LYMPHOMA

Dr. Riva Fineman

Overview

- Concepts, classification, lymphoma genesis
- Epidemiology
- Clinical presentation
- Diagnosis
- Staging
- Three important types of lymphoma

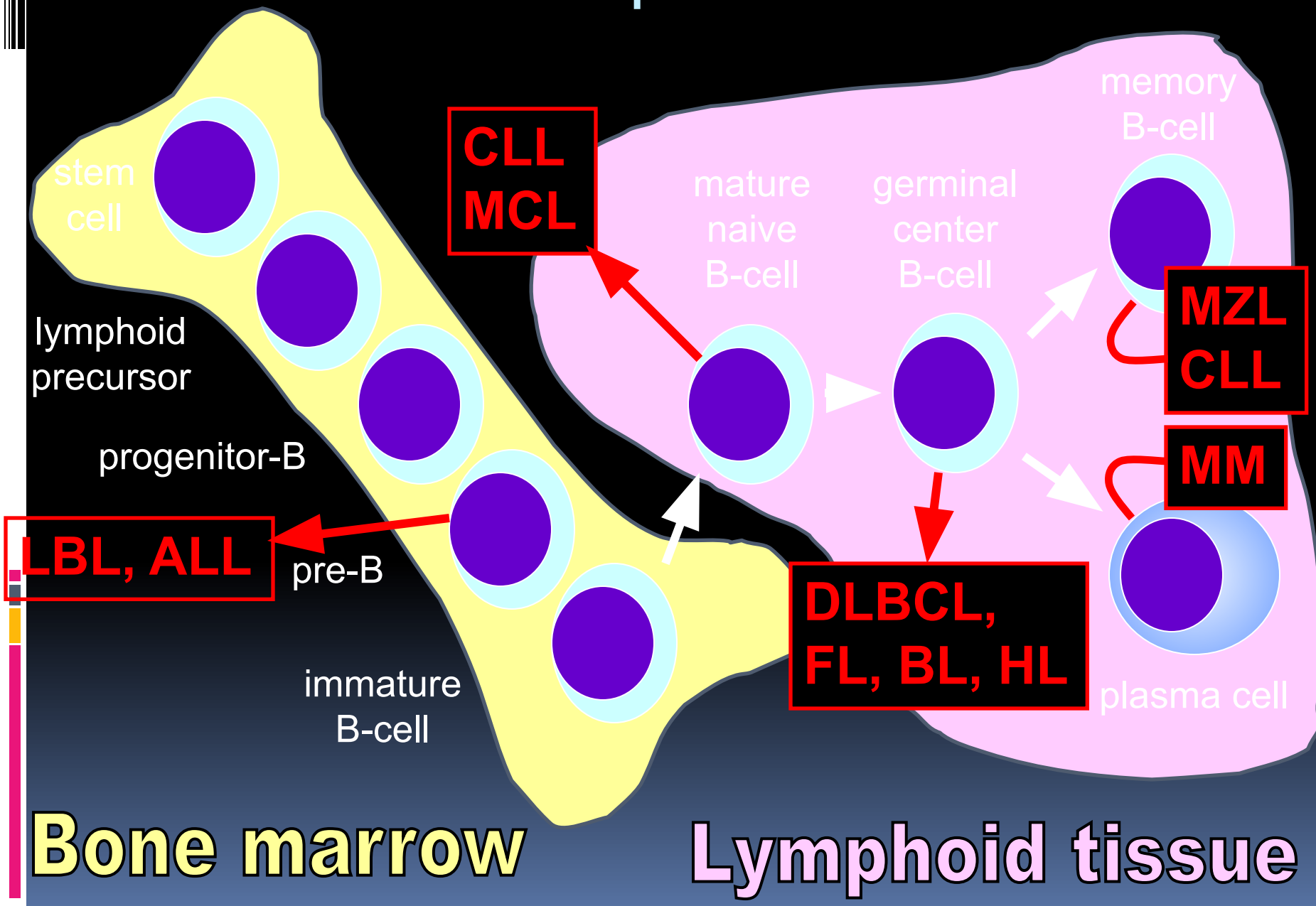
Conceptualizing lymphoma

- neoplasms of lymphoid origin (lymph nodes or extra nodal lymphatic tissues), typically causing lymphadenopathy
- leukemia vs. lymphoma
- lymphomas as clonal expansions of cells (B or T lymphocytes or NK cells) at certain developmental stages

Conceptualizing lymphoma

- Hodgkin Lymphoma – relatively uniform in histology, clinical presentation and course of the disease
- Non Hodgkin Lymphoma – a large and heterogeneous category with various cell origin, histology, clinical course. Comprises most of lymphomas

B-cell development



The challenge of lymphoma classification

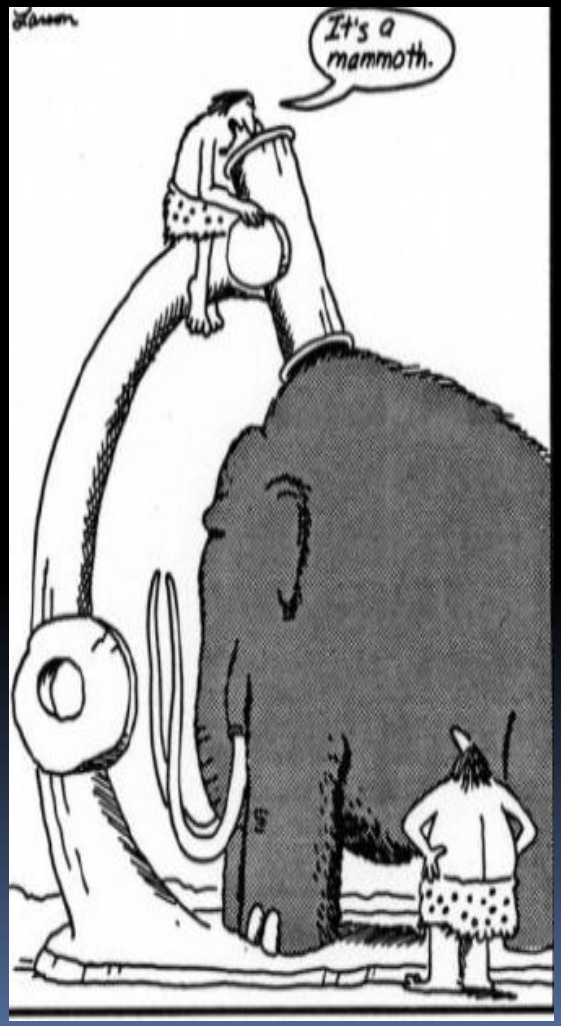
Biologically rational classification

Diseases that have distinct
- morphology
- immunophenotype
- genetic features
- clinical features

Clinically useful classification

Diseases that have distinct
- clinical features
- natural history
- prognosis
- treatment

Principles of the WHO classification



- 1.Morphology2.Immunophenotype3.Molecularbiology4.Genetic5.Clinicalpresentationand course
- I love pathologists who can diagnose lymphomas without immunohistochemistry!

Lymphoma classification (based on 2001 WHO)

- T-cell & NK-cell neoplasms
  - Precursor T-cell neoplasms (3)
  - Mature T-cell and NK-cell neoplasms (14)
  - T-cell proliferation of uncertain malignant potential (1)
- Hodgkin lymphoma
  - Classical Hodgkin lymphomas (4)
  - Nodular lymphocyte predominant Hodgkin lymphoma (1)

- B-cell neoplasms
  - Precursor B-cell neoplasms (2 types)
  - Mature B-cell neoplasms (19)
  - B-cell proliferations of uncertain malignant potential (2)

WHO Classification 2001-2008

- Precursor B-and T-cell neoplasms
- Mature B cell neoplasms
- Mature T-cell and NK neoplasms
- Hodgkin lymphoma
- Immunodeficiency associated lymphoproliferativedisorders
- Histiocyticand dendritic cell neoplasms

WHO/REAL Classification of Lymphoid Neoplasms

B-Cell Neoplasms

- Precursor B-cell neoplasm
  - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-acute lymphoblastic leukemia)
- Mature (peripheral) B-neoplasms
  - 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 and NK-Cell Neoplasms

- Precursor T-cell neoplasm
  - Precursor T-lymphoblastic leukemia/lymphoma (precursor T-acute lymphoblastic leukemia
- Mature (peripheral) T neoplasms
  - T-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
  - T-cell prolymphocytic leukemia
  - T-cell granular lymphocytic leukemia‖
  - Aggressive NK leukemia
  - Adult T-cell lymphoma/leukemia (HTLV-1+)
  - Extranodal NK/T-cell lymphoma, nasal type#
  - Enteropathy-like T-cell lymphoma**
  - Hepatosplenic γδ T-cell lymphoma*
  - Subcutaneous panniculitis-like T-cell lymphoma*
  - Mycosis fungoides/Sézary syndrome
  - Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
  - Peripheral T-cell lymphoma, not otherwise characterized
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, T/null cell, primary systemic type

Hodgkin's Lymphoma (Hodgkin's Disease)

- Nodular lymphocyte predominance Hodgkin's lymphoma
- Classic Hodgkin's lymphoma
  - Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
  - Lymphocyte-rich classic Hodgkin's lymphoma
  - Mixed cellularity Hodgkin's lymphoma
  - Lymphocyte depletion Hodgkin's lymphoma

Table 70–1. Clinical Classification of Lymphoid Malignancies

Indolent B-cell lymphomas
- *Chronic lymphocytic leukemia*
- *Lymphoplasmacytoid lymphoma/immunocytoma/Waldenström macroglobulinemia*
- *Hairy cell leukemia*
- Marginal zone B-cell lymphoma
  - Nodal: Monocytoid B-cell lymphoma
  - Extranodal: MALT lymphoma
  - Spleen/peripheral blood: Splenic lymphoma with villous lymphocytes or splenic marginal zone lymphoma
- Follicle center lymphoma, grade I and II
- Mantle cell lymphoma of mantle zone type
- Primary cutaneous follicle center lymphoma

Aggressive B-cell lymphomas (intermediate risk)
- *Prolymphocytic leukemia*
- Mantle cell lymphoma (diffuse, nodular, and blastic variants)
- Follicle center lymphoma grade III
- Diffuse large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Primary cutaneous large cell lymphoma
- Lymphomatoid granulomatosis
- Immunoproliferative small intestinal disease
- *Plasmacytoma/plasma cell leukemia*

Very aggressive B-cell lymphoma
- Precursor B-lymphoblastic lymphoma/leukemia
- Burkitt lymphoma/B-cell ALL
- *Plasma cell leukemia*

Indolent T-cell and NK cell lymphomas
- T-cell large granular lymphocyte leukemia
- Chronic NK cell lymphocytosis
- Mycosis fungoides/*Sézary syndrome*
- *Smoldering and chronic adult T-cell leukemia/lymphoma, HTLV-1 related*

Aggressive T-cell and NK cell lymphomas (intermediate risk)
- *T-cell prolymphocytic leukemia*
- Peripheral T-cell lymphoma, unspecified
- Angiocentric sinonasal lymphoma
- Intestinal T-cell lymphoma
- Anaplastic large cell lymphoma (T- and null cell type)
- Hepatosplenic γδ T-cell lymphoma.
- CD56+ T-cell large granular lymphocyte leukemia

Very aggressive T-cell and NK cell lymphomas
- Adult T-cell lymphoma/leukemia (HTLV-1 related)
- Precursor T-lymphoblastic lymphoma/leukemia
- Aggressive NK cell lymphoma
- *CD3+, CD33−, DR+, promyelocyte-like NK cell leukemia*
- *ALL-like NK cell leukemia*
- *Undifferentiated myeloid/NK cell leukemia*

Note: Disorders that are not discussed in this chapter are in *italic*.
Adapted from Hiddemann,[2] with permission.

