Evidence Based Radiation Oncology Fact Sheets
Hodgkin Lymphoma 2023

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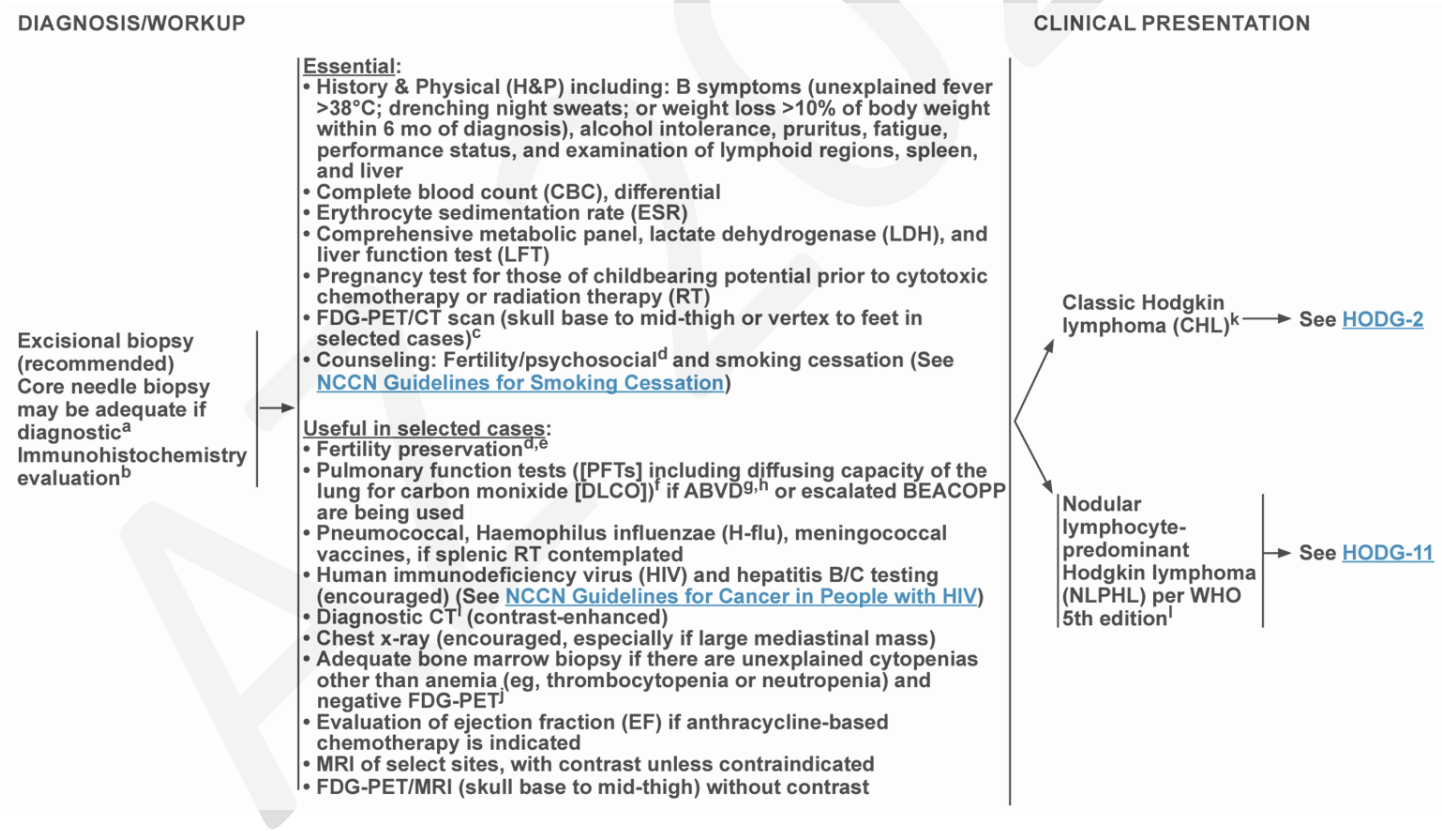
Overview:

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).



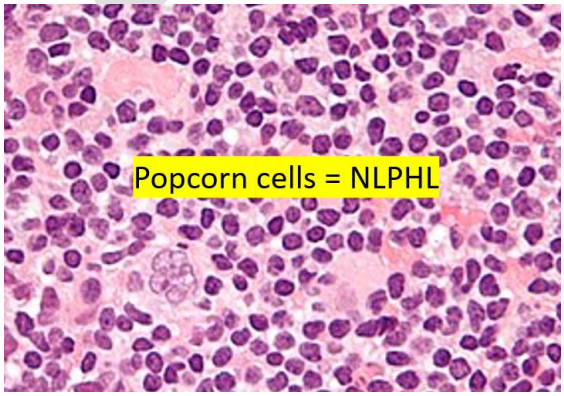
Pathology:

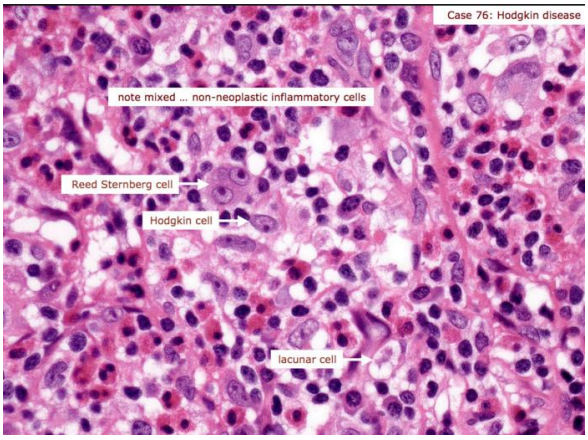
- **Classic HL**: Presence of classic Hodgkin/Reed-Sternberg (HRS) cells
  - Do not exhibit phenotypes typical of any normal cell
  - CD15+; marker is expressed on granulocytes
  - Somatic hypermutation of immunoglobulin genes, with VDJ rearrangement. This is typically seen only in germinal B cells and 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

Stage	Bulky Mediastinal Disease[m] or >10 cm Adenopathy	ESR >50 or # Sites >3	Type	Guidelines Page
IA/IIA	No	No	Favorable Disease	HODG-4
	No	Yes	Favorable/Unfavorable Disease	HODG-4 or HODG-5
	Yes	Yes/No	Unfavorable Disease	HODG-5
IB/IIB	Yes/No	Yes/No	Unfavorable Disease	HODG-5
III–IV	Yes/No	N/A	Advanced Disease	HODG-6

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

Classic Hodgkin Lymphoma in Adults 18–60 Years

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)
• ABVD[a,b] (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± ISRT[c,1,2,3,4,5]
• ABVD[a,b] followed by escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)[d] ± ISRT[c,5]
• BV + AVD (doxorubicin, vinblastine, and dacarbazine)[d,6]
• Escalated BEACOPP[d,7,8]
• Escalated BEACOPP[d] followed by ABVD[a,b] with ISRT[c,9]

Classic Hodgkin Lymphoma in Adults Age >60 Years or Adults With Poor Performance Status or Substantial Comorbidities

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
Stage I–II Favorable Disease	• A(B)VD[a,b,e] (2 cycles) ± AVD (2 cycles) + ISRT[c] (preferred)[10,11,12] • CHOP (4 cycles) + ISRT[c,13]
Stage I–II Unfavorable or Stage III–IV Disease	• A(B)VD[a,b,e] (2 cycles) followed by AVD (4 cycles),[f] if FDG-PET scan is negative after 2 cycles of ABVD.[14] ▸ Patients with a positive FDG-PET scan after 2 cycles of ABVD need individualized treatment. • BV followed by AVD, conditionally followed by BV in patients with CR or PR and no neuropathy[15] • CHOP (6 cycles) ± ISRT[c,13]
Patients with Low EF	• Add dexrazoxane to ABVD[a,b] or CHOP, with close cardiology follow-up • BV-DTIC (dacarbazine)[16,17]

Nodular Lymphocyte-Predominant Hodgkin Lymphoma
• The most common chemotherapy regimens used at NCCN Member Institutions for NLPHL are listed below[g]

Primary Systemic Therapy Regimens (listed in alphabetical order)
• ABVD[a,b] (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab[h,18,19]
• CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab[h,20,21]
• CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab[h,22]
• Rituximab[h,23,24,25,26,27,28]

Radiation:

NCCN Guidelines

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),[1-3] deep-inspiratory breath hold (DIBH) or respiratory gating,[4,5] image-guided RT (IGRT),[5] and proton therapy[6-8] may offer significant and clinically relevant advantages in specific instances to spare important normal OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.**
- **The demonstration of significant dose-sparing for OARs reflect 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 HL, use of four dimensional (4D)-CT or DIBH at the time of simulation to deal with respiratory motion and minimize dose to OARs is essential. DIBH, in particular, has been shown to decrease incidental dose to the heart, lungs, and other OARs in many disease presentations.[5] Further, IGRT during treatment delivery is essential to ensure accurate target localization. In certain circumstances, the use of protons for mediastinal lymphoma provides dosimetric advantages that may reduce long-term toxicity. The potential advantage of protons is related to the localization of disease within the mediastinum as well as patient gender assigned at birth and age.[9-11]**
- **Although the advantages of tightly conformal dose techniques, such as IMRT, includes steep dose gradients between targets and OARs, the "low-dose bath" to normal structures is often increased. Particular attention to treatment technique and adherence to dose constraints is essential to minimize dose to high-risk OARs such as breast tissue in young premenopausal individuals. Target definition 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, FDG-PET, 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.**

PRINCIPLES OF RADIATION THERAPY

Involved-Site Radiation Therapy (ISRT): Dose

- Combined Modality Therapy (CMT)
  - 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 (all stages): 30–36 Gy; 1.5–2.0 Gy per fraction
  - Partial response/refractory disease (Deauville 4–5): 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 fields for NLPHL generally include adjacent but clinically uninvolved nodes when treated with RT alone.
- Palliative RT: 4–30 Gy

