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Introduction

Evidence Based Radiation Oncology Fact Sheets
Hodgkin Lymphoma 2021

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Overview:

Epidemiology:

- About 10-14% of lymphomas; 1% of all cancers.
- Adult HD has bimodal age distribution: peaks at age 20-29 and again in the 50+ range
- Pediatric HD typically occurs 4-14 years old; marked male predominance 4:1
- 90% have disease in contiguous nodes (assuming para-aortics are contiguous to SCV via thoracic duct)
- Visceral involvement may be local extension or hematogenous; rare to GI lymphatics (Waldayer's ring or Peyer's patch)
- **Note**: **EBV**: associated with mixed cellularity type or pediatric HD.

Workup:

- History: look for B symptoms. Also fatigue, alcohol-induced pain, pruritus.
  - **FERTILITY COUNSELING** (please remember to say this during oral boards).
- PE: Palpable nodes, palpable viscera (liver and spleen).
- Labs: CBC, blood chemistry, albumin, ESR
- Radiology: CXR (PA more than AP), CT with contrast, PET, ± MRI to select sites.
- Biopsy:
  - LN excisional.
  - **Bone marrow biopsy really no longer used unless 1. cytopenia or 2. PET shows something.**
    - **NOTE: Bone Marrow Biopsy is NOT done for DLBCL!!!**
  - Staging laparotomy no longer used
- Special:
  - MUGA if Adriamycin (**A**BVD).
  - PFT if bleomycin (A**B**VD).

DIAGNOSIS/WORKUP

- **Excisional biopsy (recommended)**
- **Core needle biopsy may be adequate if diagnostic[a]**
- **Immunohisto-chemistry evaluation[b]**

Essential:
- **H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examination of lymphoid regions, spleen, liver**
- **CBC, differential, platelets**
- **Erythrocyte sedimentation rate (ESR)**
- **Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)**
- **Pregnancy test for women of childbearing age**
- **PET/CT scan[c] (skull base to mid-thigh or vertex to feet in selected cases)**
- **Counseling: Fertility, smoking cessation, psychosocial (See NCCN Guidelines for Supportive Care)**

Useful in selected cases:
- **Fertility preservation[d]**
- **Pulmonary function tests (PFTs incl. diffusing capacity [DLCO])[e] if ABVD or escalated BEACOPP are being used**
- **Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated**
- **HIV and hepatitis B/C testing (encouraged)**
- **Diagnostic CT[f] (contrast-enhanced)**
- **Chest x-ray (encouraged, especially if large mediastinal mass)**
- **Adequate bone marrow biopsy if there are unexplained cytopenias other than anemia (eg, thrombocytopenia or neutropenia) and negative PET[g]**
- **Evaluation of ejection fraction if anthracycline-based chemotherapy is indicated**
- **MRI to select sites, with contrast unless contraindicated**
- **PET/MRI (skull base to mid-thigh) without contrast**

CLINICAL PRESENTATION

- **Classic Hodgkin lymphoma (CHL)[h]** → **See HODG-2**
- **Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)** → **See HODG-8**

[a] Fine-needle aspiration (FNA) alone, in distinction from a core biopsy, is generally insufficient for diagnosis.

[b] Typical immunophenotype for CHL: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-. Typical immunophenotype for NLPHL: CD20+, CD45+, CD79a+, BCL6+, PAX-5+; CD3-, CD15-, CD30- (Swerdlow SH, Campo E, Harris NL, et al; WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2017). EBER is recommedned at initial diagnosis. An expanded panel of markers (eg, MUM-1,BOB-1, OCT-2) may be required, especially if equivocal diagnosis. See NCCN Guidelines for B-Cell Lymphomas. For NLPHL, immunoarchitectural pattern should be specified as typical vs. variant.

[c] See Principles of FDG-PET/CT (HODG-A). PET/CT should be done with patient on a flat table with arms up, if possible. In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1).

[d] Fertility preservation options include: semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

[e] In general, a DLCO threshold of ≥60% is acceptable for use of bleomycin.

[f] Imaging should be obtained in accordance with the American College of Radiology (ACR) practice guidelines. CT is considered diagnostic if it is enhanced with oral and/or IV contrast. CT component of a conventional PET/CT is often not IV contrast-enhanced. Although the diagnostic CT will often be neck/chest/abdomen/pelvis, at minimum include the areas identified as abnormal on PET/CT.

[g] In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is not assumed. If there are multifocal (three or more) skeletal PET/CT lesions, marrow may be assumed to be involved. In general, bone marrow biopsies are no longer indicated.

[h] CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

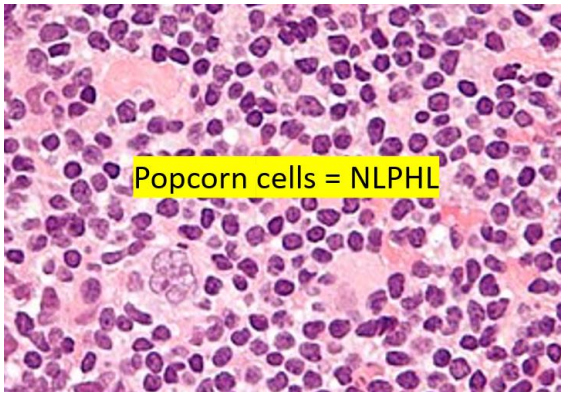
Pathology:

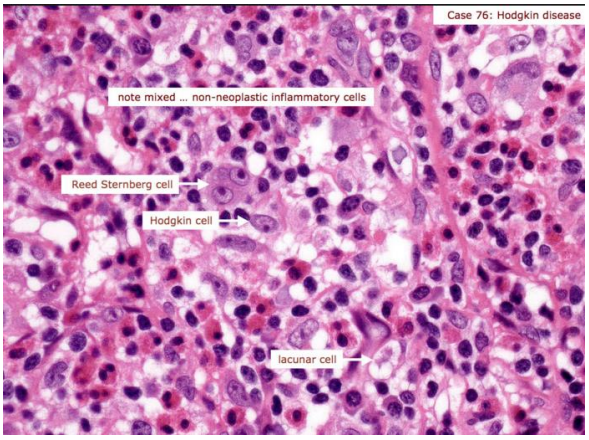
- **Classic HL**: Presence of classic Hodgkin/Reed-Sternberg (HRS) cells
  - Do not exhibit phenotypes typical of any normal cell
  - CD15+; marker is expressed on granulocytes
  - Somatic hypermutation of immunoglobulin genes, with VDJ rearrangement. This is typically seen only in germinal B cells and post-germinal B cells
  - Study of patients with both HL and NHL shows they are clonally related, suggesting that initial transformation occurred in a germinal B cell. Subsequently, there are two distinct sets of molecular lesions, which lead to divergent phenotypes of HL and NHL
  - HRS cells appear to lose their germinal B cell characteristics, and become unable to transcribe RNA for immunoglobulin due to impaired activation of Ig promoters
  - There is also activation of NF-kB pathway, which leads to c-REL increase and promotion of lymphocyte transformation and prevention of apoptotic deletion
  - There is a widespread genomic instability, which contributes to the strange nuclear appearance

- **Nodular lymphocyte predominant HL (Very FAVORABLE):** Prevalent tumor cell is "lymphocytic and histiocytic" (L&H) subtype of HRS cells.
  - Compared to most other Hodgkin these do NOT GO TO MEDIASTINUM.
  - RADIATION more than CHEMO for these.
  - Pathologically looks like popped corn
  - Express B-cell markers
  - Have multiple features that resemble normal germinal B-cells
  - Classic HRS rare or absent; appears with multiple nuclear lobes and large nucleoli

	Histology	Frequency	Features	Markers
Classical	Nodular Sclerosis	≥ 70%	**Less favorable than Lymphocyte Rich.** Broad band of birefringent collagen surrounding nodules of lymphocytes, eosinophils, plasma cells, and tissue histiocytes intermixed with RS cells. Median Age 26. Mediastinum usually involved. 1/3 have B symptoms	CD 15+, CD 30+ Occasional CD 20+ **50% EBV+**
	Mixed Cellularity	20%	**Less favorable than nodular sclerosis.** Diffuse effacement of LNs by lymphocytes, E, P, and atypical mononuclear, and RS cells. Males and Older patients Abdominal involvement and advanced disease. 1/3 have B symptoms.	
	Lymphocyte Rich	5%	**Best Prognosis.** Occasional RS cells. But mostly diffused effaced with NORMAL lymphocytes. Median Age 30. Early stage I-II. Usually no abdominal or mediastinal diagnosis. < 10% B symptoms.	
	Lymphocyte Depleted	< 5%	**Worst prognosis.** Paucity of normal appearing cells and abundance of abnormal mononuclear cells, RS cells and variants. Difficult to differentiate from anaplastic large cell lymphoma. Males and older patients. Usually advanced disease 2/3 B symptoms.	
NLP	Nodular Lymphocyte Predominant	5%	Likely distinct entity from other HD with natural history similar to low-grade NHL. Lacks RS cells. Significant transformation to DLBCL and frequent late relapse. Some respond to rituximab. **POPCORN CELLS!**	CD 15-, CD 30- CD 20+, CD 19+, CD 45+ **EBV negative.**

NOTE: DLBCL ± CD10, CD19, CD20, CD22, CD 45, bcl2, bcl6, MUM1.





Prognostic/Diagnostic Tables

Clinical Stage	Bulky Mediastinal Disease[l] or >10 cm Adenopathy	Guidelines Page
I/IIA	No	Favorable Disease (HODG-3)
	Yes	Unfavorable Disease (HODG-4)
IB/IIB	Yes/No	Unfavorable Disease (HODG-4)
III–IV	Yes/No	HODG-5

- Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- Most patients will benefit from multidisciplinary input prior to final treatment decisions.

PRINCIPLES OF UNFAVORABLE RISK FACTORS

Definitions of Lymph Node Regions*

		Ann Arbor	EORTC	GHSG
Supradiaphragmatic Nodal Regions	R Cervical/SCL			
	R ICL/Subpectoral			
	R Axilla			
	L Cervical/SCL			
	L ICL/Subpectoral			
	L Axilla			
	Mediastinum			
	R Hilum			
	L Hilum			
Infradiaphragmatic Nodal Regions	Celiac/Spleen hilar			
	Paraortic			
	Mesenteric			
	R Iliac			
	L Iliac			
	R Inguinal/Femoral			
	L Inguinal/Femoral			

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.

EORTC thoracic mass width measure at T 5-6

German = Infraclavicular is part of supraclav and cervical. Hilars are part of mediastinum.
BULKY DISEASE = you can ADD UP SEPARATE NODES which all may be 2 cm each → if you have 6 of them, it is 12 cm and bulky.
Per Lugano classification: ≥10 cm for Hodgkin lymphoma 7.0 cm in Max transverse diameter.

UNFAVORABLE RISK FACTORS FOR STAGE I–II CLASSIC HODGKIN LYMPHOMA

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	≥50 or any B symptoms
Mediastinal mass	MMR > 0.33	MTR > 0.35	MMR > 0.33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

- **ADVANCED DISEASE STAGE III/IV = IPSS (International Prognostic Score System). SAM HALL**
  - One point is given for each of the characteristics below present in the patient, for a total score ranging from 0 to 7.
    - Stage IV disease
    - Age >45 years
    - Male gender
    - Hemoglobin <10.5 g/dL
    - Albumin <4 g/dL
    - Leukocytes (WBC) ≥ 15,000/microL
    - Lymphocyte count < 600/microL and/or <8 percent of the total WBC

5141 patients with Chemo ± RT prior to 1992. Hasenclever N Engl J Med 1998.		
Score	Five-year FFP, percent	Five-year OS, percent
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
5 or more	42	56
740 patients with ABVD. Moccia J Clin Oncol 2012; 30:3383.		
Score	Five-year FFP, percent	Five-year OS, percent
0	88	98
1	84	97
2	80	91
3	74	88
4	67	85
5 or more	62	67

Score 1: no uptake
Score 2: uptake ≤ mediastinum
Score 3: uptake > mediastinum but ≤ liver
Score 4: moderately increased uptake > liver
Score 5: markedly increased uptake > liver and/or new lesions related to lymphoma

Score X:
New areas of uptake unlikely to be related to lymphoma

Staging

Definitions of Stages in Hodgkin's Disease[2]

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A No systemic symptoms present

B Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1.

