Hodgkin Lymphoma – Disease Specific Biology and Treatment Options

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My Disclaimer

- This is where I work…

Objectives

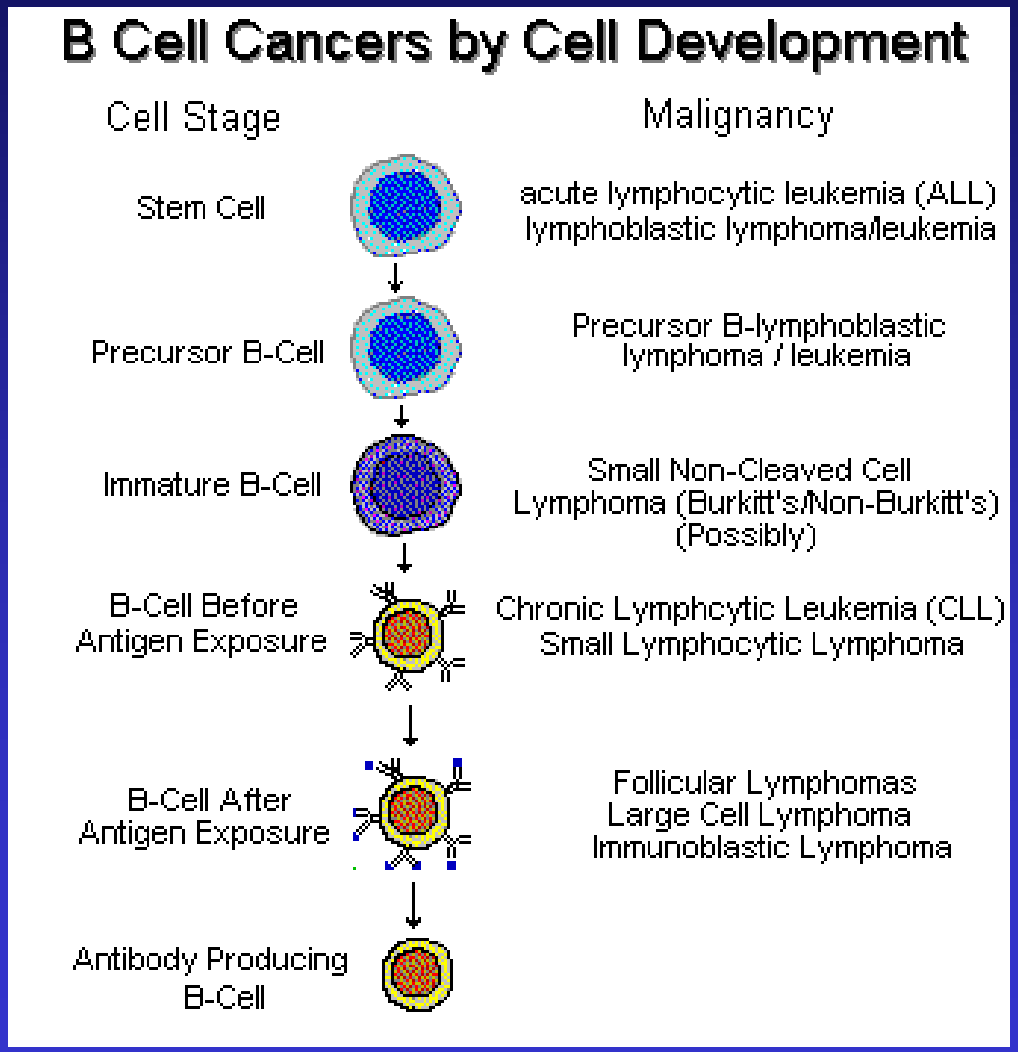
- Pathobiology – what makes HL different
- Diagnosis
- Staging
- Treatment Philosophy and Approach
  - Primary Treatment
  - Second-line Therapy
- Summary and Recommendations
- A look forward…

