Lymphoma

Objectives

• Review the diagnosis, natural history, treated course, therapeutic goals, possible complications, and prognosis of classical Hodgkin lymphoma.

• Review the diagnosis, natural history, treated course, therapeutic goals, and prognosis of “indolent” and “aggressive” non-Hodgkin lymphoma.
Cancer in the United States
New Cases and Deaths 2012

<table>
<thead>
<tr>
<th>Type</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>1,638,910</td>
<td>577,190</td>
</tr>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>28,170</td>
</tr>
<tr>
<td>Lung</td>
<td>226,160</td>
<td>160,340</td>
</tr>
<tr>
<td>Breast</td>
<td>229,060</td>
<td>39,920</td>
</tr>
<tr>
<td>Colorectal</td>
<td>143,460</td>
<td>51,690</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>79,190</td>
<td>20,130</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>9,060</td>
<td>1,190</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>70,130</td>
<td>18,940</td>
</tr>
<tr>
<td>Melanoma</td>
<td>76,250</td>
<td>9,180</td>
</tr>
<tr>
<td>Bladder</td>
<td>73,510</td>
<td>14,880</td>
</tr>
<tr>
<td>Kidney</td>
<td>64,770</td>
<td>13,570</td>
</tr>
<tr>
<td>Thyroid</td>
<td>56,460</td>
<td>1,780</td>
</tr>
<tr>
<td>Uterus</td>
<td>47,130</td>
<td>8,010</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,920</td>
<td>37,390</td>
</tr>
</tbody>
</table>

Siegel, CA Cancer J Clin 2012; 62: 10

Lymphoma
Introduction

- Heterogeneous group of malignant neoplasms arising from B-cells (~90%), T-cells, & NK cells (rare)
- Lymph nodes > bone marrow > blood >> organs
- Multiple distinct clinicopathological entities
- Variable manifestations, clinical behavior, management, and prognosis
Lymphoma
WHO Classification 2008

**Mature B-cell Neoplasms**
- Small lymphocytic lymphoma (chronic lymphocytic leukemia)
- Splenic marginal zone lymphoma
- Splenic lymphoma, unclassifiable
- Lymphoplasmacytic lymphoma
- Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Primary cutaneous follicle centre lymphoma
- Diffuse large B-cell lymphoma, NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary diffuse large B-cell lymphoma of the central nervous system
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Epstein Barr virus positive diffuse large B-cell lymphoma of the elderly
- Diffuse large B-cell lymphoma with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmaclastic lymphoma
- Large B-cell lymphoma arising in HfR8-associated multicentric Castleman disease
- Burkitt lymphoma
- B-cell lymphoma with features intermediate between diffuse large B-cell and Burkitt lymphoma
- B-cell lymphoma with features intermediate between diffuse large B-cell and Hodgkin lymphoma

**Hodgkin lymphoma**
- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

**Precursor Lymphoid Neoplasms**
- B lymphoblastic lymphoma (leukemia) NOS
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma, NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary diffuse large B-cell lymphoma of the central nervous system
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Epstein Barr virus positive diffuse large B-cell lymphoma of the elderly
- Diffuse large B-cell lymphoma with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmaclastic lymphoma
- Large B-cell lymphoma arising in HfR8-associated multicentric Castleman disease
- Burkitt lymphoma
- B-cell lymphoma with features intermediate between diffuse large B-cell and Burkitt lymphoma
- B-cell lymphoma with features intermediate between diffuse large B-cell and Hodgkin lymphoma

**Immunodeficiency-associated lymphoproliferative disorders**
- Lymphoproliferative diseases associated with primary immune disorders
- Lymphomas associated with HIV infection
- Post-transplant lymphoproliferative disorders
- Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

---

**Case 1**

**ID**
20 year old woman

**HPI**
Migratory pruritis for 6 months and painless, enlarging neck “lumps” for 2 months

**PE**
- Multiple, nontender, rubbery, mobile, 1-2 cm bilateral cervical lymph nodes
- Normocytic, normochromic anemia
- Cervical, supraclavicular, and mediastinal adenopathy plus splenic lesions
- No evidence of disease