A practical way to think of lymphoma

Category		Survival of untreated patients	Curability	To treat or not to treat
Non-Hodgkin lymphoma	Indolent	Years	Generally not curable	Generally defer Rx if asymptomatic
	Aggressive	Months	Curable in some	Treat
	Very aggressive	Weeks	Curable in some	Treat
Hodgkin lymphoma	All types	Variable – months to years	Curable in most	Treat

Mechanisms of lymphoma genesis

- Genetic alterations - lack of apoptosis (bcl-2), proliferation (c-myc)
- Infection – viral (EBV, HCV, HTLV-1), bacterial – H. Pylori
- Environmental factors – chemicals, diet
- Immunosuppression – AIDS, post transplant (solid organs, BMT)
- Chronic antigen stimulation - autoimmunity
- Family history – 3.3 times increase risk

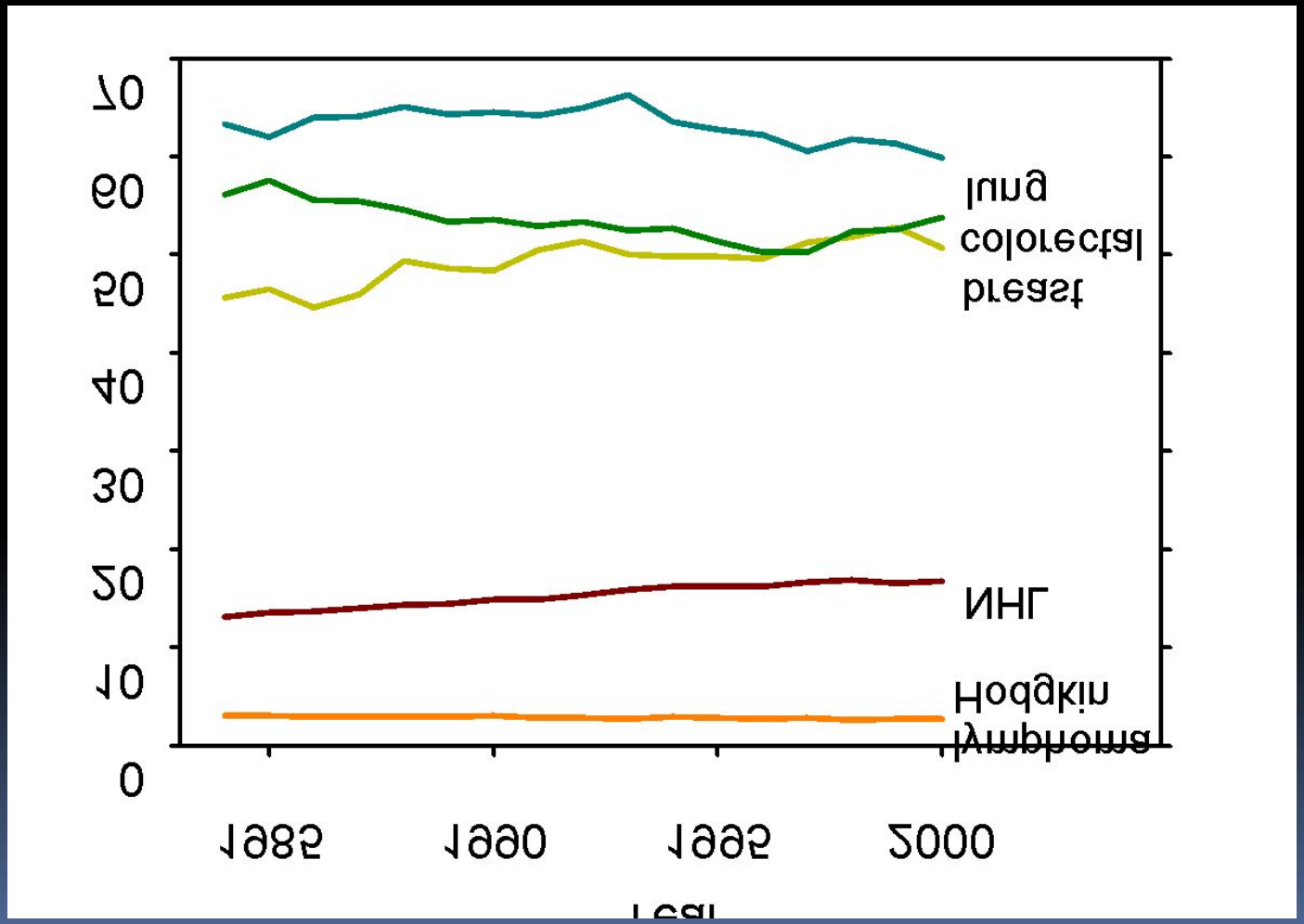
Epidemiology of lymphomas

- 5th most frequently diagnosed cancer, ±4% of all cancers and cancer deaths in USA
- males > females
- whites > other races
- incidence
  - NHL increasing over time
  - Hodgkin lymphoma stable

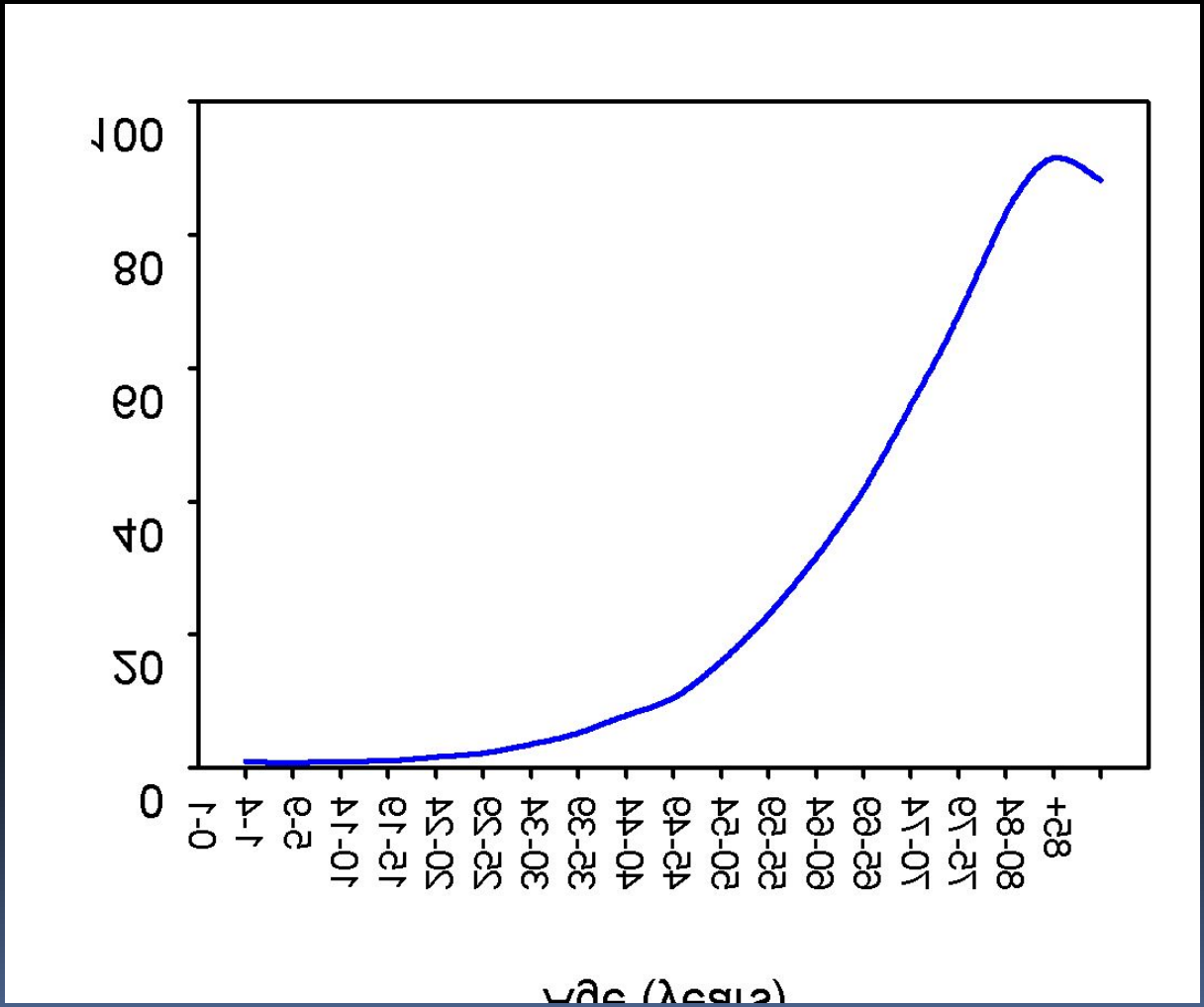
Epidemiology of lymphomas

- Geographic variability – B cell lymphoma common in Western world, T and NK cell lymphoma – most of lymphomas in South East Asia

Incidence of lymphomas in comparison with other cancers in Canada

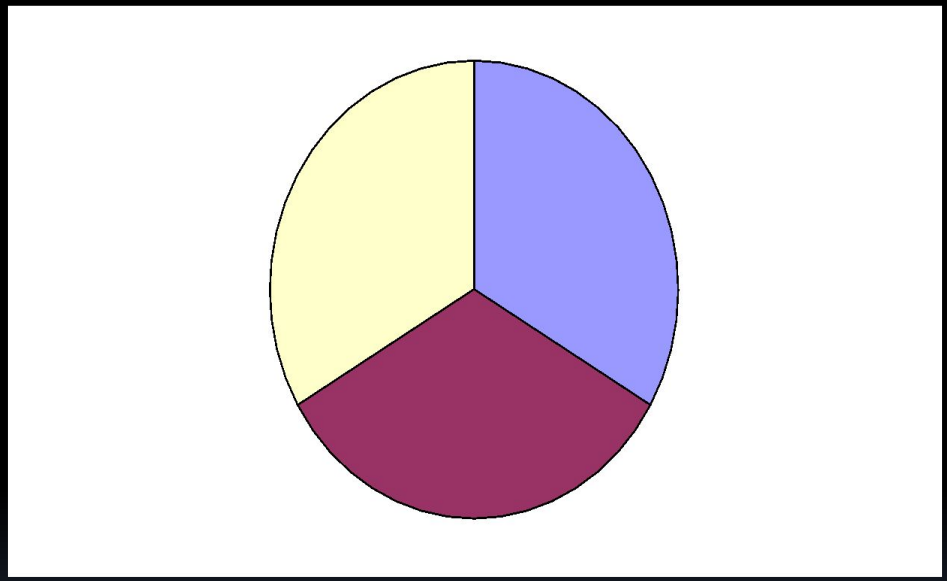


Age distribution of new NHL cases in Canada



Non-Hodgkin lymphoma
Incidence

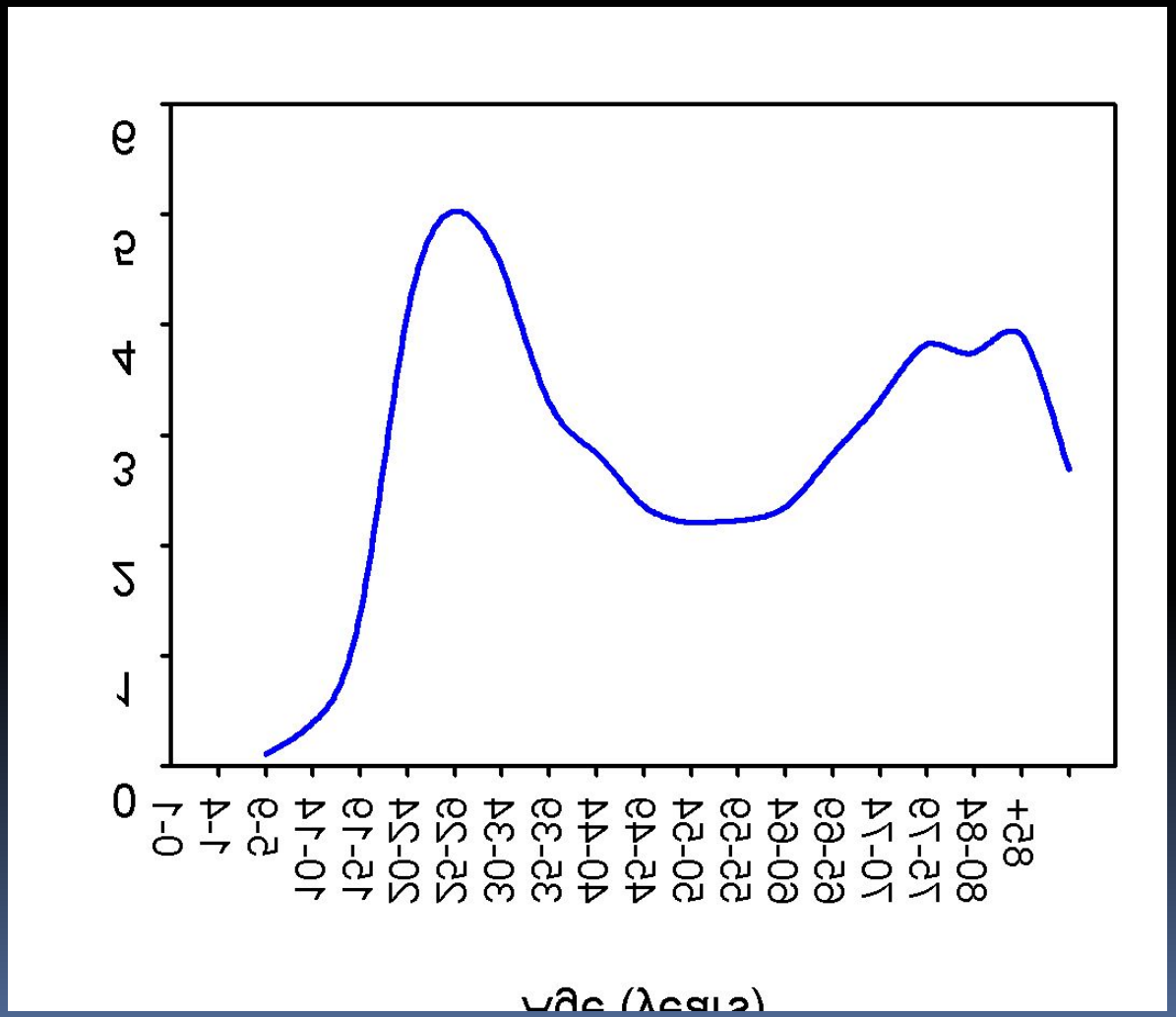
Diffuse large B-cell lymphoma



Follicular lymphoma

Other NHL

Age distribution of new Hodgkin lymphoma cases in Canada



Risk factors for NHL

- immunosuppression or immunodeficiency
- connective tissue disease
- family history of lymphoma
- infectious agents
- chemicals
- dietary
- ionizing radiation

Clinical manifestations

- Variable
  - severity: asymptomatic to extremely ill
  - time course: evolution over weeks, months, or years
- Systemic manifestations
  - Weakness, fever, night sweats, weight loss, anorexia, pruritus
- Local manifestations
  - lymphadenopathy, splenomegaly - most common
  - any tissue potentially can be infiltrated

