LYMPHOMA CANADA

SAVE THE DATE RESEARCH
EXPERT SPEAKERS HOPE
NATIONAL NETWORKING
AID CONFERENCE FORUM
ON LYMPHOMA SUPPORT
CAREGIVERS EDUCATION
SEPTEMBER 15 - 16, 2017
SURVIVORS MONTRÉAL, QC
THERAPIES SIDE EFFECTS

Indolent Lymphomas: Current

Dr Kelly Davison
MUHC

Why does indolent mean?

- Slow growth
- Often asymptomatic
- Chronic disease with periods of relapse (long natural history possible)
- Incurable with current standard therapy, but long remissions possible
- Goal of treatment is to maximize quality of life

Indolent lymphomas

	Incidence (per 100,000)
• Follicular	3.4
• Marginal zone or MALT	1.8
• Mycosis fungoides	0.4
• Waldenstrom's macroglobulinemia	0.3
• Hairy cell leukemia	0.3
• Primary cutaneous	0.1

SEER Database Incidence 2011-12

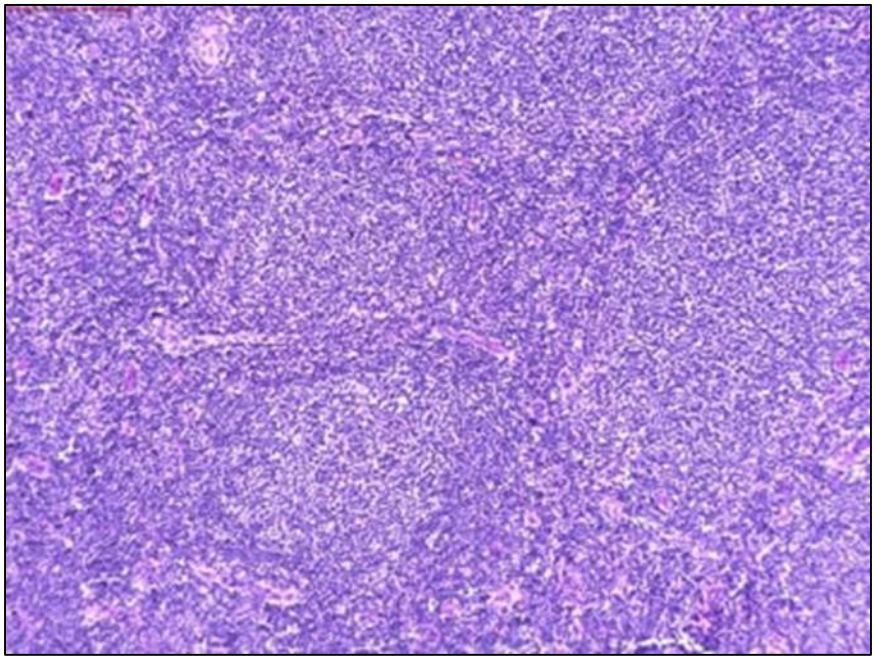
Lymphocytes

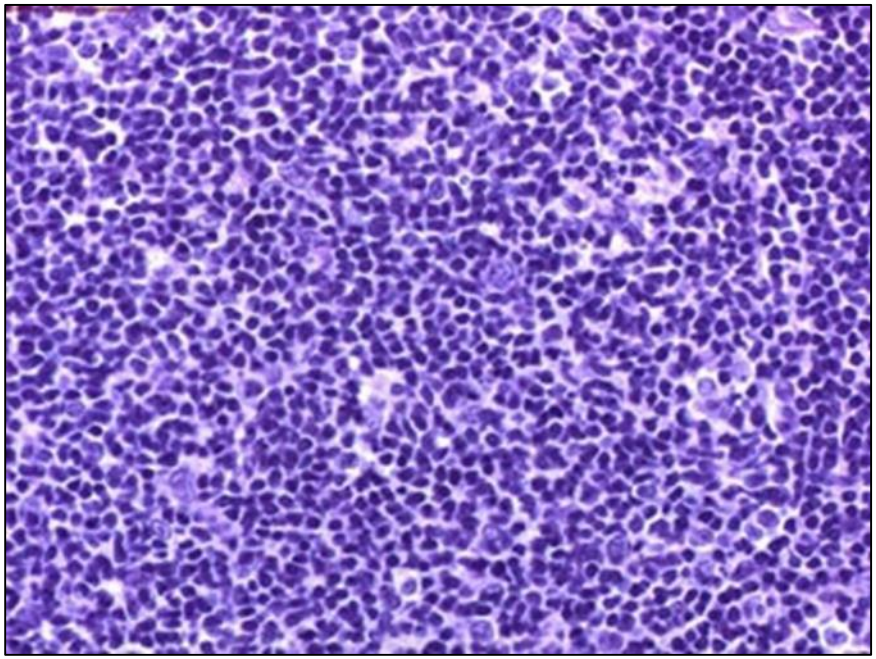
- **B cells** develop in the bone marrow
  - form antibodies against foreign bodies
    - 90% of all lymphomas
- **T cells** mature in the thymus gland
  - orchestrate the immune response
    - 10% of lymphomas
- **NK** (natural killer) **cells**
  - destroy viruses and cancers through direct attack
    - Very rare lymphomas, rarely indolent

How do we figure out which type you have?

