Aggressive lymphomas

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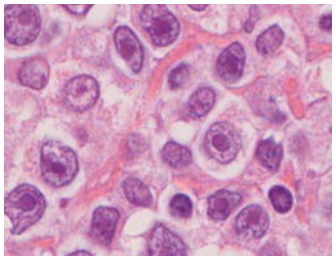
What are the aggressive lymphomas?

- Diffuse large B cell
- Mediastinal large B cell
- Anaplastic large cell
- Burkitt lymphoma
- (transformed lymphoma: see next talk)

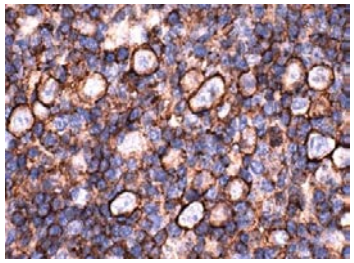
- T cell lymphomas

lymphoma classification 2012

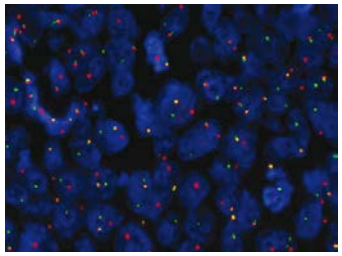
- Morphology



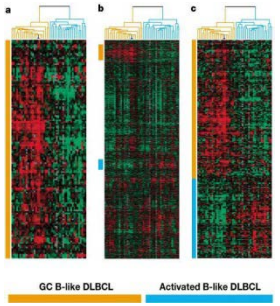
- Immunohistochemistry



- Cytogenetics



- (gene expression profiling)



Incidence of Follicular Lymphoma: US Cancer Registries 2001

WHO histology	Rate/100,000
DLBCL	7.1
Follicular	3.2
CLL/SLL	5.2
Mantle cell	0.5
Myeloma	5.3
Hodgkin's	2.7

Morton, Blood 2006

What are the aggressive lymphomas?

- Duration of symptoms generally shorter than indolent lymphomas
- Generally need treatment at time of diagnosis
  - Immediate, few days, few weeks
- Treatment generally given with the expectation of remission, goal of possible cure

Why pathology is so important in aggressive lymphomas

- Many/most are potentially cureable—so need to determine the most appropriate therapy
- Some of the criteria for diagnosis are very specific—and lead to specific treatment choices
  - Primary mediastinal lymphoma: use of radiation after chemotherapy
  - CD20 “positive” by immunohistochemistry: use of rituximab
  - T cell lymphoma: type and length of chemotherapy
  - Burkitt lymphoma: specific chromosome change in lymphoma cells, specific chemotherapy treatment programme

Why pathology is so important in aggressive lymphomas

- Specific types of lymphoma may require more or less testing for staging
  - eg lumbar puncture, bone marrow, nuclear medicine tests (Gallium, PET)
- Different subtypes of aggressive lymphoma have variable prognosis—important to know what type you have

Diagnosis starts with a biopsy

- Lymph node biopsies:
- Fine needle aspiration:
  - gives pathologist cells, able to tell lymphoma from other cancer or benign cause.
  - Can provide a lot of information and often the specific type… but is not considered definitive
- Core biopsy , removal of lymph node (excision):
  - Gives pathologist enough tissue to determine arrangment, size of cells, etc… more likely to be definitive

(but not always)

Lymphomas don’t just arise in lymph nodes

Nodal Sites	Extranodal
Neck	GI tract (stomach)
supraclavicular	bone marrow
axillary	liver
groin	skin
(spleen)	head and neck bone

Staging tests

- CT scans: neck, chest, abdomen, pelvis

  purpose: where is the lymphoma located
  - Needed to determine stage, information re: prognosis, help decide if treatment is working
  - Very important for circumstances where radiation may be considered as part of the treatment plan—generally only if lymphoma is localized to one area

