



LYMPHOMA
CANADA

EXPERT SPEAKERS HOPE
NATIONAL NETWORKING
AID CONFERENCE FORUM
ON LYMPHOMA SUPPORT
CAREGIVERS EDUCATION
SEPTEMBER 29 - 30, 2017
SURVIVORS TORONTO, ON
THERAPIES SIDE EFFECTS

Indolent Lymphomas: Current

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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, none indolent

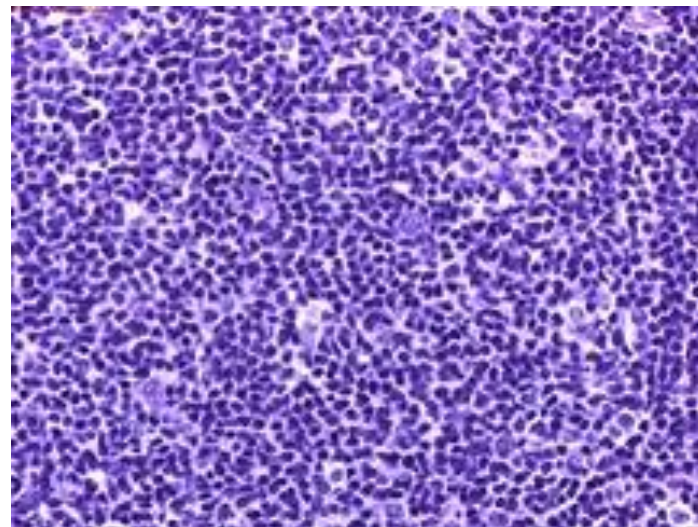
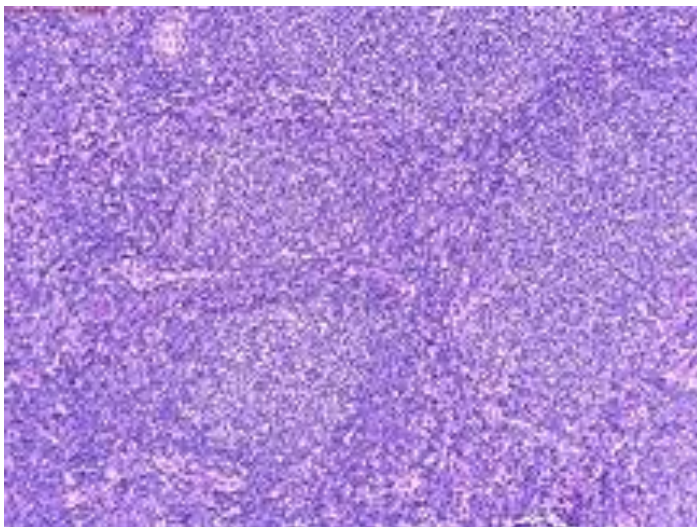


How do we figure out which type you have?

- **Physical Exam**
 - Cardiac, respiratory, abdominal
 - Lymph nodes
- **Biopsy**
 - FNA
 - 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

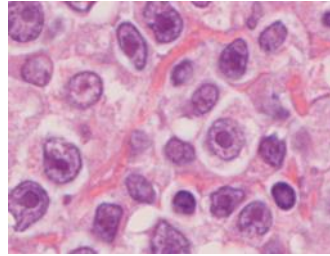
For example:

- CD20 “positive” by immunohistochemistry: use of rituximab

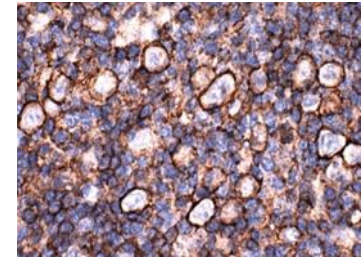


Molecular analysis

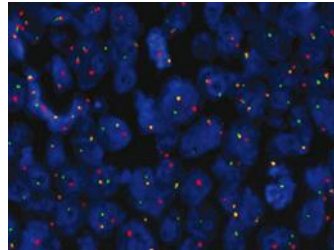
- Morphology



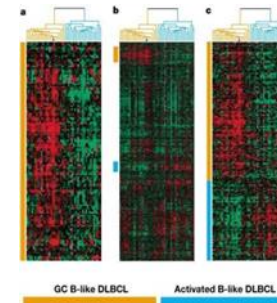
- Immunohistochemistry



- Cytogenetics



- Gene expression profiling



Staging

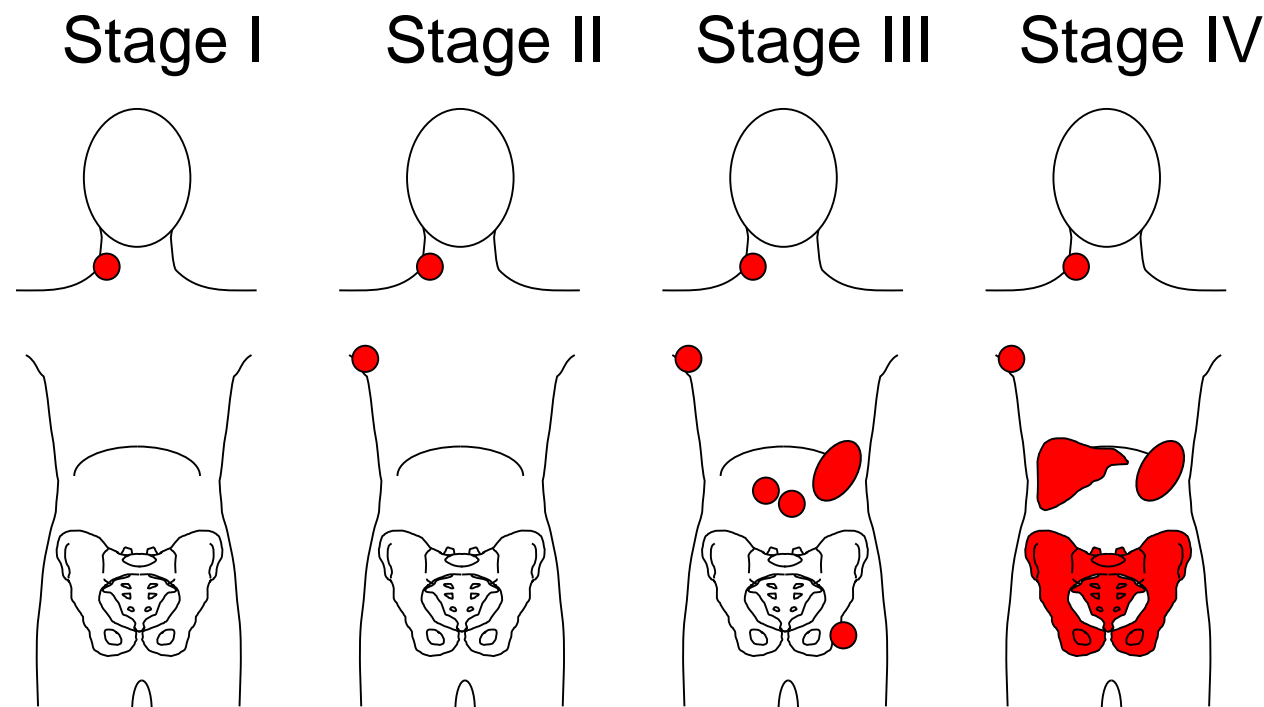
The # of staging investigations is dependent on the type of lymphoma and goals of therapy.

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



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International Prognostic Index (IPI)

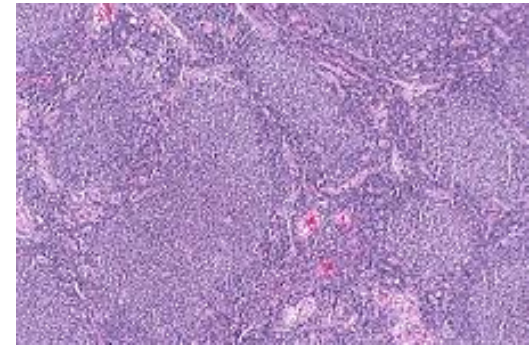
Evaluates 5 variables:

- 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



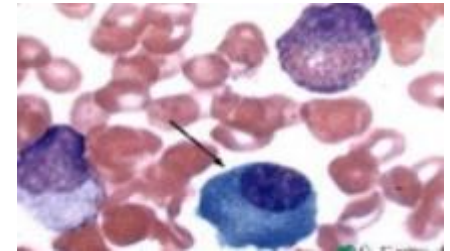
Marginal zone lymphoma

- 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 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



