Team Medicine

3. Lymphomas

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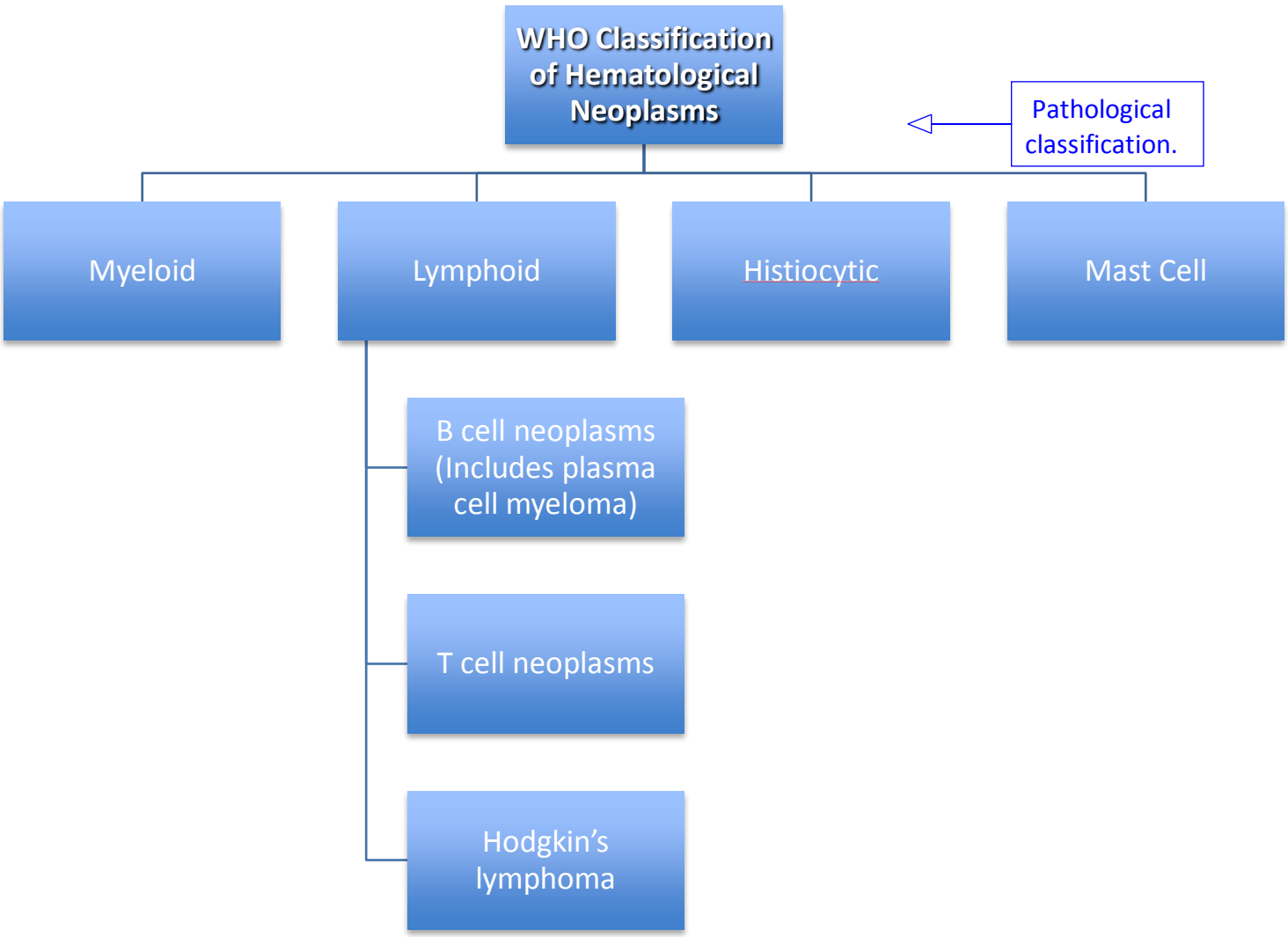
■ Slides ■ Doctors notes ■ Additional

431 Teams

* Was not mentioned by the doctor.