Staging tests for aggressive lymphoma

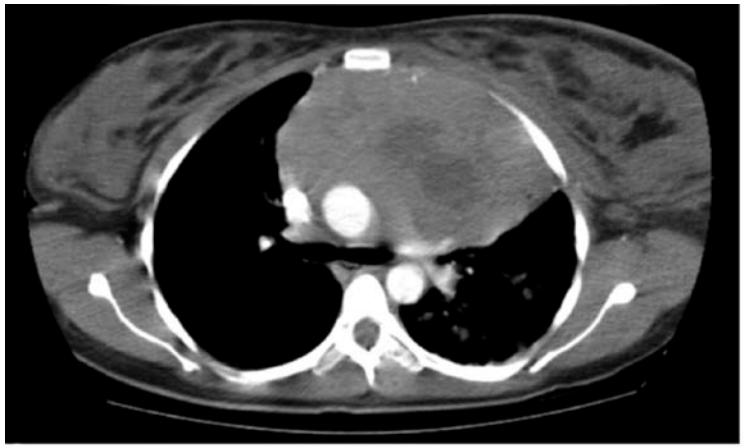
- Bone marrow biopsy

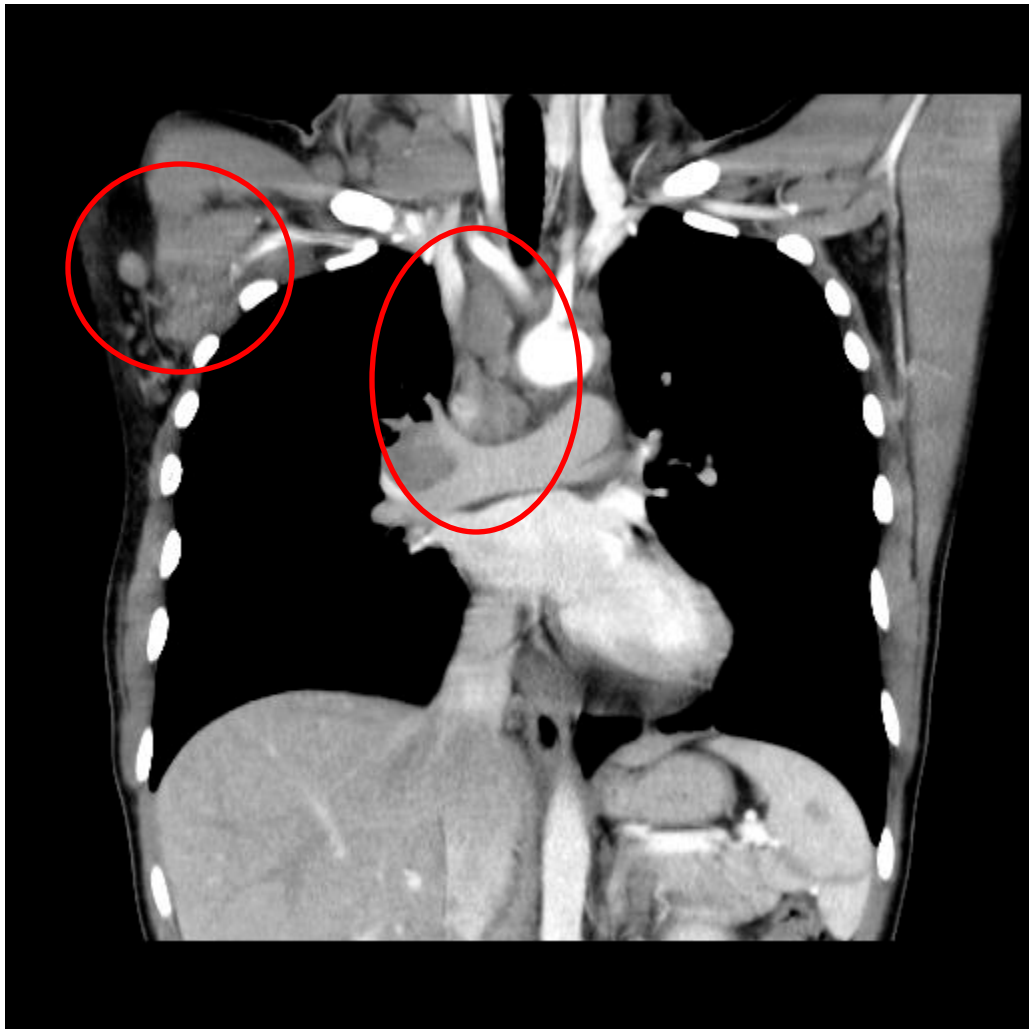
  Needed for

  – most patients with diffuse large cell lymphoma
  – all patients with T cell lymphoma (bone marrow more likely to be involved)
- Lumbar puncture
  – Some patients where risk of lymphoma in spinal fluid may be higher
  – All patients with symptoms suggesting nervous system involved (Brain MRI would also be done for this concern)

Functional imaging tests: Gallium, PET scan

- Can have role in clarifying if areas of involvement on CT scan represent lymphoma
  - "hot" on scan: likely (but not always)
- Important to determine response if there are still abnormalities on CT at end of treatment



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- Staging contributes information about overall prognosis, expected outcomes from treatment
- Along with
  - Performance status: what is the impact of lymphoma (or other medical problems) on daily life – how sick are you?
  - Number of extranodal sites of disease
  - LDH: blood test reflecting amount of lymphoma
  - Age

International prognostic index (IPI)

Treatment of aggressive lymphoma

- CHOP chemotherapy
- Cyclophosphamide
- Doxorubicin
- Vincristine

Intravenous
Every 3 weeks

- Prednisone— pills daily x 5 days

4 cycles—if radiation is also part of the plan
6 cycles—most often
8 cycles—in some circumstances (young people with big masses or other problems)

Why are we so certain that CHOP is the right chemotherapy for aggressive lymphoma?

- Numerous randomized trials of comparing different chemotherapy combinations (>40)
  - CHOP was always as good as other 6-9 drug combinations,
  - less side effects
- Number of cycles (6 v 8) and interval between cycles (2 weeks or 3 weeks) have also been compared: 6 cycles, given every 3 weeks is recommended

