



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Pediatric Hodgkin Lymphoma

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### [NCCN Pediatric Hodgkin Lymphoma Panel Members](#) [Summary of the Guidelines Updates](#)

#### [Diagnosis and Workup \(PHL-1\)](#)

#### [Clinical Staging of Classic Hodgkin Lymphoma \(PHL-2\)](#)

#### Primary Treatment of CHL

- [Low-Risk Disease \(PHL-3\)](#)
- [Intermediate-Risk Disease \(PHL-4\)](#)
- [High-Risk Disease \(PHL-5\)](#)

#### [Follow-up After Completion of Treatment and Monitoring for Late Effects \(PHL-6\)](#)

#### [Suspected Relapsed/Refractory CHL \(PHL-7\)](#)

#### [Principles of Criteria for Response-Adapted Radiation Therapy \(PHL-A\)](#)

#### [Principles of Pathology \(PHL-B\)](#)

#### [Principles of Imaging \(PHL-C\)](#)

#### [Principles of Staging \(PHL-D\)](#)

#### [Principles of Systemic Therapy \(PHL-E\)](#)

#### [Principles of Radiation Therapy \(PHL-F\)](#)

#### [Staging \(ST-1\)](#)

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To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/member\\_institutions.aspx](#).

**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 3.2021 of the NCCN Guidelines for Pediatric Hodgkin Lymphoma from Version 2.2021 include:

[MS-1](#)

- The Discussion section was added.

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Updates in Version 2.2021 of the NCCN Guidelines for Pediatric Hodgkin Lymphoma from Version 1.2021 include:

[PHL-E \(2 of 3\)](#)

- Footnote f modified: Pembrolizumab is indicated for the treatment of adult and pediatric patients with refractory CHL, or who have relapsed after 3 or more prior lines of therapy.

[PHL-E \(3 of 3\)](#)

- Reference added: Georger 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;21:121–33.



## 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  $\leq 18$  years, and may be applicable to adolescent and young adult (AYA) patients up to the age of 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](#).
- The guidelines do not currently address nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), as data are limited in pediatric patients.

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# NCCN Guidelines Version 3.2021

## Pediatric Hodgkin Lymphoma

### DIAGNOSIS

- Excisional or incisional biopsy<sup>a</sup>
- Immunohistochemistry evaluation<sup>b</sup>

### WORKUP

#### Essential:

- H&P including:
  - ▶ 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)
  - ▶ Examination of lymphoid regions, spleen
- CBC with differential
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
- Comprehensive metabolic panel
- Echocardiogram (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)<sup>c</sup>
- CT neck/chest/abdomen/pelvis with contrast or CT chest and MRI neck/abdomen/pelvis<sup>c</sup>
- PET/CT scan<sup>d</sup> or PET/MRI scan<sup>d</sup> (whole-body)<sup>c</sup>
- Pregnancy test for women of childbearing age
- Counseling: Fertility, smoking/drug cessation, psychosocial ([See NCCN Guidelines for Supportive Care](#))

#### Useful in selected cases:

- Fertility preservation<sup>e</sup>
- PFTs (including diffusing capacity [DLCO] if bleomycin indicated)<sup>f</sup>
- ECG
- HIV and hepatitis B/C testing (encouraged)
- Only consider bilateral bone marrow biopsy if there are cytopenias and negative PET<sup>g</sup>

### CLINICAL PRESENTATION

Classic Hodgkin lymphoma (CHL)<sup>h</sup> → [See Clinical Staging \(PHL-2\)](#)

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

<sup>b</sup> For typical immunophenotype, [see Principles of Pathology \(PHL-B\)](#).

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

<sup>d</sup> In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if there is an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage the patient. [See Principles of Staging \(PHL-D\)](#). If PET negative for anatomic lesions of concern, biopsy should be considered.

<sup>e</sup> Fertility preservation is an option for some patients. Refer to fertility clinic for further discussion when able prior to initiation of chemotherapy.

<sup>f</sup> In general, FEV1/FVC >60% by PFT 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.

<sup>g</sup> In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is *not* assumed. If there are multifocal (>2–3) skeletal 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(26):3523-3528.)

<sup>h</sup> CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, [see NCCN Guidelines for B-Cell Lymphomas](#). Management of NLPHL is not included in these guidelines.

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# NCCN Guidelines Version 3.2021

## Pediatric Hodgkin Lymphoma

### CLINICAL STAGING OF CLASSIC HODGKIN LYMPHOMA

Risk stratification is evolving. This table represents clinical trials with published data. Consider consultation with a center of expertise for patient management; 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 (See ST-1)	Bulk (See PHL-D)	E-lesions <sup>j</sup> (See PHL-D)	Risk Group <sup>k</sup>
IA IIA	No	No	Low risk (per EuroNet-PHL-C1 <sup>l</sup> )
	Yes	No	Low risk (per EuroNet-PHL-C1 <sup>l</sup> ) or Intermediate risk (per AHOD0031)
	Yes	Yes	Intermediate risk (per EuroNet-PHL-C1 <sup>l</sup> or AHOD0031)
IB	Any	No	Low risk (per EuroNet-PHL-C1 <sup>l</sup> )
	Any	Any	Intermediate risk (per AHOD0031)
IIB <sup>i</sup>	No	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1 <sup>l</sup> )
	No	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1 <sup>l</sup> )
	Yes	Any	High risk (per AHOD1331 <sup>l</sup> )
	Yes	Yes	High risk (per EuroNet-PHL-C1 <sup>l</sup> )
IIIA	Any	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1 <sup>l</sup> )
	Any	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1 <sup>l</sup> )
IIIB, IV	Any	Any	High risk (AHOD1331 <sup>l</sup> or EuroNet-PHL-C1 <sup>l</sup> )



<sup>i</sup> 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.

<sup>j</sup> 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.)

<sup>k</sup> GPOH-HD-2002: Mauz-Körholz C, et al. J Clin Oncol 2010;28:3680-3686; EuroNet-PHL-C1: Landman-Parker J, et al. Hematologica/ISHL10, 2016 [Abstract #P064];101:35; 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. Klin Padiatr 2020; 232(02):82-83.

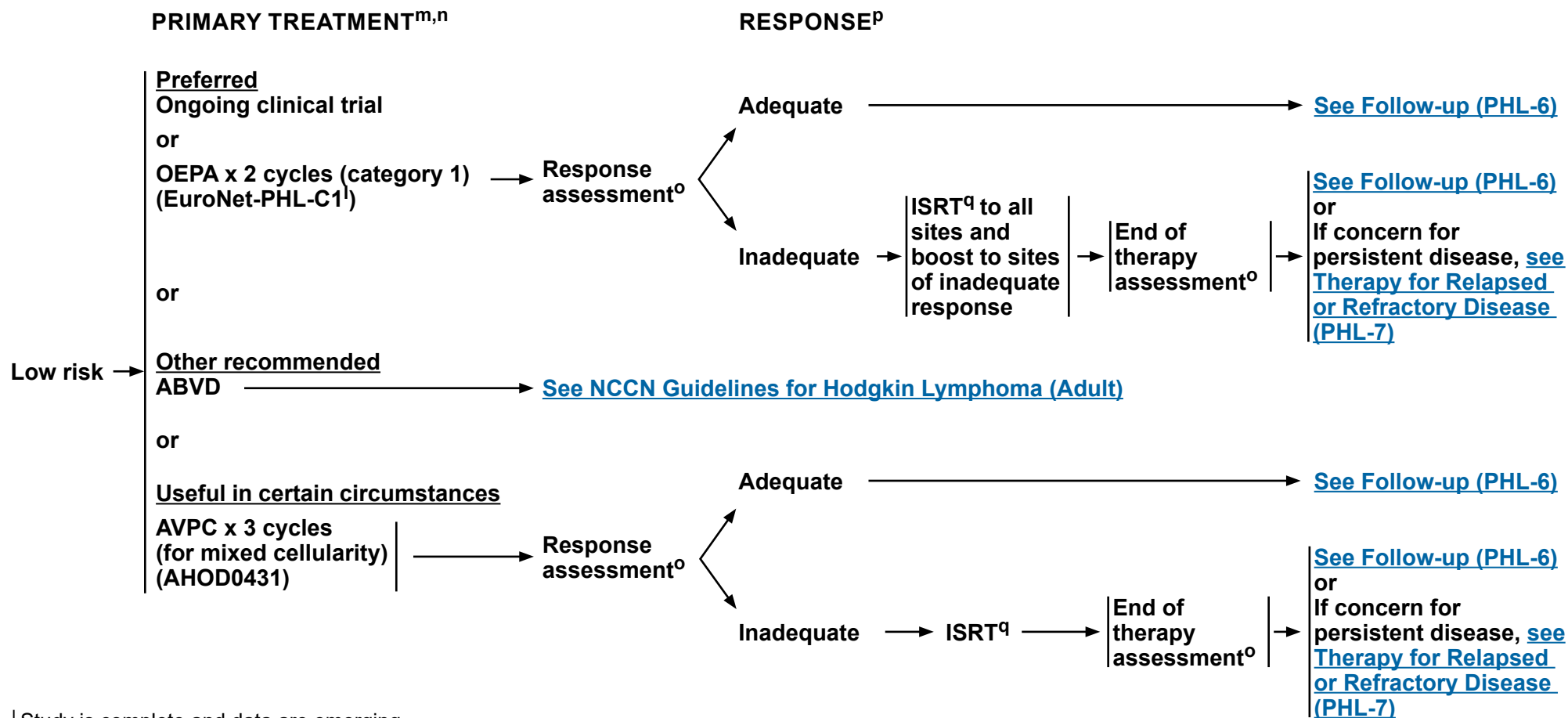
<sup>l</sup> Study is complete and data are emerging.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



### CLINICAL PRESENTATION: Classic Hodgkin Lymphoma



<sup>l</sup> Study is complete and data are emerging.

