National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Hodgkin Lymphoma

Version 1.2024 — May 14, 2024

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 1.2024 of the NCCN Guidelines for Pediatric Hodgkin Lymphoma from Version 2.2023 include:

Global Changes
- References updated throughout the Guideline

PHL-1
- Essential, bullet 10 modified: ~~Fertility/fertility preservation~~ *Counseling on infertility risk* (*see* NCCN Guidelines for AYA Oncology) (Also for PHL-E 3 of 4)

PHL-2
- Footnote i added: Risk stratification and staging criteria differ for adult trials/regimens. See NCCN Guidelines for Hodgkin Lymphoma (Adult).

PHL-3
- Footnote removed from EuroNet-PHL-C1: Study is complete and data are emerging.
- Footnote q added: Omission of ISRT should be more strongly considered for patients who meet the GPOH-2002 response criteria (Mauz-Korholz C, et al. J Clin Oncol 2010;28:3680-3686).

PHL-4
- Useful in certain circumstances, new regimen added: Nivolumab-AVD (category 2B) (S1826)

PHL-5
- Other recommended regimens, new regimen aded: Nivolumab-AVD (category 2B) (S1826)
- Useful in certain circumstances
  - Regimen removed: ABVE-PC x 2 cycles (AHOD1331)
  - Regimen removed: ABVD

PHL-7
- Footnote y modified: Data are limited on the use of rituximab for *early-stage* NLPHL. (Also for PHL-E 2 of 4)
- Footnote aa modified: *Advanced-stage* NLPHL is rare in pediatric patients. Confirm pathologic diagnosis prior to treatment. See Principles of Pathology (PHL-B).

PHL-8
- Disease surveillance/follow-up after completion of treatment
  - Imaging, bullet 1 modified: Consider *end-of-therapy* ECHO.

PHL-9
- Footnote ff modified: Recommendations for those who may avoid ASCR: initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, *and* absence of extranodal disease or B symptoms at relapse. *Harker-Murray PD, et al. J Clin Oncol 2023;41(Suppl):7515-Abstract 7515.*

PHL-A (1 of 3)
- Protocol Rationale column removed for all regimens. (Also for PHL-A 2 of 3)
- OEPA/OEPA-COPDAC (EuroNet-PHL-C1), Criteria for RT
  - Bullet 1 modified: < CR on imaging after 2 cycles of OEPA *(applies to patients with low-risk [LR] disease on GPOH 2002)*
  - Bullet 3 modified: Patients with *LR*/IR/HR disease on C1 ~~(emerging data)~~ received RT only if FDG-PET positive (Deauville 3–5) or not in at least *partial response (*PR*)* after 2 cycles of OEPA
    - ◊ Sub-bullet added: Consider boost for residual mass >100 mL or <75% volume reduction and minimum volume >5 mL at early response assessment.
- ABVE-PC, high-risk (AHOD1331) category removed.
- Footnotes
  - Footnote a modified: Stage IVA was included in the *intermediate-risk* group in the trial, although *is* not recommended for standard care. (Also for PHL-A 2 of 3)
  - Footnote removed: Study is complete and data are emerging. (Also for PHL-A 2 of 3)

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Updates in Version 1.2024 of the NCCN Guidelines for Pediatric Hodgkin Lymphoma from Version 2.2023 include:

PHL-A (2 of 3)
- Bv-AVE-PC
  - Criteria for RT, bullet 4 modified: Consider treating without a boost for ~~lesions that were~~ *LMA that was* Deauville 3 after 2 cycles and continue*s* to be Deauville 3 after 5 cycles.

PHL-B (1 of 5)
- Histologic classification
  - Bullet 1 modified: Diagnosis should be established according to guidelines in the ~~2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues~~ *2022 World Health Organization (WHO) Classification of Haematolymphoid Tumours, 5th edition or the 2022 International Consensus Classification (ICC) of Mature Lymphoid Neoplasms.*
- NLPHL
  - Bullet 2 modified: Variant histologic patterns in NLPHL should be documented in the pathology report, where possible, as *T-cell-rich and/or diffuse* patterns ~~C–F~~ may be associated with higher risk of disease progression and relapse and shorter time to relapse.
- Footnotes
  - Footnote a revised: The different morphologic variants of CHL have different clinicopathologic associations and differential diagnoses. Refer to the ~~2017~~ *2022* WHO Classification *or ICC 2022* for more details.
  - Footnote b added: Per WHO 2022, NLPHL remains under the family of HL, while ICC 2022 replaces the term NLPHL with nodular lymphocyte-predominant B-cell lymphoma (NLPBL). Both classifications recognize the clinical and biologic similarities of NLPHL to an indolent B-cell lymphoma and NLPBL is an acceptable term per WHO 2022 (Alaggio R, et al. Leukemia 2022;36:1720-1748; Campo E, et al. Blood 2022;140:1229-1253).

PHL-C (1 of 3)
- Footnote c added: Measures to reduce brown fat activation, such as warming or pharmacologic suppression, may be considered to minimize false-positive findings.

PHL-D (1 of 2)
- Bullet 1 modified: These are only guiding principles of initial staging adapted from criteria of various protocols. This table is not intended to replace *protocol-specific* staging. Refer to applicable study protocol for complete staging details.
- Lung
  - Protocols, bullet 1 modified: E-lesions: *Extralymphatic* structures (lung lesions) contiguous with nodal masses are considered to be E-lesions.
- Bone
  - Protocols, bullet 3 modified: *Extralymphatic* structures (bone lesions) contiguous with nodal masses are considered to be E-lesions.

PHL-E (1 of 4)
- AVPC, note modified: *Cyclophosphamide* and doxorubicin dosing in AHOD0431 differs from AHOD03P1.
- ABVE-PC, high-risk (AHOD1331) category removed.

PHL-E (3 of 4)
- Footnote g modified: ~~Emerging d~~*D*ata are showing utility as a re-induction option; consider for subsequent therapy if not previously used.

PHL-F (2 of 4)
- Footnote a added: In HLHR13, post-chemotherapy volumes were irradiated.

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

INTRODUCTION

- **Consultation with centers participating in pediatric cooperative group trials is encouraged. The recommendations in these Guidelines are from the previous and most recently published trials.**
- **Referral to current clinical trials is encouraged where available.**
- **The pediatric Hodgkin lymphoma (HL) panel considers "pediatric" to include any patient aged ≤18 years, and may be applicable to adolescent and young adult (AYA) patients aged ≤39 years. Therefore, these Guidelines are intended to include AYA patients and may apply to patients treated in adult oncology settings. For general oncologic care of AYA patients, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.**

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DIAGNOSTIC WORKUP

- Excisional or incisional biopsy[a]
- Immunohisto-chemistry evaluation[b]

ADDITIONAL WORKUP

Essential:

- History and physical (H&P) including:
  - B symptoms (unexplained recurrent fever >38°C within the last month; drenching night sweats; or weight loss >10% of body weight within 6 months of diagnosis)
  - Examination of lymphoid regions, spleen
- Complete blood count (CBC) with differential
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
- Comprehensive metabolic panel
- Echocardiogram (ECHO) (especially if anthracycline-based chemotherapy is indicated)
- Chest x-ray posteroanterior (PA) and lateral views (if cross-sectional imaging not available or necessitated to determine bulk of disease for a clinical trial)[c]
- CT neck/chest/abdomen/pelvis with (IV ± oral) contrast or CT chest and MRI neck/abdomen/pelvis[c]
- FDG-PET/CT[d] or FDG-PET/MRI[d] (whole-body)[c]
- Pregnancy test for patients of childbearing potential
- Counseling on infertility risk[e] (see NCCN Guidelines for AYA Oncology)
- Psychosocial assessment (for AYA, see NCCN Guidelines for AYA Oncology)
- Counseling on cessation of smoking, drugs/illicit substances, vaping, and alcohol (see NCCN Guidelines for Smoking Cessation)

Useful in selected cases:

- Pulmonary function tests (PFTs) (including diffusing capacity [DLCO] if bleomycin indicated)[f]
- Electrocardiogram (ECG)
- HIV and hepatitis B/C testing (encouraged)
- Consider immunodeficiency workup (if young age [<5 years], recurrent infections, atypical presentation, personal or family history of immunodeficiency)
- Only consider bilateral bone marrow biopsy if there are cytopenias and negative FDG-PET[g]

CLINICAL PRESENTATION

- Classic Hodgkin lymphoma (CHL)[h] → Clinical Staging (PHL-2)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) → PHL-6

[a] Core needle biopsy may be adequate if it is diagnostic. Fine-needle aspiration (FNA) is discouraged in establishing a diagnosis. See Principles of Pathology (PHL-B).

[b] For typical immunophenotype, see Principles of Pathology (PHL-B).

[c] Diagnostic imaging should be done prior to initiating chemotherapy to allow for staging and risk stratification. Consultation with radiation oncologist when considering treatment options and adequacy of imaging for potential future radiation therapy (RT) is strongly recommended. See Principles of Imaging (PHL-C) and Principles of Staging (PHL-D).

[d] In cases of FDG-PET positivity where sites of disease are inconsistent with usual presentation of HL or if there is an unusual disease presentation [ie, HIV], additional clinical evaluation may be required for staging. See Principles of Staging (PHL-D). If FDG-PET negative for anatomic lesions of concern, biopsy should be considered.

[e] Fertility preservation is an option for some patients. Refer to fertility clinic for further discussion when able, prior to initiation of chemotherapy.

[f] In general, FEV1/FVC >60% by PFT is acceptable for use of bleomycin, unless due to large mediastinal mass from HL. For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry reading of >92% on room air.

[g] In most instances, if the FDG-PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is *not* assumed. If there are multifocal (≥3) skeletal FDG-PET lesions without cortical destruction on CT, marrow involvement may be assumed and a bone marrow biopsy is not needed to confirm involvement (Purz S, et al. J Clin Oncol 2011;29:3523-3528).

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

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CLINICAL STAGING OF CHL

Risk stratification is evolving. This table represents clinical trials with published data. Consider consultation with a center of expertise for patient care; enrollment in a clinical trial is preferred. Clinical trial staging may differ from this table, and close attention to trial eligibility and staging should be followed.

Clinical Stage[i] (ST-1)	Bulk (PHL-D)	E-lesions[k] (PHL-D)	ESR	Risk Group[l]
IA IIA	No	No	Any	Low risk (per EuroNet-PHL-C1)
	Yes	No	<30	Low risk (per EuroNet-PHL-C1) or Intermediate risk (per AHOD0031)
			≥30	Intermediate risk (per EuroNet-PHL-C1 or AHOD0031)
	Yes	Yes	Any	Intermediate risk (per EuroNet-PHL-C1 or AHOD0031)
IB	Any	No	<30	Low risk (per EuroNet-PHL-C1)
			≥30	Intermediate risk (per EuroNet-PHL-C1)
	Any	Any	Any	Intermediate risk (per AHOD0031)
IIB[j]	No	No	Any	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1)
	No	Yes	Any	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1)
	Yes	Any	Any	High risk (per AHOD1331)
	Yes	Yes	Any	High risk (per EuroNet-PHL-C1)
IIIA	Any	No	Any	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1)
	Any	Yes	Any	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1)
IIIB, IV	Any	Any	Any	High risk (AHOD1331 or EuroNet-PHL-C1)

Low-risk disease (PHL-3)

Intermediate-risk disease (PHL-4)

High-risk disease (PHL-5)

[i] Risk stratification and staging criteria differ for adult trials/regimens. See NCCN Guidelines for Hodgkin Lymphoma (Adult).
[j] Only IIB with bulk was upstaged to high risk in the most recent series of COG clinical trials. The panel acknowledges that current trials have modified these groupings.
[k] E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by contiguous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation (Engert A, et al. N Engl J Med 2010;363:640-652; Lister TA, et al. J Clin Oncol 1989;7:1630-1636; Spijkers S, et al. Pediatr Radiol 2019;49:266-276).
[l] GPOH-HD-2002: Mauz-Körholz C, et al. J Clin Oncol 2010;28:3680-3686; EuroNet-PHL-C1: Mauz-Körholz C, et al. Lancet Oncol 2022;23:125-137; AHOD0031: Friedman DL, et al. J Clin Oncol 2014;32:3651-3658; AHOD1331: Kelly KM, et al. Br J Haematol 2019;187:39-48; Castellino SM, et al. N Engl J Med 2022;387:1649-1660.

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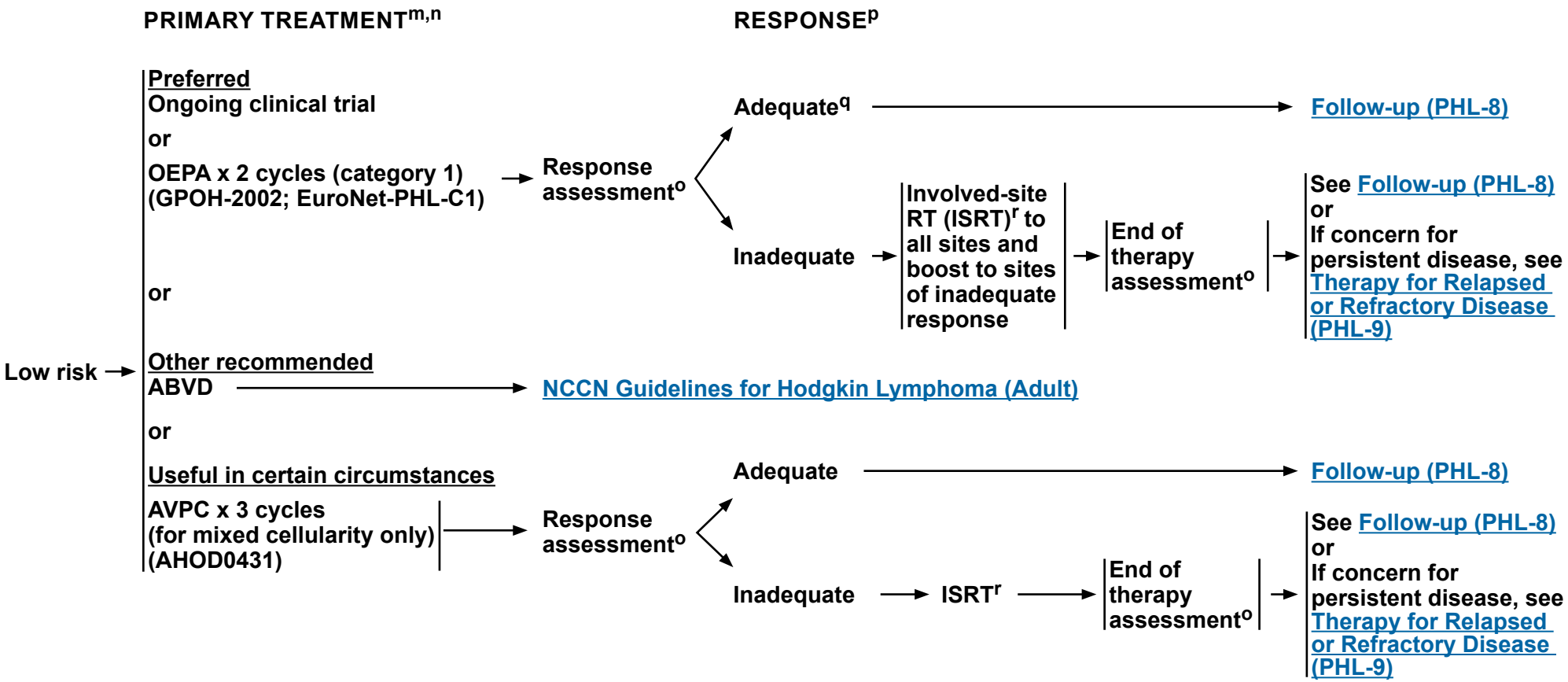
CLINICAL PRESENTATION: CHL



[m] Regimens are based off of studies with pediatric data.
[n] Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or FDG-PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with FDG-PET.
[p] Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[q] Omission of ISRT should be more strongly considered for patients who meet the GPOH-2002 response criteria (Mauz-Korholz C, et al. J Clin Oncol 2010;28:3680-3686).
[r] Principles of Radiation Therapy (PHL-F).

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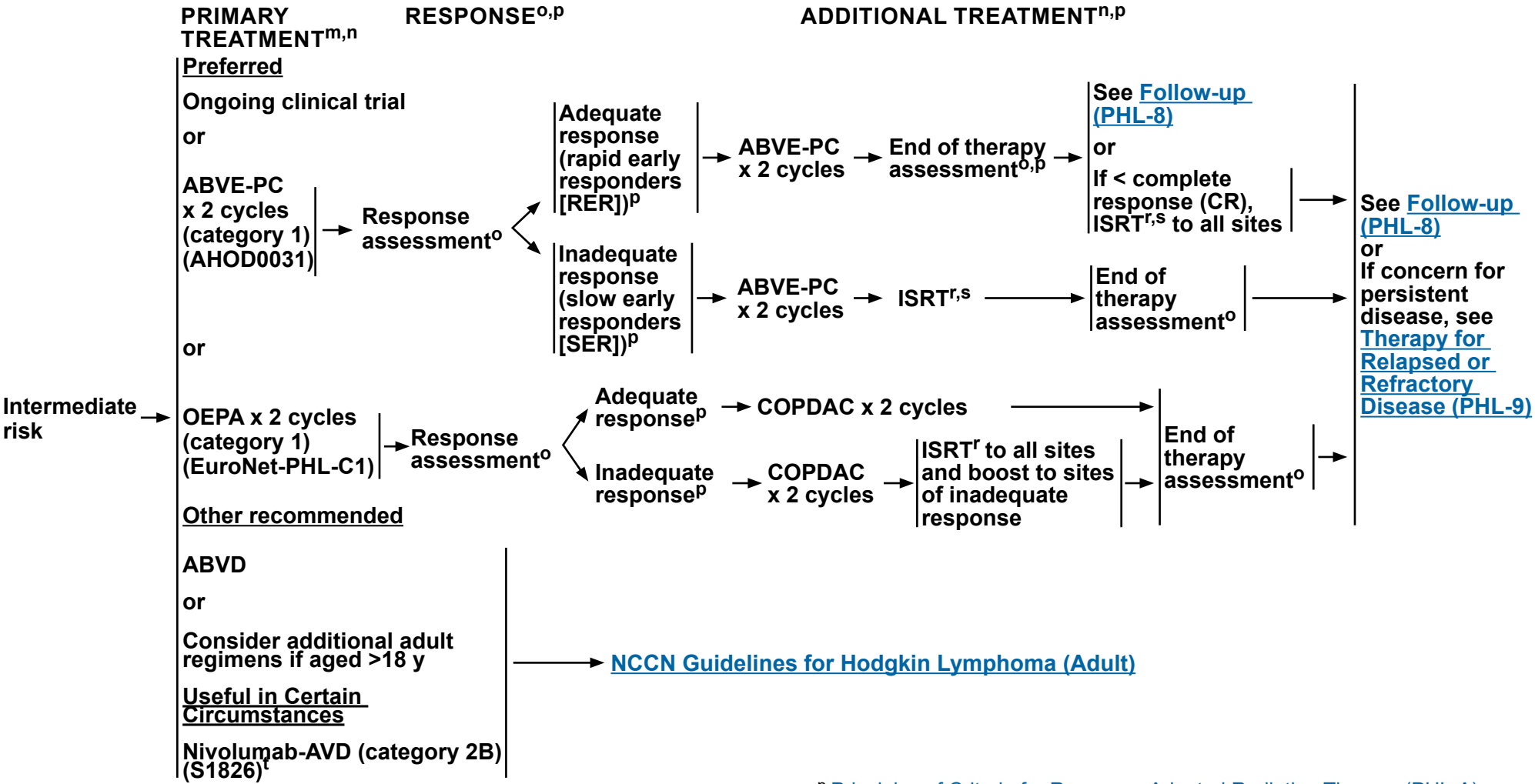
CLINICAL PRESENTATION: CHL



[m] Regimens are based off of studies with pediatric data.
[n] Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or FDG-PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with FDG-PET.
[p] Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[r] Principles of Radiation Therapy (PHL-F).
[s] ISRT can safely replace involved-field RT (IFRT) (PHL-F).
[t] This regimen is only for patients ≥12 years of age with stage III-IV disease. Nivolumab is dosed per kg in patients <18 years of age.

