Disease 3

Non Hodgkin Lymphoma
Follicular Lymphoma

APPROVED
Non Hodgkin Lymphoma
Overview

**WHO classification:** 40 types of lymphoma that are defined or in provisional status. *We only need to know 3:* low grade, high grade, and intermediate grade. Look at chart. Note that it is hard to kill cells that aren't dying. Therefore, we don't cure low grade lymphomas.

<table>
<thead>
<tr>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis</td>
<td>Apoptosis + Proliferative</td>
<td>Proliferative Proliferative</td>
</tr>
<tr>
<td>Slow accumulating</td>
<td>Accumulating but active growth</td>
<td>Tremendously active growth</td>
</tr>
<tr>
<td>Treatable Not curable</td>
<td>Treatable Curable</td>
<td>Curable</td>
</tr>
</tbody>
</table>

Follicular Non hodgkin lymphoma.

Blend of the two types

Burkett's lymphoma.
Case 3

- 59 year old man with lymphadenopathy in the neck, supraclavicular area, inguinal area. He states that he has had LN for at least 18 months and they have waxed and waned.

- Physical examination:
  - LN: 1-2 cm LN in cervical, supraclavicular, axillary, inguinal areas
  - ABD: questionable enlargement of spleen

- LAB:
  - Hct: 32%
  - WBC: 8,250/mm³
  - Platelet: 187,000/mm³
  - LDH: 112 IU/dL
Low Grade NHL: Pathophysiology
Apoptosis Defective – Cells Accumulate

Apoptosis: Programmed cell death

Myeloid Stem Cell

Myeloblast
N. Promyelocyte
N. Myelocyte
N. Metamyelocyte
N. Band
Neutrophil

Apoptotic problem. End up with too many slow growing, non-dying cells.
Follicular Non Hodgkin Lymphoma Diagnosis

Ways to diagnose Follicular Non-Hodgkin Lymphoma:

- Morphology
- Immunophenotype
- Cytogenetics
Follicular Lymphoma

Pathology
Morphology: **Normal Lymph Node, B Cell Zone**

**B-cell follicles**

Normal lymph node with lymphoid follicles around edges of lymph node (cortex). Most follicles have germinal center (selecting B-cells that are going to be avid for particular antigens.) We don't see follicles in middle of the lymph node.
Morphology: **Follicular Lymphoma**

Gross Photo

See round nodules. This is not what normal lymph node looks like.
Morphology: Follicular Lymphoma

Lymphoid follicles expand and take up whole node because of abnormal germinal centers. There are too many and they are too big.

Normal lymph node  Follicular lymphoma
Microscopic: Follicular Lymphoma

Germinal centers are made up of "squiggled up cells". A follicular lymphoma cell looks like normal follicular center cell on a "cell to cell" basis, so you need the architecture to differentiate.

Remember: Patient had anemia. This could be a result of lymphoma involvement of bone marrow.
Follicular Lymphoma: Flow Cytometry

Generally small cells that don't scatter light. Antigens on surface are characteristic of cells born in germinal center with CD10 and CD 19.
Follicular Lymphoma: Flow Cytometry

Monoclonal kappa+

To determine if something is a lymphoma, you look for monoclonality. Normally you'll see some kappa and some lambda immunoglobulin light chain expression (2:1). In follicular lymphoma, you have predominantly one type.

Polyclonal (normal)
Follicular Lymphoma: Immunohistochemistry
t(14;18) $\rightarrow$ Bcl-2 over-expression

Characterized by translocation between chromosome 14 and BCL2. (Antiapoptotic molecule.) Keeps cell from dying.