- **Physical Exam**
  - Cardiac, respiratory, abdominal
  - Lymph nodes
- **Biopsy**
  - FNA or core biopsy
  - Incisional biopsy
  - Excisional biopsy
- **Laboratory**
  - CBC and differential
  - LDH (prognostic marker in NHL)
  - ESR (important in HL)
  - Bone marrow aspirate/biopsy
- **Imaging**
  - Chest X-ray
  - Ultrasound
  - CT scan neck/ chest/ abdomen/pelvis
  - Gallium Scan
  - PET
- **Other**
  - LP – if CNS symptoms, or in certain high risk cases of aggressive lymphoma (sinus, testicle, bone marrow)

Biopsies





Why is pathology important?

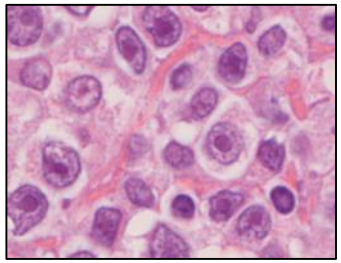
- Need to determine the most appropriate therapy
- Some of the criteria for diagnosis are very specific—and lead to specific treatment choices

  For example:

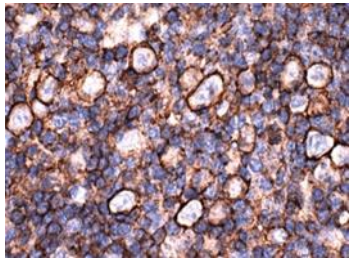
  - CD20 “positive” by immunohistochemistry: use of rituximab
- May provide prognostic information