For comparison…NHL is slightly different (see below)

Stage III/IV, THERE IS NO MORE X or E (but you must document size).
There is no more A and B for NHL.
There is an S (for spleen).
IIIE = Now part of IV.

Staging

**Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)**

Stage	Involvement	Extranodal (E) status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky**	II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm	Not applicable
	Nodes above the diaphragm with spleen involvement	
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

Chemotherapy

CHOP – Cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone.
ABVD – Adriamycin (25), bleomycin (10), vinblastine (6), dacarbazine (325 mg/m²)
COPP - Cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone
BEACOPP – Bleomycin, etoposide, + COPP
EBVP - Epirubicin, bleomycin, vinblastine, and prednisone. Used in EORTC H7.
MOPP - Mechlorethamine, vincristine (Oncovin), procarbazine, prednisone
Stanford V (1989-) - essentially MOP/ABV + etoposide

MOP: mechlorethamine, vincristine (oncovin), prednisone
ABV: Adramycin, bleomycin, vinblastine.
Etoposide.
Uses decreased doxo, bleo, and mustard cumulative doses and is a shorter course over 12 wks.

TABLE 3: Chemotherapeutic regimens used for the treatment of Hodgkin lymphoma

Regimen	Dosage and schedule	Frequency
MOPP		
Mechlorethamine	6 mg/m² IV on day 1	
Vincristine (Oncovin)	1.4 mg/m² IV on day 1 (maximum dose, 2.0 mg)	
Procarbazine	100 mg/m² PO on days 1–7	Repeat cycle
Prednisone[a]	40 mg/m² PO on days 1–14	every 28 days.
ABVD		
Doxorubicin (Adriamycin)	25 mg/m² IV on days 1 and 15	
Bleomycin	10 mg/m² IV on days 1 and 15	
Vinblastine	6 mg/m² IV on days 1 and 15	Repeat cycle
Dacarbazine	375 mg/m² IV on days 1 and 15	every 28 days.
BEACOPP		
Bleomycin	10 mg/m² IV on day 8	
Etoposide	100 mg/m² (200 mg/m²)[b] IV on days 1–3	
Doxorubicin (Adriamycin)	25 mg/m² (35 mg/m²)[b] IV on day 1	
Cyclophosphamide	650 mg/m² (1,250 mg/m²)[b] IV on day 1	
Vincristine (Oncovin)	1.4 mg/m² IV on day 8[c]	
Procarbazine	100 mg/m² PO on days 1–7	
Prednisone	40 mg/m² PO on days 1–14	Repeat cycle
G-CSF from day 8		every 21 days.
Stanford V		
Doxorubicin	25 mg/m² IV on days 1 and 15	Repeat cycle
Vinblastine	6 mg/m² IV on days 1 and 15	every 28 days for
Mechlorethamine	6 mg/m² IV on day 1	a total of 3 cycles.
Vincristine[d]	1.4 mg/m² IV on days 8 and 22	Radiotherapy to
Bleomycin	5 U/m² IV on days 8 and 22	initial sites ≥ 5 cm
Etoposide	60 mg/m² IV on days 15 and 16	(dose: 36 cGy).
Prednisone[e]	40 mg/m² PO every other day	

[a] In the original report, prednisone was given only in cycles 1 and 4.
[b] Increased dose for escalated BEACOPP
[c] Maximal dose of 2 mg
[d] Vinblastine dose was decreased to 4 mg/m² and vincristine dose to 1 mg/m² during cycle 3 for patients ≥ 50 years of age.
[e] Tapered by 10 mg every other day starting at week 10
G-CSF = granulocyte colony-stimulating factor

PRINCIPLES OF SYSTEMIC THERAPY
RELAPSED OR REFRACTORY DISEASE

Relapsed/Refractory Disease

	Second-Line Options[c] (in alphabetical order)	Subsequent Options[c,d] (in alphabetical order)
CHL	• Brentuximab vedotin[1] • Brentuximab vedotin + bendamustine[2] • Brentuximab vedotin + nivolumab[3] • DHAP (dexamethasone, cisplatin, high-dose cytarabine)[4,5] • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)[6,7,8] • Gemcitabine/bendamustine/vinorelbine[9] • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[10] • ICE (ifosfamide, carboplatin, etoposide)[5,11] • IGEV (ifosfamide, gemcitabine, vinorelbine)[12] • Pembrolizumab[25,26] (for patients not candidates for transplant)	• Bendamustine[13] • Bendamustine + carboplatin + etoposide[14] • C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) • Everolimus[15] • GCD (gemcitabine, carboplatin, dexamethasone)[16,17] • GEMOX (gemcitabine, oxaliplatin)[18] • Lenalidomide[19] • MINE (etoposide, ifosfamide, mesna, mitoxantrone)[20] • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)[21,22] • Nivolumab[23,24] (see indications below) • Pembrolizumab[25,26] (see indications below)
NLPHL[d]	• R (rituximab)[b] + DHAP[4,5] • R[b] + ESHAP[6,7,8] • R[b] + ICE[5,11] • R[b] + IGEV[12] • R[b] + Bendamustine[27] • If not previously used: ▸ R[b]-CHOP[28] ▸ R[b]-ABVD[29] ▸ R[b]-CVP[30]	

General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed/Refractory CHL[e,f]
- **CPI are recommended for any patients with CHL that has relapsed or progressed after autologous HSCT ± brentuximab vedotin.[31]**
- **CPI are also an option for patients with relapsed/refractory CHL who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy.**
- **Post-allogeneic transplant, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic transplantation; CPI should be used with caution before allogeneic transplantation due to increased risk of GVHD (graft-versus-host disease) and other immunologic complications.**

Radiation:

PRINCIPLES OF RADIATION THERAPY

General Principles

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced RT technologies such as intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), breath hold or respiratory gating, and/or image-guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important OARs such as the heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. For optimal mediastinal treatment planning, organs/tissues to be contoured should include the lungs, heart, coronary arteries, and left ventricle.
- The demonstration of significant dose-sparing for these OARs reflects best clinical practice, as it reduces the risk of late complications from normal tissue damage. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- In mediastinal Hodgkin lymphoma, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion and minimize dose to OARs are essential, especially deep inspiration breath-hold techniques, respiratory gating, and image-guided RT during treatment delivery. Breath-hold techniques have been shown to decrease incidental dose to the heart and lungs in many disease presentations.
- Although the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, the "low-dose bath" to normal structures such as the breasts must be considered in choosing the final radiation therapy technique. In any case, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound, and other imaging modalities facilitate target definition. Image guidance may be required to provide assurance of accurate daily delivery.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to develop. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

Involved-Site Radiation Therapy (ISRT) Dose

- Combined Modality Therapy
  - Non-bulky disease (stage I–II): 20[a]–30 Gy (if treated with ABVD); 1.5–2.0 Gy per fraction
  - Non-bulky disease (stage IB–IIB): 30 Gy; 1.5–2.0 Gy per fraction
  - Bulky disease sites (all stages): 30–36 Gy; 1.5–2.0 Gy per fraction
  - Sites of partial response to chemotherapy: 36–45 Gy
- ISRT Alone (uncommon, except for NLPHL)
  - Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5–2.0 Gy per fraction
  - Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT for NLPHL includes extension to clinically relevant initially uninvolved nodes.
- Palliative RT: 4–30 Gy

[a] A dose of 20 Gy following ABVD x 2 is sufficient if the patient has non-bulky stage I–IIA disease with an ESR <50, no extralymphatic lesions, and only one or two lymph node regions involved. See HODG-B for definition of nodal sites according to GHSG.

Expansions and Definitions

- Used to be the only curative treatment for HL → continues to play a great role.

- INRT: (Prechemo GTV + post-chemo GTV) + NO expansion + carve off post-chemo planning CT normal structures = INRT CTV.
  To do this you MUST do prechemo GTV in TREATMENT POSITION.
-
- ISRT: (Prechemo GTV + post-chemo GTV) + 1.5 cranial caudal expansion ALONG LYMPH PATTERN OF SPREAD = ISRT CTV. In the transverse radial expansion, this is debatable. Usually, 6-8 mm if mediastinal. Neck is 4 mm. All expansions are based on potential lymphatic spread. Your pre-chemo GTV may be bigger than ISRT CTV. Why? Because your ISRT CTV must carve off like muscle, and bone, etc.

- Unless your pre-chemo scans are in treatment position, the most important thing your prechemo scans help you is determine cranial caudal expansion. If you muscle is involved, then you cannot carve off and spare muscle obviously. You must include it.

  Note: NODULAR PREDOMINANT while giving RT ALONE without CHEMO → EXPAND (not 1 or 1.5 cm) actually 2 cm because → Rationale: CTV needs to increase in size since you are not giving chemo.

    - **Mantle field** - suggestions per Fletcher's textbook, 3rd edition.
        - Place isocenter midway between superior and inferior edges. Usually is near or slightly below the suprasternal notch.
        - Borders: Superior - Midpoint of chin, along mandible, 2-3 cm above tip of mastoid. Inferior - near diaphragm, ~4 cm above xiphoid. Inferior axillary - 4th costochondral junction. Include ~1 cm of lung in lower axilla and 2-4 cm of lung in upper axilla. Lateral axillary - junction of lateral margin of pectoralis with deltoid. Exclude humeral heads. Mediastinum / hilum -
        - Shield: larynx - thyroid notch to cricoid.
        - Superior border of the PA field can be lowered to avoid irradiation of the oral cavity and cerebellum. Place border at thyroid notch.
    - **Modified mantle / mini-mantle** - includes mediastinum, bilateral hila, supraclavicular. Excluded axilla and neck/occipital unless bulky disease present. From larynx to T10-12
        - Used in Stanford V protocol - PMID 7537796
    - **Waldeyer's ring (typically for NHL)** - Lateral fields matched to lower neck field.
        - Borders: Inferior - thyroid notch. Superior - 1 cm above zygomatic arch. Posterior - tragus, then posterior to sternocleidomastoid muscle. Anterior - orbital rim posteroinferiorly to 2nd molar and then forward along the mandible.
        - Lower neck field: Superior - matches inferior border of lateral fields. Midline larynx shielding from thyroid notch to 1-2 cm below cricoid. Laterally to junction of trapezius with clavicles. Inferiorly 1-2 cm below clavicles.
    - Para-aortic - top of T11 to bottom of L4
    - Inverted Y - includes para-aortic + iliac + inguinal
    - **Total nodal irradiation (TNI)** - Mantle followed by Inverted Y and spleen (usually after a break of 2-3 weeks between mantle and inverted Y).
    - **Sub-total nodal irradiation (STNI)** - Mantle plus para-aortic + spleen. Excludes iliac + inguinal. Often not used in females because of concern for fertility.
    - **Involved field (IFRT)** – Historic technique.:
        - Involved field recommendations:
            - Mediastinal disease - treat mediastinum + SCLV
            - SCLV disease - treat ipsilateral neck
    - Involved site radiotherapy
    - Involved node radiotherapy

- Dose
    - Typically for early-stage favorable following C 20-30 Gy / 10-15 fx.
    - Early-stage unfavorable following C 30 Gy / 15 fx
    - Bulky disease 30-36 Gy / 15-20 fx.
    - Advanced disease residual 30-36 / 15-20 fx.

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  - **Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT for NLPHL includes extension to clinically relevant initially uninvolved nodes.**
- **Palliative RT: 4–30 Gy**

NOTE: A retrospective study of 734 female Hodgkin lymphoma patients demonstrated that the 20-year estimate risk of secondary breast cancer was 7.5% after mantle field radiation therapy compared to 2.2% after chemotherapy only. References: Conway JL, et al. Int J Radiat Oncol Biol Phys, 2017 Jan 1, Page 35-41.