Hodgkin Lymphoma – Incidence and Prevalence

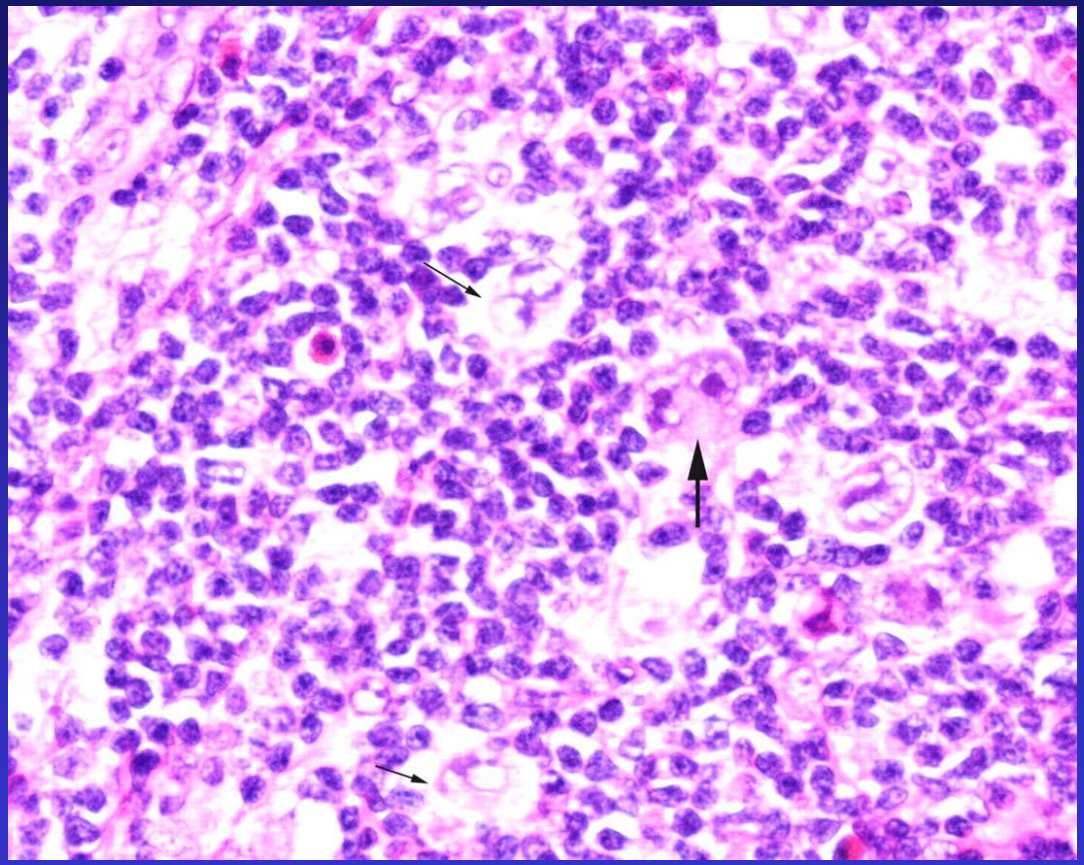
	Total	Male	Female
New HL Cases - Canada	775	436	339
HL Deaths - Canada	131	72	59
ESTIMATES FOR EUROPE and NORTH AMERICA			
Incidence -	3 / 100 000		
Prevalence	350 000		
Lifetime Risk	1 / 250		

Canadian Cancer Society 2001

Current Lymphoma Classification is based on relating disease to normal cell types and development



Hodgkin Lymphoma - Pathology



- Background of inflammatory cells, eosinophils, fibrosis
- Reed-Sternberg cell is the “malignant cell”
- Immunophenotype shows CD30+ CD15+
- Cell of origin recently shown to be a B lymphocyte

Lazarchick, J. ASH Image Bank 2009;2009:9-00002

Subtypes based on Pathology

- Classical HL
  - Nodular Sclerosis – 55%
  - Mixed Cellularity – 25%
  - Lymphocyte Rich – 5%
  - Lymphocyte Deplete – 1-2%
- Lymphocyte Predominant HL – 5%

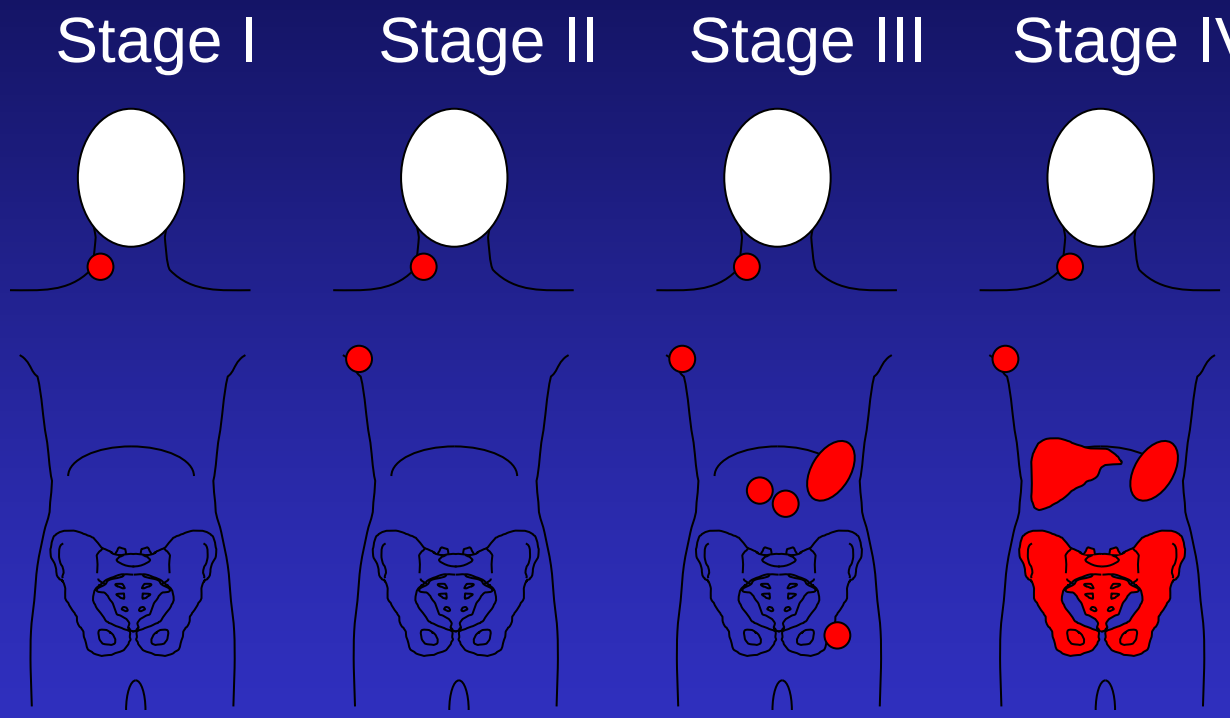
Diagnosis – gold standard is biopsy!