Other complications of lymphoma

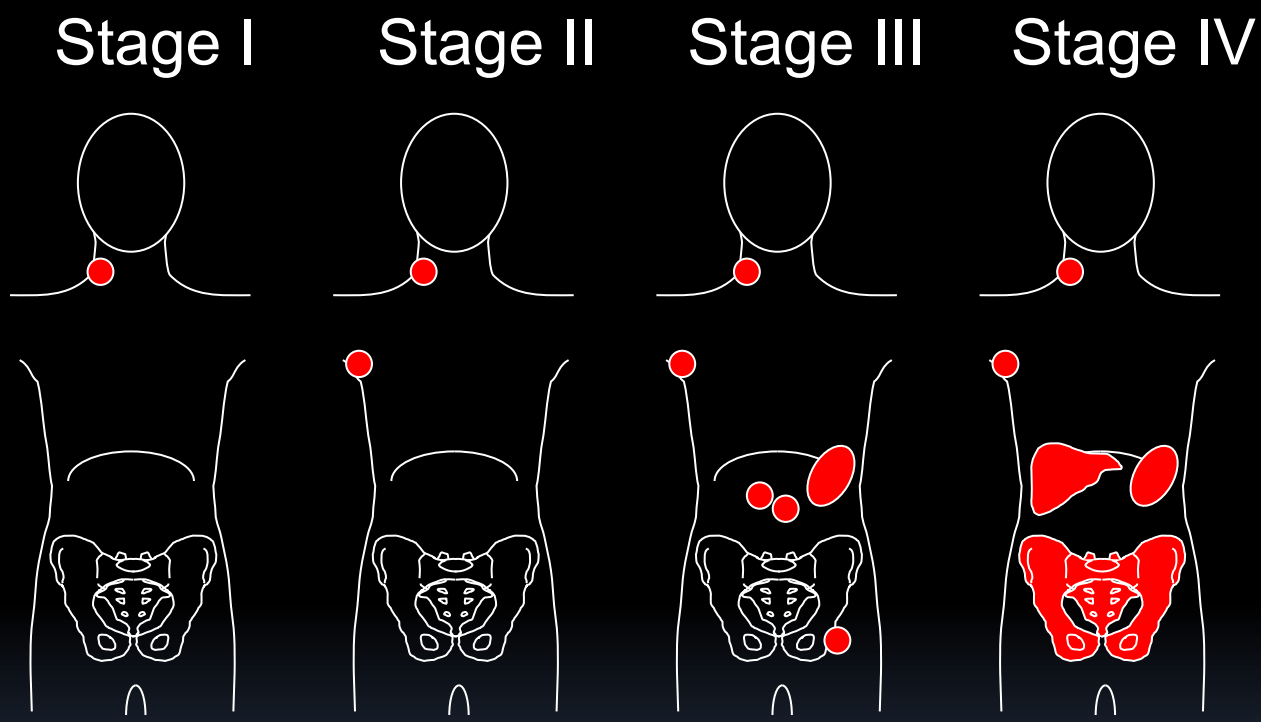
- bone marrow failure (infiltration)
- CNS infiltration
- immune hemolysis or thrombocytopenia
- compression of structures (eg spinal cord, ureters) by bulky disease
- pleural/pericardial effusions, ascites

Diagnosis requires an adequate biopsy

- Diagnosis should be biopsy-proven before treatment is initiated
- Need enough tissue to assess cells and architecture, immunopenotyping, cytogenetics and molecular studies

  - open vs core needle biopsy vs FNA

Staging of lymphoma – Ann Arbor system



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

Staging Pocedures

- History and physical examination
- Bone marrow aspiration and biopsy
- Imaging – anatomical: X-ray, CT scan – neck, chest, abdomen; functional – radio isotope scanning - gallium^{67}, PET-CT

Prognostic factors

- Histologic type
- Age
- Performance status
- Ann Arbor stage
- Size of tumor mass
- Extranodal involvement
- LDH, β2-microglobulin
- Molecular or cytogenetic abnormalities
- Response to treatment

Prognostic models - IPI

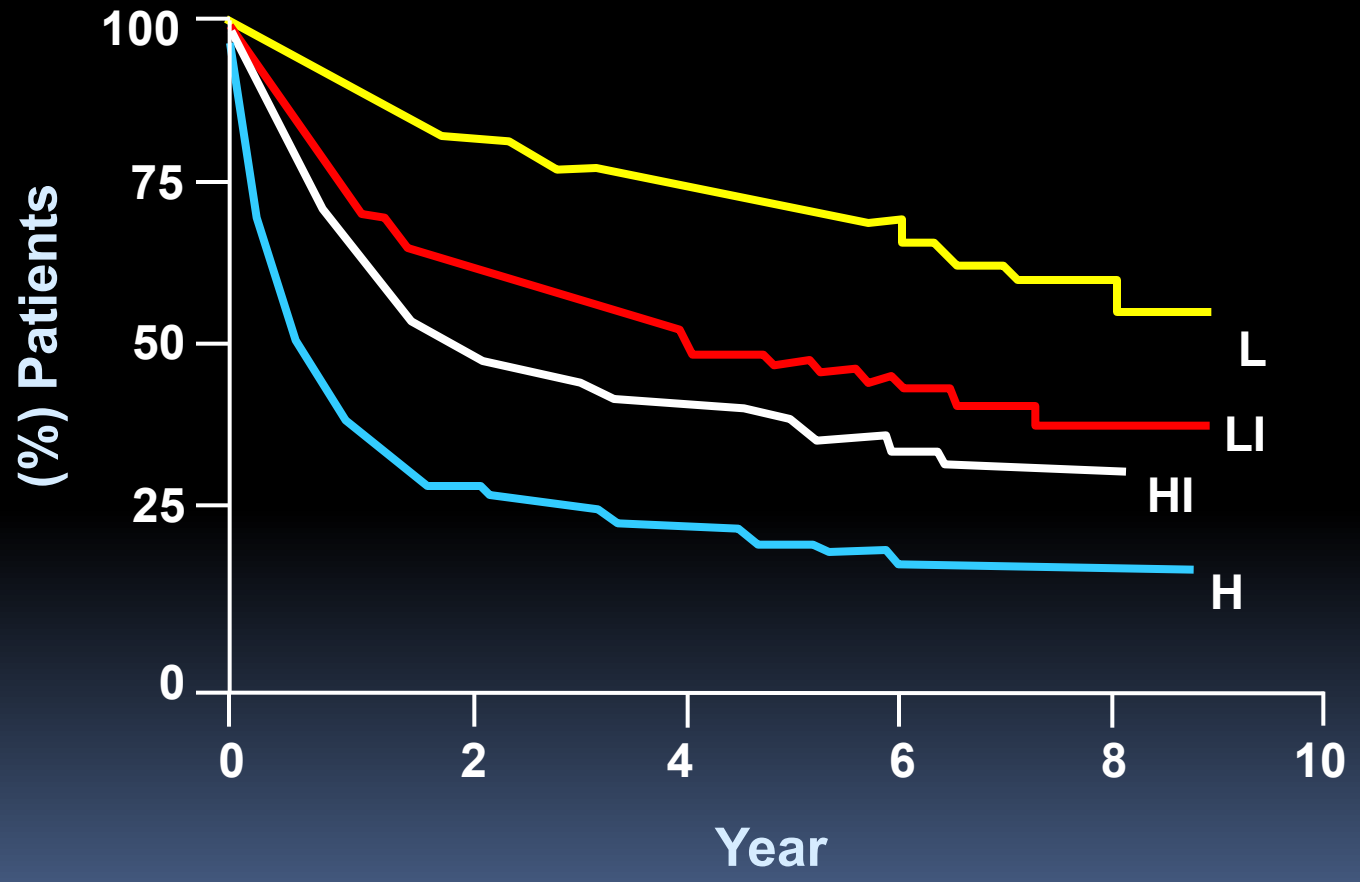
- A – age > 60 ► 1 pt.
- P – performance status > 2 ►1 pt.
- L – LDH ↑ ► 1 PT.
- E – extranodal sites > 1 ► 1 pt.
- S – stage ≥ 3 ► 1 pt.

Table 70–3. Prognostic Indices in Large Cell Lymphoma[a]

Risk Category	Score	Patients in Risk Group (%)	Complete Responses (%)	5-Year Disease-Free Survival for Patients with Complete Responses (%)	5-Year Survival (%)
International Prognostic Index[42]					
Low	0 or 1	35	87	70	73
Low–intermediate	2	27	67	50	51
High–intermediate	3	22	55	49	43
High	4 or 5	16	44	40	26
Age-Adjusted International Index[42]					
Low	0	22	92	86	83
Low–intermediate	1	32	78	66	69
High–intermediate	2	32	57	53	46
High	3	14	46	58	32
Tumor score[47]					
Low	0–2	61	91	92[b]	83[b]
High	≥3	39	46	46[b]	24[b]

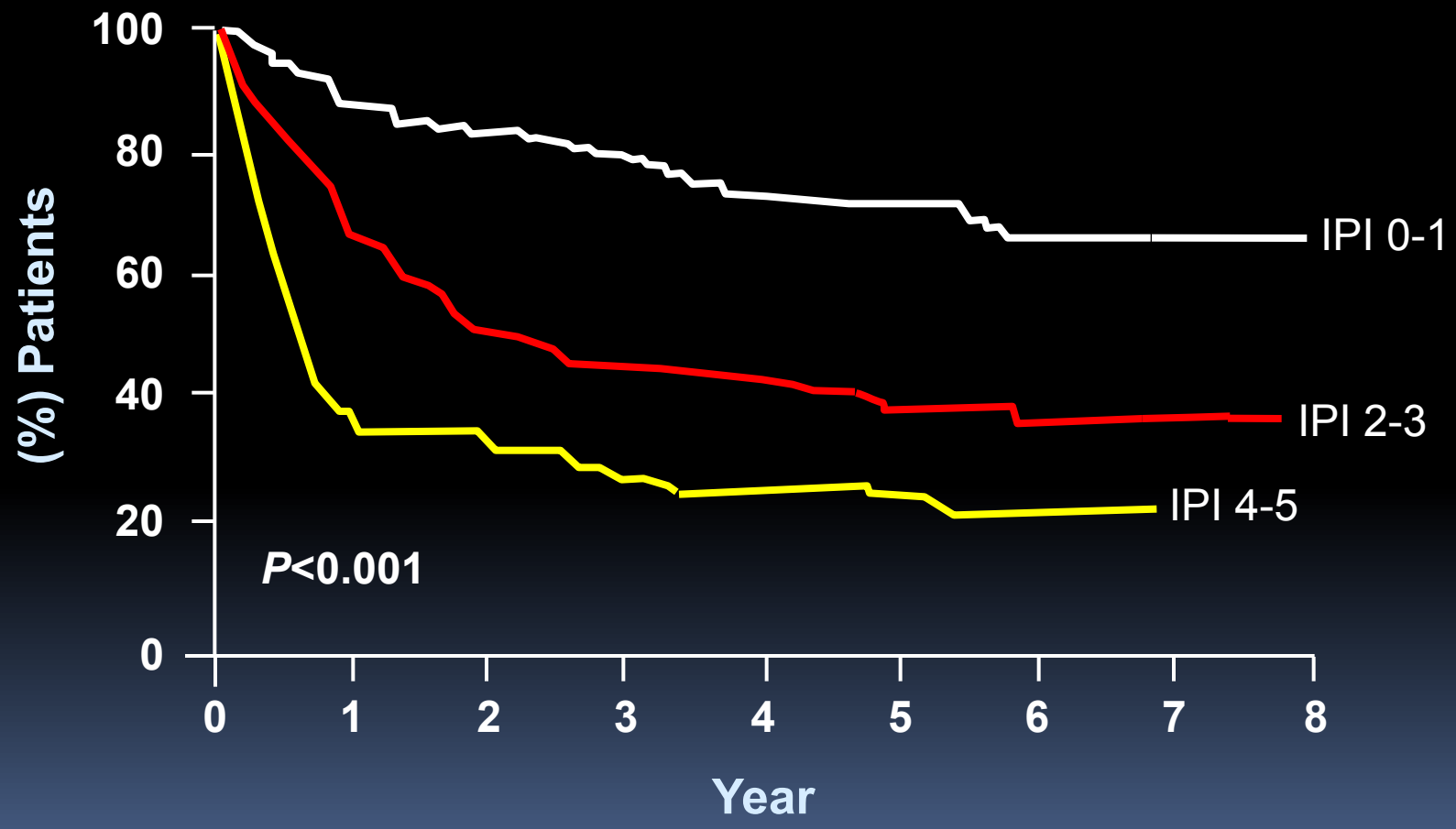
Age-Adjusted International Index: one point each is assigned for performance status <1, elevated lactate dehydrogenase level, stage III or stage IV disease.
Tumor score: one point each is assigned for elevated lactate dehydrogenase level >110%, elevated β_2-microglobulin >3, presence of constitutional symptoms, stage III or stage IV disease, each mass >7cm.
International Prognostic Index: one point each is assigned for age >60, performance status <1, elevated lactate dehydrogenase level, involvement of more than one extranodal site, stage III or stage IV disease.
[b] 3 year survival.