<sup>m</sup> Regimens are based off of studies with pediatric data.

<sup>n</sup> See [Principles of Systemic Therapy \(PHL-E\)](#).

<sup>o</sup> FDG-PET/CT or PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with PET.

<sup>p</sup> See [Principles of Criteria for Response-Adapted Radiation Therapy \(PHL-A\)](#).

<sup>q</sup> See [Principles of Radiation Therapy \(PHL-F\)](#).

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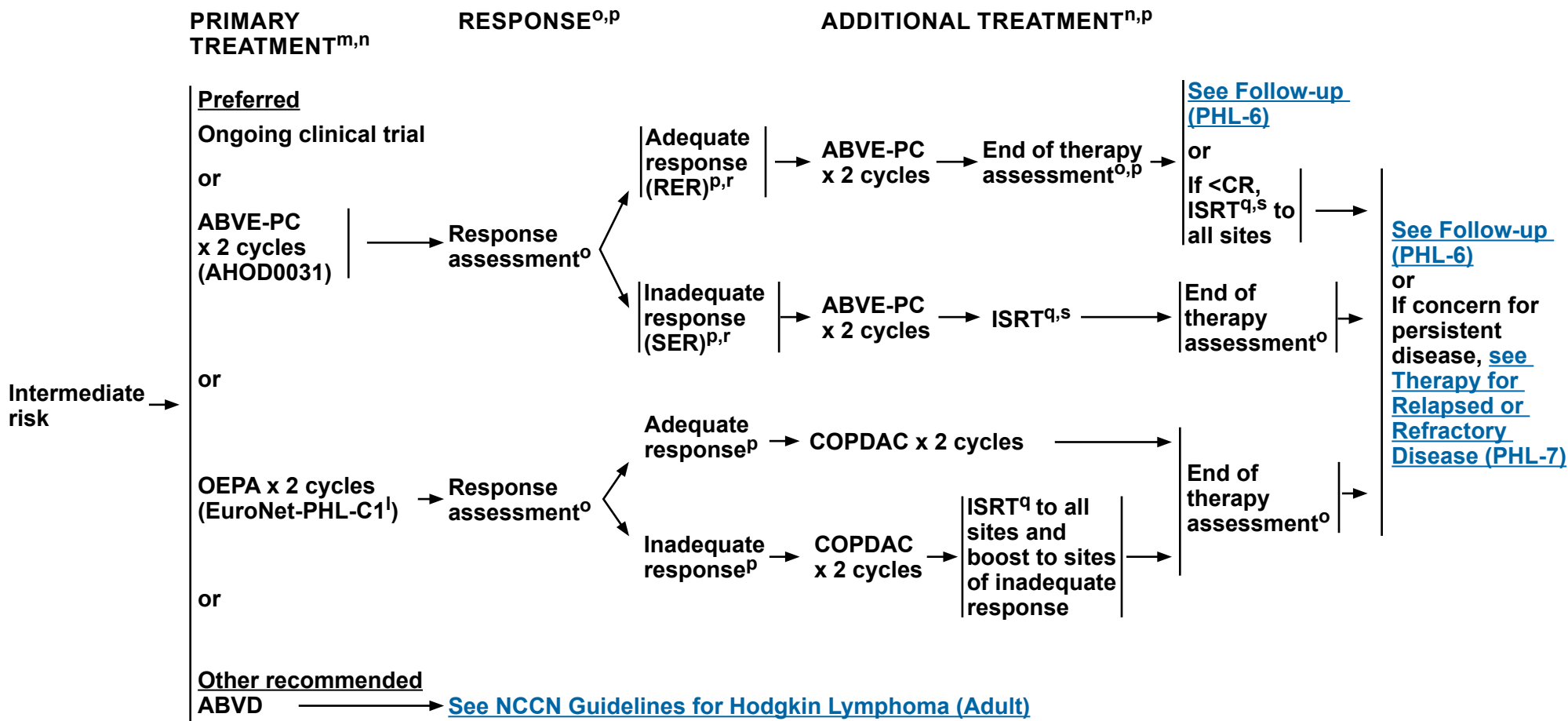
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<sup>p</sup> See Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).

<sup>q</sup> See Principles of Radiation Therapy (PHL-F).

<sup>r</sup> RER = Rapid early responders; SER = Slow early responders.

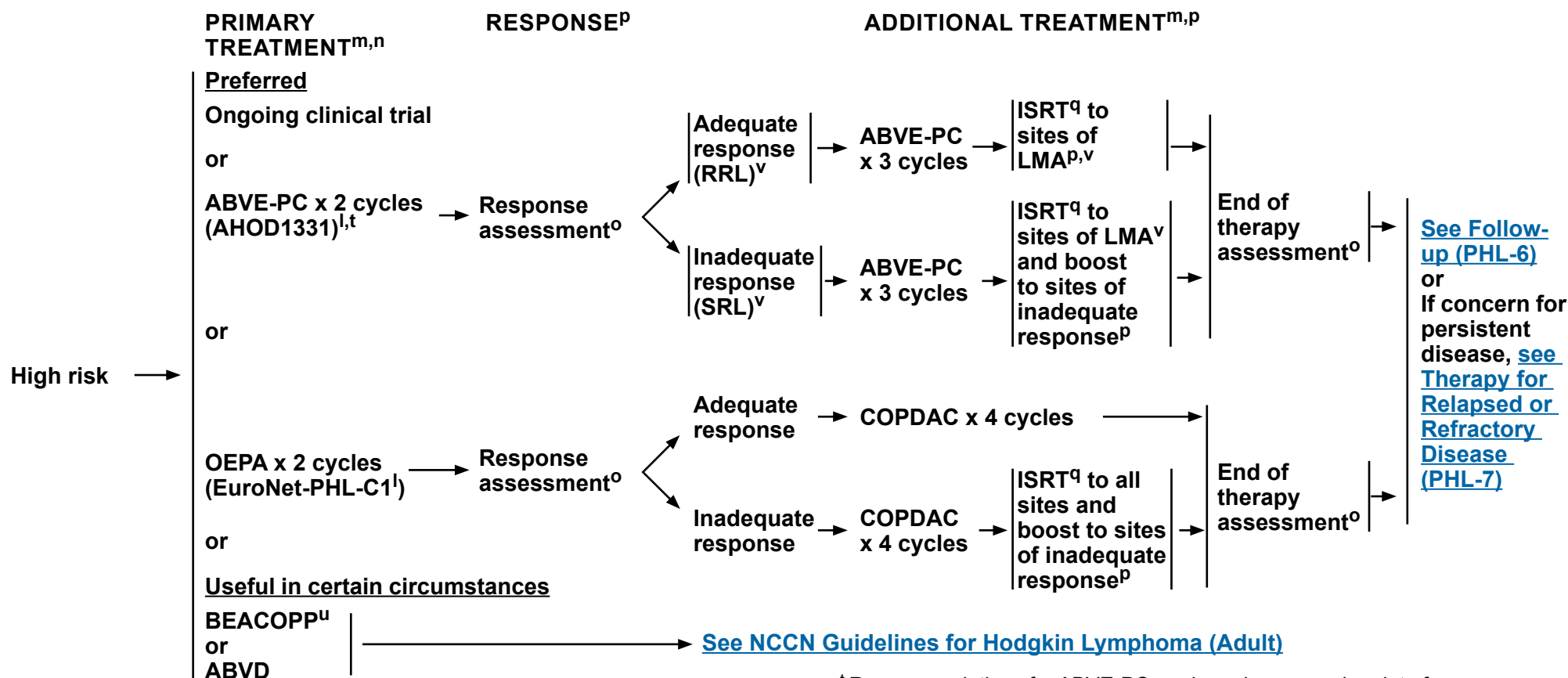
<sup>s</sup> ISRT can safely replace IFRT (see PHL-F).

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## CLINICAL PRESENTATION: Classic Hodgkin Lymphoma



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<sup>o</sup> FDG-PET/CT or PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with PET.

<sup>p</sup> See Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).

<sup>q</sup> See Principles of Radiation Therapy (PHL-F).

<sup>t</sup> Recommendations for ABVE-PC are based on emerging data from AHOD1331. Cyclophosphamide dosing in AHOD0031 differs from AHOD1331. See Principles of Systemic Therapy (PHL-E).

<sup>u</sup> 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.

<sup>v</sup> RRL = Rapidly responding lesions; SRL = Slow responding lesions; LMA= Large mediastinal adenopathy.

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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 months for 1–2 years,
  - ▶ then every 6–12 months until year 3,
  - ▶ then annually until 5 years
- **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)**
- **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, 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.
  - ▶ PET/CT or PET/MRI if previous PET was positive (Deauville 3–5), to confirm complete response (CR) at end of all prescribed therapy including RT. Once negative, repeat PET should not be done unless evaluating suspicious findings on H&P or CT or MRI.
    - ◊ Wait at least 8–12 weeks after end of RT to perform PET to minimize false-positive results.
    - ◊ Surveillance PET is not recommended due to risk for false positives.
  - ▶ If concern for relapse, management decisions should not be based on PET scan alone; clinical and pathologic correlation is needed. [See Principles of Pathology \(PHL-B\)](#) and [See Therapy for Relapsed/Refractory Disease \(PHL-7\)](#).
- **Immunizations**
  - ▶ Annual influenza vaccine is recommended, even during therapy.
  - ▶ Other vaccines as per CDC Guidelines, typically starting 6 months 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 \(PHL-F\)](#).

