National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Hodgkin Lymphoma

Version 2.2021 — October 21, 2020

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Pediatric Hodgkin Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

***Jamie E. Flerlage, MD, MS/Chair** €
St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

***Susan M. Hiniker, MD/Vice Chair** §
Stanford Cancer Institute

Saro Armenian, DO, MPH € ‡
City of Hope National Medical Center

Ellen C. Benya, MD ф
Ann & Robert H. Lurie Children's Hospital of Chicago/Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Adam J. Bobbey, MD ф
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Vivian Chang, MD €
UCLA Jonsson Comprehensive Cancer Center

Stacy Cooper, MD ‡
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Don W. Coulter, MD €
Fred & Pamela Buffett Cancer Center

Branko Cuglievan, MD €
The University of Texas MD Anderson Cancer Center

Bradford S. Hoppe, MD, MPH §
Mayo Clinic Cancer Center

Leidy Isenalumhe, MD, MS € ‡
Moffitt Cancer Center

Kara Kelly, MD €
Roswell Park Comprehensive Cancer Center

Leslie Kersun, MD, MSCE, MSEd € ‡
Children's Hospital of Philadelphia; Abramson Cancer Center at the University of Pennsylvania

Adam J. Lamble, MD €
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Nicole A. Larrier, MD, MSc §
Duke Cancer Institute

Kwadwo Oduro, MD, PhD ≠ ‡
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Anita P. Price, MD ф
Memorial Sloan Kettering Cancer Center

Kenneth B. Roberts, MD §
Yale Cancer Center/Smilow Cancer Hospital

Christine M. Smith, MD € ‡
Vanderbilt-Ingram Cancer Center

Aliyah R. Sohani, MD ≠
Masschusetts General Hospital Cancer Center

Erin M. Trovillion, MD € ‡
UC San Diego Moores Cancer Center

Emily Walling, MD, MPHS €
University of Michigan Rogel Cancer Center

Ana C. Xavier, MD €
O'Neal Comprehensive Cancer Center at UAB

NCCN
Jennifer Burns
Ndiya Ogba, PhD

NCCN Guidelines Panel Disclosures

Continue

‡ Hematology/Hematology oncology
€ Pediatric oncology
ф Diagnostic radiology
≠ Pathology
§ Radiotherapy/Radiation oncology
* Discussion Section Writing Committee

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Pediatric Hodgkin Lymphoma

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)

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

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.

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~~ *2* or more prior lines of therapy.**

PHL-E (3 of 3)

- **Reference added: Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. Lancet Oncol. 2020;21:121–33.**

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 ≤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.**

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Pediatric Hodgkin Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSIS

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

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)[c]
- CT neck/chest/abdomen/pelvis with contrast or CT chest and MRI neck/abdomen/pelvis[c]
- PET/CT scan[d] or PET/MRI scan[d] (whole-body)[c]
- 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[e]
- PFTs (including diffusing capacity [DLCO] if bleomycin indicated)[f]
- ECG
- HIV and hepatitis B/C testing (encouraged)
- Only consider bilateral bone marrow biopsy if there are cytopenias and negative PET[g]

CLINICAL PRESENTATION

Classic Hodgkin lymphoma (CHL)[h] → See Clinical Staging (PHL-2)

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

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

[c] Diagnostic imaging should be done prior to initiating chemotherapy to allow for staging and risk 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).

[d] 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.

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

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

[g] In most instances, if the 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.)

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

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 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[j] (See PHL-D)	Risk Group[k]
IA IIA	No	No	Low risk (per EuroNet-PHL-C1[l])
	Yes	No	Low risk (per EuroNet-PHL-C1[l]) or Intermediate risk (per AHOD0031)
	Yes	Yes	Intermediate risk (per EuroNet-PHL-C1[l] or AHOD0031)
IB	Any	No	Low risk (per EuroNet-PHL-C1[l])
	Any	Any	Intermediate risk (per AHOD0031)
IIB[i]	No	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1[l])
	No	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1[l])
	Yes	Any	High risk (per AHOD1331[l])
	Yes	Yes	High risk (per EuroNet-PHL-C1[l])
IIIA	Any	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1[l])
	Any	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1[l])
IIIB, IV	Any	Any	High risk (AHOD1331[l] or EuroNet-PHL-C1[l])

See Low-Risk Disease (PHL-3)
See Intermediate-Risk Disease (PHL-4)
See High-Risk Disease (PHL-5)

[i] 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.