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

Organ at Risk		Dose Recommendation (1.5-2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA[c]	Xerostomia[18,19]
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA[c]	Xerostomia[20]
	Oral Cavity (surrogate for minor salivary glands)	Mean <11 Gy	Xerostomia, dysgeusia, oral mucositis[20]
	Thyroid	V25 Gy <63.5% Minimize V30 Gy	Hypothyroidism[21]
	Lacrimal glands	V20 Gy <80%	Dry eye syndrome[22]
	Larynx/Pharyngeal constrictors	Mean <25 Gy	Laryngeal edema, dysphagia[23]
	Carotids	Ipsilateral: Avoid hotspots Contralateral: ALARA[c]	Carotid artery atherosclerosis
Thorax	Heart	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Major adverse cardiac events[d,24-27]
	Aortic and mitral valves	Dmax <25 Gy	Valvular heart disease[25,28,29]
	Tricuspid and pulmonic valves	Dmax <30 Gy	
	Left ventricle	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Heart failure[25,30]
	Pericardium	D100 (heart) <5 Gy	Pericarditis[31]
	Coronary vessels	Avoid hotspots	
	Lungs	Mean dose <13.5 Gy V20 <30% V5 <55%	Pneumonitis[32]

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

Organ at Risk		Dose Recommendation (1.5-2 Gy/fraction)	Toxicity
Abdomen	Liver	Mean <15 Gy V20 <30% V30 <20%	Hepatic toxicity[35,36]
	Stomach	Dmax <45 Gy	Ulceration[37]
	Spleen	Mean <10 Gy; V5 ≤30% V15 ≤20%	Late infections[38] Lymphopenia[39]
	Pancreas	Minimize volume >36 Gy (especially to pancreatic tail)	Diabetes[40]
	Small Bowel	V15 <120 cc Dmax <45 Gy	Diarrhea[37] Obstruction, ulceration, fistula[37]
	Kidneys	Mean <8 Gy V10 <30% V20: <15% (recommended); <25% (acceptable)	Renal insufficiency[41,42]
Other	Bone marrow[e]	V5: ALARA[c] V10 < 50% V25 < 25%	Acute cytopenias[43,44] Chronic cytopenias[45]
	Long Bone	V40 < 64%	Fracture[46]

SECONDARY MALIGNANCIES[f]

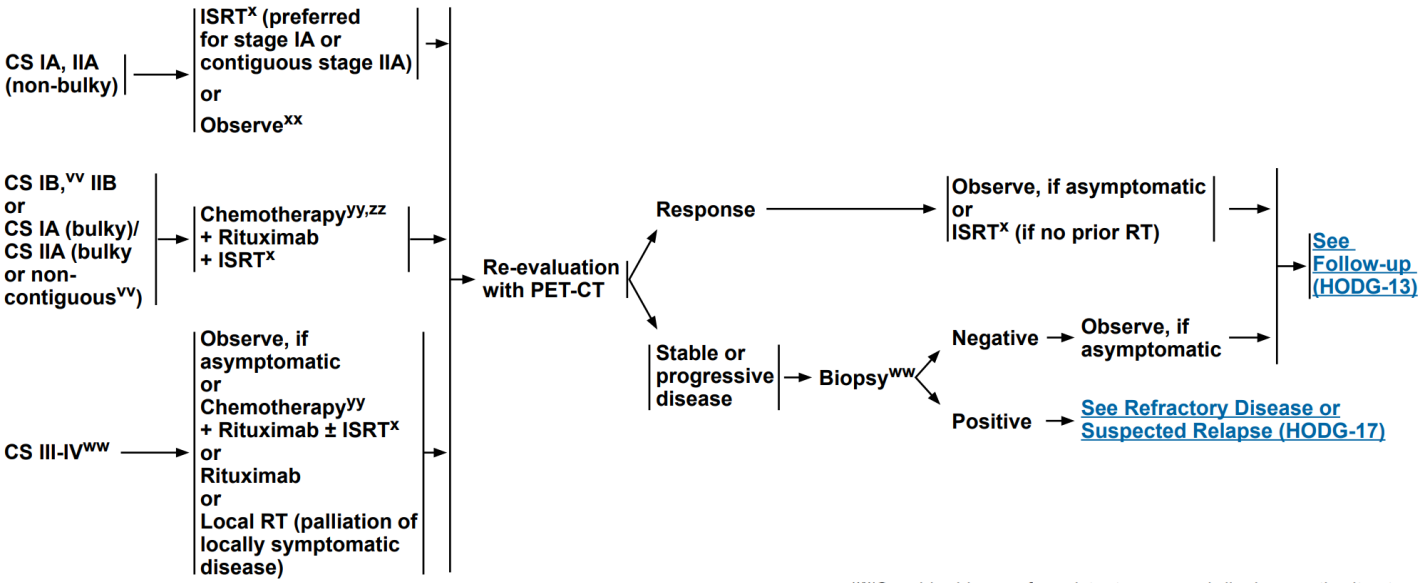
Organ at Risk	Dose Recommendation (1.8-2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy	Breast cancer (adenocarcinoma)[50]
Esophagus	Minimize volume >30 Gy	Esophagus cancer[51]
Stomach	Minimize volume >25 Gy	Stomach cancer[52]
Pancreas	Minimize volume >5-10 Gy	Pancreas cancer[53]

Nodular Lymphocyte Predominant

≈ Follicular

CLINICAL PRESENTATION:
Nodular Lymphocyte-Predominant Hodgkin Lymphoma[i]

PRIMARY TREATMENT



[i]NLPHL has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL. Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma. Data suggest outcomes differ for typical immunoarchitectural patterns (A/B) versus variant patterns (C/D/E/F).

[x]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[vv]For select patients with CS IB, or CS IIA non-contiguous disease, ISRT alone may be an option.

[ww]Consider biopsy of persistent or new subdiaphragmatic sites to rule out transformation.

[xx]Observation may be an option for stage IA patients with a completely excised solitary lymph node. See Follow-up (HODG-13).

[yy]See Principles of Systemic Therapy (HODG-B 2 of 4).

[zz]Generally a brief course of chemotherapy (3–4 months) would be given with radiation therapy.

Radiation alone is a good recommendation of early stage favorable non-bulky NLPHL.

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens

Nodular Lymphocyte-Predominant Hodgkin Lymphoma
• The most common chemotherapies used at NCCN Member Institutions for NLPHL are listed below.[a]

Regimens and References

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab[b]

Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood 2011;118:4585-4590.

Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's Lymphoma? J Clin Oncol 2010;28:e8.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab[b]

Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood 2017;130:472-477.

CVP (cyclophosphamide, vinblastine, prednisolone) + rituximab[b]

Shankar A, Hall GW, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma - an Anglo-French collaborative report. Eur J Cancer 2012;48:1700-1706.

Rituximab[b]

Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. Blood 2013;122:4182-4188.

Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. J Clin Oncol 2014;32:912-918.

Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008;111(1):109-111.

Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 2011;118:4363-4365.

Eichenauer DA, Plutschow A, Fuchs M, et al. Long-term course of patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma: A report from the German Hodgkin Study Group. J Clin Oncol 2015;33:2857-2862.

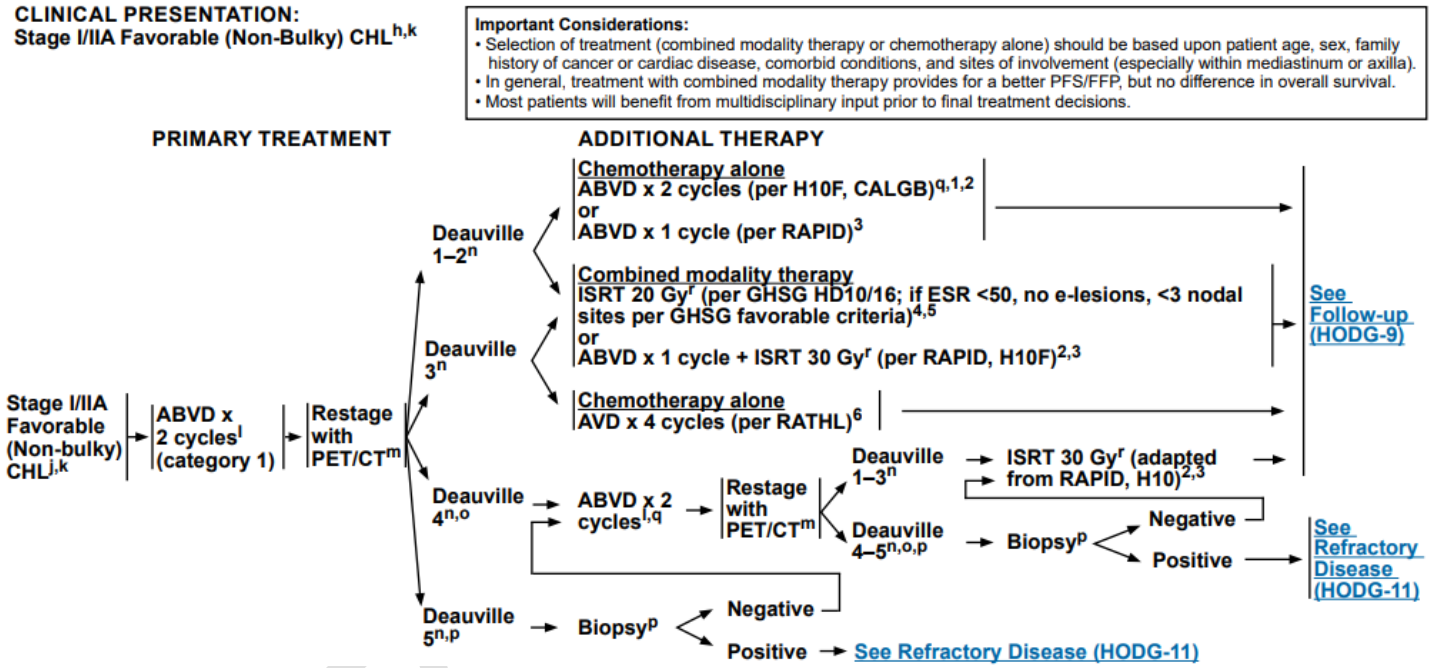
HL Treatment Chart 2021

HL	Risk Factors	Primary TX	Lugano Response	Consolidation
Limited Stage I-II	Favorable, non-bulky	ABVD x 2 * Neg 1-3, Pos 4	If Negative *	ISRT **20 Gy (only GHSG HD10)** **Unique** ABVD x 1 → ISRT **30 Gy** (All others) **Unique**
		~~ABVD x 2 (no RT)~~		
	Unfavorable, non-bulky	ABVD x 2 *"2+2" eBEACOPP / ABVD only! Age < 60, ECOG < 2.* *(HD 17 - no RT option)* ** Neg 1-2, Pos 3-4.*	If Positive *	ABVD x 2 → PET→ **(1-3) ISRT 36-45 Gy** or C±RT **escBEACOPP x 2** → PET→ **(1-3) ISRT 36-45 Gy** or C±RT → (4-5) Biopsy See NR (5)
			If NR (5)	Biopsy - → see Positive * Biopsy + → See Relapse /Refractory *or escBEACOPP x 2 → PET → evaluate*
			If no RT…	Neg (1-2) → ABVD (total 3-4) or obs. Pos (3) → ABVD (total 6) Pos (4) → eBEACOPP (total 6) NR (?4- **5**) → see Relapse / Refractory
	BULKY	ABVD x 2 *"2+2" eBEACOPP / ABVD Age < 60 (HD 14)* * Neg 1-3, Pos 4	if Negative *	ABVD x 2 → ISRT 30-36 Gy AVD x 4 → **± ISRT 30-36 Gy**
			if Positive *	ABVD x 2 → PET → (1-3) ISRT 36-45 Gy escBEACOPP x 2 → PET → (1-3) escBEACOPP x 1 → (4-5) Biopsy See NR (5)
			if NR (5)	Biopsy - → see Positive * Biopsy + → See Relapse /Refractory *or escBEACOPP x 2 → PET → evaluate (RT)*
Advanced Stage III-IV	Preferred	ABVD x 2 * Neg 1-3, Pos 4	if Negative	**AVD** x 4 → **± ISRT 30 Gy** **Unique**
			if Positive	ABVD x 2 → PET → *evaluate (**C→**RT)* escBEACOPP x 2 → PET → *evaluate (**C→**RT)*
	Select Cases (Age < 60)	*escBEACOPP x 2* *Brentuximab V. + AVD*	if NR (5)	Biopsy - → see Positive * Biopsy + → See Relapse /Refractory *or escBEACOPP x 2 → PET → eval (**C→**RT)*
Relapse Refractory 10-20% of Stg I-II 15-30% of Stg III-IV 10-15% RR pts do NOT respond to therapy.	**Must Biopsy to Prove Disease**	<u>If planned ASCT…</u> HDT Chemo	CR (1-3)	1. ASCT + post ISRT 36-45 Gy 2. Clinical Trial → All followed by BV maintenance.
			PR (4)	**1. 2nd line Salvage → Repeat PET** 2. Consider pre or post ISRT 36-45 Gy 3. ± Immediate ASCT ± ISRT **w/o 2nd line chemo** 4. Clinical Trial → All followed by BV maintenance.
			No Δ or Progressive	Institutional Protocol. No real guidance.
		<u>If NOT ASCT candidate…</u> HDT Chemo Palliative ISRT Clinical Trial	Any	Follow-up CT C/A/P q 6 months. Clinical Trial, Palliative ISRT, etc.

