Non-Hodgkin's Lymphoma

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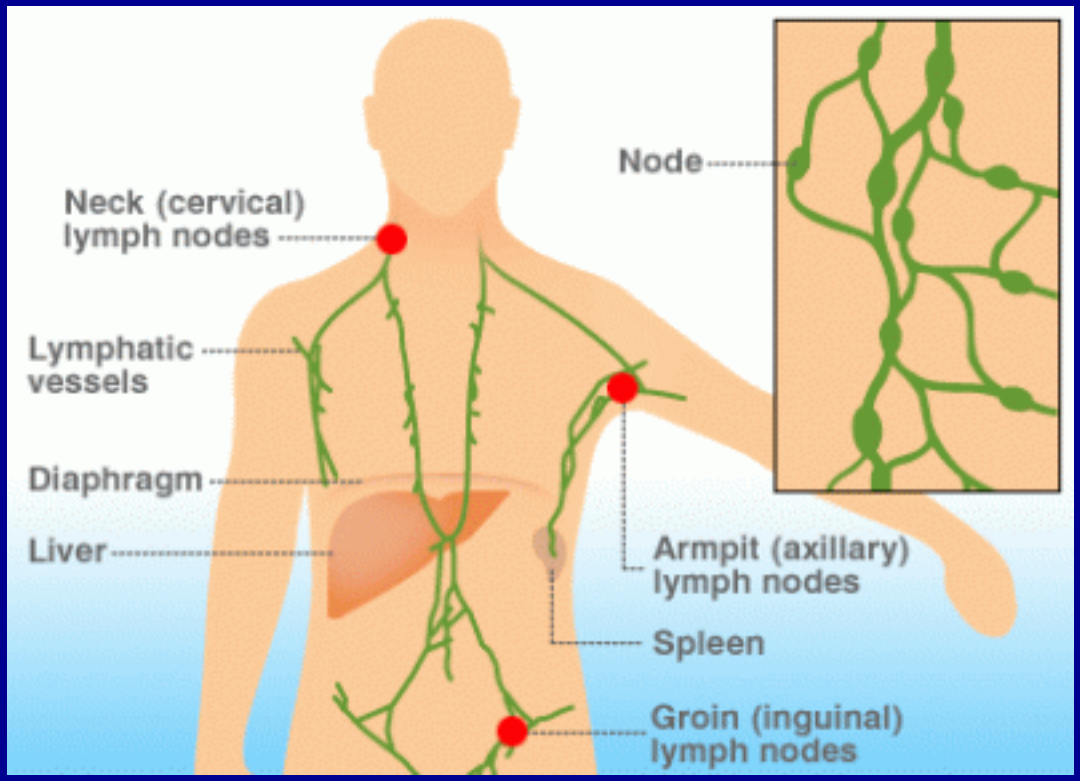
Department of Internal Medicine

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NHL: Definition

- Malignant disease of the lymphoid system, highly heterogeneous, both histologically and clinically.
- Extranodal presentation is 30%
  - The most common site is GIS



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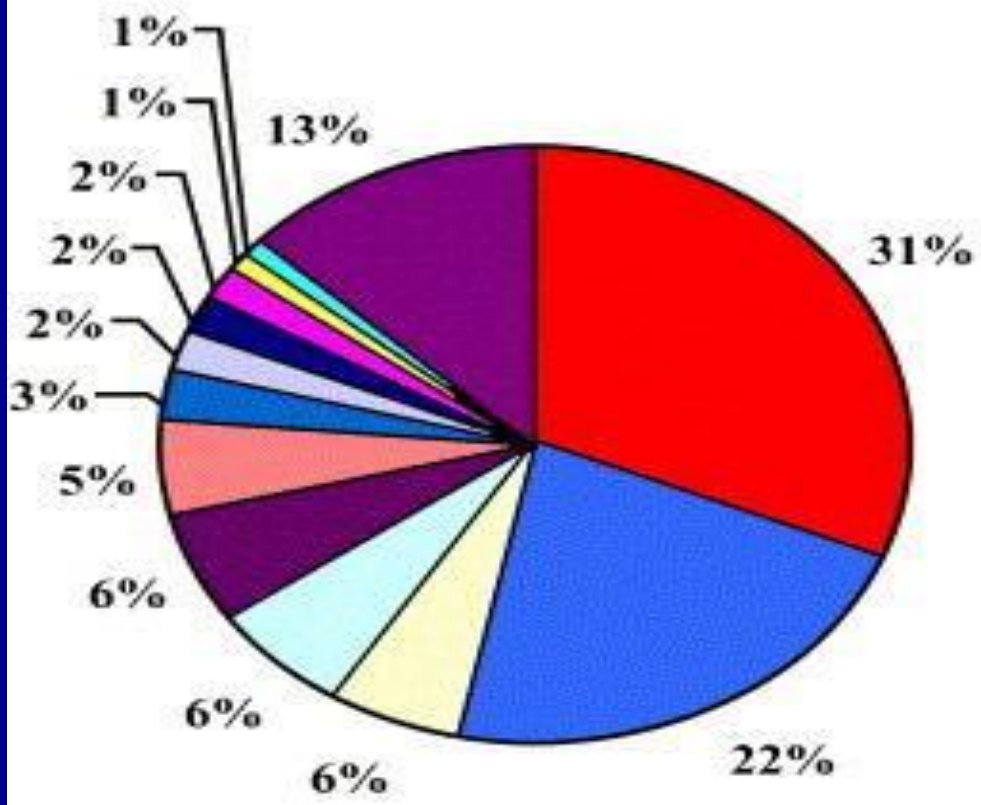
NHL: Epidemiology

- Annual incidence: 5-10 new cases per 100 000 persons
- Age distribution: middle-age patients and the elderly
- Males are affected more often than females (1.5:1.0).
- Mature B-cell neoplasms comprise over 90% of lymphomas worldwide.
- The incidence of lymphomas is increasing worldwide.

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NHL: Subtype Frequency

The most common type is **DLBCL**



- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Small lymphocytic lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Burkitt lymphoma/Burkitt cell leukemia
- Mediastinal large B-cell lymphoma
- Anaplastic large T-/Null-cell lymphoma
- Lymphoblastic lymphoma
- Nodal marginal zone B-cell lymphoma
- Lymphoplasmacytic lymphoma
- Composite cymphomas

NHL: Risk factors

- Infectious agents like Epstein-Barr virus (EBV), Human T-cell leukemia virus, H. Pylori, HHV-8 & HIV.
- Environmental factors such as chemicals.
- Medical treatments such as radiation therapy and chemotherapy.
- Genetic diseases, like Klinefelter's syndrome, Chediak-Higashi syndrome, ataxia telangiectasia syndrome.
- Autoimmune diseases, like Sjögren’s syndrome, celiac sprue, rheumatoid arthritis and systemic lupus erythematosus (SLE).

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Conditions associated with the development of lymphoma

Inherited immunodeficiency states
Klinefelter's syndrome
Chediak-Higashi syndrome
Ataxia telangiectasia syndrome
Wiscott-Aldrich syndrome
Common variable immunodeficiency disease
X-linked lymphoproliferative disease
Autoimmune lymphoproliferative syndrome
Bloom Syndrome
Acquired immunodeficiency states
Iatrogenic immunosuppression (eg, treatment of autoimmune disease or malignancy, organ transplantation)
HIV-1 infection
Acquired agammaglobulinemia
Multicentric Castleman's disease
Autoimmune disorders
Autoimmune hemolytic anemia
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome (sicca complex)
Hashimoto's thyroiditis
Inflammatory disorders
Acquired angioedema (acquired C1 esterase inhibitor deficiency)
Celiac disease, dermatitis herpetiformis
Inflammatory bowel disease treated with azathioprine/6-MP
Chemicals and drugs
Phenytoin
Dioxin, phenoxy-herbicides (Agent Orange), agricultural pesticides
Ionizing radiation
Chemotherapy, radiation therapy
Tumor necrosis factor antagonists
Hair dyes
Infectious agents (other than HIV)
Epstein-Barr virus
Human T-cell leukemia/lymphoma virus (HTLV)-I
Human herpesvirus type 8 (HHV-8, primary effusion lymphoma)
Helicobacter pylori
Campylobacter jejuni (Mediterranean lymphoma)
Chlamydia psittaci (ocular adnexal lymphoma)
Borrelia afzelii (Cutaneous B-cell lymphoma)
Hepatitis C virus (mixed cryoglobulinemia, splenic marginal zone lymphoma)
Mycobacterium tuberculosis, EBV (pyothorax-assoc. lymphoma)

Adapted from Freedman, AS, Nadler, LM. Malignancies of lymphoid cells. In: Harrision's Principles of Internal Medicine, 14th edition, Fauci, AS, Braunwald, E, Isselbacher, KJ, et al (Eds), McGraw-Hill, New York 1998. *Copyright © 1998 McGraw-Hill.*