- Fine needle aspirate (FNA) – quick, easy no OR but…
- Excisional LN biopsy
  - Lymph node architecture
  - Enough tissue to do additional testing
- Diagnostic sample should be reviewed by expert hematopathologist

Staging – Really simple

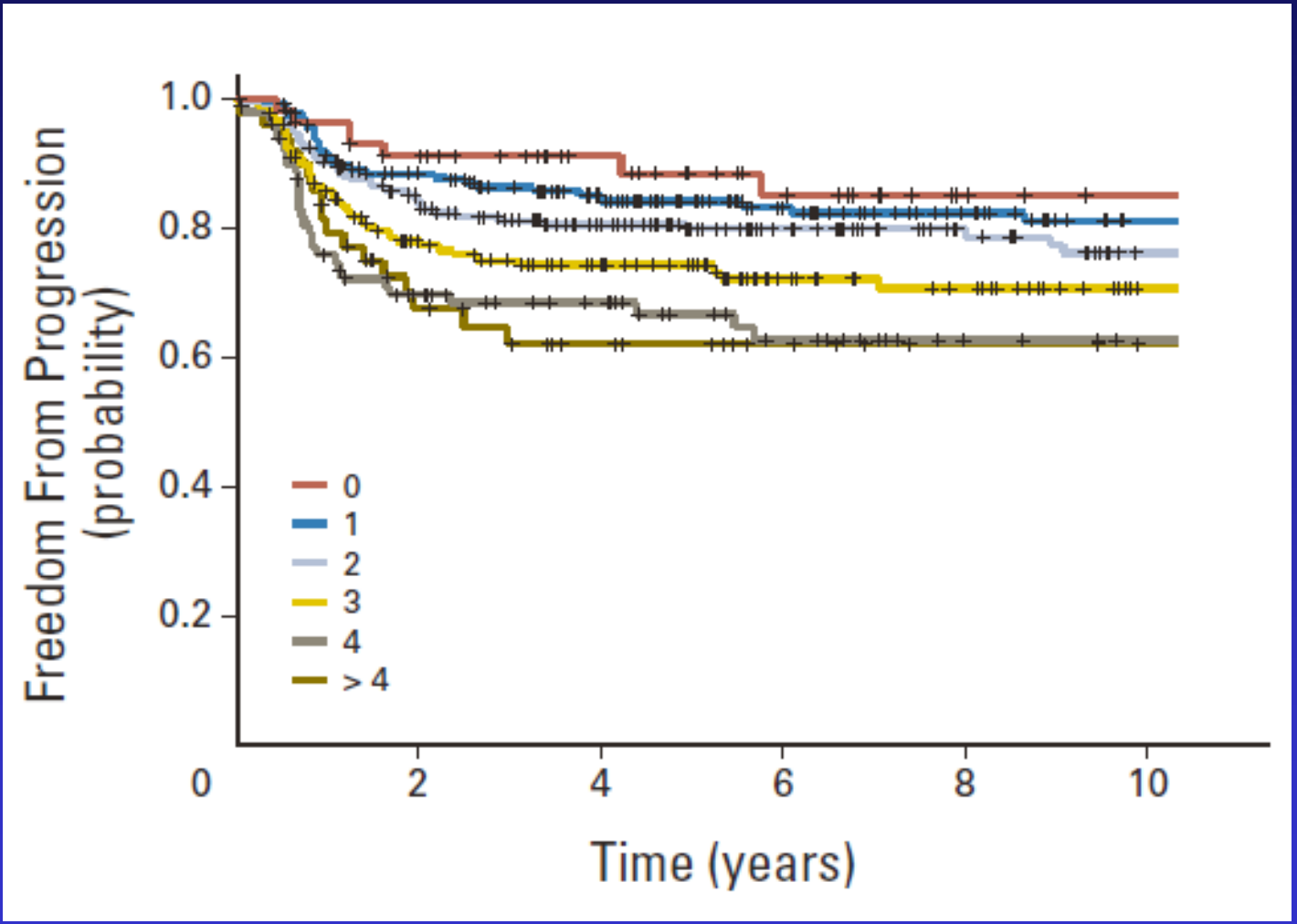
- Standard staging includes:
  - A history and physical exam
  - Bloodwork (usually CBC and chemistry tests)
  - CT scans (neck, chest, abdomen and pelvis)
  - Functional imaging (gallium or PET scan)
  - Bone marrow aspirate and biopsy (if stage III/IV disease or B symptoms)