Bcl-2 negative: Normal follicle center

Bcl-2 positive: Follicular lymphoma
Low Grade Lymphoproliferative Disease: Diagnosis

Immunophenotype: CD Markers

<table>
<thead>
<tr>
<th></th>
<th>CD5</th>
<th>CD2</th>
<th>CD3</th>
<th>CD19</th>
<th>CD20</th>
<th>SIg</th>
<th>CD11c</th>
<th>CD25</th>
<th>CD22</th>
<th>CD10</th>
<th>HLA-Dr</th>
<th>CD23</th>
<th>FMC7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Dim)</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>++</td>
<td>Br</td>
<td>-</td>
</tr>
<tr>
<td>MCL</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Br)</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Br)</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>FSC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Br)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HCL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Br)</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SLVL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++ (Br)</td>
<td>-</td>
<td>+/-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MBCL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>++</td>
<td>++ (Br)</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

++ = marker present in 80+%  
+  = marker present in 40-80%  
+/- = marker present in 10-40%  
- = marker present in <10%  
Br = bright

CLL = chronic lymphocytic leukemia
MCL = mantle cell lymphoma
PLL = prolymphocytic leukemia
PSC = follicular small cleaved NHL
HCL = hairy cell leukemia
SLVL = splenic lymphoma with villous lymphocytes
MBCL = monocytoid B-cell lymphoma

Major subdivisions of low grade lymphomas: treat and act the same. Here are the major cell surface markers they look at.
Non Hodgkin Lymphoma: Classification

**B-Cell Disease**

- CLL/SLL/prolymphocytic leukemia/mantle-cell lymphoma
- Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
- Splenic marginal-zone lymphoma
- Extranodal marginal-zone lymphoma, MALT type
- Nodal marginal-zone lymphoma
- Diffuse large B-cell lymphoma NOS
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Mediastinal large B-cell lymphoma
- Multiple myeloma/plasma cell leukemia
- Plasma cell neoplasm
- Plasmacytoma

This is the B-cell variety

- B-cell NHL
  - Precursor B-cell NHL
  - Mature B-cell NHL
## Non Hodgkin Lymphoma

### Overview

<table>
<thead>
<tr>
<th>Grade</th>
<th>Apoptosis</th>
<th>Proliferative</th>
<th>Treatability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade</td>
<td>Apoptosis</td>
<td></td>
<td>Treatable</td>
</tr>
<tr>
<td>Intermediate Grade</td>
<td>Apoptosis + Proliferative</td>
<td></td>
<td>Treatable and curable</td>
</tr>
<tr>
<td>High Grade</td>
<td>Proliferative</td>
<td></td>
<td>Curable</td>
</tr>
</tbody>
</table>

- **Apoptosis**
  - Low Grade: Apoptosis
  - Intermediate Grade: Apoptosis + Proliferative
  - High Grade: Proliferative

- **Proliferative**
  - Low Grade: None
  - Intermediate Grade: Accumulating but active growth
  - High Grade: Tremendously active growth

- **Treatability**
  - Low Grade: Treatable
  - Intermediate Grade: Treatable and curable
  - High Grade: Curable
## Low Grade NHL (follicular): Staging
### Anatomic

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>LN one location</td>
</tr>
<tr>
<td>II</td>
<td>LN 1+ locations, same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>LN on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Extranodal sites of disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms A</th>
<th>No symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms B</td>
<td>Fever, sweats, weight loss</td>
</tr>
<tr>
<td>E</td>
<td>Organ involvement adjacent to lymph node</td>
</tr>
</tbody>
</table>

Staging system adapted from Hodgkin diseases. **Doesn't work for NHL.** See lecture 3 to understand.
Manikin Used for Counting the Number of Involved Areas

- **CERVICAL**
  - PRE-AURICULAR
  - UPPER CERVICAL
  - MEDIAN OR LOWER CERVICAL
  - POSTERIOR CERVICAL
  - SUPRACLAVICULAR

- **AXILLARY**
  - AXILLARY

- **MESENTERIC**
  - CELIAC
  - SPLENIC (HEPATIC) HILAR
  - PORTAL
  - MESENTERIC

- **INGUINAL**
  - INGUINAL
  - FEMORAL

**OTHERS**: EPITROCHLEAR, POPLITEAL
**Low Grade NHL (follicular): Staging**  
(All dots are lymphoma)

Images of different stages. See slide 18 for the details.