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NHL: Risk factors

- **Age**:
  - Most people with non-Hodgkin lymphoma are older than 60.
- **Infections:**
  - Some viruses are implicated in the pathogenesis of NHL, probably because of their ability to induce chronic antigenic stimulation and cytokine dysregulation, which leads to uncontrolled B- or T-cell stimulation, proliferation, and lymphomagenesis.
  - *Human immunodeficiency virus* (HIV)
  - *Epstein-Barr virus* (EBV): linked to ***Burkitt lymphoma***.
  - *Helicobacter pylori:* Extranodal tissues generating lymphoma include **MALT** (Mucosa associated lymphoid tissue)
  - *Human T-cell leukemia/lymphoma virus* (**HTLV-1**)- adult T-cell leukemia or lymphoma.
  - *Hepatitis C virus*- lymphoplasmacytic lymphoma, Waldenström macroglobulinemia
  - HHV8-body cavity-based lymphomas

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NHL: Risk factors

- Genetic:
  - Accumulation of genetic lesions that affect:
    - Proto-oncogenes
    - Tumor suppressor genes
  - Chromosomal translocations
    - t(14;18) - overexpression of bcl-2 an apoptotic inhibitor oncogene- Follicular lymphoma
    - t(11;14) - overexpression of bcl-1 - Mantle cell lymphoma
    - t(8;14) - c-myc dysregulation – Burkitt's Lymphoma
    - t(2;5) - expression of an aberrant fusion protein - Anaplastic large cell lymphomas

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NHL: Risk factors

- t(14;18)
  - The t(14;18)(q32;q21) translocation is the most common chromosomal abnormality associated with NHL.
  - This translocation occurs in 85% of follicular lymphomas and 28% of higher-grade NHLs.
  - This translocation results in the juxtaposition of the *bcl* -2 apoptotic inhibitor oncogene at chromosome band 18q21 to the heavy chain region of the immunoglobulin (Ig) locus within chromosome band 14q32.
- t(11;14)
  - The t(11;14)(q13;q32 translocation has a diagnostic nonrandom association with mantle cell lymphoma.
  - This translocation results in the overexpression of *bcl* -1 (cyclin D1/PRAD 1), a cell-cycle regulator on chromosome band 11q13.
- t(8;14) / t(8;2) / t(8;22)
  - The 8q24 translocations lead to c-*myc* dysregulation.
  - This is frequently observed in high-grade small noncleaved lymphomas (Burkitt and non-Burkitt types), including those associated with HIV infection.

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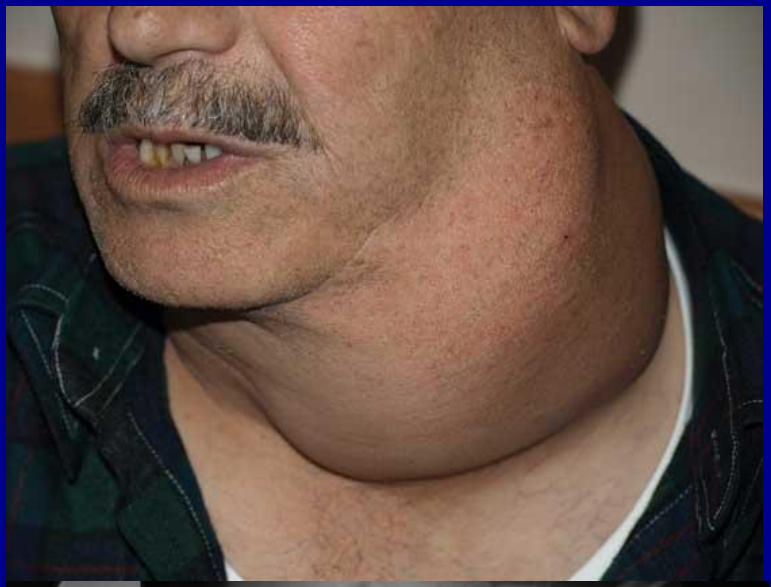
NHL: Risk factors

- t(2;5)
  - The t(2;5)(p23;q35) translocation occurs between the nucleophosmin (*NPM*) gene and the anaplastic lymphoma kinase (*ALK1*) gene.
  - It results in the expression of an aberrant fusion protein found in a majority of anaplastic large cell lymphomas.
- t(11;18) and t(1;14)
  - Two chromosomal translocations, t(11;18)(q21;q21) and t(1;14)(p22;132), are associated with mucosa-associated lymphoid tissue (MALT) lymphomas.
  - The more common (ie, t[11;18][q21;q21]) translocates the apoptosis inhibitor AP12 gene with the MALT1 gene, resulting in the expression of an aberrant fusion protein.
  - The other translocation, t(1;14)(p22;132), involves the translocation of the bcl -10 gene to the immunoglobulin gene enhancer region.

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NHL: Clinical Presentation

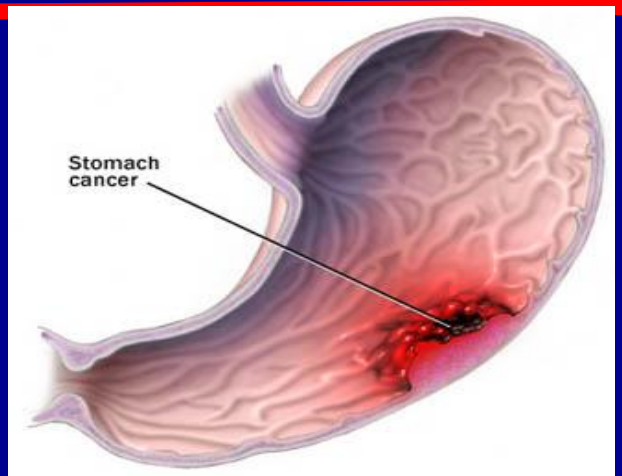
1. Constitutional/systemic symptoms (B symptoms)
   - Fever >38C,
   - Night sweats
   - Weight loss > 10% within 6 months
2. Lymphadenopathy (LAP)
   - Nontender lymph nodes enlargement
     - Painless & Mobile
     - Cervical, supraclavicular, axillary, inguinal, mediastinal, retroperitoneal, mesenteric, pelvic
3. Mediastinal adenopathy (T cell lymphoma)



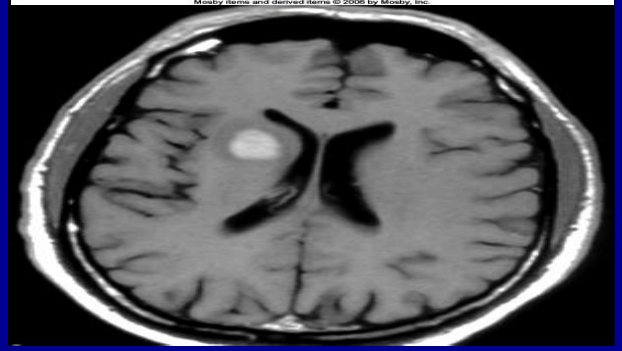


NHL: Clinical Presentation

4. Extralymphatic involvement/Extranodal disease
   - Gastrointestinal (most common)
   - Testicular masses
   - Solitary bone lesions
   - CNS
5. Other symptoms
   - Fatigue, weakness, lack of energy
   - Itching,
   - Cough, chest pain, shortness of breath, vena cava syndrome
   - Abdominal pain, bowel disturbances, ascites
   - Neurological symptoms
   - Cytopenia, unexplained anemia and thrombocytopenia (bone marrow infiltration)
   - Autoimmunologic reaction







NHL: Clinical Presentation

- Depends upon type of lymphoma and the areas of involvement.
- Some have mild presentation with lymphadenopathy waxing and waning over years whereas others can have a very aggressive presentation.
- **Aggressive lymphomas**:
  - Commonly have an acute presentation with rapid growth in size of tumor, systemic ‘B’ symptoms of fever, night sweats, weight loss, etc..
  - **Examples**: diffuse large B cell lymphoma, Burkitt lymphoma and adult T cell leukemia-lymphoma.
- **Indolent lymphomas:**
  - Slow growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenias.
  - **Examples**: Follicular lymphoma, small lymphocytic lymphoma.

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NHL: Clinical Presentation

- Clinical presentation is the same as for Hodgkin lymphoma.
- The difference is that Hodgkin is localized to cervical and supraclavicular nodes 80%-90% of the time whereas NHL is localized 10-20% of the time.
- CNS involvement is more common with NHL.
- HIV positive patients often have CNS involvement.

