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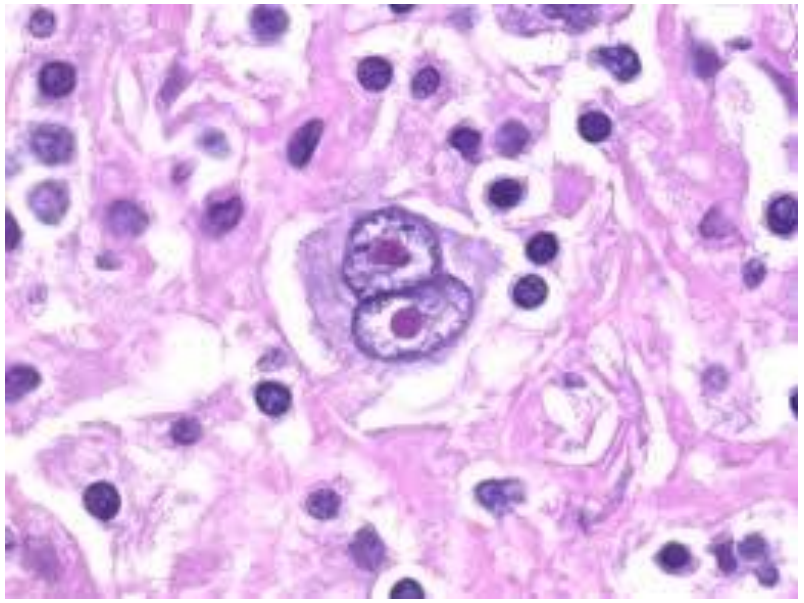
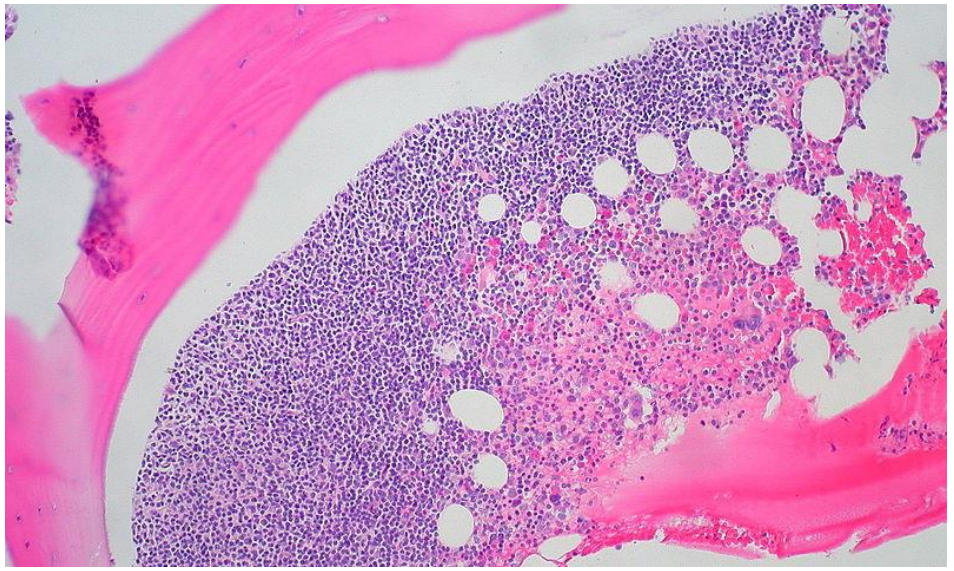
Lymphoma:
A Multidisciplinary Approach.

Presented By

Jennifer Mills





Outline of Lecture.

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- Overview of Lymphoma vs. Lymphoproliferative Disease.
- The role of Blood Sciences in Lymphoma diagnosis.
  - Haematology
  - Biochemistry
  - Immunology.
- How lymphomas are staged and treated.
- The role of Blood Sciences in monitoring and support.
- Further Treatment options.

Introduction.

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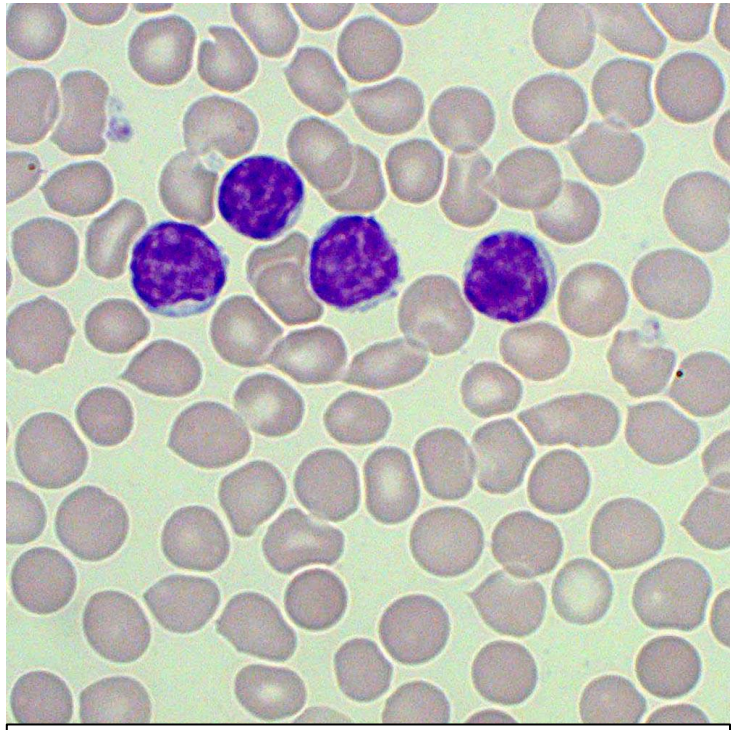

Normal Lymphocytes in Peripheral Blood.

- Malignancy affecting lymphocytes.
- Not the ONLY type of lymphocyte malignancy.
  - Differentiating between lymphoma and other disorders is key in diagnosis.
- **Lymphoma originates in lymph nodes**.
  - Can spread to the bone marrow.
  - Can “spill over” into peripheral blood.
- Different to other haematological malignancies.
  - Blurs the line between haematological and solid organ malignancy.
  - This is reflected in diagnosis and management.

