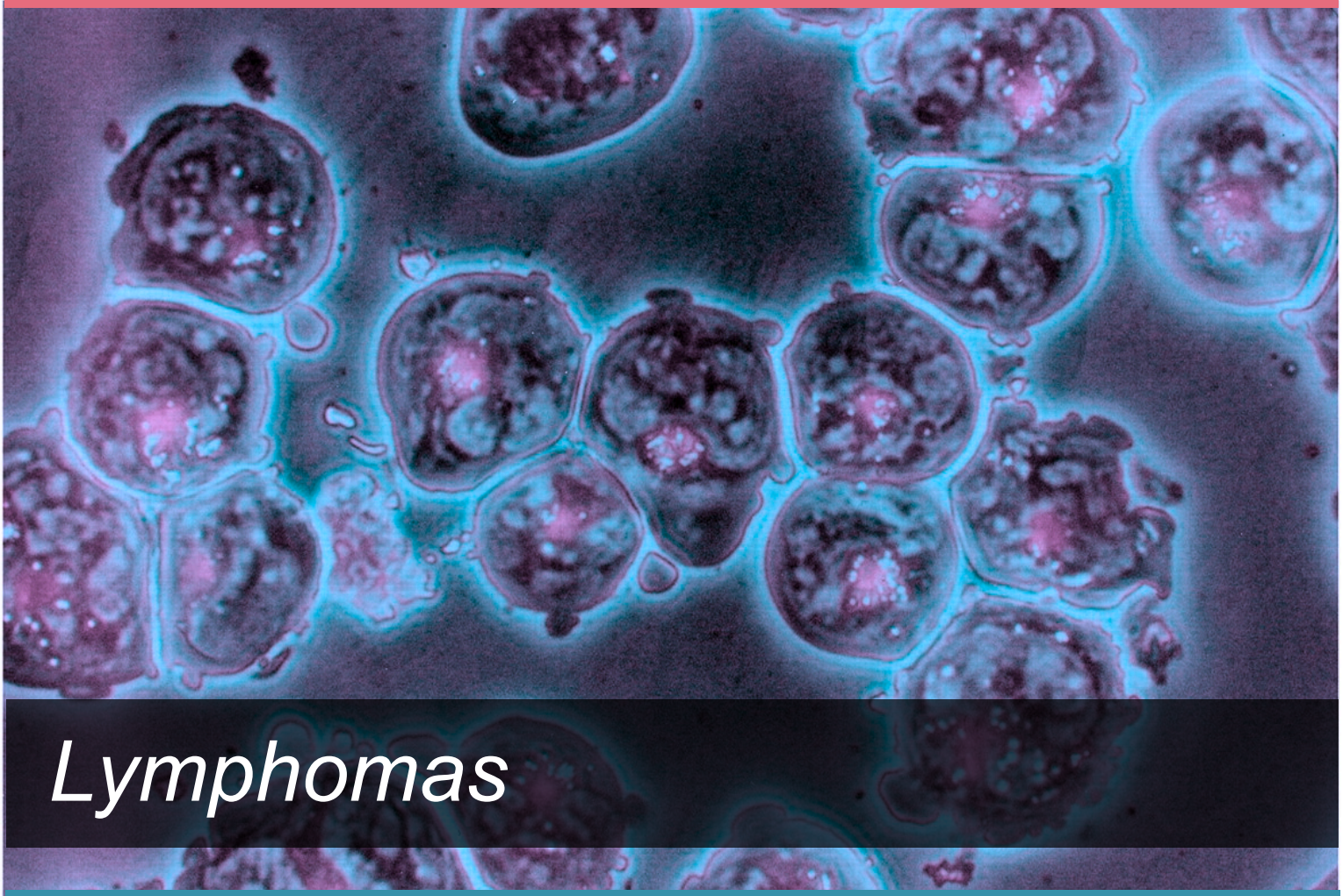

Lymphomas

429 Medicine Team

Sources: 427 Clinical Medicine Notes, Dr. Eyad Alsaeed's lecture, Step-Up to Medicine 7E, Kumar & Clark's Clinical Medicine 7E

Note: additional points from 427 Clinical Medicine & points the doctor did not stress on are in gray – do not ignore these, but focus on anything that is marked important. Notes from Step-Up are in orange boxes.

