Hodgkin's Lymphoma

Prof. Dr. Fevzi ALTUNTAŞ
Ankara Yıldırım Beyazıt Medical School
Department of Internal Medicine
Division of Hematology

Term-IV, 2020, Ankara

HL: Definition

- Neoplastic disorder with development of specific infiltrate containing pathologic Reed-Sternberg cells.
- It usually arises in lymph nodes and spreads to contiguous groups.
- Extranodal presentation are rare.
- Disease is associated with defective cellular immunity.

HL: Epidemiology

- 2-4 cases per 100.000 population / year
- Bimodal age distribution
  - 15-35 years and above 50 years
- Male predominance M:F = 1.7:1
  - Female predominance in NS type

HL: Risk factors

1) Certain *viruses*:

- *Epstein-Barr virus* (EBV)
- *Human immunodeficiency virus* (HIV)

2) Weakened immune system:

- *Inherited* condition
- Certain drugs used after an organ transplant

3) Age:

- Hodgkin lymphoma is most common among teens and adults aged 15 to 35 years and adults aged 55 years and older.

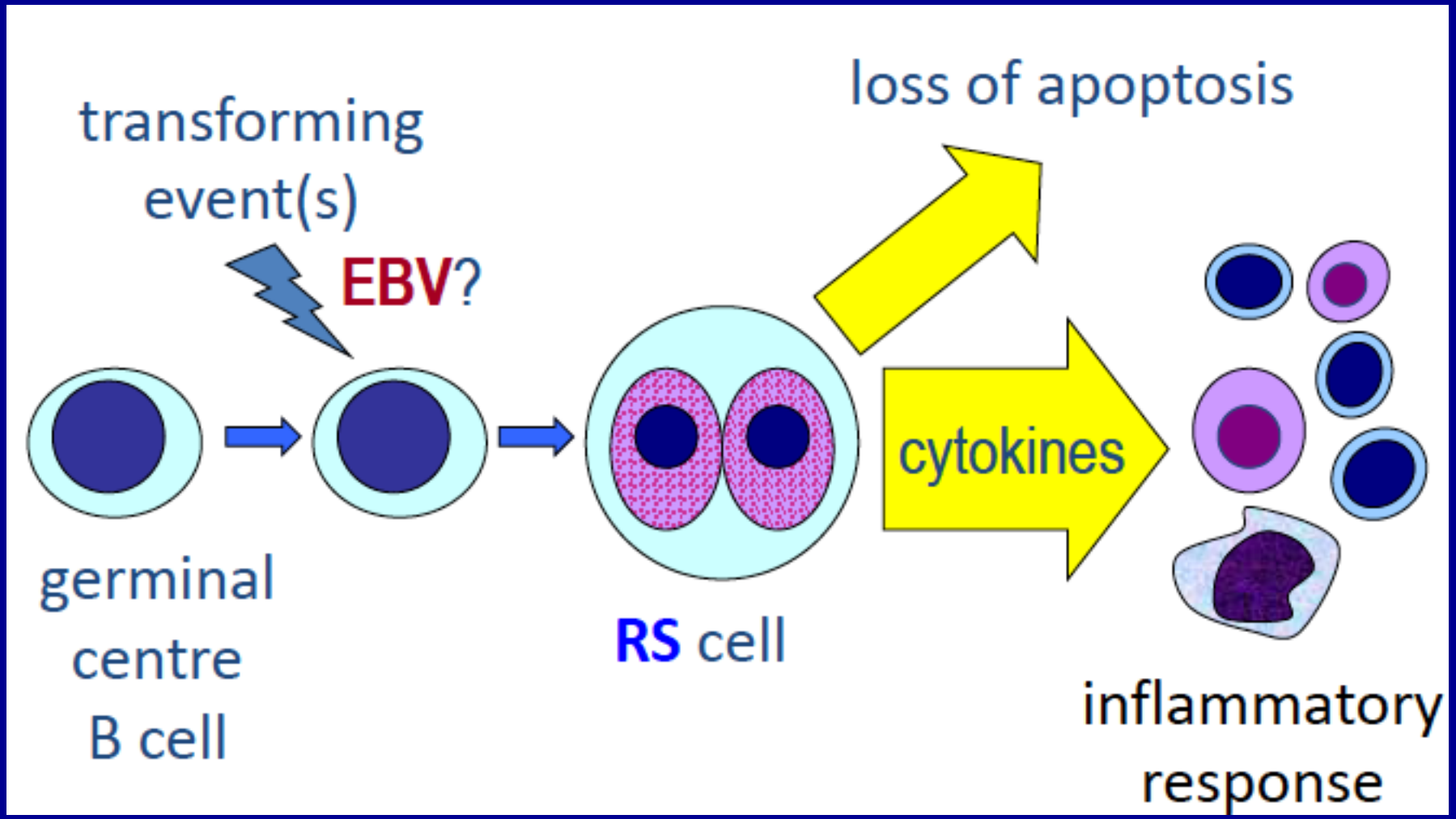
4) Family history:

- Family members, especially brothers and sisters, of a person with HL or other lymphomas may have an increased chance of developing this disease.

HL: Risk factors

- First degree relatives have five fold increase in risk for HL.
- Associated with EBV infection mainly with mixed cellularity type.
- Associated with Infectious Mononucleosis. Incidence is about 2.55 times higher.
- High socio economic status.
- Prolonged uses of human growth hormone.

HL: Pathogenesis

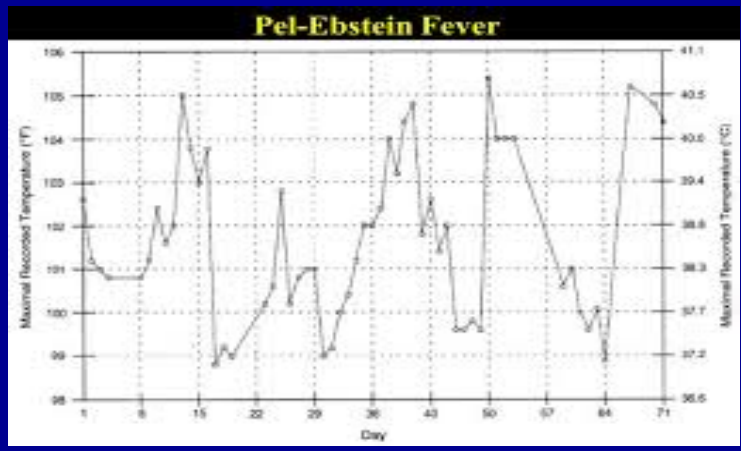


HL: Natural History

- Hodgkins lymphoma arises in a single node or a chain of nodes and spreads first to anatomically contiguous lymphoid tissue.
- Visceral involvement by HL may be secondary to extension from adjacent lymph nodes.
- Haematogenous spread occurs to liver or multiple bony sites.
- It rarely involves the gut associated lymphoid tissue such as Waldeyer ring and Peyers patches.
- Mechanism of spleen involvement is unclear but all pts with hepatic and bone involvement are associated with splenic involvement.

HL: Clinical features

- **Systemic symptoms (B symptoms)**
  - About 25-35% presents with B symptoms overall.
  - Only 15-20% of stage I-II have B symptoms like
  - **Fever >38 ° C**
    - May first present as fever of unknown origin.
    - Fever persists for days to weeks followed by afebrile intervals and then recurrence.
    - Such type of pattern is called Pel Ebstein Fever.
  - Drenching **Night sweats**
  - **Weight loss > 10% within 6 months.**
- Although pruritus is common in the disease it is not one of the ‘’B’’ symptoms.

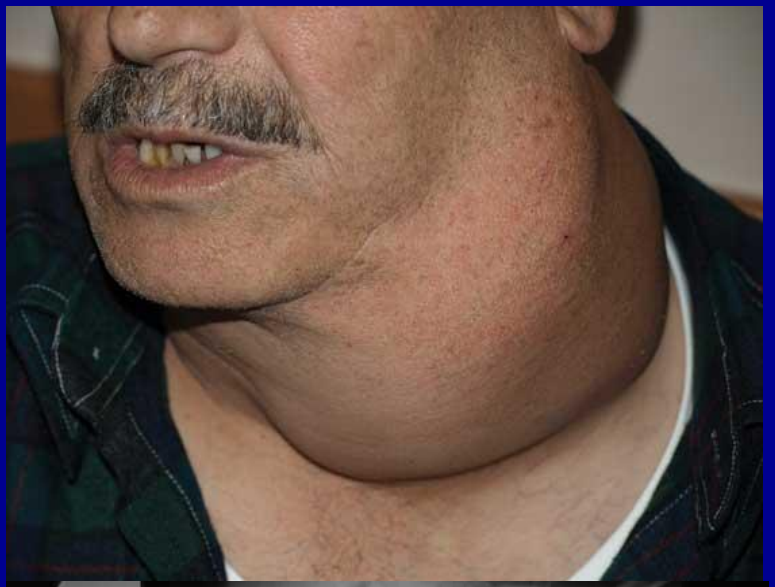


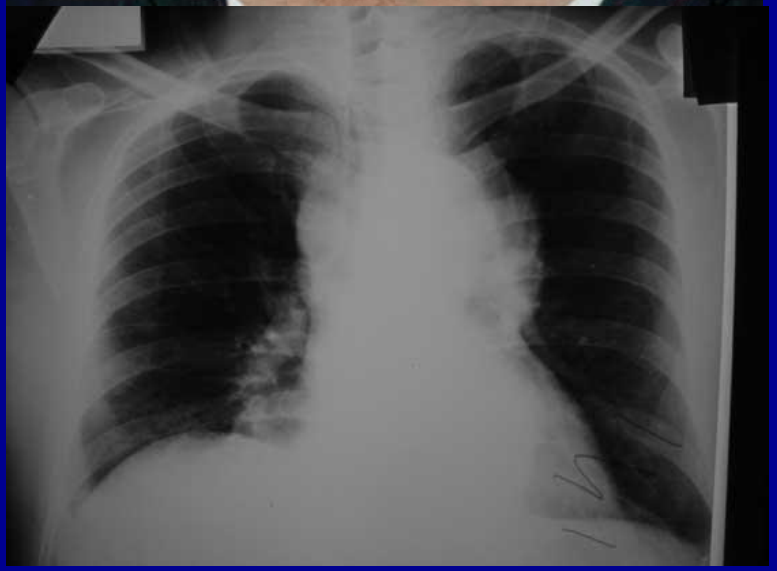
HL: Clinical features

Lymphadenopathy (LAP)

- Enlarged, painless, rubbery, non- erythematous, nontender lymph nodes are the hallmark of the disease.
- Painless & Mobile
- Cervical, supraclavicular and axillary lymphadenopathy are the most common initial signs of the disease.
  - Cervical, supraclavicular = 60-80%
  - Mediastinal adenopathy = 50% (NS type)
  - Axillary, inguinal, mediastinal, retroperitoneal, mesenteric, pelvic

❖ May become painful after drinking alcohol





HL: Clinical features

- **Extralymphatic sites may be involved such as:**
  - **Spleen**
  - **Liver**
  - **Bone marrow**
  - **Lung**
  - **CNS**

  Extralymphatic involvement is more common with NHL.
- **Emergency presentation:**
  - ❖ Infections
  - ❖ SVC obstruction (facial edema, increased JVP and Dyspnea)

HL: Clinical features

- Other less frequently symptoms are
  - Fatigue, weakness
  - Pruritus
  - Alcohol induced pain over involved lymph nodes
  - Cough, chest pain, shortness of breath, vena cava superior syndrome
  - Abdominal pain, bowel disturbances, ascites
  - Nephrotic syndrome
  - Erythema nodosum
  - Cerebellar degeneration
  - Immune hemolytic anaemia, Thrombocytopenia
  - Hypercalcaemia
  - Bone pain

HL: Laboratory

- CBC:
  - Anemia
  - Eosinophilia
  - Lymphopenia
  - Leukomoid reaction
  - Increased erythrocyte sedimentation rate & CRP
- Chemistries:
  - Hypoalbuminemia (<4 g)
  - LDH (associated with tumor burden – poor prognosis)
  - Serum copper, alkaline phosphatase, elevated levels of lysozyme
- Viral serology:
  - EBV may be present depending on tumor histopathology.

