National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 3.2024 — March 18, 2024

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***Richard T. Hoppe, MD/Chair §**
Stanford Cancer Institute

***Ranjana H. Advani, MD/Vice Chair †**
Stanford Cancer Institute

Richard F. Ambinder, MD, PhD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Philippe Armand, MD, PhD ‡
Dana-Farber/Brigham and Women's Cancer Center

Celeste M. Bello, MD, MSPH †
Moffitt Cancer Center

Cecil M. Benitez, MD, PhD ¥ §
UCLA Jonsson Comprehensive Cancer Center

Weina Chen, MD, PhD ≠
UT Southwestern Simmons Comprehensive Cancer Center

Sheen Cherian, MD §
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Bouthaina Dabaja, MD §
The University of Texas MD Anderson Cancer Center

Megan E. Daly, MD §
UC Davis Comprehensive Cancer Center

Zachary Frosch, MD, MSHP ‡
Fox Chase Cancer Center

Kara Kelly, MD €
Roswell Park Comprehensive Cancer Center

Leo I. Gordon, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Neil Hansen, MD ф
Fred & Pamela Buffett Cancer Center

Alex F. Herrera, MD ‡ ξ
City of Hope National Medical Center

Ephraim P. Hochberg, MD †
Mass General Cancer Center

Iris Isufi, MD ‡
Yale Cancer Center/Smilow Cancer Hospital

Patrick B. Johnston, MD, PhD ‡ † Þ
Mayo Clinic Comprehensive Cancer Center

Christopher R. Kelsey, MD §
Duke Cancer Institute

Vaishalee P. Kenkre, MD ‡
University of Wisconsin Carbone Cancer Center

Justin Kline, MD †
The UChicago Medicine Comprehensive Cancer Center

Ryan C. Lynch, MD † ‡
Fred Hutchinson Cancer Center

Kami Maddocks, MD ‡
The Ohio State University Comprehensive Cancer Center- James Cancer Hospital and Solove Research Institute

Jonathan McConathy, MD, PhD ϕ
O'Neal Comprehensive Cancer Center at UAB

Monica Mead, MD †
UCLA Jonsson Comprehensive Cancer Center

David Morgan, MD † ‡ ξ
Vanderbilt-Ingram Cancer Center

Carolyn Mulroney, MD † ‡ ξ
UC San Diego Moores Cancer Center

Alex Niu, MD Þ † ‡
Roswell Park Comprehensive Cancer Center

Rachel Rabinovitch, MD §
University of Colorado Cancer Center

Dahlia Sano, MBChB ‡
University of Michigan Rogel Cancer Center

Harsh Shah, DO ‡
Huntsman Cancer Institute at the University of Utah

Michael Spinner, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Jakub Svoboda, MD †
Abramson Cancer Center at the University of Pennsylvania

Randa Tao, MD §
Huntsman Cancer Institute at the University of Utah

Jane N. Winter, MD ‡ †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Joachim Yahalom, MD §
Memorial Sloan Kettering Cancer Center

Joanna C. Yang, MD, MPH §
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

NCCN
Sarah Montgomery, BA
Katie Stehman, PA-C, MMS

ξ Bone marrow transplantation	ϕ Nuclear medicine
ф Diagnostic radiology	≠ Pathology
‡ Hematology/ Hematology oncology	¥ Patient advocacy
Þ Internal medicine	€ Pediatric oncology
† Medical oncology	§ Radiation oncology
	* Discussion writing committee member

NCCN Guidelines Panel Disclosures

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See the NCCN Guidelines for Pediatric Hodgkin Lymphoma for additional recommendations for pediatric patients (including adolescents and young adults [AYAs]).

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.

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2024 include:

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

Updates in Version 2.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2024 include:

Global Changes
• References updated throughout the guideline.

HODG-6
• Stage III-IV, primary treatment regimen removed from useful in certain circumstances: Escalated BEACOPP (in select patients if international prognostic score [IPS] ≥4)
  ▸ Footnote removed: See International Prognostic Score (IPS) (HODG-3).
• Stage III-IV, primary treatment regimen added under useful in certain circumstances: BrECADD (for ages 18-61)
• Stage III-IV, primary treatment regimen added under useful in certain circumstances: Nivolumab-AVD (category 2B)
  ▸ Footnote w added: In the SWOG S1826 trial, growth factor support was optional. Herrera AF, et al. J Clin Oncol 2023;41:LBA4-LBA4. (Also for HODG-8 and HODG-B 1 of 7)

HODG-8
• New primary treatment option pathway added for CHL Stage III-IV (age 18-60 years): BrECADD (for ages 18-61)
• New primary treatment option pathway added for CHL Stage III-IV (age 18-60 years): Nivolumab + AVD

HODG-B (1 of 7)
• Primary systemic therapy regimen added for CHL (age 18-60 years): BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) +/- ISRT
• Primary systemic therapy regimen added for CHL (age 18-60 years): Nivolumab + AVD
• Primary systemic therapy regimen removed for CHL (age 18-60 years): Escalated BEACOPP
• Primary systemic therapy regimen removed for CHL (age 18-60 years): Escalated BEACOPP followed by ABVD with ISRT
• Footnotes
  ▸ Footnote c added: In times of vinblastine shortage, consider capping the dose at 10 mg to avoid wasting a vial. Consideration can also be made for substituting vinblastine with vincristine 1 mg. In times of both vinblastine and dacarbazine shortage, consideration can be made for substituting ABVD with CHOP temporarily. (Also for HODG-B 2 of 7, HODG-B 3 of 7, and HODG-B 5 of 7)
  ▸ Footnote f added: In times of vinblastine shortage, consideration can be made for substituting BV + AVD with BV-CHP (BV, cyclophosphamide, doxorubicin, prednisone) temporarily.

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Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

Global Changes

- References updated throughout the guidelines
- FDG added to all instances of PET/CT or PET/MRI
- Primary treatment and principles of systemic therapy pages for newly diagnosed classic Hodgkin lymphoma now separated by age given differences in management: 18-60 years and >60 years.
- Footnotes added to all instances of ABVD:
  - Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.
  - Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.

HODG-1

- Diagnosis/Workup
  - Useful in selected cases, bullet 4, link added: (See NCCN Guidelines for Cancer in People with HIV)
- Clinical presentation, NLPHL modified: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) *per WHO 5th edition*

HODG-1A

- Footnote l added: Referred to as nodular lymphocyte predominant B-cell lymphoma (NLPBL) in ICC.

HODG-4

- Additional Therapy
  - Deauville 1–2
    - ◊ Combined modality therapy, first option modified: Involved-site radiation therapy (ISRT) 20 Gy (adapted from GHSG HD16; if ESR <50, no e-lesions, ~~<3~~ ≤2 nodal sites per GHSG favorable criteria) (Also for Deauville 3)
    - ◊ Chemotherapy alone option modified: ABVD x 2 cycles (adapted from H10F, CALGB) ~~(preferred)~~
    - ◊ Chemotherapy alone option removed: ABVD x 1 cycle (adapted from RAPID)
- Footnote t added: Special considerations for Deauville 4–5 after ABVD x 2 cycles

HODG-8

- Footnote v added: All cycles include growth factor support.

HODG-9

- Header modified: MANAGEMENT OF CHL IN ADULTS AGE >60 YEARS *OR ADULTS WITH POOR PERFORMANCE OR SUBSTANTIAL COMORBIDITIES*
- Bullet 4 modified: The regimens listed ~~below~~ *in Principles of Systemic Therapy* should be considered in patients >60 years *or those with poor performance status or substantial comorbidities* to lessen/minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in patients >60 years.

HODG-10

- New page added: Management of CHL During Pregnancy

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

HODG-11
- Primary Treatment
  - Stage IB, IIB, or Stage IA (Bulky)/Stage IIA (Bulky or non-contiguous), primary treatment regimen added: Rituximab
- Footnote cc added: Per WHO 2022, NLPHL remains under the family of Hodgkin Lymphoma, while in the ICC 2022 update, the term NLPHL was replaced with new terminology, nodular lymphocyte predominant B-cell lymphoma (NLPBL). (Alaggio R, et al. Leukemia 2022;36:1720-1748; Campo E, et al. Blood 2022;140:1229-1253).
- Footnote ii added: Rituximab monotherapy can be used for palliation in select cases.

HODG-12
- Follow-up After Completion of Treatment and Monitoring for Late Effects
  - Bullet 1 modified: Complete response *(CR)* should be documented including reversion of FDG-PET/*CT* to "negative" within 3 mo following completion of therapy.
- Follow-up After Completion of Treatment Up to 5 Years
  - Counseling, bullet modified: Reproduction, health habits, psychosocial, cardiovascular, breast ~~self-examination~~ *awareness*, skin cancer risk, end-of-treatment discussion.
  - Imaging
    - ◊ Bullet removed: Consider neck/chest/abdomen/pelvis CT scan with contrast no more often than every 6 mo for the first 2 y following completion of therapy, or as clinically indicated after 2 y, especially in NLPHL where late relapse may occur. FDG-PET/CT only if last FDG-PET was Deauville 4–5, to confirm complete response.
    - ◊ Bullet added: Imaging should only be obtained if significant clinical concern for relapse or as mandated if enrolled in an active protocol.
      - – Sub-bullet added: If imaging is necessary, it may include diagnostic CT at 3- to 6-month intervals for up to 2 years as clinically indicated, or after 2 years if relapse is suspected.
      - – Sub-bullet added: FDG-PET/CT should only be done if last FDG-PET/CT was Deauville 4–5, to confirm CR at the end of all prescribed therapy including RT. Once negative, repeat FDG-PET/CT should not be done unless evaluating suspicious findings on H&P or CT.

HODG-12A
- Bullet 1, sub-bullet 4 modified: For guidance on COVID-19 vaccination, ~~see NCCN COVID-19 Vaccination Guide for People with Cancer.~~ *please see the CDC for Use of COVID-19 Vaccines in the US.*
- Bullet 6 modified: Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast ~~self-examination~~ *awareness*, and skin cancer risk (see NCCN Guidelines for Survivorship).
- Footnote ll added: There is limited data on screening in individuals with increased risk assigned male at birth *(AMAB)*.

HODG-13
- Second-line therapy, pathway added: Clinical trial, if available and Refer to or consult with a center with expertise

HODG-14
- Second-line therapy, positive, pathway added: Clinical trial, if available and Refer to or consult with a center with expertise

HODG-B (1 of 7)
- Footnote c addded: Principles of Radiation Therapy (HODG-C).
- Footnote d added: All cycles include growth factor support.

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Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

HODG-B (2 of 7)

- Header modified: Classic Hodgkin Lymphoma in Adults Age >60 Years *Or Adults With Poor Performance Status Or Substantial Comorbidities*
- Table Header modified: *Primary Systemic Therapy* Regimens (Listed in Alphabetical Order)
  - Stage I–II Unfavorable or Stage III-IV Disease
    - ◊ Regimen modified: ~~Brentuximab vedotin~~ *BV* followed by AVD, conditionally followed by *BV* in ~~responding~~ patients with CR or PR *and no neuropathy*
    - ◊ Regimen removed and added to new category: Brentuximab vedotin + DTIC (dacarbazine)
  - Category added: Patients with Low EF
    - ◊ Regimen added: Add dexrazoxane to ABVD or CHOP, with close cardiology follow-up
    - ◊ Regimen added: BV-DTIC (dacarbazine)

HODG-B (4 of 7)

- Table header added: Adults Age 18–60
  - Second-line and subsequent therapy
    - ◊ Regimen added: Pembrolizumab + ICE
  - Therapy for Disease Refractory to at least 3 Prior Lines of Therapy
    - ◊ Regimen removed: C MOPP (cyclophosphamide, vincristine, procarbazine, prednisone)
    - ◊ Regimen removed: MINE (etoposide, ifosfamide, mesna, mitoxantrone)
    - ◊ Regimen removed: Mini BEAM (carmustine, cytarabine, etoposide, melphalan)
- Table added: Adults Age >60 Years Or Adults With Poor Performance Status or Substantial Comorbidities
  - Palliative therapy option modified: Nivolumab ~~and~~ *or* pembrolizumab
- General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed or Refractory CHL
  - Bullet removed: CPI are recommended for any patients with CHL that has relapsed or progressed after HDT/ASCR ± brentuximab vedotin.
  - Bullet removed: CPI are also an option for patients with relapsed or refractory CHL who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy.
  - Bullet added: Checkpoint inhibitors can be continued despite progression on imaging if patients are deriving clinical benefit, as imaging progression may be indicative of immune flare rather than true progression.

HODG-B (5 of 7)

- Page added to separate Relapsed or Refractory NLPHL Regimens from Relapsed or Refractory CHL Regimens
  - Second-line and subsequent therapy
    - ◊ Regimen added: R (rituximab)

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

HODG-C (1 of 13)

- Bullet 2 modified: Advanced RT technologies such as intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), *deep-inspiratory* breath hold *(DIBH)* or respiratory gating, ~~and/or~~ image-guided RT (IGRT), *and* ~~or~~ proton therapy may offer significant and clinically relevant advantages in specific instances to spare important *normal* OAR*s* ~~such as the heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands~~ and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. ~~For optimal mediastinal treatment planning, organs/tissues to be contoured should include the lungs, heart, coronary arteries, and left ventricle.~~
- Bullet 4 modified: In mediastinal HL, ~~the~~ use of four dimensional (4D)-CT *or DIBH at the time of* ~~for~~ simulation ~~and the adoption of strategies~~ to deal with respiratory motion and minimize dose to OAR*s* ~~are~~ *is* essential.~~, especially deep inspiration breath-hold techniques, respiratory gating, and image-guided RT during treatment delivery. breath-hold techniques have~~ *DIBH, in particular, has* been shown to decrease incidental dose to the heart*,* ~~and~~ lungs*, and other OARs* in many disease presentations. *Further, IGRT during treatment delivery is essential to ensure accurate target localization..."*
- Bullet 5 modified: Although the advantages of ~~these techniques include~~ tightly conformal dose~~s~~ *techniques, such as IMRT, includes* ~~and~~ steep *dose* gradients *between targets and* ~~next to normal tissues~~ *OARs*, the "low-dose bath" to normal structures *is often increased. Particular attention to treatment technique and adherence to dose constraints is essential to minimize dose to high-risk OARs such as breast tissue in young premenopausal* ~~women~~ *individuals.* ~~such as the breasts must be considered in choosing the final RT technique. In any case, t~~ *T*arget definition and ~~delineation and~~ treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, FDG-PET~~, ultrasound~~, and other imaging modalities facilitate target definition. Image guidance may be required to provide assurance of accurate daily delivery.

HODG-C (2 of 13)

- Involved-Site Radiation Therapy (ISRT): Dose
  - Bullet 1, sub-bullet 3 modified: Bulky disease ~~sites~~ (all stages): 30–36 Gy; 1.5–2.0 Gy per fraction
  - Bullet 1, sub-bullet 4 modified: *Partial response/refractory disease* (~~Sites of~~ Deauville 4–5*)* ~~and partial response (PR) to chemotherapy~~: 36–45 Gy
  - Bullet 2 modified: ISRT Alone (uncommon, except *for NLPHL*)
  - Bullet 2, sub-bullet 2 modified: Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT *fields* for NLPHL *generally* include~~s extension to~~ *adjacent but* clinically ~~relevant initially~~ uninvolved nodes *when treated with RT alone.*
- ISRT: Volumes
  - Bullet 1 modified: ISRT *principles should be followed when designing RT fields for HL* ~~is recommended as the appropriate field for HL.~~
  - Bullet 2, sub-bullet 1 modified: The ~~volume~~ *clinical target volume (CTV)* encompasses the original or suspected extent of disease prior to chemotherapy or surgery. *This volume is then modified to account for tumor shrinkage and* ~~However, it~~ spares adjacent uninvolved organs (eg, lungs, bone, muscle, kidney) when lymphadenopathy regresses following chemotherapy.

HODG-C (4 of 13)

- OAR removed: Pericardium
- Heart, dose recommendation modified: Mean <15 Gy (acceptable): *ALARA given increased risk with even lower doses*
- Lungs, dose recommendation modified: Mean dose <13.5 Gy
  V20 <~~30~~ *20% (recommended); <30 Gy (acceptable)* V5 <55%
- Footnote c modified: "As cardiac toxicity is likely related to dose to specific substructures, *and not just mean heart dose,* it is recommended that these are contoured, constraints are applied, and doses are recorded..."

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

HODG-C (5 of 13)
- OAR modified: Kidney~~s~~
  - Sub-section added: Single Organ
  - Sub-section added: Bilateral
    - ◊ Dose recommendation added: V5 <58%

HODG-C (6 of 13)
- OAR added: Colon
  - Dose recommendation added: Minimize volume >10 Gy
  - Secondary Malignancy added: Colon cancer
- OAR added: Lung
  - Dose recommendation added: Minimize volume >9 Gy
  - Secondary Malignancy added: Lung cancer

HODG-C (7 of 13)
- General Principles of RT Dose Constraints
  - Bullet 1 modified: "...Doses to OAR*s* should follow principles of ALARA ~~(as low as reasonably achievable)~~. In some scenarios, target coverage may require dose constraints to be exceeded if the OAR is within*, or adjacent to,* the PTV. *For example, it may be difficult to meet thyroid constraints in the setting of bilateral supraclavicular lymphadenopathy."*
- Heart
  - Bullet 3 modified: "...The risk appears to be linear, without a clear safe threshold dose, with the risk of heart disease increasing by 4.1%–7.4% per 1 Gy of cardiac radiation dose administered. *As such, radiation treatment planning should aim to decrease exposure to cardiac structures following ALARA principles.* One of the best data sets relating radiation dose to cardiac disease risk in adult patients is an HL case-control study from the Netherlands..."

HODG-C (9 of 13)
- Heart (continued)
  - Bullet 3 modified: "...While the data regarding cardiac constraints for modern RT of lymphomas are imperfect, we recommend that the mean heart dose be kept as low as possible, ideally <8 Gy, although in some patients a higher dose will be necessary given lymphoma extent. *Conversely, treatment plans for patients with superior mediastinal disease should achieve doses far less than 8 Gy.* This also recognizes that patients with lymphoma tend to also receive anthracycline chemotherapy, although cumulative chemotherapy doses in modern practice tend to be lower than historical cohorts..."