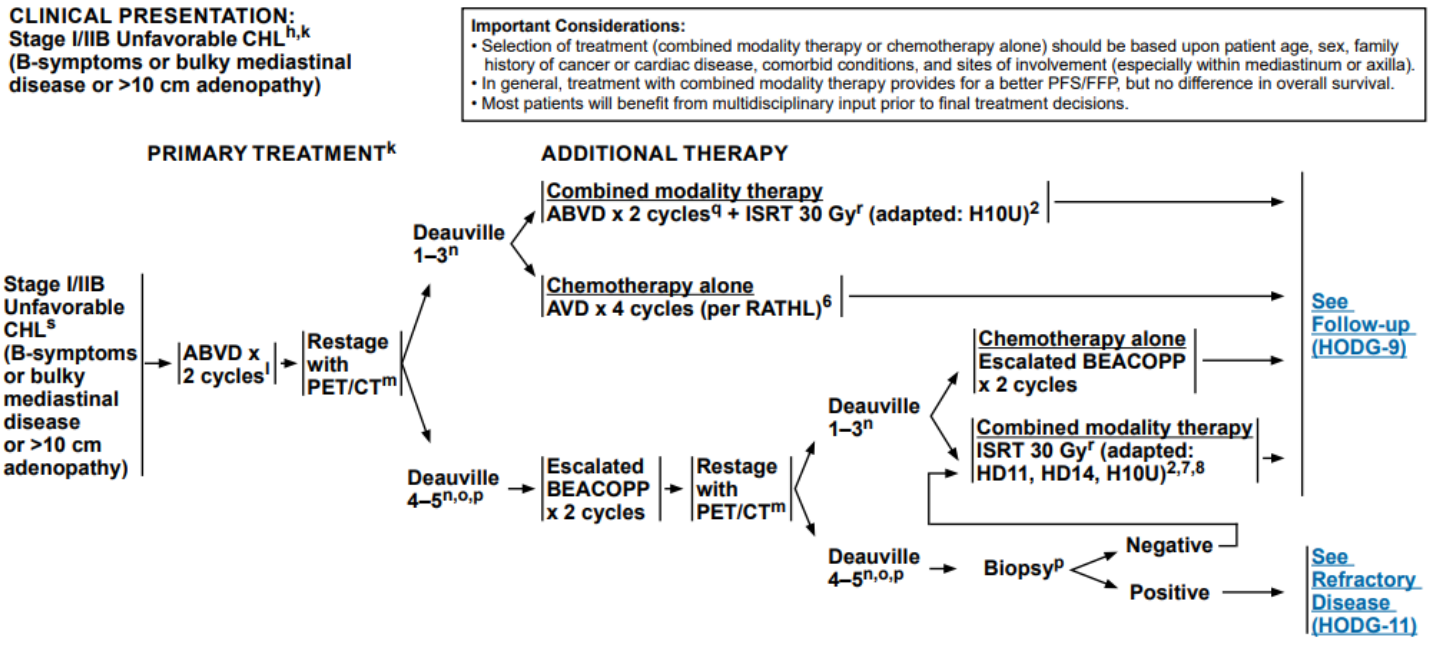
Early-Stage HL: Favorable (Stage I – II without risk factors).

Overview:

- Initially, high cure rate was achieved through prophylactic extended field radiation, to adjacent areas next to involved regions.
- Since staging laparotomy showed infradiaphgragmatic occult disease in ~20% patients with supradiaphragmatic disease, prophylactic radiation was extended to para-aortic fields or all lymph node areas. Spleen was either removed or irradiated.
- Local and distant relapses continued to occur despite extensive RT; combined chemotherapy (MOPP) and radiation (EFRT) was shown to result in 80-90% 5-year survival. Randomized trials showed that combined chemotherapy + EFRT and combined chemotherapy + IFRT was superior to RT alone.
- Because maximal combined treatment resulted in significant toxicity (late sepsis in splenectomy patients, second malignancies, heart and lung disease, and sterility), efforts were undertaken to reduce radiation field size after administration of chemotherapy.
- German HD8 and EORTC H9 showed ABVD x4 cycles + IFRT 30 Gy as the superior approach for unfavorable disease over chemotherapy + EFRT.



For comparison…



Radiation Alone and Field Determination:

Princess Margaret Hospital: Gospodarowicz MK et al. IJROBP. 1992.
Retrospective. 250 patients. Stage cI-II with supradiaphragmatic disease; no adverse prognostic factors. Variety of radiation techniques (involved field, mantle, or extended field).
Conclusions: 90% cause-specific survival at 8-years with RT alone.

International HD Collaborative Group. **Metaanalysis** of 23 randomized trials. Specht L, JCO. 1998.
Outcome: More extensive RT ↓ risk of failure (31% vs. 43%, SS), but there was no impact on 10-year OS (77% vs 77%). Addition of chemotherapy ↓ risk of failure (15% vs. 33%), with no impact on 10-year OS (79% vs. 76%)
Conclusion: More extensive RT field or addition of chemo improve disease control, but have no effect on OS due to effective salvage. Less intensive primary treatment appears to achieve similar survival rates as more intensive treatment.

British Columbia. Campbell BA, JCO 2008.
Retrospective. 325 patients with limited-stage HD Stage (IA 29%, IIA 71%), treated with chemotherapy + RT. EFRT used 1989-1996 (39%), IFRT used 1996-2001 (30%), INRT used 2001-2005 (31%). INRT = prechemo nodal volume + margin ≤ 5 cm. No PET. Median F/U 6.7 years
Outcome: Relapse rate EFRT 3% vs. IFRT 5% vs. INRT 3% (NS). No marginal recurrences after INRT. 5-year PFS 97% and OS 95%. 10-year PFS 95% and OS 90%.
Conclusion: Reduction in field size to involved nodes + 5cm appears safe, without increased risk of recurrence

Standard Studies (The "7" "10s")

Major Studies: EORTC H10, GHSG HD10, UK RAPID, (G4)

GSHD HD7 **C ± RT**
←R→ 650 patients IA to IIB without risk factors | 1. 30 Gy EFRT + 10 Gy to the involved field | 2. Two cycles ABVD → same RT |.
7-year CR 94-95% (NS). 7-year OS 92-94% (NS).
7-year FFTF 67% vs. 88% (SS). Due mainly to ↑ relapses 22% vs. 3%. (SS). No patient treated with CMT experienced relapse before year 3.
Relapses were treated mainly with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, or with the combination cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD; treatment of relapse was significantly more successful in arm A than in arm B (P = .017). In total, there were 39 second malignancies, with 21 in arm A and 18 in arm B, respectively. The incidence was approximately 0.8% per year during years 2 to 9 and was highest in older patients (P < .0001) and those with "B" symptoms (P = .012).
CONCLUSION: CMT consisting of two cycles of ABVD plus EF-RT is more effective than EF-RT.

GHSG HD10 – 4 arm trial: ABVD x2 vs ABVD x4; IFRT 30 Gy vs 20 Gy RT = IFRT
←R→ 1131 patients. Stage I-II without risk factors.
Randomization 1. ABVD x4 cycles vs ABVD x2 cycles 2. IFRT 30 Gy vs IFRT 20 Gy. **1^{O} FFTF.**

[n]The GHSG HD10 trial did not use PET after ABVD x 2 cycles to define eligibility for ISRT. GHSG HD10 study: Engert A, et al. N Engl J Med 2010;363:640-652.

Engert, NEJM, 2010; Median F/U 7.5 years. **NOT A 2 x 2, but a FOUR ARM TRIAL**.
ABVD Outcome: NS 5-year OS, FFTF, or PFS between ABVD x 4 | ABVD x 2 (OS 97% vs 97%; FFTF 93% vs 91%; PFS 93% vs 91%).
IFRT Outcome: NS 5-year OS, FFTF, or PFS between IFRT 30 Gy | 20 Gy (OS 98% vs 97%, FFTF 93% vs 93%, PFS 94% vs 93%).
No difference when all 4 arms compared.
Toxicity: Grade III/IV: 51.7% ABVD x 4 | 33.2% ABVD x 2 (P<0.001). Grade III / IV: 8.7% 30 Gy IFRT | 2.8% 20 Gy IFRT (P<0.001).
Conclusion: Go with lower Tx. 2 cycles of ABVD followed by 20 Gy IFRT is the new standard for GHSG for early favorable HD.

Sasse JCO 2017.
10 years PFS and OS the same.
In HD 7 (which the also published the results) or HD 10, there is no difference in secondary malignancy with either subtotal RT vs combined CT+IFRT.

UK Rapid Non-inferiority Trial. RT = IFRT

420 randomized patients. Non-inferiority trial. Clinical stage IA (n = 200) or IIA (n = 402).
Since nodal sites is NOT an exclusion factor, about 35% have unfavorable disease.
3 cycles ABVD → PET → NEGATIVE → **1. 30 Gy IFRT** (a small # did NOT get RT) or **2. Obs** (2 pt got RT)
→ POSITIVE (Deauv 3-5) → 4th cycle of ABVD + IFRT.

Results: PET findings were negative in 426 of these patients (74.6%). 60 mo. FU, 8 disease progression in the radiotherapy group, and 8 patients had died (3 with disease progression, 1 of whom died from Hodgkin lymphoma); there had been 20 instances of disease progression in the group with no further therapy, and 4 patients had died (2 with disease progression and none from Hodgkin lymphoma).
Note: 32% were unfavorable by German standard and 31% had ≥ 3 nodal sites.

Radford, NEJM 2015.
3-yr PFS 94.6% RT vs. 90.8% obs (intent to treat p=0.16) 97% vs 90.8% (per protocol p=0.02)
In RT arm, 26 (12%) did NOT get RT. 20 declined RT, 5 died, 1 pneumonia
In the No TX arm, 2 received RT.
PET Positive 3-year OS 97-99% PET Positive 3-year OS 87.6%
Conclusion: Non-inferior. Pet-neg after chemo possibly benefit from RT to reduce risk of relapse.

Deauville criteria is INDEPENDENT READS. But they are not blinded. They just sit in a room and all agree.

Cutter, JCO 2021 30-year CV risk study
CV dose varied widely and was negligible for those with disease outside the neck or mediastinum.
Over half of patients had a mean heart dose < 1 Gy and ⅔ had a MHD < 5 Gy.
For the entire cohort, the average 30-year risk of CVD mortality 5.02%.
Baseline risk (3.52%), anthracycline (0.94% excess risk), and IFRT risk (0.56%).
Just as CV dose varied widely, excess CVD mortality risk from IFRT ranged from 0.01% to 6.79%.
Two-thirds of patients had < 0.5% excess CVD mortality risk at 30 years from IFRT.
And of note, nearly ⅔ of patients actually had a higher excess CVD mortality risk from anthracyclines than from IFRT.
The point is that a majority of HL patients could derive disease benefit from radiation with minimal ↑ in excess cardiovascular risk.
TBL: Among patients treated with radiation for early stage HL, "the magnitude of [CVD mortality] risk varies widely and, for a majority of patients, the benefit of reduced HL relapse substantially outweighs the risk of CVD.

