

***LYMPHOPROLIFERATIE
DISORDERS
OVERVIEW***

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TABLE 3: WHO classification of lymphoid neoplasms

B-cell neoplasms

Precursor B-cell neoplasm

Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)

Mature (peripheral) B-cell neoplasms

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Splenic marginal zone B-cell lymphoma (\pm villous lymphocytes)

Hairy cell leukemia

Plasma cell myeloma/plasmacytoma

Extranodal marginal zone B-cell lymphoma of MALT type

Nodal marginal zone B-cell lymphoma (\pm monocytoid B cells)

Follicular lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma

Mediastinal large B-cell lymphoma

Primary effusion lymphoma

Burkitt lymphoma/Burkitt-like lymphoma

T-cell and NK-cell neoplasms

Precursor T-cell neoplasm

Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

Mature (peripheral) T-cell neoplasms

T-cell prolymphocytic leukemia

T-cell granular lymphocytic leukemia

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia (HTLV-1+)

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-type T-cell lymphoma

Hepatosplenic γ/δ T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides/Sézary syndrome

Anaplastic large cell lymphoma, T-/null-cell, primary cutaneous type

Peripheral T-cell lymphoma, unspecified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma, T-/null-cell, primary systemic type

Hodgkin lymphoma (Hodgkin disease)

Nodular lymphocyte-predominant Hodgkin lymphoma

Classic Hodgkin lymphoma

Nodular sclerosis Hodgkin lymphoma (grades 1 and 2)

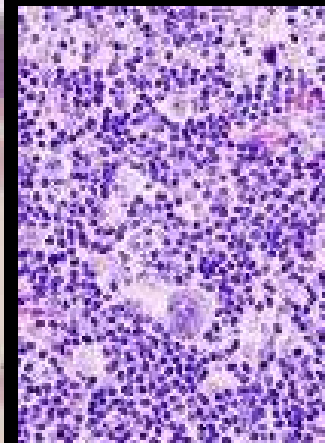
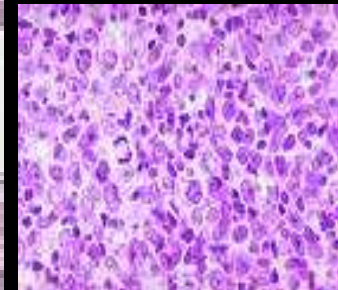
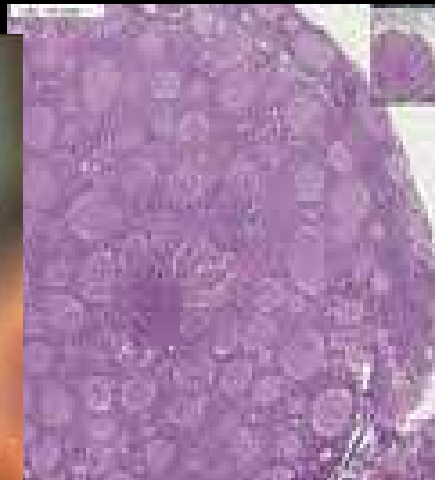
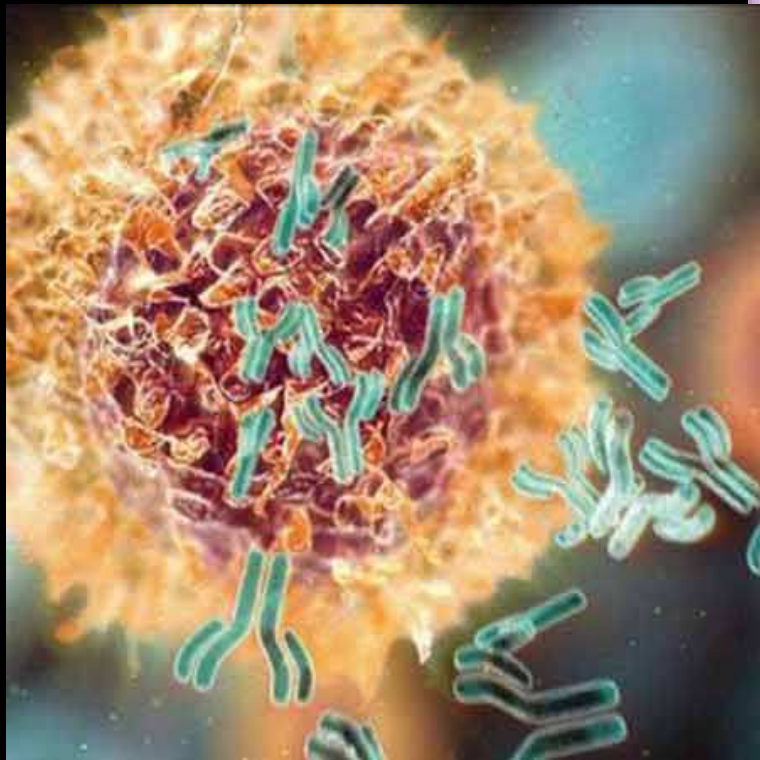
Lymphocyte-rich classic Hodgkin lymphoma

