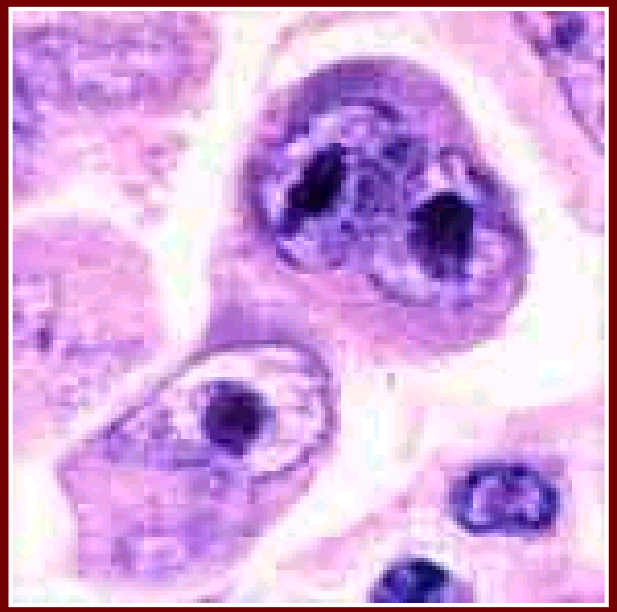
Νόσος Hodgkin

….belongs to the most curable tumor diseases in adults

- Hodgkin's disease is a group of cancers characterized by Reed-Sternberg cells in an appropriate reactive cellular background

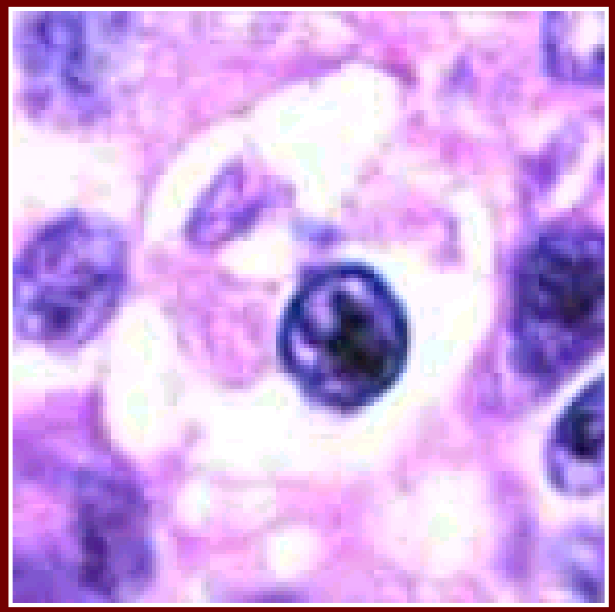
- An important clinical feature is its tendency to arise within lymph node areas and to spread in an orderly fashion to contiguous areas of lymph nodes. Late in the course of the disease,vascular invasion leads to widespread hematogenous dissemination.

RS cell and variants



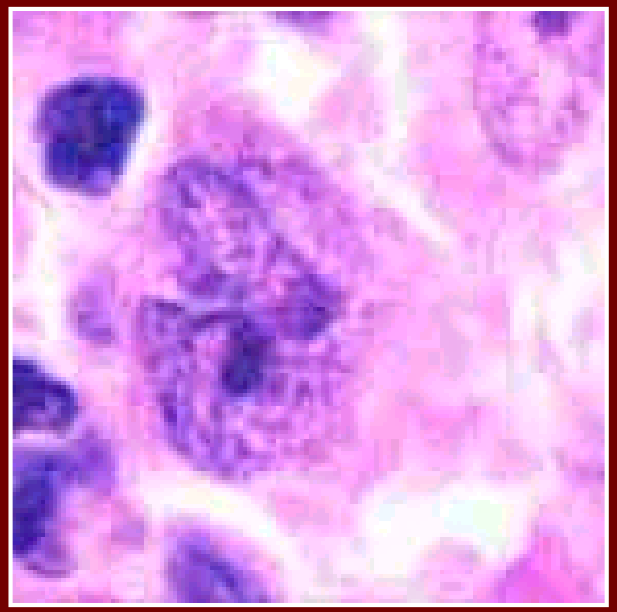
classic RS cell

(mixed cellularity)



lacunar cell

(nodular sclerosis)



popcorn cell

(lymphocyte predominance)

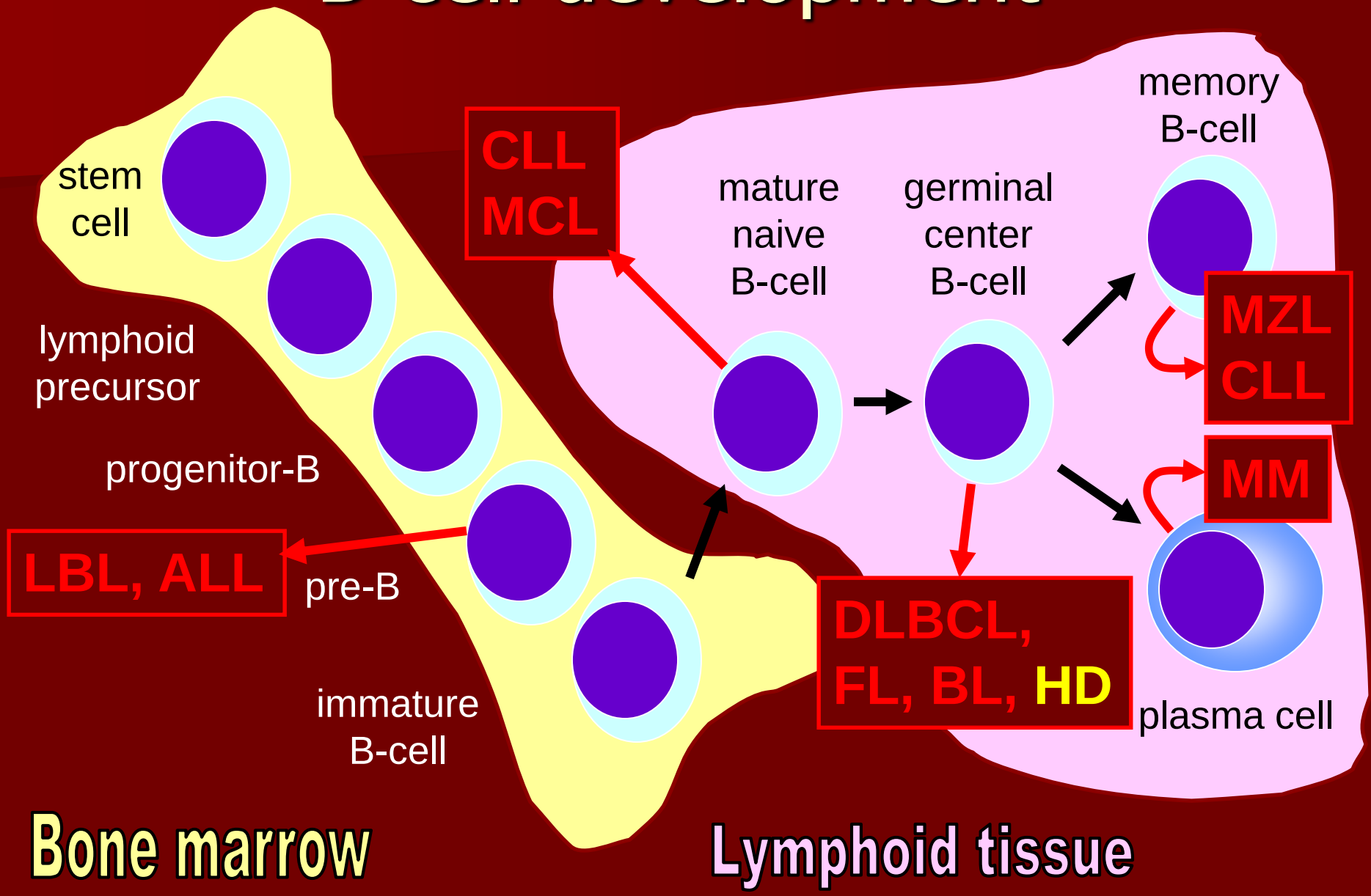
Difficulty in identifying the tumor due to:

1. Tumor cells are rare in the mass of the tumor and fail to express many B cell markers—most notably immunoglobulin

2. Most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells. In most biopsies, the Reed-Sternberg cell accounts for only 1% of the cells present, with the remainder consisting of lymphocytes, granulocytes, histiocytes, plasma cells, and fibroblasts

- The hallmark: HRS cell
- RS: of B cell origin (monoclonal, pre-apoptotic,germinal centre derived) in 100% of LPHL, 98-99% of cHL. Residual cases of cHL are derived from T cells
- This finding induced WHO to rename HD to HL
- Pathological definition is the identification of RS cells in the appropriate environment. What varies is the background!

B-cell development



WHO classification

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis (60-80%)
  - Lymphocyte-rich (5%)
  - Mixed cellularity (15-30%)
  - Lymphocyte-depleted (1%)

Nodular lymphocyte predominant (NLP) Hodgkin's lymphoma

- While the 4 types above are "Classical" types, NLP is in a category of its own. Typical Reed-Sternberg cells are rare to non-existent; instead variants called L & H cells ("popcorn cells") are seen.

- Additional distinctive clinical features setting apart nodular lymphocyte predominance HL include:
  - an indolent though relapsing course with an excellent prognosis;
  - occasional cases relapsing as high-grade B-cell non-Hodgkin's lymphoma;
  - a peak incidence in males in their 30's and 40's, without the bimodal age pattern of classic HL;
  - a greater tendency to be restricted to cervical lymph nodes

- Classical phenotype: CD15+ CD30+ CD45-. The tumor cells of cHL have lost their capacity to express Ig in all instances
- The non expression of Ig is due to a transcription defect. Epigenetic factors are involved
- The pathways of NF-kB, CD30, AP-1 and Notch-1 are deregulated ⟶
- ⟶ upregulation of several antiapoptotic molecules, pro-proliferative molecules and certain chemokine receptors
- *Carbone et al:* CD40 antigen is strongly represented on the surface of R-S cells and can help in the distinction between NSHD and other lymphoid malignancies
- *Stetler-Stevenson et al,1990* :bcl-2 rearrangement detected in ≤ 40% cases of HD

- Other nonspecific markers have been found, including IL-2 receptors, transferrin receptors, and HLA-DR.

- For these reasons, the diagnosis of Hodgkin's disease should be based on:
  1. adequate tissue samples
  2. the opinion of expert hematopathologists

- Diff.Diagn: T cell rich large B cell lymphoma, CD30+ anaplastic LCL
- NS most common, young women w mediastinal mass
- MC 2nd most common, older male pts, commonest in HIV+
- NLPHL differs in that CD20+ and CD30-. Males, localized disease, wo mediastinal involvement
- Accurate staging is the most important factor in determining the therapeutic approach

epidemiology

- 0.7% of all malignancies
- 8000 cases/yr in USA, 1400/yr in UK (2004 data)
- The NS subtype has a female predominance, with the remaining subtypes occurring more commonly in men
- developed > underdeveloped countries
- bimodal incidence pattern. Average age of 30 yrs at diagnosis although there is a second smaller peak at >50 yrs
- first peak occurs at an earlier age in patients in underdeveloped countries

Causative factors

- EBV has been implicated, because cases of this malignancy have occurred following of IM
- The EBV genome and EBV early RNAs can be found in many of the cells present in involved lymph nodes.
- Expression of the EBV protein LMP-1 has been found in the RS in 30-50% of patients
- Immunodeficiency, induced by HIV-1, has also been associated (unclear) with the development of HD, especially the mixed-cellularity subtype.
- Pts having MTX therapy for RA were found to have increased incidence of HL (one study)

Clinical Presentation

The majority of patients present with overt disease, most often as an asymptomatic enlarged lymph node *or* a mass on chest x-ray.

However, the presenting symptoms and signs may be relatively nonspecific and more compatible with infection than malignant disease.

Occult presentation of Hodgkin's disease is unusual, but the incidence of clinically occult disease has been an important influence in the development of therapeutic strategies.

Clinical Presentation-2

1. Asymptomatic lymphadenopathy,70% (painless mass)
2. Mediastinal mass (routine CXR)
3. Systemic symptoms
4. Fever
5. Pruritus
6. Intraabdominal disease
7. Cholestatic liver disease (extremely unusual)
8. Alcohol-induced pain (NS the predominant histology)
9. Skin lesions
10. Neurologic syndromes
11. Nephrotic syndrome (MCD or FGS)
12. Other (Hyper-Ca^{+2} , Eos)

Patterns of disease presentation

- Disease starts at a single site within the lymphatic system and then progresses to adjacent lymph nodes via lymphatic channels before disseminating to distant nonadjacent sites and organs.
- Noncontiguous spread and hematologic distribution are more common with recurrent disease.
- It is likely that Hodgkin's disease can spread via the thoracic duct, possibly in either direction, without clinical involvement of the mediastinum.