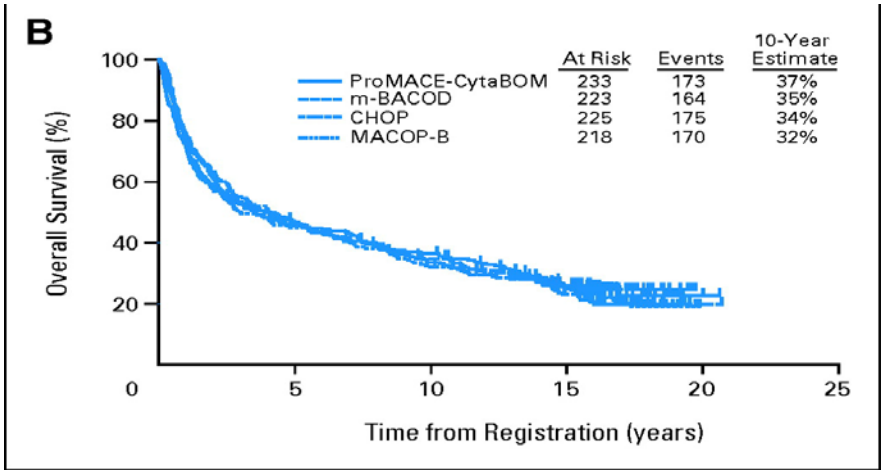
….at least for B cell lymphomas

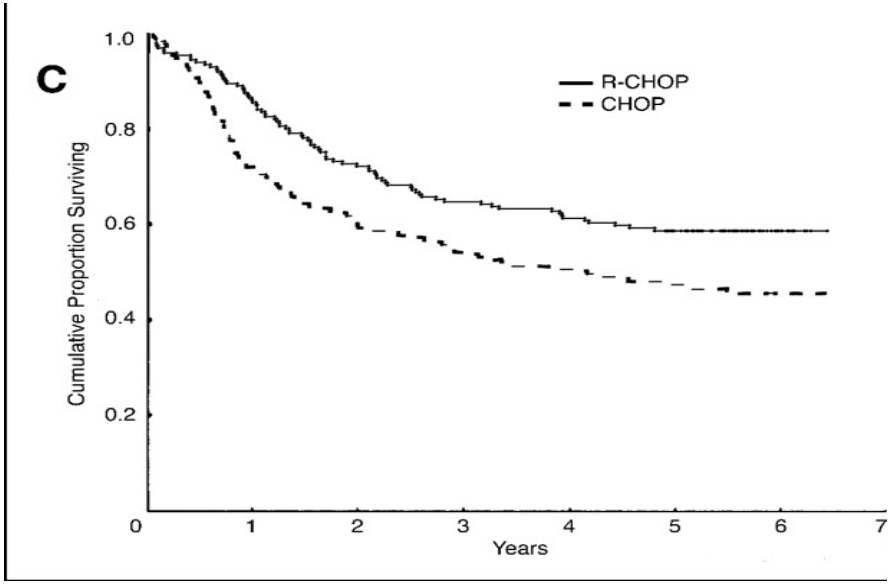
Progress in therapy of aggressive NHL subtypes: 1985-present

Comparison of multi-agent chemotherapy regimens : no progress