Mixed cellularity Hodgkin lymphoma

Lymphocyte-depletion Hodgkin lymphoma

Italic type denotes more common clinical entities. WHO = World Health Organization; MALT = mucosa-associated lymphoid tissue; NK = natural killer; HTLV-1 = human T-cell lymphotropic virus-1

Non-Hodgkin Lymphoma (NHL)



- **Increasing incidence**
- **11/100,000 in 1956 to 33/100,000 in 1996**
- **20-30% rise from 1997 to 2011¹**
- **Another 10% rise in the coming 10 yrs²**
- **Ranked 5th (M), 6th (F) for cancer mortality**

1. Ministry of Health: Cancer in New Zealand: Trends and Projections, Chapter 26: Non Hodgkin's Lymphoma, November 2002

2. Ministry of Health: Feb 2010

NZ Incidence

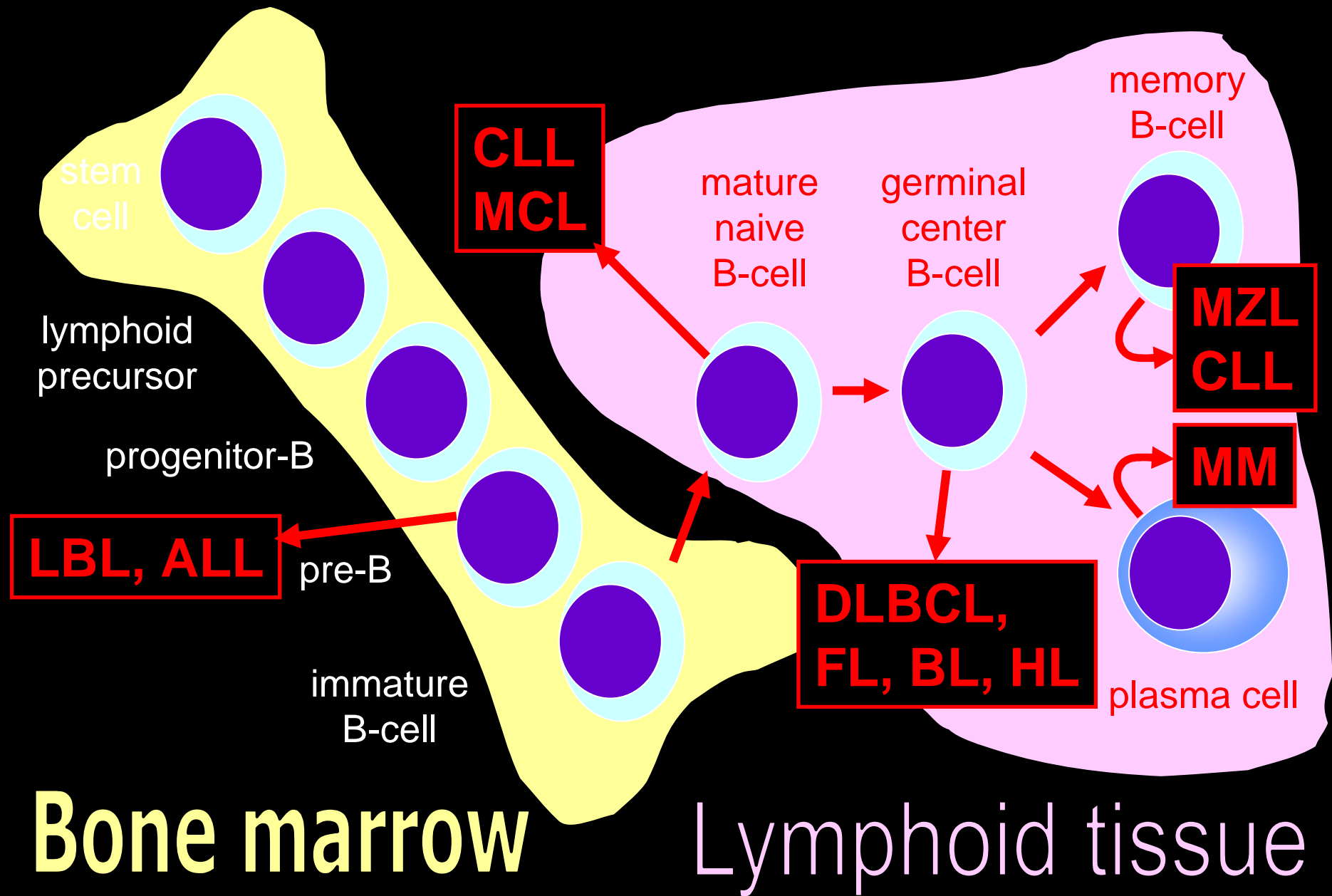
- **637 new cases in 2002, 47.1 % males**
- **Incidence is predicted to rise over the coming 10 years** (*cancer registry data 2010*)
 - **11.3 males***
 - **11.0 females***
 - **0.9 Maori males***

	Male		Female	
	Number	Rate*	Number	Rate*
2002 new registrations	297	11.3	340	11.0
2002 deaths	137	4.9	146	4.0

Types of NHL

- **Indolent Lymphoma (low grade)**
 - Life expectancy in years
 - 85-90% advanced stage (III or IV)
 - Incurable
- **Aggressive Lymphoma (high grade)**