Frequency of involved sites in pathologically staged untreated pts with HD

Nodal	Percent involved %
Cervical Nodes	
Left	60-70
Right	50-60
Mediastinal	50-60
Paraortic	30-40
Axillary	
Left	30-35
Right	25-35
Spleen	30-35
Hilar Nodes	15-35
Iliac Nodes	15-20
Inguinal	8-15
Liver	2-6
Mesenteric	1- 4
Waldeyer	1- 2
Extranodal	
Total	10-15
BM	1- 4
Other	10-12

Tips in diagnosis

- It is rare to have Hodgkin's disease in the neck and the lower abdomen without disease in the upper abdomen.
- It is unusual to have bilateral axillary involvement without disease in the lower neck areas.
- It is extremely unusual to have hepatic or bone marrow infiltration without disease in the spleen.
- It is uncommon to have pulmonary disease at presentation without Hodgkin's disease being present within the hilar lymph nodes, usually on the ipsilateral side.
- Most patients with nodular lymphocyte-predominant Hodgkin's disease presented with localized peripheral disease often in the upper neck, whereas patients with the lymphocyte depletion subtype usually presented with abdominal nodal involvement and often have extranodal disease.
- The majority of patients with nodular sclerosis histology had disease above the diaphragm and mediastinal node involvement.
- Disease in the liver was most often seen in patients with the mixed cellularity or lymphocyte depletion subtypes and systemic symptoms.

Staging Classification

Ann Arbor modified by Cotswolds

- **Stage I:** **involvement of single lymph node region or lymphoid structure**
- **Stage II:** **involvement of two or more lymph node regions on same side of diaphragm**
- **Stage III:** **involvement of lymph node regions or structures on both sides of diaphragm**
  III_1: with splenic hilar,celiac,portal nodes
  III_2: with para-aortic,iliac,mesenteric nodes
- **Stage IV:** **involvement of extranodal site(s)**

A. Asymptomatic

B. Symptomatic (B symptoms)

X. Bulky disease (> 1/3 widening of mediastinum, > 10cm max.dimension of nodal mass)

E. Involvement of a single, localised, extranodal site

Staging evaluation for Hodgkin's Disease (1)

- Essential
  - pathologic documentation by hemopathologist
  - physical examination
  - documentation of B symptoms
  - laboratory evaluation
    - complete blood count, ESR
    - liver function tests
    - renal function tests
    - lactate dehydrogenase
  - chest radiograph
  - ultrasonography
  - CT scan of chest, abdomen and pelvis
  - bone marrow aspiration / biopsy (?)

Staging evaluation for Hodgkin's Disease (2)

- Essential under certain circumstances
  - liver biopsy
  - gallium scan
  - technetium bone scan
  - bone radiographs
  - MRI
  - bipedal lymphangiogram
  - staging laparotomy
- Useful but not essential tests
  - cell-surface marker phenotypic analysis
  - gene rearrangement analysis

Diagnosis and Work Up

- Fine Needle Aspiration: alone insufficient
- Core Needle Biopsy: often adequate
- Recommendation: excisional nodal biopsy
- Immunohistochemistry is recommended but not necessary for cHD
- Immunostaining for CD15, CD30, CD3, CD20, and CD45 is recommended for typical cHD
- Immunostaining for CD20,CD57, CD15, CD30, CD3, and CD21 is recommended for NLPHD

Bone Marrow Biopsy or Not?

- Marrow infiltration by malignant cells occurs in 6.5 % of pts with newly diagnosed HD and < 1% of early stage. Closely associated w advanced disease
- 613 patients, bone marrow biopsy influenced the mode of treatment in < 1% of cases, usually in those with B symptoms. Furthermore, among patients with advanced disease, demonstration of bone marrow involvement does not identify a high risk group that needs to be treated differently
- UK: bone marrow biopsy was inappropriately performed in pts with newly diagnosed HD by 74% of hematologists and 40% of clinical oncologists

- Current recommendations:

  bone marrow biopsy from at least one site is appropriate in patients with newly diagnosed Hodgkin's disease if they have one or more of the following characteristics:

  - B symptoms
  - Clinical stage IIB to IV
  - Anemia, leukopenia, or thrombocytopenia

Choice of Treatment

- A subset of pts with stage I or II disease can be considered for localized Tx. All pts w advanced disease require systemic Tx
- Recent reports suggest that even early stage pts benefit from limited Chemo w or wo XRT
- Early stage: Stage I or II, no bulky disease, no B symptoms
- Advanced stage: stage III or IV, bulky stage II, or B symptoms

1995 to present: Patient groups

In recent years, Hodgkin's lymphoma patients have usually been grouped on the basis of prognostic or risk factors:

- Favorable: stage I and II without risk factors
- Unfavorable: stage I and II with risk factors, stage IIIA, with or without risk factors
- Advanced: stage IIIB and IV, low risk, stage IIIB and IV, high risk

Table 1. Definition of treatment groups for Hodgkin's lymphoma*

Treatment groups	EORTC/GELA	GHSG
Early-stage favorable	CS I-II without risk factors, supradiaphragmatic	CS I-II without risk factors
Early-stage unfavorable, intermediate	CS I-II with ≥ 1 risk factors, supradiaphragmatic	CS I, CSIIA ≥ 1 risk factors; CS IIB with C/D but without A/B
Advanced stage	CS III-IV	CS IIB with A/B; CS III-IV
Risk factors (RF)	A, large mediastinal mass	A, large mediastinal mass
	B, age ≥ 50 years	B, extranodal disease
	C, elevated ESR†	C, elevated ESR
	D, ≥ 4 involved regions	D, ≥ 3involved regions

*Definitions based on findings of the European Organization for Research and Treatment of Cancer (EORTC), Groupe d'Etude des Lymphomes de l'Adulte (GELA), and German Hodgkin Study Group (GHSG).
†ESR—erythrocyte sedimentation rate (≥ 50 mm/h without or ≥30 mm/h with B-symptoms.

Goal of the treatment

- Favorable disease: cure with minimal side effects
- Unfavorable disease: cure with some (acceptable) side effects
- Advanced disease: cure without serious side effects.

ABVD

- In 1975, *Bonadonna et al* introduced the ABVD regimen in an attempt to develop a regimen for patients whose disease had recurred after MOPP

- The Milan group started to compare MOPP and ABVD, using 3 cycles of each drug combination, followed by extended field irradiation and 3 additional cycles of the same chemotherapy. This comparison demonstrated a significant superiority for ABVD

- Nowdays, ABVD is considered the gold standard,but this assumption is challenged by the fact that 5% of patients progress under therapy and 5–10% relapse rather early, many of those appearing resistant to salvage therapy.

