Recommendations for Initial Evaluation, Staging and Response Assessment of Lymphomas

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Disclosures

Nothing relevant to disclose.
Rationale for Staging

• Defines location and extent of disease
• Suggests prognostic information
• Directs choice of therapy
• Provides a baseline against which response is assessed
• Facilitates comparisons amongst studies
### CLINICAL CLASSIFICATION OF HODGKIN’S DISEASE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of only one lymph node region or a single lesion elsewhere, with no constitutional symptoms</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of two or more proximal lymph node regions confined to either upper or lower trunk, with or without constitutional symptoms</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of multiple lymph node regions with or without constitutional symptoms or acute Hodgkin’s disease with no obvious lymphatic involvement</td>
</tr>
</tbody>
</table>
Report of the Committee on the Staging of Hodgkin's Disease

SAUL A. ROSENBERG

Departments of Medicine and Radiology, Stanford University School of Medicine, Palo Alto, California

Report of the Committee on Hodgkin's Disease Staging Classification

Paul P. Carbone (Chairman), Henry S. Kaplan, Karl Musshoff, David W. Smithers, and Maurice Tubiana

National Cancer Institute, Bethesda, Maryland 20014 [P. P. C.]; Stanford University, Stanford, California 94305 [H. S. K.]; Roentgen-Radium-Abteilung, Freiburg, Germany [K. M.]; Royal Marsden Hospital, London, England [D. W. S.]; and Institut Gustave Rousset, Villejuif, France [M. T.]
SYMPOSIUM

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American Cancer Society
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and
with the Assistance of The Whiting
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STAGING
IN
HODGKIN'S DISEASE

Held at the
Towsley Center for Continuing Education
University of Michigan
Ann Arbor, Michigan
April 26–28, 1971
The History of Hodgkin’s Lymphoma Staging: Ann Arbor Classification

• Based on curative treatment with RT
• Assumptions
  – HL in early stages spreads contiguously
  – Extended field RT is treatment of choice
  – Combination chemo reserved for advanced disease – unproven efficacy/unknown toxicity
• Pathologic stage (PS) from staging laparotomy (N, H, S, L, M, P, O, D – +/-)
• Clinical stage (CS) without laparotomy

The Ann Arbor classification for describing the stage of Hodgkin’s disease at initial presentation has formed the basis upon which treatment is selected and has allowed comparison of results achieved by different investigators for almost two decades. A meeting was convened to review the classification and modify it in the light of experience gained in its use and new techniques for evaluating disease. It was concluded that the structure of the classification be maintained. It was particularly recommended: (1) that computed tomography (CT) be included as a technique for evaluating intrathoracic and in diaphragmatic lymph nodes; (2) that the criteria for clinical involvement of the spleen and liver be modified to include evidence of focal defects with two imaging techniques and that abnormalities of liver function be ignored; (3) that the suffix ‘X’ to designate bulky disease (greater than 10 cm maximum dimension) be introduced; and (4) that a new category of response to therapy, unconfirmed/uncertain complete remission (CR[u]), be introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance.

Cotswold’s Recommendations 1989

- CT scans were included
- Laparotomy no longer needed
- “X” designation for bulky disease
- Introduced “CRu”
The History of Imaging

- Lymphangiogram
- IV pyelogram
- Ultrasound
- Liver/spleen scan
- CT
- Gallium scan
- MRI
PET/CT SCANNING

Concept originated in 1974 by Hoffman and Phelps
Invented by Dr David Townsend and Dr Ron Nutt
First applied to lymphoma in 1990
Medical Invention of the year, TIME magazine 2000

By Cheson
Progression-free survival by the International Workshop Criteria and IWC plus PET

PET(CT) in Staging of HL

- First used in lymphoma assessment ~1990
- Incorporated into response criteria - 2007
- Increased sensitivity vs CT
- Should improve staging accuracy
  - Fewer patients overtreated
  - Fewer patients undertreated
- 2007 - Not yet incorporated into standardized staging criteria
- Already being used by some physicians
Issues With PET in Staging Lymphoma

- How do CT and PET compare?
- How often does PET alter stage/therapy/outcome?
- Can PET/CT replace (CE)CT scans?
- Can PET replace BM Bx?
- Should PET be incorporated into routine staging?
# Sensitivity/Specificity of PET vs CT in Hodgkin’s/NHL Staging