 - Life expectancy in weeks
 - Potentially curable

B Cell Development



Aetiology

- **Unknown**
- **Immune suppression**
- **Chronic inflammation and antigenic stimulation**
- **DNA repair defects**
- **Viral & bacterial pathogenesis**

Clinical Features

- **Lymphadenopathy**
- **Hepatosplenomegaly**
- **B symptoms: fever, night sweats, wt loss**
- **Extranodal presentation**
 - **Skin - T cell NHL**
 - **CNS - especially HIV positive**
 - **GI tract, bone, lung, bone marrow**
 - **Panniculitis**
- **Cytopenia (BM involvement)**
- **Others: fatigue, pruritis**

Investigation of LN Enlargement

- **Careful history & examination**
- **Blood tests: FBC, infectious mononucleosis screen, other viral serology (CMV), throat swab, LFTs etc**
- **FNA – morphology & phenotype**
- **Tissue biopsy - usually lymph node but may be extra- nodal (marrow/spleen/skin/bone)**
- **Imaging: US scan, CT scan**

Staging

- **Examination and history**
- **FBC, ESR, LFT, biochemistry**
- **LDH, B2microglobulin**
- **Bone marrow biopsy**
- **Chest radiograph, ultrasound, CT scan chest, abdo, pelvis**
- **Lumbar puncture: AIDS lymphoma, T cell lymphoblastic lymphoma, High grade lymphoma with positive marrow**

