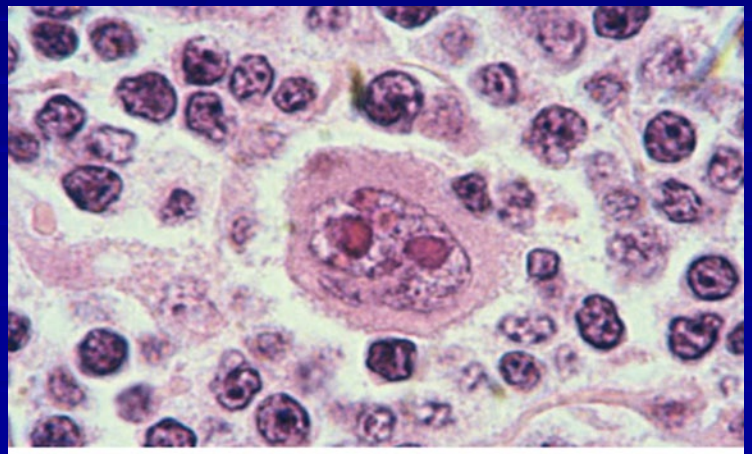
LYMPHOMAS

Dr.Mousa Qasim Hussein
Professor Internal Medicine



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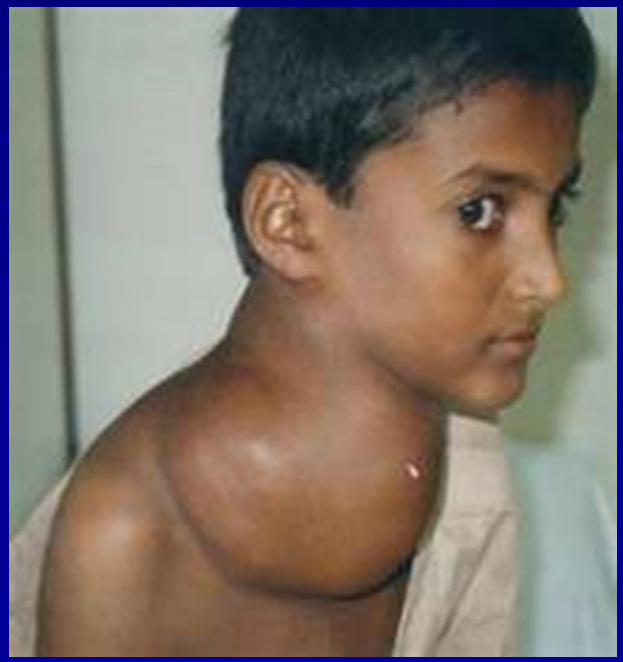


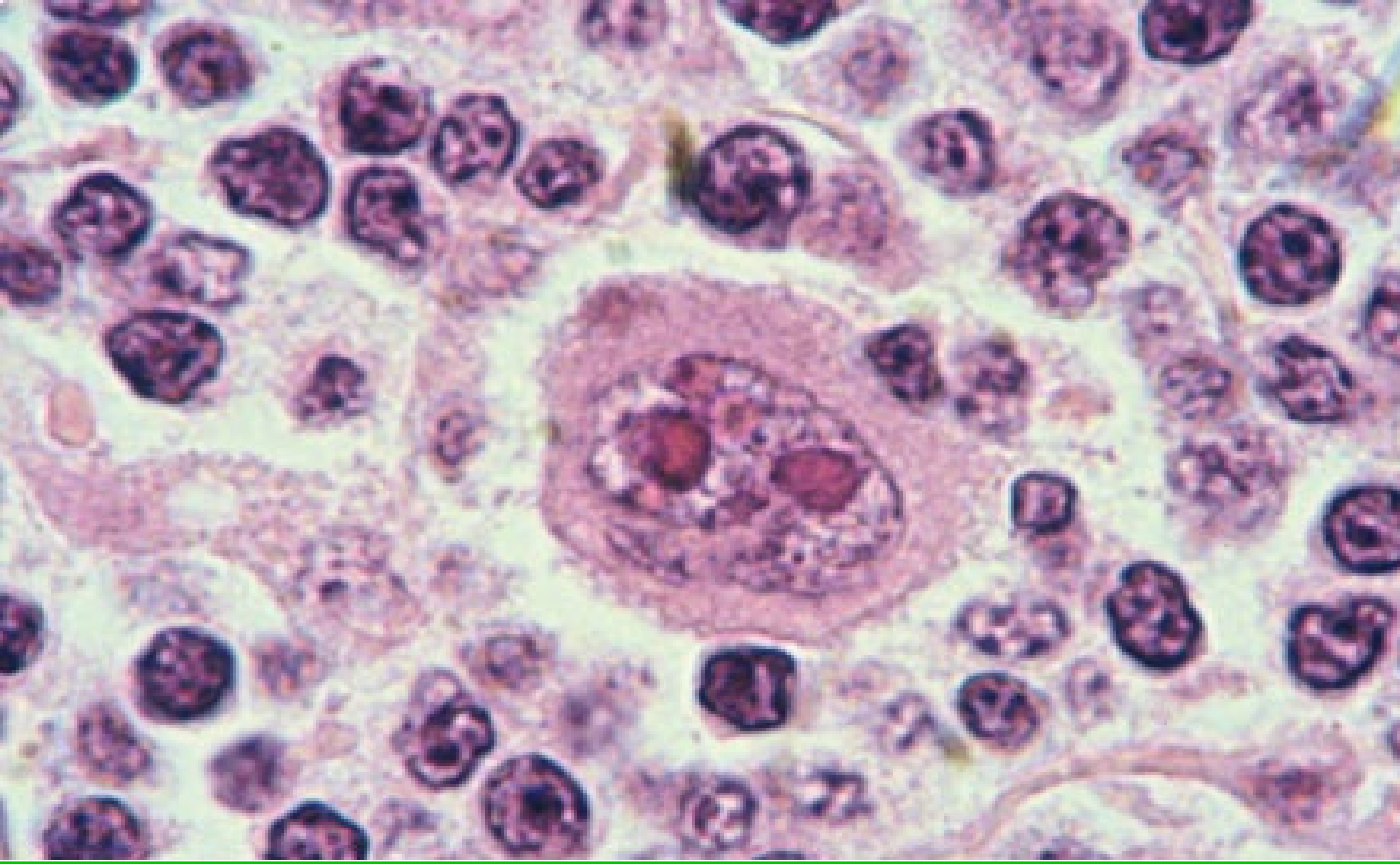
Lymphomas

These neoplasms arise from lymphoid tissues, and are diagnosed from the pathological findings on biopsy as Hodgkin or non- Hodgkin lymphoma. The majority are of B-cell origin.

Hodgkin lymphoma :

The histological hallmark is the presence of Reed-Sternberg cells, which are large, malignant lymphoid cell Of B-cell origin .

They are often only present in small numbers but are Surrounded by large numbers of reactive normal T-cells, Plasma cells and eosinophils.



In the center of the photomicrograph is a classic Reed-Sternberg cell,a binucleate cell with large “owl’s eyes” eosinophilic nucleoli.

Epidemiology :

Incidence :approximately 4 new cases/ 100 000 population/ year.

Sex ratio :slight male excess (1.5: 1).

Age :median age 31 years; first peak at 20-35 year and second at 50-70 years.

Aetiology :

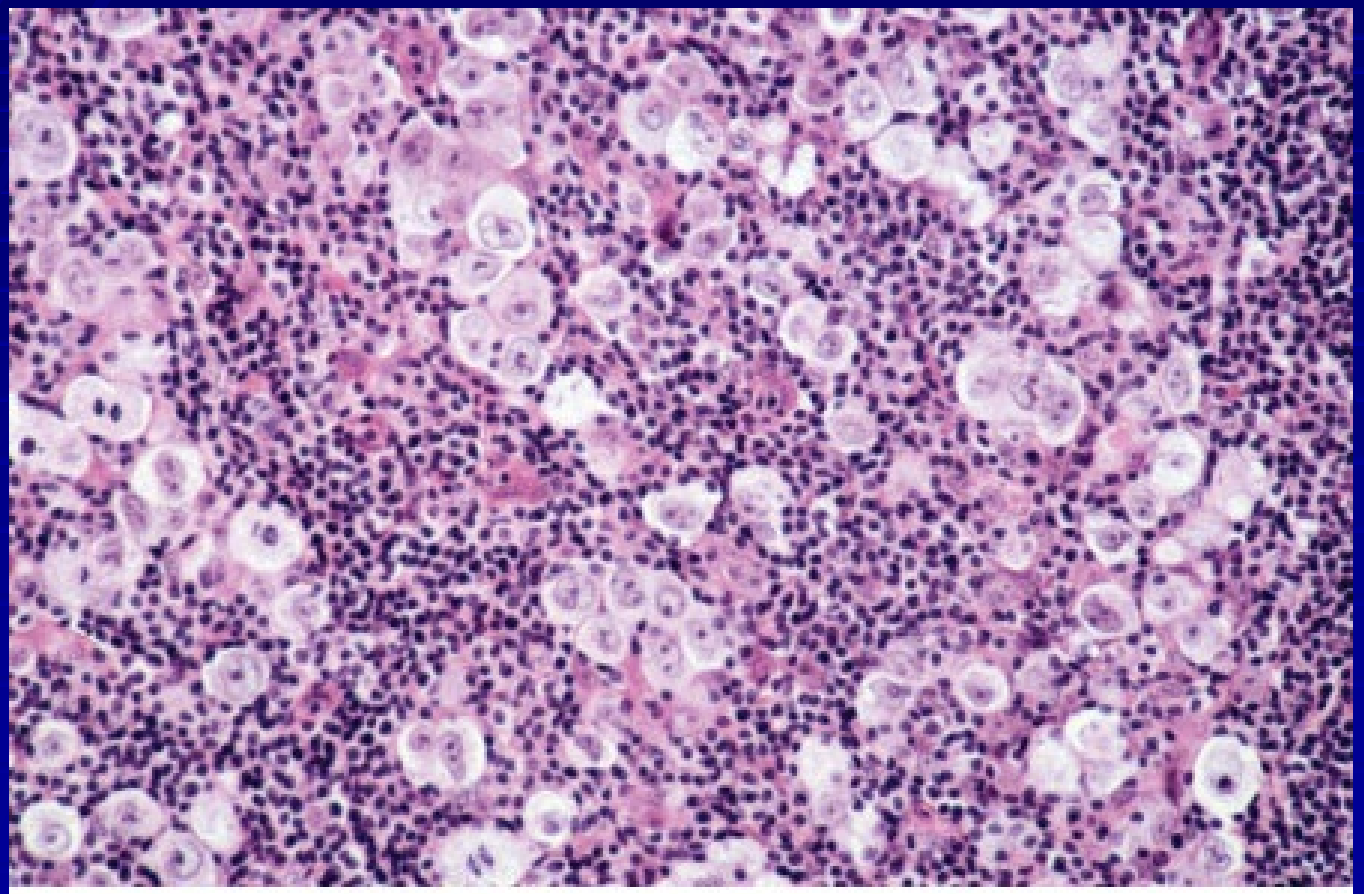
-Unknown.
-More common in patients from well-educated Background and small families.