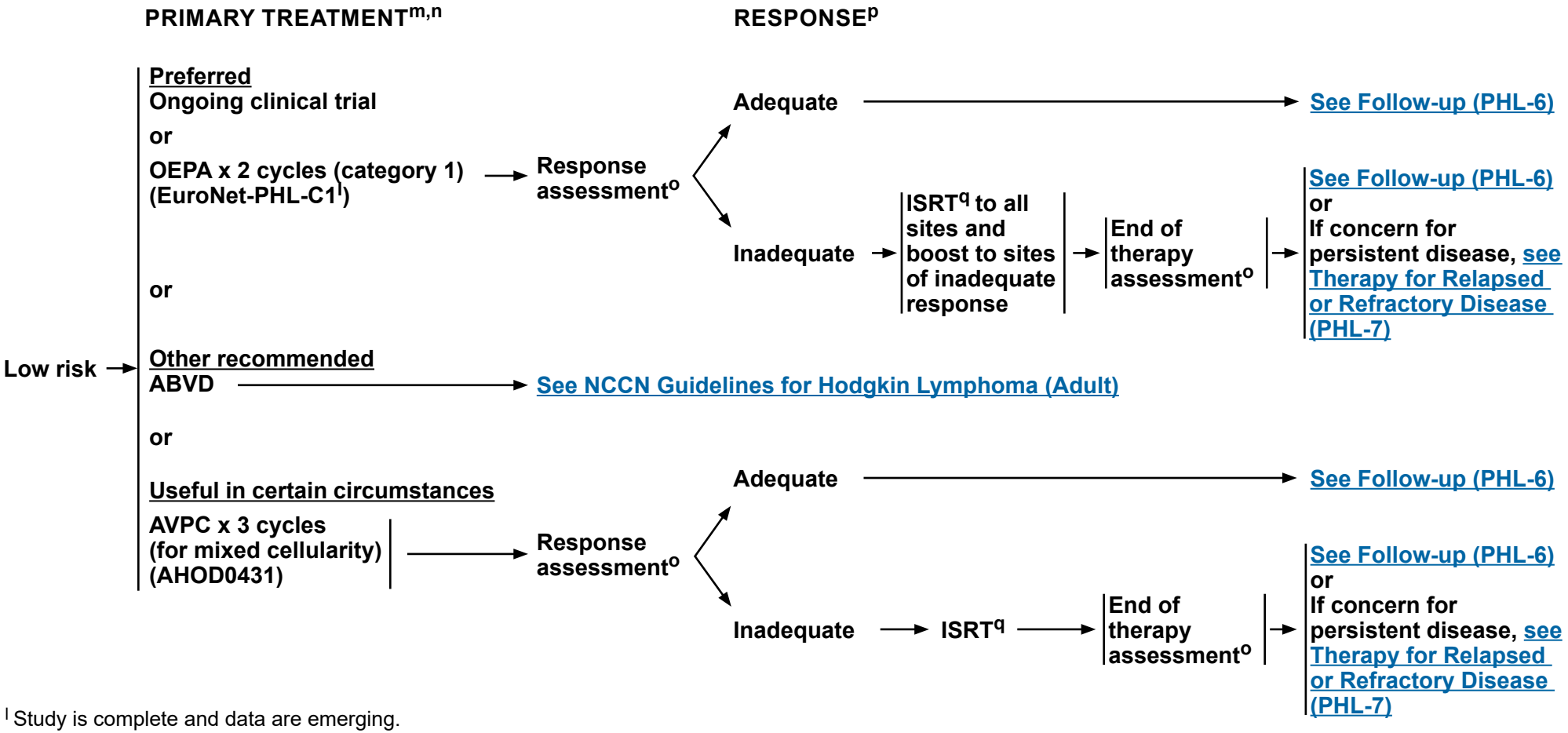
[j] E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by contiguous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation. (Engert A, et al. N Engl J Med 2010;363:640-652; Lister TA, et al. J Clin Oncol 1989;7:1630-1636.)

[k] 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.

[l] 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.