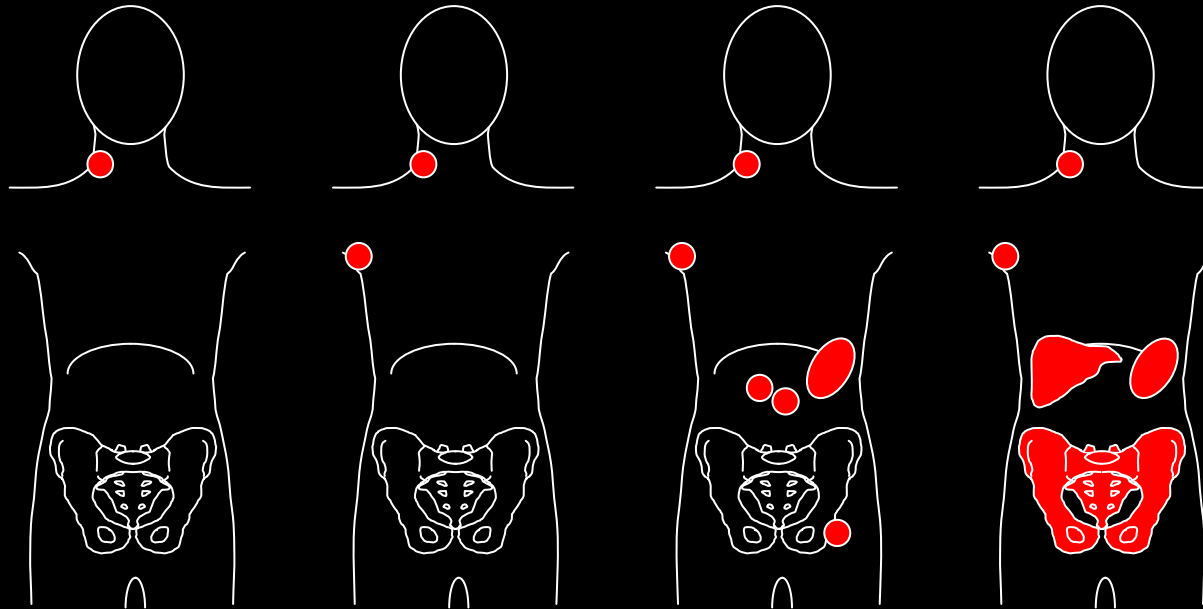
Staging of lymphoma

Stage I

Stage II

Stage III

Stage IV



A: absence of B symptoms

B: fever, night sweats, weight loss

International Prognostic Index (IPI) for DLBCL

score 0 to 5

Age > 60

High LDH

Poor performance status of patient

Stage 3, 4

Extranodal disease

Management

- **Review histology / confirm diagnosis**
 - Regional weekly lymphoma conference at ACH
 - Second opinions histology, marrow, radiology
 - Clinical input from haematologists, oncologists, radiotherapists
 - Consensus management plan

Therapy

Low grade NHL

– Stage I/II

- Involved field radiotherapy

– Stage III/IV

- Asymptomatic - wait and watch
- Symptomatic – chemo-immunotherapy (alkylating agents, fludarabine, etc..with Rituximab)
- When progress chemotherapy, immunotherapy, radioimmunotherapy, stem cell transplantation
- Median survival 8 - 10 years

