Lymphoma Imaging:
Diagnosis to Follow-up

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Outline

1. Clinical Background
2. Staging System
3. Imaging
   • Modalities
   • Staging
   • Treatment response
   • Surveillance
4. Cases
Classification: Hodgkin

- 10% of all lymphomas
- Characterized by the presence of (few) Reed-Sternberg cells in an inflammatory background
- Subtypes:
  - Classical (95%)
    - Nodular sclerosing
    - Mixed cellularity
    - Lymphocyte-rich
    - Lymphocyte-deplete
  - Nodular lymphocyte predominant (5%)

WHO classification 2008
<table>
<thead>
<tr>
<th>Type</th>
<th>B-cell</th>
<th>T-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent</strong></td>
<td><strong>Follicular (22%)</strong></td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td>Small lymphocytic/CLL</td>
<td>Primary cutaneous anaplastic large cell</td>
</tr>
<tr>
<td></td>
<td>Lymphoplasmacytic</td>
<td>Lymphoproliferative disease of large granular lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Marginal zone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>extranodal (MALT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nodal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>splenic</td>
<td></td>
</tr>
<tr>
<td><strong>Aggressive</strong></td>
<td><strong>Diffuse large B-cell lymphoma (31%)</strong></td>
<td>Peripheral T-cell, NOS</td>
</tr>
<tr>
<td></td>
<td>Mantle cell</td>
<td>Peripheral T-cell, specified</td>
</tr>
<tr>
<td></td>
<td>DLBCL with features intermediate between</td>
<td>Angioimmunoblastic (AILD**+-type)</td>
</tr>
<tr>
<td></td>
<td>DLBCL and Burkitt lymphoma</td>
<td>Nasal T/NK cell-type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous panniculitic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal enteropathy associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatosplenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaplastic large cell including null cell</td>
</tr>
<tr>
<td><strong>Very</strong></td>
<td><strong>B-cell Lymphoblastic</strong></td>
<td>T-cell Lymphoblastic</td>
</tr>
<tr>
<td><strong>Aggressive</strong></td>
<td>Burkitt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Double-hit lymphoma)</td>
<td></td>
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</tbody>
</table>

WHO classification 2008
Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>HL</th>
<th>NHL (variable depending on histology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Young adults</td>
<td>40-70 yo</td>
</tr>
<tr>
<td>B –Symptoms</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Spread</td>
<td>Contiguous nodal groups</td>
<td>Multiple remote nodal groups</td>
</tr>
<tr>
<td>Stage at</td>
<td>&gt;80% early (I &amp; II)</td>
<td>&gt;85% late (III and IV)</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal Groups</td>
<td>Thoracic: 65-85% 25-35% 5%</td>
<td>25-40% 45-55% 50-60%</td>
</tr>
<tr>
<td></td>
<td>Para-aortic: 25-35% 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesenteric: 5%</td>
<td></td>
</tr>
<tr>
<td>Extra-nodal</td>
<td>CNS: &lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>disease</td>
<td>GI: &lt;1%</td>
<td>5-15%</td>
</tr>
<tr>
<td></td>
<td>GU: &lt;1%</td>
<td>1-5%</td>
</tr>
<tr>
<td></td>
<td>BM: 5%</td>
<td>20-40%</td>
</tr>
<tr>
<td></td>
<td>Lung: 8-12%</td>
<td>3-6%</td>
</tr>
<tr>
<td></td>
<td>Bone: &lt;1%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
Workup

• H & P
• Blood work
  • CBC, diff, platelets, electrolytes, LFTs, uric acid, LDH, beta 2 microglobulin, SPEP, viral serologies for hepatitis B, C and HIV
• Initial imaging
• Tissue biopsy
• Staging scan
• +/- BM biopsy
Tissue Diagnosis

- Morphology, architecture, immunohistochemistry, flow cytometry +/- molecular studies
- **Excisional biopsy preferred**
- Core biopsy can be considered when excision is not possible. However, non-diagnostic sample must be followed by excisional biopsy
- **FNA is inadequate**
Staging

- Define location and extent
- Prognostic information
- Allow comparison among studies
- Provides baseline for assessing response or progression.
Staging

- Ann Arbor Classification
- Cotswold Classification
- Lugano Classification (2014)
* Tonsils, Waldeyer’s Ring, and spleen are considered nodal tissue
Staging - Qualifiers

- “Bulky / X”
  - Bulk is a negative prognostic factor for some lymphoma, but little agreement on its definition
  - Largest measurement of single nodal mass
  - **NHL**
    - Various threshold suggested (6-10 cm as cut-off)
  - **HL**
    - Single nodal mass > 10 cm or >1/3 of transthoracic diameter
  - None of the proposed sizes have been validated in current therapeutic era.
  - Lugano Classification: Give longest measurement rather than designation of “X” for bulky disease
  - BCCA: “X” still used. Stage II bulky disease in HL treated as advanced disease
Staging - Qualifiers