→ Relapse →

[See Principles of Pathology \(PHL-B\)](#) and [See Therapy for Relapsed/Refractory Disease \(PHL-7\)](#)

##### Monitoring for Late Effects (≥2 years after completion of systemic therapy)

- **Appropriate screening and counseling related to: thyroid, cardiac, pulmonary, bone, reproductive health; subsequent cancers (with special attention to breast cancer), and other treatment-associated late effects** ([See Children’s Oncology Group Survivorship Guidelines](#))

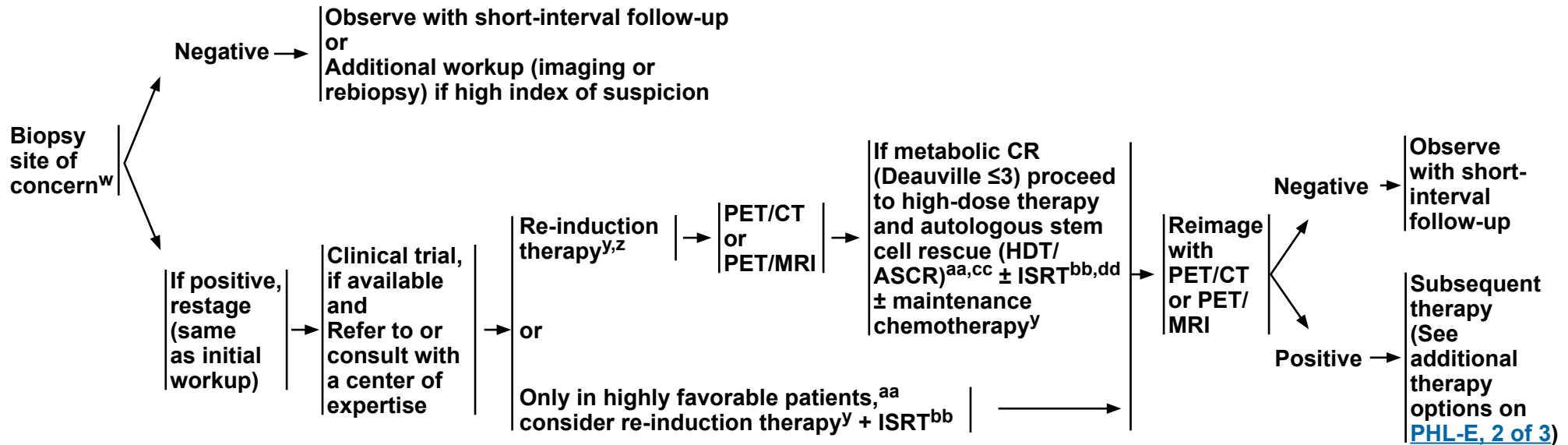
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## CLINICAL PRESENTATION: Classic Hodgkin Lymphoma

### SUSPECTED RELAPSED/ REFRACTORY DISEASE

### RE-INDUCTION THERAPY<sup>x</sup>



<sup>w</sup> A biopsy must be obtained to confirm relapse and pathology. [See Principles of Pathology \(PHL-B\)](#).

<sup>x</sup> There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

<sup>y</sup> [See Principles of Systemic Therapy for Relapsed or Refractory Disease \(PHL-E, 2 of 3\)](#).

<sup>z</sup> 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.

<sup>aa</sup> Recommendations for those who may avoid ASCR: initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease or B symptoms at relapse.

<sup>bb</sup> Strongly consider radiation therapy for selected sites that have not been previously irradiated.

<sup>cc</sup> Allotransplant is an option in select patients who relapse post-ASCT as a category 3 recommendation.

<sup>dd</sup> RT is usually performed as consolidation after transplant, unless unable to get to a metabolic CR, then can utilize RT prior to transplant.

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## Pediatric Hodgkin Lymphoma

### PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY

Regimen <sup>a</sup>	Risk Group/Stage	Criteria for RT	Protocol Rationale
<b>OEPA/OEPA-COPDAC (EuroNet-PHL-C1<sup>d</sup>)<sup>2,3</sup></b>	<b>Low Risk</b> • IA/B without E • IIA without E	<ul style="list-style-type: none"> <li>• &lt;CR on imaging after 2 cycles of OEPA                             <ul style="list-style-type: none"> <li>▶ CR: Volume reduction &gt;95% and ≤2 mL</li> <li>▶ CRu: Volume reduction &gt;75% or ≤2 mL</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 5-year EFS from GPOH-HD-2002 (C1 results pending)                             <ul style="list-style-type: none"> <li>▶ TG1: 92% (overall) (92% + RT; 93% without RT)</li> <li>▶ TG2/3: 87% 5-year EFS (overall)<sup>2</sup></li> </ul> </li> <li>• Limits total doxorubicin dose to 160 mg/m<sup>2</sup> (less than the 250 mg/m<sup>2</sup> maximum dose)</li> <li>• Estimate elimination of RT in ~30% of patients</li> <li>• Refer to EuroNET-PHL-C1 Radiotherapy Manual                             <ul style="list-style-type: none"> <li>▶ No mandatory RT to any sites</li> <li>▶ RT was only done for poor response, not for all patients.<sup>3</sup></li> </ul> </li> </ul>
	<b>Intermediate Risk</b> • IA/B + E • IIA + E • IIB, IIIA	<ul style="list-style-type: none"> <li>• All IR/HR patients on HD-2002 received RT</li> <li>• IR/HR patients on C1 (emerging data) received RT only if PET positive or not in at least PR after 2 cycles of OEPA,                             <ul style="list-style-type: none"> <li>▶ PR: No CR or CRu and &gt;50% volume reduction or residual tumor volume &lt;5 mL</li> </ul> </li> </ul>	
<b>ABVE-PC<sup>4,7</sup></b>	<b>High Risk</b> • IIB + E • IIIA + E • IIIB, IVA/B ± E	Note: Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate	
	<b>Intermediate Risk (AHOD0031)<sup>4</sup></b> • IA, IIA with bulk ± E • IB, IIB without bulk ± E • IIIA ± E <sup>b</sup>	<ul style="list-style-type: none"> <li>• Slow early responders (SER) on imaging after 2 cycles if &lt;60% reduction in product of perpendicular diameters (PPD)<sup>c</sup> for all target lesions or</li> <li>• Rapid early responders (RER) on imaging after 2 cycles if not in CR on imaging after 4 cycles                             <ul style="list-style-type: none"> <li>▶ CR: ≥80% reduction in PPD<sup>c</sup> with negative PET at end of therapy (comparable to Deauville 1–2)</li> </ul> </li> <li>• Consider boost for persistent PET-positive (Deauville 3-5) lesions at end of chemotherapy.</li> </ul>	<ul style="list-style-type: none"> <li>• 4-year EFS                             <ul style="list-style-type: none"> <li>▶ RER/CR: 88% vs. 84% (+RT)</li> <li>▶ SER: 79% vs. 75% (+ DECA)</li> </ul> </li> <li>• Response-adapted therapy</li> </ul>
<b>Useful in certain circumstances: AVPC (for mixed cellularity) (AHOD0431)<sup>1</sup></b>	<b>High Risk (AHOD1331<sup>d</sup>)<sup>5,6</sup></b> • IIB with bulk • IIIB, IV <sup>b</sup>	<ul style="list-style-type: none"> <li>• Slow responding lesions (SRL) on imaging after 2 cycles<sup>7</sup> <ul style="list-style-type: none"> <li>▶ Inadequate or SRL: Deauville 4–5</li> <li>▶ Adequate or rapidly responding lesions (RRL): Deauville ≤3</li> </ul> </li> <li>• All large mediastinal adenopathy (LMA)</li> <li>• Boost for persistent PET-positive lesions (Deauville 3-5) at end of chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Response-adapted therapy</li> <li>• Significant decrease in the number of patients receiving radiation therapy</li> </ul>
	<b>Low Risk</b> • IA, IIA without bulk • For mixed cellularity only	<ul style="list-style-type: none"> <li>• &lt;CR on imaging after 3 cycles                             <ul style="list-style-type: none"> <li>▶ CR: ≥80% reduction in PPD<sup>c</sup> and FDG-PET negative; only mediastinal nodes &gt;2 cm</li> <li>▶ PET positive (Deauville 3–5): Uptake greater than mediastinal blood pool</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 80% 4-year EFS</li> <li>• Those with mixed cellularity histology, who had a particularly excellent response (4-year EFS 95.2%)</li> <li>• Limits total doxorubicin dose to 150 mg/m<sup>2</sup> (less than the 250 mg/m<sup>2</sup> maximum dose)</li> </ul>

<sup>a</sup> FDA has only approved brentuximab vedotin for ages 18+. Refer to clinical trial.

<sup>b</sup> Stage IVA was included in the intermediate risk group in the trial, although not recommended for standard care.

<sup>c</sup> PPD = Transverse x axial plane.

<sup>d</sup> Study is complete and data are emerging.

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[References](#)



### PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY

#### References

- <sup>1</sup> 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.
- <sup>2</sup> 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.
- <sup>3</sup> 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.
- <sup>4</sup> 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.
- <sup>5</sup> Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk. Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. *Br J Haematol* 2019;187:39-48.
- <sup>6</sup> Castellino S, Parsons S, Pei Q, et al. A randomized Phase III trial of Brentuximab vedotin (Bv) for de novo High-Risk Classical Hodgkin Lymphoma (cHL) in children and adolescents - Study Design and Incorporation of secondary endpoints in Children's Oncology Group (COG) AHOD1331. *Klin Padiatr* 2020; 232(02):82-83.
- <sup>7</sup> Flerlage J, Kelly K, 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(7):e26421.