IPI: Overall Survival (OS) by Risk Strata



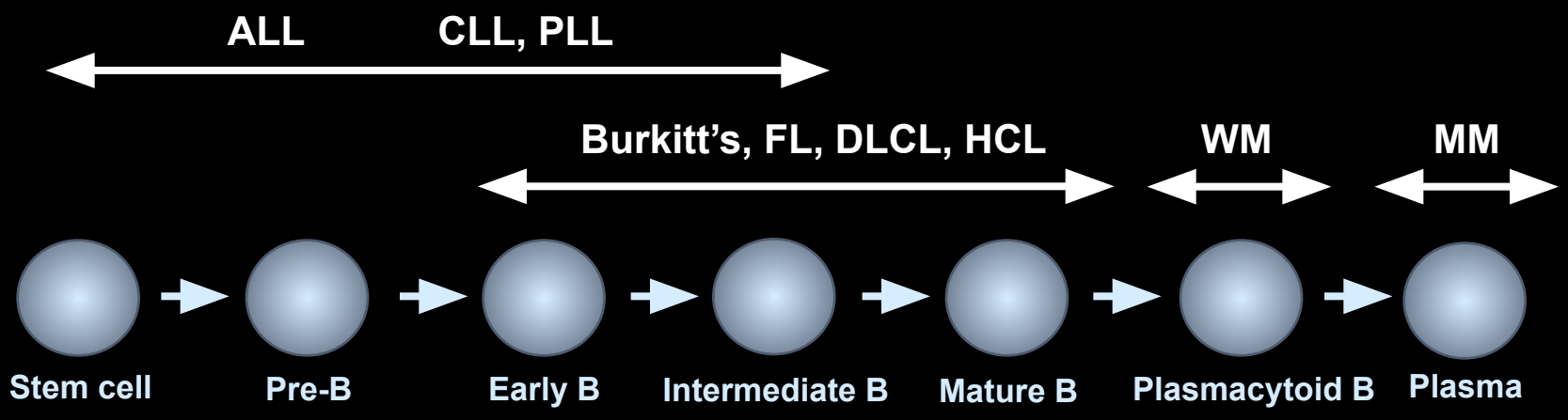
.The Non-Hodgkin's Lymphoma Pathologic Classification Project. *Cancer*. 1982;49:2112

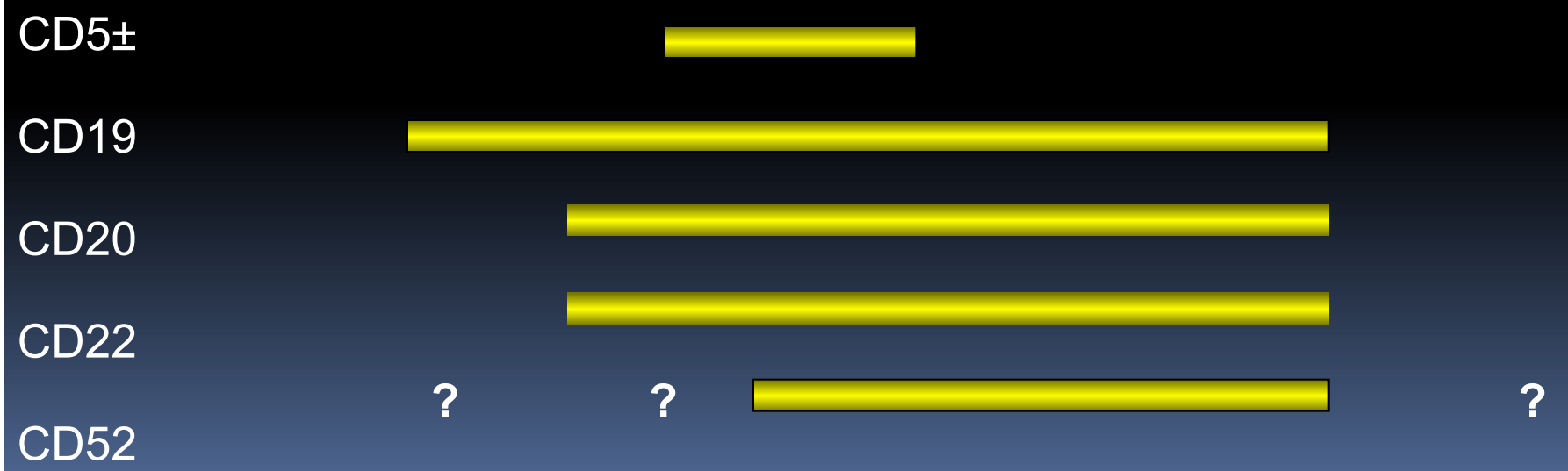
Diffuse Large B-Cell Lymphoma (DLCL): OS



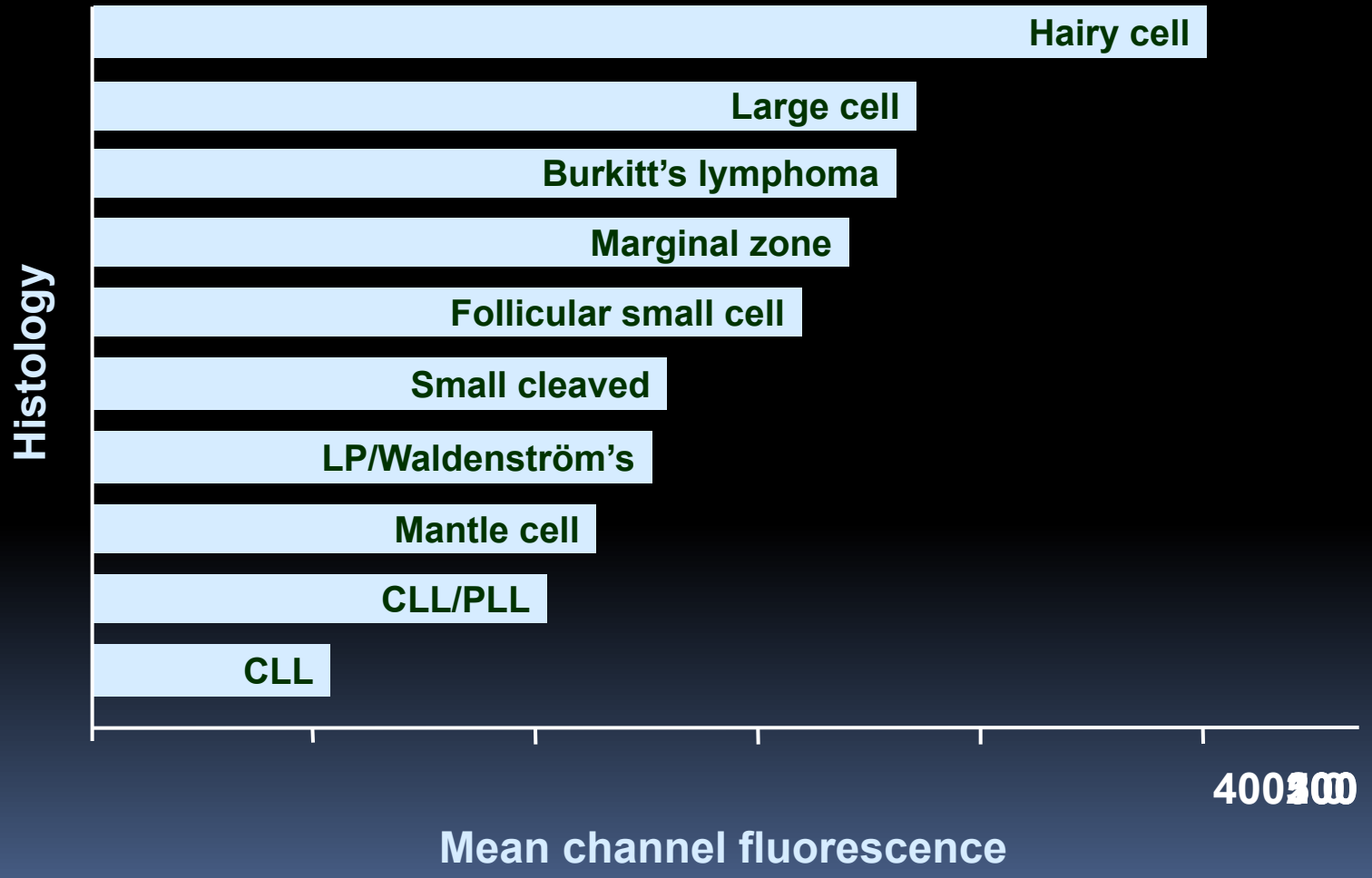
.Adapted from Armitage. *J Clin Oncol.* 1998;16:2780

Antigen Expression in B-Cell Lineage





CD20 Expression in B-Cell Malignancies



.Adapted with permission from G.D. Maloney

Three types of lymphoma worth knowing about

- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Hodgkin lymphoma

Follicular lymphoma

- most common type of “indolent” lymphoma in the Western world
- usually widespread at presentation
- often asymptomatic
- not curable (some exceptions)
- associated with BCL-2 gene rearrangement [t(14;18)]
- cell of origin: germinal center B-cell

- defer treatment if asymptomatic ("watch-and-wait")
- several chemotherapy options if symptomatic
- median survival: years
- although considered "indolent", morbidity and mortality can be considerable
- transformation to aggressive lymphoma can occur

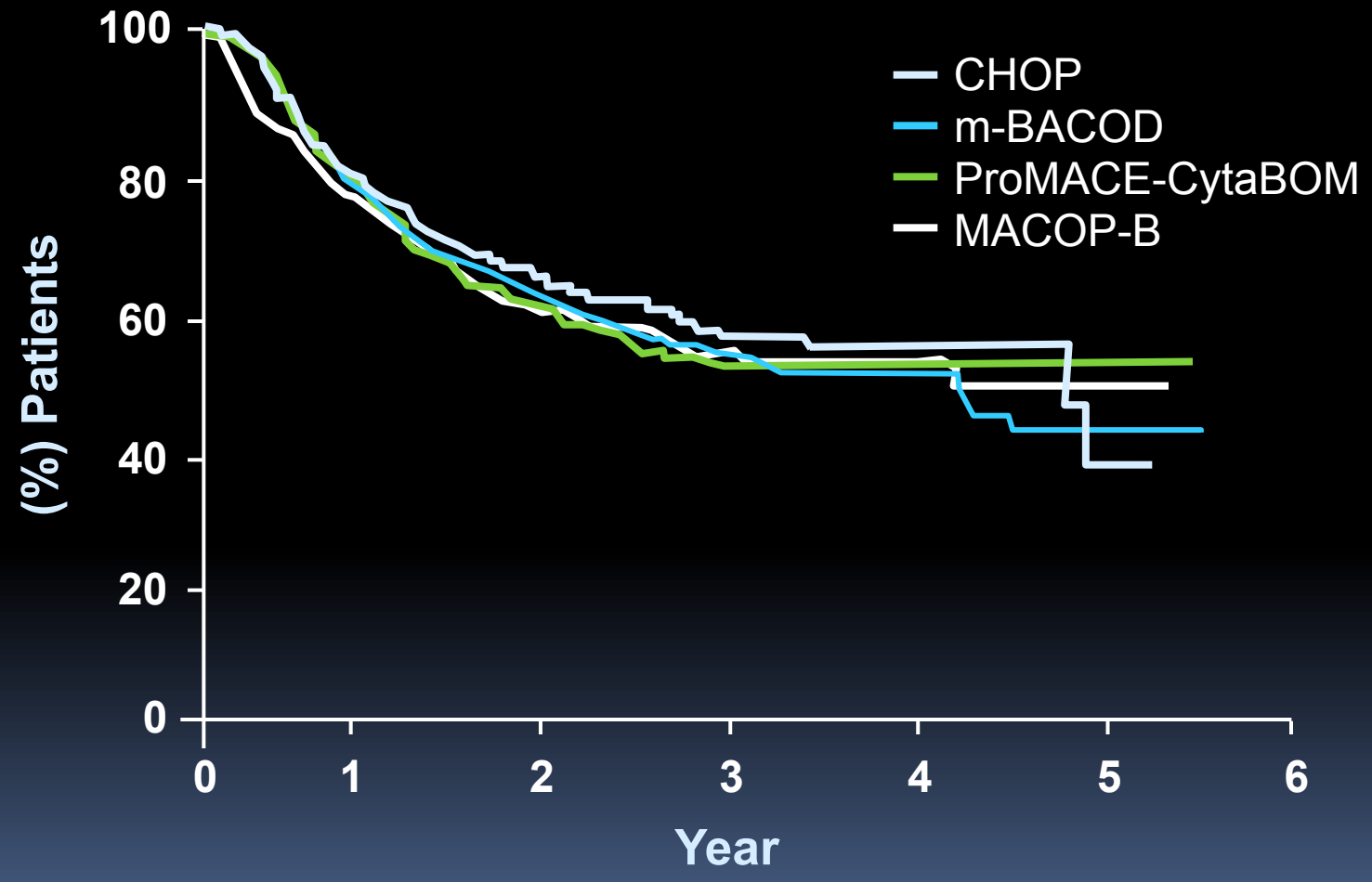
Treatment

- Chemotherapy – single agent ± corticosteroids, combination – CVP, CHOP etc.
- Monoclonal Ab – anti-CD20, anti-CD22, anti-CD30, anti-CD25, anti-CD52 etc.
- Combination of chemotherapy and monoclonal antibodies
- Radiotherapy - involved field, extended, adjuvant
- Radioimmunotherapy

