Lymphoma Part I: Hodgkin Lymphoma

Edited by: Layla Nazzal.

History

- Described by Sir Thomas Hodgkin in 1832
- Mortality decreased faster than any other malignancy in last 5 decades
  - First cure at Stanford – early stage HL with xrt in 1962
  - First cure with chemo (MOPP) at NCI in 1964
  - ABVD chemo introduced in 1975
    - ↳ still used till now

* Decreased significantly in the last 5 decades despite using the same protocol since 1975, why ?
- we are now much better in "Supportive treatment"
- " in staging properly (Due to better imaging and treating
* so for example : we treat patient and thought he's fine → PET image shows more chemo needed

Hodgkin Lymphoma: General Features

- Epidemiology
  - 7400 cases in USA annually
  - 30% of lymphomas
- Bimodal age distribution
  - Young adults (age 15-35), older adults (7th decade)
- Lymph node-based disease, preferentially involves cervical LNs
- Spreads in contiguous fashion

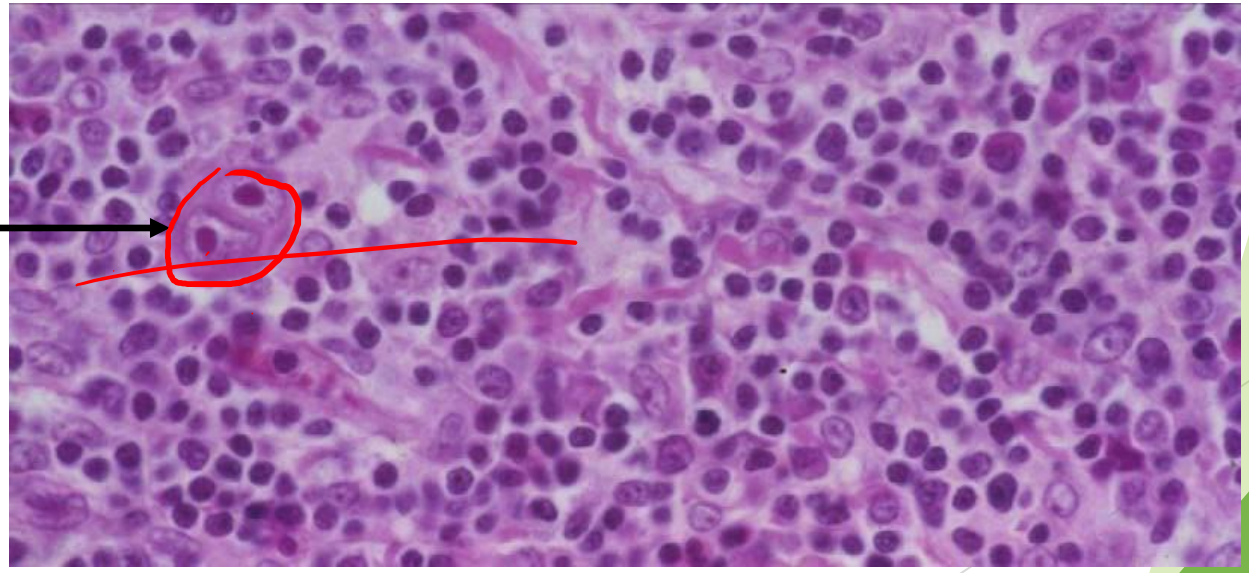
cervical LN
female
contiguous
prurtis!

Hodgkin Lymphoma: Presentation

1. Lymphadenopathy ✓ usually painless
2. B Symptoms ✓
   - Fevers, night sweats, weight loss
3. Pruritus !
5. Alcohol induced pain in lymph nodes
4. SVC syndrome (mass effect)
   - plethora
   - Edema
   - Dilated veins.

Hodgkin Lymphoma: Pathology

- Reed-Sternberg cell = malignant cell
- Reactive cells in background (eosinophils, B cells, plasma cells, etc.) often outnumber R-S cells



Hodgkin Lymphoma: WHO Classification

1. Classical Hodgkin Lymphoma (based on background cells)
   - Nodular sclerosis — most common HL
   - Mixed cellularity — RS cells ⊕ CD15+, CD30+
   - Lymphocyte-rich
   - Lymphocyte-depleted
2. Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL or LP)

↳ it differs from classic type by:

① Reed sternberg cells (popcorn cells) are CD20+ and CD15, CD30 negative

② NLPHL may progress to DLBCL, while classic don't

③ Better prognosis (rituximab?)

Hodgkin Lymphoma: Staging

(eg Hodgkin Lymphoma type B stage 3)

- Ann Arbor Staging System (diff than TNM system)
  - Stage I: Single LN region
  - Stage II: >1 LN region on same side of diaphragm
  - Stage III: LN regions on both sides of diaphragm
  - Stage IV: Extranodal disease (i.e. bone marrow, liver, etc.
- A (no B sx) or B (presence of B sx)

Symptoms

Lymphomas with the same staging but with or without B-symps differ

worse prognosis

Better prognosis

Staging for most tumors

T tumor size

N LN involvement

M metastasis

- it guides doctors in treatment and prognosis

Grading = pathological description of cells and how they look under microscope.

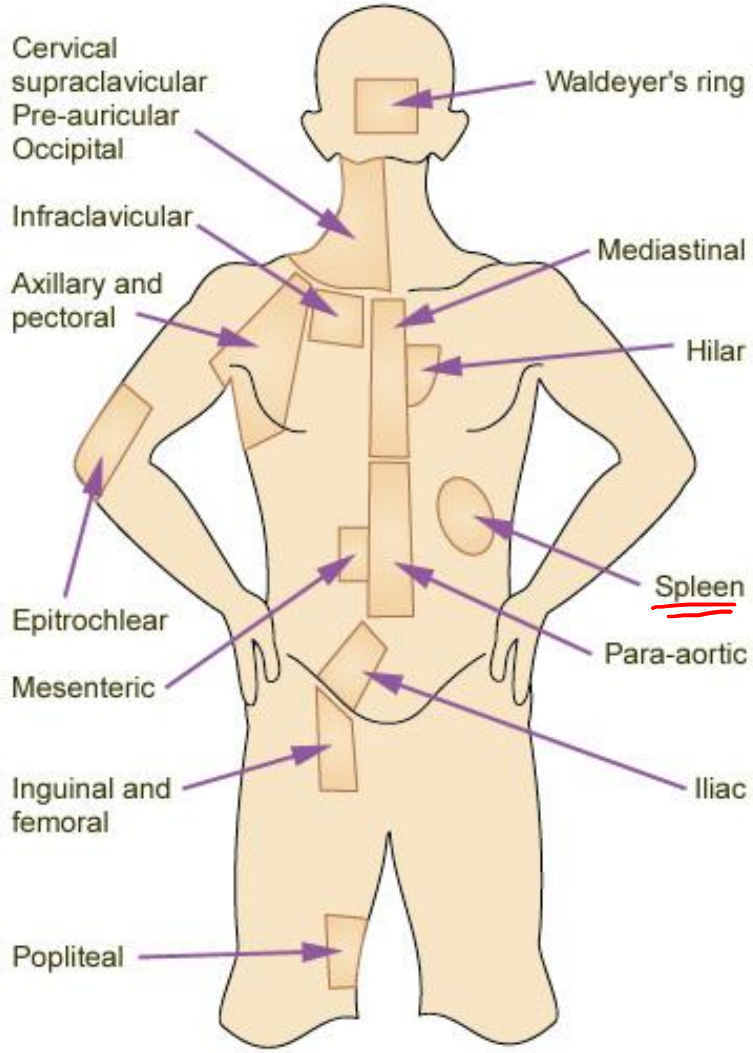
Diagnosis and Staging

- Based on pathological examination of lymph nodes.
- Standard is to do excisional lymph node biopsy.
- If no lymph node is palpable, cutting needle biopsy is an alternative .
- Fine needle aspiration is not adequate.
- Staging with CT scan or PET-CT scan and bone marrow biopsy.
- ESR and LDH are important for prognosis

