Disease 3

APPROVED

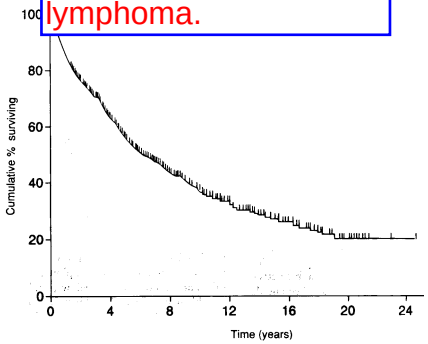
Non Hodgkin Lymphoma
Follicular Lymphoma

Non Hodgkin Lymphoma Overview

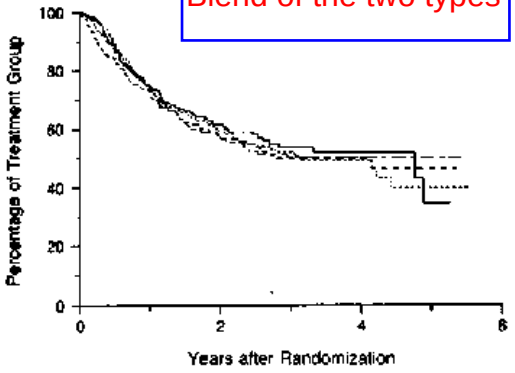
WHO classification: 40 types of lymphoma that are defined or in provisional status. *We only need to know 3:* low grade, high grade, and intermediate grade. Look at chart. Note that it is hard to kill cells that aren't dying. Therefore, we don't cure low grade lymphomas.

Low Grade	Intermediate Grade	High Grade
Apoptosis	Apoptosis + Proliferative	Proliferative Proliferative Proliferative
Slow accumulating	Accumulating but active growth	Tremendously active growth
Treatable Not curable	Treatable Curable	Curable

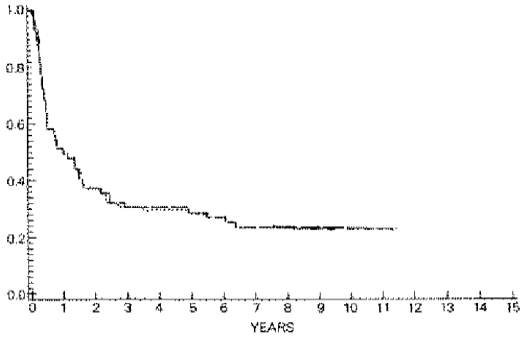
Follicular Non hodgkin lymphoma.



Blend of the two types



Burkett's lymphoma.



Case 3

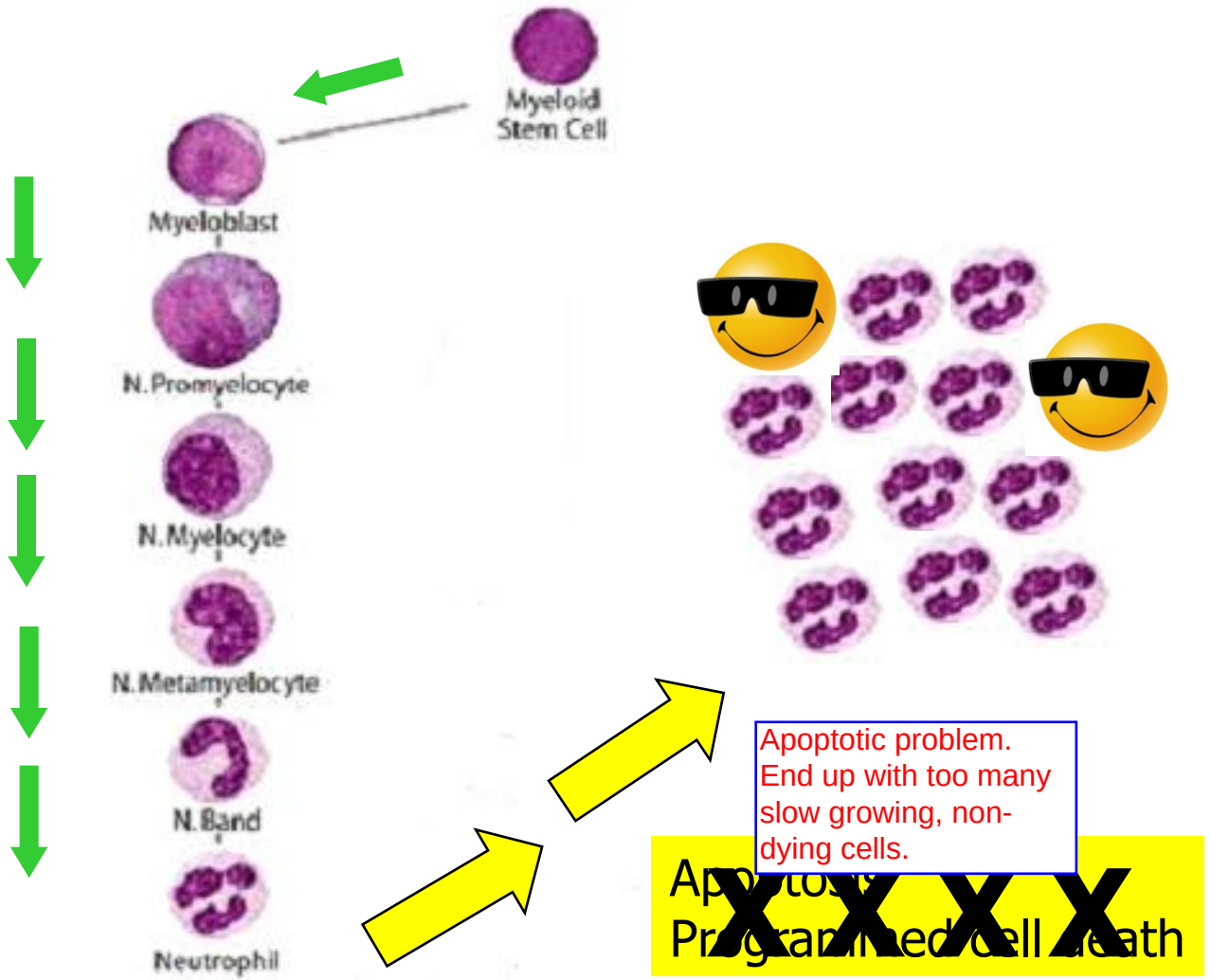
Important aspects of this case are highlighted. The lecturer focused on the fact that patient has multiple lymph node areas affected that have persisted for a while and that have waxed and waned.

- 59 year old man with lymphadenopathy in the neck, supraclavicular area, inguinal area. He states that he has had LN for at least 18 months and they have waxed and waned.

- Physical examination:
  - LN: 1-2 cm LN in cervical, supraclavicular, axillary, inguinal areas
  - ABD: questionable enlargement of spleen

- LAB:
  - Hct: 32%
  - WBC: 8,250/mm^3
  - Platelet: 187,000/mm^3
  - LDH: 112 IU/dL

Low Grade NHL: Pathophysiology
Apoptosis Defective – Cells Accumulate



Follicular Non Hodgkin Lymphoma Diagnosis

Ways to diagnose Follicular Non-Hodgkin Lymphoma:

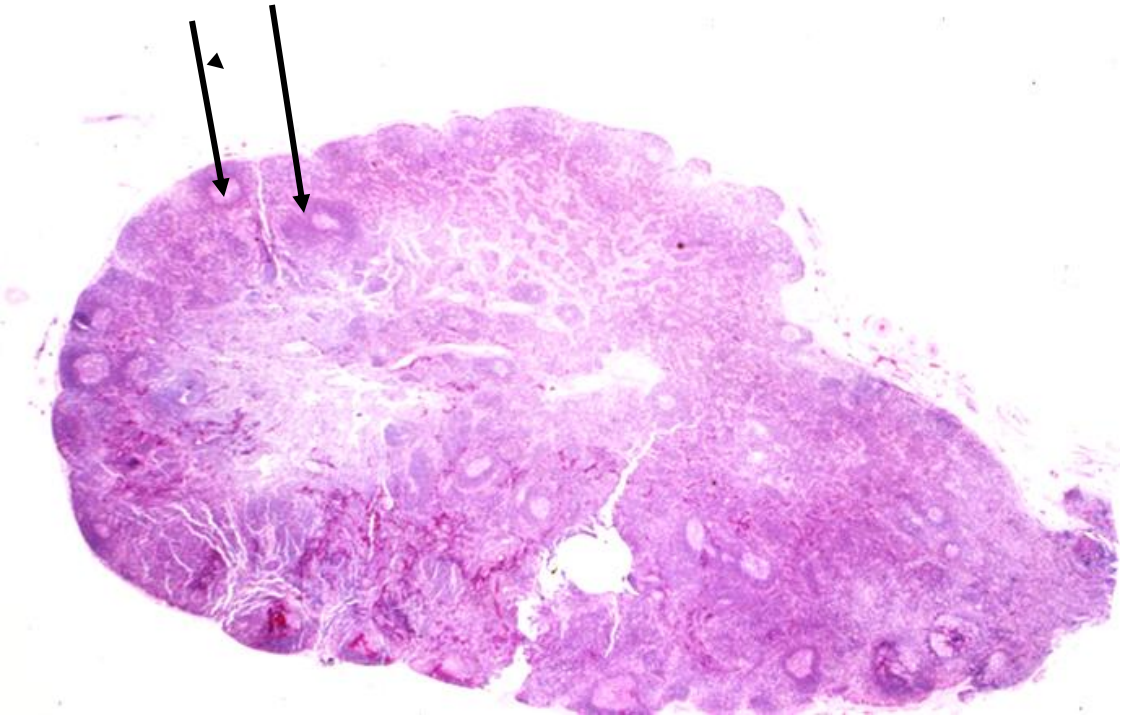
- Morphology
- Immunophenotype
- Cytogenetics

Follicular Lymphoma

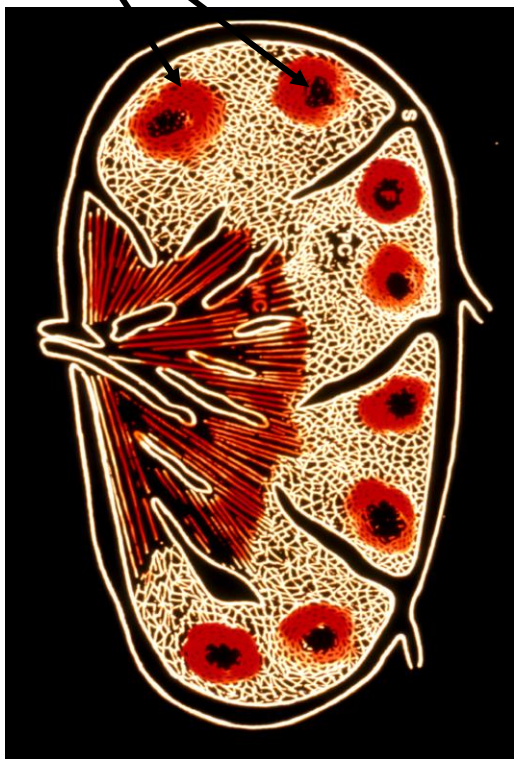
Pathology

Morphology: Normal Lymph Node, B Cell Zone

B-cell follicles



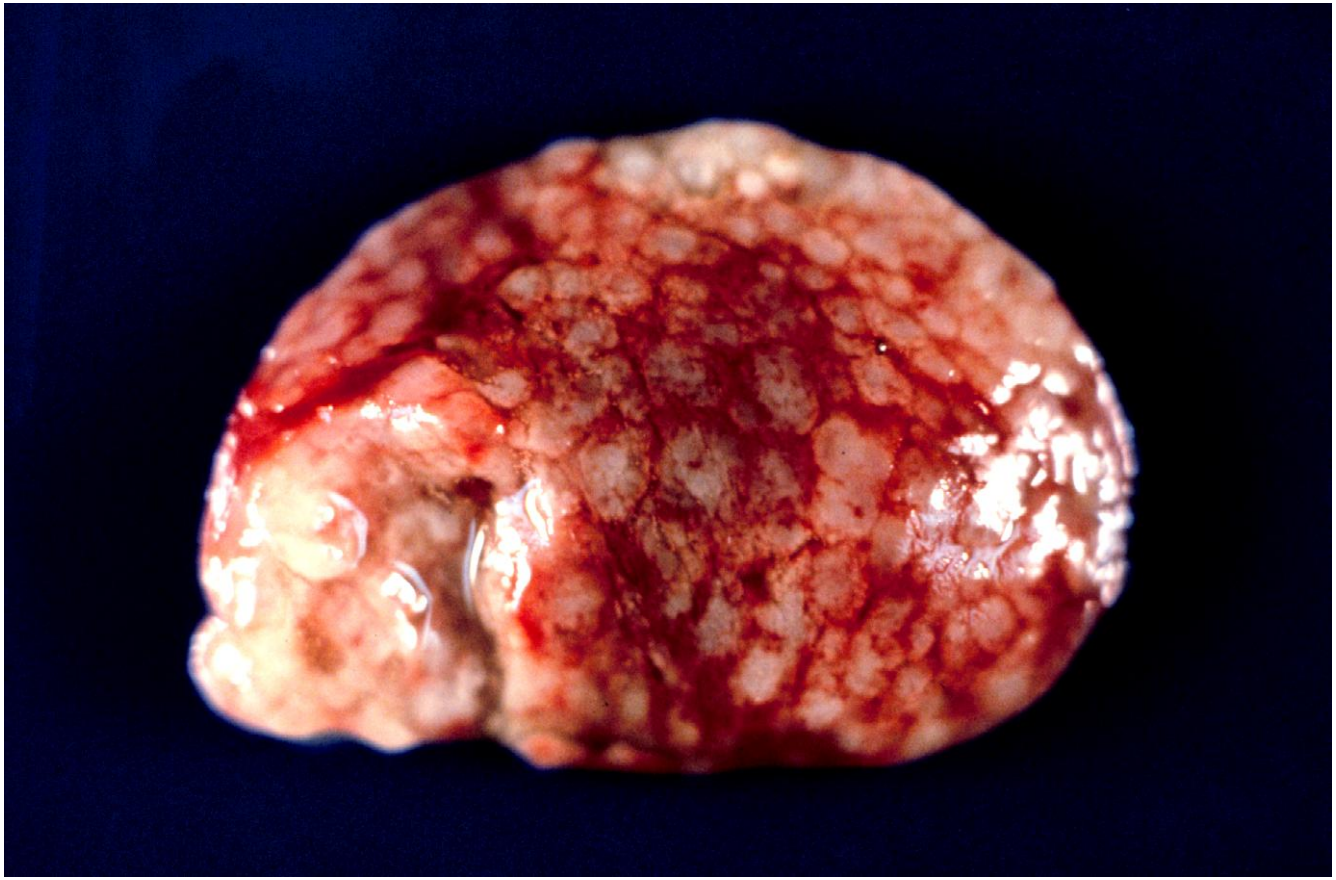
B-cell follicles



Normal lymph node with lymphoid follicles around edges of lymph node (cortex). Most follicles have germinal center (selecting B-cells that are going to be avid for particular antigens.) We don't see follicles in middle of the lymph node.

Morphology: Follicular Lymphoma Gross Photo

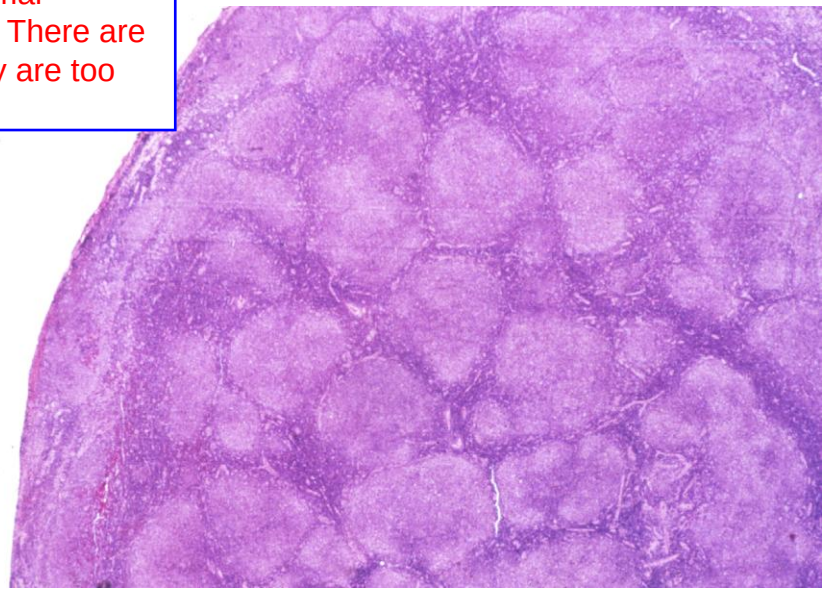
See round nodules. This is not what normal lymph node looks like.



Morphology: Follicular Lymphoma

Lymphoid follicles expand and take up whole node because of abnormal germinal centers. There are too many and they are too big.

