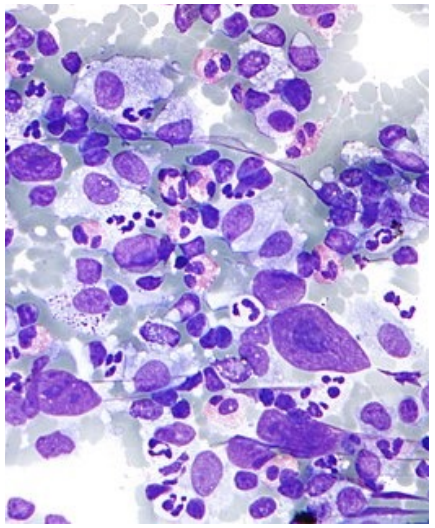
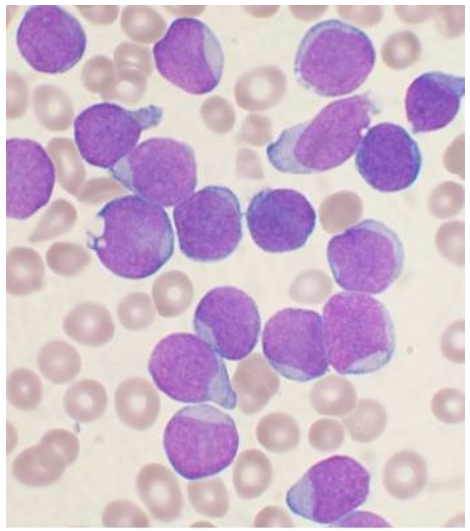
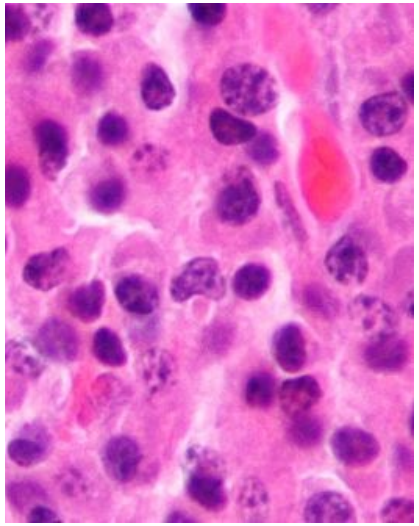
Lymphoma, leukaemia, myeloma.





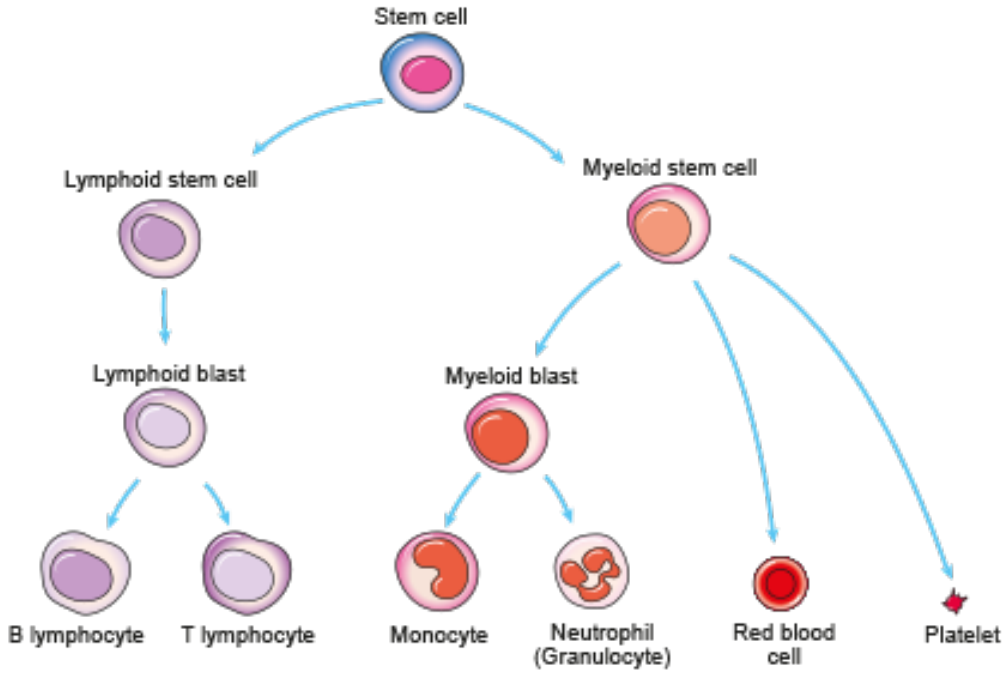


Christopher Whitty

Gresham College 2021

Lymphoma, leukaemia and myeloma.

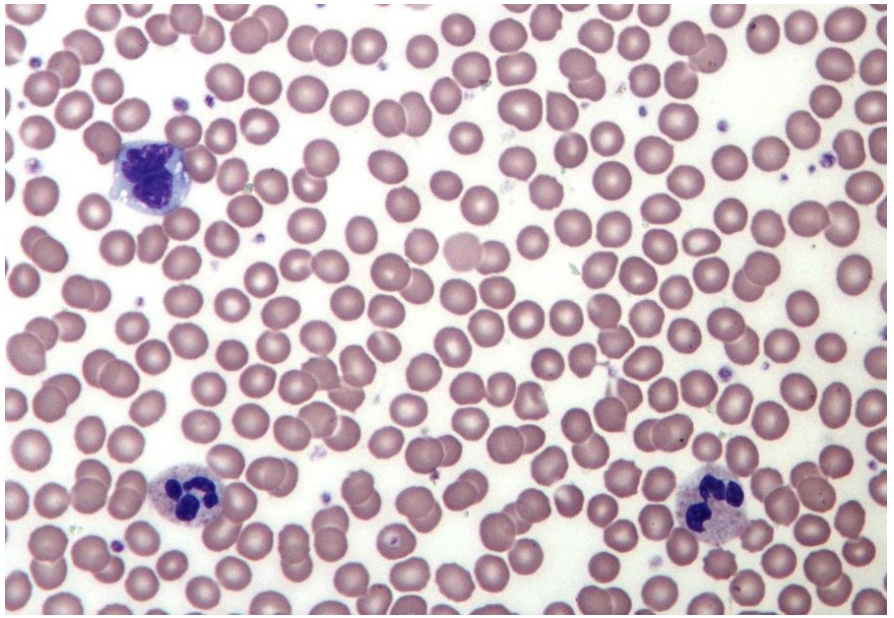
- Cancers of the blood cells or bone marrow.
- Outlook has improved substantially for many lymphomas, leukaemias and myeloma.
- Some are curable, others are treatable and can be managed as a chronic condition for many years or decades.



CRUK

What does blood do?

- White cells- fight infection.
- If not working get repeated infections.
- Red cells- transport oxygen.
- If anaemia become breathless, tired.
- Platelets- clotting.
- If low platelets may have bleeding, bruising.

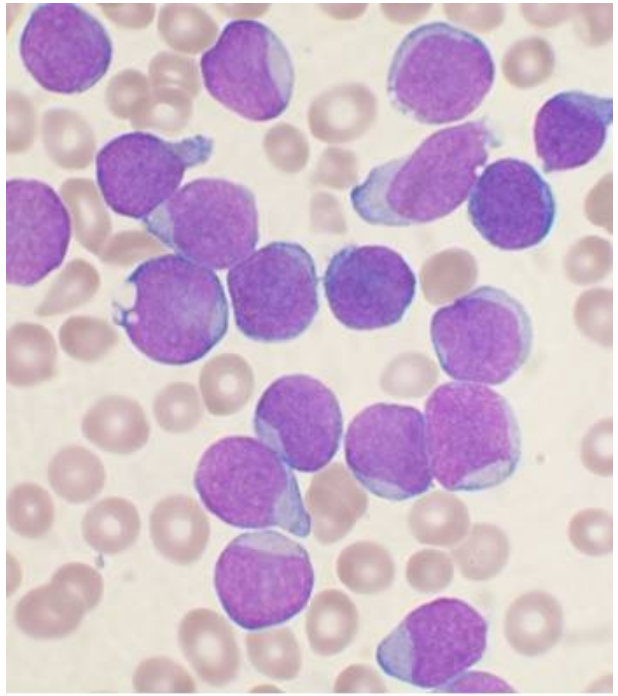


Normal blood film. Keith Chambers.

Occur over the age spectrum from childhood to old age.

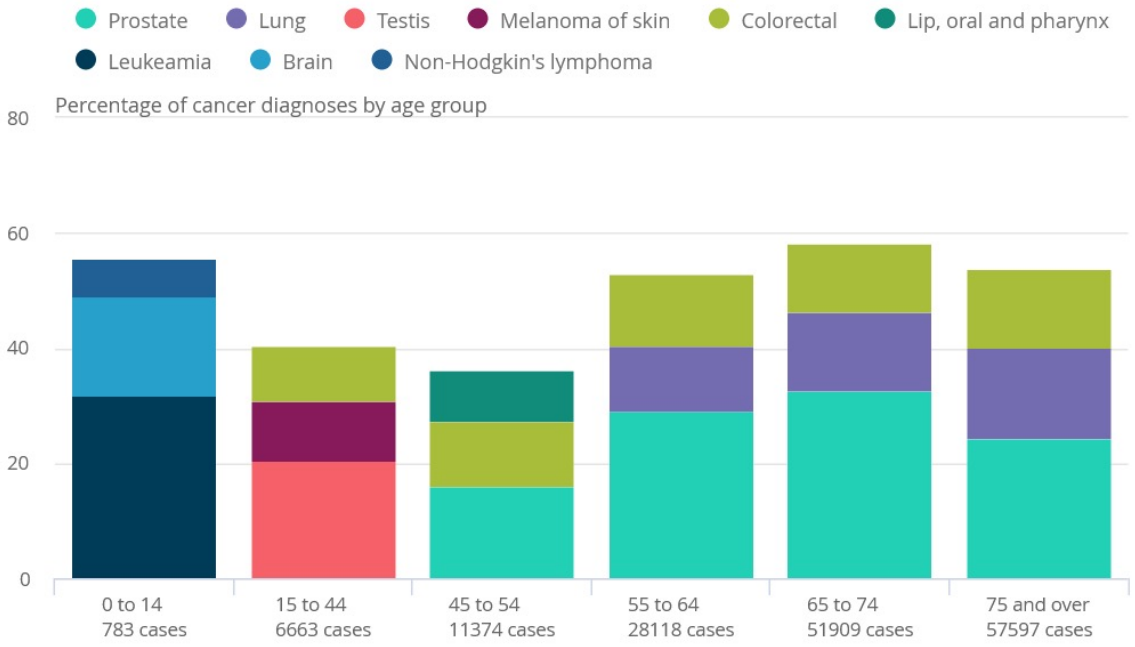
In the UK:

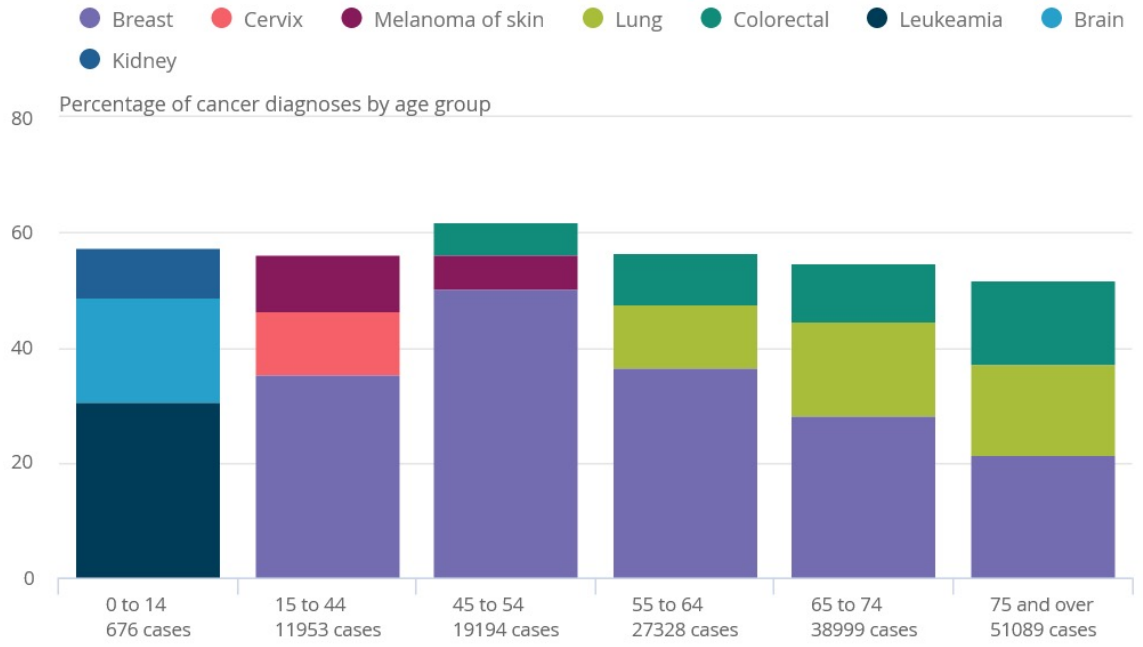
- Around 10,000 new cases and 4700 deaths a year from leukaemia.
- Around 2000 cases and 300 deaths from Hodgkin lymphoma.
- Around 14,000 cases and 4900 deaths from non-Hodgkin lymphoma.
- Around 5800 cases and 3000 deaths from myeloma.



Acute lymphoblastic leukaemia (ALL). VashiDonsk.

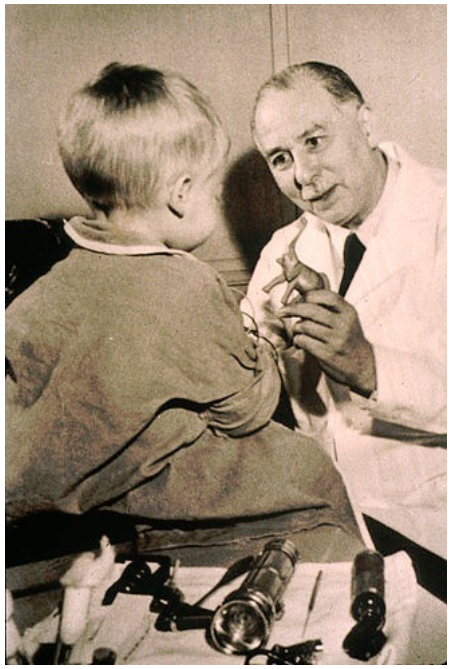
Lymphoma and leukaemia are particularly important causes of cancer in children (all rare). Top 3 cancers by age- male (L) female (R).





These cancers should be seen as disseminated diseases.

- For solid cancers like breast, prostate, lung and bowel cancer the degree of spread determines outlook and treatment.
- Surgery or targeted radiotherapy are central treatments for most solid tumours, especially early disease.
- Leukaemia, myeloma and lymphoma should be seen as disseminated from the outset.
- Outlook can be very good.
- Drugs are central to treatment.

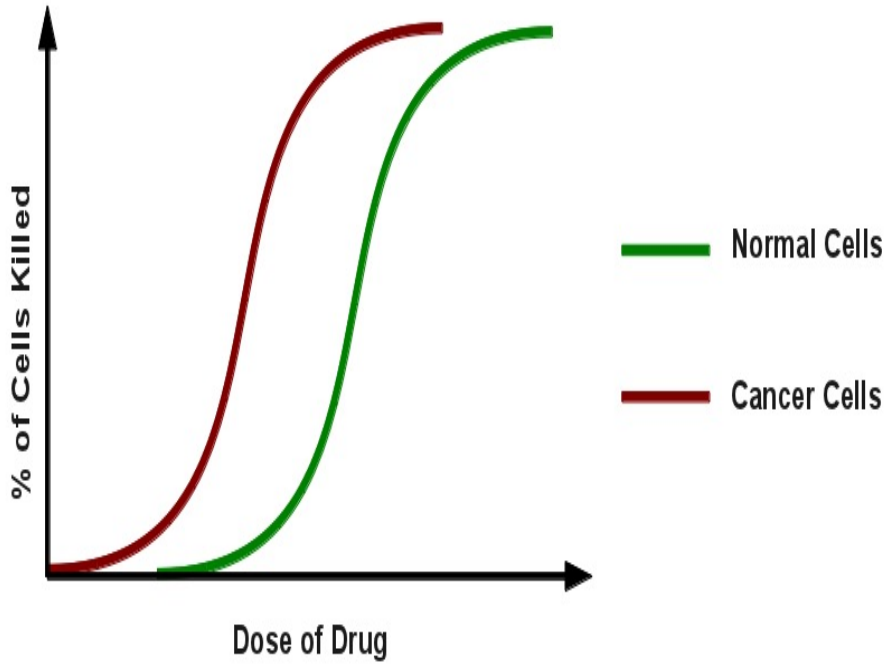


Sydney Farber first used antifolates to treat leukaemia 1948.