ISRT: Volumes

- ISRT principles should be followed when designing RT fields for HL[12]
  - Planning for ISRT requires modern CT-based simulation and treatment planning capabilities.
  - Incorporating other modern imaging such as FDG-PET and MRI often enhances treatment volume determination.[13]
- ISRT targets the site of the originally involved lymph node(s).
  - The clinical target volume (CTV) encompasses the original or suspected extent of disease prior to chemotherapy or surgery. This volume is then modified to account for tumor shrinkage and spares adjacent uninvolved organs (eg, lungs, bone, muscle, kidney) when lymphadenopathy regresses following chemotherapy.
- For CHL, the pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the CTV.
  - Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment.
- For NLPHL, the CTV will depend on whether treatment consists of ISRT alone or CMT.
  - ISRT alone: The CTV should be expanded to include potential microscopic disease in the immediate region of the FDG-PET–positive disease.
  - CMT: Similar to CHL after chemotherapy [treating originally involved lymph node(s) only]
- Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume, [ITV]) should also influence the final CTV.
- The planning target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations and may differ by site and immobilization technique.
  - See ICRU definitions[14]
- OARs should be outlined for optimizing treatment plan decisions.
- The treatment plan can be designed using conventional, 3-D conformal, proton therapy, or IMRT techniques using clinical treatment planning considerations of coverage and normal tissue avoidance.
- The treatment of extranodal disease is individualized, but similar principles of GTV/CTV/PTV definition should be applied as for nodal disease.
  - Chest wall extension – Effort should be made to include regions of initial chest wall extension to definitive doses.
  - Lung involvement – Areas of extension into the lung from mediastinal or hilar disease may be treated with lower doses (~15 Gy) unless the relative volume is small, in which case higher doses may be utilized. Careful consideration of partial lung tolerance is essential. Pulmonary nodular disease is usually not treated following chemotherapy unless residual disease is present.
  - Pleural or pericardial effusions are not included in the GTV. Nodular pericardial involvement may be included with consideration of cardiac tolerance.
  - Bone – Areas of osseous disease may be treated with a CTV expansion beyond the GTV defined by imaging. In vertebral body disease, the entire vertebra is generally treated.

[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 1 or 2 lymph node regions involved. See HODG-3 for definition of nodal sites according to GHSG.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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.

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.

Dose Constraints NCCN

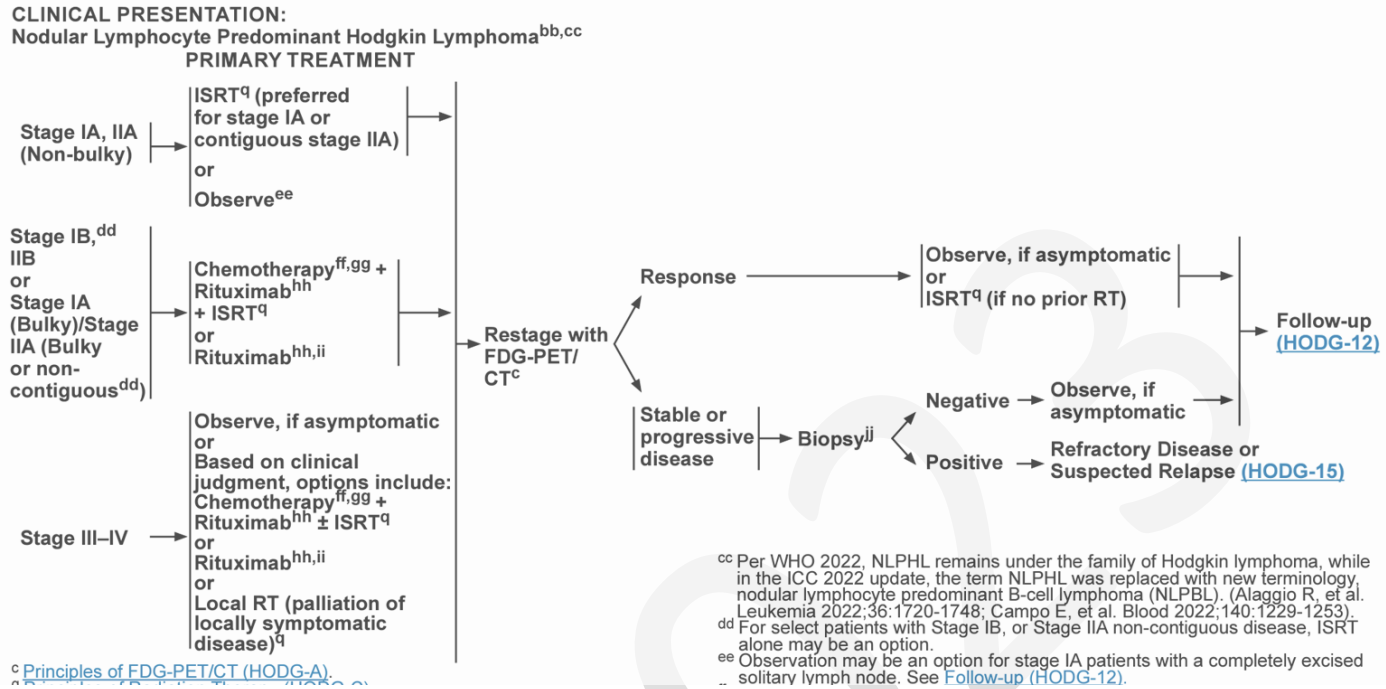
OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: as low as reasonably achievable (ALARA)	Xerostomia[15,16]
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA	Xerostomia[17]
	Oral cavity (surrogate for minor salivary glands)	Mean <11 Gy	Xerostomia, dysgeusia, oral mucositis[17]
	Thyroid	V25 Gy <63.5% Minimize V30 Gy	Hypothyroidism[18]
	Lacrimal glands	V20 Gy <80%	Dry eye syndrome[19]
	Larynx/Pharyngeal constrictors	Mean <25 Gy	Laryngeal edema, dysphagia[20]
	Carotids	Ipsilateral: Avoid hotspots Contralateral: ALARA	Carotid artery atherosclerosis

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Thorax	Heart[c]	Mean <8 Gy (recommended) Mean <15 Gy (acceptable); ALARA given increased risk with even lower doses	Major adverse cardiac events[21-24]
	Aortic and mitral valves	Dmax <25 Gy	Valvular heart disease[22,25,26]
	Tricuspid and pulmonic valves	Dmax <30 Gy	
	Left ventricle	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Heart failure[22,27]
	Coronary vessels including the left main, left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA)[c]	LAD V15 Gy <10%[c] LCx V15 Gy <14% Coronary vessels (total)- Mean <7 Gy Minimize the maximum dose to individual coronary arteries	Major adverse cardiac events[28]
	Lungs	Mean dose <13.5 Gy V20 <20% (recommended); <30 Gy (acceptable) V5 <55%	Pneumonitis[29-31]

OAR		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]
	Kidney	Single organ Mean <8 Gy V10 <30% V20 <15% (recommended); <25% (acceptable)	Bilateral V5 <58%	Renal insufficiency[41-43]
Other	Bone marrow[d]	V5: ALARA V10 <50% V25 <25%		Acute cytopenias[44,45] Chronic cytopenias[46]
	Long bone	V40 <64%		Fracture[47]

Nodular Lymphocyte Predominant

≈ Follicular



<u>Radiation alone is a good recommendation of early stage favorable non-bulky NLPHL.</u>

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]

<u>Regimens and References</u>

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.

HD16 HD17 Subgroup NLPHL

Key Points
In early-stage fav NLPHL, consolidation RT appears necessary to achieve the optimal disease control irrespective of the iPET result.
In early-stage NLPHL, Hodgkin lymphoma–directed approaches result in a 5-year PFS >90% and a 5-year overall survival of 100%.

Eichenauer, Blood 2023

100 NLPHL patients treated in the randomized HD16 (early-stage favorable; n = 85) and HD17 (early-stage unfavorable; n = 15) studies.
Patients with NLPHL treated in the HD16 and HD17 studies 5-year PFS 90.3% and 92.9%, respectively.
<u>Thus, the 5-year PFS NS from that of patients with classical Hodgkin lymphoma treated within the same studies</u> (HD16: P = .88; HD17: P = .50).
If early-stage fav. NLPHL with NEG iPET after 2× ABVD **and NO consolidation RT** tended = ↓ 5-year PFS (no RT 83% vs yes RT 100%; P = .05).
There were 10 cases of NLPHL recurrence. However, no NLPHL patient died during follow-up. Hence, the 5-year overall survival rate was 100%.
Conclusion: Taken together, contemporary Hodgkin lymphoma-directed treatment approaches result in excellent outcomes for patients with newly diagnosed early-stage NLPHL and, thus, represent valid treatment options. In early-stage favorable NLPHL, consolidation RT appears necessary after 2× ABVD to achieve the optimal disease control irrespective of the iPET result.

