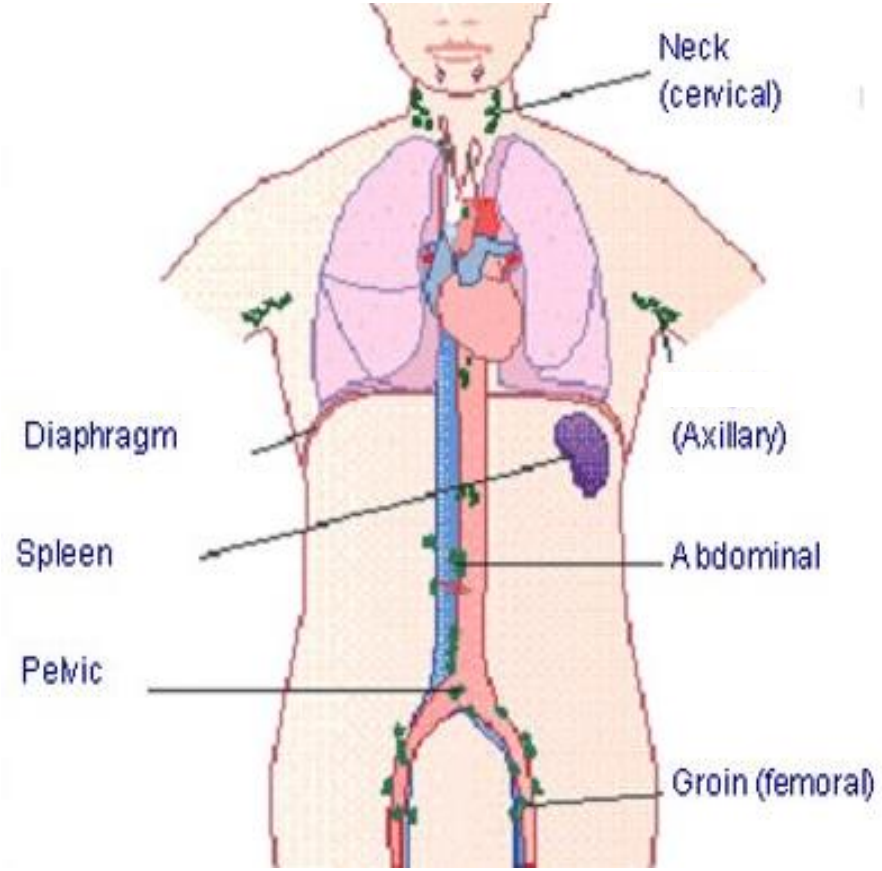
Hodgkin Lymphoma (HL)

HL: disease description



The lymphatic system showing sites commonly affected by Hodgkin's lymphoma[1]

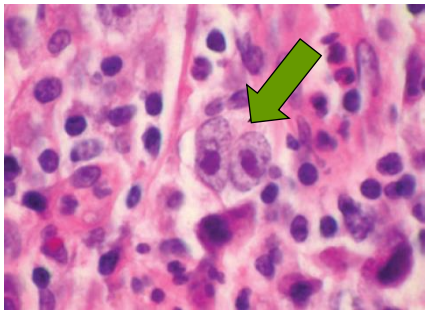
- HL is a cancer of the lymphatic system[1]
- HL commonly occurs in the lymph nodes of the neck[1]
- The WHO classifies HL into two variants[2]:
  - Classical Hodgkin lymphoma (CHL), comprising 95% of all cases
  - Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), comprising 5% of all cases

Figure reproduced with permission from Cancer Research UK.

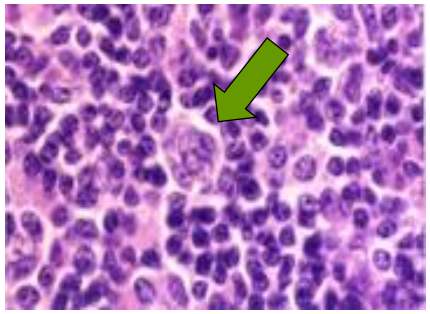
1. Cancer Research UK website: http://www.cancerhelp.org.uk/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma Accessed 260111.
2. Kuppers R. Hematology A, Soc. Educ. Program. 2009: 491-6.
Classification of Tumours of Haematopoietic and Lymphoid Tissues.Lyon: IARC Press; 2008:323–325.

HL: morphological characteristics

- CHL is characterised by the presence of Reed-Sternberg (RS) cells[1]
- NLPHL lacks RS cells and is instead characterised by the presence of popcorn cells, also known as lymphocyte predominant (LP) cells[2]



RS cells in lymphocyte-rich CHL [1]



Popcorn cells in NLPHL[2]

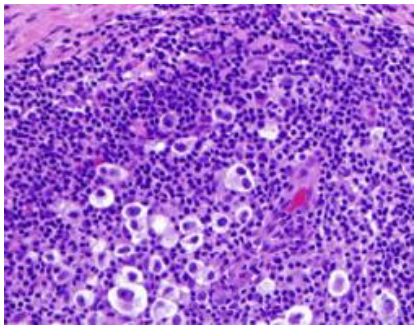
Figures reproduced with permission from

1. Glass C. Am Fam Physician. 2008;78:615-622.
2. Lichtman MA et al. *Lichtman's Atlas of Hematology*. Access Medicine:McGraw-Hill;2007.

