A Case Based Approach to Lymphoma

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Disclosures

- None

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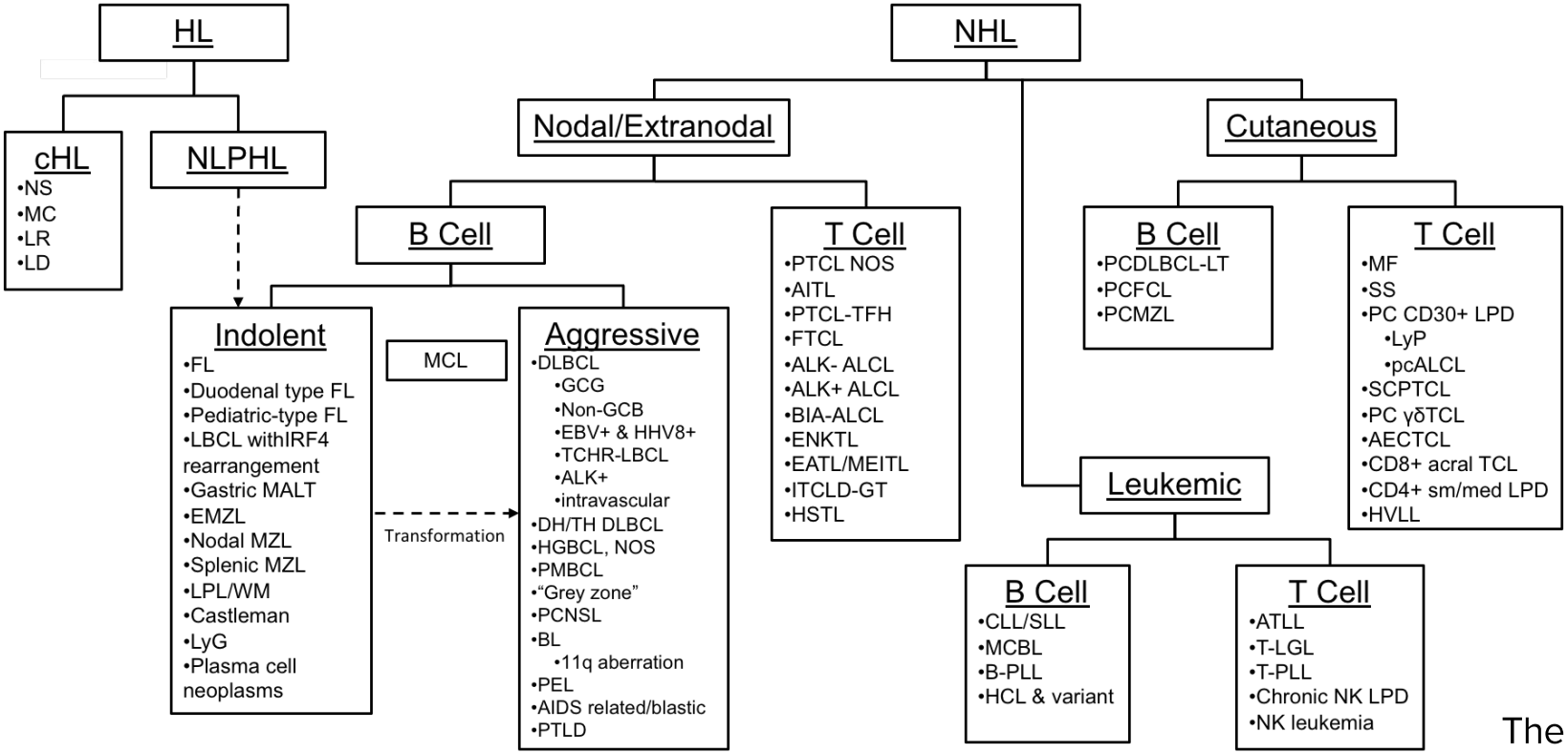
Objectives

- To understand the epidemiology Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL)
- To recognize the clinical presentation, initial work-up, and risk stratification for patients with Diffuse Large B-cell Lymphoma (DLBCL) and HL
- To be familiar with the basic treatment options for frontline DLBCL and HL
- To identify key survivorship concerns for patients with HL

Mature Lymphoid Neoplasms



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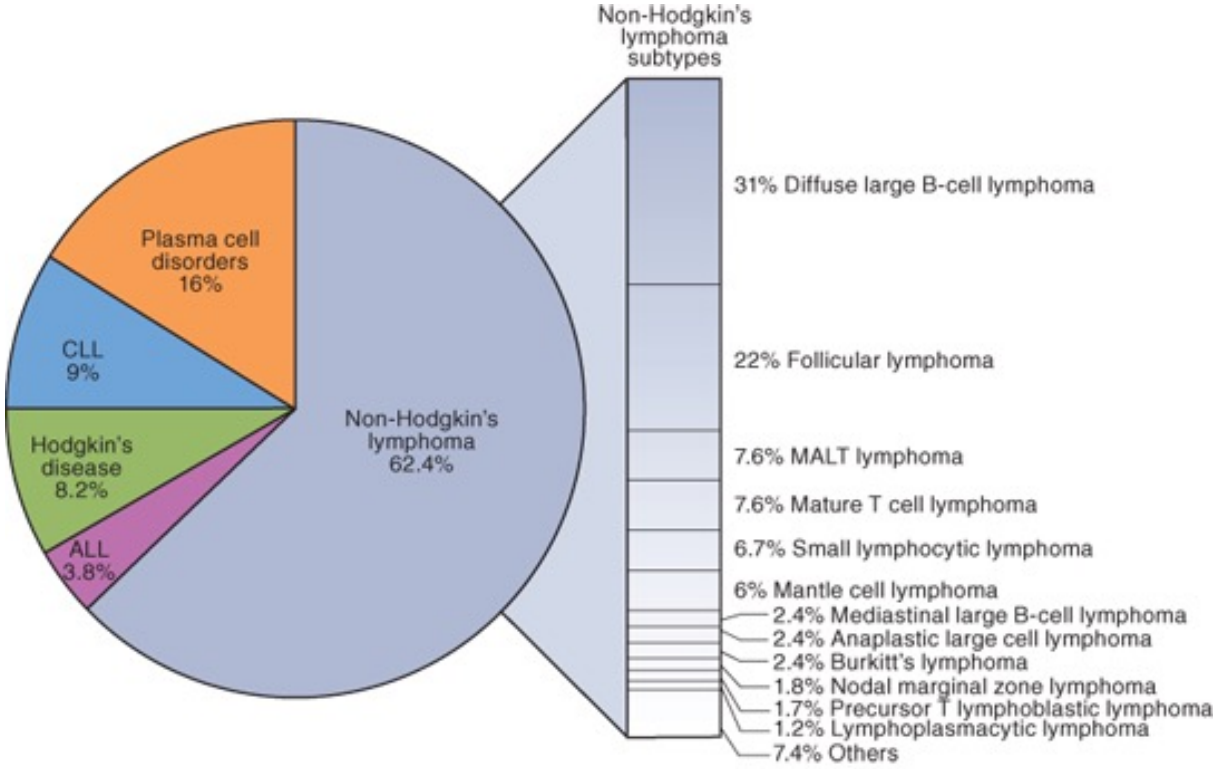
NHL is the Most Common Lymphoid Malignancy



Source: J.L Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Manual of Medicine, Twentieth Edition.