- Lymphoma is very common in Saudi Arabia.
- The difference between Hodgkin's and Non-Hodgkin's lymphoma is pathological. Non-Hodgkin: a malignant proliferation of T or B cells (the entire mass is malignant). Hodgkin's: characterized by the presence of the malignant Sternberg Reed cells that are few and scattered, surrounded by lymphoid inflammatory tissue. (About 15% of the mass is malignant **'Sternberg Reed cells'** while the majority of the mass is **inflammatory)**.
- Non-Hodgkin lymphoma is the 3rd most common cancer in KSA, preceded by breast and colorectal cancers.
- In the cancer registry the 2 types are regarded as 2 different diseases, Hodgkin's lymphoma is the 8th. If the 2 types of lymphoma were to be combined, lymphoma altogether is regarded the 2nd most common cancer.
- Lymphoma is divided into 2 main subdivisions: non-Hodgkin's and Hodgkin's lymphomas.
- Lymphoma is very common in KSA but not as common in the west, not in even in the top 10 malignancies.
- **Lymphoma (especially Hodgkin's) presents with lymphadenopathy**; hence, the way of approaching lymphadenopathy is important.
- **Lymphoma is one of the differential diagnoses of lymphadenopathy.**
- It is very common in bedside teaching to have patients with lymphadenopathy and you should know how to approach and analyze that by taking proper history, examination to know the differential diagnosis.



The purpose of these slides is to show that lymphoma is not a single disease, which has many classifications. Some types have the same treatment generally, but the characteristics and prognoses differ from one type to another.
No need to memorize any of that.

Proposed WHO Classification of. Lymphoid Neoplasms:
B-Cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/Iymphoma (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 lymphama of MALT type
Nodal marginal zone B-cell lymphoma *(+1*— monocytoid B cells)
Follicular lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphama
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burlcitt cell leukemia

← These are examples of B cell lymphoma, which arise from lymphoid origin.

T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymnphoblastic 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
Hepotosplenic 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-celllymphoma
Amaplastic large-cell lymphoma, T/null cell, primary systemic type

← Examples of T cell lymphoma.

Hodgkin's lymphoma (Hodgkin's disease), which has 5 main types.
Nodular lymphocyte-predominant Hodgkin's)ymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's Iymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

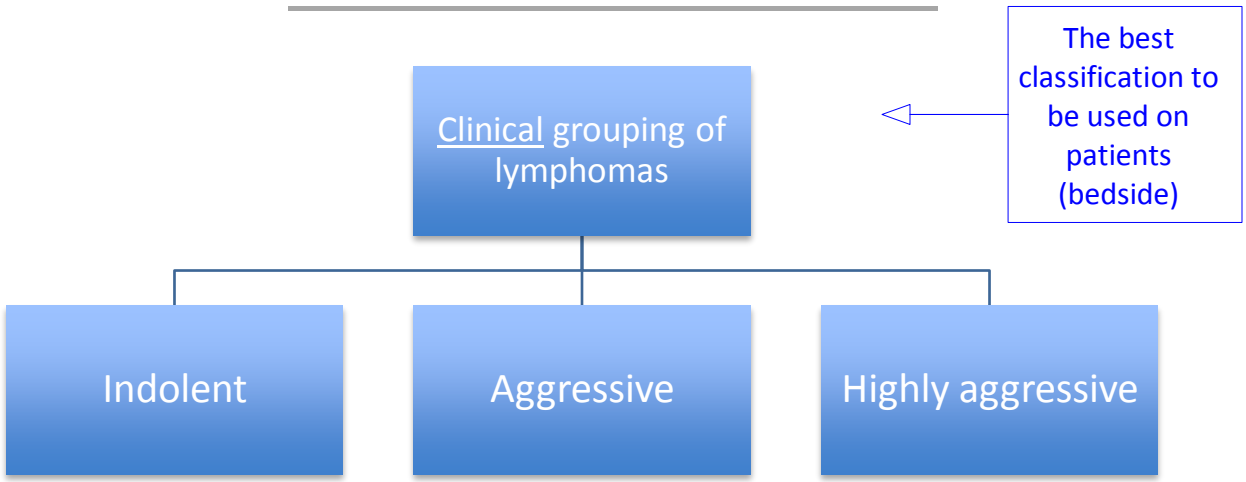
- Due to the wide spectrum of the disease, it has many classifications clinically and pathologically

NOTE: Only major categories are included. Subtypes and variants will be discussed in the WHO book[2] 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).**

1-Non-Hodgkin's Lymphoma



A. **Indolent (low grade):** **progresses very slowly**, you may wait 18 months before starting the treatment but with regular follow-up.Bad news: **not curable**, the patient will live with a chronic disease.