Pathology and molecular analysis

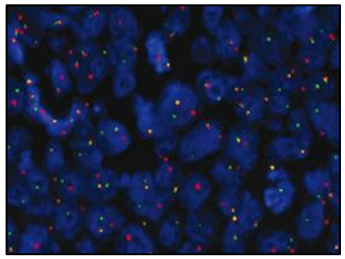
- Morphology



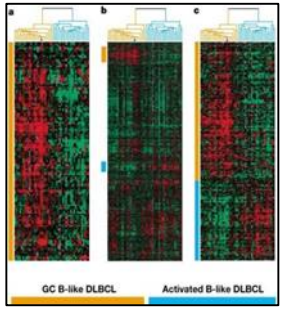
- Immunohistochemistry



- Cytogenetics



- Gene expression profiling



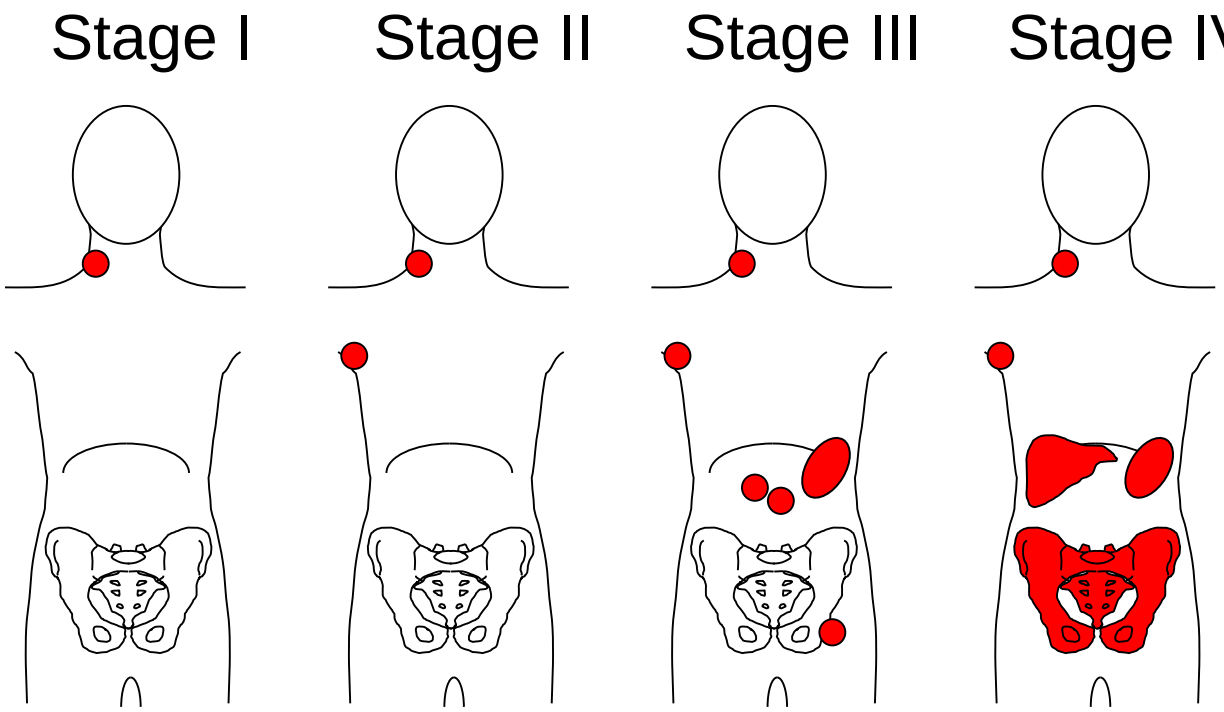
Staging

The # of staging investigations is dependent on the type of lymphoma and goals of therapy.

Staging is used to determine:

- Extent of disease
- Bulk of tumour mass
- Potential for complications
- Type of treatment

Ann Arbor Staging System



A – absence of any “B” symptoms

B – unexplained fever, drenching sweats or weight loss

Bulky > 10 cm mass on imaging

E – extranodal involvement

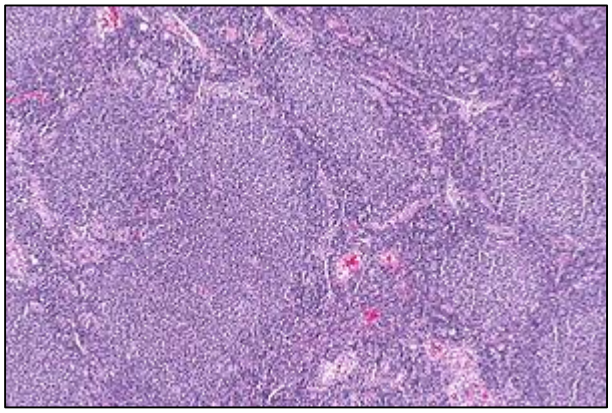
International Prognostic Index (IPI)

Evaluates 5 variables:

- Age
- Stage
- Performance status: what is the impact of lymphoma (or other medical problems) on daily life – how sick are you?
- Number of extranodal sites
- LDH

Follicular lymphoma

- Typically affects middle-aged and older adults
- Abnormal follicles give disease its name
- Causes few symptoms in early stages
- Usually responds well to treatment, but can return
- Can transform into aggressive lymphoma



FLIPI- Follicular Lymphoma International Prognostic Index

Parameter	Adverse factor	RR	95% CI
Age	≥ 60 y	2.38	2.04-2.78
Ann Arbor stage	III-IV	2.00	1.56-2.58
Hemoglobin level	< 120 g/L	1.55	1.30-1.88
Serum LDH level	> ULN	1.50	1.27-1.77
Number of nodal sites	> 4	1.39	1.18-1.64

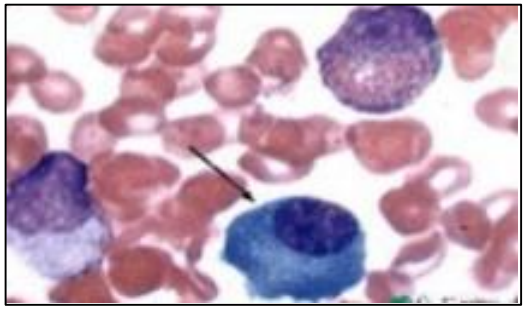
Score	Prognosis	% Patients	OS (10 yr)
0-1	good	36	71
2	moderate	37	51
3-5	poor	27	36

Marginal zone lymphoma

- Accounts for ~10% of NHL
- Affects older adults usually
- 3 types:
  - **Extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT)**
    - Occurs outside the lymph nodes, for example in the stomach, small intestine, salivary glands, thyroid, eyes or lungs
  - **Nodal marginal zone lymphoma**
    - Occurs within lymph nodes
  - **Splenic marginal zone lymphoma**
    - Usually occurs in spleen and blood