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

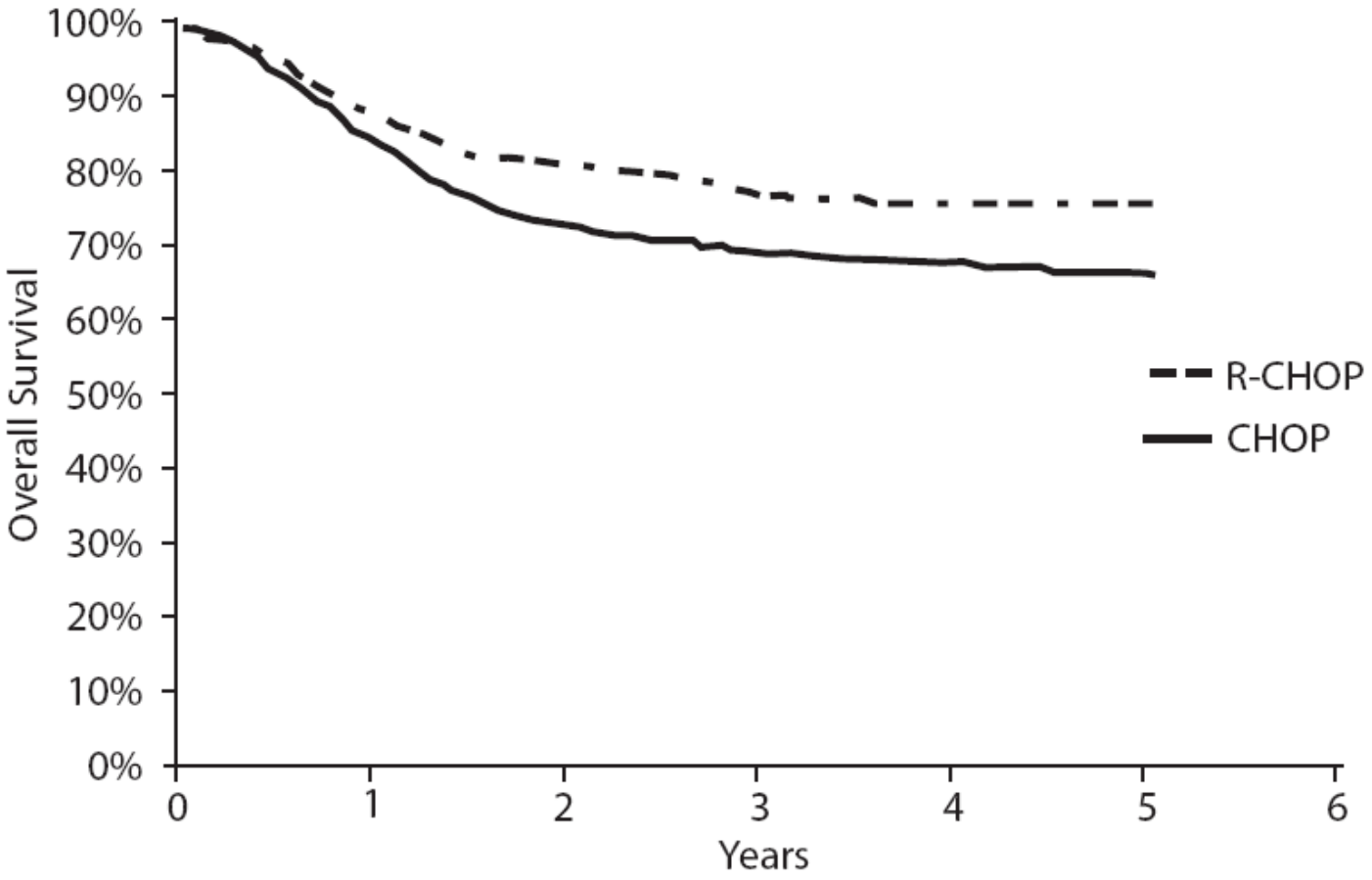
targets surface protein which is not prognostic, role in pathophysiology unknown