Questions/feedback: http://ask.fm/TeamNotes429

Lymphomas

Introduction

- *Lymphomas are commoner than the leukemias and are increasing in incidence for reasons that are unclear*
- *They arise as the result of abnormal proliferation of the lymphoid system, and hence occur at any site where lymphoid tissue is found*
- *Most common presentation: **lymphadenopathy** at single or multiple sites*
    - *Primary extra-nodal presentations account for up to 20% of non-Hodgkin's lymphoma*

- *Malignant lymphomas are the 5th most frequently occurring type of cancer in both genders in the western countries*
- ***2nd common cancer after breast and prostate CA in Saudi Arabia***
- *Lymphomas are clustered in some families*

Lymphomas are currently classified on the basis of histological appearance into:

- *Hodgkin's lymphoma*
- *Non-Hodgkin's lymphoma*

Now, classification is of immunophenotype NOT of morphology. The distinction between lymphoid leukemia & lymphoma is not always clear

WHO classification:

Don't memorize

B cell lymphomas	
Precursor B cell lymphoma	Precursor B lymphoblastic lymphoma/leukaemia (*highly aggressive*)
Mature B cell lymphoma	Chronic lymphocytic leukaemia/small lymphocytic lymphoma
	Lymphoplasmacytic lymphoma
	Splenic marginal zone lymphoma
	Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
	Nodal marginal zone B cell lymphoma
	Follicular lymphoma (*aggressive*)
	Mantle cell lymphoma
	Diffuse large B cell lymphoma (*aggressive*)
	Mediastinal (thymic) large B cell lymphoma
	Intravascular large B cell lymphoma
	Primary effusion lymphoma
	Burkitt's lymphoma/leukaemia (*highly aggressive*)
T/NK cell lymphomas	
Precursor T cell lymphoma	Precursor T cell lymphoblastic leukaemia/lymphoma (*highly aggressive*)
	Blastic NK cell lymphoma
Mature T/NK cell lymphoma	Adult T cell leukaemia/lymphoma (*very aggressive*)
	Extranodal NK/T cell lymphoma, nasal type
	Enteropathy-type T cell lymphoma
	Hepatosplenic T cell lymphoma
	Subcutaneous panniculitis-like T cell lymphoma
	Mycosis fungoides
	Sézary syndrome
	Primary cutaneous anaplastic large cell lymphoma
	Peripheral T cell lymphoma, unspecified (*aggressive*)
	Angioimmunoblastic T cell lymphoma
	Anaplastic large cell lymphoma (*aggressive*)

Table 9-16. Hodgkin's lymphoma - pathological classification

Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma:
Nodular sclerosis HL
Lymphocyte-rich HL
Mixed cellularity HL
Lymphocyte-depleted HL

Staging

IMPORTANT

Important for management plan

Table 1: Ann Arbor Staging System

Stage	Description
Stage I	***Involvement of a single lymph-node region or lymphoid structure*** *(e.g. spleen, thymus, Waldeyer's ring) or involvement of a single extra-lymphatic site*
Stage II	***Involvement of two or more lymph-node regions*** *on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extra-nodal organ or site and lymph-node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g. II_3)*
Stage III	***Involvement of lymph-node regions on both sides of the diaphragm*** *(III), which may also be accompanied by involvement of the spleen (IIIS) or by localized involvement of only one extra-nodal organ site (IIIE) or both (IIISE)*
III1	*With or without involvement of splenic, hilar, celiac or portal nodes*
III2	*With involvement of para-aortic, iliac and mesenteric nodes*
Stage IV	***Extensive extra-nodal disease.*** *Diffuse or disseminated involvement of one or more extra-nodal organs or tissues, with or without associated lymph-node involvement*
Designations applicable to any disease state (subscripts)	
A	*No symptoms*
B	*B symptoms: Fever (temperature > 38°C), drenching night sweats, unexplained loss of more than 10% of body weight within the previous 6 months*
X IMPORTANT	*Bulky disease (a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension >10 cm)* *In other words: >1/3 internal transverse diameter @ T5/6 (level of carina) on PA CXR. If >1/3 doesn't have to be >10 cm to be called bulky.*
E	*Involvement of a single (limited) extra-nodal site from adjacent nodal site*