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**PRINCIPLES OF PATHOLOGY****Histologic Classification**

- **Diagnosis should be established according to guidelines in the 2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.<sup>1</sup>**
- **There are two types of Hodgkin lymphoma (HL): classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Distinction between these types is important for therapy and prognosis. Management of NLPHL is not included in these guidelines.**
- **There are four morphologic variants of CHL:<sup>a</sup>**
  - ▶ **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.<sup>a</sup> If considering treatment based on the AHOD0431 trial,<sup>2</sup> discussion with a 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.**

**Tissue Adequacy for Diagnosis**

- **An excisional or incisional biopsy where possible is recommended. A core biopsy may be appropriate in some settings.<sup>b</sup> Fine-needle aspiration (FNA) is discouraged in establishing a diagnosis.<sup>c</sup>**
- **Ample tissue may be necessary to exclude other entities in the differential diagnosis<sup>d</sup> and for specific morphologic subtyping.<sup>e</sup>**
- **Most cases of CHL will not need a bone marrow biopsy; clinically relevant staging information can often be determined from radiologic findings. [See Principles of Imaging \(PHL-C\).](#)**

<sup>a</sup> The different morphologic variants of CHL have different clinicopathologic associations and differential diagnoses. Refer to the 2017 WHO Classification for more details.

<sup>b</sup> For example, less accessible anatomic sites such as retroperitoneum.

<sup>c</sup> Sparse neoplastic cells, extensive fibrosis, and presence of Reed Sternberg-like cells in some conditions other than in CHL are some reasons a limited biopsy may not be diagnostic.

<sup>d</sup> 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.

<sup>e</sup> 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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**PRINCIPLES OF PATHOLOGY****Immunohistochemical Considerations and Ancillary Testing**

- Consider clinical differential diagnoses (eg, T lymphoblastic lymphoma) and pathologic differential diagnoses: HL vs. non-Hodgkin lymphoma (NHL),<sup>f</sup> CHL vs. NLPHL, HL vs. infection (cytomegalovirus [CMV], Epstein-Barr virus [EBV]), and HL vs. reactive proliferations.<sup>9</sup>
- Diagnosis is based on morphologic AND immunohistochemical findings.
- Typical immunophenotype of HL:
  - ▶ CHL: Neoplastic cells are PAX5+ (weak), CD30+, CD15+, 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, CD45-, 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 cells are PAX5+, CD20+, OCT2+ (strong), CD30-, CD15-, or CD3-. They are also CD45+, CD79a+, BCL6+, EMA+, or MUM1-/weak.
- EBV+ CHL cases (EBV often assessed by EBER ISH<sup>h</sup>) may benefit from additional studies, such as EBV serology and evaluation for underlying immunodeficiency.
- Flow cytometry is not helpful in diagnosing HL.<sup>i</sup> However, it may be helpful in the evaluation of other entities in the clinical or pathologic differential diagnosis.

**Pathology Considerations in the Relapse/Refractory Disease Setting**

- Pathologic confirmation is necessary to confirm relapse, particularly if >12 months after original diagnosis, given the high false-positive rate of PET-CT. Re-biopsy is also recommended for residual PET-avid disease at the end of therapy.<sup>3</sup>
- 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, to consider mediastinal gray zone lymphoma<sup>4,5</sup> and other lymphoma subtypes. For NLPHL cases, consider the possibility of diffuse large B-cell lymphoma transformation from NLPHL<sup>6</sup> or reactive lymph node with progressive transformation of germinal centers.<sup>7</sup>
- 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 is insufficient data to recommend PDL1 testing by immunohistochemistry as a pre-requisite for checkpoint inhibitor therapy. Robust cut-offs for optimally predicting response to checkpoint inhibitor therapy have not been established.

<sup>f</sup> NHL examples, primary mediastinal large B-cell lymphoma, ALK+ anaplastic large cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, and EBV+ diffuse large B cell lymphoma.

<sup>g</sup> For example, reactive lymph node with CD30+ immunoblasts (vs. CHL) and progressive transformation of germinal centers (vs. NLPHL).

<sup>h</sup> EBER ISH: Epstein-Barr virus-encoded RNA (EBER) in situ hybridization (ISH).

<sup>i</sup> 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 REFERENCES

- <sup>1</sup> Swerdlow SH, et al (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition). 2017, Lyon: International Agency for Research on Cancer (IARC).
- <sup>2</sup> Keller F, Castellino S, 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.
- <sup>3</sup> El-Galaly TC, Gormsen L, Hutchings M. PET/CT for Staging; Past, Present, and Future. *Semin Nucl Med* 2018;48:4-16.
- <sup>4</sup> 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.
- <sup>5</sup> 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.
- <sup>6</sup> 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.
- <sup>7</sup> 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<sup>1-5</sup>****Staging or Initial Workup (should be performed within 2–4 weeks prior to initiation of therapy)**

- CT neck/chest/abdomen/pelvis with contrast or CT chest and MRI neck/abdomen/pelvis
- 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)
- PET/CT<sup>a,b</sup> or PET/MRI<sup>c</sup>
  - Whole-body is recommended
  - Diagnostic-quality CT or MRI is still needed for initial staging

**Interim and End-of-Therapy**

- PET/CT<sup>a,b</sup> or PET/MRI<sup>c</sup>
  - Wait at least 8–12 weeks after end of RT to perform 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.
  - Example: Follow-up imaging may include diagnostic-quality CT or MRI at 3- to 6-month intervals for up to 2 years.
- PET/CT<sup>a,b</sup> or PET/MRI is not advised due to risk of false positives.
  - May consider repeat PET with persistent positive disease or equivocal finding on post-therapy PET.<sup>a,b</sup>

**Relapsed or Refractory (confirmed or highly suspected)**

- CT neck/chest/abdomen/pelvis with contrast or CT chest and MR neck/abdomen/pelvis
- PET/CT<sup>a,b</sup> or PET/MRI<sup>c</sup>

<sup>a</sup> PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy. PET/CT should be obtained in accordance with American College of Radiology (ACR) practice guidelines.

<sup>b</sup> In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if there is an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage the patient. [See Principles of Staging \(PHL-D\)](#). If PET negative at anatomic lesion of concern, biopsy should be considered. In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is not assumed. If there are multifocal (>2–3) skeletal PET lesions without cortical destruction on CT, marrow involvement may be assumed.

<sup>c</sup> If PET/MRI obtained, diagnostic CT of chest is needed.

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## PRINCIPLES OF IMAGING References

- <sup>1</sup> Cerci J, Etchebehere E, Nadel H, et al. Is true whole-body 18F-FDG-PET/CT required in pediatric lymphoma? An IAEA multicentre prospective study. *J Nucl Med* 2019;60:1087-1093.
- <sup>2</sup> Kluge, R, Kurch, L, Georgi, T, and Metzger, M. Current role of FDG-PET in Pediatric Hodgkin's Lymphoma. *Semin Nucl Med* 2017;47:242-257.
- <sup>3</sup> 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.
- <sup>4</sup> McCarten K, Nadel H, Shulkin B, Cho S. Imaging for diagnosis, staging, and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. *Pediatr Radiol* 2019;49:1545-1564.
- <sup>5</sup> Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. *Pediatr Radiol*. 2019;49(11):1565-1573.

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**PRINCIPLES OF STAGING<sup>a</sup>**

- 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.

Site involvement	Imaging modality <sup>b,c,d</sup>	
Peripheral nodes	PET/CT or PET/MRI	<ul style="list-style-type: none"> <li>• ≥2 cm is considered involved on CT scan</li> <li>• &lt;2 cm if FDG-PET positive</li> </ul>
Splenic	Ultrasound	<ul style="list-style-type: none"> <li>• Any lesion large enough to characterize unless imaging characteristics indicate an alternative etiology irrespective of the FDG-PET result</li> </ul>
	PET/CT or PET/MRI	<ul style="list-style-type: none"> <li>• Focal PET-positive lesions that are confirmed by CT or MRI or ultrasound</li> <li>• Splenic involvement has to be focal lesions and not diffuse uptake or splenomegaly</li> </ul>
Lung <sup>e</sup>	PET/CT	<ul style="list-style-type: none"> <li>• E-lesions: Extra-lymphatic structures (lung lesions) contiguous with nodal masses are considered to be E-lesions</li> <li>• At least 1–2 small foci (between 5–10 mm) within whole lung if no other etiology is suspected</li> <li>• At least 1 intrapulmonary focus &gt;1 cm on CT if no other etiology is suspected</li> <li>• PET-positive lesions &lt;1 cm if no other etiology is suspected</li> </ul> <p>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.</p>
Liver	Ultrasound	<ul style="list-style-type: none"> <li>• Any lesion large enough to characterize unless imaging characteristics indicate an alternative nature irrespective of the FDG-PET result</li> </ul>
	PET/CT or PET/MRI	<ul style="list-style-type: none"> <li>• ≥1.5 cm on CT, if FDG uptake greater than or equal to that of normal liver or spleen parenchyma, respectively, should be considered positive</li> <li>• &lt;1.5 cm on CT, if FDG uptake greater than that of normal liver or spleen parenchyma should be considered positive</li> </ul>
Bone marrow	Bilateral biopsy	<ul style="list-style-type: none"> <li>• Positive by histopathology on previous high-risk trials; current trial recommendations are based on FDG-PET alone</li> <li>• European-based GPOH-HD-2002 staging: Not recommended</li> </ul>
	PET/CT or PET/MRI	<ul style="list-style-type: none"> <li>• ≥3 FDG-PET–positive lesions in bone marrow without cortical bone destruction</li> </ul>
Bone	PET/CT or PET/MRI	<ul style="list-style-type: none"> <li>• FDG-PET–positive lesion with cortical bone destruction on CT or MRI<sup>f</sup></li> </ul>

<sup>a</sup> 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.

<sup>b</sup> PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy.

<sup>c</sup> There may be PET-avid lesions that need clinical correlation to determine if it is related to lymphoma.

<sup>d</sup> [See Principles of Imaging \(PHL-C\).](#)

<sup>e</sup> 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.

<sup>f</sup> Lewis J et al. *Pediatr Blood Cancer* 2020;67(4):e28142.