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NHL: Physical Examination

- The physical examination needs to be directed to all potentially involved lymphoid sites, these include:
  - Waldeyer's ring (tonsils, base of the tongue, nasopharynx)
  - Standard lymph node sites (cervical, supraclavicular, axillary, inguinal, femoral)
  - Liver and spleen
  - Abdominal nodal sites (mesenteric, retroperitoneal)
  - Less commonly involved nodal sites
- Chest and Lungs
  - Mediastinal adenopathy
- Abdomen and Pelvis
  - Retroperitoneal, mesenteric and pelvic nodes.
- Extranodal Sites:
  - GI tract
  - Skin
  - Testicular

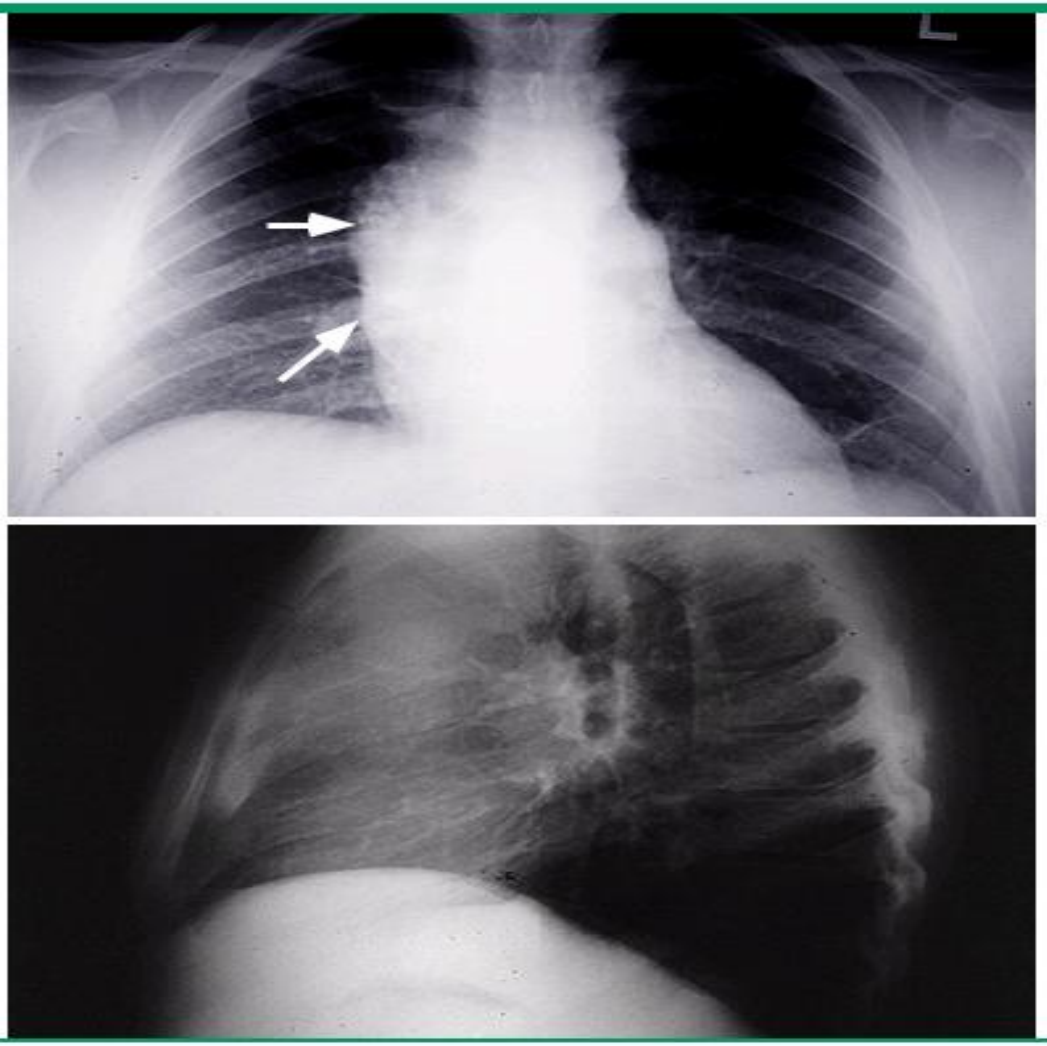
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NHL: Laboratory

- CBC:
  - Normal counts in early disease
  - Cytopenias due to bone marrow infiltration or autoimmune causes
  - Lymphocytosis with circulating malignant cells
  - Thrombocytosis (paraneoplastic syndrome or reactive)
- Chemistries:
  - LDH (associated with tumor burden – poor prognosis)
  - Beta-2 microglobulin (poor prognosis)
  - LFTs (hepatic involvement, hyper metabolism, chronic inflammation)
  - Calcium (raised in T-ALL)
- Viral serology:
  - HIV or HTLV-1 may be present depending on tumor histopathology
- PET scan:
  - Post-treatment - differentiate between recurrence and residual disease

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Mediastinal lymphoma chest radiograph



PA (upper panel) and lateral (lower panel) radiographs of a patient with a large right-sided mediastinal mass (arrows). The biopsy was consistent with diffuse large B-cell non-Hodgkin's lymphoma.

Courtesy of Arnold S Freedman, MD, Jonathan W Friedberg, MD, and Pam DePiro, MD.

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Lymphadenopathy and splenomegaly on CT scan in a patient with non-Hodgkin lymphoma



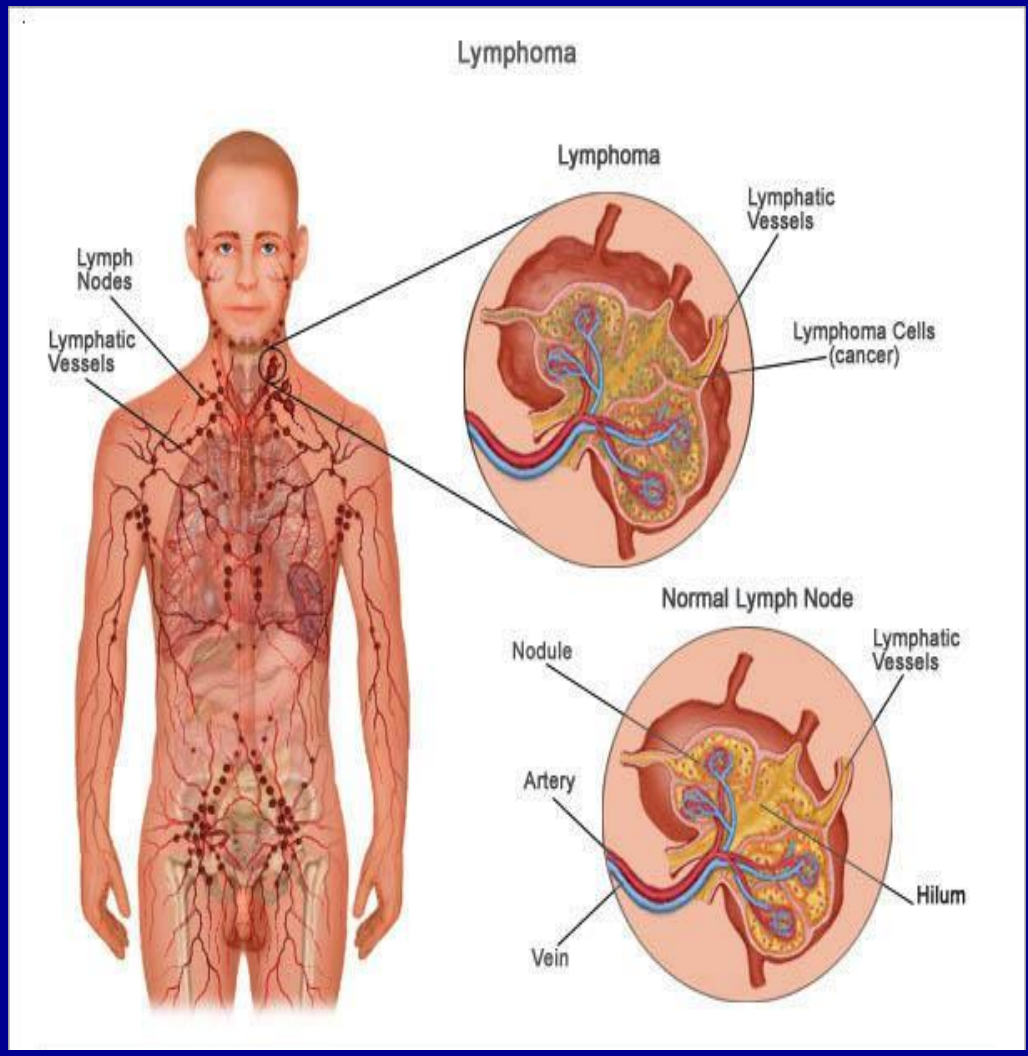
Computed tomography (CT) scan of the abdomen at the level of the kidneys in a patient with extensive B-cell non-Hodgkin lymphoma. There is massive enlargement of the retroperitoneal nodes (arrows) as well as enlarged nodes at the base of the small bowel mesentery. The spleen is also enlarged (dashed arrow).

