LYMPHOMA

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WHO Classification of Hematological Neoplasms

Myeloid    Lymphoid    Histiocytic    Mast Cell

↓

B cell neoplasms *

T cell neoplasms

Hodgkin’s lymphoma

* Includes plasma cell myeloma
**B-Cell neoplasms**

**Precursor B-cell neoplasm**
- Precursor B-lymphoblastic leukemia/Lymphoma (precursor B-cell acute lymphoblastic leukemia)

**Mature (peripheral) B-cell neoplasm***
- B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (+/— villous lymphocytes)
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type

**Nodal marginal zone B-cell lymphoma (+/— monocytoid B cells)**
- Follicular lymphoma
- Mantle-cell lymphoma
- Diffuse large B-cell lymphoma
  - Mediastinal large B-cell lymphoma
  - Primary effusion lymphoma
- Burkitt’s lymphoma/Burkitt cell leukemia
**T-cell and NK-cell neoplasms**

**Precursor T-cell neoplasm**
- Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

**Mature (peripheral) T-cell neoplasms**
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia (HTLV1 +)
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma-delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Amaplastic large-cell lymphoma, T/null cell, primary systemic type

**Hodgkin’s lymphoma (Hodgkin’s disease)**
- Nodular lymphocyte-predominant Hodgkin’s lymphoma
- Classical Hodgkin’s lymphoma
  - Nodular sclerosis Hodgkin’s Lymphoma (grades 1 and 2)
  - Lymphocyte-rich classical Hodgkin’s lymphoma
  - Mixed cellularity Hodgkin’s lymphoma
- Lymphocyte depletion Hodgkin’s lymphoma

**NOTE:** Only major categories are included. Subtypes and variants will be discussed in the WHO book² and are listed in Tables 7 through 16. Common entities are shown in boldface type.

Abbreviations: HTLV1 +, human T-cell leukemia virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*B-and T-/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).
Clinical Grouping of Lymphomas

1. Indolent
2. Aggressive
3. Highly aggressive

Formerly
1. Low Grade
2. Intermediate Grade
3. High Grade
Clinical Grouping of Lymphomas

1. **Indolent** (≡ “low grade”)  
   - Follicular lymphoma Grade 1,2  
     22%  
   - Marginal zone lymphoma  
     - Nodal  
       1%  
     - Extranodal (MALT)  
       5%  
   - Small lymphocytic lymphoma  
     6%  
   - Lymphoplasmacytic*  
     1%  

*association with Waldenstrom’s macroglobulinemia
Clinical Grouping of Lymphomas

2. Aggressive (≡ “intermediate grade”)  
   - Diffuse large B-cell lymphoma  21%
   - Primary mediastinal large B cell lymphoma  2%
   - Anaplastic large T / null cell lymphoma  2%
   - Peripheral T cell lymphoma  6%
   - Extranodal NK / T cell lymphoma, nasal type
   - Follicular lymphoma Gd 3  
   - Mantle cell lymphoma  6%

Approximate International Incidence
Clinical Grouping of Lymphomas

3. Highly Aggressive (≡ "High grade")

- Lymphoblastic lymphoma 2%
- Burkitts lymphoma 1%
- Burkitt-like lymphoma 2%

Approximate International Incidence
Clinical Grouping of Lymphomas
(further simplified for radiation oncology exam purposes)

- **INDOLENT**
  - Follicular lymphoma Gd 1, 2
  - **MALT** (marginal zone lymphoma, extranodal (MALT type))

- **AGGRESSIVE**
  - Diffuse large cell
Lymphoma – Staging System
(Cotswold’s Meeting modification of Ann Arbour Classification)

I  Single lymph node region
   (or lymphoid structure) *

II 2 or more lymph node regions

III Lymph node regions on both sides of diaphragm

IV Extensive extranodal disease
   (more extensive then “E”)

Lymphoma – Staging System

Subscripts

A  Asymptomatic

B  Fever  
   Night sweats  
   Weight loss  
   > 38°, recurrent  
   drenching, recurrent  
   > 10% body wt in 6 mos

X  Bulky disease  
   ≥ 10 cm  
   or  
   > 1/3 internal transverse diameter @ T5/6 on PA CXR

E  Limited extranodal extension from adjacent nodal site
Lymphoma – Essential Staging Investigations