• “A / B”
  • A: absence of constitutional symptoms
  • B: presence of constitutional symptoms
    • Unexplained weight loss > 10% baseline during 6 months prior to staging
    • Recurrent unexplained fever > 38 degrees
    • Recurrent night sweats
“E” – Extra-nodal disease

- Only apply in the setting of limited disease
- Stage 1E = Single extranodal lesion without nodal involvement
- Stage 2E = Stage 1 or 2 by nodal extent with limited contiguous extranodal involvement
- Designation “E” is not applicable in stage 3 and 4
Staging

Limited
  • Stages I and II (non-bulky)

Advanced
  • Stages III and IV

Stage II bulky
  • Limited or advanced as determined by histology and number of prognostic marker
  • Usually treated as advanced
Staging – Bone Marrow Biopsy

- Previously standard in lymphoma staging
- Often performed even if likelihood of involvement is low

- **Hodgkin**
  - If PET-CT is performed, BMB is not required.

- **Non-Hodgkin (DLBCL)**
  - PET-CT more sensitive than BMB, but may miss low-volume diffuse involvement (<20%)
  - If PET-CT is positive and indicate bone marrow involvement, BMB is not required. However, it is still routinely performed in BC currently

- **Non-Hodgkin (Other)**
  - Data insufficient to change standard of practice
  - 2.5 cm unilateral BMB is recommended

Imaging

Goal:

1. Define local extent of clinically overt disease
2. To seek occult disease elsewhere

Primary modalities: CT and PET-CT
Other: X-ray, ultrasound, MRI
Computed Tomography

- High spatial resolution
- Detection of lymphadenopathy by size/morphology
- Staging scan:
  - Neck
  - Chest
  - Abdomen
  - Pelvis
PET-CT

• CT
  • Detailed anatomic information

• PET
  • Functional information

• Overall
  • More accurate than CT for staging in HL and NHL, with increased sensitivity, particularly extranodal disease
# PET-CT

## Studies Comparing PET or PET-CT With CT Alone for Staging of Lymphomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>PET or PET-CT</th>
<th>No. of Patients</th>
<th>Disease</th>
<th>Upstaging (%)</th>
<th>Downstaging (%)</th>
<th>Management Change (%)</th>
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<tbody>
<tr>
<td>Bangerter et al</td>
<td>1998</td>
<td>PET-CT</td>
<td>44</td>
<td>HL</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Partridge et al</td>
<td>2000</td>
<td>PET</td>
<td>44</td>
<td>HL</td>
<td>41</td>
<td>7</td>
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<td>Jerusalem et al</td>
<td>2001</td>
<td>PET</td>
<td>33</td>
<td>HL</td>
<td>10</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Weihrach et al</td>
<td>2002</td>
<td>PET</td>
<td>22</td>
<td>HL</td>
<td>18</td>
<td>0</td>
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<tr>
<td>Munker et al</td>
<td>2004</td>
<td>PET</td>
<td>73</td>
<td>HL</td>
<td>29</td>
<td>3</td>
<td>NS</td>
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<td>Naumann et al</td>
<td>2004</td>
<td>PET</td>
<td>88</td>
<td>HL</td>
<td>13</td>
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<td>Hutchings et al</td>
<td>2006</td>
<td>Mostly PET-CT</td>
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<td>HL</td>
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<td>Rigacci et al</td>
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<td>Mostly PET</td>
<td>186</td>
<td>HL</td>
<td>14</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Buchmann et al</td>
<td>2001</td>
<td>PET</td>
<td>52</td>
<td>HL (n = 27), NHL (n = 25)</td>
<td>8</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Wirth et al</td>
<td>2002</td>
<td>PET</td>
<td>50</td>
<td>HL (n = 19), NHL (n = 31)</td>
<td>14</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Raanani et al</td>
<td>2006</td>
<td>PET-CT</td>
<td>103</td>
<td>HL (n = 32), NHL (n = 68)</td>
<td>31</td>
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<td>25</td>
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<td>Eistrom et al</td>
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<td>PET-CT</td>
<td>61</td>
<td>HL and NHL</td>
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<td>Pelosi et al</td>
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<td>PET</td>
<td>65</td>
<td>HL (n = 30), NHL (n = 35)</td>
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<td>5</td>
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<td>Karam et al</td>
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<td>PET</td>
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<td>Janikova et al</td>
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<tr>
<td>Wirth et al</td>
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<td>PET</td>
<td>42</td>
<td>FL stages I-II on CT</td>
<td>29</td>
<td>0</td>
<td>45</td>
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<tr>
<td>Le Dortz et al</td>
<td>2010</td>
<td>PET-CT</td>
<td>45</td>
<td>FL</td>
<td>8</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Luminari et al</td>
<td>2013</td>
<td>PET-CT</td>
<td>142</td>
<td>FL</td>
<td>11</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abnormal PET CT
Pitfalls