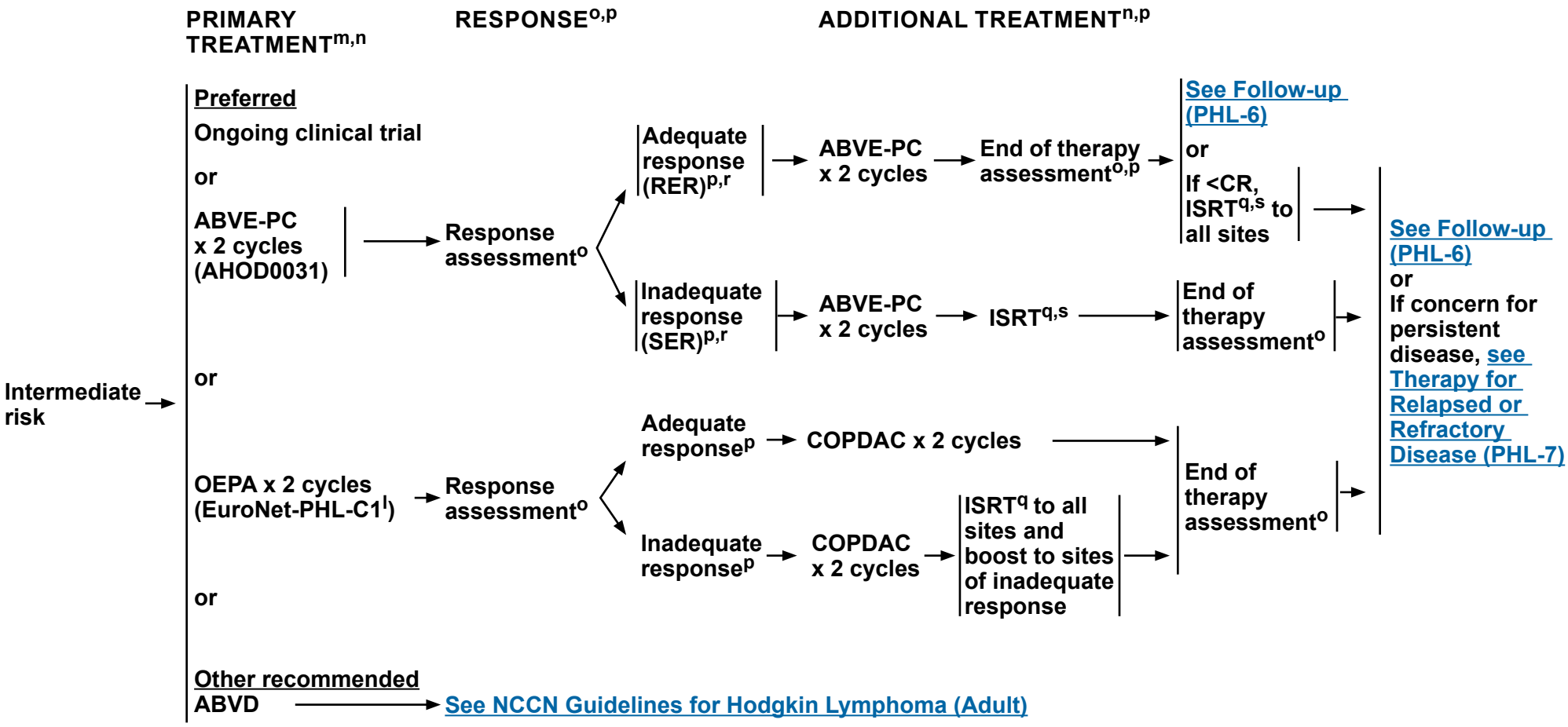
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma



[l] Study is complete and data are emerging.
[m] Regimens are based off of studies with pediatric data.
[n] See Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with PET.
[p] See Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[q] See Principles of Radiation Therapy (PHL-F).

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.