Stanford G4.
Single arm 87 patients Prospective. For non-bulky early stage HL. Sage I-IIA supradiaphragmatic HL. Stanford V chemotherapy was administered for 8 weeks → RT 30 Gy to involved fields (IF). Treatment 12 weeks → 8 weeks (12 weeks is standard for early stage UNFAVORABLE).

Advani, Ann Oncol 2013.
At a median follow-up of 10 years, FFP, DSS and OS are 94%, 99% and 94%, respectively.
Therapy was well tolerated with no treatment-related deaths.
CONCLUSIONS: Mature results of the abbreviated Stanford V regimen in nonbulky early-stage HL are excellent and comparable to the results from other contemporary therapies.

Lower dose of Bleomycin = great! But the mustard causes infertility Mechlorethamine.
NOTE: NO OS why? Salvage. Only 10% progression and do not response. Of those 50% are salvaged with stem cells and still cure.

EORTC / GELA H10: Early PET guided treatment in supradiaphragmatic stage I/II Hodgkin lymphoma.

←R→ 1950 patients **RT = INRT**

Favorable: randomized to:

1. Standard arm: ABVD x 2 → PET → Any PET Result → ABVD x 1 + INRT 30 Gy (+6 Gy boost for residual lesions).
2. Experimental: ABVD x 2 → PET. ~~If PET negative → ABVD x 2 additional cycles (total 4) without RT.~~ If PET positive → BEACOPP x 2 + INRT 30 Gy (+6 Gy boost).

Unfavorable: randomized to:

1. Standard arm: ABVD x 2 → PET → Any PET Result → ABVD x 2 + INRT 30 Gy (+6 Gy boost).
2. Experimental: ABVD x 2 → PET. ~~If PET negative → ABVD x 4 additional (total 6) without RT.~~ If PET positive → BEACOPP x 2 + INRT 30 Gy (+6 Gy boost)

ABVD q4 weeks	BEACOPP escalated q3 weeks
Doxorubicin 25 mg/m2 i.v. day 1 and 15	Cyclophosphamide 1250 mg/m2 i.v. day 1
Bleomycin 10 mg/m2 i.v./i.m. day 1 and 15	Doxorubicin 35 mg/m2 i.v. day 1
Vinblastine 6 mg/m2 i.v. day 1 and 15	Vincristine 1.4 mg/m2 i.v.(max.2mg) day 8
Dacarbazine 375 mg/m2 i.v. day 1 and 15	Bleomycin 10 mg/m2 i.v./i.m. day 8
	Etoposide 200 mg/m2/ i.v. day 1 to 3
	Procarbazine 100 mg/m2 orally day 1 to 7
	Prednisone 40 mg/m2 orally day 1 to 14
	G-CSF 5 mcg/kg s.c. day 9 to recovery leukocytes>1.0x109

Interim results; Raemaekers, JCO 2014.

Favorable pts (441) 85.8% had negative early PET. 9 events (Exp. group) vs 1 event (Standard). 1-yr PFS 94.9% vs 100% (SS).

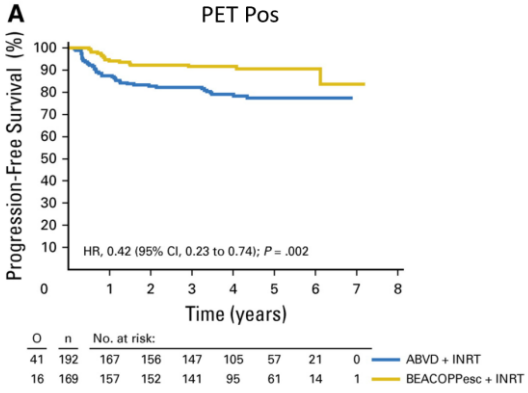
Unfavorable pts (683): 74.8% had negative early PET. 16 events vs 9. 1-yr PFS 94.7% vs 97.3% (SS).

Stopping random assignment for early PET–negative patients (aka you cannot be randomized to NO RT anymore).

Conclusion: "On the basis of this analysis, combined-modality treatment resulted in fewer early progressions in clinical stage I/II HL, although early outcome was excellent in both arms. The final analysis will reveal whether this finding is maintained over time."

REAL TAKEAWAY: Omitting Radiotherapy in Early PET-Negative Stage I/II Hodgkin Lymphoma = ↑ Risk of Early Relapse.

If PET-, 5-year PFS ABVD alone 89.6% vs. ABVD+INRT 92.1% ("NOT non-inferior").



Andre JCO 2017. **ALL no Δ OS**

Analyzed PET-positive population (361, 18.8% PETs were +).

LUMPED favorable and unfavorable TOGETHER.

5-year PFS, ABVD 77.4% vs BEACOPP 90.6% (p = 0.002).

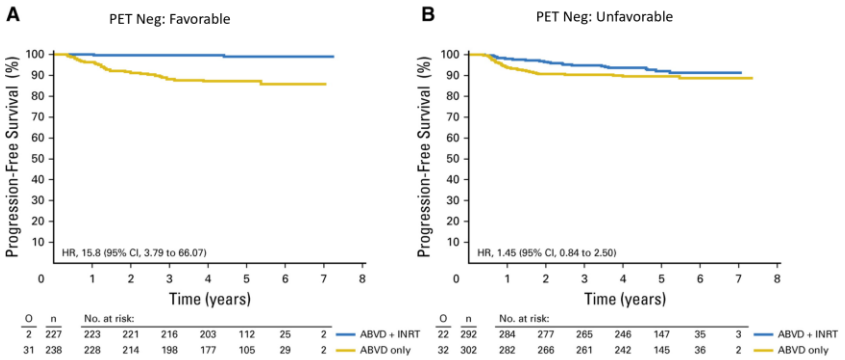
So, if you are just favorable, you really don't know if you should ABVD or BEACOPP. Perhaps the benefit is solely driven by unfavorable.

BEACOPPesc grade ≥3 toxicity, MUCH higher everything. Grade 3-4 neutropenia (50% v 30%), anemia (5% v. 0%), thrombocytopenia (20% v 0%), febrile neutropenia (24% v 0%).

Analyzed PET-negative population (1059 initial protocol + 505 tx per safety amendemnt). Enough patients to separate favorable and unfavorable.

FAVORABLE: 5-year PFS **ABVD+RT** 99% vs. **ABVD** 87% (SS).

UNFAVORABLE 5-year PFS **ABVD+RT** 92.1% vs. **ABVD** 89.6%
(non-inferiority margin was 2.1, but HR was only 1.45
∴ ABVD is "NOT NON-inferior" to IFRT)



Conclusion: When ePET + after two cycles of ABVD, switching to BEACOPPesc + INRT significantly improved 5-year PFS.

In ePET-negative patients, noninferiority of ABVD only could **not be demonstrated**: risk of relapse is increased when INRT is omitted, especially in patients in the F group.

OMISSION of RADIATION LEADS TO ↑ RISK OF PROGRESSION, but no Δ OS.

De-Escalation HD 16

GHSG HD 16
←R→ 1150 Early Stage Favorable HL Phase III. | 1. ABVD x 2 → 20 Gy IFRT | 2. ABVD x 2 → PET-guided and no RT if PET-neg 1-2, and yes PET if 3-5 |.
1^{o} exclude inferiority of 10% or more in 5-year progression-free survival (PFS) of ABVD alone compared with CMT in a per-protocol analysis. Noninferiority margin for hazard ratio, 3.01.

Fuchs, JCO 2019.
Among 628 PET 1-2-negative 5-year PFS CMT 93.4% vs. ABVD alone 86.1%. 5-year OS 98.1% vs. 98.4%.
Among 693 assigned to CMT, 5-year PFS PET-neg-1-2 93.2% vs. PET-pos->3 88.4%.
When using the more common liver cutoff (Deauville score, 4) for PET-2 positivity, the difference was more pronounced (5-year PFS, 93.1% [95% CI, 90.7% to 95.5%] *v* 80.9% [95% CI, 72.2% to 89.7%]; *P* = .0011).
Conclusion: In early-stage favorable HL, a positive PET after two cycles ABVD indicates a high risk for treatment failure, particularly when a Deauville score of 4 is used as a cutoff for positivity. In PET-2-negative patients, radiotherapy cannot be omitted from CMT without clinically relevant loss of tumor control.

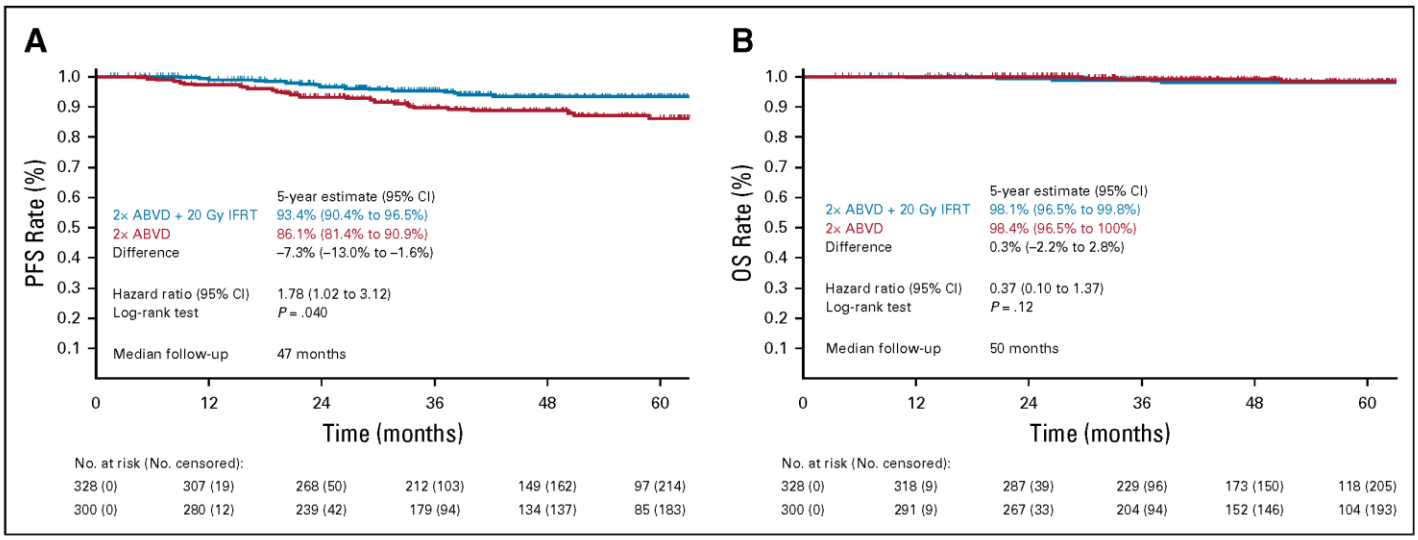
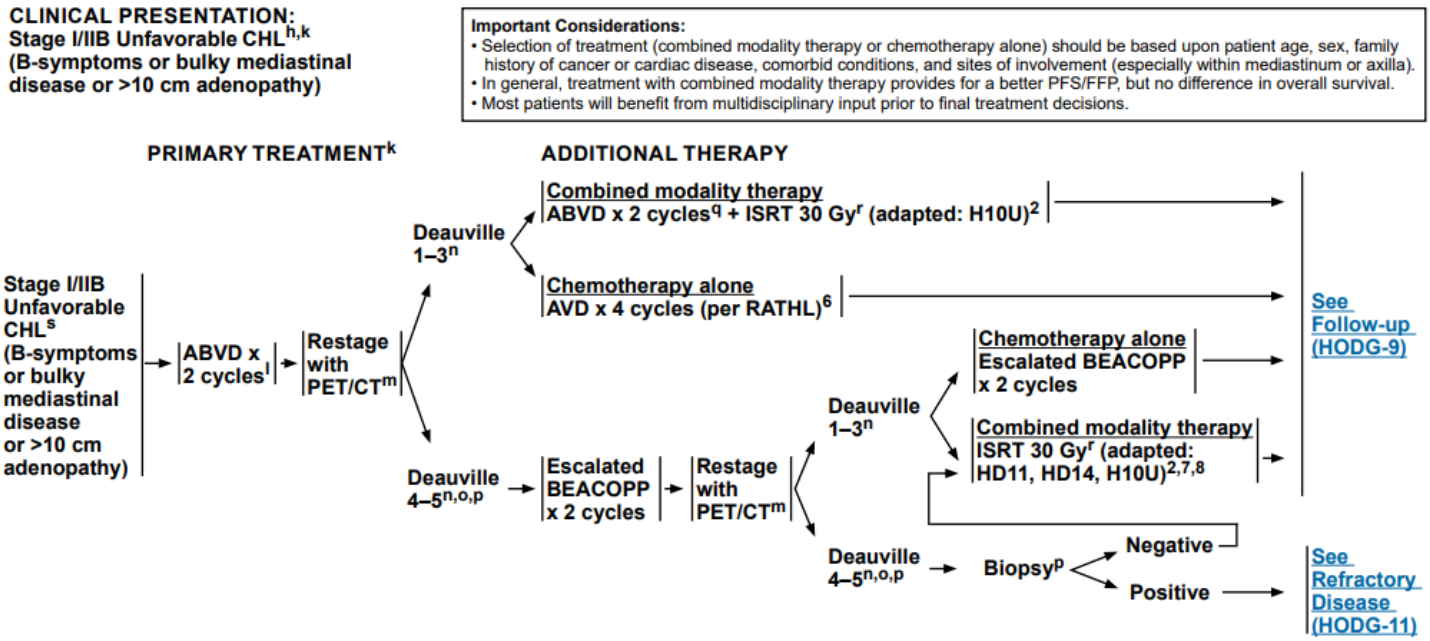


FIG 2. Kaplan-Meier estimates for the PET-2 (positron emission tomography after two cycles of chemotherapy) –negative per-protocol population. (A) Progression-free survival (PFS). (B) Overall survival (OS). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IFRT, involved-field radiotherapy.