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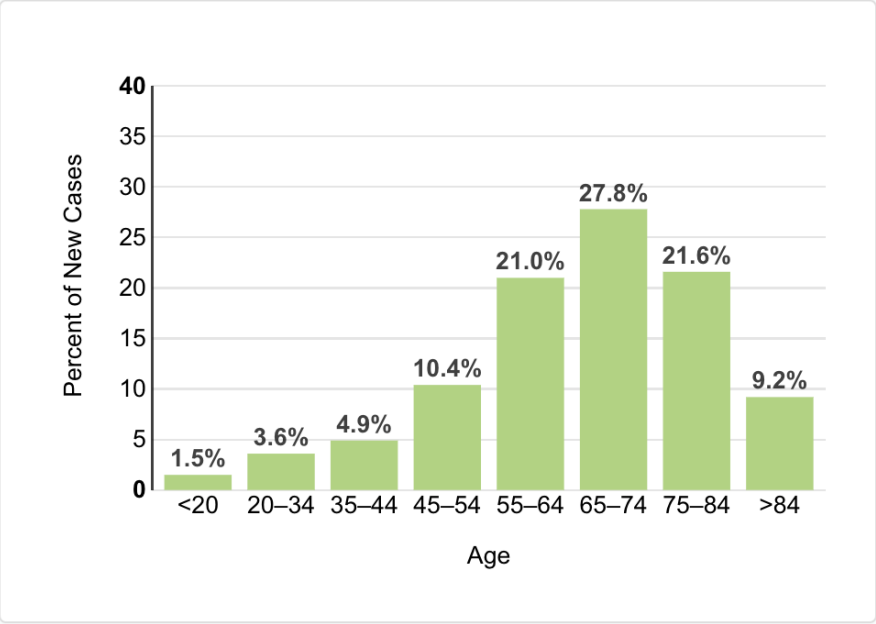
Prevalence of NHL and CHL

Age at Onset – NHL

Percent of New Cases by Age Group: Non-Hodgkin Lymphoma



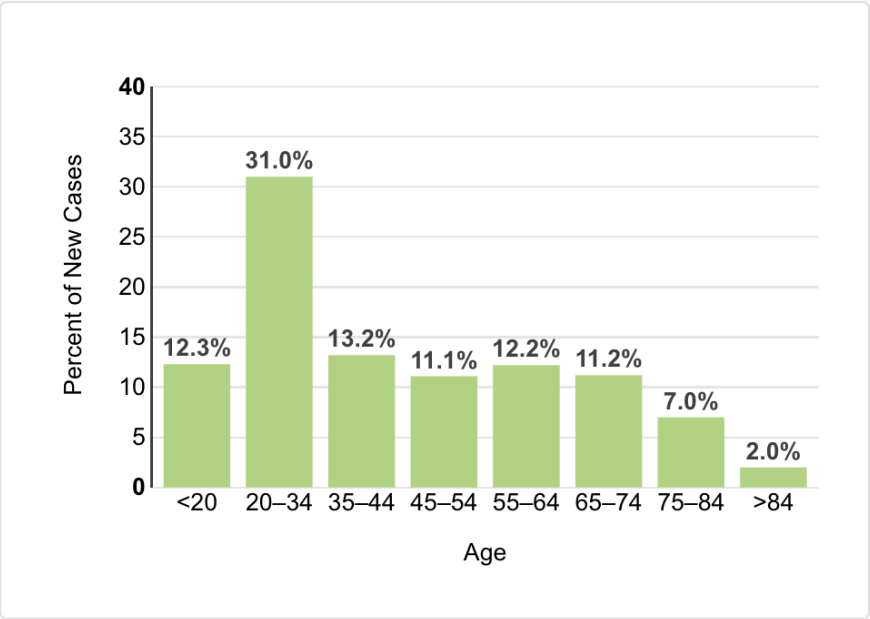
Non-Hodgkin lymphoma is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis
68

SEER 22 2016–2020, All Races, Both Sexes

Age at Onset – HL

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

Bimodal incidence peaks in the third and eighth decades of life

SEER 22 2016–2020, All Races, Both Sexes

Risk Factors – NHL

Viral infections	EBV, HTLV-1, HHV-8, hepatitis C
Bacterial infections	Heliobacter pylori, Chlamydophila psittaci
Acquired conditions of immunodeficiency	HIV, Organ or stem cell transplantation, Aging, Chronic immunosuppressive medications
Autoimmune and rheumatologic disease	Rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, Celiac disease
Environmental or occupational	Herbicides, pesticides
Congenital disorders	Wiskott Aldrich syndrome, X-linked lymphoproliferative syndrome, severe combined immunodeficiency, other immunodeficiency states

Adapted from Table 22-1: Risk Factors in the development of Non-Hodgkin Lymphoma. ASH SAP 8th Edition.

Risk Factors – CHL

- History of infectious mononucleosis caused by **Epstein-Barr virus** (EBV)
- **Immunodeficiency:** HIV, transplant
- **Autoimmune disorders:** Rheumatoid Arthritis, SLE, sarcoidosis
- Increased risk among close relatives with Hodgkin lymphoma (3-5 fold increase)

Clinical Differences Between NHL and CHL

NHL	CHL
More frequent involvement of multiple peripheral nodes	More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)
Noncontiguous spread	Orderly spread by contiguity
Waldeyer ring and mesenteric nodes commonly involved	Mesenteric nodes and Waldeyer ring rarely involved
Extranodal presentation common	Extranodal presentation rare

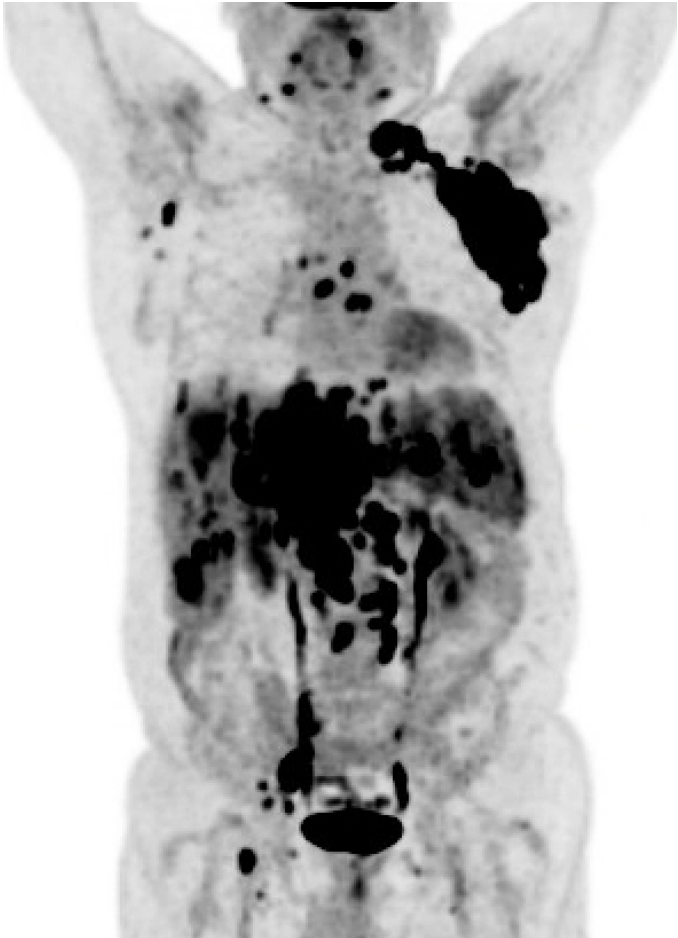
Adapted from Table 13.7. Robbins & Cotran Pathologic Basis of Disease. 2021.