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NHL: Diagnosis

For the diagnosis of non-Hodgkin's lymphomas the <u>histological examination</u> of a lymph node is necessary!



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NHL: Genetics Features

Genetic Features of Non-Hodgkin's Lymphoma (NHL) Subtypes

NHL Histologic Type	Translocation	% of Cases Affected	Proto-oncogene Involved	Mechanism of Proto-oncogene Activation	Proto-oncogene Function
Lymphoplasmacytic lymphoma	t(9;14)(p13;q32)	50	*PAX5*	Transcriptional deregulation	Transcription factor regulating B-cell proliferation and differentiation
Follicular lymphoma	t(14;18)(q32;q21) t(2;18)(p11;q21) t(18;22)(q21;q11)	90	*bcl-2*	Transcriptional deregulation	Negative regulator of apoptosis
Mantle cell lymphoma	t(11;14)(q13;q32)	70	*bcl-1*/cyclin D1	Transcriptional deregulation	Cell cycle regulator
MALT lymphoma	t(11;18)(q21;q21) t(1;14)(p22;q32)	50 Rare	*API2/MLT* *bcl-10*	Fusion protein Transcriptional deregulation	*API2* has antiapoptotic activity Antiapoptosis (?)
Diffuse large B-cell lymphoma	der(3)(q27)	35	*bcl-6*	Transcriptional deregulation	Transcriptional repressor required for GC formation
Burkitt's lymphoma	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	80 15 5	c-*myc*	Transcriptional deregulation	Transcription factor regulating cell proliferation and growth
Anaplastic large T-cell lymphoma	t(2;5)(p23;q35)	60	*NPM/ALK*	Fusion protein	*ALK* is a tyrosine kinase

Modified from Pasqualucci L, Dalla-Favera R: Molecular pathogenesis of non-Hodgkin's lymphoma. Hematology (Am Soc Hematol Educ Program) 200–205, 2001.

NHL: Diagnosis

Biopsy

- Biopsy is required for diagnosis and classification of NHL.
- Modalities:
  - FNA
  - Definitive Tissue Biopsy
- Studies on Excised Tissue:
  - Histology
  - Immunophenotype
  - Genetic studies

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NHL: Biopsy

- Histologic evaluation includes:
  - Assessment of the morphology;
  - Pattern of lymph node involvement.
- **Morphology**: Morphological changes have prognostic impact.

Favorable Prognosis	Unfavorable Prognosis
• Nodular/follicular architecture	• Diffuse architecture
• Small cell size	• Large cell size
• Cleaved nucleus	• Un-cleaved nucleus

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NHL: Biopsy

- **Immunophenotype:** is determined through flow cytometry.

Markers commonly used for assessment of lymphocyte subsets by flow cytometry

Marker name	Cell type	Comment
CD3	T cells	Expressed on all T cells and no other cell type
CD4	T cell subset	Predominantly helper/inducer T cells
CD8	T cell subset	Predominantly cytotoxic T cells; expressed by up to one- third of natural killer cells
CD19 or CD20	B cells	
CD16	Natural killer cells	Some NK cells may not express CD16
CD56	Natural killer cells	Expressed on the majority of NK cells
CD57	Natural killer cells	Expressed on the majority of NK cells; combinations of CD16, CD56, and CD57 will more reliably evaluate NK cell number than any marker alone
CD45RA	Naive T cells	
CD45RO	Memory T cells	

NK: natural killer.

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NHL: Origin

- NHL represents a progressive clonal expansion of B cells or T cells and/or NK cells arising from an accumulation of lesions affecting proto-oncogenes or tumor suppressor genes, resulting in cell immortalization.
  - **85% : B-cell origin**
  - 15% : T/NK cells
  - Rarely from Macrophages

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Immunophenotyping in B-lymphomas

B-cell lymphomas:

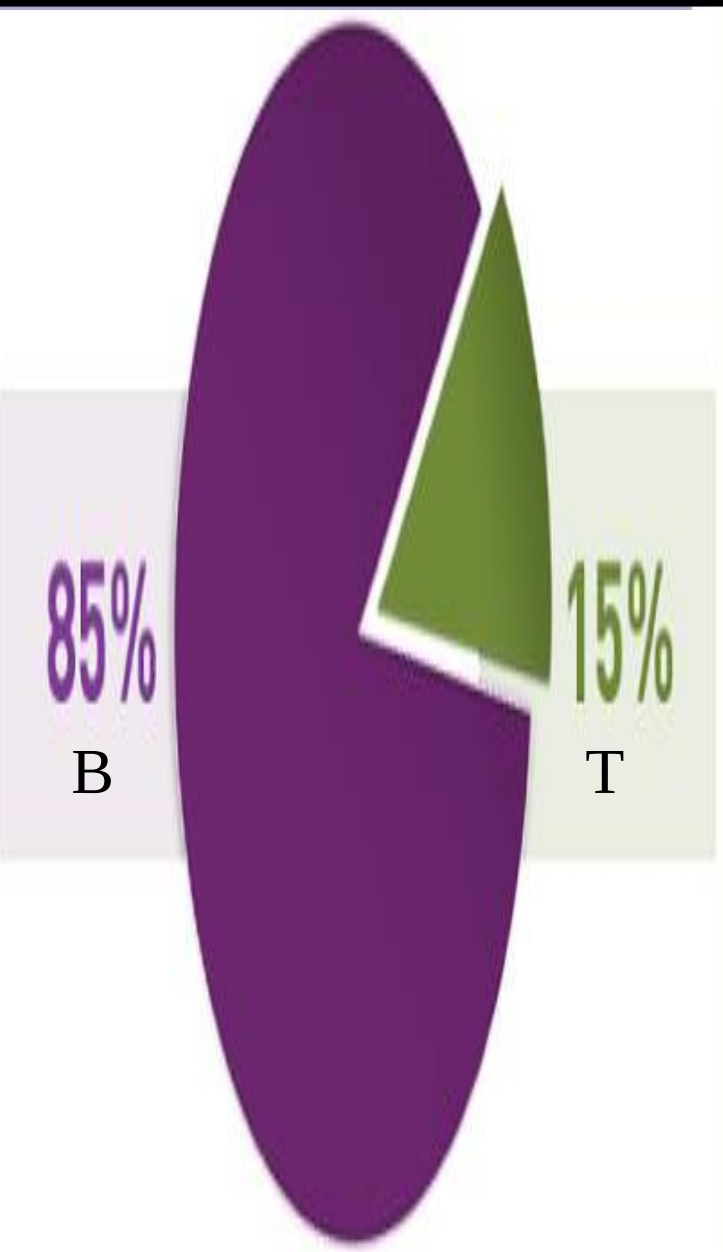
- Small lymphocytic lymphoma:
  - CD5+, CD23+, CD10-, CD43+
- Mantle cell lymphoma:
  - CD5+, CD23-, CD10±, CD43+
- Follicular lymphoma:
  - CD5-, CD23 ±, CD10+, CD43-
- MALT lymphoma:
  - CD5-, CD23± ve CD10-, CD43 ±

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Histologic classification of NHLs

1. Rappaport	-	1966
2. Lukes and Collins	-	1974
3. Dorfman	-	1974
4. Bennet et al.,	-	1974
5. Lennert	-	1974
6. WHO	-	1976
7. Working Formulation	-	1982
8. REAL	-	1994
9. WHO	-	1999-2008

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WHO Classification

B-cell neoplasms

Precursor B-cell lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

- B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma (lymphoplasmacytoid lymphoma)
- Mantle cell lymphoma
- Follicular lymphoma (follicle center lymphoma)
- Cutaneous follicle center lymphoma
- Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type
- Nodal marginal zone lymphoma =/- monocytoid B-cell
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Diffuse large B-cell lymphoma
  - Mediastinal (thymic)
  - Intravascular
  - Primary effusion lymphoma
- Burkitt's lymphoma
- Plasmacytoma
- Plasma cell myeloma

