDG-negative**

**PR if FDG-positive**

*the cases in which the tumor remains on the image but does not change its size over 3 months without treatment*
The International Harmonization Project (IHP) Interpretation Criteria 2007 *

PET-negative residual mass
FDG uptake lower than the local background for lesions less than 2 cm or lower than mediastinal blood pool for lesions equal or greater than 2 cm

Use:
Widely accepted for end-of-treatment evaluation

*Juweid et al. JCO 2007
Recommendations

PET/CT is the standard of care for remission assessment in FDG-avid lymphoma

Biopsy of residual metabolically active tissue is advised prior to institution salvage treatment

If clinical suspicion of residual disease is low, a repeat scan could be performed in 3 months to determine if uptake has diminished.
• FDG-PET is standard care for remission assessment.

• FDG-PET distinguish between viable lymphoma and necrosis/fibrosis in residual masses (CT-scan) after treatment of HL and aggressive NHL

• Post-treatment FDG-PET is highly predictive of PFS and OS in HL and (aggressive) NHL
An early reliable prediction of response to therapy may separate high-risk poor prognosis patients from those with good prognosis.

For the high-risk group, a more intensive regimen can be started at an earlier point.

For the good prognosis group, harmful side effects by unnecessary treatment might be reduced with a less intensive and less toxic regimen.
Early response evaluation

Predictor of treatment outcome

- Several studies, in Hodgkin lymphoma and in aggressive non-Hodgkin lymphoma, have showed that an *early* FDG-PET scan (iPET), after 1 to 3 cycles of chemotherapy, is a strong predictor of treatment outcome outperforming IPS and IPI.
- However, no conclusive evidence that changing treatment according to iPET improves outcome (ongoing trials) and it is not recommended to do so.
- iPET seems less predictive for response with immunochemotherapy (end-treatment PET is better)
Size reduction is not an accurate predictor of outcome. In HL tumor cells make up a very small fraction of the tumor (surrounded by reactive). Shrinking depends on the cell type and the patient’s immune system, and takes time.
NPV of interim PET is over 80% in aggressive NHL and 90% in HL. Because of the high NPV value and significant difference of outcome between PET-positive and -negative patients, interim FDG-PET is increasingly being used in the sense of risk-adapted therapy.
Conclusions
The prognostic power of negative FDG is outstanding, and there is a consensus that FDG-PET provides an accurate prognosis in patients who have received 1–4 cycles of chemotherapy or immunochemotherapy.

However, close attention should be paid when evaluating the patient prognosis using a positive interim FDG-PET scan by visual assessment, because the PPVs of such scans are limited.
Problems/controversies:
There is no consensus on criteria able to early identify good and bad responders to treatment.

Visual interpretation using the International Harmonization Project (IHP) criteria, primarily established for end of treatment evaluation.
The IHP criteria (2007) specified that uptake should be less than or equivalent to the mediastinal blood pool for lesions 2 cm or larger, or the adjacent background for smaller lesions to define metabolic response at the end-of-treatment.

In early response assessment, treatment is incomplete so the emphasis is on the degree of response and a continuous scale is desirable rather than positive/negative response categories.
The International Harmonization Project (IHP) Interpretation Criteria 2007 *

PET-negative residual mass (definition):
FDG uptake lower than the local background for lesions less than 2 cm or or lower than mediastinal blood pool for lesions equal or greater than 2 cm

Use:
Widely accepted for end-of-treatment evaluation, but generate false-positive interpretations when applied to interim evaluation because minimal residual uptake (MRU) should probably be tolerated after a few cycles of chemotherapy.

The necessity for measuring residual node size on CT adds inter observer variability to the existing variability of PET image Interpretation

*Juweid et al. JCO 2007
Early attempts to address this used three response groups (negative, minimal residual uptake [MRU] and positive).

