PET/CT in Lymphoma

FDG-avidity
Staging (nodal & extra nodal)
Response evaluation
   Early / interim
   Post-treatment
Evaluation criteria
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"
Based on size alone
- benign lymph node enlargement may lead to overstaging
- malignant small lymph nodes may be understaged

Limited detection of spleen, liver, and bone marrow involvement

Equivocal lesions require additional imaging or biopsy

Limitations of conventional imaging
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 was lower in indolent disease (83%) than in aggressive disease (97%). Indolent subtypes (e.g., 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>18F-FDG-avid</th>
<th>Negative</th>
<th>% 18F-FDG avidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin disease</td>
<td>233</td>
<td>233</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>18</td>
<td>18</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>100</td>
</tr>
<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>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Plasmyctoma</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>222</td>
<td>216</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>140</td>
<td>133</td>
<td>7</td>
<td>95</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>29</td>
<td>24</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>Marginal zone lymphoma, splenic</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>MALT marginal zone lymphoma</td>
<td>50</td>
<td>27</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large T-cell lymphoma</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>All</td>
<td>766</td>
<td>718</td>
<td>48</td>
<td>94</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Clinical subtype</th>
<th>n</th>
<th>18F-FDG-avid</th>
<th>Negative</th>
<th>% 18F-FDG avidity</th>
</tr>
</thead>
<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
FDG-PET detects more nodal and extranodal disease sites, than CT

The higher sensitivity leads to significant upward stage migration in 10-40%. In about half of these patients treatment strategy is changed

PET seems to be at least as sensitive as blind bone marrow biopsy in HD

Buchmann i et al Cancer 2001
Carr R Blood 1998
FDG-PET is more accurate

In HL and aggressive NHL FDG-PET is more accurate for diagnosing both nodal and extranodal disease than CT, thus having a strong potential impact on the staging.

Gastric lymphoma (lesser curvature)
Whether the changes in treatment strategy caused by FDG-PET will eventually lead to improvement in treatment outcome is at present unknown and being tested in randomized trials.
Response evaluation - general

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.

• Response has hitherto been based mainly on morphological criteria with a reduction in tumor size on CT as the most important factor.
PET-negative responders and PET-positive non-responders after 2 cycles of chemotherapy

Early treatment evaluation

FDG-PET after two cycles

FDG-PET negative
61 Patients, prog=3
2-year PFS 96%

FDG-PET positive
16 Patients, prog=11
2-year PFS 0%

CT after two cycles

Unsatisfactory remission
2 Patients, prog=0
2-year PFS 100%

Satisfactory remission
62 Patients, prog=11
2-year PFS 82%

CT cannot predict outcome

$P < .001$
Predictor of treatment outcome

• Several studies, in Hodgkin lymphoma and in aggressive non Hodgkin lymphoma, have showed that an *early* FDG-PET scan, after 1 to 3 cycles of chemotherapy, is a strong predictor of treatment outcome.
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
Post treatment evaluation

- 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

- FDG-PET is incorporated into the definition of end-of-treatment response evaluation (the International Harmonization Project)

Clinical example
Microscopic disease

- It is, however, clear that a negative FDG-PET scan after therapy does not exclude the presence of microscopic disease.

- The new recommendations for response criteria are not as yet supported by clinical data, and long-term follow-up of lymphoma patients evaluated by these criteria is awaited with great interest.
Quantitative assessment

Semiquantitative analysis using standardized uptake value (SUV) represents the metabolic activity of the tumor compared with that of surrounding tissue, corrected for injected dose and (usually) patient weight.
SUV
Standardized uptake value
a widely used, simple PET quantifier

\[ SUV = \frac{CPET(T)}{(Injected \ dose / body \ weight)} \]
SUVs

- 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
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


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 chemoinmunotherapy, 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 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.

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Abstract
One hundred and ninety-three hemato-oncologists and nuclear medicine specialists from 23 countries joined the 2-day Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in September 2011. Forty scientific posters were presented or discussed in the plenary session. Final results of international validation studies of Deauville criteria and change in maximum standardized uptake value (ΔSUV(MAX)) analysis in Hodgkin lymphoma (HL) as well as non-Hodgkin lymphoma (NHL) were reported. These studies were confirmatory of the prognostic value of interim positron emission tomography (PET) in 261 patients with advanced HL after two cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) when reported with the 5-point scale and in 120 patients with diffuse large B-cell lymphoma (DLBCL) after two cycles of a rituximab-containing immunochemotherapy regimen when using ΔSUV analysis. A preliminary consensus on interim PET was established among experts on the assessment of marrow response, refinement of scores 4 and 5 of the 5-point scale, the need to focus on interim PET results for NHL other than DLBCL, methods to compute ΔSUV and factors affecting ΔSUV measurements. Recommendations were given on how to use ΔSUV analysis in NHL taking into account the levels of initial SUV(MAX) and interim SUV(MAX). For the next meeting (October 2012), the majority of the audience strongly favored extending the topics, including in the workshop all aspects of PET in lymphoma, rather than just limiting it to interim PET.
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 (1).