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>IV</th>
<th>IIIE</th>
<th>IIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two sites of disease in the same region on the same side of the diaphragm</td>
<td>In the lung, away from lymph node.</td>
<td>Disease of both sides of the diaphragm and in lung next to lymph node</td>
<td>Disease in both in the neck and in the mediastinum and disease in lung right next to lymph node.</td>
<td></td>
</tr>
</tbody>
</table>
Study of almost 4,000 people: Unrelenting downhill course. 5% mortality/year. Clinical effort focused on keeping quality of life high and preventing deterioration of organ function.

**Figure 2.** Overall survival of the study population (n = 4167).
### Low Grade NHL (follicular): Prognosis

**FLIPI (Five Independent Factors)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adverse factor</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60 y</td>
<td>2.38</td>
<td>2.04-2.78</td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td>III – IV</td>
<td>2.00</td>
<td>1.56 – 2.58</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt; 12 g/dL</td>
<td>1.55</td>
<td>1.30 – 1.88</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>&gt; Upper limit normal</td>
<td>1.50</td>
<td>1.27 – 1.77</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>&gt; 4</td>
<td>1.39</td>
<td>1.18 – 1.64</td>
</tr>
</tbody>
</table>

1 point for each of the adverse factors. The more points the worse the disease prognosis.

LDH= Lactate dehydrogenase. Can be a marker of hemolysis. Ann Arbor Stage- staging based on HL.
Low Grade NHL (follicular): Prognosis
FLIPI (Five Independent Factors): SCORE

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number of factors</th>
<th>Distribution of Patients</th>
<th>5-year OS</th>
<th>10-year OS</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 – 1</td>
<td>36%</td>
<td>90.6</td>
<td>70.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37%</td>
<td>77.6</td>
<td>50.9</td>
<td>2.3</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>27%</td>
<td>52.5</td>
<td>35.5</td>
<td>4.3</td>
</tr>
</tbody>
</table>

We still can't define groups that do "really really well" and "really really poorly."
Low Grade NHL (follicular): Prognosis
FLIPI SCORE and SURVIVAL

As you can see, survival declines at a steady rate in all three groups. Hard to change these curves.
Non-Hodgkin’s Lymphomas: Statistics
SEER Incidence Rates by Year

SEER (Surveillance, Epidemiology and End Results program). Sample across hospital. Incidence of cancers. NHL has leveled off. He believes it was increasing because of chemicals in environment and that it’s leveled off because we are better about it now.
Non-Hodgkin’s Lymphomas: Statistics
SEER Incidence Rates by Age of Patient

The older we are, the more likely we are to get NHL.
Non-Hodgkin’s Lymphomas: Statistics
SEER Incidence Rates by Year by Diagnosis

Only diffuse large cell is increasing in frequency.
## Non-Hodgkin’s Lymphomas: Statistics

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk of being diagnosed</td>
<td>2.10%</td>
<td>1.76%</td>
</tr>
<tr>
<td>Lifetime risk of dying</td>
<td>0.99%</td>
<td>0.89%</td>
</tr>
</tbody>
</table>
## Non-Hodgkin’s Lymphomas: Statistics

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100,000 persons</td>
<td>19.5</td>
<td>12.4</td>
</tr>
<tr>
<td>White</td>
<td>20.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Black</td>
<td>16.0</td>
<td>8.7</td>
</tr>
</tbody>
</table>

To explain demographics, look at jobs associated with follicular lymphoma (farming, woodworking, manufacturing). These were traditionally jobs for white males.
Non-Hodgkin’s Lymphomas: Epidemiology Overview

- **15 cases per 100,000 per year in the United States**
  - 1/6600 people per year
  - 1/2000 people age > 50 per year
  - 1/960 people age > 80 per year

- **Life time risk**
  - **Diagnosis:** 2%
  - **Dying:** 1%

- **Incidence increasing:**
  - 8.6/100,000 in 1973
  - 10.5/100,000 in 1980
  - 15.3/100,000 in 1990
  - 15.6/100,000 in 1998
  - Incidence has leveled off.

- **Rises with age:**
  - 24 cases per 100,000 at age 50;
  - 104 cases per 100,000 at age 80
# Non-Hodgkin’s Lymphomas: Epidemiology By Category

Chemical agents, immune stimulation, immunosuppression, infectious agents linked to NHL.