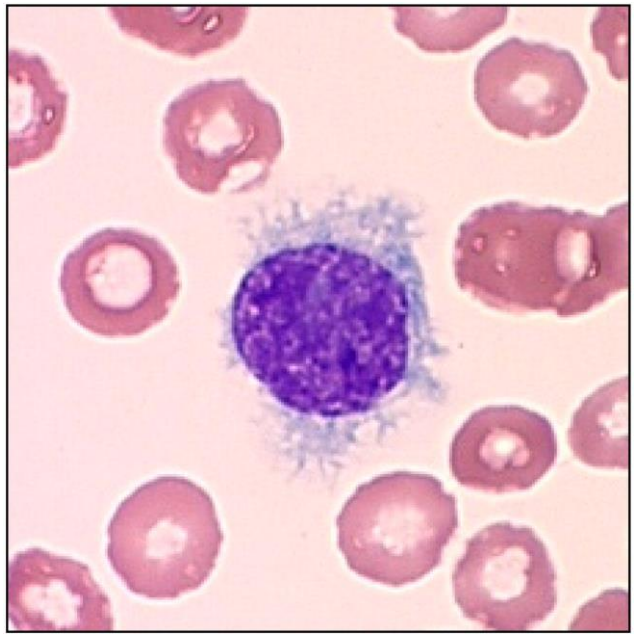
Waldenstrom's macroglobulinemia

- Dr. Jan Waldenstrom first described the condition in 1948
- Rare, 1-2% of NHLs, usually affecting older adults
- Primarily found in bone marrow
- Overproduction of IgM protein, causing thickening of blood
- Plasmapheresis may temporarily reverse or prevent symptoms associated with blood thickening.



Hairy cell leukemia

- Surface of cells look hairy under microscope
- Called ‘leukemia’ as cancerous lymphocytes can be found in the blood, though they mainly collect in the bone marrow and spleen
- Rare subtype usually found in middle-aged or older adults



Cutaneous lymphoma

- Lymphoma in the skin
- Usually T cell, but can be B cell
- Most common subtype: mycosis fungoides
- Most common in those aged 50+, but can occur in younger adults
- Often small, raised, red patches on skin that may look like eczema or psoriasis
- Ulcerating tumours (open sores) can appear
- Treatment may include ultraviolet light

Watch & wait

Randomized trial of "Watch and Wait" vs. early chemotherapy

British National Lymphoma Investigation Trial of 309 patients with indolent NHL

Results	"Watch and Wait"	Early chemotherapy
Lymphoma-specific survival	No difference	
Overall Survival	No difference	

- On average, patients needed treatment ~2.5 years from diagnosis
- However, 1 in 5 participants did not require treatment by 10 years
- 2 in 5 over the age of 70 did not require treatment

Coping with watch & wait

- Be gentle with yourself
- Talk it out
- Take care of yourself (healthy living)
- Learn about lymphoma (dispelling the myths)
- Ask for support

Indications for starting treatment

- Symptoms attributable to the lymphoma
- Low blood counts because of bone marrow involvement
- Threat to organ function
- Bulky disease or spleen
- Disease that has transformed to an aggressive lymphoma

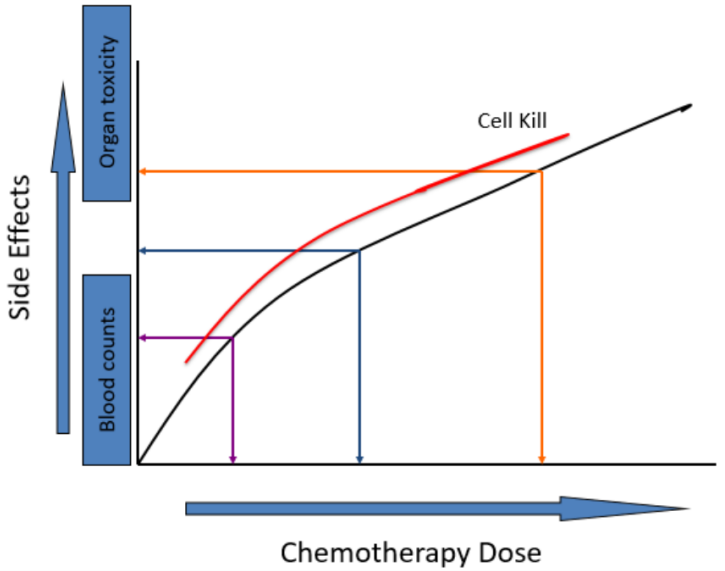
Overview of primary treatment options

Treatment Option	Description
Chemotherapy	Use of drugs to kill lymphoma cells
Radiation Therapy	Use of high-energy rays to kill lymphoma cells or slow their growth
Immunotherapy	Use of agents designed to target and destroy lymphoma cells
Transplantation	Infusion of healthy stem cells/bone marrow after high dose chemotherapy, to help the body restore its supply of healthy blood cells