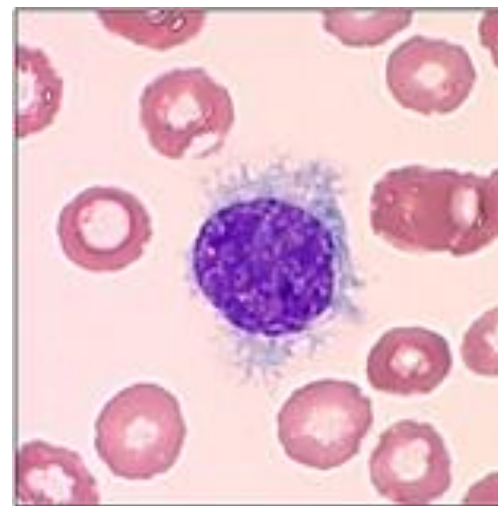
Waldenstrom's macroglobulinemia

- 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

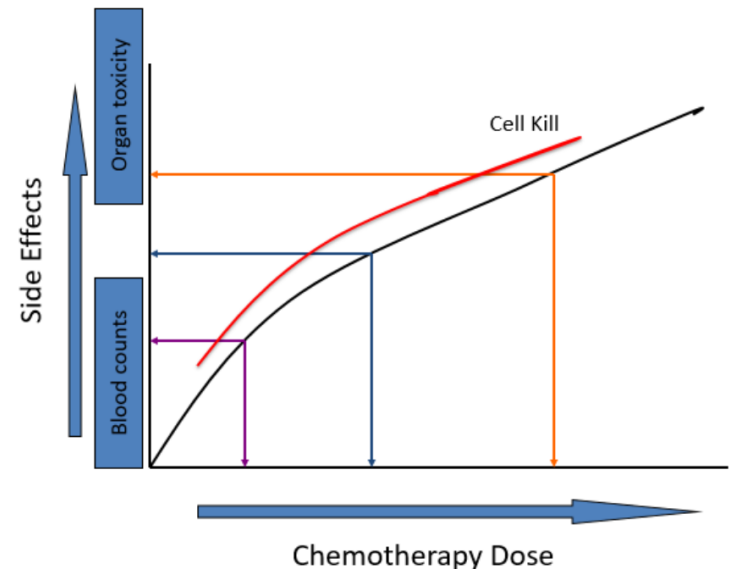
Treatment Option	Description
Chemotherapy	Use of drugs to kill lymphoma cells
Radiation Therapy	Use of high-energy rays to kill lymphoma cells or slow their growth
Immunotherapy	Use of agents designed to target and destroy lymphoma cells
Transplantation	Infusion of healthy stem cells/bone marrow to help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

Balance potential toxicity against effectiveness



Chemotherapy

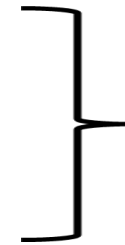
- Backbone of many cancer treatments
- Damages DNA, leading to cell death
- Systemic
- Affects all growing cells
 - Cancer cells
 - Blood cells
 - Lining of GI tract
 - Hair



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

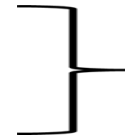
8 cycles—in some circumstances



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

FCM – with or without R

- Fludarabine
- Cyclophosphamide
- Mitoxantrone



By IV every
4 weeks

F & C infused on days 1, 2, 3; M only infused on day 1



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



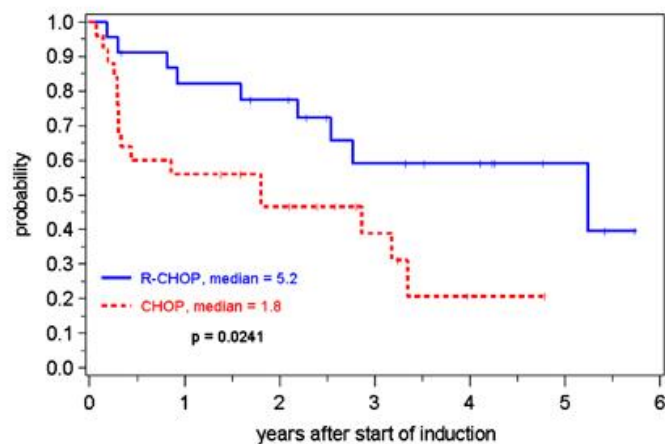
Immunotherapy

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



Why add rituximab?