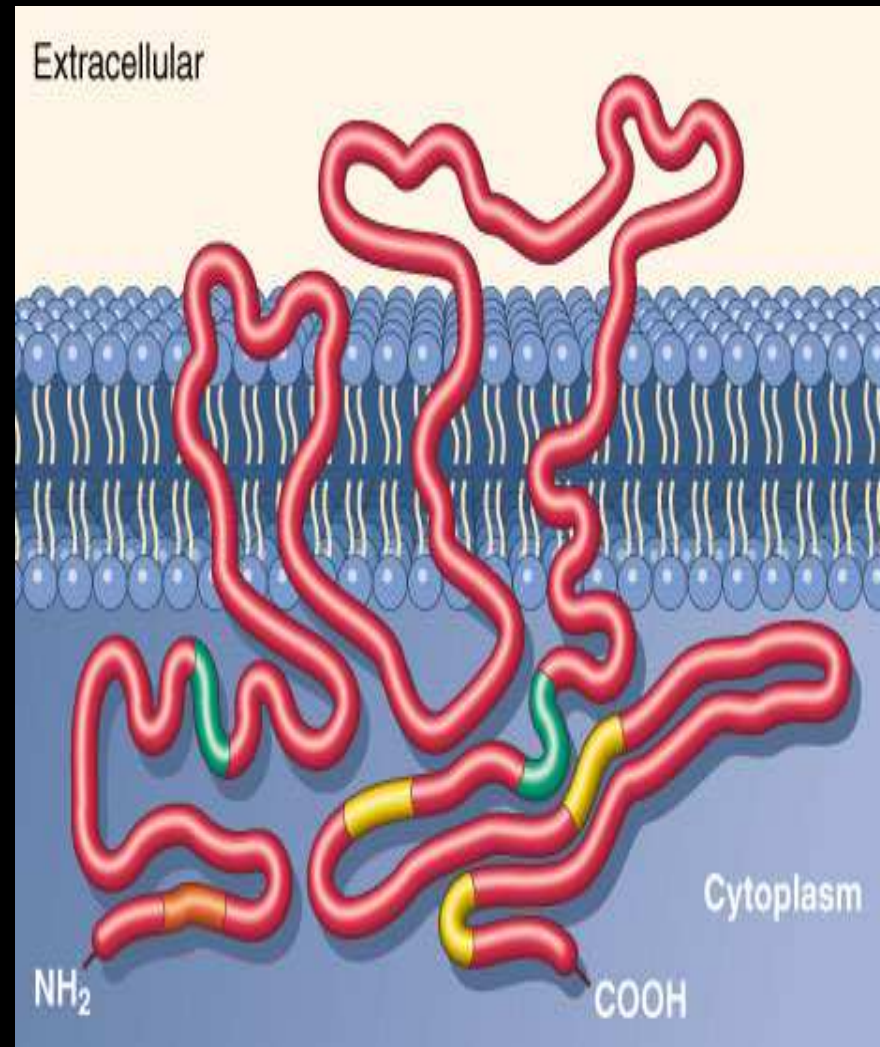
High grade NHL

- **Chemo-immunotherapy - RCHOP for diffuse large B cell lymphoma**
- **Early stage I/II - short chemotherapy and local RT**
- **If relapse - high dose therapy and autologous stem cell transplantation**