Balance potential toxicity against effectiveness

Chemotherapy

- Backbone of many cancer treatments
- Damages DNA, leading to cell death
- Systemic
- Affects all growing cells
  - Cancer cells
  - Blood cells
  - Lining of GI tract
  - Hair



Common chemotherapy regimens

CHOP - with or without R (Rituxan)

- ✓Cyclophosphamide
- ✓Doxorubicin
- ✓Vincristine
- ✓Prednisone— pills daily x 5 days

} By IV every 3 weeks

4 cycles—if radiation is also part of the plan
6 cycles—most often
8 cycles—in some circumstances

Common chemotherapy regimens

CVP – with or without R

- Cyclophosphamide
- Vincristine
- Prednisone — pills daily x 5 days

} By IV every 3 weeks

For a usual total of 6 to 8 cycles unless disease progression or unacceptable toxicity occurs

Common chemotherapy regimens

Single Agents, with or without R

Bendamustine

- Infuse on days 1 & 2
- By IV every 4 weeks
- Maximum 6 cycles

Chlorambucil

- Pill
- Dosage varies

Fludarabine

- Pill or IV for 5 days
- Repeat every 4 weeks
- Maximum 8 cycles

Cladribine

- IV for 5 days

Immunotherapy

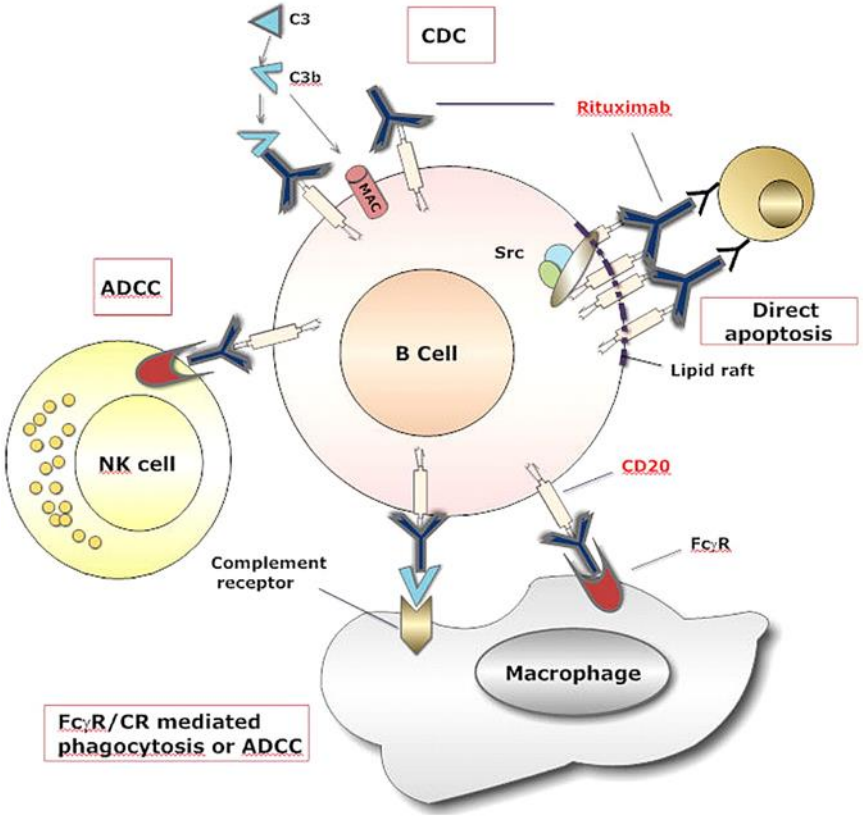
- Also called biologic therapy
- Drugs designed to boost the body's natural defenses against cancer
- Generally fewer side effects than traditional chemotherapy

Monoclonal antibodies

Antibodies developed against cancer cells can be administered to patients to destroy the tumour