-Three times more likely a past history of infectious Mononucleosis but no causal link to Epstein-Barr virus Infection proven.

WHO pathological classification and incidence :

Type	histology	incidence
Nodular lymphocyte-Predominant		5%
Classical HL	*nodular sclerosing	70%
	*Mixed cellularity	20%
	*Lymphocyte-rich	5%
	*lymphocyte-depleted	Rare

Nodular sclrosis H.L.is the most common subtype and is composed of large tumor *nodules* showing scattered lacunar classical RS cells set in a background of reactive lymphocytes, eosinophils and plasma cells with varying degrees of collagen fibrosis/*sclerosis*.



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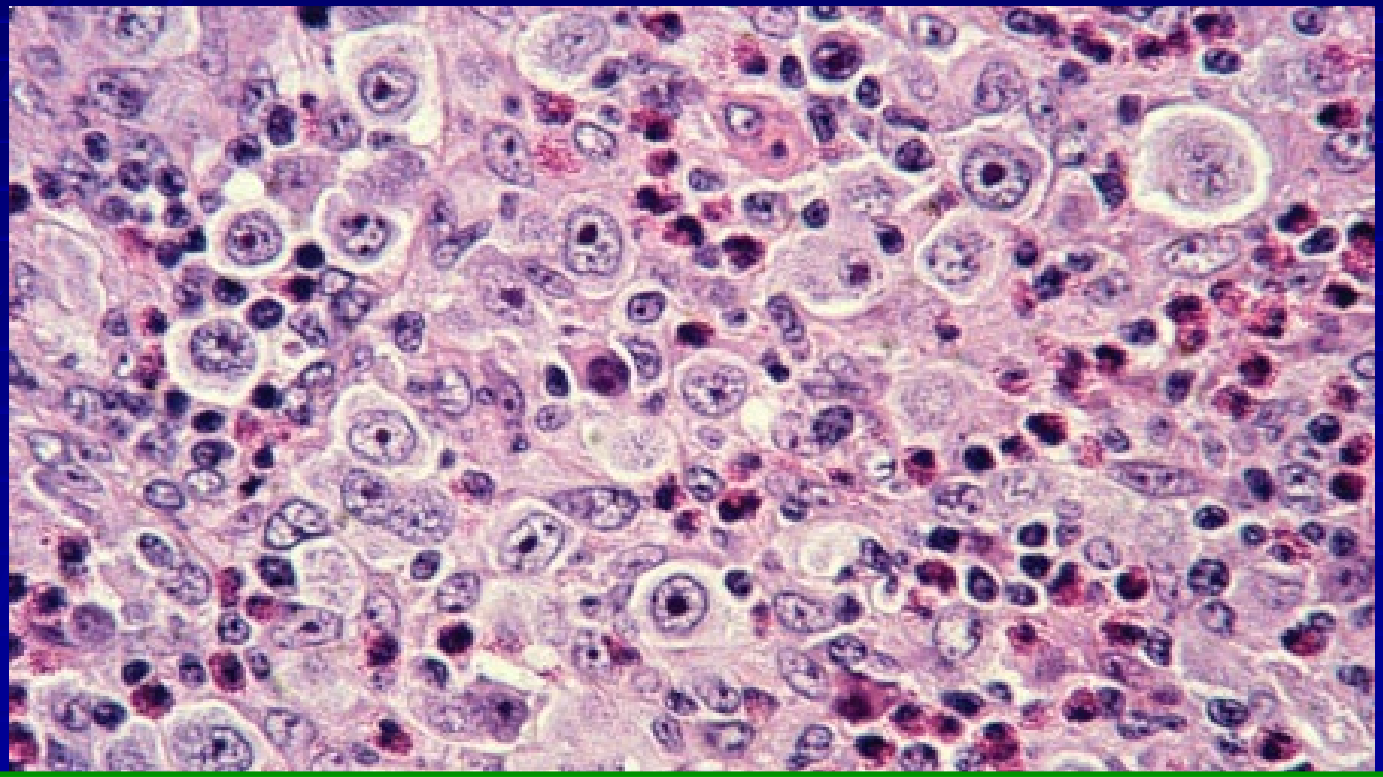
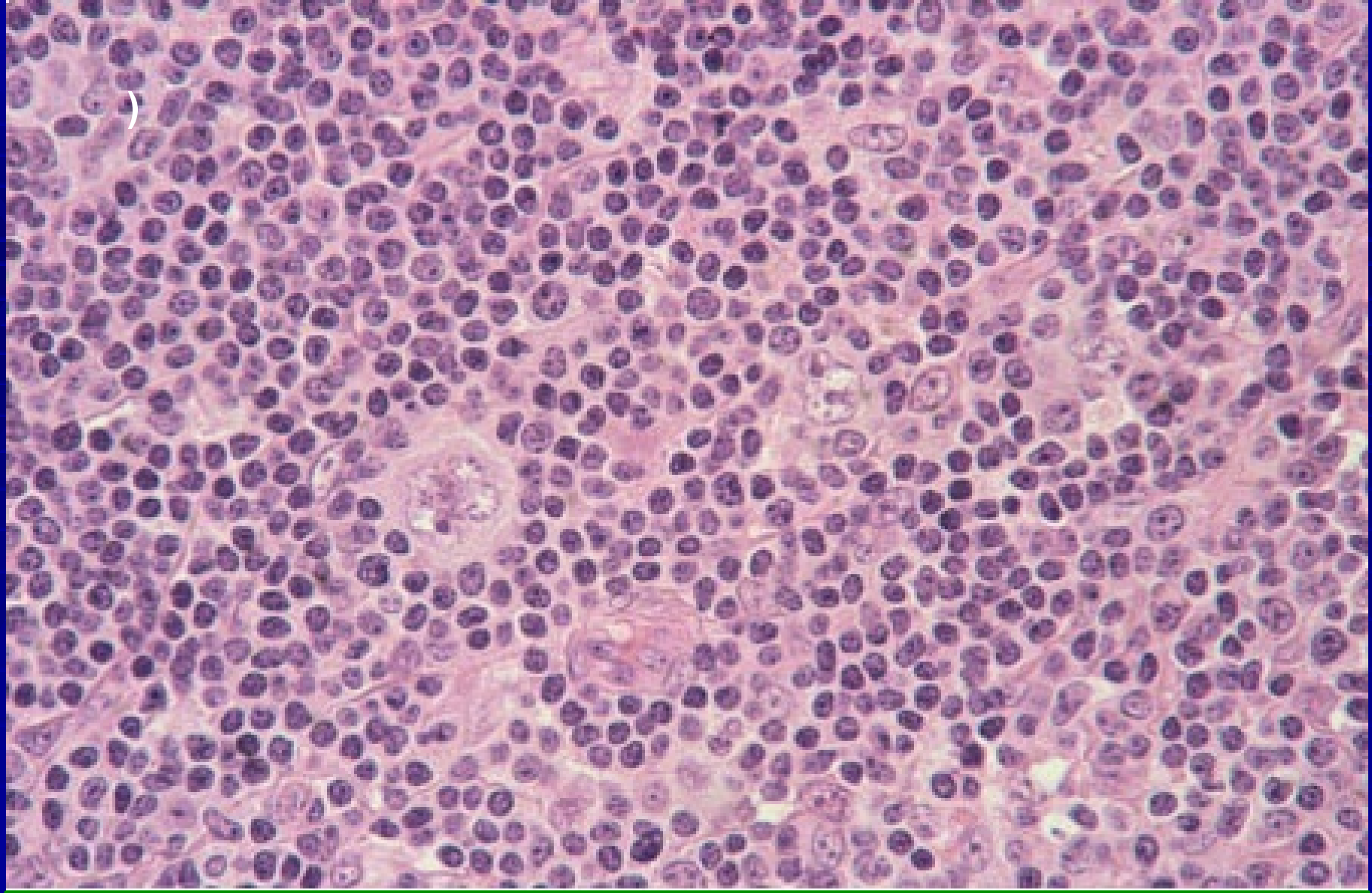
Mixed cellularity Hodgkins Lymphoma

Is a common subtype and is composed of numerous classic RS cells admixed with numerous inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells without sclerosis.