Diffuse large B-cell lymphoma

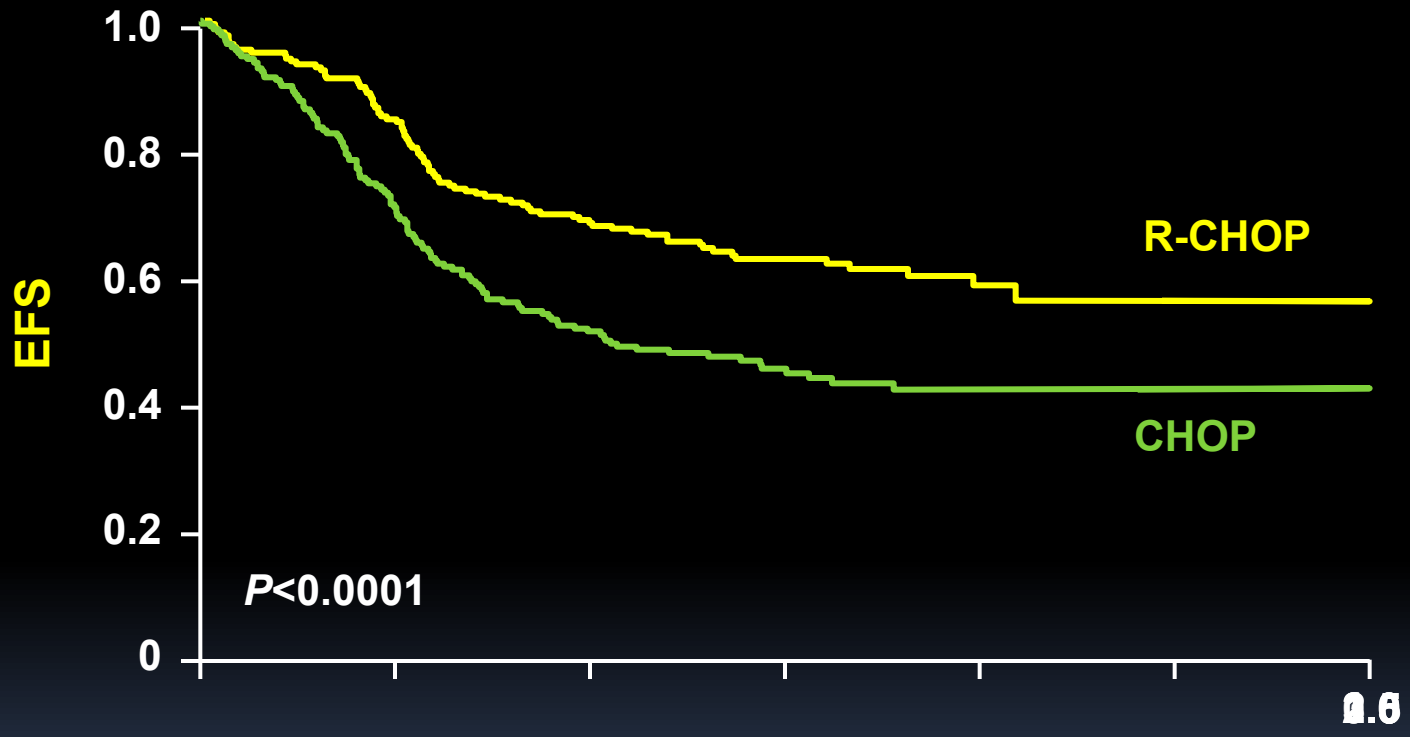
- most common type of “aggressive” lymphoma
- usually symptomatic
- extranodal involvement is common
- cell of origin: germinal center B-cell
- treatment should be offered
- curable in ~ 40%

National High Priority Lymphoma Study: Progression-Free Survival



.Adapted from Fisher. *N Engl J Med.* 1993;328:1002

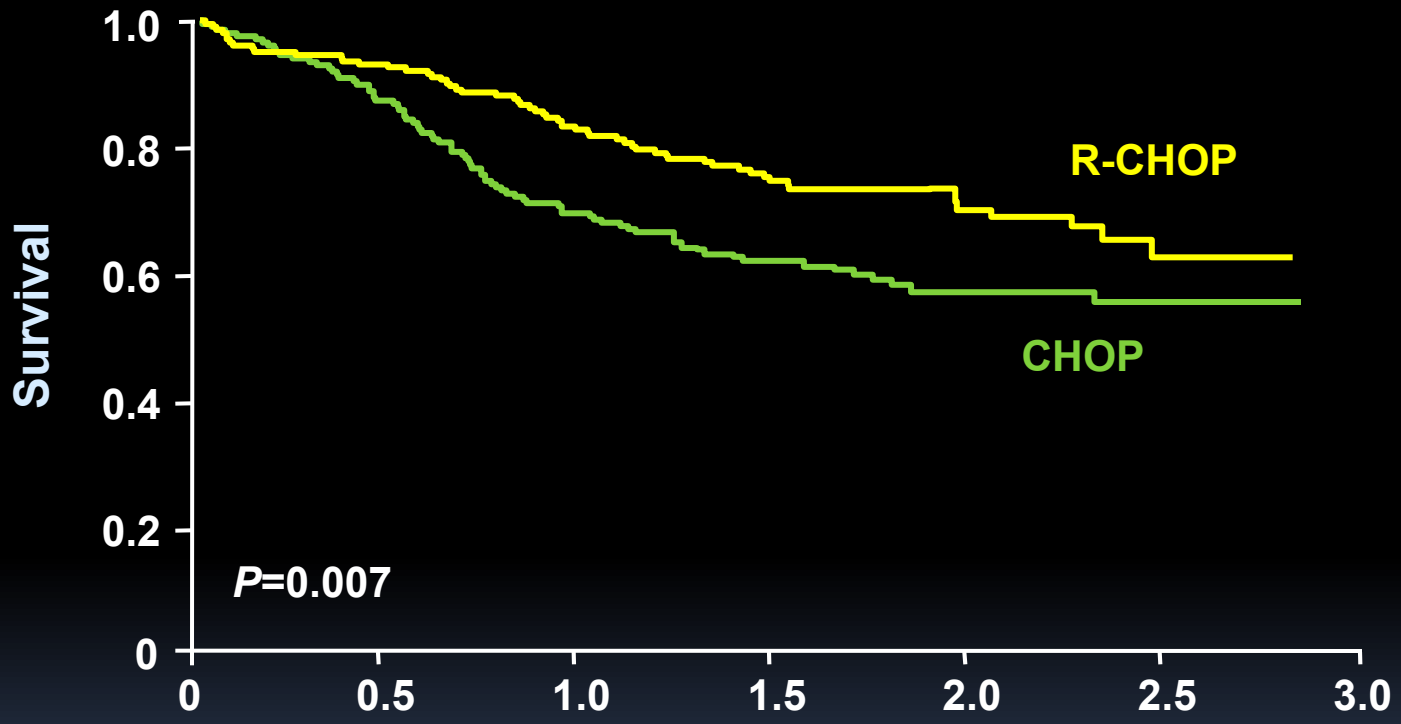
GELA Phase III Trial: EFS



No. at Risk						
R-CHOP	20	17	13	10	6	1
CHOP	19	14	10	7	4	1
P	7	4	1	2	2	7

.Coiffier et al. *N Engl J Med.* 2002;346:235

GELA Phase III Trial: OS



No. at Risk

R-CHOP	20	18	16	811	6	2
CHO	19	17	13	9	5	1
P	7	1	6	6	8	6

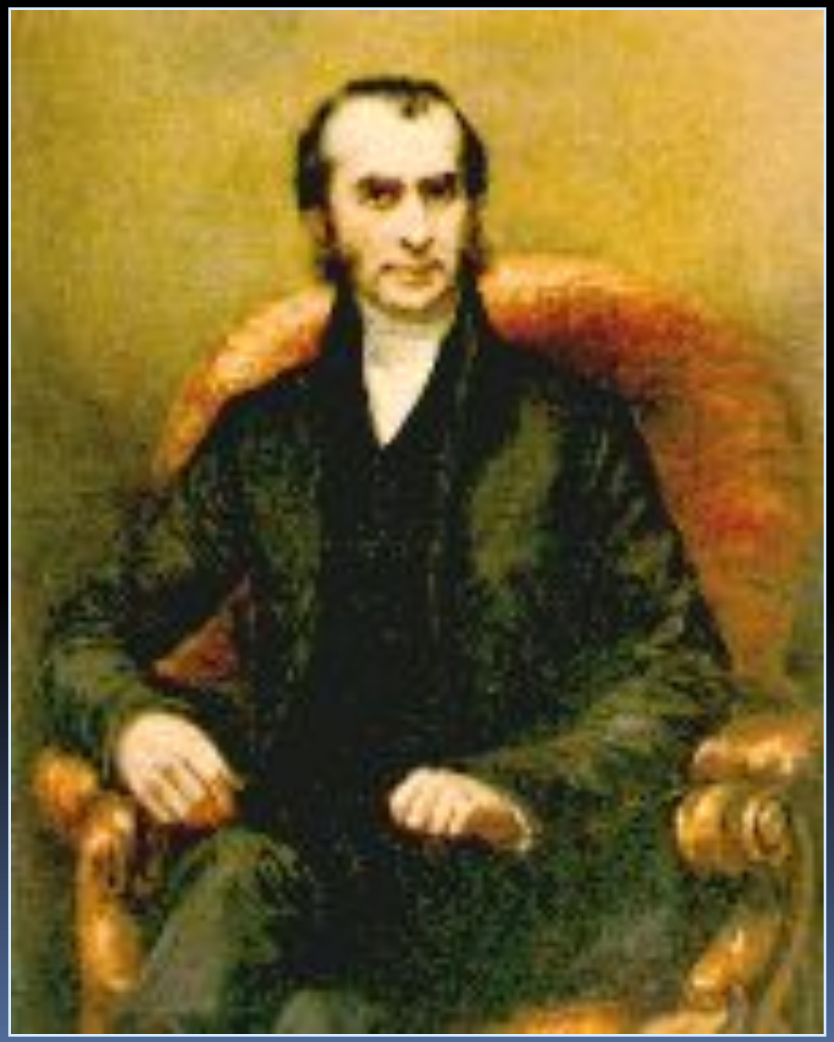
.Coiffier et al. *N Engl J Med.* 2002;346:235

GELA Phase III Trial: Summary

- Significantly higher CR/CRu rate with Rituxan® + CHOP (75% vs 63% with CHOP alone; *P*=0.005)
- Significantly longer EFS and OS rates with Rituxan® + CHOP
- Rituxan® does not increase apparent toxicity of CHOP

.Coiffier et al. *N Engl J Med.* 2002;346:235

Hodgkin lymphoma

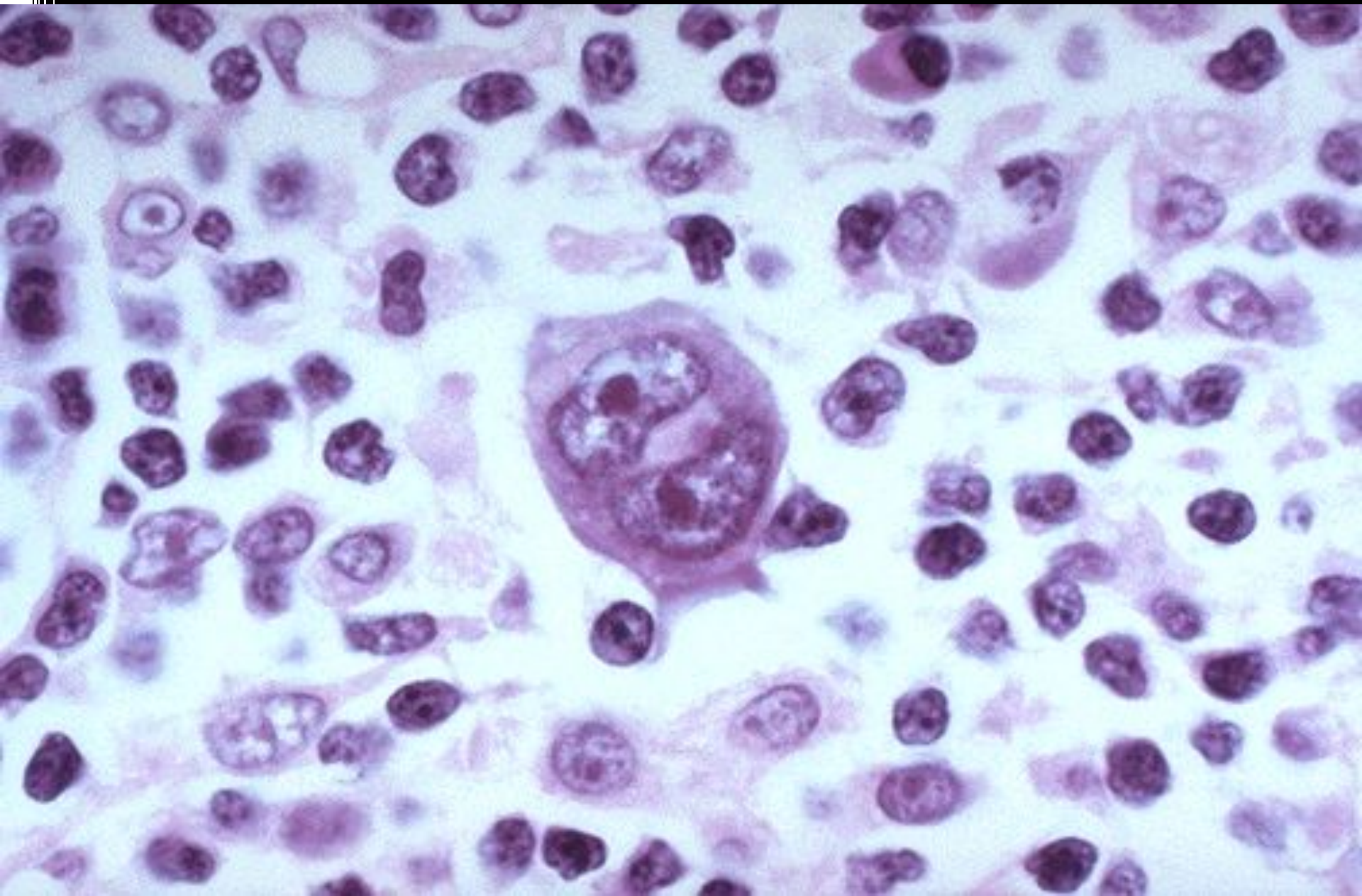


Thomas Hodgkin
(1798-1866)