Lucy Wills, who discovered folate in India, C1937.

Cytotoxic chemotherapy mechanisms.

- The basic mechanisms of chemotherapy are simple.
- Kill any cell that is dividing- cancer cells more sensitive and slower to recover.
- Good effect depends on the cancer. Rapidly dividing = more effective.
- Given in combinations- single drugs alone lead to relapse.
- Generally given in cycles.

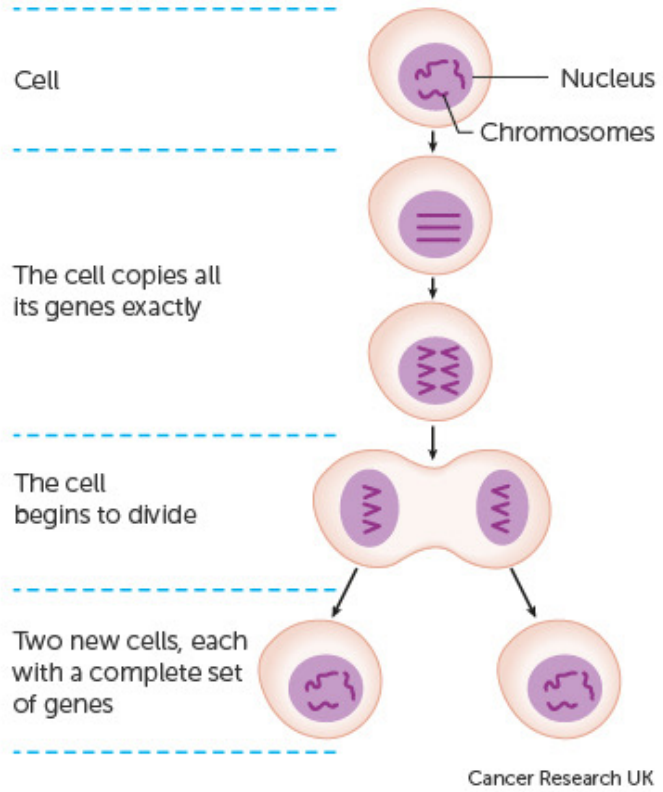


Chemotherapy- some examples.

- Vinblastine from the Madagascar periwinkle 1958.
- Bleomycin. *Streptomyces verticillus* 1960s.
- Anthracyclines derived from antibiotic produced by Streptomyces bacteria from the soil around Castel del Monte in 1950s. Doxorubicin.
- Dacarbazine 1975.
- Cyclophosphamide 1950s. From nitrogen mustards, initially derived from mustard gas.

Many mechanisms of chemotherapy.

- Alkylating agents like cyclophosphamide damage DNA.
- Antitumour antibiotics like doxorubicin attack enzymes which assist in DNA replication.
- Mitotic inhibitors like vinblastine stop cancer cells making copies of themselves e.g. via microtubule system.



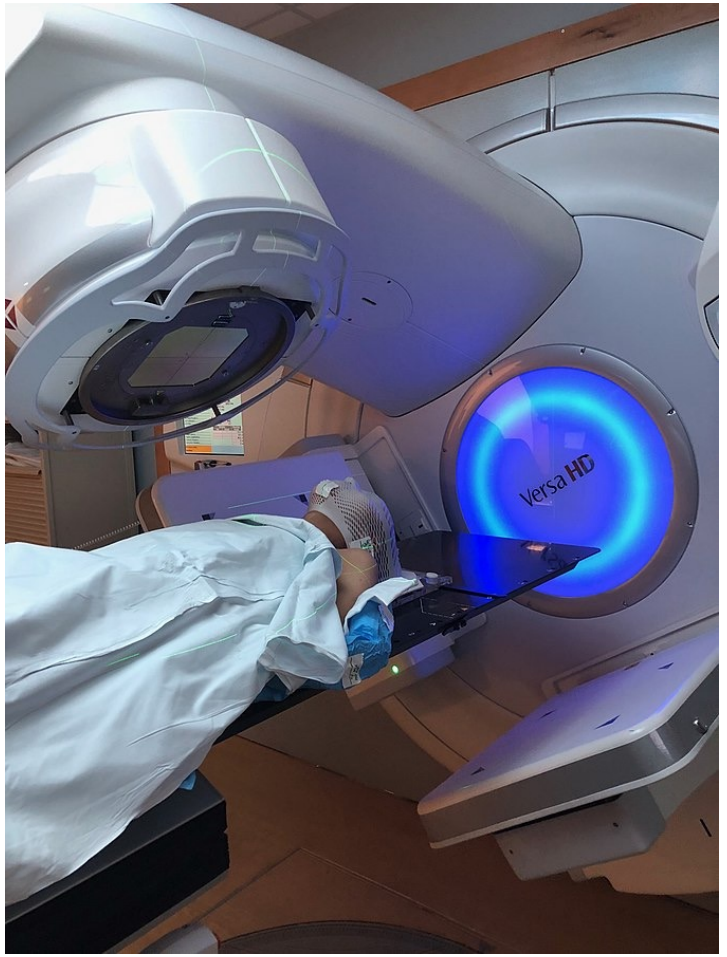
Side effects- depend on which drugs you need.

- Biggest impact on cells that are rapidly dividing: gut, hair follicles, mouth, bone marrow.
- Nausea, vomiting.
- Immune system.
- Bleeding and bruising.
- Diarrhoea / constipation.
- Hair loss.
- Most last for a short period.

Macmillan Cancer Support

Radiotherapy- only a minority.

- Radiotherapy damages dividing cells, especially cancer cells.
- May be localised or general.
- Often very well tolerated, with only local effects.
- Tiredness common.
- Sore skin.
- Nausea, diarrhoea in generalised radiotherapy. Generally shortlived.



Radiotherapy for Hodgkin lymphoma. Jakembradford.

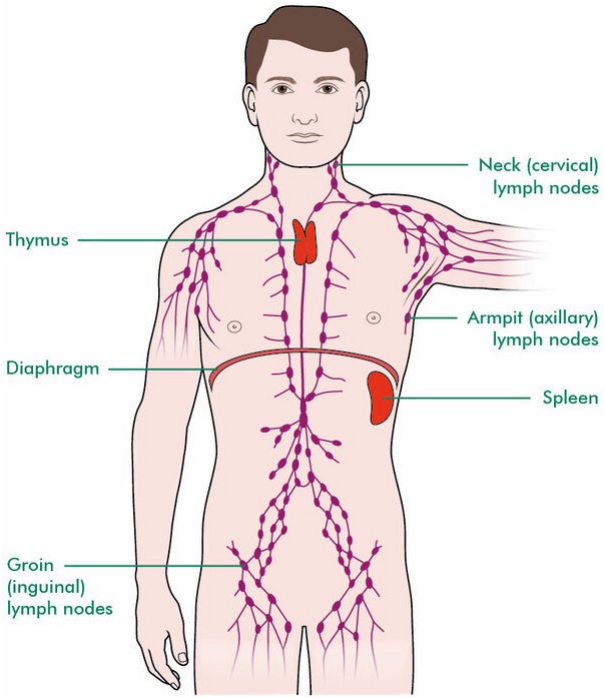
Stem cell transplants. Only a minority.

- Some highly effective treatments will kill cancer but also healthy bone marrow cells.
- Need stem cells or bone marrow transplant to recover.
- Stem cells harvested from you before treatment eg for lymphoma.
- In some, especially leukaemias (eg AML) may be a matched donor.
- Given back into your blood after the treatment.

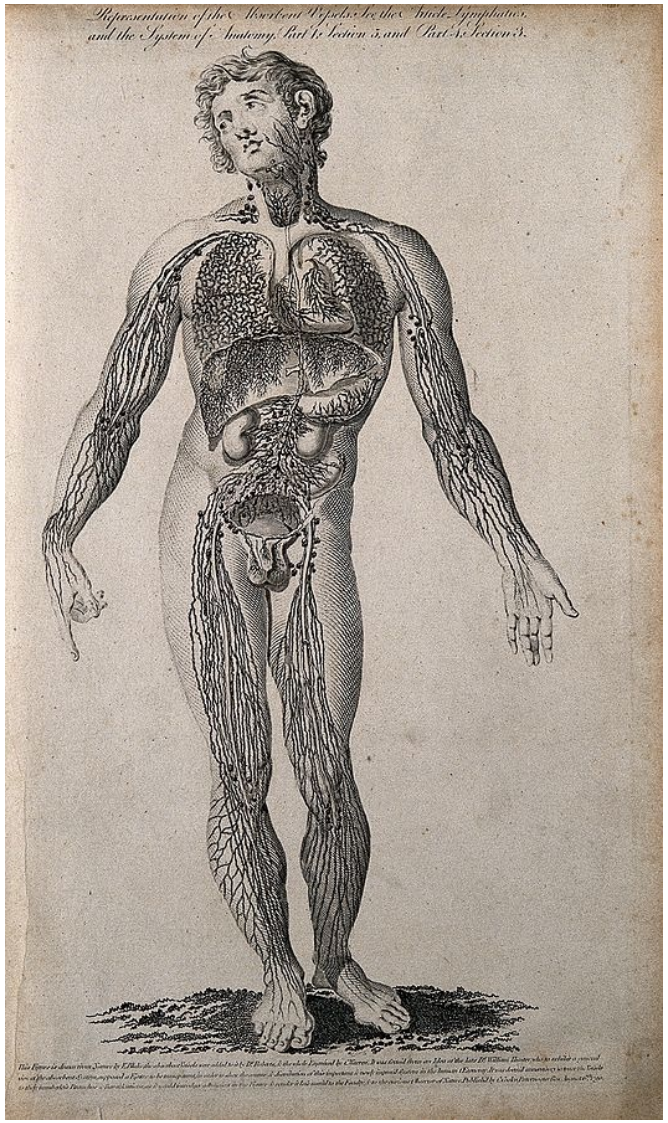
CRUK

Lymphoma.

- Cancer of the lymphatic system and lymphocytes.
- Lymphatics drain fluid and waste, help fight infection with lymphocyte white cells.
- Lymphoma may be noticed as lumps in the lymph gland distribution-
- Or when invades bone marrow.
- Or may be picked up incidentally.
- Hodgkin and non-Hodgkin.
- Many types of lymphoma.



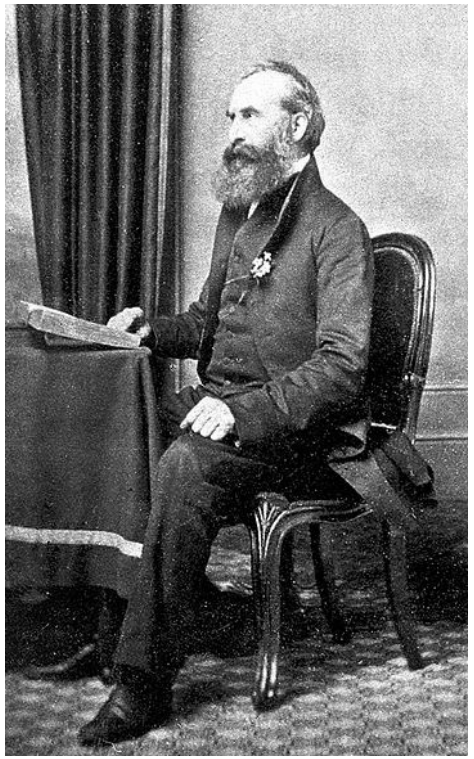
MacMillan



C. Warren after F. Blake, 1790

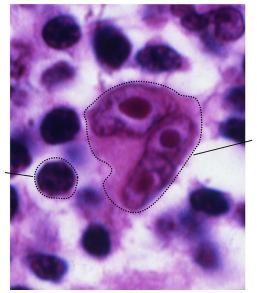
Hodgkin lymphoma.

- First described by Thomas Hodgkin in 1832. Reed-Sternberg cell described by Dorothy Reed 1901 (aged 28).
- Nymph nodes, especially of neck and shoulders (80-90%).
- Night sweats, weight loss, fatigue, fever, itching- ‘B’ symptoms.