---

Cleveland Clinic
Case 1
Question 1

Which procedure has the highest diagnostic yield?

a) Fine needle aspiration of an enlarged lymph node
b) Core needle biopsy of an enlarged lymph node
c) Excisional biopsy of an enlarged lymph node
**Lymphoma**

**Diagnosis**

- Biopsy required
  - Establish diagnosis
  - Determine type
- Biopsy types
  - Excisional
  - Incisional
  - Core needle (sometimes adequate)
  - Fine needle aspiration (rarely adequate)

**Hodgkin Lymphoma**

**Pathology**

- Derived from precursor B-cell
- Disrupted nodal architecture
- Reed-Sternberg cells or variants
- CD 30+, CD 15 +/-, CD 3-, CD 20-
- Non-malignant reactive background
Hodgkin Lymphoma
Clinical Presentation

• Young adults
• Asymptomatic
• Pruritis +/- rash
• B symptoms (fever, night sweats, weight loss)
• Cervical and supraclavicular adenopathy
• Anterior mediastinal mass

Case 1

ID 20 year old woman
HPI Migratory pruritis for 6 months and painless, enlarging neck “lumps” for 2 months
PE Multiple, nontender, rubbery, mobile, 1-2 cm bilateral cervical lymph nodes
Labs Normocytic, normochromic anemia
CT/PET Cervical, supraclavicular, and mediastinal adenopathy plus splenic lesions
BM No evidence of disease
Case 1
Question 2
What is the correct stage?

a) III A  
b) III B  
c) IV A  
d) IV B
Hodgkin Lymphoma
Ann Arbor Staging System

- Stage I  One lymph node region
- Stage II  More than one lymph node region on the same side of the diaphragm
- Stage III  More than one lymph node region on both sides of the diaphragm
- Stage IV  Extranodal site(s)

- A  No B symptoms
- B  B symptoms (unexplained fever >38°, drenching night sweats, and/or >10% unintentional weight loss < 6 months)

---

Hodgkin Lymphoma
Treatment Goals

- Cure the lymphoma
- Minimize side effects
**Hodgkin Lymphoma**

**Treatment  Disease Status and Stage**

- **Newly-diagnosed**
  - Stage I-II: Chemotherapy +/- radiation therapy
  - Stage III-IV: Chemotherapy

- **Relapsed/refractory**
  - Salvage chemotherapy followed by autologous hematopoietic progenitor cell transplantation

---

**Hodgkin Lymphoma**

**Prognosis  Disease Status and Stage**

- **Newly-diagnosed**
  - Stage I-II: 60-99%
  - Stage III-IV: 40-95%

- **Relapsed or refractory**: 20-80%
**Case 1**

**Question 3**

Which feature predicts a good prognosis?

a) Age 20 years  
b) Female sex  
c) Both age 20 years and female sex
Hodgkin Lymphoma
Prognosis  High Risk Features

• Male sex
• Stage IV
• Age ≥ 45 years
• WBC ≥ 15,000/mm$^3$
• Hemoglobin < 10.5 g/dl
• Serum albumin < 4 g/dl
• Lymphocyte count < 600/mm$^3$ or < 8%

Hodgkin Lymphoma
Prognosis  International Prognostic Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>5-year Freedom from Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
</tr>
<tr>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>≥ 5</td>
<td>42</td>
</tr>
</tbody>
</table>

Hodgkin Lymphoma
Complications

- Infection (bacterial, varicella-zoster virus)
- Cardiovascular and pulmonary disease
- Premature menopause and infertility
- Thyroid dysfunction and neoplasms
- Psychosocial dysfunction
- Secondary malignancies

Hodgkin Lymphoma
Summary

- Hodgkin lymphoma is curable
- Therapy is evolving
  - Maintain or improve cure rates
  - Minimize complications
- Monitor patients indefinitely
  - Recurrent disease
  - Complications
Case 2