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2023 include:

HODG-C (10 of 13)

- Lungs
  - Bullet 1 modified: The primary pulmonary toxicity related to mediastinal RT is radiation pneumonitis. Other complications, such as symptomatic fibrosis or ~~bronchopleural fistula~~ *bronchial stenosis*, are rarely encountered given the lower doses used for lymphoma management. Radiation pneumonitis is a clinical diagnosis consisting of dry cough, dyspnea, and occasionally low-grade fevers. Radiation pneumonitis must be distinguished from other entities including infectious pneumonia, acute bronchitis, pulmonary embolism, etc. Pulmonary complications, including pneumonitis, can arise from systemic modalities also, including bleomycin and immunotherapy. *Bleomycin pulmonary toxicity does not preclude consolidation thoracic radiation therapy.*
  - Bullet 3 modified: We recommend limiting MLD <13.5 Gy and V20 <~~30~~*20*%, ~~although dose to the lungs in most patients with lymphoma can be kept below these thresholds.~~ *though higher incidental dose to the lungs may occasionally be necessary. Rarely should the lung V20 exceed 30%.* More pertinent to IMRT or volumetric arc techniques, we recommend limiting the V5 <55%. *DIBH can help meet MLD and V5 recommendations. Adherence to pulmonary constraints is particularly important in patients who have been heavily pre-treated, particularly those who have received regimens with known lung toxicity.*
- Breast
  - Bullet removed: Doses for epithelial breast cancer are significantly greater than doses utilized for lymphomas involving the mediastinum and axilla. As such, dose to the breast would fall well within acceptable dose constraints for breast tissue with regard to toxicity and cosmesis.
  - Bullet removed: Whole breast RT increases the risk of subsequent malignancies within the irradiated tissue. A latency period of >8 years is considered necessary before observation of this phenomenon and routine breast exams 1–2 times per year are indicated after this time frame. Patients should also undergo annual mammography beginning at age 40 or 8 years after RT to the breast, whichever comes first. Patients who received breast radiation between ages 10–30 should undergo screening with both MRI and mammography, often alternated every 6 months. While MRI can begin earlier, mammography should not be pursued until the patient is at least 30 years of age.
  - Bullet added: RT doses prescribed for thoracic lymphomas are significantly lower than doses utilized for epithelial breast cancer. As such, breast tissue exposure resulting from lymphoma RT falls well within acceptable dose constraints for breast tissue toxicity and cosmesis.
  - Bullet added: Breast tissue radiation exposure results in an increased lifetime risk for secondary malignancies. A minimum latency period of 8 years is considered necessary before radiation induced cancers develop. After this latency period, routine breast exams 1–2 times per year are indicated. Individuals AFAB previously treated with thoracic RT between ages 10 and 30 should begin annual screening mammography and MRI (typically alternating every 6 months) 8 years after undergoing treatment (but not before age 25) or by age 40, whichever comes first.
  - Footnote f added: There is limited data on screening in individuals with increased risk AMAB.

ST-1

- Footnote 2 modified: FDG-PET scans are useful for upstaging in stage I–II disease. If there is FDG-PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. ~~FDG-PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.~~ *FDG-PET scans may demonstrate increased avidity in lymphoid tissue unrelated to lymphoma in persons with HIV, particularly if HIV is not well-controlled (i.e. acute/subacute HIV infection, advanced immunosuppression and or viremia) and in the presence of opportunistic infections.*

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DIAGNOSIS/WORKUP

Excisional biopsy (recommended)
Core needle biopsy may be adequate if diagnostic[a]
Immunohistochemistry evaluation[b]

Essential:
- History & Physical (H&P) including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, and examination of lymphoid regions, spleen, and liver
- Complete blood count (CBC), differential
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for those of childbearing potential prior to cytotoxic chemotherapy or radiation therapy (RT)
- FDG-PET/CT scan (skull base to mid-thigh or vertex to feet in selected cases)[c]
- Counseling: Fertility/psychosocial[d] and smoking cessation (See NCCN Guidelines for Smoking Cessation)

Useful in selected cases:
- Fertility preservation[d,e]
- Pulmonary function tests ([PFTs] including diffusing capacity of the lung for carbon monixide [DLCO])[f] if ABVD[g,h] or escalated BEACOPP are being used
- Pneumococcal, Haemophilus influenzae (H-flu), meningococcal vaccines, if splenic RT contemplated
- Human immunodeficiency virus (HIV) and hepatitis B/C testing (encouraged) (See NCCN Guidelines for Cancer in People with HIV)
- Diagnostic CT[i] (contrast-enhanced)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- Adequate bone marrow biopsy if there are unexplained cytopenias other than anemia (eg, thrombocytopenia or neutropenia) and negative FDG-PET[j]
- Evaluation of ejection fraction (EF) if anthracycline-based chemotherapy is indicated
- MRI of select sites, with contrast unless contraindicated
- FDG-PET/MRI (skull base to mid-thigh) without contrast

CLINICAL PRESENTATION

Classic Hodgkin lymphoma (CHL)[k] → See HODG-2

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) per WHO 5th edition[l] → See HODG-11

Footnotes on HODG-1A

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.

FOOTNOTES

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

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

[c] See Principles of FDG-PET/CT (HODG-A).

[d] See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology for more details on fertility/fertility preservation and psychosocial assessments in AYA patients.

[e] Fertility preservation options include: semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

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

[g] Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.

[h] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.

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

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

[k] 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.

[l] Referred to as nodular lymphocyte predominant B-cell lymphoma (NLPBL) in ICC. See HODG-11.

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.

STAGING/RISK CLASSIFICATION OF CHL[m]

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

- **Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).**
- **Most patients will benefit from multidisciplinary input prior to final treatment decisions**
- **See HODG-9 for the Management of CHL in Adults Age >60 Years or Adults with Poor Performance Status or Substantial Comorbidities**
- **See HODG-10 for the Management of CHL During Pregnancy**

[m] For definitions of bulky disease and lymph node regions, see HODG-3.

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.

UNFAVORABLE RISK FACTORS

Unfavorable Risk Factors for Stage I–II Hodgkin Lymphoma

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

GHSG = German Hodgkin Study Group
EORTC = European Organization for Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5–6

International Prognostic Score (IPS) 1 point per factor (advanced disease)†

- **Albumin <4 g/dL**
- **Hemoglobin <10.5 g/dL**
- **Male**
- **Age ≥45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count ≥15,000/mm³)**
- **Lymphocytopenia (lymphocyte count <8% of white blood cell count, and/or lymphocyte count <600/mm³)**

†From: Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339:1506-1514. Copyright © 1998 Massachusetts Medical Society. Adapted with permission.

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

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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.

Continued

UNFAVORABLE RISK FACTORS

Definitions of Lymph Node Regions*

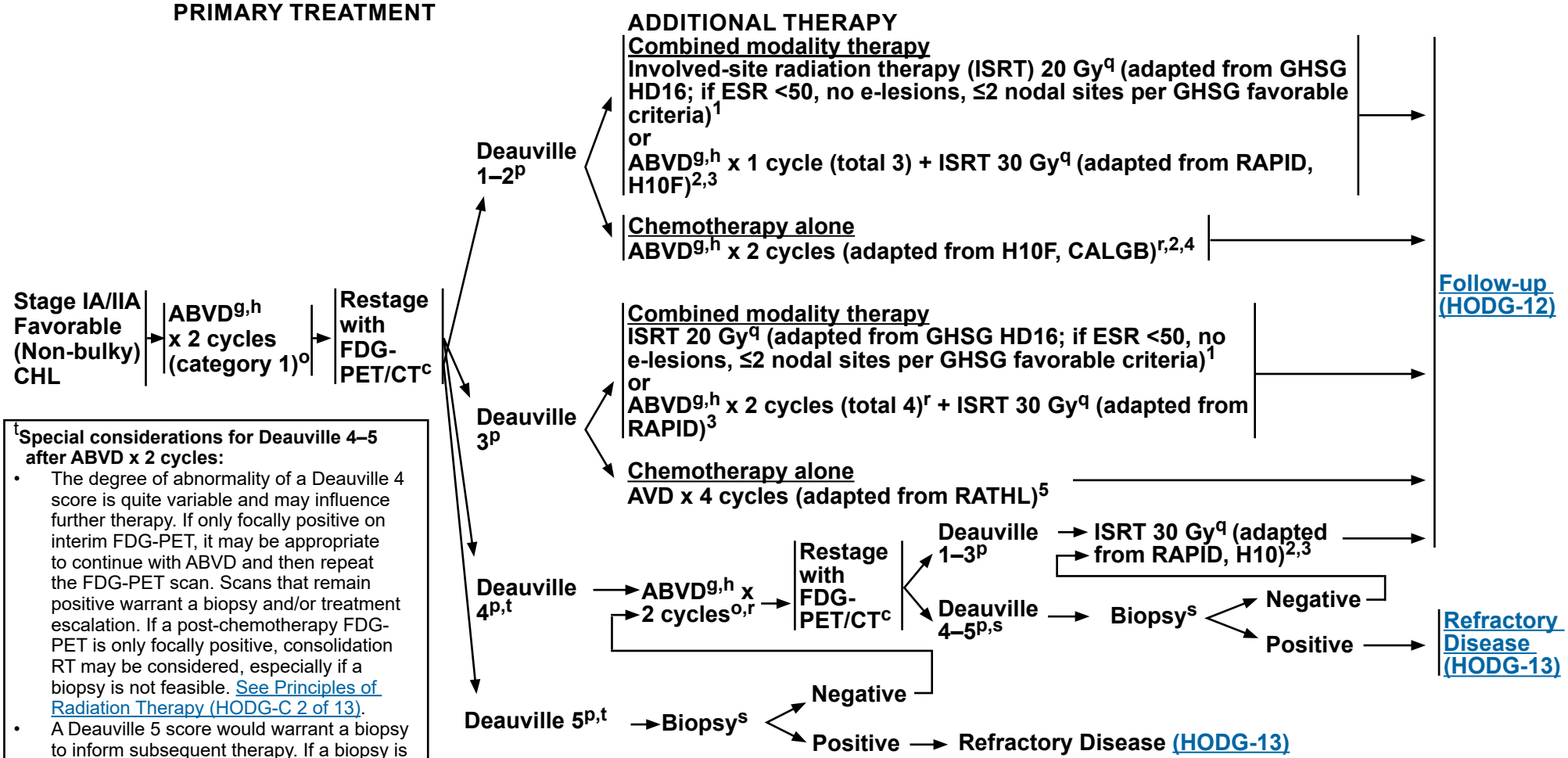
		Ann Arbor	EORTC	GHSG
Supradiaphragmatic Nodal Regions	R Cervical/Supraclavicular			
	R ICL/Subpectoral			
	R Axilla			
	L Cervical/Supraclavicular			
	L Infraclavicular/Subpectoral			
	L Axilla			
	Mediastinum			
	R Hilum			
	L Hilum			
Infradiaphragmatic Nodal Regions	Celiac/Spleen hilar			
	Paraortic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

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

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: Stage IA/IIA Favorable (Non-Bulky)[n]

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- In general, treatment with combined modality therapy provides for a better progression free survival (PFS)/freedom from progression (FFP), but no difference in overall survival.
- Most patients will benefit from multidisciplinary team input prior to final treatment decisions.



[t]**Special considerations for Deauville 4–5 after ABVD x 2 cycles:**
- The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy. If only focally positive on interim FDG-PET, it may be appropriate to continue with ABVD and then repeat the FDG-PET scan. Scans that remain positive warrant a biopsy and/or treatment escalation. If a post-chemotherapy FDG-PET is only focally positive, consolidation RT may be considered, especially if a biopsy is not feasible. See Principles of Radiation Therapy (HODG-C 2 of 13).
- A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.

For footnotes, see HODG-4A

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.

For references 1–5, see HODG-8A

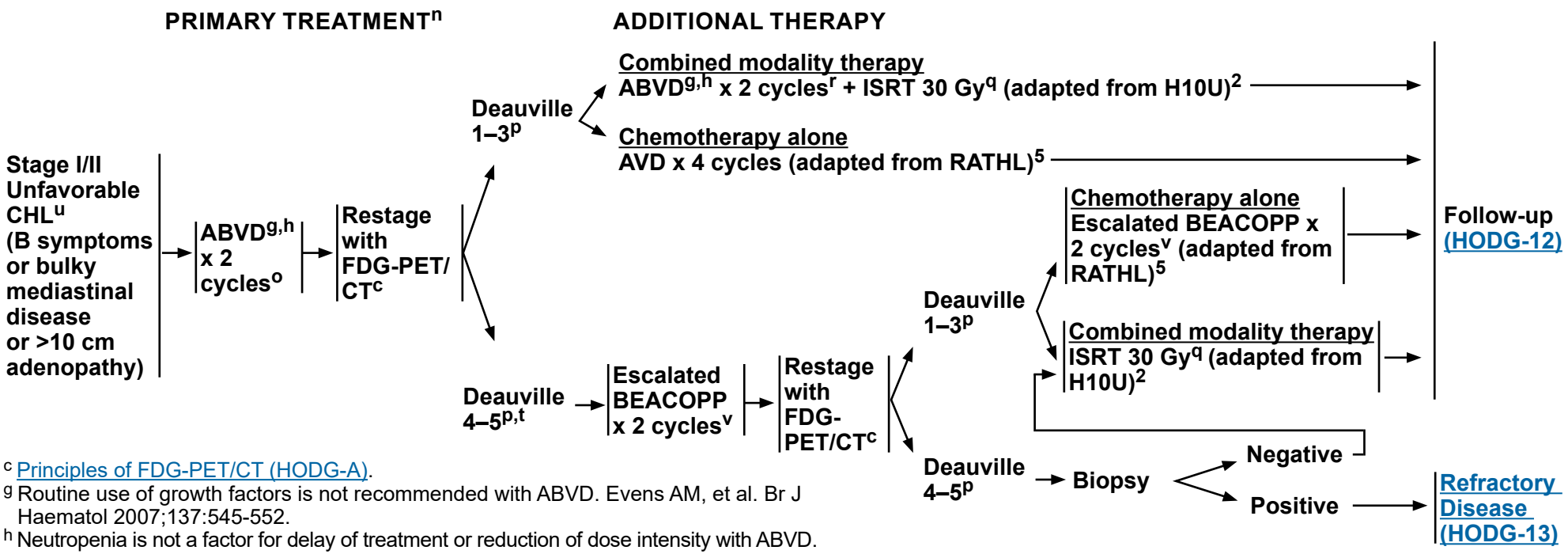
FOOTNOTES

[c] Principles of FDG-PET/CT (HODG-A).
[g] Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.
[h] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[n] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults Age >60 Years or Adults with Poor Performance Status or Substantial Comorbidities (HODG-9).
[o] Principles of Systemic Therapy (HODG-B 1 of 7).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[q] Principles of Radiation Therapy (HODG-C).
[r] Consider PFTs after 4 cycles of ABVD.
[s] A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.

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: Stage I/II Unfavorable (B symptoms or bulky mediastinal disease or >10 cm adenopathy)[n]

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- In general, treatment with combined modality therapy provides for a better PFS/FFP, but no difference in overall survival.
- Most patients will benefit from multidisciplinary team input prior to final treatment decisions.



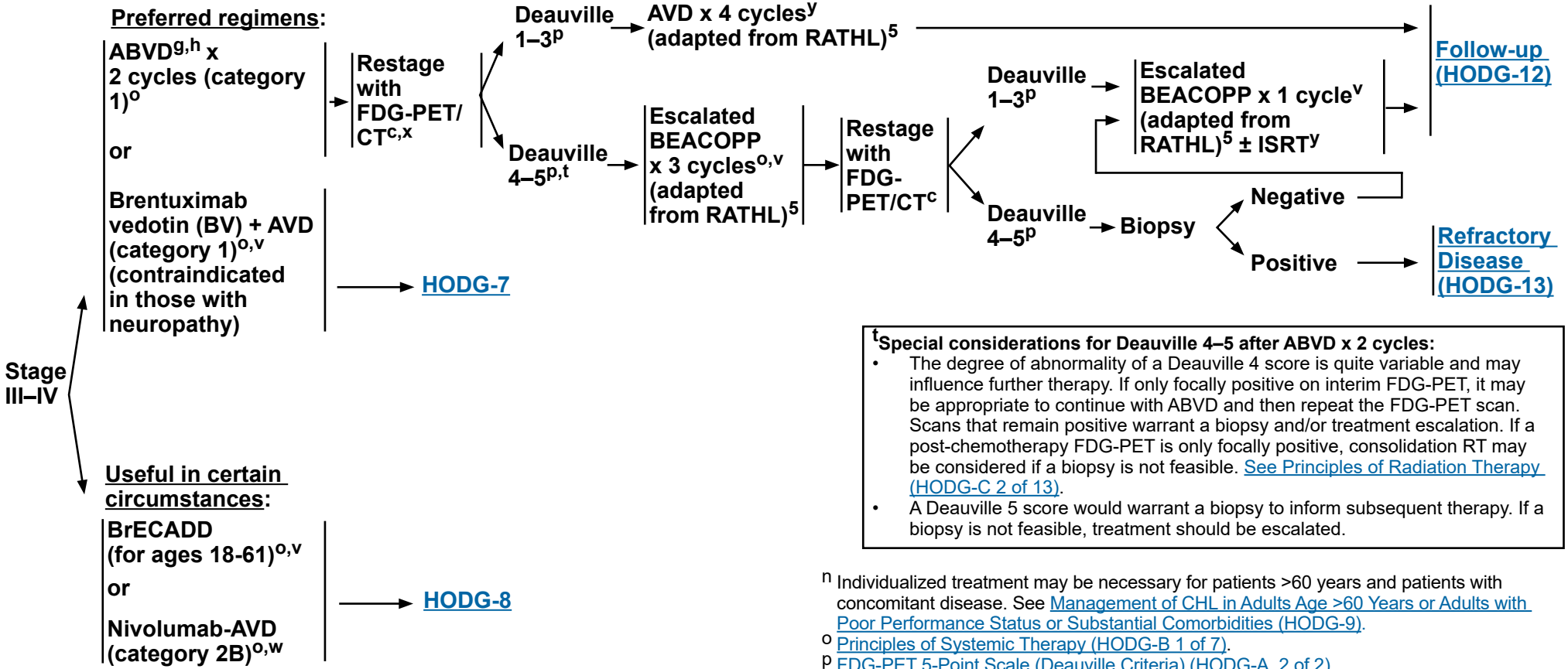
[c] Principles of FDG-PET/CT (HODG-A).
[g] Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.
[h] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[n] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults >60 Years or Adults with Poor Performance Status or Substantial Comorbidities (HODG-9).
[o] Principles of Systemic Therapy (HODG-B 1 of 7).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[q] Principles of Radiation Therapy (HODG-C).
[r] Consider PFTs after 4 cycles of ABVD.
[u] NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (HODG-3).
[v] All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.

[t] Special considerations for Deauville 4–5 after ABVD x 2 cycles:
- The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy. If only focally positive on interim FDG-PET, it may be appropriate to continue with ABVD and then repeat the FDG-PET scan. Scans that remain positive warrant a biopsy and/or treatment escalation. If a post-chemotherapy FDG-PET is only focally positive, consolidation RT may be considered if a biopsy is not feasible. See Principles of Radiation Therapy (HODG-C 2 of 13).
- A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.

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.

For references 2 and 5 see HODG-8A

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage III–IV[n]
PRIMARY TREATMENT[n]



[t] **Special considerations for Deauville 4–5 after ABVD x 2 cycles:**
- The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy. If only focally positive on interim FDG-PET, it may be appropriate to continue with ABVD and then repeat the FDG-PET scan. Scans that remain positive warrant a biopsy and/or treatment escalation. If a post-chemotherapy FDG-PET is only focally positive, consolidation RT may be considered if a biopsy is not feasible. See Principles of Radiation Therapy (HODG-C 2 of 13).
- A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.