• False negative
  Lesions smaller than 8mm
  Diabetes/Non-fasting patient
  Tumor histology

• False positive
  Granulomas and infections
  Adenomas
  Normal physiology
PET - CT

• CT component can be done in 2 ways:

<table>
<thead>
<tr>
<th>Full Dose with Contrast</th>
<th>Low Dose without Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Improve detection of abdominal and pelvic disease</td>
<td>-Lower radiation</td>
</tr>
<tr>
<td>-Helps with planning for RT</td>
<td>-Less error in measurement of FDG uptake in tumor (10-15% overestimation with contrast)</td>
</tr>
<tr>
<td>-Accurate nodal measurement for trial purposes</td>
<td></td>
</tr>
</tbody>
</table>

* Rare alters management*

**Recommendation**: ceCT ideally should occur during single visit in combination with PET-CT as baseline, if not already performed. Baseline findings will determine whether cePET-CT or lower-dose unenhanced PET-CT will suffice for additional exams.

Chest X-ray

- Cheap and accessible
- No added information compared to CT
- Initial imaging that raises suspicion for lymphoma
- BCCA
  - Often performed on follow-up visits after treatment
Ultrasound

- Limited role
- Provide guidance for biopsy
- Primary modality for evaluation of testicular lymphoma
- Non-specific appearance on US
MRI

- Limited availability. Not routinely used for staging.
- Accuracy overall comparable to CT in staging
- Detection of lymphadenopathy by size
- Compared to CT:
  - Superior to CT for CNS and bone marrow
  - Inferior to CT for thorax
- Whole-body MRI and diffusion-weighted imaging are radiation-free alternatives (i.e. for children)
STAGING

PET-CT for FDG-avid lymphomas

CT for non-FDG-avid lymphomas
  - Small lymphocytic lymphoma
  - Lymphoplasmacytic lymphoma
  - Waldenstrom macroglobulinemia
    - Mycosis fungoides
    - Marginal zone NHL
      (unless suspicion for aggressive transformation)

Interim PET-CT (early treatment response)

- Ensure effectiveness of treatment and exclude possibility of progression
- iPET-CT is a strong prognostic indicator in HL and aggressive NHL
- Frequently performed in clinical practice and trials and is recommended by some international guidelines.
- No conclusive evidence that changing treatment based on iPET-CT improves outcome.
- Lugano classification: Do not change treatment solely on the basis of iPET-CT unless clear evidence of disease progression.
- In BC, the established guidelines are that interim PET scan will guide treatment in limited and advanced-stage Hodgkin lymphoma, and limited-stage aggressive NHL.

Limited-stage Hodgkin's BC approach

Stages 1 to 2A*
Non-bulky (<10 cm)

ABVD x 2

PET/CT

Negative PET (Score 1, 2)
ABVD x 2

Positive PET (Score 3, 4, 5)
Radiation therapy

*Stage 2B Rx following the advance-stage algorithm
Advanced-stage Hodgkin: BC approach

Stages 2B, 3 or 4
Stages 1 or 2 with bulky dz (≥ 10 cm)

ABVD x 2

PET/CT

Negative PET (Score 1, 2, 3)

AVD x 4

Positive PET (Score 4, 5)

ABVD x 4

Radiation Therapy
Limited-stage aggressive NHL: BC approach

Stages 1, 2
Non-bulky

R-CHOP x 3

PET/CT

Negative PET
(Score 1, 2)

R-CHOP x 1

Positive PET
(Score 3, 4, 5)

Radiation therapy
End of Treatment

- Lugano classification
  - PET-CT for FDG-avid lymphoma
  - CT for non-FDG-avid lymphoma
- BCCA
  - Start with CT (neck, chest, abdo, pelvis) for all histologies (limited resources)
  - If CT shows complete response, stop. (Usually PET would be negative)
  - If CT shows lesion > 2 cm, then get PET-CT
- PET-CT done at least 4-6 weeks after end of treatment to avoid false positive.