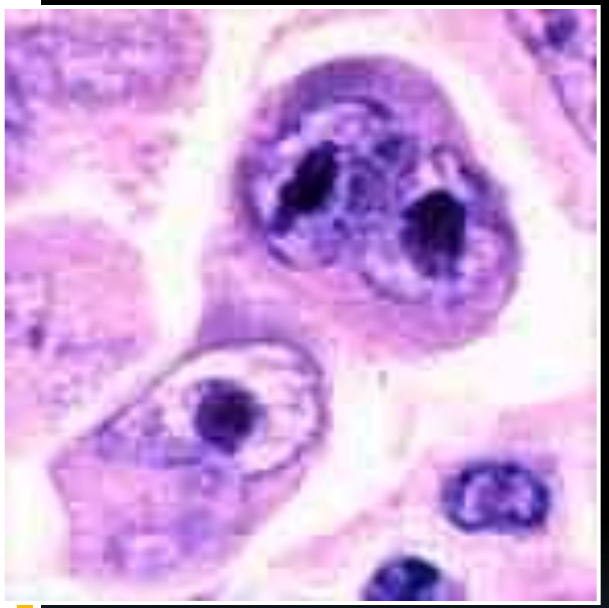
Hodgkin lymphoma

- cell of origin: germinal centre B-cell
- Reed-Sternberg cells (or RS variants) in the affected tissues
- most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells

Reed-Sternberg cell

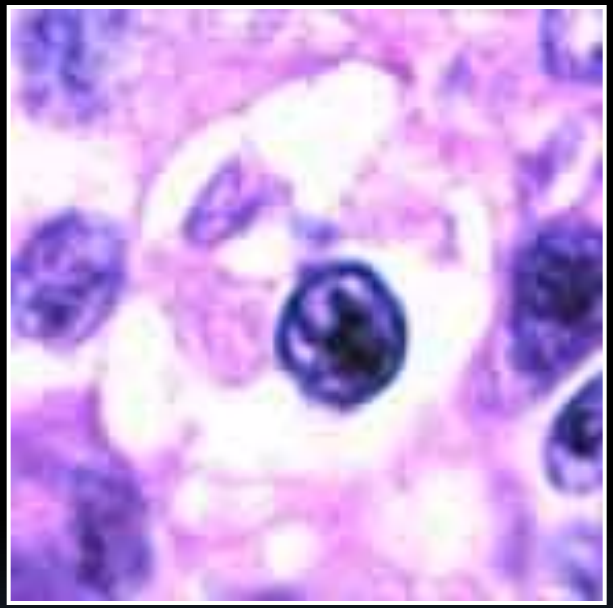


RS cell and variants



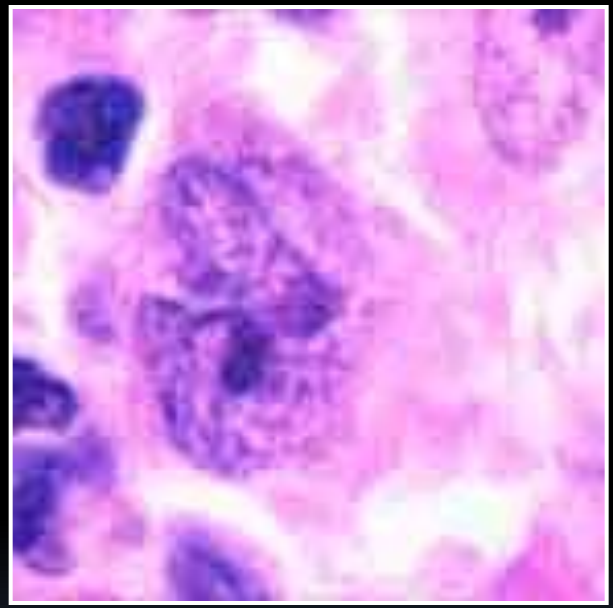
classic RS cell

(mixed cellularity)



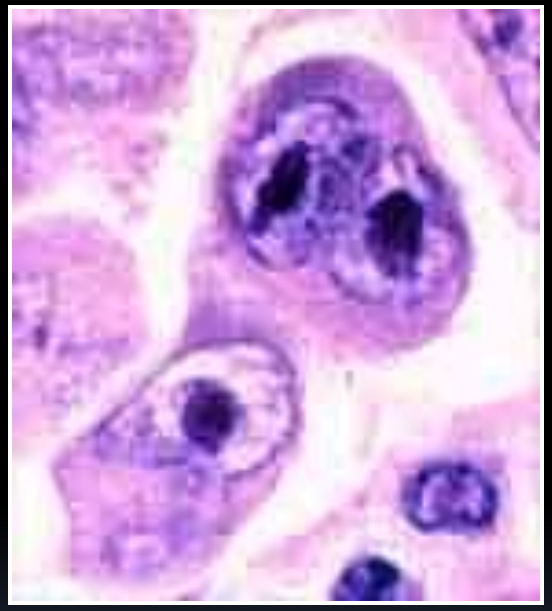
lacunar cell

(nodular sclerosis)



popcorn cell

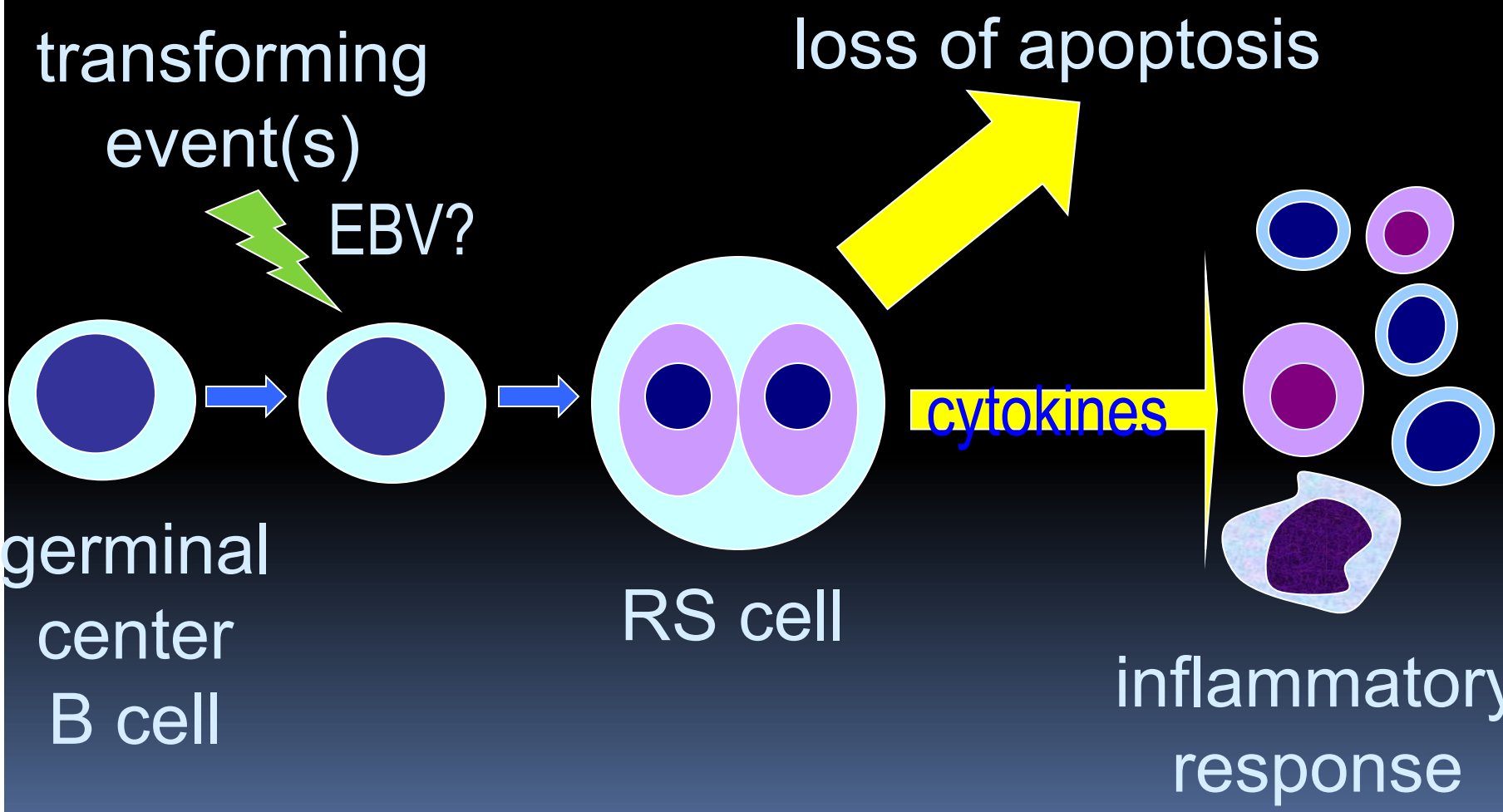
(lymphocyte predominance)



Reed-Sternberg cell

The Scream, 1893
Edvard Munch

A possible model of pathogenesis



Hodgkin lymphoma
Histological subtypes

- Nodular lymphocyte predominance Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - nodular sclerosis (most common subtype)
  - mixed cellularity
  - lymphocyte-rich
  - lymphocyte depleted

Epidemiology

- less frequent than non-Hodgkin lymphoma
- males 3.5/100000; females 2.5/100000
- peak incidence in 3rd decade
- **Stage at Diagnosis, Proportion**

  Stage I - 24.4%

  Stage II - 30.8%

  Stage III - 15.4%

  Stage IV - 12.8%

  Stage not known - 16.7%

Associated (etiological?) factors

- EBV infection
- smaller family size
- higher socio-economic status
- Caucasian > non-Caucasian
- possible genetic predisposition
- other: HIV? occupation? herbicides?

:Clinical manifestations

- lymphadenopathy, mostly mediastinal
- contiguous spread
- extra nodal sites relatively uncommon except in advanced disease
- “B” symptoms
- very rare causes obstruction, like superior vena cava syndrome

Treatment and Prognosis

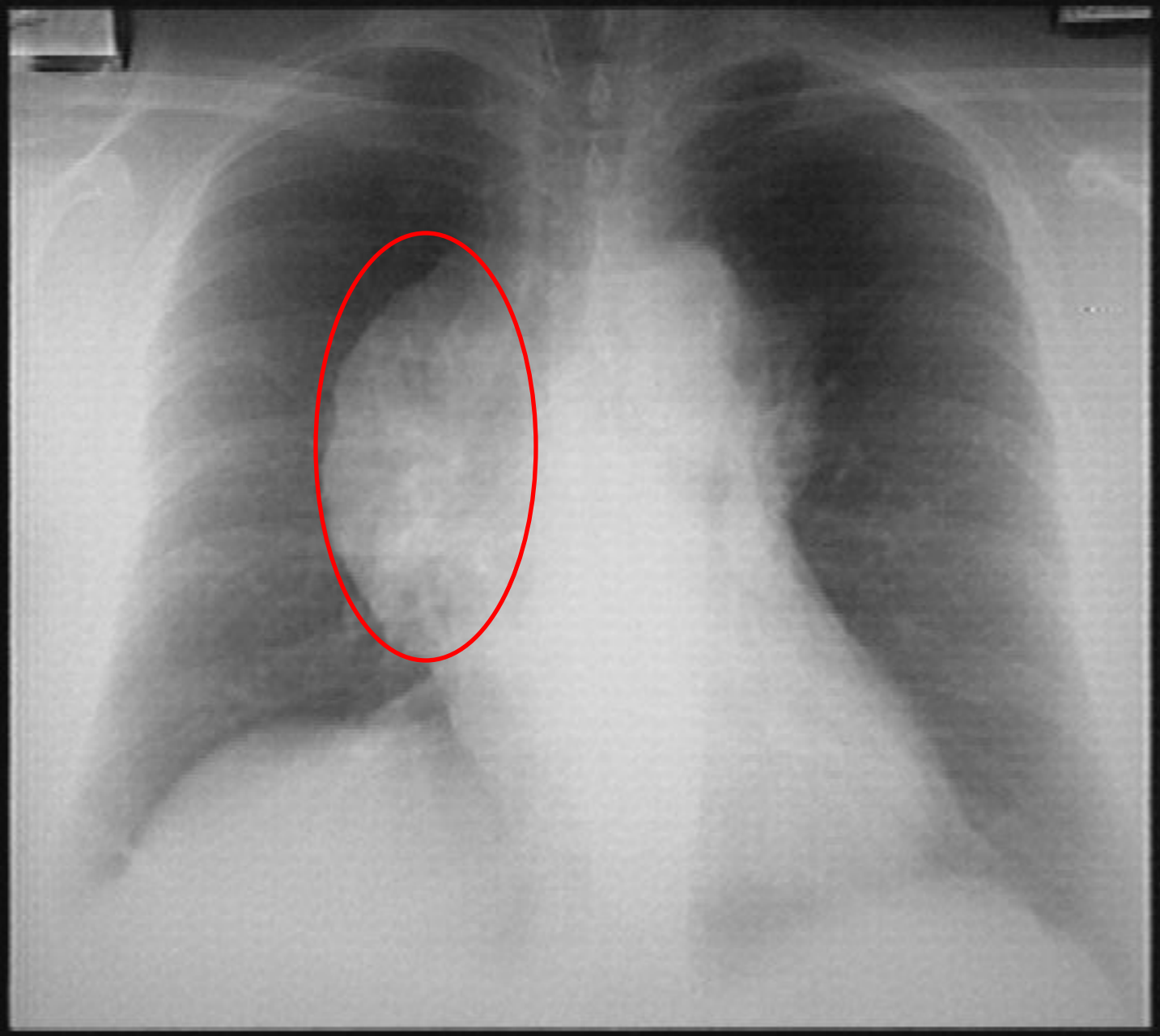
Stage	Treatment	Failure-free survival	Overall 5 year survival
I,II	ABVD x 4 & radiation	70-80%	80-90%
III,IV	ABVD x 6 or BEACOPP	60-70%	70-80%