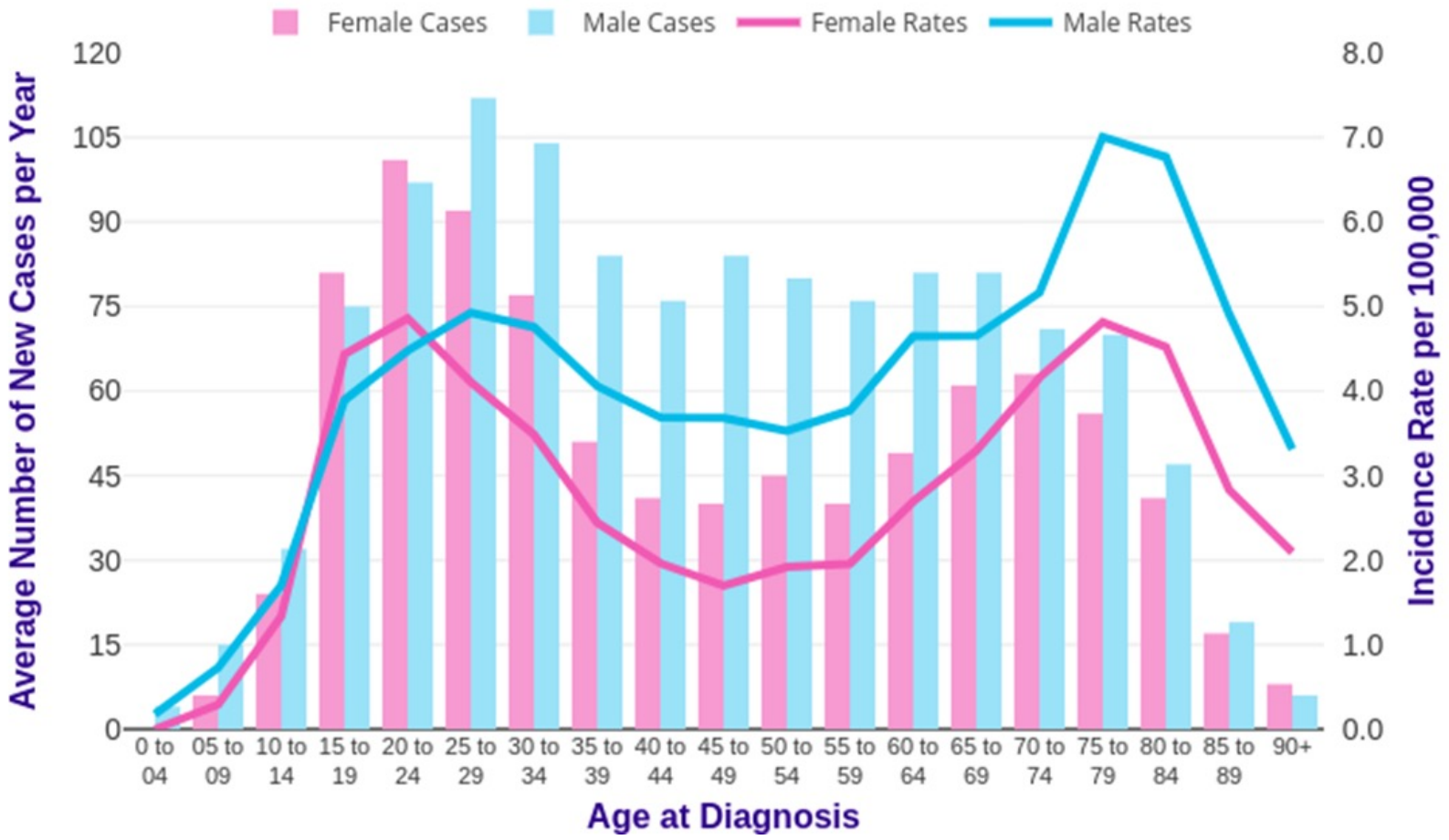
Thomas Hodgkin 1798-1866

Dorothy Reed 1874-1964



NCI

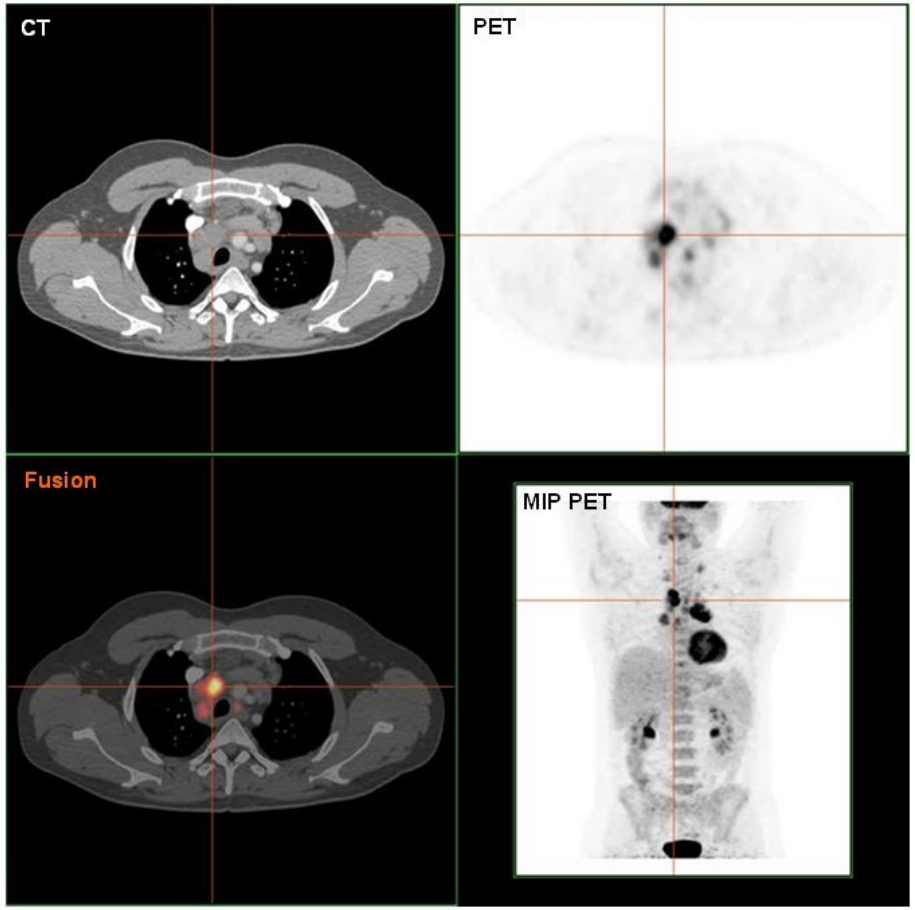
Age and Hodgkin lymphoma.
Two peaks- in late adolescence/early adulthood older age.



CRUK

Investigations.

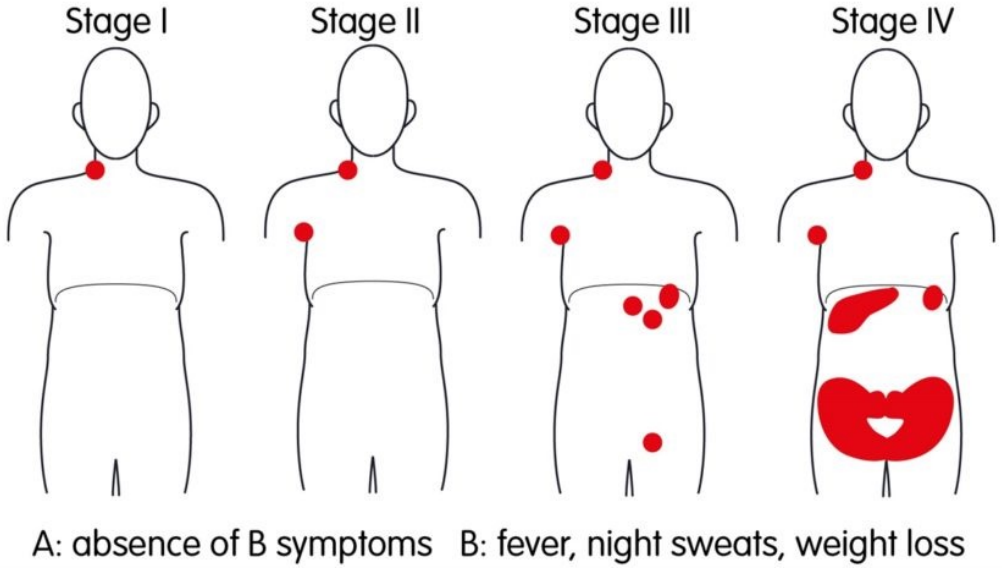
- Biopsy of lymph node.
- PET scan, PET/CT (18-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography).
- How extensive the lymphoma is, and whether it has spread to both sides of the diaphragm is important for staging.



PET/CT Hodgkin lymphoma. Hg6996

Treatment of Hodgkin lymphoma.

- Chemotherapy in almost all cases (e.g. ABVD).
- Radiotherapy in some.
- Stem cell transplant in some relapsed cases (rare).

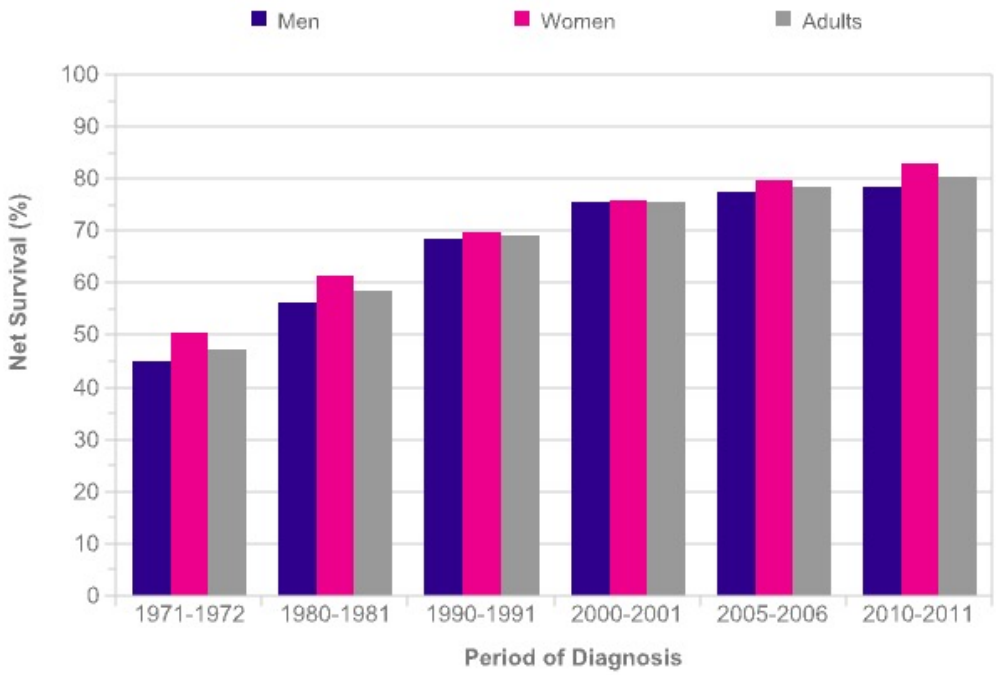


Staging of lymphoma in children.
American Childhood Cancer Org.

Hodgkin Lymphoma- treatment and survival. 75% survive ≥10 years.

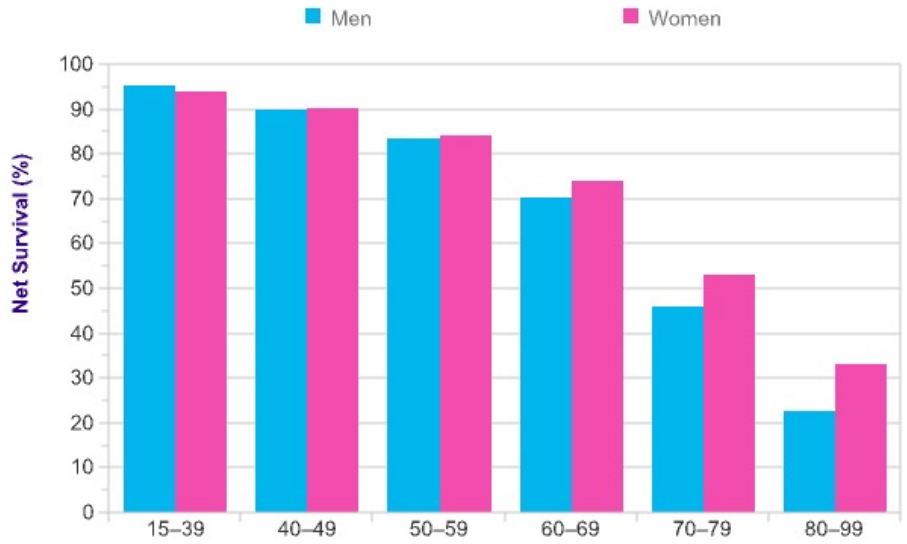
- Stage 1 and 2a disease- limited stage.
- Generally 2-4 cycles of chemotherapy +/- radiotherapy.
- Around 90% survive 5 years or more.
- Stage 2b, 3 and 4- advanced stage.
- Generally 6-8 cycles, +/- steroids +/- radiotherapy.
- Around 80% survive ≥ 5 years Stage 3.
- Around 70% survive ≥ 5 years Stage 4.

10 year survival over time. CRUK.



Age and Hodgkin Lymphoma. Survival by age (R).

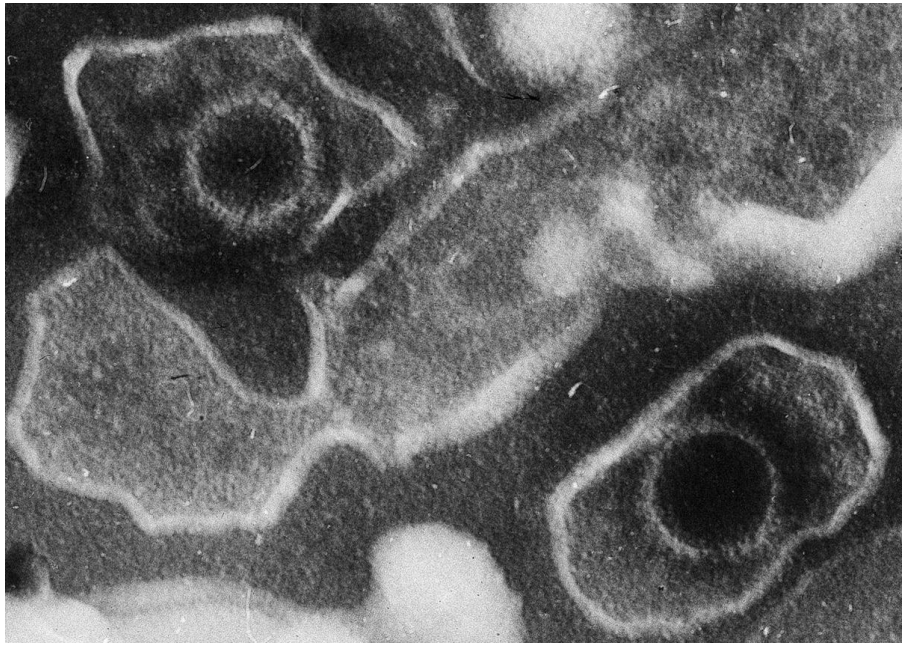
- Most people with Hodgkin lymphoma are cured.
- Particularly high cure rate in younger people.



CRUK

Around 40% of Hodgkin lymphoma is thought to be associated with infections. Other modifiable risk factors minor.

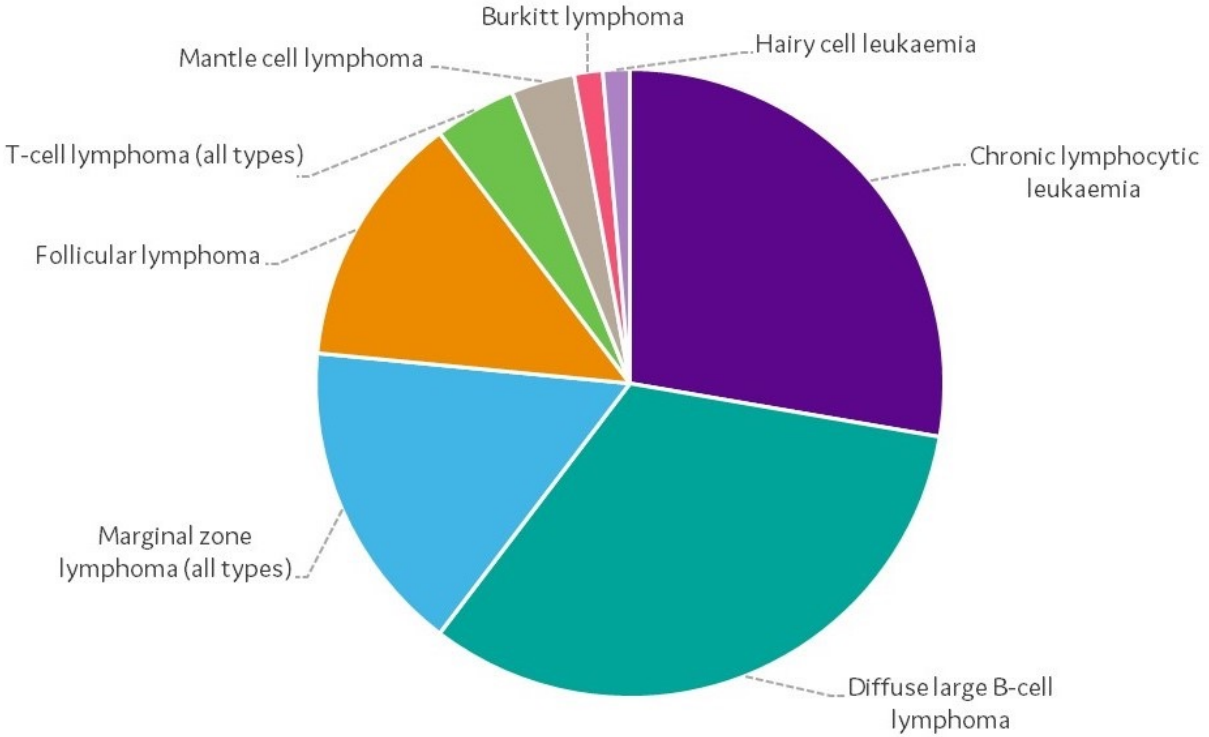
- Epstein-Barr virus (EBV, glandular fever) most common.
- HIV.



Liza Gross. EBV.

Non-Hodgkin lymphoma.

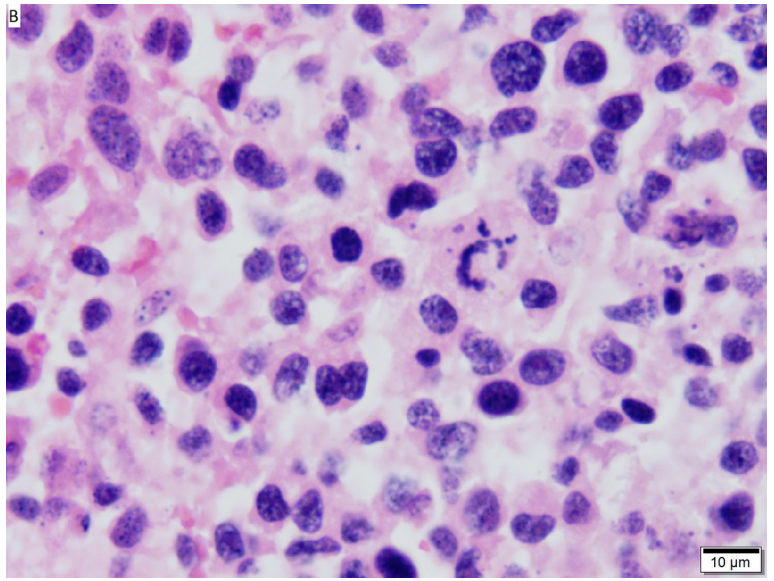
- Many types.
- Fast growing. ‘High-grade’.
- Slow growing. ‘Low-grade’.
- B-cell (the great majority) or T-cell lymphoma.
- Chronic lymphocytic leukaemia
- Diffuse large B-cell lymphoma (high-grade)
- Follicular (low-grade).



UK distribution lymphomas.
Lymphoma action.

High-grade lymphoma.