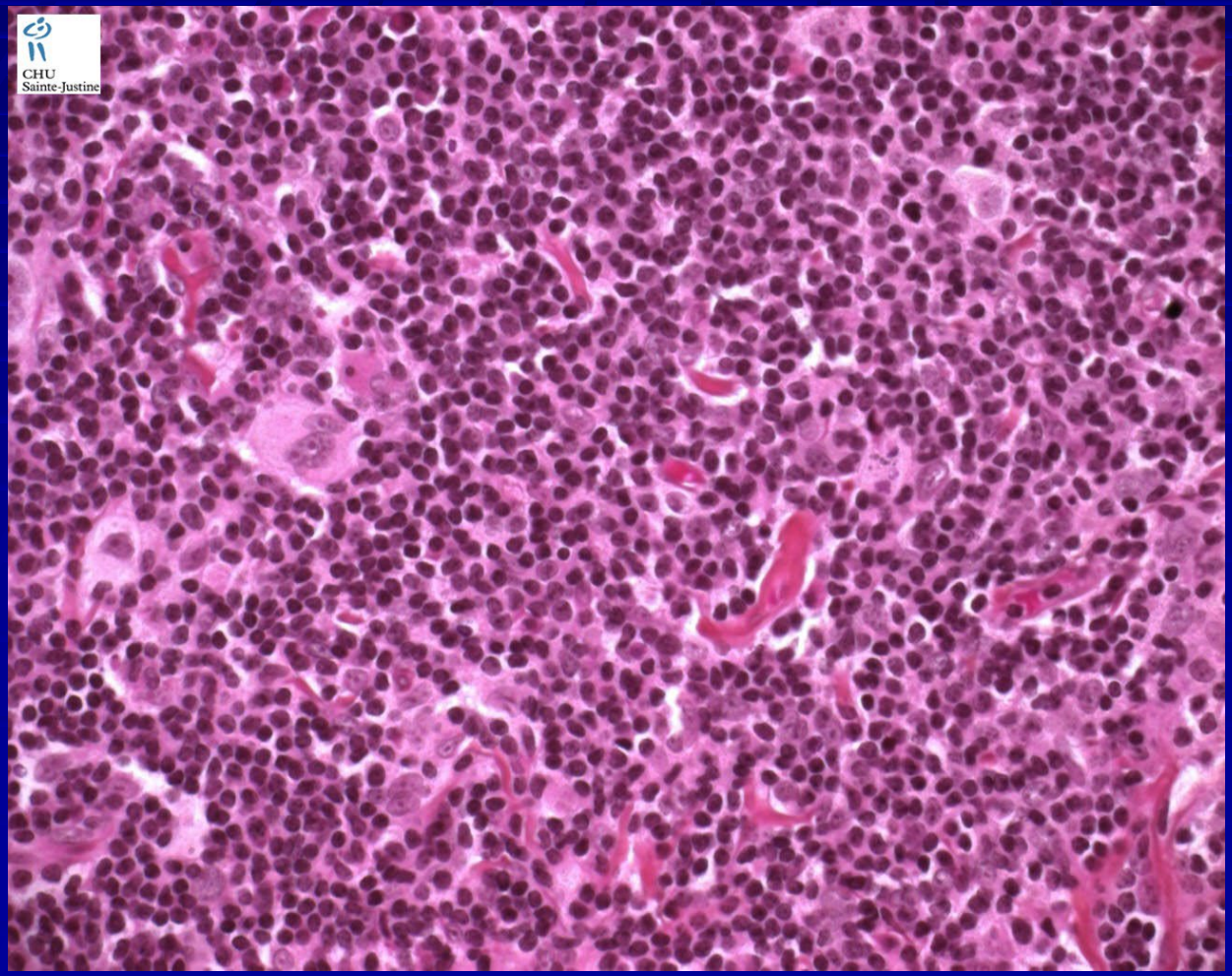


Mixed cellularity Hodgkins lymphoma

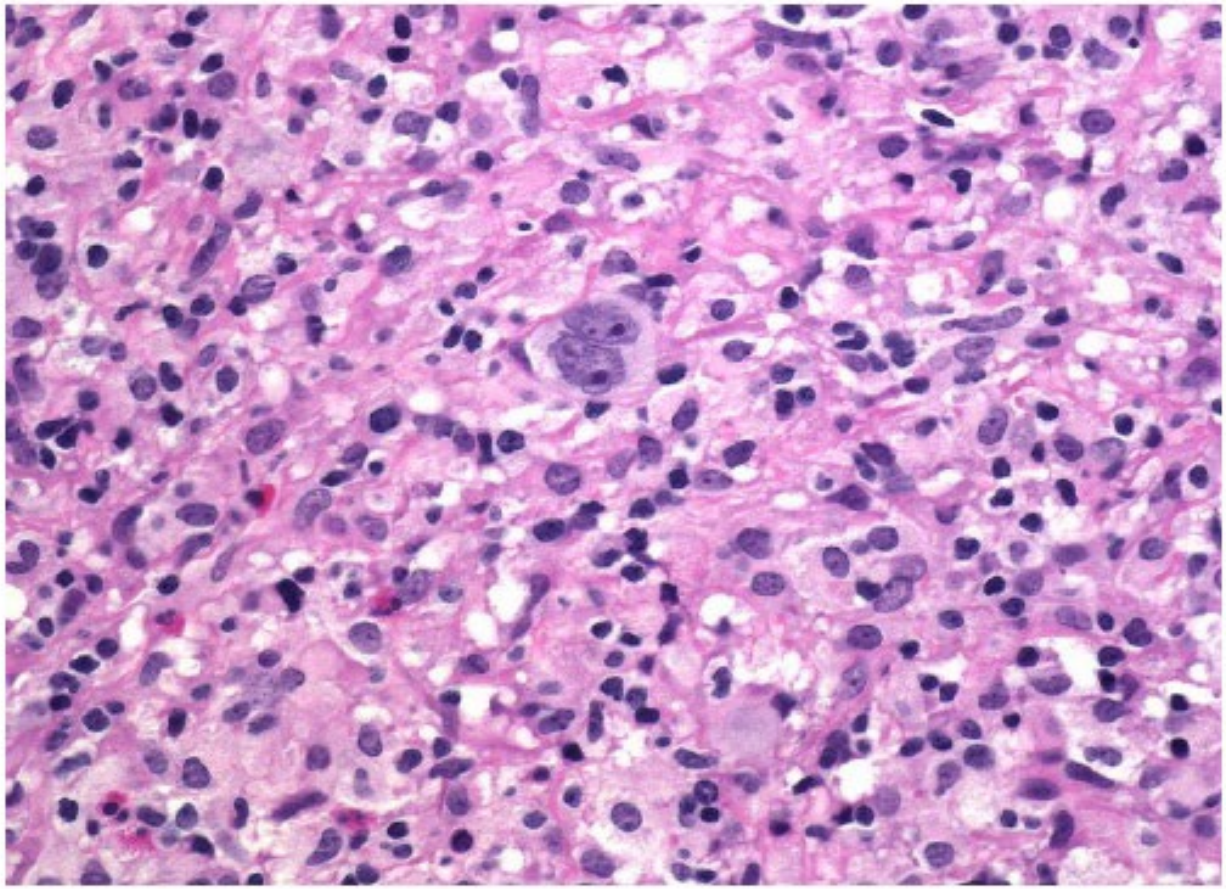


Nodular lymphocyte predominance showing characteristic L and H cells(popcorn cells)

Lymphocyte rich H.L.Is a rare subtype, show many features which may cause diagnostic confusion with nodular lymphocyte predominant B-cell Non-Hodgkin's Lymphoma (B-NHL). This form also has the most favorable prognosis.



Classical Hodgkin's Lymphoma : Lymphocyte Depleted



A Reed-Sternberg cell is seen in a background of eosinophils, lymphocytes, and macrophages. Lymphocyte-depleted is the most aggressive type of Hodgkin's lymphoma, commonly associated with advanced stages at presentation

Nodular lymphocyte predominant HL is a slow-growing , localised And rarely fatal. It has biological features such as CD20 –positive Hodigkin cells and clinical features that make it more akin to low Grade B cell non-Hodigkin lymphoma.

*the nodular sclerosing type accounts for the initial peak in young Patients and is more common in women.

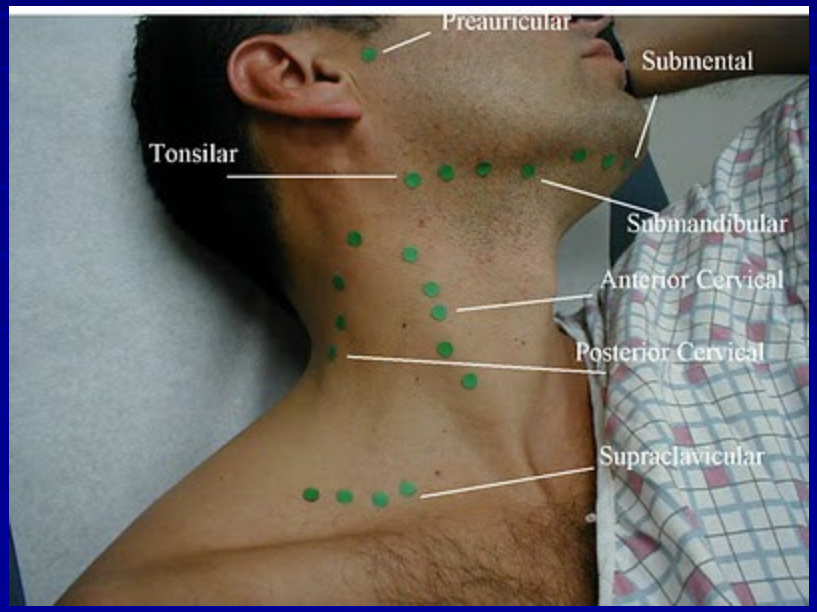
*Mixed cellularity is more common in the elderly peak.

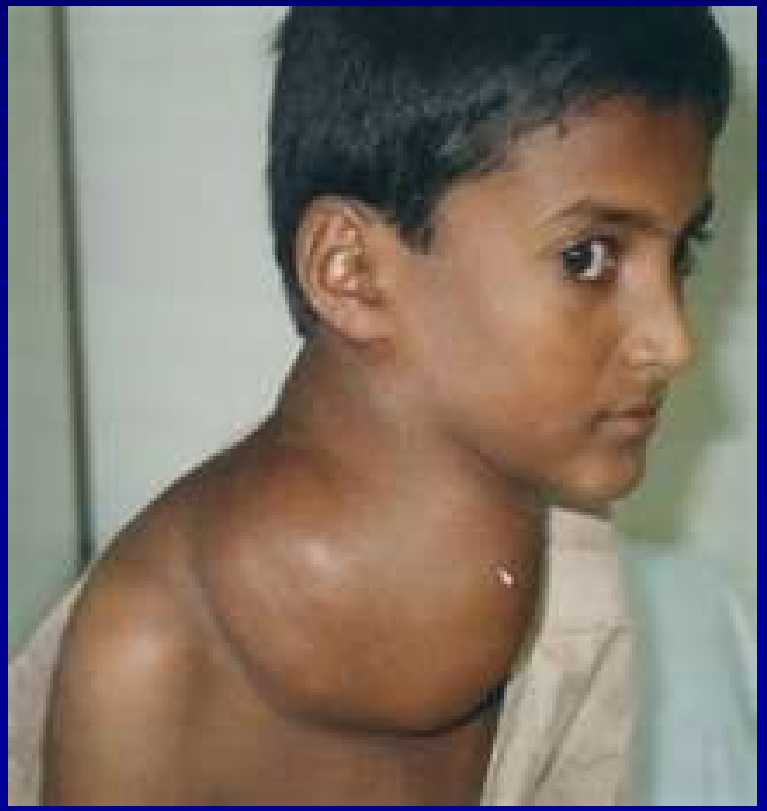
*lymphocyte rich HL usually present in men.