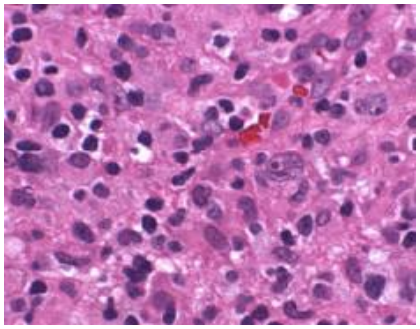
HL: CHL

- CHL is further subdivided into four histological subtypes1

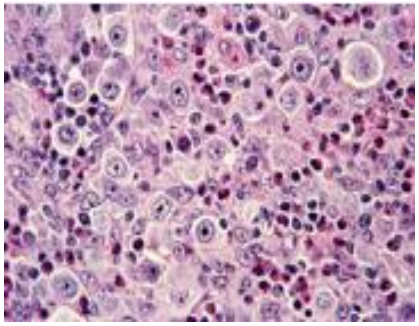
1) Nodular sclerosis (NS)[1,2]



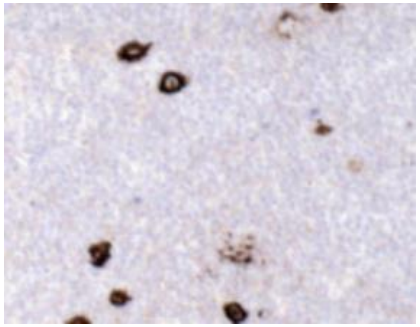
3) Lymphocyte-depleted (LD)[1,2]



2) Mixed cellularity (MC)[1,3]



4) Lymphocyte-rich (LR)[1,2]

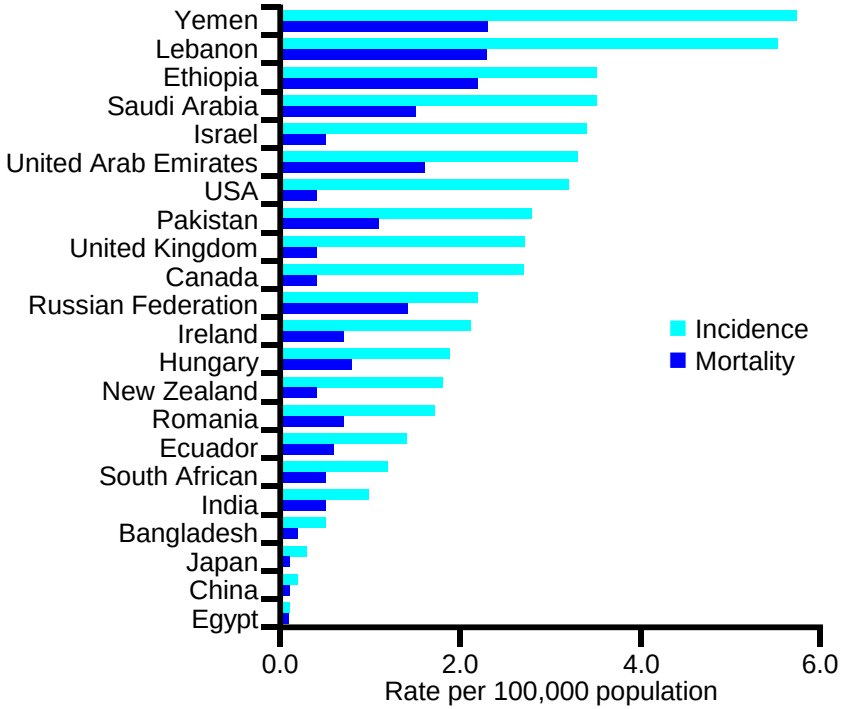


Figures reproduced with permission from

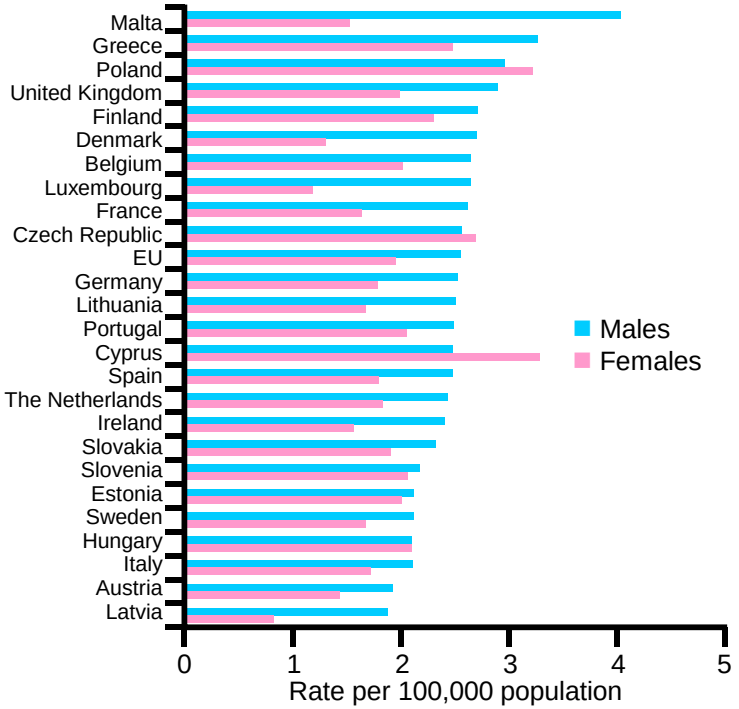
1. Swerdlow SH, Campo E, Harris NL, et al, eds. Classification of Tumours of Haematopoietic and Lymphoid Tissues.Lyon: IARC Press; 2008 2. Mani H, Jaffe ES, Clin Lymphoma Myeloma 2009;9:206–16
3. Lichtman MA et al. *Lichtman's Atlas of Hematology*. Access Medicine:McGraw-Hill;2007.

