



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Lymphoma

David Qualls, MD

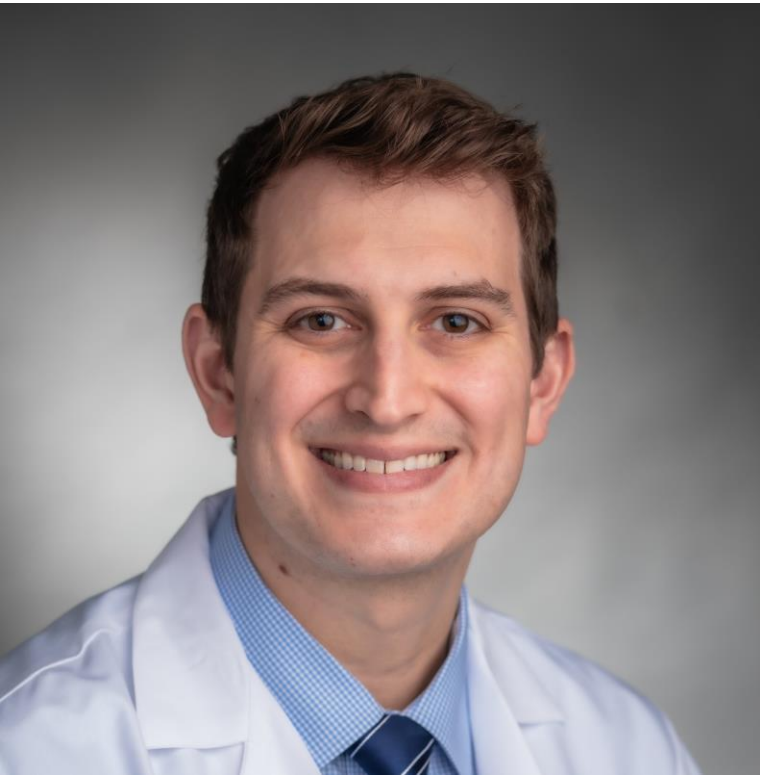
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DISCLOSURES

Honoraria for consulting	ADC Therapeutics, Genmab, Kite/Gilead, Nuvalent
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Presentation includes a description of the following off-label use of a drug or medical device	None



Overview: Two Key Learning Objectives

- Understand characteristics of common lymphoma subgroups
- Be able to describe most common management approaches for lymphoma



Overview

- Classification of lymphoid malignancies
- Epidemiology
- Clinical presentation
- Work-up and staging
- Complications of lymphoma
- Non-Hodgkin lymphoma – common subtypes and treatment
 - Common subtypes
 - Common treatment approaches
- Hodgkin lymphoma
 - Presentation
 - Treatment and Toxicities



Classification

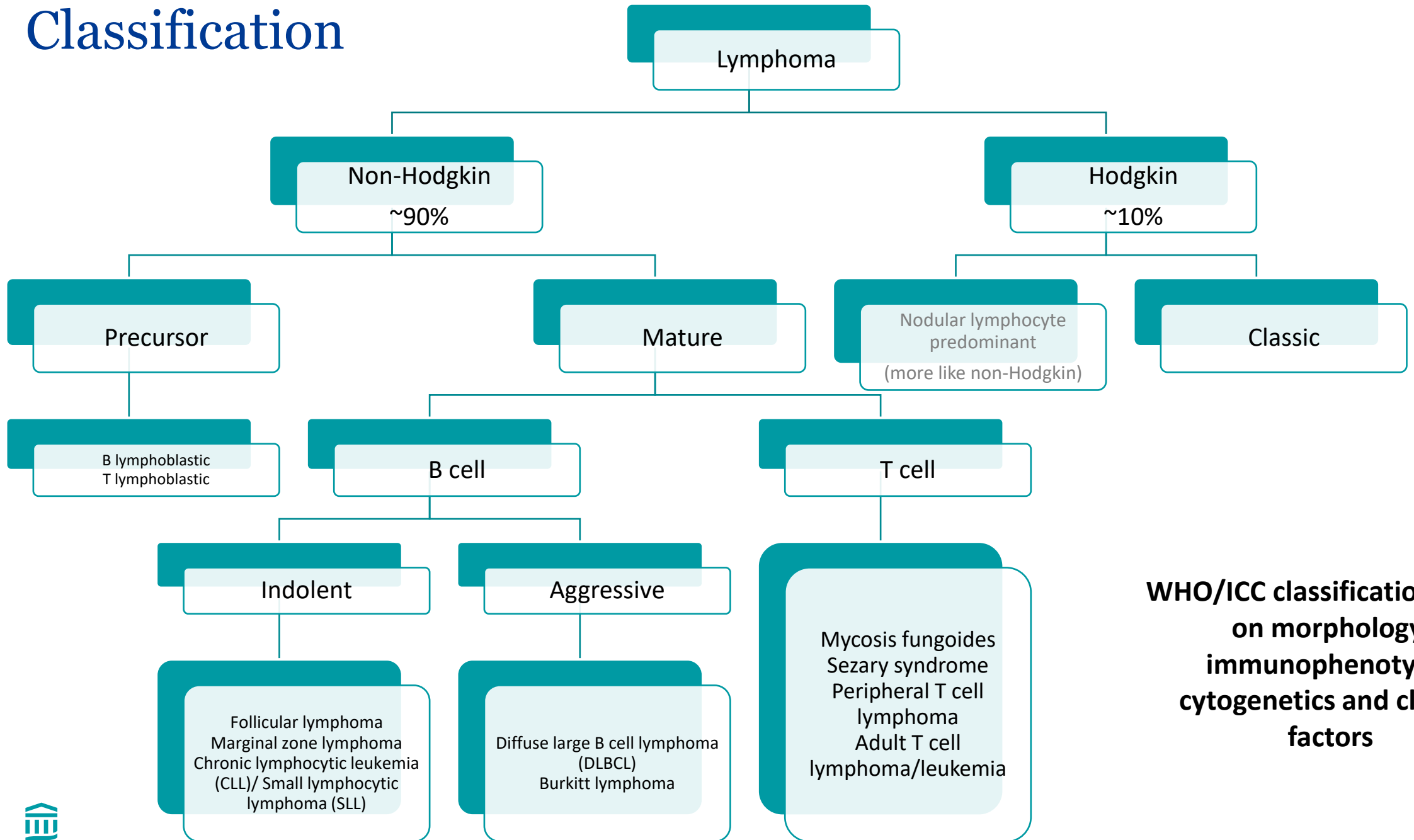
WHO Hematolymphoid classification: over 80 diagnoses

WHO Classification, 5 th edition	WHO Classification, revised 4 th edition
Tumour-like lesions with B-cell predominance	
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma	<i>Not previously included</i>
IgG4-related disease	<i>Not previously included</i>
Unicentric Castleman disease	<i>Not previously included</i>
Idiopathic multicentric Castleman disease	<i>Not previously included</i>
KSHV/HHV8-associated multicentric Castleman disease	Multicentric Castleman disease
Precursor B-cell neoplasms	
B-cell lymphoblastic leukaemias/lymphomas	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with IAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features	B-lymphoblastic leukaemia/lymphoma, BCR-ABL1-like
B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); KMT2A-rearranged
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23p13.3); TCF3-PBX1
B-lymphoblastic leukaemia/lymphoma with TCF3::IL3 fusion	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); IGH/IL3
B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)
Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (Entity deleted)	(Same)
Splenic B-cell lymphomas and leukaemias	B-cell prolymphocytic leukaemia
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	<i>Not previously included</i> (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	<i>Not previously included</i> (originally included under "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)
Follicular lymphoma	
In situ follicular B-cell neoplasm	In situ follicular neoplasia
Follicular lymphoma	(Same)
Paediatric-type follicular lymphoma	(Same)
Duodenal-type follicular lymphoma	(Same)
Cutaneous follicle centre lymphoma	
Primary cutaneous follicle centre lymphoma	(Same)
Mantle cell lymphoma	
In situ mantle cell neoplasm	In situ mantle cell neoplasia
Mantle cell lymphoma	(Same)
Leukaemic non-nodal mantle cell lymphoma	(Same)
Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	<i>Not previously included</i>
Large B-cell lymphomas	

Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements	High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with IRF4 rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	<i>Not previously included</i> (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	<i>Not previously included</i>
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	<i>Not previously included</i> , encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4 th edition (plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)
Burkitt lymphoma	
Burkitt lymphoma	(Same)
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation	
Hyperplasias arising in immune deficiency/dysregulation	<i>Not previously included</i> , encompassing non-destructive post-transplant lymphoproliferative disorders, among others
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation	<i>Not previously included</i> , encompassing polymorphic posttransplant lymphoproliferative disorders, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, among others
EBV-positive mucocutaneous ulcer	(Same)
Lymphomas arising in immune deficiency / dysregulation	<i>Not previously included</i> , encompassing monomorphic posttransplant lymphoproliferative disorders, classic Hodgkin lymphoma posttransplant lymphoproliferative disorders, lymphomas associated with HIV infection, among others
Inborn error of immunity-associated lymphoid proliferations and lymphomas	Lymphoproliferative diseases associated with primary immune disorders
Hodgkin lymphoma	
Classic Hodgkin lymphoma	(Same)
Nodular lymphocyte predominant Hodgkin lymphoma	(Same)
Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	<i>Not previously included</i>
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	<i>Not previously included</i>
Diseases with monoclonal immunoglobulin deposition	
Immunoglobulin-related (AL) amyloidosis	Primary amyloidosis
Monoclonal immunoglobulin deposition disease	Light chain and heavy chain deposition disease
Heavy chain diseases	
Mu heavy chain disease	(Same)
Gamma heavy chain disease	(Same)
Alpha heavy chain disease	(Same)
Plasma cell neoplasms	
Plasmacytoma	(Same)
Plasma cell myeloma	(Same)
Plasma cell neoplasms with associated paraneoplastic syndrome	(Same) Except AESOP syndrome <i>not previously included</i>
-POEMS syndrome	
-TEMPI syndrome	
-AESOP syndrome	



