THE LUGANO CLASSIFICATION

RECOMMENDATIONS FOR HODGKIN’S AND NON-HODGKIN’S LYMPHOMA: STAGING, RESPONSE ASSESSMENT AND FOLLOW UP

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RECOMMENDATIONS:
INITIAL EVALUATION
BACKGROUND

1971 Ann Arbor Classification

1988 Cotswolds modification

1999 NCI criteria

2007 IWG revised guidelines

2011 workshop at 11-ICML

2013 2nd workshop at 12-ICML

2014 Lugano Classification
11-ICML & 12-ICML WORKSHOPS

- Recommendations for initial evaluation, and response assessment of HL and NHL
- To update 2007 IHP criteria
- For use in clinical practice and late phase trials
- Two consensus paper in JCO 2014
OVERARCHING GOALS OF THE REVISION: Lugano Classification 2014

- Universally applicable
- Improve lymphoma patient evaluation
- Eliminate ambiguity
- Facilitate the comparison of patients and results amongst studies
- Simplify the evaluation of new therapies by regulatory agencies
Lugano classification:
Lymphoma disease compartments

- Nodal disease
- Extranodal disease
- Spleen/liver
- Clinical parameters
- Bone marrow
WHAT’S NEW IN THE LUGANO CLASSIFICATION?

- FDG-PET-CT
  - Standard staging for FDG-avid lymphomas
  - Response assessment in FDG-avid subtypes using the 5-point scale
- Progressive disease evaluation
  - PPD progression of single site defines progression. SPD eliminated for progression
- Spleen evaluation
  - Quantified: >13 cm is enlarged on CT
- Modification of the Ann Arbor Classification
- Bone marrow biopsy
  - No longer indicated for the routine staging of HL and most DLBCL
- Scan frequency
  - Routine surveillance scans are discouraged
WHAT’S THE LUGANO CLASSIFICATION DEALING WITH?

- **Initial evaluation**
  - Diagnosis
  - Patient evaluation
  - Anatomic stage
- **Staging criteria revision**
  - Imaging
  - Tumour bulk
  - Spleen liver and bone marrow involvement
- **Prognostic groups**
- **Assessment of response**
- **Follow up and surveillance**
INITIAL DIAGNOSIS

- Fine-needle aspirate is inadequate for initial diagnosis
- Excisional biopsy is recommended
- Core-needle biopsy may suffice when excision not feasible
## CRITERIA FOR INVOLVEMENT OF SITE

<table>
<thead>
<tr>
<th>Tissue site</th>
<th>Clinical</th>
<th>Type</th>
<th>Test</th>
<th>Positive finding</th>
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<tbody>
<tr>
<td>Lymph nodes</td>
<td>Palpable</td>
<td>FDG-avid</td>
<td>PET-CT</td>
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</tr>
<tr>
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<td></td>
<td>Non-avid</td>
<td>CT</td>
<td>Unexplained node enlargement</td>
</tr>
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<td>Spleen</td>
<td>Palpable</td>
<td>FDG-avid</td>
<td>PET-CT</td>
<td>Diffuse uptake, solitary mass, miliary lesions, nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-avid</td>
<td>CT</td>
<td>&gt;13 cm in vertical length, mass, nodules</td>
</tr>
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<td>Liver</td>
<td>Palpable</td>
<td>FDG-avid</td>
<td>PET-CT</td>
<td>Diffuse uptake, mass, nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-avid</td>
<td>CT scan</td>
<td>Mass, nodules</td>
</tr>
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Organomegaly is formally defined by CT

Splenomegaly is quantified >13 cm
# CRITERIA FOR EXTRANODAL SITES

<table>
<thead>
<tr>
<th>Tissue site</th>
<th>Clinical</th>
<th>Type</th>
<th>Test</th>
<th>Positive finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Signs, symptoms</td>
<td></td>
<td>CT scan</td>
<td>Mass lesion(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MRI</td>
<td>Leptomeningeal infiltration, mass lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSF assessment</td>
<td>Cytology, flow cytometry</td>
</tr>
<tr>
<td>Other (e.g., skin, lung, gastrointestinal tract, bone, bone marrow)</td>
<td>Site-dependent</td>
<td></td>
<td>PET-CT, Biopsy</td>
<td>Lymphoma involvement</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal status (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong></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><strong>Stage II bulky</strong></td>
<td>II as above with bulky disease</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Revised Staging System for Primary Nodal Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal status (E)</th>
</tr>
</thead>
<tbody>
<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>N/A</td>
</tr>
</tbody>
</table>
ABNORMAL/SUSPECTED DISEASE SITES