- Biopsy – pathology review
- History – B symptoms, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC
- creatinine, liver function tests, LDH, calcium
- Bone marrow aspiration & biopsy
- CT neck, thorax, abdomen, pelvis
Additional Staging Investigations

- PET or $^{67}$Ga scan
- CT / MRI of head & neck
- Cytology of effusions, ascites
- Endoscopy
- Endoscopic U/S
- MRI - CNS, bone, head & neck presentation
- HIV
- CSF cytology - testis, paranasal sinus, peri-orbital, paravertebral, CNS, epidural, stage IV with bone marrow involvement
**International Prognostic Index for NHL**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Criteria</th>
<th>Number of Risk Factors</th>
<th>5 yr OS*</th>
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<tbody>
<tr>
<td>Age</td>
<td>&gt; 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>3, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>ECOG ≥ 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>&gt; normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extranodal</td>
<td>&gt; 1 site</td>
<td></td>
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</table>

*Diffuse large cell lymphoma*
**Indolent Lymphoma**

e.g. Follicular Gd 1/2, small lymphocytic, marginal zone

**Limited Disease**
(Stage 1A, 2A if 3 or less adjacent node regions)

- IFRT* 30-35 Gy
- Expect ~ 40% long term FFR
- Alternate:
  - CMT
  - Observation. Treat when symptomatic.

* Involved Field Radiotherapy. Use 35 Gy for follicular. 30 Gy for SLL, marginal
Indolent Lymphoma

e.g. Follicular Gd 1/2, small lymphocytic, marginal zone

Advanced Stage

( some Stage 2, Stage 3, 4 )

- Palliative RT* for localized symptomatic disease
- Palliative chemotherapy** for disseminated symptomatic disease
- Observation only if low bulk, asymptomatic
  - Treat when symptomatic

* IFRT 15 – 20 Gy / 5
** CVP, chlorambucil
Aggressive Lymphoma (e.g. Diffuse large B cell)

Stage I, some Stage II
- CHOP* x 3 + IFRT (35-45 Gy)**
  Expect ~ 75% long term FFR

Stage III, IV, B symptoms, or bulky disease
- CHOP* x 6-8
  IFRT (35-45 Gy) to
  - sites of initial bulk
  - residual disease (i.e. PR)

* or CHOP-R (see next slide)

** higher radiation dose if residual disease
Aggressive Lymphoma (e.g. Diffuse large B cell)

CHOP q 21 days

- Cyclophosphamide
- doxorubicin (formerly Hydroxydaunorubicin)
- vincristine (“Oncovin”)
- Prednisone (p.o. x 5 days)

CHOP-R x 8 → ~40 % ↑ 3 yr EFS, OS (vs. CHOP x 8)
Extranodal Lymphoma

- Same treatment as nodal lymphoma

Notable Exceptions:
- Gastric MALT
- Testis
- CNS
- Skin
MALT = “mucosa associated lymphoid tissue”

MALT Lymphoma
≡ Marginal zone B-cell lymphoma of extranodal (MALT) type

• Stomach. assoc. with Helicobacter pylori infection*
• Salivary Gland. assoc. with Sjogren’s syndrome*
• Thyroid. assoc. with Hashimoto’s thyroiditis*
• Orbital (lacrimal, conjunctiva)
• Other: Waldeyer’s ring, breast, bladder, lung, skin

* → chronic antigen stimulation
**Gastric MALT Lymphoma**

- **Stage I^E^, H. pylori +**
  - → PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin)
  - F/U gastroscopy + Bx q6mo for 2 yrs, then q1yr

- **Stage I^E^, H. pylori - or antibiotic failure**
  - → IFRT 30 Gy (95% local control)

- **Stage 2 or higher**
  - → Treat as indolent lymphoma + H. pylori eradication
Hodgkin at ease
WHO Classification of Lymphoid Neoplasms

Hodgkin’s Lymphoma (≡ Hodgkin’s disease)

1. Nodular lymphocyte-predominant HL*
2. Classical HL
   • Nodular sclerosis HL
   • Lymphocyte-rich classical HL*
   • Mixed cellularity HL
   • Lymphocyte depletion HL

* formerly, both of these were classified as lymphocyte predominance Hodgkin’s Disease
Hodgkin’s Disease - Staging Investigations