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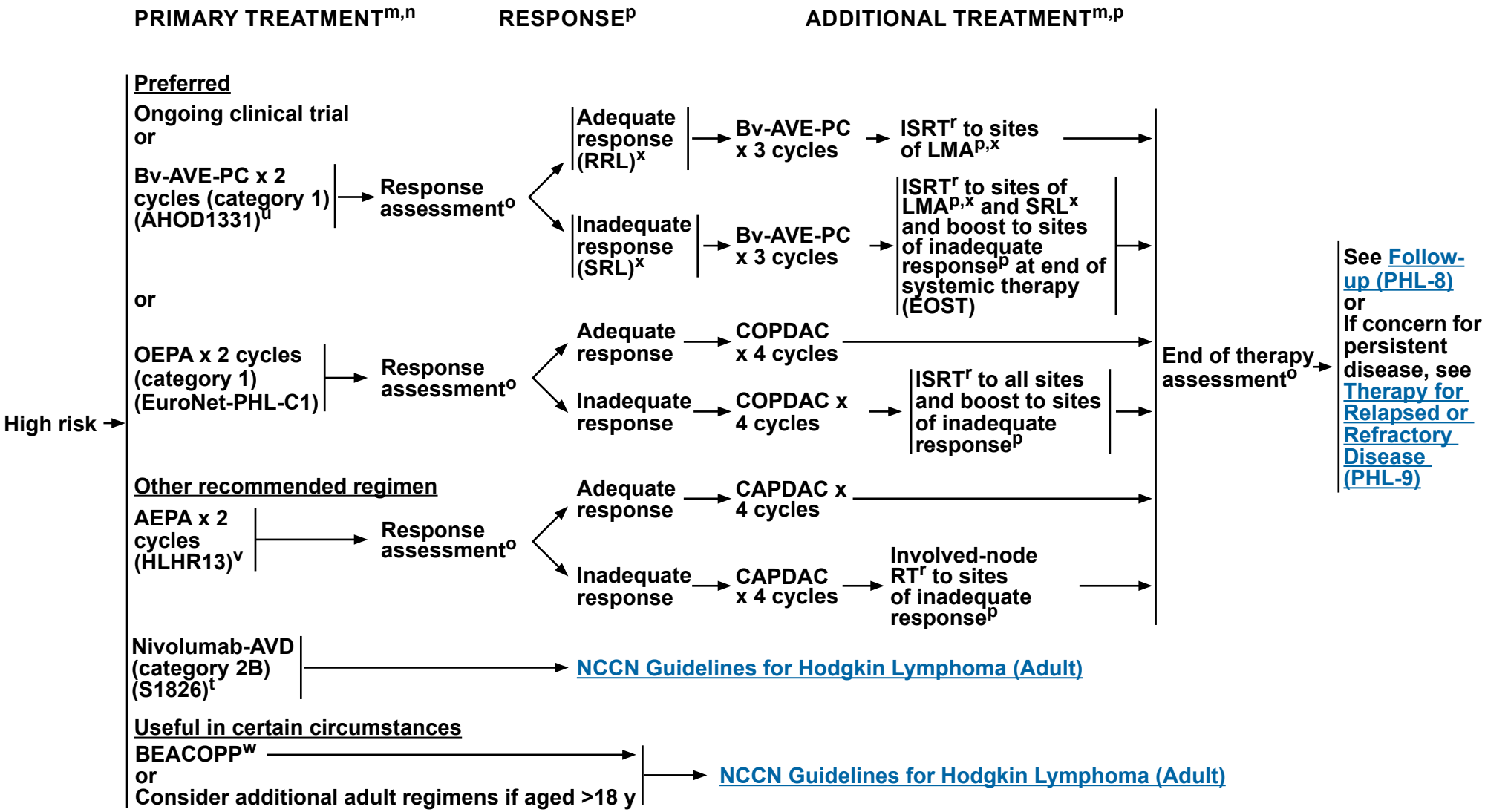
CLINICAL PRESENTATION: CHL



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Footnotes on PHL-5A

FOOTNOTES

[m] Regimens are based off of studies with pediatric data.
[n] Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or FDG-PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with FDG-PET.
[p] Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[r] Principles of Radiation Therapy (PHL-F).
[t] This regimen is only for patients ≥12 years of age with stage III-IV disease. Nivolumab is dosed per kg in patients <18 years of age.
[u] Cyclophosphamide dosing in AHOD0031 differs from AHOD1331. Castellino SM, et al. N Engl J Med 2022;387:1649-1660. See Principles of Systemic Therapy (PHL-E).
[v] Metzger ML, et al. J Clin Oncol 2021;39:2276-2283.
[w] BEACOPP has been studied in pediatric trials (ie, CCG-59704). Consider only for select patients with extensive disease given concerns for acute and long-term toxicity risk. See NCCN Guidelines for Hodgkin Lymphoma where regimens with reduced number of cycles of BEACOPP have been developed.
[x] LMA = Large mediastinal adenopathy; RRL = Rapidly responding lesions; SRL = Slow responding lesions.

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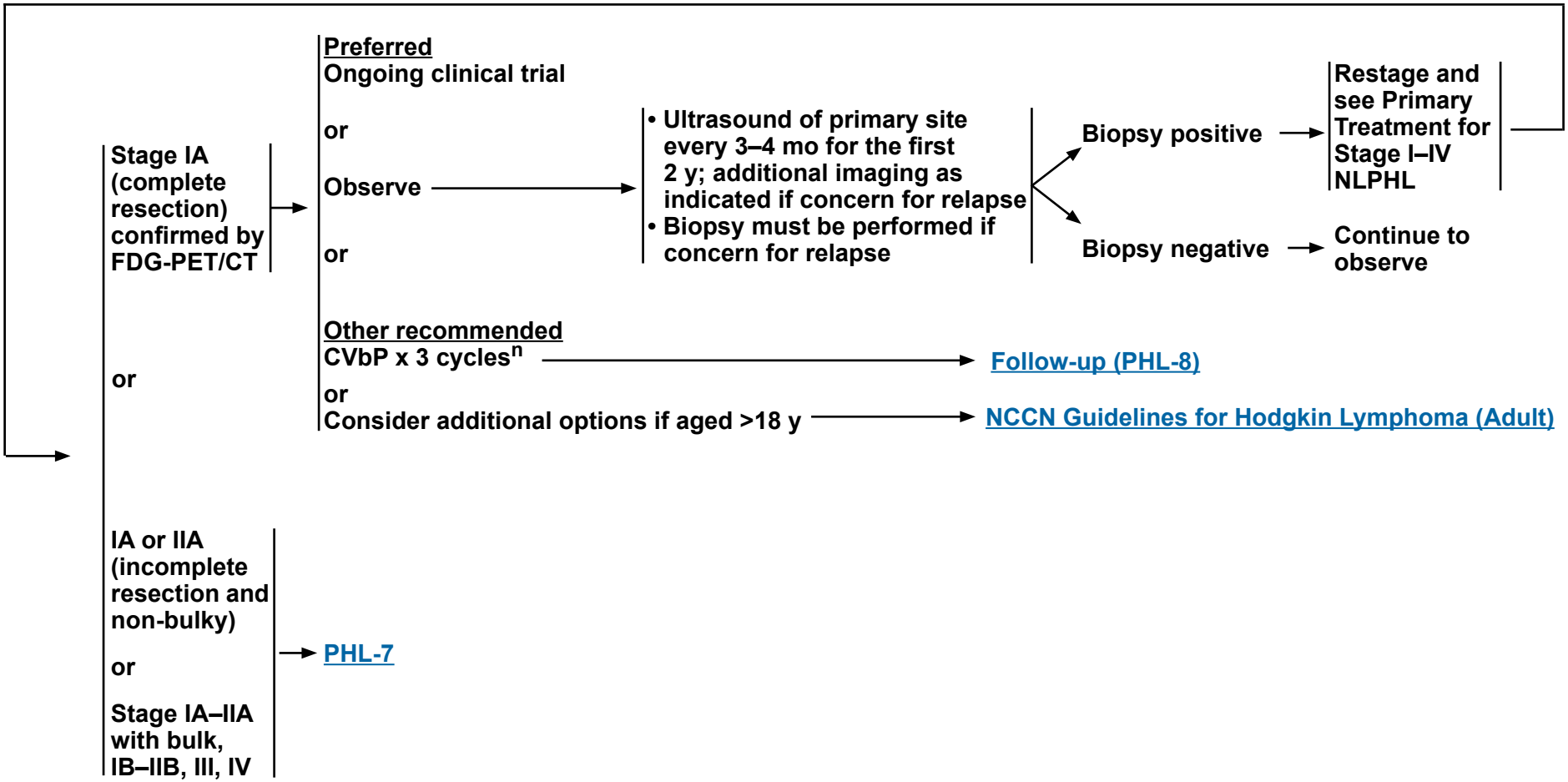
CLINICAL PRESENTATION: NLPHL

PRIMARY TREATMENT[m,n]



[m] Regimens are based off of studies with pediatric data.
[n] Principles of Systemic Therapy (PHL-E).

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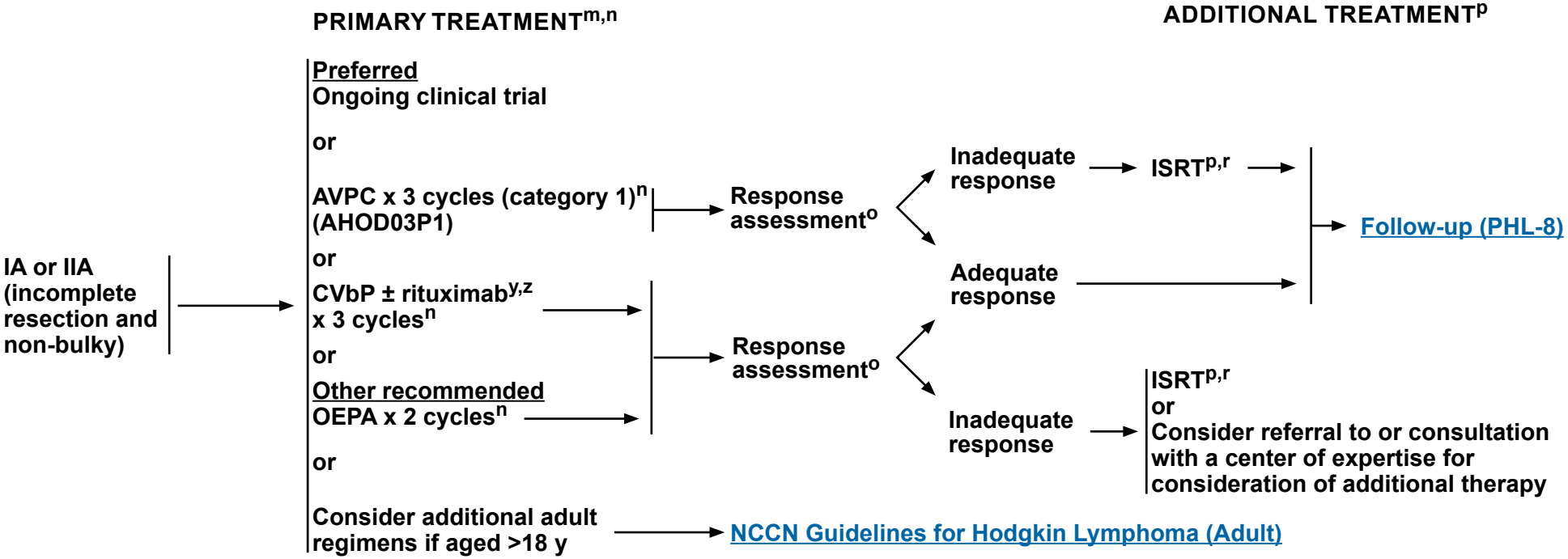
CLINICAL PRESENTATION: NLPHL



Stage IA–IIA with bulk, IB–IIB, III, IV → **Confirm pathologic diagnosis[aa]** → **There are limited data on the treatment of intermediate/advanced NLPHL. It is commonly treated similar to CHL. Given rarity, consider referral to, or consultation with, a center of expertise.**

[m] Regimens are based off of studies with pediatric data.
[n] Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or FDG-PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with FDG-PET.
[p] Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[r] Principles of Radiation Therapy (PHL-F).
[y] Data are limited on the use of rituximab for early-stage NLPHL.
[z] An FDA-approved biosimilar is an acceptable substitute for rituximab.
[aa] Advanced-stage NLPHL is rare in pediatric patients. Confirm pathologic diagnosis prior to treatment. See Principles of Pathology (PHL-B).

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

Pediatric CHL		
Disease Surveillance/ Follow-up After Completion of Treatment	• Interim H&P: ▸ Every 3–4 mo for 1–2 y, then every 6–12 mo until year 3, then annually until 5 y • Laboratory studies: ▸ CBC with differential, ESR or CRP, chemistry profile as clinically indicated. ▸ Thyroid-stimulating hormone (TSH) at least annually if RT to neck. • Consider PFTs (if bleomycin, pulmonary RT, significant pulmonary involvement, or other clinical concerns) • Immunizations: ▸ Annual influenza vaccine is recommended, even during therapy. ▸ Other vaccines as per CDC Guidelines, typically starting 6 mo after completion of therapy (see Children's Oncology Group Survivorship Guidelines). • If spleen is irradiated, vaccines should be given prior to or after RT (ie, pneumococcal, haemophilus influenzae type b, meningococcal). See Principles of Radiation Therapy (PHL-F). • Psychosocial assessment (for AYA, see NCCN Guidelines for AYA Oncology)	• Imaging: ▸ Consider end-of-therapy ECHO. ▸ Imaging studies are only recommended when relapse is suspected, because most patients will clinically declare themselves and there is no survival advantage in pre-emptive imaging. ▸ If clinical concern, chest x-ray PA and lateral views, CT with contrast, or MRI of original sites of disease may be performed and followed at 3- to 6-mo intervals up to 2 y following completion of therapy. ▸ MRI is acceptable in place of CT scan for neck/ abdomen/pelvis, but not for chest; diagnostic CT of chest is needed to evaluate lung parenchyma. ▸ FDG-PET/CT or FDG-PET/MRI if previous FDG-PET was positive (Deauville 4–5), to confirm CR at the end of all prescribed therapy including RT. Once negative, repeat FDG-PET should not be done unless evaluating suspicious findings on H&P or CT or MRI. ◊ Wait at least 8–12 wk after end of RT to perform FDG-PET to minimize false-positive results. ◊ Surveillance FDG-PET is not recommended due to risk for false positives. ▸ If concern for relapse, management decisions should not be based on FDG-PET scan alone; clinical and pathologic correlation is needed. See Principles of Pathology (PHL-B) and Therapy for Relapsed or Refractory Disease (PHL-9).
Monitoring for Late Effects (≥2 years after completion of systemic therapy)	• Appropriate screening and counseling related to: thyroid, cardiac, pulmonary, bone, fertility and reproductive health; subsequent cancers (with special attention to thyroid and breast cancer); and other treatment-associated late effects (see Children's Oncology Group Survivorship Guidelines)	

CHL relapse → See Principles of Pathology (PHL-B) and Therapy for Relapsed/ Refractory Disease (PHL-9)

NLPHL relapse → Refer to a center of expertise. See NCCN Guidelines for Hodgkin Lymphoma (Adult)

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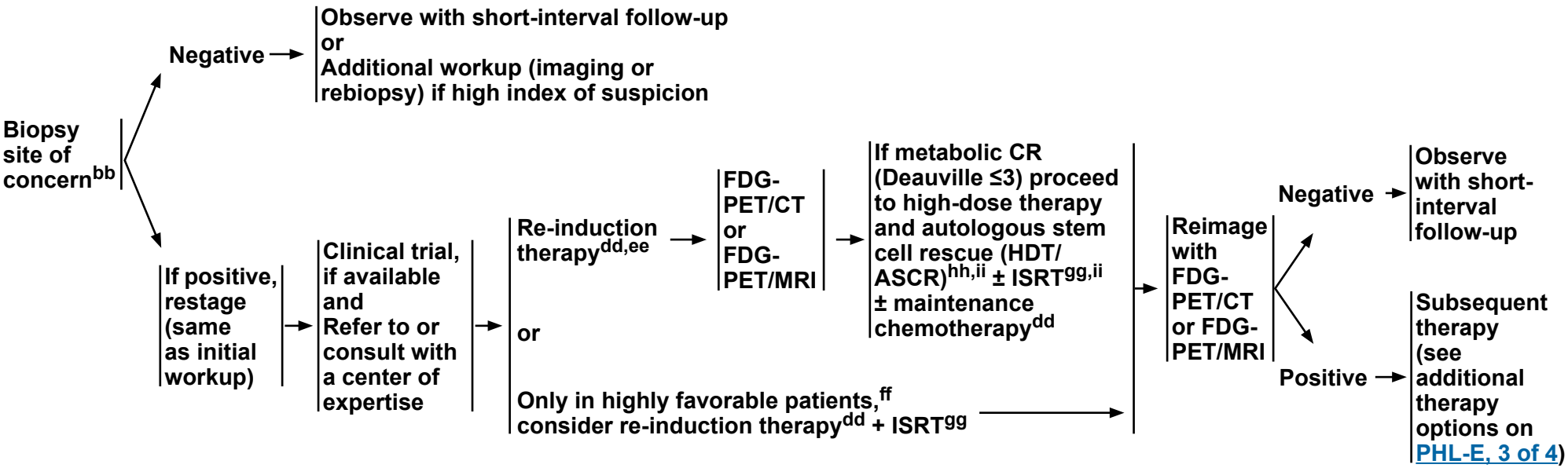
CLINICAL PRESENTATION: CHL

SUSPECTED RELAPSED/ REFRACTORY DISEASE

RE-INDUCTION THERAPY[cc]



[bb] A biopsy must be obtained to confirm relapse and pathology. See Principles of Pathology (PHL-B).

[cc] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

[dd] Principles of Systemic Therapy for Relapsed or Refractory Disease (PHL-E, 3 of 4).

[ee] It is reasonable to try multiple different re-induction regimens as needed prior to ASCR to minimize disease burden with a goal of achieving a metabolic CR prior to transplant. If less than a metabolic CR, proceed to subsequent therapy.

[ff] Recommendations for those who may avoid ASCR: initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, and absence of extranodal disease or B symptoms at relapse. Harker-Murray PD, et al. J Clin Oncol 2023;41(Suppl):Abstract 7515.

[gg] Strongly consider RT for selected sites that have not been previously irradiated.

[hh] Allogeneic transplant is an option in select patients who experience relapse post-ASCT as a category 3 recommendation.

[ii] RT is usually performed as consolidation after transplant, unless unable to get to a metabolic CR, then can use RT prior to transplant.