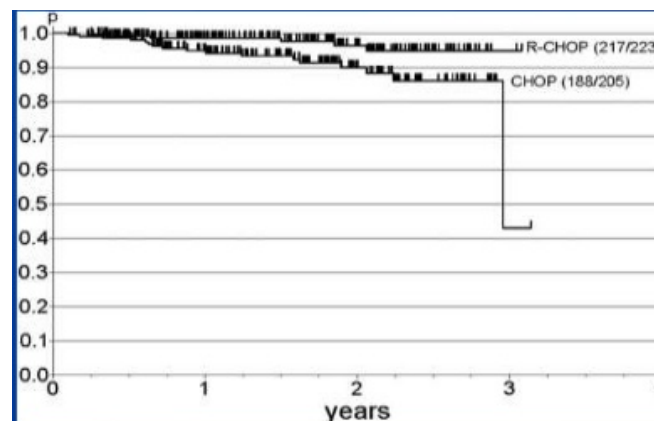
Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.



numbers of patients at risk

R-CHOP	23	18	16	9	7	3	0
CHOP	25	14	10	5	1	0	

Waldenstrom's Macroglobulinemia CHOP vs R-CHOP, German Low Grade Lymphoma Study Group, Phase III Trial Results



Follicular Lymphoma CHOP vs R-CHOP, Hiddemann et al, 2005



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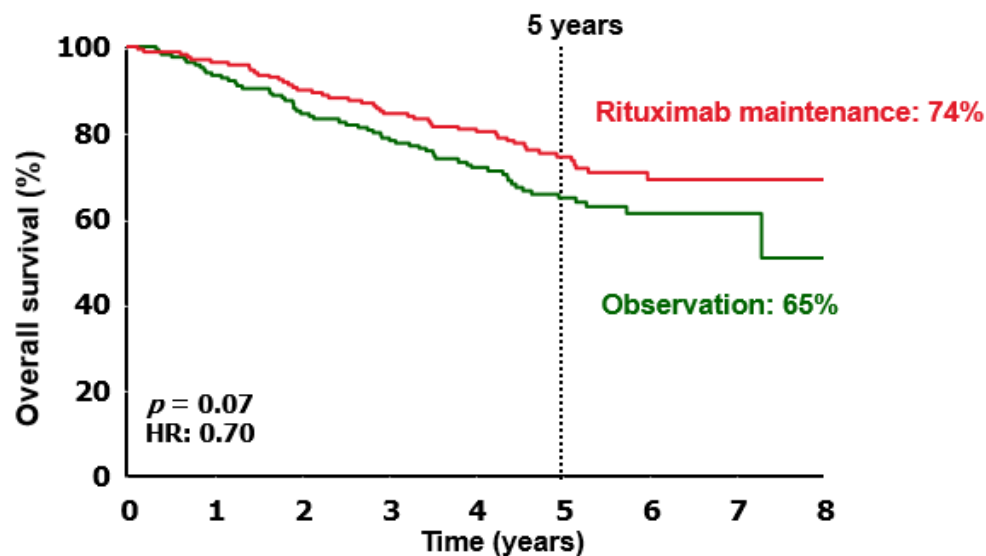


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Rituximab maintenance

- Rituximab maintenance for 2 years
- Administered every 3 months, 8 cycles

FL



van Oers MHJ, et al. *J Clin Oncol* 2010; 28:2853–2858.



Targeted therapies

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

Bortezomib

- IV twice a week for 2 weeks, then 10 day rest period

Ibrutinib

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



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.

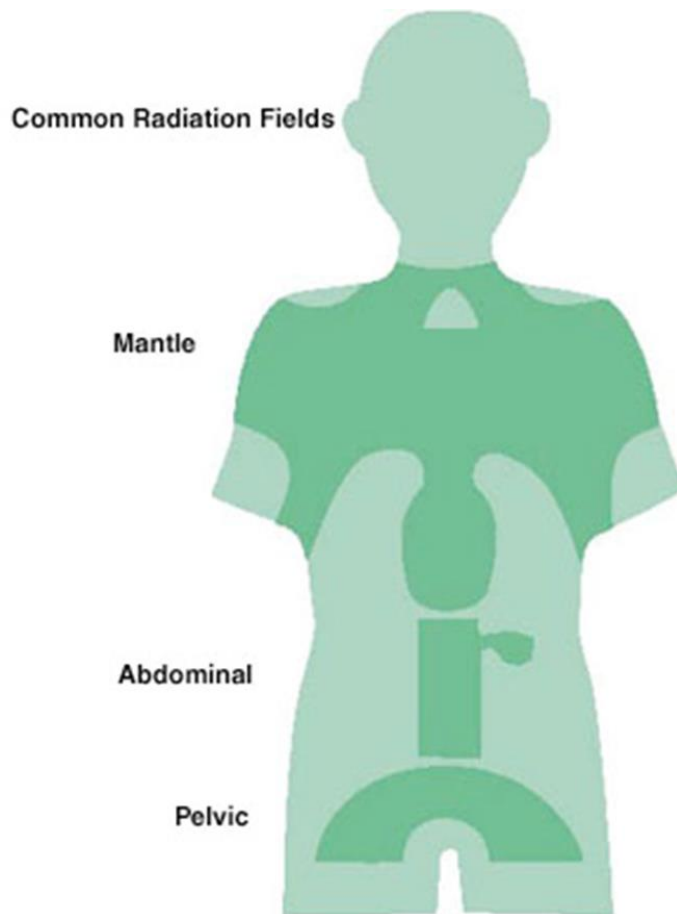


Radiation

- 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)



