



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

# **Lymphoma**

# **Multiple Myeloma**

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**CONTINUING MEDICAL EDUCATION**  
**DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL**  
**TEACHING HOSPITAL**



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# Disclosures for Eric Jacobsen, MD

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Presentation includes a description of the following off-label use of a drug or medical device	No relevant conflicts of interest to declare



# Objectives

- Classification of lymphoid malignancies
- Presentation
- Work- up and staging
- Serious complications
- Non-Hodgkin lymphoma
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
- Hodgkin lymphoma
  - Therapy
  - Complications of therapy
- Multiple Myeloma



# Classification of lymphoma

WHO classification based on  
morphology,  
immunophenotype,  
cytogenetics and clinical factors

## Non-Hodgkin lymphoma

- B-cell (90% of NHL in US)
  - Precursor vs mature
- T and NK-cell
  - Precursor vs mature

## Hodgkin lymphoma

- Classic (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted)
- Nodular lymphocyte predominant Hodgkin lymphoma



# Cancer Stat Facts: Non-Hodgkin Lymphoma

[Expand All](#)[Collapse All](#)

## Reports on Cancer

[Annual Report to the Nation](#)[Cancer Stat Facts](#)[Cancer Statistics Review](#)

+

[Preliminary Incidence Rates for 2017](#)

+

[SEER Publications](#)