HL Treatment Chart 2023

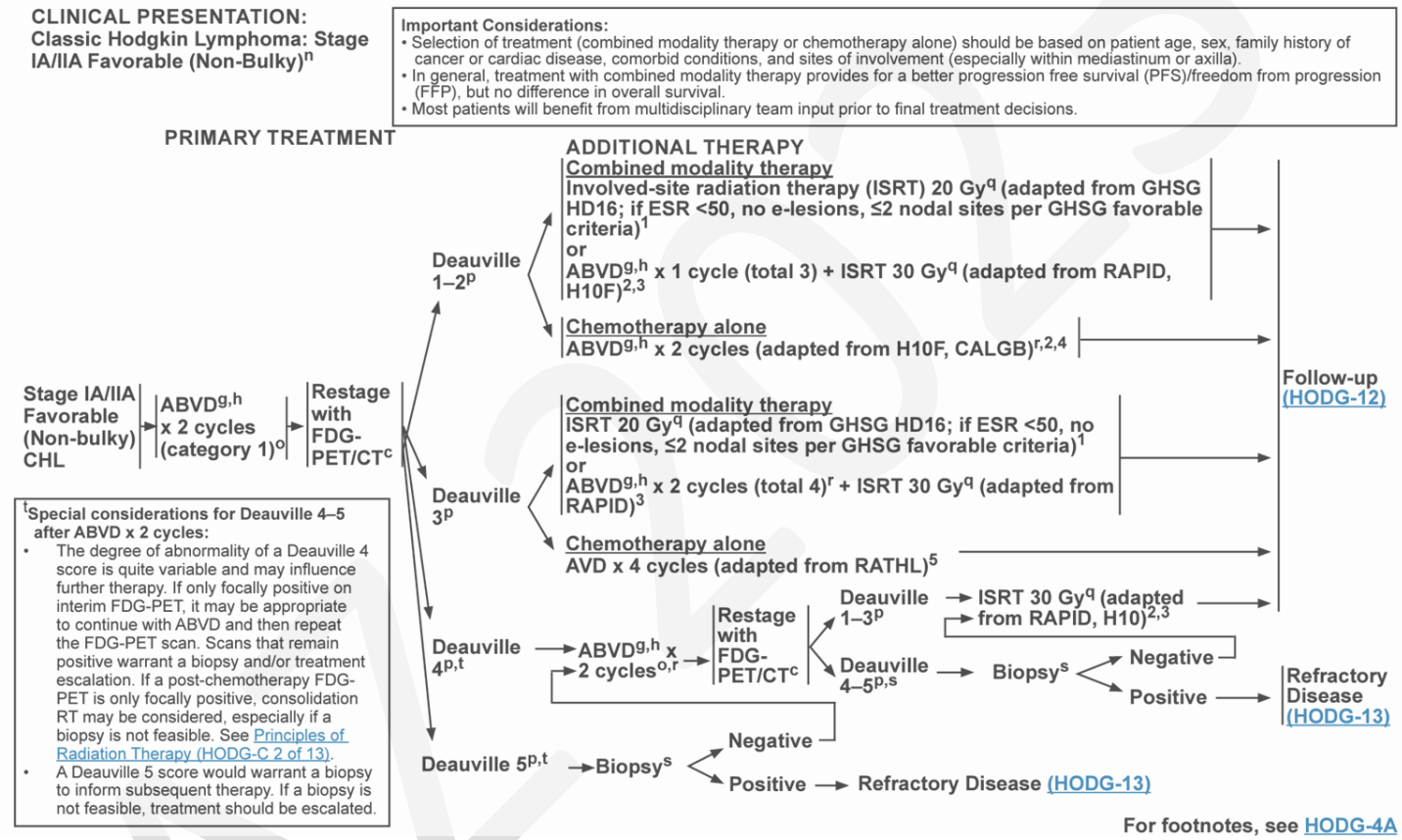
HL	Risk Factors	Primary TX	Lugano Response		Consolidation
Limited Stage I-II	Favorable, non-bulky	ABVD x 2 * Neg 1-3, Pos 4 ~~ABVD x 2~~ (no RT = bad idea)	If	Negative *	ISRT **20 Gy** **(HD10, HD16)** **Meets GHSG Criteria** ABVD x 1 → ISRT **30 Gy** (Rapid, H10F) **STD**
				Positive *	ABVD x 2 → PET→ **(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)
	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.*		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 ABVD x 2 (No RT option) CALGB 50801 → PET(2) * Neg 1-3…	if	Negative *	ABVD x 2 → ISRT 30-36 Gy AVD x 4 → **± ISRT 30-36 Gy** ***(Rathl)*** ABVD x 4 **(No RT option) CALGB 50801**
				Positive *	escBEACOPP x 2 → PET → (1-3) ISRT 30 Gy (H10U) or (1-3) escBEACOPP x 2 → (4-5) Biopsy See NR (5)
				NR (5)	Biopsy - → see Positive * Biopsy + → See Relapse /Refractory *or escBEACOPP x 2 → PET → evaluate (RT)*
Advanced Stage III-IV	Preferred (Cat. 1)	ABVD x 2 * Neg 1-3, Pos 4	if	Negative	**AVD** x 4 → **± ISRT 30 Gy** ***(Rathl)***
				Positive	escBEACOPP x 3 → PET → *evaluate (**C → ± RT**)* ***(Rathl)***
	Age < 60 yo (Cat. 1)	*escBEACOPP x 2* *Brentuximab V. + AVD*		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 **Nivo + BV induction x4c (Low-risk RRHL*)*		Any *If CMR…	Follow-up CT C/A/P q 6 months. Clinical Trial, Palliative ISRT, etc. ** Consider Systemic Tx + Consol. RT (Checkmate 744)*

Low-risk RRHL

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. ←R→ trials showed 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.



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).

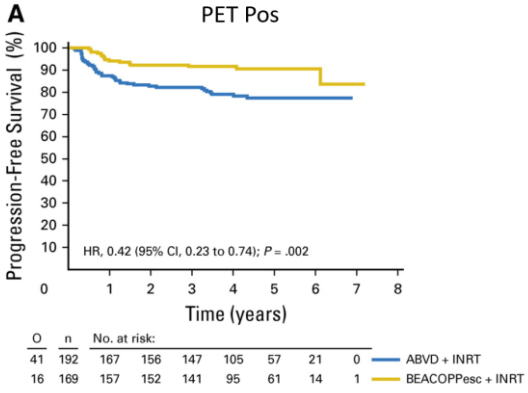
Unfavorable pts (683): 74.8% had negative early PET. 16 events vs 9. 1-yr PFS 94.7% vs 97.3% (SS).

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).

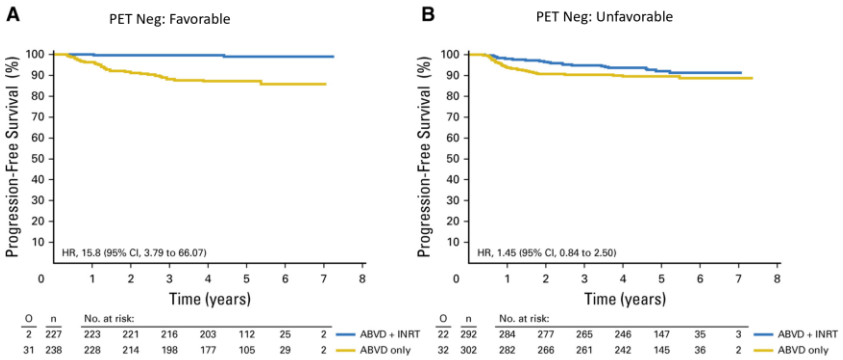
So, if you are just favorable, you really don't know if you should ABVD or BEACOPP. Perhaps the benefit is solely driven by unfavorable.

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.

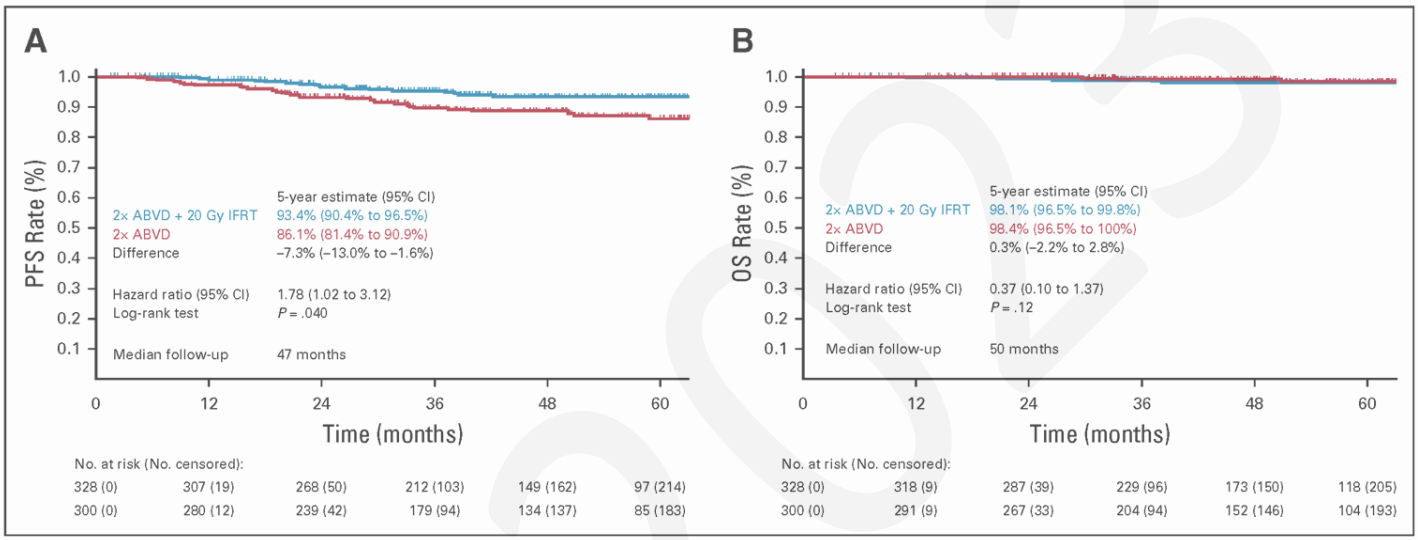


FIG 2. Kaplan-Meier estimates for the PET-2 (positron emission tomography after two cycles of chemotherapy) –negative per-protocol population. (A) Progression-free survival (PFS). (B) Overall survival (OS). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IFRT, involved-field radiotherapy.

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.