**ID** 65 year old man  
**HPI** Several months asymptomatic neck “knots”  
**PE** Cervical, axillary, and inguinal adenopathy  
**Labs** CBC, differential, CMP, and LD – normal  
**CT** Diffuse non-bulky adenopathy

---

**Case 2**  
**Question 4**  
What is the most likely diagnosis?  

a) Mycosis fungoides  
b) Burkitt lymphoma  
c) Follicular lymphoma

---
Case 2
Question 4

What is the most likely diagnosis?

a) Mycosis fungoides
b) Burkitt lymphoma
c) Follicular lymphoma

Non-Hodgkin Lymphoma
Pathology

• Morphology
• Histology
• Immunophenotype
  – CD 19+, 20+ B cell
  – Kappa or lambda light chain restriction B cell
  – CD 3+ T cell
• Genotype
  – Ig gene rearrangement B cell
  – TCR gene rearrangement T cell
  – c-MYC translocation Burkitt
Non-Hodgkin Lymphoma
Clinical Presentation

• Incidence increases with age
• Asymptomatic or symptomatic
• B symptoms (fever, night sweats, weight loss)
• Adenopathy, splenomegaly, or mass
• Extranodal involvement (stomach, lung, skin, kidneys, liver, CNS, testis, bone, sinus, orbit)
• Anemia or thrombocytopenia

Non-Hodgkin Lymphoma
Clinical Classification

• Indolent
• Aggressive
Indolent Non-Hodgkin Lymphoma
Natural History and Treated Course

• Approximately 50% of NHL
  – Follicular lymphoma
  – Marginal zone lymphoma (nodal, MALT, splenic)
  – Small lymphocytic lymphoma (chronic lymphocytic leukemia)
  – Lymphoplasmacytic lymphoma (Waldenström’s)

• B-cell origin; express CD20
• Indolent clinical behavior
• May “transform” to more aggressive lymphoma
• Incurable (with few exceptions)
• Median survival ~10-20 years

Case 2
Question 5

Which statement about newly-diagnosed, follicular lymphoma has been proven true in prospective, randomized, controlled, clinical trials?

a) Immediate (vs delayed) treatment prolongs survival.

b) Intensive (vs mild) treatment prolongs survival.

c) Chemotherapy + rituximab anti-CD20 monoclonal antibody (vs chemotherapy alone) prolongs survival.
Case 2

Question 5

Which statement about newly-diagnosed, follicular lymphoma has been proven true in prospective, randomized, controlled, clinical trials?

a) Immediate (vs delayed) treatment prolongs survival.

b) Intensive (vs mild) treatment prolongs survival.

c) Chemotherapy + rituximab anti-CD20 monoclonal antibody (vs chemotherapy alone) prolongs survival.

Indolent Non-Hodgkin Lymphoma

Treatment Goals

• Alleviate symptoms
• Improve cytopenias
• Prevent complications
• Extend time off therapy
• Prolong survival
Indolent Non-Hodgkin Lymphoma

Treatment Options

• Expectant observation
• External beam irradiation
• Single agent or combination chemotherapy
• Monoclonal antibodies & radioimmunoconjugates
• Autologous hematopoietic progenitor cell transplant
• Allogeneic hematopoietic progenitor cell transplant

Indolent B-Cell Non-Hodgkin Lymphoma

Treatment  Rituximab

• Chimeric monoclonal antibody
• Binds specifically to CD20
• Induces apoptosis
• Activates CDC and ADCC
• Synergizes with chemotherapy
• Active in indolent & aggressive B-cell non-Hodgkin lymphoma
• Minimal side effects
Chemotherapy ± Rituximab
Phase III Clinical Trials in Follicular Lymphoma