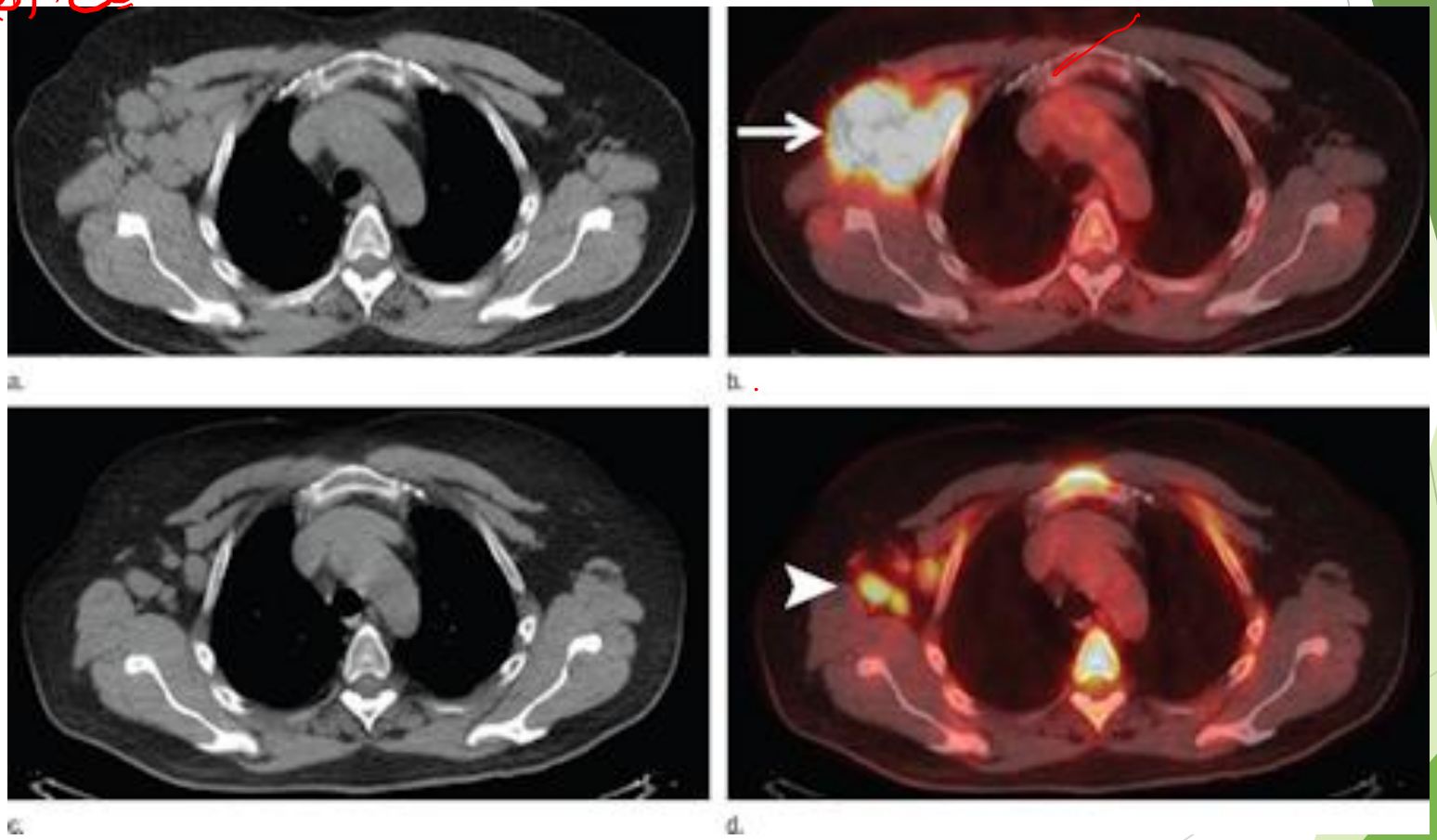
not just fine needle aspiration (bcz remebr RS cells are only 15% of cells. so just FNA may miss these cells and thus diagnosis).

Elevated LDH- phenomena is not very specific phenomenon, but may indicate the Turnover of cells and the burden of cancer and thus is now considered Tumour marker

Lymph Node Regions



CT versus PET



PET Scans in HL

Uses
1. At beginning → staging
2. In the middle → to see pt is responding or not
3. At the end → to document remission.

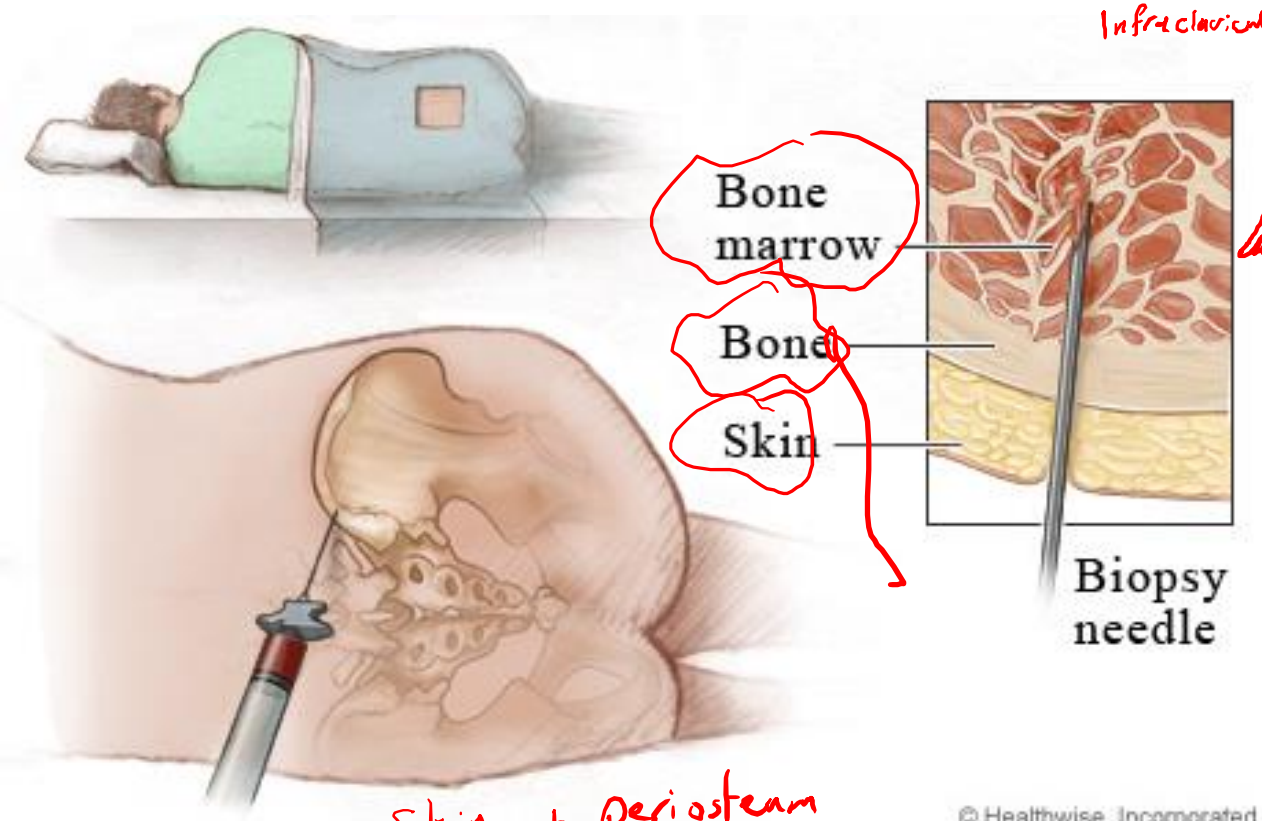
- At diagnosis
  - Upstages 19% of patients
- Completion of therapy (so after treating the pt, we thought he's fine but after PET we realized that still he's not cured yet)
  - Residual masses
- Interim PET after 2 cycles very sensitive prognostic indicator
- Not for routine surveillance