PRINCIPLES OF RADIATION THERAPY

RT-ALONE DOSES (uncommon scenario):
- Involved regions: 30-44 Gy[1]
- Uninvolved regions: 30-36 Gy

COMBINED MODALITY-RT DOSES:
- Stage I-IV; bulky disease: 20-36 Gy
- Stage I-IV, nonbulky disease: 20-30 Gy

RADIATION FIELDS

- When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.

Minimantle: bilateral cervical/supraclavicular and axillary nodes
Mantle: minimantle and mediastinal and bilateral hilar nodes
Subtotal lymphoid: mantle and para-aortic/spleen field
Inverted Y: bilateral pelvis, para-aortic/spleen field
Involved-field: involved lymphoid region(s) only
Regional-field: involved and immediately adjacent lymphoid regions

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Early stage – general aspects

- Challenge: To maintain low risk for relapse minimazing long term Tx-related toxicity
- XRT was used when pts were pathologically staged to have IA or IIA disease
- But: Laparotomy is no longer indicated
- Current approach: ABVD x 2-4 +XRT induces DFS>94% in median follow up of 2-3 yrs
- EU & NA cts in progress to further define 2 vs 4 cycles, XRT involved vs extended and rad doses required
- Studies in children favour chemo alone in terms of EFS and RespRates
- Pts presenting w early stage BUT unfavourable characteristics definitely require Chemo: ABVD x 6-8
- Pts w bulky mediastinal mass (> 1/3 max diameter of the chest) require adjuvant XRT
- Evidence: XRT of residual mass post chemo can convert PR into durable CR
- To determine whether PET will be useful in identifying bulky disease pts w active residual disease vs fibrosis and thus the need for local XRT
- The optimal therapy for patients with clinically staged I or II remains controversial. Most centres recommend combined modality therapy. However, XRT or chemo alone may suffice in appropriate situations

Early stage with favorable prognosis

Definition:

clinical stage I or II without any of the following risk factors:

a. Age > 50 y

b. Erythrocyte sedimentation rate > 50 mm/h or > 30 mm/h in the presence of B symptoms

c. Four or more separate sites of nodal involvement

d. Mediastinal mass ratio > 0.35

Treatment: combined modality preferred

First choice: ABVD x 4 cycles + involved field radiotherapy36-40 Gy

Alternative choices if first choice contra-indicated:

Sub-total nodal irradiation 36-40 Gy

EBVP x 6 cycles + involved field radiotherapy 36-40 Gy

Early stage with unfavorable prognosis

Definition:

stage I or II with any of the following risk factors:

a. Age > 50 y

b. Erythrocyte sedimentation rate > 50 mm/h or > 30 mm/h in the presence of B symptoms

c. Four or more separate sites of nodal involvement

d. Mediastinal mass ratio > 0.35

e. In addition, patients with stage IIIA could also reasonably be included in this group

Treatment: combined modality treatment essential

First choice: ABVD x 6 cycles + involved field radiotherapy 36-40 Gy

Alternative choice if first choice contra-indicated:

MOPP/ABV x 6 cycles + involved field radiotherapy 30-40 Gy

The treatment of early stage Hodgkin's lymphoma has become more complicated over the past 10 years. Initial treatment decisions may have profound long-term effects on patients. It is debatable if 'routine' cases exist and it is still advisable to treat patients in controlled clinical trials.

Mauch PM,Ann Oncol 1996

Advanced stage

- Pts w stage III or IV disease require chemo
- MOPP developed in 60's and achieved long term survival in 50-60% of pts
- ABVD was subsequently demonstrated to be active in MOPP-resistant disease.
- ABVD less toxicity, fewer 2ary malignancies. The current standard regimen
- Stanford V weekly chemo for 12 weeks, myelosuppressive agents alternating non myelosuppressive + 36 Gy to sites of >5cm disease
- DFS 89% w median follow up of 5.4 yrs
- GHSG studied a dose escalated and accelerated regimen, BEACOPP. Compared to COPP/ABVD it had improved freedom from Tx failure at 5 yrs

Results of treatment modalities in advanced stage Hodgkin's disease

Regimen	RT %	CR %	EFS/FFP/FFTF %	y		Survival %	y	Ref.
ABVD	0	82	61	5	FFP	73	5	25
MOPP/ABVD	0	83	65	5	FFP	75	5	26
MOPP/ABV	0	83	64	8	FFP	79	5	27
ABVD	0	71	63	5	FFS	82	5	28
MOPP/ABV	ns	73	66	5	FFS	81	5	28
ChlVPP/EVA	58	65	82	5	FFP	95	5	29
COPP/ABVD	64	85	69	5	FFTF	83	5	30
BEACOPP baseline	71	88	76	5	FFTF	88	5	30
MOPP/ABV	67	95	82	5	EFS	84	5	31
Stanford V	86	99	89	5	FFP	93	5	18
BEACOPP escalated	71	96	87	5	FFTF	91	5	28
BEACOPP-14	60	94	90	3	FFTF	97	3	31
4 ABVD + BEAM	ns	90	75	4	FFP	88	4	32
MEC	44	92	87	3	FFS	96	3	26