Further refinement led to the development of a five-point scale (5PS, Deauville) which better represents different grades of uptake.
In an effort to harmonize *interim* PET interpretation criteria in the PET/CTera, The First International Workshop on Interim PET in Lymphoma was held in Deauville in 2009.

Deauville, France

International Harmonization Project 2007
London criteria 2010
Gallamini criteria 2007
Deauville criteria 2010, 2011
October 2012 in Menton

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

Melik E. Javidi, Sigrid Streubel, Otto S. Hoekstra, Felix M. Moraghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Luis Esteban, Eleonora Scheisler, Andreas Buck, Ralph Nastasio, Karoline Spacan, Rodney J. Hicks, Wolfgang A. Weber, Sven W. Barts, Markus Schwaiger, Lawrence M. Schwaitz, Joes M. Zeltner, Barry A. Siegel, and Bruce D. Cheson

**ABSTRACT**

**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 chemoradiation therapy, 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 (≤ 1 x 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.

NHS PET/CT South - Guidance on Lymphoma Reporting

August 2010

During the lymphoma master class at the reporters’ meeting on 22nd July 2010, the consensus of opinion was that the Deauville PET Criteria are adopted by the PET/CT South reporters. The criteria will be used for reporting interim and post treatment lymphoma FDG PET/CTs and reporters are asked to change from the SELCN (South East London Cancer Network) Criteria to the Deauville Criteria with immediate effect.

The Deauville PET Criteria were developed at the first international workshop and focussed on interim-PET scanning in lymphoma. It was highlighted that one of the reasons for the wide range of sensitivity and specificity of interim PET in published studies was the different criteria used for PET interpretation. The workshop aimed to correct this and recommended a 5 point system for describing FDG uptake in residual lesions on interim PET/CTs.

Deauville PET Criteria

The 5 point scale
1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new sites of disease.

The reporters agreed that it is preferable to describe the appearances rather than designate a number alone. If a number only is given, it must be prefixed by the classification that is applied e.g. Deauville 3.
Interpretation of 5PS (Deauville)

1. no uptake
2. uptake ≤ mediastinum
3. uptake > mediastinum but ≤ liver
4. uptake moderately higher than liver
5. uptake markedly higher than liver and/or new lesions

X new areas of uptake unlikely to be related to lymphoma

**Score 1-2:** CMR

**Score 3:**
iPET: Probably CMR in patients receiving standard treatment
End of treatment PET: good prognosis

**Score 4-5:**
*Reduced uptake from baseline*
iPET: PMR
End of treatment PET: residual metabolic disease

*Increased uptake from baseline*
*No decrease in uptake from baseline*
*New foci*

Treatment failure and/or progression
Why is Deauville better than IHP?

The liver is a better reference background than the mediastinal blood pool or nearby background, because of its higher SUV level.

A residual mass with an FDG uptake higher than the liver background better differentiates from the background noise and has less risk to be attributed to a nonspecific uptake.

Minimal residual uptake (MRU) corresponds to foci of low-grade uptake in an area of previously noted disease and is likely to represent inflammation, but small-volume malignancy cannot be excluded.

In addition, the 5PS eliminates the reference to the size of the residual mass, which prevents different readers to compare the same residual uptake to different backgrounds, mainly when a residual tumor of about 2 cm is assessed.

IHP is not recommended for early or mid-treatment response evaluation. Deauville is preferred. SUV is for research......
The Deauville criteria – clinical application

Baseline

Deauville 4

Deauville 1
It is strongly recommended that a baseline scan is available for comparison.

The scan is performed with either lower dose or diagnostic (ce). If the baseline ceCT demonstrates no relevant findings, then lower dose CT is sufficient for response assessment.