Kim, PRO 2023 Cost Analysis
"The base case analysis showed that CMT is cost-effective compared with ABVD alone, with an incremental cost-effectiveness ratio of $8028 per QALY gained and an incremental cost of $236 gaining 0.029 QALYs. On sensitivity analyses, the results were the most sensitive to changes in recurrence rates. If the recurrence rate differences were ≥6%, CMT was cost-effective."
Conclusions
CMT is a cost-effective strategy for early-stage, favorable-risk Hodgkin lymphoma based on currently available evidence. However, small variations in recurrence-rate estimates dramatically affect strategy cost-effectiveness.

COG AHOD0431

Background: Children's Oncology Group (COG) trial AHOD0431 reduced systemic therapy and used response-adapted involved-field radiotherapy (IFRT) in early-stage pediatric classic Hodgkin lymphoma. We investigated the impact of positron emission tomographic response after 1 cycle (PET1) and on IFRT outcomes and pattern of relapse.

←R→ 276 age < 21 Stage IA or IIA HL → 3c AVPC (doxorubicin, vincristine, prednisone, and cyclophosphamide) → PET1 response assessment.

"Rapid early responders" (RERs) had a negative PET1 (PET1−)

"Slow early responders" (SERs) had a positive PET1 (PET1+). | 1. If PR by CT and PET imaging → 21-Gy IFRT | 2. If CR → no IFRT |.

IFRT = 21 Gy in 1.5 fx.

CR = anatomic ↓ ≥80% product of the perpendicular dimension (PPD) and as an FDG-PET-negative result after 3 cycles of chemotherapy cycles (PET3).

Progression-free survival (PFS) was evaluated for RERs and SERs treated with or without IFRT. Recurrence sites were initial, new, or both. Relapses involving initial sites were characterized as "within the PET1+ site" or "initially involved but outside the PET1+ site."

Keller, Cancer 2018 **4-years**

4 years → 49.0% had received minimal chemotherapy and no radiation
88.8% were in remission without receiving high-dose chemotherapy with stem cell rescue or >21 Gy IFRT
OS = 99.6%.

4-year EFS mixed cellularity histology 95.2% vs. nodular sclerosis 75.8% (SS).

A red blood cell sedimentation rate ≤20 mm/hour and a negative fluorodeoxyglucose-positron emission tomography scan after 1 cycle of chemotherapy (PET1) were associated with a favorable EFS outcome. **The study was closed early when the receipt of radiation therapy exceeded the predefined monitoring boundary.**

CONCLUSIONS

This limited chemotherapy response-based approach was successful in patients who had a negative PET1 result, had MC histology, or had a low red blood cell sedimentation rate. In this treatment paradigm, evaluation of increased chemotherapy intensity or the integration of active new agents is indicated for patients who have nodular sclerosis histology with a high ESR or who have a positive PET1 result.

Parekh, Blood 2022 118 months.

10-year PFS RERs Yes IFRT 96.6% vs. no IFRT 84.1% (P = .10).

10-year PFS SERs Yes IFRT 80.9% vs. no IFRT 64.0% (P = .03).

Among 90 RERs who did not receive IFRT, all 14 relapses included an initial site.

Among 45 SERs receiving no IFRT, 14 of 16 relapses were in the initial site (9 PET1+ site only).

Among 58 patients receiving IFRT, 5 of 10 relapses were in the PET1+ site.

After 3 cycles of AVPC alone, RERs showed favorable results.

Conversely, SERs had unfavorable outcomes with AVPC alone, although they improved with 21-Gy IFRT.

RT remains an important component of treatment for SERs.

EuroNet-PHL-C1

Background: Children and adolescents with early-stage classical Hodgkin lymphoma have a **5-year event-free survival of 90% or more** with vincristine, etoposide, prednisone, and doxorubicin (OEPA) plus radiotherapy, but late complications of treatment affect survival and quality of life. We investigated whether radiotherapy can be omitted in patients with adequate morphological and metabolic responses to OEPA.

←R→ 2131 children < 18 yo newly diagnosed stage IA, IB, and IIA classical Hodgkin lymphoma | 1. 2C OEPA |
→ If no adequate response (a partial morphological remission or greater and PET negativity) → IFRT 19·8 Gy (11 fractions of 1·8 Gy per day).

1^{O} EFS = Maintaining 5-year EFS of 90% in patients with an adequate response to OEPA without radiotherapy.

OPEA = (vincristine 1·5 mg/m2 IV, capped at 2 mg, on days 1, 8, and 15; etoposide 125 mg/m2 IV, on days 1–5; prednisone 60 mg/m2 PO on days 1–15; and doxorubicin 40 mg/m2 IV on days 1 and 15).

Mauz-Körholz, Lancet 2023 63·3 months

714 patients assigned to and treated on treatment group 1 → ITT population 713 patients with 323 (45%) male and 390 (55%) female patients.

In 440 of 713 patients ITT = adequate response **→ NO RT → 5-year EFS 86·5% (95% CI 83·3–89·8) = < 90% target rate.**

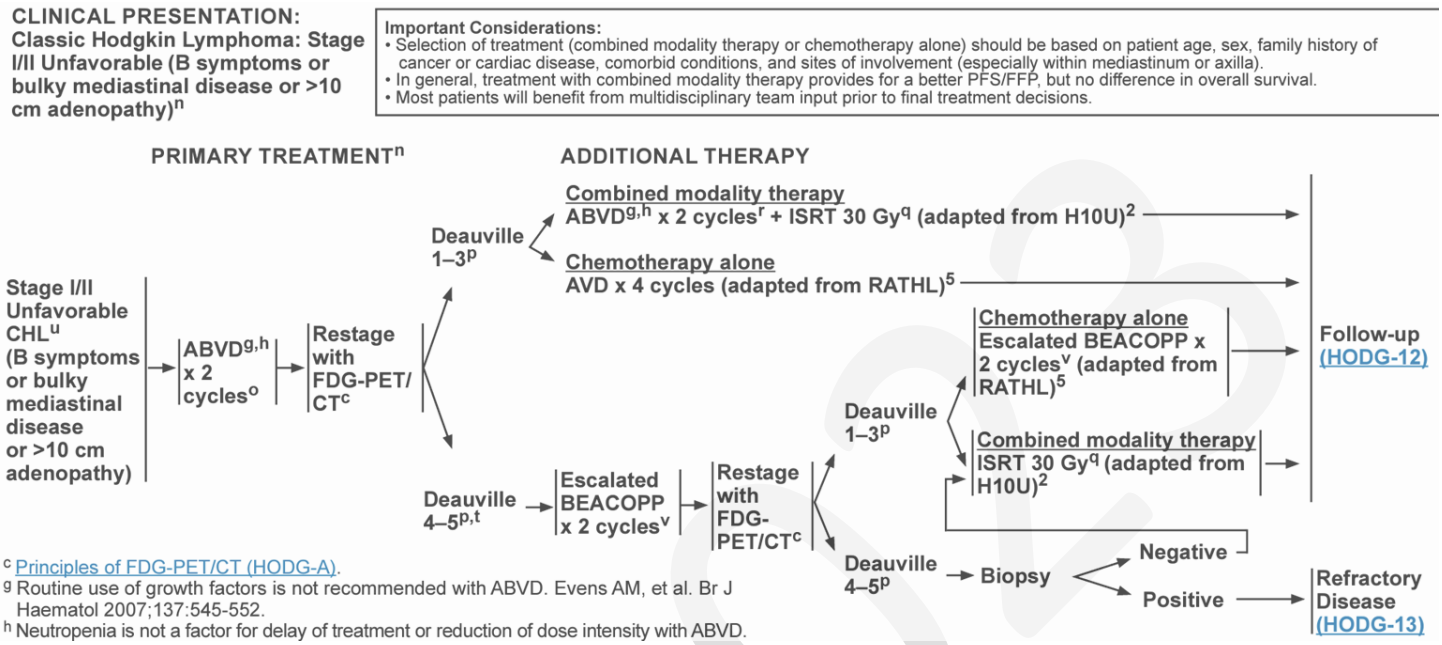
In 273 of 713 patients ITT = inadequate response → YES RT → 5-year EFS 88·6% (95% CI 84·8–92·5) → 95% CI included 90% target rate.

The most common grade 3–4 adverse events were neutropenia (in 597 [88%] of 680 patients) and leukopenia (437 [61%] of 712). There were no treatment-related deaths.

Interpretation On the basis of all the evidence, radiotherapy could be omitted in patients with early-stage classical Hodgkin lymphoma and an adequate response to OEPA, but patients with risk factors might need more intensive treatment.

Early-Stage HL: Unfavorable

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



[c] Principles of FDG-PET/CT (HODG-A).
[g] Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.
[h] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.

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

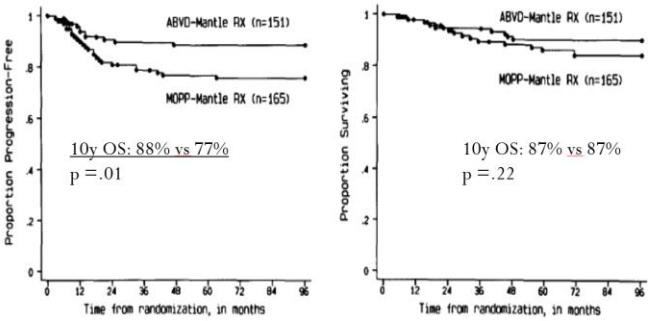


Fig 4. EORTC H6U trial: progression-free survival by treatment group. Log-rank test: P = .01.

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%**.