70% response rate, 40 - 50% long term DFS

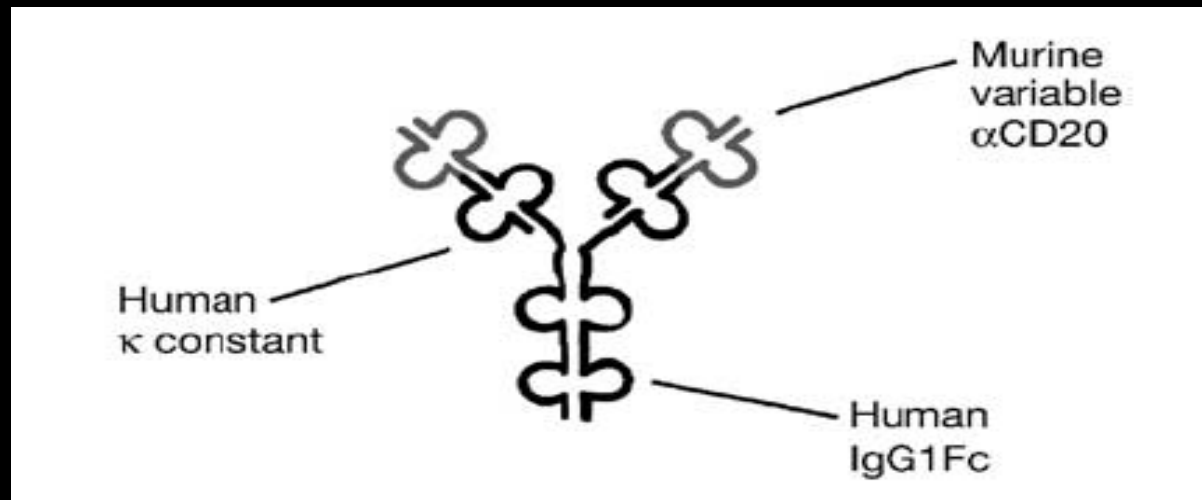
CD20: An Ideal B-cell Target

- **297 amino acid membrane-associated phosphoprotein (33–37 kD)**
 - Not shed
 - No known membrane/secreted molecular analogues (target interference)
 - Calcium channel function (?)
- **B-cell lineage antigen, *not* on:**
 - Stem cells, early pre-B cells, or plasma cells
- **Anti-CD20 binding:**
 - Does not down-modulate expression of CD20
 - Does not cause internalization of CD20



Rituximab

- Chimeric monoclonal antibody
- Developed 1980s by IDEC Pharmaceuticals
- Phase I trial 1994
- FDA approval 1997
- Targets the CD-20 antigen
 - Expressed on B-cell precursors and mature B-cells
 - NOT expressed on stem cells, plasma cells, dendritic cells, and other normal tissues
- Ideal treatment for CD20 +ve NHL



Hodgkin Lymphoma

- **Less common than NHL**
- **Highly treatable and curable**
- **? Cell of origin**
- **Hallmark Reed-Sternberg (RS) cells**
- **Most cells in affected lymph node are polyclonal reactive lymphoid cells**

Subtypes of Hodgkin Disease

- **Classical Hodgkin lymphomas (HL):**
 - Nodular sclerosis
 - Mixed cellularity
 - Lymphocyte-rich
 - Lymphocyte depleted or not depleted
- **Nodular lymphocyte-predominant HL**

Unlike NHL, histological subtype does not determine how the disease is treated, excepting in Nodular lymphocyte-predominant HL which is treated similar to low grade NHL

Clinical Manifestations

- **lymphadenopathy**
- **Hepatosplenomegaly**
- **“B” symptoms (night sweats, wt loss, fevers) are common**
- **Others: fatigue, pruritis**

Diagnosis

Fine needle aspirate is usually not sufficient to make the diagnosis of HL as it is hard to see the RS cells hence LN excisional biopsy is more informative

Staging of Hodgkin Disease

Same as for NHL

Treatment and Prognosis

Stage	Treatment	Failure-free survival	Overall survival
Early stage (I,II)	Short course chemo and/ or radiotherapy	70-80%	80-90%
Advanced Stage (III,IV)	Long course chemo +/- radiotherapy	60-70%	70-80%

Long Term Complications of Treatment

- **Infertility**
- **Secondary malignancy**
- **Premature cardiac disease**
- **Fatigue**
- **Social & Financial**

UNDERSTANDING LYMPHOMA

The lymphatic system

The lymphatic system is part of the immune system, playing a major role in the body's defence against infection and disease. The lymph nodes, which are filled with lymphocytes, act as trap doors for germs, clearing the lymph fluid as it passes through them. Like a coffee strainer and other household filters, as one germ is removed and destroyed, lymph fluid is constantly fed from the lymphatic system. When fighting infection, they become enlarged. Nodes are located throughout the body and normally do not feel like lumps, glands or nodes. There are thousands of nodes in the abdomen, pelvis and chest.

What is lymphoma?