<table>
<thead>
<tr>
<th>Chemical Agents</th>
<th>Immune stimulation</th>
<th>Immuno suppression</th>
<th>Infectious agents</th>
<th>Controversial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticide (Organo-phosphates, phenoxyacetic acid, chlorophenols)</td>
<td>Rheumatoid arthritis</td>
<td>Organ transplant</td>
<td>EBV</td>
<td>Diet high in animal protein</td>
</tr>
<tr>
<td>Solvents (benzene, butadiene, carbon tetrachloride)</td>
<td>Sjogrens</td>
<td>HIV/AIDS</td>
<td>HTLV-I</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Wood preservatives (creosote, pentachlorophenol)</td>
<td>Systemic lupus</td>
<td></td>
<td>Helicobacter pylori</td>
<td>Hair coloring products</td>
</tr>
<tr>
<td>Drugs (alkylating agents)</td>
<td></td>
<td></td>
<td>Chlamydia psittacosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Campylobacter jejuni</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C</td>
<td></td>
</tr>
</tbody>
</table>
## Non-Hodgkin’s Lymphomas: Clinical Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>54</td>
<td>56.8</td>
<td>29.8</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>1.3</td>
<td>1.0</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Usually none Related to LN</td>
<td>Usually none Related to LN</td>
<td>Symptoms related to location of LN</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td>Multiple LN in multiple locations LN are usually soft, multiple, matted</td>
<td>Single LN, often in single site, may be multiple LN harder</td>
<td>LN grow rapidly firm LN firm</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Low as disease progresses</td>
<td>Low as disease progresses</td>
<td>Low in end stages</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>Usually normal, may be high</td>
<td>Correlates with spread of disease</td>
<td>High and correlates with prognosis</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>K⁺, PO⁴, Uric acid normal</td>
<td>K⁺, PO⁴, Uric acid increased or normal</td>
<td>K⁺, PO⁴, Uric acid often increased</td>
</tr>
</tbody>
</table>

Clinical differences: LN= lymph node
In high grade lymphomas, get single, firm LN.
In low grade, get multiple soft LN.
Non-Hodgkin’s Lymphomas: Clinical Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow +</td>
<td>47%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Radiographs</td>
<td>Small, multiple LN in the mediast, hilar, retrocrural, RP, mesentery</td>
<td>Fewer, larger LN in the mediast, hilar, retrocrural, RP, mesentery</td>
<td>Abdominal and mediastinal masses, can be very large, single often</td>
</tr>
<tr>
<td>Complete response</td>
<td>don’t cure 73%</td>
<td>59%</td>
<td>48%</td>
</tr>
<tr>
<td>Median survival YR</td>
<td>7.2</td>
<td>1.5</td>
<td>.7</td>
</tr>
<tr>
<td>5 YR survival</td>
<td>70%</td>
<td>35%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Response doesn't always last.

Median survival is a year, but if you survive it, you survive "indefinitely"
Non Hodgkin Lymphoma (Follicular): Treatment Overview

- Chlorambucil
- Cyclophosphamide, vincristine, prednisone
- Cyclophosphamide, vincristine, doxorubicin, prednisone
- Fludarabine
- Fludarabine combinations
- Rituximab – monoclonal antibody added to above

- Many change rate of progression, recurrence, response
  BUT

- Only rituximab combinations change survival

Use lots of different combinations of drugs. Community moving towards Fludarabine.
Non Hodgkin Lymphoma (Follicular): Treatment

Overall Survival

Lister and Armitage, Clinical Oncology, 1995

Mortality 4-5% per year. 20% alive at 20 years.
Non Hodgkin Lymphoma (Follicular): Treatment

**Overall Survival vs Failure Free Survival**

**Failure free survival means that disease doesn't progress. Median survival is different than progression (slow).**

Low Grade Lymphoma
5 YR survival 70%
Median survival: 7.2 years
Overall survival much longer than failure free survival
Low Grade (Follicular) NHL

Summary

- Older patient
- Men more common than women
- Slowly accumulating lymphocytes
- Multiple small – soft – lymph nodes
- Slowly progressive
- Treatment controls disease, no cure
- 4% die of disease per year
Disease 4

Non Hodgkin Lymphoma
Diffuse Large Cell Lymphoma
History I

- 32 year old man with diffuse large cell B-cell NHL

- November, 2006, noted shortness of breath, cough, right sided chest pain
- PMD: CXR showed mass in the lung and scheduled for CT but...