+

## Statistics at a Glance

### At a Glance

Estimated New Cases in 2023

80,550

% of All New Cancer Cases

4.1%

Estimated Deaths in 2023

20,180

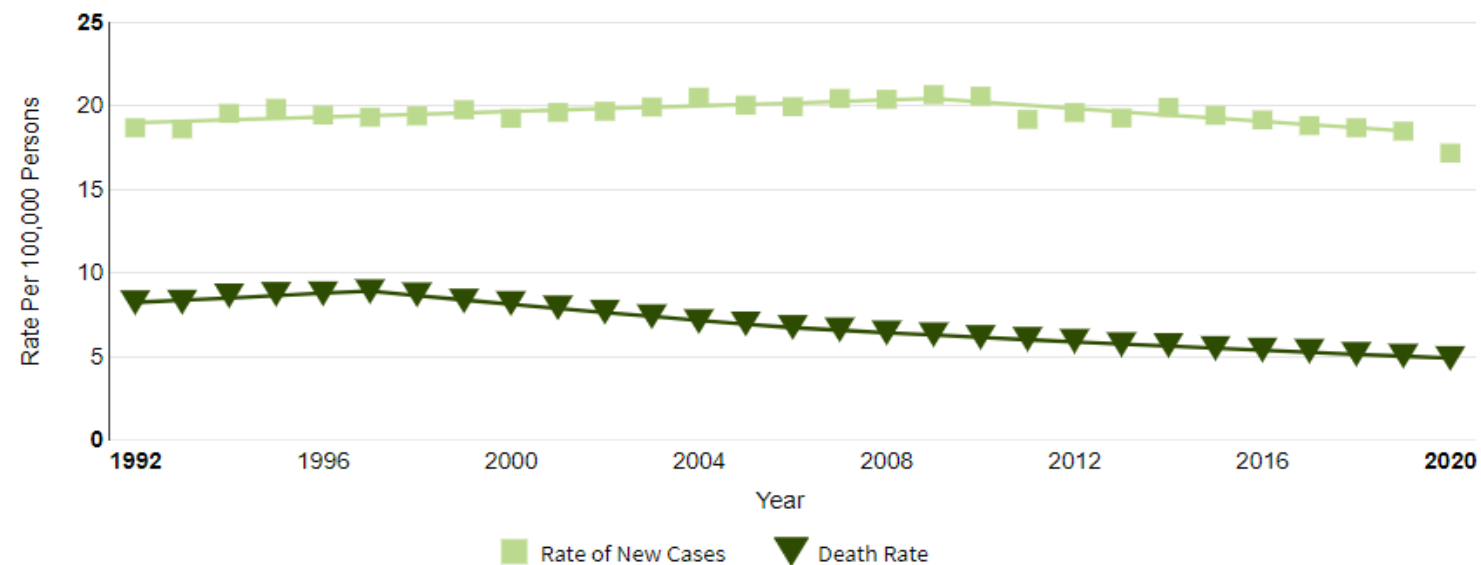
% of All Cancer Deaths

3.3%

5-Year  
Relative Survival

74.3%

2013-2019



# Risk factors

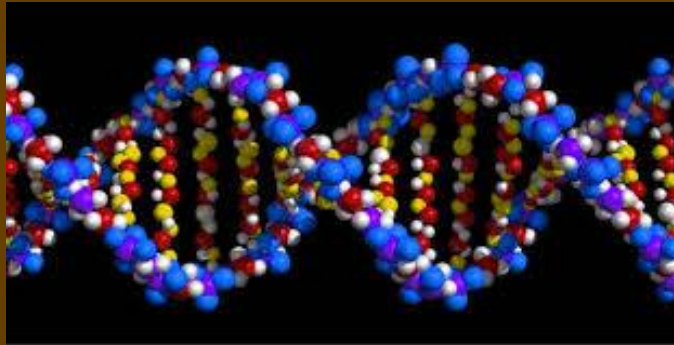
**Exposures:**

**Occupational  
Environmental**

**Immune dysfunction:**

**Autoimmune disease  
Immunodeficiency  
Immune suppression**

**Genetics:**



# Infectious associations

## **EBV:**

**Burkitt lymphoma**

**DLBCL**

**NK-T cell lymphoma**

**Hodgkin lymphoma**

**Plasmablastic lymphoma**

## **HTLV-1:**

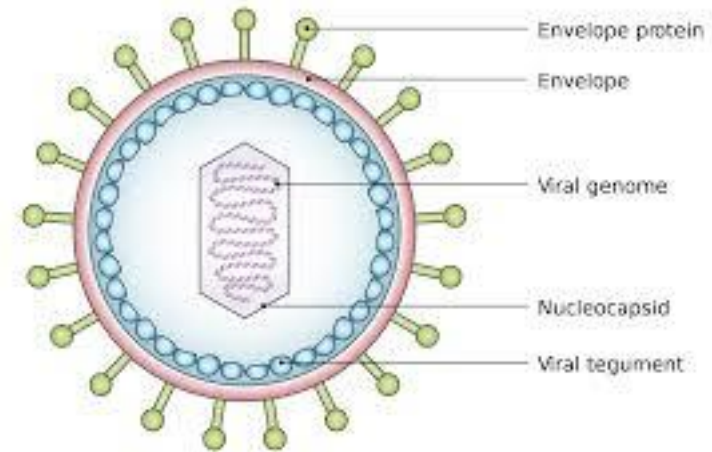
**Adult T-cell leukemia/lymphoma**

## **HHV-8:**

**Primary effusion lymphoma**

**Large B cell lymphoma**

**associated with Castleman's**



**Marginal zone lymphoma :**

**H pylori**

**B burgdorferi**

**C jejuni**

**Hepatitis C**



# Presentation

## Lymphadenopathy (2/3)

**B symptoms - fever ( $>38$ ), drenching night sweats, weight loss  $> 10\%$  in 6 months**

**Extra