T-cell neoplasms

Precursor T-cell lymphoblastic leukemia/lymphoma

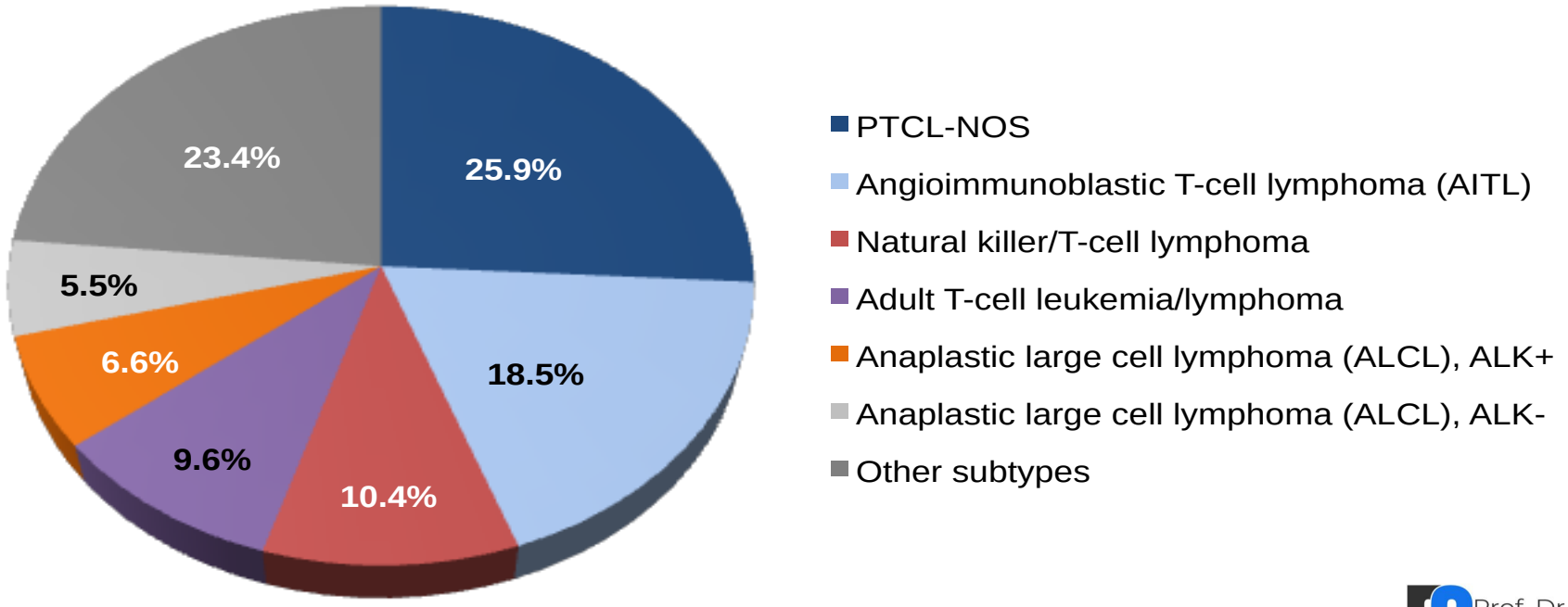
Mature T-cell and natural killer cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive natural killer cell leukemia
- T/natural killer cell lymphoma, nasal and nasal-type (angiocentric lymphoma)
- Mycosis fungoides
- Sezary syndrome
- Angio immunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma (unspecified)
- Adult T-cell leukemia/lymphoma (HTLV1 +)
- Anaplastic large-cell lymphoma (T – and null-cell types)
- Primary cutaneous CD 30 positive T-cell lymphoproliferative disorders (cutaneous
  - Anaplastic large cell lymphoma)
- Subcutaneous panniculitis-like T-cell lymphoma
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic g/d T-cell lymphoma

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Most common PTCL subtypes

- **PTCL-NOS** is the most common subtype
- Angioimmunoblastic T-cell lymphoma (AITL) and Anaplastic large cell lymphoma (ALCL), ALK+/- are also common subtypes



1. Adapted from: Vose J, et al. *J Clin Oncol.* 2008;26(25):4124-4130.

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NHL: Grades

- NHL divided into **Low** or **high grade**
- A high grade lymphoma has cells which look quite different from normal cells.
  - They tend to grow fast (aggressive)
  - Usually look follicular
  - Incurable
  - Wider dissemination at presentation
- Low grade lymphomas have cells which look much like normal cells and multiply slowly (indolent).
  - Usually look diffuse
  - Long term treatment maybe achievable

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NHL: Grades

Indolent non-Hodgkin's lymphoma	Aggressive non-Hodgkin's lymphoma
Follicular lymphoma	Diffuse large B-cell lymphoma
Diffuse small cleaved cell lymphoma	Mantle cell lymphoma
MALT lymphoma	Adult lymphoblastic lymphoma
Small lymphocytic lymphoma	Primary mediastinal large B-cell lymphoma
Waldenstrom macroglobulinemia	Burkitt's lymphoma

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NHL: Low-grade

- Many low-grade lymphomas remain indolent for many years.
- Treatment of the non-symptomatic patient is often **Avoided**.
- In this case **watchful waiting** is often the initial course of action. This is carried out because the harms and risks of treatment outweigh the benefits.
- If a low-grade lymphoma is becoming **symptomatic**, radiotherapy or chemotherapy are the treatments of choice.
- They don’t cure the lymphoma, they can alleviate the symptoms.
- Patients with these types of lymphoma can live near-normal lifespans, but the disease is **Incurable**.

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NHL: High-grade

- Treatment of the aggressive, forms of lymphoma can result in a cure in the majority of cases.
- However, the prognosis for patients with a poor response to therapy is worse.
- Treatment for these types of lymphoma typically consists of aggressive chemotherapy, including the **CHOP** or **R-CHOP** regimen.

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Small Lymphocytic Lymphoma

- 4% of all NHL
- Older age group
- Generalized lymphadenopathy with enlarged liver and spleen
- The only non-follicular low-grade lymphoma
- Prolonged survival
- But not treatable

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Follicular Lymphomas

- 20-40% of adult NHL
- Generally low grade
- Usually age > 50 years
- Characteristic t(14;18) in 90% of cases
- Generalized, painless, lymphadenopathy
- Spleen and marrow often involved at time of diagnosis (75%)
- Long natural history (6-8 years) - but not affected by treatment
- Treatment options: watchful waiting, purine nucleoside analogues, monoclonal antibodies to CD20.
- Becomes aggressive if progress to diffuse lymphoma - but still not treatable

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Diffuse Large Cell Lymphoma

- 50% of NHL (most common NHL)
- Most of B cell origin
- Dual age peak: twenties and sixties
- Rapidly enlarging, symptomatic mass at a single site
- Commonly extranodal: GI, skin, bone, brain, testis - although liver, spleen and marrow not often involved at presentation.
- Diagnosis: Typical immunophenotype- CD20+, CD45+ and CD3-
- Requires intensive therapy and CNS prophylaxis
- Curable in 50% or more of the cases
- Median survival: weeks to months if not treated

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Mantle Cell Lymphoma

- B-Cell tumor believed to arise from the mantle of the follicle (as opposed to the other lymphomas that arise from the middle)
- Older males: disseminated disease
- Aggressive and incurable
- T(11; 14) - cyclin D1 driven monoclonal expansion

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Lymphoblastic Lymphoma

- 40% of all childhood lymphomas: mostly males under 20 years
- High grade lymphoma; closely related to T-cell Acute Lymphocytic Leukemia - and treated accordingly
- Present with a rapidly progressive mediastinal mass (50-70%)
- Early bone marrow spread, and onward to blood and meninges

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Burkitt's Lymphoma

- Endemic in parts of Africa – presents with maxillary/mandibular mass
- North America – presents with a progressive abdominal mass
- Children and young adults (30% of childhood NHL)
- Fastest growing human neoplasm
- Intensive chemotherapy: 50% long term survival
- 20-30% risk of CNS involvement – provide intrathecal prophylaxis

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PTCL- Clinical presentation

- PTCL commonly presents with widespread dissemination

Clinical Characteristics (%) in the LNH87 Trial		
	PTCL (n = 288)	**B-Cell Lymphomas (n = 1595)**
Disseminated disease	78%	58%
B symptoms	57%	40%
Bone marrow positive	31%	17%
Skin lesions	21%	4%

- Clinical features alone are insufficient for the diagnosis of PTCL; biopsy of tissue involved is required to aid in diagnosis
  - » Different types of biopsies include excisional/incisional, fine needle aspiration, core needle, and bone marrow aspiration biopsies

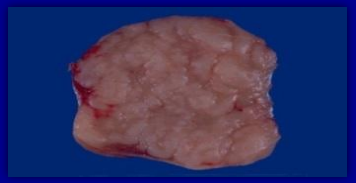
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Diagnosis of PTCL

- Differentiating PTCL from B-cell lymphoma early on is important due to differences in prognosis and treatment
- Diagnosis must be based on a combination of findings:

Clinical + **Histologic** + **Pheno/Genotypic**

- Immediate formalin fixation prevents certain immunophenotyping, flow cytometry, and cytogenetic studies from being able to be performed



Tissue biopsy

→



Histologic analysis

+



Pheno/genotypic analysis

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Common subtypes differential diagnosis

PTCL-NOS

Clinical Features
Lymph node enlargement,
B symptoms,
eosinophilia, pruritus

Rule out other diagnoses

Presentation

Median age
60

Stage III/IV
69%

Marrow +
22%

ALCL

Clinical Features
Peripheral and/or abdominal
lymphadenopathy with
B symptoms, high fever