Staging of Lymphoma – Ann Arbor System



- A – absence of any “B” symptoms
- B – Unexplained fever, drenching sweats or weight loss
- Bulky > 10 cm mass on imaging

Prognostic Score in HL discriminates Overall Survival



Moccia JCO 2012

Decisions regarding Therapy

- Modified for specific instances but *not* individualized yet
- Balance potential toxicity against effectiveness
- Remission ≠ Cure – *why?*
  - Remission is just a state at a specific time
  - Cure is remission maintained forever

Treatment Philosophy in Hodgkin Lymphoma

- Cure!
- In circumstances where cure rate is high
  - ie. localized disease – minimize late effects
- When cure rate is not as high
  - Consider more intensive treatment

IS MORE BETTER?

Chemotherapy

- Works typically through a DNA damaging mechanism – affects all growing cells
  - Lymphoma Cells
  - Blood Cells
  - Lining of GI Tract
  - Hair
- A systemic therapy – treatment travels everywhere through the bloodstream

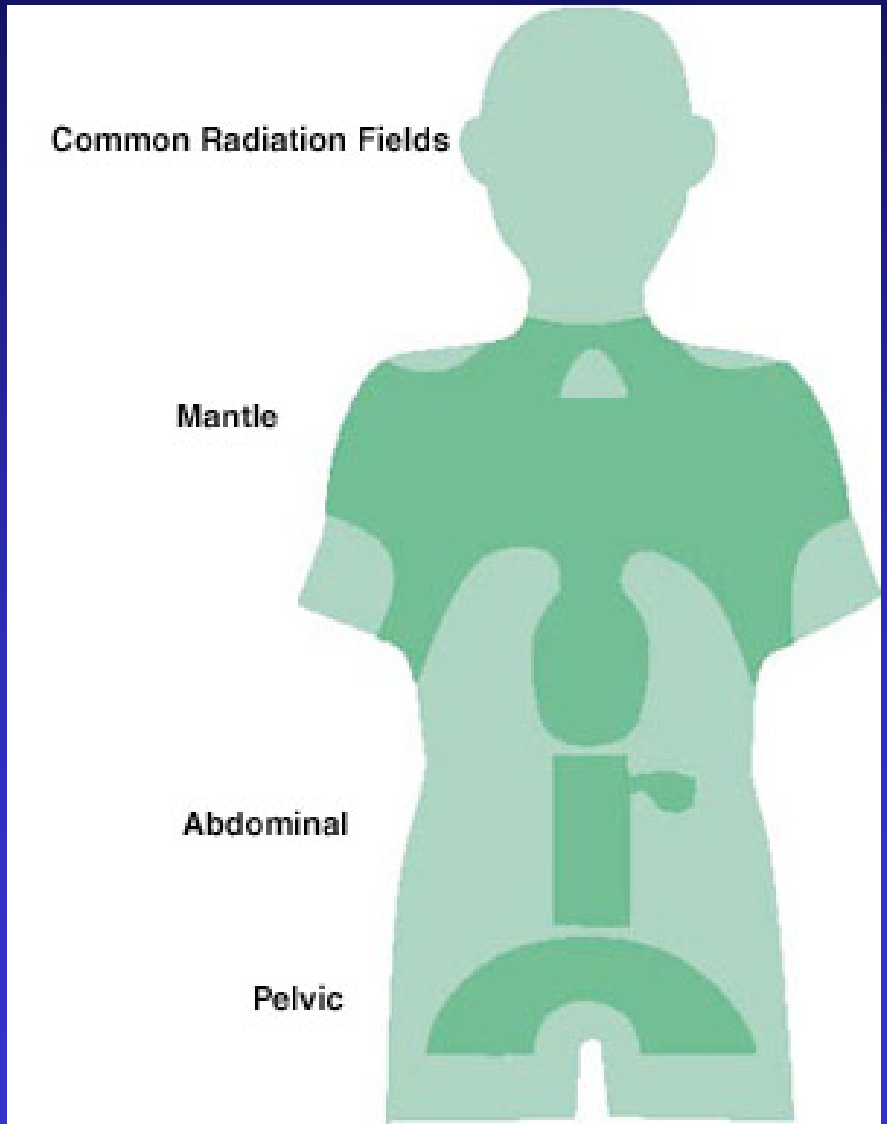
ABVD – Typical HL Chemotherapy

- ABVD is given every 2 weeks (A and B parts)
  - 1 cycle = 2 treatments and is given over 4 weeks
  - Adriamycin 25 mg/m^2
  - Bleomycin 10 u/m^2
  - Vinbastine 6 mg/m^2
  - Dacarbazine 375 mg/m^2