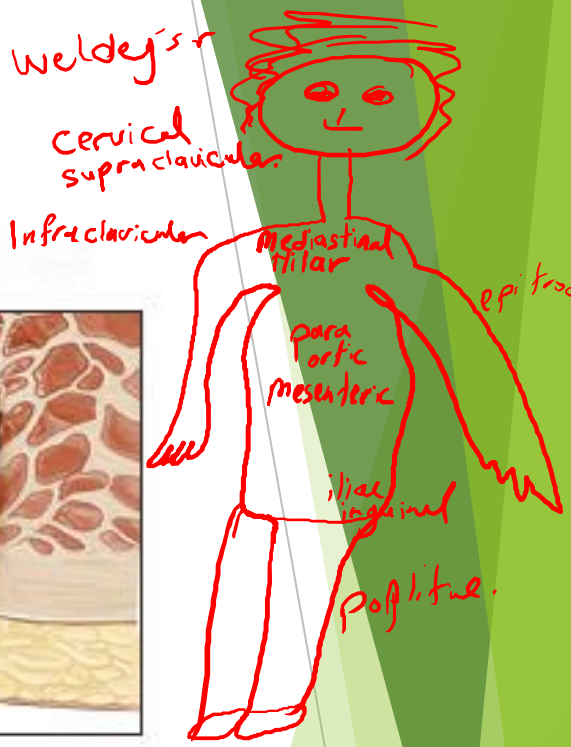
↳ A lot of false-positive
* Infection cause FP

physiological uptake in CT-PET

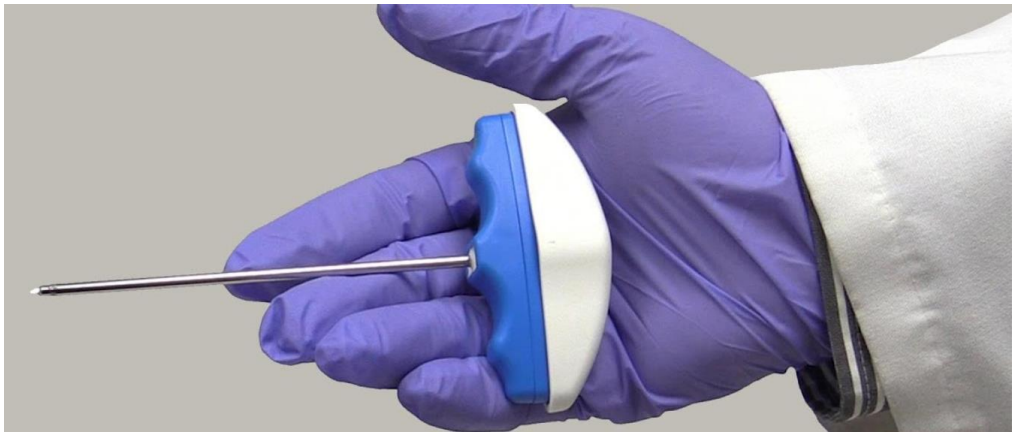
Brain, kidney, Heart, Liver } High metabolism rate in these

Bone Marrow Biopsy





Skin + periosteum are the structures that causes pain.



Favorable vs. Unfavorable Disease (subjective somehow).

- Unfavorable features
  - Bulky disease (mass ≥ 10 cm on CT scan, or ≥ 1/3 intrathoracic diameter (width of mediastinum))
  - ESR >50 if asx
  - >3 sites
  - B sx
  - ≥2 extranodal sites (Liver, Lung, Bone marrow)

IPS Score or "Hasenclever Index"
7 prognostic factors (objective) prognosis

- Albumin <4 1
- Hgb <10.5 1
- Male 1
- Age >45 1
- Stage IV 1
- WBC >15K 1
- Lymph <600 or <8% total WBC 1

normal 4g/dL (3.4-5.4)

IPS score /7

Normal (4500-11,000)

Lymphocytes

within the same stage, higher IPS is worse HL

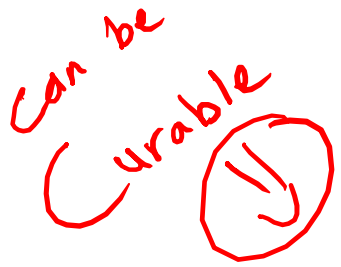
IPS Score

Progression free survival (time pt lives with his disease not getting worse).

0-4 7 50%

Score	5 year PFS
0	84%
1	77%
2	67%
3	60%
4	51%
≥ 5	42%

Hodgkin Lymphoma: Treatment



- Early Stage
  - Short-course chemotherapy (ABVD) +/- radiation therapy
    - >85% cure rate
- Advanced Stage
  - Chemotherapy (ABVD)
    - 55-65% cure rate

Note: Some labs used in HL

LDH ↑
ESR ↑ >50

IPS

Albumin <4
Hb <10.5
WBC >15K
Lymphocytes < 600

Chemotherapy in HL

ABVD

- Adriamycin (Doxorubicin) → cytotoxic and anti-mitotic [cardiomyopathy] side effect
- Bleomycin // (pulmonary toxic)
- Vinblastine microtubule binding (neuropathy)
- Dacarbazine (neuropathy)

All are chemotherapies for cancers (anti mitotics, cytotoxic, interfering with DNA,..)

* While taking a history from pt complain about heart and seems as heart failure, he told you he had Lymphoma or breast cancer before 15 years.
  - ↳ consider Adriamycin chronic cardiomyopathic effect!
  - ↳ irreversible

Bleomycin Pulmonary Toxicity Has a Negative Impact on the Outcome of Patients With Hodgkin's Lymphoma

William G. Martin, Kay M. Ristow, Thomas M. Habermann, Joseph P. Colgan, Thomas E. Witzig, and Stephen M. Ansell

Bleomycin Pulmonary Toxicity

- 0-46% affected (18% Mayo series)
- Risk factors: age>40, G-CSF
- Pulmonary sx, bilateral interstitial infiltrates, decreased diffusing capacity, absence of infection
- 24% mortality rate
- Treatment: withhold bleo, steroids

JCO 2005; 23:7614-20

Treatment: Relapsed/Refractory

- Rule of thumb: always biopsy PET positive findings to confirm!
  - Fat necrosis
  - Inflammation
- If initially stage I-II, tx'd with chemo alone, local relapse – consider XRT
- Otherwise: salvage chemo (DHAP, ICE) followed by auto PBSCT
  - OS 50-60%

If PET positive → Always make biopsy.
↳ could be False positive
↳ " " other malignancy.

Question

- A previously healthy 20 year old woman presented to her physician with a 2 month history of pruritus, drenching night sweats, unintentional weight loss, and non productive cough. On examination she has 2 cm cervical lymphadenopathy. A CT scan shows a 12 cm diameter anterior mediastinal mass. An excision biopsy of a cervical lymph node shows nodular sclerosing Hodgkin lymphoma. She is treated with ABVD combination chemotherapy followed by involved field radiation therapy and achieved a complete remission. Ten years later you see her for the first time for an annual physical examination. She remains in complete remission.
- Compared to her peers, this patient is at increased risk of:

Question

The patient took Radiation on chest and neck

- A. Breast cancer
- B. Coronary artery disease
- C. Hypothyroidism
- D. Skin cancer
- E. All of the above.

A + C + D → Due to radiation she took

B → Radiation causes coronary A. disease

so Adriamycin → Kardiomyopathy | Radiation → Coronary A. D

Question - answer

- E - All of the above

Complications of Treatment

- 6.8x more likely to die than general population

even if resolved from his cancer...