Lymphocytes: Basics.

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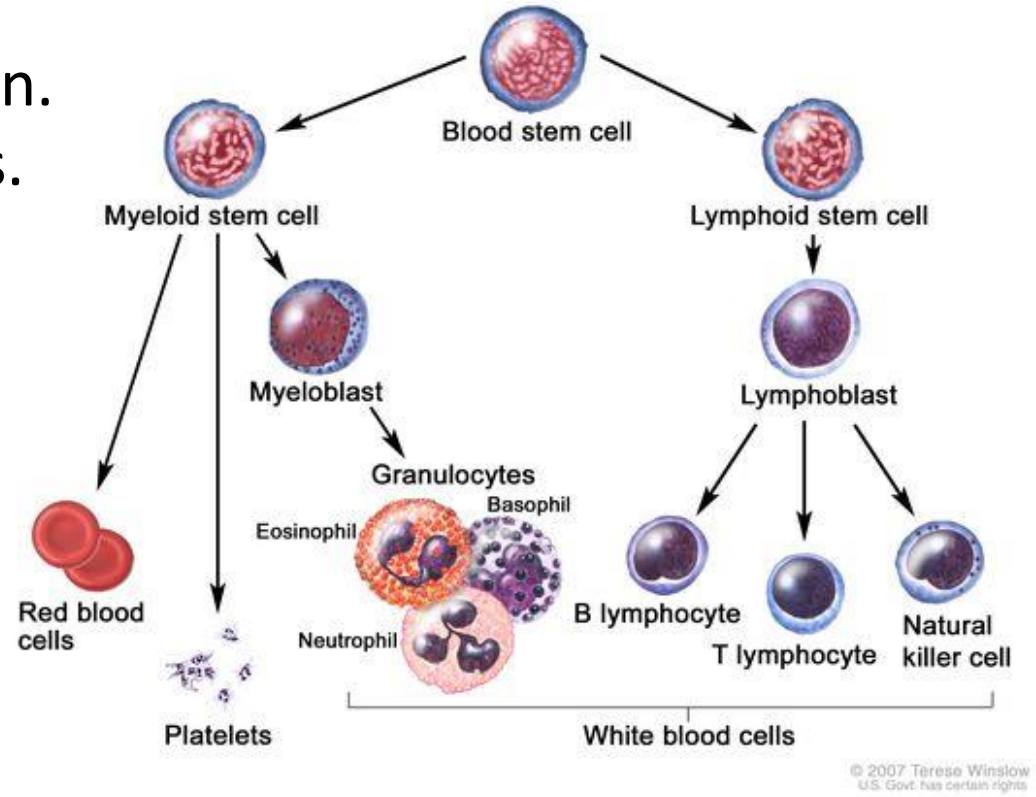
- Part of the **adaptive** immune response.
  - Make antibodies to help fight of infection.
  - Retain memory to fight future infections.
- Come in **three** main types:
  - B-cells.
  - T-cells.
    - T-helper cells.
    - Cytotoxic T-cells.
  - Natural Killer Cells.
- Initially made in the bone marrow.
- Circulate in small numbers in the peripheral blood.
- Function in the lymph nodes.



Lymphoma vs. Lymphoproliferative.

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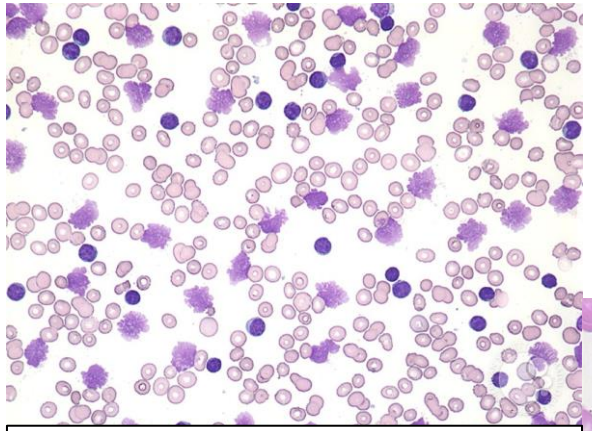
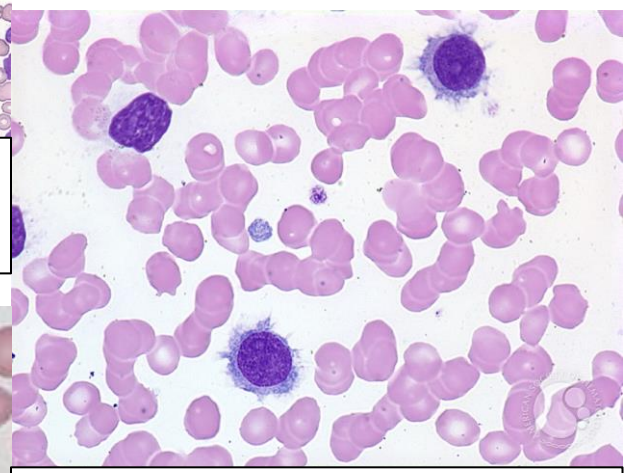
- Lymphomas are not the only type of lymphocyte malignancy.
- Other types of Lymphoproliferative disorders (LPDs) originate in bone marrow.
  - Present in peripheral blood and are diagnosed using bone marrow.
- LPD's can still found in lymph nodes.

- **Both** are **chronic** diseases.
  - Mature cells with <20% blast population.
  - That doesn't mean they can't be dangerous!
- **Both** fall under the following WHO classifications:
  - **Mature B-cell neoplasms.**
  - **Mature T- and NK-cell neoplasms.**
  - **Hodgkin Lymphoma**.

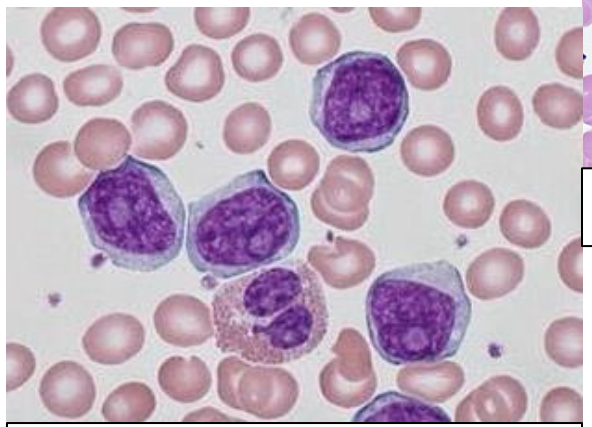
Examples of LPD's.