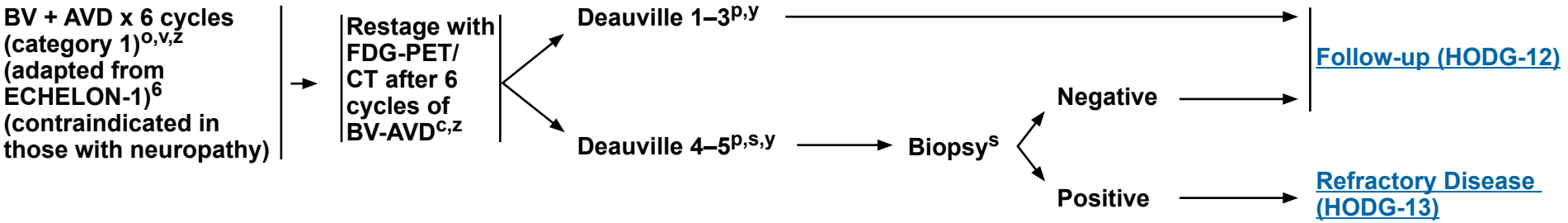
[c] Principles of FDG-PET/CT (HODG-A).
[g] Routine use of growth factors is not recommended with ABVD. Evens AM, et al. Br J Haematol 2007;137:545-552.
[h] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[n] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults Age >60 Years or Adults with Poor Performance Status or Substantial Comorbidities (HODG-9).
[o] Principles of Systemic Therapy (HODG-B 1 of 7).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[v] All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[w] In the SWOG S1826 trial, growth factor support was optional. Herrera AF, et al. J Clin Oncol 2023;41:LBA4-LBA4.
[x] The value of interim FDG-PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[y] Consider ISRT to initially bulky or FDG-PET–positive sites. See Principles of Radiation Therapy (HODG-C).

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.

For reference 5, see HODG-8A

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage III–IV[n]

PRIMARY TREATMENT[n]
(continued from HODG-6)



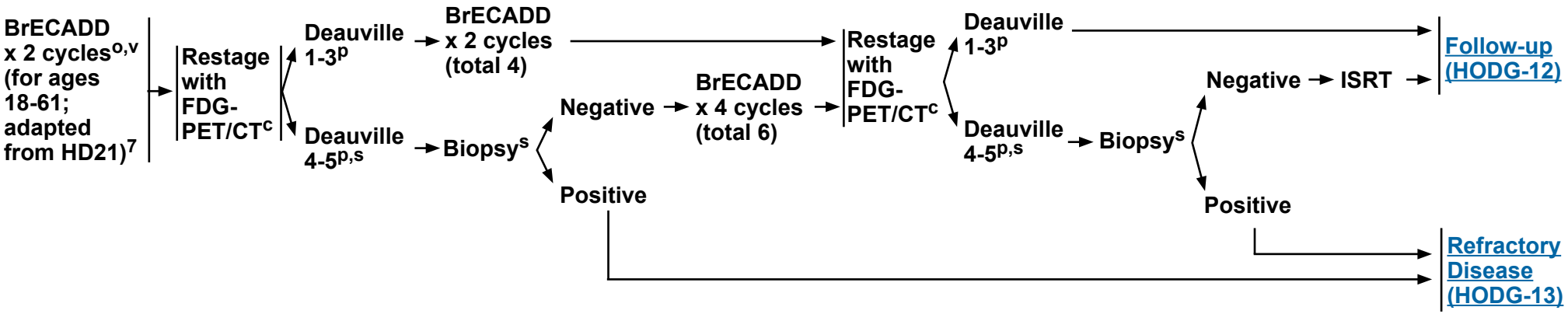
[c] Principles of FDG-PET/CT (HODG-A).
[n] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults Age >60 Years or Adults with Poor Performance Status or Substantial Comorbidities (HODG-9).
[o] Principles of Systemic Therapy (HODG-B 1 of 7).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[s] A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.
[v] All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[y] Consider ISRT to initially bulky or FDG-PET–positive sites. See Principles of Radiation Therapy (HODG-C).
[z] An interim FDG-PET/CT after 2 cycles may be helpful in further defining therapy. If performing an interim FDG-PET/CT before completion of 6 cycles, and FDG-PET is positive (Deauville 5), conduct a biopsy; if biopsy positive, change therapy.

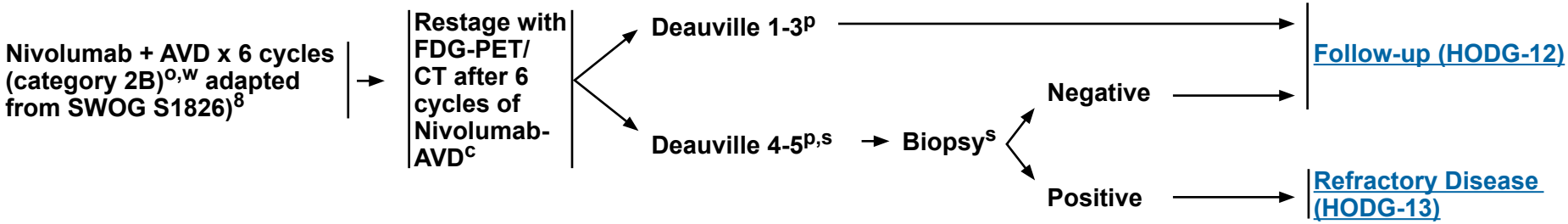
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

For reference 6, see HODG-8A

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage III–IV[n]

PRIMARY TREATMENT[n]
(continued from HODG-6)





[c] Principles of FDG-PET/CT (HODG-A).
[n] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults Age >60 Years or Adults with Poor Performance Status or Substantial Comorbidities (HODG-9).
[o] Principles of Systemic Therapy (HODG-B 1 of 7).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[s] A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.
[v] All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[w] In the SWOG S1826 trial, growth factor support was optional. Herrera AF, et al. J Clin Oncol 2023;41:LBA4-LBA4.

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For references 7 and 8, see HODG-8A

CLASSIC HODGKIN LYMPHOMA IN ADULTS AGE 18–60 YEARS
PRIMARY TREATMENT REFERENCES

[1] GHSG H16: Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 2019;37:2835-2845.
[2] EORTC/LYSA/FIL H10: André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017;35:1786-1794.
[3] RAPID study: Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598-1607.
[4] CALGB 50604: Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood 2018;132:1013-1021.
[5] RATHL study: Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med 2016;374:2419-2429.
[6] ECHELON-1: Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Eng J Med 2022;387:310-320.
[7] Borchmann P, Moccia AA, Greil R, et al. BreECADD Is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin Lymphoma: Efficacy results of the GHSG Phase III HD21 trial. Hematological Oncology 2023;41:881-882.
[8] Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). Journal of Clinical Oncology 2023;41:LBA4-LBA4.

Note: All recommendations are category 2A unless otherwise indicated.
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MANAGEMENT OF CHL IN ADULTS AGE >60 YEARS OR ADULTS WITH POOR PERFORMANCE STATUS OR SUBSTANTIAL COMORBIDITIES

- **CHL in patients who are older is associated with poorer disease outcomes.[1] B symptoms, poor performance status, mixed cellularity, histologic subtype, EBV+ disease, and medical comorbidities are more frequent in this population.[2]**
- **Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and treatment-related mortality in patients who are older.[3-6]**
- **There are limited prospective data evaluating alternatives to standard therapies for patients >60 years. Selection of standard versus alternate first-line therapy for a patient >60 years should be based on clinical judgment, with the goal of minimizing toxicity while maximizing efficacy.**
- **The regimens listed in Principles of Systemic Therapy (HODG-B 2 of 7) should be considered in patients >60 years or those with poor performance status or substantial comorbidities to lessen/minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in patients >60 years.**
- **Clinical trial is recommended when available.**
- **ISRT alone is an option when systemic therapy is not considered feasible or safe.**

[1] Jagadeesh D, Diefenbach C, Evens AM. XII. Hodgkin lymphoma in older patients: challenges and opportunities to improve outcomes. Hematol Oncol 2013;31 Suppl 1:69-75.
[2] Evens AM, Sweetenham JW, Horning SJ. Hodgkin lymphoma in older patients: an uncommon disease in need of study. Oncology (Williston Park) 2008;22:1369-1379.
[3] Ballova V, Rüffer JU, Haverkamp H, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). Ann Oncol 2005;16:124-131.
[4] Halbsguth TV, Nogová L, Mueller H, et al. Phase 2 study of BACOPP (bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in older patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). Blood 2010;116:2026-2032.
[5] Böll B, Görgen H, Fuchs M, et al. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 trials. J Clin Oncol 2013;31:1522-1529.
[6] Evens AM, Hong F, Gordon LI, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol 2013;161:76-86.

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.

MANAGEMENT OF CHL DURING PREGNANCY

General Principles

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

SUGGESTED TREATMENT APPROACH BY GESTATIONAL AGE AND SYMPTOMATIC DISEASE BURDEN

First Trimester

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

Second or Third Trimester

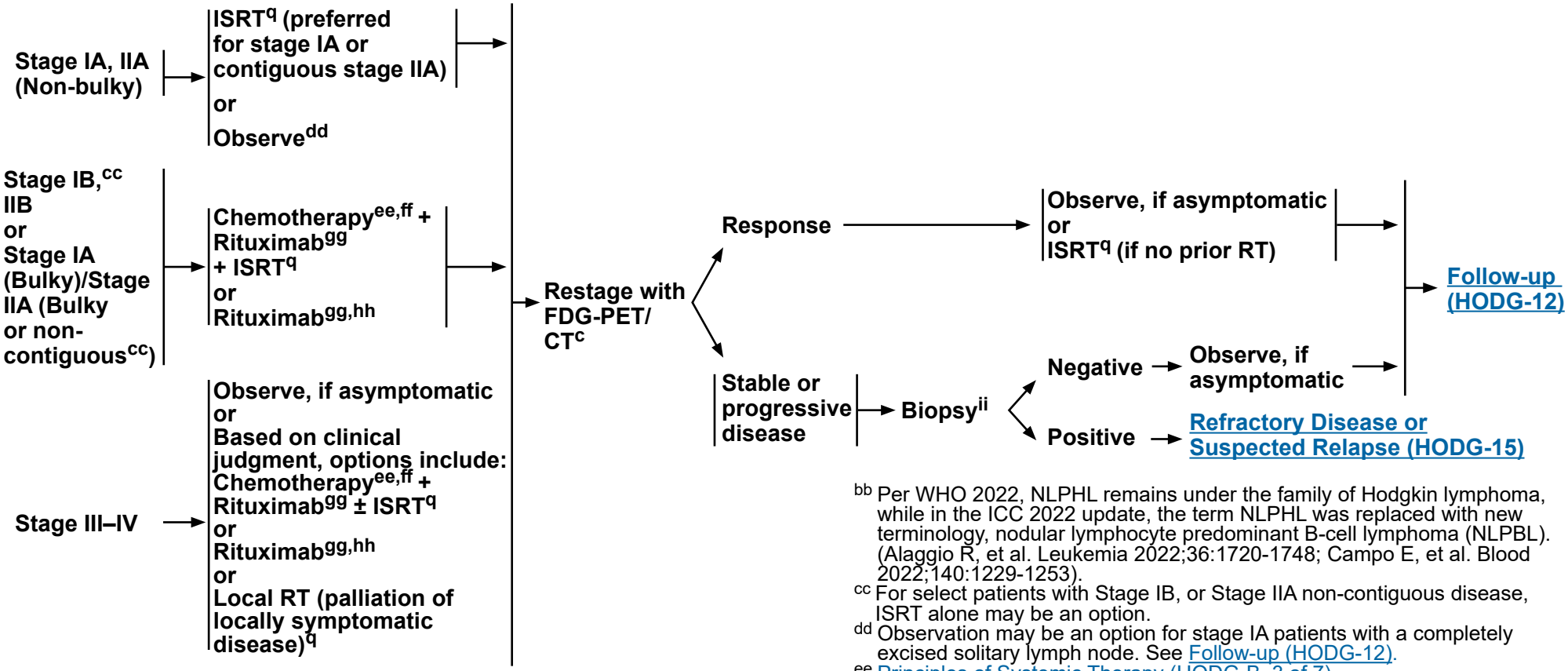
- **If asymptomatic or minimally symptomatic: delay treatment with close observation until after delivery**
- **If severe symptoms or organ compromise: treat with ABVD; work with high-risk obstetrics to avoid delivery while at nadir**

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

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:
Nodular Lymphocyte Predominant Hodgkin Lymphoma[aa,bb]

PRIMARY TREATMENT



[c] Principles of FDG-PET/CT (HODG-A).
[q] Principles of Radiation Therapy (HODG-C).
[aa] NLPHL has a different natural history and response to therapy than CHL, especially stages I–II. For that reason, separate guidelines are presented for NLPHL. Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma. Data suggest outcomes differ for typical immunoarchitectural patterns (A/B) versus variant patterns (C/D/E/F). (Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2017).
[bb] Per WHO 2022, NLPHL remains under the family of Hodgkin lymphoma, while in the ICC 2022 update, the term NLPHL was replaced with new terminology, nodular lymphocyte predominant B-cell lymphoma (NLPBL). (Alaggio R, et al. Leukemia 2022;36:1720-1748; Campo E, et al. Blood 2022;140:1229-1253).
[cc] For select patients with Stage IB, or Stage IIA non-contiguous disease, ISRT alone may be an option.
[dd] Observation may be an option for stage IA patients with a completely excised solitary lymph node. See Follow-up (HODG-12).
[ee] Principles of Systemic Therapy (HODG-B, 3 of 7).
[ff] Generally, a brief course of chemotherapy (2–4 mo) would be given with RT.
[gg] An FDA-approved biosimilar is an acceptable substitute for rituximab. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[hh] Rituximab monotherapy can be used for palliation in select cases.
[ii] Biopsy is recommended for sites of progressive disease, especially subdiaphragmatic sites, to rule out transformation.

Note: All recommendations are category 2A unless otherwise indicated.
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FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

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

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

[1] Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol Suppl 2005;(66):68-76.
[2] Lynch RC, Sundaram V, Desai M, et al. Utility of routine surveillance laboratory testing in detecting relapse in patients with classic Hodgkin lymphoma in first remission: Results from a large single-institution study. JCO Oncol Pract 2020;16:e902-e911.
[jj] Appropriate medical management should be instituted for any abnormalities.

Suspected Relapse CHL (HODG-14) or NLPHL (HODG-15)
Follow-Up and Monitoring After 5 Years (HODG-12A)

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

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

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

[jj] Appropriate medical management should be instituted for any abnormalities.
[kk] There is limited data on screening in individuals with increased risk assigned male at birth (AMAB).

[1] Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation-Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol Suppl 2005;(66):68-76.

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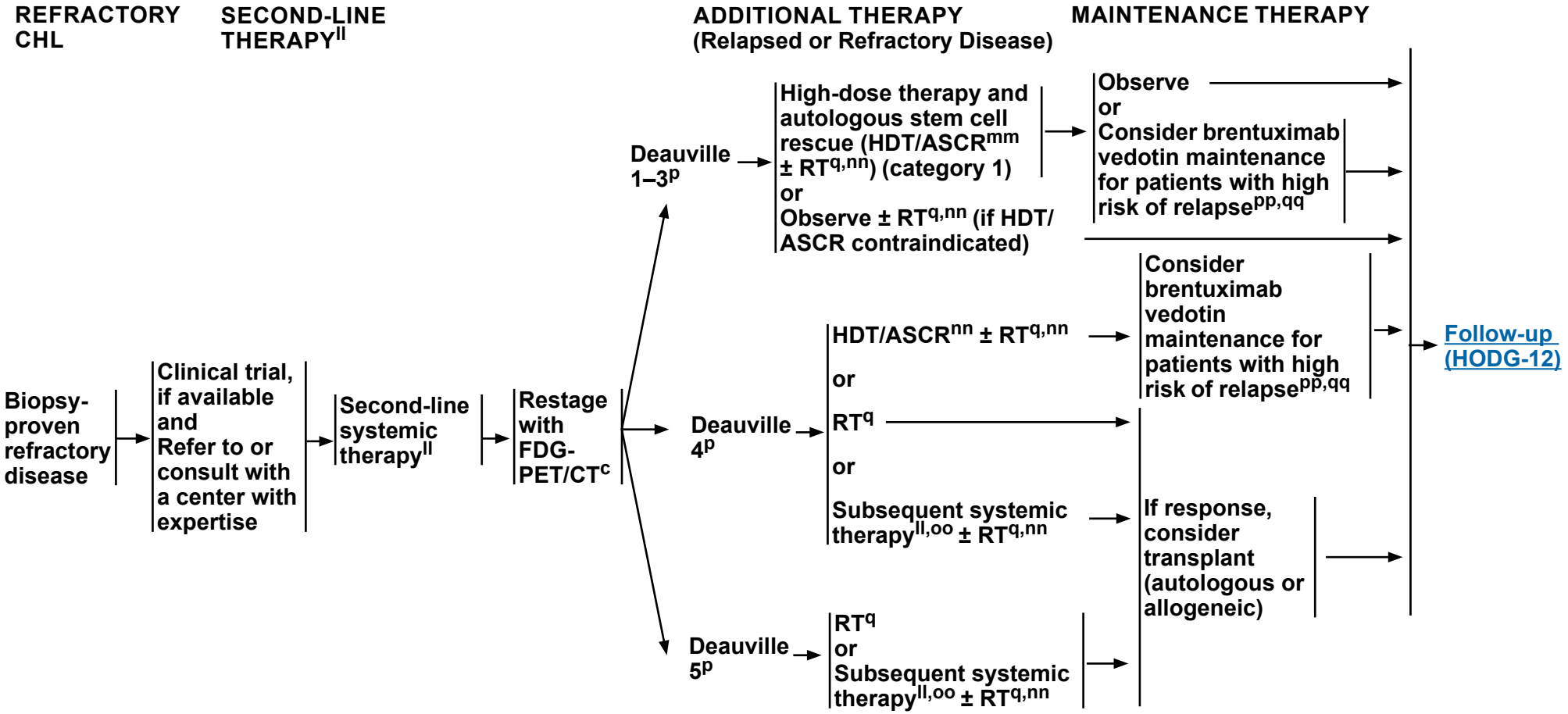
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] Principles of FDG-PET/CT (HODG-A).
[p] FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[q] Principles of Radiation Therapy (HODG-C).
[ll] Principles of Systemic Therapy for Relapsed or Refractory Disease: CHL (HODG-B, 4 of 7).
[mm] Strongly consider RT for selected sites that have not been previously irradiated. In patients without prior history of RT, total lymphoid irradiation (TLI) may be an appropriate component of HDT.
[nn] Conventional-dose chemotherapy may precede HDT. Timing of RT may vary.
[oo] Subsequent systemic therapy options include second-line therapy options that were not previously used (HODG-B, 4 of 7).
[pp] Patients with 2 or more of the following risk factors are considered to be at high risk: Remission duration <1 year, extranodal involvement, FDG-PET–positive response at time of transplant, B symptoms, and/or >1 second-line/subsequent therapy regimen. AETHERA Trial: Moskowitz CH, et al. Blood 2018;132:2639-2642.
[qq] The role of maintenance brentuximab vedotin has not been well-defined in patients who received brentuximab vedotin prior to maintenance therapy.