IHC: CD30+; EMA+, CD25+, CD43+, ALK+/-

Presentation

ALK–	ALK+
Median age 58	Median age 34
Stage III/IV 58%	Stage III/IV 65%
Marrow + 7%	Marrow + 12%

AITL

Clinical Features
Lymphadenopathy,
rash, ascites
hepatosplenomegaly,
polyclonal
hypergammaglobulinemia,
pleural effusion, arthritis,
immunodeficiency

IHC: CXCL13+, PD1+, EBV+, BCL6+/-, CD10+/-

Presentation

Median age
65

Stage III/IV
89%

Marrow +
29%

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Staging evaluation for lymphoma (1)

- Pathologic documentation by hemopathologist
- Physical examination
- Documentation of B symptoms
- Laboratory evaluation
  - CBC, ESR
  - Liver function tests
  - Renal function tests
  - LDH, B_2M
  - Monoclonal protein
  - Viral tests (HIV, CMV, EBV, HCV, HBV)

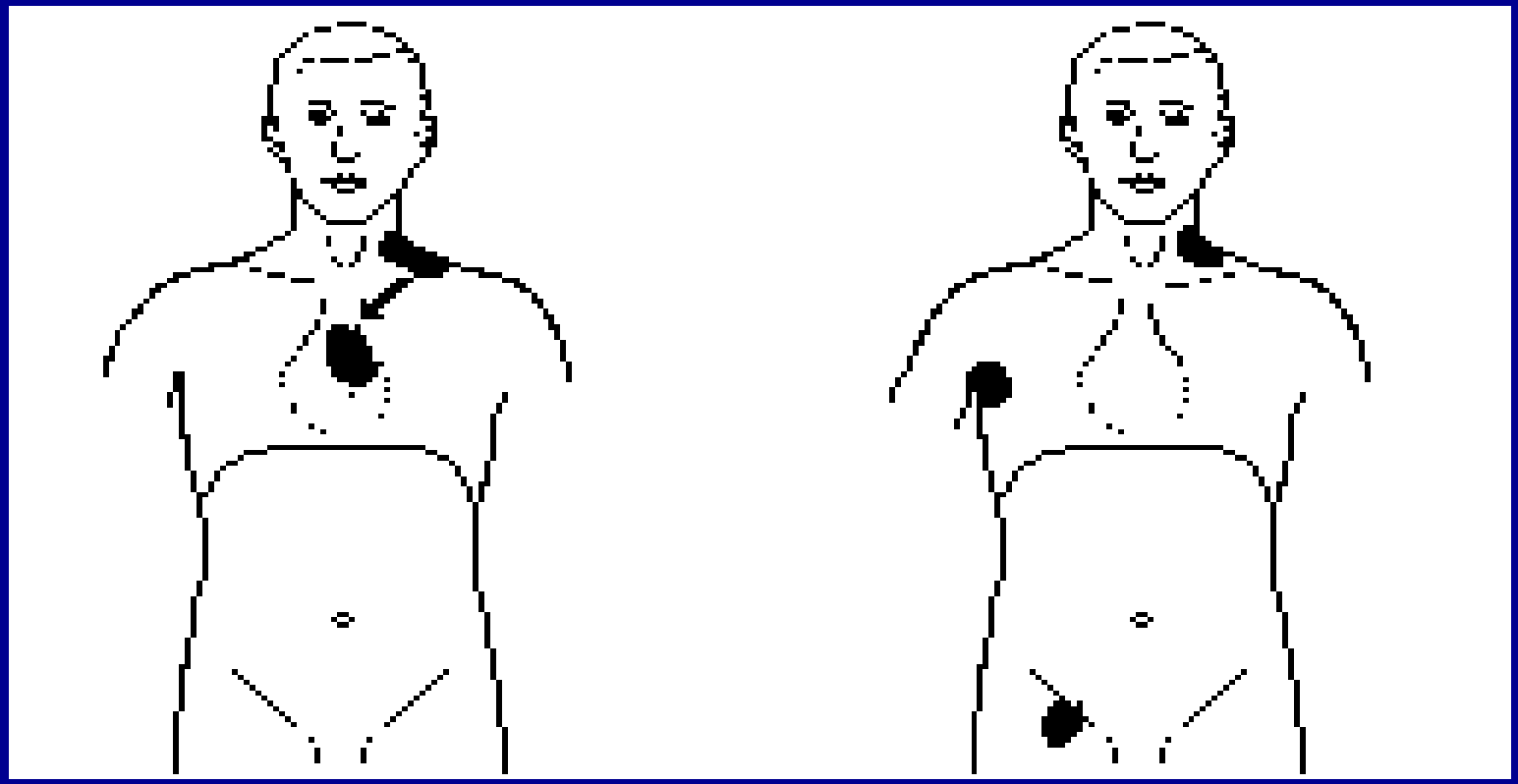
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Staging evaluation for lymphoma (2)

- **Laboratory evaluation**
  - **Chest radiograph**
  - **Ultrasonography**
  - **CT scan of chest, abdomen and pelvis**
  - **Bone marrow aspiration / biopsy**
  - **PET/CT**
  - **Endoscopy**
  - **Bone radiographs**
  - **MRI**
  - **Cell-surface marker phenotypic analysis**
  - **Cytogenetics / gene rearrangement analysis**

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Contiguous ve Non-contiguous Spread



HL

NHL

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Staging Classification

Ann Arbor

- **Stage I: involvement of single lymph node region or a single extralymphatic organ or site**
- **Stage II: involvement of two or more lymph node regions on same side of diaphragm or localized involvement of an extralymphatic organ or site**
- **Stage III: involvement of lymph node regions on both sides of the diaphragm or localized involvement of an extralymphatic**
- **Stage IV: diffuse or disseminated involvement of one or more extralymphatic organs with or without lymph nod involvement**

A. Asymptomatic

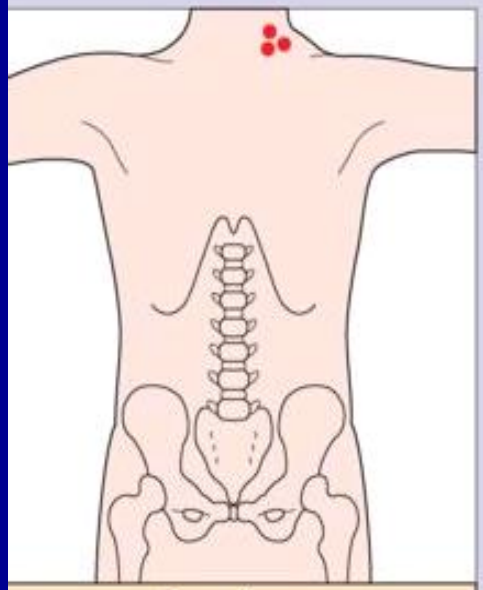
B. Symptomatic (B symptoms)

X. Bulky disease (> 1/3 widening of mediastinum, > 10cm max.dimension of nodal mass)

E. Involvement of a single, localised, extranodal site

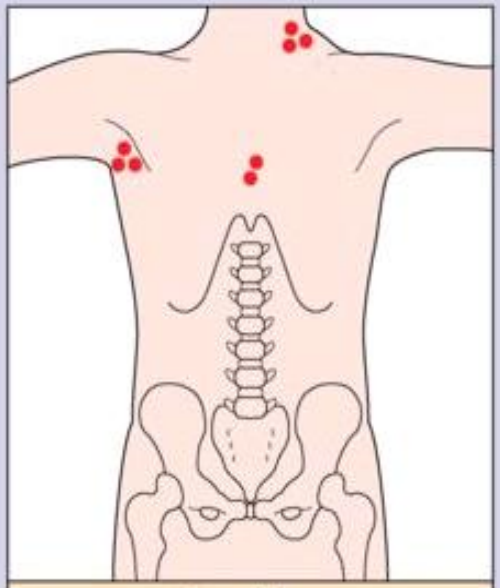
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Ann arbor staging system for hodgkin's disease and non-hodgkin's lymphomas



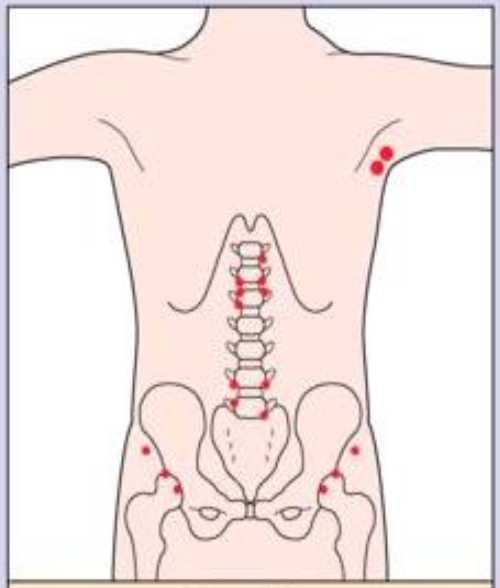
Stage I

- involvement of single lymph node region
- or involvement of single extralymphatic site (stage I_E)