Chronic Lymphocytic Leukaemia



Hairy Cell Leukaemia



B-cell prolymphocytic leukaemia

- Chronic Lymphocytic Leukaemia.
- B-cell prolymphocytic leukaemia.
- Hairy Cell Leukaemia.
- T-cell Prolymphocytic leukaemia.
- T-cell large granular lymphocytic leukaemia.
- Chronic lymphoproliferative disorder of NK cells.
- Aggressive NK cell leukaemia.
- Sézary syndrome.

Lymphoma: Statistics.

- Like most haematological malignancies, lymphoma is rare.

Incidence.

- Accounts for 1-4% of total cancer cases in the UK.
- Non-Hodgkin Lymphoma is the 7th most common cancer in the UK.
- Hodgkin Lymphoma is the 19th most common cancer for males.

Risk Factors.

- Slightly more common in males.
- Typically affects older people (75-84 years old.)
- Exposure to mutagenic chemicals.
- Other conditions e.g. HIV.

Hodgkin vs. Non-Hodgkin.

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There are two main “types” of lymphoma.

Hodgkin Lymphoma.

- Specific type of lymphoma.
- Often present in cervical (neck) lymph-nodes.
- **Identified by the presence of Hodgkin and Reed-Sternberg Cells (HRS)**
- No HRS? Likely Not Hodgkin Lymphoma!

Non-Hodgkin Lymphoma.

- **ALL other types of lymphoma!**
- Can vary significantly in the way cells look, which lymph-nodes they originate in, aggression etc.
- Can be difficult to distinguish from LPDs.

Hodgkin Lymphoma: Examples.

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- There are **6 Entries** under the WHO classification of **Hodgkin Lymphoma.**
- These are ALL lymphoma.

World Health Organization

Hodgkin Lymphoma.
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma, introduction
Nodular sclerosis classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

Non-Hodgkin Lymphoma: Examples.

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- There are **34 Entries** **Mature B-cell neoplasms.**
- There are **23 Entries** **Mature T- and NK-cell neoplasms.**

Not all of these are lymphoma!

Mature B-cell neoplasms lymphomas	Mature T- and NK-cell neoplasms lymphomas.
Splenic marginal zone lymphoma	Adult T-cell leukaemia/lymphoma
Lymphoplasmacytic lymphoma	Enteropathy-associated T-cell lymphoma
Nodal marginal zone lymphoma	Angioimmunoblastic T-cell lymphoma
Follicular lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Mantle cell lymphoma	Peripheral T-cell lymphoma, NOS
Burkitt lymphoma	Primary cutaneous peripheral T-cell lymphomas
Diffuse large B-cell lymphoma (DLBCL), NOS	Hepatosplenic T-cell lymphoma

Non-Hodgkin: Aggressive vs. Indolent

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Indolent lymphomas:

- Grow slowly.
- May not spread from original site.
- Often asymptomatic.
- May not require treatment.
- Also known as **low grade**.

Aggressive lymphomas:

- Grow rapidly.
- Spread faster.
- Will always have symptoms e.g. pain, weight loss.
- Higher mortality.
- Also known as **high grade**.

Non-Hodgkin: Aggressive vs. Indolent

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Aggressive Types.	Indolent Types.
Burkitt's Lymphoma	Follicular Lymphoma
Diffuse large B-cell Lymphoma	Marginal Zone Lymphoma
Peripheral T-cell lymphoma	Cutaneous T-Cell Lymphoma
Angioimmunoblastic lymphoma	Lymphoplasmacytic lymphoma

- Some types of lymphomas are **always** aggressive.
- Some low grade types can **transform** to high grade.

Clinical Presentation.

- Lymph node enlargement.
  - **Key Feature**.
  - Often painless.
- T-cell types can present with skin infiltration (sores/rashes).
- Constitutional Symptoms (B-Symptoms).
  - Weight loss (>10% of body weight in 6 months.)
  - Extreme Fatigue.
  - Hepatosplenomegaly.
- May have cytopenia symptoms.
  - Anaemia: ↓**Red Cells**
  - Easily bruising and bleeding: ↓**Platelets**
  - Increased incidence of infection: ↓**Neutrophils**

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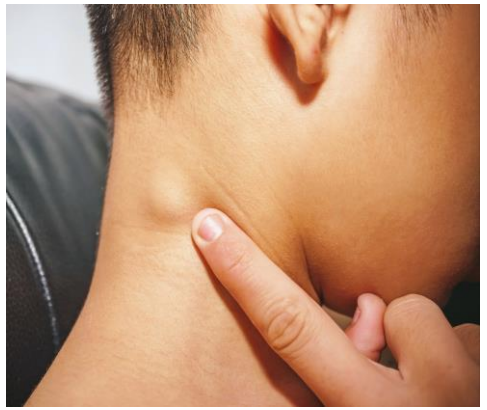

Diagnosis: Biochemistry

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- **May be normal!**

- **Common abnormal markers:**
  - **↑LDH:** Cell turn over marker.
  - **↑β2M:** General tumour cell marker.
  - **↑CRP:** Inflammation marker.
  - **↑Total Protein**: **IF** a paraprotein is produced.

- Other organs may be damaged by lymphoma infiltration.
  - **Liver Dysfunction** (↑Bilirubin ↑ALT/AST)
  - **Renal Dysfunction** (↑Urea ↑Creatine)

Diagnosis: Other Specialities

- **Immunology.**
  - Some Lymphomas produce a paraprotein.
    - Lymphoplasmacytic lymphoma: IgM

- **Microbiology.**
  - Patients with HIV/AIDS are at higher risk of:
    - Burkitt's Lymphoma.
    - Primary CNS lymphoma.
  - Epstein Barr Virus can trigger:
    - Burkitt's Lymphoma.
    - Hodgkin Lymphoma.
    - Diffuse Large B cell Lymphoma.