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

Deauville 3 = FDG-positive SUV only for research

The reporters agreed that 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
The PET/CT South reporters agreed that it in addition to describing FDG uptake of the lesion(s), it may be useful to comment on the likely significance of the FDG uptake e.g.

**Clinical details:**
Hodgkin’s lymphoma (mediastinal nodes) post 6 cycles chemotherapy, residual mass.

**Findings:**
There is minimal residual FDG uptake (MRU) less than mediastinum (Deauville 2) in the mediastinal mass measuring 2cm x 2cm.

**Comment:**
There is minimal residual uptake in the mediastinal mass more likely due to sequelae of treatment than residual disease.

Wai Lup Wong
Gill Vivian
Sarah Wilson
Vicki Major

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The Deauville criteria – clinical application
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The Deauville criteria – clinical application
The Deauville criteria – clinical application
It is strongly recommended that

a baseline scan is available for comparison.

the scan is performed with either low-dose or diagnostic CT.

the time from chemotherapy to scan is no less than 10 days.
Ten days later: 11 cm abscess, communicating with duodenum.
The Role of PET in Lymphoma* 

Mollya S. Jamuar1 and David J. Stein2

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Malignant lymphomas are a heterogeneous group of diseases whose treatment and prognosis depend on accurate staging and evaluation of histologic features. The conventional imaging procedures is CT; however, nuclear medicine imaging has also had a prominent role. Single-photon imaging with 99mTc-diethylenetriamine pentaacetic acid (DTPA) has been widely used for lymphomas. PET with 18F-FDG has gained a role in the staging and follow-up of lymphomas, largely replacing gallium as the nuclear medicine study of choice. 18F-FDG PET has proved useful in the staging and follow-up of Hodgkin’s disease and non-Hodgkin’s lymphoma (especially more aggressive types), and the widespread use of PET/CT has also increased the sensitivity and specificity. It is useful for the staging of a low-grade lymphoma, but not for the staging of high-grade lymphoma. After the advent of staging and classification of lymphomas, it has been found that PET/CT is a useful tool in the management of patients with lymphomas. PET is more sensitive than 18F-FDG, such as positron-emitting isotopes of gallium, and the cell membrane marker 18F-fluorodeoxyglucose (FDG) will be discussed at future directions for PET in lymphoma.

Key Words: PET; Non-Hodgkin’s lymphoma; PET/CT

Malignant lymphomas are the fifth most frequently occurring type of cancer in the United States. In 2005, an estimated 73,350 new cases of Hodgkin’s disease (HD) and 56,300 new cases of non-Hodgkin’s lymphoma (NHL) were diagnosed (1). The NHLs are a heterogeneous group of diseases that vary in prognosis according to histologic and clinical features. We will begin by reviewing the classifications of HDs and NHLs.

HD Histologic Subtypes

There are 4 histologic subtypes of HD. Currently, the Rye modification of the Lukes and Butler classification is in use throughout the world. Nodular sclerosis is the most common subtype in North America and Western Europe.

NHL Tumoral Classification

The classification of NHL is continuing to evolve. In 1994, an international panel of pathologists published a Revised European-American Classification of Lymphoid Tumors (REAL classification) (2). Another international panel of pathologists made minor revisions to the REAL classification under the auspices of the World Health Organization in 1998 (3). This classification recognizes...
Routine long-term follow up is not recommended (subclinical disease). If transformation of Indolent NHL is suspected PET is recommended for biopsy guidance.
PET/CT in Lymphoma

FDG-avidity: high (exceptions)
Staging (nodal & extra nodal): yes
Response evaluation: yes
  Early / interim
  Post-treatment
Evaluation criteria: Deauville

- FDG-avidity is lower in indolent disease than in aggressive disease
- Upward stage migration in 10-40%
- Strong predictor of treatment Output (HL, aggressive NHL)
- Incorporated into the definition of end-of-treatment response (IHP)
- 5 point scale
  Work in progress

Work in progress