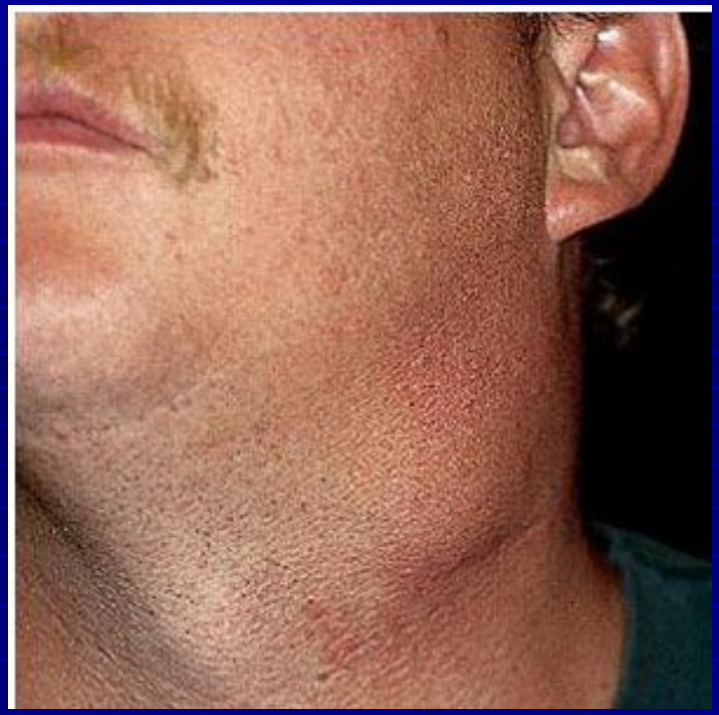
Lymphocyte-depleted HL is rare and probably represents large cells Or anaplastic non-Hodgkin lymphoma.

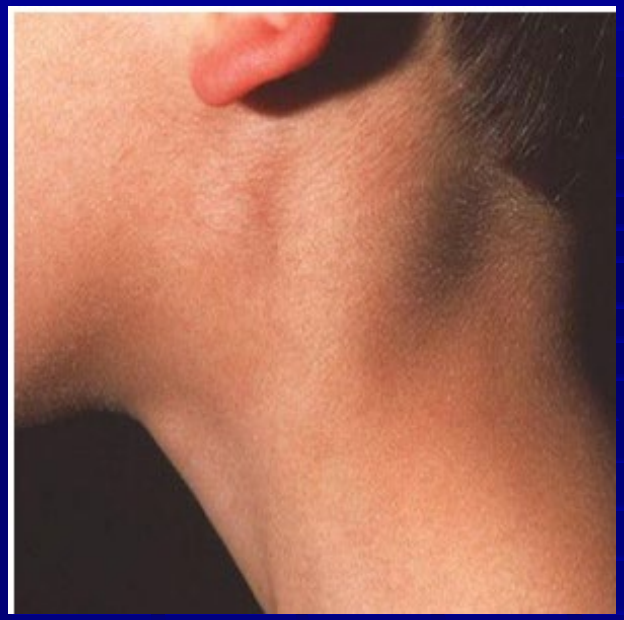
Clinical features :

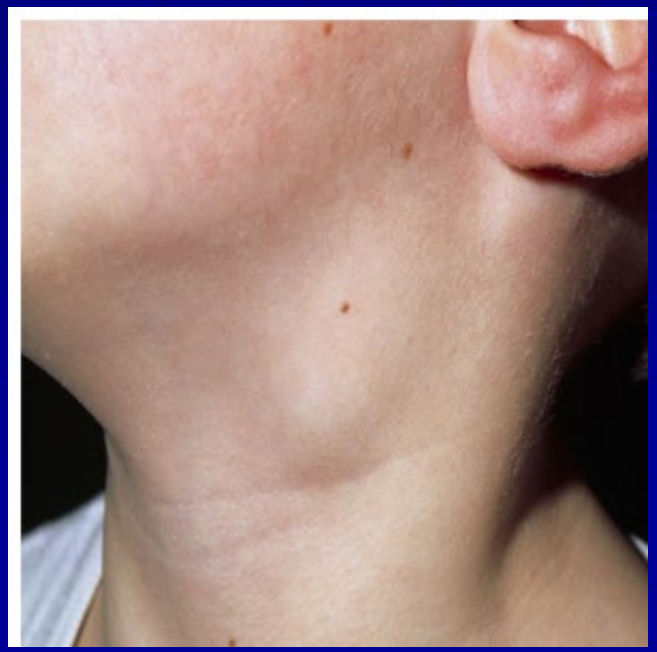
There is painless rubbery Lymphadenopathy , usually in the neck Or supraclavicular fossa; the lymph nodes may fluctuate in size.











Young patients with nodular sclerosing disease may have large Mediastinal mass which are surprisingly asymptomatic but may cause Dry cough and some breathlessness.

Isolated subdiaphragmatic nodes occur in fewer than 10% at diagnosis. Hepatosplenomegaly may be present but does not always indicate disease in those organs. Spread is contiguous from one node to the next and extranodal disease, such as bone, brain or skin involvement, is rare.

Systemic symptoms include so-called ‘B symptoms’ of drenching night sweats, fever and loss of 10% body weight. Other symptoms can include pruritis and rarely, but dramtically, alcohol- induced pain within lymph nodes

Clinical stages of Hodgkin lymphoma (Ann Arbor classification)

Stage	Definition
I	Involvement of a single lymph node region (I) or extralymphatic* site (IE)
II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm with (IIIE) or without (III) localised extralymphatic involvement or involvement of the spleen (IIIs), or both (IIISE)
IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow

Each stage is subclassified:

A No systemic symptoms

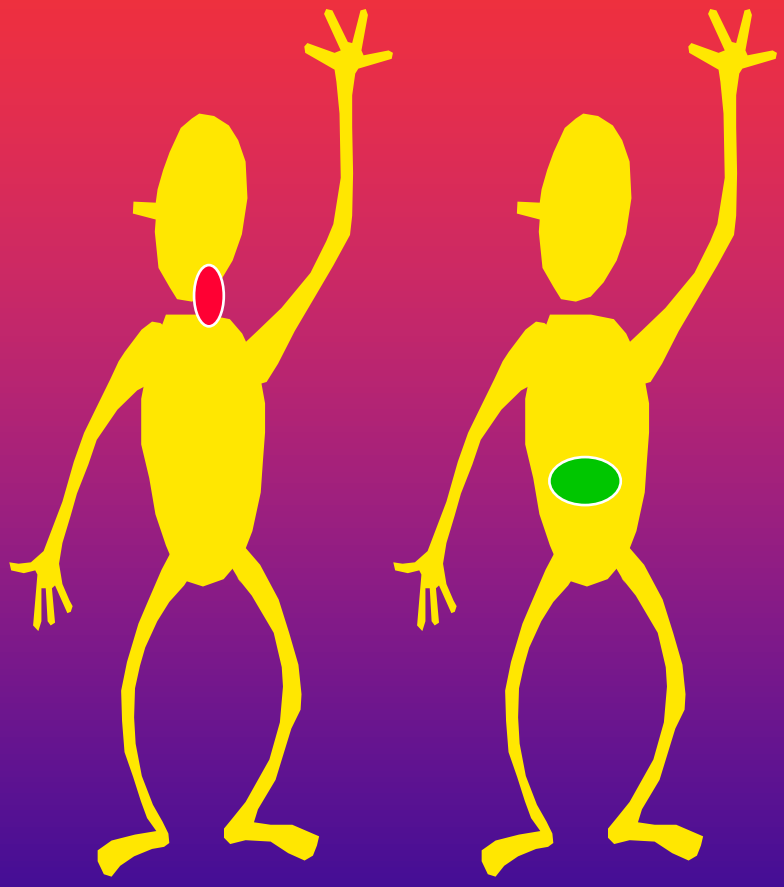
B Weight loss > 10%, drenching sweats, fever

*The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches

Ann Arbor staging

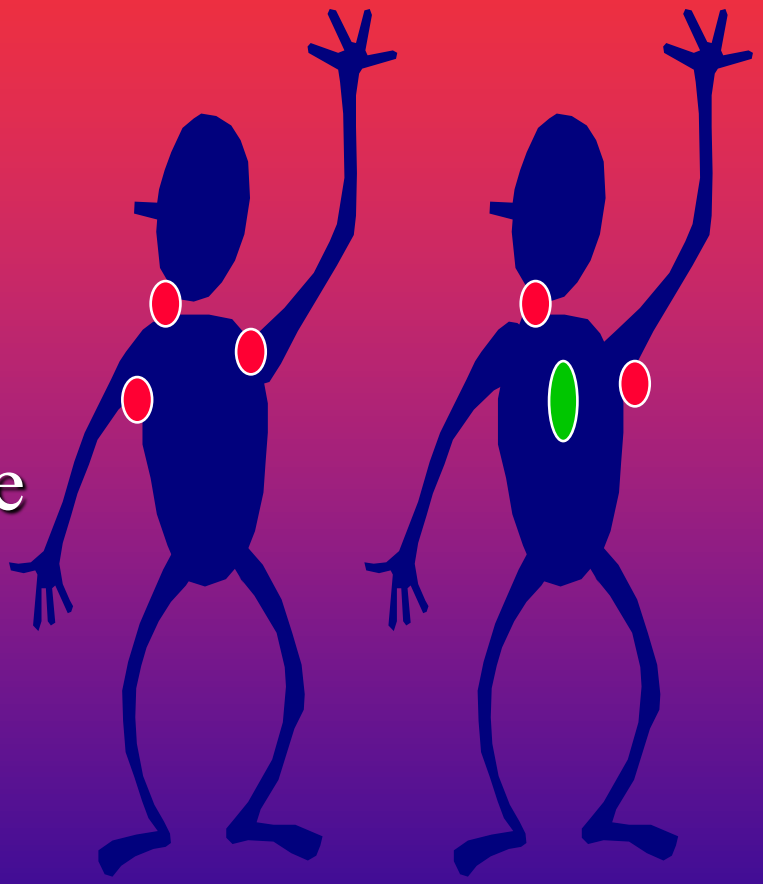
- **Stage I**

  Involvement of a single lymph node region or of a single extranodal organ or site(I_E)