Impact of Rituximab on Overall Survival of Patients with DLBCL

Age < 60 years



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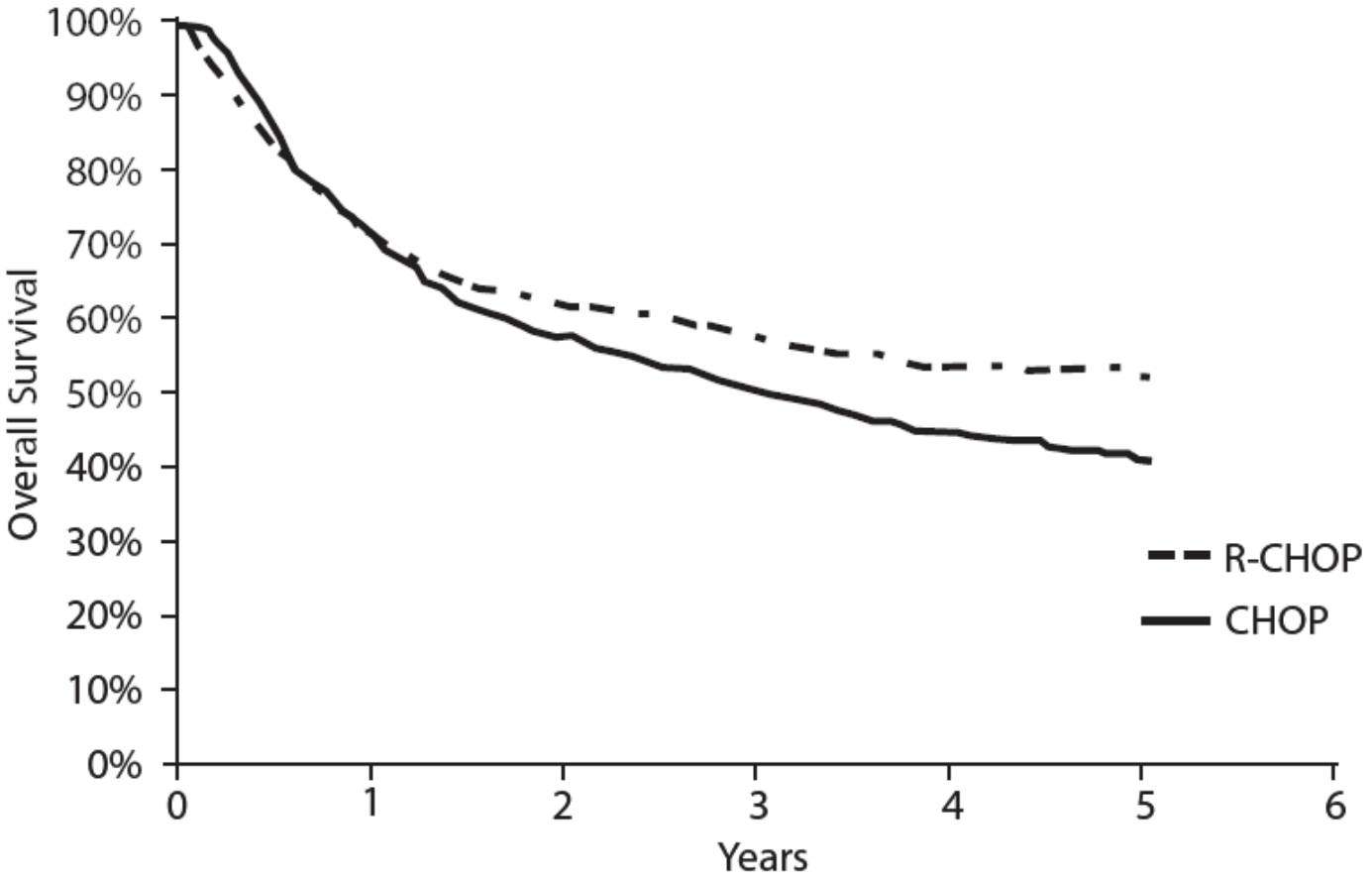
Impact of Rituximab on Overall Survival of Patients with DLBCL