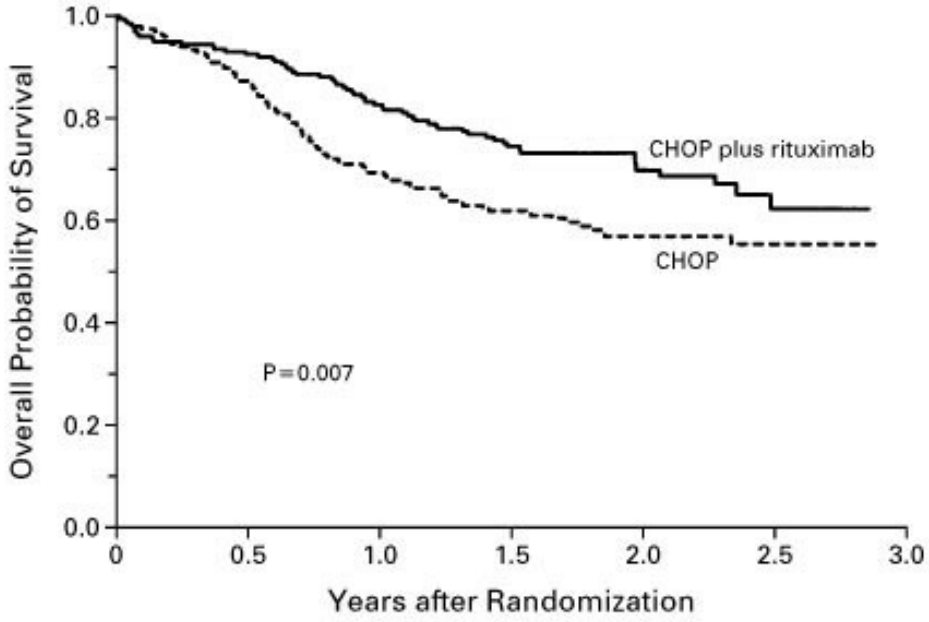
- Most common symptoms swollen lymph glands that don’t go down after a couple of weeks.
- Usually not painful. Groin, armpit, neck.
- ‘B’ symptoms- including fever, severe night sweats.
- Most common in older people.
- Diagnosis usually by biopsy.
- Imaging (CT, PET, MRI) for staging.



High grade B cell lymphoma involving liver.
TexasPathologistMSW

For most high-grade lymphoma the aim of treatment is complete remission (cure).

- Get to no detectable lymphoma with minimum side effects.
- Chemotherapy. Most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone).
- CD20 Antibody therapy (e.g. rituximab).
- May have radiotherapy.
- May have stem cell transplant.



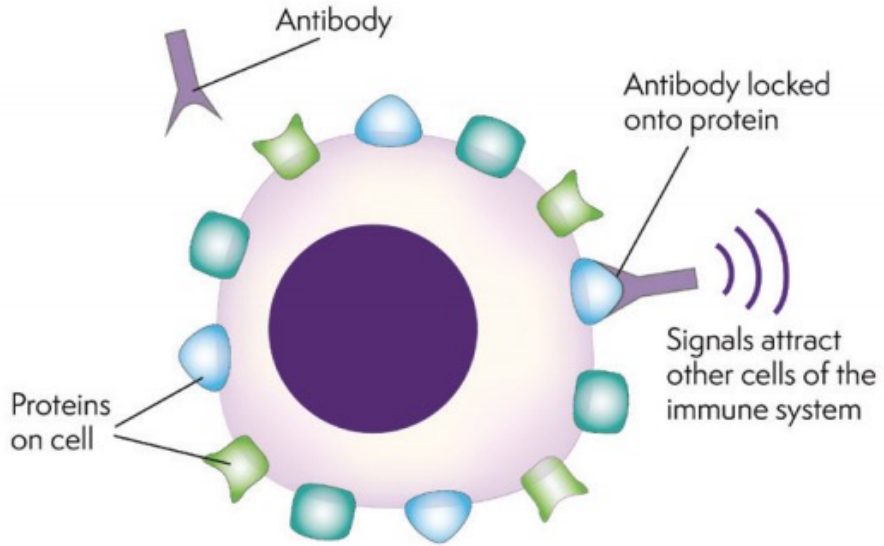
CHOP v CHOP+ritixumab.
Coiffier et al NEJM 2002

Targeted therapy- antibodies.

Ritixumab. Oguenther.

- Ritixumab an example of monoclonal antibody against CD20, found on B cells. Used in various non-Hodgkin lymphomas (NHL), and CLL.

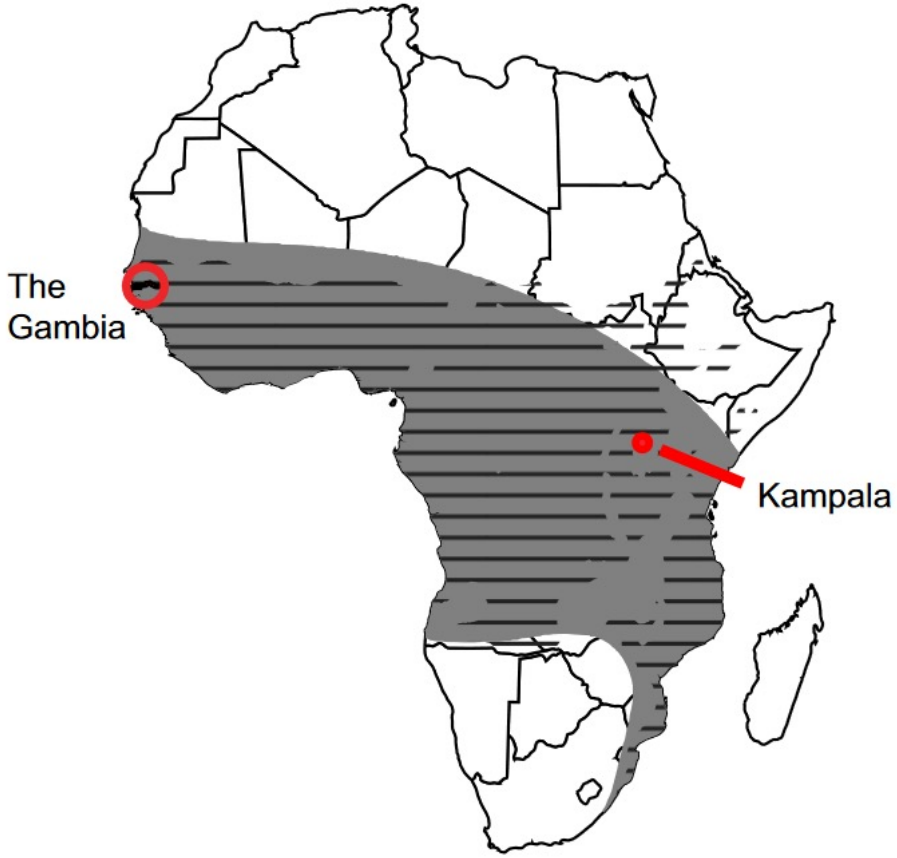
- Brentuximab. Targets CD30 and delivers a chemotherapy drug precisely to kill the cell.



Lymphoma Action.

Burkitt lymphoma in children.

- Predominantly a rapidly growing lymphoma of children.
- Rare in the UK (around 200 cases a year) but commonest non-Hodgkin lymphoma in children. Sporadic type.
- In Africa more common, in areas where EBV and malaria overlap. Endemic type. Can affect face.
- Also with immunosuppression.



B. Sugden PLOS Biology
Grey- Burkitt lymphoma.
Hatched holoendemic malaria.

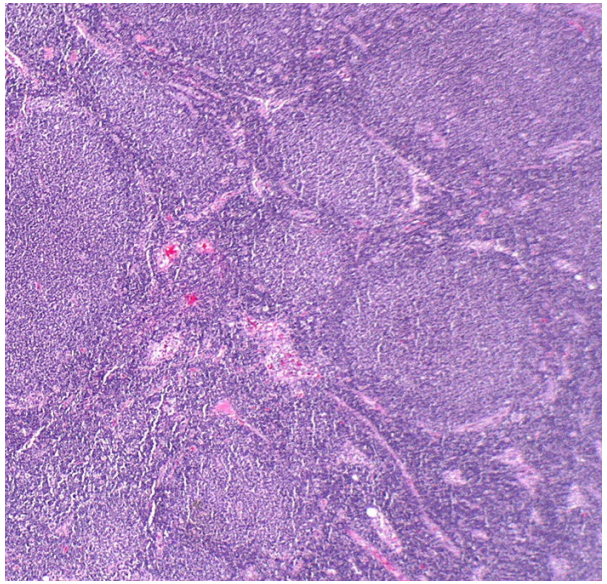
Treatment of Burkitt lymphoma.

- Combination of chemotherapy drugs and targeted therapy ritixumab.
- Survival for limited stage (Stage I and II) Burkitt lymphoma over 90%.
- Survival for advanced stage (III and IV) 80-90%.

Ritixumab. Oguenther.

Low-grade lymphoma.

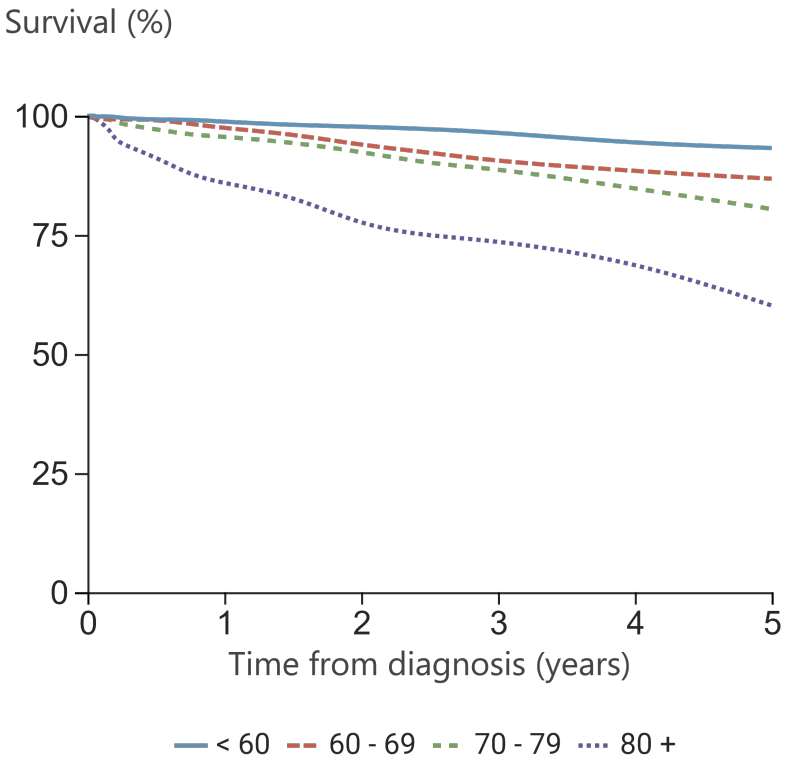
- Generally much more slowly growing.
- Most commonly aged 60-90.
- Can present with enlarged lymph nodes or B symptoms.
- May have mild symptoms or be diagnosed incidentally after blood test for another reason.
- Diagnosis by biopsy, and staging tests.



Follicular lymphoma.
Nephron.

Low-grade lymphoma treatment.

- Although full remission can occur, the main aim is control.
- People can live for many years with low grade lymphoma, receiving intermittent treatment. 55% survive 10 years or more.
- May not need treatment initially- active monitoring.
- Chemotherapy.
- Targeted CD20 antibodies. May be used also for maintenance therapy.
- Sometimes radiotherapy.
- Sometimes stem cell transplant.

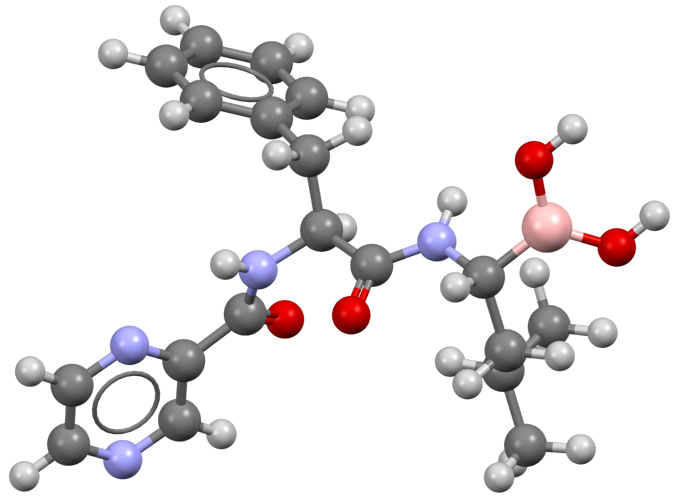


Follicular lymphoma.
Survival by age. HMRN

Targeted therapies- an example proteasome inhibitors.

- Bortezomib a proteasome inhibitor.
- Proteasomes in cells break down proteins that are no longer needed. Bortezomib blocks them.
- The proteins build up in the cell and it dies.
- Mantel cell lymphoma (a low-grade lymphoma), multiple myeloma.

- Other targeted therapies if relapse occurs.

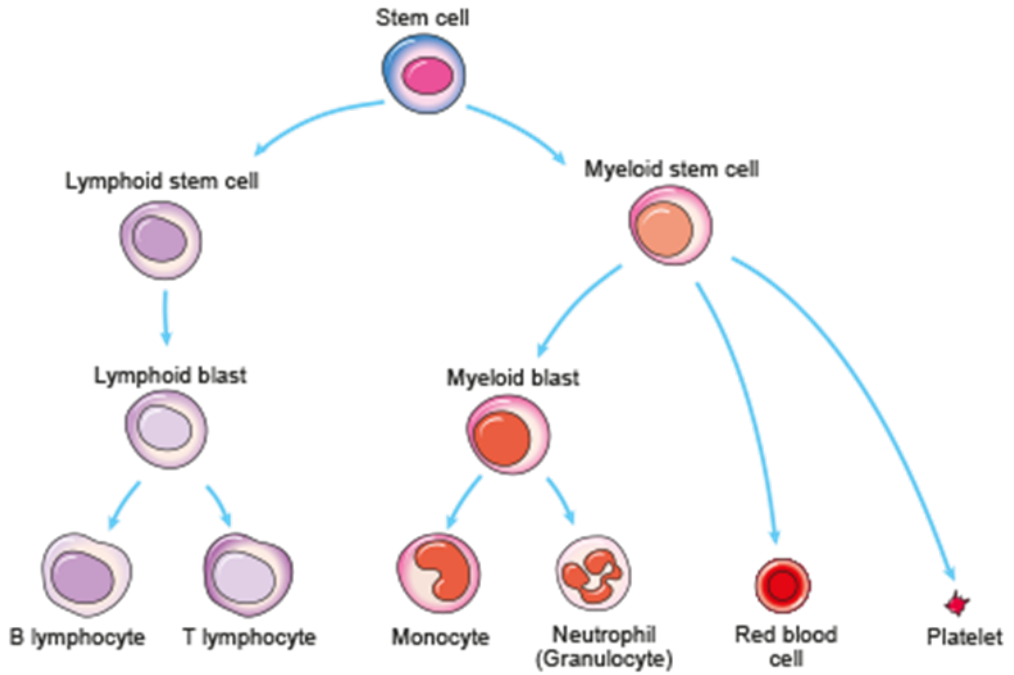


Bortezomib. Ben Mills.

Leukaemias.

- Leukaemias are cancers of the white blood cells.
- Acute (rapid) and chronic (slow) onset.
- Lymphocytic (ALL, CLL).
- Myeloid (AML, CML).

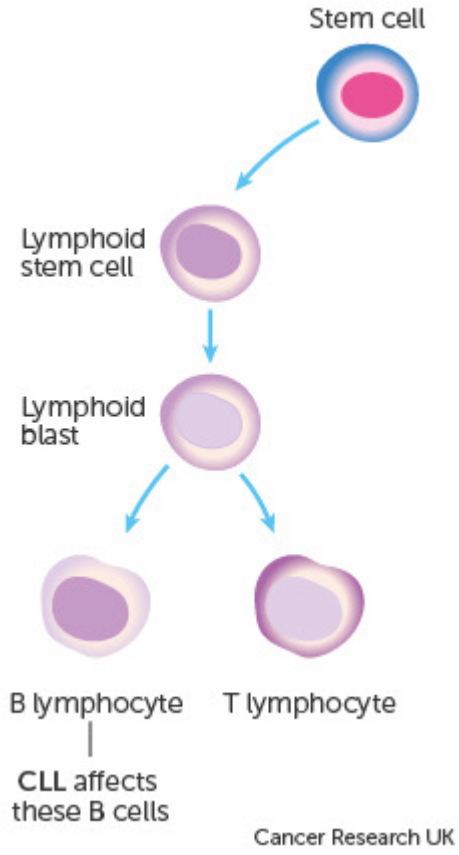
	Acute	Chronic
Lymphocytic	ALL	CLL
Myeloid	AML	CML

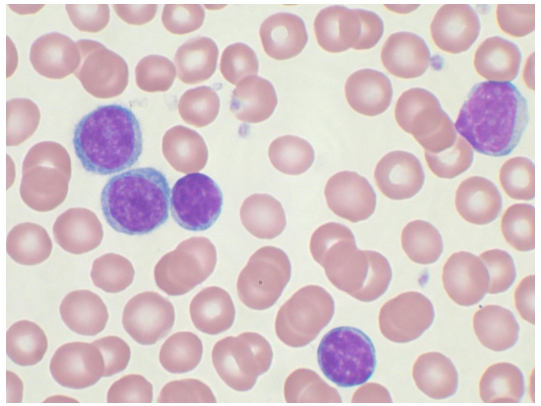


Chronic lymphocytic leukaemia (CLL).