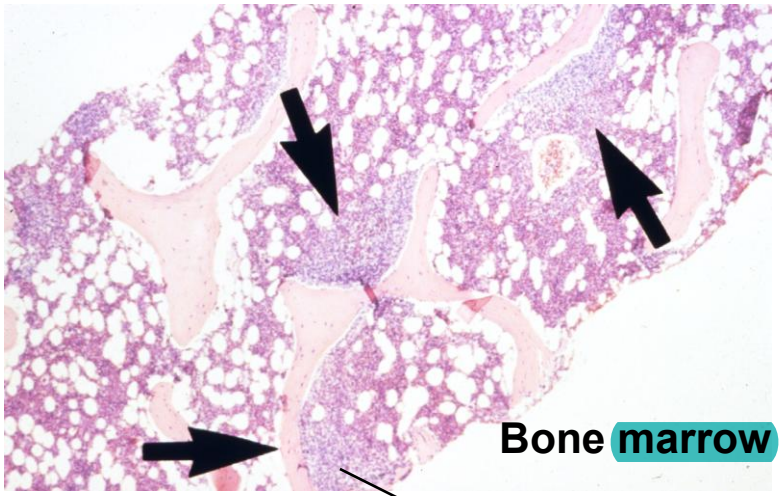
Normal lymph node

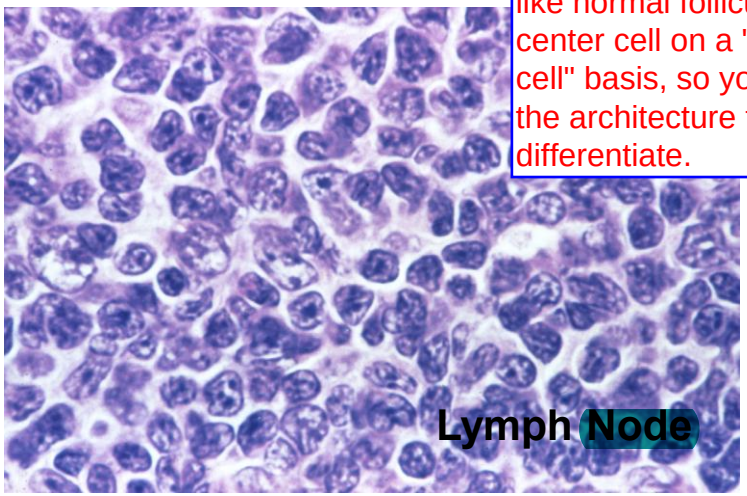


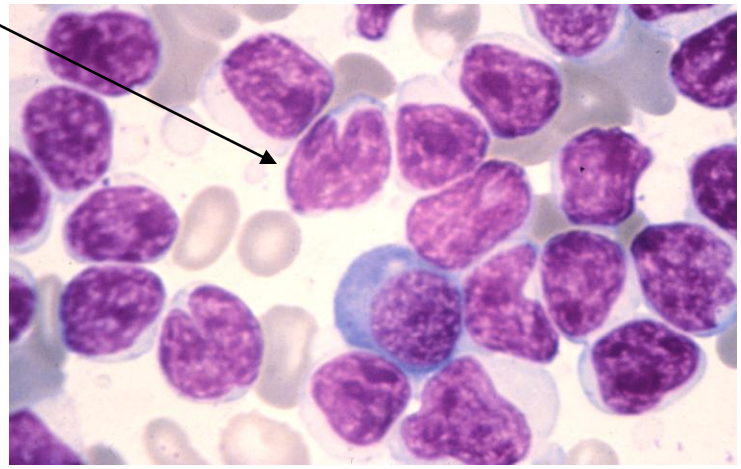
Follicular lymphoma

Microscopic: Follicular Lymphoma

Germinal centers are made up of "squiggled up cells" A follicular lymphoma cell looks like normal follicular center cell on a "cell to cell" basis, so you need the architecture to differentiate.

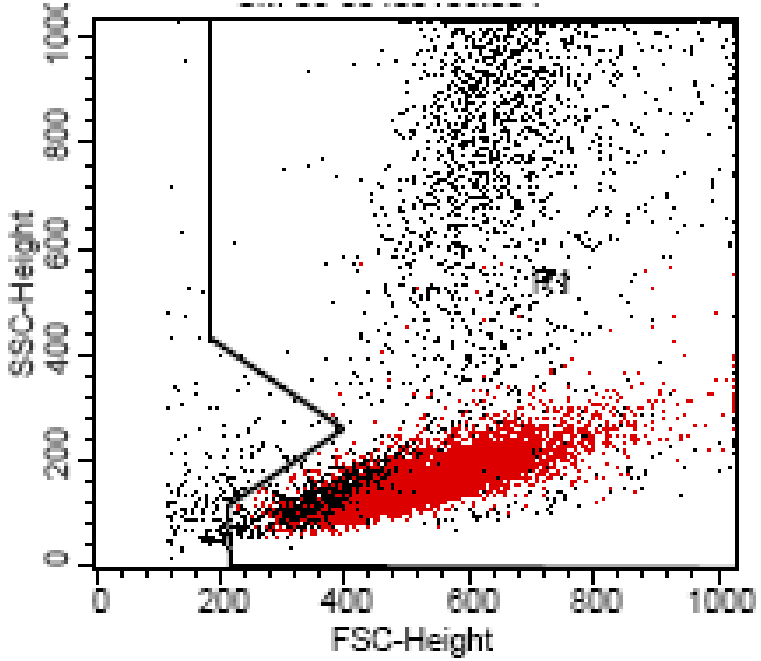




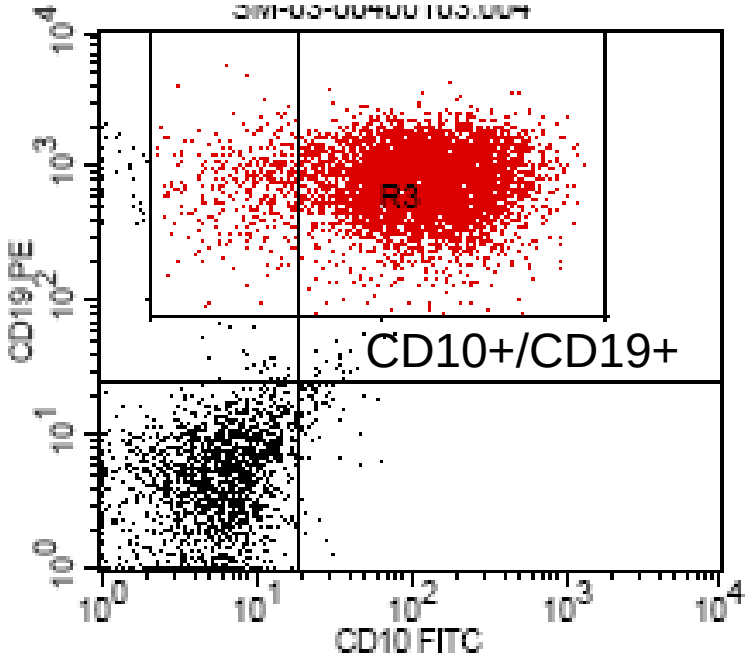


Remember: Patient had anemia. This could be a result of lymphoma involvement of bone marrow.

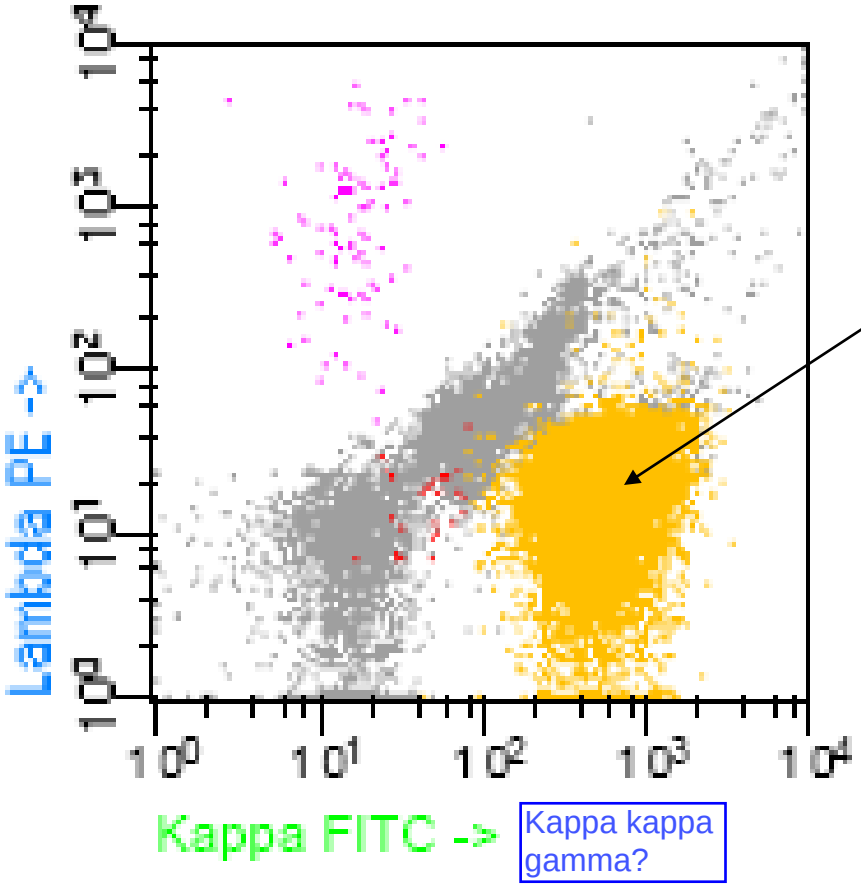
Follicular Lymphoma: Flow Cytometry



Generally small cells that don't scatter light. Antigens on surface are characteristic of cells born in germinal center with CD10 and CD 19.



Follicular Lymphoma: Flow Cytometry

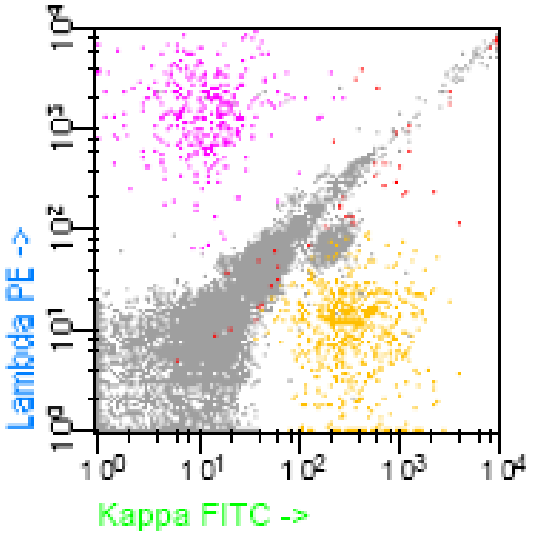


Kappa kappa gamma?

Monoclonal kappa+

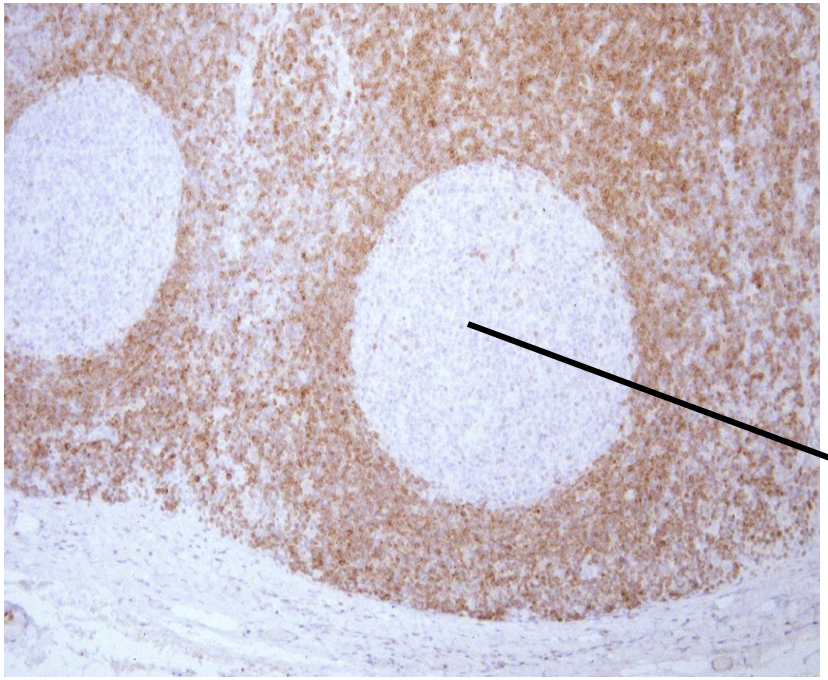
To determine if something is a lymphoma, you look for monoclonality. Normally you'll see some kappa and some lambda immunoglobulin light chain expression (2:1). In follicular lymphoma, you have predominantly one type.

Polyclonal (normal)

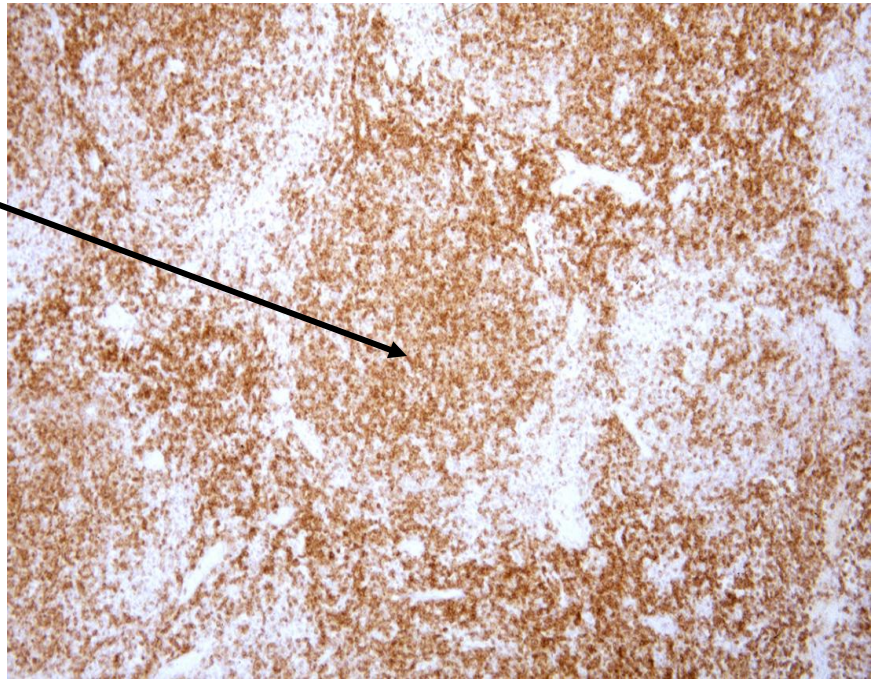


Follicular Lymphoma: Immunohistochemistry t(14;18)→Bcl-2 over-expression

Characterized by translocation between chromosome 14 and BCL2. (Antiapoptotic molecule.) Keeps cell from dying.



Bcl-2 negative: Normal follicle center



Bcl-2 positive: Follicular lymphoma

Low Grade Lymphoproliferative Disease: Diagnosis

Immunophenotype: CD Markers

Major subdivisions of low grade lymphomas: treat and act the same. Here are the major cell surface markers they look at.