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## PRINCIPLES OF STAGING<sup>a</sup>

### ASSESSMENT OF BULK DISEASE

Site involvement	US-based protocols	European-based <sup>c</sup>
Peripheral nodes	<ul style="list-style-type: none"> <li>Contiguous extramediastinal nodal aggregate &gt;6 cm in the longest transverse diameter (transaxial measurement) or craniocaudal dimension (measured on reformatted CT)</li> </ul>	<ul style="list-style-type: none"> <li>Volume of the largest contiguous lymph node mass ≥200 ml</li> </ul>
Mediastinal mass	<ul style="list-style-type: none"> <li>Tumor diameter &gt;1/3 of the maximal thoracic diameter of an upright PA chest radiograph</li> </ul>	<ul style="list-style-type: none"> <li>Tumor volume ≥200 ml</li> </ul>

### PET 5-POINT SCALE (DEAUVILLE CRITERIA)<sup>b</sup>

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(27):3048-3058.

<sup>a</sup> 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.

<sup>b</sup> PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy. This is a visual analysis and does not include standardized uptake value (SUV).

<sup>c</sup> Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate

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**PRINCIPLES OF SYSTEMIC THERAPY**  
**Primary Systemic Therapy****Primary Systemic Therapy - Recommended Dosing****AVPC<sup>1</sup>**

- Doxorubicin<sup>a</sup> 25 mg/m<sup>2</sup> IV days 1 and 2
- Vincristine 1.4 mg/m<sup>2</sup> IV days 1 and 8; 2.8 mg/dose maximum
- Prednisone 20 mg/m<sup>2</sup> PO twice daily on days 1–7
- Cyclophosphamide 600 mg/m<sup>2</sup> IV days 1 and 2
- Regimen repeated every 21 days for 3 cycles

**ABVE-PC**

*Note: cyclophosphamide dosing in AHOD0031 differs from AHOD1331.*

- **Intermediate Risk (AHOD-0031)<sup>2</sup>**

- ▶ Doxorubicin<sup>a</sup> 25 mg/m<sup>2</sup> IV days 1 and 2
- ▶ Bleomycin 5 U/m<sup>2</sup> IV day 1, 10 U/m<sup>2</sup> IV day 8
- ▶ Vincristine 1.4 mg/m<sup>2</sup> IV days 1 and 8; 2.8 mg/dose maximum per dose
- ▶ Etoposide 125 mg/m<sup>2</sup> IV daily on days 1–3
- ▶ Prednisone 40 mg/m<sup>2</sup> PO divided into two doses daily on days 1–7
- ▶ Cyclophosphamide 800 mg/m<sup>2</sup> IV on day 1
- ▶ Regimen repeated every 21 days for 4 cycles

- **High Risk (AHOD-1331)<sup>3,4</sup>**

- ▶ Doxorubicin<sup>a</sup> 25 mg/m<sup>2</sup> IV days 1 and 2
- ▶ Bleomycin 5 U/m<sup>2</sup> IV day 1, 10 U/m<sup>2</sup> IV day 8
- ▶ Vincristine 1.4 mg/m<sup>2</sup> IV days 1 and 8; 2.8 mg/dose maximum per dose
- ▶ Etoposide 125 mg/m<sup>2</sup> IV daily on days 1–3
- ▶ Prednisone 40 mg/m<sup>2</sup> PO divided into two doses daily on days 1–7
- ▶ Cyclophosphamide 600 mg/m<sup>2</sup> IV on day 1 and 2
- ▶ Regimen repeated every 21 days for 5 cycles

**OEPA (GPOH-HD-2002)<sup>5</sup>**

- Vincristine 1.5 mg/m<sup>2</sup> IV days 1, 8, 15; 2 mg/dose maximum
- Etoposide 125 mg/m<sup>2</sup> IV daily on days 2–6
- Prednisone 60 mg/m<sup>2</sup> PO daily on days 1–15
- Doxorubicin<sup>a</sup> 40 mg/m<sup>2</sup> IV days 1 and 15
- Regimen repeated every 28 days for 2 cycles

**OEPA-COPDAC (GPOH-HD-2002)<sup>5</sup>**

- **OEPA:**

- ▶ Vincristine 1.5 mg/m<sup>2</sup> IV days 1, 8, 15; 2 mg/dose maximum
- ▶ Etoposide 125 mg/m<sup>2</sup> IV daily on days 2–6
- ▶ Prednisone 60 mg/m<sup>2</sup> PO daily on days 1–15
- ▶ Doxorubicin<sup>a</sup> 40 mg/m<sup>2</sup> IV on days 1 and 15
- ▶ Regimen repeated every 28 days for 2 cycles

- **COPDAC:**

- ▶ Cyclophosphamide 500 mg/m<sup>2</sup> IV days 1, 8
- ▶ Vincristine 1.5 mg/m<sup>2</sup> IV days 1, 8; 2 mg/dose maximum
- ▶ Prednisone 40 mg/m<sup>2</sup> PO daily on days 1–15; 80 mg maximum per day
- ▶ Dacarbazine 250 mg/m<sup>2</sup> IV daily on days 1–3
- ▶ Regimen repeated every 28 days for 2 cycles for intermediate risk or 4 cycles for high risk

<sup>a</sup> Dexrazoxane may be utilized as clinically indicated. (Chow EJ, et al. J Clin Oncol. 2015;33(24):2639-2645; Shaikh F, Det al. J Natl Cancer Inst. 2015;108(4):dju357; van Dalen EC, et al. Cochrane Database Syst Rev 2011;2011:CD003917.)

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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
  - Fertility preservation (option for some patients); refer to fertility clinic for further discussion when able prior to initiation of chemotherapy.
- Consider use of RT as part of therapy for relapsed/refractory disease.
- Additional options may be considered for patients over the age of 18, see [NCCN Guidelines for Hodgkin Lymphoma](#).

#### Relapsed/Refractory Disease

	Re-Induction Therapy Options <sup>b</sup> (in alphabetical order)	Subsequent Therapy Options <sup>d</sup> (in alphabetical order)	Maintenance (post-transplant)
CHL	<ul style="list-style-type: none"> <li>• Brentuximab vedotin + bendamustine<sup>c,6</sup></li> <li>• Brentuximab vedotin + gemcitabine<sup>c,7</sup></li> <li>• Brentuximab vedotin + nivolumab<sup>c,8</sup></li> <li>• DHAP (dexamethasone, cytarabine, cisplatin)</li> <li>• GV (gemcitabine, vinorelbine)<sup>c</sup></li> <li>• IEP-ABVD (ifosfamide, etoposide, prednisone; doxorubicin, bleomycin, vinblastine, dacarbazine)<sup>9</sup></li> <li>• IGEV (ifosfamide, gemcitabine, vinorelbine)<sup>10</sup></li> <li>• IV (ifosfamide, vinorelbine)<sup>11</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Bortezomib, ifosfamide, + vinorelbine<sup>12</sup></li> <li>• Nivolumab<sup>c,e,13,14</sup></li> <li>• Pembrolizumab<sup>c,e,f,15,16</sup></li> <li>• GDP (gemcitabine, dexamethasone, cisplatin)<sup>17</sup></li> <li>• ICE (ifosfamide, carboplatin, etoposide)<sup>18</sup></li> <li>• EPIC (etoposide, prednisolone, ifosfamide, cisplatin)<sup>19</sup></li> </ul>	Useful in certain circumstances, for select high-risk <sup>g</sup> patients: <ul style="list-style-type: none"> <li>• Brentuximab vedotin<sup>h,20</sup></li> </ul>

#### [References](#)

<sup>b</sup> Reasonable to try multiple different re-induction regimens as needed prior to ASCT to minimize disease burden with a goal of achieving a metabolic CR prior to transplant.

<sup>c</sup> Should be considered in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed.

<sup>d</sup> Subsequent therapy options include re-induction options that were not previously used.

<sup>e</sup> Emerging data are showing utility as a re-induction option; consider for subsequent therapy if not previously used.

<sup>f</sup> Pembrolizumab is indicated for the treatment of pediatric patients with refractory CHL, or who have relapsed after 2 or more prior lines of therapy.

<sup>g</sup> High-risk: any patient with progressive disease, refractory disease, or relapse within 1 year of original diagnosis.

<sup>h</sup> For relapsed CHL, brentuximab vedotin is indicated for the treatment of adult patients after failure of autologous hematopoietic stem cell transplant (HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates. It is not currently approved for pediatric patients.

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**PRINCIPLES OF SYSTEMIC THERAPY**  
**References**

- <sup>1</sup> 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.
- <sup>2</sup> 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(32):3651-3658.
- <sup>3</sup> Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. *Br J Haematol* 2019;187:39-48.
- <sup>4</sup> Castellino S, Parsons S, Pei Q, et al. A randomized phase III trial of Brentuximab vedotin (Bv) for de novo High-Risk Classical Hodgkin Lymphoma (cHL) in children and adolescents - Study design and incorporation of secondary endpoints in Children's Oncology Group (COG) AHOD1331. *Klin Padiatr* 2020;232(02):82-83.
- <sup>5</sup> 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(23):3680-3686.
- <sup>6</sup> 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. *The Lancet Oncol* 2018 Feb;19:257-266.
- <sup>7</sup> 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.
- <sup>8</sup> Cole PD, Mauz-Körholz C, Mascarini 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.
- <sup>9</sup> Schellong G, Dorffel W, Claviez A, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: results from a multicenter study of the pediatric DAL/GPOH-HD study group. *J Clin Oncol* 2005;23:6181-6189.
- <sup>10</sup> 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.
- <sup>11</sup> 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.
- <sup>12</sup> 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.
- <sup>13</sup> Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin lymphoma after autologous stem-cell transplantation and brentuximab vedotin failure: a prospective phase 2 multi-cohort study. *Lancet Oncol* 2016 Sept;17:1283-1294.
- <sup>14</sup> 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.
- <sup>15</sup> 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.
- <sup>16</sup> Georger 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;21:121-33.
- <sup>17</sup> 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.
- <sup>18</sup> 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.
- <sup>19</sup> 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.
- <sup>20</sup> 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.