Lymphoma is the general term for cancers that develop in the lymphatic system. Lymphoma often starts in developing B-lymphocytes and T-lymphocytes, which have undergone malignant change. This means they multiply without any proper code for regulation, which are collectors of cancer cells. These cancer cells usually swell in the lymph nodes and other parts of the body. One type, called lymphocyte (diffuse) lymphoma, only crowd out normal lymphocytes and eventually the immune system becomes weakened and infection is more likely to happen.

Signs & symptoms

Lymphoma commonly presents to others usually a slight swelling of lymph nodes. This is usually in the neck, under the arm or in the groin. It may include an enlarged spleen, which is a lymphatic organ in the abdomen.

Other symptoms may include

- Swollen, aching, enlarged lymph nodes
- Fatigue
- Recurrent fevers
- Persistent cough
- Unexplained weight loss
- Abdominal swelling and pain

The signs and symptoms of lymphoma can often be mistaken for other less serious illnesses.

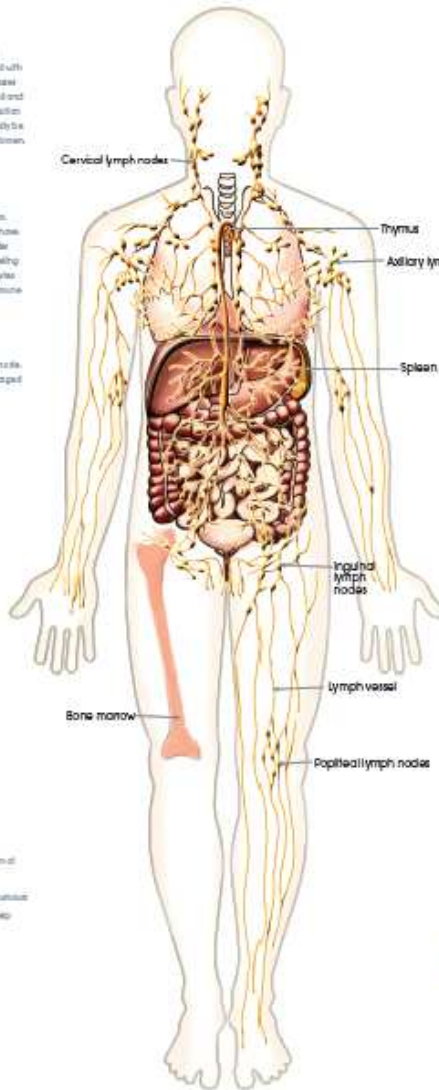
Diagnosis

To confirm a diagnosis the following investigations may be required:

- Physical examination
- Blood tests
- Lymph node biopsy
- Bone marrow biopsy
- Imaging (ultrasound, CT scan, MRI scan)

Treatment options

- Curative chemotherapy without active treatment
- Supportive therapy - treatment using steroids
- Chemotherapy - treatment using anti-cancer drugs, which is a combination of cytotoxic drugs given in set cycles
- Radiotherapy - because of high energy rays to kill cancer cells and shrink tumours
- Biological therapies - harness the power of the body's immune system to help fight lymphoma
- Stem cell transplant
- Supportive care to assist the patient and their family during treatment and recovery



Types of lymphoma

There are many different sub-types of lymphoma. The diffuse sub-types belong to a group of diseases called Hodgkin lymphoma. All other sub-types are commonly grouped together and called non-Hodgkin lymphoma.

Non-Hodgkin lymphoma

Both in terms of being a single disease or through lymphoma actually represents many different sub-types of lymphoma. In addition lymphoma can arise from cells (lymphocytes) that normally act as T-lymphocytes. For example, some lymphomas can be broadly divided into two main groups: indolent lymphoma or aggressive lymphoma.

Low grade lymphoma (or indolent lymphoma)

This type of lymphoma grows slowly, causes few symptoms and may not need to be treated urgently. Follicular lymphoma is one type of low grade lymphoma. It is the most common type of lymphoma, representing 33% of all cases.