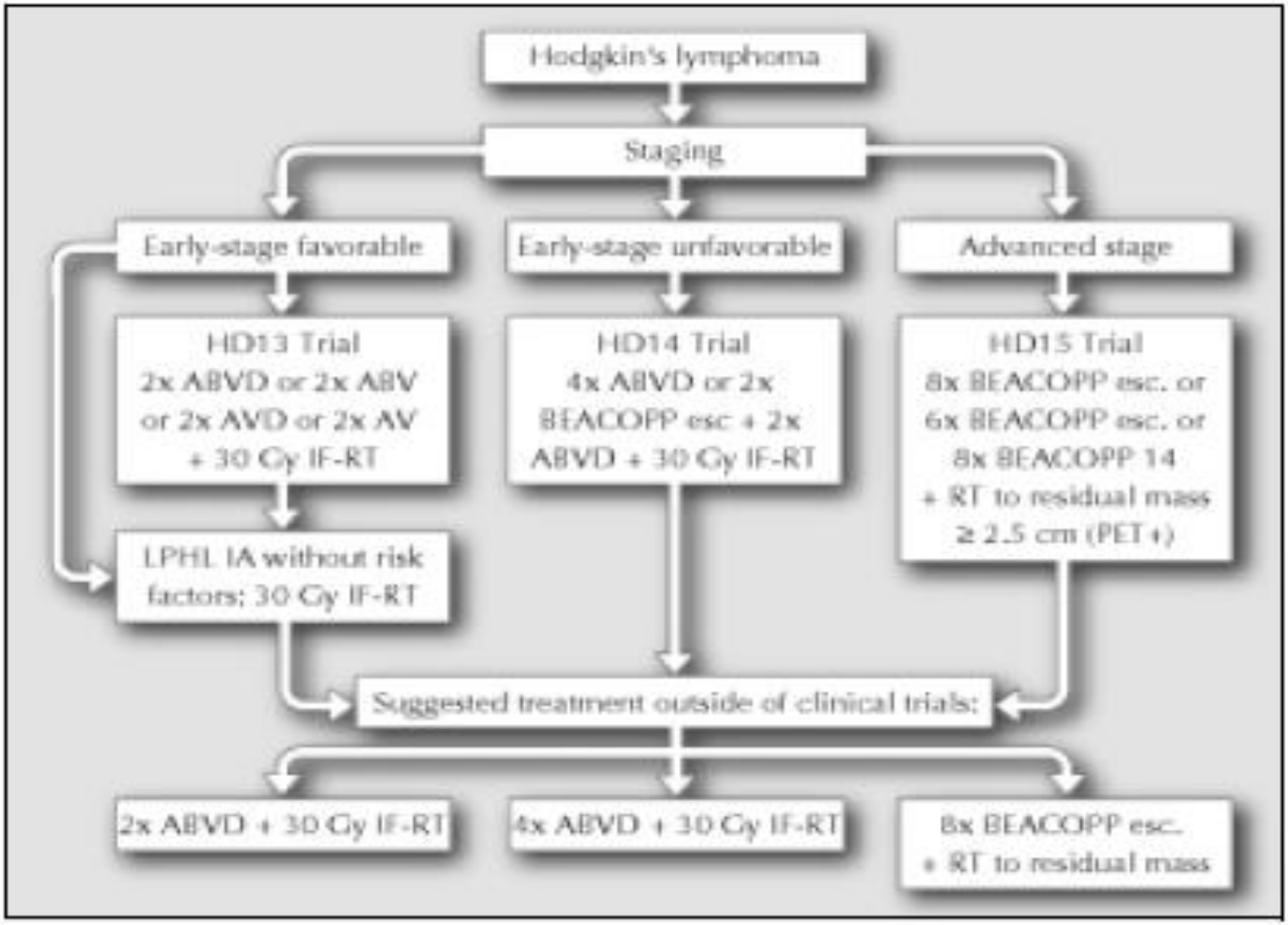
! *Note: The majority of pts in GHSG received combined modality therapy*

Table 3. Treatment results in bulky and advanced Hodgkin's disease.

Group/ Reference	Patients/ Treatment	N	FFS%	OS%	Time (Yr)
Chemotherapy Only					
CALGB	$IIIA_2$, IIIB, IV, after RT	361			5
	ABVD		61*	76	
	MOPP/ABVD		65*	75	
	MOPP		50*	66	
ECOG	$IIIA_2$, IIIB, IV, after RT	691			8
	MOPP → ABVD		54*		
	MOPP/ABV		64*		
CALGB	III, IV, after RT	856			3
	ABVD		65	87	
	MOPP/ABV		67	85	
Chemotherapy + Radiotherapy					
Milan	IB, IIA_{bulky}, IIB, III, IV	427			10
	MOPP/ABVD + RT		67	74	
	Hybrid + RT		69	72	
NCI-C	IIIB, IV, after RT	301			5
	MOPP/ABVD + RT		67	83	
	Hybrid + RT		71	81	
GHSG	IIB-$IIIA_{risk}$, IIIB, IV	1180			3
	COPP/ABVD + RT		70*	86*	
	BEACOPP + RT		79*	91*	
	EscBEACOPP + RT		89*	92*	

Table 4. Second cancers after treatment for Hodgkin's disease.

Group/ Reference	Patients/ Treatment	N	MDS/ Leukemia	Solid Tumors	Time (Yr)
Chemotherapy Only					
ECOG	$IIIA_2$, IIIB, IV, after RT	691			8
	MOPP → ABVD		9	N/A	
	MOPP/ABV		1	N/A	
CALGB	III, IV, after RT	856			3
	ABVD		0	2	
	MOPP/ABV		6	6	
Chemotherapy + Radiotherapy					
Milan	IB, IIA_{bulky}, IIB, III, IV	427	11	12	10
	MOPP/ABVD + RT				
	Hybrid + RT				
GHSG	IIB-$IIIA_{risk}$, IIIB, IV	1180			3
	COPP/ABVD	233	0	6*	
	BEACOPP	457	2	4*	
	EscBEACOPP	460	8	4*	

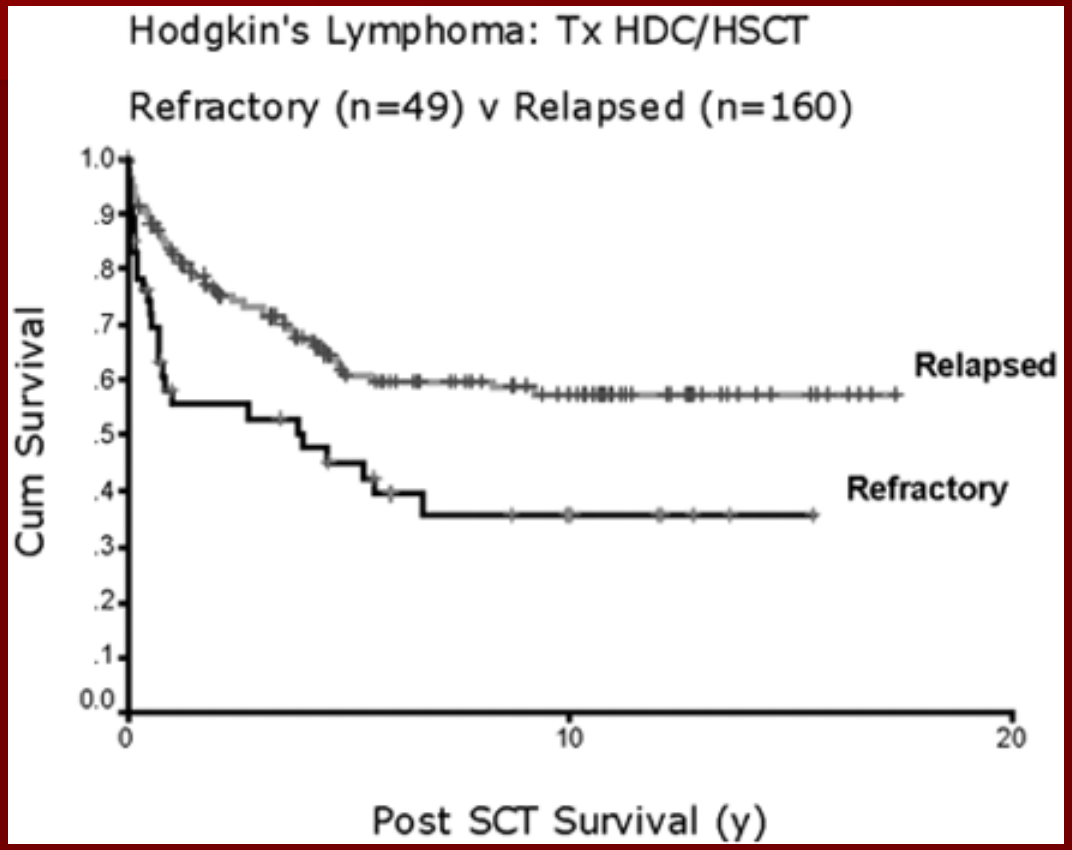


Algorithm of the first-line treatment of Hodgkin's lymphoma in the German Hodgkin Lymphoma Study Group