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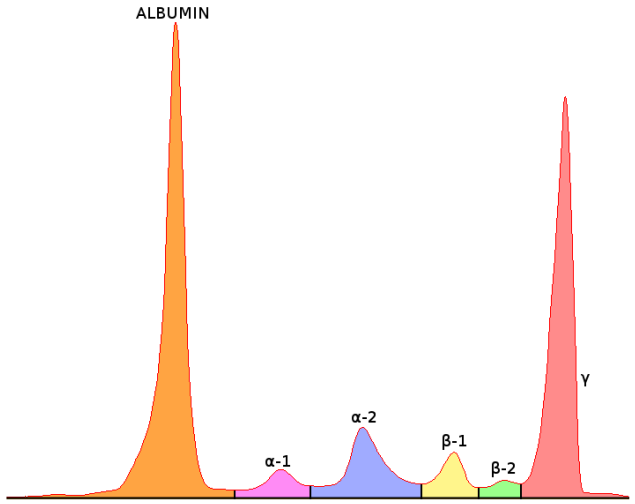

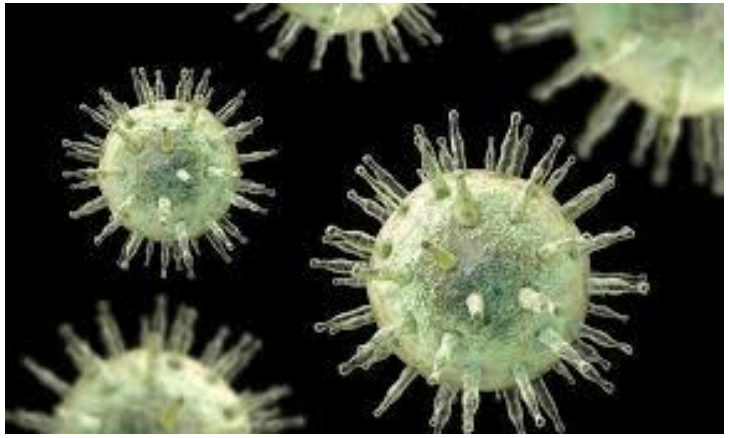

Diagnosis: Haematology

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- **May be normal!**

- **Full Blood Count:**
  - ↓**Red cells and**↓ **Platelets:** Bone marrow infiltration.
  - Changes to **white cells**:
    - ↑ **Lymphocytes:** Spill-over from affected organs.
    - ↓ **Other white cells** e.g. neutrophils: Marrow infiltration.
- **ESR**: Increased if there's a paraprotein.
- **Blood Film:**
  - Identifies LPD’s or other leukaemia's.
  - **MAY** identify lymphoma cells if there is spill-over from organs.

Diagnosis: Morphology.

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- Lymphoma is identified in lymph nodes.
- A biopsy is taken of a suspicious node.
  - Different methods depending on node location:
    - Fine Needle Aspirate.
    - Core Needle Biopsy.
    - Open Biopsy.
- Reviewed by Histologists or Lymphoma specialists.
- Bone marrow biopsies are part of diagnosis.
- Peripheral blood shouldn’t be used for diagnosis.

Diagnosis: Morphology: Hodgkin.

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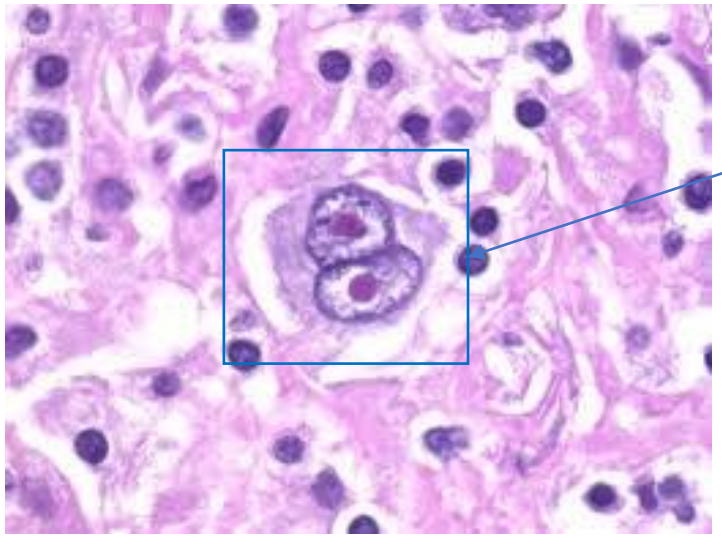
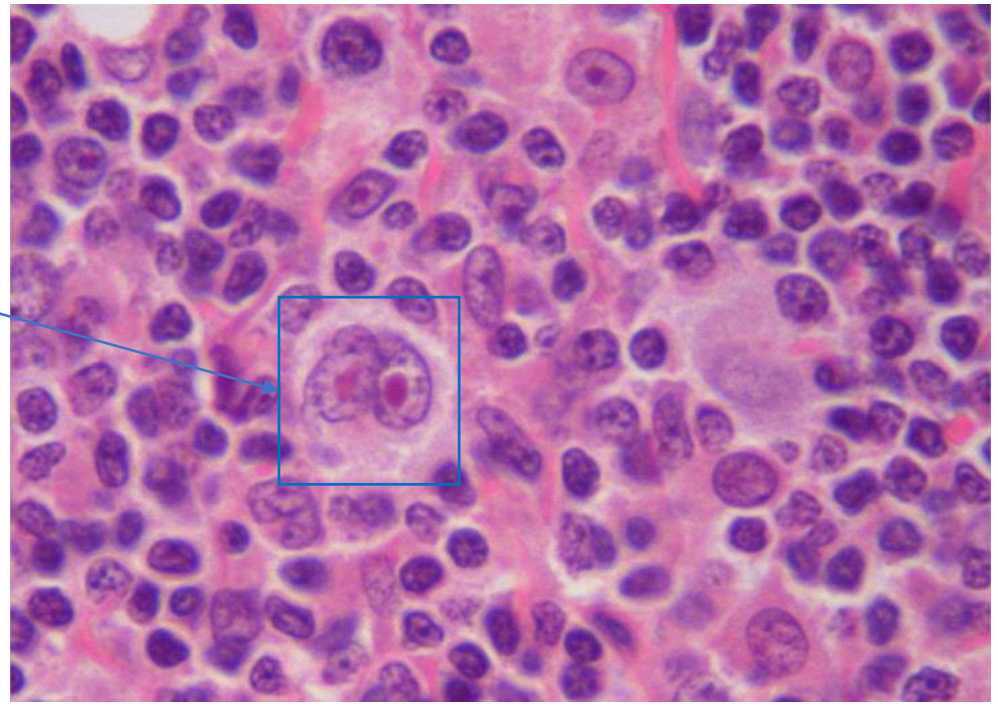
- Hodgkin lymphoma is rarely seen in marrow.
- Never seen in peripheral blood.
- Key feature is the **Hodgkin Reed-Sternberg Cells.**
  - May be infiltration of other lymphoid cells such as T-cells around the HRS cells.
- Eosinophilia is common.