Commonest chronic leukaemia, around 3800 a year in UK.

- Mainly people over 60. Rare under 40. More common in males (around 2x).
- Caused by various genetic mutations.
- Both too many B lymphocytes (crowd out others in the bone marrow) and lymphocytes do not work well.
- Increased infections, tiredness, bleeding/bruising, swollen lymph glands.
- Usually diagnosed on a blood film.

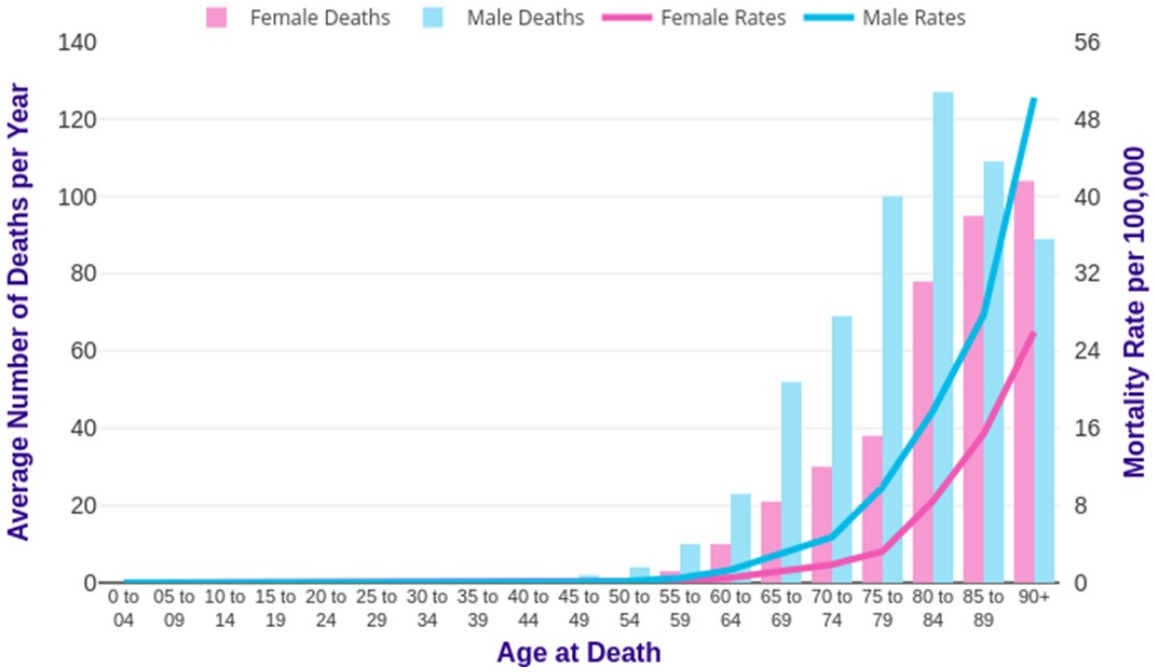




CLL. VashiDonsk.

Prognosis of CLL.

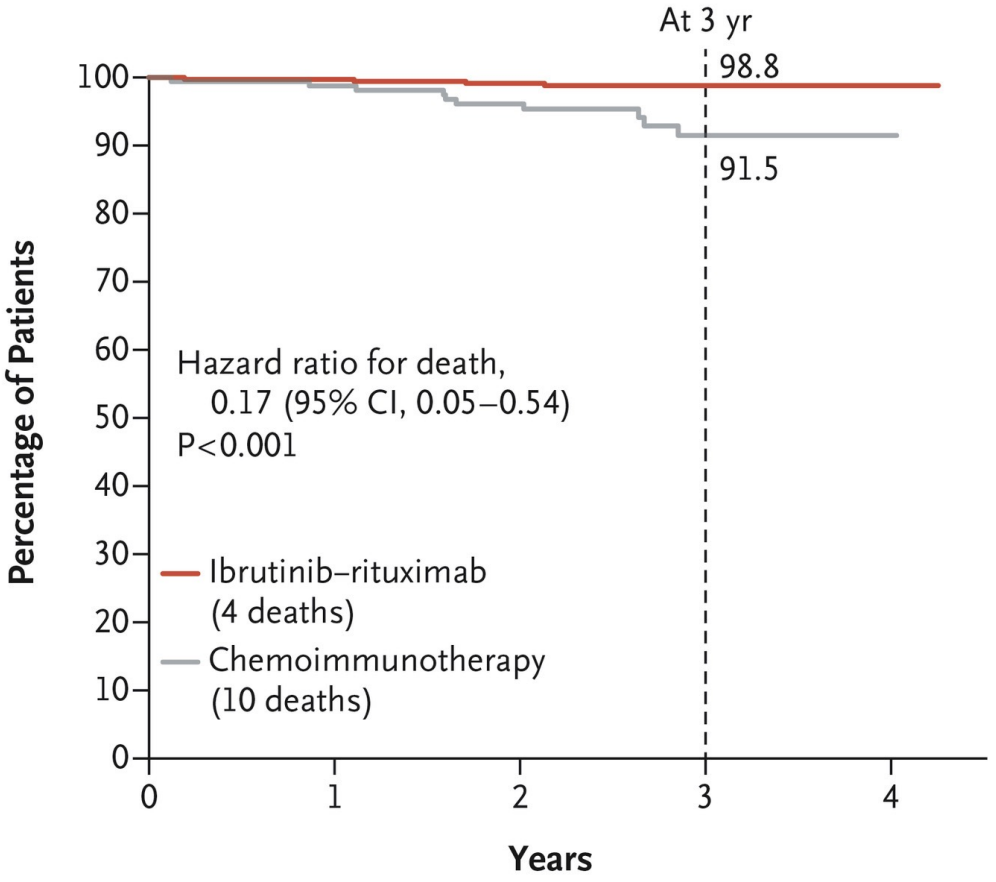
- Around 85% survive for 5 years or more in UK. Younger better.
- Genetic mutations guide prognosis.
- IgVH region mutation associated with median survival over 20 years.
- Worst prognosis del(17p); 7-year median survival.



Age and mortality CLL. CRUK/ONS

Treatment of CLL.

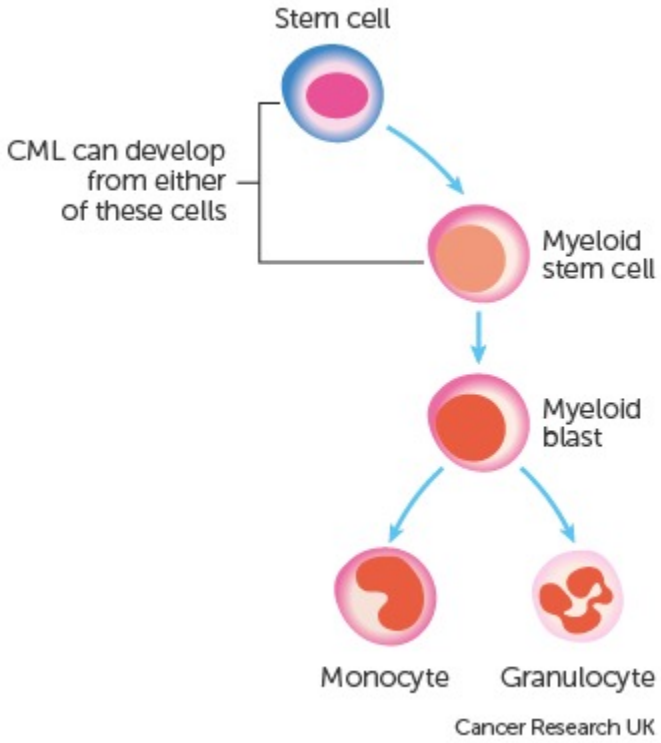
- In people with early disease no treatment may be best (no survival advantage to treatment in trials).
- In more advanced disease the aim is to control, not cure. Side effects important.
- Clinical state and mutations guide treatment.
- Some combination of newer targeted therapies like ibrutinib, acalabrutinib, venetoclax, rituximab and chemotherapy.

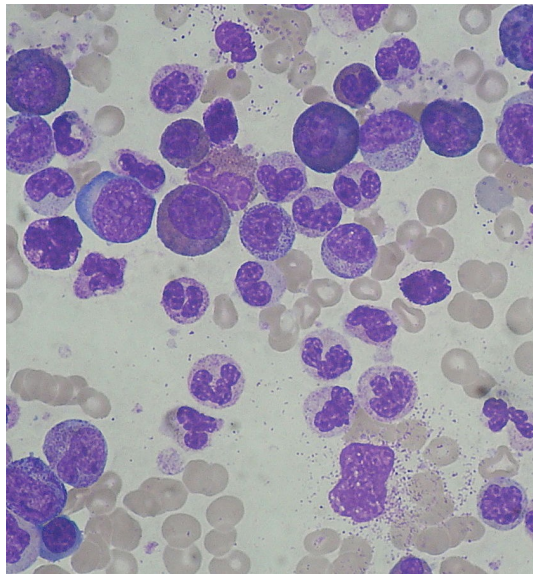


Overall survival CLL <70 years. Ibrutinib-rituximab v chemoimmunotherapy. Shanafelt et al NEJM 2019.

Chronic myeloid leukaemia (CML).
Around 800 new cases a year UK.

- Much rarer than CLL.
- Much improved outlook over time (around 75% reduction mortality since 1970s).
- Incidence increases steadily with age.
- Infections, tiredness, bruising, bleeding, night sweats, bone pain.
- Diagnosis mainly by blood film.

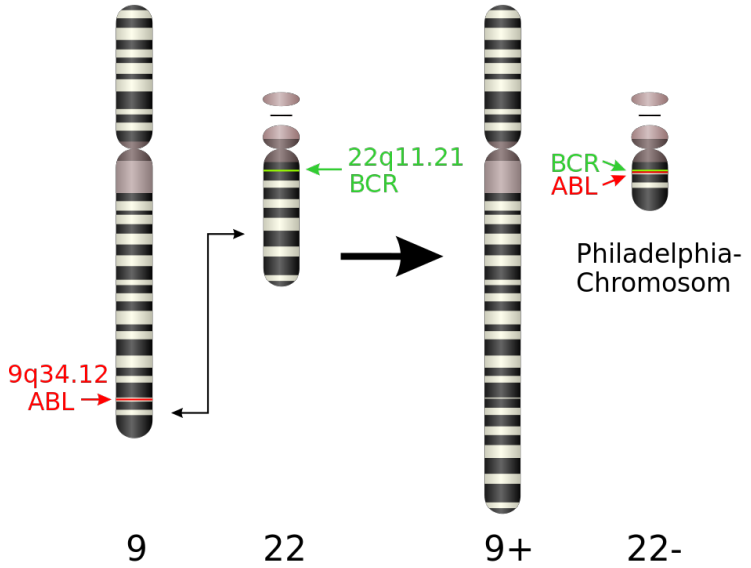




CML. PHO Mourao

CML- BCR-ABL and the Philadelphia chromosome.

- ABL1 gene on chromosome 9 breaks off and sticks to BCR gene on chromosome 22. Not inherited.
- The resulting mutated protein BCR-ABL causes CML.
- Everyone with CML has acquired the BCR-ABL mutation.
- Key drugs are tyrosine kinase inhibitors.

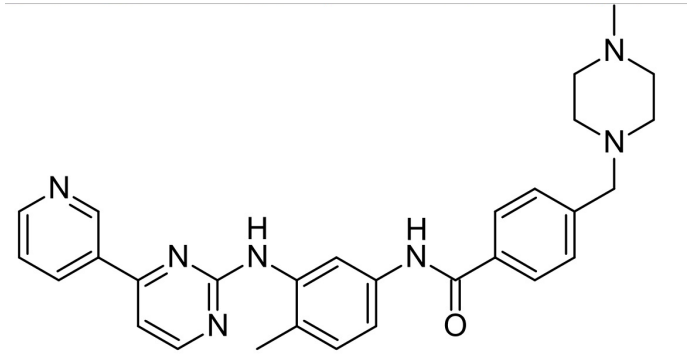


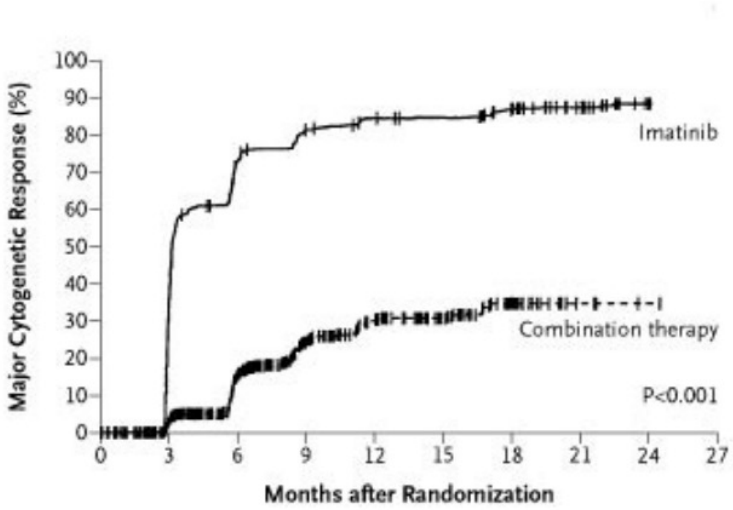
Master Uegly

Philadelphia chromosome. described by Janet Rowley 1973

Imatinib.

- Small molecule.
- Drug by design- Glivec.
- Inhibits (blocks) *bcr-abl* protein.
- Overall survival now 85%- a chronic disease for many.
- May require lifelong treatment.
- Cost has been a major issue. Reached over $120,000 a year by 2016.

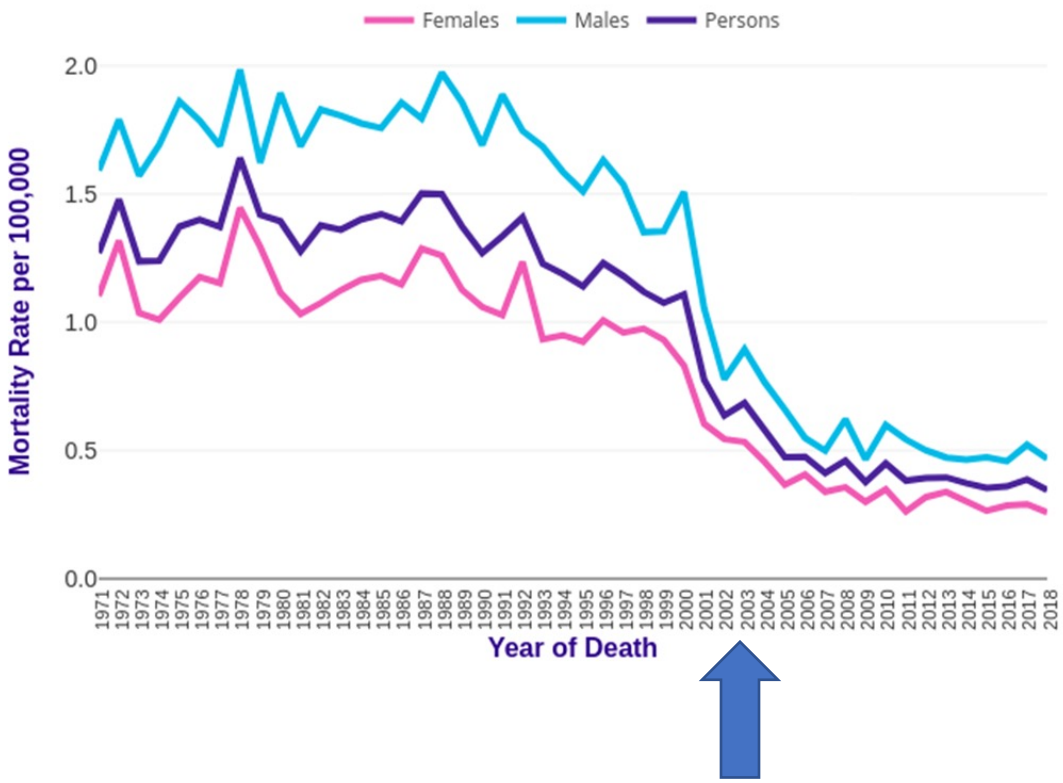




O'Brien S et al 2003 NEJM

Tyrosine kinase inhibitors (TKIs) have transformed CML outlook.