Type	**Approximate International Incidence**
Follicular lymphoma Grade 1,2 Grows very slowly	22% you must know **it is the most common**type.
Marginal zone lymphoma A) Nodal B) Extranodal (MALT)	1% 5%
Small lymphocytic lymphoma	6%
Lymphoplasmocytic*	1%

*association with Waldenstrom's macroglobulinemia

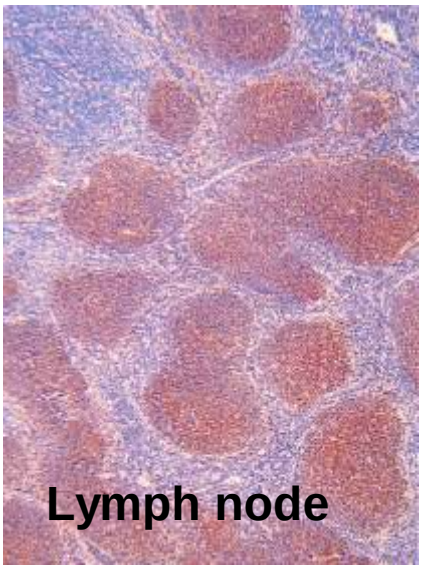
Follicular Lymphoma:

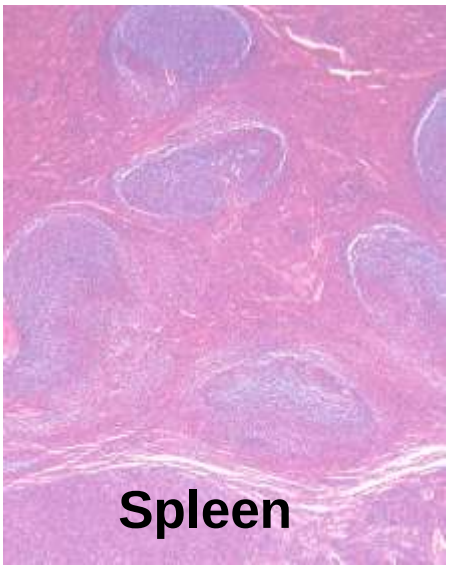
Grade	1	2	3
Number of large cells	0 – 5 / hpf	6 - 15 / hpf	>15/ hpf

The lower the grade, the slower the growth is.
Grade 1&2: You may wait before starting the treatment.
Grade 3: do not observe and start treating immediately, the lymphoma is becoming aggressive.

There is little clinical difference between grade 1 & 2 and no difference in the treatment between them.

- Most patients have disseminated disease at diagnosis:
  - Lymph nodes, spleen, bone marrow
  - < 20 % Stage I at diagnosis





- A patient presented with a small mass in the neck that grew very slowly over the period of 2 years until it reached 2 cm in diameter, then he was commenced on treatment. (indicating that you may wait before treatment)
So, follicular lymphoma: Grows very slowly, local and not usually metastatic but might spread in some cases.
Why wait before treating? In indolent lymphoma some doctors may wait for the mass to become large or cause complications, each doctor has a different philosophy. In opposition to aggressive lymphoma, most doctors treat the same way.
Treatment of indolent lymphoma also depends on age and the site of the mass whether it's causing any danger.
70 yo with multiple medical problems presented with a large lymph node or small follicular lymphoma → wait and see if they it's causing a problem, no need to intervene immediately.
Age and performance status are very important to pick up the right treating method.

B. Aggressive (intermediate grade) is like a solid tumor, should be treated without waiting.

Diffuse large B-cell lymphoma **Most common. Up to 30-40% in KSA.**	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	

Percentages in North America.

Gd 3 is regarded as aggressive, not indolent and requires immediate treatment.
Gd 1&2 are indolent.

C. Highly aggressive (high grade) **if you wait even for investigation results it will get worse (high proliferation rate/growing rapidly).** It is an emergency, must start treating as soon as possible.