nodal sites - GI tract, skin, bone**

**Rare - kidney, bladder, adrenal, heart, lungs, breast, testes, thyroid**



# Biopsy

Supraclavicular > cervical/axillary > inguinal

Excisional biopsy when possible

CT guided core needle

Send for pathology, immunohistochemistry/flow cytometry, cytogenetics



# Work-up

**CT scans chest/abdomen/pelvis**

**PET scan**

**Bone marrow biopsy (select cases)**

**CBC/diff**

**Renal/LFT/electrolytes/Uric acid**

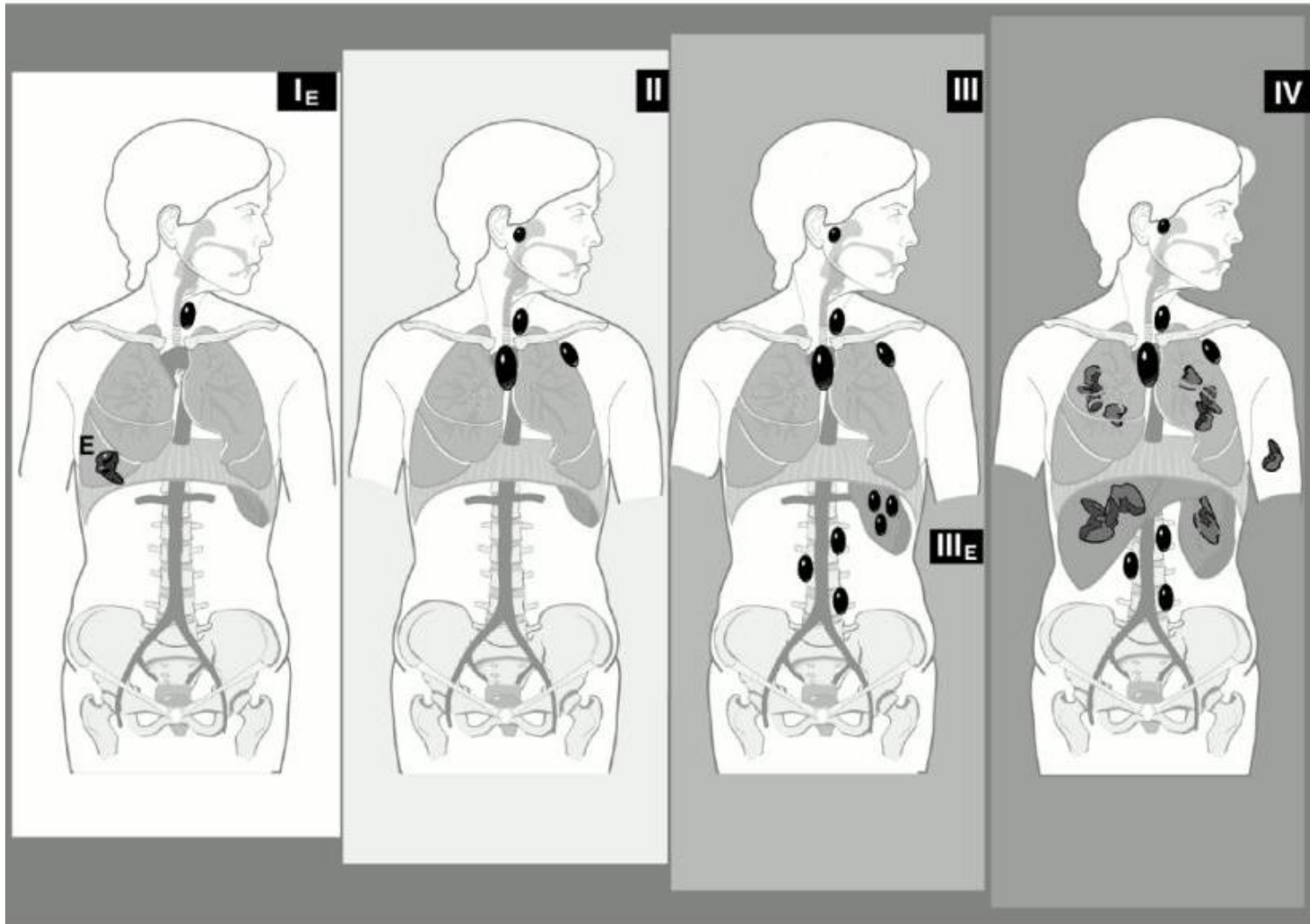
**B2 microglobulin (indolent)**

**LDH**

**SPEP**



# Staging



**A:** asymptomatic  
**B:** fever  
night sweats  
> 10% wt loss in 6 months

# Serious complications

**Cord compression**  
**Pericardial disease/tamponade**  
**Hypercalcemia**  
**SVC/airway compromise**  
**Hyperviscosity**  
**Intestinal obstruction**  
**Ureteral obstruction**  
**Tumor lysis syndrome**  
**ITP/AIHA**



# 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

- B-cell CLL/SLL
- lymphoplasmacytic
- Hairy cell leukemia
- Follicular (gr 1-2)
- Marginal zone
  - Nodal
  - Extranodal (MALT)