HL: epidemiology

- In 2010 the global incidence of HL was estimated at 69,970 in both males and females1
- HL incidence typically manifests as two peaks in both genders, either in early (20–34 years) or late (70–79 years) adulthood2



Age-standardised incidence and mortality rates for HL in selected countries, 2002[2]



Age-standardised incidence rates for HL by sex in the EU, 2002[2]

Figures reproduced with permission from Cancer Research UK.

1. GLOBOCAN website: http://globocan.iarc.fr/
2. CR UK website: http://info.cancerresearchuk.org/cancerstats/types/hodgkinslymphoma/incidence/

Knowledge Check

- What percentage of patients have CHL and what percentage of patients have NLPHL?
  - CHL: 95%, NLPHL 5%
  - CHL: 85%, NLPHL 15%
  - CHL: 75%, NLPHL 25%
  - CHL: 65%, NLPHL 35%

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HL: survival rates

- Improvement in 5-year survival rates is unmatched in any other cancer type over the past four decades[1]
- In the UK, compared with survival in the early 1970s, the 10 year survival rate for 2010 was predicted to have increased from less than 50% to approximately 78%[2]

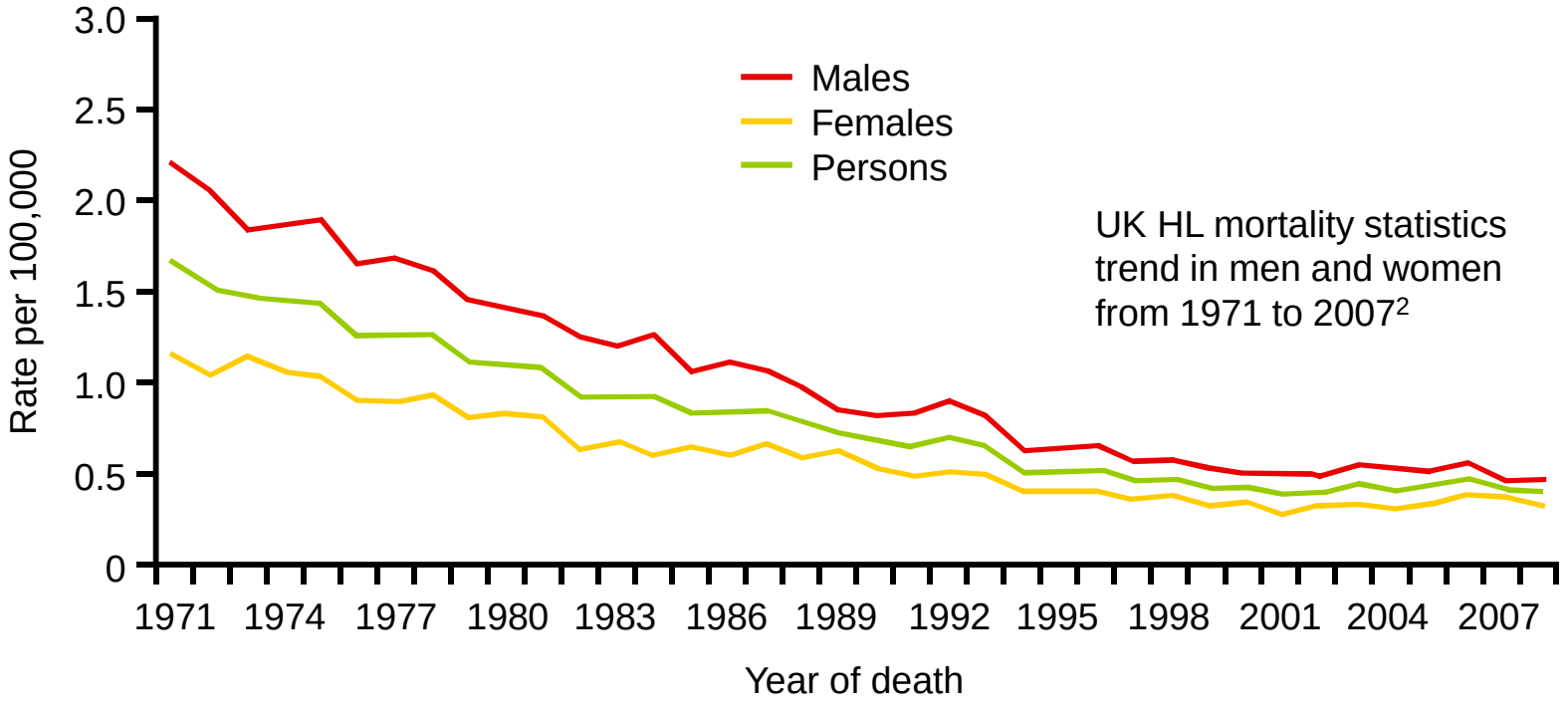


Figure reproduced with permission from Cancer Research UK.