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PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY

Regimen	HL Type	Risk Group/Stage	Criteria for RT
OEPA/OEPA-COPDAC (EuroNet-PHL-C1)[1,2,3]	**CHL**	**Low Risk** • IA/B without E • IIA without E **Intermediate Risk** • IA/B + E • IIA + E • IIB, IIIA **High Risk** • IIB + E • IIIA+ E • IIIB, IVA/B ± E	• < CR on imaging after 2 cycles of OEPA (applies to patients with low-risk [LR] disease on GPOH 2002) ▸ CR: FDG-PET negative (Deauville 1–2) and volume reduction >95% and ≤2 mL ▸ CR, unconfirmed (CRu): Volume reduction >75% or ≤2 mL • All patients with intermediate-/high-risk (IR/HR) disease on HD-2002 received RT • Patients with LR/IR/HR disease on C1 received RT only if FDG-PET positive (Deauville 3–5) or not in at least partial response (PR) after 2 cycles of OEPA ▸ PR: No CR or CRu and >50% volume reduction or residual tumor volume <5 mL ▸ Consider boost for residual mass >100 mL or <75% volume reduction and minimum volume >5 mL at early response assessment. Note: Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate
ABVE-PC[4]	**CHL**	**Intermediate Risk (AHOD0031)[4]** • IA, IIA with bulk ± E • IB, IIB without bulk ± E • IIIA ± E[a]	• SER on imaging after 2 cycles if <60% reduction in product of perpendicular diameters (PPD)[b] for all target lesions or • RER on imaging after 2 cycles if not in CR on imaging after 4 cycles ▸ CR: ≥80% reduction in PPD[b] with negative FDG-PET at end of therapy (comparable to Deauville 1–2) • Consider boost for persistent FDG-PET–positive (Deauville 3–5) lesions at end of chemotherapy.

[a] Stage IVA was included in the intermediate-risk group in the trial, although is not recommended for standard care.

[b] PPD = Transverse x axial plane.

Continued
References

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PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY

Regimen	HL Type	Risk Group/Stage	Criteria for RT
Bv-AVE-PC[5]	**CHL**	**High Risk (AHOD1331)**[6] • IIB with bulk • IIIB, IV[a]	• SRL on imaging after 2 cycles[6] ▸ Inadequate or SRL: Deauville 4–5 ▸ Adequate or RRL: Deauville ≤3 • All LMA • Boost for persistent FDG-PET–positive lesions (Deauville 3–5) at end of chemotherapy • Consider treating without a boost for LMA that was Deauville 3 after 2 cycles and continues to be Deauville 3 after 5 cycles
AEPA-CAPDAC (HLHR13)[7]	**CHL**	**High Risk** • IIB • IIIB • IV	• Residual FDG-PET–positive lesions (Deauville 4–5) after 2 cycles of therapy, or • FDG-PET–negative (Deauville 1–3) lesions with <75% anatomic response (as measured by the product of 2 perpendicular diameters of lesions by CT or MRI
AVPC	**CHL (mixed cellularity only) (AHOD0431)**[8]	**Low Risk** • IA, IIA without bulk • For mixed cellularity only	• <CR on imaging after 3 cycles ▸ CR: ≥80% reduction in PPD[b] and FDG-PET negative; only mediastinal nodes >2 cm ▸ FDG-PET positive (Deauville 3–5): Uptake greater than mediastinal blood pool
	NLPHL (AHOD03P1)[9]	• IA, single node with incomplete resection; • IA multiple nodes • IIA	• Residual FDG-PET–positive lesions after 3 cycles of AVPC, or • FDG-PET–negative lesions with <80% anatomic response (as measured by the product of 2 perpendicular diameters of lesions by CT or MRI), or • Not returned to normal size with residual nodal max dimension >2.0 cm

[a] Stage IVA was included in the intermediate-risk group in the trial, although is not recommended for standard care.
[b] PPD = Transverse x axial plane.

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References

PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY
REFERENCES

[1] Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28:3680-3686.
[2] Mauz-Körholz C, Landman-Parker J, Balwierz W, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. Lancet Oncol 2022;23:125-137. Erratum in Lancet Oncol 2022;23:125-137.
[3] Mauz-Körholz C, Landman-Parker J, Fernández-Teijeiro A, et al. Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study. Lancet Oncol 2023;24:252-261.
[4] Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32:3651-3658.
[5] Castellino SM, Pei Q, Parsons SK, et al. Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. N Engl J Med 2022;387:1649-1660.
[6] Flerlage JE, Kelly KM, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL): Methodology statement. Pediatr Blood Cancer 2017;64:e26421.
[7] Metzger ML, Link MP, Billett AL, et al. Excellent outcome for pediatric patients with high-risk Hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. J Clin Oncol 2021;39:2276-2283.
[8] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-3219.
[9] Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: A report from the Children's Oncology Group. J Clin Oncol 2016;34:2372-2379.

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PRINCIPLES OF PATHOLOGY

Histologic Classification

- **Diagnosis should be established according to guidelines in the 2022 World Health Organization (WHO) Classification of Haematolymphoid Tumours, 5th edition or the 2022 International Consensus Classification (ICC) of Mature Lymphoid Neoplasms.[1,2]**
- **There are two types of HL: CHL and NLPHL. Distinction between these types is important for therapy and prognosis.**

CHL

- **There are four morphologic variants of CHL[a]:**
  - **Nodular sclerosis**
  - **Mixed cellularity**
  - **Lymphocyte-rich**
  - **Lymphocyte-depleted**
- **CHL subtyping is not necessary for treatment in the vast majority of cases and may not be possible in all cases.[a] If considering treatment based on the AHOD0431 trial,[3] discussion with a pediatric pathologist or hematopathologist is recommended to determine if tissue is sufficient to establish a diagnosis of mixed-cellularity subtype.**
- **CHL can occur in patients with immunodeficiency (primary immunodeficiency, HIV infection, post-transplant immunodeficiency, and iatrogenic immunodeficiency). Other polymorphic lymphoproliferative disorders and Hodgkin-like lesions are also associated with immunodeficiency and should be distinguished from CHL since management and treatment recommendations differ. These are challenging cases and expert hematopathology evaluation is suggested. Referral to a center of expertise may be necessary.**

NLPHL[b]

- **There are six immunoarchitectural patterns of NLPHL and a mixture of patterns is commonly seen histologically[c,4]:**
  - **B-cell-rich nodular (pattern A)**
  - **Serpiginous/interconnected nodular (pattern B)**
  - **Nodular with prominent extranodular LP cells (pattern C)**
  - **T-cell-rich nodular (pattern D)**
  - **T-cell-rich diffuse or T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)-like (pattern E)**
  - **Diffuse B-cell-rich (pattern F)**
- **Variant histologic patterns in NLPHL should be documented in the pathology report, where possible, as T-cell-rich and/or diffuse patterns may be associated with higher risk of disease progression and relapse and shorter time to relapse.[5,6]**

[a] The different morphologic variants of CHL have different clinicopathologic associations and differential diagnoses. Refer to the 2022 WHO Classification or ICC 2022 for more details.

[b] Per WHO 2022, NLPHL remains under the family of HL, while ICC 2022 replaces the term NLPHL with nodular lymphocyte-predominant B-cell lymphoma (NLPBL). Both classifications recognize the clinical and biologic similarities of NLPHL to an indolent B-cell lymphoma and NLPBL is an acceptable term per WHO 2022 (Alaggio R, et al. Leukemia 2022;36:1720-1748; Campo E, et al. Blood 2022;140:1229-1253).

[c] The different immunoarchitectural patterns of NLPHL have different prognostic implications and differential diagnoses. In particular, pattern E (T-cell-rich diffuse or THRLBCL-like) is similar to de novo THRLBCL at the molecular level and behaves more aggressively than other NLPHL variants (Hartmann S, et al. PLoS One 2013;8:e78812). There are insufficient data directly comparing the clinical behavior of NLPHL with predominant T-cell-rich diffuse histology with that of THRLBCL to determine whether such cases are best managed like NLPHL or a large B-cell lymphoma.

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References

PRINCIPLES OF PATHOLOGY

Tissue Adequacy for Diagnosis

- **An excisional or incisional biopsy where possible is recommended. A core biopsy may be appropriate in some settings.[d] Fine-needle aspiration (FNA) is discouraged in establishing a diagnosis.[e]**
- **For CHL, ample tissue may be necessary to exclude other entities in the differential diagnosis[f] and for specific morphologic subtyping.[g]**
- **For NLPHL, ample tissue may be necessary to assess for the presence of variant histologic patterns and, in cases with predominantly T-cell-rich or diffuse patterns (patterns D–F), to exclude other entities in the differential diagnosis, such as THRLBCL, peripheral T-cell lymphoma, or another non-Hodgkin lymphoma (NHL). For cases with predominantly T-cell-rich histology, at least one nodule with lymphocyte predominant (LP) cells in a B-cell-rich background is needed to distinguish a variant NLPHL pattern from THRLBCL. Examination of additional sections of submitted tissue and/or immunohistochemical staining of additional slides may be necessary in such cases.**
- **NLPHL may be associated with concomitant diffuse large B-cell lymphoma (DLBCL) at the same or different site.[7-9] Excision specimens should be adequately sampled. A re-biopsy may be considered in situations where imaging findings are discordant with the rendered histopathologic diagnosis or discordant between different sites. Splenic involvement has been associated with increased risk of transformation.[10,11]**

[d] For example, less accessible anatomic sites such as mediastinal mass with sedation risks or retroperitoneum.
[e] Sparse neoplastic cells, extensive fibrosis, and presence of Reed Sternberg-like cells in some conditions other than in HL are some reasons a limited biopsy may not be diagnostic.
[f] For example, mediastinal gray zone lymphoma or rare composite tumors of CHL and primary mediastinal large B-cell lymphoma may not be demonstrable in limited biopsies.
[g] Fibrotic bands completely surrounding nodules are important in distinguishing nodular sclerosis CHL from mixed cellularity CHL but may not be demonstrable in small biopsies.

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References

PRINCIPLES OF PATHOLOGY

Immunohistochemical Considerations and Ancillary Testing

- **Consider clinical differential diagnoses (eg, T-cell lymphoblastic lymphoma) and pathologic differential diagnoses: HL versus NHL,[h] CHL versus NLPHL versus progressive transformation of germinal centers, HL versus infection (cytomegalovirus [CMV], Epstein-Barr virus [EBV]), and HL versus reactive proliferations.[i]**
- **Diagnosis is based on morphologic AND immunohistochemical findings.**
- **Typical immunophenotype of HL:**
  - **CHL: Neoplastic Hodgkin/Reed-Sternberg (HRS) cells are PAX5+ (weaker expression than background B lymphocytes), CD30+, CD15+, CD45-, CD3-, or CD20- (majority). This serves as an essential panel of markers for immunohistochemical evaluation of CHL. Evaluation of an expanded panel of markers (ie, CD79a-, ALK-, MUM1+, OCT2-/weak, BOB1-/weak) should be considered in cases with equivocal or imperfect morphologic or immunophenotypic features or to exclude entities in the differential diagnosis.**
  - **NLPHL: Neoplastic LP cells are PAX5+, CD20+, OCT2+ (strong), CD30-, CD15-, or CD3-. They are also CD45+, CD79a+, BCL6+, EMA+, or MUM1-/weak. Characteristics of the immune microenvironment (identification of small B cells, T-follicular helper cells, and follicular dendritic cells) are also helpful in the diagnostic workup.**
- **EBV+ CHL cases (EBV often assessed by EBER-ISH[j]) may benefit from additional studies, such as EBV serology and evaluation for underlying immunodeficiency. EBV+ LP cells have been reported only rarely in NLPHL and this finding should prompt consideration of other entities in the differential diagnosis.[12]**
- **Flow cytometry is not helpful in diagnosing HL.[k] However, it may be helpful in the evaluation of other entities in the clinical or pathologic differential diagnosis.**

[h] NHL examples, primary mediastinal large B-cell lymphoma, ALK+ anaplastic large cell lymphoma, THRLBCL, EBV+ DLBCL, and peripheral T-cell lymphoma.
[i] For example, reactive lymph node with CD30+ immunoblasts (vs. CHL) and progressive transformation of germinal centers (vs. NLPHL) and granulomatous lymphadenitis (vs. CHL or NLPHL).
[j] EBER-ISH = EBV-encoded RNA (EBER) in situ hybridization (ISH).
[k] Identification of CD4+ CD8dim+ T cells can support a diagnosis of NLPHL, but this population may also be seen in progressive transformation of germinal centers. Neoplastic cells in CHL may also be identified using sophisticated flow cytometry techniques, which are not readily available.

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PRINCIPLES OF PATHOLOGY

Pathology Considerations in the Relapse/Refractory Disease Setting

- **Pathologic confirmation is necessary to confirm relapse or refractory disease given the risk for transformation and high false-positive rate of FDG-PET/CT. Re-biopsy is also recommended for residual FDG-PET–avid disease at the end of therapy.[13] In the case of NLPHL, such residual FDG-PET–avid disease could represent foci of concurrent or transformed DLBCL.**
- **If original diagnosis slides are available, limited immunohistochemical evaluation may be performed on the relapse/refractory specimen.**
- **For CHL cases, consider the possibility of misdiagnosis at original presentation (eg, primary mediastinal large B-cell lymphoma, mediastinal gray zone lymphoma,[14,15] or other lymphoma subtypes).**
- **For NLPHL cases, consider the possibility of DLBCL (either conventional with sheets of large cells or THRLBCL-like) transformation from NLPHL[16] or reactive lymph node with progressive transformation of germinal centers.[17] Although advanced-stage NLPHL can occur, particularly in cases with variant morphology, this is uncommon. Therefore, expert hematopathology re-evaluation of original pathology slides is suggested for patients with advanced disease. Misdiagnosed CHL or THRLBCL are diagnostic considerations in this setting and should be excluded. Referral to a center of expertise may be necessary.**
- **Prior monoclonal antibody therapy targeting CD30 (for CHL) or CD20 (for NLPHL) may result in weak or negative staining for these antigens by immunohistochemistry.**
- **There are insufficient data to recommend programmed death ligand 1 (PD-L1) testing by immunohistochemistry as a prerequisite for immune checkpoint inhibitor therapy. Robust cut-offs for optimally predicting response to immune checkpoint inhibitor therapy have not been established.**

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References

PRINCIPLES OF PATHOLOGY
REFERENCES

[1] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748.

[2] Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.

[3] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-3219.

[4] Fan Z, Natkunam Y, Bair E, et al. Characterization of variant patterns of nodular lymphocyte predominant hodgkin lymphoma with immunohistologic and clinical correlation. Am J Surg Pathol 2003;27:1346-1356.

[5] Hartmann S, Eichenauer DA, Plütschow A, et al. The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). Blood 2013;122:4246-4252; quiz 4292.

[6] Hartmann S, Plütschow A, Mottok A, et al. The time to relapse correlates with the histopathological growth pattern in nodular lymphocyte predominant Hodgkin lymphoma. Am J Hematol 2019;94:1208-1213.

[7] Cotta CV, Coleman JF, Li S, Hsi ED. Nodular lymphocyte predominant Hodgkin lymphoma and diffuse large B-cell lymphoma: a study of six cases concurrently involving the same site. Histopathology 2011;59:1194-1203.

[8] Hartmann S, Eray M, Döring C, et al. Diffuse large B cell lymphoma derived from nodular lymphocyte predominant Hodgkin lymphoma presents with variable histopathology. BMC Cancer 2014;14:332.

[9] Song JY, Egan C, Bouska AC, et al. Genomic characterization of diffuse large B-cell lymphoma transformation of nodular lymphocyte-predominant Hodgkin lymphoma. Leukemia 2020;34:2238-2242.

[10] Al-Mansour M, Connors JM, Gascoyne RD, et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010;28:793-799.

[11] Kenderian SS, Habermann TM, Macon WR, et al. Large B-cell transformation in nodular lymphocyte-predominant Hodgkin lymphoma: 40-year experience from a single institution. Blood 2016;127:1960-1966.

[12] Huppmann AR, Nicolae A, Slack GW, et al. EBV may be expressed in the LP cells of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) in both children and adults. Am J Surg Pathol 2014;38:316-324.

[13] El-Galaly TC, Gormsen LG, Hutchings M. PET/CT for staging; past, present, and future. Semin Nucl Med 2018;48:4-16.

[14] Pilichowska M, Pittaluga S, Ferry J, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. Blood Adv 2017;1:2600-2609.

[15] Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-1421.

[16] Al-Mansour M, Connors J, Gascoyne R, et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010;28:793-799.

[17] Shaikh F, Ngan B, Alexander S, Grant R. Progressive transformation of germinal centers in children and adolescents: an intriguing cause of lymphadenopathy. Pediatr Blood Cancer 2013;60:26-30.

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PRINCIPLES OF IMAGING[1-8]

Staging or Initial Workup (should be performed within 2 to 4 weeks prior to initiation of therapy)
- CT neck/chest/abdomen/pelvis with contrast (IV ± oral) or CT chest and MRI neck/abdomen/pelvis
- Chest x-ray PA and lateral views (if cross-sectional imaging not available or necessitated to determine bulk of disease for a clinical trial)
- FDG-PET/CT[a,b,c] or FDG-PET/MRI[d]
  - Whole-body is recommended.
  - Diagnostic-quality CT or MRI is still needed for initial staging; when available FDG-PET/CT and diagnostic CT should be performed as a combined examination to limit radiation exposure.

Interim and End of Therapy
- FDG-PET/CT[a,b,c] or FDG-PET/MRI[d]
  - Wait at least 8 to 12 weeks after end of RT to perform FDG-PET to minimize false-positive results.
- Diagnostic-quality CT with contrast or MRI only for original sites of disease.

Follow-up/Surveillance
- 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-quality chest x-ray PA and lateral views, and CT or MRI at 3- to 6-month intervals for up to 2 years.
- FDG-PET/CT[a,b,c] or FDG-PET/MRI is not advised due to risk of false positives.
  - Repeat FDG-PET may be considered for persistent positive disease or equivocal finding on post-therapy FDG-PET.[a,b]

Relapsed or Refractory (confirmed or highly suspected)
- CT neck/chest/abdomen/pelvis with contrast (IV ± oral) or CT chest and MR neck/abdomen/pelvis
- FDG-PET/CT[a,b,c] or FDG-PET/MRI[d]

[a] FDG-PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for FDG-PET–adapted therapy. FDG-PET/CT should be obtained in accordance with American College of Radiology (ACR) practice guidelines.
[b] In cases of FDG-PET positivity where sites of disease are inconsistent with usual presentation of HL or if there is an unusual disease presentation (ie, HIV), additional clinical evaluation may be required for staging. See Principles of Staging (PHL-D). If FDG-PET negative at anatomic lesion of concern, biopsy should be considered. In most instances, if the FDG-PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is not assumed. If there are multifocal (≥3) skeletal FDG-PET lesions without cortical destruction on CT, marrow involvement may be assumed.
[c] Measures to reduce brown fat activation, such as warming or pharmacologic suppression, may be considered to minimize false-positive findings.
[d] If FDG-PET/MRI obtained, diagnostic CT of chest is needed to evaluate lung parenchyma.