- 12/6/06 – DUMC ED with shortness of breath
  - Clinical evidence for SVC syndrome
  - CT demonstrated large mediastinal mass
  - ECHO demonstrated pericardial fluid

- 12/9/06 – pericardial window placed and mediastinal mass biopsy was taken
History II

- 12/9/06 – pericardial window placed and mediastinal mass biopsy was taken – failure to wean from respirator

- 12/18/06 – Radiation 250 cGy per day x 2 days to mediastinal mass AP/PA

- Weaned from respiratory and extubated day 12/25/06 (day 17 of ventilatory support)

- FDG-PET – Positive
  - Mediastimum
  - Subcarinal
  - Spleen
  - periaortie
History III

- **PMH:**
  - Osgood-Schlatter disease

- **Family History:** non contributory

- **Social History:** Non contributory
Physical Examination:

- **Signs of SVC syndrome**
  - Plethora
  - Dilated veins

- No organomegaly

- No peripheral lymph nodes

Superior Vena Cava syndrome is the obstruction of blood flow through the SVC. It is a medical emergency. Most common symptoms include dyspnea, facial swelling, head fullness, cough, arm swelling, chest pain, dysphagia, orthopnea, distorted vision, hoarseness, stridor, headache, nasal stuffiness, nausea, pleural effusions and light headedness.
Laboratory Studies

- WBC 7,000   Hb 12.4   Plat 255,000
  - PMN 73%   Lym 17%   Mono 7%

- Comprehensive panel normal

- LDH 1117 U/L

Relatively normal other than LDH. LDH (marker of badness) was 5x upper limits of normal.
Pathology

- Biopsy mediastinal mass

- Large atypical lymphoid cells with open chromatin, several small distinct nucleoli and moderate amount of pale to clear cytoplasm

- Immunoperoxidase stains
  - BCL-2, BCL-6, MUM-1 positive
  - Myeloperoxidase and EBV negative
  - Ki-67 approximately 50%

- Diffuse Large Cell B-cell NHL
Radiographs

Usually don't see anything poking out from right mediastinum. Compressing trachea and bronchus. Enlarged cardiac silhouette is from pericardial effusion and tampanade.
CT: Pretreatment

At this level, we should only see the blood vessels. This is all neoplasm.
Aggressive NHL (DLC): Pathophysiology Not Proceed Through Development Cycle

Mature cells provide signals to myeloid stem cells to prevent overgrowth. In this case, however, cells don't mature/die.
Aggressive NHL (DLC): Pathophysiology and Aggressive Growth (Second Defect)
Diffuse Large Cell Lymphoma

Pathology
Morphologic features are variable from case to case as is the proportion of neoplastic large B cells.

Cells in DLBCL tend to be larger and have no architecture (wipes out nodal architecture). Diffuse growth pattern. Lots of variability in cytologic and histologic features.

Verigated appearance with large cells and small cells. (Large B-cell lymphoma with lots of reactive T cells in it.)
DLBCL: Immunohistochemistry

B-cell antigen positive, e.g., CD20

Make diagnosis with immunohistochemistry. CD20 is a marker of B cells. See the variability between individuals.
DLBCL: Molecular Techniques

- Gene expression profiles have shown that DLBCL derived from lymphoid follicle (germinal) centers may have a better prognosis than those that are non-GC derived.

- A small number of key gene products can be used to define GC origin using immunohistochemistry (IHC).
Using IHC to Define GC vs Non-GC Origin of DLBCL

- CD10
  - + GC B cell
  - - BCL6
    - + MUM1
      - + Non-GC B cell
      - - GCB cell
    - - Non-GC B cell

Translate expression data with diagnostic tools.
As stem cell develops in lymphoid system, you can see where it goes from a stem cell to the most mature plasma cell. In middle area, becomes activated cell before it becomes plasma cell. This is where **DLBCL happens**.