Relapsed/refractory disease

- Depends on the primary therapy and the duration of initial remission
- Pts who relapse >12 mo after a CR may be treated w combination chemo. 30-50% remain DF at 5 yrs
- Those who relapse <12 mo are less likely to achieve remission and long DFS w Chemo alone
- Poor prognostic signs in pts at relapse include advanced stage and B symptoms
- Pts w chemosensitive disease and poor prognostic factors should considered for High Dose Chemo + Auto SCT
- Without high dose therapy estimated 5 yrs survival is <20% for patients relapsing <1 yr after initial chemotherapy

Long term follow up from British Columbia since 1985



Diehl et al. ASH Education Program Book 2003

Definitions

- Primary progressive HD – never achieved CR
- Early relapse - within 12 months of CR
- Late relapse - after CR lasting >12 months

Salvage chemotherapy (Conventional Dose)

- Early relapse: Crossover therapy(MOPP vs. ABVD) CR 35%, FFS 20% at 3-5 yrs (NEJM 327: 1478, 1992)*

- Late relapse: Previous regimen or other appropriate regimen CR 50-80%, FFS 50% at 5 yrs (JCO 15: 528, 1997)

* *In this trial, ABVD therapy for 6 to 8 months was as effective as 12 months of MOPP alternating with ABVD, and both were superior to MOPP alone in the treatment of advanced Hodgkin's disease. ABVD was less myelotoxic than MOPP or ABVD alternating with MOPP.*

Prognostic factors in Salvage therapy (Favorable)

- NCI, Bethesda: age < 30 yrs, CR duration > 12 months (J Clin Oncol 10: 210, 1992)
- GELA, France: CR > 12 months, disease status at relapse (untreated vs. refractory) (Ann Oncol 6: 543, 1995)
- Hôpital Saint-Louis, Paris: CR duration > 12 months, stage I or II at relapse (Cancer 78: 1293, 1996)
- Cancer Control Agency, British Columbia: no B symptoms at relapse, CR duration > 12 months, Stage I-III at original diagnosis (Blood 77: 2292, 1991)
- Instituto Nazionale Tumori, Milan: nodal only relapse, CR duration > 12 months, disease extent at relapse (J Clin Oncol 15: 528, 1997)

Prognostic Factors for Relapse

- Age greater than 40 or 45 years
- Male gender
- Stage IV tumor
- More than three nodal sites
- Bulky disease
- Multiple extranodal sites
- Involvement of chest wall by direct extension
- B symptoms
- Low serum albumin
- Bone marrow and/or inguinal node involvement
- Anemia
- Low lymphocyte count
- High serum lactic acid dehydrogenase
- Leukocytosis
- Expression of BCL-2 by Hodgkin-Reed-Sternberg cells
- High circulating levels of CD30

Only <u>some</u> of them are used in clinical practice

Prognostic Factors used vary per Stage

UNFAVORABLE FACTORS
(localized presentations)

- Bulky disease:
  - Mediastinal mass:

$$\frac{\text{Maximum mass width}}{\text{Maximum intrathoracic diameter}} > \frac{1}{3}$$

  - Any other mass > 10 cm
- Erythrocyte sedimentation rate ≥ 50, if symptomatic
- > 3 sites
- B symptoms

UNFAVORABLE FACTORS
(advanced disease)[1,2]

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm^3)

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HSCT

- Benefit 10-15% of those w primary refractory disease and 40-50% of patients in 2nd CR
- Important to demonstrate the chemosensitivity of disease at relapse
- 2-4 cycles w 2nd line regimen which can also be used to mobilize stem cells

Table 9. Characteristics of patients best treated with high dose chemotherapy/hematopoietic stem cell transplantation (HDC/HSCT) for relapse of Hodgkin's lymphoma after primary chemotherapy.

Definite

- Relapse < 1 year after completion of primary chemotherapy
- Relapse with B symptoms
- Relapse in extranodal sites
- Relapse in previously irradiated sites

Controversial but probably indicated

- Relapse only in previously unirradiated lymph nodes, in the absence of B-symptoms, occurring > 1 year after completion of primary chemotherapy

PROGNOSTIC FACTORS FOR RECURRENCE AFTER TRANSPLANTATION

- Duration of CR of less than twelve months
- Chemotherapy resistant disease (induction failure or resistant relapse)
- Increasing number of failed chemotherapy regimens
- More than minimal disease at transplant
- Bulky residual disease at transplant
- B symptoms at relapse
- Extranodal disease at relapse
- Poor performance status
- Relapse within a prior radiation field
- Slow recovery of absolute lymphocyte count post-transplant
- High International Prognostic Factors Project score

Relapse after ABMT

- Second ABMT
- Mini allo
- Various regimens which include drugs like VP 16, nitrosoureas, gemcitabine, vinorelbine
- Monoclonal anti-CD30 antibody - being studied
- EBV specific cytotoxic T–lymphocytes generated ex-vivo can be reinfused to target EBV positive tumor cells - being studied

Rituximab in HD

- The use in Hodgkin's is in trials now.
- Cannot be considered as standard therapy for Hodgkin's disease

- The theory explained after the 2003 ASH meetings is the Reed-Sternberg cells are surrounded by many normal B cells

- The nearly universal expression of CD20 on the neoplastic cells of LPHL suggests that this lymphoma may be usefully treated with rituximab.

- Preliminary data from several small series show response rates exceeding 50%.
- Such responses may be of short duration and associated with transformation to large B-cell non-Hodgkin's lymphoma

Monitoring during and after therapy

- One month following the completion of planned therapy (or sooner if the outcome is unfavorable), the response should be documented by history and clinical examination.
- Follow-up imaging studies should first be obtained 3 (to 6) months after completion of therapy.
- If chemotherapy alone is used these studies should be obtained 1 month after finishing chemotherapy

Imaging studies - Chest CT scan

- Following mediastinal irradiation, the reassessment chest CT should be postponed for three to six months; regression of disease may be slow after radiation therapy and, if evaluation is performed too early, a residual mass may still be visible.