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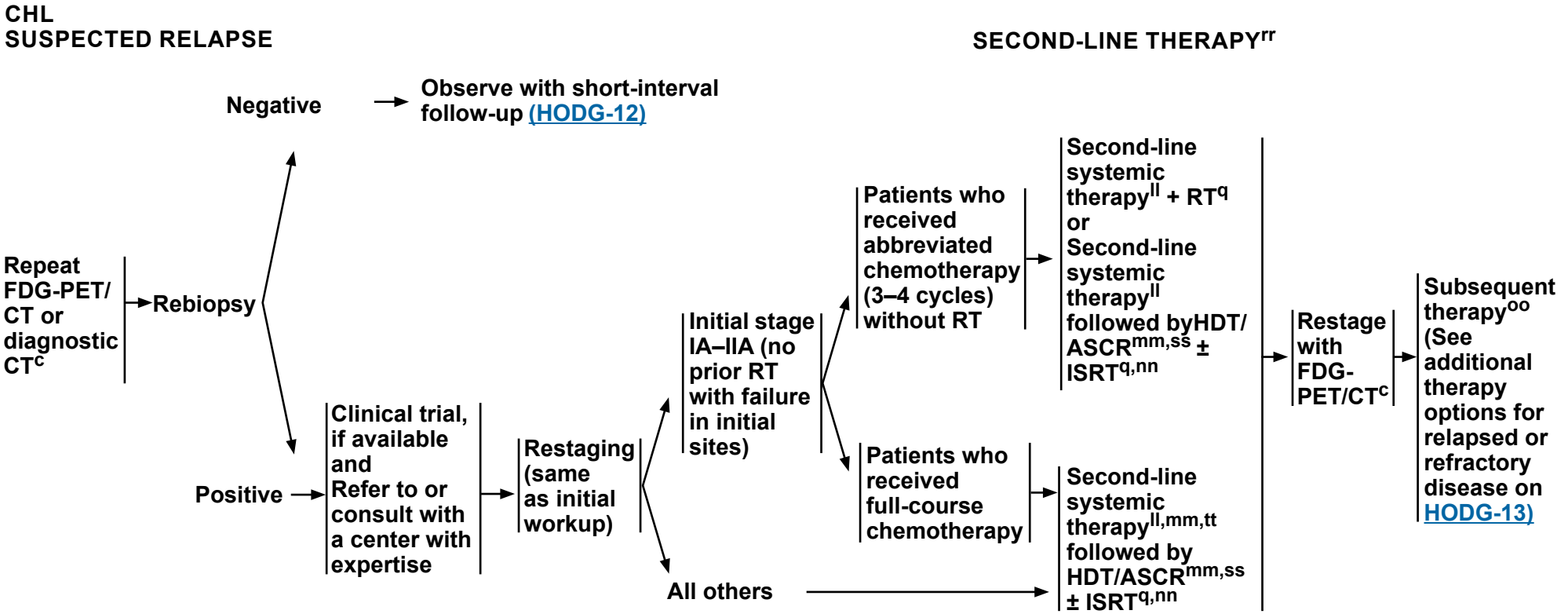

[c] Principles of FDG-PET/CT (HODG-A).
[q] Principles of Radiation Therapy (HODG-C).
[ll] Principles of Systemic Therapy for Relapsed or Refractory Disease: CHL (HODG-B, 4 of 7).
[mm] Strongly consider RT for selected sites that have not been previously irradiated. In patients without prior history of RT, TLI may be an appropriate component of HDT.
[nn] Conventional-dose chemotherapy may precede HDT. Timing of RT may vary.
[oo] Subsequent systemic therapy options include second-line therapy options that were not previously used (HODG-B, 4 of 7).
[rr] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[ss] Allogeneic hematopoietic cell transplantation (HCT) is an option in select patients as a category 3 recommendation.
[tt] For select patients with long disease-free interval and other favorable features, selection of chemotherapy should be individualized.

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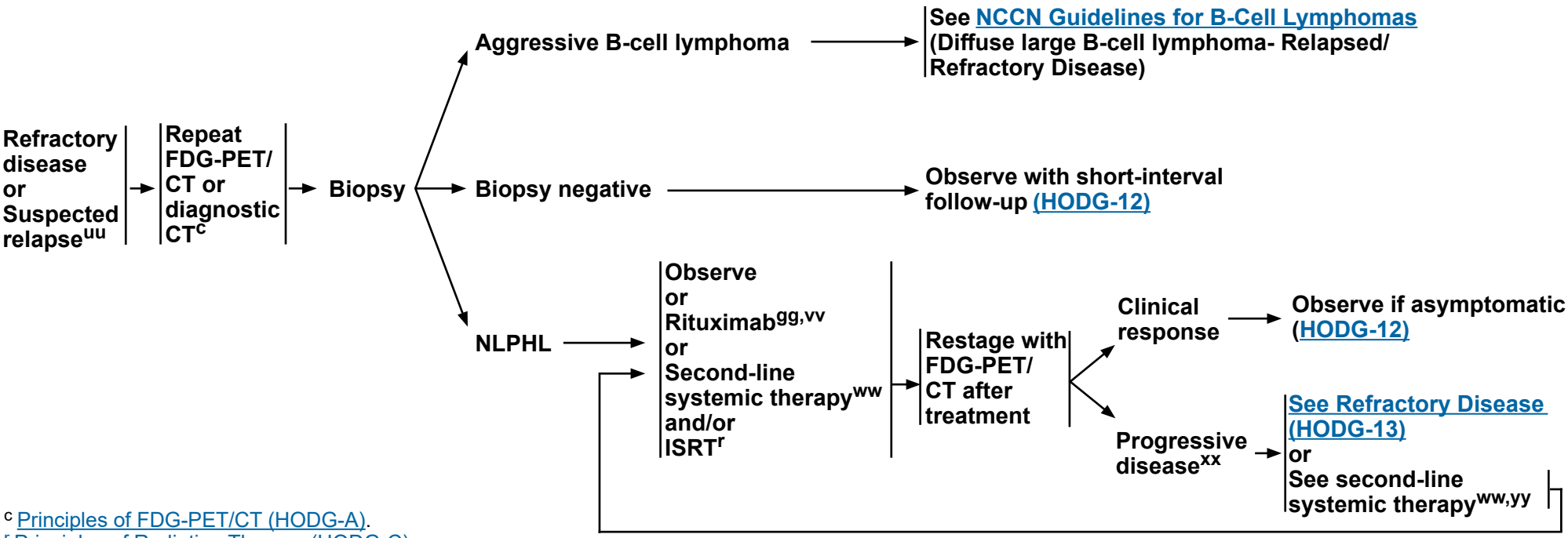
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NLPHL
REFRACTORY OR SUSPECTED RELAPSE **SECOND-LINE THERAPY[rr]**



[c] Principles of FDG-PET/CT (HODG-A).
[r] Principles of Radiation Therapy (HODG-C).
[gg] An FDA-approved biosimilar is an acceptable substitute for rituximab. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[rr] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[uu] At relapse, rebiopsy should be considered because of risk for transformation, especially if intra-abdominal or splenic disease. Some patients with NLPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed.
[vv] In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years (Schulz H, et al. Blood 2008;111:109-111; Advani RH, et al. J Clin Oncol 2014;32:912-918).
[ww] See Principles of Systemic Therapy for Relapsed or Refractory Disease: NLPHL (HODG-B, 5 of 7).
[xx] Consider rebiopsy to rule out transformation.
[yy] Subsequent systemic therapy options include second-line therapy options that were not previously used (See HODG-B, 5 of 7).

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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 FDG-PET/CT

Technique

- An integrated FDG-PET/CT or an FDG-PET with a diagnostic CT is recommended for initial diagnosis and restaging.
- For FDG-PET/CT performed in the staging or response assessment in Hodgkin lymphoma (HL), image acquisition should be obtained in accordance with the American College of Radiology (ACR) practice parameter guidelines[1] or the Society of Nuclear Medicine and Molecular Imaging (SNMMI), which adopted the European Association of Nuclear Medicine (EANM) procedure guidelines for tumor imaging: version 2.0 (with the exception that the "standardized uptake value (SUV) max" is used in the United States as the quantitative measurement).[2]
  - FDG-PET/CT should be performed with the patient on a flat table with arms up, if possible. In cases of FDG-PET positivity where disease sites are inconsistent with usual presentation of HL or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required for staging. See (ST-1).
- FDG-PET/CT scans obtained outside of these parameters (eg, in outdated mobile tomographs) can result in both false-negative and false-positive tests, and lead to inappropriate disease management. In these cases, consideration should be made for repeating the study on an acceptable FDG-PET/CT tomograph.

Timing

- Initial staging of FDG-PET/CT for patients with lymphoma should be obtained no longer than 1 month prior to the initiation of therapy.
- The initial study should include a contrast-enhanced diagnostic CT if it is expected that RT may be a component of initial treatment.

Interpretation

- The panel supports the ACR[1] and SNMMI[2] recommendation for FDG-PET/CT interpretation, including the requirement that FDG-PET/CT examinations should be performed under the supervision of and interpreted by a physician with the following qualifications:
  - Board certification in radiology or diagnostic radiology, nuclear radiology, or nuclear medicine
    OR
  - Completion of a formal Accreditation Council for Graduate Medical Education (ACGME)-approved general nuclear medicine program in addition to 1000 hours of clinical training in general nuclear medicine, 20 hours of continuing medical education (CME) in FDG-PET, and at least 150 oncologic FDG-PET/CT examinations interpreted or multi-read during the previous 3 years.[1]
- Continuing experience/education should include interpretation of a minimum of 150 FDG-PET/CT examinations in 3 years (multi-read is acceptable) and completion of 150 hours (including 75 hours of Category 1 CME) during the preceding 3 years pertinent to the physician's practice patterns, including FDG-PET imaging.[1]
- The interpreting radiology or nuclear medicine physician should have adequate training and CME/experience in interpreting FDG-PET/CT for patients with lymphoma, including use of the Deauville 5-point scoring system.
- The final report for any FDG-PET/CT examination to define response should include the Deauville 5-point scale score, which is a visual score.
- A second opinion/overread is encouraged of scans that are not initially interpreted by qualified individuals, when there is a discrepancy between the clinical presentation and radiology report, and/or when no appropriate Deauville score has been provided.

[1] American College of Radiology. ACR-SPR Practice Parameters for Performing FDG-PET/CT in Oncology. 2016. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/FDG-PET-CT.pdf?la=en. Accessed November 19, 2021.
[2] Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42:328-354.

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PET 5-POINT SCALE (DEAUVILLE CRITERIA)

Score		PET/CT Scan Result
Negative	1	No uptake
	2	Uptake ≤ mediastinum
	3	Uptake > mediastinum but ≤ liver
Positive	4	Uptake moderately higher than liver and visually above adjacent background activity
	5	Uptake markedly higher than liver and/or new lesions
	X[a]	New areas of uptake unlikely to be related to lymphoma

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

[a] Watchful waiting, biopsy, or additional imaging tests may be appropriate depending on clinical circumstances. Obtaining a second opinion/overread of the imaging may be beneficial.

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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens

Classic Hodgkin Lymphoma in Adults 18–60 Years

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

[a] Routine use of growth factors is not recommended with ABVD. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552.
[b] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[c] In times of vinblastine shortage, consider capping the dose at 10 mg to avoid wasting a vial. Consideration can also be made for substituting vinblastine with vincristine 1 mg. In times of both vinblastine and dacarbazine shortage, consideration can be made for substituting ABVD with CHOP temporarily.
[d] Principles of Radiation Therapy (HODG-C).
[e] All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[f] In times of vinblastine shortage, consideration can be made for substituting BV + AVD with BV-CHP (BV, cyclophosphamide, doxorubicin, prednisone) temporarily.
[g] In the SWOG S1826 trial, growth factor support was optional. Herrera AF, et al. J Clin Oncol 2023;41:LBA4-LBA4.

[1] Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 2019;37:2835-2845.
[2] Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598-1607.
[3] André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017;35:1786-1794.
[4] Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010;28:4199-4206.
[5] Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood 2018;132:1013-1021.
[6] Borchmann P, Moccia AA, Greil R, et al. BreECADD Is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin Lymphoma: Efficacy results of the GHSG Phase III HD21 trial. Hematological Oncology 2023;41:881-882.
[7] Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Eng J Med 2022;387:310-320.
[8] Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). Journal of Clinical Oncology 2023;41:LBA4-LBA4.

See Principles of Systemic Therapy for Relapsed or Refractory CHL (HODG-B, 4 of 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.

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens

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

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
Stage I–II Favorable Disease	• A(B)VD[a,b,c,h] (2 cycles) ± AVD (2 cycles) + ISRT[d] (preferred)[9,10,11] • CHOP (4 cycles) + ISRT[c,12]
Stage I–II Unfavorable or Stage III–IV Disease	• A(B)VD[a,b,c,h] (2 cycles) followed by AVD (4 cycles),[i] if FDG-PET scan is negative after 2 cycles of ABVD.[13] ▸ Patients with a positive FDG-PET scan after 2 cycles of ABVD need individualized treatment. • BV followed by AVD, conditionally followed by BV in patients with CR or PR and no neuropathy[14] • CHOP (6 cycles) ± ISRT[d,12]
Patients with Low EF	• Add dexrazoxane to ABVD[a,b,c] or CHOP, with close cardiology follow-up • BV-DTIC (dacarbazine)[15,16]

[a] Routine use of growth factors is not recommended with ABVD. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552.
[b] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[c] In times of vinblastine shortage, consider capping the dose at 10 mg to avoid wasting a vial. Consideration can also be made for substituting vinblastine with vincristine 1 mg. In times of both vinblastine and dacarbazine shortage, consideration can be made for substituting ABVD with CHOP temporarily.
[d] Principles of Radiation Therapy (HODG-C).
[h] Bleomycin should be used with caution as it may not be tolerated in patients >60 years, and it should not be used beyond 2 cycles.
[i] If stage I–II is unfavorable, consider a total of 4 cycles.

9 Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 2019;37:2835-2845.
10 Stamatoullas A, Brice P, Bouabdallah R, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. Br J Haematol 2015;170:179-184.
11 Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. Lancet 2015;385:1418-1427.
12 Kolstad A, Nome O, Delabie J, et al. Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. Leuk Lymphoma 2007;48:570-576.
13 Johnson P, Federico M, Fossa A, et al. Response-adapted therapy based on interim FDG-PET scans in advanced Hodgkin lymphoma: first analysis of the safety of de-escalation and efficacy of escalation in the international RATHL study (CRUK/07/033) [abstract]. Hematol Oncol 2015;33 (Suppl S1):Abstract 008.
14 Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. J Clin Oncol 2018;36:3015-3022.
15 Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL. Blood 2017;130:2829-2837.
16 Friedberg JW, Forero-Torres A, Holkova B, et al. Long-term follow-up of brentuximab vedotin ± dacarbazine as first line therapy in elderly patients with Hodgkin lymphoma [abstract]. J Clin Oncol 2018;36 (Suppl 15):Abstract 7542.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens

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

Primary Systemic Therapy Regimens (listed in alphabetical order)
• ABVD[a,b,c] (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab[k,17,18]
• CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab[k,19,20]
• CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab[k,21]
• Rituximab[k,22,23,24,25,26,27]

[a] Routine use of growth factors is not recommended with ABVD. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552.
[b] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[c] In times of vinblastine shortage, consider capping the dose at 10 mg to avoid wasting a vial. Consideration can also be made for substituting vinblastine with vincristine 1 mg. In times of both vinblastine and dacarbazine shortage, consideration can be made for substituting ABVD with CHOP temporarily.
[j] Ongoing clinical trials will help to clarify the role of a watch-and-wait strategy or systemic therapy, including anthracycline (epirubicin or doxorubicin), bleomycin, and vinblastine-based chemotherapy or antibody-based approaches, in the treatment of these patients.
[k] An FDA-approved biosimilar is an acceptable substitute for rituximab. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.

17 Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood 2011;118:4585-4590.
18 Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's lymphoma? J Clin Oncol 2010;28:e8.
19 Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood 2017;130:472-477.
20 Binkley MS, Advani, RH. SOHO State of the Art Updates and Next Questions |Treatment Approaches for Nodular Lymphocyte-Predominant Hodgkin Lymphoma. Clin Lymphoma Myeloma Leuk 2023;23:471-476.
21 Shankar A, Hall GW, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma - an Anglo-French collaborative report. Eur J Cancer 2012;48:1700-1706.
22 Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. Blood 2013;122:4182-4188.
23 Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. J Clin Oncol 2014;32:912-918.
24 Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 2011;118:4363-4365.
25 Eichenauer DA, Plütschow A, Fuchs M, et al. Long-term course of patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma: A report from the German Hodgkin Study Group. J Clin Oncol 2015;33:2857-2862.
26 Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol 2017;4:e272-e282.
27 Lugtenburg P, Avivi I, Berenschot H, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. Haematologica 2017;102:1913-1922.

See Principles of Systemic Therapy for Relapsed or Refractory NLPHL (HODG-B, 5 of 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.

PRINCIPLES OF SYSTEMIC THERAPY
Relapsed or Refractory Disease

Classic Hodgkin Lymphoma

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

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

Adults Age >60 Years or Adults With Poor Performance Status or Substantial Comorbidities

• Outcomes are uniformly poor for patients with relapsed or refractory disease.[26]
• No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended.
• Individualized treatment is necessary. Palliative therapy options include:
  ▸ Bendamustine
  ▸ BV
  ▸ ISRT[d]
  ▸ Nivolumab or pembrolizumab

General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed or Refractory CHL[27,28]

- Post-allogeneic HCT, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic HCT. If a CPI is used, the HCT regimen will need to be carefully considered.
- Checkpoint inhibitors can be continued despite progression on imaging if patients are deriving clinical benefit, as imaging progression may be indicative of immune flare rather than true progression.[29]

[d] Principles of Radiation Therapy (HODG-C).
[l] Choice depends on prior therapies and prior toxicities. There are no preferred second-line or subsequent therapy options.
[m] Subsequent systemic therapy options include second-line therapy options that were not previously used.