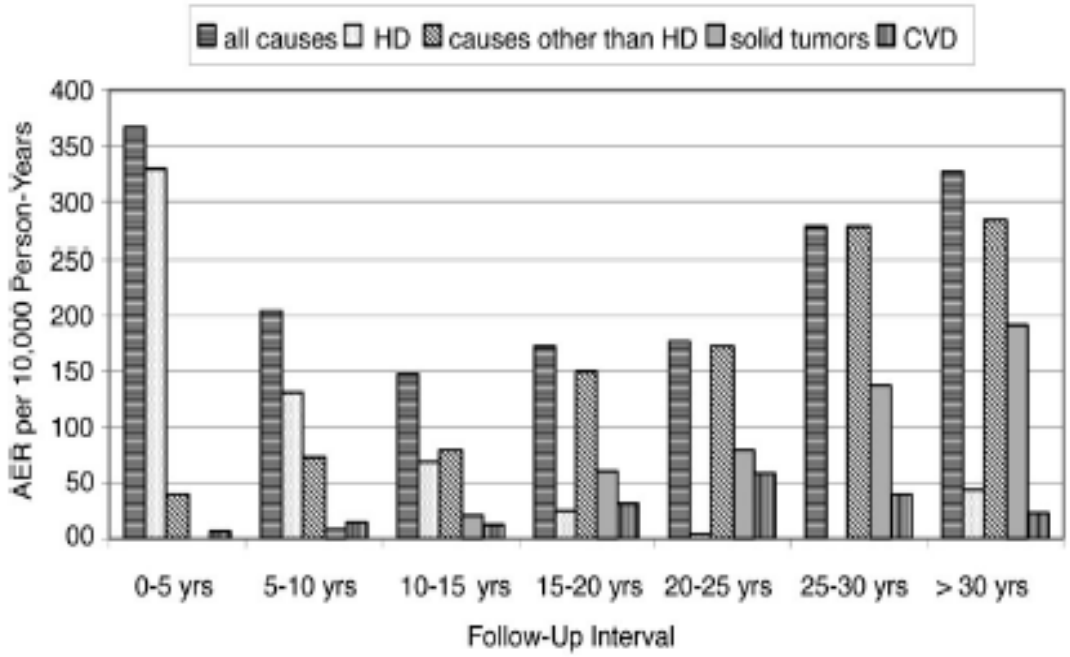


Fig 3. Absolute excess mortality from various disease categories over time. HD, Hodgkin's disease; CVD, cardiovascular disease.

JCO 2003;21:3431-39

Hodgkin Lymphoma: Complications

مشكلة بالقلب / بالرئة / بالكلى
أو سرطان آخر
أو عفو من الله ..

- Historically high dose radiation, staging splenectomy, MOPP chemotherapy
- Secondary malignancies
  - Solid tumors
  - Leukemia/MDS
- Cardiac disease
  - Anthracycline chemotherapy: CHF
  - Radiation: CAD, pericarditis, valvular disease, arrhythmias

malignancy you get as a result of chemotherapy
Like (acute myeloid Leukemia AML)

Hodgkin Lymphoma: Complications

- Pulmonary disease
  - Bleomycin chemotherapy
- Hypothyroidism
- Infertility : Remember, chemotherapuetic agents affect all actively growing and dividing cells, including these in genitals.

A

Lymphoma Part II: NHL

- It is not a disease entity by itself, actually it is a group of lymphomas, that are not Hodgkin (No RS cells in them).

Edited by:
Layla Nuzzal

Non-Hodgkin Lymphoma: Epidemiology

- Diverse group of malignant tumors of the lymphoid tissues variously derived from the clonal expansion of B cells, T cells, natural killer (NK) cells or precursors of these cells
- >40 subtypes
- 50,000 cases annually - 6th most common cause of death by cancer in the US
- No known etiology in majority
  - In minority, a predisposing factor may be present:
    - Immunosuppression
      - AIDS-defining condition→ CNS lymphoma
      - Congenital, immunosuppresive medications
    - H. pylori→ MALT

Etiology

3 viruses + 1 Bacteria.

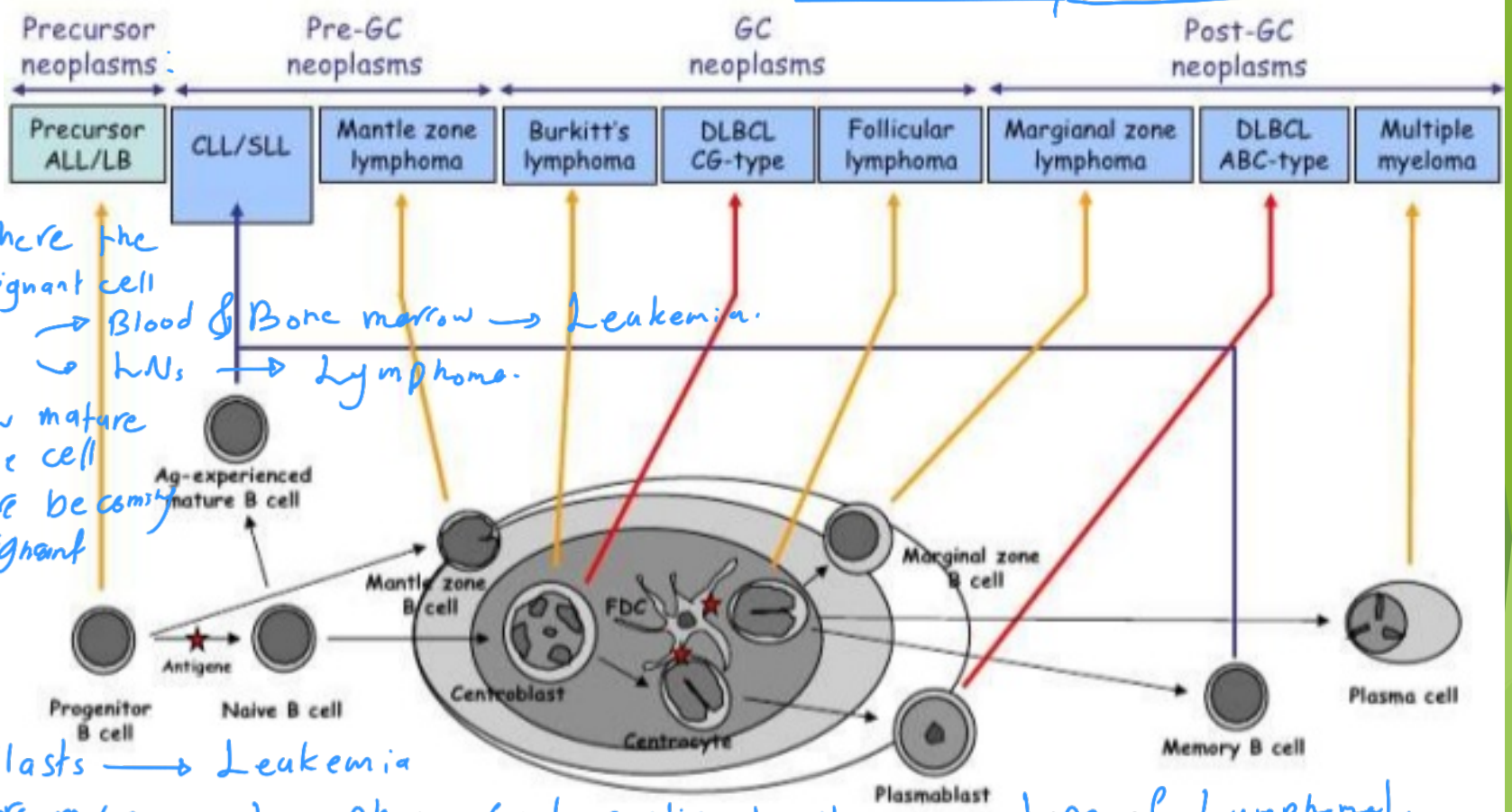
Oncogenic viruses introduce foreign genes into their target cells.

- Epstein-Barr virus (EBV) —Burkitt lymphoma and lymphoma in the setting of immunosuppressive therapy
- Human T cell lymphotropic virus I (HTLV-I) —T cell leukemia-lymphoma (ATL)
- Human Herpesvirus-8 (HHV-8) — Involved in the development of body-cavity-based lymphomas (eg, primary effusion lymphoma)

↳ They arise in serous cavities like pericardium, pleura, peritonium.