Long term complications of treatment

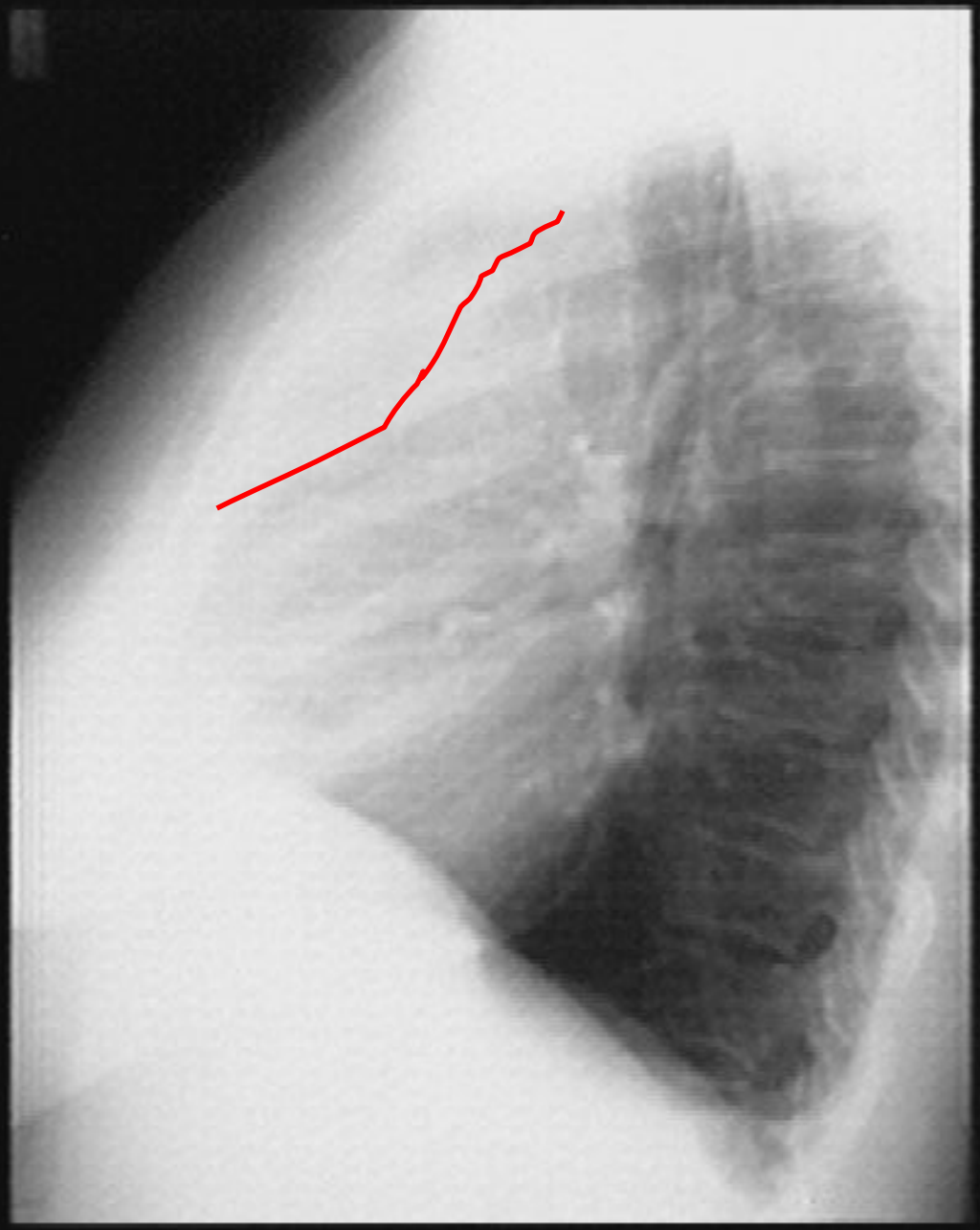
- infertility
  - MOPP > ABVD; males > females
  - sperm banking should be discussed
  - premature menopause
- secondary malignancy
  - skin, AML, lung, MDS, NHL, thyroid, breast…
- cardiac disease

.Case: W.P

- 25 year old woman
- persistent dry cough
- fever, night sweats, weight loss x 3 months
- left cervical lymphadenopathy (2 cm)
- left supraclavicular node (2 cm)
- no splenomegaly



W.P. at presentation



W.P. at presentation

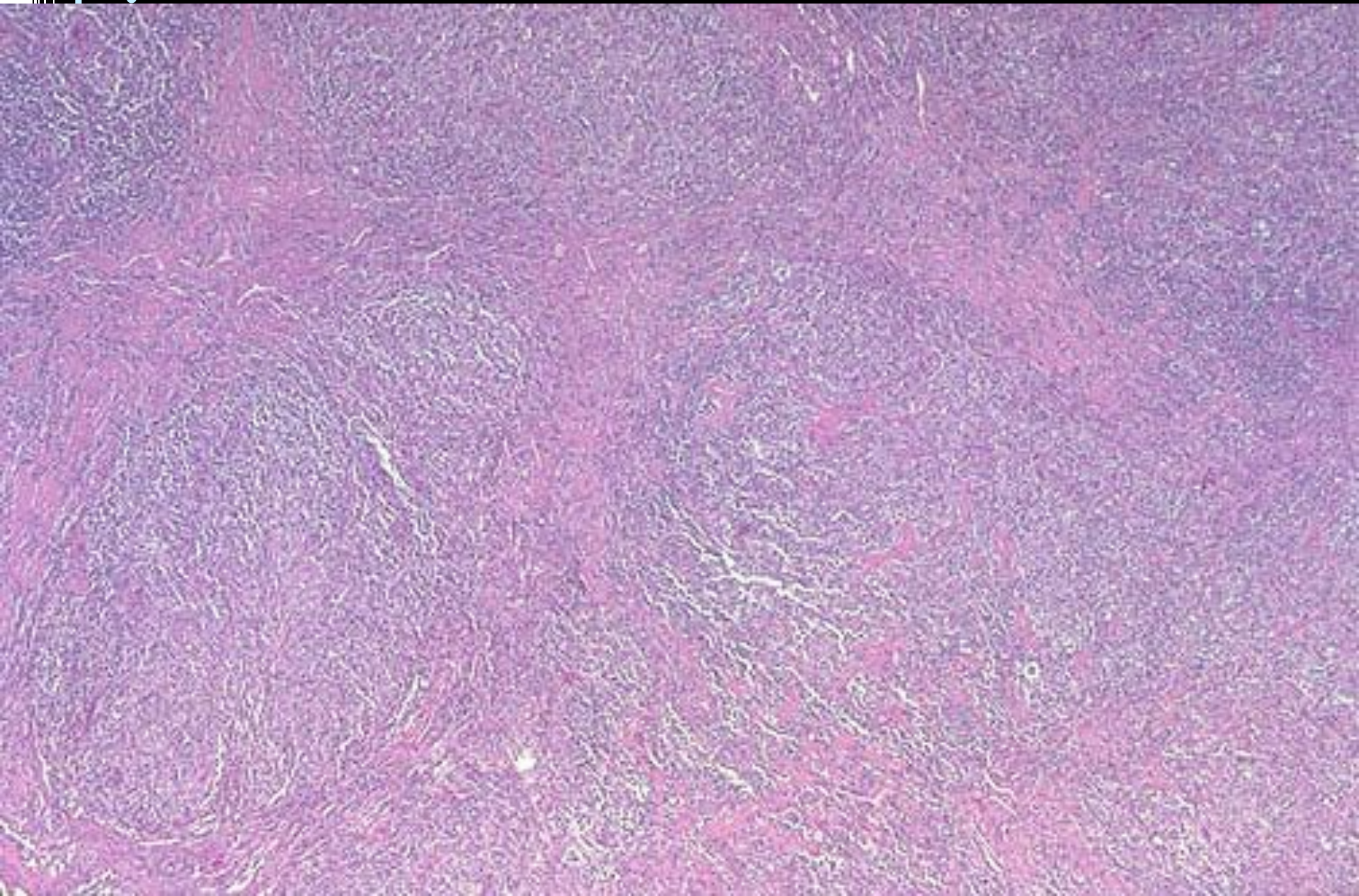
Case: W.P. differential diagnosis

- lymphoma
  - Hodgkin
  - non-Hodgkin
- lung cancer
- other neoplasms: thyroid, germ cell
- non-neoplastic causes less likely
  - sarcoid, TB, …

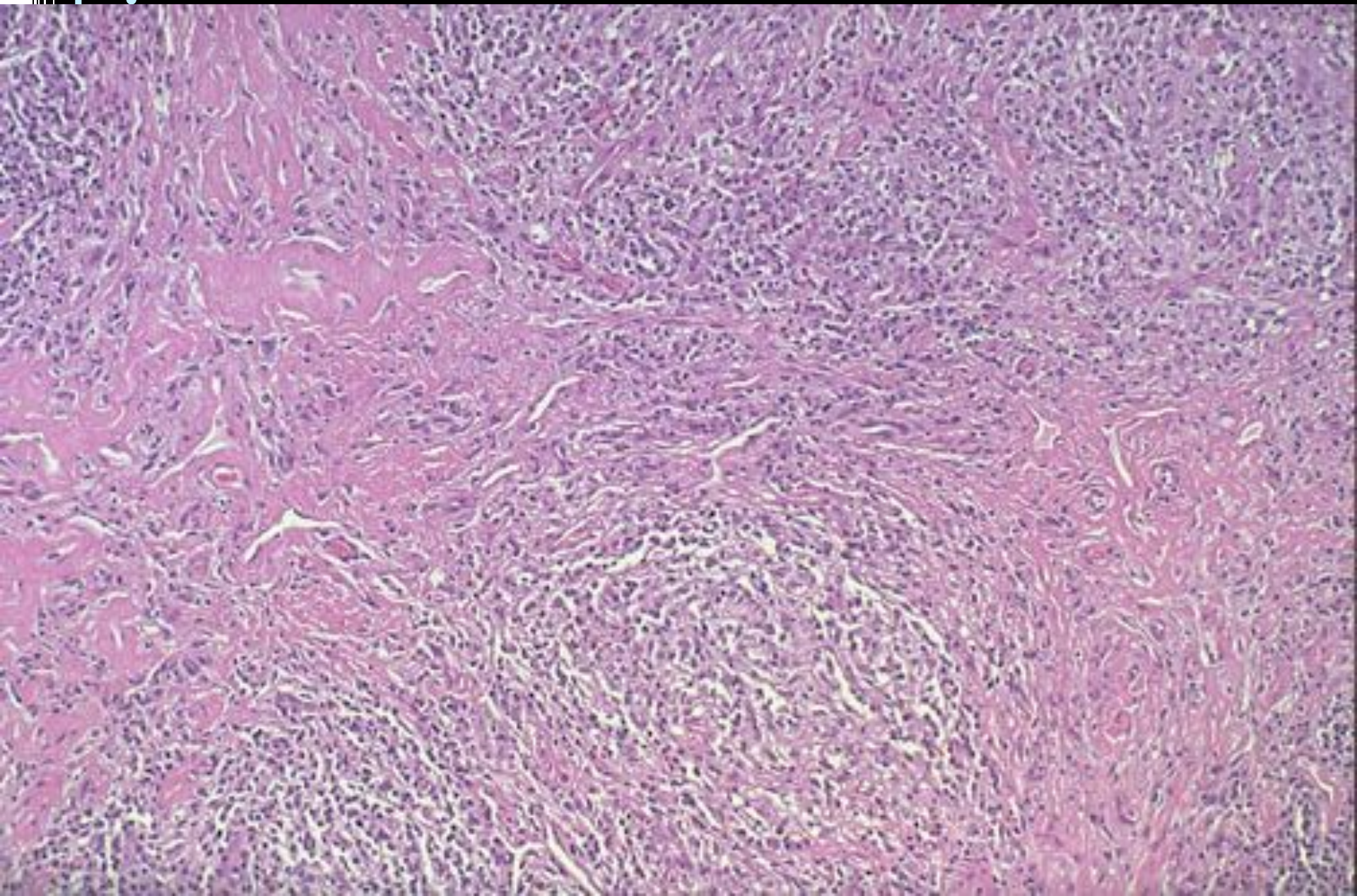
?What next

- Needle aspirate of LN: a few necrotic cells
- Needle biopsy of LN: admixture of B- and T-lymphocytes. A few atypical cells.