  - Splenic
- Mantle cell\*
- Plasma cell myeloma

## T-cell lymphomas

- T-cell LGL leukemia
- Mycosis fungoides

# Aggressive lymphomas

**Diffuse large B-cell lymphoma**

**Follicular lymphoma (grade 3)**

**Peripheral T-cell lymphoma**

**Anaplastic large cell lymphoma**

**NK/T cell lymphoma**





# Highly aggressive lymphomas

**Burkitt Lymphoma**

**Precursor B lymphoblastic lymphoma**

**Precursor T lymphoblastic lymphoma**

**Adult T-cell lymphoma/leukemia**



# Diffuse large B-cell lymphoma



# International Prognostic Index

## Pre-Rituximab Era

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

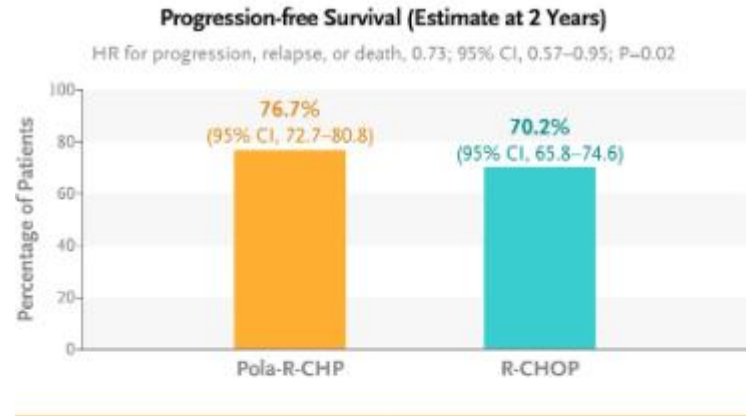
## Rituximab Era

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

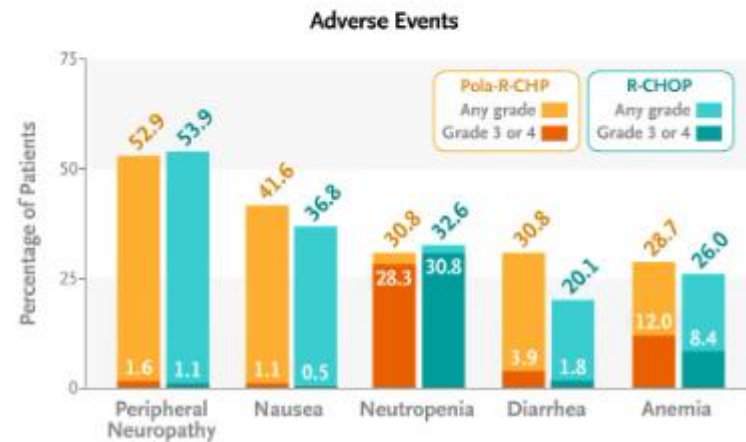
**Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH**



# Polatuzumab for frontline diffuse large B cell lymphoma



FDA approves polatuzumab vedotin-piiq for previously untreated diffuse large B-cell lymphoma, not otherwise specified, and high-grade B-cell lymphoma on April 19, 2023