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Hodgkin Lymphoma. V.2.2010.
2. CR UK website: http://info.cancerresearchuk.org/cancerstats/types/hodgkinslymphoma/mortality/

HL: predisposing factors

- Factors that may be associated with HL include:
  - age with the highest risk of developing HL during adolescence and early adulthood[1]
  - occupational exposure, including uranium radiation and smoking[2]
  - childhood environment, increased susceptibility to young/adolescent HL may be due to a reduction in the cumulative microbial exposures of childhood[3]
  - viral infections with Epstein Barr virus (EBV)[4] and HIV,[5] both of which affect the immune system

1. American Cancer Society, Cancer Facts & Figures, 2010.
2.Karunanayake CP, Singh GV, Spinelli JJ, et al. J Occ Environ Med 2009;51:1447–54.
3. Cozen W, Hamilton AS, Zhao P, et al. Blood 2009;114:4014–20.
4. Bechtel D, Kurth J, Unkel C, et al. Blood 2005;106:4345–50.
5.Clifford GM , Polesel J , Rickenbach M J Natl Cancer Inst. 2005;97:425–32.

HL: clinical presentation (1)

- Patients with CHL typically present with asymptomatic lymph node enlargement, commonly in the neck[1]
- Occasionally mass lesions may be found in other organs, such as the spleen, bone marrow, liver, bone or lungs[2]

Common manifestations of HL	Occurrence
Lymphadenopathy	
Supradiaphragmatic	90%
Infradiaphragmatic	10%
Extranodal disease	
No extranodal extension	75%
Localised, contiguous with involved lymph nodes	10%
Disseminated (liver, lung, bone, bone marrow)	
Classical	15%
Nodular lymphocyte predominant	5%
B-Symptoms	35%

1. Gospodarowicz MK, Cancer J. 2009;15:138–42.
2. Connors JM, Cancer J. 2009;15:124–28.

HL: clinical presentation (2)

- Clinical presentation of CHL depends on the geographic region, age of the patient and co-infections, or diseases affecting the immune status of the patient[1], for example:
  - in developing countries clinical presentation may lack bimodal age pattern[1]
  - immunocompromised patients (with HIV), typically present with extranodal disease with B symptoms[1]
  - older patients (>60 years) often show subdiaphragmatic disease, mixed cellularity histology and B symptoms[1]
- In comparison NLPHL is associated with less aggressive tumour growth and lymphadenopathy, usually preceding diagnosis for many years[1,2]

1. Banerjee D, Adv. in Hematol 2011; Volume 2011 (2011), Article ID 439456.
2. Nogová L, et al. J. Clin. Oncol. 2008;26:434–9.

HL: staging

- HL is defined by four stages which are further described according to the presence of A, B, E, or X symptoms

HL Stage		Description
I	Early stage favourable* or unfavourable†	Single lymph node region, or localised involvement of single extralymphatic organ/site.
II		Involvement of ≥2 lymph node regions on same side as diaphragm, or localised involvement of single associated extralymphatic organ/site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm.
III	Advanced stage	Involvement of lymph nodes regions on both sides of diaphragm, which may also be accompanied by localised involvement of an associated extralymphatic organ or site, by involvement of the spleen, or by both.
IV		Disseminated (multifocal) involvement of ≥1 extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

*no B symptoms or large mediastinal adenopathy; † with/without B symptoms with large mediastinal mass or with B symptoms accompanied by numerous sites of disease or elevated erythrocyte sedimentation rate (ESR)

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Hodgkin Lymphoma. V.2.2010.

HL: work up and diagnosis

- The work up and assessment of patients with newly diagnosed HL should include:

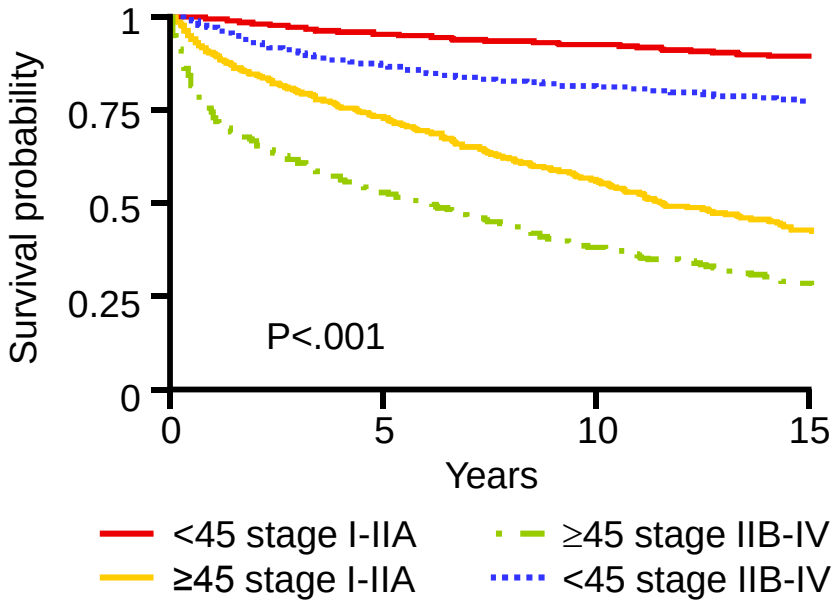
History	❑ presence of B symptoms ❑ pruritus and alcohol-related pain ❑ HIV status, hepatitis B and C ❑ cardiac, pulmonary, renal disease
Physical examination	❑ peripheral lymph node area, liver, and spleen
Laboratory tests	❑ complete blood count, LDH, liver function tests, ESR
Imaging	❑ CT scan – head, neck, chest, abdomen, and pelvis ❑ PET-CT scan
Bone marrow biopsy	❑ stages III–IV ❑ B symptoms

CT = computed tomography; ESR = erythrocyte sedimentation rate;
LDH = lactate dehydrogenase; PET = positron emission tomography