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References

PRINCIPLES OF SYSTEMIC THERAPY
Relapsed or Refractory Disease

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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

Relapsed or Refractory NLPHL	
Second-Line and Subsequent Therapy[l,m] (in alphabetical order)	

• R (rituximab)[k]
• R[k] + bendamustine[30]
• R[k] + DHAP[4,5]
• R[k] + ICE[5,10]
• R[k] + IGEV[13]
	• If not previously used[31]:
	  ▸ R[k] + ABVD[a,b,c]
	  ▸ R[k] + CHOP
	  ▸ R[k] + CVbP

[a] Routine use of growth factors is not recommended with ABVD. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552.
[b] Neutropenia is not a factor for delay of treatment or reduction of dose intensity with ABVD.
[c] In times of vinblastine shortage, consider capping the dose at 10 mg to avoid wasting a vial. Consideration can also be made for substituting vinblastine with vincristine 1 mg. In times of both vinblastine and dacarbazine shortage, consideration can be made for substituting ABVD with CHOP temporarily.
[k] An FDA-approved biosimilar is an acceptable substitute for rituximab. Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[l] Choice depends on prior therapies and prior toxicities. There are no preferred second-line or subsequent therapy options.
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References

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE
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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE
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PRINCIPLES OF RADIATION THERAPY

General Principles

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced RT technologies such as intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT),[1-3] deep-inspiratory breath hold (DIBH) or respiratory gating,[4,5] image-guided RT (IGRT),[5] and proton therapy[6-8] may offer significant and clinically relevant advantages in specific instances to spare important normal OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.
- The demonstration of significant dose-sparing for OARs reflect best clinical practice as it reduces the risk of late complications from normal tissue damage. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- In mediastinal HL, use of four dimensional (4D)-CT or DIBH at the time of simulation to deal with respiratory motion and minimize dose to OARs is essential. DIBH, in particular, has been shown to decrease incidental dose to the heart, lungs, and other OARs in many disease presentations.[5] Further, IGRT during treatment delivery is essential to ensure accurate target localization. In certain circumstances, the use of protons for mediastinal lymphoma provides dosimetric advantages that may reduce long-term toxicity. The potential advantage of protons is related to the localization of disease within the mediastinum as well as patient gender assigned at birth and age.[9-11]
- Although the advantages of tightly conformal dose techniques, such as IMRT, includes steep dose gradients between targets and OARs, the "low-dose bath" to normal structures is often increased. Particular attention to treatment technique and adherence to dose constraints is essential to minimize dose to high-risk OARs such as breast tissue in young premenopausal individuals. Target definition and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, FDG-PET, and other imaging modalities facilitate target definition. Image guidance may be required to provide assurance of accurate daily delivery.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to develop. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

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PRINCIPLES OF RADIATION THERAPY

Involved-Site Radiation Therapy (ISRT): Dose

- Combined Modality Therapy (CMT)
  - Non-bulky disease (stage I–II): 20[a]–30 Gy (if treated with ABVD); 1.5–2.0 Gy per fraction
  - Non-bulky disease (stage IB & IIB): 30 Gy; 1.5–2.0 Gy per fraction
  - Bulky disease (all stages): 30–36 Gy; 1.5–2.0 Gy per fraction
  - Partial response/refractory disease (Deauville 4–5): 36–45 Gy
- ISRT Alone (uncommon, except for NLPHL)
  - Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5–2.0 Gy per fraction
  - Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT fields for NLPHL generally include adjacent but clinically uninvolved nodes when treated with RT alone.
- Palliative RT: 4–30 Gy

ISRT: Volumes

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

[a] A dose of 20 Gy following ABVD x 2 is sufficient if the patient has non-bulky stage I–IIA disease with an ESR <50, no extralymphatic lesions, and only 1 or 2 lymph node regions involved. See HODG-3 for definition of nodal sites according to GHSG.

References

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

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

[b] General Principles of RT Dose Constraints, see HODG-C (7 of 13).

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

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

[b] General Principles of RT Dose Constraints, see HODG-C (7 of 13).

[c] As cardiac toxicity is likely related to dose to specific substructures, and not just mean heart dose,[32] it is recommended that these are contoured, constraints are applied, and doses are recorded. Contouring atlases are available.[33,34] It is recognized that contouring the coronary arteries is challenging given anatomical variations and lung/heart motion. This may warrant designing a planning OAR volume in some patients. Further, it is important to preferentially spare high-dose overlap with the proximal coronary arteries (left main, proximal LAD). For example, a plan may achieve an LAD V15 Gy <10%, but it is not ideal if most of the 15 Gy or higher dose overlap is surrounding the proximal LAD while the distal LAD is spared to meet the volumetric dose goal. Reviewing both dose to the entire coronary tree and the individual components, particularly the proximal vessels, is important.

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

OAR		Dose Recommendation (1.5–2 Gy/fraction)		Toxicity
Abdomen	Liver	Mean <15 Gy V20 <30% V30 <20%		Hepatic toxicity[35,36]
	Stomach	Dmax <45 Gy		Ulceration[37]
	Spleen	Mean <10 Gy V5 ≤30% V15 ≤20%		Late infections[38] Lymphopenia[39]
	Pancreas	Minimize volume >36 Gy (especially to pancreatic tail)		Diabetes[40]
	Small bowel	V15 <120 cc Dmax <45 Gy		Diarrhea[37] Obstruction, ulceration, fistula[37]
	Kidney	Single organ Mean <8 Gy V10 <30% V20 <15% (recommended); <25% (acceptable)	Bilateral V5 <58%	Renal insufficiency[41-43]
Other	Bone marrow[d]	V5: ALARA V10 <50% V25 <25%		Acute cytopenias[44,45] Chronic cytopenias[46]
	Long bone	V40 <64%		Fracture[47]

[b] General Principles of RT Dose Constraints, see HODG-C (7 of 13).
[d] Active bone marrow can be delineated using various imaging modalities and is most abundant in the pelvic bones, thoracic-lumbar spine, and sacrum.[48-50]

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PRINCIPLES OF RADIATION THERAPY
RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

SECONDARY MALIGNANCIES[e]

OAR	Dose Recommendation (1.8–2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy (ideally <10%)	Breast cancer (adenocarcinoma)[51]
Colon	Minimize volume >10 Gy	Colon cancer[52]
Lung	Minimize volume >9 Gy	Lung cancer[53]
Esophagus	Minimize volume >30 Gy	Esophageal cancer[54]
Stomach	Minimize volume >25 Gy	Gastric cancer[55]
Pancreas	Minimize volume >5–10 Gy	Pancreatic cancer[56]

[b] General Principles of RT Dose Constraints, see HODG-C (7 of 13).
[e] The linear no-threshold model supports limiting RT dose to susceptible organs as low as reasonably achievable. The following dose guidelines, based on published data, may further guide treatment decisions.

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

General Principles of RT Dose Constraints

- Patients with hematologic malignancies typically receive far lower doses than patients with epithelial or mesenchymal malignancies and generally have more favorable long-term outcomes. Therefore, more stringent dose constraints, often proportionally reduced from acceptable thresholds in other malignancies, are recommended. Doses to OARs should follow principles of ALARA. In some scenarios, target coverage may require dose constraints to be exceeded if the OAR is within, or adjacent to, the PTV. For example, it may be difficult to meet thyroid constraints in the setting of bilateral supraclavicular lymphadenopathy.
- A relatively rare but serious complication of RT is induction of secondary malignancies. Most studies have shown that increasing dose is associated with increasing risk without a safe threshold dose (linear no-threshold model).[57] Therefore, limiting radiation dose to susceptible organs as much as possible is vital. Disease- and patient-related factors are also contributory (eg, age, tobacco exposure).
- In addition to secondary malignancies, cardiac and pulmonary complications after RT are most concerning and are reviewed further in the following sections.

Heart

- Multiple cardiac complications can develop from mediastinal RT, including pericarditis, arrhythmias, coronary artery disease (CAD), valvular heart disease (VHD), and cardiomyopathy/congestive heart failure.[24,58] In addition to RT factors, the risk of cardiac events is also influenced by chemotherapy administration (eg, doxorubicin), pre-existing cardiovascular disease, age, and other cardiac risk factors (eg, diabetes, hypertension, hyperlipidemia).[24,32,59,60] While global heart metrics such as mean heart dose are most commonly used to assess risk, there is an increasing recognition that radiation dose-fractionation to cardiac substructures must be accounted for. Atlases for radiation oncologists to assist with contouring cardiac substructures are available.[33,34,61]
- Because of the long-term survival of thousands of patients with breast cancer and HL, many large cohort studies have been able to explore the relationship of heart RT dose with cardiac toxicity and death. Mediastinal RT for lymphomas, relative to breast cancer and other thoracic malignancies, is characterized by radiation exposures to larger volumes of the heart and substructures, albeit to lower doses (20–40 Gy). Common for both breast and lymphoma RT, there is typically a latency of >20 years for secondary cardiac disease.[24,62-64]
- As mentioned previously, most studies have associated cardiac events with either prescribed mediastinal radiation dose or mean heart dose. In both the breast cancer and lymphoma radiotherapy literature, mean heart dose has been related to the risk of cardiac events despite the variable volume of whole heart exposed in these two diseases. The risk appears to be linear, without a clear safe threshold dose, with the risk of heart disease increasing by 4.1%–7.4% per 1 Gy of cardiac radiation dose administered.[24,62-64] As such, radiation treatment planning should aim to decrease exposure to cardiac structures following ALARA principles. One of the best data sets relating radiation dose to cardiac disease risk in adult patients is an HL case-control study from the Netherlands.[24] Patients were treated prior to 1996 mainly using anteroposterior (AP)/PA fields. Using the metric of mean heart dose as a measure of cardiac toxicity risk, Van Nimwegen et al demonstrated an excess relative risk of 7.4% per Gy mean heart dose. A statistically significant increased risk of coronary heart disease was demonstrated among patients getting a mean heart dose as low as 5–14 Gy (relative risk [RR], 2.31) compared with a mean heart dose of 0 Gy. This risk was even higher for a mean heart dose of 15 Gy or higher (RR, 2.83 for 15–19 Gy; RR, 2.9 for 20–24 Gy; and RR, 3.35 for 25–34 Gy). This study also explored different age-of-diagnosis cohorts and generally showed the same radiation dose-response relationships.

References

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Heart (continued)

- The number of studies evaluating specific dose constraints for cardiac substructures is rather limited. Dutch investigators demonstrated a relationship between heart failure and mean dose to the left ventricle.[27] Chemotherapy was a clear confounder in regards to the risk of heart failure. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean left ventricle dose <15 Gy, 15.9% for 16–20 Gy, and 32.9% for ≥21 Gy.
- In regards to VHD, increasing mediastinal radiation dose, especially >30 Gy, has been associated with an elevated risk of valvular dysfunction.[24,63] Using a large Dutch cohort of adult patients treated with radiation to the mediastinum, Cutter et al demonstrated 30-year cumulative risks of VHD of 3%, 6.4%, 9.3%, and 12.4% for mean valvular doses of <30, 31–35, 36–40, and >40 Gy.[25] VHD was related to aortic valve abnormalities in 71% of patients. Mitral valvular abnormalities, which can also be related to ischemic heart disease due to papillary muscle dysfunction after myocardial infarction, occurred in 50% of patients (some patients had multiple dysfunctional valves). Tricuspid valvular disease was uncommon and pulmonic valve dysfunction was not reported—perhaps due to right heart dysfunction tending to be less clinically problematic. There was no confounding effect of anthracycline chemotherapy on VHD risk in this study. In agreement with this Dutch study, the previously mentioned German-Austrian pediatric cohort showed that prescribed mediastinal radiation dose was the only independent risk factor for VHD.[26] No cases of VHD were observed for individuals with doses of 20 Gy, while the 25-year cumulative risks among individuals with prescribed doses of 25 Gy, 30 Gy, and 36 Gy were 2%, 1%, and 16%, respectively.
- Radiation dose constraints for coronary arteries is a work in progress. Standard CT-simulation imaging, even with contrast, does not identify the entire coronary tree very well. There are resolution issues, acquisition time issues, and cardiac motion issues. Coronary anatomy is variable along with some individual variation with collateral blood flow. Proximal coronary arteries and the mid-trunk of the LAD are often visible, since the latter is located in the epicardial fat of the left anterolateral aspect of the global heart structure, apparently with minimal motion artifact. Even with research techniques to merge coronary CT angiograms,[65,66] the important branch vessels (diagonals off the LAD; obtuse marginals off the LCx, posterior descending branch of the RCA are not well demonstrated. Nevertheless, there have been studies in breast and lymphoma radiotherapeutic management to contour the major coronary arteries and try to relate coronary dosimetry to risk of CAD. Moignier et al analyzed 33 irradiated patients with HL—21 without coronary stenosis (controls) and 12 patients with critical coronary stenosis (cases) seen on CT angiography.[66] Radiation dose to stenotic coronary segments and normal coronary segments was compared using a logistic regression. In this manner, the risk of stenosis was found to be increased by 4.9% per Gy over the median dose to the control segments. This data set is too small to be a basis of radiation dose constraints, but does support the general notion of a dose-response effect in the clinical range of lymphoma radiation prescriptions. Another study by Hahn et al used a sample of 125 patients with HL treated with mediastinal RT and analyzed various dosimetry parameters of whole heart and coronary segments, looking for a relationship to cardiac events.[67] Multivariable competing risk regression models found that when any adverse cardiac event was the outcome, models using coronary artery variables did not perform better than models using whole heart variables. However, in a subanalysis of ischemic cardiac events only, the model using coronary artery variables was superior to the whole heart. Major findings for this study were that the V5 Gy for the LAD and the V20 Gy for the LCx had predictive value when looking at ischemic endpoints such as need for coronary revascularization, myocardial infarction, or cardiac death. The modeling analysis was not robust enough to yield specific guidance on dose constraints to specific coronary arteries.

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Heart (continued)

- From the historical use of extended-field radiotherapy for HL, whole heart irradiation increases the risk of constrictive pericarditis, especially with doses >15 Gy[68]. Modern radiotherapy for lymphomas rarely requires whole heart irradiation.
- Patients who survived childhood cancers represent a unique high-risk group. In a French cohort study of pediatric survivors with HL, the relative risk of severe cardiac disease at age 40 y is 1.9 at a cardiac radiation dose of 1–5 Gy and increases to 19.5–75.2 at a dose >15 Gy for survivors of childhood cancer.[21] There are at least two other notable pediatric survivorship study cohorts that provide insights to radiation dose relationship with subsequent cardiovascular disease. Schellong et al reported on 1132 survivors of HL treated on the German-Austrian pediatric cooperative group studies from 1978–1995.[26] Patients could be binned into mediastinal radiation dose exposures of 36 Gy, 30 Gy, 25 Gy, 20 Gy, and 0 Gy. Cardiac valvular defects were the most frequent late cardiac disease, followed by CAD, cardiomyopathy, conduction disorders, and pericardial abnormalities. The cumulative incidence of cardiac disease after 25 years correlated with radiation dose with incidence of 21% for 36 Gy, decreasing to 10%, 6%, 5%, and 3% for the lower dose groups, respectively ($P < .001$). Multivariate analysis of several putative risk factors showed that mediastinal radiation dose was the only significant variable predicting for cardiac disease-free survival ($P = .0025$). Mulrooney et al published the Childhood Cancer Survivor Study (CCSS) analysis of cardiovascular disease risk in pediatric cancer survivors (not just HL) and analyzed the confounding and independent effects of anthracycline and mediastinal radiation prescribed dose showing a dose-response effect for both chemotherapy and radiotherapy.[22] In this study of 14,358 patients, doses between 15 Gy and 35 Gy were not well distinguished, but there was a suggestion that 15 Gy might be a threshold dose associated with not only future VHD but also congestive heart failure and myocardial infarction. Bates et al recently updated the CCSS experience in a 2019 publication of 24,214 5-year survivors, providing further insights into the relationships between radiation and risk of long-term cardiac disease.[23] Mean heart doses >10 Gy were associated with increasing cardiac disease risk in a dose-response manner. Volumes of the heart receiving radiation also were correlated with cardiac risk. Children receiving a heart V5 of >50% had a 1.6-fold increased risk of late cardiac disease. Those receiving at least 20 Gy to any part of the heart also were at increased risk.
- While the data regarding cardiac constraints for modern RT of lymphomas are imperfect, we recommend that the mean heart dose be kept as low as possible, ideally <8 Gy, although in some patients a higher dose will be necessary given lymphoma extent. Conversely, treatment plans for patients with superior mediastinal disease should achieve doses far less than 8 Gy. This also recognizes that patients with lymphoma tend to also receive anthracycline chemotherapy, although cumulative chemotherapy doses in modern practice tend to be lower than historical cohorts. Rarely should mean heart dose exceed 15 Gy, unless patients are being treated in the second-line setting with curative intent where larger RT doses are necessary.[23] Ideally, mean left ventricular dose should be kept lower than 8 Gy, although up to 15 Gy may be necessary in some circumstances. Aortic and mitral valve doses should be kept below 25 Gy, and ideally even lower. Tricuspid and pulmonic valves may be less critical OAR and it is recommended that doses be kept below 30 Gy. Constraints to coronary arteries are less well defined but should be as low as possible in terms of dose and volume/length.

References

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Lungs

- The primary pulmonary toxicity related to mediastinal RT is radiation pneumonitis. Other complications, such as symptomatic fibrosis or bronchial stenosis, are rarely encountered given the lower doses used for lymphoma management. Radiation pneumonitis is a clinical diagnosis consisting of dry cough, dyspnea, and occasionally low-grade fevers. Radiation pneumonitis must be distinguished from other entities including infectious pneumonia, acute bronchitis, pulmonary embolism, etc. Pulmonary complications, including pneumonitis, can arise from systemic modalities also, including bleomycin and immunotherapy. Bleomycin pulmonary toxicity does not preclude consolidation thoracic radiation therapy.[69]
- The most important risk factor for radiation pneumonitis is lung dose–volume metrics including mean lung dose (MLD), V20, and V5. Such metrics have been associated with pneumonitis risk in both epithelial[70] and hematologic malignancies.[29,31] For epithelial malignancies, such as non-small cell lung cancer, guidelines generally recommend MLD <20 Gy and V20 <35%. In most circumstances, given the lower doses used in lymphoma management, much lower doses are generally achievable with careful planning.
- We recommend limiting MLD <13.5 Gy and V20 <20%, though higher incidental dose to the lungs may occasionally be necessary. Rarely should the lung V20 exceed 30%. More pertinent to IMRT or volumetric arc techniques, we recommend limiting the V5 <55%. DIBH can help meet MLD and V5 recommendations.[71] Adherence to pulmonary constraints is particularly important in patients who have been heavily pre-treated, particularly those who have received regimens with known lung toxicity.
- RT, and possibly some chemotherapy drugs such as alkylating agents,[53] increase the risk of developing lung cancer.[53,72] The risk increases linearly with dose to the lung.[53] The increased risk is most apparent in people who smoke, particularly those who continue to use tobacco after diagnosis.[73] In fact, continuing to smoke after thoracic RT multiplies the risk of developing lung cancer. Therefore, a concerted effort should be made to help patients who currently smoke and require thoracic RT to stop smoking. Lung cancer screening with low-dose CT may also be appropriate depending upon clinical circumstances including age, pack-year tobacco exposure history, and interval since quitting. See NCCN Guidelines for Lung Cancer Screening

Breast

- RT doses prescribed for thoracic lymphomas are significantly lower than doses utilized for epithelial breast cancer. As such, breast tissue exposure resulting from lymphoma RT falls well within acceptable dose constraints for breast tissue toxicity and cosmesis.
- Breast tissue radiation exposure results in an increased lifetime risk for secondary malignancies. A minimum latency period of 8 years is considered necessary before radiation induced cancers develop. After this latency period, routine breast exams 1–2 times per year are indicated. Individuals AFAB[f] previously treated with thoracic RT between ages 10 and 30 should begin annual screening mammography and MRI (typically alternating every 6 months) 8 years after undergoing treatment (but not before age 25) or by age 40, whichever comes first. See NCCN Guidelines for Breast Cancer Screening and Diagnosis (BSCR-3).
- Chemoprevention with selective estrogen receptor modulators and aromatase inhibitors have been demonstrated to reduce the risk of breast cancer by 50%–60% in high-risk populations. These trials, however, did not include individuals who received prior breast radiation for non-epithelial breast cancers. Patients should consider discussion of chemoprevention with their oncologist or breast specialist. See NCCN Guidelines for Breast Cancer Risk Reduction.