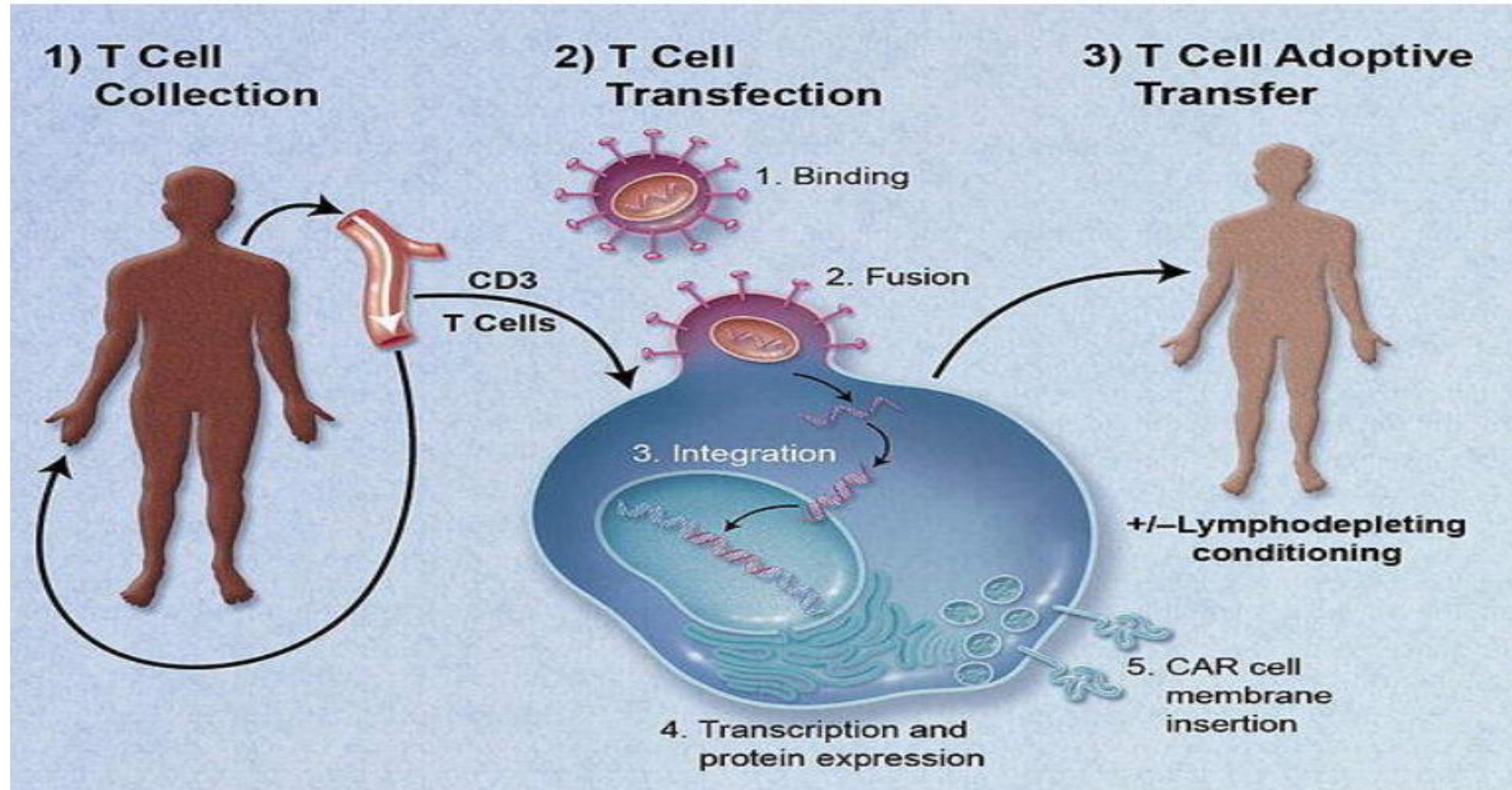


Tilly et al, NEJM 2022

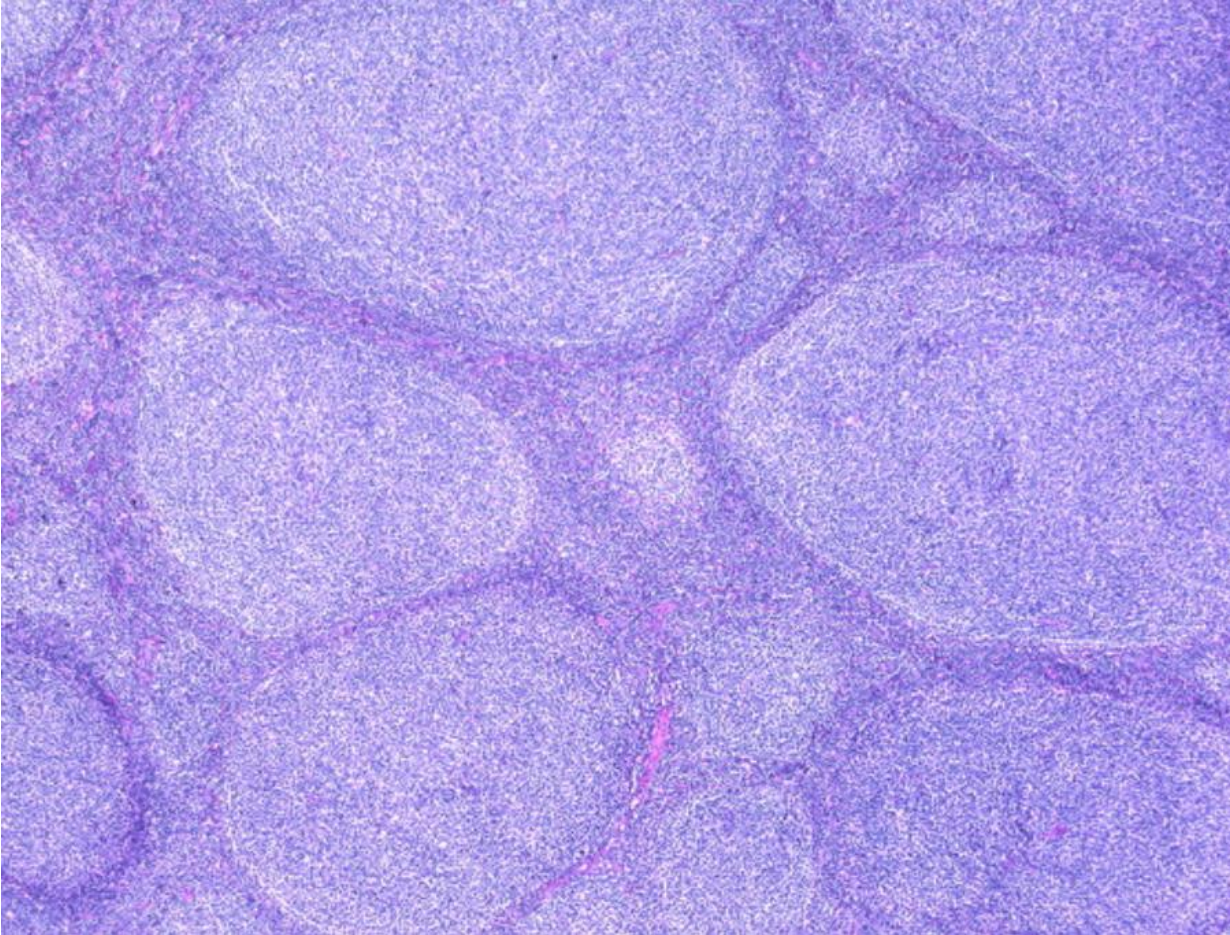




# CAR-T cells



# Follicular lymphoma



**Second most common NHL (20%)**  
**Median age at presentation - 60**  
**Male to Female – 1:1.7**



# Indolent B-cell lymphoma: clinical management

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



# Observation vs early therapy

**Not curable with conventional therapy**

**No survival disadvantage**

**Median progression to treatment**

- Grade 1: 48 months
- Grade 2: 16.5 months

**Same rate of histological transformation**

**Is an active process, requires periodic monitoring**

**Spontaneous remissions can occur**



# Indications for therapy

**Cytopenias secondary to BM infiltration**

**Threatened end-organ function**

**Symptoms attributable to disease**

**Bulk at