- The Cotswolds Committee recommended that CT be included as a technique for evaluating intrathoracic and infradiaphragmatic lymph nodes and be considered at least as useful as lymphangiography

Imaging studies - FDG-PET scan

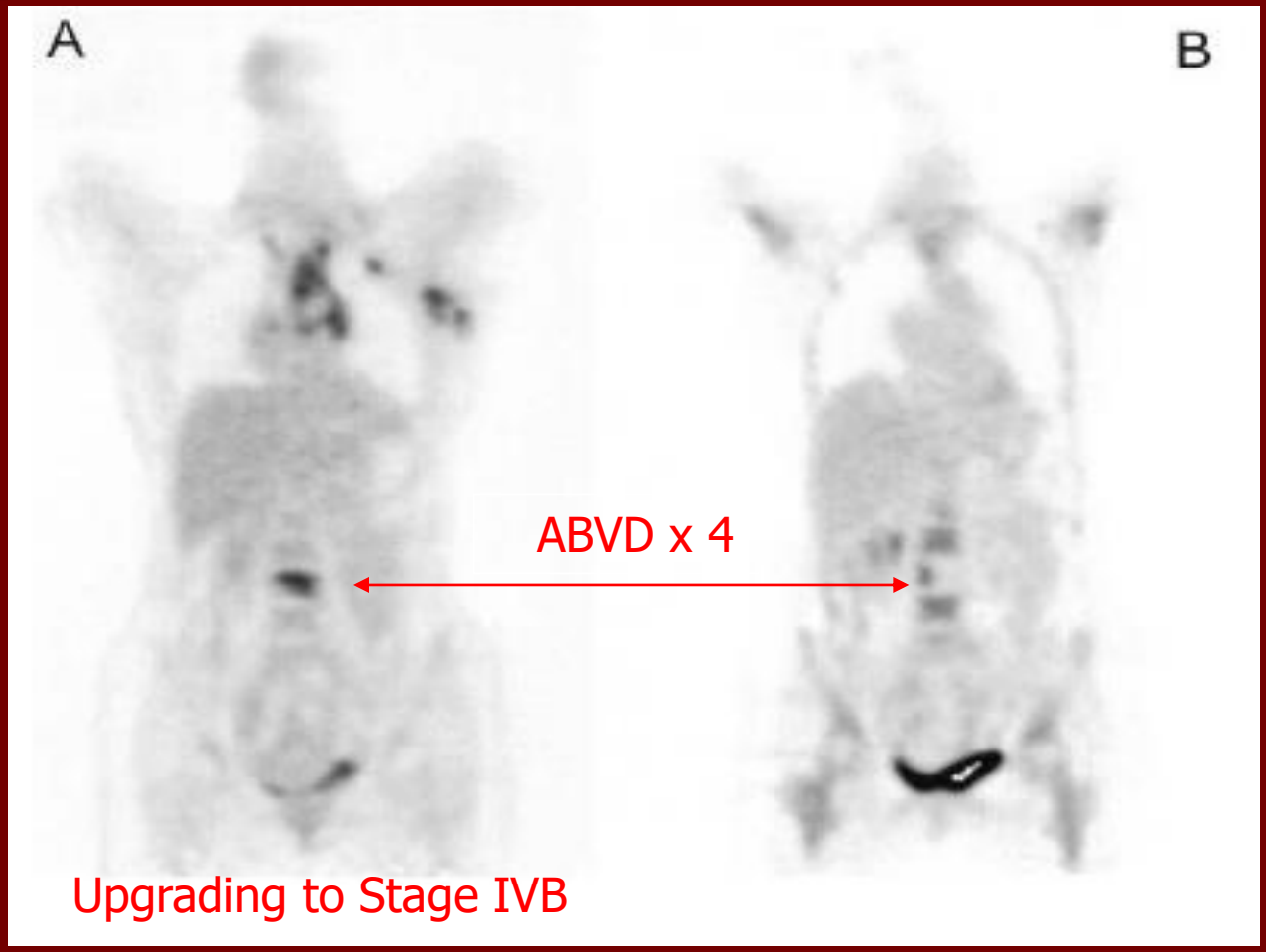
The possible role of PET scanning in the staging and restaging of patients with Hodgkin's disease is uncertain.

In a study of residual post-treatment masses in 58 patients, the negative predictive value of PET scanning was 100 percent . However, the significance of a positive scan was less certain.

Imaging studies - FDG-PET scan

- For post-treatment evaluation (residual mass is present) PET has become a standard procedure in routine clinical practice and has replaced gallium scintigraphy as an adjunct to CT.
- After first-line treatment, abnormal FDG-uptake in initially involved sites and with low suspicion of co-existing inflammation, strongly consider for providing alternative therapy.
- Negative PET results do not exclude minimal residual disease and/or the risk of late relapse.
- Dual modality PET-CT scan far better in discriminating residual lymphoma vs muscle/fat tissue

Patient with Hodgkin's lympoma,NS stage IIB based on conventional imaging modalities (CT and iliac crest biopsy)



Imaging studies - Gallium SPECT scan

- Used for monitoring and evaluating the nature of residual mediastinal disease.
- A residual mass that is gallium negative usually represents fibrosis/necrosis and follow-up without therapy may be warranted. The overall likelihood of relapse is approximately 20% in such patients.
- The relapse rate appears to vary with the initial stage of disease, ranging in one series from 7.5 percent in patients with stage I-II disease compared to 34 percent with stage III-IV disease. In early stage patients for whom chemotherapy and radiation therapy are planned, the radiation therapy should still be delivered when the Gallium scan is negative after the completion of the chemotherapy.
- Persistent gallium avidity is correlated highly with residual disease activity, with an estimated sensitivity of 76 to 100% and a specificity of 75 to 98%.
- But: Experienced interpretation of the gallium scan is required!