[f] There is limited data on screening in individuals with increased risk AMAB.

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HODGKIN LYMPHOMA STAGING[1]

Table 1

Definitions of Stages in Hodgkin Lymphoma[2]

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

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

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

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

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

A No systemic symptoms present

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

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1861.

[1] For additional information regarding the staging of Hodgkin lymphoma, refer to: 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.

[2] FDG-PET scans are useful for upstaging in stage I–II disease. If there is FDG-PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. FDG-PET scans may demonstrate increased avidity in lymphoid tissue unrelated to lymphoma in persons with HIV, particularly if HIV is not well-controlled (i.e. acute/subacute HIV infection, advanced immunosuppression and or viremia) and in the presence of opportunistic infections.

ABBREVIATIONS

4D-CT	four-dimensional computed tomography
ACGME	Accreditation Council for Graduate Medical Education
ACS	American Cancer Society
AFAB	assigned female at birth
ALARA	as low as reasonably achievable
AMAB	assigned male at birth
AP	anteroposterior
ASCR	autologous stem cell rescue
AYA	adolescent and young adult
CAD	coronary artery disease
CBC	complete blood count
CCSS	Childhood Cancer Survivor Study
CHL	classic Hodgkin lymphoma
CME	continuing medical education
CMT	combined modality therapy
CPI	checkpoint inhibitors
CR	complete response
CT	computed tomography
CTV	clinical target volume
DIBH	deep-inspiratory breath hold
DLCO	diffusing capacity of the lung for carbon monoxide
EANM	European Association of Nuclear Medicine
EBV	Epstein-Barr virus
ECHO	echocardiogram
EF	ejection fraction
EORTC	European Organisation for Research and Treatment of Cancer
ESR	erythrocyte sedimentation rate
FDG	fluorodeoxyglucose
FFP	freedom from progression
FNA	fine-needle aspiration
G-CSF	granulocyte colony-stimulating factor
GHSG	German Hodgkin Study Group
GTV	gross tumor volume
H&P	history and physical
HCT	hematopoietic cell transplant
HDT	high-dose therapy
H-flu	Haemophilus influenzae
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
ICL	infraclavicular
ICRU	International Commission on Radiation Units and Measurements
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
IPS	International Prognostic Score
ISRT	involved-site radiation therapy
ITV	internal target volume
IVF	in vitro fertilization
LAD	left anterior descending
LCx	left circumflex
LDH	lactate dehydrogenase
LDHL	lymphocyte-depleted Hodgkin lymphoma
LFT	liver function test
LRHL	lymphocyte-rich Hodgkin lymphoma
MCHL	mixed cellularity Hodgkin lymphoma
MLD	mean lung dose
MMR	mediastinal mass ratio
MRI	magnetic resonance imaging
MTR	mediastinal thoracic ratio
NLPBL	nodular lymphocyte-predominant B-Cell lymphoma
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
NSHL	nodular sclerosis Hodgkin lymphoma
OAR	organ at risk
PA	posteroanterior
PCP	primary care physician
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
RATHL	risk-adapted therapy in Hodgkin lymphoma
RCA	right coronary artery
RR	relative risk
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SUV	standardized uptake value
TLI	total lymphoid irradiation
TSH	thyroid-stimulating hormone
VHD	valvular heart disease
VMAT	volumetric modulated arc therapy

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Hodgkin Lymphoma

Discussion

This discussion corresponds to the NCCN Guidelines for Hodgkin Lymphoma. Last updated: March 18, 2024

Table of Contents

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy of B-cell origin. Most patients are diagnosed between ages 15 and 30 years, followed by another peak in adults ≥55 years. In 2024, an estimated 8570 people will be diagnosed with HL in the United States and 910 people will die from the disease.[1] The World Health Organization (WHO) classification divides HL into two main types: classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).[2] In Western countries, CHL accounts for 95% and NLPHL accounts for 5% of all HL.[3] While the WHO has maintained the term NLPHL,[2] the International Consensus Classification (ICC) has now replaced the term NLPHL with the term nodular lymphocyte predominant B-cell lymphoma (NLPBL) based on biological and clinical differences with CHL.[4]

CHL is divided into four subtypes: nodular sclerosis CHL; mixed cellularity CHL; lymphocyte-depleted CHL; and lymphocyte-rich CHL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed *popcorn cells*.

The past few decades have seen significant progress in the management of HL. The advent of more effective treatment options has improved the 5-year survival rates, which have been unmatched in any other cancer over the past 4 decades. HL is among the most curable of malignancies with modern treatments, and newly diagnosed HL has a very high likelihood of being cured with appropriate management. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to long-term toxicity. Clinical trials still emphasize improvement in cure rates for patients with advanced disease, but the potential long-term effects of treatment remain an important consideration.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma discuss the clinical management of CHL and NLPHL, focusing on adult patients ≥18 years who do not have serious intercurrent disease. The Guidelines do not address HL in pediatric patients or those with unusual situations, such as human immunodeficiency virus (HIV) positivity. Individualized treatment may be necessary for patients >60 years and those with concomitant disease or poor performance status. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Hodgkin Lymphoma, an electronic search of the PubMed database was performed to obtain key literature in Hodgkin lymphoma since the previous Guidelines update, using the following search terms: Hodgkin lymphoma, classic Hodgkin lymphoma, and nodular lymphocyte predominant. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5] Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

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

Sensitive/Inclusive Language Usage

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

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.[6,7] The system divides each stage into subcategories A and B, the latter for presence of B symptoms. “A” indicates that no systemic symptoms are present and “B” is assigned to patients with unexplained fevers above 38°C, drenching night sweats, or unexplained weight loss of more than 10% of their body weight within 6 months of diagnosis.

Patients with HL are usually classified into three groups: early-stage favorable (stage I–II with no unfavorable factors); early-stage unfavorable (stage I–II with any of the unfavorable factors such as large mediastinal adenopathy, multiple involved nodal regions, B symptoms, extranodal involvement, or significantly elevated erythrocyte sedimentation rate [ESR] ≥50); and advanced-stage disease (stage III–IV).

Mediastinal bulk, an unfavorable prognostic factor in patients with early-stage HL, is measured most commonly using the mediastinal mass ratio (MMR).[8] The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR greater than 0.33 is defined as bulky disease. This is the definition most commonly used in North America and also by the German Hodgkin Study Group (GHSG). Another definition of bulk is any single node or nodal mass that is greater than or equal to 10 cm in diameter. According to the Cotswolds modification of the Ann Arbor staging system, bulky disease is defined as the mediastinal thoracic ratio (MTR), which is the ratio of the maximum width of the mediastinal mass and the internal transverse diameter of the thorax at the T5–T6 interspace on a posteroanterior (PA) chest radiograph.[9] In this context, any mass with MTR greater than 0.35 is defined as bulky disease. This is the definition used by the European Organization for Research and Treatment of Cancer (EORTC).

The early-stage unfavorable factors are based largely on a composite of factors derived from the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, GHSG, and the National Cancer Institute of Canada (NCIC).[10,11] Of note, the nodal *regions* as defined by the GHSG and EORTC are not the same as the Ann Arbor *sites*. Both research groups bundle the mediastinum and bilateral hila as a single region. In addition, the GHSG combines subpectoral with supraclavicular or cervical, while the EORTC combines subpectoral with axilla as one region. The NCCN and EORTC unfavorable factors for stage I–II disease include bulky mediastinal disease (MMR >0.33 and MTR >0.35, respectively) or bulky disease greater than 10 cm, B symptoms, ESR greater than or equal to 50, and more than 3 involved nodal regions.

In contrast, the GHSG considers patients with more than 2 nodal regions as having unfavorable disease.

An international collaborative effort evaluating more than 5000 patients with advanced CHL (stage III–IV) identified seven adverse prognostic factors, each of which reduced survival rates by 7% to 8% per year,[12] including: age ≥45 years; male gender; stage IV disease; albumin level less than 4 g/dL; hemoglobin level less than 10.5 g/dL; leukocytosis (white blood cell [WBC] count >15,000/mm^3); and lymphocytopenia (lymphocyte count <8% of the WBC and/or lymphocyte count <600/mm^3). The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.[12,13] The IPS helps to determine the clinical management and predict prognosis for patients with stage III–IV disease.[12,13]

The Role of FDG-PET Imaging in Management of CHL

Clinical management of CHL involves initial treatment with chemotherapy or combined modality therapy (CMT; chemotherapy and radiation therapy [RT]), followed by restaging at the completion of chemotherapy to assess treatment response. Assessment of response to initial treatment is essential because the need for additional treatment is based on the treatment response. ^{18}F-fluorodeoxyglucose (FDG)-PET should not be used for routine surveillance following the completion of therapy due to risk for false positives.

FDG-PET imaging including integrated FDG-PET and CT (FDG-PET/CT) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.[14,15] In a meta-analysis, FDG-PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.[16] FDG-PET positivity at the end of treatment has been shown to be a significant adverse risk factor in patients with early-stage as well as advanced-stage disease.[17-19] In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment FDG-PET scans based on the visual assessment of FDG uptake in the involved sites. 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.[15,20,21] 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.[20,21] Interim or end-of-treatment FDG-PET scans with a score of 1, 2, or 3 are considered "negative" and FDG-PET scans with a score of 4 and 5 are considered "positive."[22] 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,[15,23,24] and treatment decisions in these cases will require clinical judgment. In addition, Deauville 4 may represent just a single area of persistent disease or lack of response in any site. The 5-PS (Deauville criteria) has been validated in international multicenter trials for FDG-PET–guided interim response assessment and risk-adapted therapy in patients with HL.[25-29] The NCCN Hodgkin Lymphoma Panel encourages a second opinion of scans when there is a discrepancy between the clinical presentation and radiology report of a scan that was not originally interpreted by a qualified individual, and/or when no Deauville score is provided.

Interim FDG-PET Imaging

Interim FDG-PET scans can be prognostic and are increasingly being used to assess treatment response during therapy,[30,31] as they can inform treatment adaptation, including treatment escalation and de-escalation.[32,33] Early interim FDG-PET imaging after chemotherapy has been shown to be a sensitive prognostic indicator of treatment outcome in patients with advanced-stage disease (stage II disease with unfavorable risk factors [with or without bulky disease] or stage III–IV disease).[34,35] Interim FDG-PET scans may also be useful to identify a subgroup of patients with early- and advanced-stage disease that can be treated with chemotherapy

alone.[29,36] The NCCN Guidelines emphasize that the value of interim FDG-PET scans remains unclear for some clinical scenarios, and all measures of response should be considered in the context of management decisions. It is important that the Deauville score be incorporated into the nuclear medicine FDG-PET scan report, since subsequent management is often dependent on that score. Individual prospective trials that use interim FDG-PET imaging are discussed below in the treatment management section.

Principles of Radiation Therapy

RT can be delivered with photons, electrons, or protons, depending on clinical circumstances.[37] Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OARs; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, 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, or deep inspiration breath hold (DIBH).[38,39] 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.[37,40-46] Although advanced RT techniques emphasize tightly conformal doses and steep gradients between targets and OARs, the "low-dose bath" to normal structures is often increased. Particular attention to treatment technique and adherence to dose constraints is essential to minimize dose to high-risk OARs such as breast tissue in young premenopausal individuals. Target definition and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, FDG-PET and other imaging modalities facilitate target definition.

For optimal mediastinal treatment planning, organs or tissues to be contoured should include the lungs, heart, and the cardiac subunits, including the coronary arteries (the left main, circumflex, left anterior descending [LAD], and right coronary arteries, with priority placed on sparing the proximal over distal portions of the arteries), valves, and left ventricle. In mediastinal HL, use of 4D-CT or DIBH at the time of simulation to deal with respiratory motion and minimize dose to OARs is essential. DIBH in particular has been shown to decrease incidental dose to the heart, lungs, and other OARs in many disease presentations.[47] Further, IGRT during treatment delivery is essential to ensure accurate target localization. In certain circumstances, the use of protons for mediastinal lymphoma provides dosimetric advantages that may reduce long-term toxicity. The potential advantage of protons is related to the localization of disease within the mediastinum as well as patient gender assigned at birth and age.[37,48,49]

Randomized prospective studies to test these concepts are unlikely to be done since these techniques are primarily designed to decrease late effects, which usually develop ≥10 years after completion of treatment. Therefore, the Guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OARs in a clinically meaningful manner without compromising target coverage should be considered in these patients, who are likely to enjoy long life expectancies following treatment.

Involved-site RT (ISRT) and involved-node RT (INRT) are being used as alternatives to involved-field RT (IFRT) in an effort to further restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long-term toxicities associated with radiation exposure.[50-52] ISRT targets the originally involved nodal sites and possible extranodal extensions, which generally defines a

smaller field than the classical IFRT that encompassed entire lymph node regions, without a demonstrable attendant decrease in efficacy.[53]

ISRT targets the initially involved nodal and extranodal sites as defined by the pre-treatment evaluation (physical examination, CT, and FDG-PET imaging). However, it 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. The incorporation of additional imaging techniques such as FDG-PET and MRI often enhances the treatment planning. The optimized treatment plan for ISRT is designed using conventional 3D conformal RT, proton therapy,[37] or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OARs. For CHL, the gross tumor volume (GTV) defined by FDG-PET/CT imaging prior to chemotherapy or surgery provides the basis for determining the clinical target volume (CTV). For NLPHL treated with ISRT alone, the CTV should be expanded to include potential microscopic disease in the immediate region of the FDG-PET–positive disease. The planning target volume (PTV) is an additional expansion of the CTV to account for any setup variations and internal organ motion.[54] PTV margins should be defined individually for each disease site.

In the setting of CMT, the panel recommends an RT dose of 30 to 36 Gy when combined with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine [DTIC]) for most patients.[55] In patients with stage I–II non-bulky disease, the recommended RT dose is 20 to 30 Gy following ABVD.[56,57] For patients treated with RT alone (uncommon, except for NLPHL) the recommended dose is 30 to 36 Gy for the involved regions and 25 to 30 Gy for uninvolved regions. The panel recommends that high cervical regions in all patients and axillae in patients assigned female at birth (AFAB) always be excluded from RT fields, if those regions are uninvolved.

Principles of RT Dose Constraints

Patients with hematologic malignancies typically receive far lower doses of RT than patients with epithelial or mesenchymal malignancies, while generally achieving more favorable long-term outcomes. More stringent dose constraints, often proportionally reduced from acceptable thresholds in other malignancies, are recommended. Doses to OARs should follow principles of ALARA (as low as reasonably achievable). In some scenarios, target coverage may require dose constraints to be exceeded if the OAR is within, or adjacent to, the PTV. For example, it may be difficult to meet thyroid constraints in the setting of bilateral supraclavicular lymphadenopathy.

A relatively rare but serious late complication of RT is the development of radiation-induced secondary cancers. Studies have reported that increasing RT dose without a safe threshold dose (linear no-threshold model) is associated with an increased risk for secondary cancers, although the pattern of risk is less well understood than those after low-dose exposure.[58] Other contributing factors include age, environmental exposure, genetic risk factors, and radiation technique, among others.[59]

RT dose constraints recommended for OARs, especially heart, lung, and breast, are described below.

Heart

Multiple cardiac complications can develop from mediastinal RT including pericarditis, arrhythmias, coronary artery disease (CAD), valvular heart disease (VHD), and cardiomyopathy/congestive heart failure.[60,61] In addition to factors related to RT, the risk of cardiac events is also influenced by chemotherapy administration (eg, doxorubicin), pre-existing cardiovascular disease, age, and other cardiac risk factors (eg, diabetes, hypertension, hyperlipidemia).[60,62-64] While global heart metrics such as

mean heart dose (MHD) are most commonly used to assess risk, there is an increasing recognition that radiation dose-fractionation to cardiac substructures must be accounted for.

Mediastinal RT for lymphomas, relative to breast cancer and other thoracic malignancies, is characterized by radiation exposures to larger volumes of the heart and substructures, albeit to lower doses (20–40 Gy). The MHD has been related to the risk of cardiac events, although the volume of the whole heart exposed to RT is variable.[65,66] In a case-control study of survivors of HL who were treated mainly with anteroposterior (AP)/PA fields, using MHD as a measure of cardiac toxicity risk, van Nimwegen et al demonstrated an excess relative risk (RR) of 7.4% per Gy MHD.[66] A significantly increased risk of coronary heart disease was reported among patients who received an MHD as low as 5 to 14 Gy (RR, 2.31) compared to an MHD of 0 Gy.[66] This risk was increased for an MHD of greater than or equal to 15 Gy (RR, 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy).[66]

The number of studies evaluating specific dose constraints for cardiac substructures is limited.[60,67,68] The prescribed mediastinal RT dose was the only independent risk factor for VHD in a pediatric cohort study, and increasing mediastinal RT dose (especially >30 Gy) has been associated with an elevated risk of valvular dysfunction.[67,68] In a large Dutch cohort of adult patients treated with mediastinal RT, the 30-year cumulative risks of VHD increased with increasing mean valvular RT doses (3% for <30 Gy, 6.4% for 31–35 Gy, 9.3% for 36–40 Gy, and 12.4% for >40 Gy) and there was no confounding effect of anthracycline chemotherapy on the risk of VHD.[68] van Nimwegen et al demonstrated a relationship between heart failure and mean left ventricular (LV) dose.[60] Chemotherapy was a clear confounder in regard to the risk of heart failure. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean LV dose less than 15 Gy, 15.9% for 16 to 20 Gy, and 32.9% for greater than or equal to 21 Gy.

RT dose constraints for coronary arteries is a work in progress and only a few studies have evaluated the effect of coronary RT dose on the risk of CAD.[69-72] In a large retrospective study of patients with non-small cell lung cancer (NSCLC) treated with thoracic RT, major adverse cardiac events were found to be associated with the volume of the LAD receiving 15 Gy (V15 Gy ≥10%).[72] Although there is no robust evidence to recommend specific guidance on dose constraints to specific coronary arteries in patients with lymphomas, limited available evidence supports the general notion of a dose-response effect in the clinical range of lymphoma RT prescriptions.