HL: Laboratory

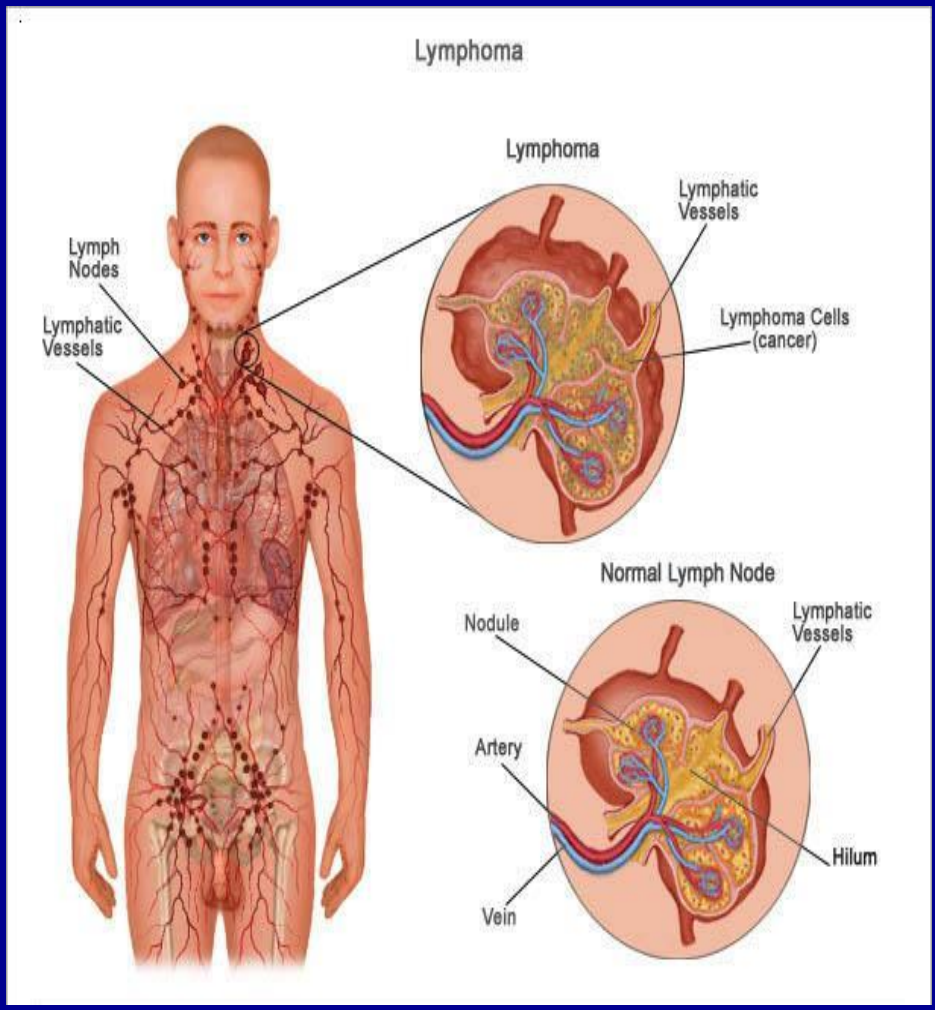
- Immunology
  - Impaired cellular immunity seen.
  - Humoral immunity is normal.
  - Anergy usually resolves in patients entered remission with treatment.
  - CD4 / CD8 ratio decreased.
  - Rarely ITP and Coombs (+) hemolytic anemia can be detected.

HL: Diagnosis

- **An excisional lymph node biopsy is the essential first step in diagnosis.**
- A biopsy is the only sure way to diagnose HL.
- The biopsy can be:
  - 1) Excisional biopsy
  - 2) Incisional biopsy
  - 3) Fine needle aspiration usually cannot remove a large enough sample for the pathologist to diagnose HL.
- **After that the most important step is to determine the extent of the disease because the stage will determine the nature of the therapy, that is, radiation vs. chemotherapy.**

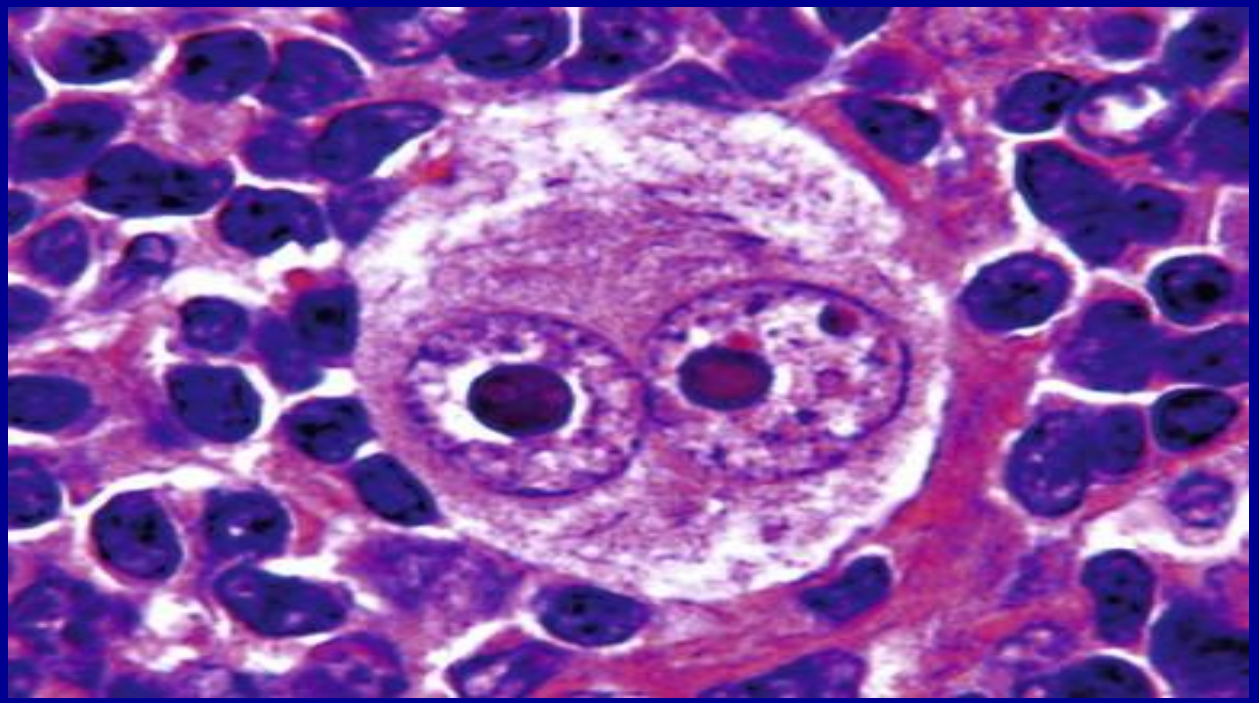
HL: Diagnosis

For the diagnosis of Hodgkin's lymphomas the histological examination of a lymph node is necessary!



HL: Diagnosis

- Based on microscopic examination of lymph node or other involved tissue
- **Malignancy of B-lymphocytes.**
- It requires identification of diagnostic **Reed-Sternberg cells.**



Dorothy Reed and Carl Sternberg first described the malignant cells of Hodgkin lymphoma call Reed Sternberg cells.

HL: Classification- WHO

I. Nodular lymphocyte predominant Hodgkin's Lymphoma

II. <u>Classical Hodgkin's Lymphoma</u>

1) Lymphocyte rich (LR)
2) Nodular sclerosis (NS)
3) Mixed cellularity (MC)
4) Lymphocyte depletion (LD)

HL: Classification- WHO

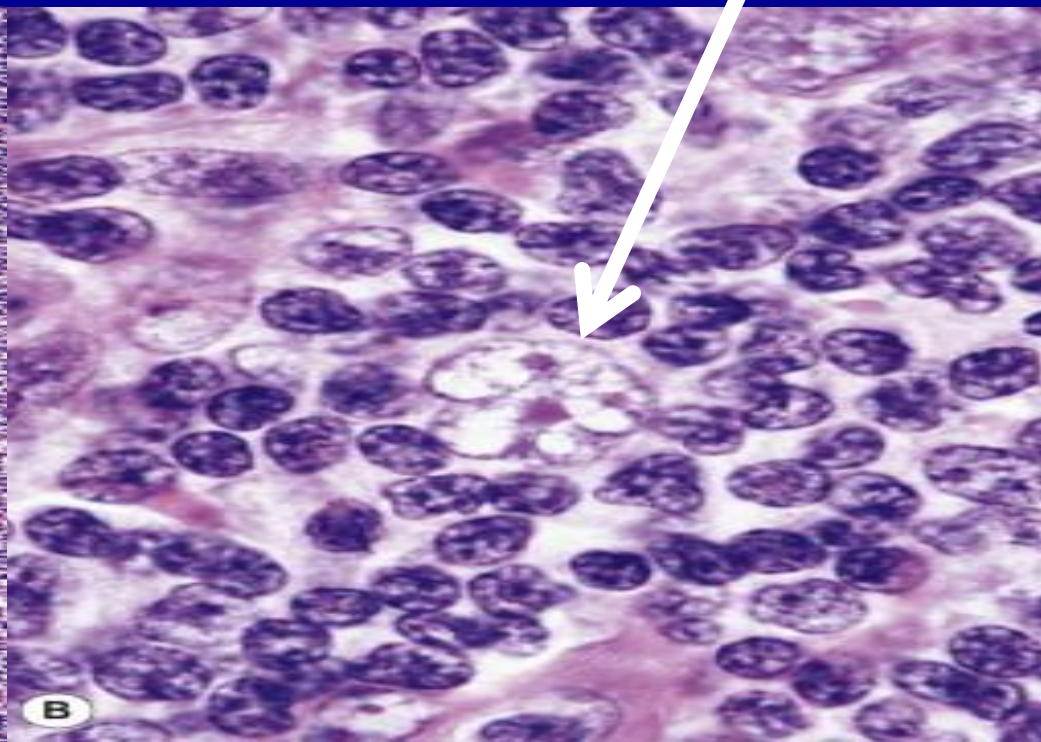
- **"Nodular sclerosis" is most common in west countries.**
- **"Mixed cellularity" is most common in Turkey.**
- Lymphocyte-predominant has the **Best prognosis**.
- Lymphocyte-depleted has the **Worst prognosis.**

HL: Immunophenotyping

	LP HL	Classical HL
J Chain	+	–
CD20, CD79a	+	–/+
CD15	–	+/–
CD30	–	+
Restin	–	+
Perforin, TIA-1	–	+
CD138 (Syndecan)	–	+
	L&H	H-RS

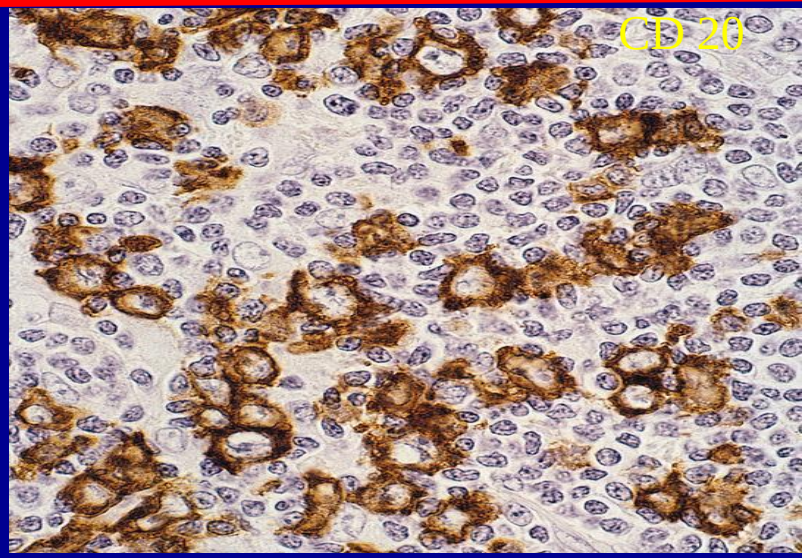
Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)