Case #1: NHL

- **HPI**
  - 70 year-old-male with no significant past medical history presents with several weeks of progressive left axillary adenopathy
  - Also endorses several weeks of weight loss and night sweats
- **Initial work-up**
  - CT C/A/P are obtained which show left axillary adenopathy
  - FNA of axillary lymph node shows B-cell lymphoma
- **Next steps?**
  - Labs: CBC with diff, CMP, uric acid, LDH, HIV, chronic hepatitis panel
  - PET/CT for staging
  - Excisional biopsy – FNA not adequate for lymphoma!

Case #1: Biopsy and Staging

- Surgical excisional biopsy of axillary lymph node is obtained which is consistent with **Diffuse Large B-cell Lymphoma (DLBCL)**
- **PET (right):**
  1. Extensive hypermetabolic lymphadenopathy above and below the diaphragm.
  2. Multiple hypermetabolic foci throughout the liver and spleen.
  3. Asymmetric hypermetabolic focus in the left tonsil.
  4. Deauville score 5.



Clinical Presentation of DLBCL

- Lymphadenopathy
- B-symptoms
  - Unexplained fevers
  - Weight loss (>10% in 6 months)
  - Night sweats: not subtle
- Specific symptoms based on site
  - Rare neoplastic syndromes

Initial Work-up of DLBCL

- Physical exam (lymphadenopathy, splenomegaly)
- Labs: CBC with diff, CMP, uric acid, LDH, HIV, Hep B testing (if rituximab planned), Hep C
- PET/CT for staging (or CTs)
- TTE (if anthracycline planned)
- Bone marrow biopsy: not needed for all patients, obtain if would change management of if unexplained cytopenias
- Lumbar puncture and/or MRI brain (based on symptoms or if high risk)
- Pregnancy testing and fertility consult

Staging of DLBCL

Stage	Involvement
Limited	
I	One node or a group of adjacent nodes
II	Two or more nodal groups on the same side of the diaphragm
II bulky	II as above with “bulky” disease
Advanced	
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement
IV	Additional noncontiguous extralymphatic involvement

Extent of disease is determined by positron emission tomograph/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Staging of DLBCL

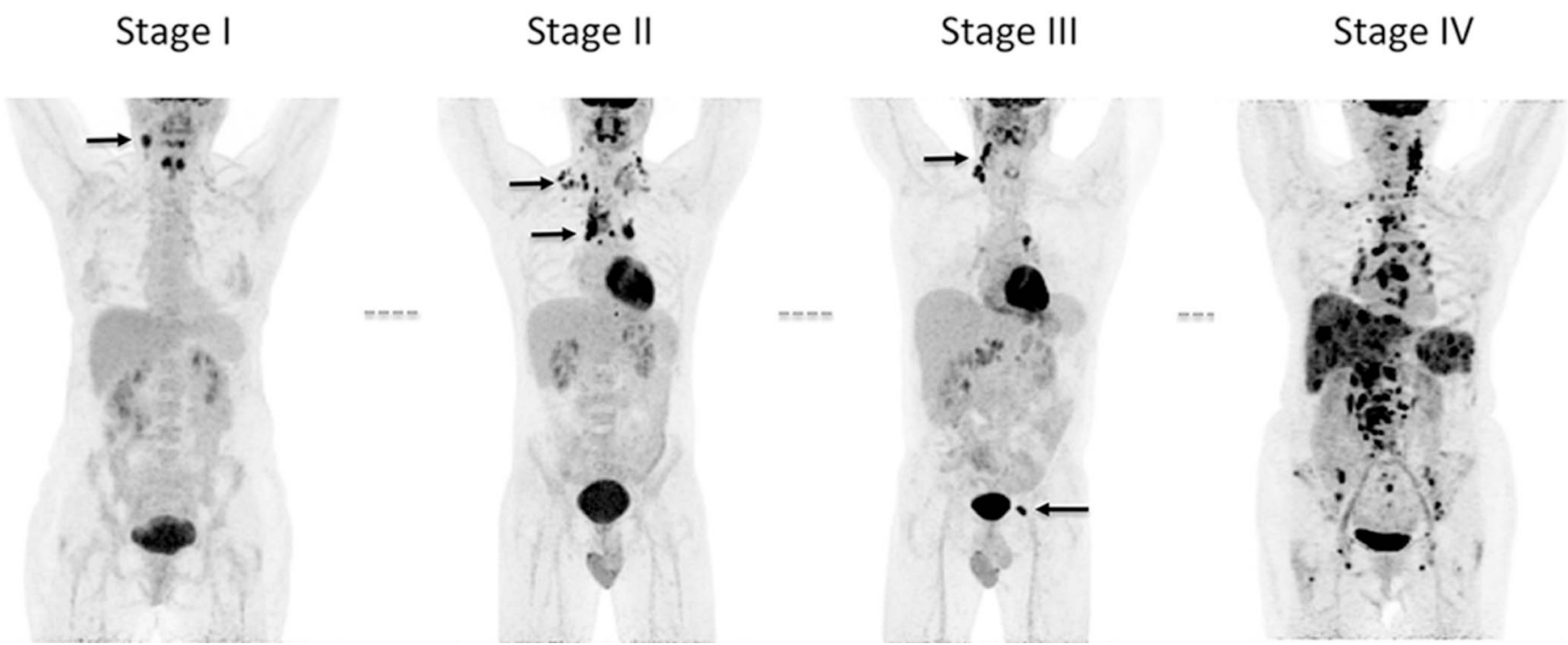


Figure 1. El-Galaly TC, Gormsen LC, Hutchings M. PET/CT for Staging; Past, Present, and Future. Semin Nucl Med. 2018 Jan;48(1):4-16.

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Risk Stratification – International Prognostic Index (IPI)

Factors	0 points	1 point
Age	≤60	>60
Ann Arbor Stage	I/II	III/IV
ECOG	0-1	≥2
Serum LDH	≤1× ULN	>1× ULN
Extra-nodal sites	≤1	>1

Score/Risk	4 yr OS	4 yr PFS
0-1: Low	82%	85%
2: Low-intermediate	81%	80%
3: High-intermediate	49%	57%
4-5: High	59%	51%

A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993;329(14):987-94.