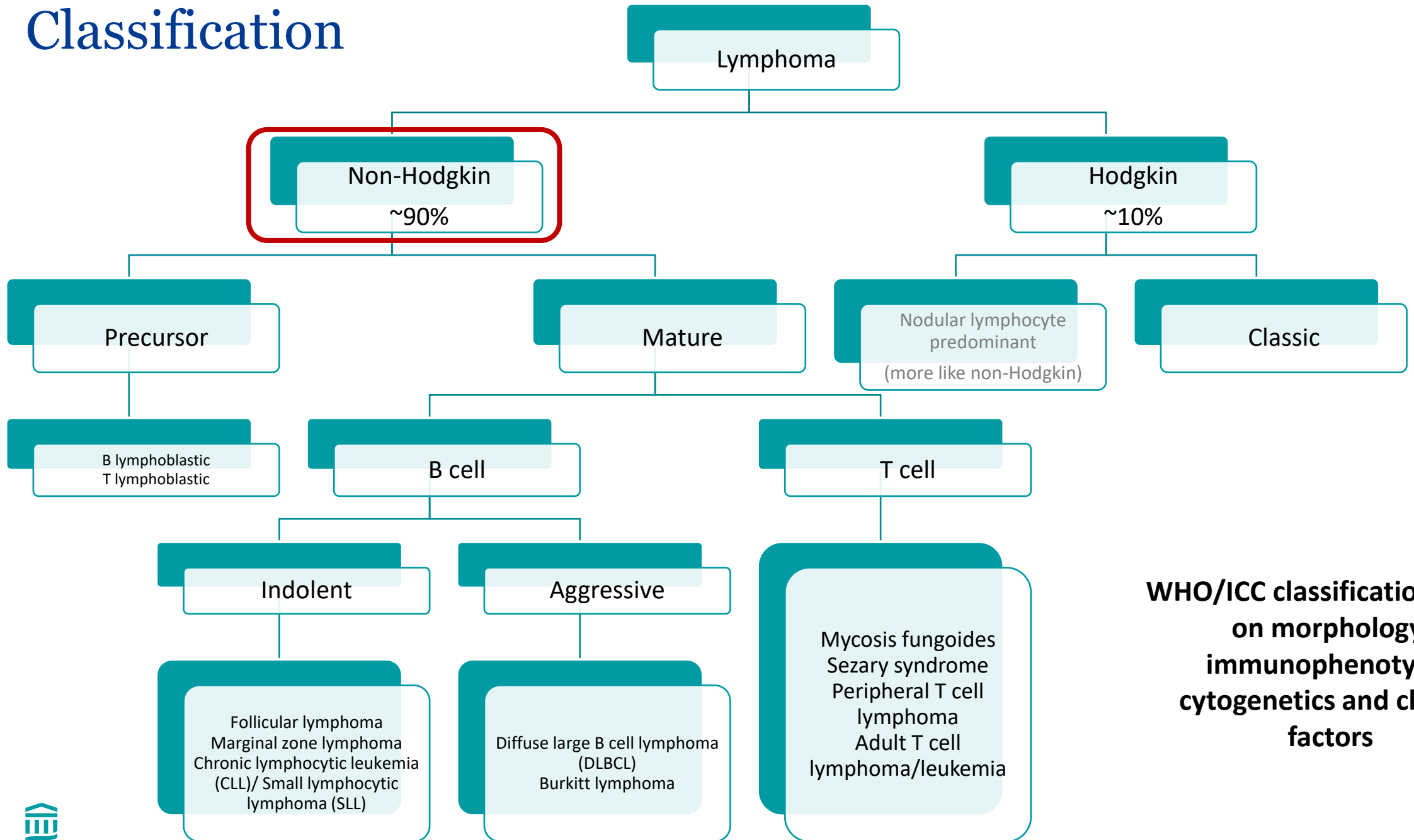
Classification



**WHO/ICC classification based
on morphology,
immunophenotype,
cytogenetics and clinical
factors**



Classification



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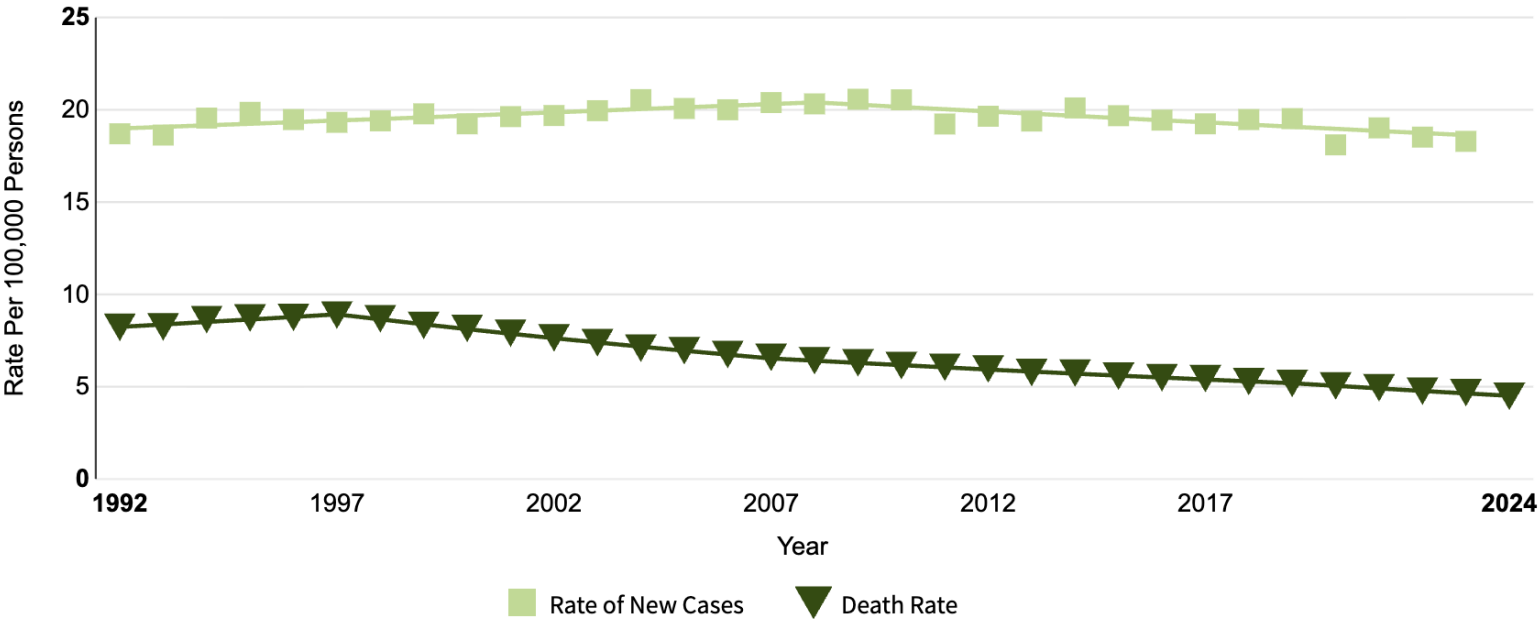
Demographics: Non-Hodgkin Lymphoma

At a Glance

Estimated New Cases in 2026	79,320
% of All New Cancer Cases	3.8%

Estimated Deaths in 2026	19,970
% of All Cancer Deaths	3.2%

5-Year Relative Survival
74.3%
2016–2022



Risk Factors for non-Hodgkin lymphoma

- Increasing age
- Exposures
 - Radiation
 - Chemicals - benzene, herbicides, insecticides
 - Infections
- Immune dysfunction
 - Autoimmune disease (SLE, Sjogren, RA, celiac, others)
 - Immunodeficiency/immunosuppression
 - HIV, organ transplant, treatments for autoimmune disease
- Genetics:
 - first-degree relatives slightly more likely to have NHL (RR 1.5-2)
 - no specific screening/testing recommended



Infectious Associations

EBV:

Burkitt lymphoma

DLBCL

NK-T cell lymphoma

Hodgkin lymphoma

Plasmablastic lymphoma

HTLV-1:

Adult T-cell leukemia/lymphoma

HHV-8:

Primary effusion lymphoma

Large B cell lymphoma associated with Castleman's

Marginal zone lymphoma :