* Side note (Herpesviridae)
1 Hsv-1
2 Hsv-2
3 VZV
4 EBV
5 CMV

B-cell ontogeny and lymphomagenesis



* where the malignant cell is?
  - → Blood & Bone marrow → Leukemia.
  - → LNs → Lymphoma.
* How mature is the cell before becoming malignant

Blasts → Leukemia

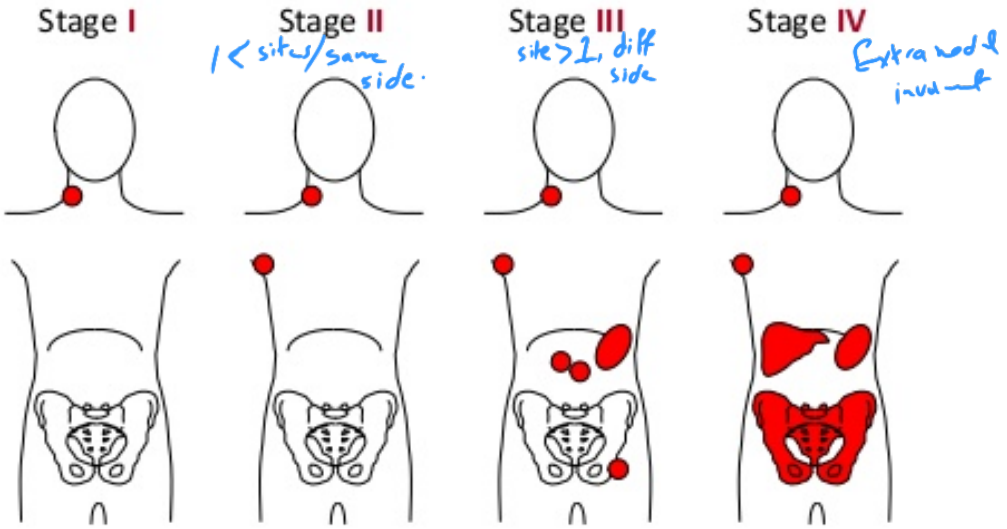
more mature → Lymphoma (and accordig where it occurs → type of Lymphoma).

Bone marrow	Interfollicular area	Follicular area	Perifollicular area	Peripheral blood Extranodal tissues

Progenitor B-cell → pro B-cell → pre B-cell → Immature B-cell → Naive B-cell → mature B-cell → Plasma cell / memory cells.

Non-Hodgkin Lymphoma: Staging

Staging of lymphoma



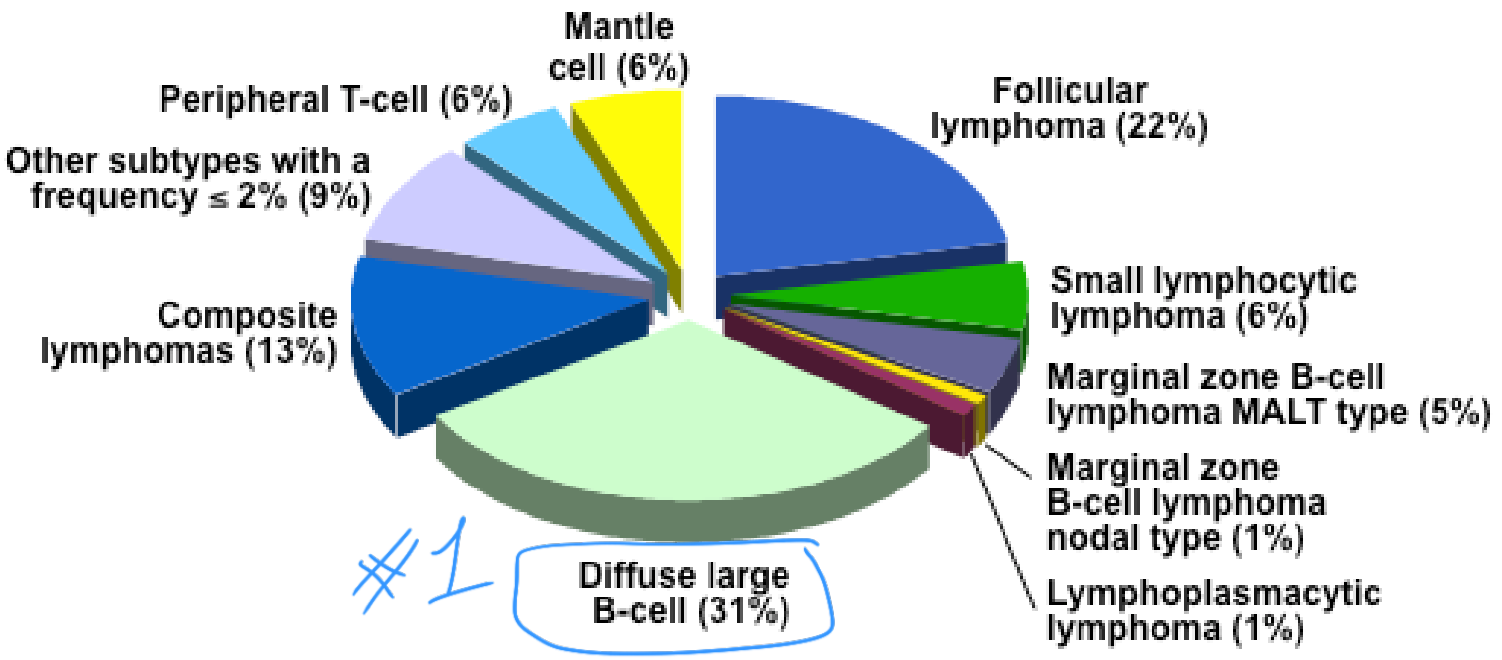
A: absence of B symptoms
B: fever, night sweats, weight loss

WHO Classification: Non-Hodgkin Lymphomas

- Precursor B-cell neoplasms
- Precursor B-lymphoblastic leukemia/lymphoma
- Mature (peripheral) B-cell neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle-cell lymphoma
- Diffuse large B-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma

- Precursor T-cell neoplasms
- Precursor T-lymphoblastic leukemia/lymphoma
- Mature (peripheral) T-cell neoplasms
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK pos
- Anaplastic large-cell lymphoma, ALK neg
- Primary cutaneous T-cell lymphomas

Non-Hodgkin Lymphoma
Subtypes



Armitage JO, et al. *J Clin Oncol*. 1998;16:2780-2795.[1]

Follicular Lymphoma: General Features

- Indolent lymphoma (slow growing)
  - Long survival (8-10 years)
  - Non-curable
- t(14;18): overexpression of **bcl-2** protein (anti-apoptotic) → **live forever protein** (prevent apoptosis either by sequestering caspases or by preventing the release of mitochondrial apoptogenic factors)
- Presentation
  - Incidentally noted lymphadenopathy
  - Usually advanced stage at diagnosis (Bcz it is indolent slowly growing).
- Can transform to aggressive lymphoma → DLBCL
  - Bad prognosis: 10 to 70% over time but 2-3% per years

Follicular Lymphoma: Treatment

- Treatment depends on symptoms
  - Observation ("watch and wait") – no benefit to early treatment
  - Immunotherapy (rituximab) → anti-CD20
  - Radioimmunotherapy
  - Chemotherapy—Rituximab + Bendamustine
- Sequential treatment
  - Treat → Remission → Progression → Treat

not curative

Rituximab (Anti CD20): any disease caused by excessive B-cell activity we may use Rituximab in treatment.

used in → RA, SLE

Extranodal marginal zone lymphoma of mucosa associated tissue (MALT)

- Non-lymph node sites with chronic antigen stimulation
  - Gastric: H. Pylori□ treat with triple therapy
  - Salivary gland: Sjogren's syndrome (autoimmune)
  - Conjunctiva: Chlamydia psittaci
- Low grade, indolent lymphoma
  - Can transform□ DLBCL □ BCL-2 and CD10 negative, but BCL-6 positive (inhibit transcription)
- Excellent prognosis