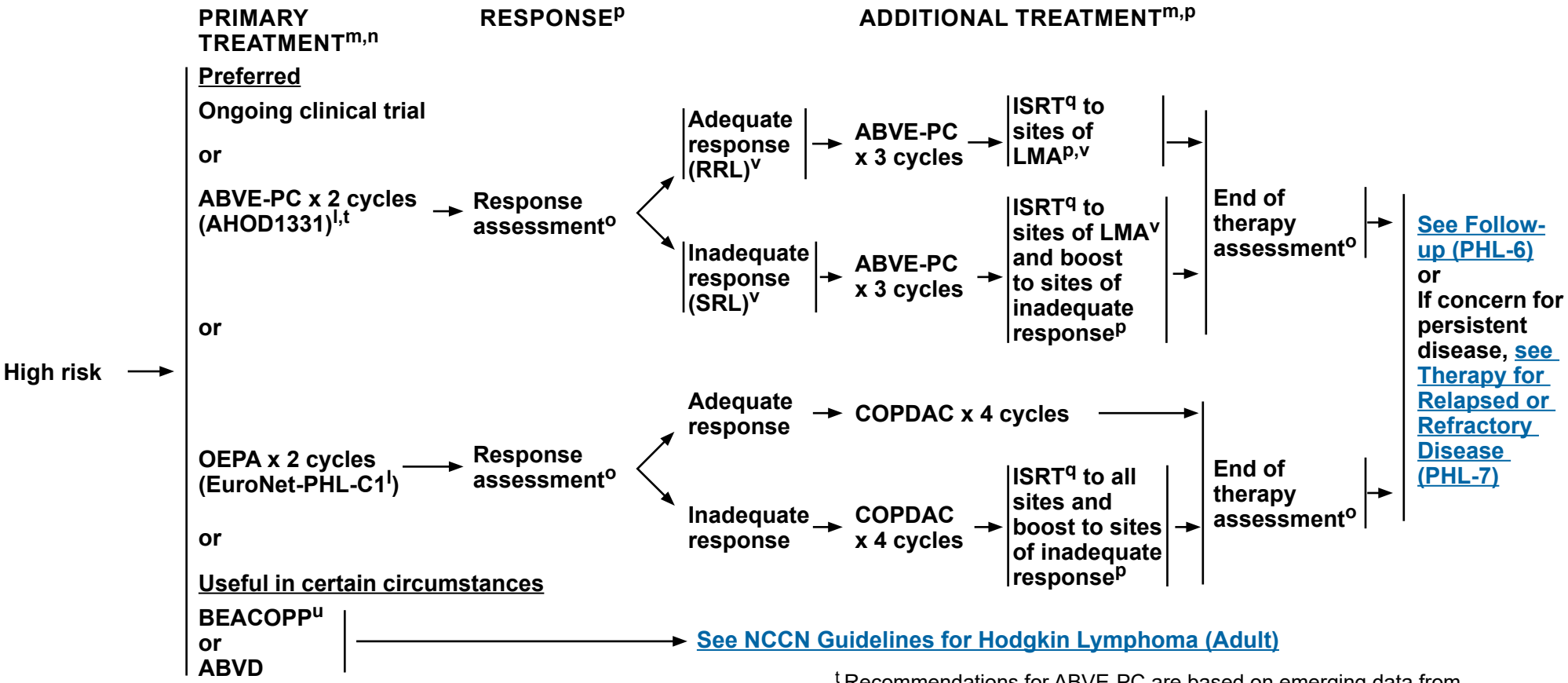
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma



[l] Study is complete and data are emerging.
[m] Regimens are based off of studies with pediatric data.
[n] See Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with PET.
[p] See Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[q] See Principles of Radiation Therapy (PHL-F).
[r] RER = Rapid early responders; SER = Slow early responders.
[s] ISRT can safely replace IFRT (see PHL-F).

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



[l] Study is complete and data are emerging.
[m] Regimens are based of off studies with pediatric data.
[n] See Principles of Systemic Therapy (PHL-E).
[o] FDG-PET/CT or PET/MRI and contrast-enhanced diagnostic CT or MRI of original sites of disease if not included with PET.
[p] See Principles of Criteria for Response-Adapted Radiation Therapy (PHL-A).
[q] See Principles of Radiation Therapy (PHL-F).
[t] 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).
[u] 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.
[v] RRL = Rapidly responding lesions; SRL = Slow responding lesions; LMA= Large mediastinal adenopathy.

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.

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).
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)