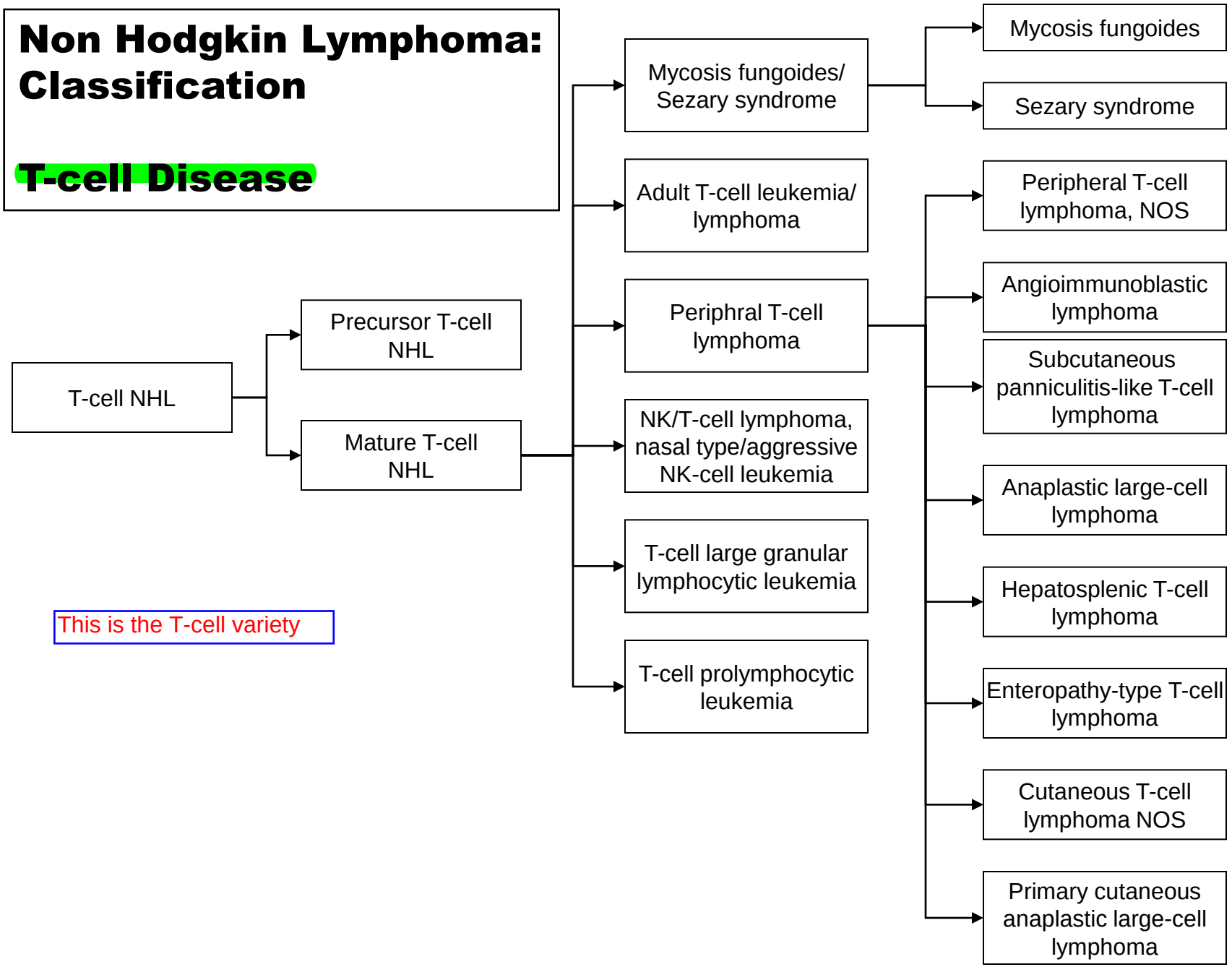
	CD5	CD2	CD3	CD19	CD20	SIg	CD11c	CD25	CD22	CD10	HLA-Dr	CD23	FMC7
CLL	++	-	-	++	++	++ (Dim)	-	-	+/-	-	++	Br	-
MCL	++	-	-	++	++	++ (Br)	-	+	++	+/-	++	-	-
PLL	-	-	-	++	++	++ (Br)	-	-	++	+/-	++	-	+
FSC	-	-	-	++	++	++ (Br)	-	-	+	+	++		-
HCL	-	-	-	++	++	++ (Br)	++	++	++	-	++		-
SLVL	-	-	-	++	++	++ (Br)	-	+/-	++	-	++		-
MBCL	-	-	-	+/-	++	++	++	-		-	++		-

++ = marker present in 80+%
+ = marker present in 40-80%
+/- = marker present in 10-40%
- = marker present in < 10%
Br = bright

CLL = chronc lymphocytic leukemia
MCL = mantle cell lymphoma
PLL = prolymphocytic leukemia
PSC = follicular small cleaved NHL
HCL = hairy cell leukemia
SLVL = splenic lymphoma with villous lymphocytes
MBCL = monocytoid B-cell lymphoma

Non Hodgkin Lymphoma: Classification

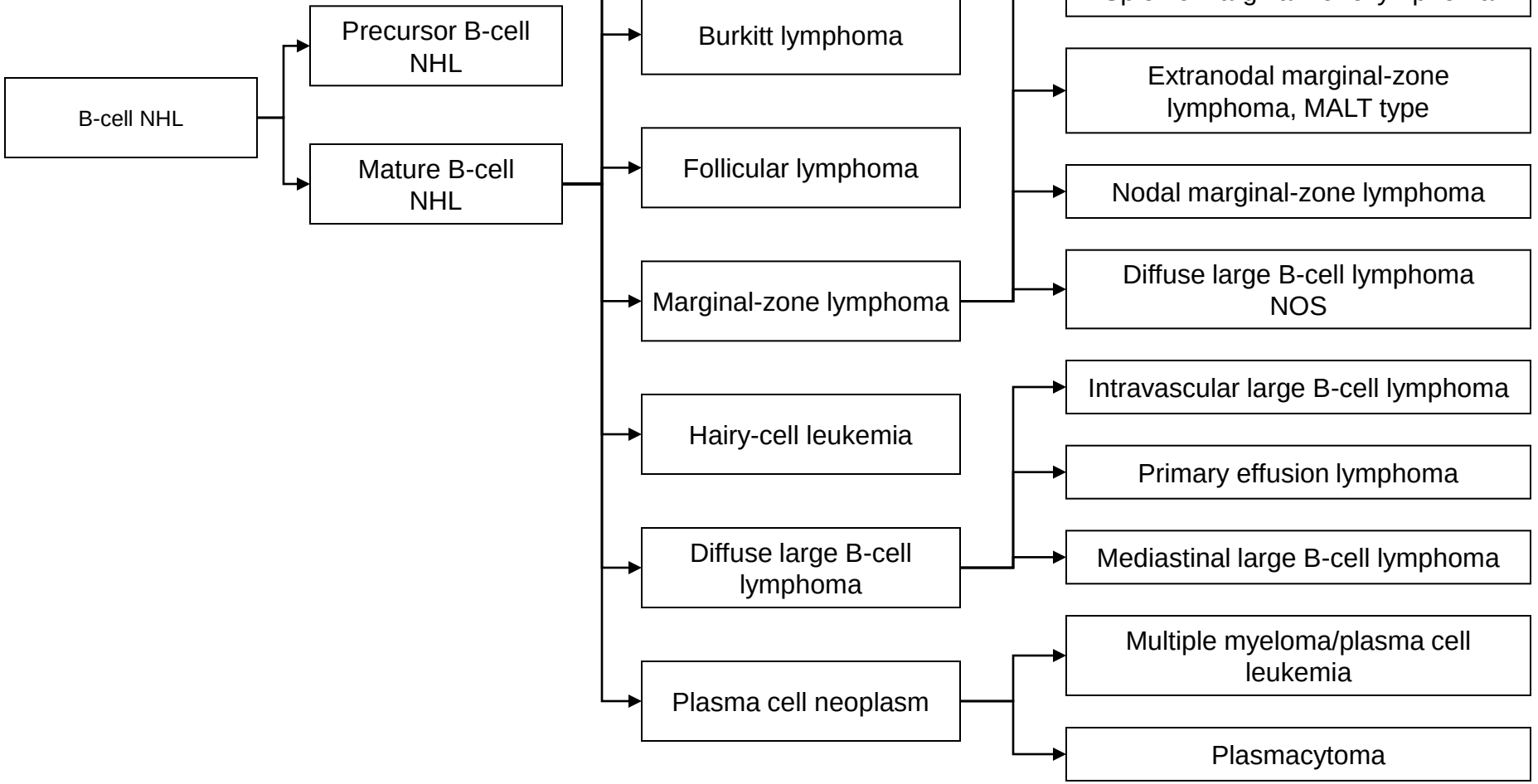
T-cell Disease



Non Hodgkin Lymphoma: Classification

B-Cell Disease

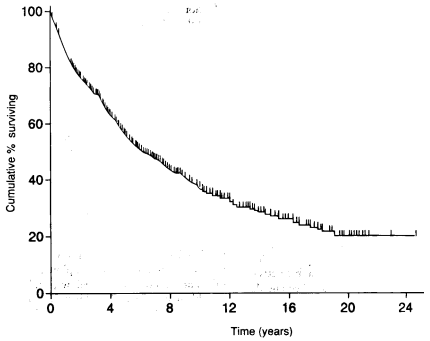
This is the B-cell variety

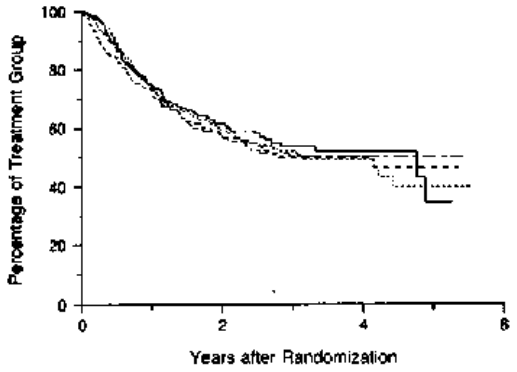


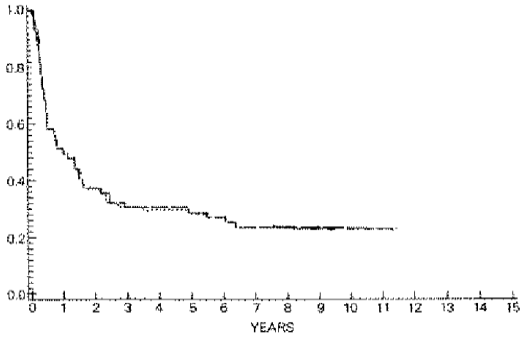
Non Hodgkin Lymphoma Overview

Know this chart.

Low Grade	Intermediate Grade	High Grade
Apoptosis	Apoptosis + Proliferative	Proliferative Proliferative Proliferative
Slow accumulating	Accumulating but active growth	Tremendously active growth
Treatable Not curable	Treatable Curable	Curable







Low Grade NHL (follicular): Staging Anatomic

Staging system adapted from hodgkin diseases. **Doesn't work for NHL**. See lecture 3 to understand.

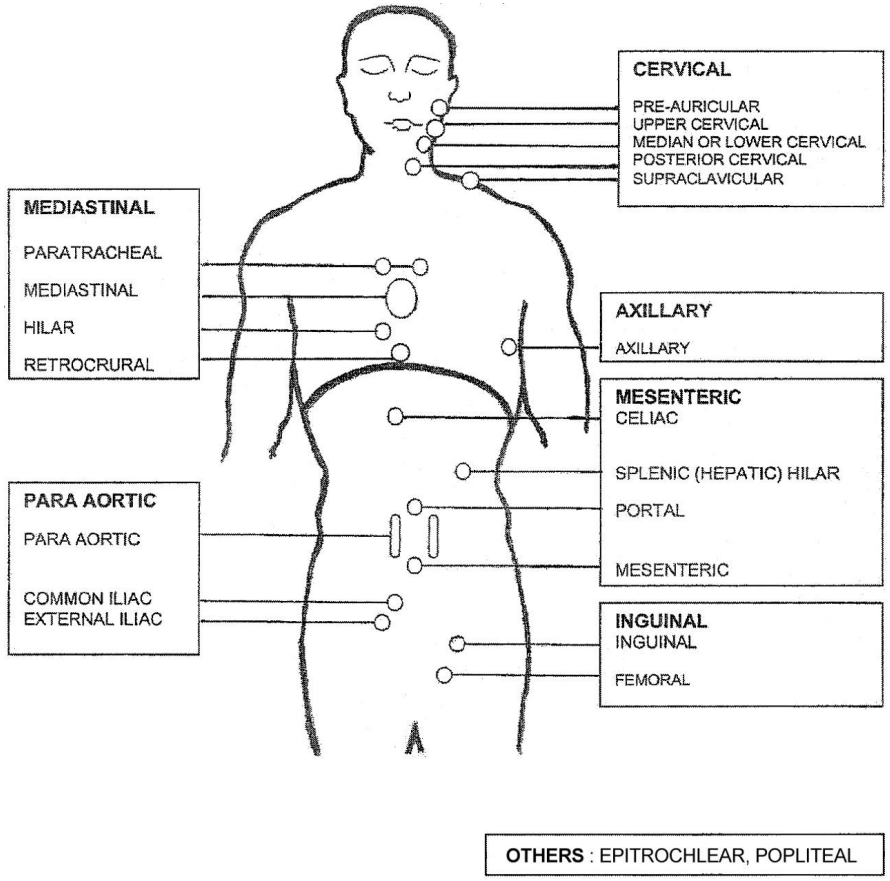
Stage	Disease
I	LN one location
II	LN 1+ locations, same side of diaphragm
III	LN on both sides of diaphragm
IV	Extranodal sites of disease

Symptoms A	No symptoms
Symptoms B	Fever, sweats, weight loss

E	Organ involvement adjacent to lymph node

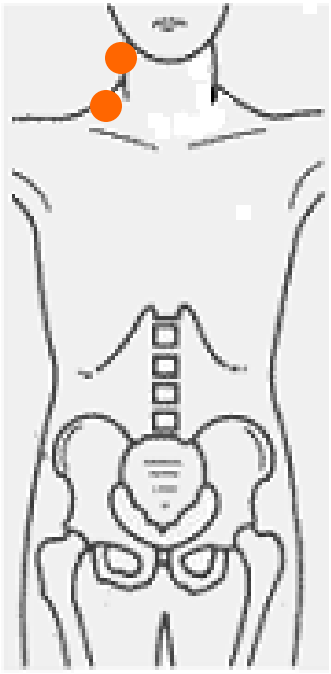
Manikin Used for Counting the Number of Involved Areas

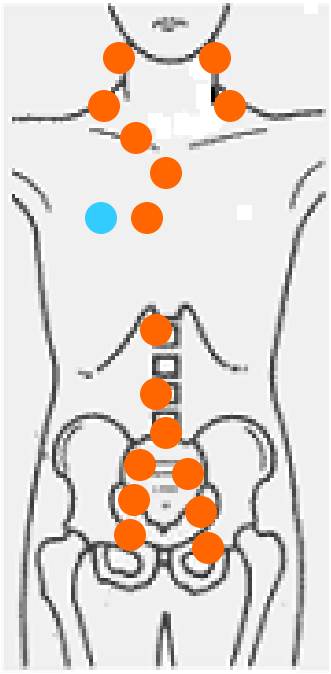
Defines regions.

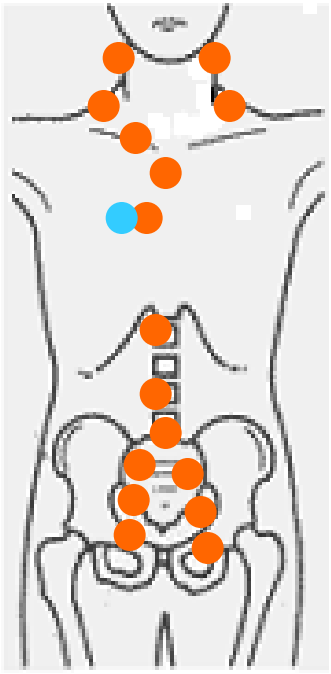


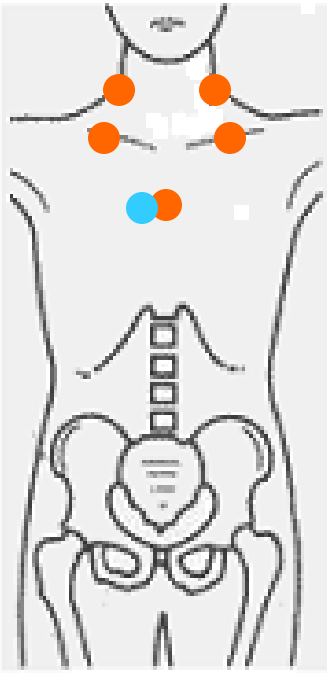
Low Grade NHL (follicular): Staging (All dots are lymphoma)

Images of different stages. See slide 18 for the details.









Stage	I	IV	IIIE	IIE
	Two sites of disease in the same region on the same side of the diaphragm	In the lung, away from lymph node.	Disease of both sides of the diaphragm and in lung next to lymph node	Disease in both in the neck and in the mediastinum and disease in lung right next to lymph node.

Low Grade NHL (follicular): Prognosis
FLIPI (Follicular Lymphoma International Prognostic Index)

Study of almost 4,000 people: Unrelenting downhill course. 5% mortality/year. Clinical effort focused on keeping quality of life high and preventing deterioration of organ function.

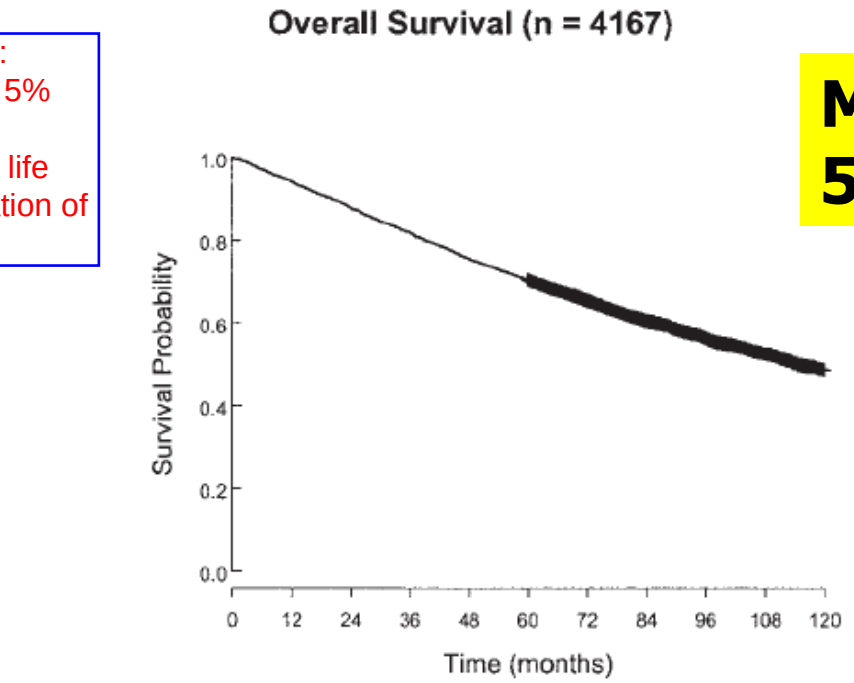


Figure 2. Overall survival of the study population (n = 4167).