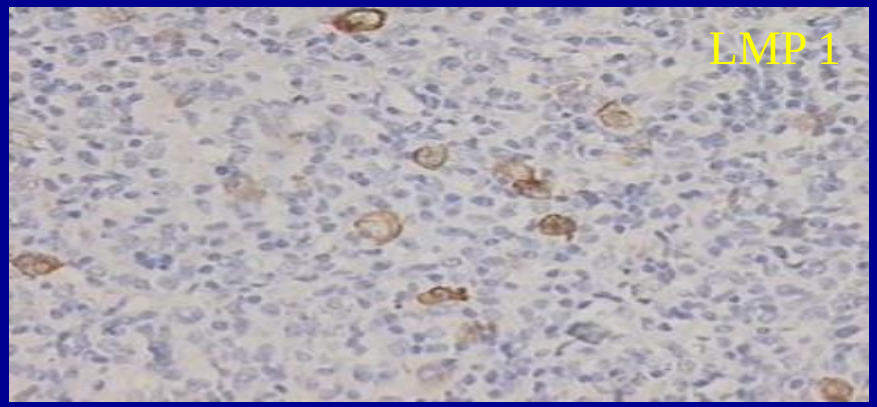
- Neoplastic cells known as LP cells or lymphocyte predominant cells
- Background- small lymphocytes, histiocytes, epithelioid histiocytes, plasma cells
- Neutrophils and eosinophils are <u>not</u> seen.

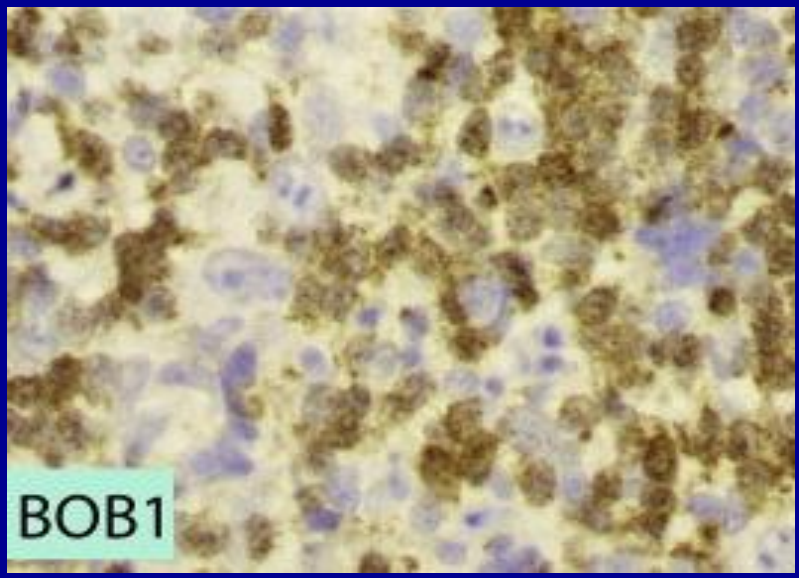


NLPHL - IHC markers

- Positive for CD 20, CD79a, CD75, BCL6, CD45 in all cases.
- EMA in >50% of cases.
- Ig heavy chains and light chains positive.
- LP cells ringed by CD 4+, CD 57+, T cells and small B cells.
- LP cells negative for CD 15, CD 30.

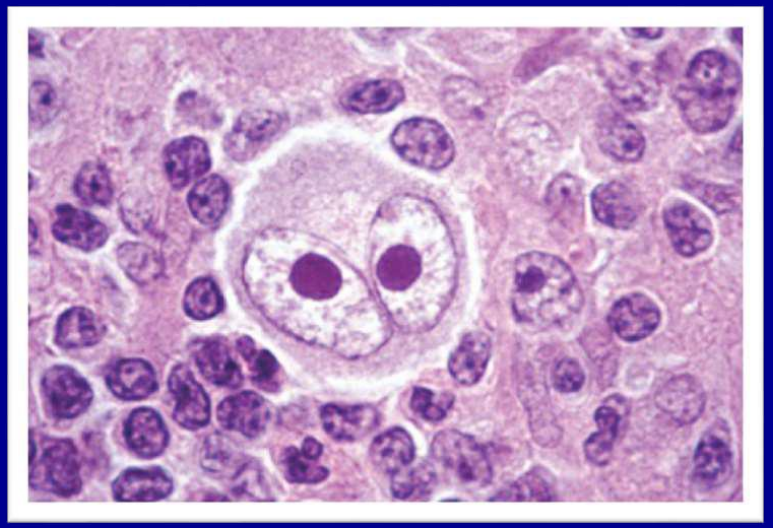






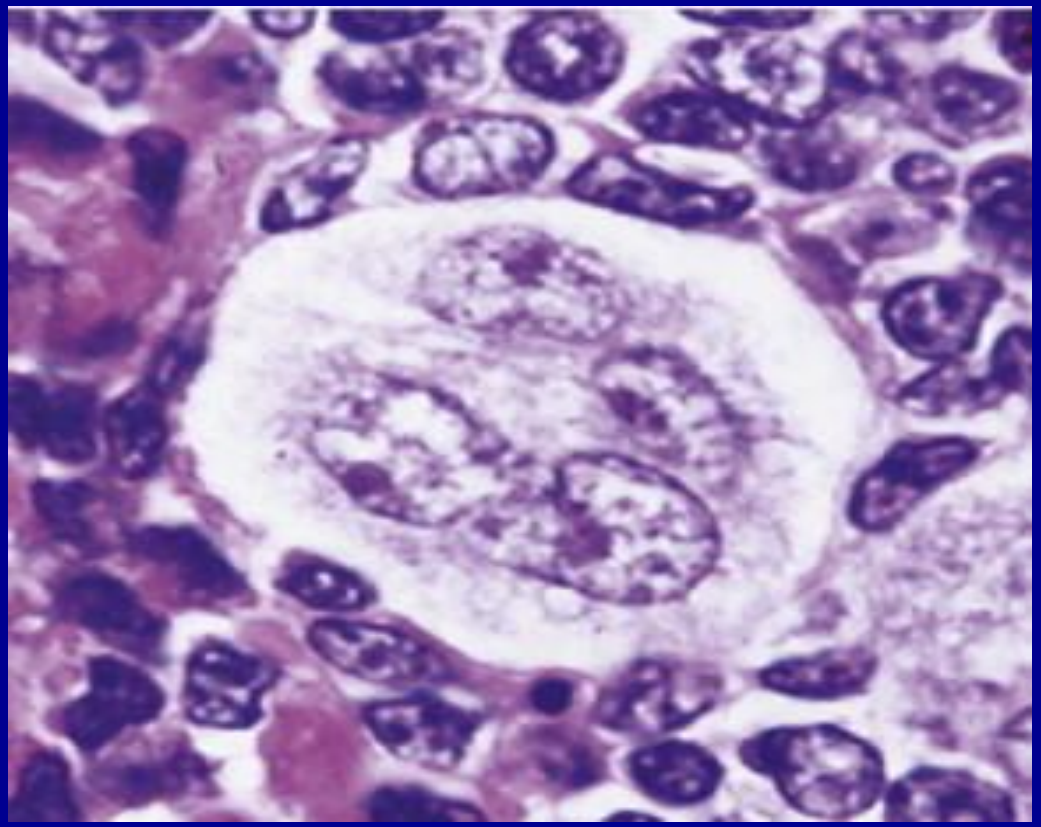
Classical HL

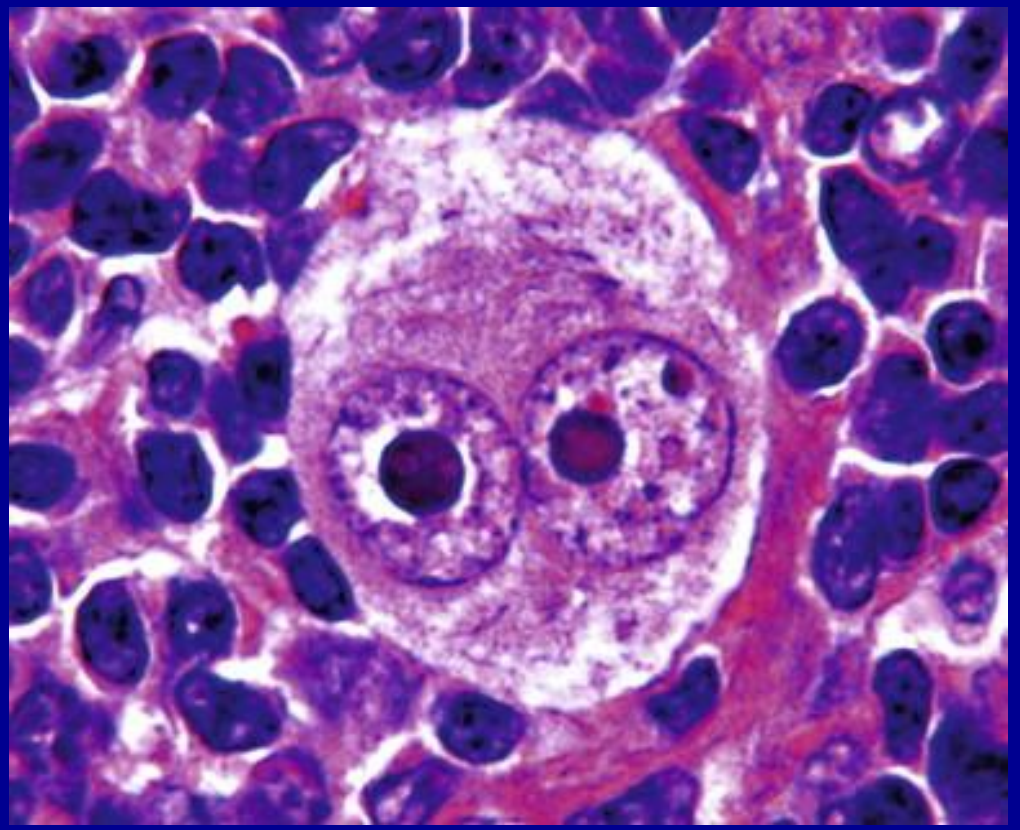
- Mononuclear Hodgkin cells and multinucleated RS cells (HRS)
- Background of small lymphocytes, histiocytes, plasma cells, eosinophils, neutrophils, collagen fibres, fibroblasts.
- Large cells (>45um in diameter) with classically binucleate or bilobed central nucleus each with a large acidophilic central nucleoli surrounded by a clear halo. "**owl's eye appearance**"
- Variants: mononuclear (Hodgkin's cell), mummified cell, lacunar cell, L/H cell.