Baues, IJROBP 2019 Pattern of Recurrence Median 47-month follow-up.
Evaluation of recurrences either in-RT field or out-of-field. Overall, 328 PET neg → chemo+RT vs. and 300 PET neg → PET-directed.
5-year IF-relapses 2.4% → 10.5% without RT (*P* = .0008).
5-year OF-relapses Equivalence 4.1% vs. 6.6% (*P* = .54).
There was no grade 4 toxicity observed during IF-RT, and incidence of second primary malignancies was similar in both groups.
Conclusions PET-negative patients of the HD16 study showed no significant toxicity after 20 Gy IF-RT, and we demonstrated that omission of IF-RT resulted in more, **particularly local**, **recurrences**. Therefore, consolidation IF-RT should still be considered as standard therapy in this setting.

Early-Stage HL: Unfavorable

- **Major Studies to Know:**
  HD 11, HD 14, EORTC H10 (Again).



Laparotomy Study:

EORTC H6F. Carde 1993.
262 patients clinical stage I-II and favorable factors (1-2 sites, no bulky disease, ESR < 50 or < 30 if B symptoms).
1. No Laparotomy (clinicaly staging) with STLI (Mantle + PA RT 40 Gy).
2. Laparotomy → if negative → mantle 40 Gy.
   If positive → ? CRT.

Outcomes: In patients undergoing lap, 33% found lap (+). 6-year FFP laparoscopy + Mantle 83% vs Mantle + PA 78% (NS); OS 89% vs 93% (NS)
Conclusions: Staging laparotomy before STNI may be deleted even in favorable patients at no cost to survival or FFP.
In unfavorable patients, ABVD achieved better results than MOPP, at lower hematologic and gonadal cost.

ABVD vs MOPP

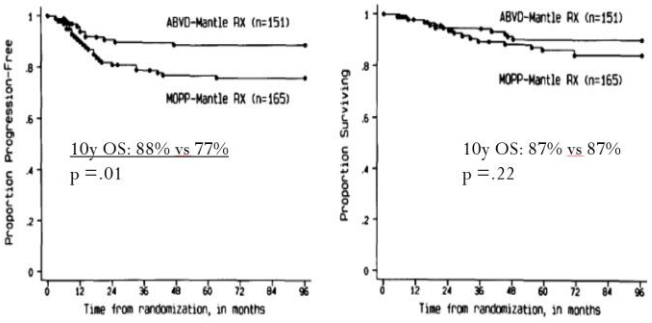


Fig 4. EORTC H6U trial: progression-free survival by treatment group. Log-rank test: P = .01.

Fig 5. EORTC H6U trial: overall survival by treatment group. Log-rank test: P = .22.

- ABVD with better 10y DFS: 88% vs 77% (p=.01); not OS

EORTC H6-Unfavorable -- MOPP x6 + Mantle RT vs ABVD x6 + Mantle RT
Randomized. 316 patients, unfavorable prognosis (at least one of: >2 nodal areas, bulky, B-symptoms, elevated ESR). No surgical staging.
1. MOPP x3 → Mantle RT → MOPP x3
2. ABVD x3 → Mantle RT → ABVD x 3.

Carde, JCO 1993. Median F/U 5.3 years
6-year FFP MOPP vs ABVD 76% vs 88% (SS);
6-year OS 85% vs 91% (NS)
Toxicity: ABVD better gonadal, but worse pulm (both gender) same <3.
Conclusion: In combination with mantle RT, **ABVD superior to MOPP**.
∴ DON'T USE MOPP. ABVD is standard.

EFRT vs IFRT (The "8s" HD8, H8 U/F)

Milan (Italy) - ABVD x 4 cycles plus subtotal nodal vs involved field RT **REMOVES SUBTOTAL NODAL**.
136 patients. Stage I (**unfavorable**) or IIA (**favorable** or **unfavorable**), clinical staging.
Randomized ABVD x4 cycles → 1. STNI 2. IFRT. RT began 4 weeks after chemo and restaging. Dose CR 36 Gy, for PR/unconfirmed CR 40 Gy.
For STNI, 30.6 Gy to uninvolved mantle + para-aortic + spleen. Treated postchemotherapy volumes

Bonadonna, JCO 2004. Median F/U 9.7 years
Outcome: CR STNI 100% vs. IFRT 97%. 12-year FFP 93% vs. 94% (NS); 12-year OS 96% vs. 94% (NS)
Conclusion: ABVD + IFRT is feasible to use involved-field instead of more extensive RT.
3 patients 4.5% had secondary malignancy with STRT vs. 0 with IFRT. Not SS, but just FYI.
If complete remission on PET after ABVD, no difference with STNI and IFRT!
Remember, this study had PET after 4 cycles.

EORTC H8-U / H8-F – INRT vs STNI.
Randomized, 3 arms. 996 patients, Stage I-II supradiaphragmatic HD, **favorable and unfavorable** (Prognostic score using EROTC H7 criteria >=9).
H8-F (favorable): 1. MOPP-ABV x3 cycles + IFRT 2. STNI alone
H8-U (unfavorable): 1. MOPP-ABV x6 cycles + IFRT 2. MOPP-ABV x4 cycles + IFRT 3. MOPP-ABV x4 cycles + STNI
RT dose CR 36 Gy, PR 40 Gy.

Ferme. NEJM 2007. Median F/U 7.7 years
H8-F Outcome: 5-year EFS MOPP-ABV + IFRT 98% vs. STNI 74% (SS); **10-year OS 97% vs. 92% (SS)**
H8-U Outcome: 5-year EFS similar 84% vs. 88% vs. 87% (NS); **10-year OS 88% vs. 85% vs. 84% (NS)**.
Conclusion: Favorable disease chemo x3 + IFRT best. Unfavorable disease = Equivalent, so the least TX: chemo x4 + IFRT best.

GHSG HD8 (1993-98) -- COPP/ABVD x2 cycles plus EFRT vs IFRT
Randomized. 1064 patients, with **early stage unfavorable HD**. Clinical stages I-II with ≥1 risk factors + stage IIIA without risk factors.
Risk factors = large mediastinal mass, extranodal, massive splenic involvement, ↑ ESR, > 2 lymph node groups.
IIB may have only elevated ESR or more than 2 lymph node groups but no other risk factors.
Tx: COPP→ ABVD → COPP → ABVD → **1.** EFRT 30 Gy **2.** IFRT 30 Gy. A 10 Gy boost given to bulky disease.
Supradiaphragmatic EF RT was a mantle + PA + splenic hilum / spleen. Subdiaphragmatic EF RT was an inverted Y plus mini-mantle.

Engert, JCO 2003. Median F/U 4.5 years
Outcome: 5-year FFTF EFRT 86% vs. IFRT 84% (NS), 5-year OS EFRT 91% vs. 92% (NS). No Δ CR, PFS, relapse rate, death, and 2nd Ca.
Toxicity: Nausea/vomiting, pharyngitis, GI toxicity, leukopenia, and thrombocytopenia worse in EFRT arms
Conclusion: RT volume reduction from EFRT to IFRT produces similar results and less toxicity.

Klimm, Ann Oncol. 2007. Subset analysis. 89 patients age >60. Poorer risk profile.
Outcome: 5-year FFTF: EFRT 58% vs. IFRT 70% (SS), OS 59% vs. 81% (SS)
Toxicity: Grade 3-4 EFRT 26% vs. IFRT 9%
Conclusion: *Treatment with EFRT of elderly patients after chemo has negative impact on survival*.

Sasse, Ann Oncol. 2012. Epub2012. 10-year EFRT vs IFRT FFTF (80% vs 80%), PFS (80% vs 80%), OS (86% vs 87%). NS.

EORTC H9-U

←R→ 808 15-70 yo with supradiaphragmatic HL with at ≥ 1 RF (age ≥ 50, involvement of 4-5 nodal areas, medias/thoracic ratio ≥ 0.35, ESR ≥ 50 without B-symptoms or ESR ≥ 30 and B-symptom. Non-inferiority H9-U trial. Non-inferiority 10% for the Δ 5-year EFS.

1. Control: 6-ABVD-IFRT 2. Exp: 4-ABVD-IFRT 3. Exp: 4-BEACOPPbaseline-IFRT

Ferme, Eur J Cancer 2017.

5-year EFS 89.4% vs. 85.9% vs. 88.8%. = Non-inferior Δ 4.0%.

5-year OS all 93-94%.

CONCLUSIONS: The trial demonstrates that **4-ABVD followed by IFRT** yields high disease control in patients with early-stage HL and risk factors responding to chemotherapy. Although non-inferior in terms of efficacy, four cycles of BEACOPPbaseline were more toxic than four or six cycles of ABVD.

GHSG HD11. **Sister Trial to the GHSG HD 10** RT = IFRT

←R→ 1395 Kinda 2 x 2 / 4 arm.. N = 1395, Stage I/II, unfavorable per GHSG.

Randomize ABVD x 4 vs BEACOPP x 4 AND 20Gy vs 30Gy 2x2 Design: ABVD 30 (A); ABVD 20 (B); BEACOPP 30 (C); BEACOPP 20 (D)
RT 20-30Gy in 1.8 – 2Gy/fx

NOT powered for each arm individually, so they compared everything to ABVD x 4 to 30 Gy.

Also, 1^{O} FFTF

Eich, JCO 2010. median follow-up: 82 months)

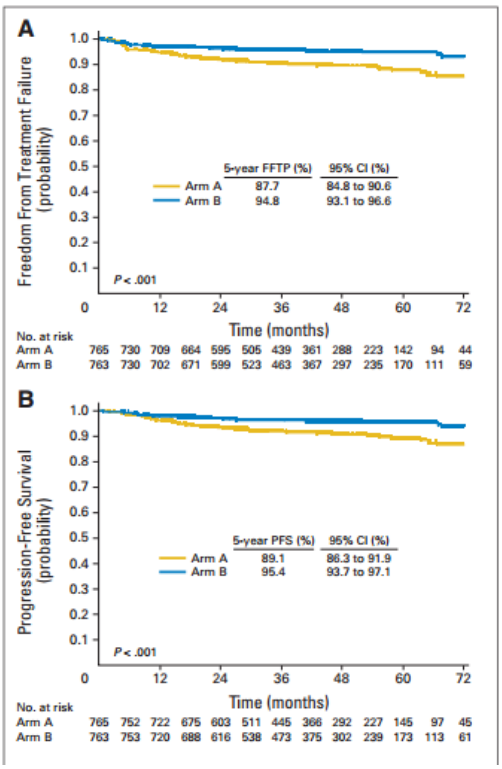
CR ~ 95% (all arms except ABVD ~ 93%). PR 1.1%; non-response <1%; 2.1% progression. **Relapse rate 9.7%**.