Abnormal Nodal Site
LDi >1.5 cm

Abnormal Extranodal Site
Present and consistent with lymphoma

Enlarged Liver
As judged by radiological interpretation on CT

Enlarged Spleen
>13 cm in vertical length (cranial to caudal)
IMAGING EVALUATION

• PET-CT is the standard for FDG-avid lymphomas
• CT is indicated for nonavid histologies
• CT based evaluation is preferred for
  - Histologies with low or variable FDG avidity
  - Regions of the world where PET-CT is unavailable.
• In absence of PET, mass that has decreased in size but persists is a PR
  - Need biopsy documenting absence of lymphoma to upgrade to CR
  - CRu (complete remission unconfirmed) is not a response category in the Lugano classification
## FDG AVIDITY ACCORDING TO WHO CLASSIFICATION

<table>
<thead>
<tr>
<th>Histology (patient numbers)</th>
<th>%FDG-avid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma (489)</td>
<td>97 - 100</td>
</tr>
<tr>
<td>Diffuse Large B cell lymphoma (446)</td>
<td>97 - 100</td>
</tr>
<tr>
<td>Follicular lymphoma (622)</td>
<td>91 - 100</td>
</tr>
<tr>
<td>Mantle cell (83)</td>
<td>100</td>
</tr>
<tr>
<td>Burkitt (24)</td>
<td>100</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma (37)</td>
<td>94 - 100</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma (80)</td>
<td>83 - 100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (31)</td>
<td>78 - 100</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma (93)</td>
<td>86 - 98</td>
</tr>
<tr>
<td>MALT (227)</td>
<td>54 - 81</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma (49)</td>
<td>47 - 83</td>
</tr>
</tbody>
</table>

FDG-AVID, NODAL LYMPHOMAS

- All histologies, except
  - Chronic lymphocytic leukaemia/small lymphocytic lymphoma
  - Lymphoplasmacytic lymphoma/Waldenstrom’s macroglobulinemia,
  - Mycosis fungoides,
  - Marginal zone lymphomas

- Unless there is a suspicion of aggressive transformation
## Disease Evaluation

<table>
<thead>
<tr>
<th>Measurable nodal site</th>
<th>Measurable extranodal disease site</th>
<th>Non-measurable disease sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDi &gt;1.5 cm</td>
<td>LDi &gt;1.0 cm</td>
<td>All other disease sites:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>♦ Nodal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>♦ Extranodal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>♦ Assessable disease</td>
</tr>
<tr>
<td><strong>Up to 6 measurable nodal/extranodal sites</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ♦ Largest target nodes, nodal masses or other lymphomatous lesions
- ♦ Measurable extranodal disease
- ♦ Measurable in two diameters (LDi and SDi)
- ♦ Represent different body regions/overall disease burden
- ♦ Include mediastinal and retroperitoneal disease, if involved

**Examples:**
- skin, GI, bone, spleen, liver, kidneys, effusions
CLINICAL EVALUATION
Systemic symptoms rarely direct treatment, their recurrence may herald disease relapse

**Lugano Classification:**

The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR
RECOMMENDATIONS: STAGING
PET-CT

Scans should be reported with visual assessment
Images scaled to a fixed SUV & colour table

- Noting location of foci in nodal & extranodal sites
- Distinguished from physiological uptake and other patterns of disease according to the distribution and/or CT characteristics
CONTRAST ENHANCED CT (CECT)

It rarely alters management, and can be reserved for:

- Measurement of nodal size for trials
- Radiation planning
- Distinguishing bowel from nodes
- Assessing compression/thrombosis of central/mediastinal vessels
CONTRAST ENHANCED CT (CECT)

- In practice many patients have separate CECT before PET-CT
- If not and CECT is required at staging, it should ideally be combined with PET-CT at a single visit
- Full dose CECT involves additional radiation, which should be considered when deciding which examination(s) to perform
# SPLEEN AND LIVER EVALUATION