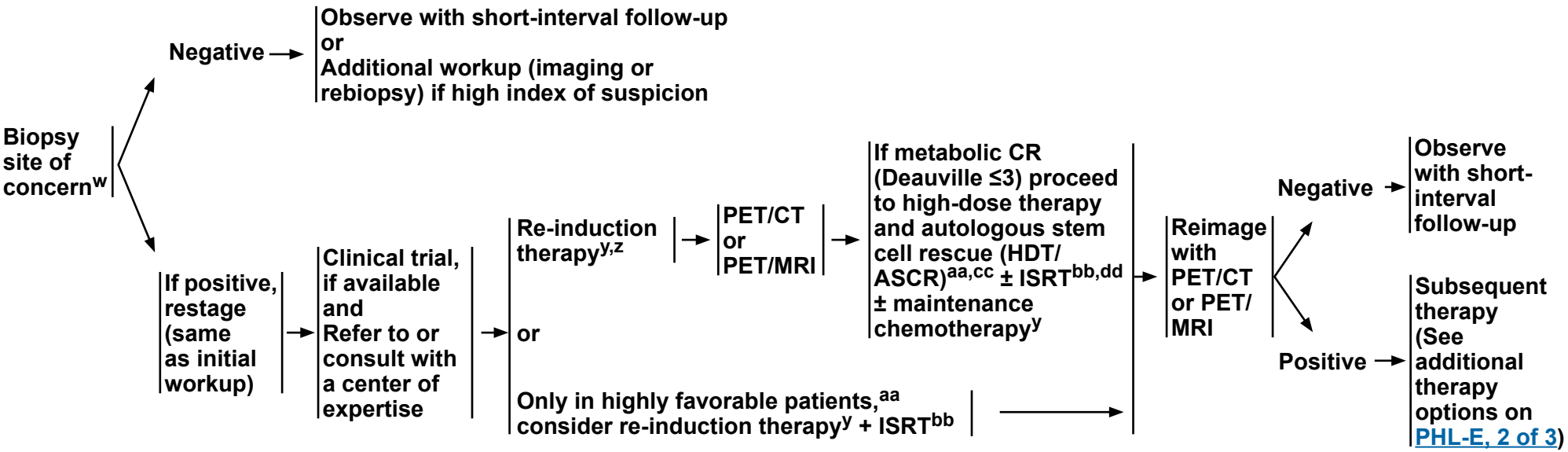
→ **Relapse** → See Principles of Pathology (PHL-B) and See Therapy for Relapsed/Refractory Disease (PHL-7)

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

SUSPECTED RELAPSED/ REFRACTORY DISEASE

RE-INDUCTION THERAPY[x]



[w] A biopsy must be obtained to confirm relapse and pathology. See Principles of Pathology (PHL-B).
[x] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[y] See Principles of Systemic Therapy for Relapsed or Refractory Disease (PHL-E, 2 of 3).
[z] 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.
[aa] 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.
[bb] Strongly consider radiation therapy for selected sites that have not been previously irradiated.
[cc] Allotransplant is an option in select patients who relapse post-ASCT as a category 3 recommendation.
[dd] RT is usually performed as consolidation after transplant, unless unable to get to a metabolic CR, then can utilize RT prior to transplant.

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 CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY

Regimen[a]	Risk Group/Stage	Criteria for RT	Protocol Rationale
OEPA/OEPA-COPDAC (EuroNet-PHL-C1[d])[2,3]	**Low Risk** • IA/B without E • IIA without E **Intermediate Risk** • IA/B + E • IIA + E • IIB, IIIA **High Risk** • IIB + E • IIIA+ E • IIIB, IVA/B ± E	• <CR on imaging after 2 cycles of OEPA ▸ CR: Volume reduction >95% and ≤2 mL ▸ CRu: Volume reduction >75% or ≤2 mL • All IR/HR patients on HD-2002 received RT • IR/HR patients on C1 (emerging data) received RT only if PET positive or not in at least PR after 2 cycles of OEPA, ▸ PR: No CR or CRu and >50% volume reduction or residual tumor volume <5 mL Note: Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate	• 5-year EFS from GPOH-HD-2002 (C1 results pending) ▸ TG1: 92% (overall) (92% + RT; 93% without RT) ▸ TG2/3: 87% 5-year EFS (overall)[2] • Limits total doxorubicin dose to 160 mg/m² (less than the 250 mg/m² maximum dose) • Estimate elimination of RT in ~30% of patients • Refer to EuroNET-PHL-C1 Radiotherapy Manual ▸ No mandatory RT to any sites ▸ RT was only done for poor response, not for all patients.[3]
ABVE-PC[4,7]	**Intermediate Risk (AHOD0031)[4]** • IA, IIA with bulk ± E • IB, IIB without bulk ± E • IIIA ± E[b]	• Slow early responders (SER) on imaging after 2 cycles if <60% reduction in product of perpendicular diameters (PPD)[c] for all target lesions or • Rapid early responders (RER) on imaging after 2 cycles if not in CR on imaging after 4 cycles ▸ CR: ≥80% reduction in PPD[c] with negative PET at end of therapy (comparable to Deauville 1–2) • Consider boost for persistent PET-positive (Deauville 3-5) lesions at end of chemotherapy.	• 4-year EFS ▸ RER/CR: 88% vs. 84% (+RT) ▸ SER: 79% vs. 75% (+ DECA) • Response-adapted therapy
	High Risk (AHOD1331[d])[5,6] • IIB with bulk • IIIB, IV[b]	• Slow responding lesions (SRL) on imaging after 2 cycles[7] ▸ Inadequate or SRL: Deauville 4–5 ▸ Adequate or rapidly responding lesions (RRL): Deauville ≤3 • All large mediastinal adenopathy (LMA) • Boost for persistent PET-positive lesions (Deauville 3-5) at end of chemotherapy	• Response-adapted therapy • Significant decrease in the number of patients receiving radiation therapy
Useful in certain circumstances: AVPC (for mixed cellularity) (AHOD0431)[1]	**Low Risk** • IA, IIA without bulk • For mixed cellularity only	• <CR on imaging after 3 cycles ▸ CR: ≥80% reduction in PPD[c] and FDG-PET negative; only mediastinal nodes >2 cm ▸ PET positive (Deauville 3–5): Uptake greater than mediastinal blood pool	• 80% 4-year EFS • Those with mixed cellularity histology, who had a particularly excellent response (4-year EFS 95.2%) • Limits total doxorubicin dose to 150 mg/m² (less than the 250 mg/m² maximum dose)