Toxicity: 20 Gy did have less mucositis, n/v, GI tract dysphagia. **BEACOPP was worse** (↑ Grade 3 tox and hospitality).

Conclusion: ***OS*** NO DIFFERENCE between the 4 arms of study

FFTF and PFS NO DIFFERENCE between ABVD+30Gy, BEACOPP+30Gy and BEACOPP+20Gy
ABVD+20Gy is NOT the same… ***decreased FFTF and PFS.***

CONCLUSION: Since BEACOPP had more toxicity and since ABVD+ 20 Gy is worse, standard is still ABVD + 30 Gy IFRT.



GHSG HD14. (Idea is, if you can based on HD 11 get away with only 20 Gy with Beacopp but not ABVD, maybe Beacopp does have some benefit). RT = IFRT

N = 1528, Stage I/II, **unfavorable**. **ALL PATIENTS < 60 yo.**

IA, IB, IIA + 1 of: Mass (≥ 1/3 thorax), >2 nodal areas, extra LN disease, ESR ≥ 50 or ≥30 if B sx.
IIB w/ +ESR or >2 nodes

EXCLUDED: B symptoms + (Extranodal or Bulky) = Treated according to Advanced.

←R→ **Also, 1^{O} FFTF**

1. escBEACOPP x2 cycles → ABVD x2 cycles ("2 + 2") → IFRT 30 Gy

2. ABVD x4 cycles → IFRT 30 Gy.

Study terminated early at 3rd interim analysis because of better outcomes seen in the 2+2 arm.

von Tresckow, JCO 2012.

More acute toxicity with 2+2 regimen (Grade 3 chemo from 50% → 80%), but no overall difference in treatment-related mortality or second malignancies.

Conclusion: For age < 60 yo, BEACOPP x 2 cycles followed by ABVD significantly improves tumor control (FFTF, PFS) in patients with early unfavorable HD.

FFTF ↑ PFS ↑ LC ↑
OS was the same.

	ABVD	BEACOPPesc
Relapse rate	8.40%	2.50%
2nd relapse rate	1.40%	0.40%
5y FFTF	87.70%	94.80%
5y PFS	89.10%	95.40%
5y OS	96.80%	97.20%

De-Escalation (The "17")

GHSG HD17

←R→ 1100 early-stage unfavorable HL (all histologies) **AGE < 60,** ECOG ≤ 2 | 1. 2+2 (eBEACOPP / ABVD) → 30 Gy I**F**RT | 1. 2+2 → PET-directed |.
PET-directed = 30 Gy I**N(ode)**RT only if after 2+2, PET was positive (Deauville ≥ 3).

Remember, for DE-ESCALATION, you want to be on the safe side…so Deauville 3 = positive.

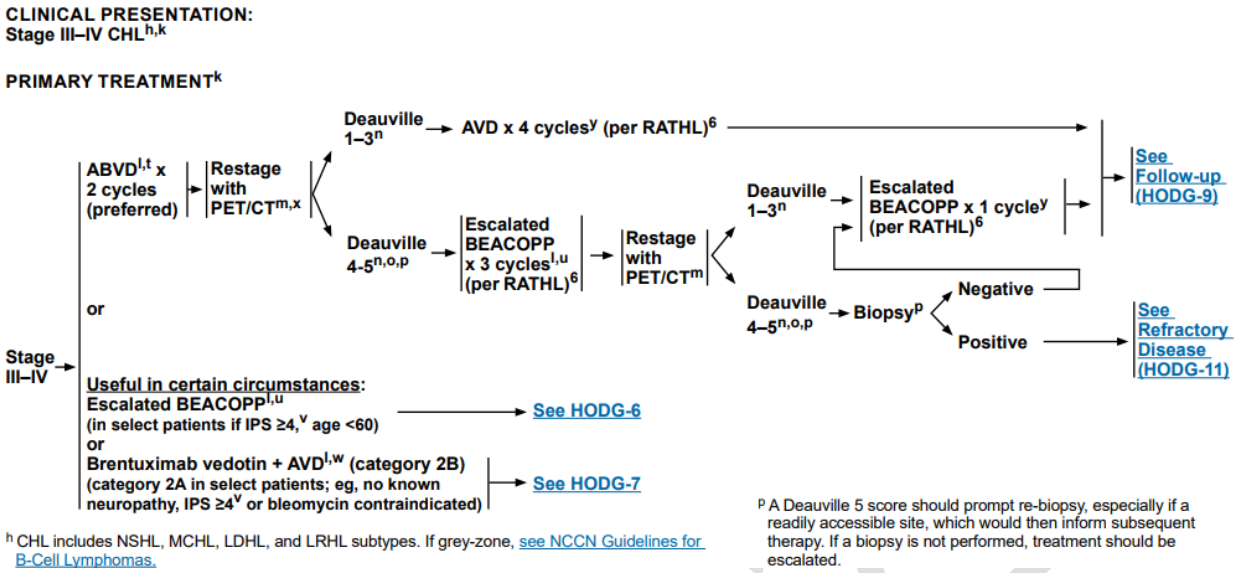
1^{O} 5-year PFS

Borchmann, Lancet 2021

5-year PFS 97.3% vs. 95.1% (NS).
G 3-4 leukopenia 83-84% NS. Dysphagia ↑ with radiation 6 % vs. 2%. "Serious adverse" 29-30% NS.
Interpretation PET4-negativity after treatment with 2 + 2 chemotherapy in patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma allows omission of consolidation radiotherapy without a clinically relevant loss of efficacy. PET4-guided therapy could thereby reduce the proportion of patients at risk of the late effects of radiotherapy.

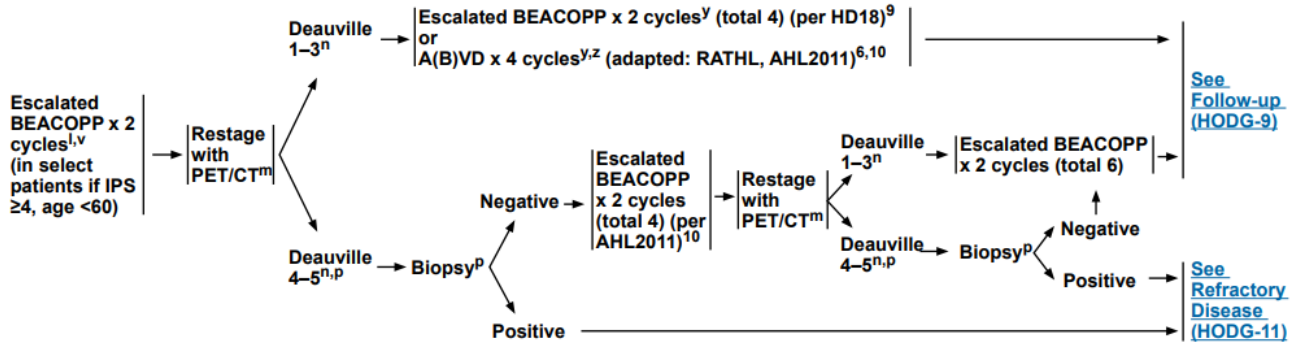
***I**mportant to notice the radiation technique IFRT vs. INRT.

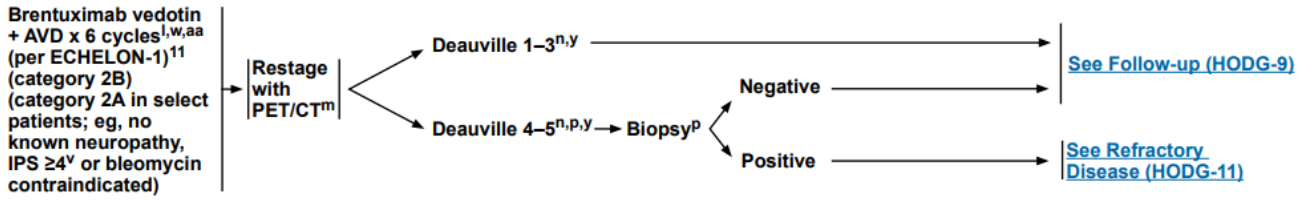
Advanced Stage HL



[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

[p] A Deauville 5 score should prompt re-biopsy, especially if a readily accessible site, which would then inform subsequent therapy. If a biopsy is not performed, treatment should be escalated.





6c ABVD → Consolidation RT

Tata Memorial **Positive Trial**

Purpose: Evaluating the role of consolidation radiation in patients achieving a complete remission after six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy using event-free survival (EFS) and overall survival (OS) as primary end points.

←R→ 251 HD induction 6c x ABVD → 179 of 251 patients (71%) achieved CR and was randomized | 1. further therapy | 2. consolidation radiation |.

Laskar, JCO 2004.

8-year OS 89% vs. 100% (SS). 8-year EFS 76% vs. 88% (SS).

Addition of RT improved EFS and OS in patients with age < 15 years (P =.02; P =.04), B symptoms (P =.03; P =.006), advanced stage (P =.03; P =.006), and bulky disease (P =.04; P =.19).

CONCLUSION: Our study suggests that the addition of consolidation radiation helps improve the EFS and OS in patients achieving a complete remission after six cycles of ABVD chemotherapy, particularly in the younger age group and in patients with B symptoms and bulky and advanced disease.

GITIL/FIL HD0607 Trial **Negative Trial**

←R→ 296 advanced HL largest diameter size 5-7 cm (34%, subgroup A), 8-10 cm (32%, subgroup B), classic > 10 cm bulky (33%, subgroup C).

All with 2 negative PETS after 2nd (PET-2) and 6th (PET-6) ABVD. | 1. Consolidation RT | 2. No RT |.

Median RT was 30.6 Gy (24-36 Gy range).

Gallamini, JCO 2020 FU 5.9 years.

6-year PFS Subgroup A 91% vs. 95% (NS) Subgroup B 98% vs. 90% (NS) Subgroup C 89% vs. 86%.

CONCLUSION cRT could be safely omitted in patients with HL presenting with an LNM and a negative PET-2 and PET-6 scan, irrespective from the LNM size detected at baseline.

Standard Studies (The "15-ER")

GHSD HD 15.

←R→ 2126 advanced HD | Stage III-IV | IIB + extranodal disease or mediastinal mass > 33% max thoracic diameter |
1. BEACOPP$_{esc}$ x 8c 2. BEACOPP$_{esc}$ x 6c 3. BEACOPP-14 x 8c (given over 14 days instead of 21 days) All followed by → PET guided therapy.
If you have residual mass ≥ 2.5 cm or PET+ → 30 Gy.

Engert, Lancet 2012.
5-year FFTF 84·4% vs. 89·3% vs. 85·4%. **5-year OS 91·9% vs. 95·3%** vs. 94·5%. **BEACOPP x 8c < 6c in FFTF and OS (SS)**.
Mortality 7·5% vs. 4·6% vs. 5·2%. Treatment-related events (2·1%, 0·8%, and 0·8%) 2^{O} malignancies (1·8%, 0·7%, 1·1%)
The negative predictive value for PET at 12 months was 94·1%
11% received additional radiotherapy.
INTERPRETATION: Treatment with six cycles of BEACOPP(escalated) followed by PET-guided radiotherapy was more effective in terms of freedom from treatment failure and less toxic than eight cycles of the same chemotherapy regimen. Thus, six cycles of BEACOPP(escalated) should be the treatment of choice for advanced stage Hodgkin lymphoma. PET done after chemotherapy can guide the need for additional radiotherapy in this setting.