- Usually start with a daily TKI imatinib. From 2001.
- Works for most people- can be maintained on this for years.
- There are other TKIs if there is relapse.
- Chemotherapy/ stem cell transplant much more rarely used.

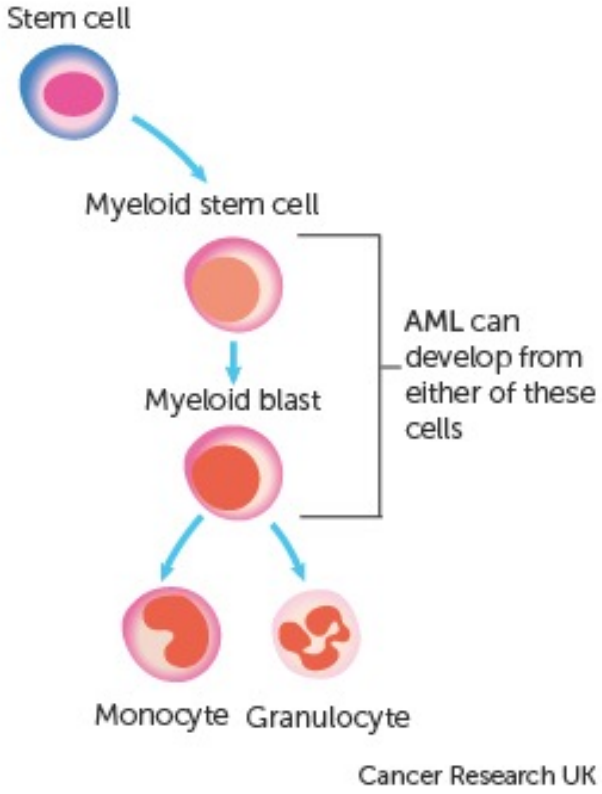


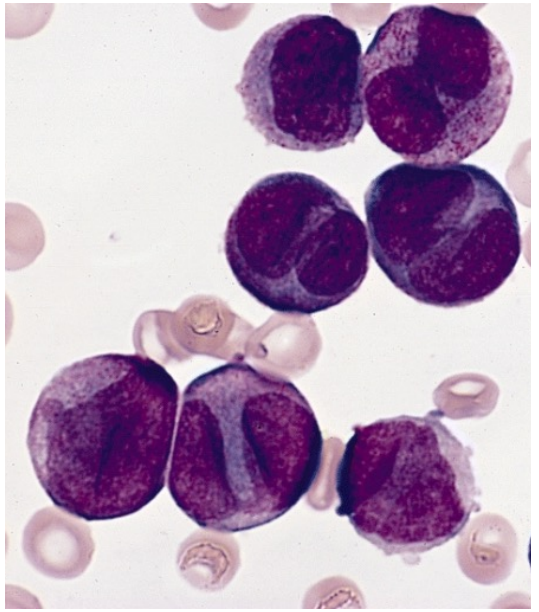
Mortality rate over time, CML. CRUK.

Acute myeloid leukaemia (AML).

Around 3,200 cases a year UK.

- Symptoms often vague- infections, tiredness, bruising/bleeding, fever, bone pain.
- Main diagnosis is by a blood test. May need a bone marrow test.
- Risk stratification based on factors including gene changes, chromosome changes, cell markers, age, white cell count.

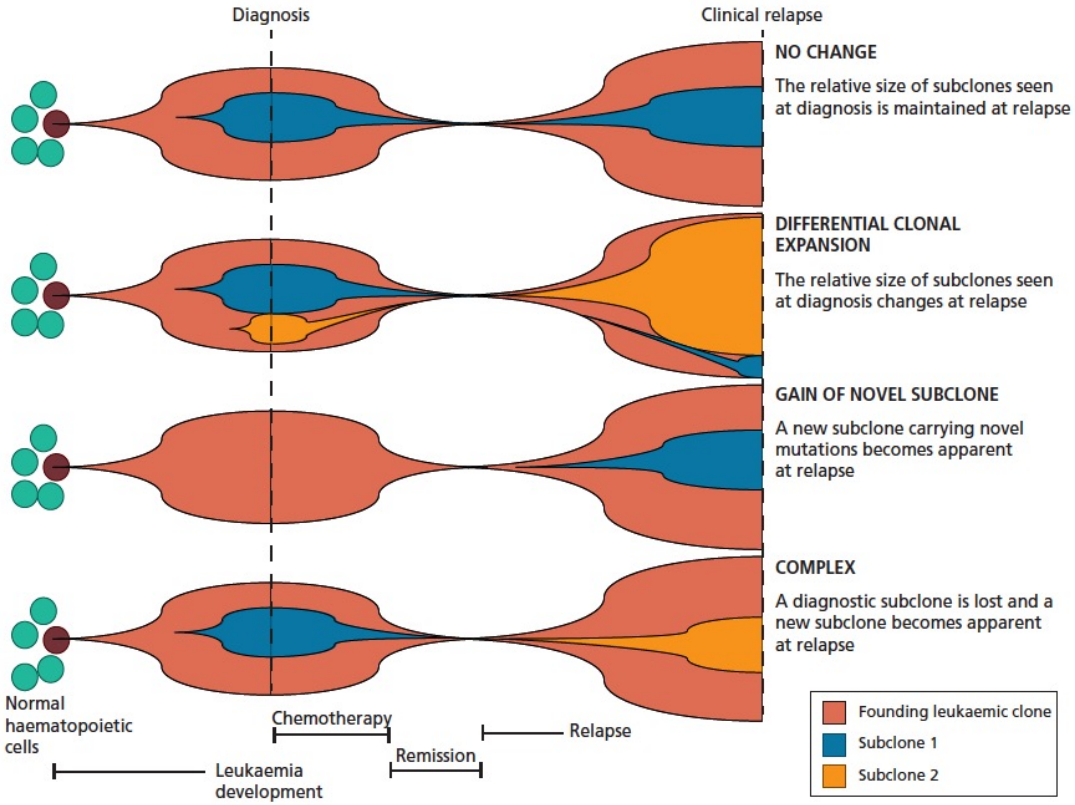




AML. AFIP.

AML is a disease of acquired genetic damage

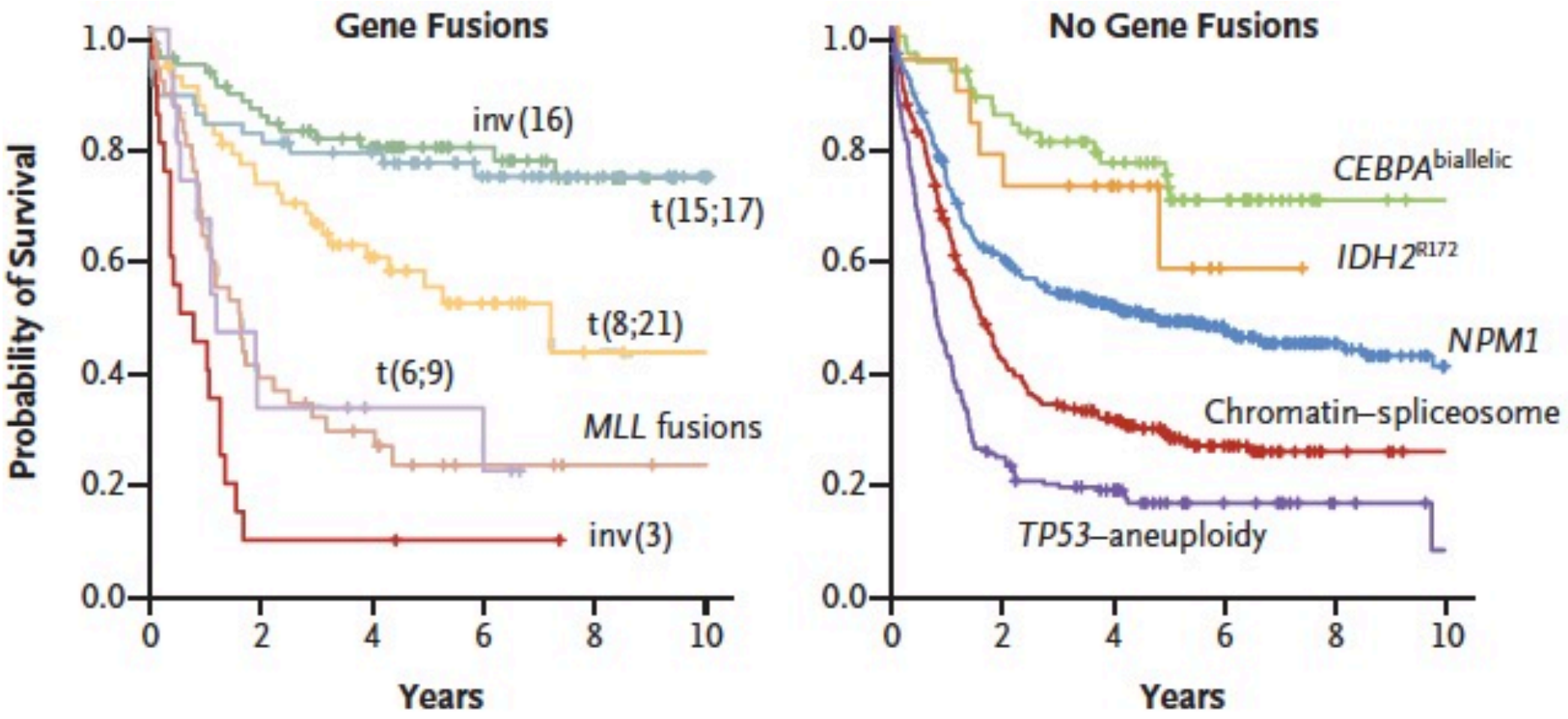
- Acquired genetic damage to bone marrow stem cells occurs throughout life.
- Most has no consequence but occasionally the damage starts a cell on the path to AML.
- Multiple genetic routes to the development of the disease.
- Subgroups of cells evolve during the illness



G Vassiliou

AML – outcome

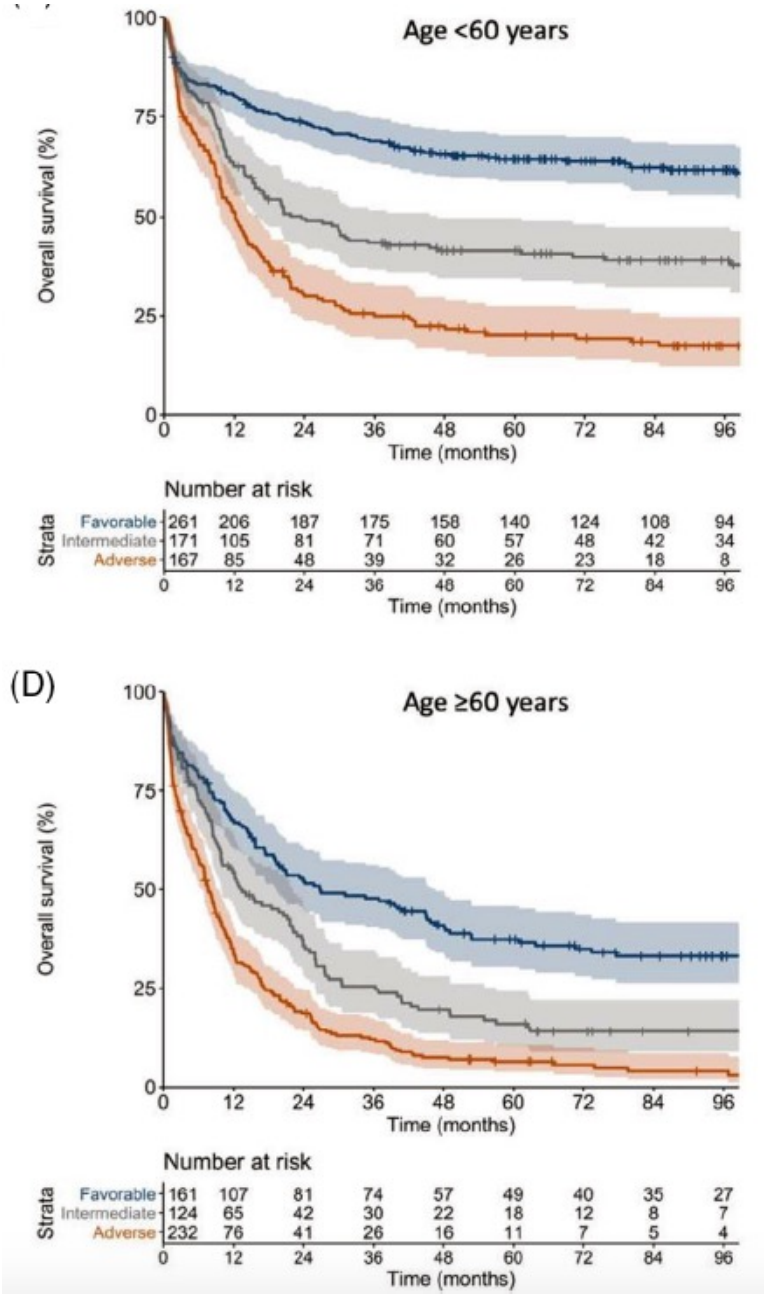
- The outcome in AML is determined by the type of genetic damage.



Courtesy Charles Crawley

AML treatment by risk.

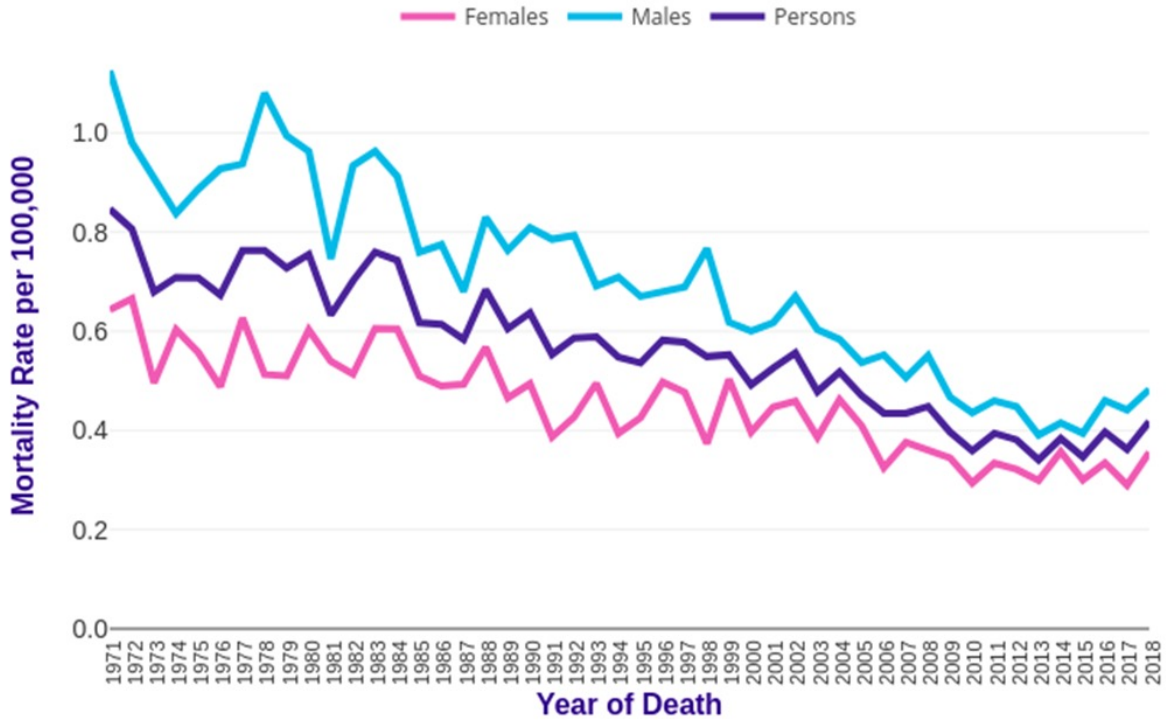
- Disease Risk – 3 groups
- Treatment
  - Lower risk – Chemotherapy
  - Higher risk – Chemotherapy + donor stem cell transplant.
- Outcome worsens with increasing age:
  - Worse genetic damage.
  - More difficulty tolerating intensive treatment.