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





## PRINCIPLES OF RADIATION THERAPY

### 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 include 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, PET, ultrasound, and other imaging modalities facilitate target definition.
  - ▶ Image guidance may be required to provide assurance of accurate daily delivery.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to develop. In light of that, the modalities and techniques (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.

[Continued](#)

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**PRINCIPLES OF RADIATION THERAPY****Volume**

- Involved-site RT (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 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. However, it spares adjacent uninvolved organs (eg, lungs, bone, muscle, kidney) when lymphadenopathy regresses following chemotherapy.
  - ▶ Pre-chemo or pre-biopsy 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 utilized.
  - ▶ Careful consideration of partial lung tolerance is essential.
  - ▶ Pulmonary nodular disease is usually not treated following chemotherapy unless residual disease is present.
- Pleural or pericardial effusions are not included in the GTV. Nodular pericardial involvement may be included with consideration of cardiac tolerance.
- Bone: Areas of osseous disease may be treated with a CTV expansion beyond the GTV defined by imaging. In 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).

[Continued](#)

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**PRINCIPLES OF RADIATION THERAPY**

- 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.
- Protocols calling for IFRT/ISRT to all sites of disease involvement for stage III/IV disease should be avoided, in favor of a regimen that only irradiates sites that are bulky, or inadequate response (SER/SRL).

**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 partial response 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 PET positive sites, 10-15 Gy (total dose 40-45 Gy).

**DOSE CONSTRAINTS**

	Goal*	Minor Dev	Major Dev	Outcome
Mean Heart	ALARA	10–20 Gy	>20 Gy	Cumulative incidence of significant heart disease at 30 years: 10–20 Gy-5.8%, >20 Gy-7.7% <sup>1</sup>
Left Ventricle (mean)	<10 Gy	10–15 Gy	>20 Gy	Adult HL: Relative risk of congestive heart failure compared with no RT: 16–20 Gy (RR, 1.65), 21–25 Gy (RR, 3.84) <sup>2</sup>
Lung (mean)	ALARA	10–15 Gy	>15 Gy	Adult HL: Pulmonary death mean lung 10–15 Gy (RR, 4.4); 15–20 Gy (RR, 7.7); Lung fibrosis mean lung dose 10–15 Gy (RR, 3.8) <sup>3</sup>
Thyroid	ALARA	V30 <63%		Hypothyroidism 11.5% if V30 <62.5%, and 70.8% if >62.5% <sup>4</sup>
Salivary Glands (mean)	ALARA		>24 Gy	Dose threshold for xerostomia in head and neck cancer <sup>5</sup>
Breast	ALARA (minimize volume receiving 4 Gy or more)			Adult HL: 3.2 fold increase in risk of breast cancer if 4 Gy delivered to breast, risk increases with dose <sup>6</sup>

\* ALARA = as low as reasonably achievable

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## PRINCIPLES OF RADIATION THERAPY REFERENCES

- <sup>1</sup> 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(13):1090-1101.
- <sup>2</sup> van Nimwegen F A, 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(16):2257-2265.
- <sup>3</sup> 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(23):3687-3696.
- <sup>4</sup> 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(5):1802-1808.
- <sup>5</sup> 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(3):577-587.
- <sup>6</sup> Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003;290(4):465-475.

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## Pediatric Hodgkin Lymphoma

### COTSWOLDS-MODIFIED ANN ARBOR STAGING SYSTEM

Stage	Definition
<b>I</b>	<b>One nodal group or lymphoid organ (e.g. spleen or thymus)</b>
	<b>IE One extranodal site</b>
<b>II</b>	<b>Two or more nodal groups, same side of the diaphragm</b>
	<b>IIE Localized extranodal site with stage II criteria, both on the same side of the diaphragm</b>
<b>III</b>	<b>Nodal groups on both sides of the diaphragm</b>
	<b>IIIS1 With splenic involvement</b>
	<b>IIIE2 With localized extranodal site</b>
	<b>IIISE Both IIIS1 and IIIS2</b>
<b>IV</b>	<b>Disseminated involvement of one or more extralymphatic organ (e.g. lung, bone) with or without any nodal involvement</b>

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

Lister T, 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.



NCCN Categories of Evidence and Consensus	
<b>Category 1</b>	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
<b>Category 3</b>	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	
<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



## Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Last updated: March 18, 2021

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# NCCN Guidelines Version 3.2021

## Pediatric Hodgkin Lymphoma

### Overview

Classical Hodgkin lymphoma (CHL) is an uncommon malignancy involving lymph nodes and the lymphatic system, and is generally characterized by the presence of large binucleate or multinucleated neoplastic cells or mononuclear variants (collectively termed Hodgkin Reed-Sternberg [HRS] cells) in a background of benign inflammatory cells.<sup>1</sup> Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. 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.<sup>2-4</sup>

The WHO classification divides Hodgkin lymphoma (HL) into two main types: CHL and nodular lymphocyte-predominant HL (NLPHL).<sup>4</sup> CHL is divided into four subtypes: nodular sclerosis CHL; mixed cellularity CHL; lymphocyte-depleted CHL; and lymphocyte-rich CHL.<sup>4</sup> CHL is characterized by the presence of HRS cells in an inflammatory background and expresses CD30, whereas NLPHL lacks HRS cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed *popcorn cells*, and differs from CHL as it is negative for CD30 and positive for CD20. Most cases of childhood HL are CHL and NLPHL and account for 5% to 10% % of childhood HL.<sup>1</sup>

In 2021, an estimated 8830 people will be diagnosed with HL in the United States and 960 people will die from the disease.<sup>5</sup> In adolescents (aged 15–19 years), HL is the most commonly diagnosed cancer;<sup>6</sup> 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.<sup>7</sup> 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.<sup>6</sup>

The past few decades have seen significant progress in the management of pediatric patients with HL, with estimated 5-year survival rates of greater than 98% after treatment with chemotherapy alone or combined with radiation therapy (RT).<sup>8,9</sup> However, the potential long-term effects of treatment remain an important consideration.<sup>8,9</sup>

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 CHL, 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 aged 18 years of age and younger, 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 HL patients 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.

### Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this inaugural version of the NCCN Guidelines for Pediatric Hodgkin Lymphoma, an electronic search of the PubMed database was performed to obtain key literature published in the field, using the following search term: pediatric Hodgkin lymphoma. The





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## Pediatric Hodgkin Lymphoma

PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.<sup>10</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at [www.NCCN.org](http://www.NCCN.org).

### Diagnosis and Workup for Classic Hodgkin Lymphoma

For evaluation and initial workup of CHL, 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.

Immunostaining for CD30, CD15, CD20, and CD3 is recommended for CHL. 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. Cases of EBV+ CHL may benefit from additional studies such as EBV serology and evaluation

for underlying immunodeficiency. 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 women of childbearing age undergo treatment. HIV and hepatitis B and C testing is encouraged for patients with risk factors for HIV or unusual disease presentations

PET scans are essential for initial staging and for evaluating residual masses at the end of treatment<sup>11</sup> (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: PET/CT or PET/MRI scans (whole-body); diagnostic contrast-enhanced CT (neck, chest, abdomen, and pelvis); or CT of chest and MRI (neck, abdomen, and pelvis). PET scans should be assessed by a nuclear diagnostic radiologist experienced in reading Deauville scores for 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 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 to stage the patient. If



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PET is negative for anatomic lesions of concern, a biopsy should be considered.

In most cases, if the PET/CT displays a homogeneous pattern of marrow uptake, which is thought to be secondary to cytokine release,<sup>12,13</sup> bone marrow involvement is not assumed. If there are multifocal skeletal PET lesions without cortical destruction on CT, marrow involvement may be assumed and a bone marrow biopsy is not needed to confirm involvement.<sup>14</sup> In select cases, if there are cytopenias and the 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, an FEV1/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.

In select cases and if the patients are interested, the panel recommends consideration of fertility preservation (eg, semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) prior to the initiation of therapy. In general, the panel also recommends providing referrals for counseling as needed that address fertility, smoking cessation or substance abuse 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.<sup>1</sup> 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.<sup>1,15,16</sup> Staging is generally defined as follows:<sup>16</sup>

- Stage I: One nodal group or lymphoid organ (eg, spleen, thymus and 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) 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 CXR 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 transverse diameter or craniocaudal dimension, and EuroNet defines bulk as >200 mL.
- E: Involvement of extralymphatic tissue on one side of the diaphragm by limited 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 extension from a site of involvement into a surrounding tissue or organ, and this does not always indicate stage IV disease. Involvement of an extranodal site that is extralymphatic and does not arise from direct extension is considered to be stage IV



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disease. The distinction between stage IV disease and E-lesions is not applied uniformly and remains an area in need of international harmonization.

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.<sup>1</sup> 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.<sup>17</sup> As the SEARCH effort for CAYAHL develops, so will the evolution of harmonized risk stratification for pediatric HL.<sup>9</sup>

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).<sup>9</sup> 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. Due to the evolving nature of risk stratification, enrollment in a clinical trial is preferred. In addition, for patient management, the panel recommends considering consultation with a center of expertise.

### Principles of Imaging

Clinical management of pediatric patients with CHL involves initial treatment with chemotherapy and assessment of treatment response with PET to determine the need for additional treatment.<sup>18-20</sup>

Given the avidity of pediatric lymphomas for <sup>18</sup>F-fluorodeoxyglucose (FDG),<sup>19</sup> the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of FDG uptake in the involved sites (See Deauville Criteria Table in *Principles of Staging*). 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.<sup>21-23</sup> 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.<sup>22,23</sup> These criteria vary across different protocols as they have yet to be validated in a large pediatric trial. However, interim or end-of-treatment PET scans with a score of 1, 2, or 3 are generally considered “negative” and PET scans with a score of 4 and 5 are considered “positive.”<sup>24</sup> 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,<sup>21,25,26</sup> 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 PET-guided interim response assessment and risk-adapted therapy in adult patients with HL.