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References

PRINCIPLES OF IMAGING[1-8]

Interpretation

- The panel supports the American College of Radiology (ACR)[9] and Society of Nuclear Medicine and Molecular Imaging (SNMMI)[10] recommendation for FDG-PET/CT interpretation, including the requirement that FDG-PET/CT examinations should be performed under the supervision of and interpreted by a physician with the following qualifications:
  - Board certification in radiology or diagnostic radiology, nuclear radiology, or nuclear medicine
    OR
  - Completion of a formal Accreditation Council for Graduate Medical Education (ACGME)-approved general nuclear medicine program in addition to 1000 hours of clinical training in general nuclear medicine, 20 hours of continuing medical education (CME) in FDG-PET, and at least 150 oncologic FDG-PET/CT examinations interpreted or multi-read during the previous 3 years.[9]
- Continuing experience/education should include interpretation of a minimum of 150 FDG-PET/CT scans in 3 years (multi-read is acceptable) and completion of 150 hours (including 75 hours of Category 1 CME) during the preceding 3 years pertinent to the physician's practice patterns, including FDG-PET imaging.[9]
- The interpreting radiology or nuclear medicine physician should have adequate training and CME/experience in interpreting FDG-PET/CT for patients with lymphoma including the use of the Deauville 5-point scoring system.
- The final report for any FDG-PET/CT examination to define response should include the Deauville 5-point scale score, ***which is a visual score***.
- A second opinion/overread is encouraged of scans that are not initially interpreted by qualified individuals, when there is a discrepancy between the clinical presentation and radiology report, and/or when no appropriate Deauville score has been provided.

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References

PRINCIPLES OF IMAGING
REFERENCES

[1] Cerci JJ, Etchebehere EC, Nadel H, et al. Is true whole-body ^{18}F-FDG-PET/CT required in pediatric lymphoma? An IAEA multicentre prospective study. J Nucl Med 2019;60:1087-1093.

[2] Kluge R, Kurch L, Georgi T, Metzger M. Current role of FDG-PET in pediatric Hodgkin's lymphoma. Semin Nucl Med 2017;47:242-257.

[3] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068.

[4] McCarten KM, Nadel HR, Shulkin BL, Cho SY. Imaging for diagnosis, staging, and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. Pediatr Radiol 2019;49:1545-1564.

[5] Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. Pediatr Radiol 2019;49:1565-1573.

[6] Verhagen MV, Menezes LJ, Neriman D, et al. ^{18}F-FDG PET/MRI for staging and interim response assessment in pediatric and adolescent Hodgkin lymphoma: a prospective study with ^{18}F-FDG PET/CT as the reference standard. J Nucl Med 2021;62:1524-1530.

[7] Rathore N, Eissa HM, Margolin JF, et al. Pediatric Hodgkin lymphoma: Are we over-scanning our patients? Pediatr Hematol Oncol 2012;29:415-423.

[8] Spijkers S, Littooij AS, Humphries PD, et al. Imaging features of extranodal involvement in paediatric Hodgkin lymphoma. Pediatr Radiol 2019;49:266-276.

[9] American College of Radiology. ACR-ACNM-SNMMI-SPR Practice Parameters for Performing FDG-PET/CT in Oncology. 2021. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/FDG-PET-CT.pdf?la=en. Accessed September 14, 2021.

[10] Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42:328-354.

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NCCN Guidelines Version 1.2024
Pediatric Hodgkin Lymphoma

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Discussion

PRINCIPLES OF STAGING[a]

- **These are only guiding principles of initial staging adapted from criteria of various protocols. This table is not intended to replace protocol-specific staging. Refer to applicable study protocol for complete staging details.**
- **While these principles are based on panel consensus, this remains an area of ongoing research.**
- **The Lugano criteria are not included in this table, because there is inadequate harmonization between adult and pediatric staging criteria. For example, size cut-offs in adults are larger than they are for children.**

Site Involvement	Imaging Modality[b,c,d]	Protocols
Lymph nodes	Diagnostic CT/ MRI and FDG-PET/CT	• Long axis ≥2 cm is considered involved on diagnostic CT/MRI • Long axis 1–2 cm, if FDG-PET positive
Splenic	Ultrasound	• Any lesion large enough to characterize unless imaging characteristics indicate an alternative etiology irrespective of the FDG-PET result
	FDG-PET/CT or FDG-PET/MRI	• Focal FDG-PET–positive lesions that are confirmed by CT with IV contrast or MRI or ultrasound • Splenic involvement must include focal imaging abnormality. Splenomegaly and diffuse uptake greater than liver alone are not considered involvement.
Lung[e]	FDG-PET/CT	• E-lesions[g]: Extralymphatic structures (lung lesions) contiguous with nodal masses are considered to be E-lesions. • At least 1–2 small foci (between 5–10 mm) within whole lung if no other etiology is suspected • At least 1 intrapulmonary focus >1 cm on CT if no other etiology is suspected • FDG-PET–positive lesions <1 cm if no other etiology is suspected Note: If all lesions are exclusively in 1 lung, then only this particular lung is considered as involved. However, even if there is just one additional smaller focus found within the other lung, then both lungs are considered involved.
Liver	Ultrasound	• Any focal mass lesion or lesions on diagnostic imaging large enough to characterize in a visceral organ is considered lymphomatous involvement unless the imaging characteristics indicate an alternative etiology.
	FDG-PET/CT or FDG-PET/MRI	• Focal FDG-PET–positive lesions
Bone marrow	Bilateral biopsy	• Positive by histopathology on previous high-risk trials; current trial recommendations are based on FDG-PET alone • European-based GPOH-HD-2002 staging: Not recommended
	FDG-PET/CT or FDG-PET/MRI	• ≥3 FDG-PET–positive lesions in bone marrow without cortical bone destruction
Bone	FDG-PET/CT or FDG-PET/MRI	• FDG-PET–positive lesion with cortical bone destruction on CT or MRI[f] • If no cortical bone destruction, a bone scan may be helpful. • Extralymphatic structures (bone lesions) contiguous with nodal masses are considered to be E-lesions.[g]

[a] Clinical interpretation of staging at diagnosis should not be based on reports alone. Treating clinician notes should summarize interpretation of sites of involvement prior to initiation of treatment.
[b] FDG-PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for FDG-PET–adapted therapy. This is a visual analysis and does not include standardized uptake value (SUV).
[c] There may be FDG-PET–avid lesions that need clinical correlation to determine if it is related to lymphoma.
[d] Principles of Imaging (PHL-C).
[e] There are inconsistencies in staging between protocols and providers. Careful attention to staging of lung involvement is important as it may change the risk group of the patient.
[f] Lewis J, et al. Pediatr Blood Cancer 2020;67:e28142.
[g] E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by contiguous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation (Engert A, et al. N Engl J Med 2010;363:640-652; Lister TA, et al. J Clin Oncol 1989;7:1630-1636; Spijkers S, et al. Pediatr Radiol 2019;49:266-276).

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PRINCIPLES OF STAGING[a]

ASSESSMENT OF BULK DISEASE

Site Involvement	US-Based Protocols	European-Based Protocols[h]
Peripheral nodes	• Contiguous extramediastinal nodal aggregate >6 cm in the longest diameter (LDi) measured in axial, coronal, or sagittal dimension (including oblique measurement)	• Volume of the largest contiguous lymph node mass ≥200 mL
Mediastinal mass	• Tumor diameter >1/3 of the maximal thoracic diameter of an upright PA chest radiograph	• Tumor volume ≥200 mL

PET 5-POINT SCALE (DEAUVILLE CRITERIA)[b]

Score	PET/CT Scan Result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

With kind permission from Springer International Publishing: Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32:3048-3058.

[a] Clinical interpretation of staging at diagnosis should not be based on reports alone. Treating clinician notes should summarize interpretation of sites of involvement prior to initiation of treatment.

[b] FDG-PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for FDG-PET–adapted therapy. This is a visual analysis and does not include SUV.

[h] Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate (in cm). Mauz-Körholz C, et al. Lancet Oncol 2022;23:125-137.

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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy

Primary Systemic Therapy - Recommended Dosing

AVPC[1]

Note: Cyclophosphamide and doxorubicin dosing in AHOD0431 differs from AHOD03P1.

- **CHL (AHOD0431)[1]**
  - Doxorubicin[a] 25 mg/m^2 IV days 1 and 2
  - Vincristine 1.4 mg/m^2 IV days 1 and 8; 2.8 mg/dose maximum
  - Prednisone 20 mg/m^2 PO twice daily on days 1–7
  - Cyclophosphamide 600 mg/m^2 IV days 1 and 2
  - Regimen repeated every 21 days for 3 cycles
- **NLPHL (AHOD03P1)[2]**
  - Doxorubicin[a] 50 mg/m^2 IV day 1
  - Vincristine 1.4 mg/m^2 IV days 1 and 8; 2.8 mg/dose maximum
  - Prednisone 20 mg/m^2 PO twice daily on days 1–7
  - Cyclophosphamide 800 mg/m^2 IV day 1
  - Regimen repeated every 21 days for 3 cycles

Bv-AVE-PC[3]

- **High Risk (AHOD1331)**
  - Brentuximab vedotin 1.8 mg/kg IV day 1 (prior to other chemotherapy); 180 mg/dose maximum per dose
  - Doxorubicin[a] 25 mg/m^2 IV days 1 and 2
  - Vincristine 1.4 mg/m^2 IV day 8; 2.8 mg/dose maximum per dose
  - Etoposide 125 mg/m^2 IV daily on days 1–3
  - Prednisone 40 mg/m^2 PO divided into two doses daily on days 1–7
  - Cyclophosphamide 600 mg/m^2 IV days 1 and 2
  - Regimen repeated every 21 days for 5 cycles

ABVE-PC

Note: Cyclophosphamide dosing in AHOD0031 differs from AHOD1331.

- **Intermediate Risk (AHOD0031)[4]**
  - Doxorubicin[a] 25 mg/m^2 IV days 1 and 2
  - Bleomycin 5 U/m^2 IV day 1, 10 U/m^2 IV day 8
  - Vincristine 1.4 mg/m^2 IV days 1 and 8; 2.8 mg/dose maximum per dose
  - Etoposide 125 mg/m^2 IV daily on days 1–3
  - Prednisone 40 mg/m^2 PO divided into two doses daily on days 1–7
  - Cyclophosphamide 800 mg/m^2 IV day 1
  - Regimen repeated every 21 days for 4 cycles

[a] Dexrazoxane may be used as clinically indicated (Chow EJ, et al. J Clin Oncol 2023;41:2248-2257; Shaikh F, et al. J Natl Cancer Inst 2015;108:djv357; van Dalen EC, et al. Cochrane Database Syst Rev 2011;2011:CD003917).

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References

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy

Primary Systemic Therapy - Recommended Dosing

OEPA (GPOH-HD-2002)[5]
- Vincristine 1.5 mg/m^2 IV days 1, 8, and 15; 2 mg/dose maximum
- Etoposide 125 mg/m^2 IV daily on days 2–6
- Prednisone 60 mg/m^2 PO daily on days 1–15
- Doxorubicin[a] 40 mg/m^2 IV days 1 and 15
- Regimen repeated every 28 days for 2 cycles

OEPA-COPDAC (GPOH-HD-2002)[5]
- **OEPA:**
  - Vincristine 1.5 mg/m^2 IV days 1, 8, and 15; 2 mg/dose maximum
  - Etoposide 125 mg/m^2 IV daily on days 2–6
  - Prednisone 60 mg/m^2 PO daily on days 1–15
  - Doxorubicin[a] 40 mg/m^2 IV on days 1 and 15
  - Regimen repeated every 28 days for 2 cycles
- **COPDAC:**
  - Cyclophosphamide 500 mg/m^2 IV days 1 and 8
  - Vincristine 1.5 mg/m^2 IV days 1 and 8; 2 mg/dose maximum
  - Prednisone 40 mg/m^2 PO daily on days 1–15; 80 mg maximum per day
  - Dacarbazine 250 mg/m^2 IV daily on days 1–3
  - Regimen repeated every 28 days for 2 cycles for intermediate risk or 4 cycles for high risk

AEPA-CAPDAC (HLHR13)[6]
- **AEPA**
  - Brentuximab vedotin 1.2 mg/kg IV days 1, 8, and 15; 120 mg/dose maximum per dose
  - Etoposide 125 mg/m^2 IV on days 1–5
  - Prednisone 60 mg/m^2/day PO divided TID on days 1–15; 30 mg/dose TID maximum
  - Doxorubicin[a] 40 mg/m^2 IV days 1 and 15
    - ◊ Regimen repeated every 28 days for 2 cycles
- **CAPDAC**
  - Cyclophosphamide 500 mg/m^2 IV days 1 and 8
  - Brentuximab vedotin 1.2 mg/kg IV days 1 and 8; 120 mg/dose maximum per dose
  - Prednisone 40 mg/m^2/day PO divided TID on days 1–15; 20 mg/dose TID maximum
  - Dacarbazine 250 mg/m^2 IV on days 1–3
    - ◊ Regimen repeated every 21 days for 4 cycles

CVbP ± Rituximab[b,c,7,8]
- Cyclophosphamide 500 mg/m^2 IV on day 1
- Vinblastine 6 mg/m^2 IV days 1 and 8
- Prednisolone 40 mg/m^2 PO on days 1–8
  - Regimen repeated at 2–3 week intervals for 3 cycles
- Rituximab 375 mg/m^2 IV day 1

[a] Dexrazoxane may be used as clinically indicated. (Chow EJ, et al. J Clin Oncol 2023;41:2248-2257; Shaikh F, et al. J Natl Cancer Inst 2015;108:djv357; van Dalen EC, et al. Cochrane Database Syst Rev 2011;2011:CD003917.)
[b] Data are limited on the use of rituximab for early-stage NLPHL.
[c] An FDA-approved biosimilar is an acceptable substitute for rituximab.

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References

PRINCIPLES OF SYSTEMIC THERAPY
Treatment for Relapsed or Refractory Disease

- **Consider the following when selecting re-induction or subsequent therapy:**
  - **Referral to a center with expertise given lack of data**
  - **Clinical trial enrollment**
  - **Primary therapy and prior RT exposure**
  - **Cumulative short- and long-term toxicity**
  - **Opportunity to harvest stem cells**
  - **Counseling on infertility risk (NCCN Guidelines for AYA Oncology)**
  - **Psychosocial assessment (for AYA, see NCCN Guidelines for AYA Oncology)**
- **Consider use of RT as part of therapy for relapsed/refractory disease.**
- **Additional options may be considered for patients >18 years; see NCCN Guidelines for Hodgkin Lymphoma (Adult).**

Relapsed/Refractory Disease

	Re-Induction Therapy Options[d] (in alphabetical order)	Subsequent Therapy Options[f] (in alphabetical order)	Maintenance (post-transplant)
CHL	• Brentuximab vedotin + bendamustine[e,9] • Brentuximab vedotin + gemcitabine[e,10] Brentuximab vedotin + nivolumab[e,11] • DHAP (dexamethasone, cytarabine, cisplatin) • GV (gemcitabine, vinorelbine)[e] • IGEV (ifosfamide, gemcitabine, vinorelbine)[12] • IV (Ifosfamide, vinorelbine)[13]	• Bortezomib, ifosfamide, + vinorelbine[14] • EPIC (etoposide, prednisolone, ifosfamide, cisplatin)[15] • GDP (gemcitabine, dexamethasone, cisplatin)[16] • ICE (ifosfamide, carboplatin, etoposide)[17] • Nivolumab[e,g,18,19] • Pembrolizumab[e,g,h,20,21]	Useful in certain circumstances, for select patients with high-risk[i] disease: • Brentuximab vedotin[22]
NLPHL	Refer to a center of expertise. See NCCN Guidelines for Hodgkin Lymphoma (Adult).		

[d] It is reasonable to try multiple different re-induction regimens as needed prior to ASCR to minimize disease burden with a goal of achieving a metabolic CR prior to transplant.
[e] Should be considered in patients with heavily pretreated (with platinum or anthracycline-based chemotherapy) disease or if a decrease in cardiac function is observed.
[f] Subsequent therapy options include re-induction options that were not previously used.
[g] Data are showing utility as a re-induction option; consider for subsequent therapy if not previously used.
[h] Pembrolizumab is indicated for the treatment of pediatric patients with refractory CHL, or who have relapsed after two or more prior lines of therapy.
[i] High-risk: any patient with progressive disease, refractory disease, or relapse within 1 year of original diagnosis.

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References

PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

[1] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: a report from the Children's Oncology Group. Cancer 2018;124:3210-3219.
[2] Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant hodgkin lymphoma: a report from the Children's Oncology Group. J Clin Oncol 2016:34;2372-2379.
[3] Castellino SM, Pei Q, Parsons SK, et al. Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. N Engl J Med 2022;387:1649-1660.
[4] Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32:3651-3658.
[5] Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28:3680-3686.
[6] Metzger ML, Link MP, Billett AL, et al. Excellent outcome for pediatric patients with high-risk Hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. J Clin Oncol 2021;39:2276-2283.
[7] 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.
[8] Shankar A, Hall GW, McKay P, et al. Management of children and adults with all stages of nodular lymphocyte predominant Hodgkin lymphoma - All StAGEs: A consensus-based position paper from the Hodgkin lymphoma subgroup of the UK National Cancer Research Institute. Br J Haematol 2022;197:679-690.
[9] O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicenter, single-arm, phase 1-2 trial. Lancet Oncol 2018;19:257-266.
[10] Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Lancet Oncol 2018;19:1229-1238.
[11] Cole PD, Mauz-Körholz C, Mascarin M, et al. Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin lymphoma (R/R cHL): Primary analysis [abstract]. J Clin Oncol 2020;38(Suppl): Abstract 8013.
[12] Marr K, Ronsley R, Nadel H, et al. Ifosfamide, gemcitabine, and vinorelbine is an effective salvage regimen with excellent stem cell mobilization in relapsed or refractory pediatric Hodgkin lymphoma. Pediatr Blood Cancer 2020;67:e28167.
[13] Trippett TM, Schwartz CL, Guillerman RP, et al. Ifosfamide and vinorelbine is an effective reinduction regimen in children with refractory/relapsed Hodgkin lymphoma, AHOD00P1: a children's oncology group report. Pediatr Blood Cancer 2015;62:60-64.
[14] Horton TM, Drachtman R, Chen L, et al. A phase 2 study of bortezomib in combination with ifosfamide/vinorelbine in paediatric patients and young adults with refractory/recurrent Hodgkin lymphoma: a Children's Oncology Group study. Br J Haematol 2015;170:118-122.
[15] Shankar A, Hayward J, Kirkwood A, et al. Treatment outcome in children and adolescents with relapsed Hodgkin lymphoma--results of the UK HD3 relapse treatment strategy. Br J Haematol 2014;165:534-544.
[16] Baetz T, Belch A, Couban S, et al. Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 2003;14:1762-1767.
[17] Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97:616-623.
[18] Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort single-arm phase 2 trial. Lancet Oncol 2016;17:1283-1294.
[19] Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: Extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. J Clin Oncol 2018;36:1428-1439.
[20] Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017;35:2125-2132.
[21] Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21:121-133.
[22] Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;385:1853-1862.