<table>
<thead>
<tr>
<th>Neoplasias:</th>
<th>Precursor B cell leukemias</th>
<th>B cell lymphomas/chronic lymphocytic leukemia</th>
<th>Waldenström's/myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TdT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Aggressive NHL:**

**Classification**

- T-cell NHL
  - Precursor T-cell NHL
  - Mature T-cell NHL
    - Mycosis fungoides / Sezary syndrome
    - Adult T-cell leukemia / lymphoma
    - Peripheral T-cell lymphoma
    - Angioimmunoblastic lymphoma
    - Subcutaneous panniculitis-like T-cell lymphoma
    - Anaplastic large-cell lymphoma
    - NK/T-cell lymphoma, nasal type / aggressive NK-cell leukemia
    - T-cell large granular lymphocytic leukemia
    - T-cell prolymphocytic leukemia
    - Enteropathy-type T-cell lymphoma
    - Hepatosplenic T-cell lymphoma
    - Cutaneous T-cell lymphoma NOS
    - Primary cutaneous anaplastic large-cell lymphoma
# Aggressive NHL (DLC): Classification

<table>
<thead>
<tr>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis</td>
<td><strong>Apoptosis + Proliferative</strong></td>
<td>Proliferative Proliferative</td>
</tr>
<tr>
<td>Slow accumulating</td>
<td>Accumulating but active growth</td>
<td>Tremendously active growth</td>
</tr>
<tr>
<td>Treatable</td>
<td>Treatable</td>
<td>Curable</td>
</tr>
<tr>
<td>Not curable</td>
<td>Curable</td>
<td></td>
</tr>
</tbody>
</table>

![Graphs showing survival analysis](image-url)
Aggressive NHL (DLC): Staging

International Prognostic Index

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>IV</th>
<th>IIIIE</th>
<th>IIE</th>
</tr>
</thead>
</table>

Diagram showing the staging of aggressive NHL (DLC) with different anatomical sites involved.
# Aggressive NHL (DLC): Prognosis

## International Prognostic Index

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristic</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 60</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>&gt; 60</td>
<td>41</td>
</tr>
<tr>
<td>Stage</td>
<td>I or II</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>III or IV</td>
<td>44</td>
</tr>
<tr>
<td>Site of Involvement</td>
<td>Extranodal ≤ 1</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Extranodal &gt; 1</td>
<td>37</td>
</tr>
<tr>
<td>Performance Status</td>
<td>Ambulatory (0 – 1)</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Non ambulatory (2-4)</td>
<td>35</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>≤ 1 x normal</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 x normal</td>
<td>44</td>
</tr>
</tbody>
</table>

International prognostic index. Five relevant factors. You either have the factor or you don’t. The more points, the worse the prognosis.
# Aggressive NHL (DLC): Prognosis

## International Prognostic Index

<table>
<thead>
<tr>
<th>Index</th>
<th>Risk Factor</th>
<th>Percent</th>
<th>CR (%)</th>
<th>Overall Survival 5 Yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 or 1</td>
<td>35</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Low Intermediate</td>
<td>2</td>
<td>27</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>High Intermediate</td>
<td>3</td>
<td>22</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4 or 5</td>
<td>16</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

Index helps direct treatment options.
Aggressive NHL (DLC): Statistics
Frequency

Frequency of Common NHL Subtypes in Adults

- Follicular (22%)
- Diffuse large B-cell (31%)
- Mantle cell (6%)
- Peripheral T-cell (6%)
- Marginal zone B-cell (6%)
- Marginal zone B-cell, nodal (1%)
- Lymphoplasmacytic (1%)
- Composite lymphomas (13%)
- MALT (5%)
- Other subtypes with a frequency <2% (9%)
Aggressive NHL (DLC): Statistics
Incidence per 100,000 People per Year
# Non-Hodgkin Lymphomas: Epidemiology By Category