Examples of **Hodgkin Reed-Sternberg Cells.**



Diagnosis: Morphology: Non-Hodgkin.

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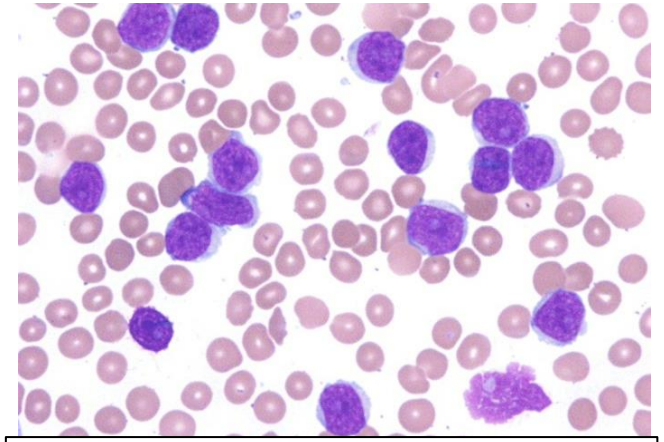
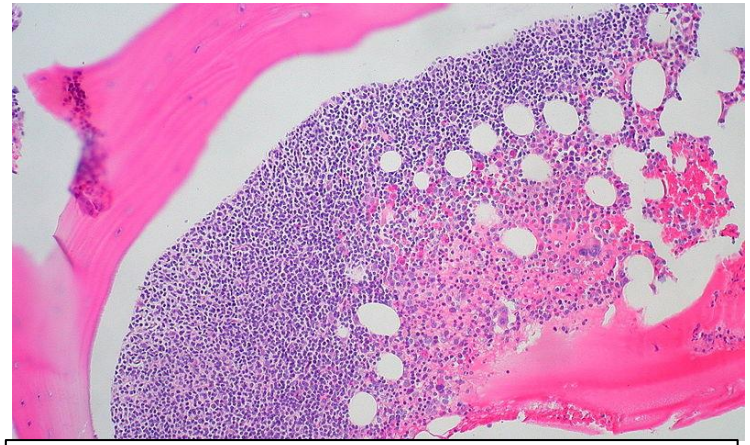
- Can be seen in the bone marrow in advanced stages.
- Sometimes seen in peripheral blood.
  - Lymphocyte counts can be >100x10^9/L. (Reference: 4-11x10^9/L)
- Lymphocytes look different depending on the lymphoma.
- There are different bone marrow distributions.
  - Nodular.
  - Interstitial.
  - Para-trabecular.
- This is a valuable part of diagnosis!

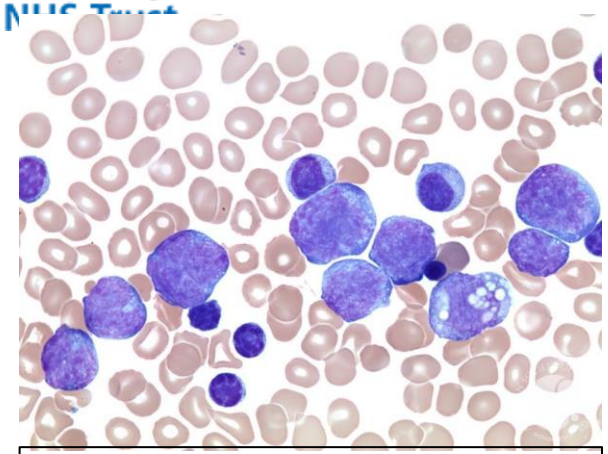
Morphological Identification: Non-Hodgkin.



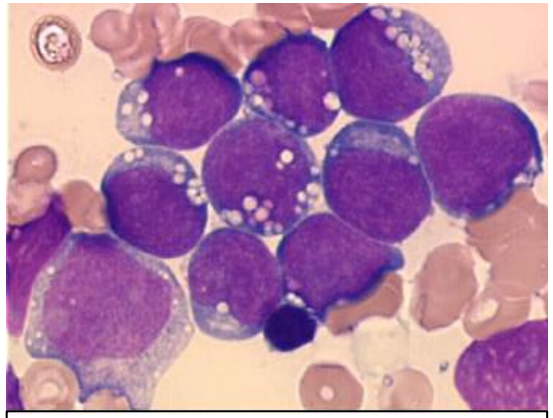
Follicular Lymphoma in Peripheral Blood.



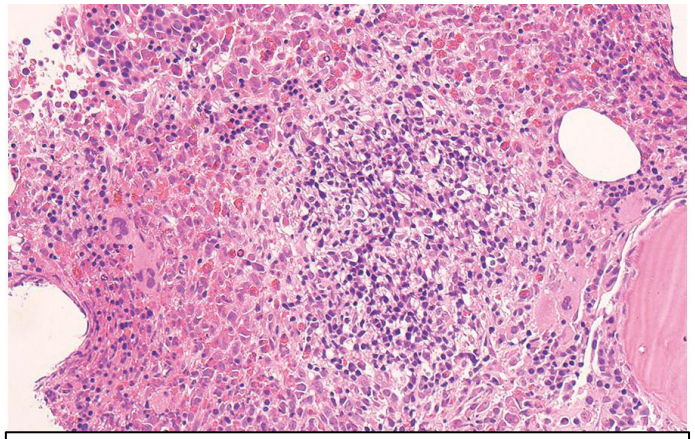
Follicular Lymphoma in Bone Marrow.