Estey Am J Hematol 2020

Improvements in AML treatment.

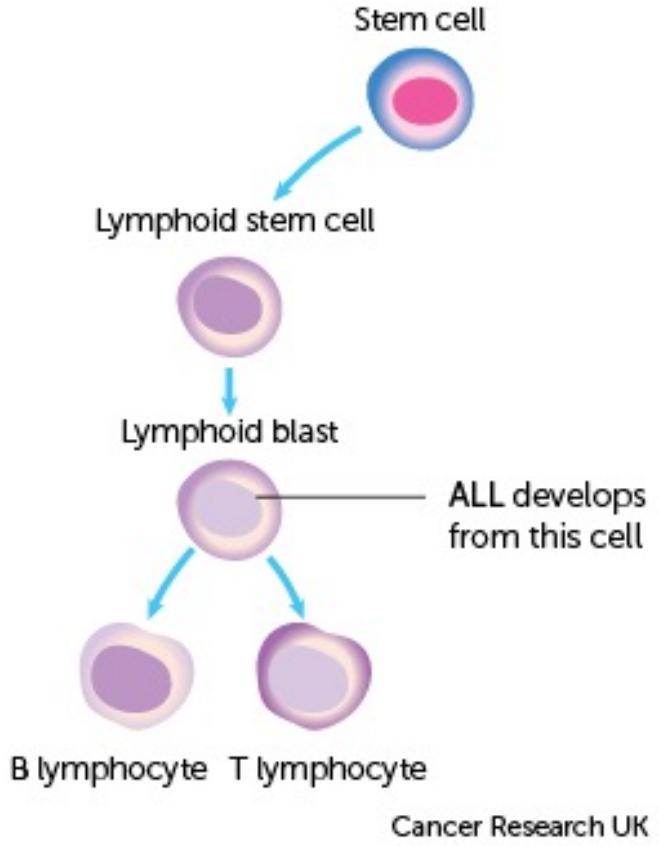
- NHS in England is supporting whole genome sequencing for newly diagnosed AML.
  - Better decisions about transplant.
  - Identification of patients with targetable mutations.
- New targeted therapies
  - Drug carrying antibodies to CD33.
  - Tryrosine kinase inhibitors.

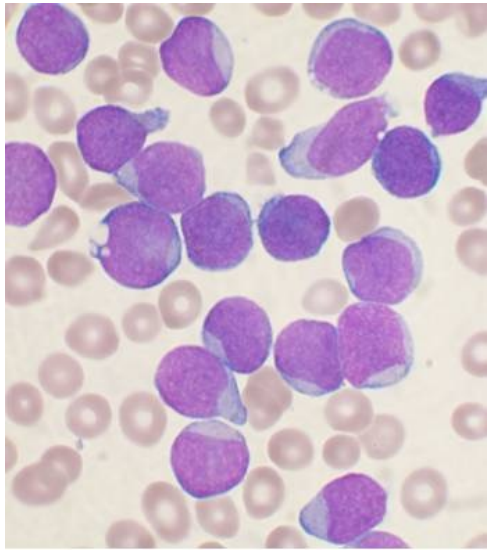


Mortality over time. CRUK.

Acute lymphoblastic leukaemia (ALL).
Around 800 diagnosed a year in the UK.

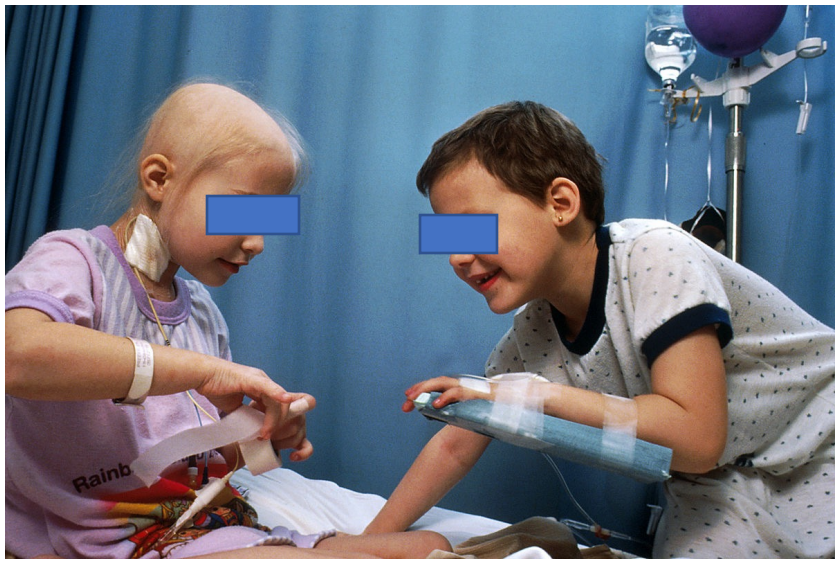
- Large number of immature lymphocytes.
- Tiredness, anaemia, bruising, fevers.
- Fatal in weeks to months if untreated.
- Outlook now good for many. Of those aged 14 or under >90% survive ≥5 years. Much lower in those over 65.



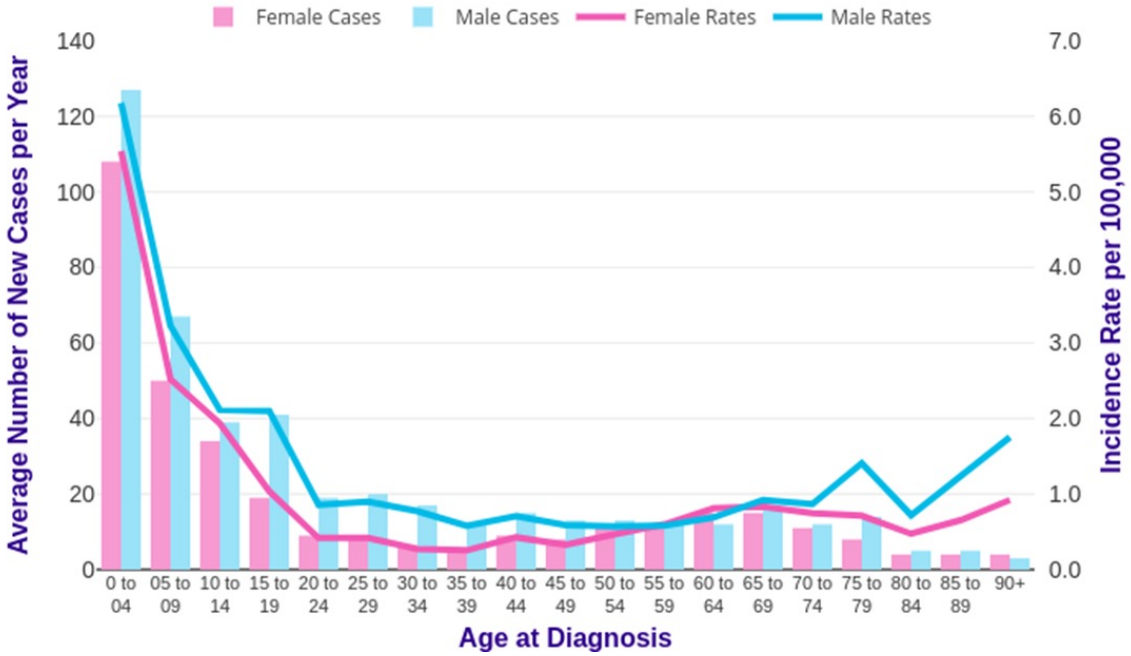


Bone marrow with B-cell ALL. VashiDonsk

ALL is mainly a disease of children.
2-5 is the most common age to develop it, rare after 24.



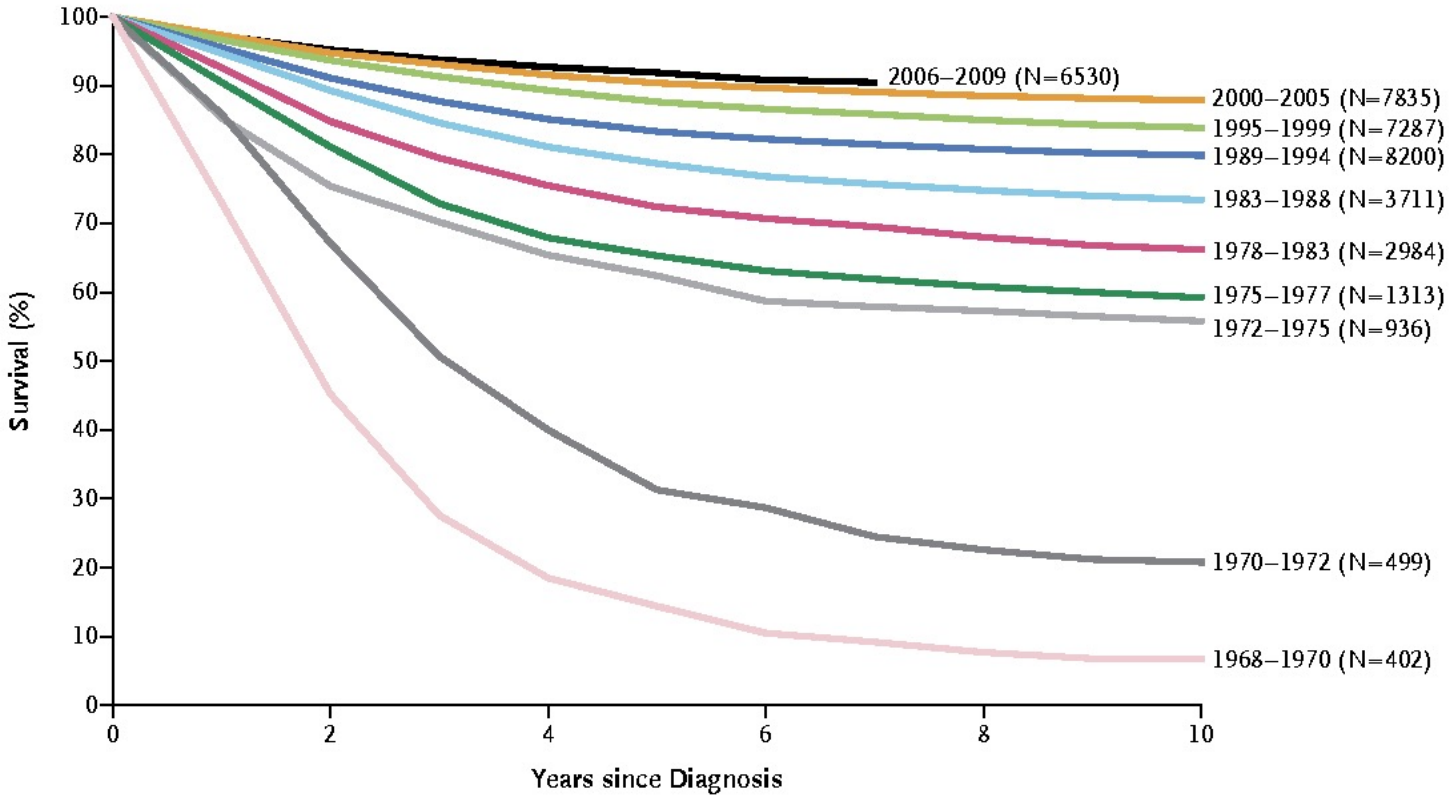
Two girls with ALL, 1985.
National Cancer Institute, USA.



CRUK

Evolution of chemotherapy for ALL.

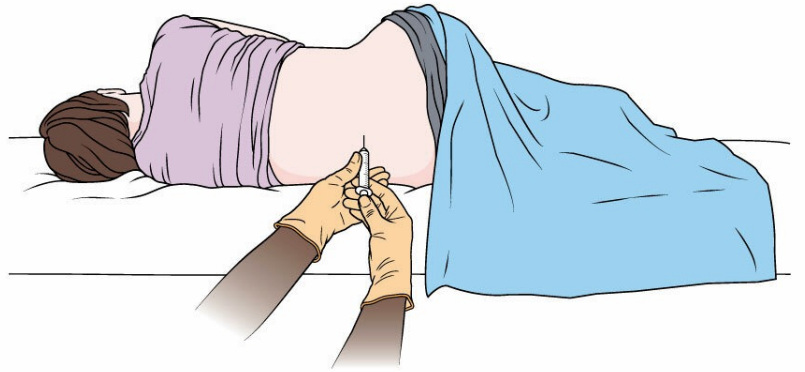
- Transient remissions with anti-folate drugs.
- Combination chemotherapy inducing complete remissions.
- Sequential studies over 50 years progressively improving survival.
- Challenge in 2021 to achieve the same with less side effects.



Hunger SP, NEJM 2015.

ALL treatment.

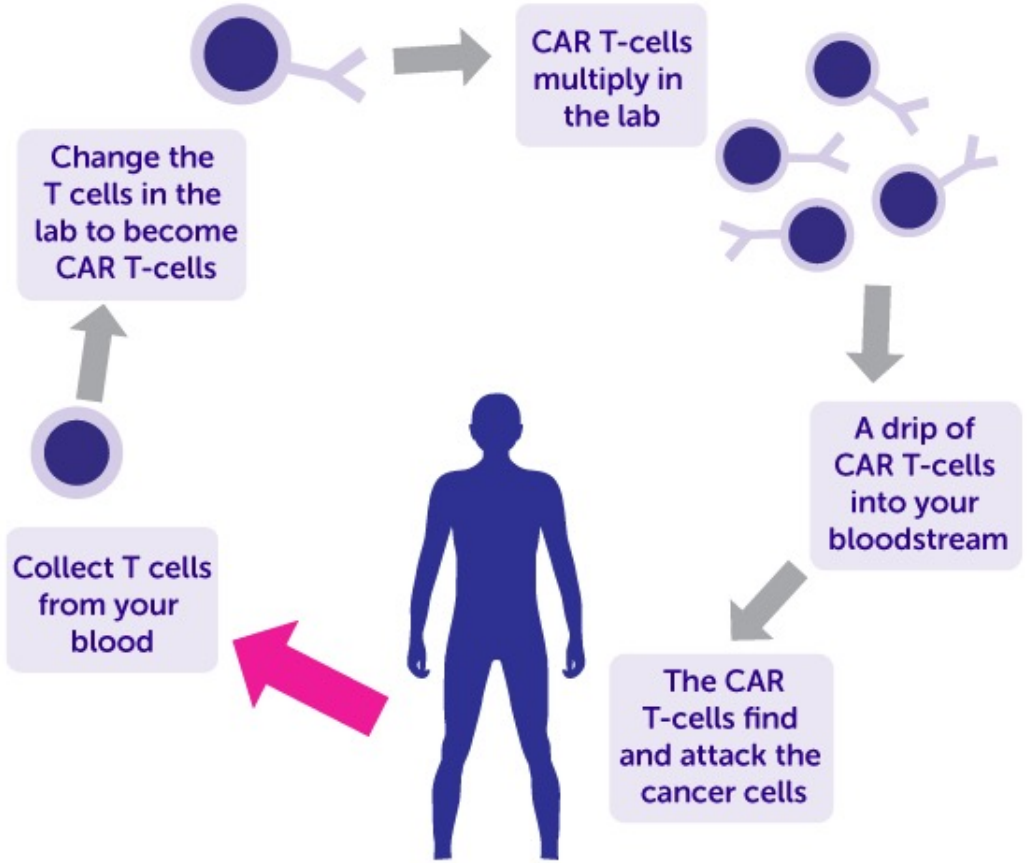
- Chemotherapy to achieve remission.
- Strongly influenced by genotype.
- May need treatment for brain ALL with intrathecal chemotherapy and/or radiotherapy.
- Then chemotherapy for some years to prevent relapse.



Intrathecal chemotherapy.
MacMillan.org

Chimeric Antigen Receptors Cell Therapy (CAR-T).