Lymphoblastic lymphoma	2%
Burkitt's lymphoma	1%
Burkitt-like lymphoma	2%

Is Burkitt's lymphoma curable? Yes, it is **very sensitive to chemotherapy** but the problem is that it commonly recurs.

Staging System of Lymphoma:

(Cotswold's Meeting modification of **Ann Arbour Classification**)

Early	**I**	Single lymph node region (or lymphoid structure)
	II	2 or more lymph node regions
Late	**III**	Lymph node regions on both sides of diaphragm
	IV	Extensive extranodal disease (more extensive then "E")

The earlier the stage, the better the prognosis.
Treatment depends on the stage.
Stages I&II: one lymph node on one of the diaphragm, either above or below.
Stage III: on both sides. Stage IV: spread allover the body.
In oncology, stage IV is also called 'metastatic stage'. The term 'metastatic lymphoma' is not used as a term, because it is still curable unlike in solid tumors.

This concept is all you need to know in staging.

Subscripts: Important

A	Asymptomatic

B	Fever Night sweats Weight loss	>38°, recurrenthigh grade Usually 38.3, fluctuates up and down (Pel-Ebstein fever) Drenching (might need to change clothes), recurrent > 10% (of ideal body weight)body weight in 6 months
X	Bulky disease: divided into mediastinal and non mediastinal	Mediastinal: Either: mass ≥ 10 cm Or:> 1/3 internal transverse diameter @ T5/6 on PA CXR*[1] Non-mediastinal: different institutes have different opinions. Hematology society in Riyadh: 6 cm or more is considered to be bulky.
E	Limited	extranodal extension from adjacent nodal site

- You must ask the patient about these symptoms to properly diagnose them with lymphoma. Lymphoma does not necessarily present with lymphadenopathy, it can occur in any part of the body through the lymphatic vessels; hence you must address the previous symptoms.
- TB for example can present with lymphadenopathy, night sweats and fever. How to differentiate between TB and lymphoma? By the character of the symptom.

*1: (>1/3 of the maximum diameter of the mediastinum which is usually on the level of T5 in CXR).
e.g. a slim patient presented with a mediastinal lymph node of 7cm, it occupies 1/3 of the maximum diameter = bulky disease.

TB: Low-grade fever (37.5°-37.7°), mild night sweats (not drenching).
- You can also ask about fatigability. In mediastinal lymph nodes ask about shortness of breath and chest pain (compression symptoms).
- There is no specific questions or symptoms about lymphoma, it depends on the site.

Essential Staging Investigations:

- History – B symptoms, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBCand differential
- Biopsy – pathology review
- Creatinine, liver function tests, LDH, calcium
- Bone marrow aspiration & biopsy(to assess infiltration), always done in non-Hodgkin & in some cases of hodgkins. In our stage you must know it's done in BOTH types.
- CT neck, thorax, abdomen, pelvis

Do not forget to examine the oral cavity, spine, spleen and liver.

Why ask for differential? The count of lymphocytes is one of the prognostic factors especially in Hodgkin's lymphoma.
CBC:
-Establishes if the cause of lymphadenopathy is an infection.
-If there's pancytopenia = bone marrow infiltration (helps in staging)

Creatinine & LFT: to assess the involvement of the kidneys and liver. Also to obtain a baseline before starting chemotherapy to assess the level of damage throughout the progress of treatment.

Additional Staging Investigations:depends on the site

- PET or ^{67}Ga scanwidely used
- CT / MRI of head & neck
- Cytology of effusions, ascites(if the patient presents with pleural effusion: examine pleuritic fluid. If it was brain lymphoma: examine CSF)
- 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

*Important

International Prognostic Index for NHL(non Hodgkin lymphoma)

This index in only used for diffused large B cell lymphoma (not in Burkitt's)

Risk factors:

Age	Stage	PS	Extranodal involvement	LDH
> 60	3,4	ECOG > 2	> 1 site	> Normal

For each risk factor you add one point.

PS: performance status. ECOG: performance status scale.

Patients with high LDH don't do well.

	Number of risk factors	5 Year OS*(survival)
Low risk	0-1	75%
Low intermediate	2	51%
High intermediate	3	43%
High risk	4-5	26%

*Diffuse large cell lymphoma

Treatment:

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

Not curable, slowly growing, you may wait before treating. Depends on the stage.