- Biopsy – pathology review
- History – B symptoms, pruritus, alcohol pain, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC, ESR
- Creatinine, liver function tests, LDH, calcium, albumin
- Bone marrow aspiration & biopsy
  - if abnormal CBC, Stage 2B or higher
- CT thorax, abdomen, pelvis
Hodgkin’s Disease - Other Investigations

- PET scan
- $^{67}$Ga scan
- Lymphangiogram – if expertise available, no PET
- Pregnancy test
- oophoropexy / semen cryopreservation  
  – if chemotherapy or pelvic RT
- Dental assessment – if oropharyngeal RT
Hodgkin’s Lymphoma

- Early Stage
  - 1A, 2A

- Advanced
  - III, IV
  - Bulky Disease
  - B Symptoms
Hodgkin’s Lymphoma

Early Stage
1A, 2A

FAVOURABLE*
• 1-3 sites
• Age ≤ 40
• ESR < 50
• NS, LRCHL

UNFAVOURABLE*
• > 3 sites
• Age > 40
• ESR > 50
• Mixed cellularity

Advanced
III, IV
Bulky Disease
B Symptoms

*NCIC HD6 Study Criteria reflecting prognosis when treated with radiation only
Early Stage Hodgkin’s Lymphoma
Favourable Prognosis

• ABVD X 3 - 4
• IFRT 30 Gy / 20

• Fewer cycles ABVD may be adequate. GHSG HD10 study, in progress, compares ABVD x 2 vs. ABVD x 4

• Lower radiation dose may be adequate. GHSG HD10 study and EORTC H9 study, in progress, compare IFRT 20 Gy with 30 Gy (HD10) and 36 Gy (H9)

• Caution: late toxicity data awaited
Favourable Prognosis — Early Stage Hodgkin’s Lymphoma

Some Other Treatment Options

• **STNI**
  Mantle + Para-aortic nodes, spleen 35 Gy/20

• **ABVD x 2 + IFRT**

• **ABVD x 6**

• historical gold standard
  • survival \( \equiv \) CMT
  • use if CTx contraindicated
  • **but:** high risk late toxicity

• as per BCCA guidelines
  • awaiting clinical trial results (GHSG HD10)

• awaiting NCIC HD.6 results
Early Stage Hodgkin’s Lymphoma
Unfavourable Prognosis

- ABVD X 4 - 6
- IFRT 30 Gy / 20

• NB: Overlap with favourable prognosis ESHL
Advanced Stage Hodgkin’s Lymphoma
Stage 3, 4, B symptoms, bulky disease

- ABVD X 6 – 8*
- IFRT
  - sites of bulky disease
  - sites of residual disease (35 Gy / 20)

* ABVD until 2 cycles past maximum response
ABVD

- doxorubicin *(Adriamycin)*
- Bleomycin
- Vinblastine
- Dacarbazine

IV Days 1, 15
Very Favourable Prognosis
Hodgkin’s Lymphoma

• Stage 1A NLPHEL*
• Stage 1A high neck NS, LRCHL

→ IFRT 35 Gy / 20

*Nodular Lymphocyte Predominant HL
–usually localized, peripheral nodal sites
–good prognosis, but some late relapses (>10yr)
Hodgkin’s Lymphoma
Rough Approximation of Prognosis

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>80 – 90%</td>
<td>85 – 95%</td>
</tr>
<tr>
<td>Advanced</td>
<td>40 – 80%*</td>
<td></td>
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</tbody>
</table>

* Depending on Hasenclever Prognostic Index: based on Age>45, male, Stage 4, albumin < 4, Hb < 10.5, WBC<600 or >15000

If RT only (STNI): Deaths from 2nd malignancy > deaths from Hodgkin’s disease by 15 – 20 yrs
Side Effects of Radiotherapy for Hodgkin’s Lymphoma

1. Depend on
   - Dose/fractionation
   - Site
   - Irradiated volume
   - Chemotherapy

2. - Acute
   - Subacute
   - Late
Toxicity of STNI for Hodgkin’s Lymphoma

ACUTE

- Skin erythema
- Local alopecia
- Xerostomia
- Dysphagia
- Fatigue
- ↓ WBC, platelets
- Para-aortic RT - nausea, vomiting
  - diarrhea
Toxicity of EFRT for Hodgkin’s Lymphoma

SUBACUTE

• Fatigue
• Xerostomia
• Pneumonitis < 5%, dependent on lung volume treated
• Herpes Zoster
• Lhermitte’s Syndrome
Toxicity of STNI for Hodgkin’s Lymphoma