Early

Advanced

Non Hodgkin's Lymphoma

Clinical grouping of NHL:

1. *Indolent (formerly low grade)*
   a. *Follicular lymphoma* Most Common, IMP *grade 1, 2*
   b. *MALT (marginal zone lymphoma, extra-nodal (MALT type)*
2. *Aggressive (formerly intermediate grade)*
   a. *Diffuse large B cell lymphoma*
3. *Highly aggressive (formerly high grade)*
   a. *Lymphoblastic lymphoma*
   b. *Burkitt's lymphoma*
   c. *Burkitt-like lymphoma*

- NHL occurs with the malignant transformation and growth of B or T lymphocytes or their precursors in the lymphatic system.
- B-cell lymphomas account for 85% of all cases; T-cell lymphomas 15%

NHL is twice as common as Hodgkin's disease. At presentation, patients with NHL tend to have more advanced disease than patients with Hodgkin's disease.

Clinical features

- *Lymph node enlargement, most often of the cervical nodes. These are usually painless and with a rubbery consistency. The pattern of spread is usually contiguous.*
- ***Systemic 'B' symptoms:*** *[Less common than in HL] fever (25%), drenching night sweats, weight loss of > 10% bodyweight.* IMP
- *Hepatosplenomegaly, abdominal fullness/pain*
- *Recurrent infections, symptoms of anemia or thrombocytopenia-due to bone marrow involvement*
- *Other constitutional symptoms, such as pruritis, fatigue, anorexia and, occasionally, alcohol-induced pain at the site of enlarged lymph nodes.*
- *Symptoms due to involvement of other organs (e.g. mediastinum - cough and breathlessness, superior vena cava obstruction)*

How many B symptoms do you need to suspect NHL?
Only one.
Fever in lymphoma vs. fever in TB:
Low-grade in TB ~37.8 °C, drenching in lymphoma (higher ~38-39 °C)

Important Staging Investigations

- ***Biopsy*** *(pathology review):* ***lymph node biopsy***
- *History – B symptoms, past history*
- *Physical Exam – nodes, liver, spleen, oropharynx*
- *CBC*
- *Creatinine, liver function tests, LDH, calcium*
- ***Bone marrow aspiration & biopsy***
- *CT neck, thorax, abdomen, pelvis*

Additional tests

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

Always start w/biopsy:
BUT: differentiate between infection & malignancy e.g. if young patient with flu symptoms, and enlarged node that is painful & fluctuating > don't biopsy, if persistent > biopsy.
Any lymph node >1 cm present for >4 weeks that cannot be attributed to infection should be biopsied
BM biopsy/aspiration:
Important in NHL > bone marrow invasion is common esp. stage IV
PET scan can give false +ve
Gallium scan:
Used to differentiate between active tumors vs. fibrosis. Low-sensitivity.
When is it useful?
If an initial scan was positive and correlated to the Dx made by CT & biopsy well – then a post-therapy scan would be useful.

International prognostic index of NHL

V.IMPORTANT

Age	*> 60*
Stage	*3, 4*
PS (performance status)	*ECOG ≥ 2*
LDH	*> Normal*
Extra-nodal	*> 1 site*

Eastern Cooperative Oncology Group's 0–4 PS assessment - question "How much of the day does the patient spend in bed?" 0 = normal activity;
1 = symptomatic without being bedridden;
2 = <50% bedtime;
3 = bedbound >50% of the day;
4 = bedbound all the time.