- H. pylori (gastric)
- Chlamydia psittaci (ocular adnexal)
- Campylobacter jejuni (small intestinal)
- Borrelia burgdorferi (solitary cutaneous)
- Hepatitis C (splenic)



Clinical Presentation

Lymphadenopathy in about 2/3

B symptoms:

- Fevers
- Drenching night sweats
- Weight loss > 10% in 6 months

Lymphoma can involve any site

- Common extra-nodal sites: GI tract, skin, bone/bone marrow
- Consider CNS involvement if neurologic s/sx (especially with more aggressive lymphomas)
- Rarer extra-nodal sites: kidney, bladder, adrenal, heart, lungs, breast, testes, thyroid



Evaluation: Biopsy

Excisional biopsy when possible

CT guided core needle biopsy often adequate

FNA usually not adequate (need intact tissue to assess architecture)

Send for pathology,
immunohistochemistry/flow cytometry,
cytogenetics



FNA – usually not diagnostic

Evaluation: Workup

Imaging:

- CT scan – CAP +/- neck
- PET/CT scan

Labs:

- CBC + differential
- CMP, uric acid
- LDH, B2 microglobulin (tumor burden)
- Consider SPEP/immunofixation, serum free light chains
- HBV surface antigen, core antibody
- HCV, HIV serologies

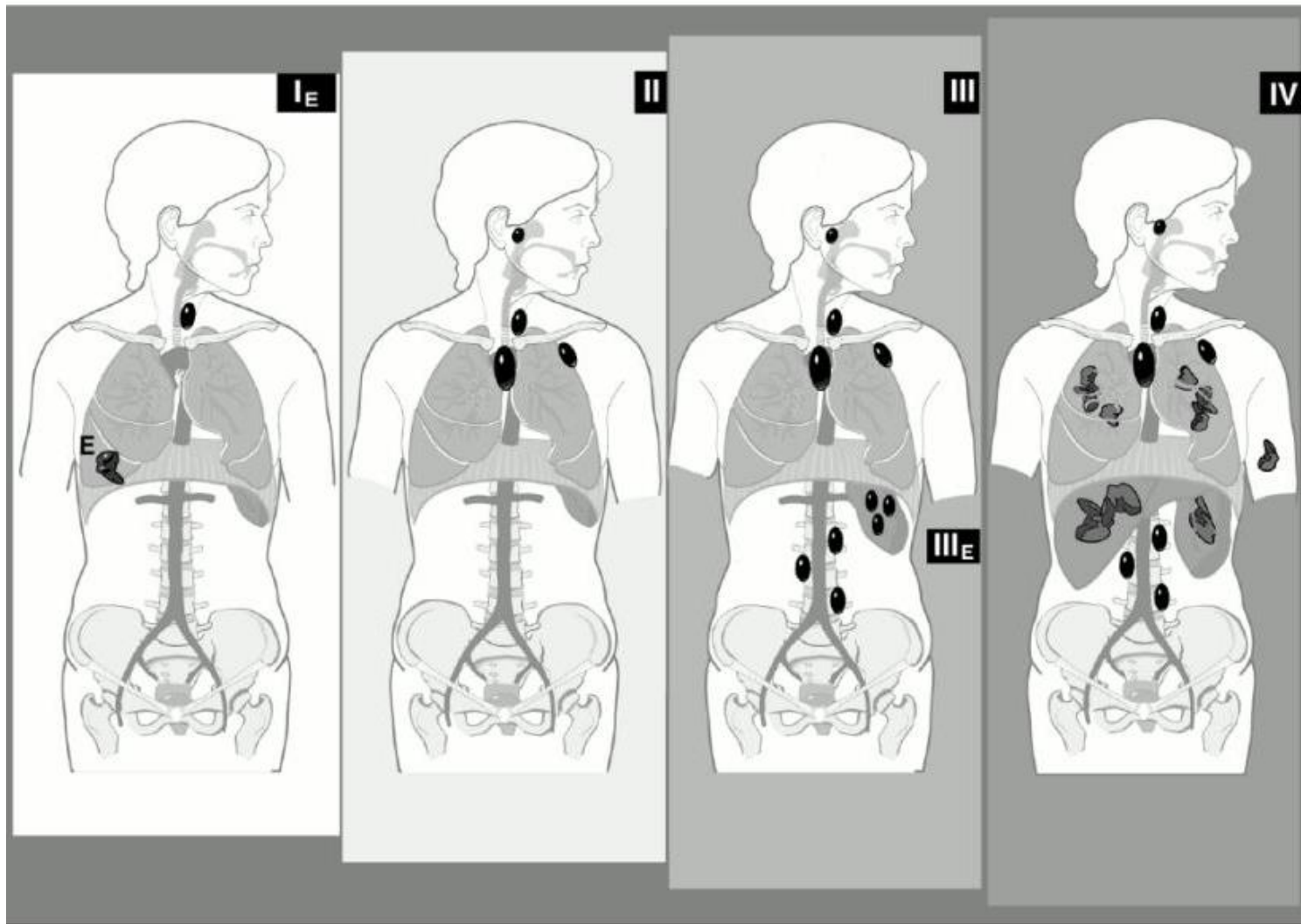
Bone marrow biopsy (select cases)

Additional pre-treatment evaluation to consider

- Echo, EKG (anthracycline-containing chemo regimens have risk of cardiotox)



Staging



A: no B symptoms

B: fever

night sweats

> 10% wt loss in 6 months

Complications from lymphoma

Mass effect

- Cord compression
- SVC syndrome
- Pericardial disease/tamponade
- Intestinal/ureteral obstruction

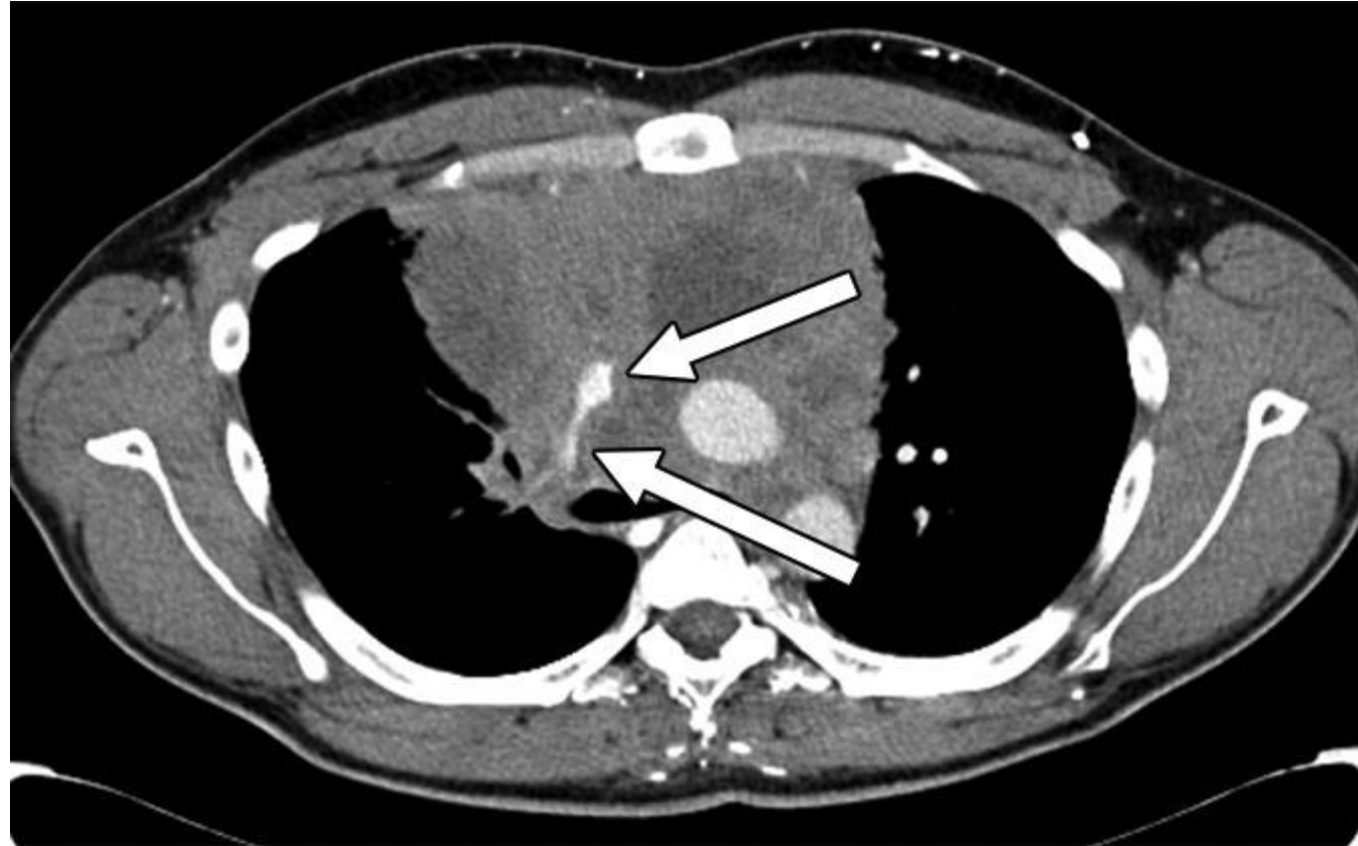
Electrolyte/metabolic

- Tumor lysis syndrome
- Hypercalcemia

Cytopenias

- Anemia, thrombocytopenia, neutropenia
- Can be autoimmune (AIHA, ITP)