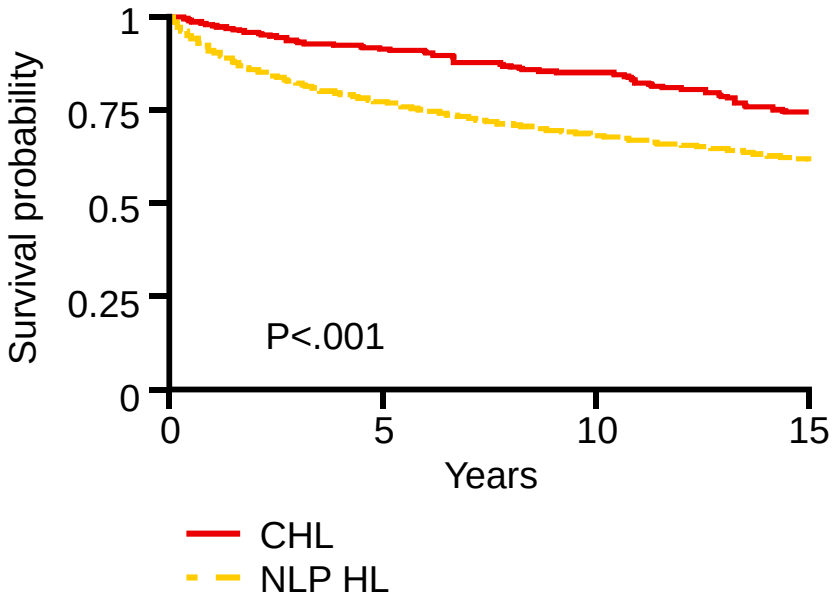
Gospodarowicz MK. Cancer J 2009;15:138–42.

HL: prognosis and survival

- Survival rates in HL are influenced by age at diagnosis, histology and stage of disease



Survival curves by age at diagnosis (<45 yrs vs ≥ 45 years) and stage (Stage I–IIA versus Stage IIB–IV



Survival curves for CHL and NLPHL

Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

HL: prognosis (early disease)

- Prognosis varies with disease stage[1]
  - Unfavourable prognostic factors for patients with stage I to II include[2,3]

Risk factor	GHSG	EORTC	NCIC
Age		≥50	≥40
Histology			MC or LD
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B sx
Mediastinal mass	MMR >0.33	MTR >0.33	MMR >0.33 or >10cm
# Nodal sites	>2	>3	> 3
E lesion	Any		

ESR and B symptoms: GHSG= ESR >50 if asymptomatic, ESR >30 if B symptoms;
EORTC= ESR >50 if asymptomatic, ESR >30 if B symptoms, NCIC = ESR >50 or any B symptoms

GHSG = German Hodgkin Study Group; EORTC = European Organization for the Research and Treatment of Cancer; LD = lymphocyte depleted; MC = mixed cellularity; MMR = mediastinal mass ratio; MTR = mediastinal thoracic ratio; NCIC = National Cancer Institute, Canada.

1. Armitage JO, N. Engl. J. Med. 2010;363:653–63.
2. Hasenclever D, N. Engl. J. Med. 1998;339:1506–14.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Hodgkin Lymphoma. V.2.2010.

HL: prognosis (advanced disease)

- The **international prognostic system** (**IPS**) is a seven-factor prognostic scoring system that predicts five-year rates of freedom from progression of disease and overall survival[1]

- These prognostic factors are:
  - age ≥45 years
  - male gender
  - stage IV disease
  - serum albumin of <4 g/dL
  - haemoglobin level <10.5 g/dL
  - white blood cell count of >15,000/mm^3
  - lymphocyte count of <600/mm^3 and/or <8% of white blood count