	Number of Risk Factors	5 yr OS*
Low Risk	**0-1**	**75%**
Low-Intermediate	**2**	**51%**
High-Intermediate	**3**	**43%**
High Risk	**4-5**	**26%**

*Diffuse large cell lymphoma

Types

Follicular lymphoma

The most common type of NHL

These comprise 20% (22%in other references) of all B cell lymphomas. Most patients with follicular lymphoma present feeling well but with painless lymphadenopathy. Investigation usually reveals multiple sites of disease: involvement of the bone marrow is common. Death occurs because of resistant disease, transformation to diffuse large B cell lymphoma (LBCL) or the effects of therapy. (Grade 1, 2)

The etiology of NHL is still unknown.

Risk factors for NHL

- HIV/AIDS
- Immunosuppression- e.g., organ transplant recipients
- History of certain viral infections (e.g., EBV, HTLV-I)
- History of *Helicobacter pylori* gastritis (risk of primary associated gastric lymphoma)
- Autoimmune disease- e.g. Hashimoto's thyroiditis or Sjogren's syndrome (risk of mucosa-associated lymphoid tissue [MALT])

Diffuse large B cell lymphoma (DLBCL)

The most common aggressive type of NHL

This is almost invariably fatal without therapy within months, and was previously classified as aggressive or high-grade lymphoma. Now > 50% of young patients are cured. The only indications for a palliative approach at the initial presentation are extreme co-morbidity and the will of the patient. Expectant management is inappropriate. Patients present with rapidly progressive lymphadenopathy and progressive infiltration of many organs, e.g. spinal cord, gastrointestinal tract

MALT Lymphoma

- *Marginal zone B-cell lymphoma of extra-nodal (MALT) type* IMP
  - *Stomach, associated with Helicobacter pylori infection**
  - *Salivary gland, associated with Sjogren's syndrome**
  - *Thyroid, associated with Hashimoto's thyroiditis**
  - *Orbital (lacrimal, conjunctiva)*
  - *Other: Waldeyer's ring, breast, bladder, lung, skin*

Chronic antigen stimulation

Testis Lymphoma

- *Usually aggressive histology*
- *Elderly patients, less tolerant of chemo*
- *High risk relapse \ need aggressive Rx*

High risk of:

- *Extra-nodal relapse*
- *Contra-lateral testis relapse > 40% by 15yrs*
- *CNS relapse > 30% 10yr actuarial risk*

Treatment of NHL

Indolent Lymphoma

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

No standard treatment – they probably won't ask about it

- *Limited Disease*
  - *(Stage 1A, 2A if 3 or less adjacent node regions)*
    - *IFRT* 30-35 Gy*
    - *Expect ~ 40% long term FFR* (freedom-from-relapse)
    - *Alternate:*
      - *CMT*
      - *Observation. Treat when symptomatic.*

IFRT: Involved Field Radio-therapy

- *Low-grade lymphomas: Cure is rare. Median survival is 5 to 7 years.*
- *Intermediate-grade lymphomas: Fifty percent of patients can be cured with aggressive therapy. Median survival is about 2 years.*
- *High-grade lymphomas: Up to 70% can be cured with aggressive therapy. Median survival without treatment is a few months*

- *Advanced Stage*
  - *(Some Stage 2, Stage 3, 4)*
    - *Palliative radiotherapy (IFRT 15 – 20 Gy /5) for localized symptomatic disease*
    - *Palliative chemotherapy (CVP, chlorambucil) for disseminated symptomatic disease*
    - *Observation only if low bulk, asymptomatic*
      - *Treat when symptomatic*

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)*

IMPORTANT
If stage 1 → chemo (short course, 3 cycles) then radio localized
If stage 2, 3 or 4 → chemo (longer course)
** Rule of radiation: Bulky or residual tumor (Local recurrence is less after radiotherapy)*

**Or CHOP-R (see next)*
*** Higher radiation dose if residual disease*

Very-high-dose chemotherapy with bone marrow transplantation is a last resort.