Evaluate spleen and liver by PET-CT

<table>
<thead>
<tr>
<th>Spleen</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Use single measurement which correlates well with volume</td>
<td>♦ Liver size by physical examination or CT scan not a reliable measure of hepatic involvement by lymphoma</td>
</tr>
<tr>
<td>♦ Most studies use 10-12 cm for vertical length (cranial to caudal)</td>
<td>♦ Diffusely increased or focal uptake, with or without focal or disseminated nodules support liver involvement</td>
</tr>
<tr>
<td>♦ Lugano recommendation: Splenomegaly &gt;13 cm</td>
<td></td>
</tr>
</tbody>
</table>

- Lugano recommendation: Splenomegaly >13 cm.
BONE MARROW EVALUATION

• HL
  - If PET-CT is performed, bone marrow biopsy no longer indicated for HL

• DLBCL
  - Biopsy if the PET is negative and identifying a discordant histology is important for patient management

• Other subtypes
  - ~2.5 cm unilateral bone marrow biopsy is recommended, along with immunohistochemistry and flow cytometry at screening/baseline

• If involved at baseline
  - Must be normal for CR
  - No evidence of FDG-avid disease in marrow for CMR
Is prognostic in some lymphomas
Largest tumour diameter should therefore be recorded at staging whenever possible on CT in HL and NHL*
Measurements of total tumour volume should be explored as potential prognosticators with PET and CT

* Term X need no longer be used
RECOMMENDATIONS:
RESPONSE ASSESSMENT
PET-CT
(FDG-avid lymphomas)

- PET-CT is recommended for response assessment using 5-Point Scale (5-PS)
- If mid therapy imaging is performed, PET-CT is superior to CT
- Trials are currently evaluating the role of PET response adapted therapy
- Meantime it is not recommended to change treatment based solely on PET-CT unless there is clear evidence of progression
- Most data relate to HL, DLBCL & high tumour burden FL
5-POINT SCALE  
(DEAUVILLE CRITERIA)

<table>
<thead>
<tr>
<th>Score</th>
<th>18-FDG uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>≤ Mediastinal blood pool</td>
</tr>
<tr>
<td>3</td>
<td>&gt; Mediastinum and ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Moderately &gt; liver at any site</td>
</tr>
<tr>
<td>5</td>
<td>Markedly¹ &gt; liver at any site and/or new sites of disease</td>
</tr>
<tr>
<td>X</td>
<td>New areas of uptake unlikely to be related to lymphoma</td>
</tr>
</tbody>
</table>

1. i.e., maximum standardized uptake value (SUVmax) of the lesion >2x liver uptake
## FDG-PET EVALUATION

<table>
<thead>
<tr>
<th>Score 1 or 2</th>
<th>♦ Considered to represent complete metabolic response (CMR) at interim and end of treatment</th>
</tr>
</thead>
</table>
| Score 3     | ♦ Dependent on the timing of assessment, the clinical context and the treatment  
           | ♦ FDG uptake declines during therapy in chemosensitive disease and residual FDG uptake higher than normal liver uptake is frequently seen at interim in patients who achieve CMR at the end of treatment |
| Score 4 or 5 at interim | ♦ Suggests chemosensitive disease provided uptake has reduced from baseline and is considered to represent partial metabolic response |
| Score 4 or 5 at end of treatment | ♦ Represents residual metabolic disease even if the uptake has reduced from baseline |
TIMING OF PET-CT SCANS

Should be:

- As long as possible after the last chemotherapy administration for interim scans
- 6-8 weeks post chemotherapy at end of treatment ideally (but a minimum of 3 weeks)
- ≥ 3 months after radiotherapy
# FDG-PET EVALUATION

<table>
<thead>
<tr>
<th>2007 Guidelines</th>
<th>Lugano Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ PET scans based on visual interpretation and intended for end of treatment evaluation</td>
<td>◦ Use the 5-point scale (MBP and liver)</td>
</tr>
<tr>
<td>◦ Used mediastinal blood pool as the comparator</td>
<td>◦ Interim PET-CT to assess early treatment response</td>
</tr>
<tr>
<td></td>
<td>◦ end of treatment PET-CT to establish remission status.</td>
</tr>
</tbody>
</table>
## CT VS. PET: CMR/CR