Overall survival (OS) in patients with advanced HL by IPS

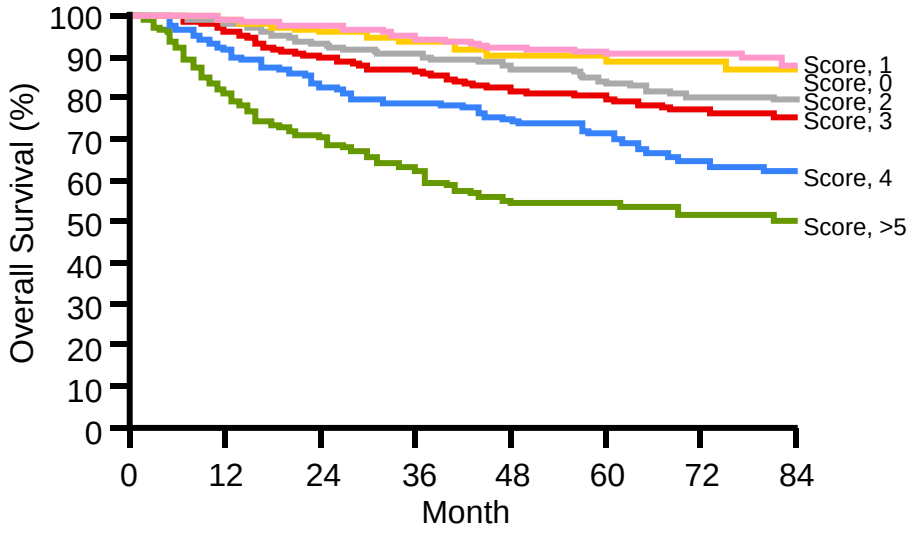
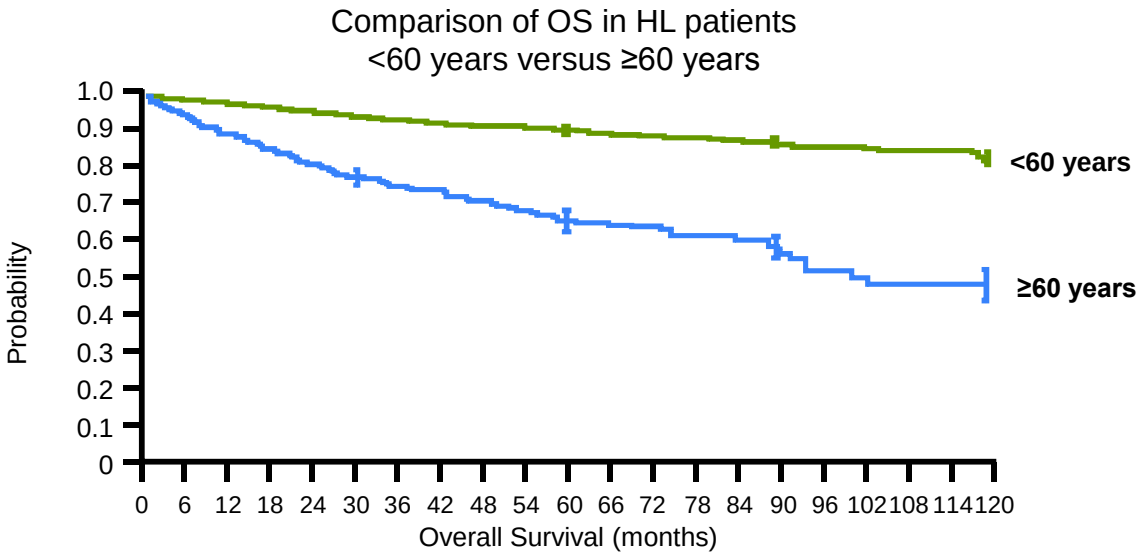


Figure reproduced with permission from Hasenclever D. N Engl J Med. 1998;339:1506–14.

Hasenclever D. N Engl J Med. 1998;339:1506–14.

HL: Elderly Patients

- Older age (>60 years) is an additional unfavourable risk factor for HL patients and poor outcomes have been attributed due to:
  - biologically less favourable disease
  - less tolerance for conventional chemotherapy
  - lower-dose intensity treatment
  - higher-treatment related mortality



Engert A, et al. J Clin Oncol 2005;23:5052–60.

Knowledge Check

What is the IPS?

- International Position Staging
- International Phase Scoring
- International Prognostic System
- International Passive Sets

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HL: treatment

- Significant progress has been made with current regimens resulting in cure rates of ~80%[1,2]
- Treatment is based on disease stage

Treatment group (stage)	Description
Early	Stage I–II without risk factors
Intermediate	Stage I–II with ≥ 1 risk factors
Advanced	Stage III–IV, large mediastinal mass, age ≥50 years, elevated ESR, ≥4 nodal areas

Table adapted with permission from Engert A, et al. ESMO Guidelines Working Group. Ann Oncol 2010;21:v168–71.

1. Jona A, Younes A. Blood Rev. 2010. doi:10.1016/j.blre.2010.08.003.
2. Czuczman M, et al. Leuk Lymphoma. 2010;51suppl 1:41–49.
3. Canellos GP, Anderson JR, Propert KJ, et al. NEJM 1992; 327:1478–1484.
4. Engert A, et al. ESMO Guidelines Working Group. Ann Oncol 2010;21:v168–71.

HL: Early stage treatment (1)

- ESMO1
- Combined modality treatment (CMT) is recommended as standard
- 2 or 3 cycles ABVD (each in 28 day cycles) followed by 30 Gy involved-field radiotherapy (IF-RT)

Adriamycin	25 mg/m^2	i.v.	Days 1 + 15
Bleomycin	10 mg/m^2	i.v.	Days 1 + 15
Vinblastine	6 mg/m^2	i.v.	Days 1 + 15
Dacarbazine	375 mg/m^2	i.v.	Days 1 + 15

Recycle: day 29

The ABVD treatment regime, administered in 28 day cycles[1]

- NCCN2
- If using CMT: 4 cycles ABVD followed by re-staging; patients with favourable disease, 2 cycles ABVD followed by 30 Gy RT
- Chemotherapy only: 2 cycles ABVD, followed by re-staging, followed by another 2 to 4 cycles ABVD
- If using Stanford V:* 2 cycles (over 8 weeks), followed by restaging; consolidative irradiation is instituted within 3 weeks (30 Gy)

*Stanford V = doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin and prednisone

1.Engert A, Eichenauer DA, Dreyling M; ESMO Guidelines Working Group Ann Oncol. 2010;21:v168–71
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Hodgkin Lymphoma. V.2.2010