CHOP q 21 days

- *Cyclophosphamide*
- *Doxorubicin (formerly Hydroxydaunorubicin)*
- *Vincristine ("Oncovin")*
- *Prednisone (p.o. x 5 days)*

** The addition of rituximab (if CD20+ve) to CHOP chemotherapy reduces the impact of large masses*

Extra-nodal Lymphoma:

Same treatment as nodal lymphoma

Notable Exceptions:

- *Gastric MALT*
- *Testis*
- *CNS*
- *Skin*

V. IMPORTANT:
The sites
Treatment of gastric MALT

Rule: in NHL, even if stage I → give aggressive systemic therapy – why? Fear of microscopic extra-nodal disease

Gastric MALT Lymphoma

- *Stage I_E, H. pylori +ve*
  - *PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin)*
  - *F/U gastroscopy + biopsy every 6 months for 2 yrs, then yearly*
- *Stage I_E, H. pylori -ve or antibiotic failure*
  - *IFRT 30 Gy (95% local control)*
- *Stage II or higher*
  - *Treat as indolent lymphoma + H. pylori eradication*

Testis Lymphoma

- *All patients: Orchidectomy (diagnostic & therapeutic)*
  - *CHOP-R x 6*
  - *Scrotal radiation 30 Gy / 15*
- *Reduces risk testis recurrence to <10%*
- *Stage II: involved field nodal RT*
- *III & IV: CNS chemoprophylaxis*
  - *Intrathecal MTX*

Cutaneous Lymphoma

E.g. Primary Diffuse Large B-cell, Primary Cutaneous Anaplastic Large Cell and Mycosis Fungoides:*

- *Local RT effective for local control*

** Mycosis Fungoides usually treated initially with topical Rx*

Hodgkin's Lymphoma (HL)

- *This is a disease involving primarily the lymph nodes*
- *It occurs slightly more frequently in males than females with a ratio of 1.3: 1*
- *Over 90% will occur in **adults** between 16 and 65 years with the peak incidence in the 3rd decade. The incidence is stable.*

In KSA, Hodgkin's lymphoma is seen more in adults. But, younger populations are affected as well.

HL vs. NHL
- HL more commonly involves lymph nodes
- HL has a better prognosis; Reed-Sternberg cells do not pose a great threat

- *There a link between HL & previous infective mononucleosis and EBV (up to 40% of patients with HL have increased **EBV antibody** titres at the time of diagnosis and several years prior to the clinical development of HL)*
- *No clear-cut of the causes of lymphomas but we know that it's multi-factorial*

Pathology

- *The typical histologic picture for HD is that of a lymphoma with characteristic types of **Reed-Sternberg (RS)** cells (look like owl's eyes) in a background of non-neoplastic cells*
- *Often the RS cells form only a small proportion of the enlarged nodes. The RS cells are usually of clonal **B-cell** origin*
- *However, it has been difficult to study these cells because it is hard to grow these cell lines*

Classification of Hodgkin's Lymphoma (Hodgkin's disease)

1. ***Nodular lymphocyte-predominant HL***.
    a. ***(5% of cases)*** *contains malignant L and H cells (lymphocytic and/or histiocytic Reed-Sternberg cell variants, also called 'popcorn' cells). It is usually localized, peripheral nodal sites with good prognosis, but some late relapses (>10yr)*.
2. ***Classical HL (the first is with best prognosis):***
    a. ***Lymphocyte-rich HL appears in 5%*** *and is characterized by an infiltrate of many small lymphocytes and Reed-Sternberg cells. It often occurs in peripheral lymph nodes. It is often an indolent disease that presents at a higher median age.*
    b. ***Nodular sclerosing HL (70% of cases):*** *This is* ***the most common form****. Demonstrates a nodular growth pattern with many fibrotic bands present. This type is typically seen in young adults,* ***without*** *sex predominance. It involves particularly cervical and supraclavicular lymph nodes and the anterior mediastinum.*
    c. ***Mixed cellularity HL. Approximately 25%*** *of cases have mixed cellularity with lymphocytes, eosinophils, neutrophils and histiocytes. Reed-Sternberg cells are present but no fibrotic bands. It is more common in men and is associated with B symptoms (see below).*