presentation**

**Steady progression during a period of observation >6 months**

**Presentation with concurrent histologic transformation**

**Massive splenomegaly**



# Other Key Lymphoma Subtypes

## Marginal zone lymphoma

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

## Mantle Cell Lymphoma

- 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)**



# Sezary Syndrome



Diffuse erythroderma, keratosis, ectropion



# Mycosis fungoides

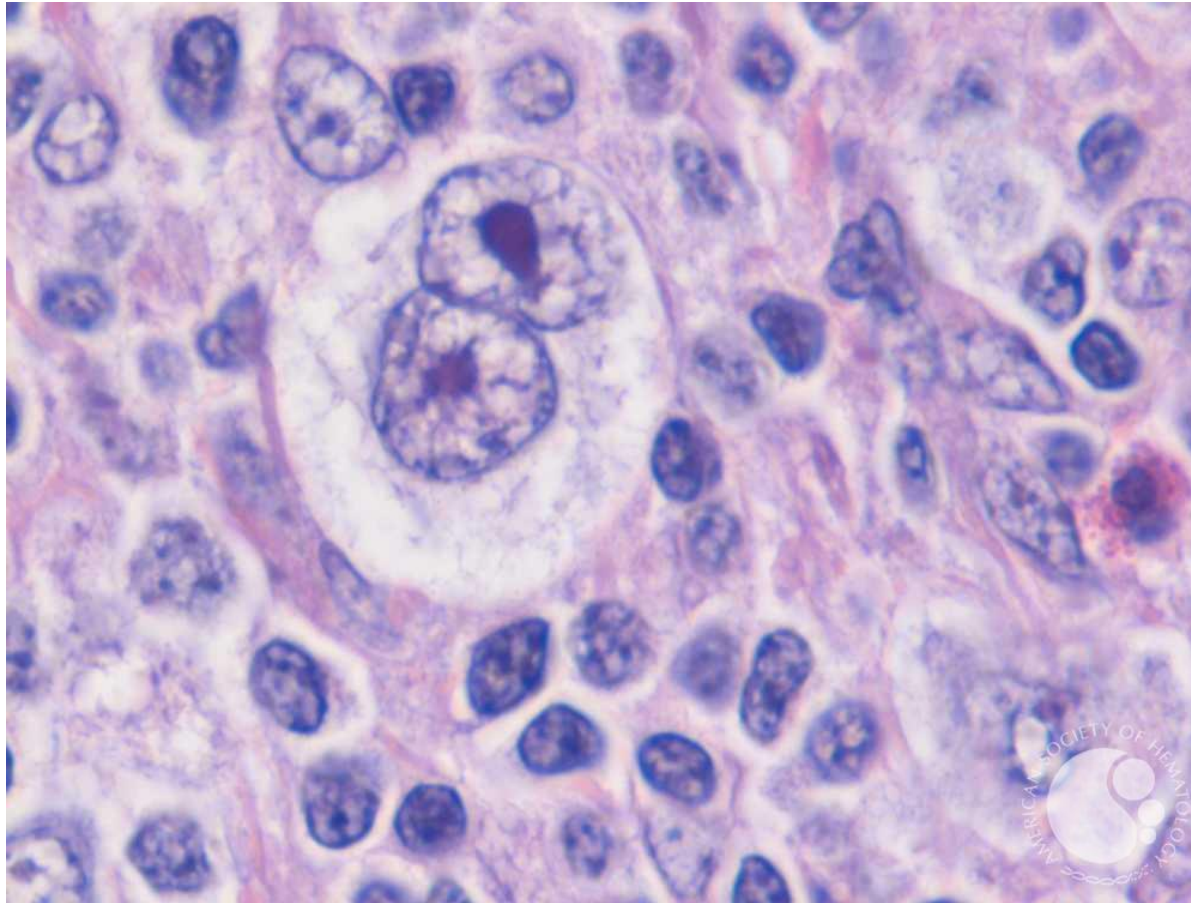


Patch, plaque, tumor stage disease

Frequently misdiagnosed as eczema, psoriasis, ringworm

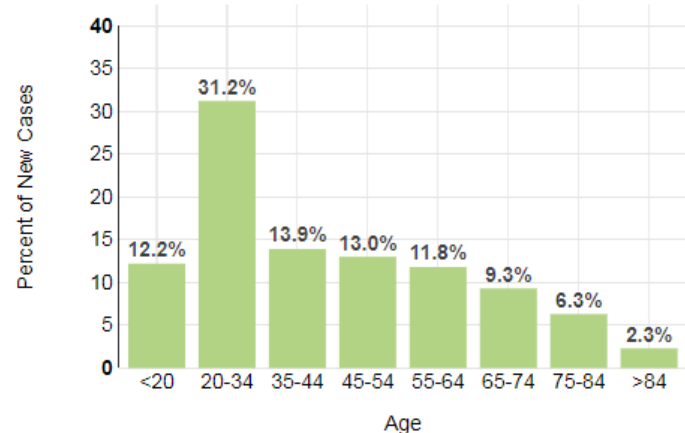
Often requires multiple biopsies to establish diagnosis

# Hodgkin lymphoma



# Epidemiology

## Percent of New Cases by Age Group: Hodgkin Lymphoma



Hodgkin lymphoma is most frequently diagnosed among people aged 20-34.