Radiation

- Applies to localized disease
- May not be used in all types of aggressive 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)
- Doses of radiation are lower than those used in solid cancers

Common Radiation Fields



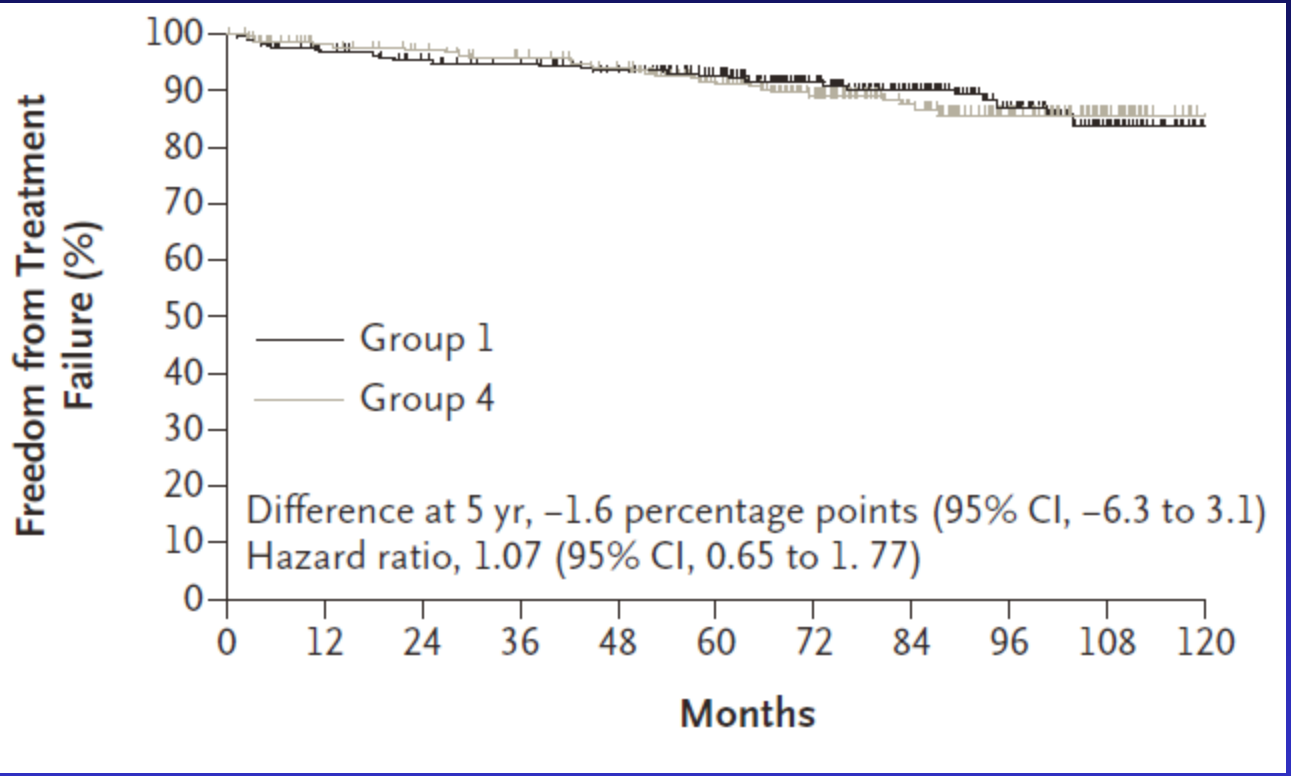
Combined modality Therapy

- Chemotherapy + Radiation = Combined Modality Therapy
- This is our current standard treatment of localized (limited stage) HL
- We do not routinely use radiation as part of the treatment of widespread (advanced stage) HL but may consider for bulky site of disease

Hodgkin Lymphoma

- Cure rate in limited stage disease is 80-95%
- Cure rate in advanced stage disease is 65-80%
- Treatment has evolved over 30-40 years based on application of multiple clinical trials
  - Radiation initially then combination chemotherapy
  - Subsequently more multi-drug regimens (MOPP or MOPP/ABV) and now ABVD