[a] FDA has only approved brentuximab vedotin for ages 18+. Refer to clinical trial.
[b] Stage IVA was included in the intermediate risk group in the trial, although not recommended for standard care.
[c] PPD = Transverse x axial plane.
[d] Study is complete and data are emerging.

References

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

PRINCIPLES OF CRITERIA FOR RESPONSE-ADAPTED RADIATION THERAPY
References

[1] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-3219.
[2] 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.
[3] 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.
[4] Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32: 3651-3658.
[5] 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.
[6] 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.
[7] 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.

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 PATHOLOGY

Histologic Classification

- **Diagnosis should be established according to guidelines in the 2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.[1]**
- **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:[a]**
  - **Nodular sclerosis**
  - **Mixed cellularity**
  - **Lymphocyte-rich**
  - **Lymphocyte-depleted**
- **CHL subtyping is not necessary for treatment in the vast majority of cases and may not be possible in all cases.[a] If considering treatment based on the AHOD0431 trial,[2] 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.[b] Fine-needle aspiration (FNA) is discouraged in establishing a diagnosis.[c]**
- **Ample tissue may be necessary to exclude other entities in the differential diagnosis[d] and for specific morphologic subtyping.[e]**
- **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).**

[a] The different morphologic variants of CHL have different clinicopathologic associations and differential diagnoses. Refer to the 2017 WHO Classification for more details.
[b] For example, less accessible anatomic sites such as retroperitoneum.
[c] 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.
[d] 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.
[e] Fibrotic bands completely surrounding nodules are important in distinguishing nodular sclerosis CHL from mixed cellularity CHL but may not be demonstrable in small biopsies.

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 PATHOLOGY

Immunohistochemical Considerations and Ancillary Testing

- Consider clinical differential diagnoses (eg, T lymphoblastic lymphoma) and pathologic differential diagnoses: HL vs. non-Hodgkin lymphoma (NHL),[f] CHL vs. NLPHL, HL vs. infection (cytomegalovirus [CMV], Epstein-Barr virus [EBV]), and HL vs. reactive proliferations.[g]
- 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[h]) may benefit from additional studies, such as EBV serology and evaluation for underlying immunodeficiency.
- Flow cytometry is not helpful in diagnosing HL.[i] 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.[3]
- 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[4,5] and other lymphoma subtypes. For NLPHL cases, consider the possibility of diffuse large B-cell lymphoma transformation from NLPHL[6] or reactive lymph node with progressive transformation of germinal centers.[7]
- 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.

[f] 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.
[g] For example, reactive lymph node with CD30+ immunoblasts (vs. CHL) and progressive transformation of germinal centers (vs. NLPHL).
[h] EBER ISH: Epstein-Barr virus-encoded RNA (EBER) in situ hybridization (ISH).
[i] 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.

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 PATHOLOGY
REFERENCES

[1] 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).

[2] 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.

[3] El-Galaly TC, Gormsen L, Hutchings M. PET/CT for Staging; Past, Present, and Future. Semin Nucl Med 2018;48:4-16.

[4] 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.

[5] 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.

[6] 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.

[7] 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.