Lymphocyte-depleted HL is rare and there is lack of cellular infiltrate with numerous Reed-Sternberg cells. It typically presents with advanced stage and B symptoms. It is seen in HL associated with HIV. It has the worst prognosis. [IMP]

Diagnosis

- ***Lymph node biopsy****—The presence of* ***Reed Sternberg cells*** *is* ***required to make the definite diagnosis.***
    - *Presence of inflammatory cell infiltrates—This distinguishes Hodgkin's lymphoma from non-Hodgkin's lymphoma (NHL). The inflammatory cells present are reactive to the Reed Sternberg cells. These include plasma cells, eosinophils, fibroblasts, and T and B-lymphocytes.*
- *CXR and CT scan (chest, abdomen, pelvis)—to detect lymph node involvement.*
- *Bone marrow biopsy— to evaluate bone marrow involvement.* ***Not as useful as in NHL.***
- *Laboratory findings— leukocytosis, eosinophilia; level of ESR elevation sometimes corresponds with disease activity, CBC (if abnormal CBC, Stage 2B or higher), creatinine, liver function tests, LDH, calcium, albumin*
- *History – B symptoms, pruritis, alcohol pain, PS*
- *Physical Exam – nodes, liver, spleen, oropharynx*

Other investigations include

- ***Positron emission tomography (PET****) is increasingly being used for staging, assessment of response and direction of therapy. Despite the fact that the evidence base is still quite small, and many hypotheses remain to be validated, there can be no doubt that it is a major advance in the management of lymphoma.*
- *^{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

IMPORTANT, *esp. in yellow boxes*

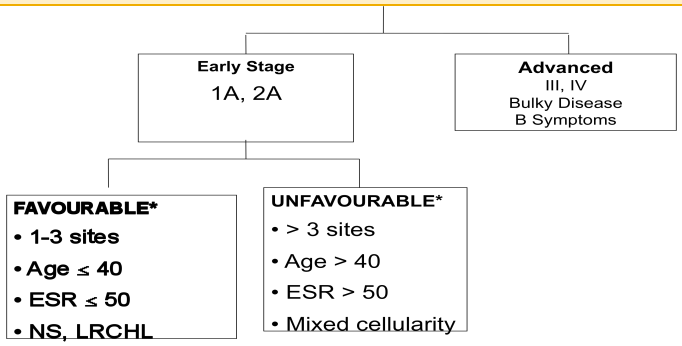

Figure 1

Management:

*Treatment is always given with a curative intent and consists of **radiotherapy**, **cyclical** combination **chemotherapy** or both. The choice of treatment depends on:*

- *Stage*
- *Involved sites*
- *'Bulk' of lymph nodes involved*
- *Presence or absence of 'B' symptoms*

Chemotherapy and radiation therapy in combination achieve cure rates of over 70% in Hodgkin's disease

- ***Standard care**: 'Moderate' chemotherapy, 2-4 cycles (i.e. non-sterilizing and low secondary cancer risk) followed by involved field irradiation (20-30 Gy) has become standard care*
- *The above approach fails for about 25% of patients. More intensive treatment programs have been tested, e.g. BEACOPP, with better results, but with greater toxicity profiles (and greater expense), and are clearly not necessary for the majority of patients*
- *An alternative is to develop a 'risk-adapted' therapy relying on an early assessment of response to 'minimal' therapy (ABVD) and escalating as appropriate*
- *In case of recurrent HL, it is conventional to consolidate remission when possible, with high-dose therapy and peripheral blood cell progenitor rescue (PBPCR)*