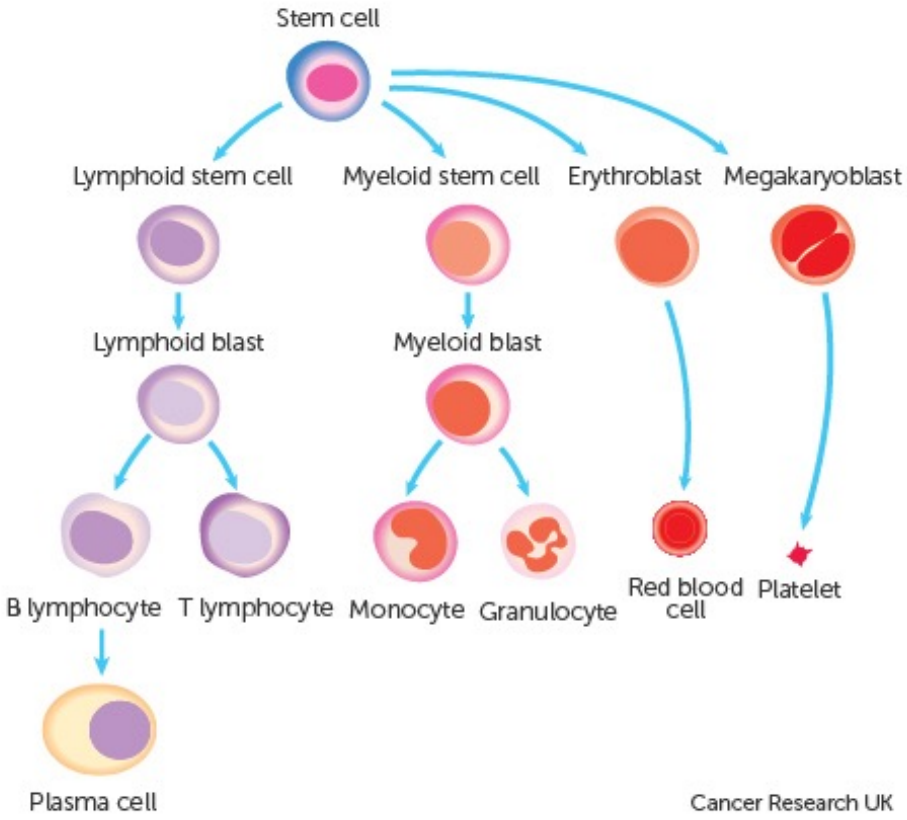
- A major scientific advance, but very complex (and expensive).
- Our immune system attacks cancer cells as well as infections.
- T-cells destroy defective cells, whether infected or damaged.
- Remove some of your T cells, reprogram them to recognise the cancer by inserting receptors for the cancer cell.
- T-cells survive for a long time, so you have to get it right…

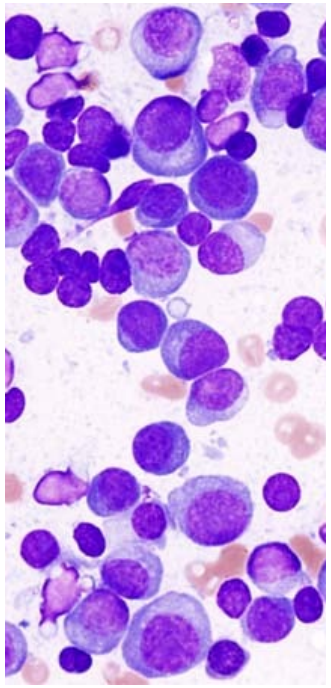


CRUK

Myeloma (multiple myeloma).
Around 5800 a year.

- Very rare in those under 40, mainly a cancer of older age.
- Plasma cells usually produce antibodies (G, A, M, D, and E)
- Antibodies attach to, and lead to killing of, viruses and bacteria.
- Myeloma is massive expansion of a clone of plasma cells, that usually produce (largely pointless) antibodies.

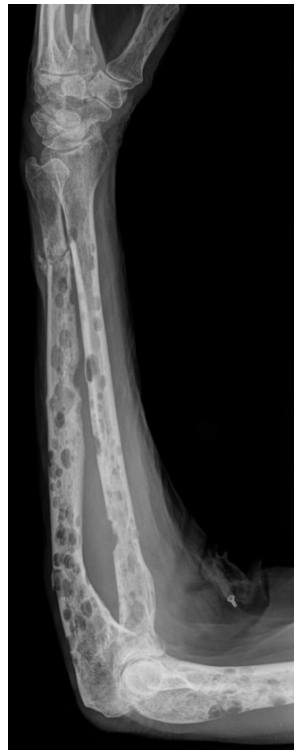




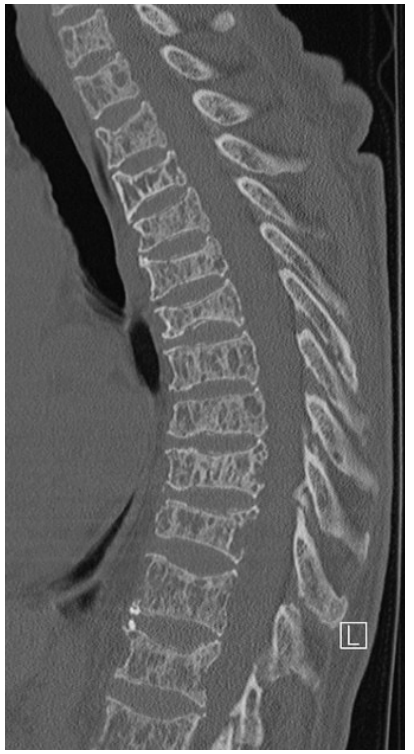
Wiki

The consequence of myeloma.

- Displacement of other bone marrow cells, similar to lymphomas and leukaemias. Anaemia, infections.
- Bone becomes eroded from the inside: collapse of vertebrae, ‘pathological fractures’, spinal cord compression, bone pain.
- Lots of immunoglobulin protein. ‘Sticky’ blood, kidney damage, clots.
- Too much calcium in the blood.



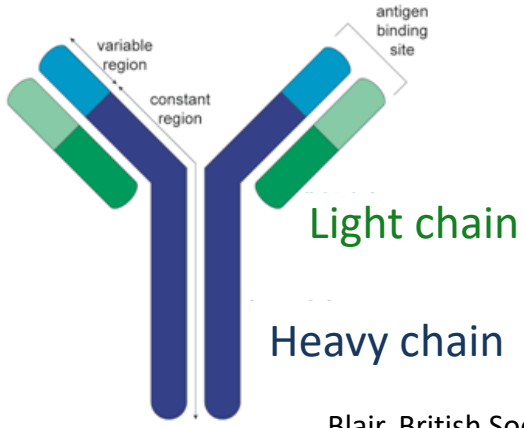
Hellerhoff.



Frank Gaillard
Radiopaedia

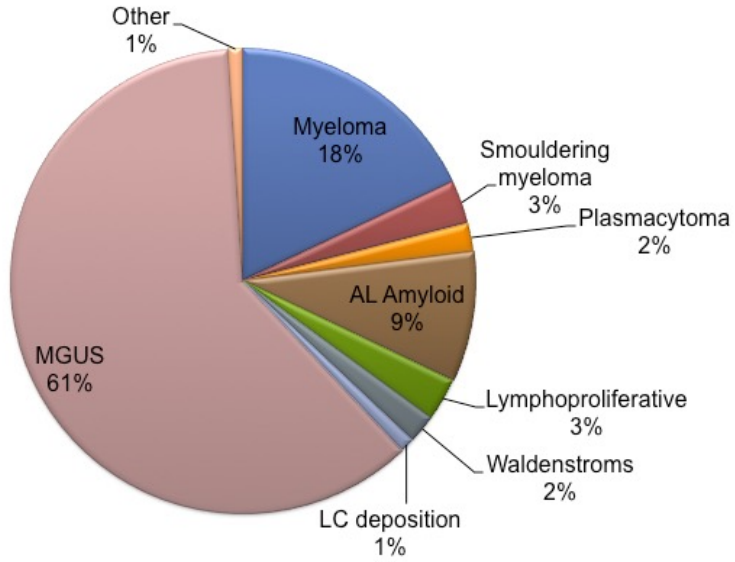
Diagnosis of myeloma.

- Blood test- for an excess of intact antibodies and a fragments of antibodies (light chains).
  - Excess of antibody = paraprotein.
  - Excess of antibody fragment = free light chain assay.
- Older test for light chains in urine test- Bence-Jones protein
- Bone marrow biopsy.
- CT, MRI or PET scans.



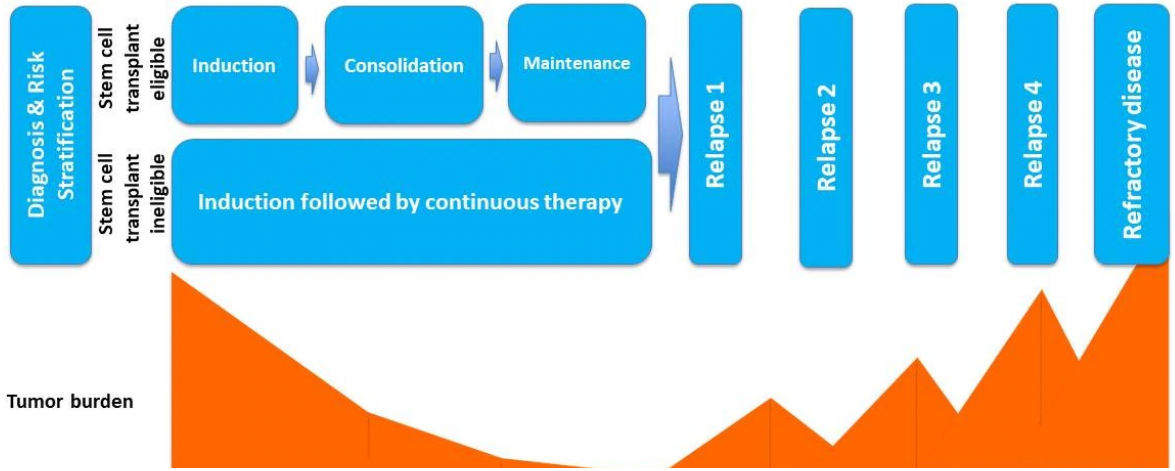
Blair, British Society for Immunology

Most paraproteins are not myeloma



Myeloma treatment.

- Not everybody diagnosed with myeloma needs immediate treatment.
- Aim in most people is long term control, and reduction of symptoms, not cure in most cases.
- Myeloma is a relapsing-remitting disease with periods of activity and periods of relatively inactive.
- More aggressive treatment in younger patients which may include self stem cell transplant.



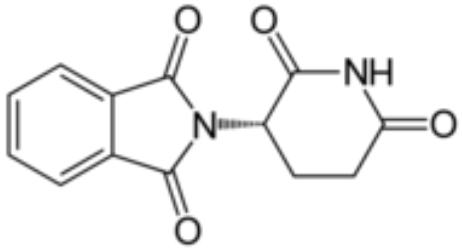
Mayo Clinic

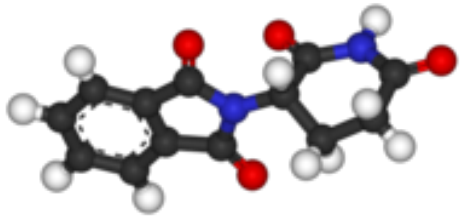
Initial treatment, and then treatments at relapse.

- Combinations often including a proteosome inhibitor, a thalidomide like drug and steroid.

Proteosome inhibitors	Imid's	Steroid
• Bortezomib • Carfilzomib • Ixazomib	• Thalidomide • Lealidomide • Pomalidomide	• Dexamethasone • Prednisolone

- Alternative combinations and antibody treatment at relapse.

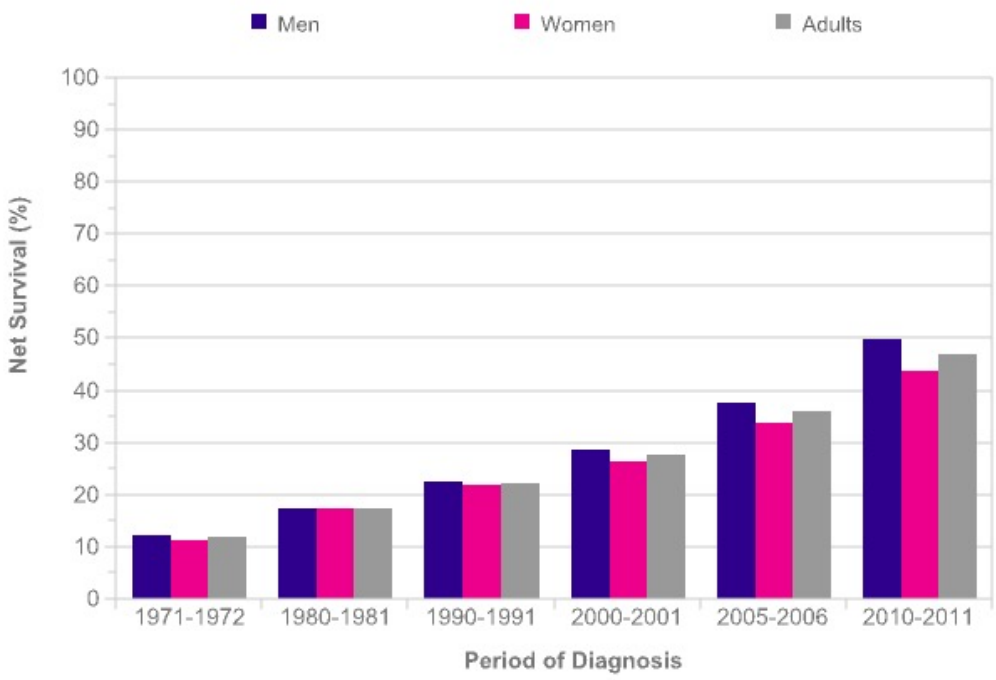




Thalidomide stops cancer cells developing, stops them growing their own blood vessels, and stimulates the immune system to attack cancer cells.

Myeloma survival is steadily improving.

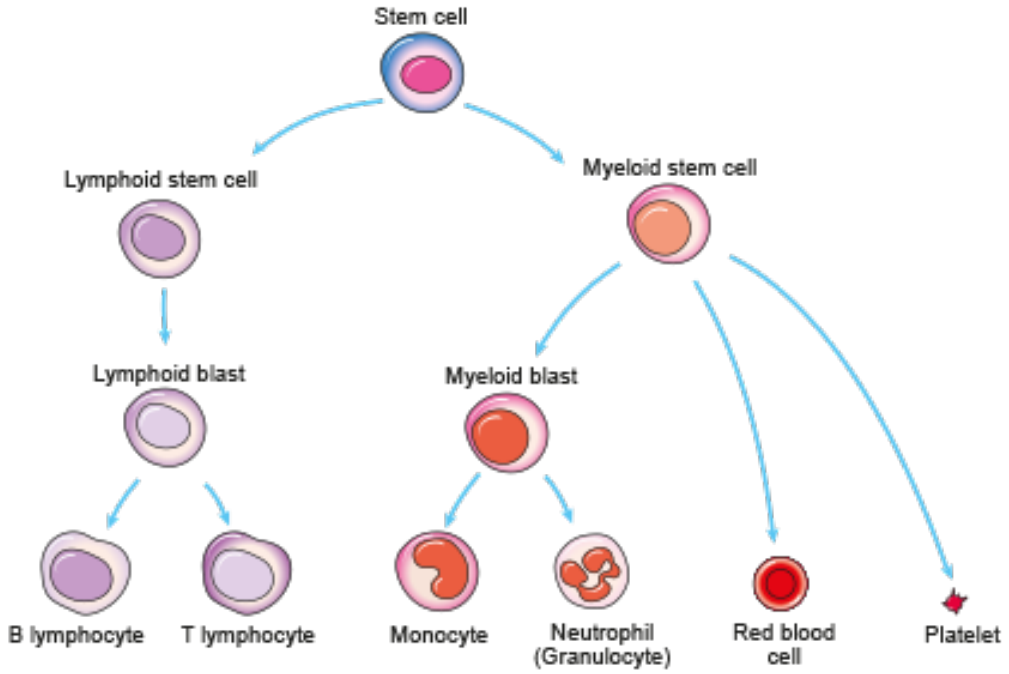
- Over 80% are alive a year after diagnosis.
- From around 10% survival at 5 years in 1970s; over 50% are now alive 5 years later, and just under 30% at 10 years.
- Better survival at younger ages; >70% 5 year survival in those aged under 50.
- Survival continues to improve.



5 year survival over time from 1970s. CRUK.

Lymphoma, leukaemia and myeloma.

- Cancers of the blood cells or bone marrow.
- Outlook has improved substantially for many lymphomas, leukaemias and myeloma.
- Some are curable, others are treatable and can be managed as a chronic condition for many years or decades.
- Genotyping, targeted therapies and novel treatments transforming the outlook.



CRUK