Treatment of DLBCL

- **R-CHOP:** given in 21 day cycles
  - **R**ituximab 375 mg/m2 IV or SQ (diff dose)
  - **C**yclophosphamide 750 mg/m2 IV
  - **H**=doxorubicin 50 mg/m2 IV
  - **O**ncovin/vincristine 2 mg IV (can sub polatuzumab for higher risk patients)
  - **P**rednisone 100 mg PO days 1-5
  - G-CSF (growth factor) given for patients age >65 or high comorbidity
- **Common toxicities**
  - Infusion reactions with rituximab
  - Risk for infection, cytopenias, nausea/vomiting
  - Hemorrhagic cystitis with cyclophosphamide, cardiotoxicity with doxorubicin, neuropathy and constipation with vincristine

Case #1: Continued

- Patient presents to clinic to start treatment with R-CHOP
- **Labs show:**
  - Cr 2 (baseline normal)
  - Uric acid of 14
  - Potassium of 5.5
  - Phosphate of 6
- What complication are you concerned about and what treatment would you recommend?
  - Spontaneous tumor lysis syndrome (TLS)

Tumor Lysis Syndrome (TLS): Overview

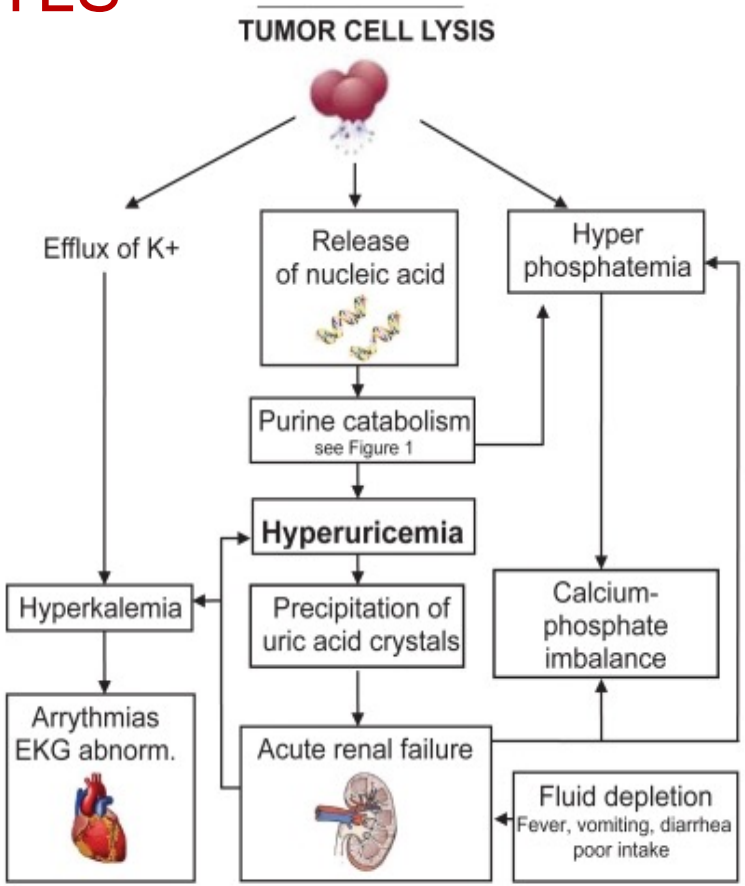
- Rapid breakdown of cancer cells→release of intracellular contents
- Intracellular contents are released too quickly for the body to remove them→metabolic abnormalities
  - Hyperuricemia
  - Hyperkalamia
  - Hyperphosphatemia
  - Hypocalcemia (2/2 phosphorus binding calcium)
- May occur spontaneously or 2/2 initiation of anti-neoplastic therapy

Frequency of TLS by Tumor Type

Risk Factors for TLS

Intrinsic tumor related risk factors

Pathogenesis of TLS



Pession et al. Biologics. 2008 Mar;2(1):129-41.

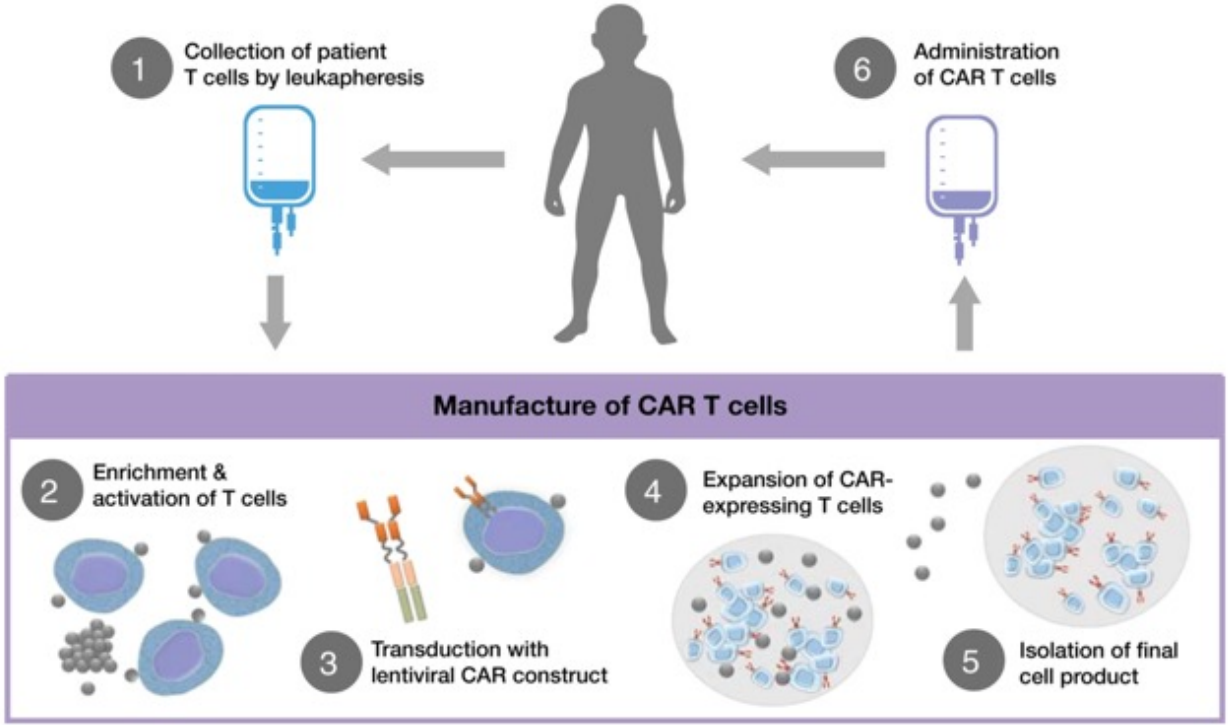
Treatment of TLS

- **Prophylaxis**
  - Allopurinol and IV fluids
  - Consider rasburicase for high-risk patients with initiation of treatment
- **Treatment**
  - Allopurinol and IV fluids
  - Rasburicase: typically given for uric acid >=8 mg/dL with signs of renal failure or other significant lab abnormalities
  - Correct electrolyte abnormalities
  - Hemodialysis can be needed in rare cases
  - **For our patient**→with AKI, uric acid 14, phosphate of 6, and potassium of 5.5→admit, fluids, allopurinol, rasburicase

Case #1: End of Treatment

- Patient completes 6 cycles of R-CHOP, end of treatment PET obtained 6 weeks after completion of chemotherapy shows concern for refractory disease
- Biopsy is obtained which confirms persistent DLBCL
- He is referred to a tertiary care center and CAR-T cell therapy is recommended
- What is CAR-T cell therapy and what are the common toxicities seen with CAR-T?

Overview of CAR-T Cell Therapy



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Hucks, et al. *Blood Cancer J*. 2019;9(2):10-19.