PET imaging is important as a baseline measurement before therapy to determine the initial sites of involvement and to perform an early response assessment (often after the initial two cycles of chemotherapy).<sup>11</sup> Although the optimum time point for assessment and criteria for response are not uniform, interim assessment of response by PET is incorporated into pediatric HL treatment.<sup>1</sup> The panel recommends diagnostic contrast-enhanced CT or MRI to adequately evaluate all sites of involvement, and PET/CT or 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 PET to minimize false-positive results.

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.<sup>27</sup> 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, 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.<sup>28-30</sup> 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  $\geq 10$  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. ISRT targets the originally involved nodal sites and possible extranodal extensions (which generally defines a smaller field than the classical IFRT),<sup>31</sup> 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 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 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



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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 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 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.<sup>32</sup> 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).<sup>32</sup> 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 TG-1 patients who achieve a CR after chemotherapy [GPOH-HD-95 trial].<sup>33</sup>

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 in boys with HL.<sup>34</sup> In this trial, all patients were aged <18 years (n = 573); for induction, boys (n = 287) received 2 courses of OEPA (vincristine, etoposide, prednisone, and doxorubicin), and girls (n = 286) received 2 courses of OPPA (vincristine, procarbazine, prednisone, and doxorubicin).<sup>34</sup> After chemotherapy, all patients received IFRT at 19 Gy except patients in TG-1 stage 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.<sup>34</sup> In TG-2 and TG-3, there was no significant difference in EFS between boys and girls (90.2% ± 2.3% vs. 84.7% ± 2.7%, respectively; *P* = .12).<sup>34</sup> 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 TG-1 patients who experience CR after chemotherapy.<sup>33,34</sup>

Building on the GPOH-HD studies, an international intergroup study for CHL in children and adolescents (EuroNET-PHL C1) aimed to: 1) demonstrate a 90% 5-year EFS in PET-negative patients (TG-1) after 2 cycles of OEPA; and 2) demonstrate that dacarbazine can safely replace procarbazine in consolidation chemotherapy (COPP vs. COPDAC) in TG-2 and TG-3 stages without impairing treatment.<sup>35</sup> In a report from an interim analysis, the 4-year overall survival (OS) and EFS were 98% and 88%, respectively.<sup>35</sup> The EFS in TG-1, TG-2, and TG-3 was 87.5%, 91%, and 86.6%, respectively (*P* = .08). The EFS in patients with or without RT was 88% and 87%. In addition, the EFS was not different between the COPP and COPDAC arms in TG-2 and TG-3. In TG-1, ESR >30 or bulky disease was associated with inferior EFS.<sup>35</sup> This trial suggests that RT can be eliminated in patients who are PET-negative after chemotherapy, and dacarbazine can safely replace procarbazine in COPP. Therefore, only the COPDAC arm is included in the Guidelines.<sup>35</sup>

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.<sup>36</sup> All patients (n = 278) were treated with 3 cycles of AVPC, and patients who were not in 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



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support for 2 cycles, and IFRT.<sup>36</sup> At 4 years, 49.0% of patients had been treated with 3 cycles of AVPC without RT and 88% were in 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 ( $P = .008$ ).<sup>36</sup> In this study, a negative PET scan after 1 cycle of chemotherapy (PET1) and an ESR rate  $\leq 20$  mm/h were associated with a favorable EFS outcome.<sup>36</sup>

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

After initial cycles of chemotherapy, patients with adequate response may receive followed-up. Patients with inadequate response receive ISRT (to all sites and boost to sites of inadequate response per EuroNet-PHL-C1). Based on an end-of-therapy PET assessment, patients may receive follow-up or may consider reinduction 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.<sup>37-41</sup> 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.<sup>42</sup> 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 early response assessment 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. RERs 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 RERs with less than CR were nonrandomly assigned to receive IFRT. In patients who experienced inadequate response (slow early response [SER]) after 2 cycles of ABVE-PC, they were randomly assigned to receive or not receive 2 cycles of chemointensification 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% for RERs and 77.4% for SERs;  $P < .001$ ), and the 4-year OS was 97.8% (98.5% for RERs and 95.3% for SERs;  $P < .001$ ).<sup>42</sup> In RER patients who experienced 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 SER patients 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 SER patients 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 RERs with CR at the end of chemotherapy, and that



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augmenting chemotherapy in SERs with PET-positive disease may be beneficial.<sup>42</sup>

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.<sup>43</sup> In addition, the 5-year EFS was higher in the LPHL subgroup compared to CHL (92.2% vs. 83.5%, respectively;  $P = .04$ ).<sup>43</sup> Based on the data, the investigators state that this subgroup may benefit from treatment with chemotherapy alone.

Other clinical studies evaluating the intermediate-risk group (TG-2) include the GPOH-HD-2002 and EuroNET-PHL C1 trials<sup>34,35</sup> as described under *Low-Risk CHL*.

### **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 AHOD0031 regimen, after 2 initial cycles of ABVE-PC, patients with adequate response are treated with 2 additional cycles of ABVE-PC. Based on an end-of-therapy PET assessment and CR achievement with CT criteria, patients may either receive follow-up or treatment with ISRT to all sites if less than CR. Patients with 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 with adequate response are treated with 2 cycles of

COPDAC. Patients with 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 PET assessment and CT scan, patients may either be followed up 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.<sup>37-41</sup> The panel recommends referring to the adult [NCCN Guidelines for Hodgkin Lymphoma](#) to review relevant data and context.

### **High-Risk CHL**

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.<sup>44</sup> After 3 cycles of ABVE-PC, early response was evaluated and patients with RER based on anatomic criteria received IFRT (21 Gy) and patients with SERs 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 intermediate and high-risk patients, respectively;  $P = .87$ ).<sup>44</sup> 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.<sup>44</sup> Overall, this trial allowed a reduction in alkylator and anthracycline exposure in 63% of patients.

In a later COG study, AHOD0831, the investigators aimed to limit alkylator exposure and decrease radiation volumes in pediatric patients



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with high-risk HL, defined as stage IIIB and IVB (n = 165; aged ≤21 years).<sup>45</sup> All patients received 2 cycles of ABVE-PC; if they experienced CR (RER), they received an additional 2 cycles of ABVE-PC and IFRT (21 Gy) only to sites of initial bulk. Patients with SER received 2 cycles of ifosfamide and vinorelbine followed by 2 more cycles of ABVE-PC and RT to sites of initial bulk disease and slow-responding sites. According to intent-to-treat analysis, the 4-year second EFS (ie, freedom from second relapse or malignancy) was 91.9% (95% CI, 86.1%–95.3%).<sup>45</sup> The 5-year first EFS and OS rates were 79.1% (95% CI, 71.5%–84.8%) and 95% (95% CI, 88.8%–97.8%), respectively. Although the projected target for second EFS was not reached (ie, 95%), the EFS and OS rates were comparable to other trials involving high-risk HL.<sup>44,46</sup> In the phase III COG AHOD1331 trial, further refinements are being investigated including substituting bleomycin with brentuximab vedotin, a CD30 antibody-drug conjugate, the results of which are pending.<sup>47,48</sup>

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; age <21 years).<sup>46,48</sup> All patients received 4 cycles of BEACOPP, and patients with rapid response received either 4 cycles of COPP/ABV and no IFRT (female patients) or 2 cycles of ABVD followed by IFRT (21 Gy) (male patients).<sup>46</sup> Patients who were slow responders received an additional 4 cycles of BEACOPP and IFRT. The 5-year EFS and OS rates were 94% and 97%, respectively.<sup>46</sup> Although this regimen is effective at maintaining disease control, it is likely to be associated with increased long-term toxicities.<sup>48</sup>

### **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 according to

AHOD1331 (based on AHOD0831) or EuroNet-PHL-C1 as the preferred strategies.

For the AHOD1331 regimen, after 2 initial cycles of ABVE-PC, patients with adequate response (rapidly responding lesions/RRL) are treated with 3 additional cycles of ABVE-PC and ISRT to sites of LMA. Patients with inadequate response (slow responding lesions/SRL) receive 3 additional cycles of ABVE-PC and ISRT to sites of LMA. The addition of boost is dependent on PET-positive lesions at end of chemotherapy.

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

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

In certain circumstances, BEACOPP and ABVD regimens may be considered for some pediatric patients.<sup>37-41,46</sup> 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.

### **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,<sup>49-57</sup> patients should be followed up with an oncologist 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





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schedule should be individualized, depending on clinical circumstances such as patient's age, gender, 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<sup>58</sup> 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 PET scans are not recommended. If relapse is suspected (based on imaging, clinical, and pathological correlations) imaging studies are recommended. It is acceptable to obtain a 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. If the previous PET was positive (Deauville 3 to 5), a PET/CT or 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 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 PET assessments.