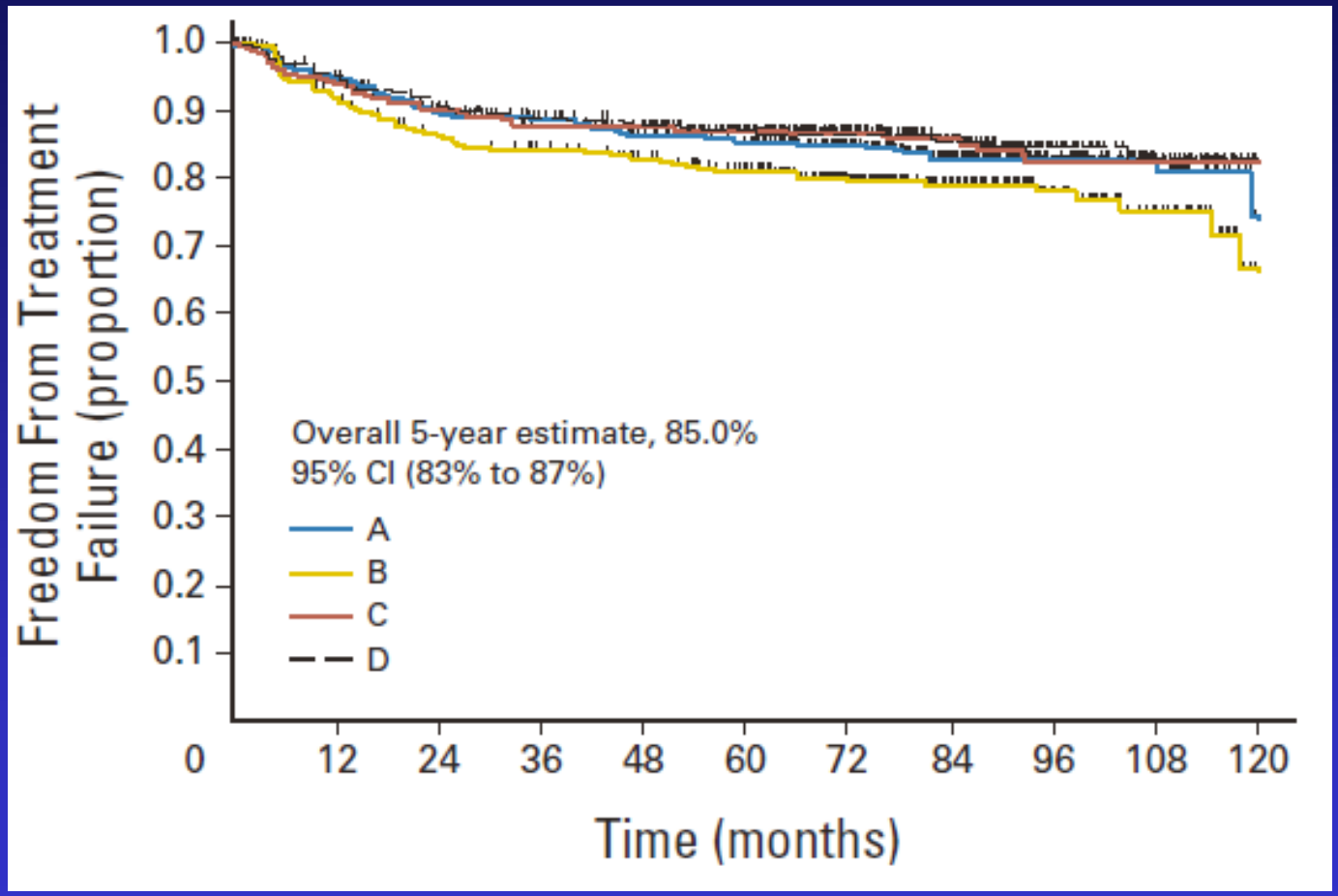
Limited HL – less treatment is just as effective



- 2 cycles of ABVD and lower dose radiation is just as effective as 4 cycles of ABVD and more RT