- Examples:
  - Rituximab
  - Obinutuzumab

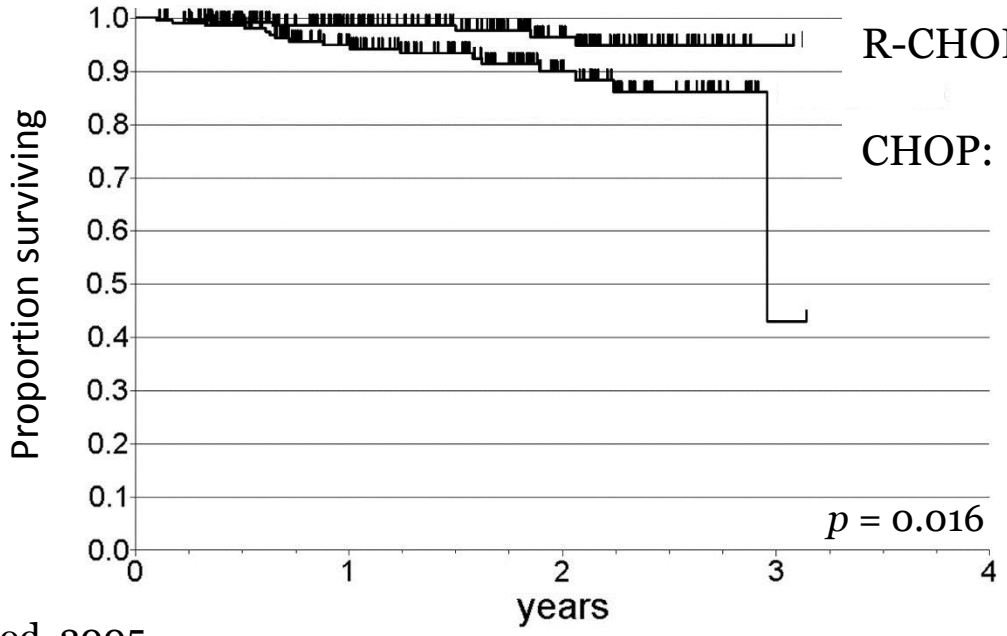
Only work for lymphomas that express the target protein



Samantha M. Jaglowski et al. Blood 2010;116:3705-3714

Why add rituximab?

Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.



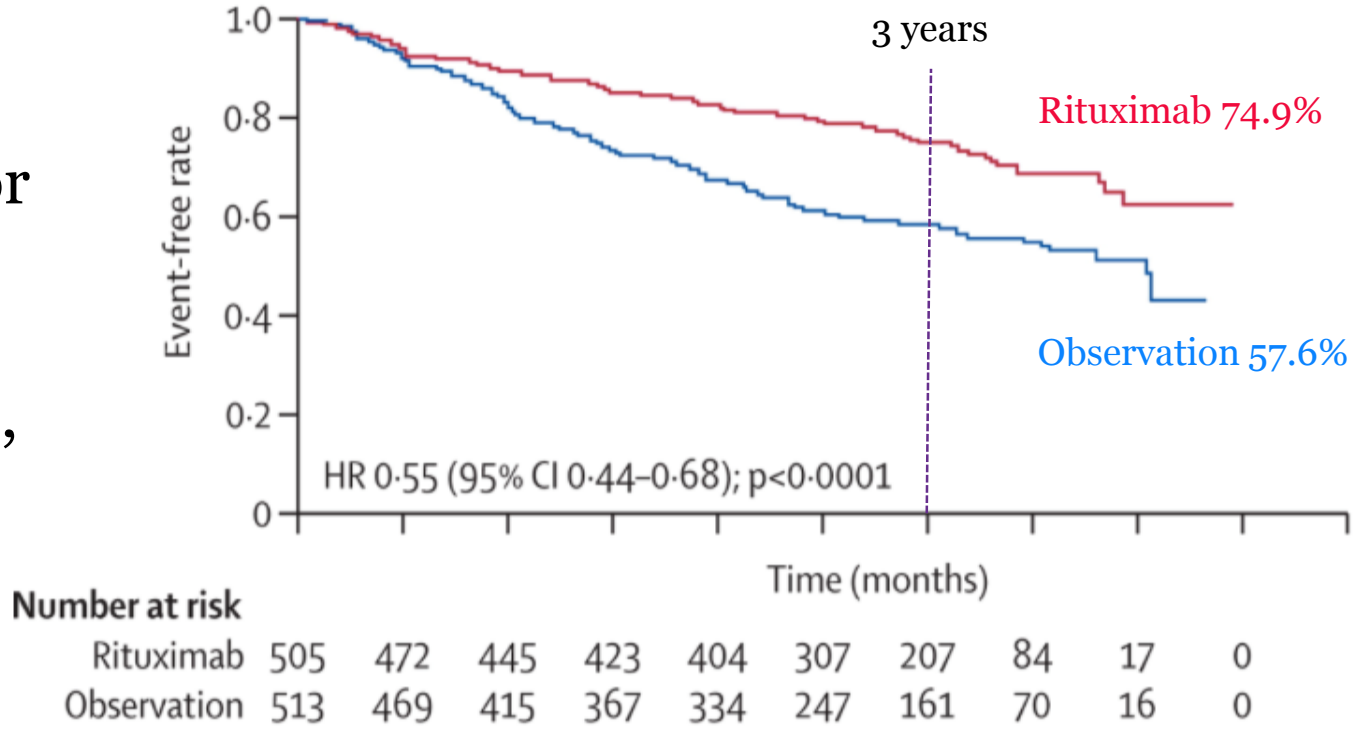
R-CHOP: 6 deaths (n = 225)

CHOP: 17 deaths (n = 203)

Hiddemann et al. Blood, 2005

Rituximab maintenance

- Rituximab maintenance for 2 years
- Administered every 2 months, 12 cycles



Salles et al, The Lancet, 2011

Targeted therapies

Drugs that target specific molecules on the surface of cancer cells or cell pathways.