Diffuse Large B-cell in Peripheral Blood.



Burkitt's in Bone Marrow.



Lymphoma Nodule.

Diagnosis: Immunophenotyping.

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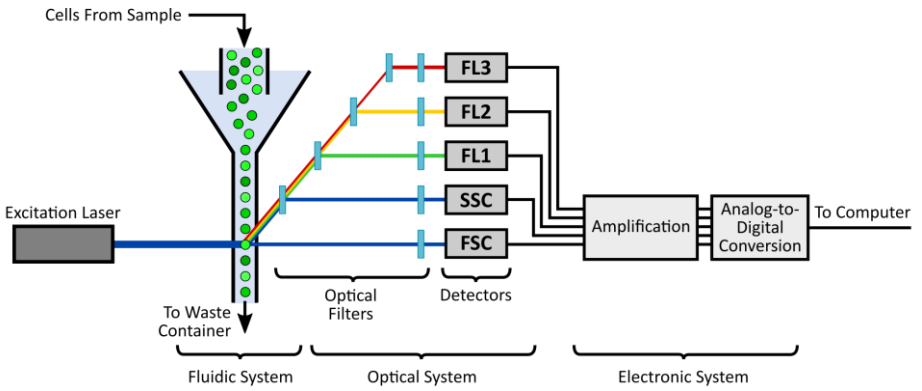
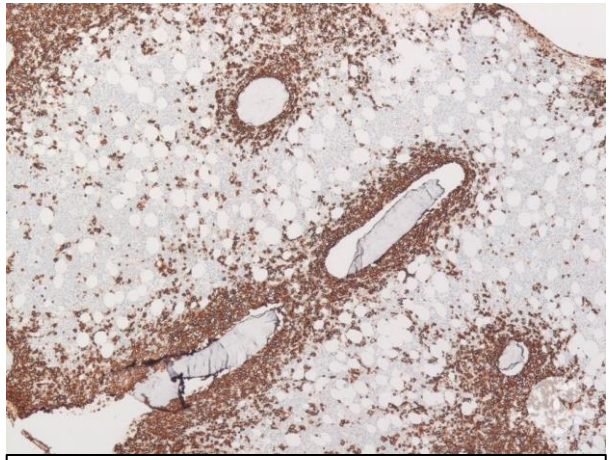
- This can be done by **flow cytometry** or by **immunohistochemistry.**
- Different cell types express different markers.
  - These are “clusters of differentiation/CD Markers.”
- Lymphoma cells can be identified by expression of surface CD markers.
  - The combination of markers can tell us what lymphoma the patient has.
  - Supports and confirms morphological findings.





CD20 staining of Follicular Lymphoma.

Diagnosis: Immunophenotyping.

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CD Marker	Normal Cells.		Lymphomas				
	B-cell	T-helper	Hodgkin	Mantle Cell	Follicular	Angioimmunoblastic T-cell	Burkitt's
CD45	+	+	-	+	+	+	+
CD19	+	-	-	+	+	-	+
CD20	+	-	+/-	+	+	+	+
CD5	-	+	-	-	+	-	-
CD10	-	-	-	+	-	+/-	+
CD30	-	-	+	-	-	-	-
CD15	-	-	+	-	-	-	-
CD4	-	+	-	-	-	+	-
CD43	+/-	+	-	+	-	+	+

Diagnosis: Genetics.

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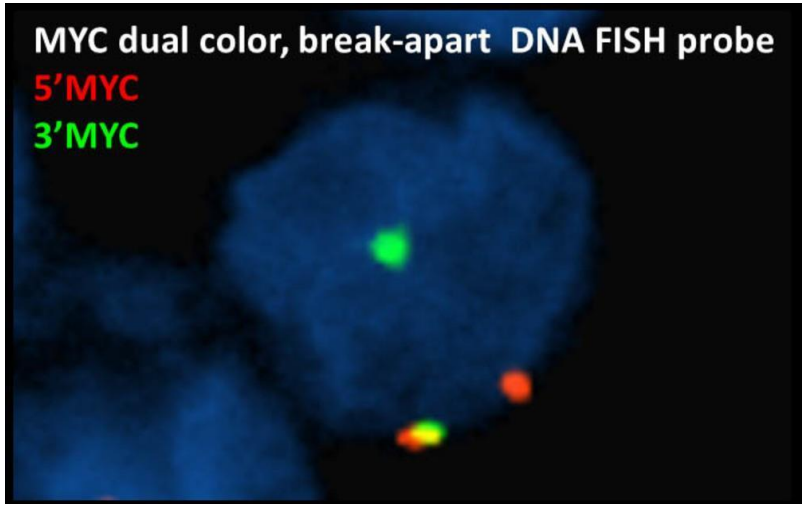
- Some lymphomas have diagnostic mutations.
- Others have generic mutations:
  - These may be diagnostic in combination with other features.
  - Or are useful for prognosis.
- Testing can be done on any tissue sample containing lymphoma cells.
- Testing includes:
  - Karyotyping.
  - Fluorescence *In Situ* Hybridisation.
  - Molecular techniques e.g. Next Generation Sequencing.



Diagnosis: Genetics: Examples.

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t(8;14)(q24;14q32) *MYC/IGH* gene rearrangement.

- The *IGH* gene is commonly involved in B-cell lymphomas.
- Mutations involving MYC are common in high grade disease e.g. **Burkitt's Lymphoma.**

t(14;18)(q32;q21) *IGH/BCL2* gene rearrangement.

- Seen in 80% of **Follicular Lymphoma.**

T-Cell Receptor Rearrangement.

- Clonal populations have the same T-cell receptor.

Del(17p) or Molecular *TP53* Mutations.

- Common in many leukaemia's.
- Associated with aggressive disease/poor prognosis.

Staging.