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 IMAGING[1-5]

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[a,b] or PET/MRI[c]
  - Whole-body is recommended
  - Diagnostic-quality CT or MRI is still needed for initial staging

Interim and End-of-Therapy
- PET/CT[a,b] or PET/MRI[c]
  - 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[a,b] 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.[a,b]

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

[a] 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.
[b] 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.
[c] If PET/MRI obtained, diagnostic CT of chest is needed.

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 IMAGING
References

[1] 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.

[2] 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.

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

[4] McCarten 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.

[5] Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. Pediatr Radiol. 2019;49(11):1565-1573.

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 STAGING[a]

- **These are only guiding principles of initial staging adapted from criteria of various protocols. This table is not intended to replace protocol specific staging. Refer to applicable study protocol for complete staging details.**
- **While these principles are based on panel consensus, this remains an area of ongoing research.**

Site involvement	Imaging modality[b,c,d]	
Peripheral nodes	PET/CT or PET/MRI	• ≥2 cm is considered involved on CT scan • <2 cm if FDG-PET positive
Splenic	Ultrasound	• Any lesion large enough to characterize unless imaging characteristics indicate an alternative etiology irrespective of the FDG-PET result
	PET/CT or PET/MRI	• Focal PET-positive lesions that are confirmed by CT or MRI or ultrasound • Splenic involvment has to be focal lesions and not diffuse uptake or splenomegaly
Lung[e]	PET/CT	• E-lesions: Extra-lymphatic structures (lung lesions) contiguous with nodal masses are considered to be E-lesions • At least 1–2 small foci (between 5–10 mm) within whole lung if no other etiology is suspected • At least 1 intrapulmonary focus >1 cm on CT if no other etiology is suspected • PET-positive lesions <1 cm if no other etiology is suspected Note: If all lesions are exclusively in 1 lung, then only this particular lung is considered as involved. However, even if there is just one additional smaller focus found within the other lung, then both lungs are considered involved.
Liver	Ultrasound	• Any lesion large enough to characterize unless imaging characteristics indicate an alternative nature irrespective of the FDG-PET result
	PET/CT or PET/MRI	• ≥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 • <1.5 cm on CT, if FDG uptake greater than that of normal liver or spleen parenchyma should be considered positive
Bone marrow	Bilateral biopsy	• Positive by histopathology on previous high-risk trials; current trial recommendations are based on FDG-PET alone • European-based GPOH-HD-2002 staging: Not recommended
	PET/CT or PET/MRI	• ≥3 FDG-PET–positive lesions in bone marrow without cortical bone destruction
Bone	PET/CT or PET/MRI	• FDG-PET–positive lesion with cortical bone destruction on CT or MRI[f]

[a] Clinical interpretation of staging at diagnosis should not be based on reports alone. Treating clinician notes should summarize interpretation of sites of involvement prior to initiation of treatment.
[b] PET should be read by an experienced nuclear diagnostic radiologist experienced in reading Deauville scores for PET-adapted therapy.
[c] There may be PET-avid lesions that need clinical correlation to determine if it is related to lymphoma.
[d] See Principles of Imaging (PHL-C).
[e] There are inconsistencies in staging between protocols and providers. Careful attention to staging of lung involvement is important as it may change the risk group of the patient.
[f] Lewis J et al. Pediatr Blood Cancer 2020;67(4):e28142.

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 STAGING[a]

ASSESSMENT OF BULK DISEASE

Site involvement	US-based protocols	European-based[c]
Peripheral nodes	• Contiguous extramediastinal nodal aggregate >6 cm in the longest transverse diameter (transaxial measurement) or craniocaudal dimension (measured on reformatted CT)	• Volume of the largest contiguous lymph node mass ≥200 ml
Mediastinal mass	• Tumor diameter >1/3 of the maximal thoracic diameter of an upright PA chest radiograph	• Tumor volume ≥200 ml

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

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

With kind permission from Springer International Publishing: Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32(27):3048-3058.

[a] Clinical interpretation of staging at diagnosis should not be based on reports alone. Treating clinician notes should summarize interpretation of sites of involvement prior to initiation of treatment.
[b] 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).
[c] Volume = (a x b x c)/2 where a, b, c are three dimensions of a node or conglomerate

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 SYSTEMIC THERAPY
Primary Systemic Therapy

Primary Systemic Therapy - Recommended Dosing

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

ABVE-PC

Note: cyclophosphamide dosing in AHOD0031 differs from AHOD1331.