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>Newman (‘94)</td>
<td>16</td>
<td>PET</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Thill (‘97)</td>
<td>27</td>
<td>PET</td>
<td>100</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
<td>CT</td>
<td>77</td>
<td></td>
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<tr>
<td>Buchman (‘01)</td>
<td>52</td>
<td>PET (N)</td>
<td>99.2</td>
<td>100</td>
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<tr>
<td></td>
<td></td>
<td>CT (N)</td>
<td>83.2</td>
<td>99.8</td>
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<td></td>
<td></td>
<td>PET (E)</td>
<td>100</td>
<td>99.4</td>
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<td></td>
<td></td>
<td>CT (E)</td>
<td>80.8</td>
<td>99.4</td>
</tr>
<tr>
<td>Schaefer (‘04)</td>
<td>60</td>
<td>PET/CT</td>
<td>94</td>
<td>100</td>
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<tr>
<td></td>
<td></td>
<td>CT</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Hutchings (‘06)</td>
<td>99</td>
<td>PET/CT (N)</td>
<td>92.2</td>
<td>99.3</td>
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<tr>
<td></td>
<td></td>
<td>CT</td>
<td>82.6</td>
<td>98.9</td>
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# PET in Staging of HL

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Upstaging (%)</th>
<th>Downstaging (%)</th>
<th>Management Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangerter</td>
<td>1998</td>
<td>44</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Partridge</td>
<td>2000</td>
<td>44</td>
<td>41</td>
<td>7</td>
<td>25</td>
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<tr>
<td>Jerusalem</td>
<td>2001</td>
<td>33</td>
<td>10</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Weirauch</td>
<td>2002</td>
<td>22</td>
<td>18</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Munker</td>
<td>2004</td>
<td>73</td>
<td>29</td>
<td>3</td>
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<tr>
<td>Naumann</td>
<td>2005</td>
<td>88</td>
<td>13</td>
<td>8</td>
<td>20</td>
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<tr>
<td>Hutchings</td>
<td>2006</td>
<td>99</td>
<td>19</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Rigacci</td>
<td>2007</td>
<td>186</td>
<td>14</td>
<td>1</td>
<td>6</td>
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</table>

# PET in Staging NHL/HL

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Upstaging (%)</th>
<th>Downstaging (%)</th>
<th>Management Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchmann</td>
<td>2001</td>
<td>52</td>
<td>8</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Wirth</td>
<td>2002</td>
<td>50</td>
<td>14</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Raanani</td>
<td>2006</td>
<td>103</td>
<td>31</td>
<td>1</td>
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<tr>
<td>Elstrom</td>
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<td>61</td>
<td>18</td>
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<tr>
<td>Pelosi</td>
<td>2008</td>
<td>65</td>
<td>11</td>
<td>5</td>
<td>8</td>
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<tr>
<td>Karam</td>
<td>2006</td>
<td>17</td>
<td>41</td>
<td>0</td>
<td>29</td>
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<tr>
<td>Janikova</td>
<td>2008</td>
<td>82</td>
<td>NS</td>
<td>NS</td>
<td>18</td>
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<tr>
<td>Wirth</td>
<td>2008</td>
<td>42</td>
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<td>0</td>
<td>45</td>
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<tr>
<td>Le Dortz</td>
<td>2010</td>
<td>45</td>
<td>8</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Luminari</td>
<td>2013</td>
<td>142</td>
<td>11</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Difficulty in Interpreting “Change in Treatment”

- Most often not stated
- Surgery to RT
- Increased RT dose/field size
- RT to chemotherapy
- Increased cycles of chemotherapy
- Not contemporary treatment strategies
Contrast enhanced CT (ceCT)

Considered for
- measurement of nodal size
- radiation planning
- distinguishing bowel from nodes or assessing compression/thrombosis of central/mediastinal vessels if required at staging
Contrast enhanced CT (ceCT): *But*

- In practice many patients have separate ceCT before PET-CT
- If not, PET-CT with low dose contrast
- Full dose ceCT involves additional radiation, which should be considered when deciding which examination(s) to perform.
PET-CT For Staging and Early Response in HL (n=1214)

- RATHL (ceCT) and PET-CT staging compared
- Concordance in 80%
  - PET-CT upstaged 14% (BM 92, lung 11, multiple 12)
  - Downstaged 6%
  - ceCT identified 7 PET-CT-neg lesions (bowel, Liver, spleen)
  - BMBx – positive 0.4% where PET was negative

Closed Workshop:
Lymphoma pretreatment assessment and response criteria in the New Millennium: Beyond Ann Arbor

Tuesday, June 14, 2011 – USI Auditorium, Lugano University

Steering Committee: B.D. Cheson, R.I. Fisher, T.A. Lister, E. Zucca
Session Co-Chair – Sally Barrington
Overarching Goals of the Revision – Lugano Classification 2014

- Improve lymphoma patient evaluation
- Eliminate ambiguity
- Universally applicable
- Facilitate the comparison of patients and results amongst studies
- Simplify the evaluation of new therapies by regulatory agencies.