The time to scan:

<table>
<thead>
<tr>
<th>Chemotherapy:</th>
<th>GCSF treatment:</th>
</tr>
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<tbody>
<tr>
<td>as long as possible</td>
<td>2 weeks</td>
</tr>
<tr>
<td>min 3 wks</td>
<td></td>
</tr>
<tr>
<td>preferably 6-8 wks</td>
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</table>

<table>
<thead>
<tr>
<th>Radiotherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
</tr>
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</table>
Quantitative assessment

- Quantitative applications of FDG-PET are also recognised as objective tools for response monitoring
  - accurate measurement relies on consistent methods for acquisition and processing and rigorous quality assurance of equipment for widespread application
SUV
Standardized uptake value
a widely used, simple PET quantifier

\[ SUV = \frac{CPET(T)}{\text{Injected dose} / \text{body weight}} \]
- tumor metabolism
- underestimation of true activity in small tumors
- heterogeneous tumors
- time (after inj) dependent
- plasma glucose dependent
- Body weight, BSA, LBM
- Scanning parameters and PET-scanner

Intraindividual variation in FDG uptake in serial PET-scans is low (CV 10%). Changes by more than 20% (1 SUV) is significant
Conclusion: Although the Deauville criteria are valid for assessing the prognostic value of early PET/CT in DLBCL, computation of the $\Delta$SUV$_{\text{max}}$ leads to better performance and inter-observer reproducibility, and should be preferred when a baseline scan is available.
## Early response evaluation

**Table 1** Evolution of PET scans in the management of DLBCL

<table>
<thead>
<tr>
<th>Era</th>
<th>Study</th>
<th>Timing of PET</th>
<th>Criteria</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>No standardized criteria available for PET interpretation</td>
<td>Kostakoglu et al., Jerusalem et al., Spaepen et al., Haioun et al., Dupuis et al., Safar et al. [5-9, 24*]</td>
<td>Mid: 1–4</td>
<td>Custom visual criteria</td>
<td>Interim PET predicts patient’s outcome</td>
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<tr>
<td></td>
<td>Han et al., Moskowitz et al. [10, 13]</td>
<td>Mid: 2–4</td>
<td>Custom visual criteria</td>
<td>No prognosis impact of interim PET because of low PPV</td>
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<tr>
<td></td>
<td>Juweid et al. [14]</td>
<td>End of treatment</td>
<td>Visual: IHP</td>
<td>Valuable for DLBCL and HL</td>
</tr>
<tr>
<td></td>
<td>Meignan et al. [18]</td>
<td>Mid: 2–4</td>
<td>Visual: 5PS</td>
<td>Valuable for DLBCL and HL</td>
</tr>
<tr>
<td></td>
<td>Casasnovas et al., Casasnovas et al., Itti et al. [15, 16*, 17*]</td>
<td>Mid: 2 &amp; 4</td>
<td>Visual: IHP</td>
<td>Low PPV</td>
</tr>
<tr>
<td>Standardized criteria available for PET interpretation</td>
<td>Casasnovas et al., Itti et al., Itti et al. [15, 17*, 19]</td>
<td>PET2</td>
<td>Visual: 5PS</td>
<td>5PS better predicts patient's outcome than IHP criteria</td>
</tr>
<tr>
<td></td>
<td>Lin et al., Itti et al. [21, 22]</td>
<td>Mid: 2 &amp; 4</td>
<td>ΔSUVmax</td>
<td>DSUVmax better predicts patient’s outcome than custom visual criteria</td>
</tr>
<tr>
<td></td>
<td><strong>Itti et al. [19]</strong></td>
<td>PET2</td>
<td>ΔSUVmax</td>
<td>Better interobserver reproducibility of ΔSUVmax compared to 5PS criteria</td>
</tr>
<tr>
<td></td>
<td>Casasnovas et al. [16*]</td>
<td>Mid: 2 &amp; 4</td>
<td>ΔSUVmax</td>
<td>ΔSUVmax better predicts patient’s outcome than both IHP and 5PS visual criteria</td>
</tr>
</tbody>
</table>

*SPS* 5-point scale; *DLBCL* diffuse large B-cell lymphoma; *HL* Hodgkin’s lymphoma; *IHP* international harmonization project; *PET* positron emission tomography; *PPV* positive predictive value; *SUVmax* maximum standardized uptake value
Assumptions:

In HL, neoplastic Reed–Sternberg is 1% of the overall cellularity. The non-neoplastic cellular compartment is switched-off very early by chemotherapy: known as “metabolic CR.”