Hyperviscosity (especially if high IgM)



Pfau et al., AJR 2019



Clinical behavior of non-Hodgkin lymphoma

	Indolent	Aggressive	Highly aggressive
Survival untreated	Years	Months	Weeks
Response to chemotherapy	Not curable	Curable	Curable
Example	Follicular lymphoma	Diffuse large B-cell lymphoma	Burkitt lymphoma



Indolent Lymphomas

B-cell lymphomas

- Follicular (gr 1-3A)
- Marginal zone
 - Nodal
 - Extranodal (MALT)
 - Splenic
- Chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL)

T-cell lymphomas

- T-cell LGL leukemia
- Mycosis fungoides



Aggressive Lymphomas

B cell lymphomas

- **Diffuse large B-cell lymphoma**
- Primary mediastinal B cell lymphoma
- Follicular lymphoma (grade 3B)

T cell lymphomas

- Peripheral T-cell lymphoma
- Anaplastic large cell lymphoma
- NK/T cell lymphoma
- Adult T-cell lymphoma/leukemia

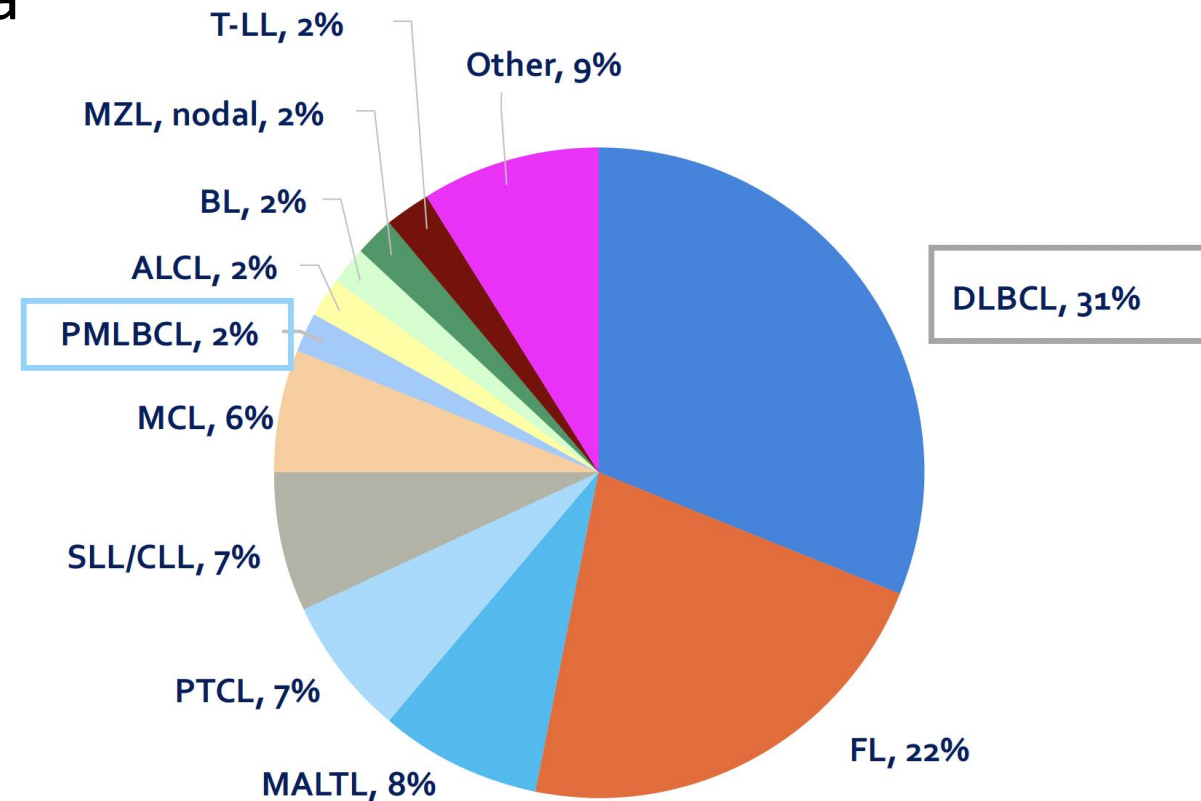
Highly Aggressive Lymphomas

- Burkitt Lymphoma
- Precursor B lymphoblastic lymphoma
- Precursor T lymphoblastic lymphoma



Diffuse large B cell lymphoma (DLBCL)

- Most common non-Hodgkin lymphoma
- Median age at diagnosis 66
- Presentation:
 - Rapidly growing mass
 - B symptoms (30%)
 - Elevated LDH (>50%)
 - Localized disease in 20-30%
- Curable with chemoimmunotherapy
- 5-year relative survival: ~70-80%

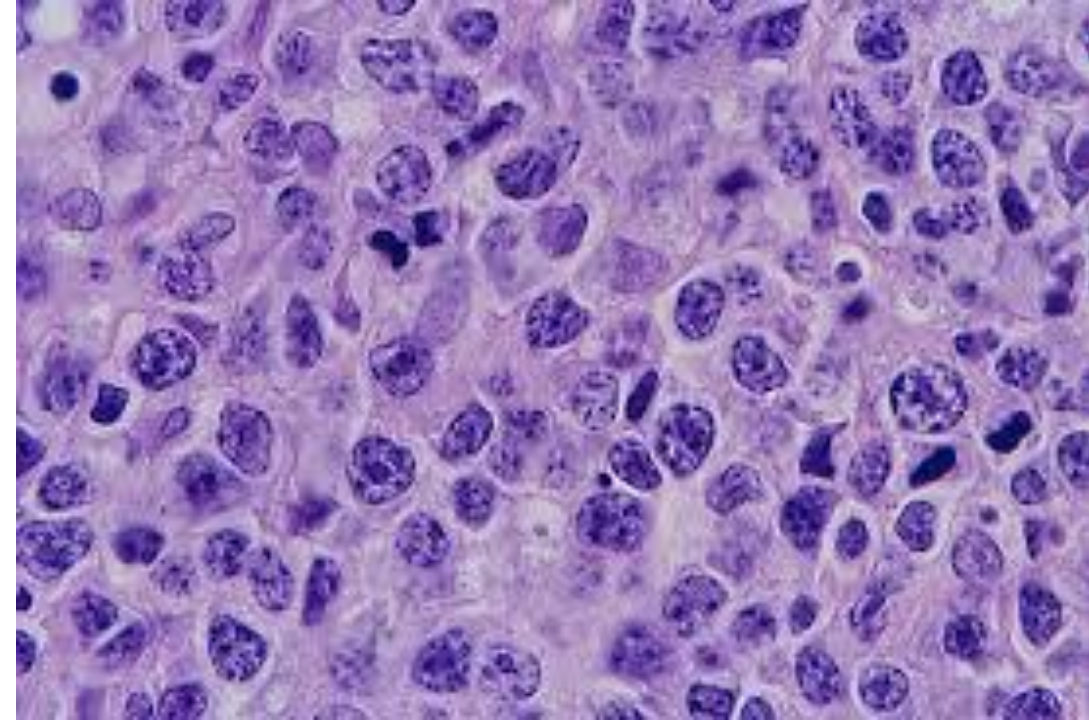


Armitage JO, Weisenburger DD. *J Clin Oncol.* 1998;16:2780-2795.



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International Prognostic Index (IPI)

Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH

Pre-Rituximab Era

Risk factors	5 yr OS
0-1	73%
2	51%
3	42%
4-5	26%

Shipp et al. NEJM 1993

Rituximab Era

Risk factors	4 yr DFS	4 yr OS
0	94%	94%
1-2	80%	79%
3-5	53%	55%

Sehn et al. Blood 2007



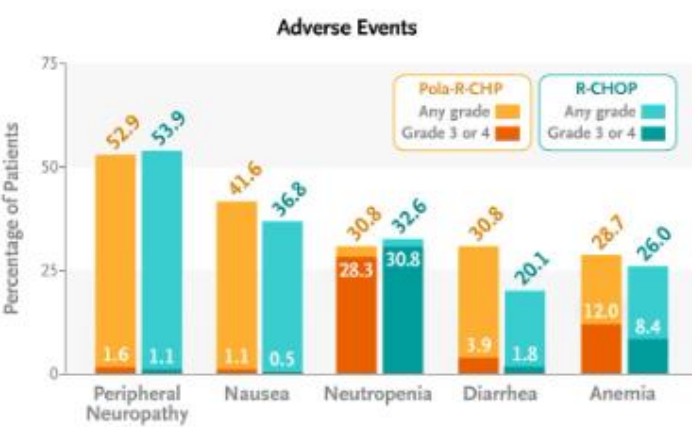
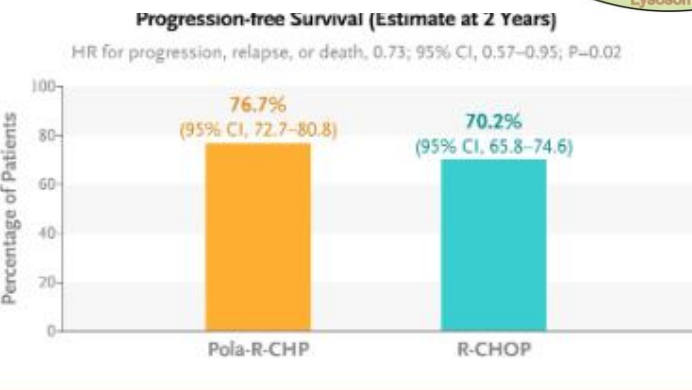
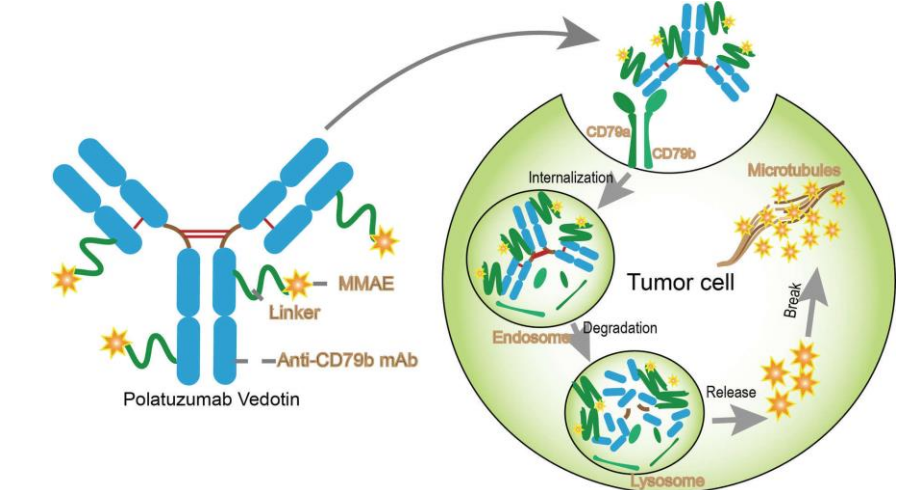
Frontline treatment for DLBCL

R-CHOP: standard of care since early 2000's

- Rituximab
- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisone

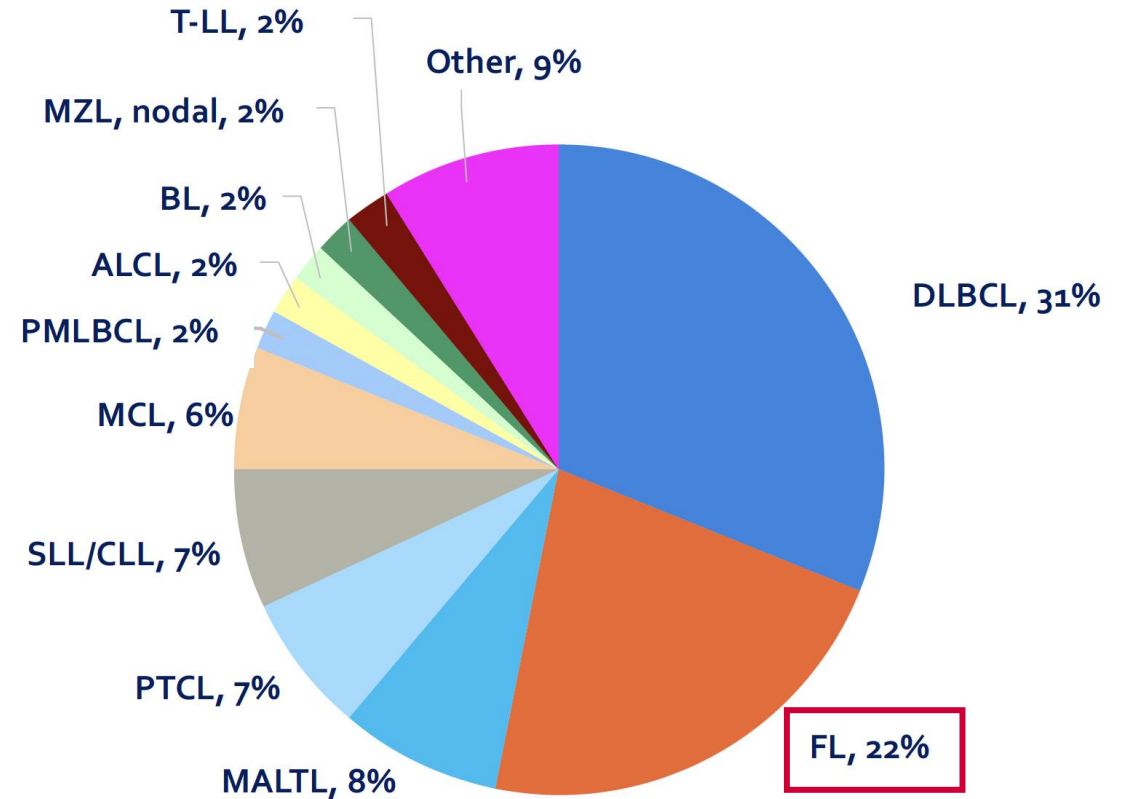
Pola-R-CHP: now often used in higher risk patients (IPI 2-5)

- Rituximab
- Cyclophosphamide
- Doxorubicin
- Polatuzumab vedotin**
- Prednisone



Follicular lymphoma

- Second most common NHL (20%)
- Most common indolent lymphoma
- Median age at presentation ~ 60
- Male to Female – 1:1.7
- Clinical presentation:
 - Many incidentally diagnosed
 - Painless lymphadenopathy
 - Often present for months
- Very responsive to treatments, but generally considered incurable (unless limited stage)
- 1-2% annual risk for transformation to aggressive lymphoma (DLBCL)

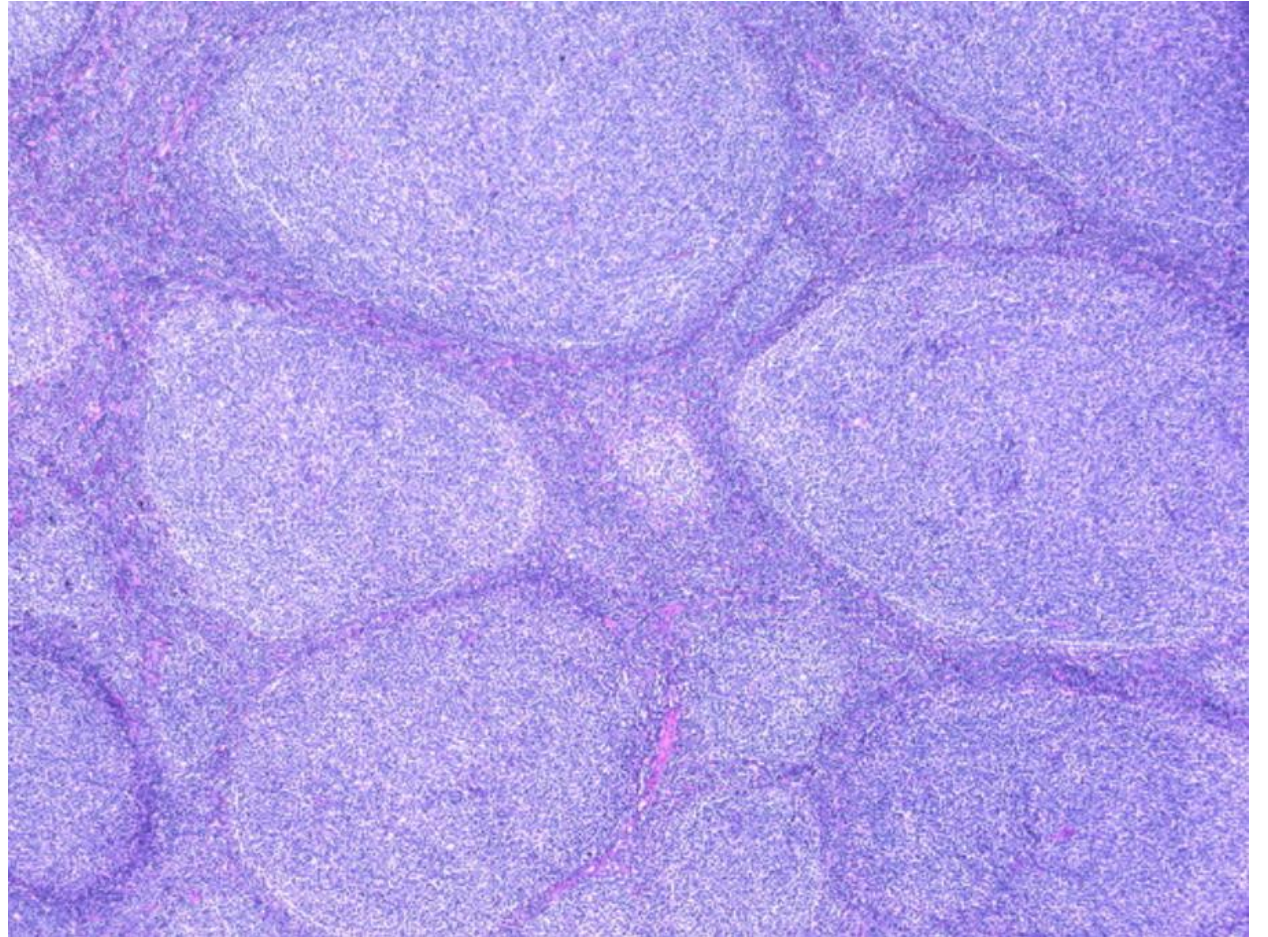


Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16:2780-2795.