In indolent lymphoma the treatment is LOCAL, especially in early stages → radiotherapy.

Limited Diseasei.e. local → radiotherapy

Stage 1: small, local and not causing problems → start treatment directly without waiting.
It was found that 5% of grade 1 follicular lymphoma could be cured up to 5-10% of cases.

(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

-You only need to know the modality of treatment.
-Local → radiotherapy
-Systemic → chemotherapy
-No need to know the doses.

Advanced Stage i.e. systemic → chemotherapy

(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 cycles+ IFRT (35-45 Gy)**

Chemotherapy, if limited to one place → use radiotherapy to boost the treatment.

Expect ~ 75% long term FFR

Stage III, IV, B symptoms, or bulky disease

CHOP* x 6-8 cycles

IFRT (35-45 Gy) to - sites of initial bulk

- Residual disease (i.e. PR)

CHOP q 21 days

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

*or CHOP-R (see next slide)

** higher radiation dose if residual disease

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

Only chemotherapy, no radiotherapy except in 2 conditions:

1. Bulky disease
2. Residual disease and the patient cannot tolerate more chemotherapy.

Note the number of chemotherapy cycles, more cycles in stage III&IV

-The treatment of lymphoma is: radiotherapy, chemotherapy or both.
-NOT surgery, surgery is for obtaining a biopsy only.
-Even if the diseased lymph node is removed, the disease is not yet cured. It is a systemic disease.
-Indolent lymphoma could be treated by resection in some cases, but large
-B cell lymphoma must be treated by chemotherapy.

Rituximab

- Chimeric anti-CD20 mAb
  - Mouse variable region
  - Human constant region (I_gG_1)
  - Direct antitumor effects
  - Complement-mediated cytotoxicity
  - Antibody dependent cellular cytotoxicity
  - Synergistic activity with chemotherapy

Chemotherapy – Rituximab Combinations

CHOP – R

- CHOP + rituximab (on day 1)

- GELA study: elderly aggressive NHL . Improved EFS, OS at 3yrs with CHOP-R x 8 vs CHOP x 8.
- MInT study: Interim results suggest superiority of CHOP-R over CHOP in younger (<60) patients.
- CVP – R
- Prolonged TTR in Indolent lymphoma. Probably not covered by most provincial plans

Extranodal lymphoma

- Same treatment as nodal lymphoma

Notable Exceptions:

- Gastric MALT
- Testis
- CNS
- Skin

MALT mucosal associated lymphoid tissue Lymphoma

MALT is one name for a wide spectrum of diseases, which has a specific behavior.

Most low grade lymphomas at the following sites are MALT type:

- Stomach most important site, associated with H.pylori
- Lung
- Ocular adnexa
- Thyroid
- Salivary glands

Patients with H.pylori must be treated adequately, otherwise the infection will cause prolonged inflammation and transform into MALT lymphoma.

- Most localized (Stage I, II)
- History of chronic antigen stimulation
  - Autoimmune disease e.g. Sjogren's, Hashimoto's
  - H. Pylori infection

Treatment of MALT lymphomas

Local treatment for Localized disease

- Radiotherapy
  - Local / regional: 30 Gy / 20
  - Surgery
- Antibiotics for gastric MALT lymphoma
- Cyclophosphamide / chlorambucil

Disseminated disease

~ 30 % of cases

- Treatment similar to

-Treatment of gastric MALT: H. pylori eradication (antibiotics).
-If the patient became resistant to antibiotics, move on to local treatment (radiotherapy) of the entire stomach.
-It is highly curable up to 96% of cases.

Stage III, IV follicular lymphomas

Gastric MALT Lymphoma

~ ½ of gastric lymphomas

- Association with:
  - Chronic gastritis
  - Helicobacter pylori infection

H. pylori infection ➔ accumulation of MALT ➔lymphoma arises in acquired MALT.

Testis Lymphoma

- usually aggressive histology
- elderly patients, less tolerant of chemo
- high risk relapse ∴ need aggressive Tx

High risk of:

- extranodal relapse
- contralateral testis relapse > 40% by 15yrs
- CNS relapse > 30% 10yr actuarial risk

Treatment of testis lymphoma:

All patients	Stage 2	Stage 3,4
• Orchidectomy (diagnostic & therapeutic) • CHOP-R x 6 • Scrotal radiation 30 Gy/ 15 - Reduces risk testis recurrence to < 10%	• Involved field nodal RT	• CNS chemoprophylaxis – intrathecal MTX

Treatment Summary:
Indolent: early → wait or radiotherapy.
Late → wait or systemic (chemo), radiotherapy if localized.
Aggressive:
Grade I&II: chemo + radiotherapy
Grade III&IV: chemo.
MALT: antibiotic → if recurrent: radiotherapy.