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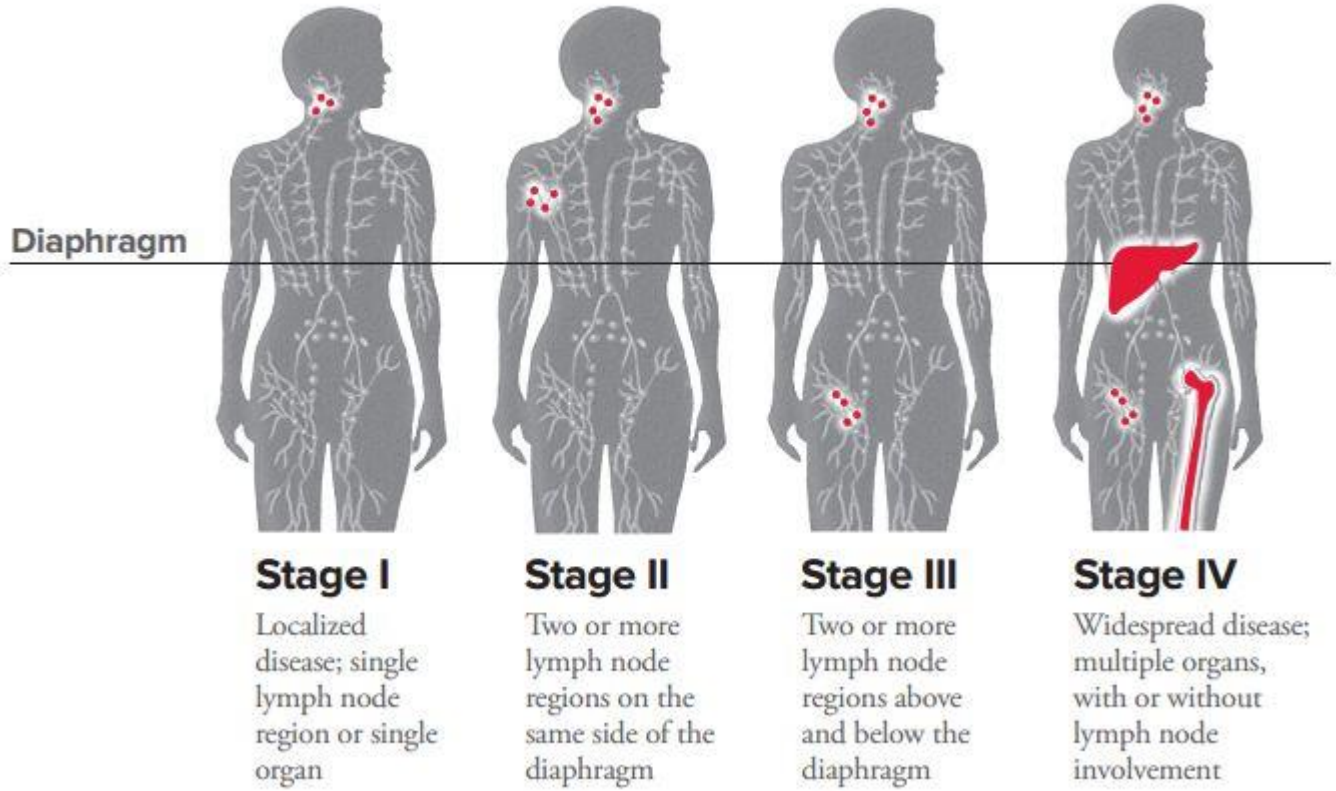
- Imaging is used stage lymphoma.
- PET/CT can show smaller areas of disease.
- Lymph nodes position is important.
- Affected nodes on **both sides** of the diaphragm suggest **increased spread.**
- Involvement of nonlymphoid organs indicates **metastasis.**
- Bone marrow analysis is part of staging, not just diagnosis!

Ann Arbor Staging Criteria.



Treatment.

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- There are lots of options.
- Depends on stage, location of nodes, comorbidities, age etc.

"Watch and Wait"

- Patients with indolent disease.
  - Only in cases where the disease is stage I or II.
- Patients who are asymptomatic.

Cytotoxic Chemotherapy.

- Advanced stages.
- Aggressive disease.
- Combinations of drugs to kill proliferating cells.
- **CHOP:** cyclophosphamide, doxorubicin, vincristine and prednisolone
- **DA-EPOCH-R:** etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, hydroxydaunorubicin and rituximab.

Treatment.

Radiotherapy.

- Can be targeted or total body depending on stage.
- Can be used to “de-bulk” large nodes.
- Used in combination with chemotherapy.

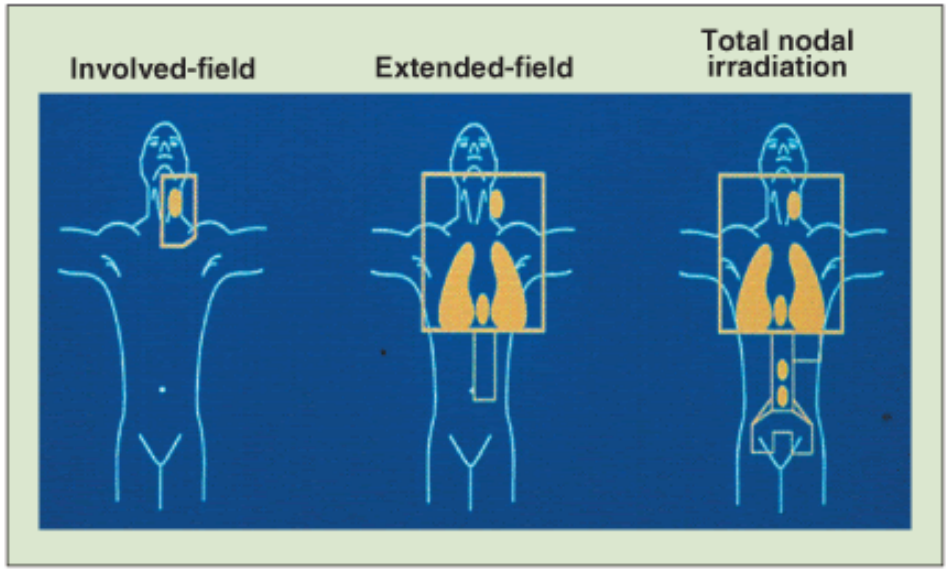

Figure 1: Radiotherapy Techniques and Fields—Involved-field, extended-field, and total nodal irradiation in a patient with left cervical involvement of Hodgkin's lymphoma (clinical stage I).