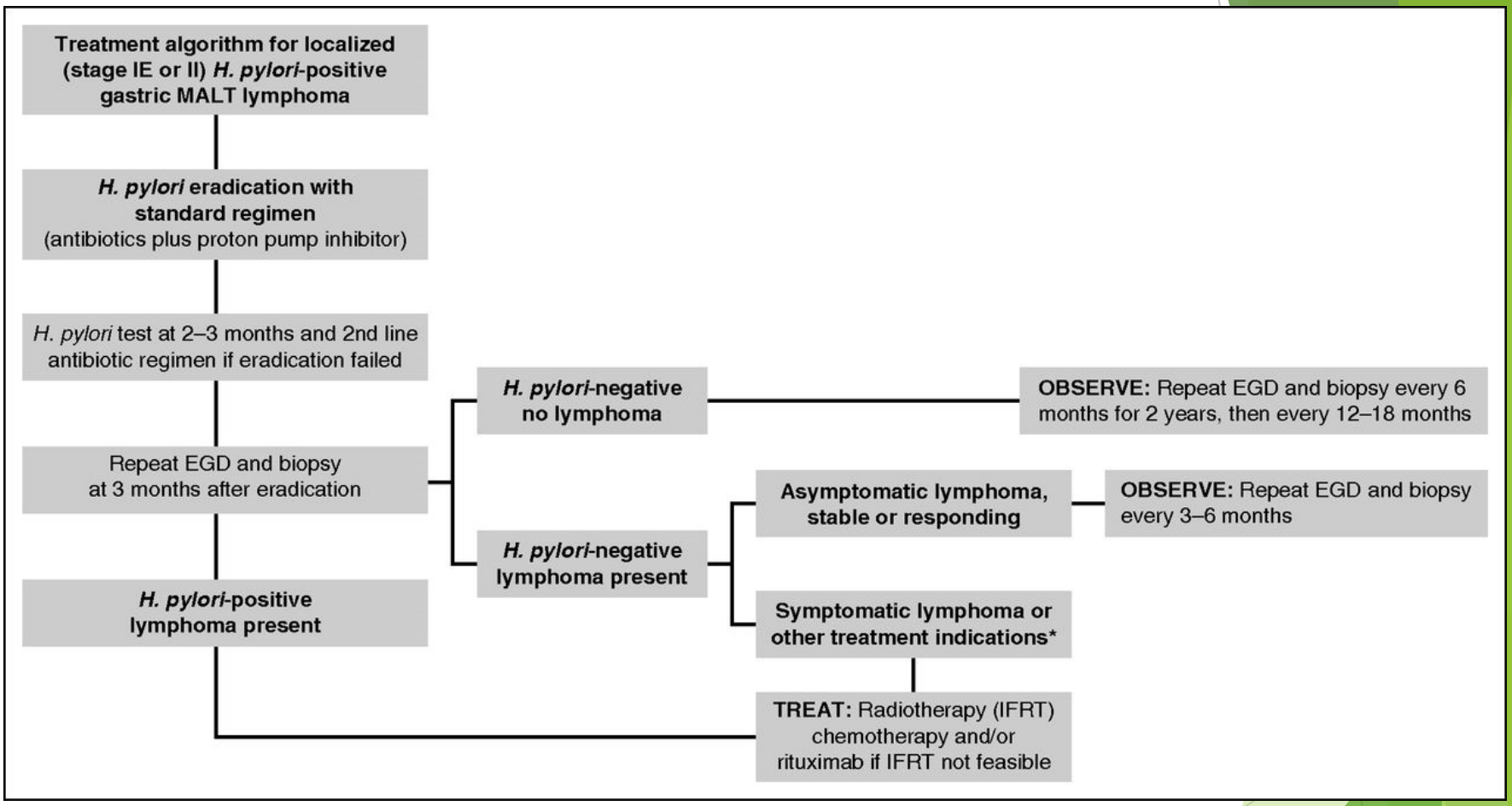
MALT: Treatment

- Treat underlying inflammatory etiology
  - Gastric MALT – H. Pylori tx
    - Antibiotic treatment alone sufficient in 70%
    - t(11;18) associated with resistance to antibiotics
  - Sensitive to radiation ✓✓

Like gastric adenocarcinoma.

* H. pylori is strongly associated with malignancy → MALToma.
  - It is hypothesized that certain strains of H. pylori causes this.
  - Hypothesis for MALToma: H. pylori induced gastritis causes an immune response → T-cell causes aberrant activation of B. cells → unstopped proliferation of B-cells
    - What supports that H. pylori is associated with malignancy is the great response for patients after treating H. pylori

or, alot of proliferation → alot of mitosis → Risk of mutation is higher.


Treatment algorithm for localized (stage IE or II) H. pylori-positive gastric MALT lymphoma
H. pylori eradication with standard regimen (antibiotics plus proton pump inhibitor)
H. pylori test at 2–3 months and 2nd line antibiotic regimen if eradication failed
Repeat EGD and biopsy at 3 months after eradication
H. pylori-positive lymphoma present
H. pylori-negative no lymphoma
OBSERVE: Repeat EGD and biopsy every 6 months for 2 years, then every 12–18 months
H. pylori-negative lymphoma present
Asymptomatic lymphoma, stable or responding
OBSERVE: Repeat EGD and biopsy every 3–6 months
Symptomatic lymphoma or other treatment indications*
TREAT: Radiotherapy (IFRT) chemotherapy and/or rituximab if IFRT not feasible

Mantle cell lymphoma: General

men predominance

- Non-curable, 6th decade
- Median survival 5 years
- Male predominance
- Generally advanced stage at presentation 70%
  - Extranodal involvement: GI tract (lymphomatous polyposis)
- CD5+, CD20+, CD19+ CD23-, cyclin D1+ (CCND1 gene)