Age < 61-79 years



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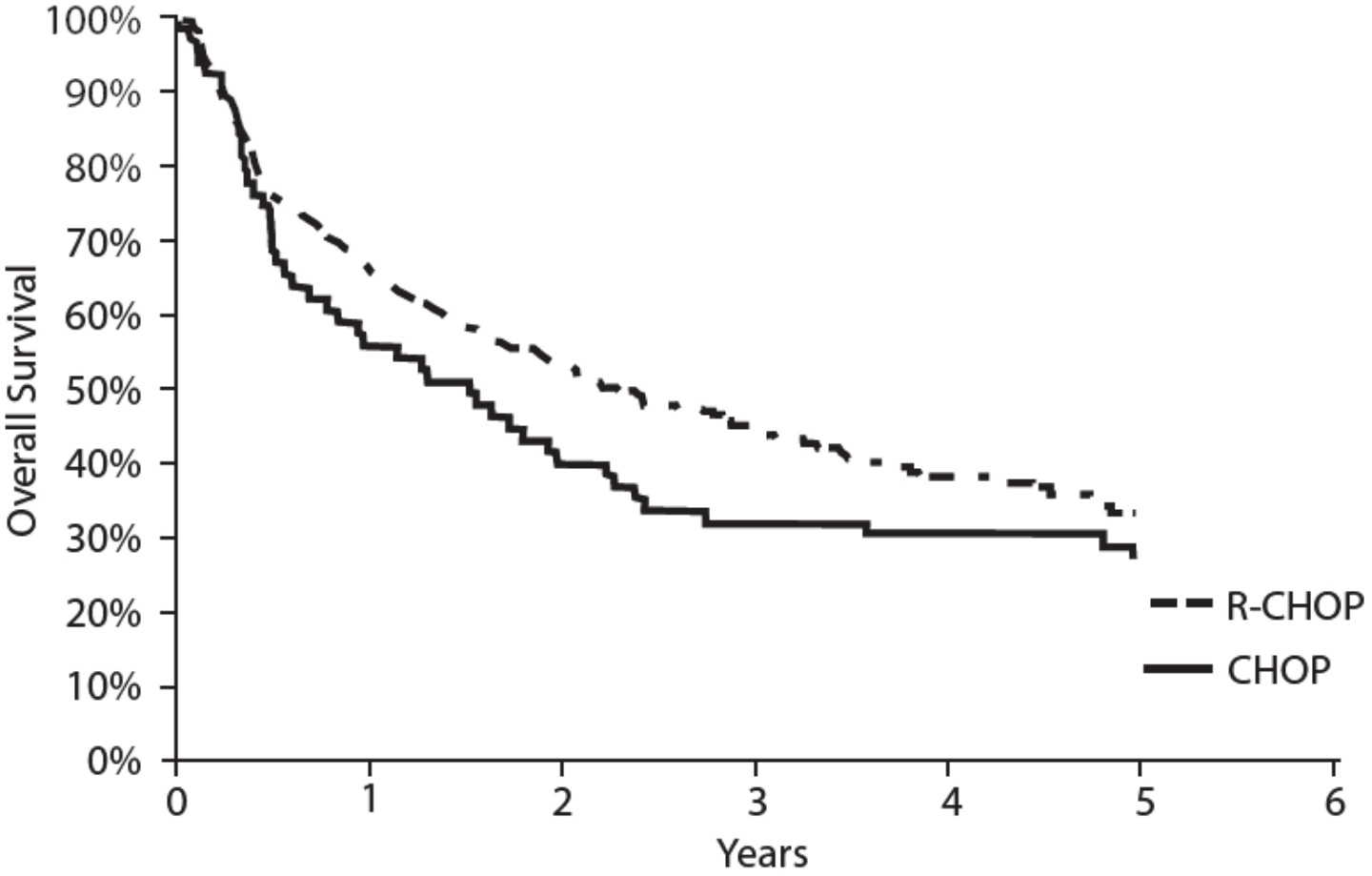
Age >79 years