Ann Arbor staging

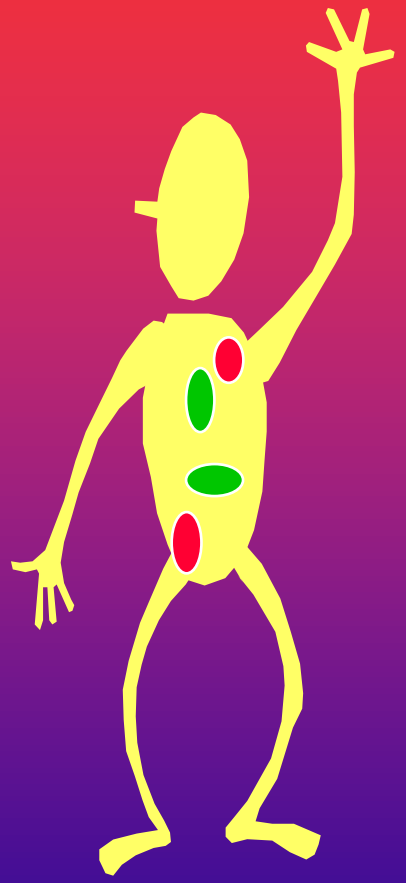
- **Stage II:**
  - two or more lymph node regions on the same side of the diaphragm
  - localized extranodal organ and one or more lymph node regions on the same side of the diaphragm(II_E)



Ann Arbor staging

- **Stage III**

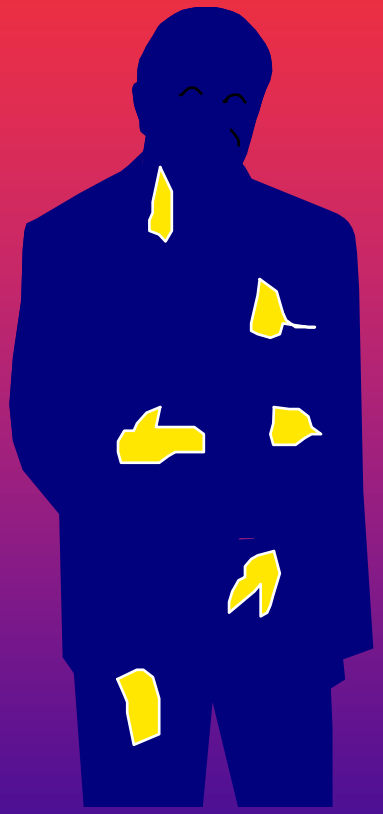
  lymph node regions on both sides of the diaphragm or with localized extranodal organ (III $_{E}$) or spleen (IIIs)or both (III $_{ES}$).



Ann Arbor staging

- **Stage IV:**
  Diffused or disseminated involvement of one or more extranodal organs, with or without associated lymph node enlargement.

BM,LIVER,CNS, EFFUSION



Ann Arbor staging

Group A

- Without general symptoms

Group B

- With general symptoms
  - unexplained fever , >38°C, lasting over 3 days
  - night sweating
  - weight loss, >10% of body weight within 6 months

Investigations

The aim of investigations not only to diagnose lymphoma but also To determine the extent of disease.

***full blood count** may be completely normal. A normochromic, normorcytic Anaemia or lymphopeia may be present this is a poor prognostic factor, particularly in advanced disease.
An eosinophilia, neutrophilia or thrombocytosis may be present.

ESR may be raised and is an adverse prognostic factor.is a poor Prognostic factor.
*
*

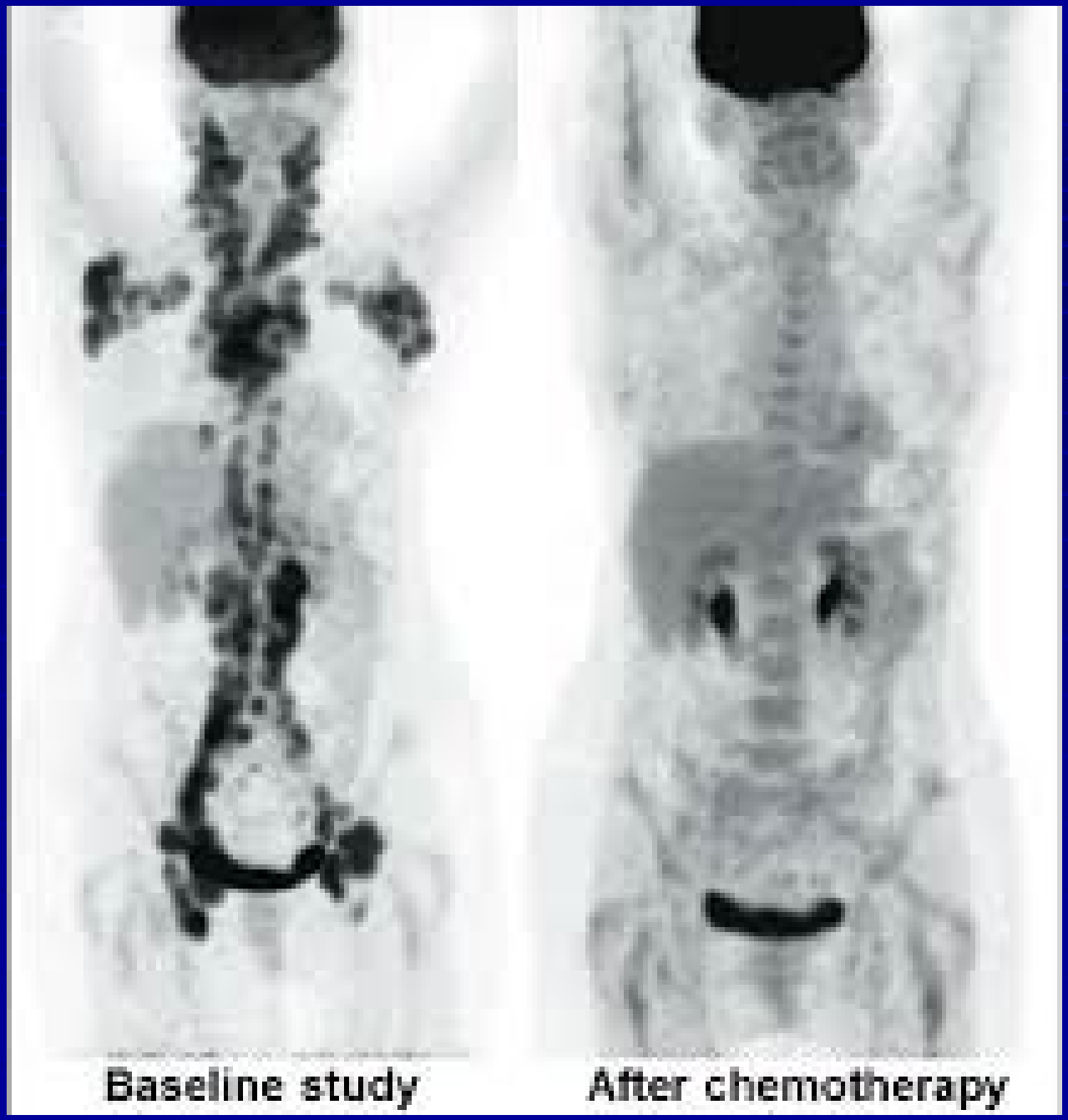
Renal function test are required to ensure function is normal prior to Treatment.

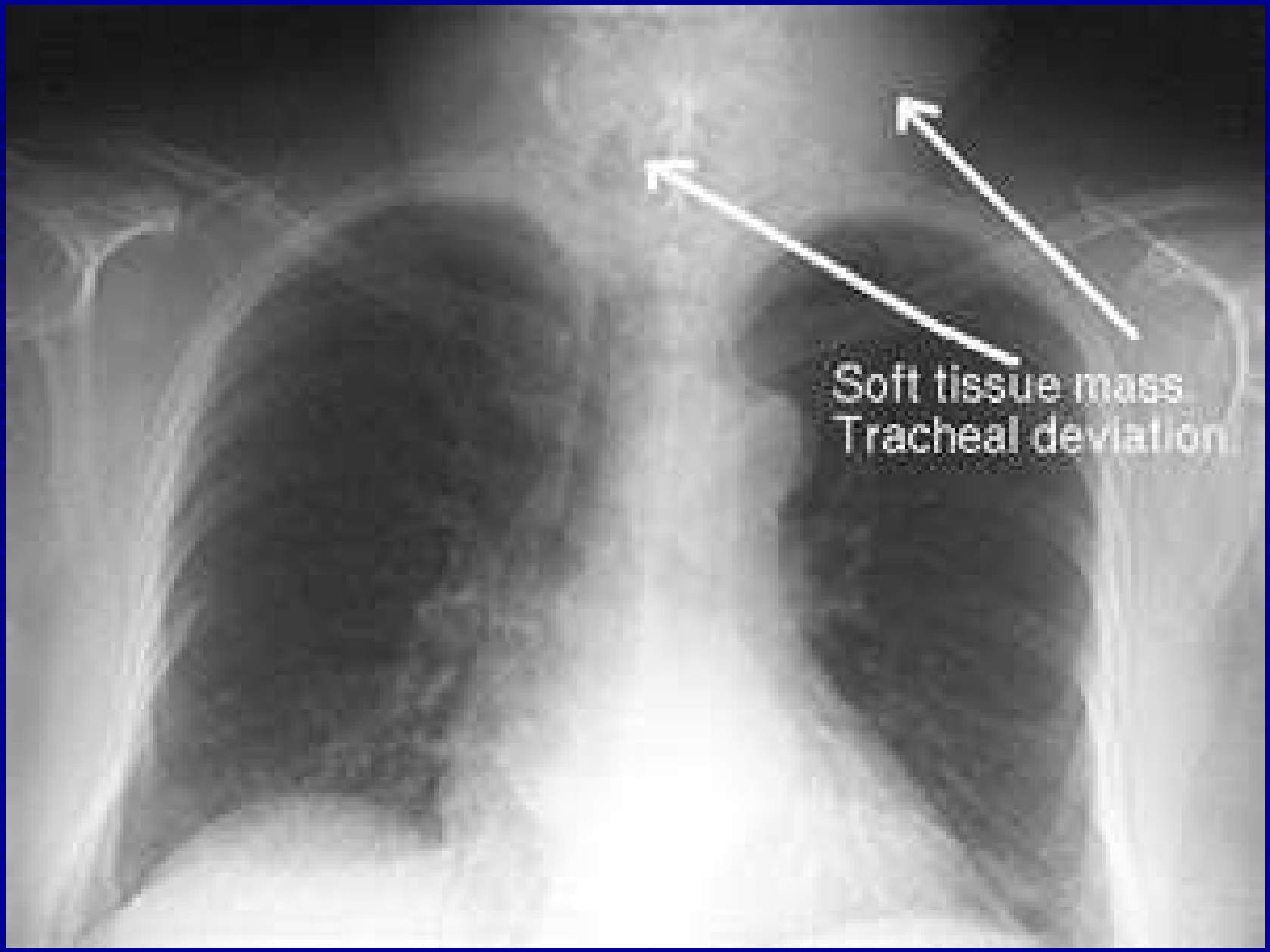
***Liver function** may be abnormal in the absence of disease or reflect Hepatic infiltration. An obstructive pattern may be caused by nodes At the porta hepatis.