Median Age  
At Diagnosis

**39**

SEER 18 2011-2015, All Races, Both Sexes

Estimated New Cases in 2018	8,500
% of All New Cancer Cases	0.5%

Estimated Deaths in 2018	1,050
% of All Cancer Deaths	0.2%

Percent Surviving  
5 Years

**86.6%**

2008-2014

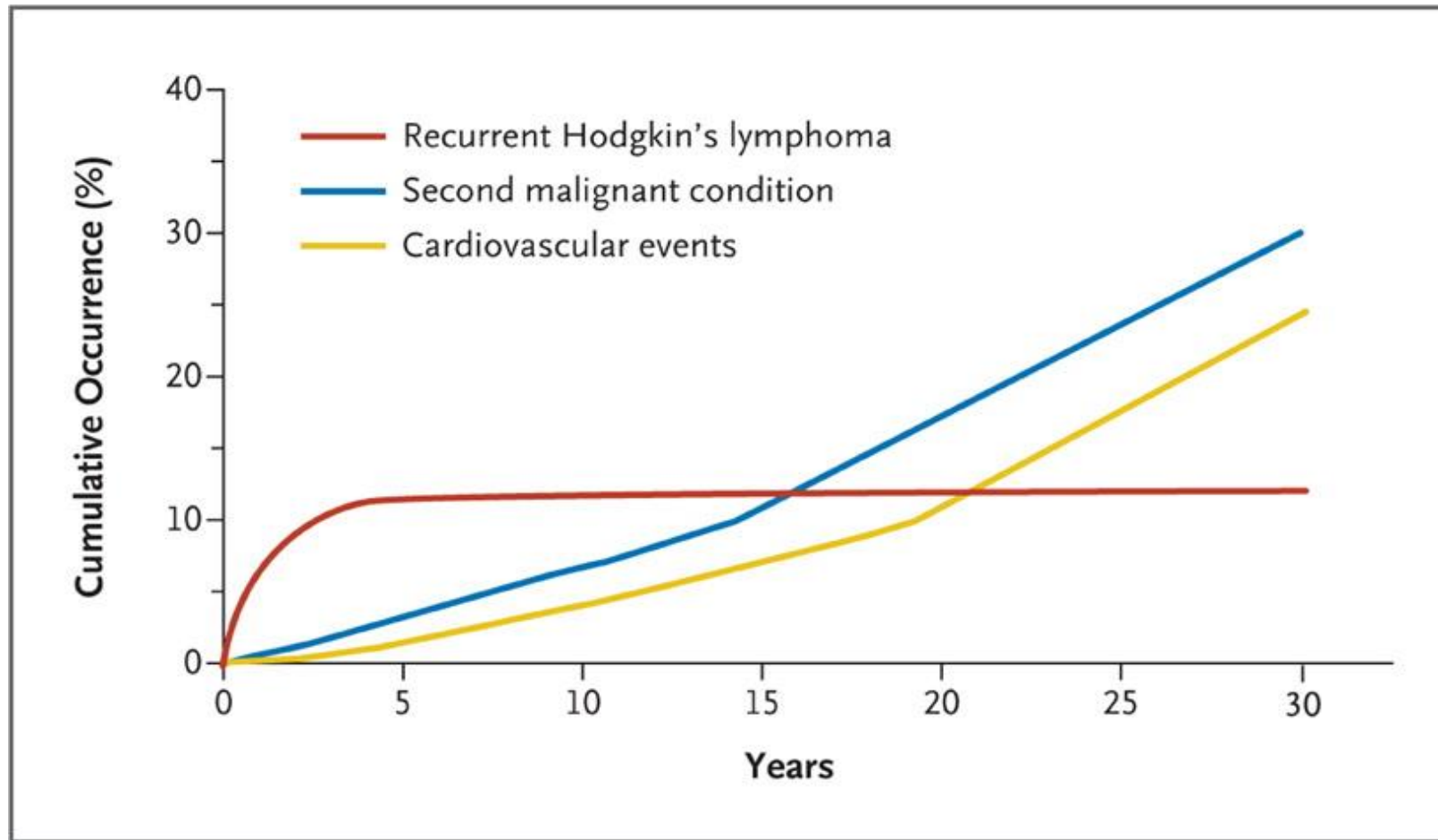
**Increased incidence in industrialized countries**