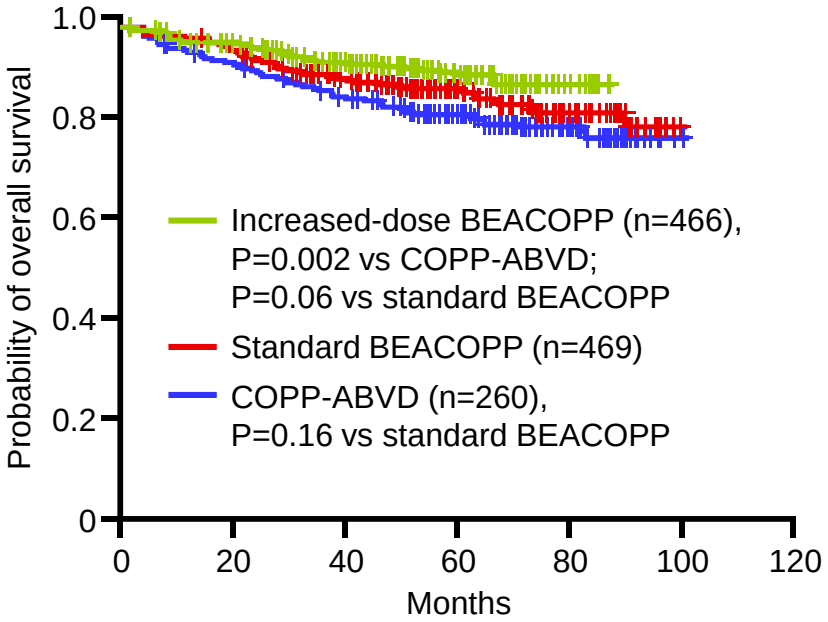
HL: intermediate stage treatment

- ESMO1
- Standard therapy of 4 cycles ABVD followed by 30 Gy IF-RT
- In patients up to 60 years, more intensive treatment is recommended with 2 cycles BEACOPPescalated

Bleomycin	10 mg/m^2	i.v.	Day 8
Etoposide	200 mg/m^2	i.v.	Days 1–3
Adriamycine	35 mg/m^2	i.v.	Day 1
Cyclophosphamide	1250 mg/m^2	i.v.	Day 1
Vincristine	1.4 mg/m^2	i.v.	Day 8
Procarbazine	100 mg/m^2	p.o.	Days 1–7
Prednisone	40 mg/m^2	p.o.	Days 1–14
G-CSF		s.c.	From day 8

Recycle: day 22

The BEACOPP dose-escalated treatment regime, in 21 day cycles[1]



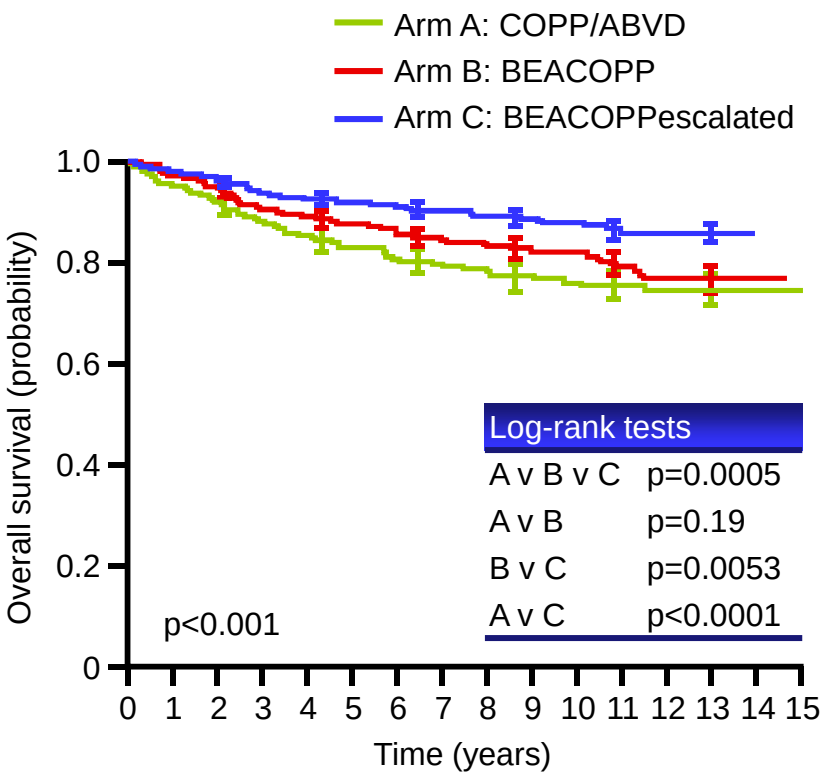
OS rate is highest in the escalated-dose BEACOPP compared to standard BEACOPP or ABVD regimes in patients with advanced HL[2]

1.Engert A, Eichenauer DA, Dreyling M; ESMO Guidelines Working Group Ann Oncol. 2010;21:v168–71.
2. Diehl V, et al. N Engl J Med. 2003;348:2386–95
3. Diehl V, Sieber M, Rüffer U, et al. Ann Oncol. 1997;8:143–8.

HL: advanced stage treatment

ESMO[1]

- Patients ≤60 years treated with a chemotherapy regimen followed by localised RT of 30 Gy to any residual lymphomas. Chemotherapy may be either:
  - ABVD (6 or 8 cycles, every 28 days)
  - BEACOPPescalated (8 cycles, every 21 days)
- Patients >60 years:
  - ABVD (6 to 8 cycles) ABVD followed by localised radiation, 30 Gy, to residual lymphoma
  - BEACOPPescalated is NOT recommended in elderly patients, as increased toxicity has been observed in this age group



In patients with advanced HL BEACOPPescalated showed improved OS compared to other regimens[2]

Figure reproduced with permission from Engert A, et al J Clin Oncol 2009;27:4548–54.

1.Engert A, Eichenauer DA, Dreyling M; ESMO Guidelines Working Group Ann Oncol. 2010;21:v168–71.
2. Engert A, et al J Clin Oncol 2009;27:4548–54.