<table>
<thead>
<tr>
<th>Lymph nodes and extralymphatic sites</th>
<th>PET-CT-based response Complete Metabolic Response (CMR)</th>
<th>CT-based response Complete Response (CR) ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 1, 2, or 3 with or without a residual mass on 5PS</td>
<td>Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease</td>
</tr>
<tr>
<td>Non-measured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Regress to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</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>Symptoms</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
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RESPONSE ACCORDING TO 5-PS

Score 1, 2 is Complete Metabolic Response (CMR)

Score 3 is also CMR with standard treatment
But in response-adapted trials exploring de-escalation, score 3 may be deemed inadequate response to avoid under-treatment
Interpretation of score 3 depends on timing of assessment, clinical context & treatment
HIGH PHYSIOLOGICAL FDG UPTAKE

Can occur in some sites…

e.g., Waldeyers ring, gut, bone marrow after chemotherapy or GCSF treatment with ‘physiologic’ uptake > normal liver

In this case, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue
RESPONSE ACCORDING TO 5-PS

Score 4, 5 with reduced uptake from baseline is partial metabolic response (PMR)
- At interim this suggests responding disease
- At end of treatment this indicates residual disease

Score 4, 5 with no change in uptake from baseline means no metabolic response (NMR)

Score 4, 5 with an increase in uptake from baseline &/or new lesions is progressive metabolic disease (PMD)
- At interim and end of treatment NMR and PMD indicates treatment failure
RESIDUAL MASSES

• Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered
  → interval scan can be considered where clinical likelihood of disease is low

• Residual size mass and location should be recorded in PET-CT reports where possible
  → as significance of the size of masses is unclear but may be complementary to metabolic information and data should be collected prospectively in clinical trials
PET-CT AND NEW THERAPIES

• Immunomodulatory agents may be associated with tumour flare or pseudo-progressions

• Biopsy or repeat assessment (> 2 weeks) are needed to determine if there is true PD
QUANTITATIVE METHODS FOR RESPONSE ASSESSMENT

• PET-CT quantitative methods (e.g. ΔSUV, MTV & TLG) may improve on visual assessment
  → require further validation in clinical trials
  → should be explored as prognosticators

• Standardisation of PET-CT assessment is mandatory for quantitative analysis of imaging parameters
  → and desirable for best clinical practice
PET-CT ROLE IN ASCT

PET-CT is prognostic in refractory & relapsed HL & DLBCL after salvage chemotherapy prior to HD chemotherapy & ASCT

PET-CT could be used:
- to select patients for HD chemotherapy & ASCT
- to identify poor prognosis patients
- as a surrogate endpoint to test novel therapies
- to current re-induction regimes
FOLLOW UP

- Clinical judgement, history & examination are cornerstones of FU
- FU is determined by histology, if patient is within a trial (or not) & clinical setting
- Frequency in **curable** lymphoma (e.g. HL, DLBCL) ↓ over time with ↓ likelihood of relapse
- Frequency of FU in **other** lymphoma (e.g. FL, MCL) ↑ over time as ↑ likelihood of recurrence
- Surveillance scans should be discouraged
- FP rate > 20% for surveillance PET leads to unnecessary investigations, radiation, biopsies, cost and anxiety
TIMING OF IMAGING EVALUATION

- **Limit the number of scans to which a patient is exposed**
- Clinical trials with time-dependent endpoints (e.g., PFS, EFS):
  - CT scan is determined by the study-designated interval
  - Indolent lymphomas, asymptomatic intra-abdominal or retroperitoneal disease progression may be a concern in patients with residual disease in those areas following therapy
- Published studies fail to support routine surveillance scans, and they are discouraged
- Follow-up scans should be prompted by clinical indications
SUMMARY OF IMAGING RECOMMENDATIONS
NEW since 2007

- PET-CT for staging of FDG-avid lymphomas
- HL and many DLBCL patients can be spared BMB
- PET-CT is recommended for mid-treatment assessment and for remission assessment
- The Deauville 5-PS is recommended for reporting response
- PD can be defined on a single site
- Splenomegaly is defined (13 cm on CT scan)
- Routine surveillance scans are discouraged
Thank you!
REFERENCES