**NS subtype associated with high standard of living**

**MC/LD in economically disadvantaged countries (EBV associated)**



# Competing risks in Hodgkin lymphoma



Minimize  
late effects



Maximize  
cure



# RT related late effects

**Secondary cancer:**  
Long latency  
Increasing risk over  
time  
Relates to dose and  
field



**Secondary cancer:**  
Breast cancer (  )  
<30)   
Lung  
GI  
Sarcoma  
Thyroid

**Cardiovascular  
disease:**  
CAD  
Valvular  
Pericardial  
Conduction





# Hodgkin lymphoma therapy

**Stage I and II Disease:**

**Chemotherapy with or  
without radiation**

**Approximately 85%-90%  
cured with initial  
chemotherapy**

**Stage III and IV Disease:**

**Chemotherapy always  
required; now typically in combination  
with brentuximab**

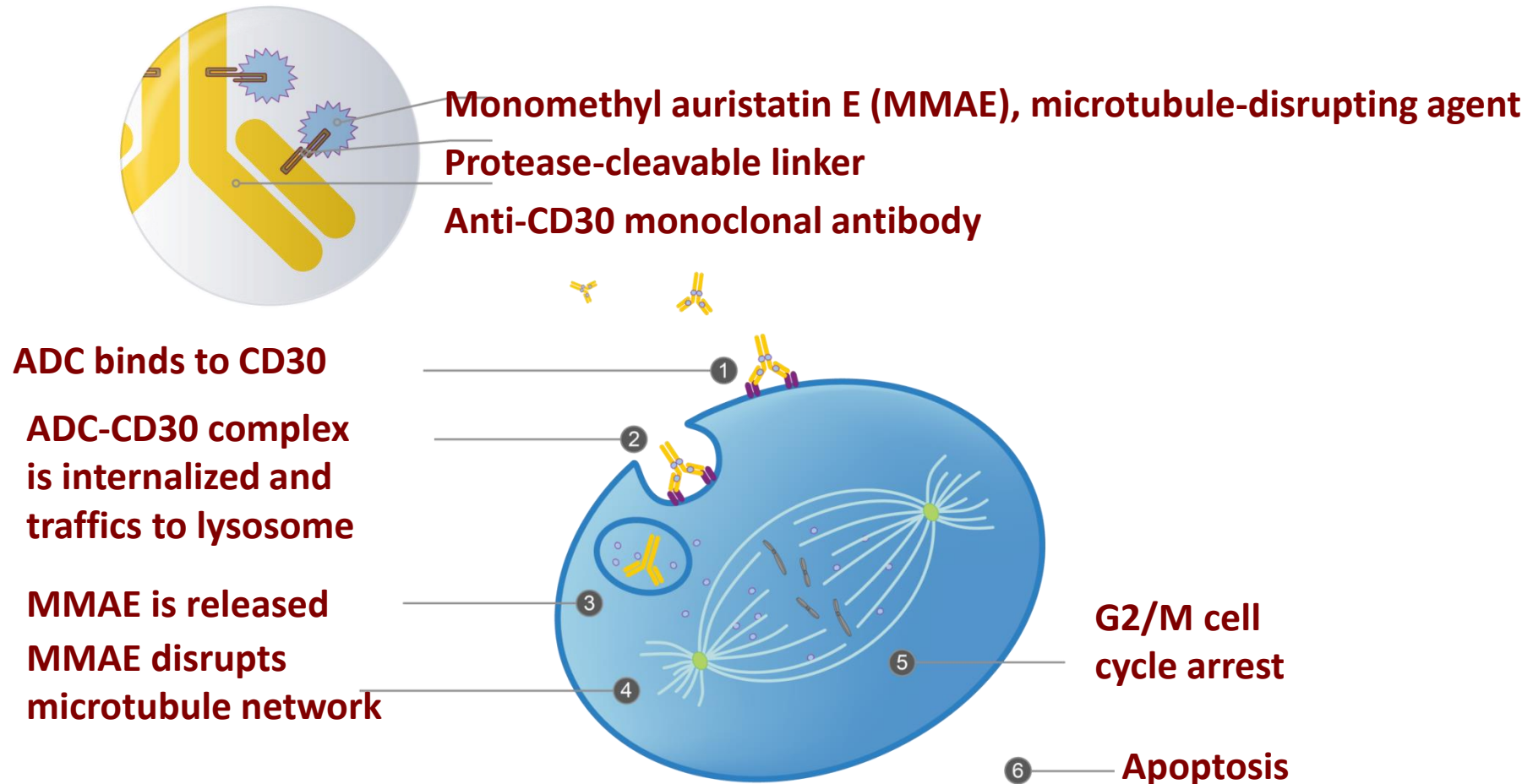
**Role of radiation therapy to sites of bulky  
disease uncertain**

**75% cured with initial therapy depending  
on risk**



# Brentuximab Vedotin

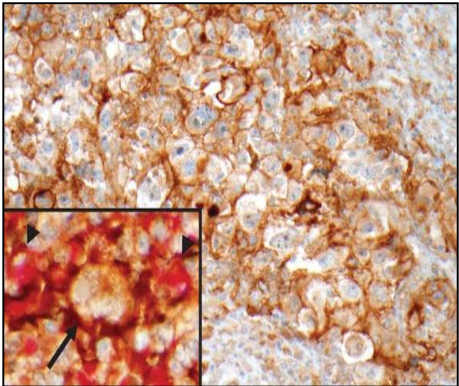
**ORR 75% (34% CR) with 96% disease control in relapsed HL**



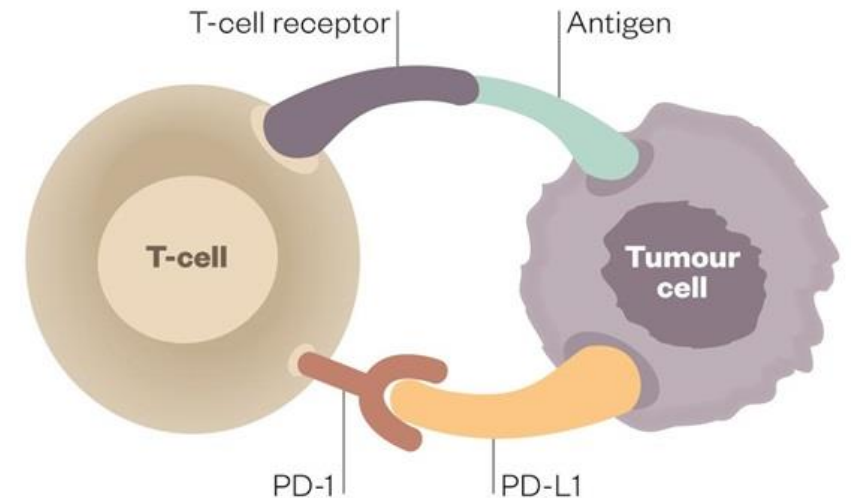
# Immunotherapy and Hodgkin lymphoma

Classical HL (cHL) is characterized pathologically by a failed immune response.

Near uniform amplification at 9p24.1  
leading to overexpression of PD-L1 and PD-L2  
cHL has a genetically driven vulnerability to  
PD-1 blockade.



PD-L1 expression in cHL



# Summary

## 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 may have long remissions and survival

# Hodgkin lymphoma:

- Often presents in neck and mediastinum
- High cure rates
- Early stage disease treated with combined modality therapy, advanced disease treated with chemotherapy
- Significant long term toxicities of therapy



# 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.**



# References

**Swerdlow et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016.**

**NCCN Clinical Practice Guidelines in Oncology. [www.nccn.org](http://www.nccn.org)**

**Evans LS, Hancock BW. Non-Hodgkin lymphoma. Lancet. 2003 362:139-46.**