Stage II

- involvement of ≥ 2 lymph node regions on same side of diaphragm
- may include localized extralymphatic involvement on same side of diaphragm (stage II_E)



Stage III

- involvement of lymph node regions on both sides of diaphragm
- may include involvement of spleen (stage III_S) or localized extranodal disease (stage III_E) or both (III_{E+S})

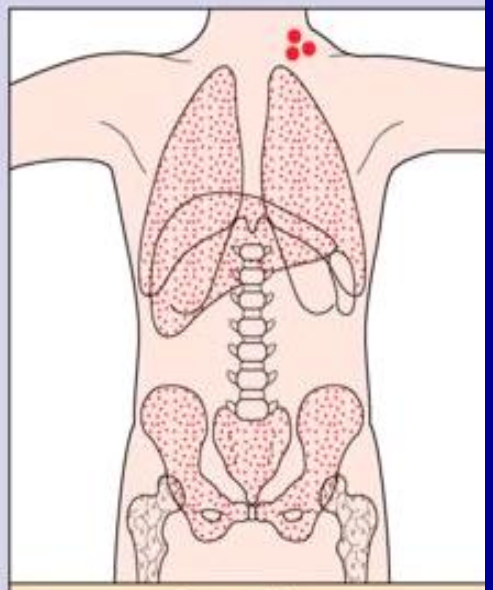
For Hodgkin's Disease:

III_1

- disease limited to upper abdomen – spleen, splenic hilar, celiac, or porta hepatic nodes

III_2

- disease limited to lower abdomen – periaortic, pelvic, or inguinal nodes



Stage IV

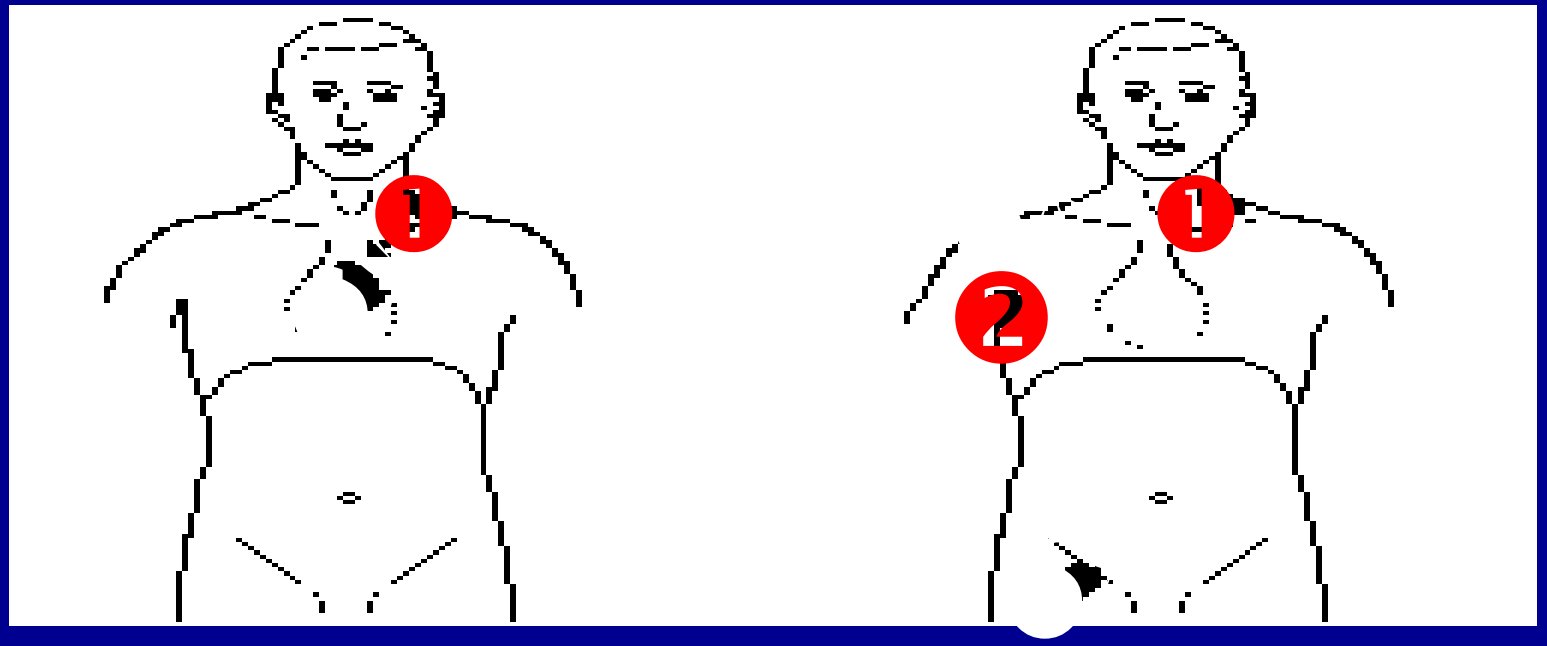
- disseminated (multifocal) extralymphatic disease involving one or more organs (e.g., liver, bone marrow, lung, skin), +/- associated lymph node involvement
- or isolated extralymphatic disease with distant (non-regional) lymph node involvement