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PRINCIPLES OF RADIATION THERAPY[1-6]

General Principles

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

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Continued
References

PRINCIPLES OF RADIATION THERAPY[1-6]

Volume

- ISRT is recommended as the appropriate field for HL. If the protocol used involved-field RT (IFRT) then it should be replaced by ISRT.
- Planning for ISRT requires CT-based simulation and treatment planning capabilities. Incorporating other modern imaging such as FDG-PET and MRI often enhances treatment volume determination.
- ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original or suspected extent of disease prior to chemotherapy or surgery.[a] However, it spares adjacent uninvolved organs (eg, lungs, bone, muscle, kidney) when lymphadenopathy regresses following chemotherapy.
  - Pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (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.
  - Movement of the CTV by respiration as determined by 4D-CT or fluoroscopy should be used to create an internal target volume (ITV).
- 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. Daily image guidance is recommended to minimize the PTV expansion.
- Outline OARs for optimizing treatment plan decisions.
  - These should include contouring of breast tissue (conventional breast tissue and glandular breast tissue) and cardiac substructures (left ventricle and coronary vessels), especially when contemporary RT techniques are being used (IMRT, VMAT, and proton therapy).
- The treatment plan can be designed using conventional, 3D conformal RT (3D-CRT), IMRT, or proton therapy 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 used.
  - 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 the presence of vertebral body disease, the entire vertebra is generally treated.
- If spleen is irradiated, vaccines should be given prior to or after RT (ie, pneumococcal, haemophilus influenzae type b, meningococcal).

[a] In HLHR13, post-chemotherapy volumes were irradiated.

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Continued
References

PRINCIPLES OF RADIATION THERAPY[1-6]

- **In general, RT fields and doses should be delivered per protocol guidelines used for systemic therapy.**

RT Fields

- **ISRT can safely replace IFRT or modified IFRT.**
- **Residual-site RT should be used only when dictated by the protocol or as a "boost" following standard ISRT.**
- **RT should be given according to the protocol being followed. For patients with stage III/IV disease it is preferable to avoid a protocol that calls for IFRT/ISRT to all sites of disease and instead use a protocol that only irradiates sites that are bulky or if inadequate response.[7]**

Low/Intermediate Risk

- **ISRT, consider**
  - **All sites of disease - 21 Gy**
  - **Sites of slow response could receive a boost of up to 9 Gy (total dose 21–30 Gy)**
  - **Sites of PR should receive a boost of 9–19 Gy (total dose 30–40 Gy)**

High Risk

- **Avoid regimens that require ISRT to all sites of disease.**
- **ISRT, consider:**
  - **Bulky disease - 21 Gy**
  - **Slow responding sites could receive a boost of up to 9 Gy (total dose 21–30 Gy)**
  - **Partial responding sites should receive a boost of 9–19 Gy (total dose 30–40 Gy)**

Relapsed/Refractory Disease

- **If no HDT/ASCR planned: ISRT 30 Gy**
- **In conjunction with HDT/ASCR**
  - **ISRT, 30 Gy to relapsed/refractory sites, and consider 21 Gy to initial sites that are no longer present (depending on the size of the field)**
  - **If Deauville 4–5 after several lines of therapy consider RT to achieve metabolic CR prior to transplant. Boost to FDG-PET–positive sites, 10–15 Gy (total dose 40–45 Gy).**

RT Dose Constraints

- **See "RT Dose Constraint Guidelines for Lymphoma" in the NCCN Guidelines for Hodgkin Lymphoma (Adult).**

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References

PRINCIPLES OF RADIATION THERAPY
REFERENCES

[1] Bates J, Howell RM, Liu Q, et al. Therapy-related cardiac risk in childhood cancer survivors: An analysis of the childhood cancer survivor study. J Clin Oncol 2019;37:1090-1101.
[2] van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257-2265.
[3] Dietz AC, Chen Y, Yasui Y, et al. Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Cancer 2016;122:3687-3696.
[4] Cella L, Conson M, Caterino M, et al. Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2012;82;1802-1808.
[5] Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577-587.
[6] Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465-475.
[7] Hall MD, Terezakis SA, Lucas JT, et al. Radiation Therapy Across Pediatric Hodgkin Lymphoma Research Group Protocols: A Report From the Staging, Evaluation, and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL) Group. Int J Radiat Oncol Biol Phys 2022;112:317-334.

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COTSWOLDS-MODIFIED ANN ARBOR STAGING SYSTEM

Stage	Definition
I	One nodal group or lymphoid organ (eg, spleen or thymus)
IE	Local extension from one nodal group to another site[a]
II	Two or more nodal groups, same side of the diaphragm
IIE	Localized extension from one nodal group to an extranodal site with stage II criteria, both on the same side of the diaphragm[a]
III	Nodal groups on both sides of the diaphragm
IIIS1	With splenic involvement
IIIE2	With localized extension from one nodal group to an extranodal site[a]
IIISE	Both IIIS1 and IIIE2
IV	Disseminated involvement of one or more extralymphatic organs (eg, lung, bone, bone marrow, liver) with or without any nodal involvement

Additional Sub-staging Variables	
A	Asymptomatic
B	Presence of B symptoms (unexplained recurrent fever >38°C within last month; drenching night sweats; or weight loss >10% of body weight within 6 months of diagnosis)
X	Bulky nodal disease: nodal mass >1/3 of intrathoracic diameter or 6 cm[b] in dimension

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636.

[a] Based on panel consensus.
[b] In adults, 10 cm dimension is used.

ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy
ASCR	autologous stem cell rescue
AYA	adolescent and young adult
CBC	complete blood count
CHL	classic Hodgkin lymphoma
CME	continuing medical education
CMV	cytomegalovirus
CR	complete response
CRu	complete response, unconfirmed
CTV	clinical target volume
DIBH	deep inspiration breath hold
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
EBER-ISH	Epstein-Barr encoding region in situ hybridization
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
EOST	end of systemic therapy
ESR	erythrocyte sedimentation rate
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume in the first second
FNA	fine-needle aspiration
FVC	forced vital capacity
GTV	gross tumor volume
H&P	history and physical
HDT	high-dose therapy
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin/Reed-Sternberg
ICC	International Consensus Classification
IFRT	involved-field radiation therapy
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
ISRT	involved-site radiation therapy
ITV	internal target volume
LDi	longest diameter
LMA	large mediastinal adenopathy
LP	lymphocyte predominant
NHL	non-Hodgkin lymphoma
NLPBL	nodular lymphocyte-predominant B-cell lymphoma
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
OAR	organ at risk
PA	posteroanterior
PD-L1	programmed death ligand 1
PR	partial response
PFT	pulmonary function test
PPD	product of perpendicular diameters
PTV	planning target volume
RER	rapid early responder
RRL	rapidly responding lesion
SER	slow early responder
SRL	slow responding lesion
SUV	standardized uptake value
THRLBCL	T-cell/histiocyte-rich large B-cell lymphoma
TSH	thyroid-stimulating hormone
VMAT	volumetric modulated arc therapy

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 1.2024
Pediatric Hodgkin Lymphoma

Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Last updated: May 14, 2024

Table of Contents

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system.[1] The WHO classification divides HL into two main types: classic Hodgkin Lymphoma (CHL) and nodular lymphocyte-predominant HL (NLPHL).[2] CHL accounts for the majority of childhood HL, with NLPHL making up 5% to 10% of cases.[1]

CHL is characterized by the presence of large binucleate or multinucleated neoplastic cells or mononuclear variants (collectively termed Hodgkin Reed-Sternberg [HRS] cells) in an inflammatory background, whereas NLPHL lacks HRS cells but is characterized by the presence of lymphocyte-predominant (LP) cells, sometimes termed *popcorn cells.*[1] In CHL, HRS cells nearly always express CD30 and often express CD15 (in ~70%), while CD20 is expressed in only ~6% to 10%. In contrast, in NLPHL, the characteristic LP cells express CD20 and rarely express CD30 and CD15.[1]

CHL is divided into four subtypes: nodular sclerosis CHL; mixed cellularity CHL; lymphocyte-depleted CHL; and lymphocyte-rich CHL.[2] There are 6 immunoarchitectural patterns of NLPHL: B-cell–rich nodular (pattern A), serpiginous/interconnected nodular (pattern B), nodular with prominent extranodular LP cells (pattern C), T-cell–rich nodular (pattern D), T-cell–rich diffuse or T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)-like (pattern E), and diffuse B-cell–rich (pattern F).[3] Most patients are diagnosed with HL between 15 and 30 years of age, followed by another peak in adults aged ≥55 years. Although the exact etiology is unknown, some risk factors for HL include prior infection with Epstein-Barr virus (EBV) and immunocompromising conditions, including immunosuppression after organ transplantation or infection with HIV.[4-6]

In 2024, an estimated 8570 people will be diagnosed with HL in the United States and 910 people will die from the disease.[7] In adolescents (aged 15–19 years), HL is the most commonly diagnosed cancer;[8] it is estimated that 4200 adolescents and young adults (AYAs) aged 15 to 39 years of age were diagnosed with HL in 2020, with 800 of those cases being ages 15 to 19 years.[9] The incidence is less common in children (aged 5–14 years); in 2014, a report estimated that 380 children would be diagnosed with HL that year.[8]

The past few decades have seen significant progress in the management of pediatric HL, with estimated 5-year survival rates of greater than 98% after treatment with chemotherapy alone or combined with radiation therapy (RT).[10,11] However, the potential long-term effects of treatment remain an important consideration.[10,11]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Hodgkin Lymphoma were developed as a result of meetings convened by a multidisciplinary panel of pediatric HL experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. The NCCN Guidelines® currently focus on clinical staging of HL, and treatment strategies are adapted according to risk. Given the complexity of HL treatment regimens and the required supportive care measures, the NCCN Pediatric Hodgkin Lymphoma Panel recommends a consultation with centers participating in pediatric cooperative group trials. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

The panel also considers the term “pediatric” to include any patient ≤18 years of age, and recommendations in the Guidelines may extend to AYA patients up to 39 years of age. Across treatment centers, practice patterns vary with regard to AYA patients in terms of whether patients with HL are treated primarily by pediatric or adult oncologists. This Guideline is intended to apply to pediatric patients, and may also apply to AYA patients treated in an adult oncology setting.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Pediatric Hodgkin Lymphoma, an electronic search of the PubMed database was performed to obtain key literature published in pediatric HL, using the following search terms: Hodgkin lymphoma and childhood or pediatric or adolescent or young adult. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[12] Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis and Workup for Hodgkin Lymphoma

For evaluation and initial workup of HL, the panel recommends that an excisional or incisional lymph node biopsy generally be performed, although a core needle biopsy may be adequate if diagnostic. A diagnostic assessment based solely on fine-needle aspiration (FNA) biopsy is discouraged. Diagnosis should be established according to guidelines in the 2022 World Health Organization (WHO) Classification Haematolymphoid Tumours, 5th edition[2] or 2022 International Consensus Classification (ICC) of Mature Lymphoid Neoplasms.[13]

Immunostaining for CD30, CD15, CD20, and CD3 is recommended. Evaluation of an expanded panel of markers (ie, CD45, CD79a, ALK, MUM1, OCT2, BOB1) should be considered in cases with equivocal or imperfect morphologic features, or to exclude entities in the differential diagnosis. The HRS cells of CHL express CD30 in all patients, express CD15 in the majority of patients, and are usually negative for CD45 and CD3. CD20 may be detectable in a minority of cases. The LP cells of NLPHL express CD20 and also express CD45. Characteristics of the immune microenvironment (identification of small B cells, T-follicular helper cells, and follicular dendritic cells) are also helpful in the diagnostic workup of NLPHL. Cases of EBV+ CHL may benefit from additional studies such as EBV serology and evaluation for underlying

immunodeficiency. EBV+ LP cells have been reported only rarely in NLPHL and this finding should prompt consideration of other entities in the differential diagnosis.[14] Per WHO 2022, NLPHL remains under the family of HL, while ICC 2022 replaces the term NLPHL with nodular lymphocyte predominant B-cell lymphoma (NLPBL).[2,13] Both classifications recognize the clinical and biologic similarities of NLPHL to an indolent B-cell lymphoma and NLPBL is an acceptable term per WHO 2022. For additional information, see *Principles of Pathology* in the algorithm.

The workup should include a thorough history and physical examination, including determination of one or more B symptoms (unexplained recurrent fevers >38°C within the last month; drenching night sweats within the last month; weight loss of >10% of body weight within 6 months of diagnosis; and examination of lymphoid regions and spleen). Other essential workup components include standard laboratory tests (complete blood count [CBC] with differential; erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP]; and a comprehensive metabolic panel). A pregnancy test should be performed before individuals of childbearing potential undergo treatment. HIV and hepatitis B and C testing are encouraged for patients with risk factors for HIV or unusual disease presentations. An immunodeficiency workup should also be considered for patients <5 years of age, those with recurrent infections, those with an atypical presentation, and those with a personal or family history of immunodeficiency.

^{18}F-fluorodeoxyglucose (FDG)-PET scans are essential for initial staging and for evaluating residual masses at the end of treatment[15] (see *Principles of Imaging* and *Principles of Staging* in the algorithm). For staging and risk assessment, diagnostic imaging should be done before initiating chemotherapy, including: FDG-PET/CT or FDG-PET/MRI scans (whole-body); diagnostic contrast-enhanced (IV +/- oral) CT (neck, chest, abdomen, and pelvis); or CT of chest and MRI (neck, abdomen, and pelvis). When available, FDG-PET/CT and diagnostic CT should be performed as a combined examination to limit radiation exposure. FDG-PET scans should be assessed by a nuclear diagnostic radiologist experienced in reading Deauville scores for FDG-PET–adapted therapy. If cross-sectional imaging is not available or is needed for a clinical trial, posterior-anterior and lateral chest x-rays are recommended to determine bulk of disease (mediastinal mass). Consultation with a radiation oncologist is strongly recommended when considering treatment options and to determine the adequacy of imaging for potential future RT.

In cases of FDG-PET positivity where sites of disease are not consistent with usual presentation of HL, or if there are unusual disease presentations (ie, HIV), additional clinical evaluation may be needed for staging. If FDG-PET is negative for anatomic lesions of concern, a biopsy should be considered.

In most cases, if the FDG-PET/CT displays a homogeneous pattern of marrow uptake, which is thought to be secondary to cytokine release,[16,17] bone marrow involvement is not assumed. If there are multifocal ($\geq$3) skeletal FDG-PET lesions without cortical destruction on CT, marrow involvement may be assumed and a bone marrow biopsy is not needed to confirm involvement.[18] In select cases, if there are cytopenias and the FDG-PET scan is negative, a bilateral bone marrow biopsy may be considered.

If anthracycline-based chemotherapy is indicated, an echocardiogram is recommended. Pulmonary function tests (PFTs), including diffusing capacity of the lungs for carbon monoxide (DLCO), are recommended for patients receiving bleomycin-based chemotherapy. In general, a forced expiratory volume (FEV1)/forced vital capacity (FVC) of at least 60% is acceptable for bleomycin use, unless this is due to large mediastinal mass from HL. For children who are unable to cooperate for PFTs, the criteria for bleomycin use are: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry reading of >92% on room air.

The panel recommends counseling on infertility risk. In select cases and if the patients are interested, the panel recommends consideration of fertility preservation (eg, semen cryopreservation, ovarian tissue or oocyte cryopreservation) prior to the initiation of therapy. In general, the panel also recommends providing referrals for counseling as needed that address smoking cessation, substance use disorders, and psychosocial concerns. For additional recommendations, see the NCCN Guidelines for Supportive Care.

Clinical Staging and Risk Stratification

Physical examination and diagnostic imaging evaluations are used to designate the clinical stage.[1] The most widely used staging scheme for both pediatric and adult HL is the Ann Arbor Staging System, which may include the Cotswolds modification—which includes the prognostic significance of bulky disease.[1,19,20] Staging is generally defined as follows:[20]

- Stage I: One nodal group or lymphoid organ (eg, spleen, thymus, Waldeyer's ring)
- Stage II: Two or more nodal groups on the same side of the diaphragm
- Stage III: Nodal groups on both sides of the diaphragm
- Stage IV: Disseminated involvement of one or more extralymphatic organs (eg, lung, bone, bone marrow, liver) with or without any nodal involvement

Additional sub-staging variables include these terms:

- A: Asymptomatic
- B: Presence of B symptoms
- X: Bulky nodal disease, which is nodal mass greater than one-third of intrathoracic diameter on a chest x-ray or as defined by the protocol. Note: Pediatric protocols have also defined bulk disease as contiguous extramediastinal nodal mass greater than 6 cm in the longest diameter, measured in axial, coronal, or sagittal dimension (including oblique measurement), and EuroNet defines bulk as volume of the largest contiguous lymph node mass ≥200 mL.
- E: Involvement of extralymphatic by direct extension from an adjacent nodal site

Note: The Ann Arbor Staging System is in need of revision, as it does not fully represent the current practice in staging pediatric HL. Refer to the original protocol for appropriate staging of "E-lesions." Many protocols today define an E-lesion as direct extension from a site of involvement into a surrounding tissue or organ, and this does not always indicate stage IV disease.[21,22] Involvement of an extranodal site that is extralymphatic and does not arise from direct extension is considered to be stage IV disease. The distinction between stage IV disease and E-lesions is not applied uniformly but is an important distinction, as E-stage disease requires a less extensive treatment schedule.[22]

Currently, there is no uniform risk stratification for pediatric HL, although several factors are considered to confer poor prognosis, including B symptoms, mediastinal and peripheral lymph node bulk, extranodal disease, number of nodal sites, Ann Arbor stage, serum markers for inflammation, gender, and response to initial chemotherapy.[1] To facilitate the interpretation and comparison of global clinical trials, an international collaborative effort was developed: the Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL) working group.[23] As the SEARCH effort for CAYAHL develops, so will the evolution of harmonized risk stratification for pediatric HL.[11]

There are several cooperative groups, including the Children's Oncology Group (COG) (which resulted from a merging of the Pediatric Oncology

Group and Children's Cancer Group) and the European Network for Pediatric Hodgkin Lymphoma (EuroNET-PHL).[11] In the Guidelines, the panel has summarized clinical stage and associated risk groups (see *Clinical Staging of Classic Hodgkin Lymphoma* in the algorithm) but notes that emerging data may be used to update different risk groups and that staging criteria and risk stratification differ for adult regimens and clinical trials (see the NCCN Guidelines for Hodgkin Lymphoma [Adult]). Due to the evolving nature of risk stratification, enrollment in a clinical trial is preferred. In addition, for patient treatment, the panel recommends considering consultation with a center of expertise.

Principles of Imaging

Clinical management of pediatric CHL involves initial treatment with chemotherapy and assessment of treatment response with FDG-PET to determine the need for additional treatment.[24-26]

Given the avidity of pediatric lymphomas for FDG,[25] the Deauville criteria were defined for the interpretation of interim and end-of-treatment FDG-PET scans based on the visual assessment of FDG uptake in the involved sites (See Deauville Criteria Table in *Principles of Staging* in the algorithm). These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.[27-29] In the 5-PS (Deauville criteria), scores of 1 to 4 refer to initially involved sites and a score of 5 refers to an initially involved site and/or new lesions related to lymphoma.[28,29] These criteria vary across different protocols as they have yet to be validated in a large pediatric trial. However, interim or end-of-treatment FDG-PET scans with a score of 1, 2, or 3 are generally considered "negative" and FDG-PET scans with a score of 4 and 5 are considered "positive."[30] A score of 4 can be difficult to assess when FDG uptake in mediastinal masses cannot clearly be differentiated from thymic uptake or inflammatory reactions,[27,31,32] and treatment decisions in these cases will require clinical judgment. In addition, Deauville 4 may represent just a single area of persistent disease or failure to respond in any site. The 5-PS (Deauville criteria) has been validated in international multicenter trials for FDG-PET–guided interim response assessment and risk-adapted therapy in adult patients with HL.