**LATE**

- Hypothyroidism
- Cardiac
  - (CAD, valvular disease, pericarditis)
  - 5% risk cardiac death in 20 yrs (2-3 x expected)
- 2nd malignancy (↑ risk of most solid tumors)
  - esp. breast ca if < 25 yrs at time of RT
  - Lung ca in smokers
  - Solid tumour risk rises after 10 years from RT
  - Absolute Excess Risk ~1% per year
52 y.o. male with dysphagia

Exam: posterior oropharyngeal mass involving L tonsil, L base of tongue, crossing over midline to involve R base of tongue.

Biopsy: “large cell lymphoma of T-cell derivation with differential diagnosis between nasal type extranodal T-cell lymphoma, and peripheral T-cell lymphoma of unspecified type.”
General Principles of Answering Lymphoma Questions - 2

• “First of all, I would take a complete history and perform a full physical examination…”

• “The pathology should be reviewed by an experienced lymphoma pathologist…”

• “This patient’s management should be discussed in a multidisciplinary setting*…”

*At least by haematologist / medical oncologist and radiation oncologist
Clinical Grouping of Lymphomas

2. **Aggressive** (≡ “intermediate grade”)

- Diffuse large B-cell lymphoma 21%
- Primary mediastinal large B cell lymphoma 2%
- Anaplastic large T / null cell lymphoma 2%
- Peripheral T cell lymphoma 6%
- Extranodal NK / T cell lymphoma, nasal type
- Follicular lymphoma Gd 3
- Mantle cell lymphoma 6%

Approximate International Incidence
“Aggressive” lymphoma

- CT head, neck, thorax, abdo, pelvis
- MRI head & neck
- CBC, creatinine, LDH, liver enzymes
- Bone marrow aspiration & biopsy
- HIV testing
- Dental consult
CT: “nodular defect arising from posterior aspect of pharynx extending into tonsillar region...3.5 x 1.5 cm...also a prominent nodular structure extending through base of tongue 3.5 x 2.5 cm.... Non-specific cervical lymph nodes, the largest 11 mm...”

No evidence of disease at other sites, normal lab work.
DM 005676

CHOP x 3

Why not CHOP-R?

Planning CT

Supine, in immobilization shell

GTV contoured
PTV: Waldeyer’s Ring. Lateral POP, 6 MV photons, compensators for dose homogeneity, 40 Gy / 20 / 4 wks
31 y.o. female with recent onset fatigue, night sweats, and mass in right neck

Seen in ER: R supraclavicular node ~2 cm

CXR: Huge ant mediastinal mass

Biopsy: Nodular sclerosis type Hodgkin’s disease

CT Chest: “Large, lobulated mass in anterior mediastinum extending from suprasternal notch to cardiophrenic angle…also an enlarged subcarinal node…”
Referral to Radiation Oncology

• History & Physical
• Pathology Review
• Discuss with Haematologist / Medical Oncologist
• CBC, ESR, creatinine, liver enzymes
• CT abdo-pelvis
• $^{67}$Ga scan
• Bone marrow aspiration & biopsy
Hodgkin’s Lymphoma, Nodular Sclerosis type
Stage IXB
ABVD x 8 cycles. Residual 4 x 6 cm ant. Mediastinal mass
CT simulation. GTV contoured. CTV = entire mediastinum with 2 cm lateral margin. Move breasts out of field. 6 MV photons. AP POP. 35 Gy / 20 / 4 weeks. Shielding after 25 Gy to protect heart.
26 y.o. female with one year history of intermittent chest pain.

CXR: Anterior mediastinal mass

CT: 6 x 7.5 cm anterior mediastinal mass. No other lymphadenopathy seen.

Biopsy: Non-Hodgkin’s Lymphoma, large cell type. Probably mediastinal sclerosing type.
Referral to Radiation Oncology

- History & Physical
- Pathology Review
- Discuss with Haematologist / Medical Oncologist
- CBC, LDH, creatinine, liver enzymes
- CT abdo-pelvis
- $^{67}$Ga scan
- Bone marrow aspiration & biopsy

What Stage is this patient?
Bulky disease on CXR. Stage IXA
CHOP x 6 cycles. 2 x 0.9 cm residual mass

RT to mediastinum: 40 Gy / 20