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Indolent B cell lymphomas: Management

Localized	Advanced Low tumor burden	Advanced High tumor burden
Involved Field RT	Observation	Therapy



Observation vs early therapy

Advanced-stage indolent lymphoma without complications: observation typically preferred

- Not classically curable with conventional therapy
 - Allogeneic stem cell transplant curative, but high morbidity
- No survival advantage to early treatment
 - No change in rate of histological transformation
- Spontaneous remissions can occur
- After COVID-19 pandemic, increased focus on immunosuppressive effects of lymphoma treatment



Indications for treatment with indolent lymphomas

- Cytopenias secondary to bone marrow infiltration
- Threatened end-organ function (ie ureteral obstruction)
- Symptoms attributable to disease
 - Large lymph nodes causing discomfort
 - B symptoms (fevers, night sweats, weight loss)
- Bulk at presentation (typically > 7 cm or 3 sites > 3 cm)
- Presentation with concurrent histologic transformation
- Massive splenomegaly



Other key non-Hodgkin lymphoma subtypes

Marginal zone lymphoma

- nodal
- extranodal (conjunctiva, lung, GI, skin)
- splenic

Mantle Cell Lymphoma

- Can have indolent or aggressive presentation
- Propensity to affect GI tract
- Characterized by cyclin D1 overexpression

SLL/CLL

- Often detected on routine CBC
- Autoimmune complications, particularly AIHA and ITP
- Targeted therapy has mostly replaced chemotherapy
- **Key toxicities: BTK inhibitors (bleeding, cardiac); venetoclax (TLS)**



Other key non-Hodgkin lymphoma subtypes

Cutaneous T cell lymphomas:

Mycosis fungoides

- Primarily skin involvement
- Pruritic patches/plaques
- Frequently misdiagnosed as eczema, psoriasis, ringworm
- Diagnosis by skin biopsy (may require multiple biopsies)
- Topical treatment often initially used (phototherapy, topical steroids or chemo); systemic therapy for more advanced disease



Sezary syndrome

- Skin involvement + circulating disease, sometimes lymphadenopathy
- Diffuse erythroderma, keratosis, ectropion
- Diagnosis: skin biopsies, peripheral blood flow cytometry
- Treatment: topicals as above, systemic therapies, extracorporeal photopheresis



Treatment of relapsed or refractory B cell lymphoma

- Other chemotherapy
- **CAR T cell therapy**
- **Bispecific antibodies**
- Antibody-drug conjugates
- Targeted therapies
- Autologous and allogeneic stem cell transplant



CAR T cell therapy

Created using a patient's own T cells

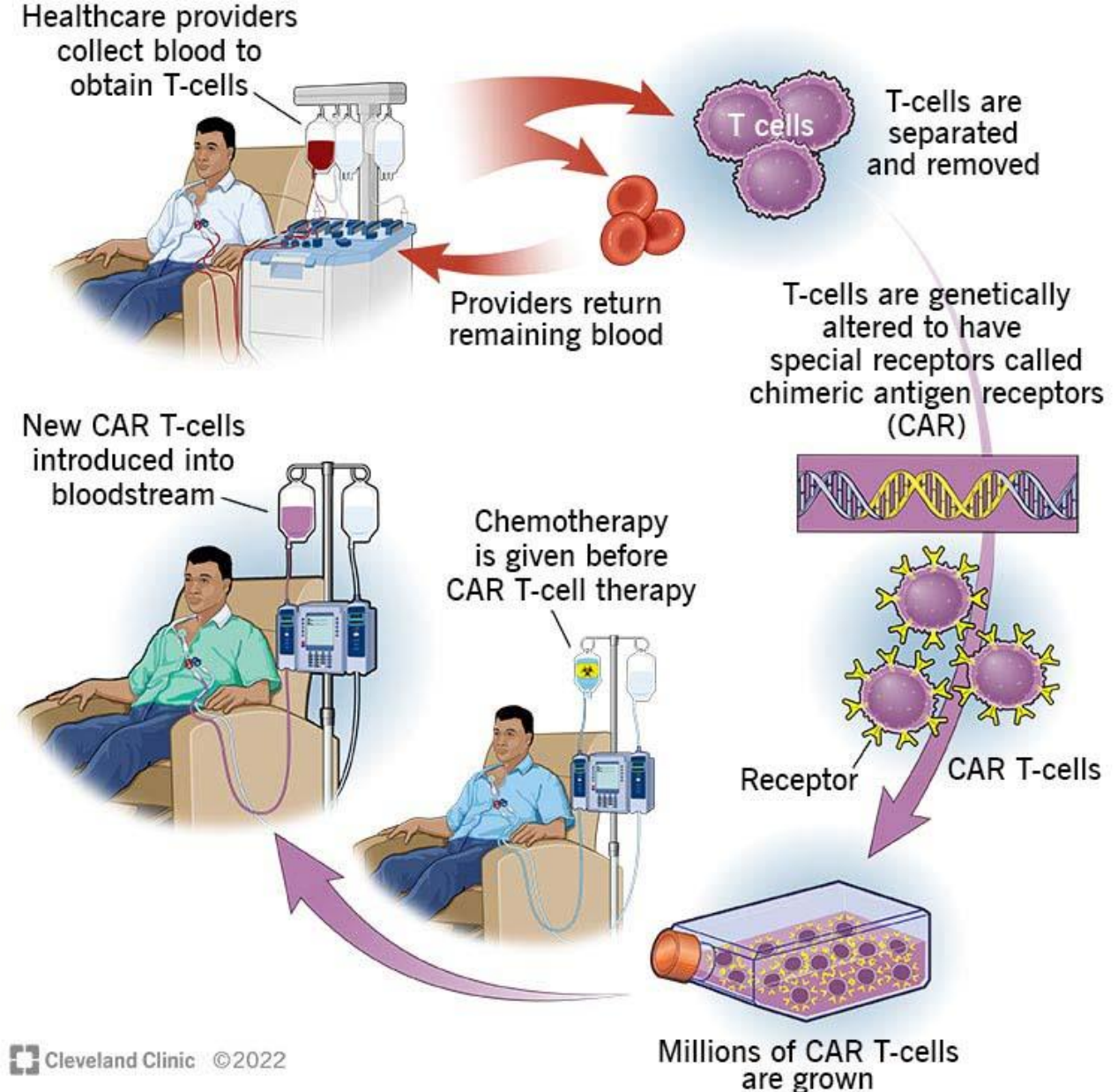
- Process takes time (usually 4-8 weeks)
- Sometimes “bridging” treatment is given to control lymphoma while waiting for CAR T

Monitoring after CAR T cell therapy is needed for side effects, including:

- Cytokine release syndrome (fevers, sepsis-like presentation)
- Immune effector cell-associated neurotoxicity (ICANS) – ranges from confusion to aphasia, seizures
- Cytopenias
- Infections