FDG-PET imaging is important as a baseline measurement before therapy to determine the initial sites of involvement and to perform an early response assessment (ERA) (often after the initial two cycles of chemotherapy).[15] Although the optimal time point for assessment and criteria for response are not uniform, interim assessment of response by FDG-PET is incorporated into pediatric HL treatment.[1] The panel recommends diagnostic contract-enhanced CT or MRI to adequately evaluate all sites of involvement, and FDG-PET/CT or FDG-PET/MRI for interim and end-of-therapy assessments. In addition, the panel recommends waiting for at least 8 to 12 weeks after the end of RT to perform FDG-PET to minimize false-positive results. The panel also recommends consideration of measures such as warming or pharmacologic suppression to reduce brown fat activation to minimize false positive FDG-PET findings.

In some cases, routine surveillance scans in the first year following completion of therapy may have utility; however, they are recommended to be limited thereafter.[33] During follow-up, scans should only be obtained if there is significant concern for relapse or for up to 2 years.

Principles of Radiation Therapy

RT can be delivered with photons, electrons, or protons, depending upon clinical circumstances. Although advanced RT techniques emphasize tightly conformal doses and steep gradients adjacent to normal tissues, the "low-dose bath" to normal structures such as the breasts must be considered in choosing the final RT technique. Therefore, target definition, delineation, and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in

tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, FDG-PET, ultrasound (US), and other imaging modalities facilitate target definition.

Data from single-institution studies have shown that significant dose reduction to organs at risk (OARs; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid arteries, bone marrow, stomach, muscle, soft tissue, salivary glands) can be achieved with advanced RT planning and delivery techniques such as four-dimensional CT (4D-CT) simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), respiratory gating, deep inspiration breath hold, or proton therapy.[34-36] These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control. However, the panel notes that randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OARs in a clinically meaningful manner without compromising target coverage should be considered in these patients, who are likely to enjoy long life expectancies following treatment.

Involved-site RT (ISRT) is recommended as the appropriate field for HL and can safely replace involved-field RT (IFRT) or modified IFRT from earlier trials, though in HLHR13 involved-node RT was used to treat post-chemotherapy volumes. ISRT targets the originally involved nodal sites and possible extranodal extensions (which generally defines a smaller field than the classical IFRT),[37] and is intended to spare the adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. Treatment planning for ISRT requires the use of CT-based simulation, and additional imaging techniques such as FDG-PET and MRI often enhance the treatment planning.

For patients with low- or intermediate-risk disease, the panel recommends an RT dose of 21 Gy to all sites of disease. Sites of slow response (usually defined with specific anatomic and/or FDG-PET criteria) can receive a boost of up to 9 Gy (total dose of 21–30 Gy). Sites of partial response (PR) should receive a boost of 9–19 Gy (total dose of 30–40 Gy). For patients with high-risk disease, the panel discourages using regimens that require ISRT to all sites of disease. Instead, for bulky disease, a dose of 21 Gy may be considered. The RT doses recommended for sites of slow response and sites of PRs in the low- or intermediate-risk disease setting are the same in this context. The panel notes that residual site RT should only be used when dictated by the protocol or as a boost following standard ISRT.

For patients with relapsed or refractory disease, if no high-dose therapy (HDT) or autologous stem cell rescue (ASCR) is planned, an RT dose of 30 Gy is recommended. If HDT/ASCR is planned, an RT dose of 30 Gy to relapsed or refractory sites may be used, with a consideration of 21 Gy to initial sites that are no longer present with active disease. If FDG-PET positive (Deauville 4 to 5) after several lines of therapy, RT may be considered to achieve metabolic complete response (CR) before transplant. Boost RT doses of 10 to 15 Gy (total dose of 40–45 Gy) to FDG-PET–positive sites may also be considered.

Management of CHL

In this section, data from select clinical trials that are recommended in the Guidelines are reviewed to provide a rationale for their inclusion in the Guidelines.

Low-Risk CHL

Approximately 26% to 34% of children and adolescents with HL present with low-risk disease.[38] Outcomes for children and adolescents with low-risk HL are high, so recent trials are focused on modifying treatment (ie, reduction or elimination of specific chemotherapeutic agents or RT).[38] For instance, the German Society of Pediatric Oncology and Hematology Hodgkin's Disease (GPOH-HD) study series has demonstrated that RT can be eliminated from a combined modality treatment scheme for patients in treatment group (TG) 1 stage (early stages: I and IIA) who achieve a CR after chemotherapy (GPOH-HD-95 trial).[39]

In the GPOH-HD-2002 study, the main goal was to replace a component of chemotherapy (ie, procarbazine with etoposide and dacarbazine) to decrease gonad toxicity.[40] In this trial, all patients were aged <18 years (n = 573); for induction, males (n = 287) received 2 courses of OEPA (vincristine, etoposide, prednisone, and doxorubicin), and females (n = 286) received 2 courses of OPPA (vincristine, procarbazine, prednisone, and doxorubicin).[40] After chemotherapy, all patients received IFRT at 19 Gy except patients in TG-1 stage (early stages: IA, IB, and IIA) who were in CR (residual tumor volume ≤95% and ≤2 mL of the initial volume). In TG-1, overall event-free survival (EFS) was 92% ± 2.0%, with no significant impact of RT on EFS.[40] In TG-2 (intermediate stages: IE, IIB, IIAE, and IIIA) and TG-3 (advanced stages: IIBE, IIIAE, IIIB, IVA, IVB, and IVE), there was no significant difference in EFS between males and females (90.2% ± 2.3% vs. 84.7% ± 2.7%, respectively; *P* = .12).[40] This trial suggested that both regimens could be used in intermediate and advanced stages, but also confirmed findings from GPOH-HD-95 that RT could be eliminated in patients in TG-1 stage who experience CR after chemotherapy.[39,40]

Building on the GPOH-HD studies, an international intergroup phase III titration study for CHL in children and adolescents (EuroNET-PHL-C1) aimed to investigate whether RT can be omitted in patients with an adequate morphological and metabolic response to OEPA. Among 714 patients assigned to and treated on TG-1, an adequate response, defined as ≥50% reduction in tumor volume and PET activity ≤ mediastinal blood pool or background activity, was achieved in 62%. In this group that did not receive RT, the 5-year EFS was 86.5% (95% CI, 83.3%-89.8%), below the target of 90%. Post hoc analyses demonstrated that the target EFS was achieved in patients without risk factors of bulky involvement or an elevated ESR.[41]

In the COG AHOD0431 trial, the goal was to evaluate the efficacy of a lower-intensity regimen, AVPC (doxorubicin, vincristine, prednisone, and cyclophosphamide), in pediatric and AYA patients (≤21 years of age) with non-bulky, stage IA and IIA CHL.[42] All patients (n = 278) were treated with 3 cycles of AVPC, and patients who did not experience CR after 3 cycles received 21 Gy of IFRT. Patients who experienced a protocol-defined, low-risk relapse after chemotherapy alone were eligible for an integrated salvage regimen composed of vinorelbine, ifosfamide, dexamethasone, etoposide, cisplatin, and cytarabine, with growth factor support for 2 cycles, and IFRT.[42] At 4 years, 49.0% of patients had been treated with 3 cycles of AVPC without RT and 88% achieved CR without receiving HDT/ASCR or >21 Gy of IFRT. The OS rate was 99.6%. Patients with mixed cellularity histology had a 4-year EFS of 95.2% compared to an EFS of 75.8% in patients with nodular sclerosis histology (P = .008).[42] In this study, a negative FDG-PET scan after 1 cycle of chemotherapy (PET1) and an ESR rate ≤20 mm/h were associated with a favorable EFS outcome.[42]

NCCN Recommendations for Low-Risk CHL

For patients with stage IA, IIA, and IB CHL (with or without bulky disease; no E-lesions), the panel recommends enrollment in an ongoing clinical trial

or treatment with OEPA according to GPOH-2002 or EuroNet-PHL-C1 (a category 1 recommendation) as the preferred strategies. In certain circumstances, for patients with mixed cellularity histology only, 3 cycles of AVPC may be considered per the AHOD0431 trial.

After initial cycles of chemotherapy, patients who experience adequate response may be followed. Omission of ISRT should be more strongly considered for patients that meet the GPOH-2002 response criteria, in recognition of the lower EFS observed among patients with risk factors treated on the PHL-C1 trial.[40] Patients who experience inadequate response receive ISRT (to all sites and boost to sites of inadequate response per EuroNet-PHL-C1). Based on an end-of-therapy FDG-PET assessment, patients may be followed or may consider re-induction therapies if there is a concern for persistent disease.

In some pediatric patients with CHL, the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) may be considered.[43-47] The panel recommends referring to the adult NCCN Guidelines for Hodgkin Lymphoma to review relevant data and context.

Intermediate-Risk CHL

The phase III COG AHOD0031 study evaluated the role of early chemotherapy response in tailoring subsequent therapy in pediatric intermediate-risk HL.[48] Patients with newly diagnosed intermediate-risk HL (n = 1,712; aged <22 years) received 2 cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone) followed by ERA with PET/CT. For patients who experienced adequate response (rapid early response [RER], based on anatomic criteria), 2 additional cycles of ABVE-PC were given followed by an evaluation for CR. Those who experienced RER with CR (80% or greater reduction in the product of perpendicular parameters [PPD] or a return to normal size for all target lesions, plus no residual extramediastinal nodal mass >2.0 cm, no residual disease in non-measurable sites, and a negative gallium or FDG-PET scan) were randomly assigned to IFRT (21 Gy) or observation, and those who experienced RER with less than CR were nonrandomly assigned to receive IFRT. Patients who experienced inadequate response (slow early response [SER]) after 2 cycles of ABVE-PC were randomly assigned to receive or not receive 2 cycles of chemo-intensification with DECA (dexamethasone, etoposide, cisplatin, and cytarabine) followed by 2 additional cycles of ABVE-PC. All patients in the SER group were randomized to receive IFRT.

The overall 4-year EFS was 85% (86.9% in the setting of RER and 77.4% in the setting of SER; $P < .001$), and the 4-year OS was 97.8% (98.5% in the setting of RER and 95.3% for in the setting of SER; $P < .001$).[48] In those who experienced RER with CR at the end of chemotherapy, there was no significant difference in the 4-year EFS rate between patients who received IFRT versus those who did not receive IFRT (87.9% vs. 84.3%, respectively). For those who experienced SER who received either DECA or no DECA, the 4-year EFS was 79.3% versus 75.2%, respectively ($P = .11$). PET response imaging was not required but was obtained for the majority of patients as part of clinical care. Analysis of these data demonstrated that those who experienced SER with PET-positive lesions after two cycles had a marginal improvement in EFS on the DECA arm (70.7% vs. 54.6%, $P = .05$). Overall, this study showed that RT can be omitted in those who experience RER with CR at the end of chemotherapy, and that augmenting chemotherapy in those who experience SER with PET-positive disease may be beneficial.[48]

In a study by the Pediatric Oncology Group (P9425), the efficacy of ABVE-PC in intermediate- or high-risk HL (n = 216; age <22 years) was assessed.[49] After 3 cycles of ABVE-PC, early response was evaluated and patients who experienced RER based on anatomic criteria received IFRT (21 Gy) and patients who experienced SER received 2 additional cycles of ABVE-PC (total of 5 cycles) followed by IFRT. Patients were also randomly assigned to receive or not receive dexrazoxane to evaluate its

effect as a protectant from anthracycline-induced cardiac and bleomycin-induced pulmonary toxicity. Of 209 evaluable patients, the 5-year EFS was 84% (84% and 85% for patients with intermediate- and high-risk disease, respectively; *P* = .87).[49] The EFS differed between patients with large mediastinal adenopathy (LMA) versus those without LMA (80% ± 4% vs. 91% ± 3%; *P* = .03). However, use of dexrazoxane did not affect EFS, but may increase risk for acute toxicity, especially typhlitis. The 5-year OS was 95% and did not differ between RER and SER groups.[49] Overall, this trial allowed a reduction in alkylator and anthracycline exposure in 63% of patients. However, RT fields were more extensive than with contemporary approaches.

A later COG study further examined long-term outcomes among children with newly diagnosed malignancies, including HL, who received dexrazoxane as part of clinical trial therapy.[Chow, 2022 #252] Patients who had been randomized to doxorubicin with or without dexrazoxane were assessed with a median follow-up period of 18.6 years. Dexrazoxane was not found to be associated with relapse (HR, 0.84), secondary cancers (HR, 1.19), all-cause mortality (HR, 1.07), or cardiovascular mortality (HR, 1.45), and serious cardiovascular outcomes occurred less commonly when dexrazoxane was used (5.6% vs. 17.6%; *P* = .02). In a retrospective study assessing outcomes among children with HL, acute lymphoblastic leukemia, or osteosarcoma who received doxorubicin with or without dexrazoxane, the use of dexrazoxane, particularly among those who received a cumulative doxorubicin dose of ≥ 250 mg/m^2, was associated with a reduced risk of reduction in lower left ventricular function or ejection fraction at 18.1 ± 2.7 years from cancer diagnosis.[50]

The randomized phase II SWOG S1826 trial compared the safety and efficacy of 6 cycles of N-AVD (nivolumab, doxorubicin, vinblastine, and dacarbazine) to BV-AVD in patients ≥12 years of age (n = 976; median age 27 years [range 12–83 years]) with stage III–IV HL.[51,52] Data from the second interim analysis revealed a superior 1-year PFS with N-AVD (94%) compared to BV-AVD (86%) (*P* = .0005) in the full cohort.[51] Among 327 patients aged 12-17 years, 1-year PFS with N-AVD was 94% and 88% with BV-AVD (*P* = .067).[52] Only 2 patients in this age group received RT.[52] While there were 7 deaths due to AEs in the BV-AVD arm compared to 3 in the N-AVD arm in the overall cohort, no deaths were reported among adolescents.[51,52] There were more grade ≥3 hematologic AEs on the N-AVD arm (48.4% vs. 30.5%; 45% vs. 41% among adolescents), as expected as growth factor use was only required with BV-AVD, but similar rates of febrile neutropenia.[51,52] Sensory and motor peripheral neuropathy were less frequent in the N-AVD arm (28.1%/4% vs. 54.4%/6.8%; 18%/8% vs. 29%/5% among adolescents).[51,52] While rates of pneumonitis and colitis were similar between the two arms[51,52], hypo/hyperthyroidism was more common yet infrequent with N-AVD (2% vs.0% among adolescents[52]). Longer follow-up and OS data are needed.

Other clinical studies evaluating the intermediate-risk group (TG-2) include the GPOH-HD-2002 and EuroNET-PHL-C1 trials[40,53] as described under *Low-Risk CHL*.

In a follow-up titration study of EuroNET-PHL-C1, patients were randomly assigned to 2 (TG-2) or 4 (TG-3) cycles of COPP or COPDAC after an initial 2 cycles of OEPA.[54] RT was omitted in patients who experienced adequate response (partial remission or greater and FDG-PET negativity [Deauville score 1–2]) following 2 cycles of OEPA. Those who experienced inadequate response received ISRT and an additional boost to sites that responded slowly to treatment. Five-year EFS in those who experienced adequate responses and for whom RT was omitted was 90.1% compared to 87.1% in those who experienced inadequate response and went on to RT. Five-year EFS in all patients treated with COPP was 89.9% versus 86.1% in all those treated with COPDAC, with a difference of -3.7%. A subgroup analysis further investigated responses to COPP versus COPDAC in those who experienced adequate versus inadequate response and found a treatment difference of -9.1% (91.9% with COPP

and 82.9% with COPDAC). There was no difference in OS between COPP and COPDAC. Results of this trial indicate that RT can be safely omitted in patients with intermediate- and advanced-stage disease who experience adequate response to OEPA when treated with either COPP or COPDAC. Results also show non-inferiority of the less gonadotoxic COPDAC compared to COPP in patients who received RT; however, COPDAC was inferior to COPP in those for whom RT was omitted.

NCCN Recommendations for Intermediate-Risk CHL

For patients with stage IA/IIA CHL (with bulky disease; with or without E-lesions), IB CHL (with or without bulky disease or E-lesions), IIB CHL (no bulky disease; with or without E-lesions), and IIIA CHL, the panel recommends enrollment in an ongoing clinical trial or treatment according to AHOD0031 or EuroNet-PHL-C1 as the preferred strategies.

For the AHOD0031 regimen, after 2 initial cycles of ABVE-PC, patients who experience adequate response are treated with 2 additional cycles of ABVE-PC. Based on an end-of-therapy FDG-PET assessment and CR achievement with CT criteria, patients may either be followed or treated with ISRT to all sites if less than CR. Patients who experience inadequate response receive 2 additional cycles of ABVE-PC and ISRT.

For the regimen based on EuroNet-PHL-C1, after 2 initial cycles of OEPA, patients who experience adequate response are treated with 2 cycles of COPDAC. Patients who experience inadequate response are treated with 2 cycles of COPDAC and ISRT (to all sites and boost to sites of inadequate response).

In both cases, based on an end-of-therapy FDG-PET assessment and CT scan, patients may either be followed or considered for biopsy to confirm persistent active disease.

As recommended for low-risk CHL, the ABVD regimen may be considered for some pediatric patients and is an other recommend treatment option.[43-47] N-AVD as per SWOG S1826 may be considered in certain circumstances in patients ≥12 years of age with stage 3A involvement.[52] The panel recommends referring to the adult NCCN Guidelines for Hodgkin Lymphoma to review relevant data and context for these regimens.

High-Risk CHL

In the phase III, randomized COG AHOD1331 trial, the anti-CD30 antibody-drug conjugate brentuximab vedotin (Bv) with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (Bv-AVE-PC) was compared to ABVE-PC in pediatric patients with previously untreated stage IIB with bulk tumor, stage IIIB, stage IVA, or stage IVB disease (n = 587; aged 2–21 years).[55] ISRT (21 Gy) was administered following cycle 5 to slow-responding lesions (defined by a Deauville score of 4 or 5 on FDG-PET following cycle 2) and to LMA present at diagnosis. With a median follow-up of 42.1 months, 3-year EFS was 92.1% (95% CI, 88.4%–94.7%) in the Bv-AVE-PC group compared to 82.5% (95% CI, 77.4%–86.5%) in the ABVE-PC group (HR, 0.41; 95% CI, 0.25–0.67; P < .001). The percentage of patients requiring ISRT did not differ significantly between the two groups (53.4% in the Bv-AVE-PC group vs. 56.8% in the ABVE-PC group, respectively). OS rates at 3 years were 99.3% (95% CI, 97.3%–99.8%) in the Bv-AVE-PC group compared to 98.5% (95% CI, 96.0%–99.4%) in the ABVE-PC group. Toxicity was similar in the two groups, with an overall incidence of clinically significant adverse events (AEs) in 73.5% of patients in the Bv-AVE-PC group versus 68.2% in the ABVE-PC group. There was no significant difference in rates of grade 2 or higher peripheral neuropathy between the two groups (25.5% in the Bv-AVE-PC group vs. 24.9% in the ABVE-PC group).