Indications for CAR-T in DLBCL

Therapy	Indications
Axi-cel	• Second line for treatment of DLBCL that is refractory to initial chemoimmunotherapy or relapses <12 months following completion of chemoimmunotherapy • Third line and beyond for all patients with relapsed/refractory DLBCL
Liso-cel	• Same as above PLUS • Patients with relapsed or refractory illness after first-line chemoimmunotherapy who are not eligible for hematopoietic stem cell transplant (HSCT) due to comorbidities or age
Tisa-cel	• Third line and beyond for all patients with relapsed/refractory DLBCL

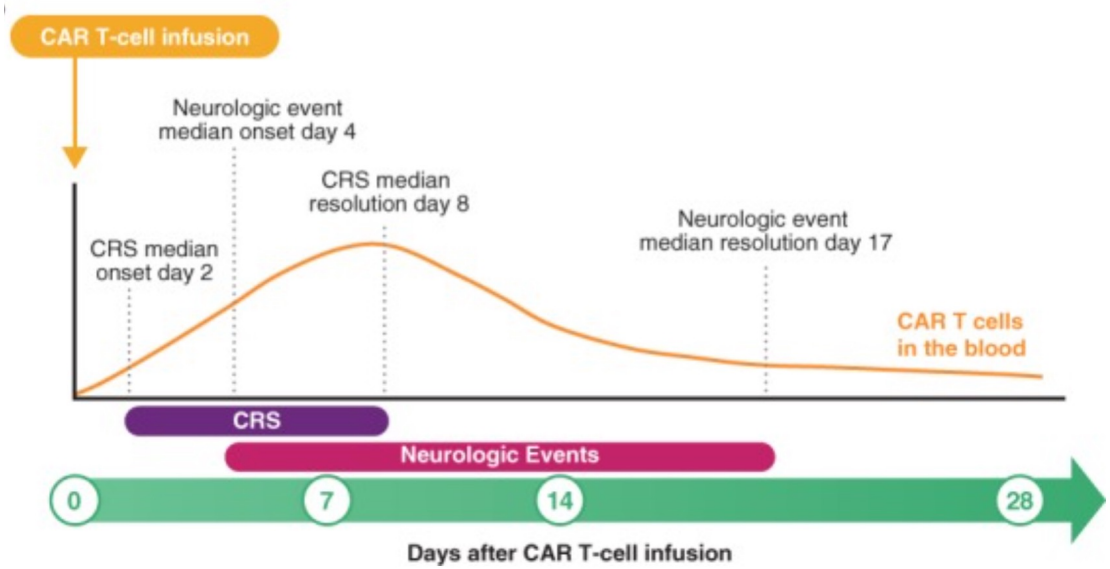
Early Toxicities of CAR-T

Cytokine Release Syndrome (CRS)		Neurologic	
Common	**Serious**	**Common**	**Serious**
▪ Fever ▪ Hypotension ▪ Tachycardia ▪ Hypoxia ▪ Chills	▪ Atrial fibrillation ▪ Ventricular tachycardia ▪ Cardiac arrest ▪ Cardiac failure ▪ Renal insufficiency ▪ Capillary leak syndrome ▪ Hypotension ▪ Hypoxia ▪ HLH/MAS	▪ Encephalopathy ▪ Tremor ▪ Dizziness ▪ Delirium ▪ Confusion ▪ Agitation	▪ Seizures ▪ Leukoencephalopathy ▪ Cerebral edema ▪ Aphasia ▪ Obtundation

Jacobson, et al. *Oncologist*. 2020;25(1):138-146.

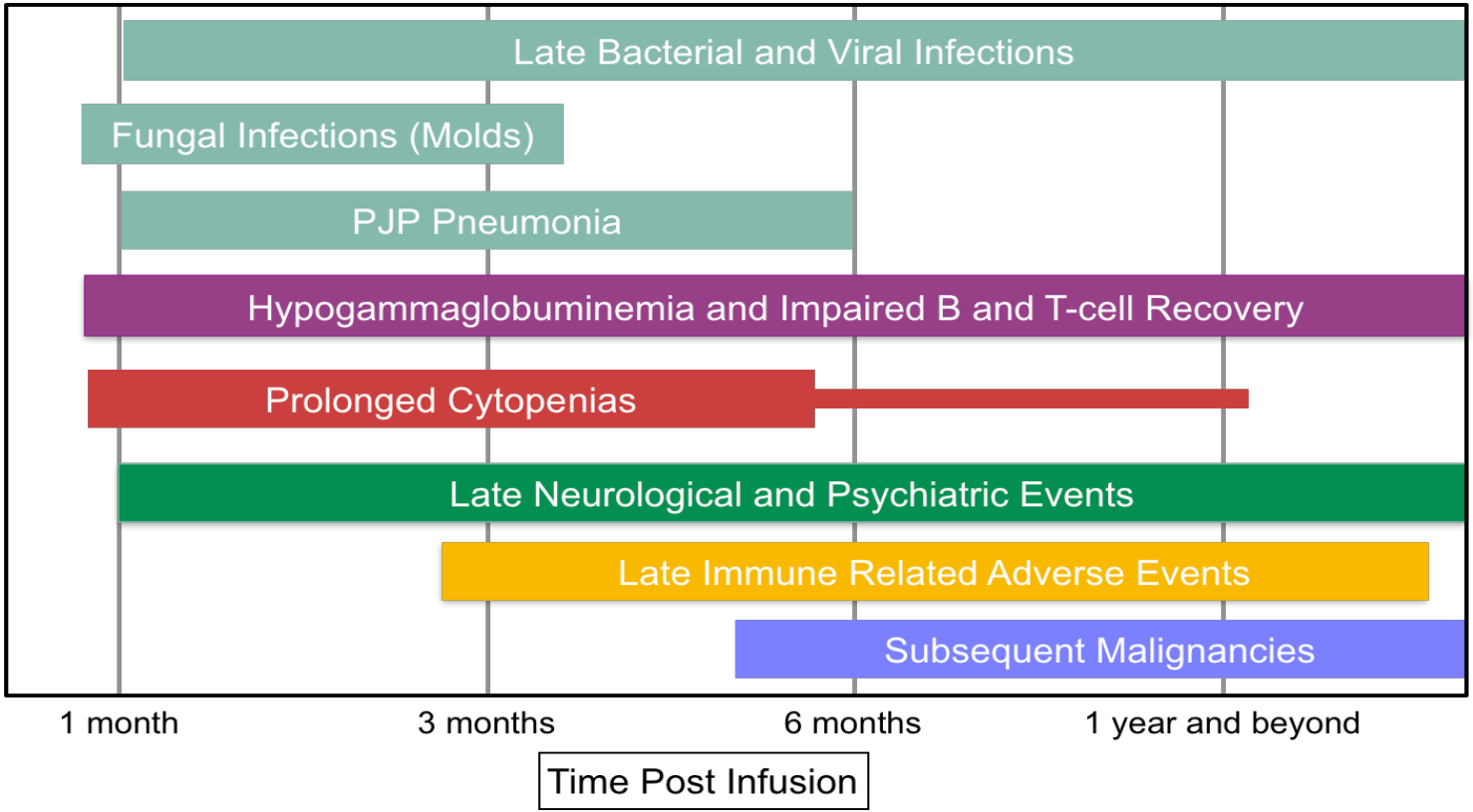
Incidence of Toxicities Based on CAR-T Product

	CRS		Neurotoxicity	
	Any	Severe	Any	Severe
Axi-cel	93%	13%	64%	28%
Tisa-cel	58%	23%	21%	12%
Liso-cel	37%	1%	25%	15%



1. Locke FL, et al. *Lancet Oncol*. 2019; 20(1): 31-42; 2. Schuster SJ, et al. *N Engl J Med*. 2019; 380: 45-56. 3. Abramson JS, et al. *Lancet*. 2020; 396(10254): 839-852. 4. Jacobson, et al. *Oncologist*. 2020;25(1):138-146.