Mortality 5%/year

Solal-Celigny (FLIPI) Blood 2004;104:1258-1265

Low Grade NHL (follicular): Prognosis
FLIPI (Five Independent Factors)

1 point for each of the adverse factors. The more points the worse the disease prognosis.

Parameter	Adverse factor	RR	95% CI
Age	≥ 60 y	2.38	2.04-2.78
Ann Arbor Stage	III – IV	2.00	1.56 – 2.58
Hemoglobin level	< 12 g/dL	1.55	1.30 – 1.88
Serum LDH level	> Upper limit normal	1.50	1.27 – 1.77
Number of nodal sites	> 4	1.39	1.18 – 1.64

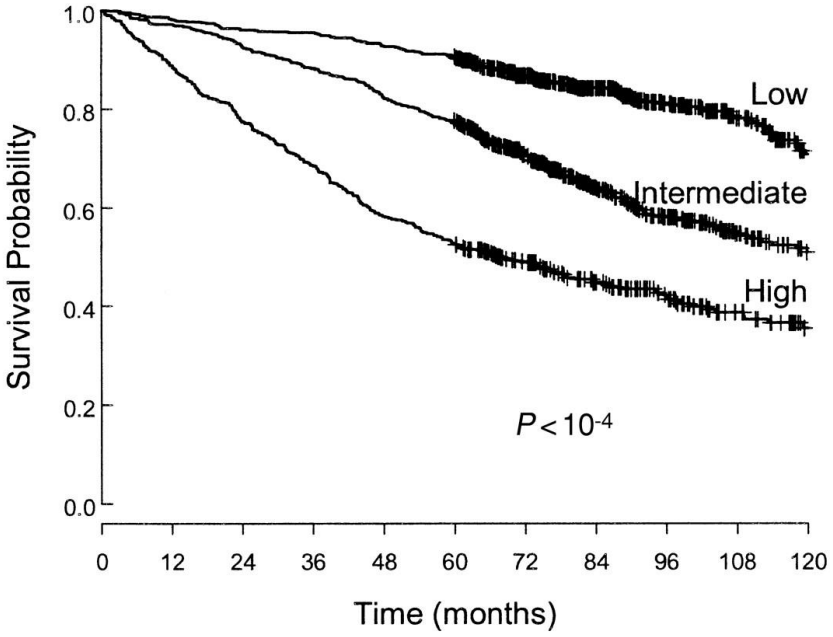
LDH= Lactate dehydrogenase. Can be a marker of hemolysis.
Ann Arbor Stage- staging based on HL.

Low Grade NHL (follicular): Prognosis
FLIPI (Five Independent Factors): SCORE

We still can't define groups that do "really really well" and "really really poorly."

Risk Group	Number of factors	Distribution of Patients	5-year OS	10-year OS	RR
Low	0 – 1	36%	90.6	70.7	1.0
Intermediate	2	37%	77.6	50.9	2.3
High	≥ 3	27%	52.5	35.5	4.3

Low Grade NHL (follicular): Prognosis
FLIPI SCORE and SURVIVAL

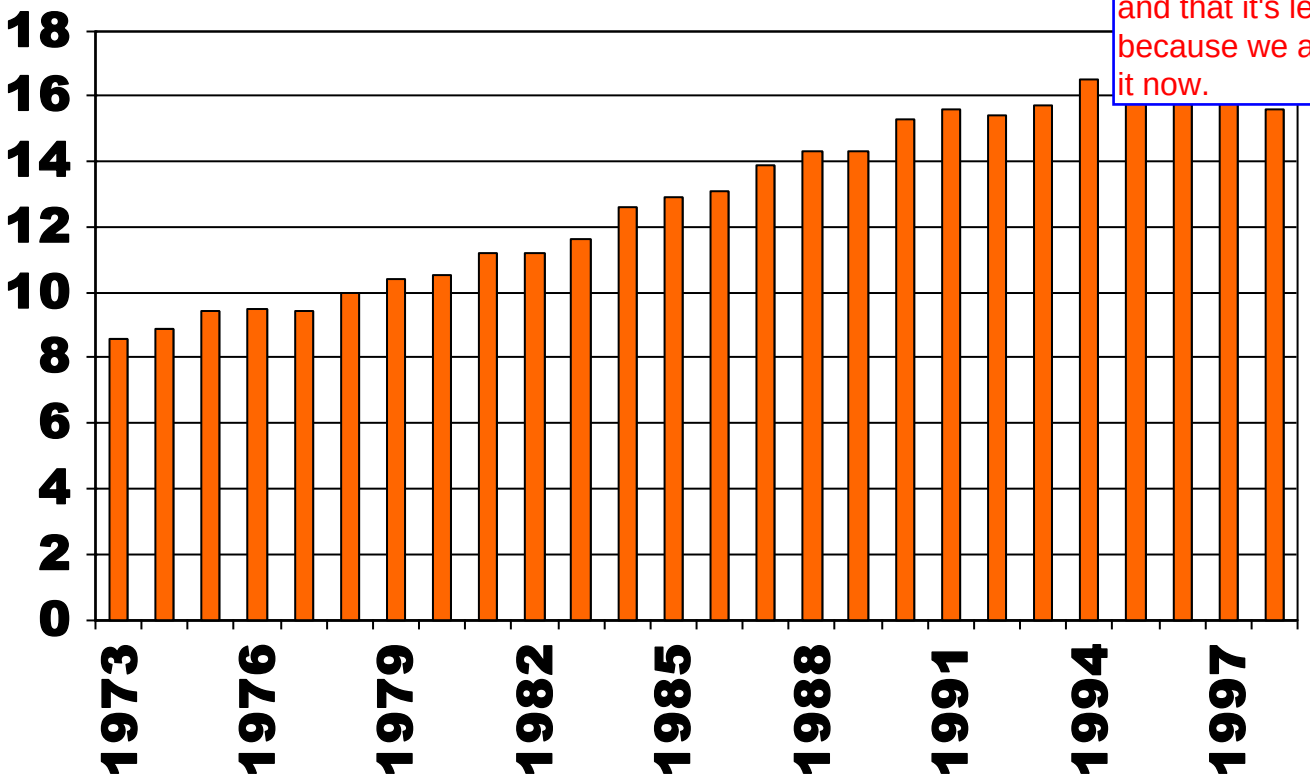


No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

As you can see, survival declines at a steady rate in all three groups. Hard to change these curves.

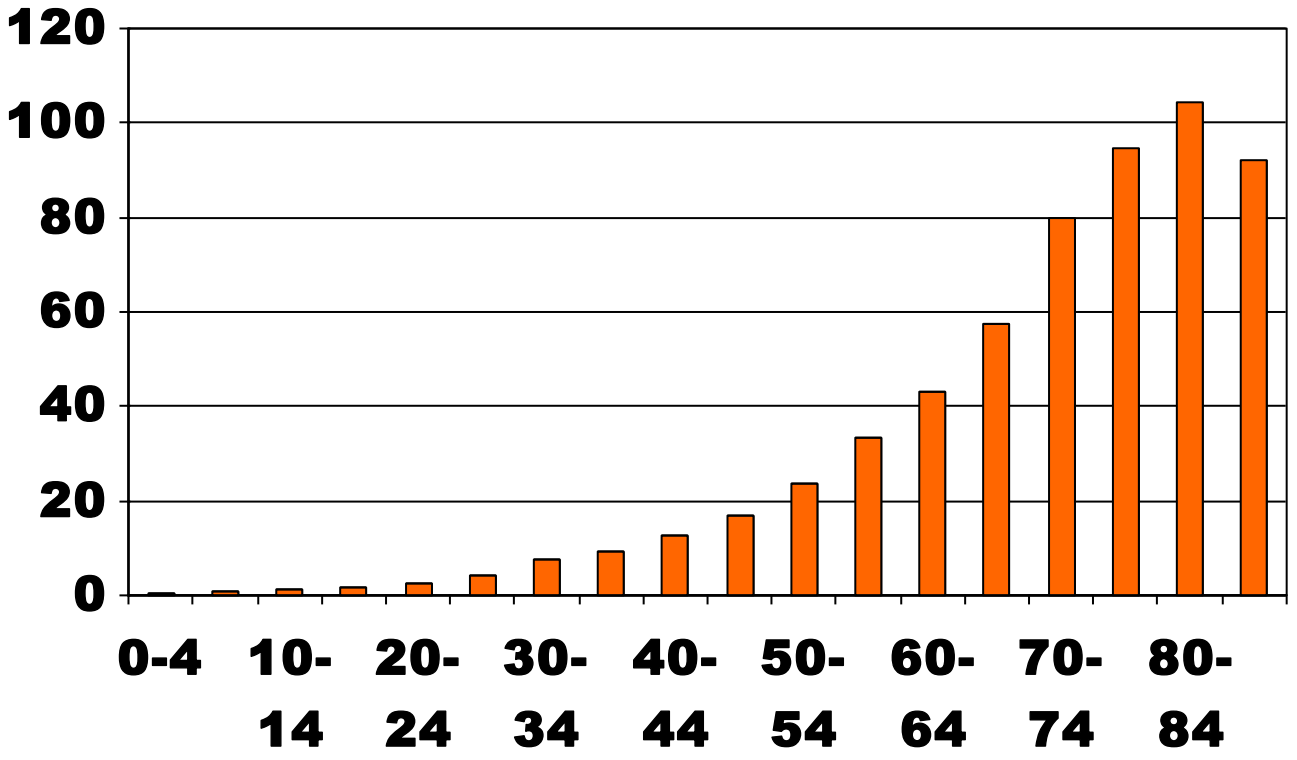
Non-Hodgkin's Lymphomas: Statistics
SEER Incidence Rates by Year

SEER (Surveillance, Epidemiology and End Results program). Sample across hospital. Incidence of cancers. NHL has leveled off. He believes it was increasing because of chemicals in environment and that it's leveled off because we are better about it now.



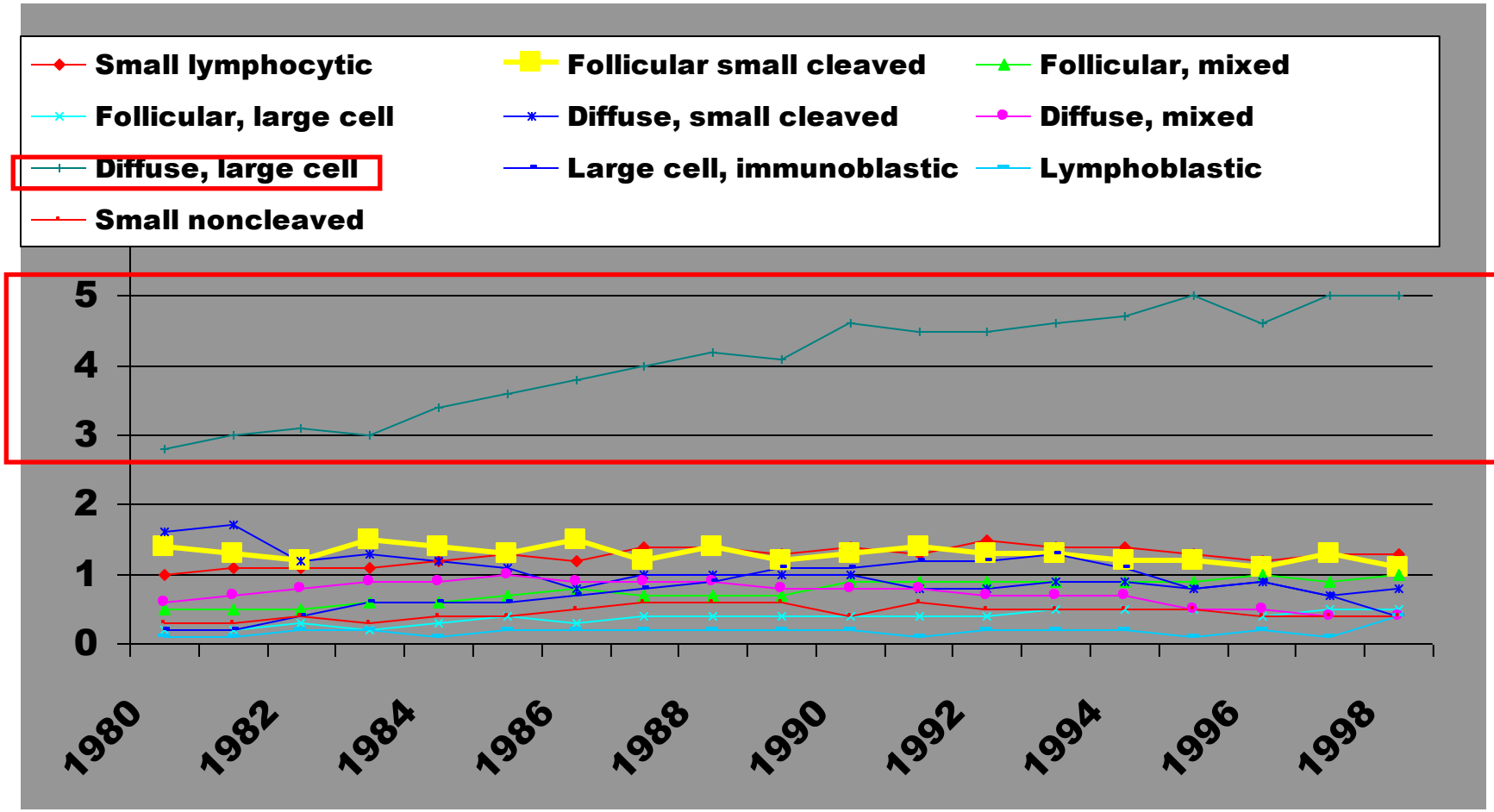
Non-Hodgkin's Lymphomas: Statistics
SEER Incidence Rates by Age of Patient

The older we are, the more likely we are to get NHL.



Non-Hodgkin's Lymphomas: Statistics
SEER Incidence Rates by Year by Diagnosis

Only diffuse large cell is increasing in frequency.



Non-Hodgkin's Lymphomas: Statistics

	Males	***Females***
Lifetime risk of being diagnosed	2.10%	1.76%
Lifetime risk of dying	0.99%	0.89%

Non-Hodgkin's Lymphomas: Statistics

To explain demographics, look at jobs associated with follicular lymphoma (farming, woodworking, manufacturing). These were traditionally jobs for white males.	***Males***	***Females***
Rate per 100,000 persons	19.5	12.4
White	20.2	13.0
Black	16.0	8.7

Non-Hodgkin's Lymphomas: Epidemiology Overview

- 15 cases per 100,000 per year in the United States
  - 1/6600 people per year
  - 1/2000 people age > 50 per year
  - 1/960 people age > 80 per year
- Life time risk
  - Diagnosis: 2%
  - Dying: 1%
- Incidence increasing:
  - 8.6/100,000 in 1973
  - 10.5/100,000 in 1980
  - 15.3/100,000 in 1990
  - 15.6/100,000 in 1998

Incidence has leveled off.

- Rises with age:
  - 24 cases per 100,000 at age 50; 104 cases per 100,000 at age 80

Non-Hodgkin's Lymphomas: Epidemiology By Category

Chemical agents, immune stimulation, immunosupression, infectious agents linked to NHL.

Chemical Agents	Immune stimulation	Immuno supppression	Infectious agents	Controversial
• Pesticide (Organo-phosphates, phenoxyacetic acid, chlorophenols) • Solvents (benzene, butadiene, carbon tetrachloride) • Wood preservatives (creosote, pentachlorophenol) • Drugs (alkylating agents)	• Rheumatoid arthritis • Sjogrens • Systemic lupus	• Organ transplant • HIV/AIDS	• EBV • HTLV-I • Helicobacter pylori • Chlamydia psittacosis • Campylobacter jejuni • Hepatitis C	• Diet high in animal protein • Cigarette smoking • Hair coloring products

Non-Hodgkin's Lymphomas: Clinical Clinical Features

Clincial differences: LN= lymph node
In high grade lymphomas, get single, firm LN.
In low grade, get multiple soft LN

	Low Grade	Intermediate Grade	High Grade
Age	54	56.8	**29.8**
M/F	1.3	1.0	**2.6**
Symptoms	Usually none Related to LN	Usually none Related to LN	Symptoms related to location of LN
PE	Multiple LN in multiple locations LN are usually soft, multiple, matted	Single LN, often in single site, may be multiple LN harder	LN grow rapidly LN firm Abdominal masses
Albumin	Low as disease progresses	Low as disease progresses	Low in end stages
LDH	Usually normal, may be high	Correlates with spread of disease	High and correlates with prognosis
Other	K^+, PO^4, Uric acid normal	K^+, PO^4, Uric acid increased or normal	K^+, PO^4, Uric acid often increased

Non-Hodgkin's Lymphomas: Clinical Clinical Features

	Low Grade	Intermediate Grade	High Grade
Bone marrow +	47%	6%	10%
Radiographs	Small, multiple LN in the mediast, hilar, retrocrural, RP, mesentery	Fewer, larger LN in the mediast, hilar, retrocrural, RP, mesentery	Abdominal and mediastinal masses, can be very large, single often
Complete response	don't cure 73%	59%	48%
Median survival YR	7.2	1.5	.7
5 YR survival	70%	35%	23%

Response doesn't always last.