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
<th>N</th>
<th>CR</th>
<th>ORR</th>
<th>PFS/EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>aU, III-IV, 1-3 FL</td>
<td>CVP x8</td>
<td>159</td>
<td>10%</td>
<td>57%</td>
<td>15 mo</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>CVP-R x8</td>
<td>162</td>
<td>41%*</td>
<td>81%*</td>
<td>34 mo*</td>
<td>83%*</td>
</tr>
<tr>
<td>bU, III-IV, 1-3 FL</td>
<td>MChlP x8 → IFN</td>
<td>96</td>
<td>25%*</td>
<td>75%</td>
<td>29 mo*</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>MChlP-R x8 → IFN</td>
<td>105</td>
<td>50%*</td>
<td>92%*</td>
<td>NR*</td>
<td>87%*</td>
</tr>
<tr>
<td>cU, II-IV, 1-3 FL</td>
<td>CHEP x12 + IFN</td>
<td>183</td>
<td>50%*</td>
<td>72%</td>
<td>37%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>CHEP-R x6 + IFN</td>
<td>175</td>
<td>67%*</td>
<td>81%*</td>
<td>53%*</td>
<td>84%</td>
</tr>
<tr>
<td>dU, III-IV, 1-2 FL</td>
<td>CHOP x6-8 → IFN/ASCT</td>
<td>205</td>
<td>17%</td>
<td>90%</td>
<td>32 mo</td>
<td>NR*</td>
</tr>
<tr>
<td></td>
<td>CHOP-R x6-8 → IFN/ASCT</td>
<td>222</td>
<td>20%*</td>
<td>96%*</td>
<td>NR*</td>
<td>87%*</td>
</tr>
<tr>
<td>eU, IV, LG NHL (70% FL)</td>
<td>FMD x8 → R → IFN</td>
<td>79</td>
<td>85%</td>
<td>96%</td>
<td>53%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>FMD-R x8 → IFN</td>
<td>82</td>
<td>88%</td>
<td>100%</td>
<td>69%*</td>
<td>96%</td>
</tr>
<tr>
<td>fRR, 1-3 FL</td>
<td>FCM x4 ± MR</td>
<td>31</td>
<td>23%</td>
<td>71%</td>
<td>21 mo</td>
<td>3.8 yr</td>
</tr>
<tr>
<td></td>
<td>FCM-R x4 ± MR</td>
<td>37</td>
<td>41%</td>
<td>95%*</td>
<td>NR*</td>
<td>NR*</td>
</tr>
<tr>
<td>gRR, 1-3 FL</td>
<td>CHOP x6 ± MR</td>
<td>234</td>
<td>16%</td>
<td>72%</td>
<td>20 mo</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>CHOP-R x6 ± MR</td>
<td>231</td>
<td>30%*</td>
<td>85%*</td>
<td>33 mo*</td>
<td>83%*</td>
</tr>
</tbody>
</table>


---

Case 3

ID 70 year old woman

HPI Fatigue, abdominal discomfort & mass; PS1

PE Right axillary adenopathy & huge LLQ mass

Labs WBC 15.4 with normal differential, Hgb 10.0, platelets 370, and LDH 897 (normal 100-220)

CT/PET Right axillary lymph nodes and massive retroperitoneal and mesenteric adenopathy

LN Bx Diffuse large B-cell lymphoma

BM Bx No evidence of lymphoma
Case 3
Question 6

This lymphoma is potentially curable.

a) True
b) False
Aggressive Non-Hodgkin Lymphoma
Natural History and Treated Course

• Approximately 50% of NHL
  – Diffuse large B cell lymphoma
  – Peripheral T cell lymphoma
  – Anaplastic large cell lymphoma
  – Lymphoblastic lymphoma
  – Burkitt lymphoma

• Aggressive clinical behavior
• Potentially curable

Aggressive Non-Hodgkin Lymphoma
Treatment Goals

• Alleviate symptoms
• Improve cytopenias
• Prevent complications
• Extend time off therapy
• Prolong survival
• Cure the lymphoma
Aggressive Non-Hodgkin Lymphoma