Long term complications of therapy

- Large cohorts of pts followed at Stanford 1960-1995 & at Dana Farber Cancer Inst & Massach. Gen Hosp showed that the risk of death form other causes at 15 yrs surpasses that from Hodgkin's
- Latent period of at least 5-10 yrs, and the risk of 2ary cancers persists for > 20 yrs from initial treatment
- Best studied secondary tumor is breast cancer. Adolescent fems treated w RT or treated before 30 yrs of age. Begin to appear at the end of 1st decade
- CV complications and hypothyroidism
- Long term depend upon the regimen. MOPP associated w sterility, MDS, AML. ABVD carries pulmonary and CV risks.
- Increased incidence of MDS/AML has been documented within 5-7 yrs of high dose therapy which is in addition to the acute toxicity of BMT
- Also increased incidence of NHL

Causes of death in treated HD

	Stanford[141] *			Joint Center[142] †		
	Patients		Deaths	Patients		Deaths
	(no.)	(%)	(%)	(no.)	(%)	(%)
Total patients	2,498	100		794	100	
Total deaths	754	30.2	100	124	15.6	100
HD	333	13.3	44	56	7.0	45
Second malig-nancy	160	6.5	21	36	4.5	29
Cardiovascular	117	4.8	16	15	1.9	12
Pulmonary	50	2.0	7	1	0.1	1
Infectious	31	1.3	4	8	1.0	6
Accidental	14	0.6	2	3	0.4	2
Other	49	2.0	7	4	0.5	3

*All stages treated from 1960-1995: estimated mean follow-up, 12 years.

†Laparotomy stage IA-IIIB only treated from 1969-1988: mean follow-up, 11 years.

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Risk of 2nd malignancies after HD treatment

Site or Type	Relative Risk	Absolute Excess Risk* (per 10,000 patients per yr)
All malignancies	3.5	56.2
ANLL	70.8	15.5
NHL	18.6	10.7
Solid tumors	2.4	29.3
Lung	4.2	13.5
Breast	2.5	11.3
GI	2.5	5.8
Sarcoma	7.0	1.0
Thyroid	4.7	0.5
Melanoma	4.2	1.6

Abbreviation: GI, gastrointestinal tract.

*Absolute (excess) risk per 10,000 patient years = [observed events − expected events/person-years] × 10,000. The absolute risk divided by 100 is the percentage likelihood of an event per year of follow-up for an individual patient.

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- Solid tumors:the most common type of second malignancy, accounting for 59%–80% of cases and 58%–75% of absolute excess risk.

- Leukemia and NHL make up a relatively small number of second cancers observed, but very high relative risk (uncommon expectation of these malignancies in the control populations).

- Younger age at treatment: higher relative risks for developing a solid tumor; this in part reflects the relatively lower incidence of malignancies expected in matched control populations. Within adult populations, absolute excess risks appears to increase with increasing age—this finding may be particularly weighted by risks associated with developing lung cancer.

- The cumulative risk of developing a solid tumor continuously increases, until at least 25 years of follow-up.
- The risk of developing acute leukemia is predominantly confined to the first 10 years of follow-up.
- Treatment received is associated with different risks of developing specific second cancers. The risk of developing a solid tumor is increased in patients receiving radiation therapy in comparison with those receiving chemotherapy alone. This risk may be further increased by use of larger radiation fields and, at least for some solid tumors, by use of combined-modality therapy.
- Risk of a second malignancy progressively increases over time in patients who have received radiation therapy, whereas a plateau in cumulative incidence is suggested in patients who receive chemotherapy alone.

SIGN Guidelines - Jan 2004

"Long term follow up of survivors of childhood cancer"

Second cancer is the leading cause of death in long term survivors of Hodgkin's disease with exceptionally high risks of breast cancer among women treated at a young age. Breast cancer risk increases with increasing radiation dose up to at least 40 Gy. A radiation dose of 4 Gy or more delivered to the breast was associated in one study with 3.2–fold excess risk. The risk increased to eight fold with a dose of more 40 Gy. Young age at treatment has a major on risk of second malignancy after Hodgkin's disease. Although absolute excess risk are greater for older patients relative risks of several important malignancies are much greater for patients who are treated when young.

Questions to be answered

Early stage HD wo Risk Factors

- Is radiation therapy (RT) alone obsolete?

- RT alone is no longer the treatment of choice in most centers in Europe and North America.

Early stage HD wo RF

- If combination CT-RT:

a. What CT, how many cycles?

b. RT: field and dose?

Combination CT-RT is the most common treatment strategy in Europe and US.

a) 2-4 cycles of ABVD are considered the international gold standard for early stage HD.

b) 30-35 Gy IF is the modern standard.

Early stage HD wo RF

- Is CT alone sufficient?

- This problem is currently being investigated in clinical trials; the answer is pending. At the ASH meeting 2003, results of the HD-6 trial of the National Cancer Institute of Canada Clinical Trials Group (ECOG trial JHD06) were announced ….

Early stage HD w RF

- Do we need an intermediate group?
- The EORTC, the GELA, and the GHSG continue to treat the early unfavorable (intermediate) group differently from the early favorable and advanced group.
- Allocating these patients into the early stage favorable group would undertreat a certain subgroup and overtreat another if one moves them up to the advanced group.

  Ongoing subgroup analyses try to discriminate these special subgroups for even better custom-tailored therapy.

Early stage HD w RF

- Is combination CT-RT the gold standard?

- Yes, CT+RT is the gold standard internationally at the moment.

Early stage HD w RF

- Which CT and how many cycles?

- ABVD is considered the gold standard at the moment, but this assumption is challenged

  by the fact that 5% of patients progress under therapy and 5–10% relapse rather early, many of those appearing resistant to salvage therapy.

Early stage HD w RF

- RT: dose and field?
- Recent studies have shown that IF-RT after ABVD x4 suffices and is less toxic and equally effective as EF-RT. Current and recently closed trials have investigated the question whether 20 Gy IF-RT is sufficient after ABVD x4 or whether in certain risk groups one needs 30 Gy or more. CT alone has not been sufficiently tested to testify its potential to cure patients in this setting.

Advanced HD

- Do we have better RF as the IPS?

- IPS is still the internationally most accepted and used risk factor score for advanced HL. Many groups are working intensively to find new biologic or gene expression profiling markers for the identification of risk groups in advanced HL. The results are curiously awaited. (*bcl-2* ?)

Advanced HD

- Is ABVD the gold standard?
- The early progression rate,the 5-year FFTF and the OS rates were significantly inferior for the 0-2 and the 3–7 RF strata if one compares patients treated with COPP/ABVD and with escalated BEACOPP.For these reasons the GHSG has decided to treat even patients with a low-risk factor score with escalated BEACOPP. The pivotal international study headed by the EORTC comparing 8 ABVD versus 4 escalated BEACOPP + 4 baseline BEACOPP in advanced HD patients will add valid information about the feasibility, toxicity, and the equality or superiority of the regimen in question.

Advanced HD

- Do we need RT after effective CT?
- The recently published paper by the EORTC demonstrated that after reaching a CR after 8 cycles of effective chemotherapy, patients with advanced HL patients do not benefit from additive RT.

  There might be a risk group, however, which needs RT for elimination of the last tumor cell.