In the Children's Cancer Group (CCG)-59704 study, the efficacy of upfront dose intensification with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, procarbazine, and prednisone) has been evaluated in pediatric patients with high-risk HL (n = 99; aged <21 years).[56,57] All patients received 4 cycles of BEACOPP, and patients who experienced rapid response received either 4 cycles of COPP/ABV and no IFRT (females) or 2 cycles of ABVD followed by IFRT (21 Gy) (males).[57] Patients who experienced slow response received an additional 4 cycles of BEACOPP and IFRT. The 5-year EFS and OS rates were 94% and 97%, respectively.[57] Although this regimen is effective at maintaining disease control, it is likely to be associated with increased long-term toxicities.[56]

Building on TG-3 from the GPOH-HD2002 trial, the HLHR13 multicenter trial studied the efficacy of Bv in frontline treatment of high-risk CHL in pediatric patients.[58] In this study, Bv replaced vincristine in the OEPA/COPDAC regimen. Patients ≤18 years with stage IIB, IIIB, or IV CHL were treated with 2 cycles of AEPA (A = Bv) followed by 4 cycles of CAPDAC. ERA was obtained following AEPA cycles and lymph nodes not achieving CR were targeted with response-based residual node radiation (RNRT). Compared to a historical control group treated with the Stanford V regimen (prednisone, nitrogen mustard, doxorubicin, vincristine, etoposide, bleomycin, and vinblastine) from the HOD99 study, more patients achieved CR at ERA with AEPA than with Stanford V (35.1% vs. 17%, *P* = .004) and did not require RT. Three-year EFS and OS rates with AEPA were 97.4% and 98.7% respectively, compared to 80.8% (*P* = .0008) and 96.5% (*P* = .311) with Stanford V.

Another clinical study evaluating high-risk CHL is the SWOG S1826 trial,[51,52] as described under *Intermediate-Risk CHL*.

NCCN Recommendations for High-Risk CHL

For patients with stage IIB, IIIA, IIIB, and IV CHL, the panel recommends enrollment in an ongoing clinical trial or treatment with Bv-AVE-PC according to AHOD1331 or treatment according to EuroNet-PHL-C1 as the preferred strategies.

For the Bv-AVE-PC regimen based on AHOD1331, after 2 initial cycles of Bv-AVE-PC, patients who experience adequate response (rapidly responding lesions [RRLs]) are treated with 3 additional cycles of Bv-AVE-PC and ISRT to sites of LMA. Patients who experience inadequate response (slow responding lesions [SRLs]) receive 3 additional cycles of Bv-AVE-PC and ISRT to sites of LMA and SRL. The addition of boost is dependent on FDG-PET–positive lesions at end of chemotherapy.

For the regimen based on EuroNet-PHL-C1, after 2 initial cycles of OEPA, patients who experience adequate response are treated with 4 cycles of COPDAC. Patients who experience inadequate response are treated with 4 cycles of COPDAC and ISRT to all sites and boost to sites of inadequate response.

Another recommended regimen is based on HLHR13. For this regimen, after 2 initial cycles of AEPA, patients who experience adequate response are treated with 4 cycles of CAPDAC. Patients who experience inadequate response are treated with 4 cycles of CAPDAC and involved node RT to sites of inadequate response.

Another recommended regimen for patients ≥12 years of age is N-AVD as per SWOG S1826. The panel recommends referring to the adult NCCN Guidelines for Hodgkin Lymphoma to review relevant data and context for this regimen.

In all cases, based on an end-of-therapy FDG-PET assessment, patients may either be followed or considered for biopsy to confirm persistent active disease.

In other circumstances, the BEACOPP regimen may be considered for some pediatric patients.[43-47,57] The panel recommends referring to the adult NCCN Guidelines for Hodgkin Lymphoma to review relevant data and context. It is worth noting that in the adult NCCN Guidelines for Hodgkin Lymphoma, regimens with reduced number of cycles of BEACOPP have been developed.

Relapsed or Refractory CHL

Although the outcomes for pediatric HL are excellent, approximately 10% of patients with early-stage disease and up to 25% of patients with advanced-stage disease experience relapse.[10,59,60] For patients with relapsed or refractory disease, treatment options include standard-dose chemotherapy (re-induction therapy), HDT with ASCR, or novel approaches.[59] Re-induction regimens can be divided into four major categories.[59]

1) **Targeted therapy and immunotherapy-based regimens** include Bv combined with bendamustine,[61,62] gemcitabine,[63] or nivolumab;[64,65] or single-agent nivolumab[66,67] or single-agent pembrolizumab.[68,69]

In a group of heavily pretreated patients ≥18 years of age with R/R HL (n = 64) and anaplastic large cell lymphoma (n = 1), the safety and clinical activity of Bv and bendamustine was evaluated.[61] An overall response was achieved in 29 of 37 patients (78%).[61] The combination of Bv and bendamustine as part of salvage therapy was also assessed in a multicenter retrospective analysis of pediatric patients with R/R HL (n = 29; median age 16 years).[62] Complete metabolic response (CMR) rate and objective response rates were 66% and 79%, respectively. Seventeen patients were able to undergo successful stem cell mobilization and 16 went on to consolidative transplant (13 autologous, 3 allogeneic). Three-year EFS and OS rates were 65% and 89%, respectively. Treatment was well tolerated overall, with the most common grade 3 or 4 AEs being hematologic. There were 2 cases of grade 3 hyperbilirubinemia and 3 episodes of grade 3 infusion reactions. There were no reports of significant neuropathy.

In a COG study (AHOD1221), the safety and efficacy of Bv and gemcitabine was evaluated in children and young adults with primary refractory or early relapsed HL (n = 46; aged <30 years).[63] Of 42 evaluable patients, 24 (57%) achieved a CR within the first 4 cycles of treatment; 4 of 13 patients (31%%) who experienced a PR or who had stable disease had all target lesions with Deauville scores of ≤2 after 4 cycles of treatment.[63] Using a Deauville score threshold of ≤3, 28 of 42 (67%) achieved a CR.

The combination of Bv and nivolumab, a human monoclonal PD-1–directed antibody, has been evaluated as initial salvage therapy in adult patients with R/R HL prior to ASCT.[70] In this phase 1/2 study, patients received up to 4 cycles of Bv and nivolumab, with staggered dosing in cycle 1 followed by same-day dosing in cycles 2–4. CR and objective response rates were 61% and 82%, respectively. The most common AEs were nausea in 49% of patients, fatigue in 41%, and infusion reactions in 44%. Grade 3 or higher AEs occurred in 31% of patients. Peripheral neuropathy was reported in 20% of patients.[70] Long-term follow-up data revealed an estimated 3-year PFS rate of 77% (91% for those who proceeded to ASCT following study treatment) and 3-year OS of 93%.[65] At a median of 34.3 months, no new AEs were observed.[65]

In a phase II study of children and AYA patients with R/R HL (n = 44; median age range, 9–30 years), patients were treated with 4 cycles of Bv and nivolumab and experienced CMR and ORR rates of 59% and 82%, respectively (according to blinded independent central review).[71] The

majority of immune-mediated AEs were grade 1 or grade 2. One patient experienced two grade 3 infusion-related reactions.

Multiple studies have also demonstrated efficacy of nivolumab and pembrolizumab, another human monoclonal PD-1–directed antibody, in adult patients with R/R HL.[66-68] In a study evaluating the efficacy of pembrolizumab in pediatric patients with R/R PD-L1–positive solid tumors or lymphomas (n = 154 evaluable patients; median age, 13 years; interquartile range [IQR], 8–15 years), 9 of 15 patients with R/R HL achieved an objective response (60%).[69] In the phase III KEYNOTE-204 study, heavily pretreated adult patients with R/R CHL were randomized to receive either pembrolizumab or Bv (n = 300 evaluable patients; pembrolizumab arm, n = 148; Bv arm, n = 152; aged ≥18 years).[72] The median PFS in the pembrolizumab treatment arm was statistically longer than the Bv treatment arm (13.2 months vs. 8.3 months, respectively; HR, 0.65; 95% CI, 0.48–0.88; *P* = .00271).[72]

Because no randomized trials have been conducted to compare reinduction regimens, none of the regimens are considered to be superior to the others.[60] At this stage, desired qualities in a regimen are low toxicity and high efficacy, and other goals of therapy are to obtain cytoreduction/CR before transplant, and to harvest peripheral blood stem cells for ASCT.[59]

In general, two post-transplant treatment options may be considered including: 1) maintenance therapy with Bv (especially useful in patients with disease with high-risk features including progressive disease, refractory disease, or relapse within 1 year of diagnosis);[73] and 2) RT consolidation after HDT/ASCR. Multiple studies support the addition of RT in the transplant setting by showing benefit for local tumor control and improved EFS/OS/disease-free survival (DFS).[60,74,75]

2) **Gemcitabine-based regimens** including: GV[76] (gemcitabine and vinorelbine); and IGEV[77] (ifosfamide, gemcitabine, and vinorelbine). The GV regimen was evaluated in heavily pretreated pediatric patients with R/R HL (n = 30; median age, 17.7 years; range, 10.7–29.4 years).[76] All patients had received at least 2 prior chemotherapy regimens and 17 patients had undergone prior HDT/ASCR. Overall, 19 of 25 patients had measurable disease responses for an observed response rate of 76%.[76] Patients who had received transplant before GV tended to be more likely to have disease response to therapy compared to patients who had not received transplant.[76] In a study of 12 pediatric patients with primary refractory or relapsed HL (age range, 8–16 years), the ORR to IGEV was 100%, with 58% CRs and 42% PRs.[77] The 5-year second EFS and OS rates were 83.0% ± 11.0% and 90.0% ± 9.5%, respectively.[77]

3) **Ifosfamide-/etoposide-based regimens** including: ICE[78] (ifosfamide, carboplatin, and etoposide); IV[79] (ifosfamide, and vinorelbine); and a regimen composed of bortezomib and IV.[80] The ICE regimen was developed to decrease non-hematologic toxicities observed with cisplatin-containing regimens.[60,78] In a study of patients with primary refractory or relapsed HL (n = 65; median age, 27 years; range, 12–59 years), after treatment with 2 biweekly cycles of ICE, patients whose disease responded to therapy received HDT/ASCR and IFRT. In this study, the response rate to ICE was 88% and the EFS for patients who underwent transplantation was 68%.[78]

In a study evaluating the efficacy of the IV regimen, 66 patients <30 years of age with R/R HL were treated with 2 cycles of IV.[79] The overall response rate (ORR) of 72% allowed most of the patients to undergo subsequent HDT/ASCR.[79] It is worth noting that this regimen eliminates etoposide, a chemotherapeutic agent associated with secondary malignancy after transplantation.[79,81] Addition of bortezomib to the IV regimen does not improve anatomic CR after 2 cycles, but may improve the ORR at the completion of therapy.[80]

4) **Platinum-based regimens** including: DHAP[82] (dexamethasone, cytarabine, and cisplatin); EPIC[83] (etoposide, prednisolone, ifosfamide, and cisplatin); and GDP[84] (gemcitabine, dexamethasone, and cisplatin). In a study of patients with relapsed/refractory (R/R) HL (n = 102; median age, 34 years; range, 21–64 years), the response rate after 2 cycles of DHAP was 89%.[82] In a retrospective study of 80 children with relapsed or primary refractory HL, treatment with the EPIC regimen (55% of patients received HDT/ASCR after first relapse following EPIC regimen) resulted in a 5-year OS and progression-free survival (PFS) from relapse of 75.8% and 59.9%, respectively.[83] In a study of patients with R/R HL (n = 23; median age, 36 years; range, 19–57 years) the response rate after 2 cycles of GDP was 69.5%.[84]

NCCN Recommendations for Relapsed or Refractory CHL

Histologic confirmation with biopsy is recommended before initiating treatment for relapsed or refractory disease given the risk for transformation and high false-positive rate of FDG-PET/CT. If the biopsy is negative, the panel recommends either observation with short-interval follow-up or additional workup if there is a high index of suspicion. If the biopsy is positive, the panel recommends enrollment in a clinical trial if available, and referral to or consulting with a center of expertise, as several options exist for the treatment of R/R disease and there is a lack of data to support one regimen over another.

Typically, patients are treated with re-induction therapies, and after an FDG-PET/CT or FDG-PET/MRI assessment, if metabolic CR is observed (Deauville score ≤3), treatment can be followed up with HDT/ASCR with or without ISRT and with or without maintenance therapy. In general, RT is performed as consolidation after transplant. If a metabolic CR is not achieved, RT may be used before transplant.

In certain cases, patients may avoid ASCR. These include patients with initial disease stages other than IIIB or IVB, patients who have no prior exposure to RT, patients with duration of first CR >1 year, and patients with no extranodal disease or B symptoms at relapse.[85] In these patients, re-induction therapy plus ISRT may be considered for initial treatment of R/R HL.

After initial re-induction therapy, an assessment with FDG-PET/CT or FDG-PET/MRI is recommended to evaluate response. If FDG-PET–negative, patients may be observed with short-interval follow-up. If FDG-PET–positive, subsequent therapy options should be considered, including re-induction options that were not previously used.

Management of NLPHL

In this section, data from select clinical trials that are recommended in the Guidelines are reviewed to provide a rationale for their inclusion in the Guidelines.

Stage IA NLPHL with Complete Resection confirmed by FDG-PET/CT

The presentation of NLPHL is clinically distinct from that of CHL. There is a strong male predominance (~70%) and pediatric patients often present at a younger age than CHL. Most patients are asymptomatic and present with early-stage disease (stage IA), with localized peripheral lymph node involvement. Mediastinal involvement is seen infrequently.[86,87]

While pediatric patients with NLPHL have historically achieved excellent responses to regimens used for early-stage CHL, the chemotherapy and RT involved in these regimens carry risks of late toxicities, including secondary cancers and transformation to non-Hodgkin lymphoma (NHL).[86] Several cooperative groups have published evidence to suggest that complete surgical resection of localized disease, confirmed post-operatively, is an effective option in a select group of patients.[86-89]

In the Children's Oncology Group AHOD03P1 study, a total of 52 patients with stage IA NLPHL limited to a single lymph node were observed without further therapy following complete resection.[86] Five-year EFS was 77.1%. Of the 52 patients in this group, 13 relapsed at a median of 11.5 months from the time of study enrollment. Twelve of the 13 relapses were stage IA, occurring at the initial site of disease or in adjacent nodes/nodal regions.

The European Network on Pediatric Hodgkin Lymphoma collected data from 58 patients with limited-stage disease treated with resection alone.[87] Fifty-four of the patients had stage IA disease, 2 had stage IIA disease, and 2 had stage IIIA disease. At a median follow-up of 43 months, PFS and OS rates were 57% and 100%, respectively. Of the patients who achieved CR after surgery (51 of 58 patients), overall PFS was 67% at 26-month follow-up. All patients who had residual disease after surgery had recurrence at a median of 17 months and 14 of the 51 patients who achieved CR after surgery had recurrence at a median of 26 months. Only 5 patients received RT. With a median follow-up of 52 months, PFS for patients who recurred was 80%.

Shankar and colleagues investigated low-intensity CVbP (cyclophosphamide, vinblastine, prednisone) in patients with early-stage NLPHL and found this to be a safe and effective upfront chemotherapy regimen for patients who were not able to be treated with surgical resection alone.[90] In this study, a total of 55 patients with either previously untreated (n = 45) or relapsed (following surgical resection) (n = 10) stage I or II NLPHL were treated with 3 cycles of CVbP prior to response assessment. Of the 45 patients who received first-line CVbP, 80% (n = 36) achieved either a CR or CRu (complete response unconfirmed) and the remaining (n = 9) patients achieved a PR. Of the 9 patients who experienced PR, all achieved CR with either salvage chemotherapy or IFRT. All 10 of the patients who received CVbP at relapse following surgical resection achieved a CR. For the entire cohort, 40-month freedom from treatment failure (FFTF) and OS were 75.4% and 100%, respectively. With a median follow-up period of 41 months, only 3 patients experienced relapse following CVbP (all 3 with stage IIA disease at diagnosis), and all 3 went on to achieve CR following OEPA +/- COPP. CVbP was well tolerated, with no grade 3 or 4 hematologic toxicities reported, and hair loss and mucositis were rare.

NCCN Recommendations for Stage IA NLPHL with Complete Resection Confirmed by FDG-PET/CT

For patients with stage IA NLPHL with complete resection confirmed by FDG-PET/CT, the panel recommends enrollment in an ongoing clinical trial or observation as the preferred strategies. Observation should consist of an US of the primary site every 3 to 4 months for the first 2 years. Additional imaging should be pursued as indicated for concern for relapsed disease. Biopsy should also be performed if there is concern for relapse. If biopsy is negative, observation can continue. If biopsy confirms relapse, patients should undergo restaging, with treatment decisions to follow based on stage.

Chemotherapy with CVbP for 3 cycles is another recommended option. For patients >18 years, additional options can be considered as per the NCCN Guidelines for Hodgkin Lymphoma (Adult).

Stage IA or IIA NLPHL with Incomplete Resection and Non-Bulky

Combination chemotherapy regimens used in the treatment of CHL have shown excellent outcomes in children with NLPHL; however, these treatment strategies carry long-term risks associated with chemotherapy and RT; thus, contemporary treatment approaches aim to limit chemotherapy cycles with or without RT.[86,88]

The COG AHOD03P1 study, as discussed above, not only aimed to evaluate the strategy of surgical resection alone for patients with early-stage NLPHL, but also evaluated the use of AVPC

(doxorubicin/vincristine/prednisone/cyclophosphamide) chemotherapy.[86] A total of 135 patients with either unresected stage IA or stage IIA disease or with recurrence following complete resection received 3 cycles of AVPC. CR was obtained in 92% of patients. The 8% of patients who experienced less than a CR went on to receive IFRT. Five-year EFS was estimated at 88.8%, with 12 relapses and the development of secondary cancer in 3 patients. AVPC was overall well tolerated, with grade 3 or 4 fever and neutropenia in 5.1% of patients.

CVbP was found to be a safe and effective first-line chemotherapy regimen for children and adolescents with stage IA or IIA NLPHL by Shanker and colleagues, as previously discussed in *Stage IA NLPHL with Complete Resection Confirmed by FDG-PET/CT*.[90] While data for the use of the anti-CD20 antibody rituximab for early-stage NLPHL are limited, it has been safely added to chemotherapy regimens in many subtypes of lymphoma and has yielded favorable PFS and response rates in adult NLPHL when combined with ABVD and CHOP. Shanker and colleagues thus support the addition of rituximab to low intensity CVbP and postulate that it would improve PFS while adding minimal toxicity.[88]

NCCN Recommendations for Stage IA or IIA NLPHL with Incomplete Resection and Non-Bulky

For patients with stage IA or IIA NLPHL with incomplete resection and non-bulky disease, the panel recommends enrollment in an ongoing clinical trial, AVPC x 3 cycles (category 1 recommendation), or CVbP with or without rituximab as preferred strategies. An FDA-approved biosimilar is an acceptable substitute for rituximab. With the AVPC approach, if an adequate response is not achieved following 3 cycles, ISRT is recommended. With the CVbP approach, if an adequate response is not achieved following 3 cycles of CVbP with or without rituximab, the panel recommends consideration of ISRT or a referral to or consultation with a center of expertise for consideration of additional therapy.

Another recommended option is OEPA x 2 cycles as studied in children and adolescents with CHL in the EuroNet-PHL-C1 study.[54] For those who experience inadequate response to 2 cycles of OEPA, the panel recommends consideration of ISRT or a referral to or consultation with a center of expertise for consideration of additional therapy. For patients >18 years, additional options can be considered as per the NCCN Guidelines for Hodgkin Lymphoma (Adult).

Stage IA–IIA with Bulk, IB–IIB, III, IV NLPHL

Intermediate and high risk NLPHL is rare in pediatric patients. Although it can occur, particularly in cases with variant morphology, this is uncommon. Therefore, expert hematopathology re-evaluation of original pathology slides is suggested to confirm pathologic diagnosis. Misdiagnosed CHL or THRLBCL are diagnostic considerations in this setting and should be excluded.