***LDH** measurement , as raised levels are an adverse prognostic factor.

***Chest X-ray** may show mediastinal mass.
***CT scan of chest and abdomen to permit staging.** Bulky Disease (greater than10 cm in a single node mass) is an Adverse prognostic factor.

- Positron emission tomography (PET) scanning identifies nodes involved with HL, which are 18fluorodeoxyglucose (FDG)-avid, and this allows more accurate staging and monitoring of response
- Lymph node biopsy may be undertaken surgically or by percutaneous needle biopsy under radiological guidance


Baseline study
After chemotherapy


Soft tissue mass
Tracheal deviation

Management

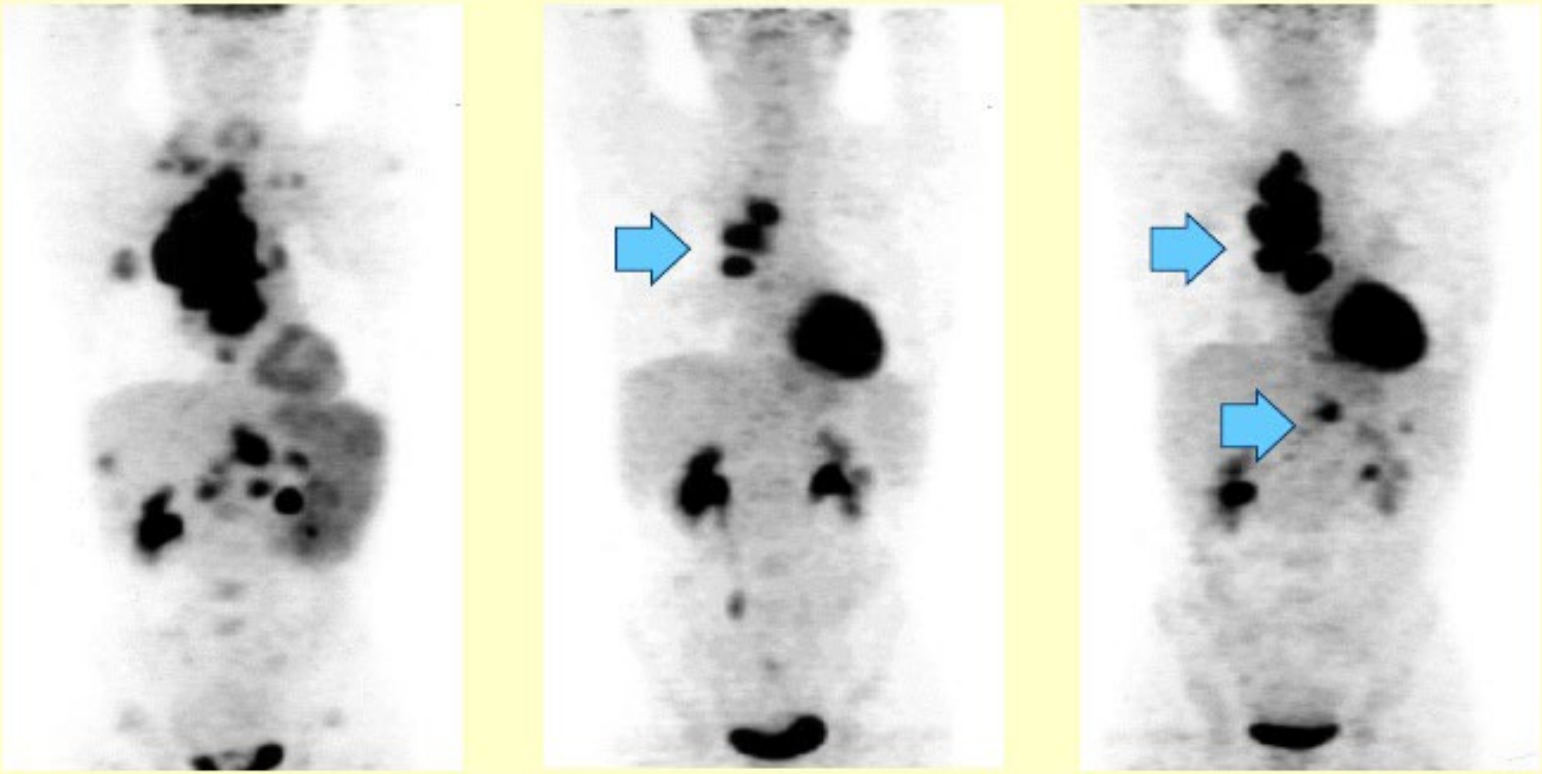
. Given the high cure rate and excellent prognosis of a majority of young and middle-aged patients with HL, the aim is to maximize cure rates while minimising long-term treatment-related toxicity. Treatment approaches involve defining patients as early-stage disease (stages IA and IIA) or advanced stage disease (IB, IIB, III and IV).

The ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) is widely used in the UK, while the more intensive BEACOPP regimen (bleomycin, etoposide, doxorubicin (adriamycin), cyclophosphamide, vincristine (oncovin), procarbazine, prednisolone) is a more effective alternative, though with a greater risk of side-effects including infertility and treatment-related MDS and AML.

Standard therapy for early-stage patients without additional risk factors, such as bulk disease or high ESR, is two cycles of ABVD combined with 20 Gy radiotherapy to the involved sites of disease

Standard therapy for early-stage patients with additional risk factors is four cycles of ABVD combined with 30 Gy radiotherapy. Careful planning of radiotherapy is required to limit the doses delivered to normal tissues and new planning techniques continue to improve targeting of radiotherapy.

Early treatment evaluation



Before treatment | At 2 cycles | At 4 cycles

FDG-PET2 (+)

Haioun C, et al. Blood 2005; 106(4): 1376–81

Combined modality consisting of

doxorubicin 25 mg/m^2 IV **plus**
bleomycin 10 units/m^2 IV **plus**
vinblastine 6 mg/m^2 IV **plus**
dacarbazine 375 mg/m^2 IV
on days 1 and 15; every 28 d generally for two to four cycles;

followed by ISRT at a dose of 20-30 Gy
(depending on German Hodgkin Study Group [GHSG] criteria)

Nevertheless, the long-term risks of second cancers and heart and lung disease within the radiation felds remain a concern, especially for young people with a high cure rate and potentially decades of life ahead of them.

Early-stage patients who have a negative FDG PET-CT scan after three or four cycles of combination chemotherapy can safely omit radiotherapy.

Young women receiving breast irradiation during the treatment of chest disease have an increased risk of breast cancer and should participate in a breast screening programme. Patients continuing to smoke after lung irradiation are at particular risk of future lung cancer .

ABVD chemotherapy can cause cardiac and pulmonary toxicity, due to doxorubicin and bleomycin, respectively. The incidence of infertility and secondary myelodysplasia/AML is low with this regimen but higher with BEACOPP.

Patients with advanced-stage disease are most commonly managed with chemotherapy alone. Standard treatment in the UK is 6–8 cycles of ABVD, followed by an assessment of response. A negative FDG PET-CT after two cycles of ABVD (interim PET-2 response) predicts a very good outcome from continuing with up to six cycles of ABVD.

Patients with relapsed disease that responds to salvage chemotherapy and ideally becomes FDG PET-CT-negative should be considered for autologous stem cell transplantation

Those with resistant disease might benefit from an allogeneic stem cell transplant

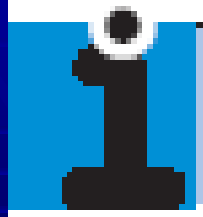
Brentuximab vedotin is an antibody–drug conjugate directed against CD30 on the Reed–Sternberg cell surface. This antibody delivers the antimitotic toxin monomethyl auristatin E to the Hodgkin cells and, as a single agent, can produce good responses in patients who have failed, or are not suitable for, an autologous transplant and can be a ‘bridge’ to an allogeneic transplant.

The immunotherapy drugs pembrolizumab and nivolumab can inhibit this ‘checkpoint’ in the immune response and allow T-cell killing of Reed–Sternberg cells. Both drugs are available for patients who have failed multiple lines of treatment and can produce further remissions.

Prognosis

Over 90% of patients with early-stage HL achieve complete remission when treated with chemotherapy followed by involved field radiotherapy, and the great majority are cured. The major challenge is how to reduce treatment intensity, and hence long-term toxicity, without reducing the excellent cure rates in this group. Omitting radiotherapy in the majority of PET-negative patients is one major step forward in this regard..

Historically, between 50 and 70% of those with advanced-stage HL were cured. The Hasenclever index can be helpful in assigning approximate chances of cure when discussing treatment plans with patients. More recent data using the PET scanner to direct therapy suggests that long-term survival is improving to beyond 80%.