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Rituximab improves outcome only when CD20 is on cell surface

- Given prior to chemotherapy drugs on each treatment day
- Infusion reactions are common
  - Fever, chills, hives; occasionally shortness of breath, low blood pressure
  - Given very slowly for first few treatments; later treatments given over 90 minutes safely

What to expect on treatment (ie, side effects)

- Hair loss
- Nausea, vomiting: controllable with medication
  - Granisetron, ondansetron; aprepitant
- Fatigue
  - Better with exercise: walking ! Exercise bike
- Fever: middle week of the 3 week cycle
  - Need a thermometer! If >38.3 or 101.5→ get a blood test (even Sunday afternoon…)

Other important things

- Heart function: may need monitoring
  - Weakening of heart muscle rare side effect of doxorubicin
- Numb hands, feet: vincristine
  - Not usually disabling but is annoying
- Difficulty with memory, concentration (multi-tasking)– “chemobrain”
  - Improves with exercise

Other important things

- Fertility
  - consequences different for women and men
- Work/school
  - Can I have a normal life? When will my life get back to normal?
- Going out in public, infection risks
  - Not as bad as you think…
- Immunization
  - Get a flu shot

Treatment outcomes

- Variable, depend on many things….
  - Favourable group (IPI score): 90% relapse-free
  - Intermdiate prognosis: 60-70%
  - Unfavourable: 40-50% relapse-free
- Long-term remission rates lower for elderly, T cell lymphoma, certain subtypes of B cell (defined by chromosomes, for instance)

What happens if first treatment doesn't work?

- Difficult question
- For young patients: stem cell transplantation considered best option
  - Autologous stem cells (patients own)
  - Uses very high dose of chemotherapy to try to eliminate resistant lymphoma cells
  - Only beneficial if lymphoma responds to a second chemotherapy regimen

When treatment stops working…

- Many other treatments available, goals of therapy change
  - Single agent chemotherapy drugs
  - Combinations (occasionally)
  - Radiation to local areas causing symptoms

  - Clinical trials of new agents (see next talk)
- Clarification of goals with your oncologist is very important