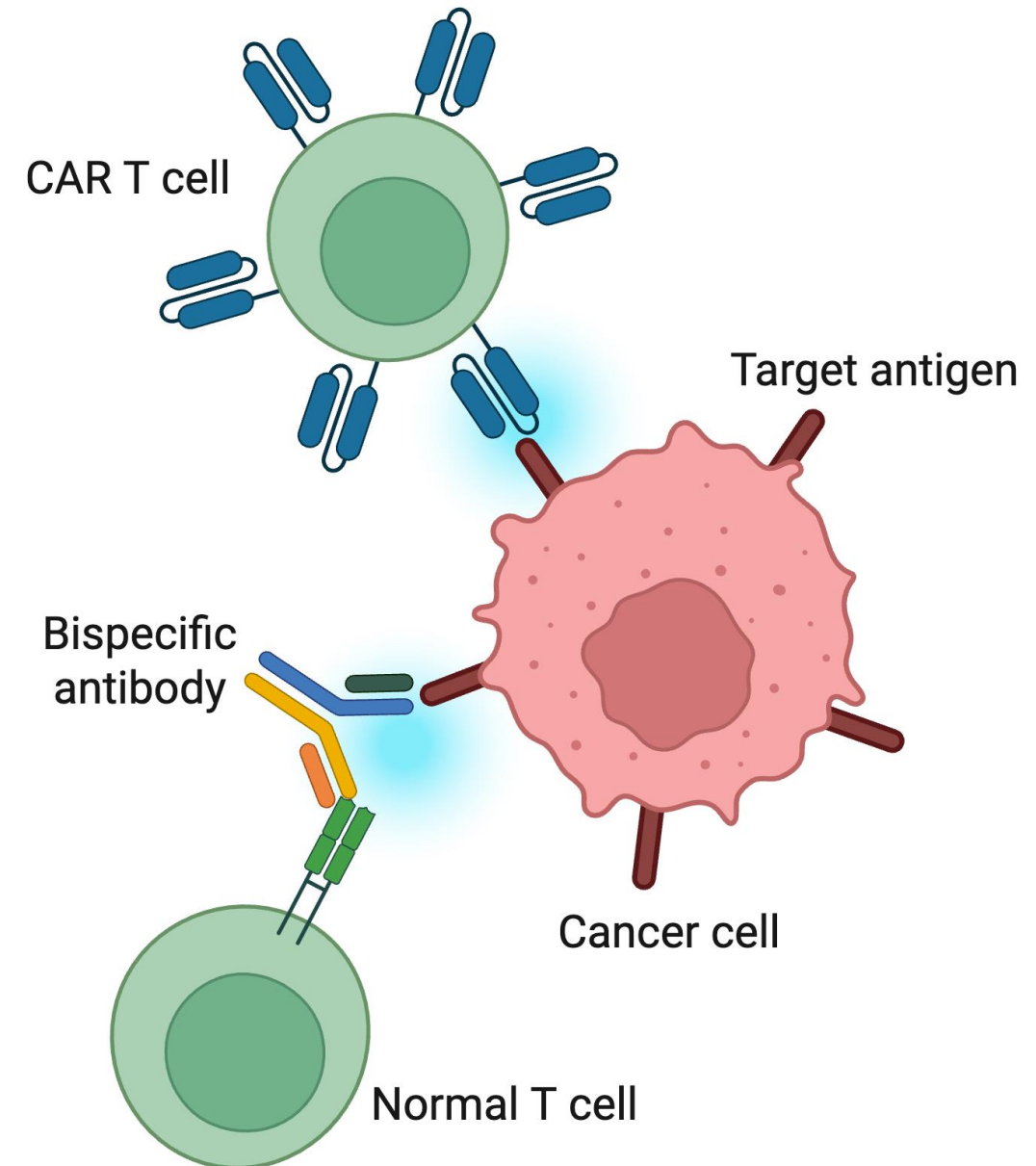


How CAR T-cell therapy is used to treat cancer



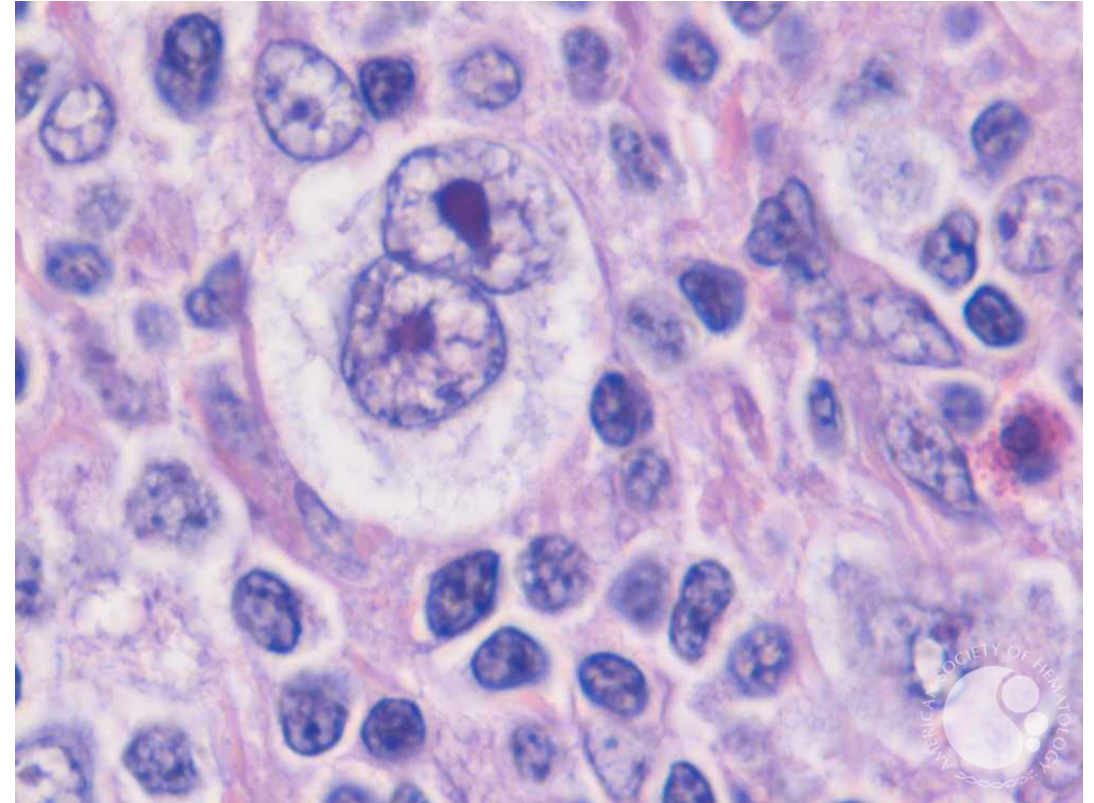
Bispecific antibodies

- Engineered antibody that can bind 2 different targets simultaneously
- Bind normal T cells (CD3) and a target on lymphoma (usually CD20)
- Given IV or injected under skin
- “Off the shelf” T cell therapy
- Can be given alone or in combinations
- Toxicities: similar to CAR T
 - Cytokine release syndrome (usually with earlier doses)
 - Neurotoxicity (rarer/milder than CAR T)
 - Immunosuppression and infections
 - low IgG common, especially over time



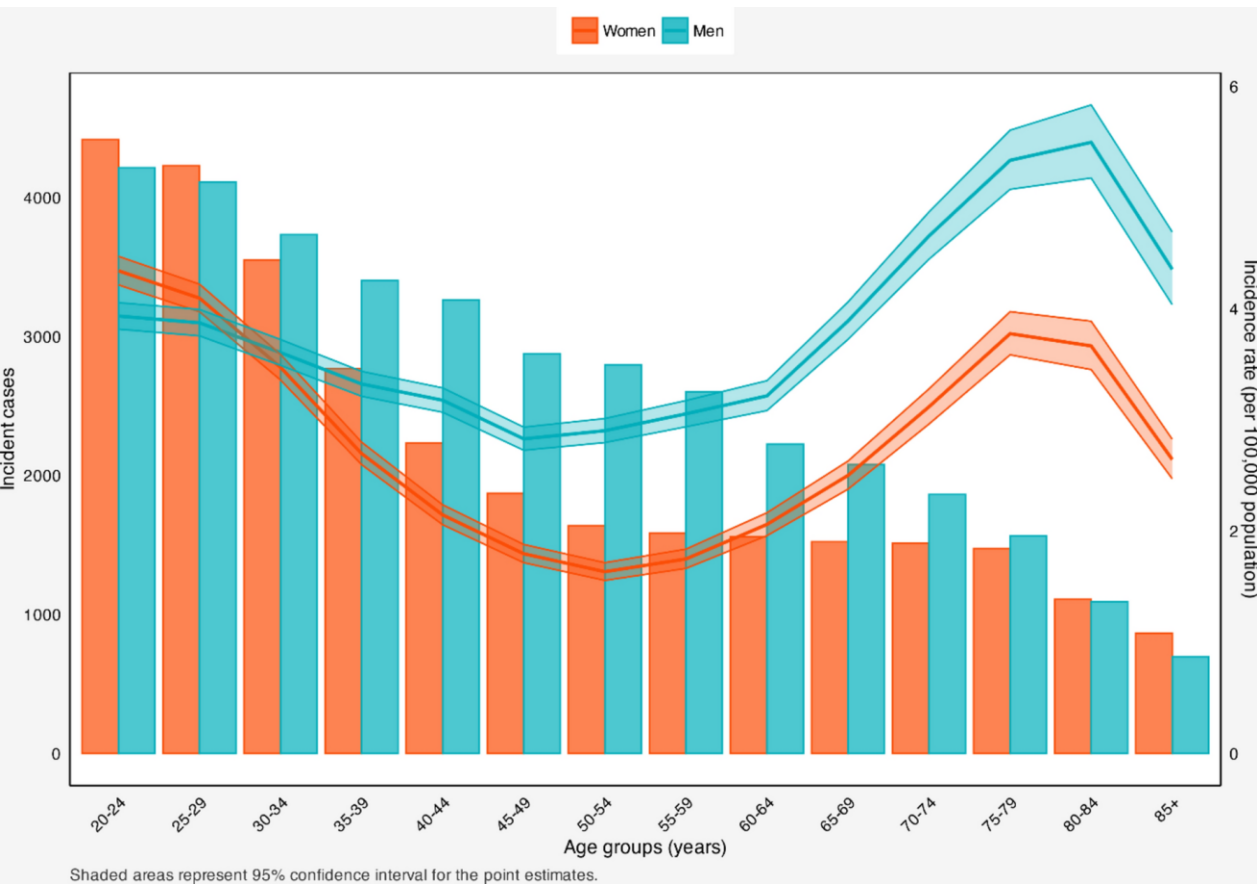
Hodgkin lymphoma

- Pathology: Reed-Sternberg cells classic finding (“Owl eyes”)
- Clinical presentation:
 - Lymphadenopathy, most often starting in neck/axilla/mediastinum
 - Can be advanced stage
 - B symptoms common
 - Painful adenopathy with alcohol reported
- Diagnosis: similar to non-Hodgkin
 - Excisional biopsy preferred
 - Similar workup