<table>
<thead>
<tr>
<th>Chemical Agents</th>
<th>Immune stimulation</th>
<th>Immuno suppression</th>
<th>Infectious agents</th>
<th>Controversial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticide (Organo-phosphates, phenoxyacetic acid, chlorophenols)</td>
<td></td>
<td></td>
<td>EBV</td>
<td>Diet high in animal protein</td>
</tr>
<tr>
<td>Solvents (benzene, butadiene, carbon tetrachloride)</td>
<td></td>
<td></td>
<td>HTLV-I</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Wood preservatives (creosote, pentachlorophenol)</td>
<td></td>
<td></td>
<td>Helicobacter pylori</td>
<td>Hair coloring products</td>
</tr>
<tr>
<td>Drugs (alkylating agents)</td>
<td>Rheumatoid arthritis</td>
<td>Organ transplant</td>
<td>Chlamydia psittacosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sjogrens</td>
<td>HIV/AIDS</td>
<td>Campylobacter jejuni</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic lupus</td>
<td></td>
<td>Hepatitis C</td>
<td></td>
</tr>
</tbody>
</table>
## Aggressive NHL (DLC): Statistics Clinical

<table>
<thead>
<tr>
<th></th>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>54</td>
<td>56.8</td>
<td>29.8</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>1.3</td>
<td>1.0</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Usually none Related to LN</td>
<td>Usually none Related to LN</td>
<td>Symptoms related to location of LN</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td>Multiple LN in multiple locations LN are usually soft, multiple, matted</td>
<td>Single LN, often in single site, may be multiple LN harder</td>
<td>LN grow rapidly LN firm Abdominal masses</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Low as disease progresses</td>
<td>Low as disease progresses</td>
<td>Low in end stages</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>Usually normal, may be high</td>
<td>Correlates with spread of disease</td>
<td>High and correlates with prognosis</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>( K^+ ), ( PO_4^4 ), Uric acid normal</td>
<td>( K^+ ), ( PO_4^4 ), Uric acid increased or normal</td>
<td>( K^+ ), ( PO_4^4 ), Uric acid often increased</td>
</tr>
</tbody>
</table>
## Aggressive NHL (DLC): Statistics

### Clinical

<table>
<thead>
<tr>
<th></th>
<th>Low Grade</th>
<th>Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow +</td>
<td>47%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Radiographs</td>
<td>Small, multiple LN in the mediast, hilar, retrocrural, RP, mesentery</td>
<td>Fewer, larger LN in the mediast, hilar, retrocrural, RP, mesentery</td>
<td>Abdominal and mediastinal masses, can be very large, single often</td>
</tr>
<tr>
<td>Complete response</td>
<td>73%</td>
<td>59%</td>
<td>48%</td>
</tr>
<tr>
<td>Median survival YR</td>
<td>7.2</td>
<td>1.5</td>
<td>.7</td>
</tr>
<tr>
<td>5 YR survival</td>
<td>70%</td>
<td>35%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Cure 1/3 patients. If you get across median, you are going to be cured.
Aggressive NHL (DLC): Treatment National High Priority Study

Patients (%)

Years after registration

N  PD/Death  5-y Estimate (%)

CHOP 1972 225 170 33

MACOP-B 218 161 34

ProMACE-CytaBOM 233 168 36

m-BACOD 223 151 38

Give all the drugs you can with non-overlapping toxicity. 1975-1990.
Drug combinations (more drugs, more expensive, more dangerous).
Every institution had own regimen claimed better than CHOP.
Compared drugs. No regimen better than CHOP.

CHOP Chemotherapy

- Cyclophosphamide 750 mg/m² IV day 1
- Vincristine 1.4 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Prednisone 100 mg PO day 1-5
- Rituximab 375 mg/m² IV day 1
CHOP vs Rituximab-CHOP

Rituximab is about 10% better. Improvement in survival has been sustained.

Feugier (Coiffier, GELA)  J Clin Oncol; 23:4117-4126 2005
Aggressive NHL (DLC): Summary

- Single or multiple areas of involvement
- Activated lymphoid cell, high proliferative rate
- Cure possible in 50% of patients