ECOG E2496

←R→ n = 794, unfavorable Stage I/II (with > 1/3 PA CXR) **OR** Stage III-IV **RT = IFRT to 36Gy: 2-3 wks after chemo**
If ABVD, only for mediastinal disease pts

Allocated to arm ABVD (n = 428)
6-8 cycles of modified IFRT 36 Gy only to patients with massive mediastinal disease

Allocated to arm Stanford V (n = 426)
12 weeks of chemotherapy with modified IFRT 36 Gy to sites > 5 cm in maximum transverse dimension plus spleen if involved on CT

Table 3. Response Rates

Response (%)	ABVD Arm (n = 394)	Stanford V Arm (n = 399)
CR and CCR	72.7	68.7
PR	7.6	7.5
SD	8.4	10.5
Progression	0.3	2.0

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CCR, clinical complete remission; CR, complete remission; PR, partial response; SD, stable disease.

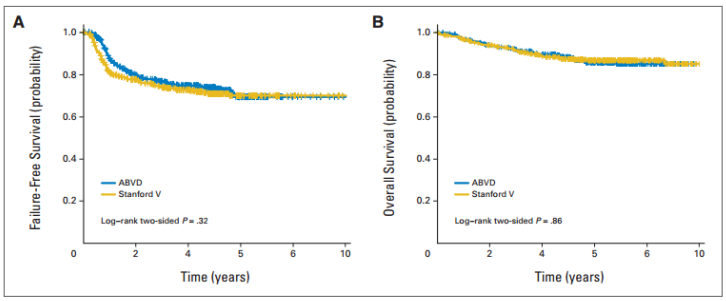


Fig 2. (A) Failure-free (*P* = .32) and (B) overall survival (*P* = .86) are shown for all patients, showing no difference between the two arms. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

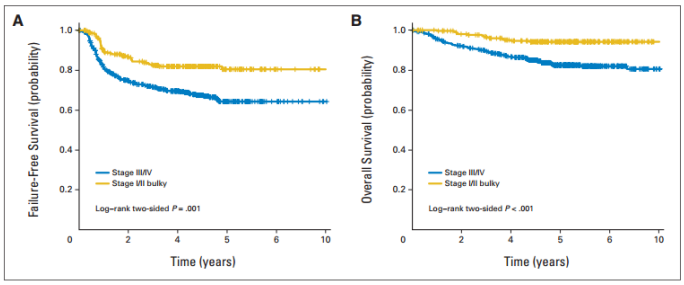


Fig 3. Patients with locally extensive disease (stage I to II bulky) were compared with patients with advanced disease (stage III to IV); patients with locally advanced disease had better (A) failure-free survival (FFS; *P* = .001) and (B) overall survival (OS; *P* = .002), but there were no differences in FFS or OS between ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and Stanford V (data not shown).

Gordon, JCO 2013
All comers: 5-year FFS: 74% vs. 71% (NS) 5-year OS 88% vs 88% (NS)
For all ABVD vs Stanford V patients – **NO DIFFERENCE** in FFS or OS at 10y.
Subgroup 1: Difference between Early Unfavorable vs Advanced Stage
Early stage vs Advanced 5y OS Early 94% vs Advanced 85% (p < .001);
5y FFS Early 82% vs Advanced 67% (p = .001)
Subgroup 2: HIGH IPS (3-7) compared to low IPS (0-2), E2496 demonstrated **IMPROVED FFS** with **ABVD vs Stanford V**.
Low IPS: 5-year FFS: ABVD 77% vs. S.V. 78% (NS) 5-year OS: 91% vs 93% (NS)
High IPS: **5-year FFS: ABVD 67% vs S.V. 57% (SS)** 5-year OS: 84% vs 77% (NS)

CONCLUSION: no Δ, ∴ ABVD remains standard of care in US.

RT specs: ABVD arm – only if mediastinal disease
Margins: .5cm lateral 5+ cm inferior below extent of disease, including bilateral hilar regions.
Superior vs inf border of larynx (sup if SCV involved)
Portal to include bilateral SCV: Does not need entire cardiac silhouette
36 Gy in 1.5 – 1.8 Gy/fx

Subgroup Advani JCO 2015

UK RATHL

←R→ noninferiority 1214 patients advanced classic HL. | Stage IIB-IV | IIA + 1. ≥ 3 involved sites or 2. Bulky disease (> 33% TDiam or > 10 cm) |
Goal: Can we omit bleomycin in patients with good PET response?

All ABVD x 2c → PET/CT if D. 1-3 ←R→ 1. ABVD x 4c 2. AVD (no bleo) x 4c
If D. 4-5 all BEACOPP (BEACOPP-14 or escalated BEACOPP)

RT was NOT recommended for patients with negative PET/CT. **(Despite what we know from PET- results from EORTC H 10)**

"…although local investigators had discretion to use radiotherapy if they believed it was necessary."

1º 3-year PFS (noninferiority comparison to exclude a difference of 5 or more percentage points).

BEACOPP-14 (repeated every 14 days)

Doxorubicin	25mg/m^2 iv	Day 1
Cyclophosphamide	650mg/m^2 iv	Day 1
Etoposide	100mg/m^2 iv	Days 1-3
Procarbazine (or Natulan)	100mg/m^2 po	Days 1-7
Prednisolone	80mg/m^2 po	Days 1-7
Bleomycin	10,000units/m^2 iv	Day 8
Vincristine*	1.4mg/m^{2}iv	Day 8
G-CSF	263/300mcg or equivalent PEG-Filgrastim single dose	Day 9-13

BEACOPP-escalated (repeated every 21 days)

Doxorubicin	35mg/m^2 iv	Day 1
Cyclophosphamide	1250mg/m^2 iv	Day 1
Etoposide	200mg/m^2 iv	Days 1-3
Procarbazine (or Natulan)	100mg/m^2 po	Days 1-7
Prednisolone	40mg/m^2 po	Days 1-14
Bleomycin	10,000units/m^2 iv	Day 8
Vincristine*	1.4mg/m^{2}iv	Day 8
G-CSF	263/300mcg or equivalent PEG-Filgrastim single dose	Day 9 until count recovered

Johnson, NEJM 2016.

Interim PET - was 83.7% (vast majority).

3-year PFS 85.7 vs. 84.4 3-year OS 97.2% vs. 97.6%. progression

The absolute Δ in the 3-year PFS **1.6% [sic] (???)**. Non-inferior margin was 5%.

Respiratory adverse events 3% vs. 1% (SS).

32 patients received consolidation RT (2.6% vs. 4.3 %).

Interim PET + was 16.3 % → BEACOPP was given to the 172 patients. Of these 74.4% had negative findings on a third PET-CT scan.

3-year PFS 67.5% 3-year OS 87.8%.

Overall

3-year PFS 82.6 3-year OS 95.8%.

CONCLUSIONS: AVD is not-noninferior but results remain excellent and bleomycin omission may be reasonable (accepted by NCCN 2017).

Table 3. Grade 3 or 4 Adverse Events among Patients with Negative PET Findings Who Started Their Assigned Treatment.*

Event	ABVD, Cycles 1 and 2 (N=1203)	ABVD, Cycles 3–6 (N=468)	AVD, Cycles 3–6 (N=457)	BEACOPP-14 (N=94)	Escalated BEACOPP (N=78)
			number (percent)		
Any blood or bone marrow event	711 (59)	280 (60)	273 (60)	68 (72)	58 (74)
Neutropenia	694 (58)	275 (59)	269 (59)	59 (63)	52 (67)
Thrombocytopenia†	16 (1)	6 (1)	15 (3)	18 (19)	33 (42)
Any cardiac event	9 (1)	6 (1)	2 (<0.5)	1 (1)	0
Any constitutional symptom	36 (3)	18 (4)	13 (3)	11 (12)	11 (14)
Fatigue†	14 (1)	14 (3)	5 (1)	8 (9)	3 (4)
Fever	16 (1)	4 (1)	7 (2)	2 (2)	9 (12)
Any infection	76 (6)	68 (15)	47 (10)	35 (37)	33 (42)
Febrile neutropenia†	24 (2)	22 (5)	10 (2)	10 (11)	20 (26)
Any neurologic event	20 (2)	23 (5)	14 (3)	9 (10)	3 (4)
Any pulmonary or upper respiratory event†	8 (1)	15 (3)	3 (1)	4 (4)	4 (5)
Dyspnea†	5 (<0.5)	9 (2)	1 (<0.5)	2 (2)	2 (3)
Pneumonitis	0	5 (1)	1 (<0.5)	0	2 (3)
Any vascular event	18 (1)	23 (5)	12 (3)	8 (9)	2 (3)
Thrombosis or embolism related to vascular access	4 (<0.5)	4 (1)	1 (<0.5)	0	0
Thrombosis, thrombus, or embolism	14 (1)	20 (4)	11 (2)	8 (9)	2 (3)
Any clinical adverse event‡§	188 (16)	143 (31)	96 (21)	52 (55)	47 (60)
Any grade 3 or 4 adverse event	771 (64)	322 (69)	299 (65)	75 (80)	65 (83)

Newer Studies (Early PET HD 18 + Rituximab, Echelon-1)

HD18 – Rituximab

Background – Could early interim PET-imaging after BEACOPPx2 + Rituximab ↑ PFS in advanced HD?
←R→ 1100 of which 440 were randomized… All 2 cycles of $BEACOPP_{esc}$ → PET-2 + → | 1. $BEACOPP_{esc}$ | 2. $R\text{-}BEACOPP_{esc}$ |. PET-2 + = Deauville 3-5.
Rituximab IV 375 mg/m ^{2} (maximum 700 mg), 24 h before starting the fourth cycle of $BEACOPP_{escalated}$ (day 0 and day 3 in cycle 4, day 1 in cycles 5–8).
1^O 5-year PFS.

Borchmann, Lancet 2017.
3-year PFS BEACOPP 91·4% vs. R-BEACOPP 93·0% (NS).
Grade 3–4 leukopenia 95% and severe infections 20-23% (NS).
Interpretation Rituximab did NOT ↑ PFS. However, PFS for PET-2 positive patients was much better than expected, exceeding even the outcome of PET-2-unselected patients in the previous HD15 trial. Thus, PET-2 cannot identify patients at high-risk for treatment failure in the context of the very effective German Hodgkin Study Group standard treatment for advanced stage Hodgkin lymphoma.

ECHELON-1

BACKGROUND Brentuximab vedotin is an anti-CD30 antibody–drug conjugate that has been approved for relapsed and refractory Hodgkin lymphoma.
←R→ 664 previously untreated stage III or IV classic Hodgkin lymphoma → | 1. BV + AVD | 2. ABVD | 1^O PFS 2^O OS.
BV: 1.2 mg of brentuximab vedotin per kilogram of body weight.
BLEOMYCIN MAY CAUSE TOO MUCH LUNG TOXICITY with BV.

Connors, NEJM 2018.
2-year PFS 82.1% vs. 77.2% (P=0.04).

	Neutropenia	Per. Neuropathy	Pulm G ≥3
1..	58%	67%	1%
2..	45%	43%	3%

CONCLUSIONS A+AVD had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin lymphoma, with a 4.9 percentage-point lower combined risk of progression, death, or noncomplete response and use of subsequent anticancer therapy at 2 years.

Relapsed/Refractory HL

Statistics:

- "In early-stage disease, rates of relapse remain in the 5% to 10% range (1, 15) and are even higher after treatment with chemotherapy alone (2, 3); in advanced disease, relapse rates can be as high as 30% to 40% (4, 16, 17)." Constine IJROBP 2018. ILROG.
  - Relapsed patients → high-dose chemotherapy and autologous stem cell rescue have an approximately 50% potential for cure.
- Refractory HL occurs in approximately 10% of patients, defying initial treatment approaches.
  - Also, can consider eligibility for transplantation, but otherwise very poor prognosis.
- Patients with high-risk features (eg, early relapse or extranodal relapse) are considered for post-transplantation BV.

Standard Studies (Athera, Ansell PD-1)

ATHERA
←R→ 329 patients cHL unfavorable risk relapsed or primary progressive → autologous SCT → | 1. BV | 2. Placebo |.

Moskowitz, Lancet 2015.
Median PFS 42.9 mo. vs. 24.1 mo. Death 16-17% both (NS). OS (NS).
5-year PFS was 59% vs. 41% (SS)

PD-1 Trial, Ansell NEJM 2015.
23 patients refractory HL 78% previous SCT and 78% previously treated with BV
Patients received Nivo 3 mg/kg q2weeks. OBJECTIVE RESPONSE 87%, CR 17%