The Hasenclever prognostic index for advanced Hodgkin lymphoma

Score 1 for each of the following risk factors present at diagnosis:

- Age > 45 yrs
- Male gender
- Serum albumin < 40 g/L
- Haemoglobin < 105 g/L
- Stage IV disease
- White blood count > 15 × 10^9/L
- Lymphopenia < 0.6 × 10^9/L

Score	5-yr rate of freedom from progression (%)	5-yr rate of overall survival (%)
0–1	79	90
> 2	60	74
> 3	55	70
> 4	47	59

Patients who fail to respond to initial chemotherapy or relapse within a year of initial therapy have a poor prognosis, but some may achieve long-term survival after autologous HSCT. Patients relapsing after 1 year may obtain long-term survival with further chemotherapy alone, but fit patients frequently proceed to autologous HSCT.

Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) represents a monoclonal proliferation of lymphoid cells of B-cell (90%) or T-cell (10%) origin. The incidence of these tumours increases with age, to 62.8/million population per annum at age 75 years, and the overall rate is increasing at about 3% per year.

Non-Hodgkin lymphomas are classified as low- or high-grade tumours on the basis of their proliferation rate.

- High-grade tumours divide rapidly, are typically present for a matter of weeks before diagnosis, and may be life-threatening with high risk of extranodal involvement.
- Low-grade tumours divide slowly, may be present for many months before diagnosis, and typically behave in an indolent fashion

Epidemiology

Incidence

*12 new cases /100 000 people per year.

Sex ratio

*slight male excess.

Age

*median age 65-70 years.

Aetiology

*no single causative abnormality described .
*lymphoma is a late manifestation of HIV Infection.
*specific lymphoma types are associated with EBV, human Herpesvirus8(HHV8) and HTLV infection.
*the development of gastric lymphoma can be associated With Helicobacter pylori infection.
*some lymphomas are associated with specific chromosome Lesions; the t(14:18) translocation in follicular lymphoma Result in the desregulated expression of the BCL-2 gene Product which inhibits apoptotic cell death.
*lymphoma occurs in congenital immunodeficiency states And in immunosuppressed patients post organ transplantation.

Previous classifications were based principally on histological appearances. The current WHO classification stratifies according to cell lineage (T or B cells) and incorporates clinical features, histology, chromosomal abnormalities and concepts related to the biology of the lymphoma. Clinically, the most important factor is grade, which is a reflection of proliferation rate.

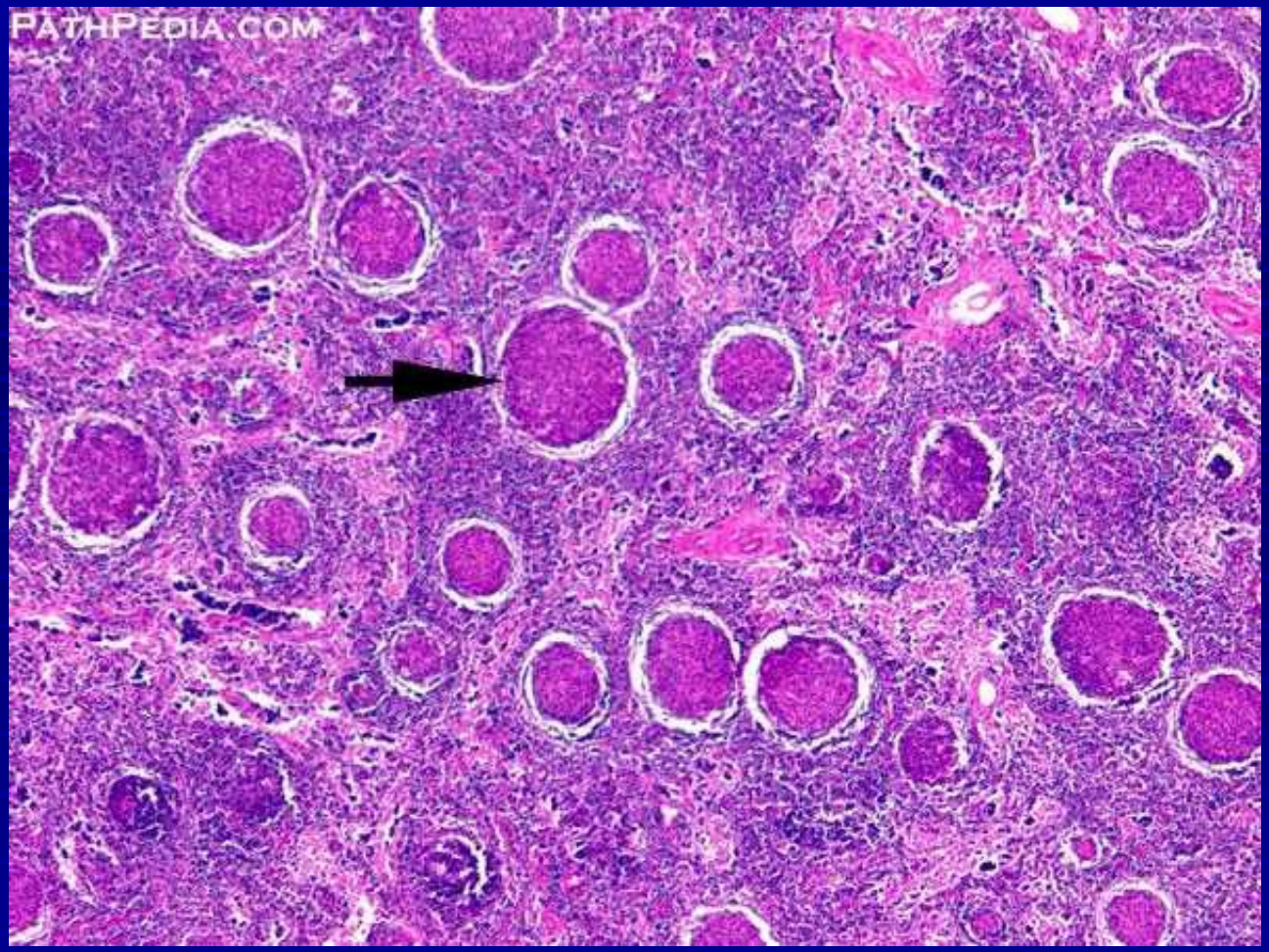
High-grade NHL has high proliferation rates, rapidly produces symptoms, is fatal if untreated, but is potentially curable.

Low-grade NHL has low proliferation rates, may be asymptomatic for many months or even years before presentation, runs an indolent course , but is not curable by conventional therapy

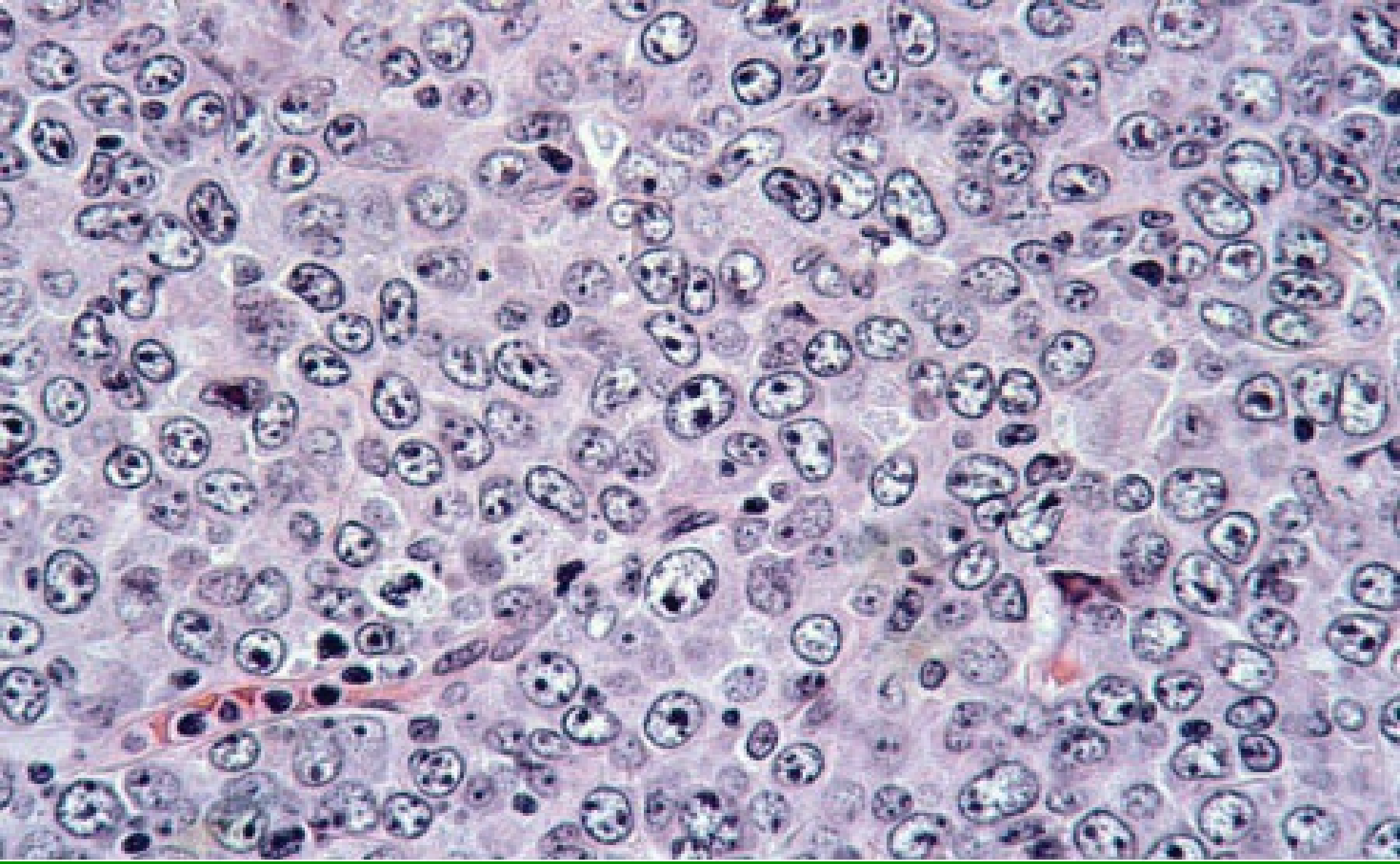
Of all cases of NHL in the developed world, over two-thirds are either diffuse large B-cell NHL (high-grade) or follicular NHL (low-grade) . Other forms of NHL, including Burkitt lymphoma, mantle cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphomas and T-cell lymphomas, are less common.