Red-Sternberg cells

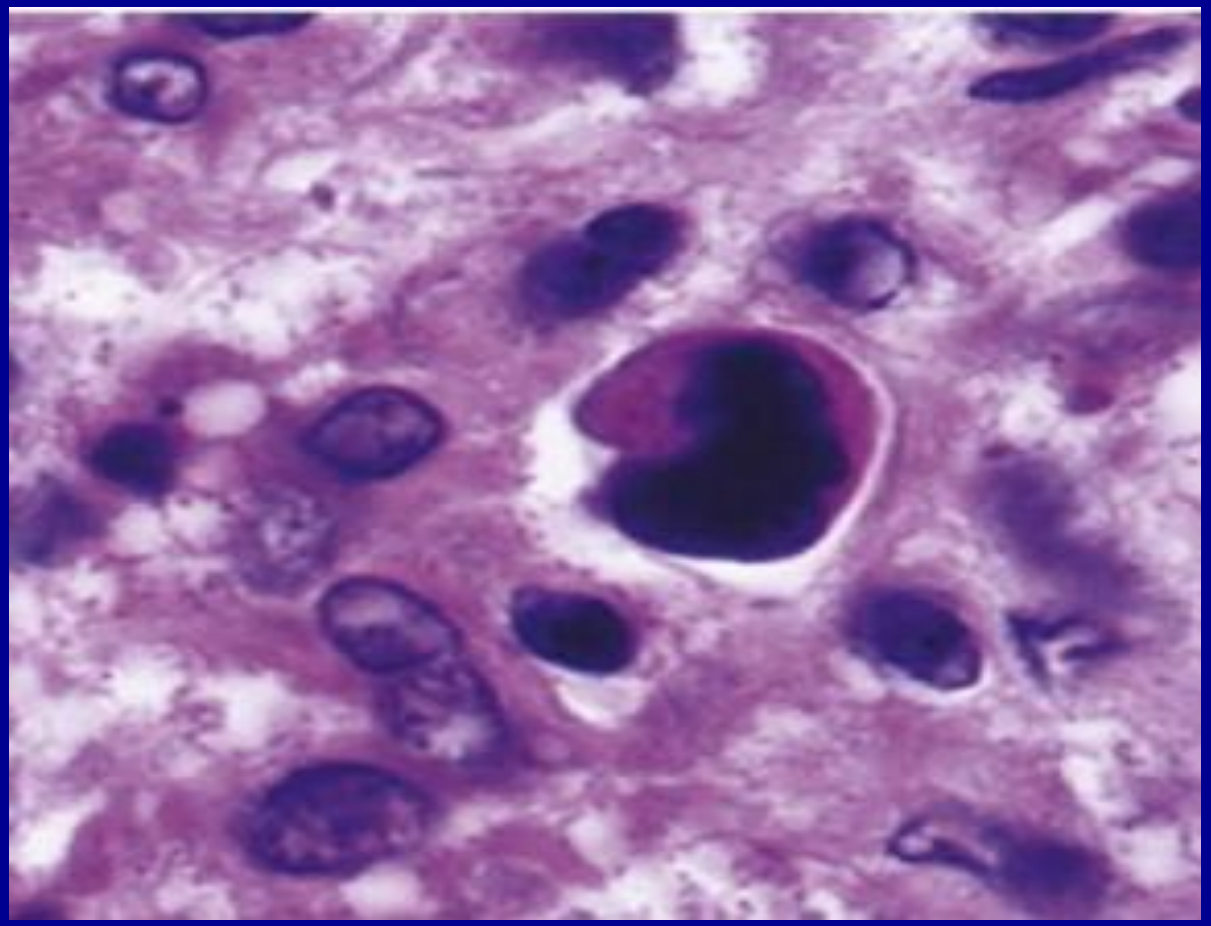
HRS: cells with *mirror image* nuclei and prominent, eosinophilic, inclusion - like nuclei.





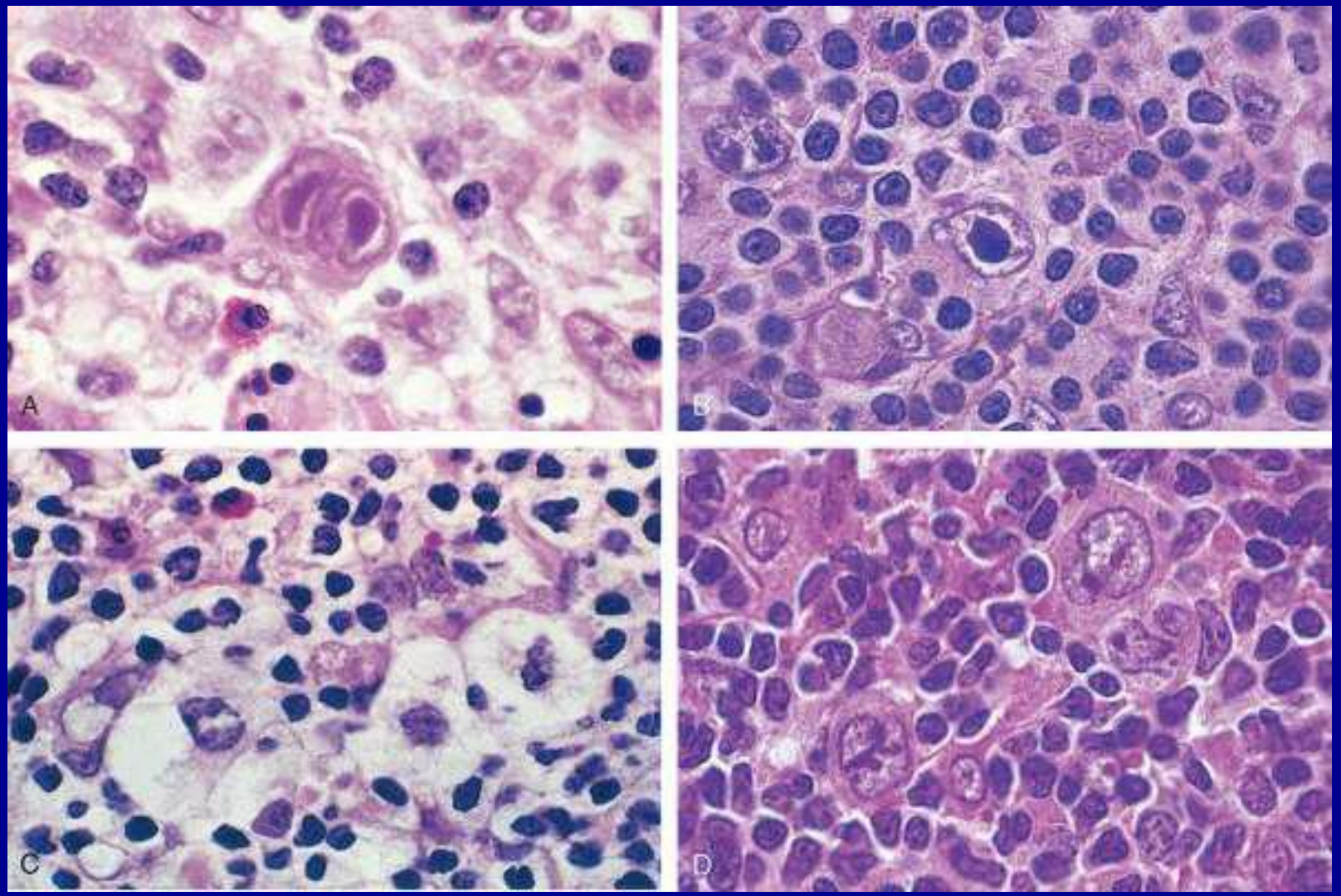
Red-Sternberg cells

The cell has a "**mummified**" appearance.



Red-Sternberg cells

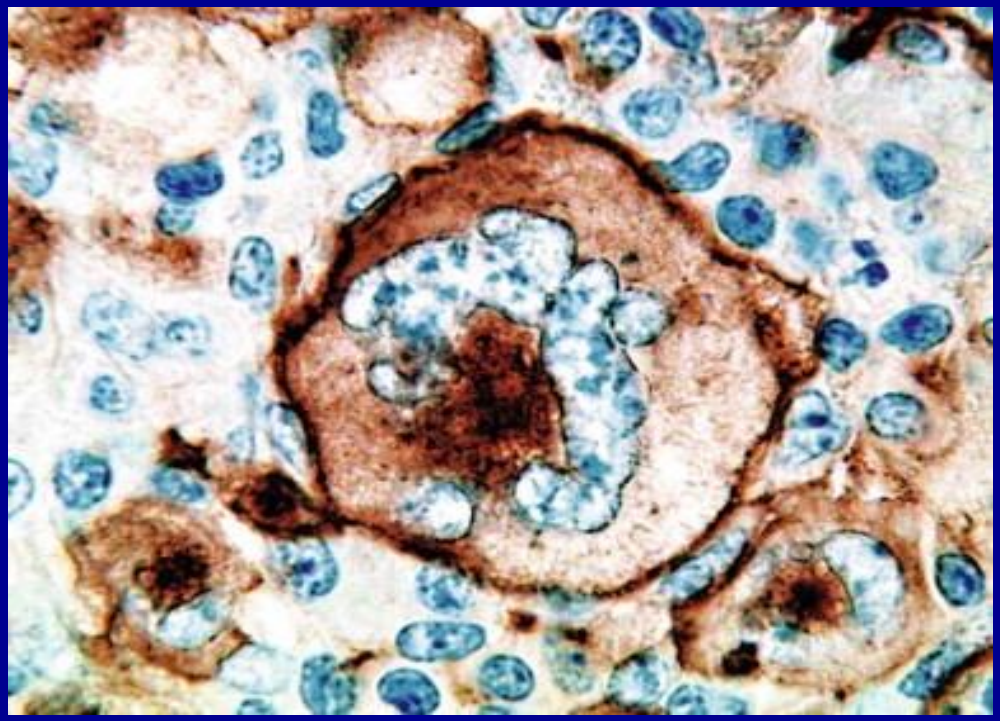
Reed–Sternberg cells variants



Classical HL - IHC markers

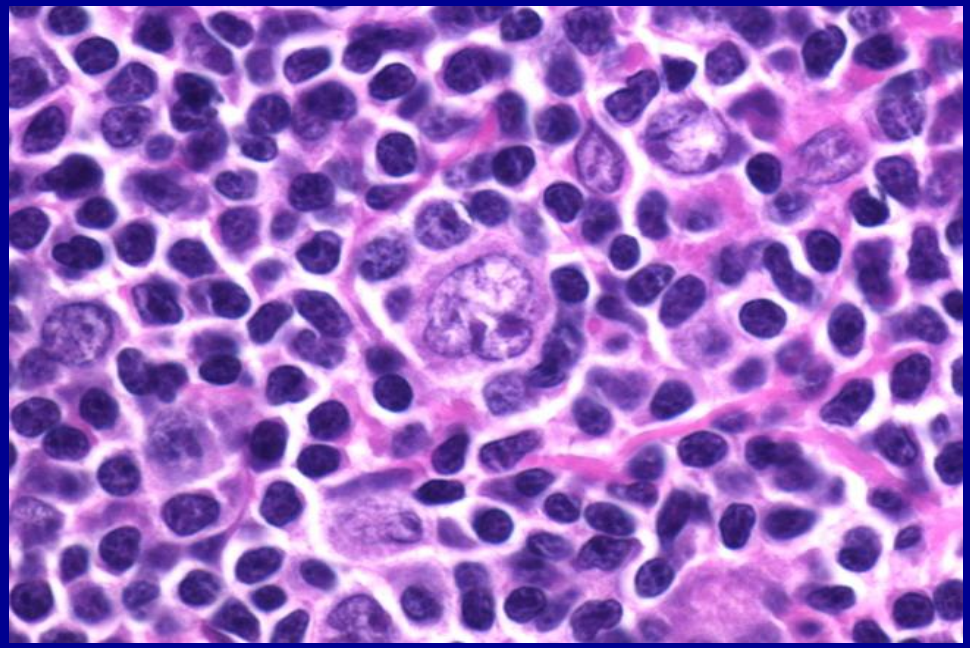
- Positive for
  - CD 30 (all cases)
  - CD 15 (75- 80% of cases)
  - Ki 67
  - CD 25
- Negative for
  - CD45 , CD75 and CD68.
  - Pan B, S-100, keratin

➢ EMA weakly positive.