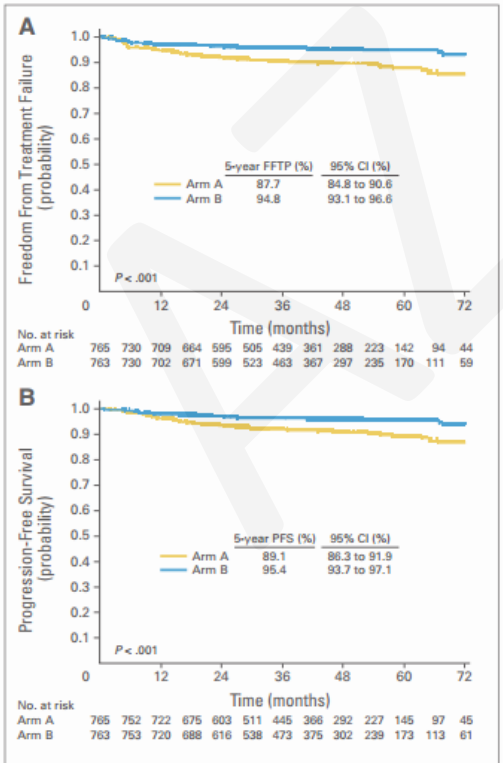
Toxicity: 20 Gy did have less mucositis, n/v, GI tract dysphagia. **BEACOPP was worse** (↑ Grade 3 tox and hospitality).

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 get away with 20 Gy + Beacopp but not ABVD (aka HD11), 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 ("17" + CALGB)

GHSG HD17

←R→ 1100 early-stage unfavorable HL (all histologies) **AGE < 60,** ECOG ≤ 2 | 1. 2+2 (escBEACOPP / ABVD) → 30 Gy I**F**RT | 2. 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.

*****Important to notice the radiation technique IFRT vs. INRT.

CALGB 50801

PURPOSE Patients with bulky stage I/II classic Hodgkin lymphoma (cHL) are typically treated with chemotherapy followed by radiation. Late effects associated with radiotherapy include increased risk of second cancer and cardiovascular disease. We tested a positron emission tomography (PET)–adapted approach in patients with bulky, early-stage cHL, omitting radiotherapy in patients with interim PET-negative (PET−) disease and intensifying treatment in patients with PET-positive (PET+) disease.

←R→ 94 patients bulky disease (mass > 10 cm or 1/3 the max diameter CXR) → 2C ABVD → PET2.

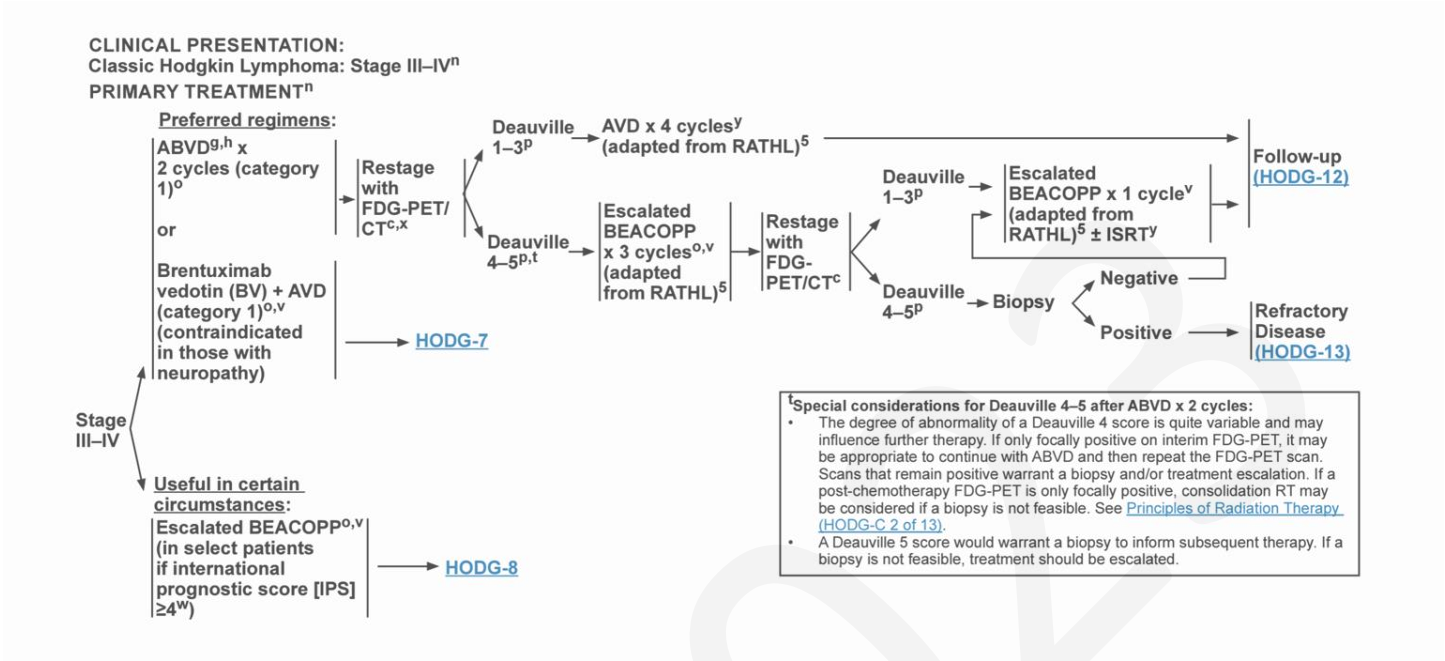
If PET2– (Score 1-**3**) → 4C ABVD.
If PET2+ → 4C escBEACOPP → 30.6 Gy IFRT

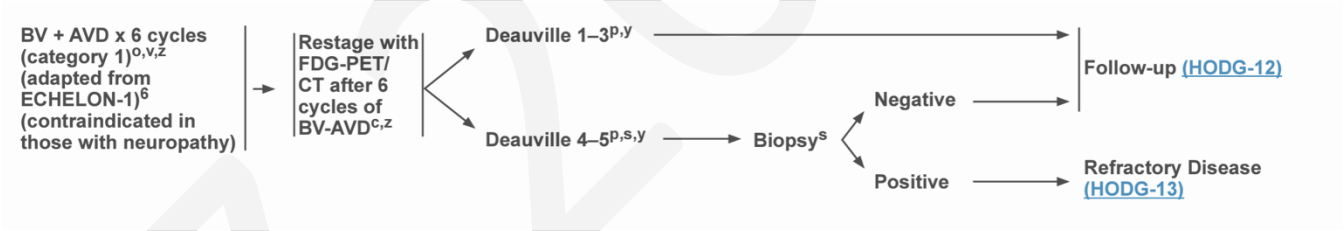
90% Stage II. 51% IIB/IIBE.

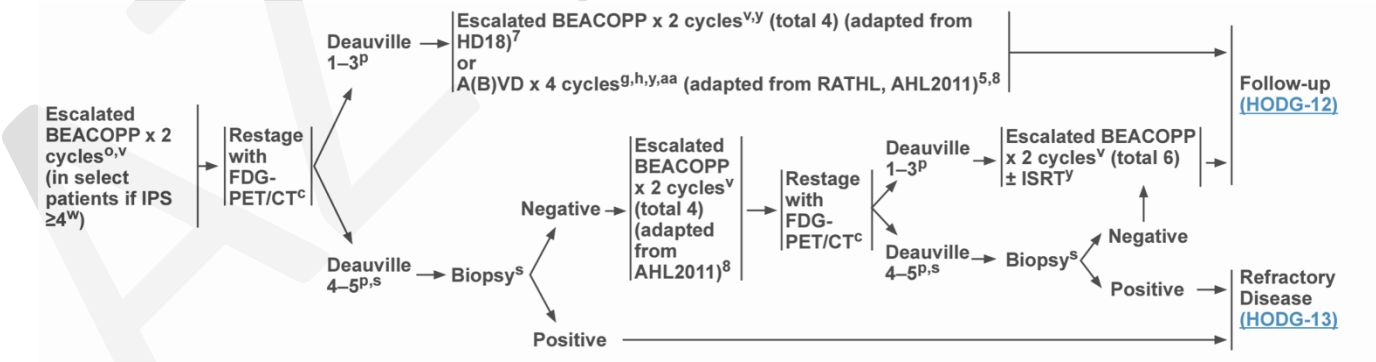
LaCasce, JCO 2022

78% were PET2– and 22% were PET2+.
3-year PFS PET2– 93.1% vs. PET2+ 89.7%. 3-year OS 98.6% vs. 94.4%.
The predominant toxicity was neutropenia, with 9% of patients developing febrile neutropenia and one developing sepsis.
CONCLUSION Our study of PET-adapted therapy in bulky stage I/II cHL met its primary goal and was associated with an excellent 3-year PFS rate of 92.3% in all patients, with the majority being spared radiotherapy and exposure to intensified chemotherapy.

Advanced Stage HL







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.

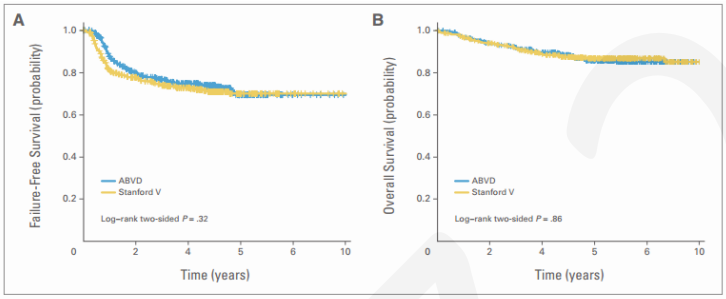


Fig 2. (A) Failure-free (P = .32) and (B) overall survival (P = .86) are shown for all patients, showing no difference between the two arms. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

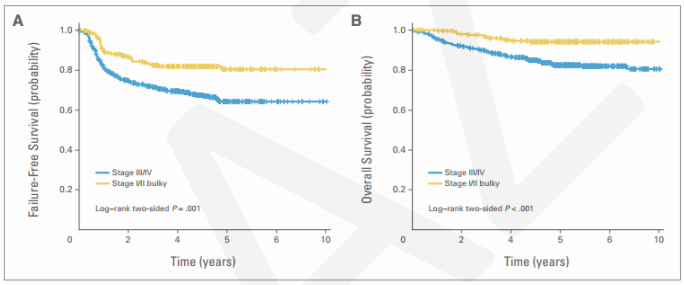


Fig 3. Patients with locally extensive disease (stage I to II bulky) were compared with patients with advanced disease (stage III to IV); patients with locally advanced disease had better (A) failure-free survival (FFS; P = .001) and (B) overall survival (OS; P = .002), but there were no differences 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

Stage 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?