Median survival is a year, but if you survive it, you survive "indefinitely"

Non Hodgkin Lymphoma (Follicular): Treatment Overview

- Chlorambucil
- Cyclophosphamide, vincristine, prednisone
- Cyclophosphamide, vincristine, doxorubicin, prednisone
- Fludarabine
- Fludarabine combinations

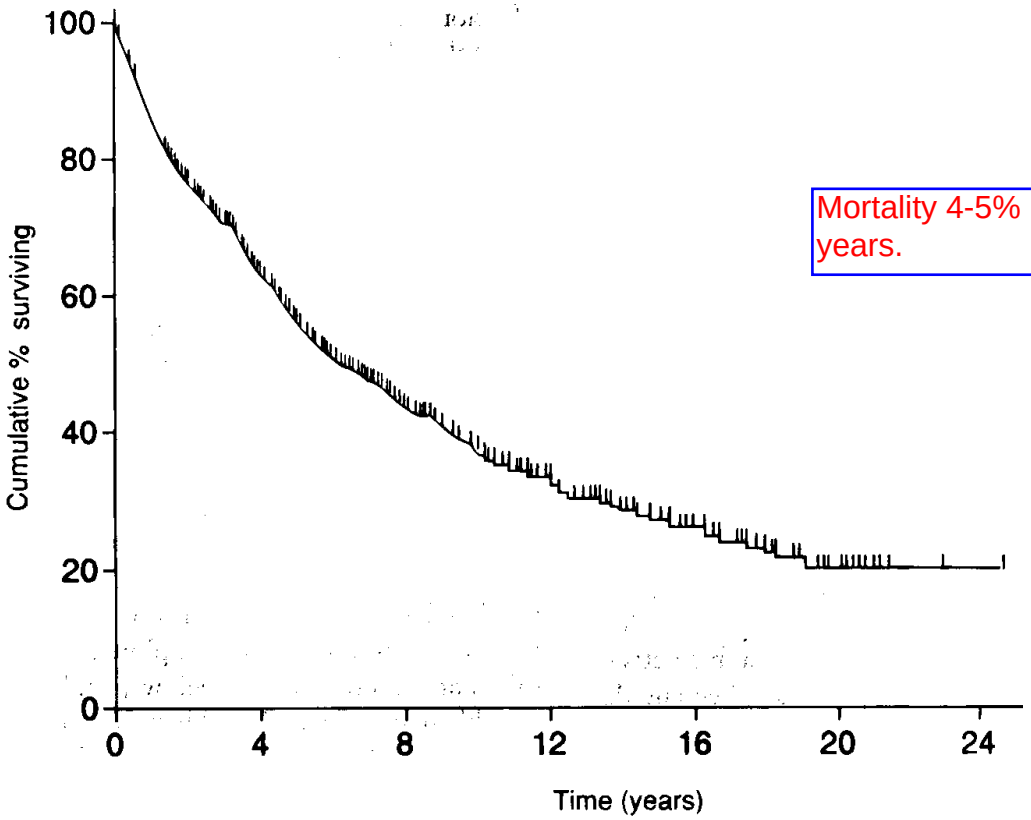
- Rituximab – monoclonal antibody added to above

- Many change rate of progression, recurrence, response BUT

- Only rituximab combinations change survival

Use lots of different combinations of drugs. Community moving towards Fludarabine.

Non Hodgkin Lymphoma (Follicular): Treatment Overall Survival



Mortality 4-5% per year. 20% alive at 20 years.

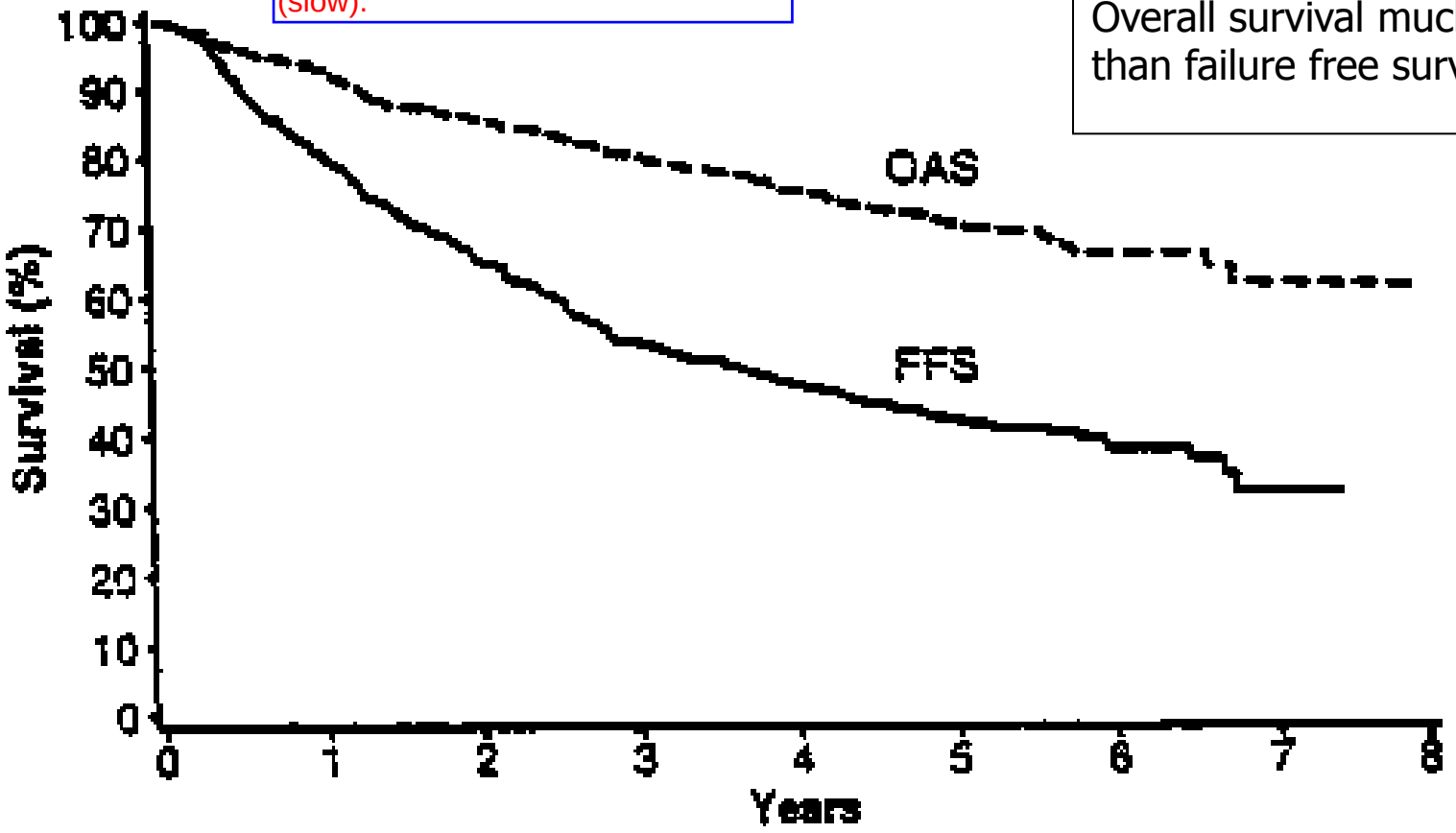
Lister and Armitage, Clinical Oncology, 1995

Non Hodgkin Lymphoma (Follicular): Treatment

Overall Survival vs Failure Free Survival

Failure free survival means that disease doesn't progress. Median survival is different than progression (slow).

Low Grade Lymphoma
5 YR survival 70%
Median survival: 7.2 years
Overall survival much longer than failure free survival



Low Grade (Follicular) NHL Summary

Read this slide

- Older patient
- Men more common than women
- Slowly accumulating lymphocytes
- Multiple small – soft – lymph nodes
- Slowly progressive
- Treatment controls disease, no cure
- 4% die of disease per year

Disease 4

Non Hodgkin Lymphoma
Diffuse Large Cell Lymphoma

History I

He just read this slide.

- 32 year old man with diffuse large cell B-cell NHL

- November, 2006, noted shortness of breath, cough, right sided chest pain
- PMD: CXR showed mass in the lung and scheduled for CT but…

- 12/6/06 – DUMC ED with shortness of breath
  - Clinical evidence for SVC syndrome
  - CT demonstrated large mediastinal mass
  - ECHO demonstrated pericardial fluid

- 12/9/06 – pericardial window placed and mediastinal mass biopsy was taken

History II

- 12/9/06 – pericardial window placed and mediastinal mass biopsy was taken – failure to wean from respirator
- 12/18/06 – Radiation 250 cGy per day x 2 days to mediastinal mass AP/PA
- Weaned from respiratory and extubated day 12/25/06 (day 17 of ventilatory support)
- FDG-PET – Positive
  - Mediastimum
  - Subcarinal
  - Spleen
  - periaortic

History III

- PMH:
  - Osgood-Schlatter disease
- Family History: non contributory
- Social History: Non contributory

Physical Examination:

- Signs of SVC syndrome
  - Plethora
  - Dilated veins
- No organomegaly
- No peripheral lymph nodes

Would make biopsy easier.

Superior Vena Cava syndrome is the obstruction of blood flow through the SVC It is a medical emergency. Most common symptoms include dyspnea, facial swelling, head fullness, cough, arm swelling, chest pain, dysphagia, orthopnea, distorted vision, hoarseness, stridor, headache, nasal stuffiness, nausea, pleural effusions and light headedness.

Laboratory Studies

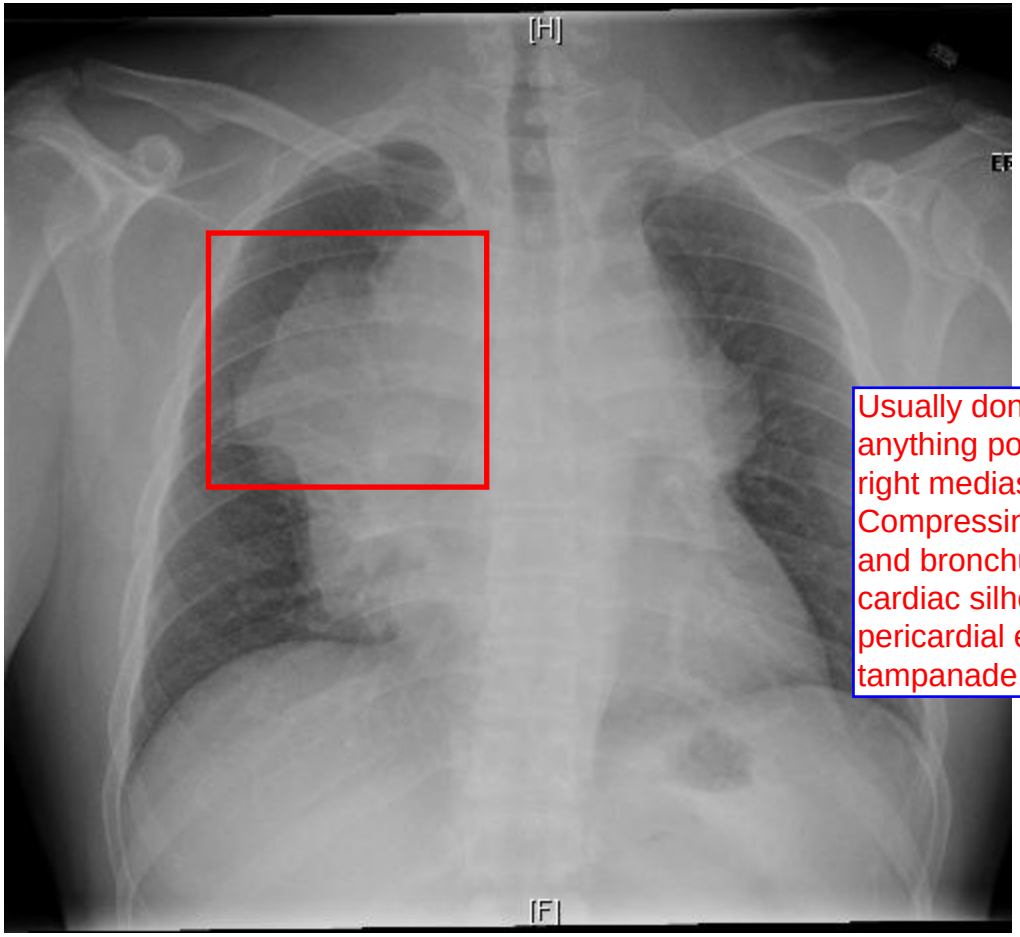
- WBC 7,000 Hb 12.4 Plat 255,000
  - PMN 73% Lym 17% Mono 7%
- Comprehensive panel normal
- LDH 1117 U/L

Relatively normal other than LDH. LDH (marker of badness) was 5x upper limits of normal.

Pathology

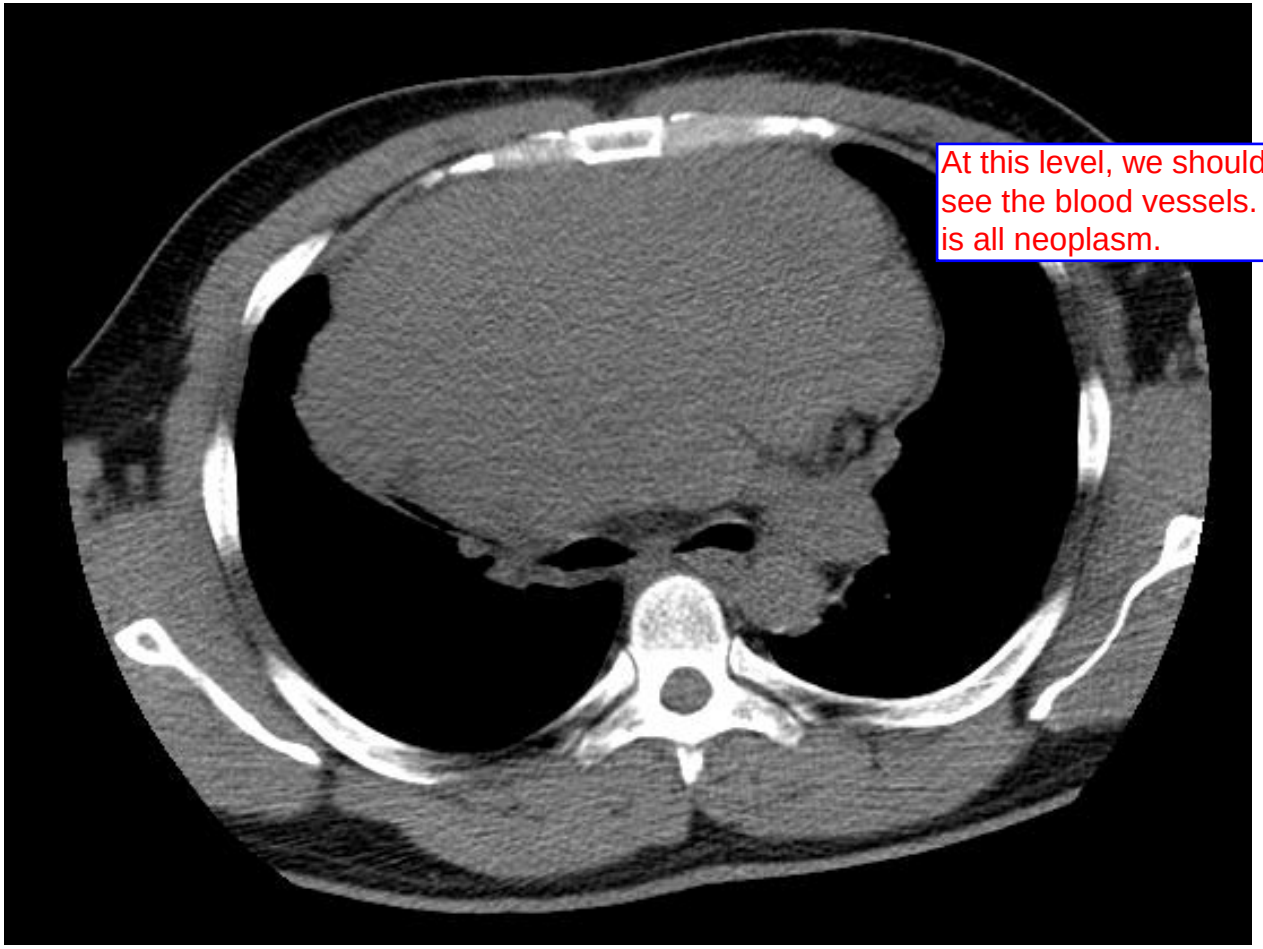
- Biopsy mediastinal mass
- Large atypical lymphoid cells with open chromatin, several small distinct nucleoli and moderate amount of pale to clear cytoplasm
- Immunoperoxidase stains
  - BCL-2, BCL-6, MUM-1 positive
  - Myeloperoxidase and EBV negative
  - Ki-67 approximately 50%
- Diffuse Large Cell B-cell NHL

Radiographs

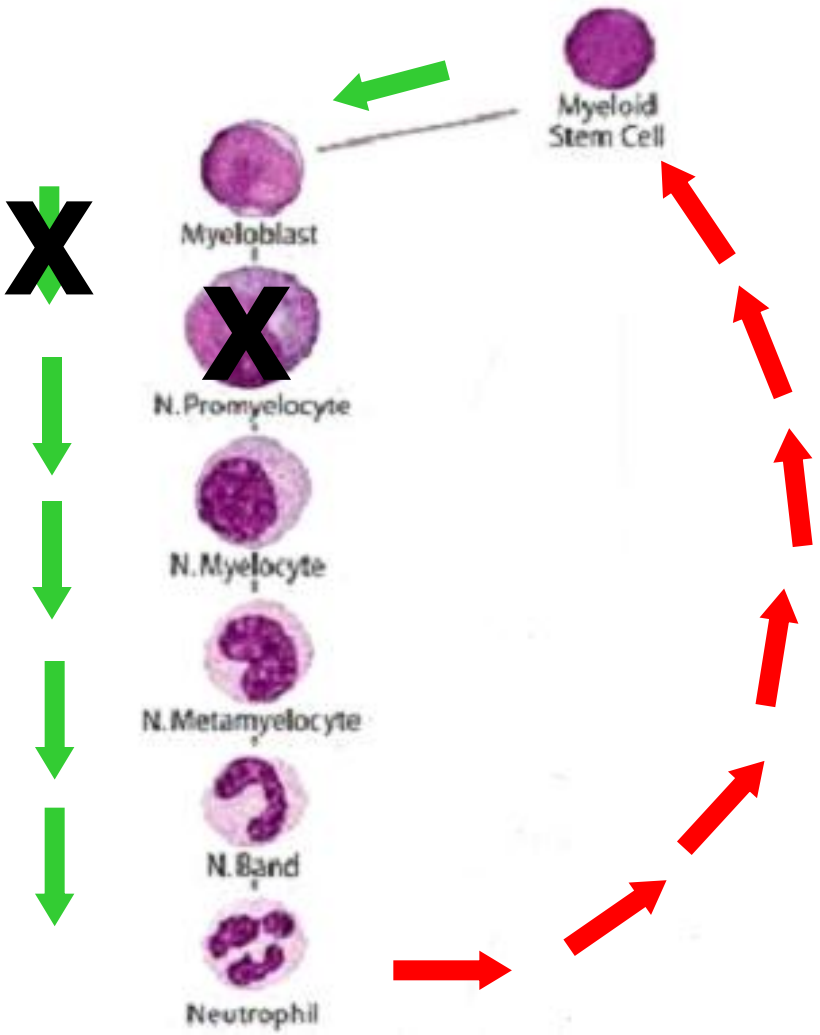


Usually don't see anything poking out from right mediastinum. Compressing trachea and bronchus. Enlarged cardiac silhouette is from pericardial effusion and tampanade.