Treatment Disease Status and Stage

- Newly-diagnosed
  - Stage I-II: Chemotherapy ± radiation therapy
  - Stage III-IV: Chemotherapy

- Relapsed / refractory: Salvage chemotherapy followed by autologous hematopoietic progenitor cell transplantation

“CHOP” ± Rituximab for DLBCL

Treatment Prospective Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Endpoint</th>
<th>CHOP</th>
<th>R-CHOP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GELA&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Age 60-80</td>
<td>5 yr EFS</td>
<td>30%</td>
<td>54%</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td></td>
<td>Stage II-IV</td>
<td>5 yr OS</td>
<td>45%</td>
<td>58%</td>
<td>.0073</td>
</tr>
<tr>
<td>ECOG&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Age &gt; 60</td>
<td>3 yr FFS</td>
<td>46%</td>
<td>53%</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>Stage I-IV</td>
<td>3 yr OS</td>
<td>58%</td>
<td>67%</td>
<td>.18</td>
</tr>
<tr>
<td>MInT&lt;sup&gt;d,*&lt;/sup&gt;</td>
<td>Age &lt; 60</td>
<td>2 yr TTF</td>
<td>61%</td>
<td>80%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Low risk</td>
<td>2 yr OS</td>
<td>86%</td>
<td>95%</td>
<td>.0002</td>
</tr>
</tbody>
</table>

*CHOP-like (CHOP, CHOEP, MACOP-B, PMitCEBO)

---

<sup>b</sup>Habermann, *J Clin Oncol* 2006;24:3121
<sup>c</sup>Feugier, *J Clin Oncol* 2005;23:4117
<sup>d</sup>Pfreundschuh, *Lancet Oncol* 2006;7:379
Case 3
Question 7

Which one of this patient’s presenting features predicts a good prognosis?

a) Age 70 years  
b) Stage III  
c) Elevated LDH  
d) Good performance status

Cleveland Clinic
Aggressive Non-Hodgkin Lymphoma
Prognosis  High Risk Features

- Age > 60 years
- LDH > normal
- Performance status ≥ 2
- Ann Arbor stage III-IV
- Extranodal sites ≥ 2

Risk Factors  5-year Survival (%)
0-1  73
2  51
3  43
4-5  26

Non-Hodgkin Lymphoma

Summary

• Heterogeneous group of clinicopathological entities
• Multitude of clinical presentations
• Variable natural history and prognosis
• New treatments → improved survival

Hodgkin and Non-Hodgkin Lymphoma
New Active Therapeutic Agents

• FDA-approved for certain types of lymphoma
  – Proteasome inhibitor (bortezomib 2006)
  – Histone deacetylase inhibitors (vorinostat 2006, romidepsin 2009)
  – Chemotherapy (bendamustine 2008, pralatrexate 2009)
  – Antibody-drug conjugate (brentuximab vedotin 2011)

• FDA-approved but not for lymphoma
  – Immunomodulatory drug (lenalidomide 2005)
  – mTOR inhibitors (temsirolimus 2007, everolimus 2009)
  – Monoclonal antibody (ofatumumab 2009)

• Not yet FDA-approved for any indication
  – Monoclonal antibodies (obinutuzumab, galiximab, inotuzumab)
  – Other targeted agents (HDAC, mTOR, ATK, BTK, PI3K, & SYC inhibitors)
Lymphoma
Points to Remember

• The diagnosis of lymphoma requires a tissue biopsy.
• Patients with Hodgkin lymphoma are highly curable.
• The addition of rituximab to conventional chemotherapy has improved the survival of patients with B-cell non-Hodgkin lymphoma.
• T-cell non-Hodgkin lymphoma remains a challenge.
• Lymphoma survivors remain at risk for late treatment-related complications.

Lymphoma
Clinical Practice Guidelines

• National Comprehensive Cancer Network
• Clinical Practice Guidelines in Oncology™
• Hodgkin Lymphoma
• Non-Hodgkin Lymphoma
• www.nccn.org