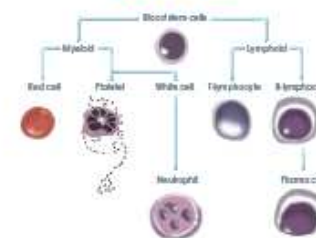
Intermediate and high grade lymphoma (or aggressive lymphoma)

This type of lymphoma grows quickly and treatment is needed at the time of diagnosis. Because these lymphomas grow quickly they tend to respond well to chemotherapy and radiation therapy. Diffuse large B-cell lymphoma is the most common type of lymphoma, representing 25% of all cases.

Hodgkin lymphoma

In terms of presentation and treatment this lymphoma is most often called diffuse large cell lymphoma. There are different sub-types, the combination chemotherapy is different to that of other aggressive lymphomas. The correct microscopic diagnosis is important in determining lymphoma type.

Blood cells



Multiple Myeloma

- **Less common than NHL**
- **Average life expectancy 30 -36 ms**
- **Some patients live for 10 yrs or more**
- **Potentially curable with high dose chemotherapy (bone marrow or stem cell transplantation)**

Etiology of Multiple Myeloma

Largely unknown

Types of Plasma Cell Disorders

- **Multiple Myeloma**
 - **Indolent Myeloma**
- **Solitary Plasmacytoma**
- **Monoclonal Gammopathy of Undetermined Significance (MGUS)**

Diagnostic Criteria

- **Symptomatic Myeloma:**
 - Clonal plasma cells >10% on BMB or (in any quantity) in a biopsy from other tissues (plasmacytoma)
 - Monoclonal protein (serum or urine)
 - Evidence of end-organ damage
 - Hypocalcaemia
 - Renal insufficiency attributable to myeloma
 - Anaemia
 - Bone lesions

- **Asymptomatic Myeloma:**
 - Serum paraprotein >30 g/L **AND/OR**
 - Clonal plasma cells >10% on BMB **AND**
 - **NO** myeloma-related organ/ tissue impairment
- **Monoclonal Gammopathy of Undetermined Significance (MGUS):**
 - Serum paraprotein <30 g/L **AND**
 - Clonal plasma cells <10% on BMB **AND**
 - **NO** myeloma-related organ/tissue impairment

Clinical Features

- **Bone marrow failure**
 - **Anemia, thrombocytopenia, neutropenia**
- **Renal failure**
- **Bone disease with skeletal destruction**
 - **lytic lesions**
- **Hypercalcemia**

Diagnosis

- **Bone marrow biopsy**
- **Serum protein electrophoresis & immunofixation**
- **Skeletal survey**
- **Serum free light chains assay**
- **Urine Bence-Jones protein**

Staging

- **Stage I:** β_2 -microglobulin ($\beta 2M$) < 3.5 mg/L, albumin ≥ 3.5 g/dL
- **Stage II:** $\beta 2M < 3.5$ and albumin < 3.5 ; or $\beta 2M \geq 3.5$ and < 5.5
- **Stage III:** $\beta 2M \geq 5.5$

Prognostic Factors

Poor prognosis

- Age > 65
- High tumor mass
- High β 2 microglobulin
- Renal failure, hypercalcemia
- Hypoalbuminaemia

Treatment

Standard Chemotherapy

- Melphalan and prednisone
- CD (cyclophosphamide, Dexamethasone)
- VAD (vincristine, adriamycin, dexamethasone)
- Thalidomide

High Dose Chemotherapy

- Peripheral stem cell transplant

Other Modalities

- **Pulse dexamethasone**
- **Local radiotherapy**
- **Pamidronate and other bisphosphonates**
- **Velcade (Bortezomib)**
- **Revlimid (Lenalidomide)**

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- “Benign” monoclonal gammopathy
- Present in 1% of healthy adults at age 40, rises with age, **5.3 % in 70 yrs or older and 7.5% in 85 yrs persons**
- Rate of progression to Plasma cell dyscrasia is 1% / year
- Follow-up should be **6 monthly (FBC, Ca, renal function, Ig level & SPE)**