CT: Pretreatment

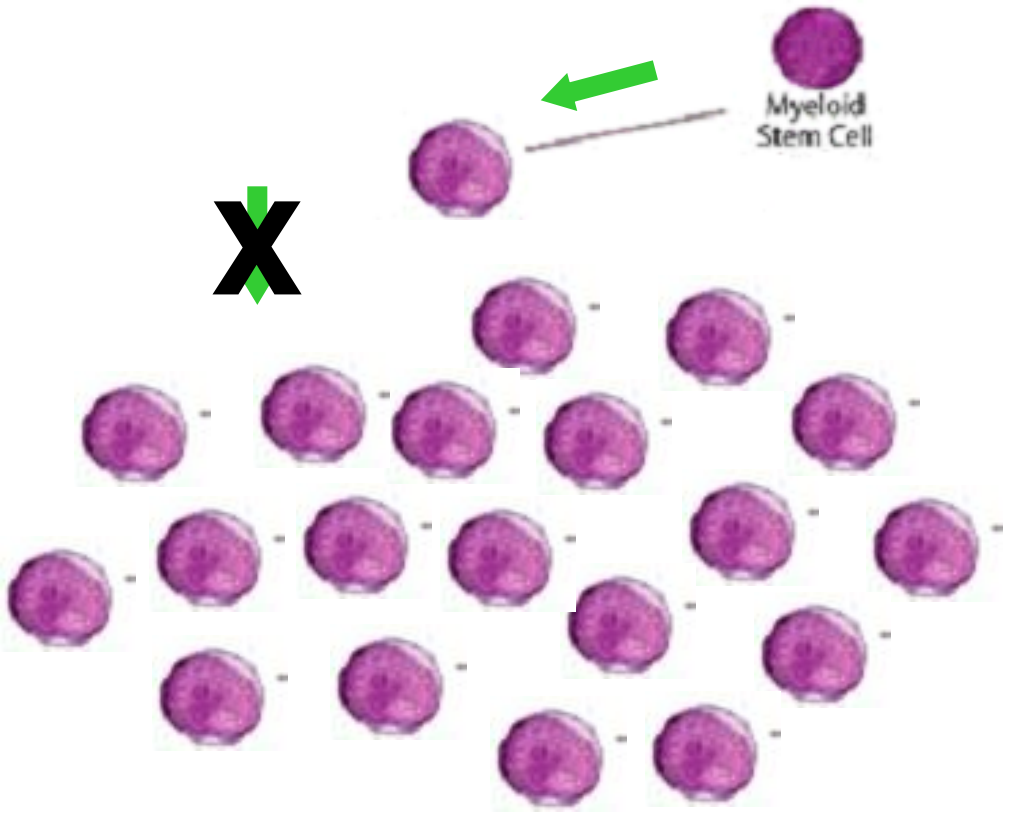


Aggressive NHL (DLC): Pathophysiology
Not Proceed Through Development Cycle



Mature cells provide signals to myeloid stem cells to prevent overgrowth. In this case, however, cells don't mature/die.

Aggressive NHL (DLC): Pathophysiology And Aggressive Growth (Second Defect)

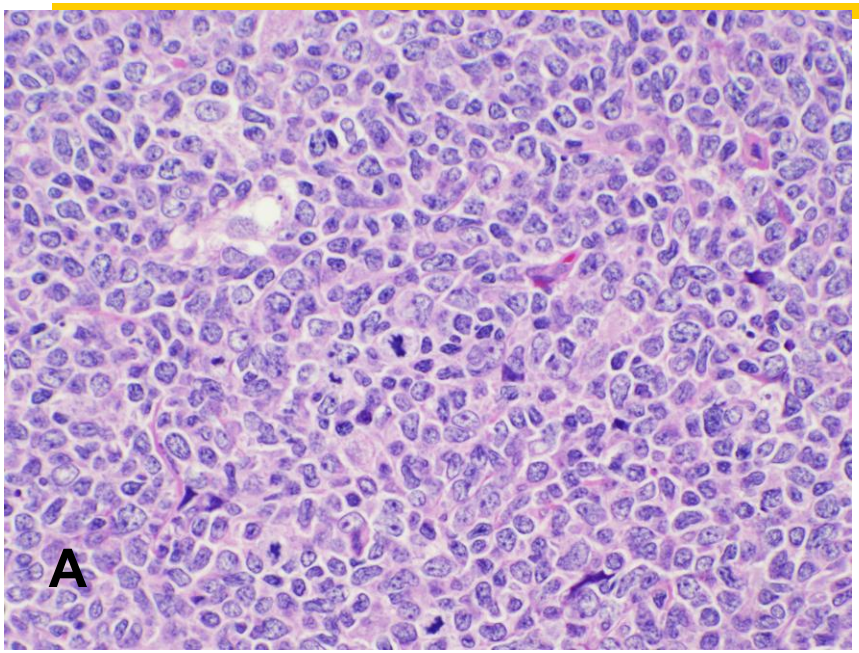


Diffuse Large Cell Lymphoma

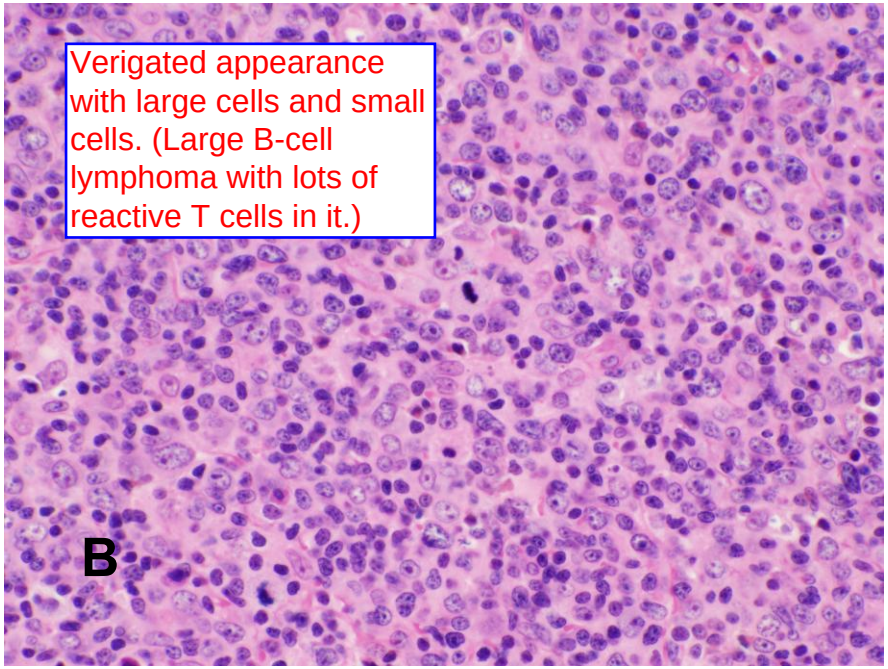
Pathology

Diffuse Large B-cell Lymphoma

DLBCL: Morphology

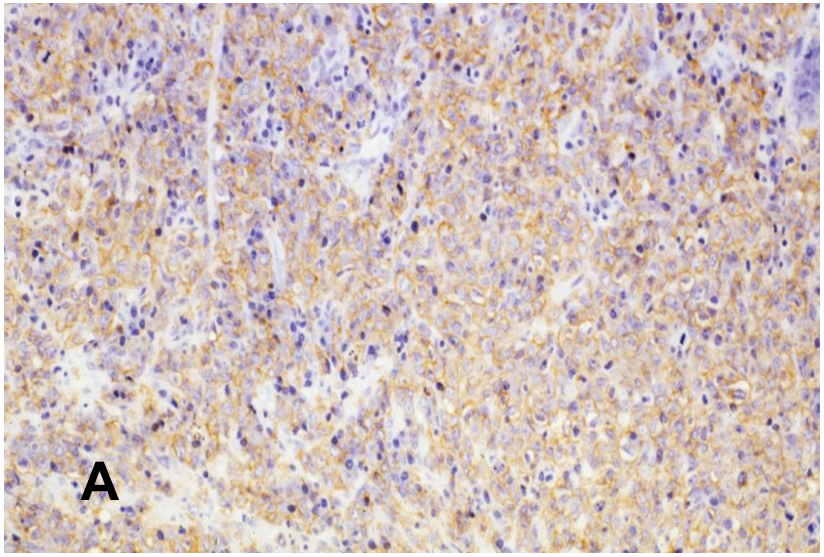


Cells in DLBCL tend to be larger and have no architecture (wipes out nodal architecture). Diffuse growth pattern. Lots of variability in cytologic and histologic features..



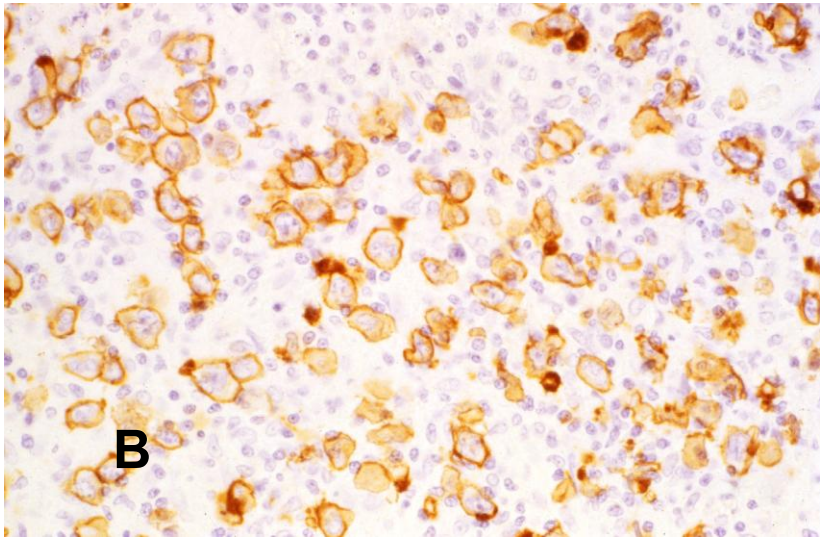
Morphologic features are variable from case to case as is the proportion of neoplastic large B cells

DLBCL: Immunohistochemistry



B-cell antigen positive, e.g., CD20

Make diagnosis with immunohistochemisty. CD20 is a marker of B cells. See the variability between individuals.

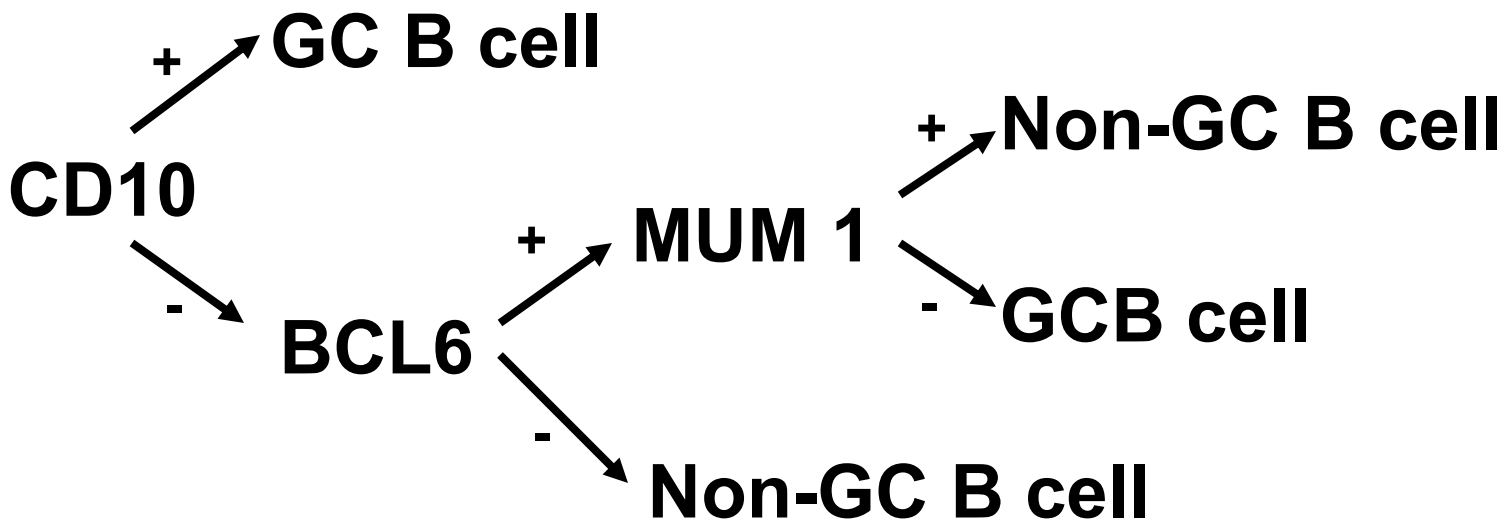


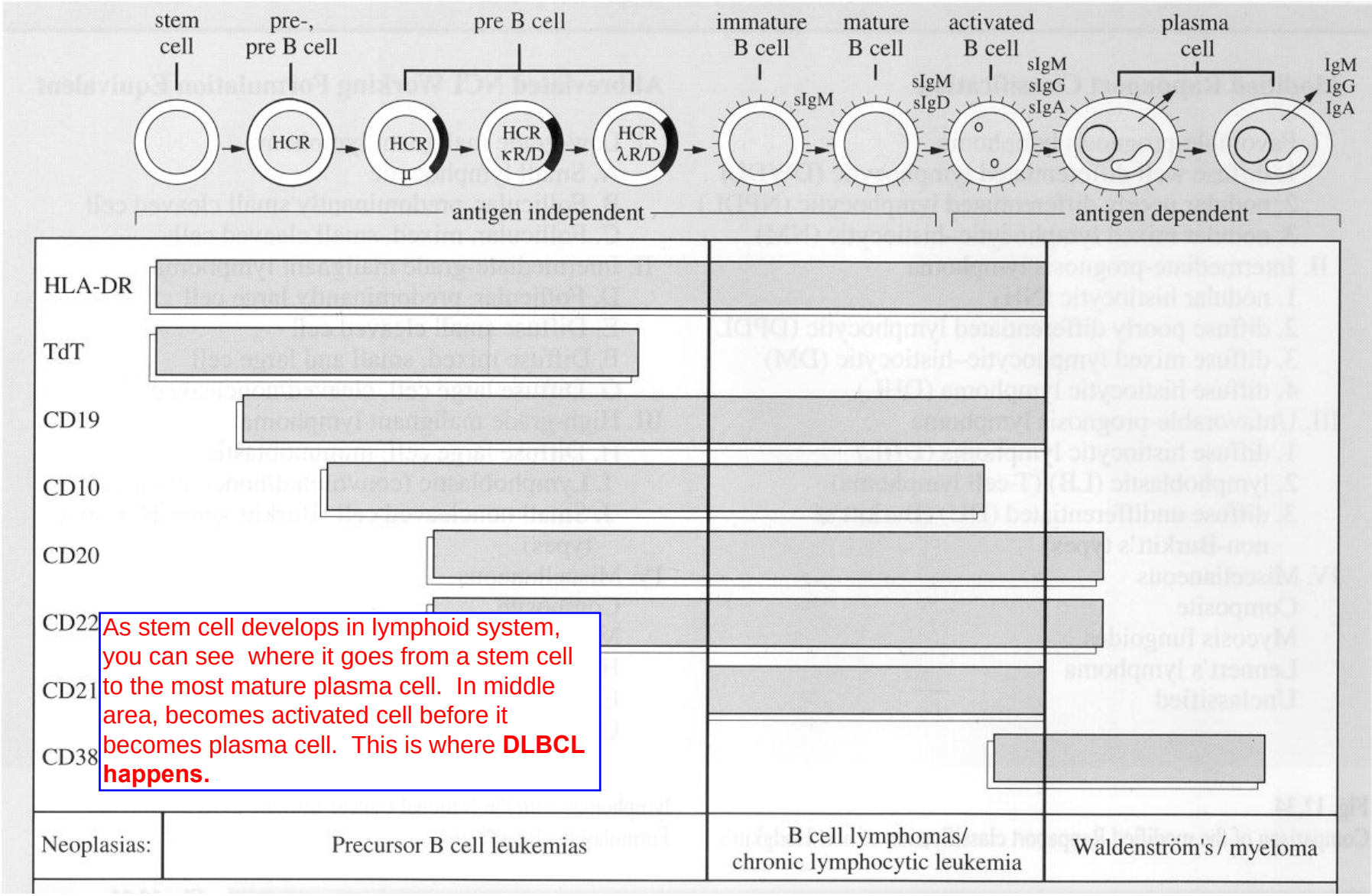
DLBCL: Molecular Techniques

- Gene expression profiles have shown that DLBCL derived from lymphoid follicle (germinal) centers may have a better prognosis than those that are non-GC derived
- A small number of key gene products can be used to define GC origin using **immunohistochemistry (IHC)**