- **Intermediate Risk (AHOD-0031)**[2]
  - Doxorubicin[a] 25 mg/m^2 IV days 1 and 2
  - Bleomycin 5 U/m^2 IV day 1, 10 U/m^2 IV day 8
  - Vincristine 1.4 mg/m^2 IV days 1 and 8; 2.8 mg/dose maximum per dose
  - Etoposide 125 mg/m^2 IV daily on days 1–3
  - Prednisone 40 mg/m^2 PO divided into two doses daily on days 1–7
  - Cyclophosphamide 800 mg/m^2 IV on day 1
  - Regimen repeated every 21 days for 4 cycles
- **High Risk (AHOD-1331)**[3,4]
  - Doxorubicin[a] 25 mg/m^2 IV days 1 and 2
  - Bleomycin 5 U/m^2 IV day 1, 10 U/m^2 IV day 8
  - Vincristine 1.4 mg/m^2 IV days 1 and 8; 2.8 mg/dose maximum per dose
  - Etoposide 125 mg/m^2 IV daily on days 1–3
  - Prednisone 40 mg/m^2 PO divided into two doses daily on days 1–7
  - Cyclophosphamide 600 mg/m^2 IV on day 1 and 2
  - Regimen repeated every 21 days for 5 cycles

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

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

[a] 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):djv357; van Dalen EC, et al. Cochrane Database Syst Rev 2011;2011:CD003917.)

References

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

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[b] (in alphabetical order)	Subsequent Therapy Options[d] (in alphabetical order)	Maintenance (post-transplant)
CHL	• Brentuximab vedotin + bendamustine[c,6] • Brentuximab vedotin + gemcitabine[c,7] • Brentuximab vedotin + nivolumab[c,8] • DHAP (dexamethasone, cytarabine, cisplatin) • GV (gemcitabine, vinorelbine)[c] • IEP-ABVD (ifosfamide, etoposide, prednisone; doxorubicin, bleomycin, vinblastine, dacarbazine)[9] • IGEV (ifosfamide, gemcitabine, vinorelbine)[10] • IV (Ifosfamide, vinorelbine)[11]	• Bortezomib, ifosfamide, + vinorelbine[12] • Nivolumab[c,e,13,14] • Pembrolizumab[c,e,f,15,16] • GDP (gemcitabine, dexamethasone, cisplatin)[17] • ICE (ifosfamide, carboplatin, etoposide)[18] • EPIC (etoposide, prednisolone, ifosfamide, cisplatin)[19]	Useful in certain circumstances, for select high-risk[g] patients: • Brentuximab vedotin[h,20]

References

[b] 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.
[c] Should be considered in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed.
[d] Subsequent therapy options include re-induction options that were not previously used.
[e] Emerging data are showing utility as a re-induction option; consider for subsequent therapy if not previously used.
[f] Pembrolizumab is indicated for the treatment of pediatric patients with refractory CHL, or who have relapsed after 2 or more prior lines of therapy.
[g] High-risk: any patient with progressive disease, refractory disease, or relapse within 1 year of original diagnosis.
[h] 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.

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 SYSTEMIC THERAPY
References

[1] Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: a report from the Children's Oncology Group. Cancer 2018;124:3210-3219.
[2] 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.
[3] 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.
[4] 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.
[5] Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28(23):3680-3686.
[6] 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.
[7] 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.
[8] 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.
[9] 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.
[10] 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.
[11] 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.
[12] 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.
[13] 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.
[14] 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.
[15] 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.
[16] Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. Lancet Oncol. 2020;21:121–33.
[17] 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.
[18] 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.
[19] 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.
[20] 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

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

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

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

- **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%[1]
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)[2]
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)[3]
Thyroid	**ALARA**	**V30 <63%**		Hypothyroidism 11.5% if V30 <62.5%, and 70.8% if >62.5%[4]
Salivary Glands (mean)	**ALARA**		**>24 Gy**	Dose threshold for xerostomia in head and neck cancer[5]
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[6]

* ALARA = as low as reasonably achievable

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
REFERENCES

[1] Bates J, Howell RM, Liu Q, et al. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. J Clin Oncol 2019;37(13):1090-1101.

[2] 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.

[3] Dietz AC, Chen Y, Yasui Y, et al. Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Cancer 2016;122(23):3687-3696.

[4] Cella L, Conson M, Caterino M, et al. Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2012;82(5);1802-1808.

[5] Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45(3):577-587.

[6] Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290(4):465-475.

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.

COTSWOLDS-MODIFIED ANN ARBOR STAGING SYSTEM

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

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

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

DISCUSSION
UNDER
DEVELOPMENT