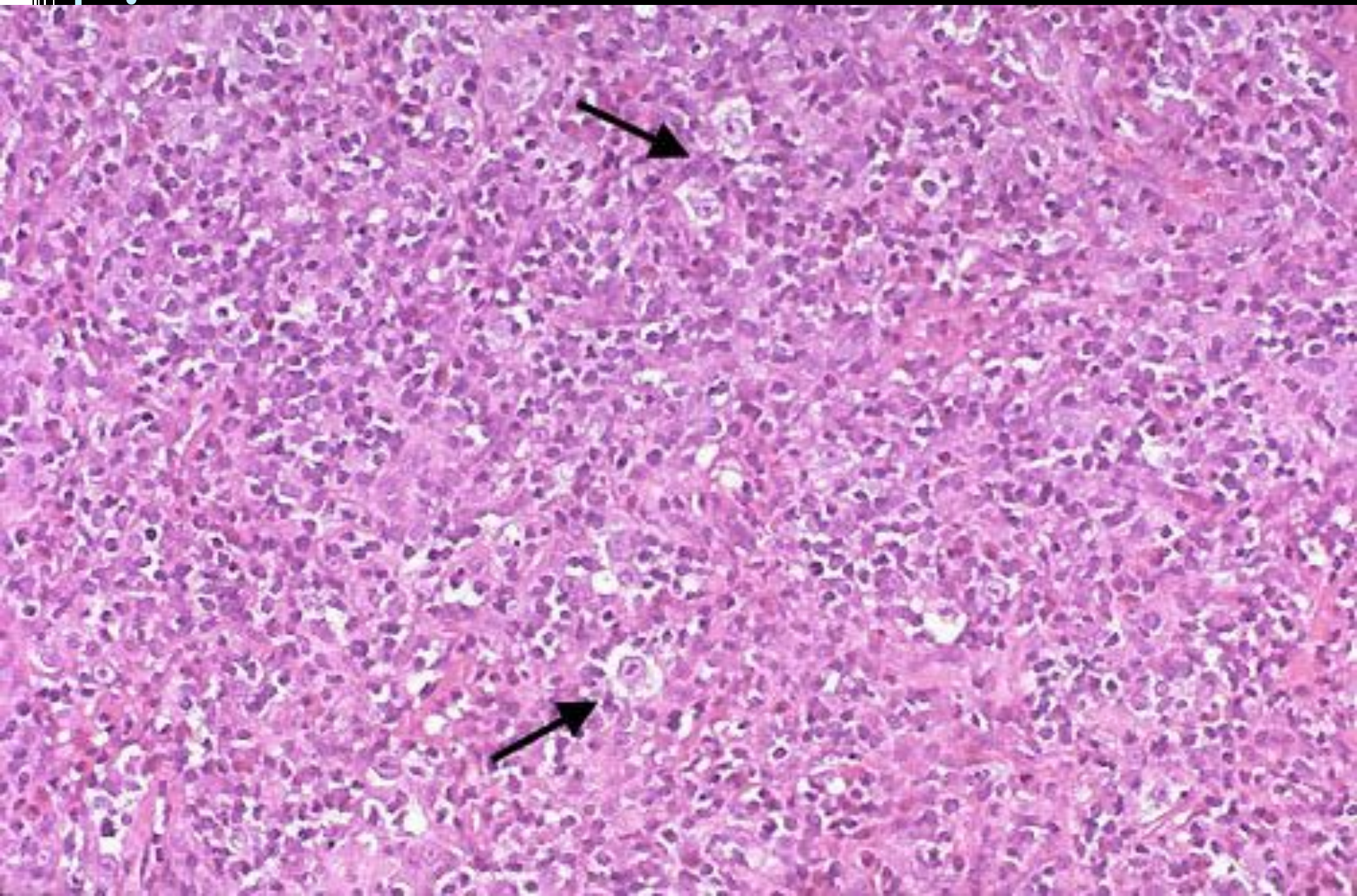
Case: W.P. lymph node



Case: W.P. lymph node

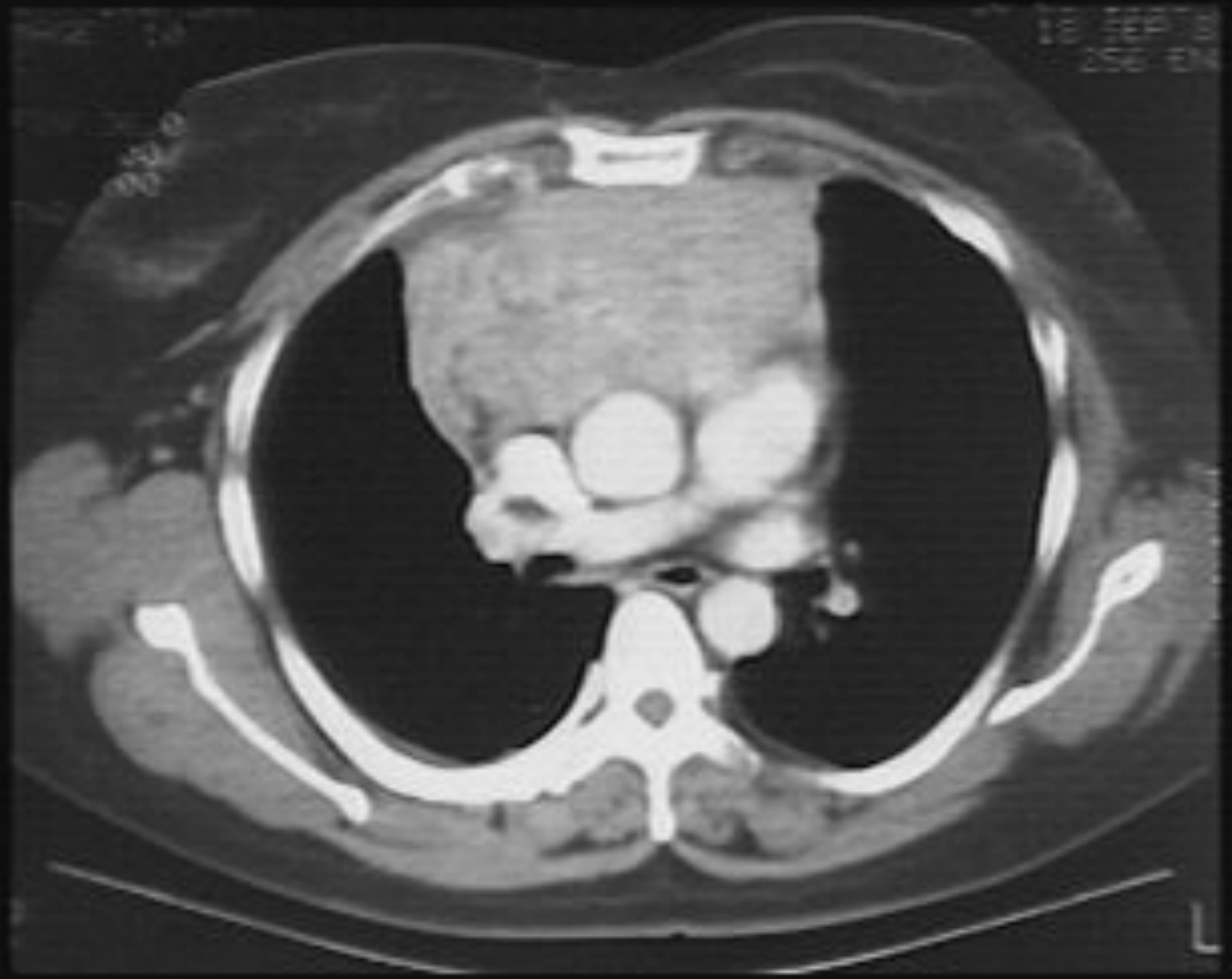


Case: W.P. lymph node



Case: W.P. staging investigations

- CT neck/chest/abdomen/pelvis
- bone marrow
- PET scan
- Blood work: normal CBC, ESR, LDH, albumin



W.P. at presentation

Staging investigations

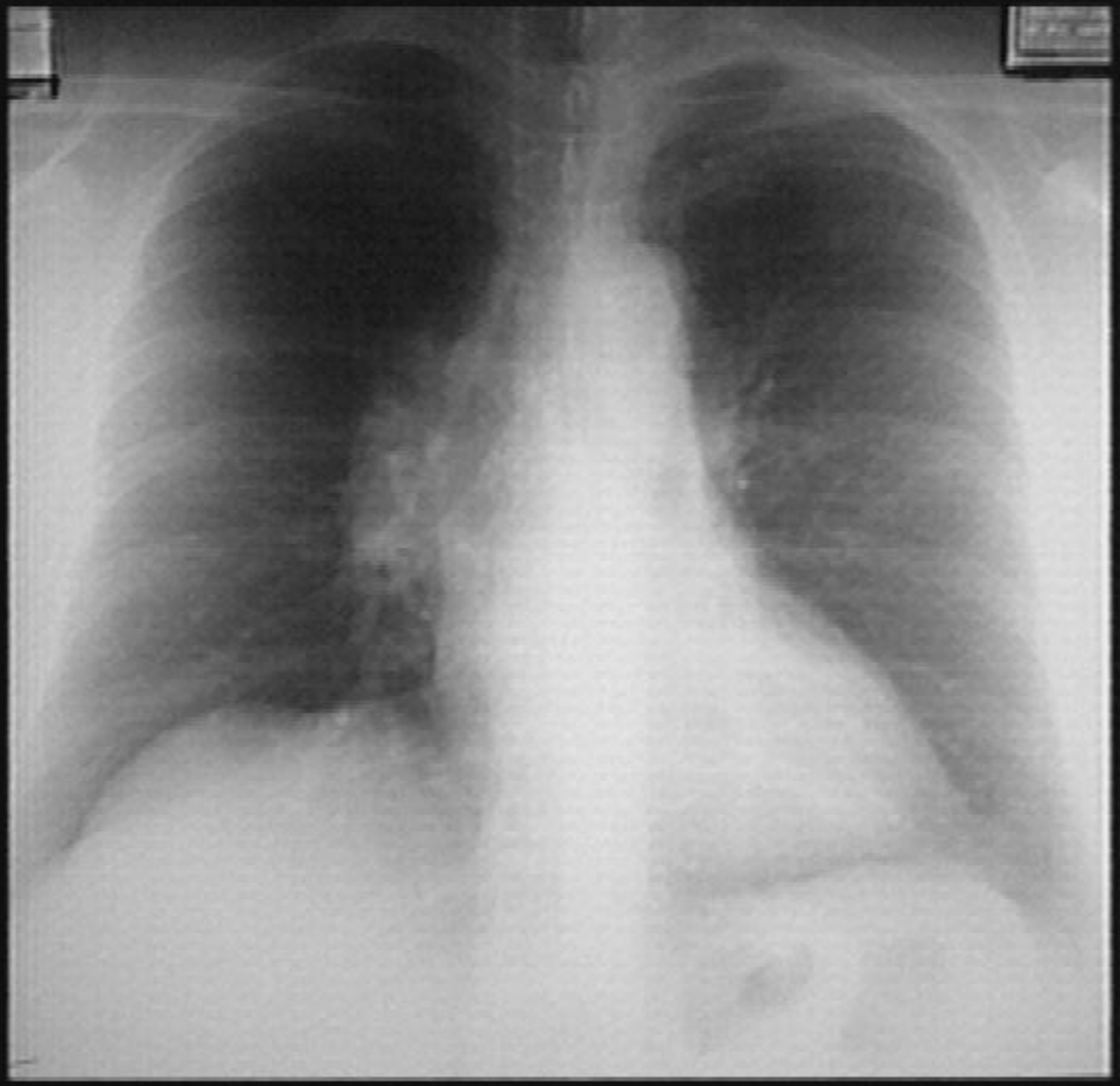
- bone marrow normal
- CT scan: Lt. supraclavicular adenopathy; large mediastinal mass; Rt. hilum; no disease below diaphragm
- PET avid

What is her diagnosis and ?stage

- nodular sclerosis HD
- stage IIB
- with bulky mediastinal mass

Case: W.P. Treatment

- discussion with patient
- treatment with ABVD x 6 cycles
  - constitutional symptoms gone after 1st cycle
- bulky mediastinal mass is a special situation that merits additional radiation after chemotherapy



W.P. post-chemotherapy

Case: W.P. post-ABVD

- response to chemo, but residual mediastinal/hilar mass
- repeat PET scan negative, suggesting that residual mass may just be fibrotic tissue
- proceed with radiotherapy as originally planned

Case: W.P. post-radiotherapy

- serial CT scans did not show progression
- patient remains in remission