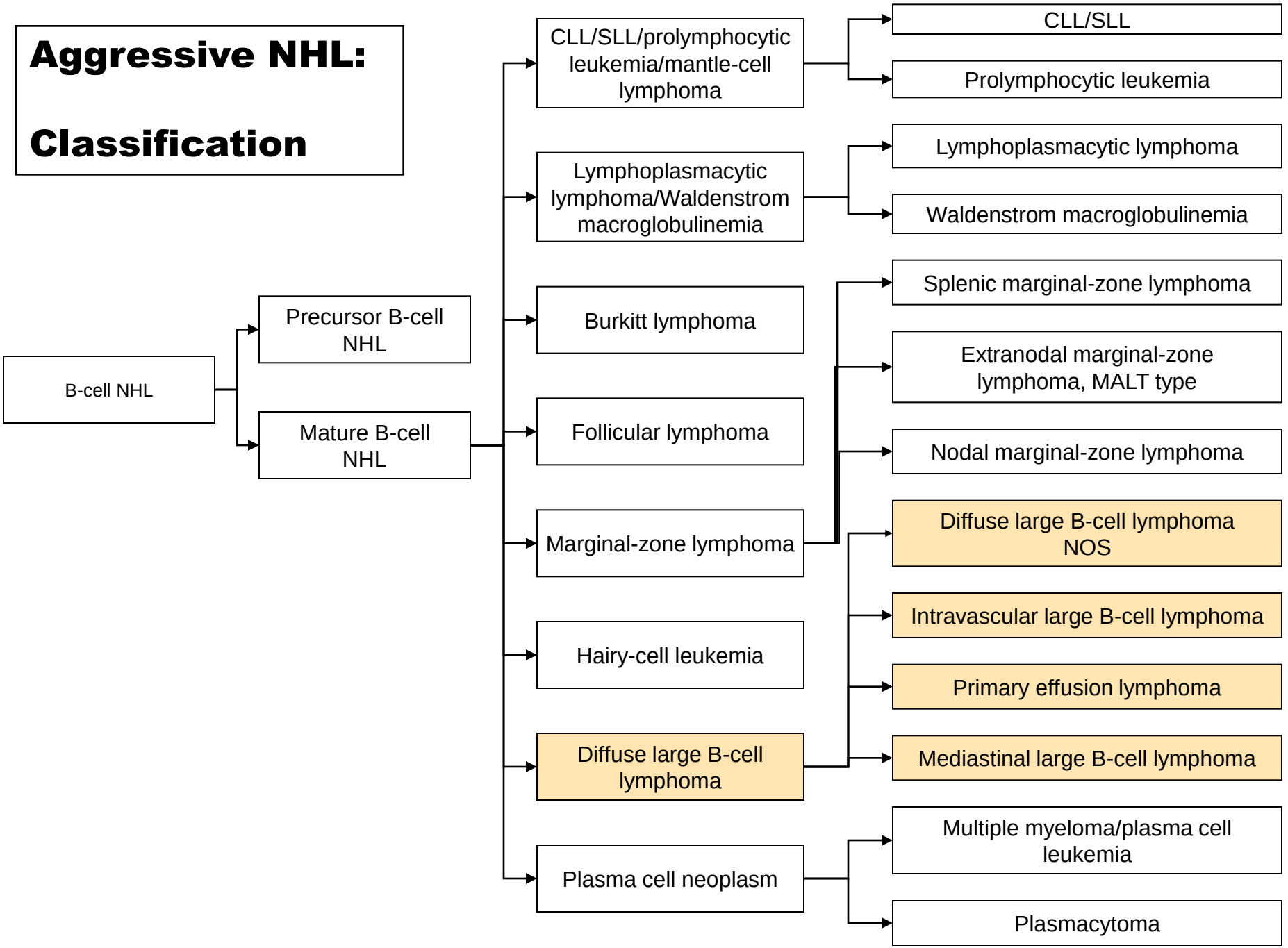
Using IHC to Define GC vs Non-GC Origin of DLBCL

Translate expression data with diagnostic tools.



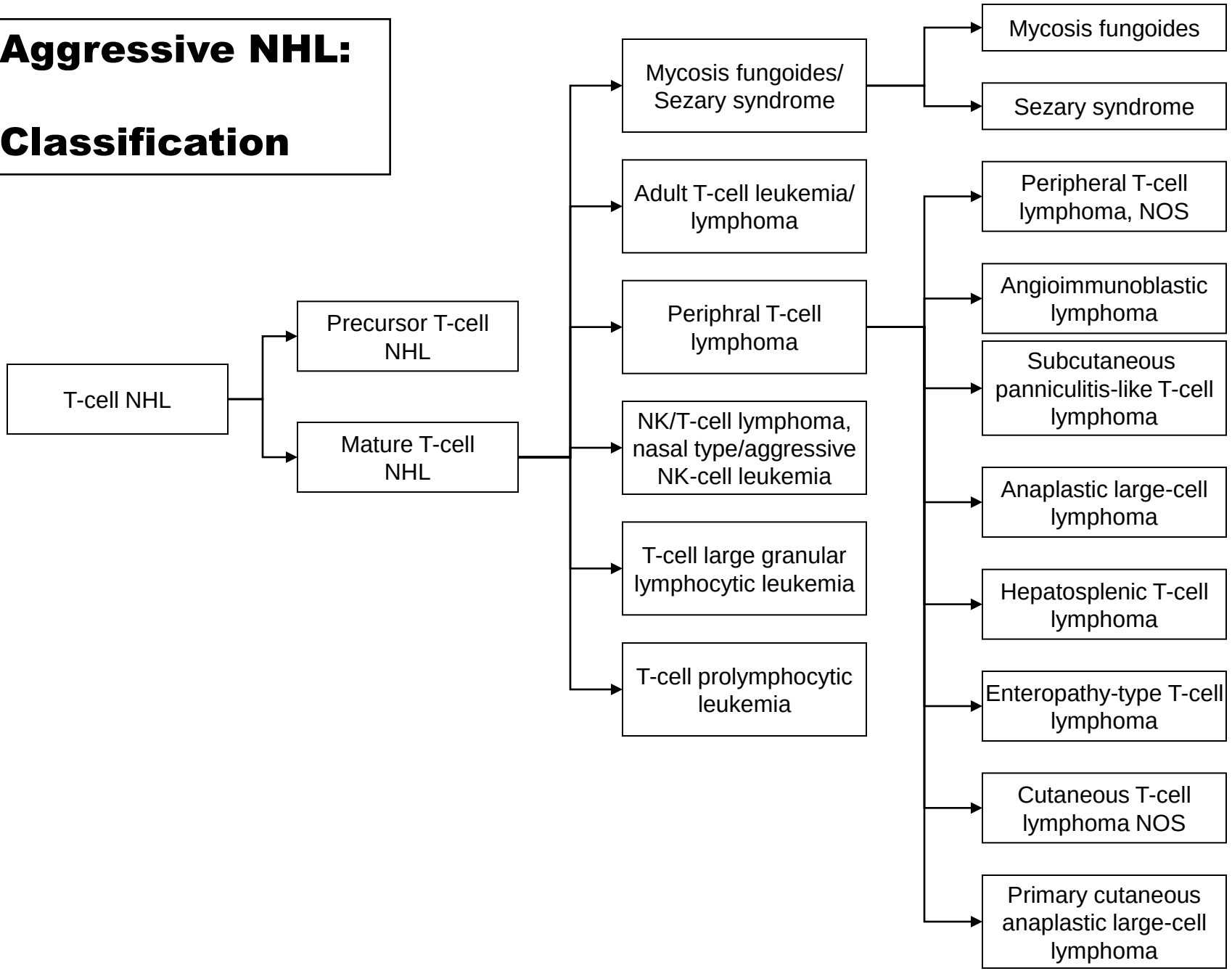

stem cell
pre-, pre B cell
pre B cell
immature B cell
mature B cell
activated B cell
plasma cell
HCR
HCR
HCR κR/D
HCR λR/D
sIgM
sIgM sIgD
sIgM sIgG sIgA
IgM IgG IgA
antigen independent
antigen dependent
HLA-DR
TdT
CD19
CD10
CD20
CD22
CD21
CD38
As stem cell develops in lymphoid system, you can see where it goes from a stem cell to the most mature plasma cell. In middle area, becomes activated cell before it becomes plasma cell. This is where **DLBCL happens.**
Neoplasias:
Precursor B cell leukemias
B cell lymphomas/ chronic lymphocytic leukemia
Waldenström's / myeloma

Aggressive NHL: Classification



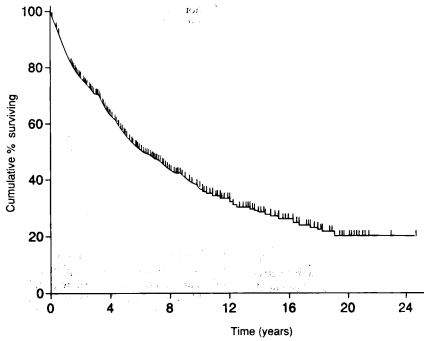
Aggressive NHL:

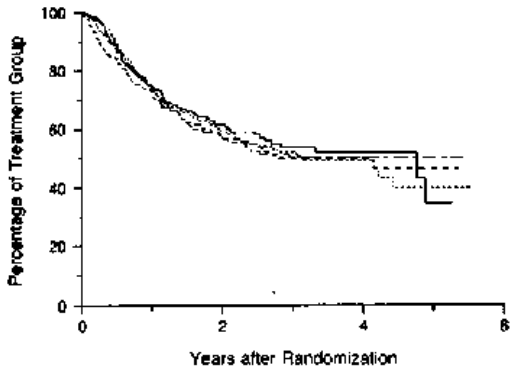
Classification

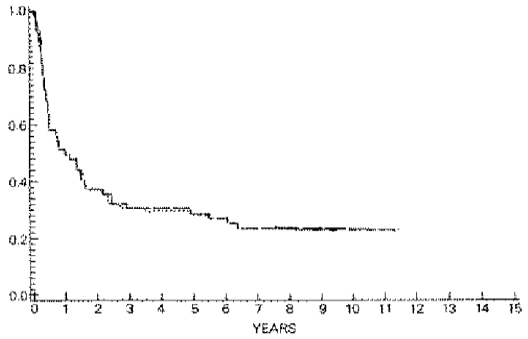


Aggressive NHL (DLC): Classification

Low Grade	Intermediate Grade	High Grade
Apoptosis	Apoptosis + Proliferative	Proliferative Proliferative Proliferative
Slow accumulating	Accumulating but active growth	Tremendously active growth
Treatable Not curable	Treatable Curable	Curable

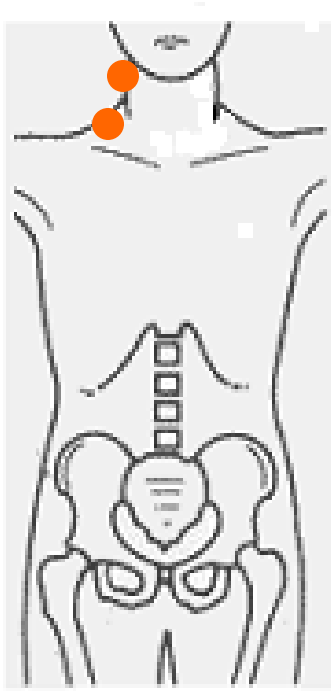


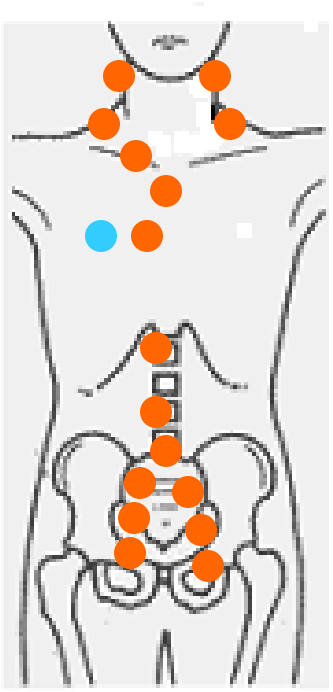


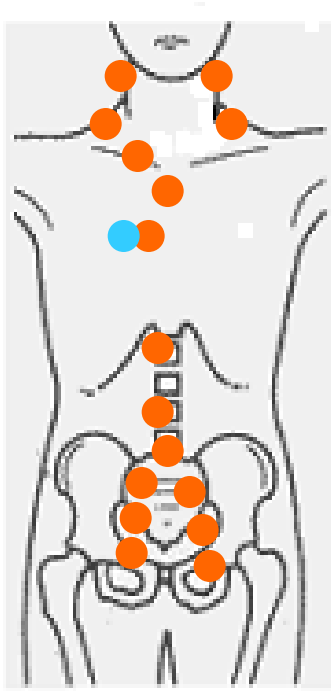


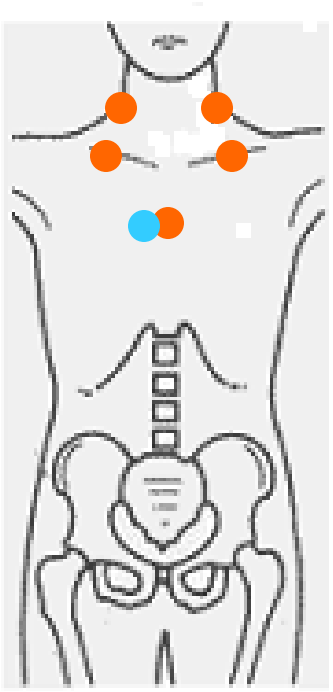
Aggressive NHL (DLC): Staging International Prognostic Index

Doesn't work.









Stage	I	IV	IIIE	IIE

Aggressive NHL (DLC): Prognosis International Prognostic Index

International prognostic index. Five relevant factors. You either have the factor or you don't. The more points, the worse the prognosis.