Hodgkin's lymphoma	*ABVD*	*Doxorubicin (**A**driamycin), **B**leomycin, **V**inblastine, **D**acarbazine*
	BEACOPP	*Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone*

Early Stage Hodgkin's Lymphoma

Favorable Prognosis

Short course & low dose chemoradiation

- *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*

- *Other treatment options:*

• STNI Mantle + Para-aortic nodes, spleen 35 Gy/20 "Subtotal nodal irradiation"	• **historical gold standard** • **Survival = CMT** • **use if CTx contraindicated** • **but: high risk late toxicity**
• ABVD x 2 + IFRT	• **as per BCCA guidelines** • **awaiting clinical trial results** (GHSG HD10)
• ABVD x 6	• **awaiting NCIC HD.6 results**

Unfavorable Prognosis

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

Chemo: 6 cycles. Radiation for bulky or residual

** NB: Overlap with favorable 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*

Very Favorable Prognosis Hodgkin's Lymphoma

- *Stage 1A NLPHL**
- *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)

Prognosis Features

*The histologic type does not greatly influence the prognosis of Hodgkin's disease (with the exception of the **lymphocyte-depleted type**, which has THE WORST PROGNOSIS). Treatment is effective in most patients with the other histologic types of Hodgkin's disease.*

	DFS (disease free survival)	OS (overall survival)
Early	80 – 90%	85 – 95%
Advanced	40 – 80%*	

If radiation therapy only (STNI): Deaths from 2nd malignancy > deaths from Hodgkin's disease by 15 – 20 yrs

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

Lymphoma follow up:

- *History, physical examination every 3 months for 2 yrs, then every 6 months for 5 yrs and then annually.*
- *CBC, LDH*
- *CT chest, abdomen, pelvis every 6 months for 5 yrs*
- *TSH at least annually after neck irradiation*
- *Breast cancer screening for women treated with chest radiation 10 yrs post radiotherapy*

Revision of Highlighted Points

- *What is the most common type of lymphoma?*
  - *NHL: follicular*
  - *HL: Nodular sclerosing HL*
- *Which type is the most aggressive?*
  - *Diffuse large B-cell*
- *Which type has the best prognosis?*
  - *Follicular NHL*
  - *Lymphocyte-predominant HL*
- *Which type has the worst prognosis?*
  - *Burkitt's (NHL)*
  - *Lymphocyte-depleted HL*
- *A 65-year-old female patient is diagnosed with stage I diffuse B cell lymphoma. She has an ECOG score of 1 and no evidence of extra-nodal disease. LDH levels were found to be in the normal range (115-221 U/L). What is the expected survival rate for this patient?*
  - *She has one risk factor (age > 60 yrs), so her OS ~75%*
- *A patient presents with lymphoma that involves hilar nodes on both sides. A chest x-ray showed that the mediastinum was widened by more than a third. What is the stage of this patient's disease?*
  - *Stage IIX (**Involvement of two or more lymph-node regions** + **Bulky disease**; a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension >10 cm)*
- *What is the management of aggressive NHL?*
  - *Stage I: chemo (short course, ~3 cycles), then localized radio*
  - *Stages II, III & IV: chemotherapy (longer course)*
- *What is the management of stage IE, H. pylori +ve gastric MALT?*
  - *PPI, 2 antibiotics e.g. clarithromycin, amoxicillin*
  - *F/U gastroscopy w/biopsy every 6 months for 2 years, then annually*
- *What is the management of early, favorable prognosis HL?*
  - *Short course chemotherapy (ABVD x3) & low dose IFRT*
- *What is the management of early, unfavorable prognosis HL?*
  - *Longer chemotherapy course (ABVD 6 cycles). Radiation only for bulky or residual disease.*

Thank you