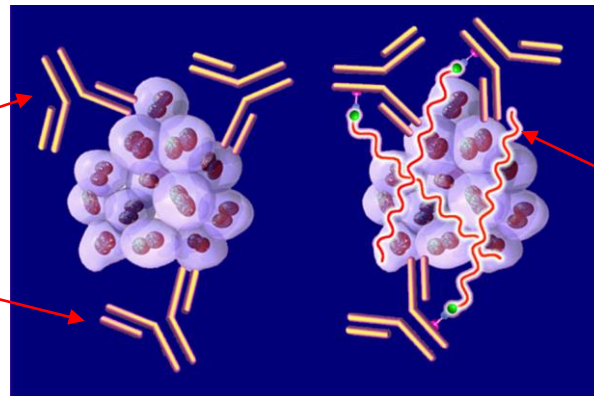
Common radiation fields



Combination therapy

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

Monoclonal antibody alone



With radioactive isotopes



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

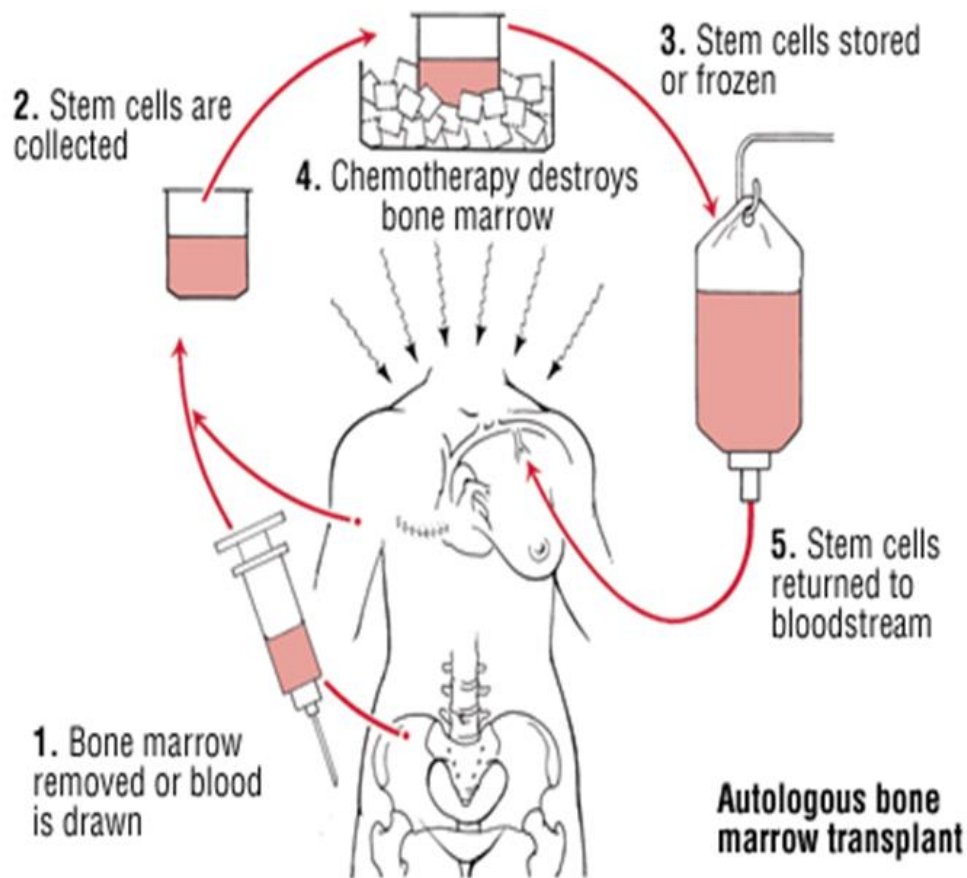
- Secondary cancers
- Work/school
- Going out in public, infection risks
- Immunization



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





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