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


See accompanying article doi: 10.1200/JCO.2003.84.8880

ABSTRACT

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 position 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 Montreux, France, and the 12th ICML in Lugano, Switzerland. To update the international harmonisation project guidance relating to 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 18F-fluorodeoxyglucose–avid lymphomas in clinical practice and late-phase trials.

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INTRODUCTION

Advances in staging and response assessment of lymphomas have occurred with the introduction of prognostic indices, molecular profiling, and more accurate imaging, with the potential to improve disease characterization and treatment selection. The International Harmonisation Project (IHP) first published guidelines about the application of position emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) in lymphoma in 2007, and PET was integrated in revised response criteria. The field has continued to evolve, PET combined with computed tomography (CT) has replaced PET alone. Mounting evidence supports the central role of PET-CT in staging and response assessment in Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Multiple international studies are under way to investigate whether PET-CT response can be used to guide therapy to improve patient outcomes. Conceptual efforts have been made to standardize PET-CT methods and interpretation in the context of trials. A five-point scale (0–5), suited to assess differing degrees of response at risk- and end-of-treatment, has been developed to score images. This scale was recommended as the standard reporting tool at the First International Workshop on PET in Lymphoma in Montreux, France, in 2009.

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


See accompanying article doi: 10.1200/JCO.2013.63.6229

Abstract

The purpose of this work was to provide 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 Lymphomas in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiotherapists, pathologists, radiologists, and nuclear medicine physicians, representing major international clinical trial groups and centers and countries. Clinical and imaging subcommittees presented that conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphomas, 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 standard staging for PET-CT. A modification of the Ann Arbor descriptory terminology will be used for anatomic distribution of disease, and when the satellites or B symptoms for example, is included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and does not influence the stage of 9 or 10 or 1 more diffuse b-cell lymphomas. However, staging of HL and advanced stage HL may require a biopsy in some cases. The recommendations are based on consensus of the recommendations of the two working groups. Routine functional scans are not recommended. These recommendations should improve the ability to evaluate patients with clinical outcomes of clinical trials.
Staging of Lymphomas: The Lugano Classification

• PET-CT is the standard for FDG-avid lymphomas; CT is indicated for non-avid histologies (CLL/SLL, MZL, LPL, MF)
• Modified AA staging for disease localization; however, patients are treated according to prognostic and risk factors
• Suffixes A and B are only required for HL
• “X” no longer used
• Splenomegaly: >13 cm
• No BMBx in HL or most DLBCL

• If the diagnostic CT and PET are acquired on the same day, it is strongly recommended that the PET is performed prior to the CT with IV contrast as to not compromise PET results.

Hodgkin Lymphoma: Protecting the Victims of Our Success

Bruce D. Cheson, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC
See accompanying article on page 4508

The only saving grace of the present is that it’s too damned stupid to question the past very closely.
—H.P. Lovecraft

In few instances in oncology has progress been so methodical. Total nodal irradiation became subtotal, then extended field, and then involved field. Randomized trials demonstrated that regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine were more
Routine Bone Marrow Biopsy in Hodgkin Lymphoma

- 454 newly diagnosed pts
- Bone marrow involvement
  - 18% focal lesions by PET
  - 8% involvement by trephine
- No pt with BM+ had CS I-II by PET
- Pts with BM+ had other evidence of stage IV
- BM Bx upstaged 5 pts from III-IV
- No treatment decisions changed by BM Bx

BMBx and PET-CT in DLBCL

- 130 pts; 35 (27%) with BM involvement: 33 by PET, 14 by BMBx
- PET identified all positive BMs
- BX did not upstage any patients
- Sensitivity/specificity
  - PET-CT – 94%, 100%
  - BMBx – 40%, 100%
- Prognosis of PET+/Bx- similar to stage IV w/o BM involvement
- Pts with BM+ had other evidence of stage IV

PET-CT For Staging and Early Response in HL (n=1214)

- RATHL (ceCT) and PET-CT staging compared
- Concordance in 80%
  - PET-CT upstaged 14% (BM 92, lung 11, multiple 12)
  - Downstaged 6%
  - ceCT identified 7 PET-CT-neg lesions (bowel, Liver, spleen)
  - BMBx – positive 0.4% where PET was negative

BM Bx in the Staging of Lymphomas

- If PET-CT is performed, BM biopsy is no longer indicated for HL, and only for DLBCL if PET is negative and identifying discordant histology is important for patient management.