Specific Agents.

- **Rituximab**
  - **Anti-CD20 antibody**: used for B-cell lymphomas.
  - Used to treat new cases, relapsed cases and maintain response.
- **Ibrutinib**
  - **Bruton’s Tyrosine Kinase inhibitor**: Signalling molecule in B-cells.
  - Used to treat: Mantle Cell, Marginal zone, *TP53* mutated cases.

Pathology In Treatment: Haematology.

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- **Cytotoxic Chemotherapy.**
  - ↓ Red Cells ↓ Platelets ↓ White cells ↓Neutrophils
- **Radiotherapy.**
  - ↓ Red Cells ↓ Platelets ↓ White cells ↓Neutrophils
- **Specific Agents.**
  - **Ibrutinib**
    - ↑ White Cells early in treatment (changes attachment to the stroma)
  - **Rituximab.**
    - ↓ Lymphocytes including non-lymphoma cells.

Pathology In Treatment: Transfusion.

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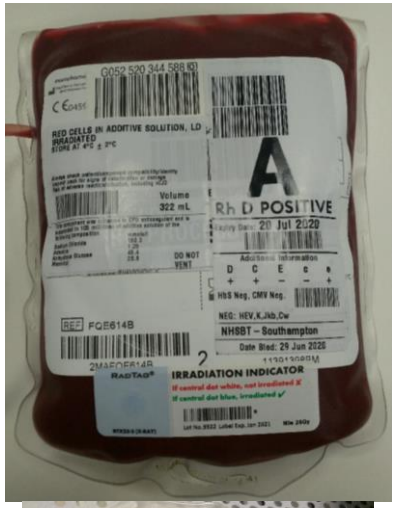
- Patients may require transfusions of:
  - Packed Red Blood Cells
  - Platelets
- Because of the suppression of the bone marrow from:
  - Chemotherapy
  - Radiotherapy.
- Less of an issue with specific agents.
- Patients may have special requirements:
  - Irradiated:
    - Specific chemotherapies e.g. fludarabine.
    - Treated Hodgkin Lymphomas.
    - Stem cell transplants.



Pathology In Treatment: Biochemistry.

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- **Cytotoxic Chemotherapy.**
  - Increased strain on the liver and kidneys.
- **Radiotherapy.**
  - Organs near the radiotherapy site may be affected.
- Biochemistry can monitor the effect of drugs to minimise organ damage.
- **LDH** and **β2M** may increase or decrease depending on treatment efficacy.
- Most patients will be immunocompromised.
  - Due to treatment or disease.
  - **CRP:** Monitors for infections.

Tumour Lysis Syndrome and the Lab.

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- Occurs when lots of cancer cells die quickly and release their contents into the blood stream.
- Can be fatal- needs to be recognised and treated rapidly.
- Is identified using pathology.

Indices	Abnormality in TLS.
White Cell Count/Lymphocytes	↑
Potassium	↑
Phosphate	↑
Calcium	↓
Urea	↑
Lactic Acid	↑

Finishing Treatment.

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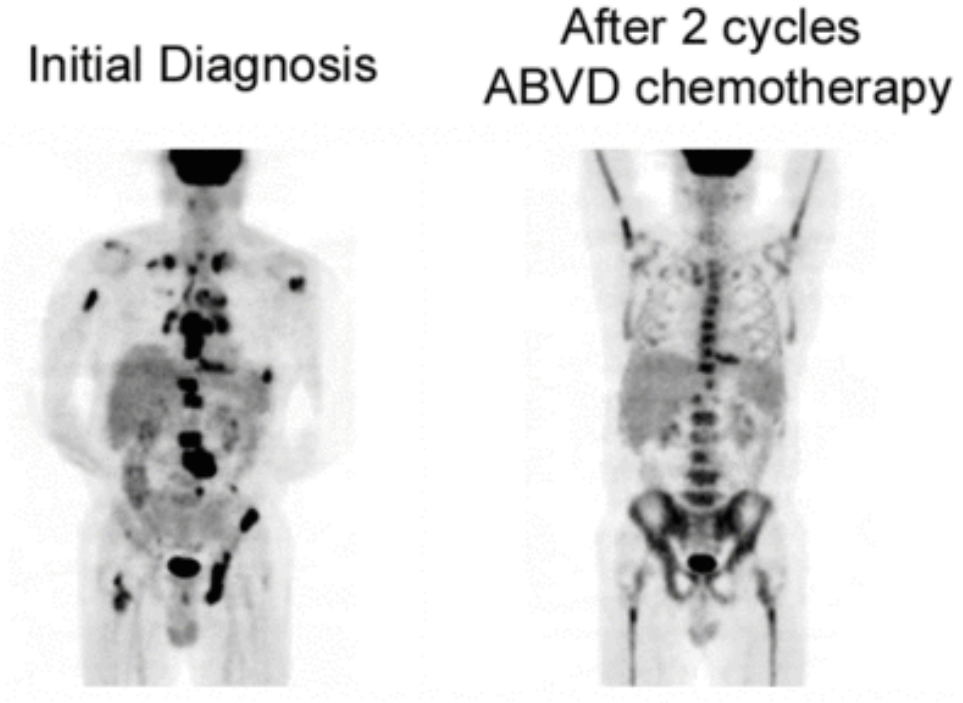
- Patients will have repeat biopsies.
- Aim is to see reduction or absence of lymphoma cells.
- This is confirmed using imaging.
  - Shows changes to size and activity.
- Ideally the patient would have no lymphoma cells after treatment.
  - Early stage disease may be completely cleared.
  - Advanced patients may have some residual disease.
  - Any reduction in disease will improve patient quality of life.



What Next?

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- All patients need regular monitoring.
  - Blood Tests.
  - Clinic and GP visits.
- Patients move onto further lines of treatment if they have not responded enough.
- Further therapies depend on the many factors.
- Patients who relapse after treatment develop more severe disease.
  - Worsening symptoms.
  - Increased white cell count.
  - Organ dysfunction.
- If patients fails treatments and meet requirements, they may have a stem cell transplant.
  - Transplants are the only true “cure” for haem malignancies.
  - They come with many risks.
  - They are highly dependant on patient status.

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Thank you for Listening.

Any Questions?