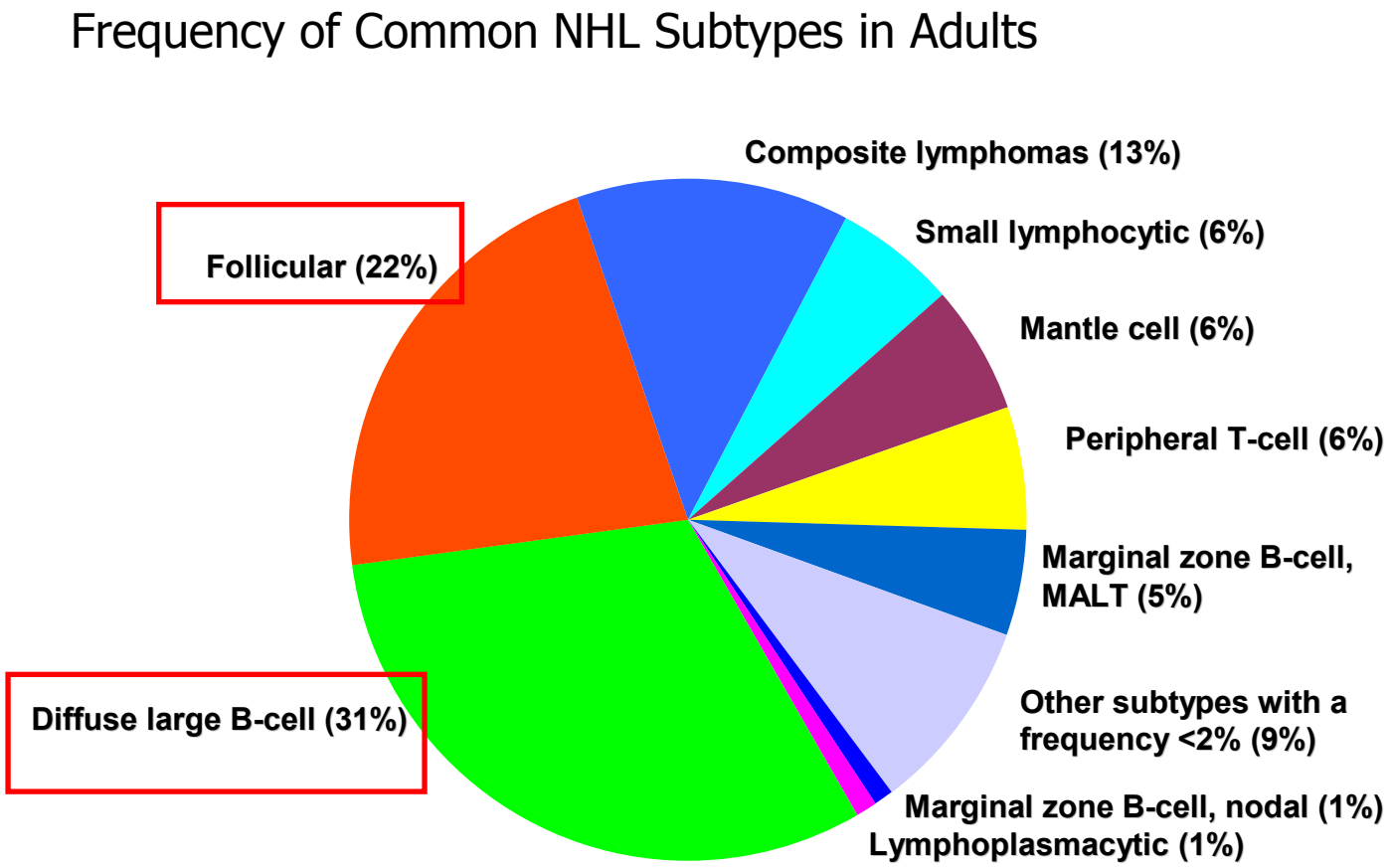
Category	*Characteristic*	*5-year Survival Rate (%)*
Age	< 60	60
	>60	41
Stage	I or II	69
	III or IV	44
Site of Involvement	Extranodal ≤ 1	56
	Extranodal > 1	37
Performance Status	Ambulatory (0 – 1)	55
	Non ambulatory (2-4)	35
Serum LDH	≤ 1 x normal	67
	> 1 x normal	44

Aggressive NHL (DLC): Prognosis
International Prognostic Index

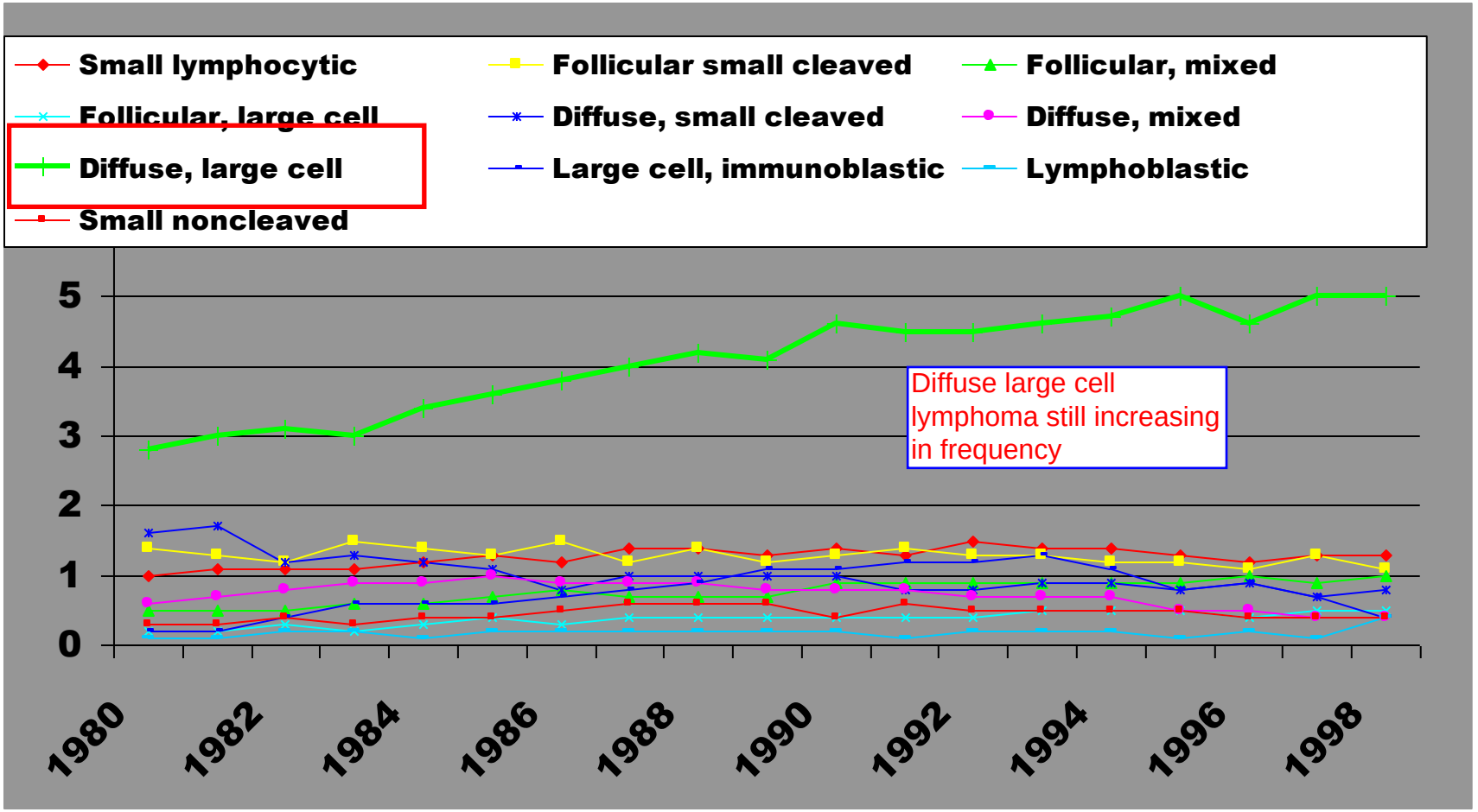
Index	Risk Factor	Percent	CR (%)	Overall Survival 5 Yr (%)
Low	0 or 1	35	70	73
Low Intermediate	2	27	50	51
High Intermediate	3	22	49	43
High	4 or 5	16	40	26

Index helps direct treatment options.

Aggressive NHL (DLC): Statistics Frequency



Aggressive NHL (DLC): Statistics
Incidence per 100,000 People per Year



Non-Hodgkin Lymphomas: Epidemiology By Category

same as low grade lymphomas

Chemical Agents	Immune stimulation	Immuno supppression	Infectious agents	Controversial
• Pesticide (Organo-phosphates, phenoxyacetic acid, chlorophenols) • Solvents (benzene, butadiene, carbon tetrachloride) • Wood preservatives (creosote, pentachlorophenol) • Drugs (alkylating agents)	• Rheumatoid arthritis • Sjogrens • Systemic lupus	• Organ transplant • HIV/AIDS	• EBV • HTLV-I • Helicobacter pylori • Chlamydia psittacosis • Campylobacter jejuni • Hepatitis C	• Diet high in animal protein • Cigarette smoking • Hair coloring products

Aggressive NHL (DLC): Statistics Clinical

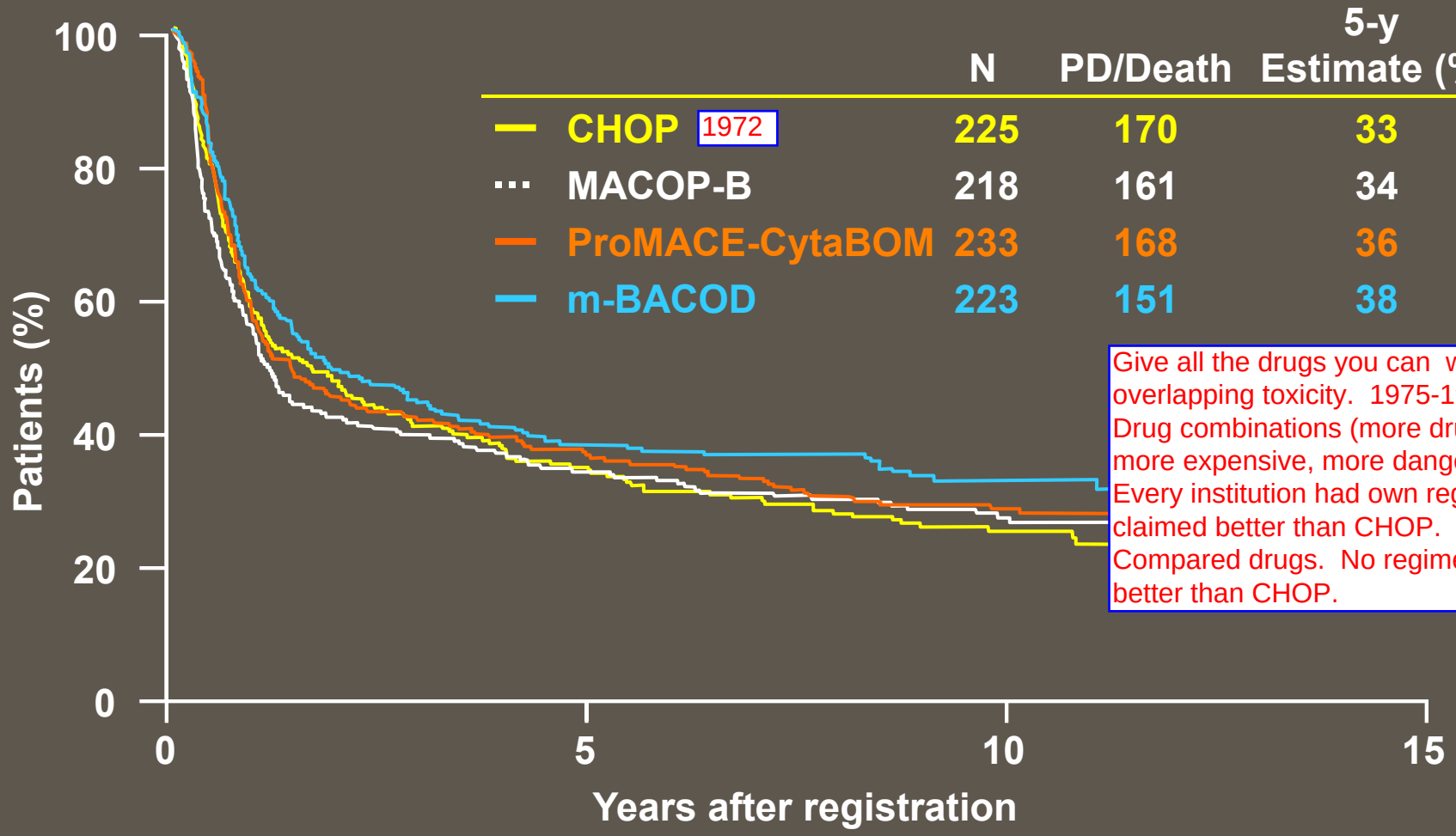
	Low Grade	Intermediate Grade	High Grade
Age	54	56.8	**29.8**
M/F	1.3	1.0	**2.6**
Symptoms	Usually none Related to LN	Usually none Related to LN	Symptoms related to location of LN
PE	Multiple LN in multiple locations LN are usually soft, multiple, matted	Single LN, often in single site, may be multiple LN harder	LN grow rapidly LN firm Abdominal masses
Albumin	Low as disease progresses	Low as disease progresses	Low in end stages
LDH	Usually normal, may be high	Correlates with spread of disease	High and correlates with prognosis
Other	K^+, PO^4, Uric acid normal	K^+, PO^4, Uric acid increased or normal	K^+, PO^4, Uric acid often increased

Aggressive NHL (DLC): Statistics Clinical

	Low Grade	Intermediate Grade	High Grade
Bone marrow +	47%	6%	10%
Radiographs	Small, multiple LN in the mediast, hilar, retrocrural, RP, mesentery	Fewer, larger LN in the mediast, hilar, retrocrural, RP, mesentery	Abdominal and mediastinal masses, can be very large, single often
Complete response	73%	59%	48%
Median survival YR	7.2	1.5	.7
5 YR survival	70%	35%	23%

Cure 1/3 patients. If you get across median, you are going to be cured.

Aggressive NHL (DLC): Treatment National High Priority Study



Update of Fisher et al. *N Engl J Med.* 1993;328:1002. Courtesy of R. Fisher, 2005.

CHOP Chemotherapy

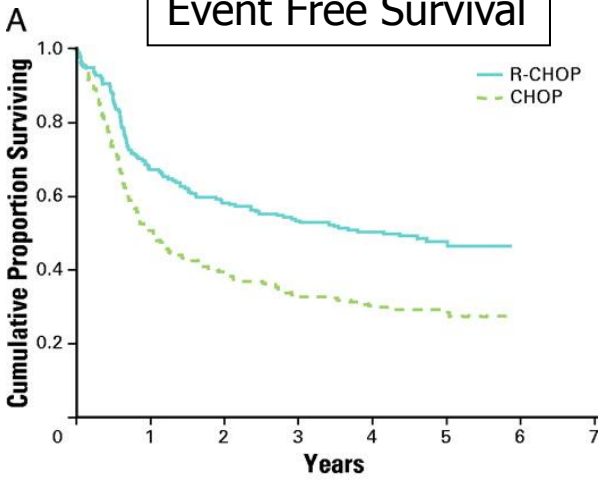
- Cyclophosphamide 750 mg/m2 IV day 1
- Vincristine 1.4 mg/m2 IV day 1
- Doxorubicin 50 mg/m2 IV day 1
- Prednisone 100 mg PO day 1-5

- Rituximab 375 mg/m2 IV day 1

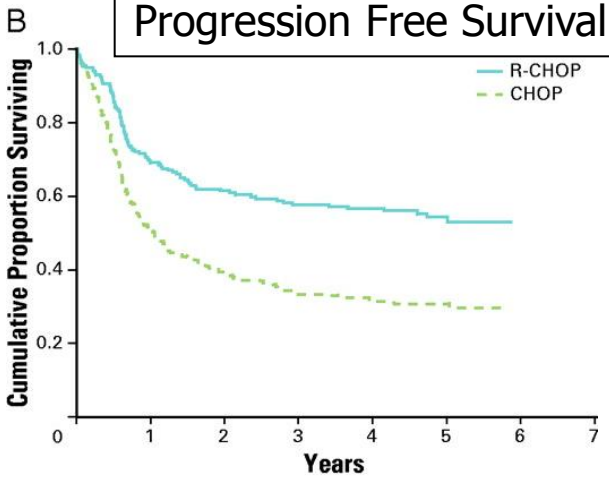
CHOP vs Rituximab-CHOP

Rituximab is about 10% better. Improvement in survival has been sustained.

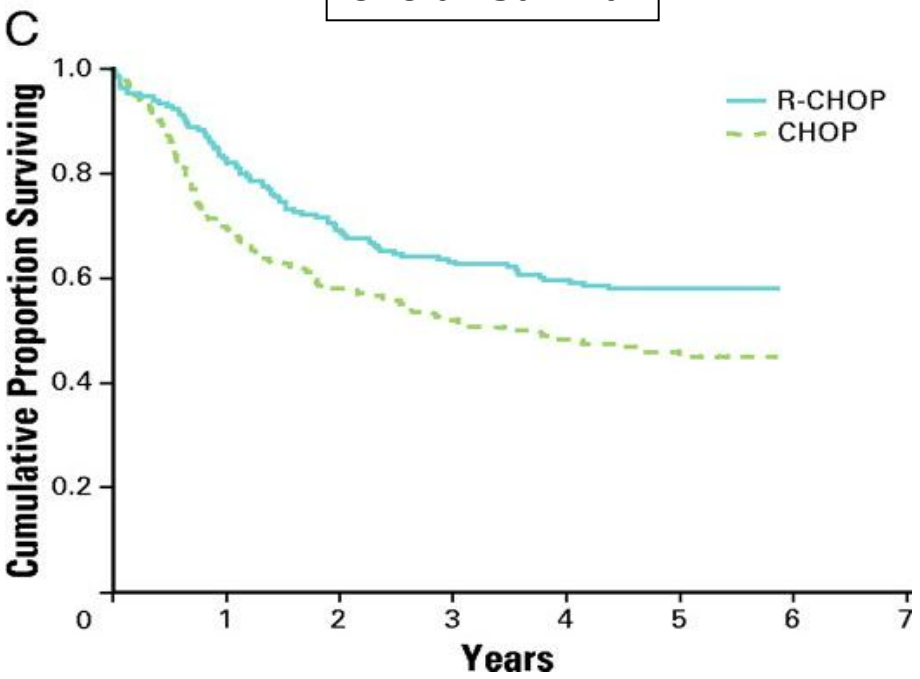
Event Free Survival



Progression Free Survival



Overall Survival



Feugier (Coiffier, GELA) J Clin Oncol; 23:4117-4126 2005

Aggressive NHL (DLC): Summary

- Single or multiple areas of involvement
- Activated lymphoid cell, high proliferative rate
- Cure possible in 50% of patients