NCCN Recommendations

While the data regarding cardiac constraints for modern RT for lymphomas are imperfect, the panel recommends that the MHD be kept as low as possible, ideally less than 8 Gy, although in some patients a higher dose will be necessary given lymphoma extent. Conversely, treatment plans for patients with superior mediastinal disease should achieve doses far less than 8 Gy. The panel recognizes that nearly all patients with lymphoma receive anthracycline-based chemotherapy, although cumulative chemotherapy doses in modern practice tend to be lower than historical cohorts. Whole heart irradiation increases the risk of constrictive pericarditis, especially with whole heart RT doses greater than 15 Gy[73]; therefore, it is recommended that MHD should rarely exceed 15 Gy. This may be reconsidered if patients are being treated in the second-line setting with curative intent where larger RT doses are necessary. Mean LV dose should not exceed 8 Gy, although in some circumstances up to 15 Gy may be necessary. Aortic and mitral valve doses should be less than 25 Gy, although lower doses would be optimal. Given that tricuspid and pulmonic valves may be less affected OARs, it is recommended that

doses less than 30 Gy be administered. Constraints to coronary arteries are less well defined,[74] but should be as low as possible in terms of dose, volume, and length. It is recognized that contouring the coronary arteries is challenging given anatomical variations and lung/heart motion. This may warrant designing a planning OAR volume in some patients. Furthermore, it is also important to preferentially spare high-dose overlap with the proximal coronary arteries. For dose recommendations for OARs, see *Principles of RT - RT Dose Constraint Guidelines for Lymphoma* in the algorithm.

Lungs

Mediastinal RT-related pulmonary toxicity is primarily radiation pneumonitis, although complications including symptomatic fibrosis or bronchopleural fistula have been encountered rarely. Radiation pneumonitis is a clinical diagnosis consisting of dry cough, dyspnea, and occasional low-grade fevers, and must be distinguished from other entities including drug-induced (especially bleomycin) pneumonitis, infectious pneumonia, acute bronchitis, and pulmonary embolism. Bleomycin pulmonary toxicity (BPT) does not preclude consolidation thoracic RT.[75] Pulmonary complications can also arise from systemic therapies such as brentuximab vedotin (BV) and immunotherapy.

The most important risk factors for radiation pneumonitis are lung dose-volume metrics, including mean lung dose (MLD), V20 Gy, and V5 Gy. Such metrics have been associated with pneumonitis risk in both epithelial[76] and hematologic malignancies.[77] For epithelial malignancies such as NSCLC, it is generally recommended that MLD be less than 20 Gy and V20 Gy be less than 35%. In most circumstances, given the lower doses used in lymphoma management, much lower doses are generally achievable with careful planning.

NCCN Recommendations

The panel recommends limiting MLD less than 13.5 Gy and V20 Gy less than 20%, though higher incidental dose to the lungs may occasionally be necessary. Rarely should the lung V20 exceed 30%. In cases where IMRT or volumetric arc techniques are appropriate, limiting the V5 to less than 55% is recommended. DIBH can help meet MLD and V5 recommendations.[78] Adherence to pulmonary constraints is particularly important in patients with heavily pretreated disease, particularly those who have received regimens with known lung toxicity.

Breast

Whole breast RT increases the risk of subsequent malignancies within the irradiated tissue. Therefore, the guidelines recommend a maximum mean breast dose of 4 Gy and a V4 of less than 10%.

Treatment Guidelines

Diagnosis and Workup

For evaluation and initial workup of HL the panel recommends that an excisional 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 generally insufficient except in unusual circumstances when, in combination with immunohistochemistry (IHC), it is judged to be diagnostic of HL by an expert hematopathologist or cytopathologist. Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, PAX5, and EBER-ISH is recommended for CHL. The Reed-Sternberg cells of CHL express CD30 in all patients, express CD15 in the majority of patients, and are usually negative for CD3 and CD45. CD20 may be detectable in less than 40% of patients. An extended panel of markers (ie, MUM-1, BOB-1, OCT-2) may be required, especially if there is an equivocal diagnosis. For NLPHL, the immunoarchitectural pattern should be specified as typical (subtypes A or B) or variant (subtypes C, D, E, or F).

Workup should include a thorough history and physical examination (H&P), including determination of B symptoms (unexplained fevers >38°C, drenching night sweats, or unexplained weight loss of >10% of body weight within 6 months of diagnosis; other associated symptoms are alcohol intolerance, pruritus, fatigue, and poor performance status). Physical examination should include all lymphoid regions, spleen, and liver; standard laboratory tests (complete blood count [CBC], differential, ESR, serum lactate dehydrogenase [LDH], albumin, and liver and renal function tests); and FDG-PET/CT scan (skull base to mid-thigh or vertex to feet in selected cases).

The panel recommends imaging be obtained in accordance with the American College of Radiology (ACR) guidelines. A diagnostic CT enhanced with oral and/or intravenous (IV) contrast may be useful in selected cases (neck, chest, abdomen, and pelvis). At minimum, diagnostic CT scans should include involved areas identified as abnormal on FDG-PET scan. PA and lateral chest x-rays are encouraged in selected cases for patients with large mediastinal masses.

The NCCN PET Task Force and the NCCN Guidelines consider FDG-PET scans essential for initial staging and for evaluating residual masses at the end of treatment.[79] An integrated FDG-PET scan plus a diagnostic CT is recommended for initial staging and should be obtained no longer than 1 month prior to the initiation of therapy. A separate contrast-enhanced diagnostic CT is not needed if it was part of the integrated FDG-PET scan. The panel supports the ACR[80] and Society of Nuclear Medicine and Molecular Imaging (SNMMI)[81] recommendations for FDG-PET/CT interpretation (see *Principles of FDG-PET/CT* in the algorithm).[82-85] However, it should be noted that FDG-PET scans may be positive in sites of infection or inflammation, even in the absence of HL. In patients with FDG-PET–positive sites outside of the disease already identified, or if the FDG-PET–positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. In patients with newly diagnosed HL undergoing pretreatment staging with FDG-PET/CT, routine bone marrow biopsy is not required if the FDG-PET scan is negative or displays a homogenous pattern of bone marrow uptake, which may be secondary to cytokine release.[86,87] The bone marrow may be assumed to be involved if the FDG-PET scan displays multifocal (≥3) skeletal lesions.[86,88] However, a bone marrow biopsy may be performed if the FDG-PET scan is negative, but unexplained cytopenias other than anemia are present (eg, thrombocytopenia, neutropenia). In select cases, MRI with contrast to select sites may be considered, unless contraindicated. FDG-PET/MRI without contrast (skull base to mid-thigh) may also be considered for anatomical imaging.

Evaluation of ejection fraction (EF) is recommended if anthracycline-based therapy is indicated. HIV and hepatitis B or C testing should be encouraged for patients with risk factors for HIV or unusual disease presentations (see NCCN Guidelines for Cancer in People with HIV). Pulmonary function tests, including diffusing capacity of the lungs for carbon monoxide (DLCO), are recommended for patients receiving bleomycin-based chemotherapy. In general, a DLCO threshold of at least 60% is acceptable for bleomycin use.[89,90] A seasonal influenza vaccine is recommended. Pneumococcal, Haemophilus influenzae (H-flu), and meningococcal vaccines are recommended if splenic RT is contemplated.

A pregnancy test should be performed before patients of childbearing potential undergo treatment. Alkylating agent-based chemotherapy is associated with a higher risk of premature ovarian failure than chemotherapy with non-alkylating agent-based chemotherapy.[91] In select cases and if the patient is interested, the Guidelines recommend consideration of fertility preservation (ie, semen cryopreservation, ovarian tissue or oocyte cryopreservation) prior to the initiation of chemotherapy with alkylating agents or pelvic RT.[92,93]

Management of Classic Hodgkin Lymphoma in Adults Aged 18–60 Years

Patients are divided into the following groups after initial diagnosis and workup:

- Stage I–II
- Stage III–IV

Patients with stage I–II are further classified into the following subgroups depending on the presence or absence of NCCN unfavorable factors:

- Stage IA–IIA (favorable with non-bulky disease)
- Stage I–II (unfavorable with B symptoms, bulky mediastinal disease, or >10 cm adenopathy)

The standard treatment for early-stage CHL is with either CMT or chemotherapy alone. Selection of CMT or chemotherapy alone should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement. Generally, CMT provides for a better progression-free survival (PFS)/freedom from progression (FFP); however, there is no difference in overall survival (OS) in prospective randomized trials. Most patients will benefit from multidisciplinary input prior to final treatment decisions.

Stage I–II

The HD10 trial from the GHSG investigated the reduction of the number of cycles of ABVD as well as the IFRT dose in patients with stage I–II disease with no risk factors.[57] The definition of favorable disease implies the absence of unfavorable risk factors outlined in *Unfavorable Risk Factors* in the algorithm. It is worth noting that for purposes of stratification, the GHSG and EORTC do not define the lymph node regions strictly according to the Ann Arbor criteria. In this trial, patients were not eligible if they had 3 or more involved lymph node regions, any E-lesions, bulky mediastinal adenopathy, ESR >50, or ESR >30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to one of the four treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT or 2 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT.[57] The final analysis of this trial showed that (with a median follow-up of 79–91 months) there were no significant differences between 4 and 2 cycles of ABVD in terms of 5-year OS (97.1% and 96.6%), freedom from treatment failure (FFTF) (93.0% vs. 91.1%), and PFS (93.5% vs. 91.2%). With respect to the dose of IFRT, the OS (97.7% vs. 97.5%), FFTF (93.4% vs. 92.9%), and PFS (93.7% vs. 93.2%) were also not significantly different between 30 Gy and 20 Gy IFRT.[57] More importantly, there were also no significant differences in OS, PFS, and FFTF among the four treatment arms. The results of the HD10 study confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment for patients with a very favorable presentation of early-stage disease with no risk factors, thereby minimizing the risk of late effects.

Subsequent studies have assessed the value of interim FDG-PET scans in defining the need for RT in patients with stage I–II disease. The UK RAPID trial showed that patients with stages IA–IIA disease with a negative FDG-PET scan after 3 cycles of ABVD have an excellent outcome with or without IFRT.[29] In this study (n = 602; 426 patients had a negative FDG-PET scan after 3 cycles of ABVD), patients with stage IA–IIA favorable disease (no B symptoms or mediastinal bulky disease) and a Deauville score of 1 to 2 on interim FDG-PET scan after 3 cycles of ABVD were randomized to either IFRT (n = 209) or observation (n = 211). After a median follow-up of 60 months, in an intent-to-treat analysis, the estimated 3-year PFS rate was 94.6% for those treated with IFRT compared to 90.8% for those who received no further treatment (*P* = .16). The corresponding 3-year OS rates were 97.1% and 99.0%, respectively.[29] In the “per protocol” (as treated) analysis, the 3-year PFS rates were 97.1% and 90.8%, respectively, favoring the use of CMT (*P* = .02). Of note,

among patients with initial disease greater than or equal to 5 cm, patients treated with CMT had a superior EFS compared to patients treated with ABVD alone.[94]

In the EORTC H10 trial, which included 754 patients in the favorable group (H10F), PET response after 2 cycles of ABVD facilitated early treatment adaptation.[32] In this study, mediastinal blood pool activity was used as the reference background activity for PET positivity of residual masses greater than or equal to 2 cm in greatest transverse diameter, regardless of location. A smaller residual mass or a normal-sized lymph node was considered positive if its activity was above that of the surrounding background. Patients with PET-negative response after receiving 2 cycles of ABVD received 1 additional cycle of ABVD (total of 3 cycles) followed by INRT in the standard arm, or 2 additional cycles of ABVD (total of 4 cycles) only in the experimental arm.[32] After a median follow-up of 10 years, the intent-to-treat PFS rates were 98.8% and 85.4% in the ABVD + RT and ABVD only arms, respectively ($P < .0001$).[95] If the interim PET was positive, patients in both the H10F and H10U (unfavorable group) were continued on ABVD for a total of 4 cycles on the standard arm or treatment was intensified to 2 cycles of escalated BEACOPP + INRT in the experimental arm.[32]

In the H10U group (n = 1196), patients were randomized into two treatment arms.[32] In the standard arm, patients were treated with 2 cycles of ABVD, underwent interim PET, and were treated with 2 additional cycles of ABVD + INRT (30–36 Gy). In the experimental arm, patients were treated with 2 cycles of ABVD, underwent interim PET scans, and if found to be PET negative, were treated with an additional 4 cycles of ABVD. For the patients with interim PET-negative response, the 10-year PFS was 91.4% following 4 cycles of ABVD + INRT versus 86.5% following 6 cycles of ABVD.[95] If patients were found to be PET positive after the initial 2 cycles of ABVD, chemotherapy was intensified with 2 cycles of escalated BEACOPP + INRT (30–36 Gy) as in the H10F group. Initial results of this trial demonstrated that in patients with stage I–II (favorable or unfavorable disease), a PET-positive response after 2 cycles of ABVD facilitates early treatment adaptation to 2 cycles of escalated BEACOPP + INRT, with improved 5-year PFS when compared to 2 additional cycles of ABVD and INRT (90.6% vs. 77.4%, respectively).[32] Longer term follow-up however revealed that at 10 years, the difference in PFS between ABVD and escalated BEACOPP in patients with PET-positive response after 2 cycles of ABVD had lost its statistical significance (79.2% vs. 85.1%, respectively; $P = .1777$).[95]

The GHSG HD16 trial (n = 1150) included patients with stage I–II favorable disease according to GHSG criteria.[96] Patients randomized to the standard arm received 2 cycles of ABVD followed by an interim PET and IFRT (20 Gy), regardless of the PET result. On the experimental arm, following 2 cycles of ABVD, patients with a negative PET (Deauville score <3) received no further therapy, while those with a positive PET received IFRT (20 Gy). Among the 628 patients in the combined arms who had a negative interim PET, the 5-year PFS was 94.2% following CMT and 86.7% following ABVD alone ($P = .14$).[97] Relapse analysis from this trial revealed a higher 5-year local recurrence rate in patients with PET-negative response with omission of IFRT, at 10.5% with chemotherapy alone compared to 2.4% with CMT ($P = .54$).[98]

The CALGB 50604 trial examined the use of interim PET to guide treatment of patients with stage I–II HL (excluding only patients with bulky disease).[99] Patients received 2 cycles of ABVD followed by PET. Patients with a PET-negative response (Deauville score of 1–3, which is different from the H10 and RAPID trials that used a score of 1–2) were given 2 more cycles of ABVD, whereas patients with a PET-positive response were treated with escalated BEACOPP + IFRT.[99] With a median follow-up time of 3.8 years, the estimated 3-year PFS for the PET-negative and

PET-positive groups were 91% and 66%, respectively.[99] The 3-year PFS was 94% for patients with Deauville 1–2 response on interim PET compared to only 77% for patients with Deauville 3 response.

The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial examined the use of interim PET to guide treatment for patients with advanced disease, which included 500 patients (41.6%) who had stage II disease with various risk factors (B symptoms, bulky disease, or ≥3 involved sites).[25,33] In the randomized trial, 1119 patients with stage II–IV disease received 2 cycles of ABVD and underwent interim PET scans. Patients with a Deauville score of 1 to 3 were assigned in a 1:1 ratio to continue treatment with 4 cycles of either ABVD or AVD. At a median of 7.3 years, the 7-year PFS and OS rates between the ABVD and AVD groups did not differ significantly (81% vs. 79.2% and 93.2% vs. 93.5%, respectively). However, the omission of bleomycin from the ABVD regimen after negative PET results (ie, Deauville score of 1–3) led to a decrease in the incidence of pulmonary toxic effects when compared to continued ABVD.[100] The potential value of added RT was not tested in this trial.

NCCN Recommendations for Stage IA–IIA Favorable, Non-Bulky Disease

The recommended primary treatment for stage I–IIA with favorable non-bulky disease is 2 cycles of ABVD (category 1), followed by restaging with FDG-PET/CT. If there is a preference to treat patients with CMT, treatment options for patients with a Deauville score of 1 to 3 include ISRT (20 Gy) if ESR is less than 50, no E-lesions are present, and there are 2 or fewer nodal sites[57,96] or 1 cycle of ABVD (total 3) plus ISRT (30 Gy) for Deauville 1–2 versus 2 cycles of ABVD (total 4) plus ISRT (30 Gy) for Deauville 3.[29,32]

If there is a preference to treat with chemotherapy alone, patients with a Deauville score of 1 to 2 are recommended to be treated with an additional 2[32,99] cycles of ABVD according to the H10F or CALGB trials. Per the RATHL trial, a Deauville score of 3 should be treated with 4 cycles of AVD.[33]

For patients with a Deauville score of 4, if only focally positive on interim FDG-PET, patients may continue with 2 additional cycles of ABVD before repeat scan. Following restaging, a biopsy is recommended for all patients with a Deauville score of 4 to 5. The panel recommends escalating therapy for patients whose scan remains positive throughout the area(s) of initial disease. ISRT (30 Gy) is recommended for patients with a Deauville score of 1 to 3, or 4 to 5 with a negative biopsy.[29,32] A Deauville score of 5 after interim restaging should be managed as described for refractory disease. Biopsy is recommended for all patients with a score of Deauville 5. If the biopsy is negative, treatment is as described for patients with a Deauville score of 4. If the biopsy is positive, or if a biopsy is not feasible, treatment is as described for refractory disease.

NCCN Recommendations for Stage I–II Unfavorable, B Symptoms, Bulky Mediastinal Disease, or Adenopathy >10 cm

For stage I–II unfavorable CHL with B symptoms, bulky mediastinal disease, or greater than 10 cm adenopathy, the preferred regimen, ABVD, is initially administered for 2 cycles followed by restaging with FDG-PET. If there is a preference to treat patients with CMT, patients with a Deauville score of 1 to 3 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT (30 Gy).[32] If there is a preference to treat with chemotherapy alone, patients with a Deauville score of 1 to 3 are recommended to receive 4 cycles of AVD.[33]

Patients with a Deauville score of 4 to 5 are treated with 2 cycles of escalated BEACOPP followed by interim FDG-PET restaging. All cycles of escalated BEACOPP should include growth factor support. A Deauville score of 5 should prompt re-biopsy to inform subsequent therapy. If a biopsy is not performed, treatment should be escalated. Patients with a

Deauville score of 1 to 3 who prefer CMT are followed up with ISRT (30 Gy).[32,101,102] Two cycles of escalated BEACOPP are recommended for those who prefer chemotherapy alone. Biopsy is recommended for patients with a Deauville score of 4 to 5 after restaging. If the biopsy is negative, treatment is as described for patients with a Deauville score of 1 to 3. For patients with a positive biopsy, or those in whom biopsy is not feasible, treatment is as described for refractory disease.

Stage III–IV

While chemotherapy is always used for patients with advanced-stage disease, CMT is an appropriate treatment approach in some instances, especially for patients with bulky disease, and is used for those who experienced poor response to chemotherapy in other treatment regimens.[103,104]

ABVD is a preferred treatment option based on several randomized clinical trials that failed to show a survival benefit for more intensive regimens.[104-107] The potential role for RT in stage III–IV disease has not been demonstrated in contemporary randomized clinical trials; however, it may be useful in selected clinical situations, such as described in the HD15 trial, below.