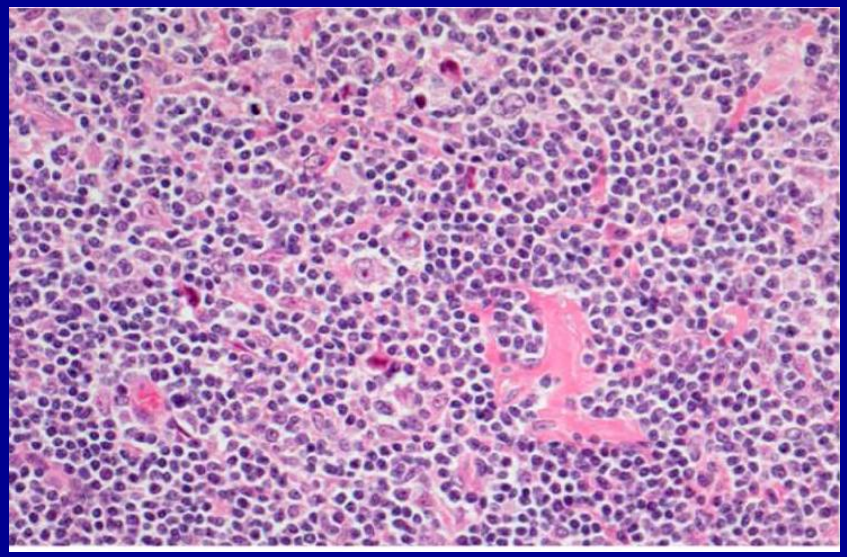
Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)

- < 5% of Hodgkins lymphoma
- Mainly involves cervical, axillary or mediastinal
- "L&H" cells or Popcorn cells are seen
- Positive for CD20, CD45
- Negative for CD15, CD30, EBV



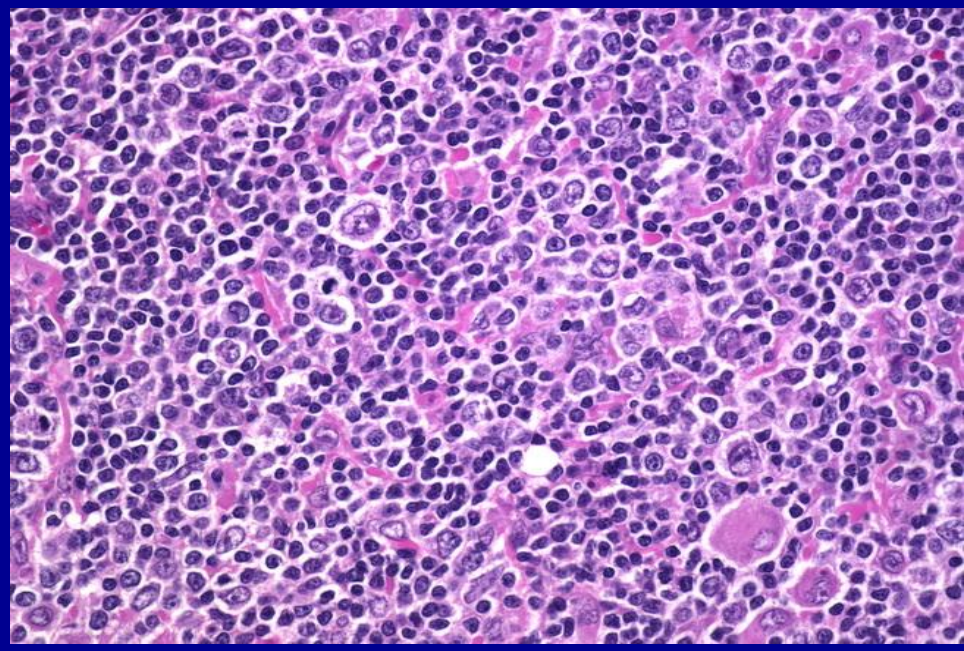
Lymphocyte Rich

- This is an uncommon form of classical HL
- Tends to be seen in older adults
- M > F
- RS cells CD15+, CD30+; 40% EBV+
- Reactive lymphocytes make up the vast majority of the cellular infiltrate.
- In most cases, involved lymph nodes are diffusely effaced, but vague nodularity due to the presence of residual B-cell follicles is sometimes seen.
- Very good to excellent prognosis



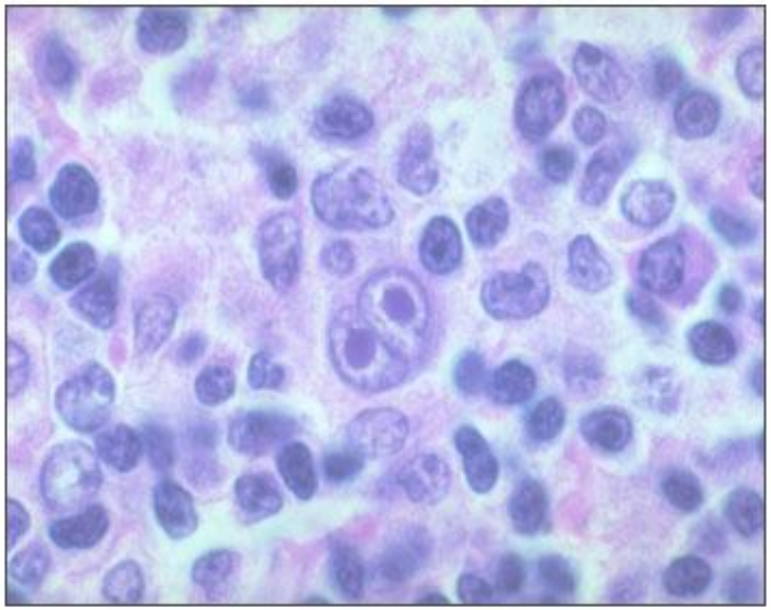
Nodular Sclerosis

- Most common type diagnosed.
  - About 70%
- Lacunar cells are seen
- CD 15 and 30 positive
- EBV negative
- Only subtype without a male predominance
- Seen in younger pts with stage I –II disease



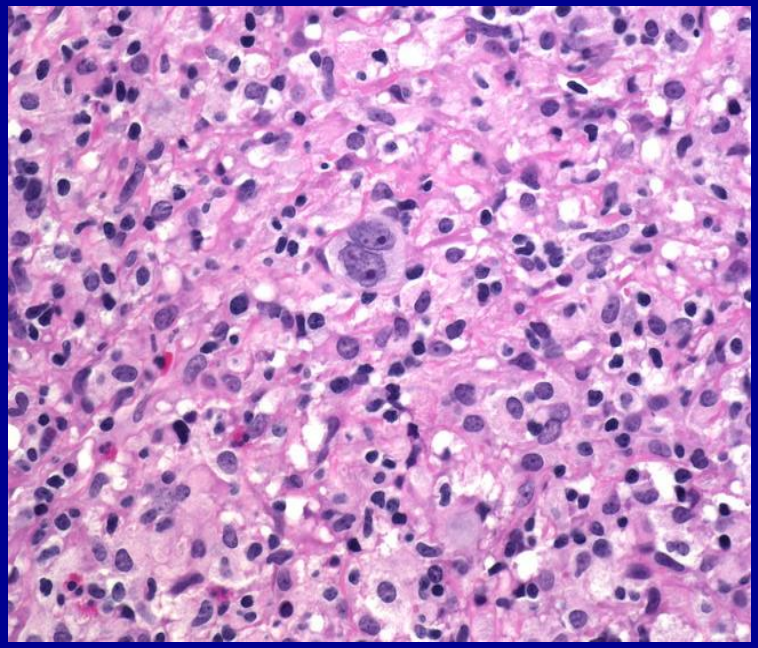
Mixed Cellularity

- Constitutes about 20%
  - Most common type diagnosed in Turkey
- More common in young children
- CD 15, CD30, EBV positive
- Presents in advanced stages
  - >50% as stage III/IV
- Tendency to involve spleen, bone marrow
- CD15+, CD30+, EBV+



Lymphocyte Depleted

- Constitutes <5%
- Worst prognosis of all subtypes
- Older males
- Advanced stage, Stage IV
- Present as febrile illness with pancytopenia, hepatomegaly, and no peripheral lymphadenopathy.
- The biologic hallmark of LD-HL is a collapse of cell-mediated immunity.
- RS cells CD15+, CD30+; most EBV+
- HIV infection



Staging evaluation (1)

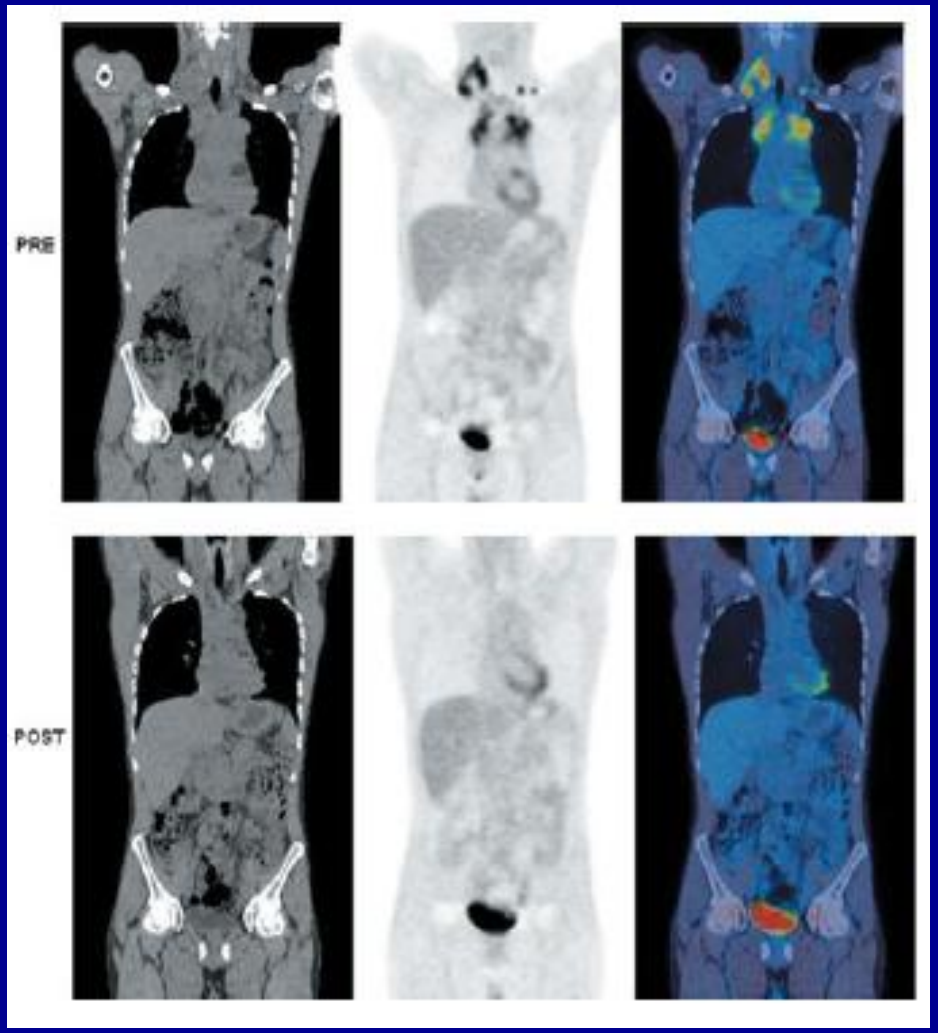
- Essential
  - Pathologic documentation by hemopathologist
  - Physical examination
  - Documentation of B symptoms
  - Laboratory evaluation
    - CBC, ESR
    - Liver function tests
    - Renal function tests
    - LDH
  - Chest radiograph
  - Ultrasonography
  - CT scan of chest, abdomen and pelvis
  - PET
  - Bone marrow aspiration / biopsy (bilateral)