In general, and in terms of monitoring late effects ( $\geq 2$  years after completion of systemic therapy), patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects (eg, secondary cancers, cardiac disease, and issues affecting the thyroid, bone, and reproductive health), health habits, and psychosocial issues. For comprehensive details, see the COG Survivorship Guidelines.<sup>58</sup>

### 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.<sup>8,59,60</sup> For patients with relapsed or refractory disease, treatment options include standard-dose chemotherapy (re-induction therapy), high-dose chemotherapy with ASCR, or novel approaches.<sup>59</sup> Re-induction regimens can be divided into four major categories.<sup>59</sup>

1) **Platinum-based regimens** including: DHAP<sup>61</sup> (dexamethasone, cytarabine, and cisplatin); EPIC<sup>62</sup> (etoposide, prednisolone, ifosfamide, and cisplatin); and GDP<sup>63</sup> (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%.<sup>61</sup> In a retrospective study of 80 children with relapsed or primary refractory HL, treatment with the EPIC regimen (55% of patients received stem cell transplant 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.<sup>62</sup> In a study of patients with R/R HL (n



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= 23; median age, 36 years; range, 19–57 years) the response rate after 2 cycles of GDP was 69.5%.<sup>63</sup>

2) **Ifosfamide-/etoposide-based regimens** including: ICE<sup>64</sup> (ifosfamide, carboplatin, and etoposide); IEP-ABVD<sup>65</sup> (ifosfamide, etoposide, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine); IV<sup>66</sup> (ifosfamide, and vinorelbine); and a regimen composed of bortezomib and IV.<sup>67</sup> The ICE regimen was developed to decrease non-hematologic toxicities observed with cisplatin-containing regimens.<sup>60,64</sup> 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 who 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%.<sup>64</sup>

In a study of patients with progressive or relapsed HL (n = 167; median age, 14.7 years; range, 4.3–24.5 years), patients were treated with 2 to 3 cycles of IEP alternating with 1 to 2 cycles of ABVD, and supplemented by additional chemotherapy.<sup>65</sup> Involved disease sites were also treated with individualized doses of RT. After 10 years, the DFS and OS rates were 62% and 75%, respectively.<sup>65</sup> This study also identified 3 risk groups defined as *progressive disease* on or within 3 months of primary treatment, which had the worst prognosis (DFS/OS rates of 41% and 51%, respectively); *early relapse* 3–12 months from primary treatment with improved OS (DFS/OS rates of 55% and 78%, respectively); and *late relapse* over 12 months from primary treatment, which had significantly better DFS (DFS/OS rates of 86% and 90%, respectively), even though this group did not receive stem cell transplantation in second CR.<sup>59,65</sup>

In a study evaluating the efficacy of the IV regimen, 66 patients younger than 30 years of age with R/R HL were treated with 2 cycles of IV.<sup>66</sup> The overall response rate (ORR) of 72% allowed most of the patients to

undergo subsequent stem cell transplantation.<sup>66</sup> It is worth noting that this regimen eliminates etoposide, a chemotherapeutic agent associated with secondary malignancy after transplantation.<sup>66,68</sup> 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.<sup>67</sup>

3) **Gemcitabine-based regimens** including: GV<sup>69</sup> (gemcitabine and vinorelbine); and IGEV<sup>70</sup> (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).<sup>69</sup> All patients had received at least 2 prior chemotherapy regimens and 17 patients had undergone prior autologous stem cell transplantation (ASCT). Overall, 19 of 25 patients had measurable responses for an observed response rate of 76%.<sup>69</sup> Patients who had received transplant before GV tended to respond to therapy over patients who had not received transplant.<sup>69</sup> 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.<sup>70</sup> The 5-year second EFS and OS rates were 83.0% ± 11.0% and 90.0% ± 9.5%, respectively.<sup>70</sup>

4) **Targeted therapy and immunotherapy-based regimens** include brentuximab vedotin combined with bendamustine,<sup>71</sup> gemcitabine,<sup>72</sup> or nivolumab;<sup>73</sup> or single-agent nivolumab<sup>74,75</sup> or single-agent pembrolizumab.<sup>76,77</sup> In a group of heavily pretreated patients at least 18 years of age with R/R HL (n = 64) and anaplastic large cell lymphoma (n = 1), the safety and clinical activity of brentuximab vedotin and bendamustine was evaluated.<sup>71</sup> An overall response was achieved in 29 of 37 patients (78%).<sup>71</sup> In a COG study (AHOD1221), the safety and efficacy of brentuximab vedotin and gemcitabine was evaluated in children and young adults with primary refractory or early relapsed HL (n = 46; aged <30 years).<sup>72</sup> Of 42 evaluable patients, 24 (57%) had a CR within the first 4 cycles of treatment; 4 of 13 patients (31%) with a PR



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or stable disease had all target lesions with Deauville scores of  $\leq 2$  after 4 cycles of treatment.<sup>72</sup> Using a Deauville score threshold of  $\leq 3$ , 28 of 42 (67%) achieved a CR.

The combination of brentuximab vedotin 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 with a CR rate of 61% after 4 cycles and no increase in toxicities compared to either agent alone.<sup>78</sup> For patients who underwent ASCT after the combination, the 2-year PFS was 91%.<sup>79</sup> 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 brentuximab vedotin and nivolumab experienced complete metabolic response (CMR) and ORR of 59% and 82%, respectively (according to blinded independent central review).<sup>73</sup> No grade 3 or 4 immune mediated adverse events were observed.

Multiple studies have also demonstrated efficacy of nivolumab and pembrolizumab, another human monoclonal PD-1–directed antibody, in adult patients with R/R HL.<sup>74-76</sup> 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%).<sup>77</sup> In the phase III KEYNOTE-204 study, heavily pretreated adult patients with R/R CHL were randomized to receive either pembrolizumab or brentuximab vedotin (n = 300 evaluable patients; pembrolizumab arm, n = 148; brentuximab vedotin arm, n = 152; aged  $\geq 18$  years).<sup>80</sup> The median PFS in the pembrolizumab treatment arm was statistically longer than the brentuximab vedotin treatment arm (13.2 months vs. 8.3 months, respectively; HR, 0.65; 95% CI, 0.48–0.88;  $P = .00271$ ).<sup>80</sup>

Because no randomized trials have been conducted to compare re-induction regimens, none of the regimens is considered to be superior to the other.<sup>60</sup> 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.<sup>59</sup>

In general, two post-transplant treatment options may be considered including: 1) maintenance therapy with brentuximab vedotin (especially useful in patients with high-risk features including progressive disease, refractory disease, or relapse within 1 year of diagnosis);<sup>81</sup> 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).<sup>60,82,83</sup>

### ***NCCN Recommendations for Relapsed or Refractory CHL***

Histologic confirmation with biopsy is recommended before initiating treatment for relapsed or refractory disease. If the biopsy is negative, the panel recommends either observation with short-interval follow-up or additional workup if high index of suspicion. If the biopsy is positive, the panel recommends enrolling the patient 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 lack of data to support one regimen over another.

Typically, patients are treated with re-induction therapies, and after a PET/CT or PET/MRI assessment, if metabolic CR is observed (Deauville score  $\leq 3$ ), 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 unable to achieve a metabolic CR, RT may be used before transplant.



In certain cases, patients may avoid ASCR. These include patients with initial 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. 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 PET/CT or PET/MRI is recommended to evaluate response. If PET-negative, patients may be observed with short-interval follow-up. If PET-positive, subsequent therapy options should be considered, including re-induction options that were not previously used.

## 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.<sup>8</sup> Emerging data will continue to inform the panel's recommendations and consistent with NCCN philosophy, participation in clinical trials is always encouraged.

**References**

- 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>.
- 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>.
- 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>.
- Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021;71:7-33. Available at: <https://pubmed.ncbi.nlm.nih.gov/33433946/>.
- 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>.
- 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>.
- 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>.
- 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>.
- U.S. National Library of Medicine Key MEDLINE® Indicators. Available at: [http://www.nlm.nih.gov/bsd/bsd\\_key.html](http://www.nlm.nih.gov/bsd/bsd_key.html). Accessed January 24, 2020.
- 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>.
- Ei-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>.
- 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>.
- 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>.
- 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>.
- 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>.
- 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>.

18. 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>.

19. 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>.

20. 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>.

21. 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>.

22. 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>.

23. 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>.

24. 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>.

25. 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>.

26. 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>.

27. 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/>.

28. 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>.

29. 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>.

30. 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>.

31. 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>.



32. 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>.
33. 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>.
34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. Zubizarreta PA, Alfaro E, Gutter 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>.
42. 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>.
43. 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>.
44. 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>.



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## Pediatric Hodgkin Lymphoma

45. Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. *Br J Haematol* 2019;187:39-48. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31180135>.

46. 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>.

47. Castellino SM, Parsons SK, Pei Q, et al. A randomized Phase III trial of Brentuximab vedotin (Bv) for de novo High-Risk Classical Hodgkin Lymphoma (cHL) in children and adolescents - Study Design and Incorporation of secondary endpoints in Children's Oncology Group (COG) AHOD1331. *Klin Padiatr* 2020;232:S-II-07. Available at:

<https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0040-1701822>.

48. 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>.

49. 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>.

50. 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>.

51. 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>.

52. Dorffel W, Riepenhausen 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>.

53. 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>.

54. 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>.

55. 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>.

56. 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>.

57. 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>.

58. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. 2018. Available at:

[http://survivorshipguidelines.org/pdf/2018/COG\\_LTFU\\_Guidelines\\_v5.pdf](http://survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf).

Accessed January 31, 2019.





# NCCN Guidelines Version 3.2021

## Pediatric Hodgkin Lymphoma

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. *Hemisphere* 2020;4:e329. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32072145>.

61. 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>.

62. 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>.

63. 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>.

64. 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>.

65. Schellong G, Dorffel W, Claviez A, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: results from a multicenter study of the pediatric DAL/GPOH-HD study group. *J Clin Oncol*

2005;23:6181-6189. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16135485>.

66. 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>.

67. 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>.

68. 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>.

69. 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>.

70. 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>.

71. 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>.



# NCCN Guidelines Version 3.2021

## Pediatric Hodgkin Lymphoma

72. 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>.

73. 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](https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8013).

74. 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>.

75. 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>.

76. 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>.

77. Georger 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>.

78. 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>.

79. Herrera AF, Manley T, Sacchi M, et al. Brentuximab Vedotin and Nivolumab for Relapsed or Refractory Classic Hodgkin Lymphoma: Long-Term Follow-up Results from the Single-Arm Phase 1/2 Study. *Blood* 2019;134:238-238. Available at: <https://doi.org/10.1182/blood-2019-122576>.

80. 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](https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8005).

81. 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>.

82. 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>.

83. 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>.