Long Term/Late Toxicities of CAR-T



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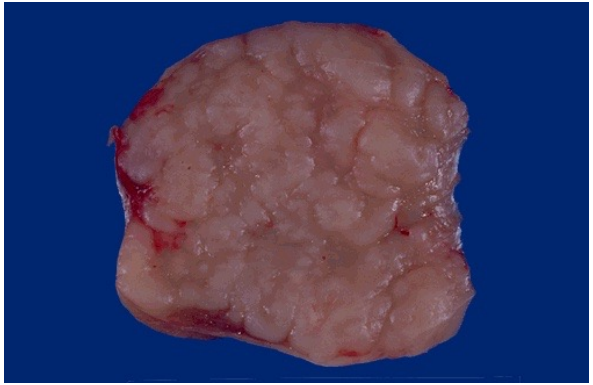
Chakraborty, et al. Transplantation and Cellular Therapy. 2021: 222- 229.

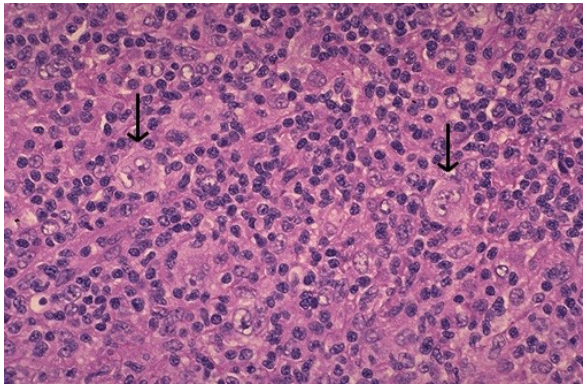
Case #2: CHL

- 22-year-old female presents with a left neck mass, fevers, and night sweats
- **Physical examination:** 2-3 cm left cervical/supraclavicular nodes that are rubbery in consistency
- **FNA:** inflammatory cells, atypical lymphocytes, flow cytometry fails to detect a clonal population of lymphocytes
- **What is the next step?**
  - Repeat biopsy→Classical Hodgkin Lymphoma, nodular sclerosis subtype

Diagnosis of Classical Hodgkin Lymphoma

- Lymph node biopsy: incisional or excisional (surgical)
- Fine needle aspirate (FNA) is NOT adequate
  - Diagnosis can be missed!
- CHL is not detected by flow cytometry





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Subtypes of CHL

Subtype	Clinical Features
Nodular Sclerosis	• Most common subtype (70%) • Most common type in adolescents and young adults, M=F • Usually stage I or II disease, mediastinal involvement common • LN: fibrous bands dividing cellular areas into nodules
Mixed Cellularity	• Second most common subtype (20-25%) • Biphasic incidence peaking in young adults and again at age >55, M>F • >50% stage III or IV, B symptoms common • LN: Frequent mononuclear and RS cells in background rich in T lymphocytes, eosinophils, macrophages, plasma cells
Lymphocyte Rich	• 5% of all CHL cases • Often seen in older adults, M>F • LN: frequent mononuclear and diagnostic RS cells in background rich in T lymphocytes
Lymphocyte Depleted	• Rarest subtype, more common in older men and HIV+ • Often presents with advanced stage disease

Adapted from Table 13.8, Subtypes of Hodgkin Lymphoma, Robbins & Cotran Pathologic Basis of Disease. 2021.

Clinical Presentation of CHL (1/2)

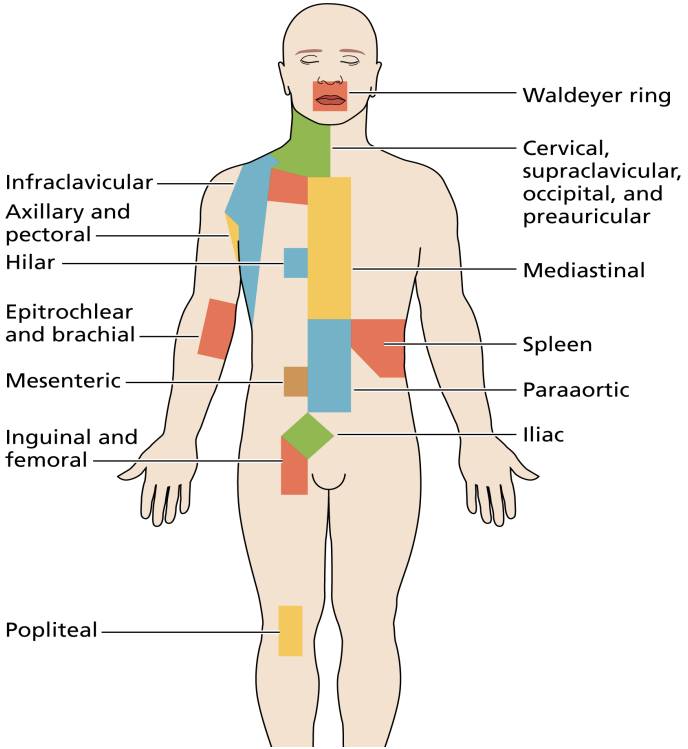
- Painless adenopathy = most common presentation
  - 60-70% cervical and supraclavicular
  - 15-20% axillary
  - Lymphadenopathy is usually nontender with “rubbery” consistency
- Pruritis (itching)
  - Can predate lymphadenopathy by months
  - Typically intense, refractory to topical and oral antihistamines
- Fatigue/malaise

Clinical Presentation of CHL (2/2)

- Cough, shortness of breath in patients with mediastinal disease
  - Rarely: hemoptysis
- 1/3 have ”B-symptoms”
  - Fevers, night sweats, weight loss
  - Can be cause of fever of unknown origin
- Rarely (<10% cases), alcohol ingestion can induce pain in lymph nodes
- Subdiaphragmatic presentations are uncommon

Orderly Progression

- CHL typically tracks from 1 lymph node basin to next in an orderly, stepwise fashion
- Rare to skip nodal sites
- Most common anatomic sites:
  - Left cervical lymph nodes (LNs): 60-70%
  - Right cervical LNs: 50-60%
  - Mediastinum: 50-60%
  - Axillary LNs: left 30-35%, right 25-35%
  - Hilar nodes: 15-35%
  - Spleen: 30-35%
  - Iliac: 15-20%
  - Bone marrow: <10%



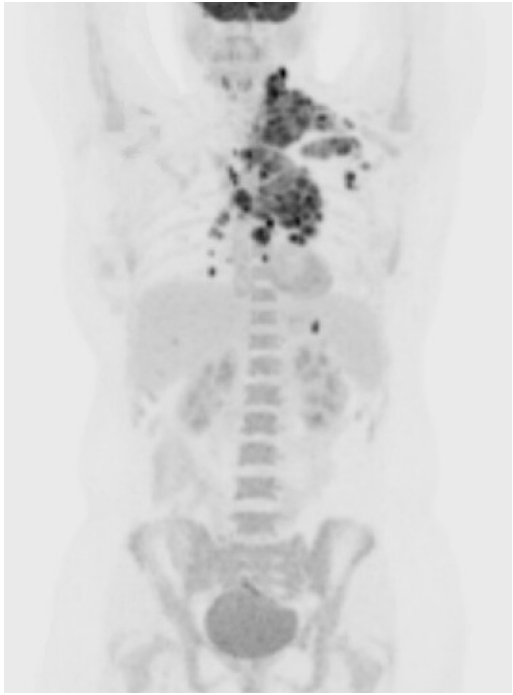
Celeste Bello, Pamela B. Allen, 2022, Hodgkin lymphoma, American Society of Hematology Self-Assessment Program, Figure 21-1.