Major Non-Hodgkin's Lymphoma Types

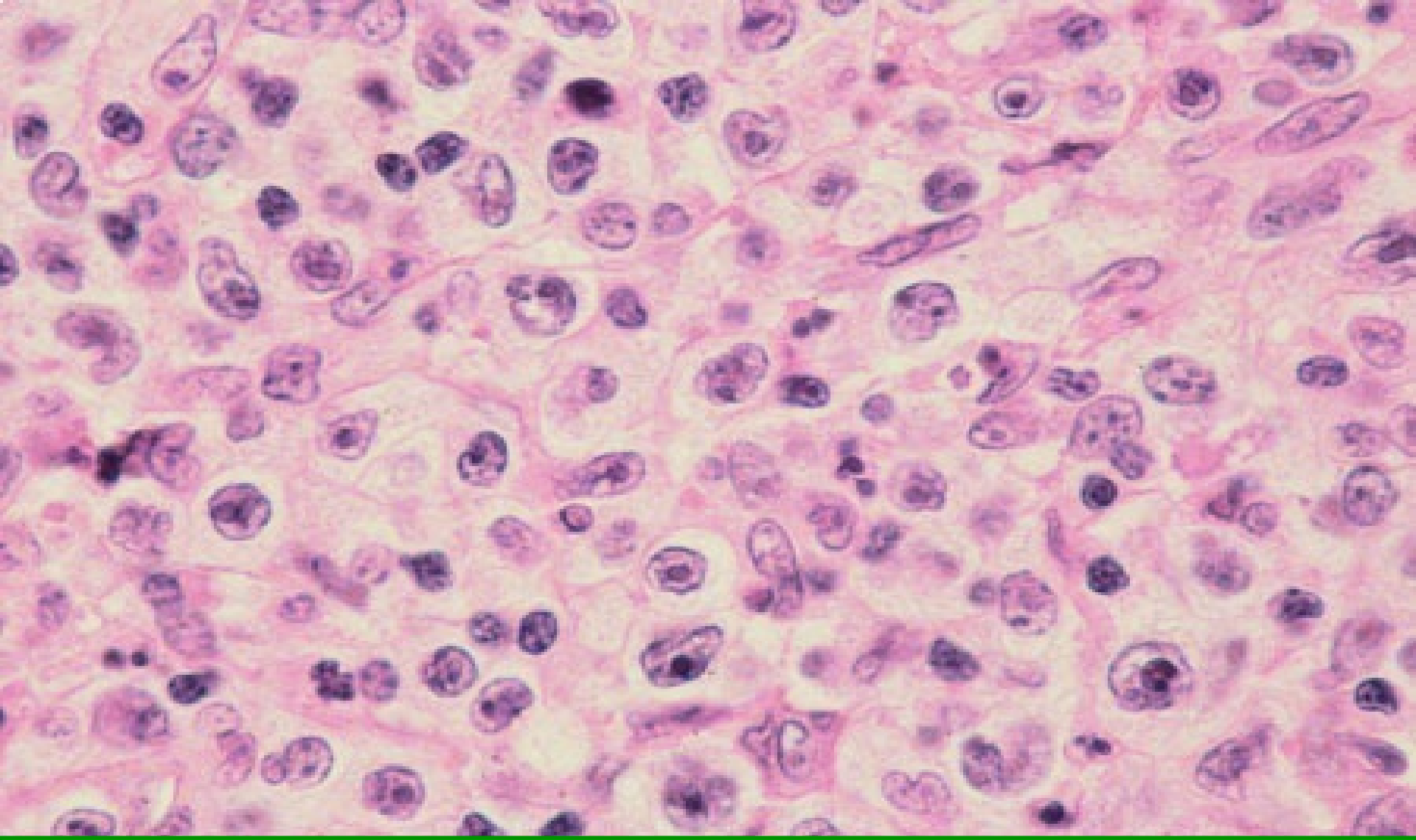
Category	Percentage Incidence
Diffuse large B-cell	31
Follicular	22
Marginal zone B-cell, MALT	8
Peripheral T-cell	7
Small B-lymphocytic (CLL)	7
Mantle Cell Lymphoma	6
Primary mediastinal large B-cell	2
Anaplastic large T/null cell	2
High grade B-cell, Burkitt-like	2
Marginal Zone B-cell, nodal	2
Precursor T-lymphoblastic	2



[FOLLICULAR LYMPHOMA]. Follicular lymphoma is the 2nd most common B-cell non-Hodgkin lymphoma after diffuse large B-cell lymphoma. It comprises up to 20% of lymphoma in adults in the USA and in Western Europe. As the name implies the lymphoma takes a “follicular” or nodular pattern of growth with or without diffuse areas.



Diffuse large B-cell lymphoma



Peripheral T-cell lymphoma

Clinical features

Unlike Hodgkin lymphoma, NHL is often widely disseminated at presentation, including in extranodal sites. Patients present with lymph node enlargement , which may be associated with systemic upset: weight loss, sweats, fever and itching.

Hepatosplenomegaly may be present.

Sites of extranodal involvement include the bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone. Bone marrow involvement is more common in low-grade (50–60%) than high-grade (10%) disease. Compression syndromes may occur, including gut obstruction, ascites, superior vena cava obstruction and spinal cord compression. The same staging system is used for both HL and NHL, but NHL is more likely to be stage III or IV at presentation.

Investigations

These are as for HL, but in addition the following should be performed:

- Bone marrow aspiration and trephine to identify bone marrow involvement.
- Immunophenotyping of surface antigens to distinguish T-cell from B-cell tumours. This may be done on blood, marrow or nodal material.

- Cytogenetic analysis to detect chromosomal translocations and molecular testing for T-cell receptor or immunoglobulin gene rearrangements.
- Immunoglobulin determination. Some lymphomas are associated with IgG or IgM paraproteins, which serve as markers for treatment response.

- Measurement of uric acid levels. Some very aggressive high-grade NHLs are associated with very high urate levels, which can precipitate renal failure when treatment is started.
- HIV testing. HIV is a risk factor for some lymphomas and affects treatment decisions.
- Hepatitis B and C testing. This should be done prior to therapy with rituximab.

Management

Low-grade NHL

The majority of patients (80%) present with advanced stage disease and will run a relapsing and remitting course over several years. Asymptomatic patients may not require therapy and are managed by 'watching and waiting'.

Indications for treatment

1-marked systemic symptoms,

2-lymphadenopathy causing discomfort or disfigurement.

3- bone marrow failure

4- compression syndromes.

In follicular lymphoma, the options are:

- **Radiotherapy.** This can be used for localised stage I disease, which is rare. FDG PET-CT-confirmed stage I disease has a 70% cure rate with radiotherapy.
- **Chemotherapy. Most patients will respond to oral therapy with chlorambucil, which is well tolerated but not curative** and is reserved nowadays for older/frail patients.

More intensive intravenous chemotherapy in younger patients produces better quality of life through long periods of remission

- **Monoclonal antibody therapy**

Humanaised monoclonal antibody can be uaed to target surface antigens on tumour cells and to induce tumour cell apoptosis directly.

The anti-CD20 antibody rituximab has been shown to induce durable clinical responses in up to 60% of patients when given alone, and acts synergistically when given with chemotherapy.

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Rituximab (R) in combination with cyclophosphamide, vincristine and prednisolone (R-CVP), cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) or bendamustine (R-bendamustine) is commonly used as first-line therapy.

Two years of maintenance therapy with single-agent rituximab, following achievement of first or second response, especially if this is only a partial response, delays the time to next treatment. As yet, however, rituximab maintenance has not shown a survival benefit. New and more potent monoclonal antibodies are in development; a recent trial of obinutuzumab combined with chemotherapy showed longer progression-free survival compared to similar chemotherapy with rituximab.

Targeted therapy.

The PI3 kinase inhibitor idelalisib is approved for relapsed follicular lymphoma and ibrutinib is approved for relapsed mantle cell lymphoma (a poor-prognosis lymphoma with low-grade histology, but aggressive clinical behaviour) and for relapsed Waldenstrom's macroglobulinaemia (also known as lymphoplasmacytic lymphoma. Newer targeted therapies are likely to become more widely used in low-grade lymphomas in the near future.

- **Transplantation.**

High-dose chemotherapy and autologous HSCT can produce long remissions in patients with relapsed disease. Decisions on the timing of such treatment are complex in the context of rituximab maintenance and newer targeted therapies. However, younger patients with short first or second remissions or who relapse during rituximab maintenance should be considered

High-grade NHL

Patients with diffuse large B-cell NHL need treatment at initial presentation:

- **Chemotherapy.**

The majority (> 90%) are treated with intravenous combination chemotherapy, typically with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone).

- **Monoclonal antibody therapy.**
  When combined with CHOP chemotherapy, rituximab (R) increases the complete response rates and improves overall survival. R-CHOP is currently recommended as first-line therapy for all relatively fit patients.

- *Radiotherapy.*

Stage I patients without bulky disease are **treated with four cycles of CHOP or R-CHOP, followed by involved site radiotherapy. Radiotherapy is also indicated for a residual localised site of bulk disease after chemotherapy, and for spinal cord and other compression syndromes.**

- **HSCT. Autologous**

  HSCT benefits patients with relapsed disease that is sensitive to salvage immunochemotherapy. As with HL, achieving PET negativity prior to autologous transplantation is desirable.

CAR-T-cell therapy

is licensed for certain patients with multiply relapsed DLBL or high-grade transformation of follicular lymphoma and can salvage patients from a desparate situation.

Prognosis

Low-grade NHL runs an indolent remitting and relapsing course, with an overall median survival of 12 years. Transformation to a high-grade NHL occurs in 3% per annum and is associated with poor survival. In diffuse large B-cell NHL treated with R-CHOP, some 75% of patients overall respond initially to therapy and 50% will have disease-free survival at 5 years.

The prognosis for patients with NHL is further refined according to the international prognostic index (IPI). For high-grade NHL, 5-year survival ranges from over 75% in those with low-risk scores

-age < 60 years,

- stage I or II,

- one or fewer extranodal sites,

-normal LDH

-good performance status)

5 years survival 25% in those with :high-risk scores

-increasing age,

-advanced stage,

-concomitant disease

- a raised LDH.

Relapse is associated with a poor response to further chemotherapy (< 10% 5-year survival), but in patients under 65 years HSCT improves survival.

THANK YOU