- BM remains part of staging for other histologies.
Revised Staging System for Primary Nodal Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>One node or group of adjacent nodes</td>
<td>Single extranodal lesion without nodal involvement</td>
</tr>
<tr>
<td>Stage II</td>
<td>Two or more nodal groups on the same side of the diaphragm</td>
<td>Stage I or II by nodal extent with limited, contiguous extranodal involvement</td>
</tr>
<tr>
<td>Bulky stage II</td>
<td>II as above with “bulky” disease</td>
<td>N/A</td>
</tr>
<tr>
<td>Advanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Nodes on both sides of the diaphragm</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Nodes above the diaphragm with spleen involvement</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Additional non-contiguous extranodal involvement</td>
<td></td>
</tr>
</tbody>
</table>


Abstract: Standardized guidelines for response assessment are needed to ensure comparability among clinical trials in non-Hodgkin’s lymphoma (NHL). To achieve this, two meetings were convened among United States and International lymphoma experts representing medical, hematology/oncology, 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 largest 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 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 cytometry, cyogenetic, 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 II trials are to identify therapies that will prolong the progression-free survival, 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.


STANDARDIZED RESPONSE criteria are essential for the conduct of clinical research. They facilitate interpretation of data, comparisons of the results among various clinical trials, and identification of new agents with promising activity, and provide a framework on which to evaluate new biologic and immunologic insights into the diseases being studied. The availability of uniform guidelines ensures a reliable analysis of comparable patient groups among studies and acquisition of similar data. Response criteria have been developed for patients with chronic lymphocytic leukemia,1,2 acute myelogenous leukemia,3 and Hodgkin’s disease (HD),4 and criteria are now standardized for solid tumors.5 In 1987, Dixon et al emphasized the need for uniform reporting of end points in clinical trials of patients with non-Hodgkin’s lymphomas (NHL) of particular importance were the complete remission rate, survival, time to treatment failure, and time to relapse of complete responders. Their recommendations were met with controversy that remained unresolved. Therefore, although the need for common reporting was obvious, the precise definitions of several major end points were neither provided nor uniformly adopted. A consequence is that there are currently no standardized response criteria for patients with NHL.

Recognizing this need, several United States lymphoma investigators from National Cancer Institute (NCI)-sponsored cooperative groups, the NCI, and the pharmaceutical industry collaborated in an effort to resolve the issues regarding response assessment in NHL. The result was a preliminary document that was subsequently reviewed and approved by European lymphoma experts.9 Eventually, a workshop was held at the NCI on February 28 to 28, 1997, with a subsequent meeting on May 16, 1997, to come to consensus on a standardized set of guidelines for response assessment in adult patients with indolent and aggressive NHL.

This report presents the recommendations from the NCI-sponsored international working group. These represent a

- Complete remission (CR)
- Complete remission/unconfirmed (CRu)
- Partial remission (PR)
- Stable disease (SD)
- Relapsed disease (RD)
- Progressive disease (PD)

Limitations of IWG Response Criteria

- Unclear/misinterpretations (e.g. CRu)
- Dependent on inadequate methods
  - Physical examination
  - CXR, CT scan, MRI
  - SPECT gallium
  - Visual bone marrow evaluation
Revised Response Criteria for Malignant Lymphoma


ABSTRACT

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 cytometry for definitions of response in non-Hodgkin’s and Hodgkin’s lymphoma. Standardized definitions of end points are provided.

Conclusion
We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new and more effective therapies to improve the outcome of patients with lymphoma.
Both PET cut-offs predictive of PFS

Score ≥3

Score ≥4

HR 3.9 (95% CI 2.5-5.9, p<.0001)
Median PFS:
16.9 (10.8-31.4) vs. 74.0 mo (54.7-NR)