Engert NEJM 2010

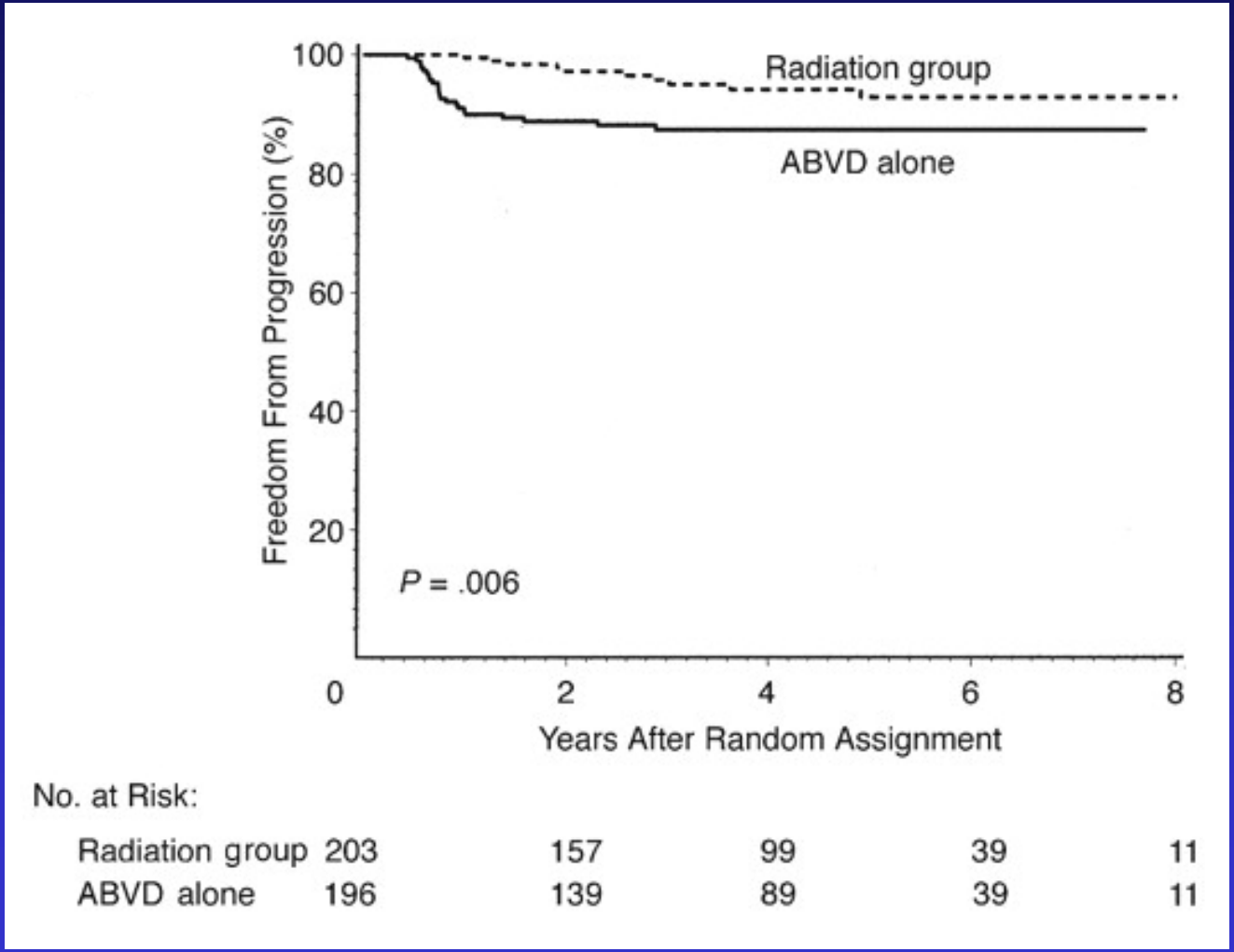
Limited HL – Less toxic treatment is just as effective



- 4 cycles of ABVD and radiation is just as effective as 4 cycles of 7 drug chemotherapy and RT

Engert NEJM 2010

Limited HL – Radiation may help maintain remission



No. at Risk:

Radiation group	203	157	99	39	11
ABVD alone	196	139	89	39	11

Meyer et al. JCO 2005

Concerns about more intensive regimens in HL

- Acute toxicities
  - Low blood counts
  - higher rates of transfusion and infection
- Late Toxicity
  - Infertility
  - Second Cancers
- Need longer follow-up to accurately understand frequencies of late effects
  - Other multi-drug regimen studies have NOT shown benefits