Lymphoma follow-up:

- Hx, Px q3mo for 2 yrs, then q6mo to 5 yrs and then annually.
- CBC, LDH
- CT chest, abdo, pelvis q6mo to 5 yrs, but most importantly the first 2 years, where more recurrences occur.
- TSH at least annually after neck irradiation
- Breast cancer screening for women treated with chest radiation 10 yrs post RT

History: always ask about B symptoms and presence of a lump. Most cases will present with a lump

Recurrent lymphoma is more aggressive.
It is possible that the patient present with A symptoms the first time, B symptoms (more aggressive) the recurrent time.

2- Hodgkin's Lymphoma

WHO Classification of Lymphoid Neoplasms

Hodgkin's Lymphoma (≡ Hodgkin's disease)

More with lymph nodes, in opposition to non-Hodgkin, which occurs in any part of the body
If a patient presents with a lymph node lymphoma: think of Hodgkin's first, then non-Hodgkin's.

1. Nodular lymphocyte-predominant HL*
2. Classical HL(**Thomas Hodgkin was a MDRS**مدرس)

-Nodular **S**clerosis HL(MOST COMMON subtype!)
-Lymphocyte-**R**ich classical HL*(rare and associated with EBV)
-**M**ixed cellularity HL
-Lymphocyte **D**epletion HL

-Know the types.
-Lymphocyte predominant HL has the best prognosis.
- First 2 types of classical HL have better prognosis than the last 2.

- Formerly, both of these were classified as lymphocyte predominance Hodgkin's disease

Staging investigations of Hodgkin's disease:

- History – B symptoms, pruritis, alcohol pain, PS
- Physical Exam – nodes, liver, spleen, oropharynx
- CBC, **ESR**
- Biopsy – pathology review
- creatinine, liver function tests, LDH, calcium, albumin
- Bone marrow aspiration & biopsy
  - If abnormal CBC, Stage 2B or higher
- CT thorax, abdomen, pelvis

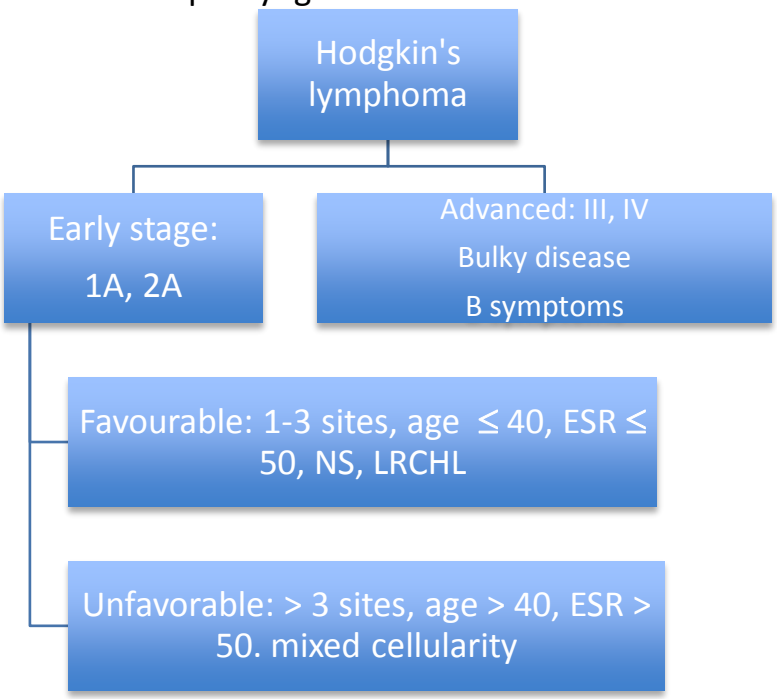
Same as in non Hodgkin. The difference is you ask for ESR here instead of LDH.