Postinduction PET status (cut-off ≥4) and Overall Survival

HR 6.7, 95% CI 2.4-18.5, p=0.0002
Median OS: 79 months vs. NR

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

**markedly** increased uptake is taken to be uptake > 2-3 times the SUV max in normal liver

Deauville 1 – Pre-treatment

Courtesy S. Barrington
Deauville 2 – Pre-treatment

Courtesy S. Barrington
Deauville 3 – Pre-treatment

Courtesy S. Barrington
Deauville 3 – Post-treatment

Courtesy S. Barrington
Deauville 4 – Pre-treatment

Courtesy S. Barrington
Deauville 4 – Post-treatment

Courtesy S. Barrington
Deauville 5 – Pre-treatment

Courtesy S. Barrington
<table>
<thead>
<tr>
<th>CMR/CR</th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete Metabolic Response (CMR)</td>
<td>Complete Radiologic Response (ALL of the following)</td>
</tr>
<tr>
<td>Target Nodal/Extranodal</td>
<td>Score 1, 2, or 3* by 5-PS with or without a residual mass</td>
<td>Nodal Disease: ≤ 1.5 cm in LDi</td>
</tr>
<tr>
<td>Non-Target Spleen</td>
<td>Score 1, 2, or 3* by 5-PS with or without a residual mass</td>
<td>Extranodal Disease: Absent</td>
</tr>
<tr>
<td>New lesions</td>
<td>Score 1, 2, or 3* by 5-PS with or without a residual mass</td>
<td>Regress to normal</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No evidence of FDG-avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, IHC negative</td>
</tr>
<tr>
<td>Score of 3</td>
<td>Good prognosis with standard treatment (interim scan) for some</td>
<td></td>
</tr>
<tr>
<td></td>
<td>De-escalation is investigated→ may consider a score of 3 as inadequate response (to avoid undertreatment).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PMR/PR</th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Nodal/Extranodal</strong></td>
<td>Partial Metabolic Response (PMR)</td>
<td>Partial Remission (PR) (ALL of the following)</td>
</tr>
<tr>
<td>Score 4,5 with reduced uptake compared with baseline and residual mass(es) of any size.</td>
<td>&gt; 50% decrease from baseline in SPD of all Target lesions</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Target Spleen</strong></td>
<td></td>
<td>No Increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Spleen</strong>: &gt; 50% decrease from baseline in enlarged portion (value over 13cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Liver</strong>: no progression</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td><strong>Bone marrow</strong></td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Persistent focal changes in the marrow with nodal response,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Further evaluation with MRI or biopsy, or an interval scan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR/SD</th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Metabolic Response (NMR)</td>
<td>Stable disease</td>
</tr>
</tbody>
</table>
| Target Nodal/Extranodal | Score 4 or 5 with no significant change in FDG uptake from baseline, at interim or EoT. | • < 50% decrease from baseline in SPD of all Target lesions  
• No criteria for PD are met |
| Non-Target   |                                                                                        | No progression                          |
| Spleen       |                                                                                        | No progression                          |
| New lesions  |                                                                                        | None                                   |
| Bone marrow  | No change from baseline                                                                | Not applicable                          |

<table>
<thead>
<tr>
<th>PMD/PD</th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Nodal/Extranodal</td>
<td>Progressive Metabolic Disease (PMD)</td>
<td>ONE of the following</td>
</tr>
<tr>
<td></td>
<td>• Score 4, 5 with increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EoT</td>
<td><strong>PPD Progression:</strong> An individual node/lesion must be abnormal with: • LDi &gt; 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND <strong>An increase in LDi or SDi from nadir</strong> • ≥ 0.5 cm for lesions ≤ 2 cm • ≥ 1.0 cm for lesions &gt; 2 cm</td>
</tr>
<tr>
<td>Non-Target</td>
<td></td>
<td>Unequivocal Progression</td>
</tr>
<tr>
<td>Spleen/Liver</td>
<td></td>
<td>Unequivocal Progression: • Progression of existing Splenomegaly • New or Recurrent Splenomegaly • New or Recurrent liver involvement</td>
</tr>
<tr>
<td>New lesions</td>
<td></td>
<td>• Regrowth of previously resolved lesions • New node &gt; 1.5 cm in any axis • New extranodal site &gt; 1.0 cm in any axis • New extranodal site &lt;1.0 cm in any axis • Unequivocal/attributable to lymphoma. • Any size assessable disease unequivocal/attributable to lymphoma</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>New/recurrent FDG avid foci</td>
<td>New/recurrent involvement</td>
</tr>
</tbody>
</table>

Summary: What is New in Lugano

Response Criteria

- PET-CT for all FDG-avid histologies
- Deauville 5-point scale standard
- CR includes persistent nodes that are PET-negative in FDG-avid histologies
- CT-PR retains SPD 6 nodes/extranodal lesions
- Single lesion adequate for PD
Summary

• PET-CT has become the gold standard for staging FDG-avid lymphomas with low dose unenhanced CT
  – More sensitive than CT
  – At least as specific as CT
• Omitting ceCT reduces radiation by 50%
• Post-treatment scan is necessary for restaging
• Staging PET-CT improves interpretation of restaging scans
• Lugano staging criteria will improve patient outcome
Thank you!