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ANN –ARBOR STAGE

Single LN region

≥2 LN region on the same side of diaphragm



STAGE-1

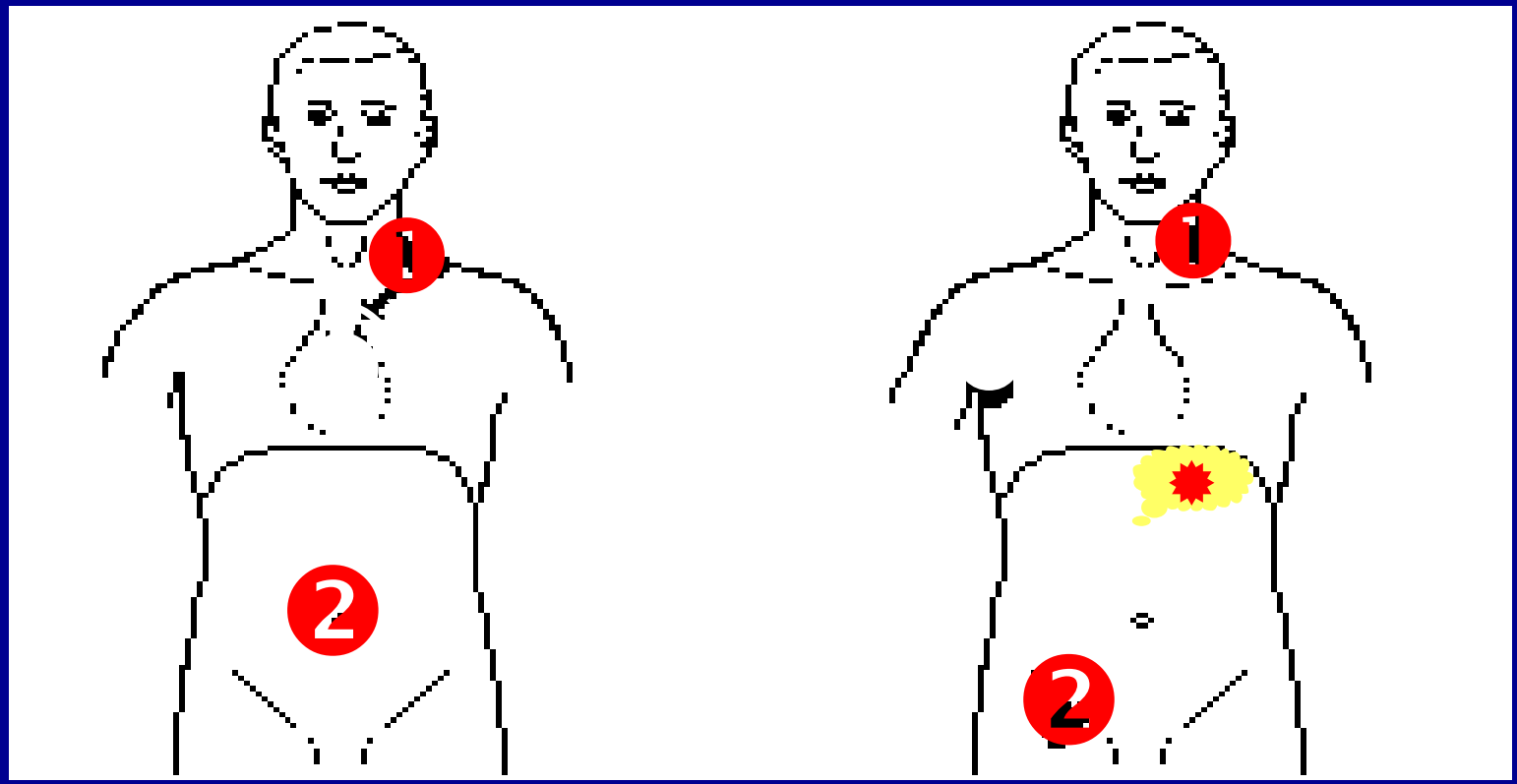
STAGE-2

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ANN –ARBOR STAGE

LN regions on both sides of diaphragm

LN regions on both sides of diaphragm + spleen



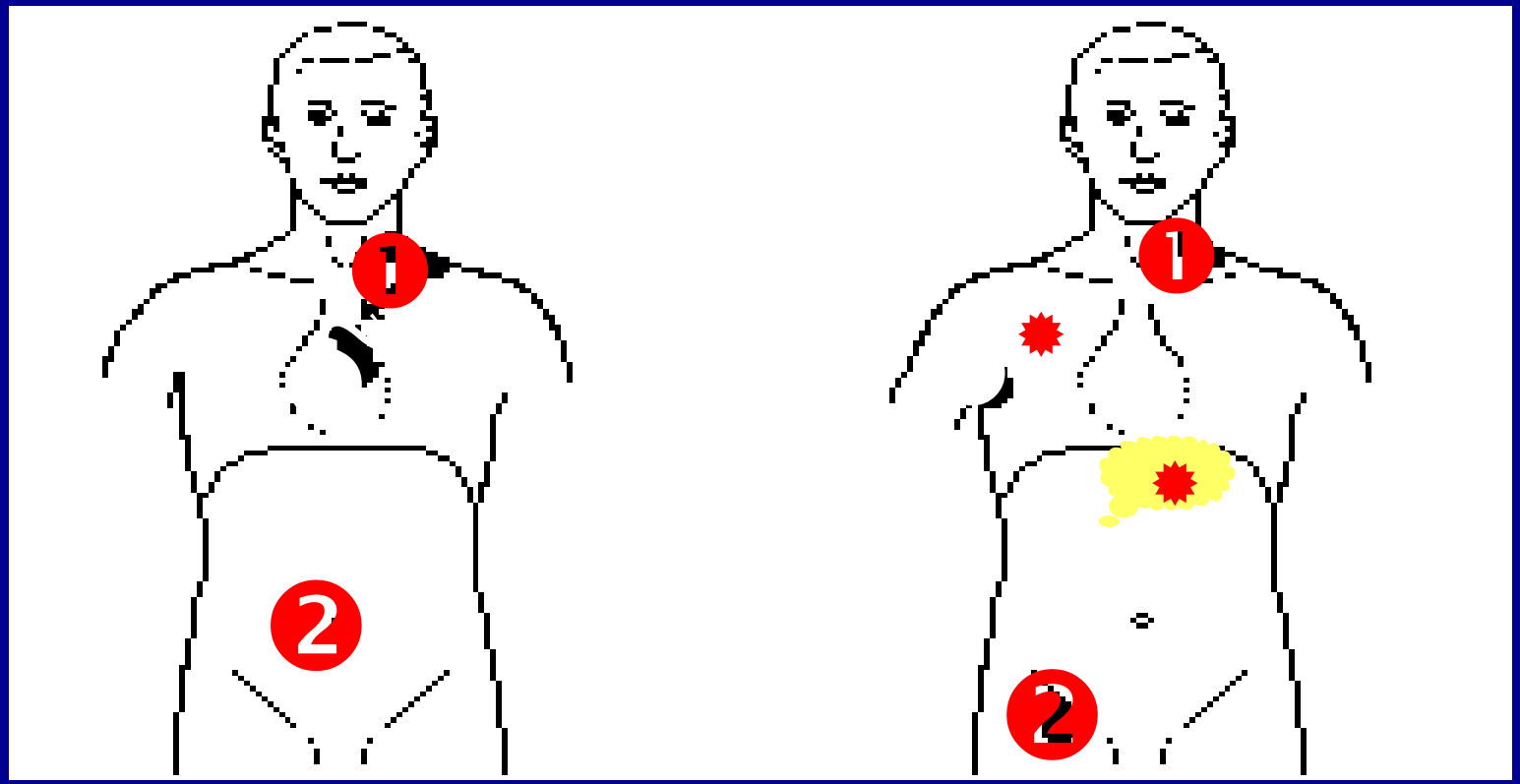
STAGE-3

STAGE-3S

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ANN –ARBOR STAGE

LN regions on both sides of
diaphragm + Extralymphatic disease



STAGE-3

STAGE-3SE

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NHL: Prognostic Factors - IPI

1. Age above 60 years
2. Disease stage III and IV
3. Extranodal involvement of more than 1 site
4. Serum LDH concentration >1 x normal
5. Performance status < 80%

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Treatment results of aggressive non-Hodgkin's lymphomas according to the risk group

Risk group	No of risk factor	CR %	5-year survival %
Low	0-1	87	73
Low intermediate	2	67	50
High intermediate	3	55	43
High	4-5	44	26

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NHL: Treatment

- Considerations:
  - Histopathology (i.e. SLL, MCL, or Burkitt)
  - Stage
  - Symptoms
  - Age
  - Comorbidities
  - Prognostic factors

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NHL: Treatment

- **Chemotherapy**
- **Radiotherapy**
- **Hematopoietic stem cell transplantation**
  - **Autologous**
  - **Allogeneic**
- **Radioimmunotherapy**
- **Immunotherapy**
- **Antibiotic therapy**

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NHL: Chemotherapy

- **Monotherapy**
  - Chlorambucil
  - Purin analogs (Fludarabine)
- **Polichemotherapy (± Rituximab)**
  - CVP
  - **CHOP**
  - CBV
  - ESHAP
  - DHAP
  - EPOCH
  - CODOX/IVAC
  - ProMACE-cytaBOM

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NHL: Treatment

- **Immunotherapy**
  - **Monoclonal antibodies**
    - **Anti-CD20 (Rituximab)**
    - **Anti-CD52 (Alemtuzumab)**
  - **Interferons**
  - **Interleukin 2**
- **Combination therapy**
  - **CHOP ± Rituximab**
- **Radioimmunotherapy**
  - **Zevalin : antiCD20+Y-ibritumomab tiuxetan**
  - **Bexxar: antiCD20+ I-tositumomab**

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NHL: Treatment

- Same principles of treating Hodgkin Lymphoma.
- The initial chemotherapeutic regimen is **CHOP**
  - Cyclophosmamide, hydroxy-adriamycine, oncovin and prednisolone
- CNS lymphoma is often treated with radiation in addition to Chemo.
- Relapses can be controlled with BM transplantation in high risk patients.
- Some pts express **CD-20** antigen in greater amount. In this case, monoclonal antibody **Rituximab** should be used.
- Rituximab is an anti-CD20 antibody that has limited toxicity and add survival benefit to the use of CHOP.

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NHL: Treatment

- Indolent – stage I and II (contiguous)
  - Involved field radiation
  - 10 year failure free survival: 50-60%
- Indolent – stage II, III, IV
  - Asymptomatic – deferral therapy with careful observation (early treatment does not improve prognosis)
  - Median progression in 4-6 years
  - Symptomatic: Purine nucleoside analogues (Fludarabine)
  - Oral alkylating agents (Cyclophosphamide)
  - Combination chemotherapy

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NHL: Treatment

- Aggressive – stage I and II (contiguous)
  - 3 cycles of CHOP followed by involved field radiation.
- Aggressive – stage II, III, IV
  - Combination chemotherapy (CHOP is better than ProMACE-CytaBOM, m-BACOD and MACOP-B; otherwise use a doxorubicin based regime)
  - Consider involved field radiation
  - Autologous/allogeneic hematopoietic stem cell transplantation

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NHL: Stem Cell Transplantation

1. Refractory disease
2. Relapse
3. High risk in CR1
   - ① T-cell lymphoma
   - ② Primary mediastinal B-cell lymphoma
   - ③ Mantle cell lymphoma
   - ④ Lymphoblastic lymphoma
   - ⑤ Burkitt's lymphoma

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Radiotherapy of aggressive NHLs

1) Exclusively in pathologic stage I and IE.
2) No indications for combined therapy.

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Non-Hodgkin's Lymphomas

RESPONSE CRITERIA FOR LYMPHOMA
(not including PET)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu (unconfirmed)	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Source: Table 2 from Cheson BD, Horning SJ, Coiffier B et al: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. J of Clin Oncol 17(4); 1999: 1244. Reprinted with permission from the American Society of Clinical Oncology.

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