Epidemiology

Biphasic age distribution: seen in younger patients (teens – 30s) and age 60+



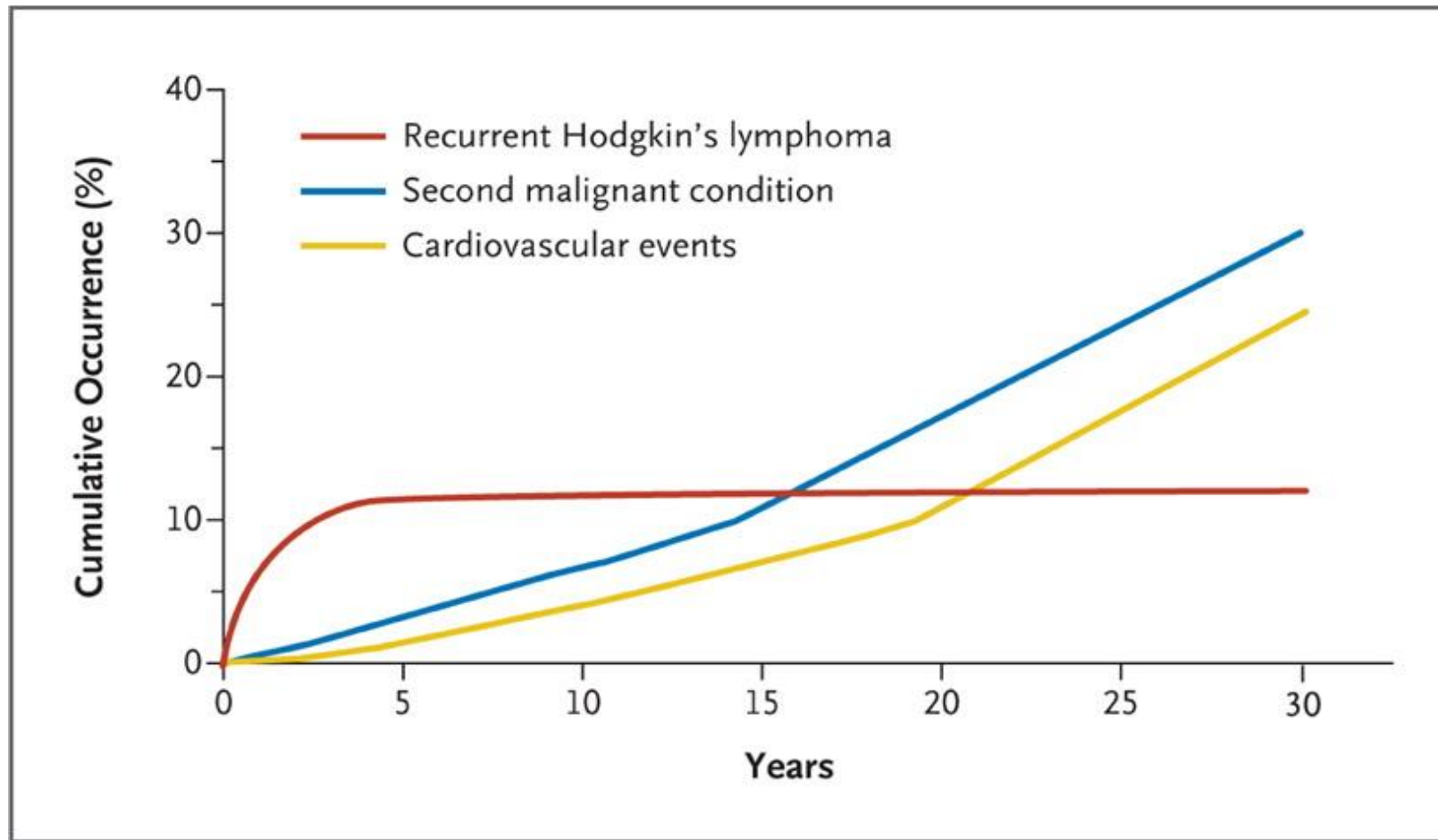
Aslani et al., Sci Rep 2024



NCI SEER Database



Competing risks in Hodgkin lymphoma



Minimize
late effects

Maximize
cure



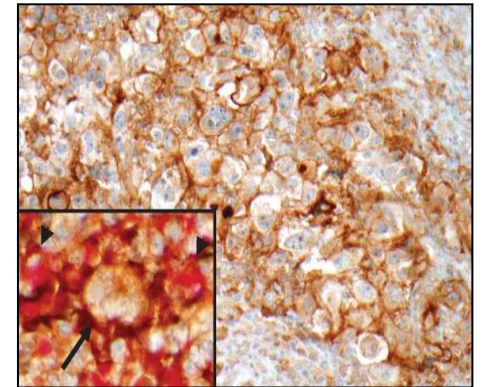
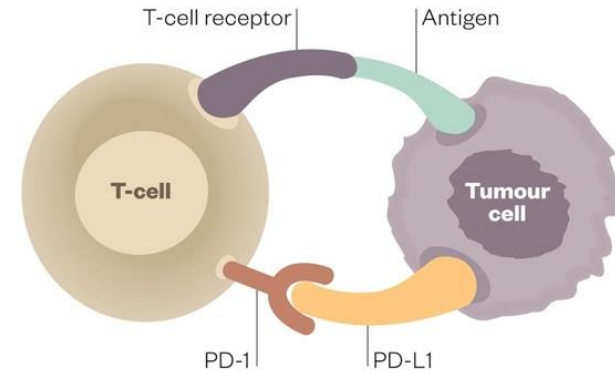
Hodgkin Lymphoma Therapy

Stage I and II disease:

- Chemotherapy +/- radiation therapy
- Response-adapted approaches often used to minimize chemo exposure
- Cure rates 85-90% or higher

Stage III and IV disease:

- Chemotherapy combinations, often with:
 - Checkpoint inhibitor immunotherapy (pembrolizumab, nivolumab)
 - Brentuximab vedotin (antibody-drug conjugate targeting CD30)
- Cure rates 80-90%



PD-L1 expression in cHL

Chen et al. *Clin Cancer Res.* 2013
Ansell et al. *N Engl J Med.* 2014

Late toxicities from Hodgkin lymphoma treatment

Secondary cancer:

Breast cancer (↑ if radiation <30 yrs)

Lung

GI

Sarcoma

Thyroid

Leukemia

Cardiovascular disease:

CAD

Valvular

Pericardial

Conduction

Heart failure

Others:

Pulmonary (bleomycin)

Endocrine (thyroid radiation)

Neuropathy

Fertility

Psychosocial

Take-Home Notes

Non-Hodgkin lymphoma

- Often presents with lymphadenopathy but any organ may be involved
- Excisional or core biopsy to determine subtype
- Staging with CT +/- PET and bone marrow biopsy (in select cases)
- Aggressive lymphoma is curable in > half of patients with combination chemotherapy
- Indolent lymphoma is not curable with standard chemotherapy, but patients often have long remissions and survival



Take-Home Notes

Hodgkin lymphoma

- Often presents in neck and mediastinum
- High cure rates
- Early-stage disease treated with combined modality therapy, advanced disease treated with chemotherapy (often with immunotherapy today)
- Emphasis on long term toxicities given curability and often young age at diagnosis



Question #1

26-year-old college student presents with cough, night sweats and 20 lb weight loss. On exam she has bilateral cervical and left supraclavicular lymphadenopathy. Chest CT scan confirms a 4 cm left supraclavicular node and a large mediastinal mass.

The most likely diagnosis is:

- a. Follicular lymphoma
- b. T-cell LGL
- c. Hodgkin lymphoma
- d. Small lymphocytic lymphoma
- e. Burkitt's lymphoma



Question #1

- a. Follicular lymphoma commonly presents in older adults with asymptomatic lymphadenopathy.
- b. T-cell LGL presents with cytopenias and splenomegaly.
- c. Hodgkin lymphoma affects young adults and presents with adenopathy in the neck and chest. B symptoms are common.
- d. Small lymphocytic lymphoma also presents with asymptomatic adenopathy with frequent splenomegaly in older adults.
- e. Burkitt's lymphoma typically presents with rapidly progressive adenopathy and high LDH.



Question #2

Which of the following are indications for therapy in the indolent lymphomas?

- a. thrombocytopenia**
- b. bulky lymphadenopathy**
- c. weight loss**
- d. transformation to diffuse large B-cell lymphoma**
- e. all of the above**



Question #2

All the above are indications for initiating therapy in follicular lymphoma. Early therapy in the absence of symptoms has not been shown to prolong overall survival.



Contact: david_qualls@dfci.harvard.edu
Feel free to reach out with questions!

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Mass General Brigham