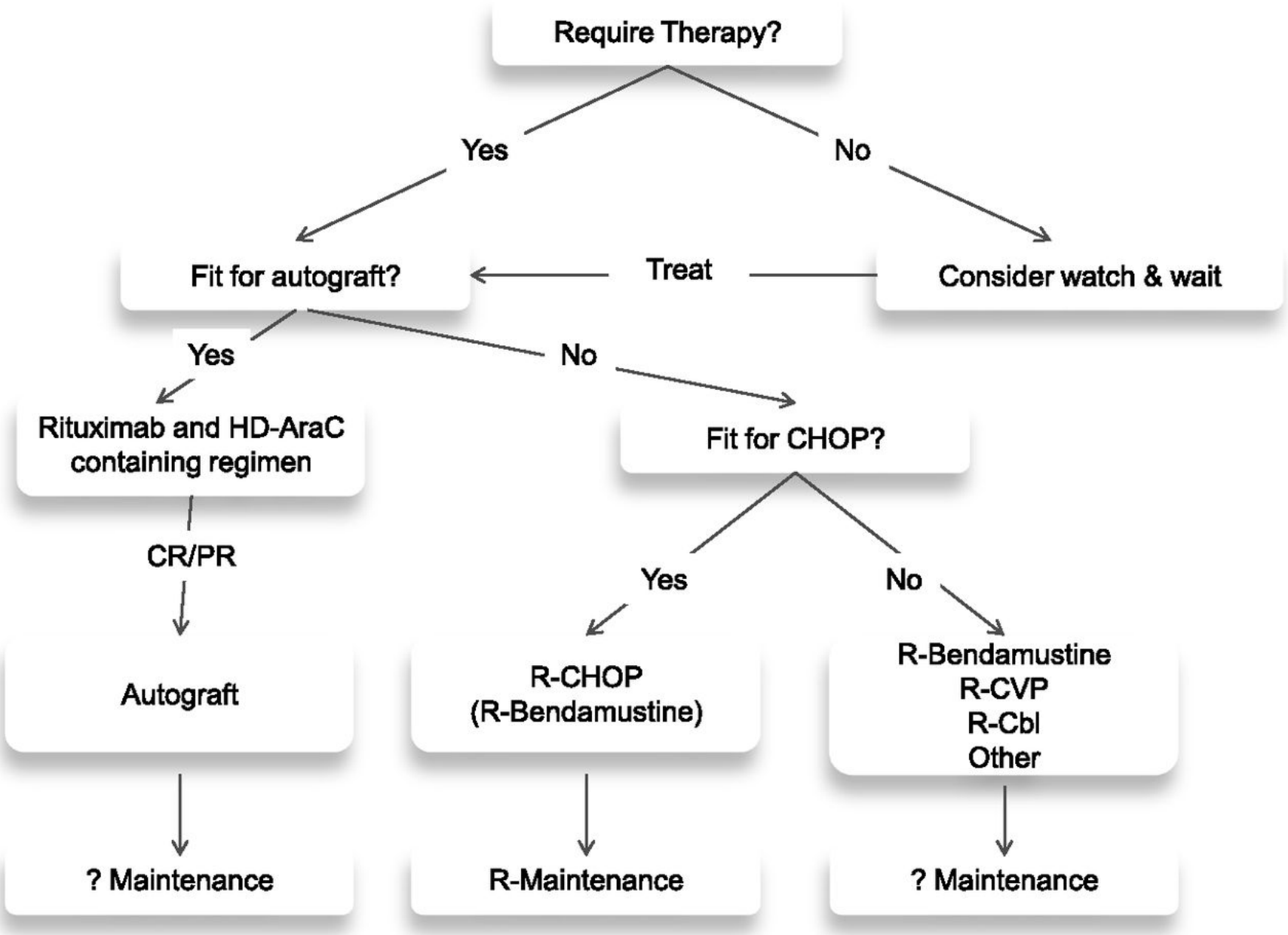
G1/S phase

- Cyclin D1: independent growth and angiogenesis via VEGF production. Down-regulate Fas expression, leading to increased chemotherapeutic resistance and protection from apoptosis
- t(11;14) translocation

Mantle cell lymphoma: Treatment

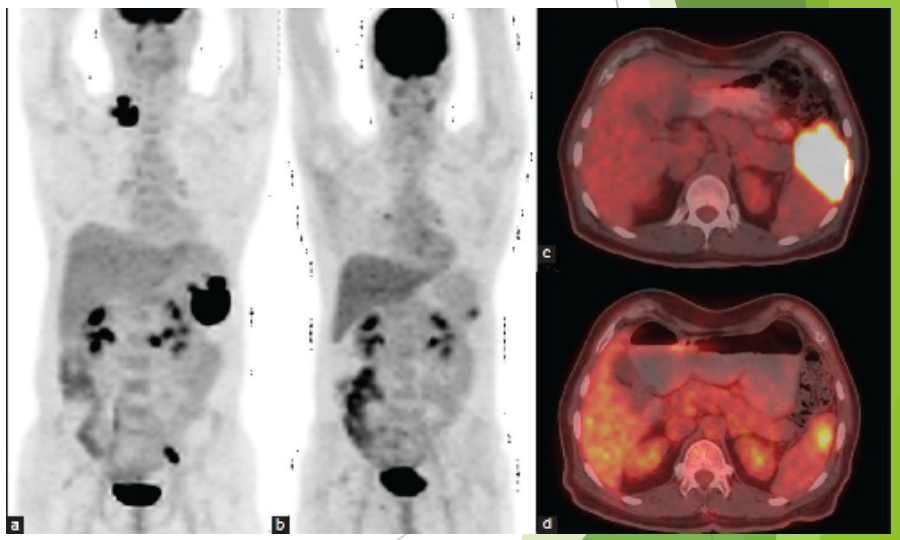
- There is a small subset of patients with MCL that will have a more indolent course and may not require treatment initially
- Chemosensitive
- For younger patients, RCHOP/RDHAP followed by auto PBSCT
  - Or R-hyperCVAD
- For non-transplant candidates, R-Bendamustine
- Clinical trials

For many indolent Lymphomas that are not curable → (Like follicular and mantle Lymphomas.
we don't have to introduce chemo and radio therapy, so as not to replace the indolent not affecting Life Lymphoma by bad side effects of chemo, and at the end it is not curable!)


Require Therapy?
Yes
No
Fit for autograft?
Treat
Consider watch & wait
Yes
No
Rituximab and HD-AraC containing regimen
Fit for CHOP?
CR/PR
Yes
No
Autograft
R-CHOP (R-Bendamustine)
R-Bendamustine
R-CVP
R-Cbl
Other
? Maintenance
R-Maintenance
? Maintenance

Diffuse Large B-cell lymphoma: General

- Aggressive lymphoma
  - But potentially curable (~50%)
- De novo or transformed low grade lymphoma (follicular for example)
- Immunodeficiency (EBV associated)
- Presentation
  - Lymphadenopathy
    - Rapidly expanding mass
  - Extranodal sites
  - B symptoms



Diffuse Large B-cell lymphoma: Prognosis

- International Prognostic Index (IPI) predicts 5 year survival
  - Age (≥60)
  - Performance status (>2)
  - LDH (> ULN)
  - Extranodal involvement (>1 site)
  - Stage (>2)
- Low risk (0-1) 73%
- Low-int (2) 51%
- High-int (3) 43%
- High risk (4-5) 26%

IPS
HL

Albumin > 4
Hb < 10.5
WBC > 15k
Lymphocyte < 600
male

Age > 45 y/o
stage IV

IPI
NHL

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Diffuse Large B-cell lymphoma: Treatment

- Combination chemotherapy
  - R=rituximab*
  - C=cyclophosphamide
  - H=doxorubicin
  - O=vincristine
  - P=prednisone
- If relapse, salvage with platinum based chemotherapy (RICE or RDHAP) followed by autologous stem cell transplant

R CHOP

Burkitt Lymphoma: General Features

- High-grade lymphoma
  - Most rapidly growing neoplasm in humans
- C-**myc** translocation (**mitosis always**!)
  - t(8;14)
  - Drives cells into cell cycle
- EBV positive in 95% of African variant
- May be associated with HIV
- Potentially curable

Ironically, this tumour enlarges significantly day by day!

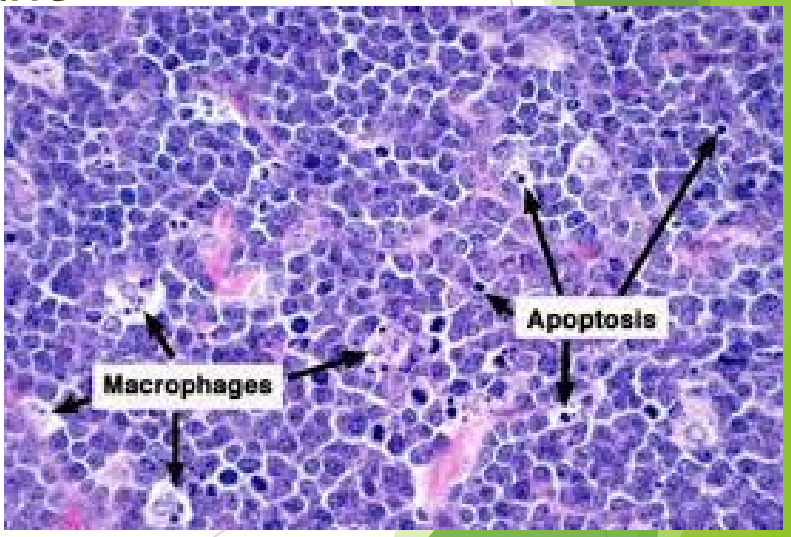


Table 2

Burkitt Lymphoma Variants

	Endemic	Sporadic	AIDS-Associated BL
Epidemiology	5–15/10^5 per year, much more common in children than adults	2–3/10^6 per year, more common in children than adults	30%–40% of HIV-related NHL
Clinically	Facial bones affected more commonly than abdominal organs, jaw tumors are more common at young age	Abdominal organs affected more commonly than facial bones, nodal involvement more common among adults than children	Disseminated disease at presentation is common
Morphologic variants	Typical variant	Typical and BLL	BL with plasmacytoid differentiation
EBV association	> 90%	15%–30%	Variable with the location
Location of breakdown in chromosome 8	More than 100 kilobase upstream to c-*myc* exon 1	Between exons 1 and 2 of the c-*myc* gene	Between exons 1 and 2 of the c-*myc* gene
Location of breakdown in chromosome 14	In the joining segments of the IgH gene	Within the Sμ switch region of IgH gene	Within the Sμ switch region of IgH gene
Bone marrow involvement	22% at presentation	30%–38% at presentation	~30% at presentation
CNS involvement	12% at presentation	13%–17% at presentation	20%–30% at presentation

AIDS = acquired immunodeficiency syndrome; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; CNS = central nervous system; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; IgH = immunoglobulin heavy-chain; NHL = non-Hodgkin lymphoma.