HL: relapsed/refractory treatment

ESMO[1]

- Most relapsed patients: high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT)
- Low-risk patient relapsing after 2 cycles followed by RT: salvage treatment with intensive chemotherapy e.g. BEACOPPescalated
- Patients with localised late relapse: salvage RT only
- Patients relapsing after high-dose chemotherapy and ASCT: no standard treatment. Should be treated on a case by case basis

1.Engert A, Eichenauer DA, Dreyling M; ESMO Guidelines Working Group Ann Oncol. 2010;21:v168–71
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Hodgkin Lymphoma. V.2.2010

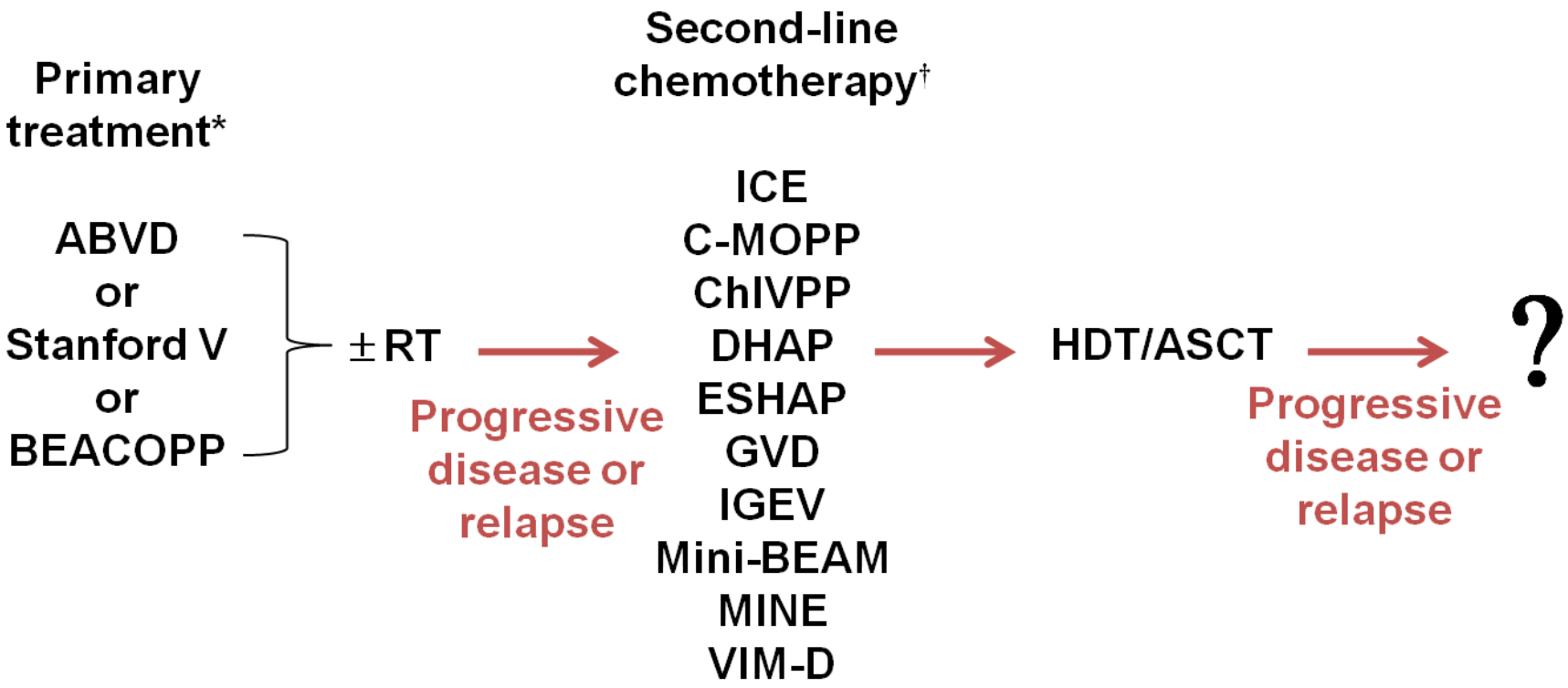
HL: relapsed/refractory treatment

NCCN[2]

- Biopsy, including bone marrow, and restaging
- Relapse in patients with initial IA to IIA who underwent chemotherapy: no standard therapy, treat individually, options include:
  - RT
  - second-line chemotherapy ± RT
  - HDT/ASCT ± RT
- Radiation naïve patients: total lymphoid irradiation recommended
- All other patients: recommendations include:
  - HDT/ASCT ± locoregional RT
  - second-line chemotherapy ± RT

1.Engert A, Eichenauer DA, Dreyling M; ESMO Guidelines Working Group Ann Oncol. 2010;21:v168–71
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Hodgkin Lymphoma. V.2.2010

HL: current treatment paradigm



*Choice of primary treatment is dependent on disease stage and presence of unfavourable risk factors.
†Selection of regimen depends on pattern of relapse and agents previously used; some patients with minimal disease at relapse may not need additional treatment prior to HDT/ASCT.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology,Hodgkin Lymphoma. V.2.2010.

Knowledge Check

- What treatment does ESMO recommend for most relapsed patients with HL?
  - High-dose therapy followed by autologous stem cell transplantation
  - High dose therapy followed by allogeneic stem cell transplantation
  - Autologous stem cell transplantation followed by radiation
  - Allogeneic stem cell transplantation followed by radiation and/or high dose therapy

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