Ibrutinib

- Pill, taken as directed until disease progression or intolerance to drug develops

Idelalisib

- Pill, taken alone or in combination with Rituximab, until progression or intolerance

Radiation

Medical uses of radiation:

1. Diagnostic: low doses of radiation to take images of internal body structure i.e. chest X-ray
2. Therapeutic: higher doses of radiation to kill cancer cells

Difference between the two is the amount of energy. Therapeutic radiation can use up to 1,000 times the energy of diagnostic radiation.

Radiation

- X-ray beams interact with atoms, creating a reaction that leads to cell DNA damage
- Damage prevents the cells from dividing and growing
- Lymphocytes are the most sensitive cells in the body to radiation, so can use lower doses of radiation compared to what is used to treat solid tumours.

Radiation

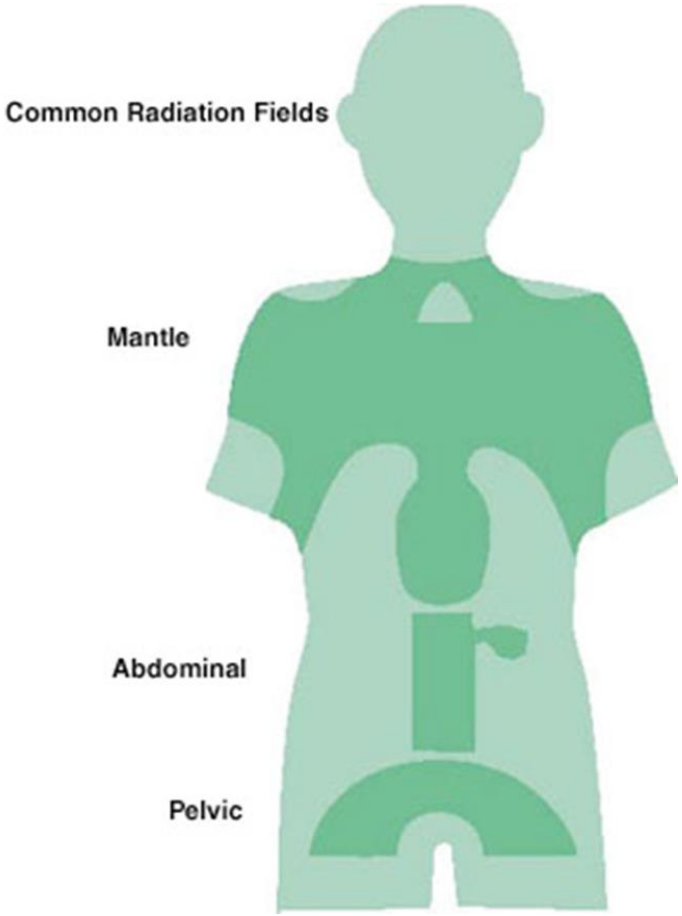
Linear Accelerators

- Machines do not use radioactive sources but instead use electricity to produce X-rays and electrons.
- Versatile as they can produce different energies of radiation, to minimize the normal tissue affected.

Radiation

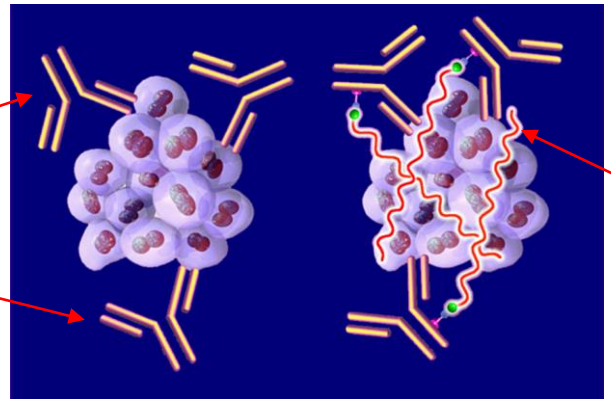
- Applies to localized disease
- May not be used in all types of indolent NHL
- Generally treatment is given daily for 4 weeks (Monday to Friday X 4 weeks = 20 treatments or “fractions”)
- Side effects based on the area that is being radiated (skin and tissue beneath it)