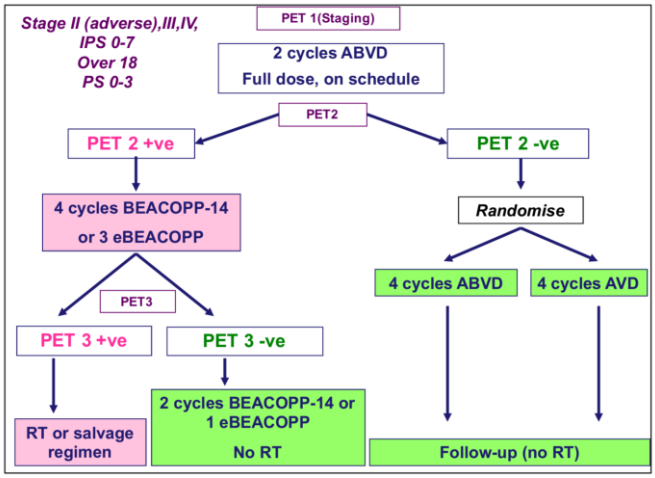
All ABVD x 2c → PET/CT if D. 1-3 ←R→ 1. ABVD x 4c 2. AVD (no bleo) x 4c

If D. 4-5 all BEACOPP (BEACOPP-14 x **4c** or escBEACOPP **x 3c**)

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

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)

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

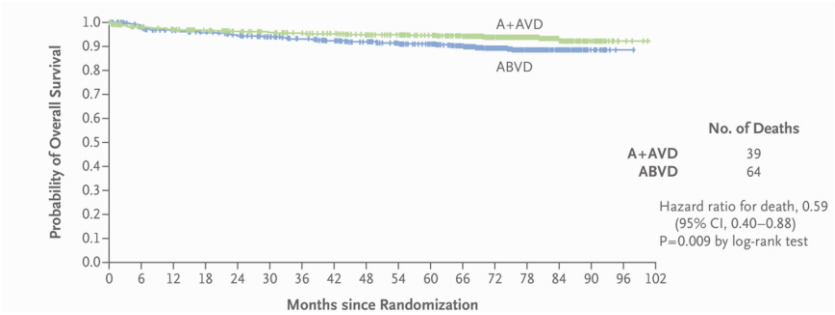
3-year PFS 82.6 3-year OS 95.8%.

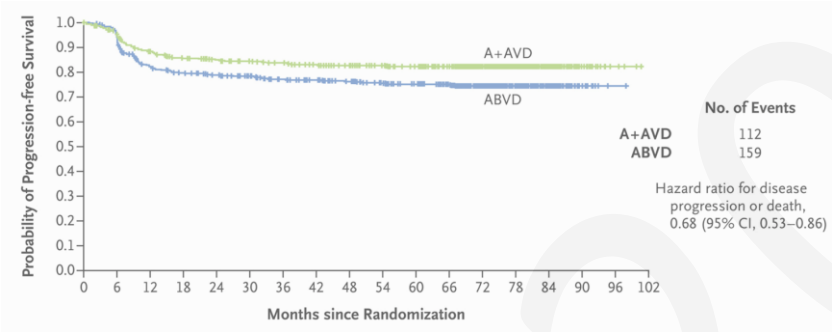
CONCLUSIONS: AVD is not-noninferior but results remain excellent and bleomycin omission may be reasonable (accepted by NCCN 2017).

Newer Studies (Echelon-1, "18")

ECHELON-1

BACKGROUND Brentuximab vedotin is an anti-CD30 antibody (A) –drug conjugate that has been approved for relapsed and refractory Hodgkin lymphoma.
←R→ 664 previously untreated stage III or IV classic Hodgkin lymphoma → | 1. A + 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.
1^{O} mod PFS.



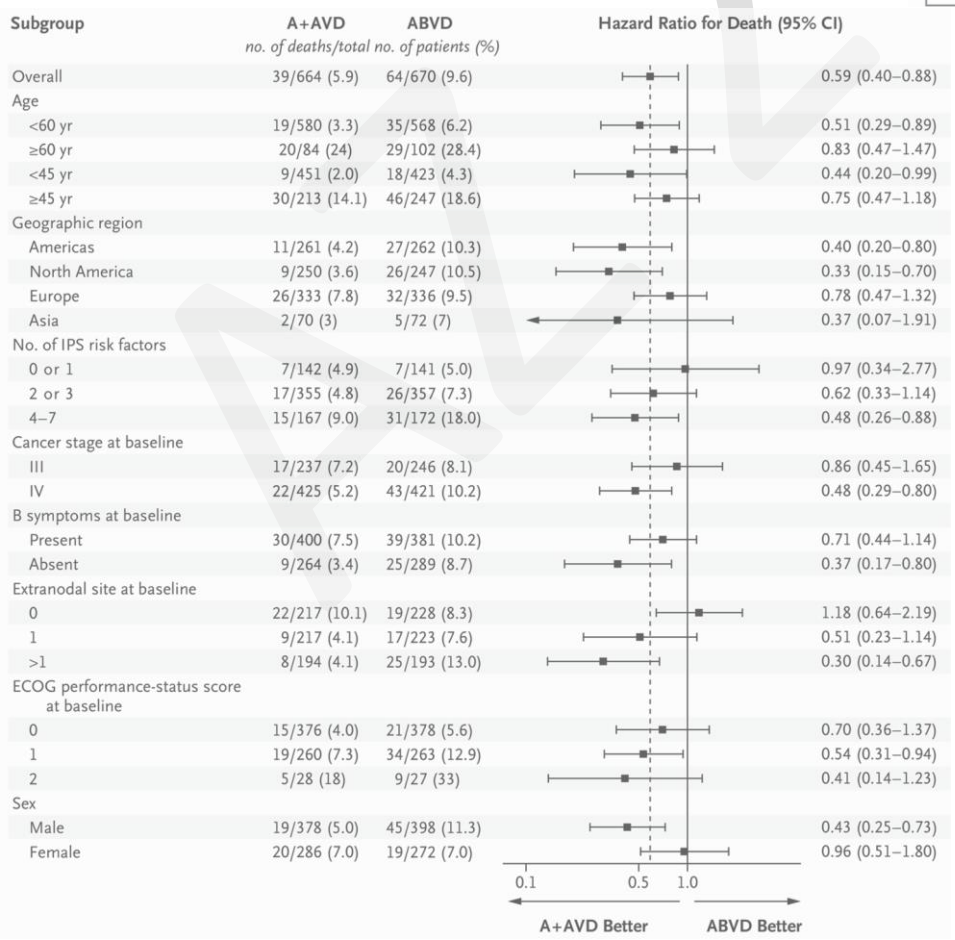


Ansel, NEJM 2022 6-years (73 months)
6-year OS 93.9% vs. 89.4% (HR 0.59, SS).

CONCLUSIONS
Patients who received A+AVD for the treatment of stage III or IV Hodgkin's lymphoma had a survival advantage over those who received ABVD

Table 1. **Summary of Causes of Death (Safety Population).***

Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1



Comment: Concurrent RT with BV may be safe
https://www.advancesradonc.org/article/S2452-1094(23)00108-2/fulltext

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.

HD18 – Rituximab

Background – Could early interim PET-imaging after BEACOPPx2 + Rituximab ↑ PFS in advanced HD?

←R→ 1100 of which 440 were randomized… <u>All 2 cycles of $BEACOPP_{esc}$ → PET-2 + → | 1. $BEACOPP_{esc}$ | 2. R-$BEACOPP_{esc}$ |</u>. 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.

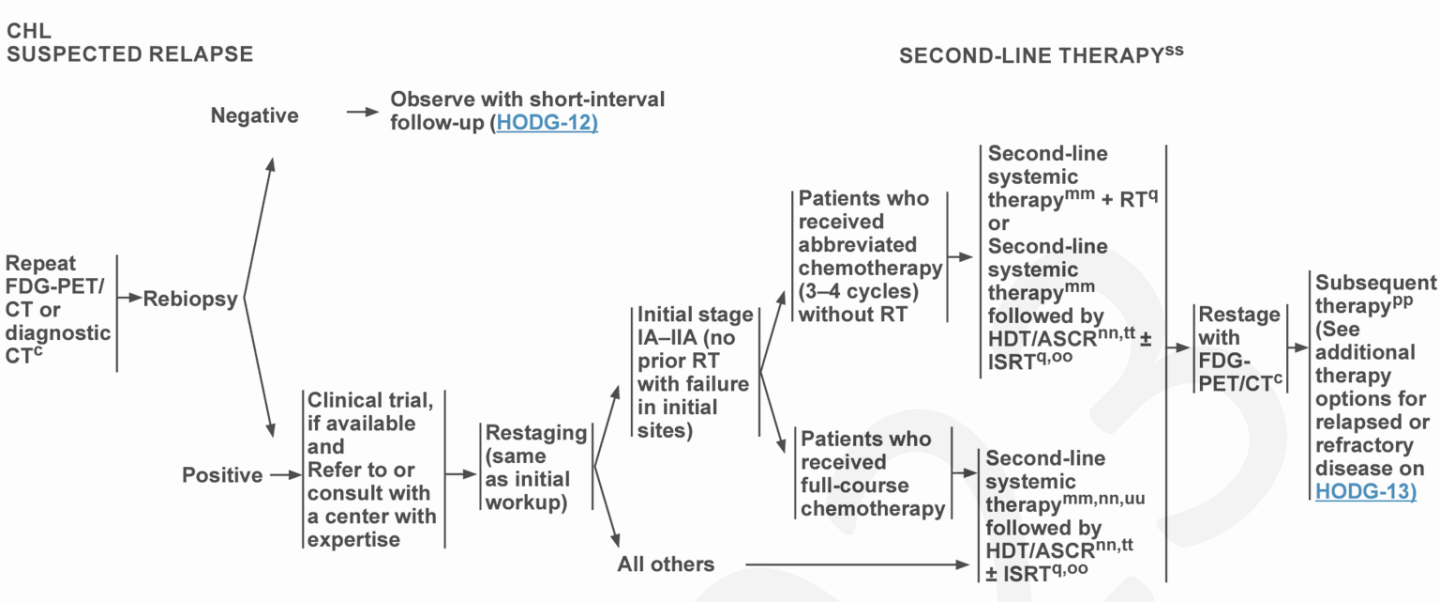
Borchmann, Lancet 2017.