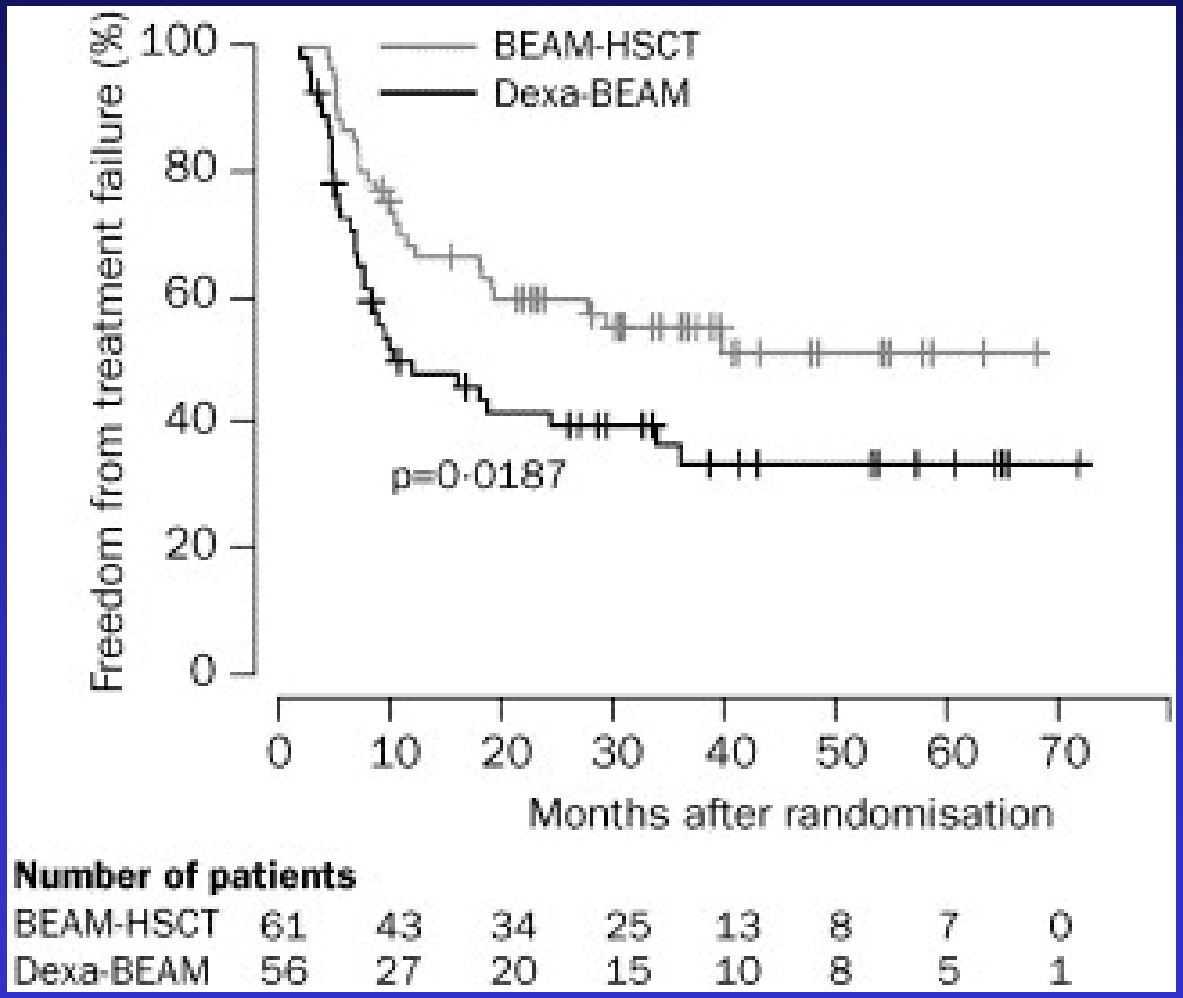
Treatment algorithm in Hodgkin Lymphoma

- Limited stage disease (short course ABVD)
  - Minimize toxicity
  - Recommend radiation but balance toxicity (second cancer, heart disease) against disease recurrence
    - Smaller radiation field, lower dose
- Advanced stage disease (longer course ABVD)
  - Lymphoma recurrence remains an important concern
  - More aggressive chemotherapy?

What happens if primary treatment doesn't work?

- A minority of patients with HL!
  - Primary refractory disease – lymphoma grows on treatment or within 3 months of completion
  - Relapsed disease – lymphoma grows after 3 months of treatment
- Lymphoma is behaving aggressively – signs that cancer cells have developed drug/radiation resistance
  - But this can be overcome – different drugs and doses

GHSG Transplant Trial – Autologous Transplant improves Outcome in relapsed HL



Schmitz et al. Lancet 2002

Transplant strategies vary center to center

- No studies demonstrate the superiority of one approach over another – variation in:
  - Type of second-line chemotherapy (ICE, GDP)
  - Technique of mobilizing peripheral blood stem cells
  - High dose therapy regimen of the transplant
  - Role of radiation as part of second-line treatment
- Generally, lymphoma needs to respond to second-line chemotherapy for transplant to be successful

A (Canadian) Transplant Strategy

- Second-line chemotherapy (GDP)
  - Gemcitabine 1000 mg/^{2} day 1 and 8
  - Dexamethasone 40 mg days 1-4
  - Cisplatin 75 mg/m^2 day 1
- Stem Cell Mobilization
  - Cyclophosphamide 2 g/m ^{2} day 1
  - Etoposide 200 mg/m ^{2} days 1-3
  - Neupogen 10 ug/kg starting day 6
- High Dose Chemotherapy
  - Etoposide 60 mg/kg day -4
  - Melphalan 180 mg/m^{2}day –3
  - Stem Cell Infusion Day 0

PMH Treatment Policy – Limited Stage Hodgkin Lymphoma

- Definition
  - Stage IA (non Bulky)
  - Stage II A (non Bulky)
- Treatment
  - ABVD chemotherapy 2-4 cycles + Involved Field Radiation (30 Gy) depending on amount of disease and some lab parameters

PMH Treatment Policy – Advanced Stage Hodgkin Lymphoma

- Definition
  - Stage III or IV
  - Any Stage with B symptoms
  - Bulky Disease
- Treatment
  - ABVD chemotherapy X 6-8 cycles
  - Radiation if bulky site

PMH Treatment Policy – Relapsed / Refractory Hodgkin Lymphoma

- ASCT eligible patients
  - Second-line chemotherapy with GDP
  - Mobilization of stem cells
  - ASCT procedure
  - Consider radiation if bulky disease pre-ASCT
- Non-ASCT eligible patients
  - Alternate chemotherapy regimen
  - Radiation

Summary – The Fundamentals of HL

- Confirm the diagnosis
- Accurate Staging
- Treatment is chemotherapy based (ABVD)
  - Remember to think about radiation if the disease is localized
- Second chance of cure with ASCT