Staging evaluation (2)

- **Essential under certain circumstances**
  - **Liver biopsy**
  - **Technetium bone scan**
  - **MRI**
  - **Staging laparotomy**
- **Useful but not essential tests**
  - **Cell-surface marker phenotypic analysis**
  - **Gene rearrangement analysis**

PET SCAN

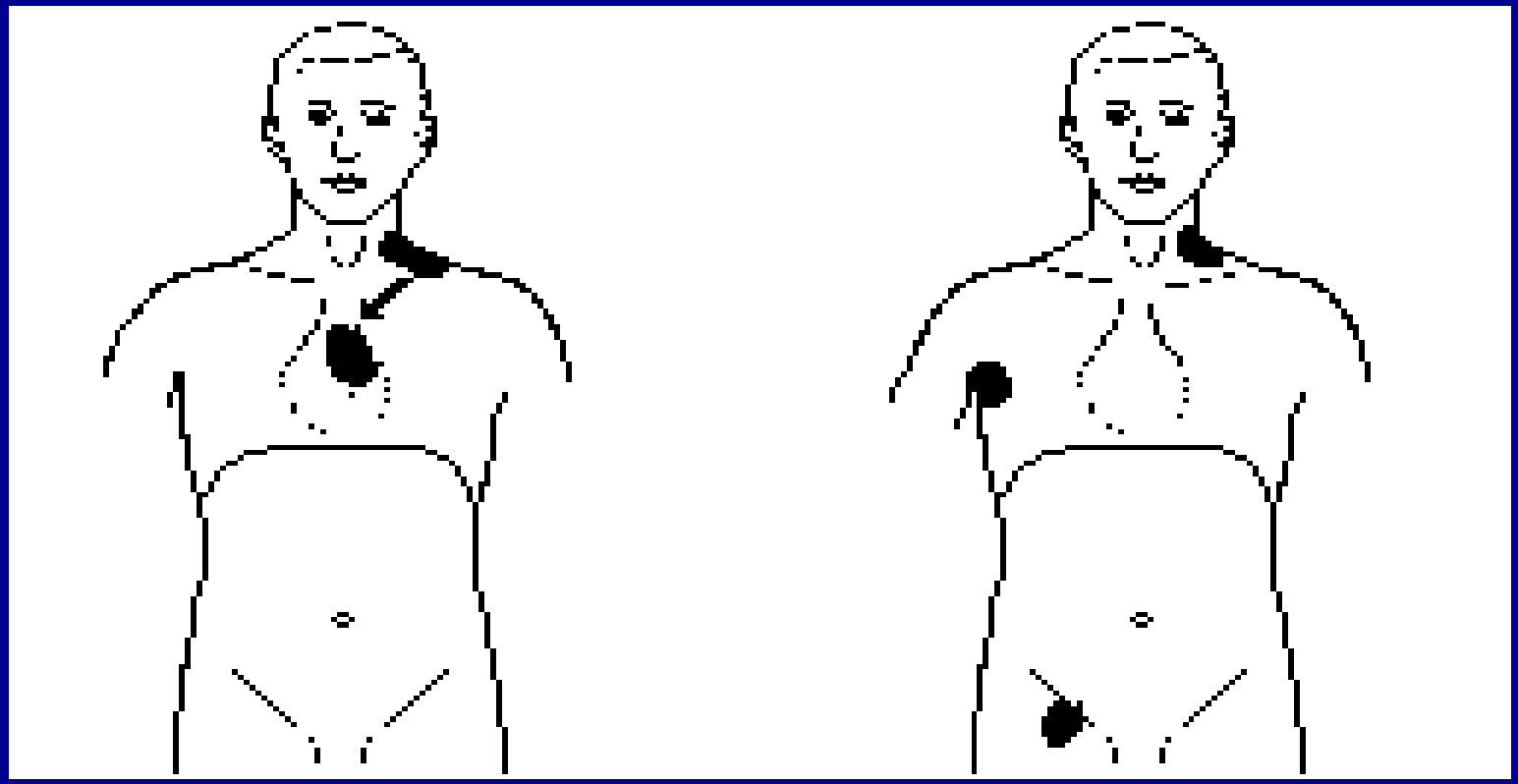
- PET Scan has become an integral component of initial staging.
- Information provided by PET has been recently incorporated in the lymphoma guidelines for response evaluation after completion of treatment.
- Useful for follow up study to evaluate residual masses , dx of early recurrence and predicting outcome.
- It has a specificity of 90-95%.



Bone Marrow Biopsy

- Less commonly put into practice
- Overall involvement of bone marrow in Hodgkins lymphoma is 5%.
- Indicated in patients with
  - B symptoms
  - Clinical evidence of sub diaphragmatic disease
  - Stage III-IV
  - Recurrent disease

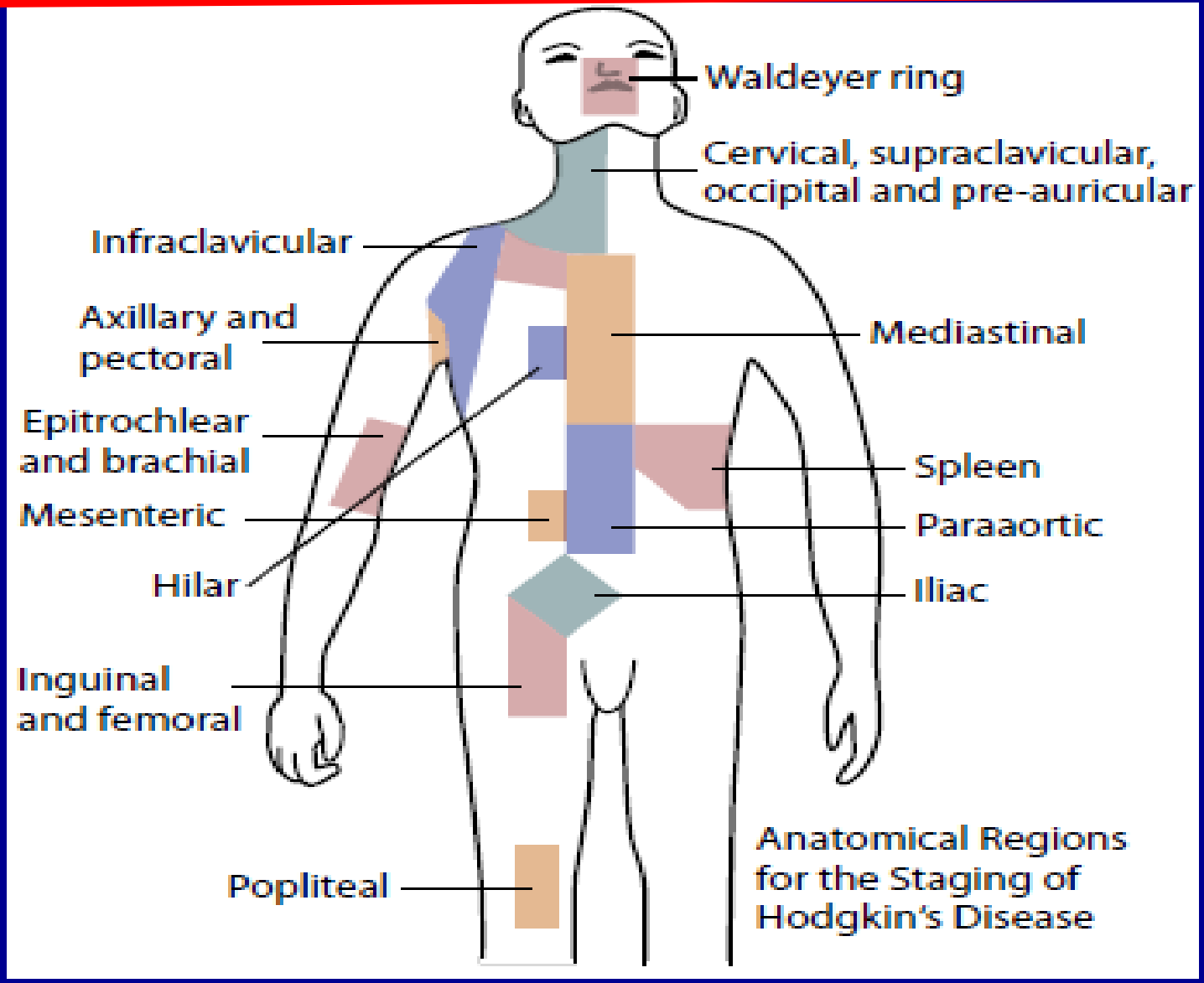
Contiguous ve Non-contiguous Spread



HD

NHL

Lymph nodes group



Staging

Ann Arbor modified by Cotswolds

- Stage I: involvement of single lymph node region or lymphoid structure
- Stage II: involvement of two or more lymph node regions on same side of diaphragm
- Stage III: involvement of lymph node regions or structures on both sides of diaphragm

  III_1: with splenic hilar,celiac,portal nodes

  III_2: with para-aortic, iliac, mesenteric nodes
- Stage IV: involvement of extranodal site(s)

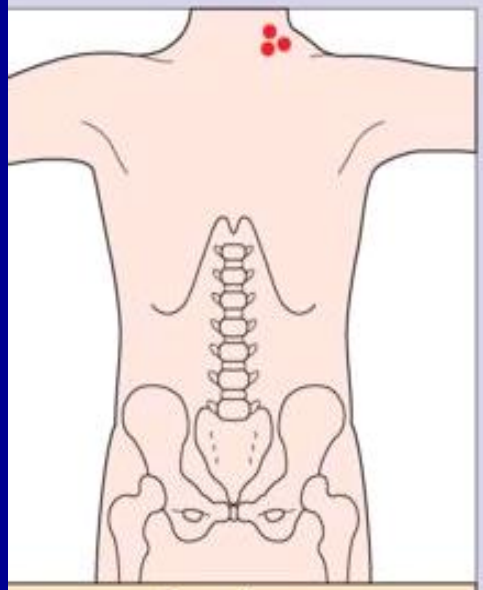
A. Asymptomatic

B. Symptomatic (B symptoms)

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

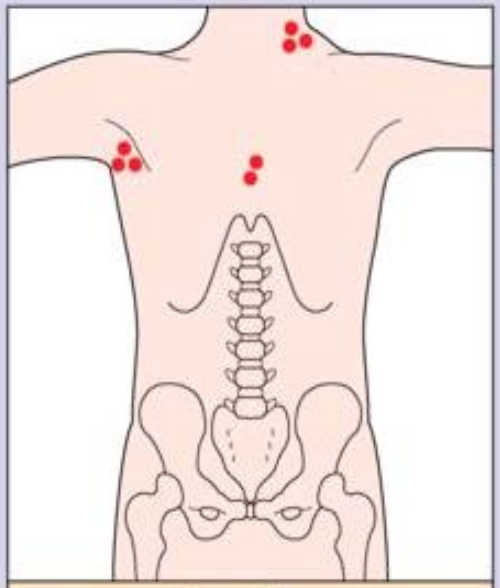
E. Involvement of a single, localised, extranodal site

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



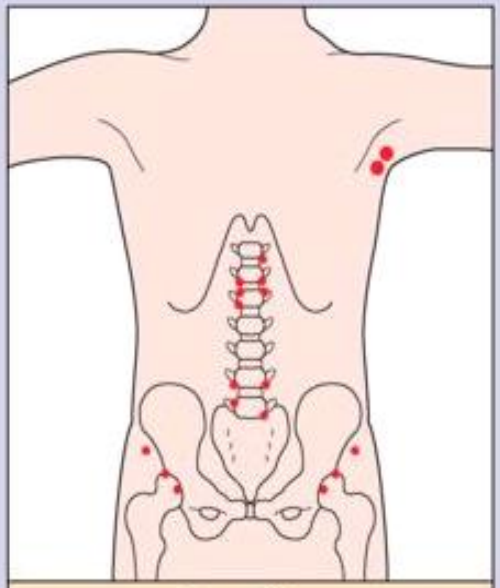
Stage I

- 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})