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.

Relapsed/Refractory HL



Classic Hodgkin Lymphoma

- **Consider the following when selecting re-induction or subsequent therapy:**
  - **Clinical trial enrollment**
  - **Referral to a center with expertise**

Adults Age 18–60 Years	
Second-Line and Subsequent Therapy[i,j] (in alphabetical order)	**Therapy for Disease Refractory to at Least 3 Prior Lines of Therapy (in alphabetical order)**
• BV[1] • BV + bendamustine[2] • BV + nivolumab[3] • DHAP (dexamethasone, cisplatin, high-dose cytarabine)[4,5] • Gemcitabine/bendamustine/vinorelbine[6] • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[7] • GVD + pembrolizumab[8] • ICE (ifosfamide, carboplatin, etoposide)[5,9,10] • ICE + brentuximab vedotin[11] • ICE + nivolumab[12] • IGEV (ifosfamide, gemcitabine, vinorelbine)[13] • Pembrolizumab[14,15] • Pembrolizumab + ICE[16]	• Bendamustine[17] • Bendamustine + carboplatin + etoposide[18] • Everolimus[19] • GCD (gemcitabine, cisplatin, dexamethasone)[20] • GEMOX (gemcitabine, oxaliplatin)[21] • Lenalidomide[22] • Nivolumab[23,24] • Vinblastine[25]

Adults Age >60 Years or Adults With Poor Performance Status or Substantial Comorbidities
• Outcomes are uniformly poor for patients with relapsed or refractory disease.[26] • No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended. • Individualized treatment is necessary. Palliative therapy options include: ▸ Bendamustine ▸ BV ▸ ISRT[c] ▸ Nivolumab or pembrolizumab. See Checkpoint Inhibitors (CPI) HODG-B (4 of 7)

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.

Studies (Checkmate 744, Athera, Ansell PD-1)

CheckMate 744 Single Arm **Low-Risk Relapsed Classic HL**

Purpose/Objective(s): Standard of care treatment for patients with relapsed and refractory classic Hodgkin lymphoma (RRHL) involves second line therapy followed by high dose therapy and autologous stem cell transplant (HDT/ASCT) and carries with it significant costs and toxicities to the patient. Some patients with RRHL may not require such intensive therapy, especially in the era of targeted chemotherapy and checkpoint inhibitors. CheckMate 744 (NCT02927769) evaluated a novel second-line therapy that omits HDT/ASCT by combining brentuximab vedotin (BV) and a nivolumab (N) followed by consolidative ISRT for low risk RRHL.

Single Arm Prospective: 28 patients aged 5–30 y with 1 prior treatment **without HDT/ASCT**.

Median age (range) was 17 (6–27) years old and 64% of patients were aged < 18 y

Low-risk RRHL = relapse without B symptoms
extranodal disease
limited sites of relapse (=4 sites ↑ diaphragm or =3 sites ↑/↓ the diaphragm)
+ AND with initial Stage IA, IIA with relapse <1 year if they received =3 cycles of chemotherapy and **no RT**
OR Stage IA/B, IIA/B, IIIA = 1 year.

Patients received 4 cycles of N + BV induction

→ IF complete metabolic response (CMR) → additional 2 cycles of N + BV before → **RT consolidation**.

→ IF suboptimal response → received 2 cycles of BV + bendamustine intensification.
→ IF THEN CMR → **RT consolidation**.

RT was delivered to a dose of 30-30.6 Gy at 1.5-1.8 Gy/fraction to an ISRT volume. RT consolidation was delivered using 3D-CRT, IMRT, or proton therapy.

Hoppe, ASTRO 2023 31.2 months follow-up

Most (79%) pts had stage II disease at diagnosis and 82% had relapsed = 12 mo after first line treatment.

Of 27 pts continuing in study after induction N + BV
6 received bendamustine + BV intensification
92.9% achieved CMR

22 patients received RT consolidation.

3-year EFS 86.9% 3-year PFS 95%.

Conclusion: A novel combination of N + BV followed by ISRT was an effective second line therapy. This treatment regimen allowed patients to forgo high dose therapy and transplant in favor of consolidative radiotherapy using ISRT. Larger studies challenging the role of high dose therapy and transplant are needed for RRHL.

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.

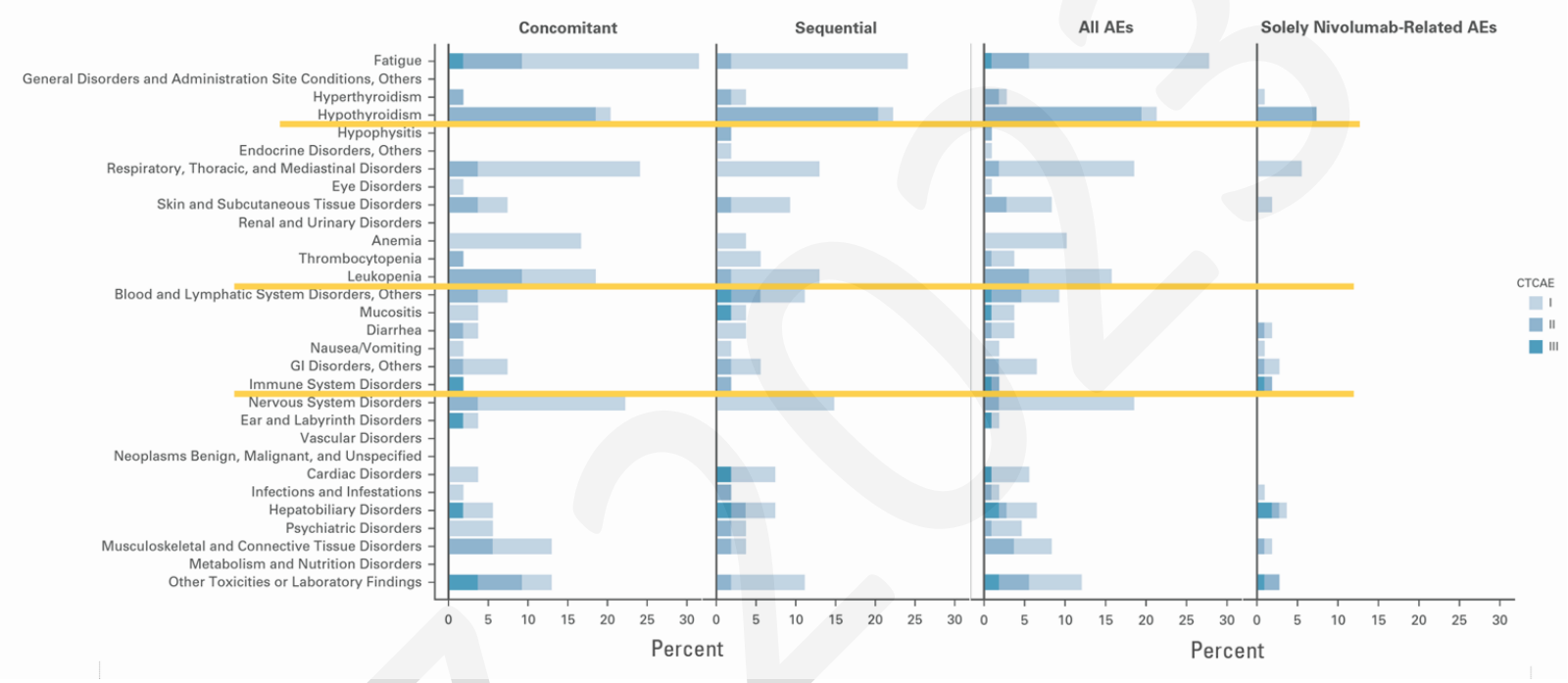
23 patients refractory HL 78% previous SCT and 78% previously treated with BV

Patients received Nivo 3 mg/kg q2weeks. OBJECTIVE RESPONSE 87%, CR 17%

Immunotherapy

NIVAHL
←R→ Phase II 109 patients early-stage unfavorable classical Hodgkin lymphoma (HL), by GHSG criteria.
| 1. concomitant 4 × cycles of N-AVD (4 × N-AVD, group A) | 2. sequential 4 × nivo → 2 × N-AVD, → 2 × AVD (Group B) |.
All → consolidated by 30 Gy involved-site radiotherapy (ISRT).

Bröckelmann, JCO 2023 **41 month**
OS = 100% in both treatment groups. PFS 98% and 100%. in the sequential and concomitant nivolumab, doxorubicin, vinblastine, and dacarbazine treatment groups, respectively.
1 failure was seen with the single agent nivo treatment period in Group B. Planned BEACOPP + ISRT = CR.
Nivo-related toxicity = hypothyroidism (21%). Correlation of hypothyroidism with female gender (87%).