Common radiation fields



Combination therapy

- Chemotherapy + radiation
- Chemotherapy + immunotherapy = chemoimmunotherapy
- Radiation (radioactive isotopes) + immunotherapy = radioimmunotherapy



Side effects of treatment

Short term:

- Hair loss
- Mouth sores
- Nausea, vomiting: controllable with medication
- Fatigue
- Fever: need a thermometer! If >38.3 or 101.5° get a blood test (even Sunday afternoon…)
- Low blood counts

Other possible issues

- Heart function: may need monitoring
- Peripheral neuropathy (numb hands, feet)
- Difficulty with memory, concentration (multi-tasking)– “chemobrain”
- Fertility

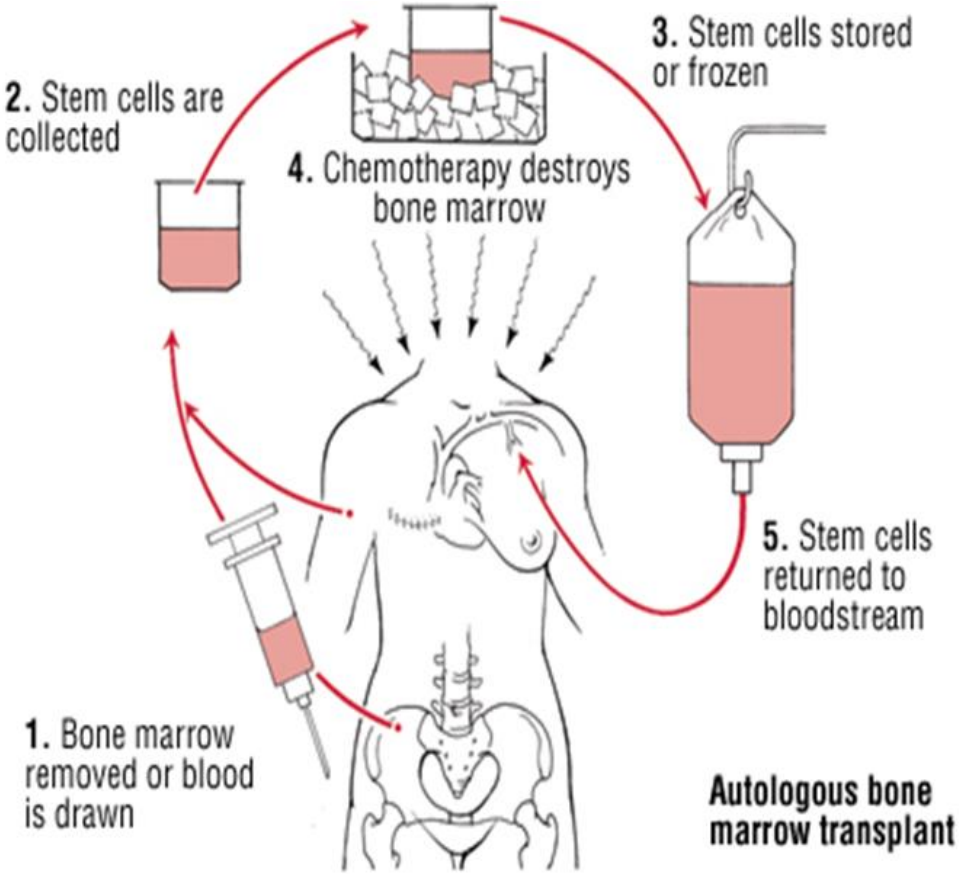
Other possible issues

- Secondary cancers
- Work/school
- Going out in public, infection risks
- Immunization

Stem cell transplant (SCT)

Autologous

- Use own cells
- Low treatment related mortality
- High rates of remission
- Transplant strategies vary centre-to-centre



Stem cell transplant (SCT)

Allogeneic

- Rare
- HLA matched sibling or matched unrelated donor
- 1 in 4 chance of sibling being a match
- Graft versus lymphoma: good!
- Graft versus host disease: can be very bad, including fatal, and life long
- Higher treatment related mortality

After treatment is completed

- Repeat staging tests to determine if the lymphoma is “in remission”
  - Hope that we have attained a long period of disease control before we have to re-treat the lymphoma
- Follow-up with your family MD (~annually)
  - Screening for secondary cancers
  - Vaccines
- Follow-up with your oncologist (~3 months)

Relapse/refractory

- Many other treatments available
- Goals of therapy may change
- Clarification of goals with your oncologist is very important
- Clinical trials of new agents