In a subsequent report from the AHOD0031 study, the investigators evaluated the outcomes of a subgroup of patients in the study who had lymphocyte-predominant HL (LPHL) (n = 96 of 1,711), and found that compared to CHL, patients with LPHL were more likely to achieve RER (93.6% vs. 81.0%; *P* = .002) and CR (74.2% vs. 49.3%; *P* = .000005) after chemotherapy.[91] In addition, the 5-year EFS was higher in the LPHL subgroup compared to CHL (92.2% vs. 83.5%, respectively; *P* = .04).[91] Based on the data, the investigators state that this subgroup may benefit from treatment with chemotherapy alone.

There are limited data on the treatment of intermediate/high risk NLPHL. It is commonly treated similar to CHL. Given its rarity, consideration of referral to or consultation with a center of expertise is recommended.

Relapsed or Refractory NLPHL

Histologic confirmation with biopsy is recommended before initiating treatment for relapsed or refractory disease given the risk for

transformation and high false-positive rate of FDG-PET/CT. In the case of NLPHL, residual FDG-PET–avid disease can represent foci of concurrent or transformed diffuse large B-cell lymphoma (DLBCL) or reactive lymph node with progressive transformation of germinal centers.[92,93]

Follow-Up After Completion of Treatment

Given the long-term risks of the therapies for HL, including secondary cancers, fatigue, pulmonary toxicity, thyroid dysfunction, and reproductive issues,[94-102] patients should be followed by an oncologist or survivorship specialist who is aware of these risks and complications, in coordination with the primary care provider, especially during the first 2 years after treatment. The follow-up schedule should be individualized, depending on clinical circumstances such as patient's age, sex, stage of disease, and initial treatment modality.

The panel recommends an interim history and physical examination every 3 to 4 months for 1 to 2 years, then every 6 to 12 months until year 3, and then annually until 5 years. Recommended laboratory studies include: CBC with differential, ESR or CRP, and a chemistry profile as clinically indicated. If the patient's neck was treated with RT, thyroid-stimulating hormone (TSH) should be evaluated annually. If patients were exposed to regimens that contain bleomycin or pulmonary RT, or have significant pulmonary involvement or other clinical concerns, PFTs should be considered. At the end of therapy, an echocardiogram may be considered, with repeat echocardiograms thereafter based on specific risk profile (eg, Children's Oncology Group Long-Term Follow-up Guidelines).

An annual influenza vaccination and other vaccines per the Centers for Disease Control and Prevention (CDC) is recommended for all patients (see the COG Survivorship Guidelines[103] for more details). In addition, in patients treated with splenic RT, vaccinations should be given prior to or following RT (ie, pneumococcal, meningococcal, and Haemophilus influenzae type b).

Due to the risk of false positives, routine or surveillance FDG-PET scans are not recommended. If relapse is suspected (based on imaging, clinical, and pathologic correlations) imaging studies are recommended. It is acceptable to obtain a posterior-anterior and lateral chest x-ray, CT scan with contrast, or MRI of original sites of disease, followed at 3- to 6-month intervals for up to 2 years following completion of therapy. Although an MRI scan may substitute CT scan for neck, abdomen, and pelvic regions, a diagnostic CT of the chest is required to evaluate lung parenchyma. If the previous FDG-PET was positive (Deauville 3 to 5), an FDG-PET/CT or FDG-PET/MRI scan is recommended to confirm CR at the end of all prescribed therapy, including RT. The panel notes that once negative, a repeat FDG-PET should not be done unless evaluating suspicious findings on the history and physical, CT, or MRI. In addition, to minimize false-positive results, it is important to wait at least 8 to 12 weeks after the end of RT to perform FDG-PET assessments.

In general, and in terms of monitoring late effects (≥2 years after completion of systemic therapy), patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects (eg, secondary cancers [with special attention to thyroid and breast cancer], cardiac disease, and issues affecting the thyroid, bone, and fertility and reproductive health), health habits, and psychosocial issues. For comprehensive details, see the COG Survivorship Guidelines.[103]

Summary

Pediatric HL is now curable in most patients because of the introduction of more effective and less toxic regimens. However, survivors may experience late treatment-related side effects. For this reason, long-term follow-up is essential after completion of treatment. In addition, improvements in harmonization of staging and response criteria, and risk stratification will improve the therapeutic index.[10] Emerging data will

continue to inform the panel's recommendations and consistent with NCCN philosophy, participation in clinical trials is always encouraged.

References

1. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. Pediatr Clin North Am 2015;62:139-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25435117.

2. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-1748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732829.

3. Fan Z, Natkunam Y, Bair E, et al. Characterization of variant patterns of nodular lymphocyte predominant Hodgkin lymphoma with immunohistologic and clinical correlation. Am J Surg Pathol 2003;27:1346-1356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14508396.

4. Jarrett RF. Risk factors for Hodgkin's lymphoma by EBV status and significance of detection of EBV genomes in serum of patients with EBV-associated Hodgkin's lymphoma. Leuk Lymphoma 2003;44 Suppl 3:S27-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15202522.

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31912902.

6. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. IARC Press: Lyon 2017.

7. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38230766.

8. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83-103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24488779.

9. Miller KD, Fidler-Benaoudia M, Keegan TH, et al. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 2020;70:443-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32940362.

10. Kelly KM. Hodgkin lymphoma in children and adolescents: improving the therapeutic index. Hematology Am Soc Hematol Educ Program 2015;2015:514-521. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26637767.

11. Mauz-Korholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin Lymphoma. J Clin Oncol 2015;33:2975-2985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26304892.

12. U.S. National Library of Medicine Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed January 24, 2020.

13. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-1253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35653592.

14. Huppmann AR, Nicolae A, Slack GW, et al. EBV may be expressed in the LP cells of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) in both children and adults. Am J Surg Pathol 2014;38:316-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24525501.

15. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25113753.

16. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 2012;30:4508-4514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23150698.

17. Salaun PY, Gastinne T, Bodet-Milin C, et al. Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? Eur J Nucl Med Mol Imaging 2009;36:1813-1821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19499219.

18. Purz S, Mauz-Korholz C, Korholz D, et al. [18F]Fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. J Clin Oncol 2011;29:3523-3528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21825262.

19. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5121694.

20. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2809679.

21. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20818855.

22. Spijkers S, Littooij AS, Humphries PD, et al. Imaging features of extranodal involvement in paediatric Hodgkin lymphoma. Pediatr Radiol 2019;49:266-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30515533.

23. Flerlage JE, Kelly KM, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL): Methodology statement. Pediatr Blood Cancer 2017;64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28097818.

24. Kluge R, Kurch L, Georgi T, Metzger M. Current Role of FDG-PET in Pediatric Hodgkin's Lymphoma. Semin Nucl Med 2017;47:242-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28417854.

25. McCarten KM, Nadel HR, Shulkin BL, Cho SY. Imaging for diagnosis, staging and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. Pediatr Radiol 2019;49:1545-1564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31620854.

26. Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. Pediatr Radiol 2019;49:1565-1573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31620855.

27. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32:3048-3058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25113771.

28. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma 2010;51:2171-2180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077737.

29. Meignan M, Gallamini A, Itti E, et al. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. Leuk Lymphoma 2012;53:1876-1881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432519.

30. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37:1824-1833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20505930.

31. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. Eur J Nucl Med Mol Imaging 2017;44:97-110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28411336.

32. Schaefer NG, Taverna C, Strobel K, et al. Hodgkin disease: diagnostic value of FDG PET/CT after first-line therapy--is biopsy of FDG-avid lesions still needed? Radiology 2007;244:257-262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17581905.

33. Petrausch U, Samaras P, Veit-Haibach P, et al. Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG-PET/CT for follow-up? Ann Oncol 2010;21:1053-1057. Available at: https://pubmed.ncbi.nlm.nih.gov/19914963/.

34. Filippi AR, Ragona R, Piva C, et al. Optimized volumetric modulated arc therapy versus 3D-CRT for early stage mediastinal Hodgkin lymphoma without axillary involvement: a comparison of second cancers and heart disease risk. Int J Radiat Oncol Biol Phys 2015;92:161-168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863763.

35. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22386373.

36. Hoppe BS, Flampouri S, Zaiden R, et al. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. Int J Radiat Oncol Biol Phys 2014;89:1053-1059. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24928256.

37. Hoskin PJ, Diez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol) 2013;25:49-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22889569.

38. Giulino-Roth L, Keller FG, Hodgson DC, Kelly KM. Current approaches in the management of low risk Hodgkin lymphoma in children and adolescents. Br J Haematol 2015;169:647-660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25824371.

39. Dorffel W, Luders H, Ruhl U, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. Klin Padiatr 2003;215:139-145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12838937.

40. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28:3680-3686. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20625128.

41. Mauz-Korholz C, Landman-Parker J, Fernandez-Teijeiro A, et al. Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study. Lancet Oncol 2023;24:252-261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36858722.

42. Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-3219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29738613.

43. Bhethanabhotla S, Jain S, Kapoor G, et al. Outcome of pediatric advanced Hodgkin lymphoma treated with ABVD and predictors of inferior survival: a multicenter study of 186 patients. Leuk Lymphoma 2017;58:1617-1623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27919174.

44. Jain S, Kapoor G, Bajpai R. ABVD-Based Therapy for Hodgkin Lymphoma in Children and Adolescents: Lessons Learnt in a Tertiary Care Oncology Center in a Developing Country. Pediatr Blood Cancer 2016;63:1024-1030. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26855007.

45. Marr KC, Connors JM, Savage KJ, et al. ABVD chemotherapy with reduced radiation therapy rates in children, adolescents and young adults with all stages of Hodgkin lymphoma. Ann Oncol 2017;28:849-854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28327925.

46. Stieglitz E, Dinh T, Phelps AS, et al. ABVD Without Radiation for Newly Diagnosed Pediatric and Young Adult Patients With Hodgkin Lymphoma: A Single Center Retrospective Analysis of 28 Consecutive Patients. J Pediatr Hematol Oncol 2018;40:290-294. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29432308.

47. Zubizarreta PA, Alfaro E, Guitter M, et al. Children and Adolescent Hodgkin Lymphoma in Argentina: Long-term Results After Combined ABVD and Restricted Radiotherapy. J Pediatr Hematol Oncol 2017;39:602-608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902084.

48. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32:3651-3658. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25311218.

49. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood 2009;114:2051-2059. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19584400.

50. Chow EJ, Aggarwal S, Doody DR, et al. Dexrazoxane and Long-Term Heart Function in Survivors of Childhood Cancer. J Clin Oncol 2023;41:2248-2257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36669148.

51. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). Journal of Clinical Oncology 2023;41:LBA4-LBA4. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.17_suppl.LBA4.

52. Castellino SM, Li H, Herrera AF, et al. Progression-free survival (PFS) and toxicity with nivolumab-AVD compared to brentuximab vedotin-AVD in pediatric advanced stage (AS) classic Hodgkin Lymphoma (cHL), Results of SWOG S1826 [abstract]. Blood 2023;142:610-610. Available at: https://www.sciencedirect.com/science/article/pii/S000649712305214X.

53. Landman-Parker J, Wallace H, Hasenclever D, et al. First International Inter-Group Study for Classical Hodgkin Lymphoma in Children and Adolescents: EuroNet-PHL-C1 European protocol Euronet PHL-C1; Report of the latest interim Analysis [Abstract# P064]. Haematologica; 10th International Symposium on Hodgkin Lymphoma Symposium (ISHL10) 2016;101:35. Available at: https://haematologica.org/article/view/7868.

54. Mauz-Korholz C, Landman-Parker J, Balwierz W, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. Lancet Oncol 2022;23:125-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34895479.

55. Castellino SM, Pei Q, Parsons SK, et al. Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. N Engl J Med 2022;387:1649-1660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36322844.

56. Kelly KM. Management of children with high-risk Hodgkin lymphoma. Br J Haematol 2012;157:3-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22188115.

57. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. Blood

2011;117:2596-2603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21079154.

58. Metzger ML, Link MP, Billett AL, et al. Excellent outcome for pediatric patients with high-risk Hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. J Clin Oncol 2021;39:2276-2283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33826362.

59. Daw S, Wynn R, Wallace H. Management of relapsed and refractory classical Hodgkin lymphoma in children and adolescents. Br J Haematol 2011;152:249-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21133886.

60. Daw S, Hasenclever D, Mascarin M, et al. Risk and Response Adapted Treatment Guidelines for Managing First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group. Hemasphere 2020;4:e329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32072145.

61. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial. Lancet Oncol 2018;19:257-266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29276022.

62. Forlenza CJ, Gulati N, Mauguen A, et al. Combination brentuximab vedotin and bendamustine for pediatric patients with relapsed/refractory Hodgkin lymphoma. Blood Adv 2021;5:5519-5524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34559223.

63. Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Lancet Oncol 2018;19:1229-1238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30122620.

64. Cole PD, Mauz-Körholz C, Mascarin M, et al. Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin lymphoma (R/R cHL): Primary analysis. Journal of Clinical Oncology 2020;38:8013-8013. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8013.

65. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood 2021;138:427-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33827139.

66. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol 2016;36:3733-3739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27354476.

67. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016;17:1283-1294. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27451390.

68. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017;35:2125-2132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28441111.

69. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:121-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31812554.

70. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 2018;131:1183-1194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29229594.

71. Harker-Murray P, Mauz-Korholz C, Leblanc T, et al. Nivolumab and brentuximab vedotin with or without bendamustine for R/R Hodgkin lymphoma in children, adolescents, and young adults. Blood 2023;141:2075-2084. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36564047.

72. Kuruvilla J, Ramchandren R, Santoro A, et al. KEYNOTE-204: Randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL). Journal of Clinical Oncology 2020;38:8005-8005. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8005.

73. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2015;385:1853-1862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25796459.

74. Kahn S, Flowers C, Xu Z, Esiashvili N. Does the addition of involved field radiotherapy to high-dose chemotherapy and stem cell transplantation improve outcomes for patients with relapsed/refractory Hodgkin lymphoma? Int J Radiat Oncol Biol Phys 2011;81:175-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20732769.

75. Wilke C, Cao Q, Dusenbery KE, et al. Role of Consolidative Radiation Therapy After Autologous Hematopoietic Cell Transplantation for the Treatment of Relapsed or Refractory Hodgkin Lymphoma. Int J Radiat Oncol Biol Phys 2017;99:94-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28816170.

76. Cole PD, Schwartz CL, Drachtman RA, et al. Phase II study of weekly gemcitabine and vinorelbine for children with recurrent or refractory Hodgkin's disease: a children's oncology group report. J Clin Oncol 2009;27:1456-1461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19224841.

77. Marr K, Ronsley R, Nadel H, et al. Ifosfamide, gemcitabine, and vinorelbine is an effective salvage regimen with excellent stem cell mobilization in relapsed or refractory pediatric Hodgkin lymphoma. Pediatr Blood Cancer 2020;67:e28167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31925920.

78. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97:616-623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11157476.

79. Trippett TM, Schwartz CL, Guillerman RP, et al. Ifosfamide and vinorelbine is an effective reinduction regimen in children with refractory/relapsed Hodgkin lymphoma, AHOD00P1: a children's oncology group report. Pediatr Blood Cancer 2015;62:60-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25308760.

80. Horton TM, Drachtman RA, Chen L, et al. A phase 2 study of bortezomib in combination with ifosfamide/vinorelbine in paediatric patients and young adults with refractory/recurrent Hodgkin lymphoma: a Children's Oncology Group study. Br J Haematol 2015;170:118-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25833390.

81. Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood 2000;95:1588-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10688812.

82. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13:1628-1635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12377653.

83. Shankar A, Hayward J, Kirkwood A, et al. Treatment outcome in children and adolescents with relapsed Hodgkin lymphoma--results of the UK HD3 relapse treatment strategy. Br J Haematol 2014;165:534-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24754633.

84. Baetz T, Belch A, Couban S, et al. Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 2003;14:1762-1767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14630682.

85. Harker-Murray PD, Cole PD, Hoppe BS, et al. Response-adapted therapy (tx) with nivolumab plus brentuximab vedotin (nivo + BV) without autologous hematopoietic cell transplantation (auto-HCT) in children, adolescents, and young adults (CAYA) with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL): CheckMate 744 [abstract]. Journal of Clinical Oncology 2023;41:7515-7515. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.7515.

86. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: A report from the Children's Oncology Group. J Clin Oncol 2016;34:2372-2379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27185849.

87. Mauz-Korholz C, Gorde-Grosjean S, Hasenclever D, et al. Resection alone in 58 children with limited stage, lymphocyte-predominant Hodgkin lymphoma-experience from the European network group on pediatric Hodgkin lymphoma. Cancer 2007;110:179-185. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17526010.

88. Shankar A, Hall GW, McKay P, et al. Management of children and adults with all stages of nodular lymphocyte predominant Hodgkin lymphoma - All StAGEs: A consensus-based position paper from the Hodgkin lymphoma subgroup of the UK National Cancer Research Institute. Br J Haematol 2022;197:679-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35362554.

89. Pellegrino B, Terrier-Lacombe MJ, Oberlin O, et al. Lymphocyte-predominant Hodgkin's lymphoma in children: therapeutic abstention after initial lymph node resection--a Study of the French Society of Pediatric Oncology. J Clin Oncol 2003;21:2948-2952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12885814.

90. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22093944.

91. Marks LJ, Pei Q, Bush R, et al. Outcomes in intermediate-risk pediatric lymphocyte-predominant Hodgkin lymphoma: A report from the Children's Oncology Group. Pediatr Blood Cancer 2018;65:e27375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30277639.

92. Al-Mansour M, Connors JM, Gascoyne RD, et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010;28:793-799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20048177.

93. Shaikh F, Ngan BY, Alexander S, Grant R. Progressive transformation of germinal centers in children and adolescents: an intriguing cause of lymphadenopathy. Pediatr Blood Cancer 2013;60:26-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22707034.

94. Amini A, Murphy B, Cost CR, et al. Cardiac Mortality in Children and Adolescents with Hodgkin's Lymphoma: A Surveillance, Epidemiology and End Results Analysis. J Adolesc Young Adult Oncol 2016;5:181-186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26959398.

95. Bhakta N, Liu Q, Yeo F, et al. Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. Lancet Oncol 2016;17:1325-1334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27470081.

96. Clausen CT, Hasle H, Holmqvist AS, et al. Hyperthyroidism as a late effect in childhood cancer survivors - an Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study. Acta Oncol 2019;58:227-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30585514.

97. Dorffel W, Riepenhausenl M, Luders H, et al. Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood

and Adolescence. Dtsch Arztebl Int 2015;112:320-327, i. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26037468.

98. Fernandez-Pineda I, Davidoff AM, Lu L, et al. Impact of ovarian transposition before pelvic irradiation on ovarian function among long-term survivors of childhood Hodgkin lymphoma: A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer 2018;65:e27232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29750388.

99. Inskip PD, Veiga LHS, Brenner AV, et al. Hypothyroidism after Radiation Therapy for Childhood Cancer: A Report from the Childhood Cancer Survivor Study. Radiat Res 2018;190:117-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29763379.

100. O'Brien MM, Donaldson SS, Balise RR, et al. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. J Clin Oncol 2010;28:1232-1239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20124178.

101. Oeffinger KC, Hudson MM, Mertens AC, et al. Increasing rates of breast cancer and cardiac surveillance among high-risk survivors of childhood Hodgkin lymphoma following a mailed, one-page survivorship care plan. Pediatr Blood Cancer 2011;56:818-824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21370417.

102. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2011;2011:CD003917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21678342.

103. The Children’s Oncology Group long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers. Available at: https://childrensoncologygroup.org/index.php/survivorshipguidelines. Accessed November 16, 2023.