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

Initially, obtain LDH and ESR (since you don't know which type of lymphoma you have)
For follow up:
LDH →non Hodgkin's.**(LDH level is inversely proportional with the prognosis)**
ESR → Hodgkin's.

- Dental assessment – if oropharyngeal RT



Treatment:

-Early stage: 3 cycles of chemotherapy + radiation (BOTH).
-Advanced: chemotherapy only. Add radiation only in bulky disease or residual lymphoma.
-Clinical difference: early stage has a better prognosis, especially if it was lymphocyte rich, which can be cured in 100% of cases. Unlike non-Hodgkin's lymphoma which was 75%.
-Hodgkin's lymphoma has better prognosis, and is considered more like 'a bad infection', unless it was a late stage.
-Lymphoma, especially Hodgkin's, cannot be cured completely, especially if it was in a lymph node.

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

Some Other Treatment Options

• STNI Mantle + Para-aortic nodes,spleen 35 Gy/20	• historical gold standard • survival ≡CMT • use if CTx containdicated • 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

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 1, 15 days.

Very favourable 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)

Hodgkin's Lymphoma
Rough Approximation of Prognosis

	FFS	OS
Early	80 – 90%	85 – 95%
Advanced	40 – 80%*	

If RT 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 'dies' by fibrosis. How do you know if it is residual or just fibrosis?
- PET scan can differentiate but is not available in all facilities. Done before and after treatment.
1) A biopsy study is positive for lymphoma.
2) Before starting the treatment you must do a gallium scan, if it became +ve→ gallium scan is considered sensitive and can be used later after the treatment to follow up.
3) If the scan became –ve, it cannot be used to follow up later on (not sensitive in this case).
-You have to follow this procedure to make sure that you are not giving a patient unnecessary chemotherapy (if recurrence is suspected) while it is only a remnant fibrosis.

Summary of the steps of approaching a patient with lymphadenopathy:

1. Physical examination
2. Investigations: CBC
3. Determine what the patient has by biopsy.

If +ve biopsy: determine if it was spread through the body by bone marrow aspirate.

4. CT scan from the chest to pelvis to find the location of the lymphoma (it can spread easily through the lymphatic channels).

Summary

	Hodgkin's	Non-Hodgkin's
Overall incidence	Less common (8th in KSA)	More common (2nd in KSA)
Most common type	Nodular sclerosing HL	Follicular lymphoma
Type with best prognosis	Lymphocyte-predominant HL	Follicular lymphoma
Type with worst prognosis	Lymphocyte-depleted	Burkitt's NHL
Histology	reed-sternburg cells	Varies (no reed-sternburg cells !)
Inflammatory cell infiltates	Present	Absent
Physical exam	Systemic adenopathy, hepatosplenomegaly	Regional adenopathy, hepatosplenomegaly
Systemic "B" symptoms	More common	Less common
Survival	Better	Worse

Clinically important lymphoma oncogene (extra)

c-myc →burkitt's lymphoma →t(8,14)
bcl-2→Follicular lymphoma→t(14,18)

Bcl-2 is considered as anti-apoptotic protein. It is a proto-oncogene,but when the translocation t(14,18) happens it becomes oncogene → overexpressed → it will prevent apoptosis forever leading to cancerous cells formation.
A proto-oncogene is a gene that is normally found and functioning normally , but has the potential to become an oncogene (abnormal)

Questions

Q1) which is the single most valuable investigation in the diagnosis of non- Hodgkin's lymphoma?

A- Blood count
B- Immunophenotyping of a fine needle aspirate from a lymph node
C- Lymph node biopsy
D- CT scan

Q2) which of these infectious agents has NOT been associated with development of non- Hodgkin's lymphoma?

A- *Helicobacter pylori*
B- Cytomegalovirus
C- Epstein-Barr virus
D- HTLV- 1

Q3) which ONE of the following is TRUE about Stage IA Hodgkin's lymphoma?

A- It is associated with a raised serum lactate dehydrogenase
B- It may present with weight loss
C- It is best left untreated with a 'watch and wait' approach
D- It may be confined to the lymph nodes on one side of the neck

C - B - D