In NHL, the neoplastic cells is 90% of the total cell population and a progressive fraction of neoplastic cells are lysed by the chemotherapy. The percentage of the cell destruction is predictive of the final response to the chemotherapy.

For these reasons, it is argued that a visual assessment seems preferable in HL, whereas a quantitative approach by SUVmax measurement seems more appropriate in DLBCL.
Routine long-term follow up is not recommended (subclinical disease).

If transformation of Indolent NHL is suspected PET is recommended for biopsy guidance
PET is now the standard of care for end-of-treatment response assessment in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma but not for surveillance.

The Hodgkin lymphoma guideline explicitly states that surveillance PET should not be done because of the risk of false-positives, nor is PET recommended in the non-Hodgkin lymphoma guideline.
The Lack of Evidence for PET or PET/CT Surveillance of Patients with Treated Lymphoma, Colorectal Cancer, and Head and Neck Cancer: A Systematic Review

Kamal Patel¹, Nira Hadar¹, Jounghee Lee¹, Barry A. Siegel², Bruce E. Hillner³, and Joseph Lau¹
Post treatment surveillance

6 lymphoma studies
2 prospective PET (Mantle cell and mixed)
4 retrospective PET/CT (2 Hodgkin, one non Hodgkin one mixed)
Four were rated as quality B and 2 as quality C

Quality B studies had some deficiencies in the criteria, but these deficiencies were considered unlikely to result in a major bias (retrospective studies start with a lower grade of B).

Quality C studies had serious design or reporting deficiencies

PET and PET/CT are widely used for surveillance of patients after cancer treatments. We conducted a systematic review to assess the diagnostic accuracy and clinical impact of PET and PET/CT used for surveillance in several cancers. **Methods:** We searched MEDLINE and Cochrane Library databases from 1996 to March 2012 for English-language studies of PET or PET/CT used for surveillance of patients with lymphoma, colorectal cancer, or head and neck cancer. We included prospective or retrospective studies that reported test accuracy and comparative studies that assessed clinical impact. **Results:** Twelve studies met our inclusion criteria: 6 lymphoma (n = 767 patients), 2 colorectal cancer (n = 96), and 4 head and neck cancer (n = 194). All studies lacked a uniform definition of surveillance and scan protocols. Half the studies were retrospective, and a third were rated as low quality. The majority reported sensitivities and specificities in the range of 90%–100%, although several studies reported lower results. The only randomized controlled trial, a colorectal cancer study with 65 patients in the surveillance arm, reported earlier detection of recurrences with PET and suggested improved clinical outcomes. **Conclusion:** There is insufficient evidence to draw conclusions on the clinical impact of PET or PET/CT surveillance for these cancers. The lack of standard definitions for surveillance, heterogeneous scanning protocols, and inconsistencies in reporting test accuracy preclude making an informed judgment on the value of PET for this potential indication.

**Key Words:** surveillance; PET; PET/CT; lymphoma; colorectal
PET/CT in Lymphoma

FDG-avidity: high (exceptions)
Staging (nodal & extra nodal): yes
Response evaluation: yes
Early / interim (iPET)
Post-treatment
Evaluation criteria:
  IHP
  Deauville
  Change in SUV max
Surveillance

- FDG-avidity is lower in indolent disease than in aggressive disease
- Upward stage migration in 10-40%
- Strong predictor of treatment outcome (HL, aggressive NHL)
- Standard care
- Not recommended
- 5PS recommended
- Seems better in NHL
- Not for routine
- Transformation – biopsy