Criteria for Response

PET

- **Five point scale (Deauville Criteria)** validated for use at interim and end of treatment
- Scores the most intense uptake in a site of initial disease:
  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. Area of uptake unlikely to be related to lymphoma
Criteria for Response

PET

- 1 or 2 = complete metabolic response
- 3 = complete metabolic response at interim and good prognosis at completion
- 4 or 5 (with reduced uptake) = partial metabolic response
- Increase in FDG uptake, score of 5 with no decrease in uptake, and new FDG avid foci = treatment failure / progression
Criteria for Response

CT

• Complete response:
  • Target nodes/nodal masses regress <1.5 cm (in longest transverse diameter) and no extra-lymphatic sites of disease
  • Spleen regress to normal
Criteria for Response

CT

• Complete response:
  • Target nodes/nodal masses regress <1.5 cm (in longest transverse diameter) and no extra-lymphatic sites of disease
  • Spleen regress to normal

• Partial response:
  • >50% decrease in sum of product diameter of up to 6 target measurable nodes and extranodal sites
  • Spleen regressed > 50% in length beyond normal
Criteria for Response

CT

• Complete response:
  • Target nodes/nodal masses regress <1.5 cm (in longest transverse diameter) and no extra-lymphatic sites of disease
  • Spleen regresses to normal

• Partial response:
  • >50% decrease in sum of product diameter of up to 6 target measurable nodes and extranodal sites
  • Spleen regressed > 50% in length beyond normal

• Stable disease:
  • < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites
  • No criteria for progressive disease are met
Criteria for Response

CT

• Disease progression
  • Require at least 1 of the following
    1. New or increased adenopathy
    2. Splenic volume increase
    3. New or larger non-measured lesions
    4. Recurrent previously resolved lesion
    5. New extranodal lesion > 1cm in any axis
Follow-up / Surveillance

• Clinical surveillance (history, PE, labs)

• Routine surveillance scan is **discouraged**
  • PET-CT has false-positive rate of 20% leading to unnecessary investigations, radiation, biopsies, expense, and patient anxiety

• Follow-up scan should be prompted by clinical indication

• **Exception**: Indolent lymphomas, asymptomatic intra-abdominal or retroperitoneal disease progression may be clinically occult. Judicious use of scans can be considered.

Cases
Case 1 – Limited HL
Case 1 – CMR
Case 2 – 14 yo
Case 2
Case 2 – Advanced HL
Case 2 – CMR
Case 3
Case 3 – Limited HL
Case 3 – Partial Response
Case 4 – Limited HL
Case 4 – CMR
Case - DLBCL
Case - DLBCL
Case - DLBCL
Case - Progression
Extra-nodal Disease
Orbit
Nasopharyngeal NHL
Thyroid
Vertebral Body
Primary Bone Lymphoma
Gastric
Testicular
Take Home Points

• Excisional biopsy is preferred for diagnosis, although core-needle biopsy may suffice when not feasible. FNA is considered inadequate.

• For staging, PET-CT is the standard for FDG-avid lymphomas, whereas CT is indicated for non-FDG-avid histology.

• Staging (limited vs advanced) is only one of many factors guide treatment.

• The designation X for bulky disease is no longer necessary per Lugano Classification, but still used in BC.
Take Home Points

• In HL, if PET-CT is performed, a BMB is not indicated. However, BMB are still routinely done at diagnosis for patients with NHL in order to identify discordant histology.

• PET-CT should be used for response assessment in FDG-avid histology. However, CT is still first line due limited resource in BC.

• End of treatment PET-CT should be done at least 4-6 weeks after completion of therapy to avoid false positive.

• Surveillance scans after remission are discouraged.

• Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.
Lymphoma Imaging - PET

Sharon Gershony MD
UBC Radiology and Nuclear medicine Resident
BCCA Indications for FDG-PET in the Clinical Management of Adult Cancer Patients:

**Lymphoma**

1. Post-chemotherapy for patients with advanced stage aggressive non-Hodgkin lymphoma (including primary mediastinal large B cell lymphoma) and Hodgkin lymphoma with residual CT abnormalities or initial bulky (bulky = 10 cm or larger in any single diameter) disease to assess need for radiation therapy

2. Staging of Hodgkin lymphoma

3. Staging of aggressive non-Hodgkin lymphoma

4. PET to plan duration of chemotherapy for patients with limited stage (IA or IIA, non-bulky) Hodgkin lymphoma.

5. PET to plan duration and type of treatment for limited stage (IA or IIA, non-bulky) aggressive histology (diffuse large B cell, mantle cell, peripheral T cell) lymphoma.

**NOTE:** No defined indication in the routine evaluation of low grade lymphomas.
Deauville Criteria

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 uptake > mediastinum but ≤ liver
- Score 4 uptake > liver at any site
- Score 5 uptake > liver and new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

Moskowitz C H Hematology 2012;2012:397-401

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Other cancers given specific clinical indications, as approved by the BC Cancer Agency, on an individual basis

It is well recognized in clinical practice that there may be clinical scenarios that do not meet specific guidelines but where expert medical opinion indicates the procedure could have a major impact on patient management. PET scan referrals in these cases will be reviewed on an individual basis by physician representatives from the appropriate Provincial Tumor Group and the Functional Imaging department.

If approved by consensus, the patient will be offered participation in the study.

http://www.bccancer.bc.ca/PPI/PET/indications.htm