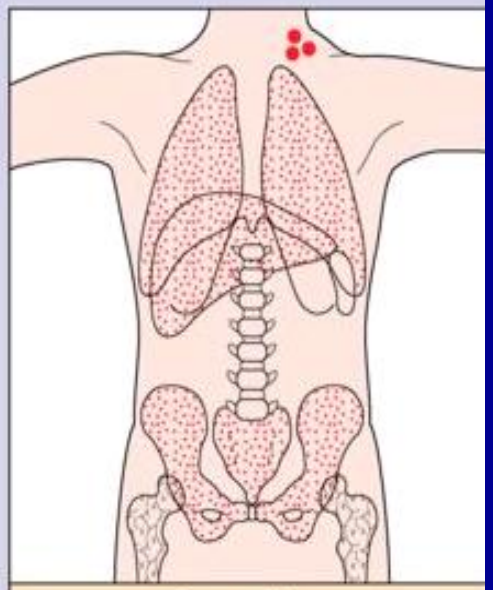
For Hodgkin's Disease:

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



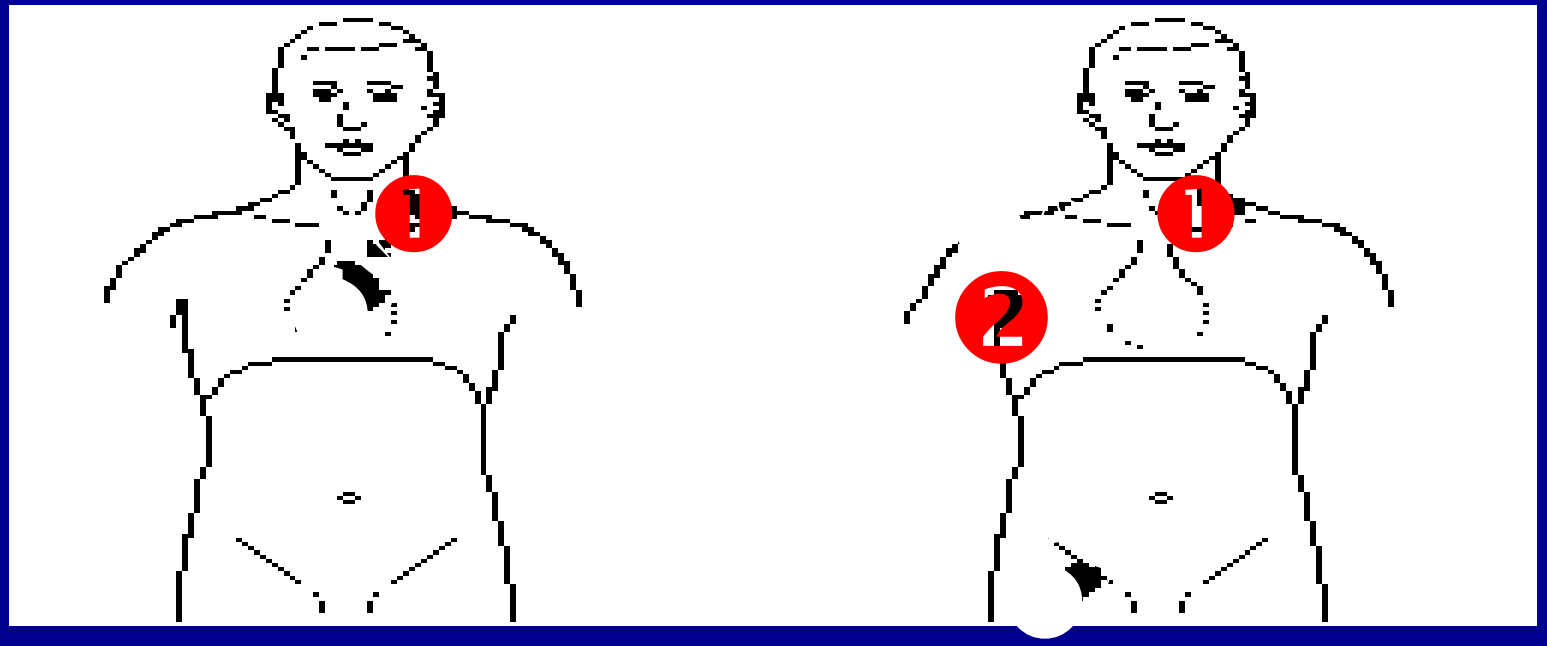
Stage IV

- 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

ANN –ARBOR STAGE

Single LN region

≥2 LN region on the same side of diaphragm



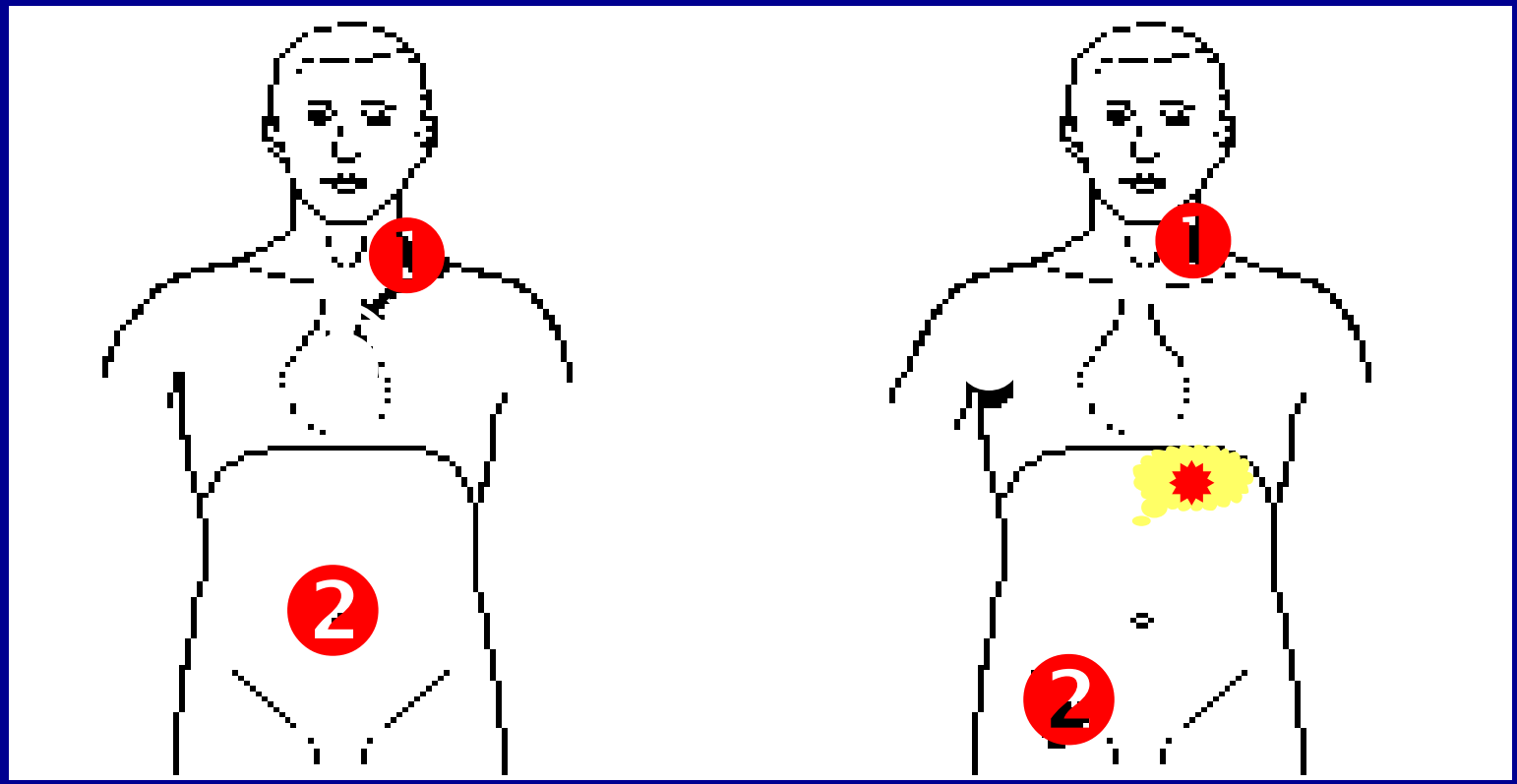
STAGE-1

STAGE-2

ANN –ARBOR STAGE

LN regions on both sides of diaphragm

LN regions on both sides of diaphragm + spleen

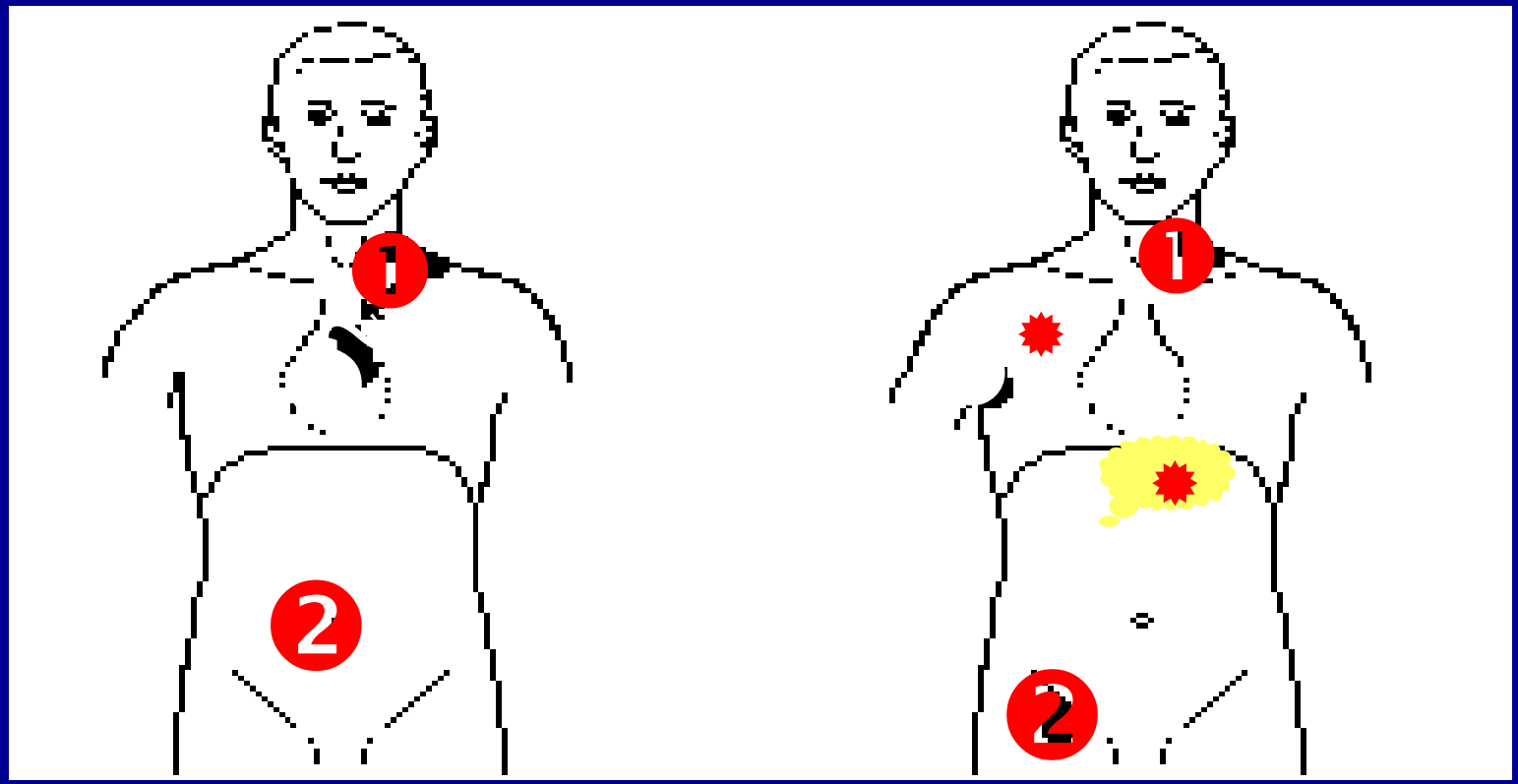


STAGE-3

STAGE-3S

ANN –ARBOR STAGE

LN regions on both sides of diaphragm + Extralymphatic disease



STAGE-3

STAGE-3SE

Prognostic factor for Early stage Hodgkin's Lymphoma

Prognostic (risk) factor	Treatment groups	Study group
Large mediastinal mass ESR ≥ 50 without B symptoms ESR ≥ 30 with B symptoms Age >50 ≥4 Nodal sites involved	*Favorable*: Stages I–II without risk factors *Unfavorable*: Stages I–II with ≥1 risk factor(s)	EORTC
Large mediastinal mass ESR ≥ 50 without B symptoms ESR ≥ 30 with B symptoms Extranodal disease ≥3 Nodal sites involved	*Favorable*: Stages I–II without risk factors *Unfavorable (or intermediate)*: Stages I–II with ≥1 risk factors (If stage IIB with bulky mass or extranodal disease: considered advanced stage)	GHSG
Histology (MC, LD) ESR ≥ 50 Age ≥ 40 years ≥4 Nodal sites involved Note: Bulky mediastinal disease excluded from trial	*Favorable:* Stages I–II without risk factors *Unfavorable:* Stages I–II with ≥1 risk factor(s)	NCIC

Prognostic factor for Advanced stage Hodgkin's Lymphoma - International Prognostic Score (IPS)

- **H**emoglobin < 10.5 g/dl
- **A**ge ≥ 45
- **G**ender - Male
- **L**ymphocytes < 600/mm^3 veya < %8
- **A**lbumin < 4 g/dl
- **W**BC ≥ 15,000/mm^3
- **S**tage – IV

Hodgkin's Lymphoma: Treatment

- With appropriate treatment about 85% of patients with Hodgkin disease are curable
  - Chemoterapy
    - ABVD, BEACOPP, Stanford
  - Radiotherapy
  - Bone marrow transplantation

Hodgkin's Lymphoma: Treatment

- Therapy is entirely based on the stage
  - The most important prognostic factor.
- Localized disease **(stage IA and IIA)**