Initial Work-up

- **History and physical**
  - Focus on symptoms, especially B-symptoms and pruritus
  - Presence of adenopathy, hepatosplenomegaly
- **Laboratory**
  - CBC with differential, erythrocyte sedimentation rate (ESR), comprehensive metabolic panel (CMP)
  - HIV and hepatitis B/C testing
- **Staging**
  - PET: positron emission testing (+/- CT with contrast)
  - Bone marrow biopsy and aspirate only for select patients
- **Additional work-up**
  - TTE for baseline EF assessment
  - Consideration for oncofertilty

Case #2: Staging PET

1. Extensive hypermetabolic adenopathy above the diaphragm consistent with lymphoma.
2. Diffuse intense uptake throughout the osseous structures could relate to bone marrow stimulation or osseous involvement.
3. Deauville score: 5



Risk Stratification: Early Stage

1. **Early-stage favorable:** stage I-II with no unfavorable factors
2. **Early-stage unfavorable:** stage I-II with unfavorable factors)

Unfavorable Factors
1. Large mediastinal adenopathy (mediastinal mass ratio >0.33) or bulky disease (any single node or nodal mass >10cm in diameter) 2. Multiple involved nodal regions (>3 sites of disease) 3. B symptoms 4. ESR (≥50)

Risk Stratification: Advanced Stage, IPS

Risk factors

Serum albumin, <4 g/dL

Hemoglobin, <10.5 g/dL

Male gender

Stage IV disease

Age ≥ 45 years

White blood cell count, ≥15,000/mm^3

Lymphocyte count, <600/mm^3 or <8% of white blood cells

Outcomes

Number of factors	5-year progression-free survival	5-year overall survival
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
≥5	42	56

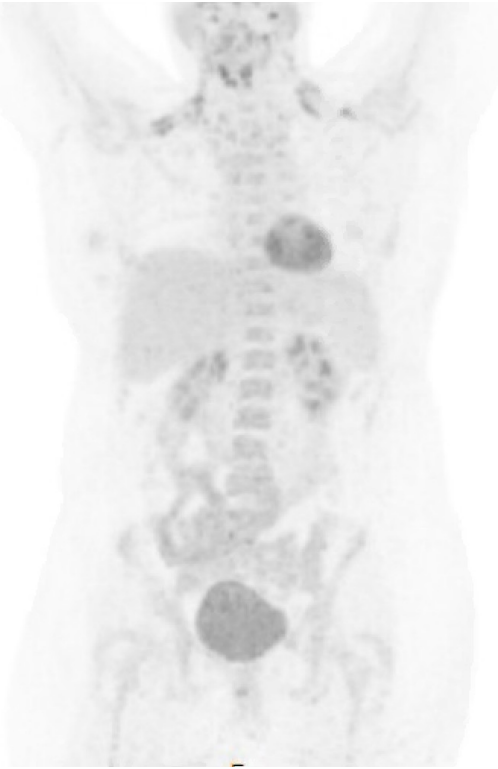
Matasar et al. (2012). Advances in the diagnosis and management of lymphoma. Blood and Lymphatic Cancer: Targets and Therapy. 2012. 29. 10.2147.

Treatment of CHL

- **Early Stage (Stage I/II)**
  - ABVD (adriamycin, bleomycin, vinblastine, dacarbazine)
  - PET after 2 cycles with risk adapted approach based on PET findings
- **Advanced Stage (Stage III/IV)**
  - Survival benefit with brentuximab (antibody drug conjugate targeting CD30) in combination with AVD over ABVD
  - Checkpoint inhibitors (nivolumab, pembrolizumab) are also moving into frontline setting
- **Relapsed**
  - Goal of treatment = cure for first relapse
  - Treatment: salvage treatment→autologous stem cell transplant

Case #2: End of Treatment Visit

- Completes 2 cycles of ABVD followed by 4 cycles of AVD
- Presents to review end of treatment PET (right)
- PET
  - Stable redemonstration of mild hypermetabolic soft tissue mass in the left anterior mediastinal region with metabolic activity less than background liver
  - Previously noted additional mildly hypermetabolic cervical and chest lymphadenopathy appear less conspicuous, Deauville score 3.
- Next steps?



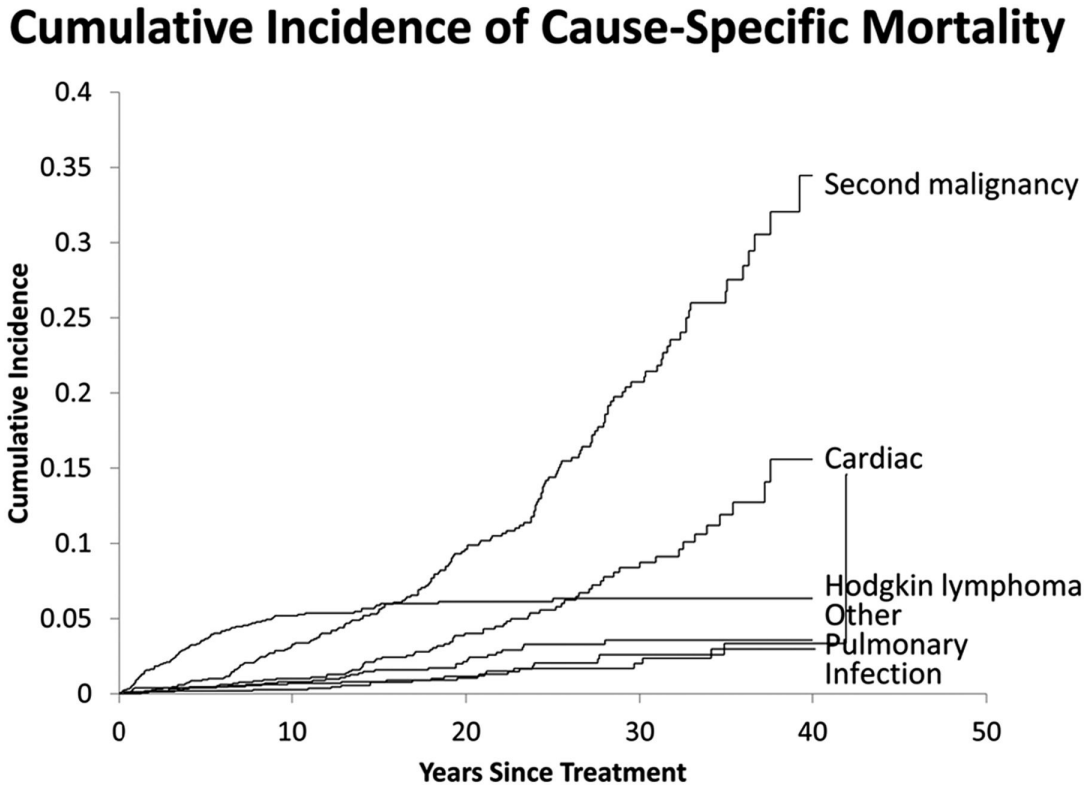
Post-Treatment Surveillance

- Clinical follow-up
  - Every 3 months for first 2-3 years
  - Every 6 months years 3-5 years
  - Relapse is very unlikely beyond 5 years
  - Annually years 5-10, can also transition to following with PCP alone during this time period
- CT scans/surveillance imaging: no longer recommend for patients who achieve a complete response