Burkitt Lymphoma: Treatment

- Intensive, short-duration chemotherapy with CNS directed-therapy
  - CODOX-M/IVAC
- Risk of tumor lysis syndrome
  - Rapid tumor cell death – spontaneous or due to treatment
    - Hyperuricemia ▫ renal failure
    - Hyperkalemia (remember K^+ is high Intracellularly).
    - Hyperphosphatemia ▫ hypocalcemia
    - Metabolic acidosis

Highly aggressive B-cell lymphoma NOS with features intermediate between DLBCL and Burkitt lymphoma

- Provisional WHO classification
- Often associated with genetic mutations
  - Double hit
    - C-MYC and BCL-2
  - Triple hit
    - Plus BCL-6
- Biologically aggressive
- Poor prognosis

NHL Summary

- Many different subtypes
  - T cell vs. B cell
  - Indolent vs. aggressive
  - Incurable vs. curable
- Histology is the key to making diagnosis
  - Excisional lymph node biopsy

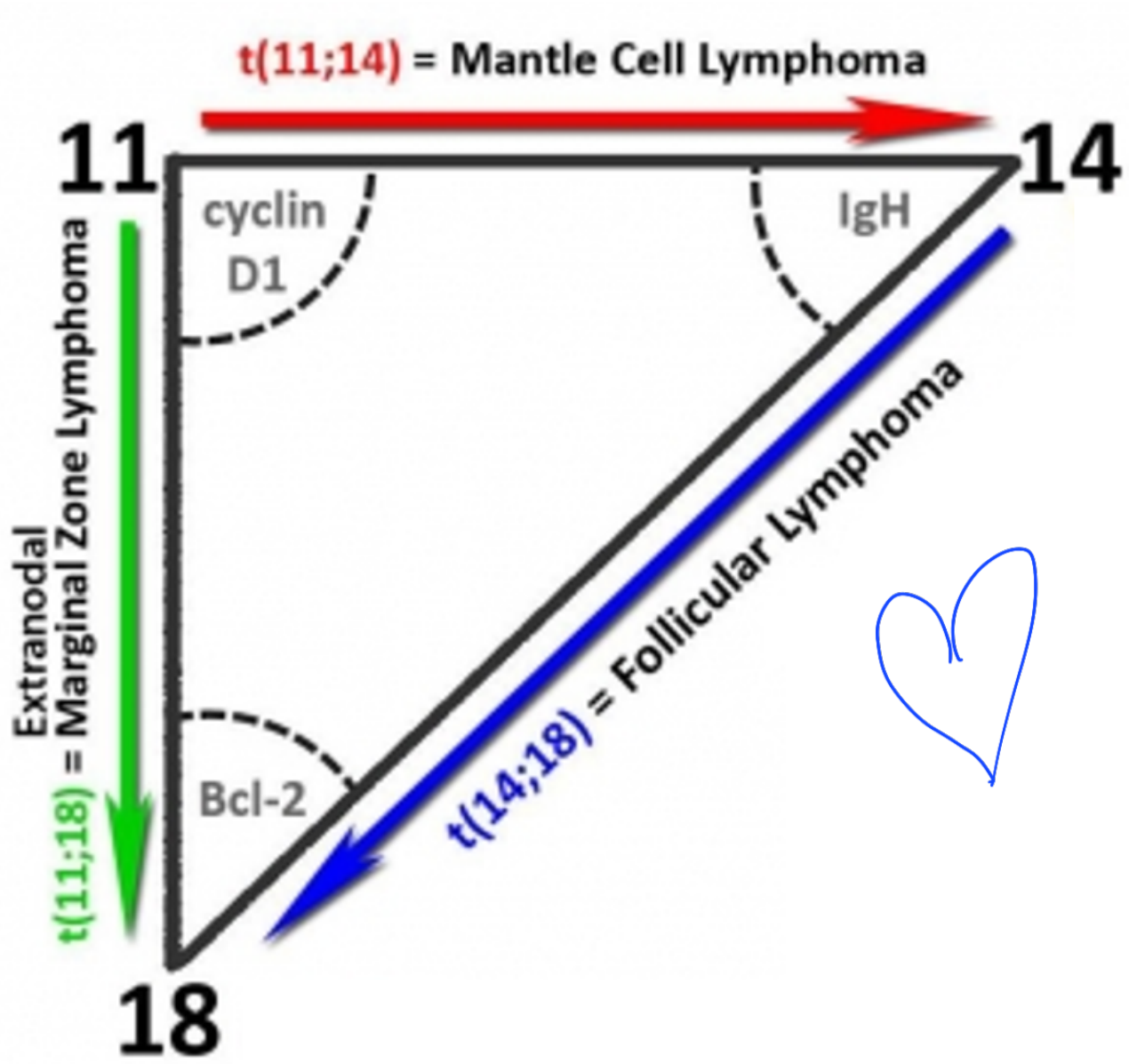

t(11;14) = Mantle Cell Lymphoma
11
14
18
cyclin
D1
IgH
Bcl-2
t(14;18) = Follicular Lymphoma
Extranodal
t(11;18) = Marginal Zone Lymphoma

TABLE 2: Immunophenotypic and histochemical markers of B-cell lymphomas/leukemias

	sIg	cIg	CD5	CD10	CD20	CD23	CD43	CD103	Cyclin D1
Follicular	+	–	–	+	+	–(+)	–	–	–
CLL/SLL	dim+	–(+)	+	–	dim+	+	+	–	–
Mantle	+	–	+	–	+	–(+)^	+	–	+
MZL/ MALT	+/+	–(+)/(+)	–/–	–/–	+/+	–/–	–(+)/–(+)	+	–/–
B-cell-PLL*	+	–	–(+)	–	+	+(–)	+	+	–
DLBCL#	+(–)	–(+)	–(+)	–(+)	+	–	–	–	–
HCL	+	–	–	–	+	–	+	–	+(–)
BL/BLL	+	–	–	+	+	–	+	NA	–
LPL	+	+	–	–	+	–	–(+)	–	–

+ = > 90% positive; +(–) = > 50% positive; –(+) = < 50% positive; – = < 10% positive; BL/BLL = Burkitt lymphoma/Burkitt-like lymphoma; cIg = cytoplasmic immunoglobulin; CLL = chronic lymphocytic leukemia; B-cell PLL = B-cell prolymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; HCL = hairy cell leukemia; LPL = lymphoplasmacytic lymphoma; MZL/MALT = splenic marginal zone/mucosa-associated lymphoid tissue; sIg = surface immunoglobulin; SLL = small lymphocytic leukemia

* = A T-cell variant is present in approximately 20% to 30% of PLL cases.

= A T-cell histiocyte-rich B-cell lymphoma variant is present in approximately 1% to 3% of DLBCL cases.

^ = 20% to 25% of cases are CD23+ by flow cytometric immunophenotyping; testing for *bcl-1* is essential.

Small B-cell

- **Follicular Lymphoma**
  - non-curable
  - t(14,18)
- **Mantle zone Lymphoma**
  - non-curable
  - t(11,14)
- **Marginal zone Lymphoma (MALToma)**
  - curable
  - * chronic inflammation
    - H. pylori
    - Sjogren synd.
  - t(11,18)

Intermediate B-cell

- **Burkitt Lymphoma**
  - Endemic / sporadic
  - t(8,14)

Large B-cell

- **Diffuse Large B-cell Lymphoma (DLBCL)**