  - Managed predominantly with **chemotherapy + Radiotherapy**.
  - 2-4 cycles ABVD + 20-36 cy RT
- All patients with evidence of **''B'' symptoms** as well as **stage III and IV**
  - Managed with **chemotherapy**.
  - 6-8 cycles ABVD or **BEACOPP**
- The most effective combination chemotherapeutic regimen for Hodgkin's lymphoma is **ABVD** (adriamycin, bleomycin, vinblastin and dacarbazine).

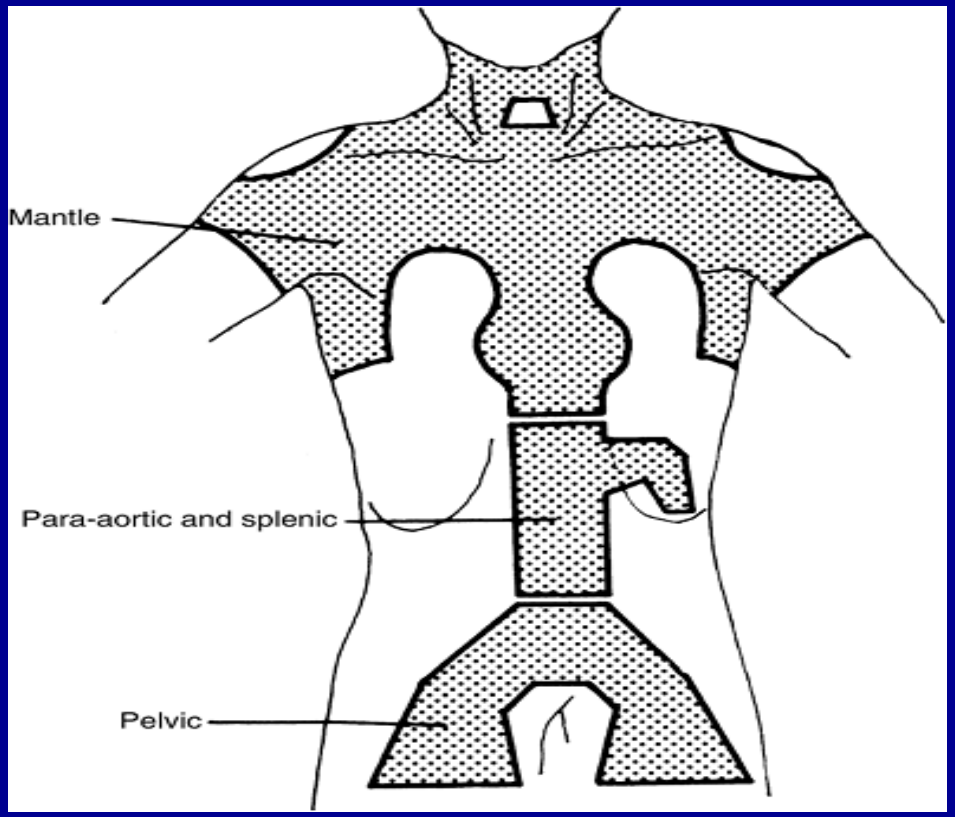
HL: Chemotherapy

Regimen	Medication		Delivery
ABVD	Adriamycin Bleomycin Vinblastine Dacarbazine	25mg/m2 10 6 375	Each agent is given intravenously on days 1 and 15 (1 cycle), each cycle repeated at 28 days
Stanford V	Adriamycin Bleomycin Vinblastine Vincristine Prednisone Mechlorethamine Etoposide		Each agent is given intravenously, except for prednisone
BEACOPP	Bleomycin Etoposide Adriamycin Cyclophosphamide Oncovin (vincristine) Procarbazine Prednisone		Each agent is given intravenously, except procarbazine and prednisone

HL: Radiotherapy

- Radiation therapy is the most effective single therapeutic agent for treating Hodgkin's lymphoma.
- The main objective of radiation in Hodgkin's lymphoma is to treat involved and contiguous field.
  - **Mantle field**
  - **Paraaortic field**
  - **Pelvic field**

  Dose: 20-36 Gy



HL: Salvage Treatment

Salvage therapy- resistance/relapse:

- **Second-line noncross-resistant regimens**

  CR= 30-40%

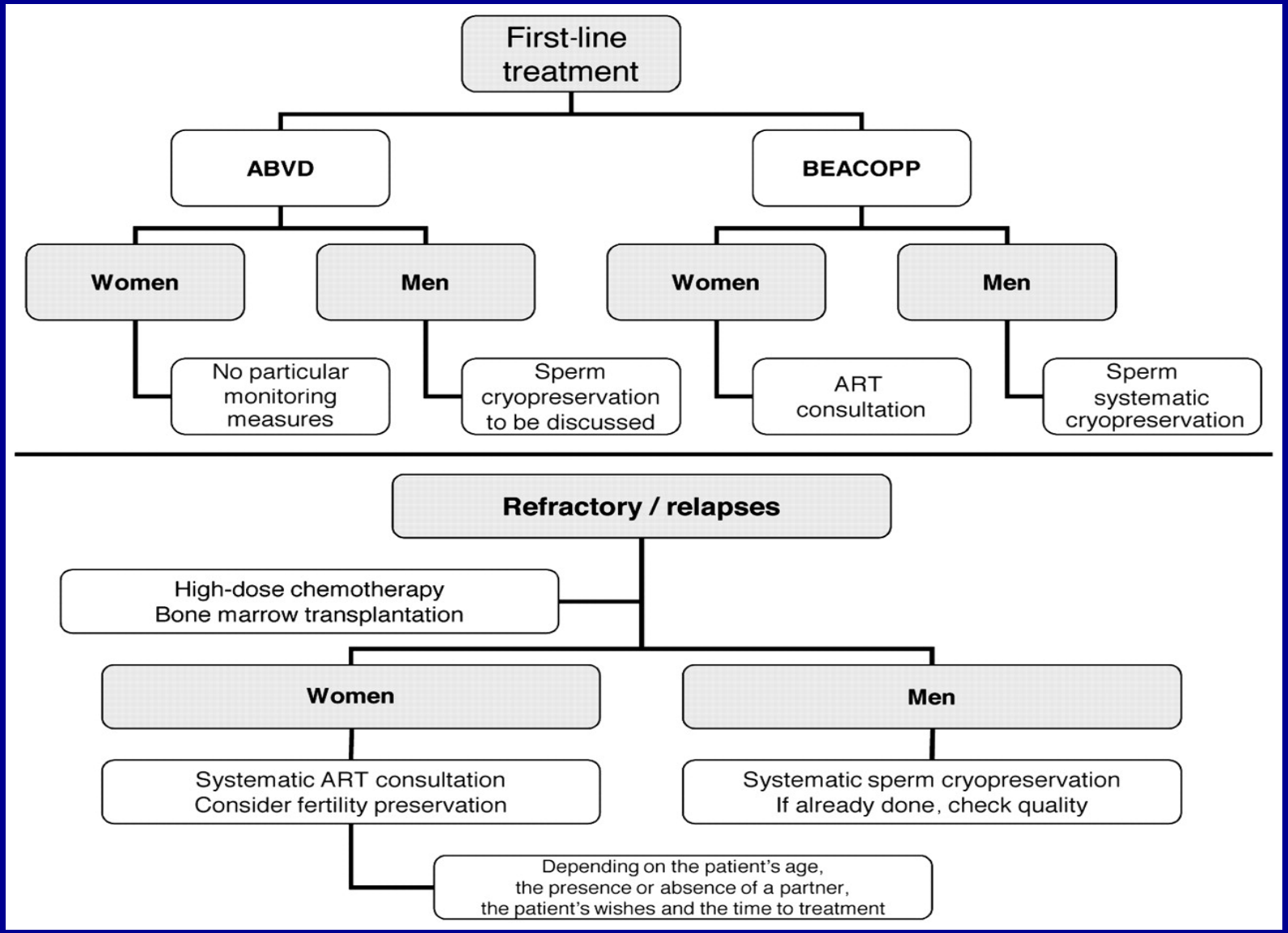
  DFS= 10-25%

  - **DHAP**
  - **CEP**
  - **EVAP**
  - **GDP**
- **High dose chemotherapy with autologous stem cell transplantation**

HL: Complications

- Radiation Pneumonitis (6-12 weeks)
- Radiation Pericarditis
- Subclinical Hypothyroidism
  - Most common delayed symptoms
- Herpes Zoster infections
- Lhermittes sign (1-2 months)
- Streptococcus pneumoniae and H influenzae infection following splenic radiation.
- Azoospermia in males
- Premature menopause in females
- Secondary malignancy
  - Leukaemia
  - Lymphoma (diffuse large cell type most common after 5 years)
  - Solid Tumors: In males Lung (>30 Gy), colorectal
    In females Breast, lung, colorectal

HL: Reproductive counseling



www.drfevzialtuntas.com
faltuntas@hotmail.com