General Health Maintenance in CHL Survivors

- Follow-up after 5 years from completion of treatment
  - Annual history and physical
  - Laboratory studies
    - CBC with differential, chemistry panel, fasting glucose, and biannual lipids
    - If neck irradiation→thyroid stimulating hormone
- Vaccinations
  - Annual influenza and pneumococcal
  - Patients undergoing stem cell transplant require repeat vaccination with childhood vaccines

Cause Specific Mortality in CHL Survivors



Andrea K. Ng, Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects, Blood, 2014, Figure 1

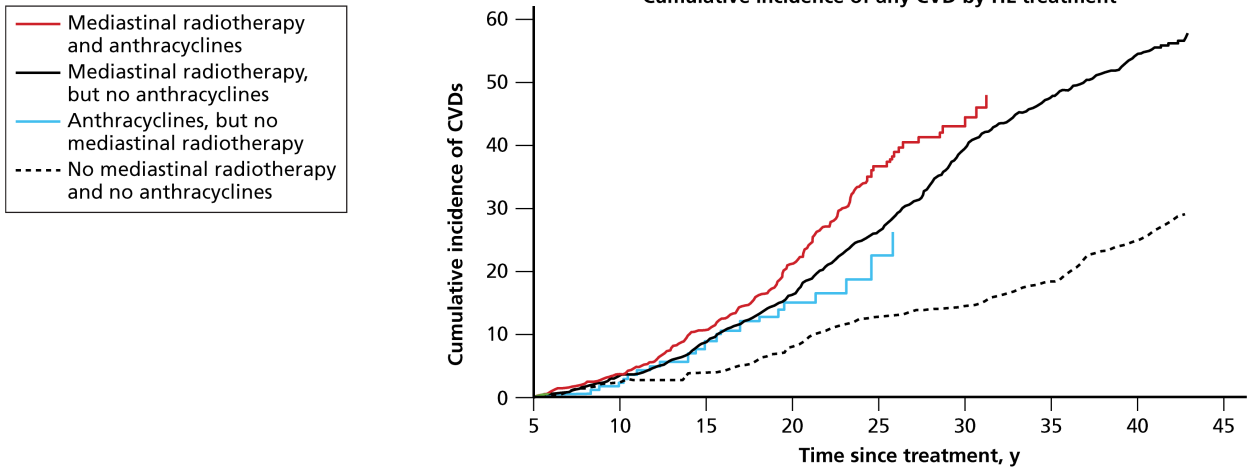
Secondary Malignancies in CHL Survivors

- 40 year cumulative incidence: 43.6%
- Most common: 75-80% solid tumor (breast, lung, GI cancers), also acute leukemia and non-Hodgkin lymphoma
- Relative risk of hematologic malignancies = higher when compared to general population
  - 10 to 80 fold increased risk of leukemia, 3 to 35 fold increased of NHL
  - >2 fold increase in solid tumor malignancies

Screening for Secondary Malignancies in CHL Survivors

Malignancy	Recommendations
Breast Cancer	Starting at age 40 years (or if chest irradiated, eight years after radiation or age 25, whichever is later): • Annual screening mammogram + annual breast MRI for women who received radiation to the chest between age 10 to 30 years old • Consider referral to high-risk breast clinic for discussion of chemoprevention
Lung Cancer	• Consider annual low dose CT scan starting 5 years after diagnosis for those with significant smoking history • Encourage smoking cessation
Skin Cancer	• Annual complete skin examination • Sun safety practice
Colon Cancer	• Begin colorectal cancer screening 10 years earlier than for general population

Cardiovascular Disease in CHL Survivors



No. at risk

Mediastinal radiotherapy and anthracyclines	604	492	364	180	46	14	1	0
Mediastinal radiotherapy, but no anthracyclines	1,448	1,269	1,097	848	552	273	119	30
Anthracyclines, but no mediastinal radiotherapy	169	139	105	59	13	6	1	0
No mediastinal radiotherapy and no anthracyclines	302	270	249	158	158	110	55	16

No. at risk

Mediastinal radiotherapy and anthracyclines	22	39	47	39	9	2	0
Mediastinal radiotherapy, but no anthracyclines	48	75	102	119	123	58	32
Anthracyclines, but no mediastinal radiotherapy	3	10	8	3	1	0	0
No mediastinal radiotherapy and no anthracyclines	6	5	11	11	3	5	5

Celeste Bello, Pamela B. Allen, 2022, Hodgkin lymphoma, American Society of Hematology Self-Assessment Program, Figure 21-6

Monitoring for Cardiovascular Disease

Screening and counseling techniques are similar to those used for other high-risk populations	
Cardiac Disease	• Consider referral to cardiologist for baseline evaluation after treatment for patients who received an anthracycline or radiation therapy. • Minimization of traditional risk factors (ex. smoking, obesity, hyperlipidemia, hypertension)
Non-coronary Vascular Disease	• Annual examination for carotid bruits; obtain carotid ultrasound if suspicious clinical findings • Modification of traditional risk factors as above

Endocrine Complications

- **Infertility**
  - <10% with ABVD, higher risk for women >30 years old
  - Management: involve onco-fertility early in treatment course, referral to reproductive Endocrinologist as needed
- **Diabetes Mellitus**
  - 8.3% of CHL survivors developed after 30 years in one study
  - Fasting glucose or hemoglobin A1c every two years in HL survivors whose treatment included radiation to the chest or abdomen
- **Hypothyroidism**
  - Incidence of 47% at 26 years for patients receiving neck irradiation
  - Management: annual TSH for those patients who received radiation

Other Long-Term Complications of Treatment

- **Pulmonary**
  - Long-term survivors = at risk for late pulmonary complications, including pulmonary fibrosis, bronchiectasis, chronic pleural effusions, and recurrent pneumonia
  - Management: baseline PFTs for patients who underwent radiation to the chest wall +/- bleomycin, refer to pulmonologist for respiratory symptoms
- **Psychosocial**
  - Higher rates of depression and anxiety seen in CHL survivors as compared to the general population
  - Annual evaluation should include a discussion of psychiatric health including an assessment of symptoms of depression

Summary

- NHL typically presents at older ages than CHL, with a median age of onset of 68 years old as compared to 39 years old
- NHL and CHL differ in clinical presentation, with NHL more likely to present in extra-nodal sites, to have non-contiguous spread, and to involve multiple peripheral lymph nodes than CHL
- It is important to be aware of key survivorship concerns in CHL survivors including screening for secondary malignancies and cardiac disease

Questions?