MANAGEMENT OF CHL DURING PREGNANCY

General Principles

- **CHL is the most common hematologic malignancy diagnosed during pregnancy, as the peak incidence coincides with the reproductive years.[1] CHL accounts for 6% of all cancers diagnosed during pregnancy.[2]**
- **CHL in patients who are pregnant is enriched for the nodular sclerosis subtype and has a similar clinical presentation, natural history, and prognosis compared to patients who are not pregnant.[1]**
- **Management of CHL during pregnancy requires a multidisciplinary approach including medical oncology, high-risk obstetrics, and neonatology, with the goal of maximizing the cure rate for the patient and allowing for delivery of a healthy child.**
- **Radiologic staging during pregnancy should include a single view (posteroanterior [PA]) chest X-ray with abdominal shielding and an abdominal ultrasound or MRI without gadolinium.[1,2] FDG-PET and CT imaging should be avoided.**
- **Treatment of the patient who is pregnant should be individualized based on the symptomatic burden of disease, gestational age, and patient's wishes. The NCCN Panel's suggested approach to management by trimester is summarized below.**
- **Chemotherapy should be avoided in the first trimester given the high risk of congenital malformations or fetal demise.[1,2]**
- **ABVD can be safely administered in the second and third trimesters with excellent maternal and fetal outcomes.[3-5]**
- **Intensive regimens such as escalated BEACOPP and BV + AVD should be avoided during pregnancy given the paucity of data. RT should also be avoided during pregnancy given potential risks of teratogenesis, prematurity, cognitive impairment, and childhood malignancy.[6]**
- **Consultation with pharmacy is recommended to ensure supportive medications are appropriate for use in pregnancy. G-CSF is category C in pregnancy. Ondansetron and metoclopramide are the preferred antiemetics for patients who are pregnant.[7,8]**
- **Breastfeeding should be avoided in patients receiving chemotherapy in the post-partum period.[1]**

SUGGESTED TREATMENT APPROACH BY GESTATIONAL AGE AND SYMPTOMATIC DISEASE BURDEN

First Trimester

- **If asymptomatic or minimally symptomatic: delay treatment with close observation until second or third trimester**
- **If severe symptoms or organ compromise: consider referral to center with expertise, consider pregnancy termination and urgent treatment, or single-agent vinblastine followed by ABVD after end of first trimester**

Second or Third Trimester

- **If asymptomatic or minimally symptomatic: delay treatment with close observation until after delivery**
- **If severe symptoms or organ compromise: treat with ABVD; work with high-risk obstetrics to avoid delivery while at nadir**

[1] Bachanova V, Connors JM. Hodgkin lymphoma in pregnancy. Curr Hematol Malig Rep 2013;8:211-217.
[2] Dunleavy K, McLintock C. How I treat lymphoma in pregnancy. Blood 2020;136:2118-2124.
[3] Evens AM, Advani RH, Press OW, et al. Lymphoma occurring during pregnancy: antenatal therapy, complications, and maternal survival in a multicenter analysis. J Clin Oncol 2013;31:4132-4139.
[4] Pinnix CC, Osborne EM, Chihara D, et al. Maternal and fetal outcomes after therapy for Hodgkin or non-Hodgkin lymphoma diagnosed during pregnancy. JAMA Oncol 2016;2:1065-1069.
[5] Maggen C, Dierickx D, Lugtenburg P, et al. Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. Lancet Haematol 2019;6:e551-e561.
[6] Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys 2009;73:1304-1312.
[7] Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med 2013;368:814-823.
[8] Matok I, Gorodischer R, Koren G, et al. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med 2009;360:2528-2535.

Follow-up

FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

- Complete response (CR) should be documented including reversion of FDG-PET/CT to "negative" within 3 mo following completion of therapy.
- It is recommended that the patient be provided with a treatment summary at the completion of therapy, including details of RT, organs at risk (OARs), and cumulative anthracycline dosage given.
- Follow-up with an oncologist is recommended and should be coordinated with the primary care physician (PCP), especially during the first 5 y after treatment to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease (see NCCN Guidelines for Survivorship).[kk,1] Late relapse or transformation to large cell lymphoma may occur in NLPHL.
- The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.

	Follow-up After Completion of Treatment Up to 5 Years
Interim H&P	• Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually.
Vaccines	• Annual influenza vaccine and other vaccines as clinically indicated (see NCCN Guidelines for Survivorship).
Laboratory studies[2]:	▸ CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated. ▸ Thyroid-stimulating hormone (TSH) at least annually if RT to neck.
Counseling	Reproduction, health habits, psychosocial, cardiovascular, breast awareness, skin cancer risk, end-of-treatment discussion (see NCCN Guidelines for Survivorship).
Imaging	• Imaging should only be obtained if significant clinical concern for relapse or as mandated if enrolled in an active protocol. ▸ If imaging is necessary, it may include diagnostic CT at 3- to 6-month intervals for up to 2 years as clinically indicated, or after 2 years if relapse is suspected. ▸ FDG-PET/CT should only be done if last FDG-PET/CT was Deauville 4–5, to confirm CR at the end of all prescribed therapy including RT. Once negative, repeat FDG-PET/CT should not be done unless evaluating suspicious findings on H&P or CT. • Surveillance FDG-PET/CT should not be done routinely due to risk for false positives. Management decisions should not be based on FDG-PET scan alone; clinical or pathologic correlation is needed.

Follow-up and Monitoring After 5 Years[kk,1]

- Interim H&P: Annually
  - ▸ Annual blood pressure, aggressive management of cardiovascular risk factors.
  - ▸ Pneumococcal, meningococcal, and Haemophilus influenzae type b revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (See CDC recommendations).
  - ▸ Annual influenza vaccine and other vaccines as clinically indicated (see NCCN Guidelines for Survivorship).
  - ▸ For guidance on COVID-19 vaccination, please see the CDC for Use of COVID-19 Vaccines in the US.
  - ▸ For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.
  - ▸ For guidance on the adolescent and young adult population, see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
- Cardiovascular symptoms may emerge at a young age.
  - ▸ Consider stress test/ECHO at 10-y intervals after treatment is completed.
  - ▸ Consider carotid ultrasound at 10-y intervals if neck irradiation.
- Laboratory studies:
  - ▸ CBC, platelets, chemistry profile annually
  - ▸ TSH at least annually if RT to neck
  - ▸ Biannual lipids
  - ▸ Annual fasting glucose
- Annual breast screening: Initiate at age 40 y or 8 y post-therapy, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for patients assigned female at birth (AFAB)[ll] who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Perform other routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per the NCCN Guidelines for Detection, Prevention, and Risk Reduction and the ACS Cancer Screening Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast awareness, and skin cancer risk (see NCCN Guidelines for Survivorship).
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.

Side Effect Studies

Cardiac HL CHD

Background Previous efforts to predict absolute risk of treatment-related cardiovascular diseases (CVDs) have mostly focused on childhood cancer survivors. We aimed to develop prediction models for risk of coronary heart disease (CHD) and heart failure (HF) for survivors of adolescent/adult Hodgkin lymphoma (HL).

RR 1433 5-year HL survivors treated between 1965 and 2000 and age 18-50 years at HL diagnosis, with complete data on administered chemotherapy regimens, radiotherapy volumes and doses, and cardiovascular follow-up.

De Vries, JCO 2023 **24 years**

Median follow-up of 24 years, 341 survivors had developed CHD and 102 had HF.

We were able to predict CHD and HF risk at 20 and 30 years after treatment with moderate to good overall calibration and moderate discrimination (areas under the curve: 0.68-0.74), which was confirmed by external validation for the CHD model (areas under the curve: 0.73-0.74).

On the basis of our model including prescribed mediastinal radiation dose, 30-year risks ranged from 4% to 78% for CHD and 3% to 46% for HF, depending on risk factors. A male smoker age 30-50 with >35Gy to the mediastinum = 77.8% cumulative risk of CHD over 30 years vs. a female nonsmoker age 18-24 years who receives no mediastinal RT = 3.6% risk.

CONCLUSION

We developed and validated prediction models for CHD and HF with good overall calibration and moderate discrimination. These models can be used to identify HL survivors who might benefit from targeted screening for CVD and early treatment for CVD risk factors.

Utah Cancer Registry **Mental Health**

Background: Long-term mental health outcomes were characterized in patients who were diagnosed with Hodgkin lymphoma (HL), and risk factors for the development of mental health disorders were identified.

Methods: Patients who were diagnosed with HL between 1997 and 2014 were identified in the Utah Cancer Registry. Each patient was matched with up to five individuals from a general population cohort identified within the Utah Population Database, a unique source of linked records that includes patient and demographic data. In total, 795 patients who had HL were matched with 3575 individuals from the general population.

Tao, Cancer 2022

Compared with the general population, patients who had HL had a higher risk of any mental health diagnosis (hazard ratio, 1.77; 95% confidence interval, 1.57-2.00). Patients with HL had higher risks of anxiety, depression, substance-related disorders, and suicide and intentional self-inflicted injuries compared with the general population. The main risk factor associated with an ↑ risk of being diagnosed with mental health disorders was undergoing hematopoietic stem cell transplantation, with a hazard ratio of 2.06 (95% confidence interval, 1.53-2.76). The diagnosis of any mental health disorder among patients with HL was associated with a detrimental impact on overall survival; the 10-year overall survival rate was 70% in patients who had a mental health diagnosis compared with 86% in those patients without a mental health diagnosis ($p < .0001$).

Conclusions: Patients who had HL had an increased risk of various mental health disorders compared with a matched general population. The current data illustrate the importance of attention to mental health in HL survivorship, particularly for patients who undergo therapy with hematopoietic stem cell transplantation.