The results of the important RATHL trial demonstrated that the omission of bleomycin from the ABVD regimen in patients with negative interim PET scan (Deauville score 1–3) after 2 cycles of ABVD resulted in a lower incidence of pulmonary toxicity than with continued ABVD, without impacting efficacy (3-year PFS 81.6% and OS 97%).[33] In this trial, patients who had a positive interim PET (Deauville 4–5) had treatment intensified to escalated BEACOPP. With a median follow-up of 5 years, the 3-year PFS and OS were 71% and 85%, respectively. Similar PET-adapted escalation has been evaluated in the U.S. Intergroup trial S0186[108,109] and the Italian GITIL/FIL HD 0607 trial.[110] For the U.S. Intergroup trial, the 5-year PFS and OS for patients who had a positive interim PET were 65% and 97%, respectively.[108,109] Similar results were also seen in the 0607 trial for patients who had a positive interim PET, with a 3-year PFS and OS of 60% and 89%, respectively.[110]

BV-AVD has emerged as another preferred treatment option based on the results of the phase III ECHELON-1 trial.[111-113] Initial results of the ECHELON-1 trial showed that BV-AVD had superior PFS compared to ABVD in first-line treatment of patients with stage III–IV disease.[111,112] In this trial patients with previously untreated stage III or IV CHL were randomized to receive ABVD (n = 670) or BV-AVD (n = 664).[111] Patients received 6 cycles of chemotherapy without treatment adaptation based on interim restaging. The 5-year follow-up data confirmed that PFS benefit for BV-AVD compared to ABVD was consistent in all patient subgroups independent of disease stage, age, and IPS.[112] While the incidence of pulmonary toxicity was lower in the BV-AVD arm due to the elimination of bleomycin, there was a higher rate of peripheral neuropathy (19% compared to 9% for patients in the ABVD group) and febrile neutropenia (19% compared to 11% for patients in the ABVD group) mandating the use of growth factor support with this regimen.[111,112] Furthermore, the rate of pulmonary toxicity in the control group does not reflect that of modern management, as bleomycin may be omitted in the vast majority of patients after the first 2 cycles (see RATHL trial discussion above).

A more recent interim analysis revealed a significant OS benefit with BV-AVD compared to ABVD (hazard ratio [HR], 0.59; *P* = .009).[113] Estimated 6-year OS was 93.9% in the BV-AVD group versus 89.4% in the ABVD group. Consistent improvement in estimated 6-year OS was seen in both patients with positive PET scans following 2 cycles of treatment (95% vs. 77%; HR, 0.16) and in patients with negative PET scans following 2 cycles of treatment (94.9% vs. 90.6%; HR, 0.54). In the prespecified subgroups, more favorable estimates of treatment effect with BV-AVD over ABVD were observed in patients with stage IV disease,

patients <60 years (vs. patients ≥60 years), and in patients with an IPS greater than or equal to 4 (vs. IPS of 0–1). In accordance with previous reports, PFS estimates at 6 years favored BV-AVD compared to ABVD, with estimates of 82.3% and 74.5%, respectively (HR, 0.68). Consistent 6-year PFS benefit was seen with BV-AVD over ABVD across multiple subgroups, including those with stage III or IV disease and those with negative or positive PET scans following two cycles of treatment. More patients had ongoing peripheral neuropathy in the BV-AVD (18.9% compared to 9.0% in the ABVD group), though patients in both groups saw improvements (85.6% in the BV-AVD group had complete resolution or amelioration compared to 87.1% in the ABVD group). Subsequent therapy was used less frequently in the BV-AVD group compared to the ABVD group, including autologous and allogeneic HCT and immunotherapies, though the use of subsequent RT was similar between the two groups. There was a higher proportion of deaths due to a second cancer in the ABVD group compared to the BV-AVD group (4.9% vs. 3.5%).

The ongoing international phase III GHSG HD21 trial aimed to minimize treatment-related morbidity for adult patients ≤60 years of age with advanced stage CHL by investigating a remodeled escalated BEACOPP regimen referred to as BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) that eliminates bleomycin and procarbazine.[114] Fifteen hundred patients were randomized to PET-adapted 4 to 6 cycles of BrECADD versus escalated BEACOPP. Preliminary data show that with a median follow-up of 40 months, 3-year PFS was superior with BrECADD (94.9%) compared to escalated BEACOPP (92.3%) and 3-year OS was 98.5% in both groups. While the phase III data have not yet been published, data for BrECADD have been published from the original phase II portion of the study, which compared 6 cycles of BrECADD versus BrECAPP (BV, etoposide, doxorubicin, cyclophosphamide, procarbazine, prednisone).[115] With a median follow-up of 17 months, 46 of 52 patients in the BrECADD group (88%) achieved a complete response (CR). Among the entire cohort, the most common grade 3 to 4 adverse events (AEs) were hematologic. Four percent of patients in the BrECADD group experienced grade 3 to 4 organ AEs and 35% experienced grade 1 to 2 peripheral neuropathy.

The randomized phase II SWOG S1826 trial compared the safety and efficacy of 6 cycles of N-AVD (nivolumab, doxorubicin, vinblastine, and dacarbazine) to BV-AVD in patients ≥12 years of age (n = 976; median age 27 years [range 12–83 years]) with stage III–IV HL.[116] Data from the second interim analysis revealed a superior 1-year PFS with N-AVD (94%) compared to BV-AVD (86%) (*P* = .0005). There were 7 deaths due to AEs in the BV-AVD arm compared to 3 in the N-AVD arm. There were more grade ≥3 hematologic AEs on the N-AVD arm (48.4% vs. 30.5%) but similar rates of febrile neutropenia. Growth factor was optional during the trial. Sensory and motor peripheral neuropathy were less frequent in the N-AVD arm (28.1%/4% vs. 54.4%/6.8%). While rates of pneumonitis and colitis were similar between the two arms, hypo/hyperthyroidism was more common with N-AVD (7%/3% vs. <1%). Longer follow-up and OS data are needed.

NCCN Recommendations for Stage III–IV Disease

Based on the updated safety and efficacy data from the ECHELON-1 trial (discussed above),[113] BV-AVD is now included as a preferred treatment option with a category 1 recommendation along with ABVD. However, it should be noted that use of BV is contraindicated in patients with neuropathy. Additionally, all cycles of BV-AVD should include growth factor support.

ABVD is initially administered for 2 cycles followed by restaging with FDG-PET/CT. Patients with a Deauville score of 1 to 3 are treated with 4 cycles of AVD based on results from the RATHL trial.[33] After 4 cycles of

AVD, patients should be followed and monitored for relapse/late effects (see *Follow-up After Completion of Treatment*).

For patients with a Deauville score of 4 to 5, recommended treatment is 3 cycles of escalated BEACOPP per RATHL trial results,[33] followed by reassessment of response with FDG-PET/CT. As previously noted, all cycles of escalated BEACOPP should include growth factor support. For patients with a Deauville score of 1 to 3, the recommended options are to continue on therapy with 1 additional cycle of escalated BEACOPP alone or combined with ISRT to initially bulky or selected FDG-PET–positive sites. A biopsy is recommended for patients with a Deauville score of 4 or 5. If the biopsy is negative, treatment is as described for patients with a Deauville score of 1 to 3. For patients with a positive biopsy, treatment is as described for refractory disease.

BV-AVD is initially administered for 6 cycles followed by restaging with FDG-PET/CT.[113] If performing an FDG-PET/CT before completion of 6 cycles, a biopsy is recommended in patients with a Deauville score of 5. Therapy should be re-evaluated for positive biopsies. At the completion of therapy, patients with a Deauville score of 1 to 3 should be monitored for relapse/late effects (see *Follow-up After Completion of Treatment*). ISRT to initially bulky or FDG-PET–positive sites may be considered for patients with a Deauville score of 4 to 5. Alternatively, a biopsy may be considered for patients with a Deauville score of 5 and, if positive, alternative therapy for refractory disease should be pursued.

It must be underscored that the ECHELON-1 trial design was not PET-adapted; consequently, patients treated with ABVD who could have benefited from dose escalation according to current practices or for whom bleomycin could have been omitted were continued on ABVD. Consequently, the superiority of BV-AVD over PET-adapted ABVD according to RATHL study has not been established.

Based on data from the ongoing GHSG HD21 trial,[114] BrECADD is included as a treatment option in certain circumstances. BrECADD is initially administered for 2 cycles followed by restaging FDG-PET/CT. Patients with a Deauville score of 1 to 3 are treated with 2 additional cycles of BrECADD followed by reassessment with an FDG-PET/CT. Patients with a Deauville score of 1 to 3 should be followed and monitored for relapse/late effects (see *Follow-up After Completion of Treatment*), while a Deauville score of 4 to 5 warrants a biopsy. ISRT is recommended for those with a negative biopsy, while a positive biopsy warrants treatment as described for refractory disease.

For patients with a Deauville score of 4 to 5 after 2 initial cycles of BrECADD, a biopsy is recommended. If the biopsy is negative, 4 additional cycles of BrECADD are recommended followed by reassessment with FDG-PET/CT. Patients with a Deauville score of 1 to 3 should be followed and monitored. Repeat biopsy is recommended for those with a Deauville score of 4 to 5. For those with a negative biopsy, ISRT is recommended. For those with a positive biopsy, treatment is as described for refractory disease. Growth factor support should be given for all cycles of BrECADD.

Based on data from the ongoing SWOG S1826 trial,[116] N-AVD is also included as a treatment option in certain circumstances. N-AVD is initially administered for 6 cycles followed by restaging with FDG-PET/CT. Patients with a Deauville score of 1 to 3 should be followed and monitored for relapse/late effects (see *Follow-up After Completion of Treatment*). Biopsy is recommended for patients with a Deauville score of 4 to 5. If biopsy is positive, treatment is as described for refractory disease. If biopsy is negative, follow-up and monitoring for relapse/late effects is recommended.

Management of Classic Hodgkin Lymphoma in Adults Aged >60 Years or Adults with Poor Performance Status or Substantial Comorbidities

CHL in patients >60 years is associated with worse disease outcomes.[117] B symptoms, poor performance status, mixed cellularity, histologic subtype, Epstein-Barr virus-positive (EBV+) disease, and medical comorbidities are more frequent in this population.[118] Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and transplant-related mortality (TRM) in patients who are older.[119-122] However, there are limited prospective data evaluating alternatives to standard therapies for patients who are older. Selection of standard versus alternate first-line regimens for patients who are older or for patients with poor performance status or substantial comorbidities should be based on clinical judgment and patient's performance status, with the goal of minimizing toxicity while maximizing efficacy.

In the HD10 and HD13 trials led by the GHSG, the impact of bleomycin in the ABVD regimen in patients ≥60 years with stage I–II favorable HL was evaluated. Two hundred eighty-seven patients were randomized to receive: 2 cycles of ABVD or 2 cycles of AVD followed by 20 or 30 Gy IFRT (HD13 study) and 2 cycles of ABVD or 4 cycles of ABVD followed by 20 or 30 Gy IFRT (HD10 study).[123] Overall grade III–IV toxicity and grade III–IV leukopenia and infection rates were higher in patients receiving 4 cycles of ABVD. The results of the study suggested limited benefit in patients ≥60 years receiving more than 2 cycles of bleomycin.[123]

Due to pulmonary toxicity, bleomycin should be used with caution, as it may not be tolerated in patients who are older. In a retrospective analysis, 147 patients with stage I–IV HL aged ≥60 years were treated with ABVD and evaluated for toxicity and survival.[124] All patients received at least 1 full course of ABVD and 50 patients received additional RT (30–40 Gy). Bleomycin was removed or reduced in 53 patients due to pulmonary toxicity. CR was observed in 117 patients (80%) with a 5-year OS rate estimated at 67% (95% confidence interval [CI], 58–74).[124] Other risk factors that may be associated with bleomycin-induced pulmonary toxicity (BPT) include a history of smoking and use of granulocyte-colony stimulating factor (G-CSF) during treatment.[125,126]

In a phase II multicenter study, the impact of sequential BV given before and after AVD was examined in patients ≥60 years with untreated stage II–IV HL (n = 48).[127] After two lead-in doses of BV, 37 of 48 patients (77%) completed 6 cycles of AVD, and 35 patients (73%) received at least one BV consolidation.[127] Among 42 patients with evaluable response, the overall response and CR rates after 6 cycles of AVD were 95% and 90%, respectively.[127] By intent-to-treat analysis, the 2-year EFS, PFS, and OS rates were 80%, 84%, and 93%, respectively.[127]

The following regimens have also been used as front-line chemotherapy in patients who are older with HL:

- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)[128]
- BV plus DTIC[129,130]
- VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin)[131,132]
- BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)[122]
- PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine)[133]

NCCN Recommendations

The regimens listed below should be considered in patients >60 years or patients with poor performance status or substantial comorbidities to lessen or minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in patients who are older. Clinical trial is recommended when available.

Stage I–II Favorable Disease

ABVD and CHOP are included as primary treatment options for patients >60 years or patients with poor performance status or substantial comorbidities with stage I–II favorable disease.[57,123,124,128,132] In this setting, 2 cycles of ABVD, with or without 2 cycles of AVD, followed by ISRT is the preferred option. The other treatment regimen includes 4 cycles of CHOP with ISRT.

Stage I–II Unfavorable or Stage III–IV Disease

ABVD, BV lead in followed by AVD and BV maintenance, and CHOP with or without ISRT are included as primary treatment options for patients >60 years or patients with poor performance status or substantial comorbidities with stage I–II unfavorable or stage III–IV disease.[33,127-130,133] For the ABVD regimen, an FDG-PET scan follows treatment with 2 cycles of ABVD. Bleomycin should not be used beyond 2 cycles if included in the regimen. If the FDG-PET scan is negative (Deauville score 1–3), patients can be treated with 4 cycles of AVD (total of 6 cycles), although 2 cycles of AVD (total of 4 cycles) followed by ISRT may be considered for stage I–II unfavorable disease. If the FDG-PET scan is positive (Deauville score 4–5) after 2 cycles of ABVD, an individualized treatment plan should be developed.

Patients with Low EF

BV plus DTIC is included as a primary treatment option for patients with low EF.[129,130] Another option is to add dexrazoxane to ABVD or CHOP, with close cardiology follow-up.

Management of Classic Hodgkin Lymphoma During Pregnancy

CHL is the most common hematologic malignancy diagnosed during pregnancy, as the peak incidence coincides with the reproductive years.[134] CHL accounts for 6% of all cancers diagnosed during pregnancy[135] and as many as 3% of patients presenting with CHL present during pregnancy.[134] CHL in patients who are pregnant is enriched for the nodular sclerosis subtype and has a similar clinical presentation, natural history, and prognosis compared to patients who are not pregnant.[134]

Management of CHL during pregnancy requires a multidisciplinary approach including medical oncology, high-risk obstetrics, and neonatology, with the goal of maximizing the cure rate for the patient as well as allowing for the delivery of a healthy child.[134] Treatment of the patient who is pregnant should be individualized based on a multitude of factors, including the symptomatic burden and stage of disease, gestational age, and the beliefs and wishes of the patient.[134]

Complete radiologic staging of CHL is not required, given the need to minimize potential harm to the unborn fetus.[134] Radiologic imaging should, however, help to estimate the stage of disease and should include a PA chest x-ray with abdominal shielding and an abdominal ultrasound (US) or MRI without gadolinium.[134,135] FDG-PET and CT imaging should be avoided in order to minimize fetal radiation exposure.[134]

As most patients diagnosed with CHL during pregnancy have early-stage disease and present with minimal or no symptoms, it is often safe to defer treatment until after delivery with close monitoring and follow-up.[134,136-138] In a retrospective analysis by Evens and colleagues that examined treatment outcomes and complications for 90 patients with HL (n = 40) and non-Hodgkin lymphoma (NHL; n = 50) during pregnancy, there were no differences in maternal complications, median birth weight of infants, or perinatal events between those in whom therapy was deferred until the postpartum period and those who received antenatal treatment.[139] Twenty-five percent of the patients with HL in this study had advanced-stage disease.

For patients requiring treatment during pregnancy due to severe symptoms or organ compromise, RT should also be avoided given

potential risks of teratogenesis, prematurity, cognitive impairment, and childhood malignancy.[140] Chemotherapy should be avoided during the first trimester given the high risk of congenital malformations or fetal demise.[134,135] ABVD can be safely administered in the second and third trimesters with excellent maternal and fetal outcomes,[139,141,142] while intensive regimens such as escalated BEACOPP and BV + AVD should be avoided during pregnancy given the paucity of data. For those receiving chemotherapy during pregnancy, consultation with pharmacy is recommended to ensure supportive medications are appropriate for use in pregnancy. G-CSF is category C in pregnancy.[143] Ondansetron and metoclopramide are the preferred antiemetics for patients who are pregnant.[144,145] Breastfeeding should be avoided in patients receiving chemotherapy in the postpartum period.[134]

In the previously discussed retrospective analysis by Evens and colleagues, 20 patients with HL received chemotherapy with either ABVD or AVD, with 13 patients starting chemotherapy in the second trimester and 7 patients starting in the third trimester.[139] An additional 4 patients received RT during the second or third trimester. The overall response rate (ORR) for patients with HL who received antenatal therapy was 96%, with 83% of patients achieving CR. As previously noted, among all patients with HL with available obstetrical information, there were no differences in preterm or perinatal complications or median birth weight of infants between those who deferred therapy versus those who received antenatal chemotherapy or RT. There was, however, a trend towards patients who received antenatal therapy having infants who were small for gestational age (41% vs. 9% for patients in whom therapy was deferred, respectively; *P* = .09). Three-year PFS and OS rates for all patients with HL were 85% and 97%, respectively.

Another retrospective study examined maternal and fetal outcomes of 39 patients with lymphoma (31 with HL, 8 with NHL) during pregnancy.[141] Three women electively terminated pregnancy. Of the remaining 36 patients, 12 (31%) deferred therapy until delivery while 24 (61%) received antenatal therapy. Two patients received chemotherapy during the first trimester, one with ABVD or an ABVD-like regimen and the other with a CHOP or CHOP-like regimen. Twenty-two patients received therapy during the second or third trimesters, with 4 receiving RT, 13 receiving ABVD or ABVD-like regimens, and 5 receiving CHOP or CHOP-like regimens. The ORR for those who received antenatal therapy was 91.7%, with 75% achieving CR. Among those who did not electively terminate pregnancy, there were no differences in PFS, OS, or rates of preterm delivery among those who received antenatal care and those who deferred antenatal care until delivery. Of the 31 patients with HL, 5-year PFS was 69.9% and 5-year OS was 80%.

In another retrospective study investigating 134 patients diagnosed with HL during pregnancy, 56 patients (42%) deferred therapy, 72 patients (54%) received antenatal chemotherapy, and 6 patients (4%) received antenatal RT.[142] There were no differences in rates of neonates being small for gestational age or requiring neonatal intensive care unit (NICU) admission among those exposed to chemotherapy versus unexposed to chemotherapy, though those exposed to chemotherapy had lower birth weight percentiles (*P* = .035). In this study, patients who received antenatal therapy did have more obstetrical complications (*P* = .005), with the most common being preterm contractions and preterm rupture of membranes. A maternal survival analysis compared patients with HL who were pregnant (n = 77) versus not pregnant (n = 211) and found similar 5-year PFS and OS rates among those with early-stage HL (PFS, 82.6% vs. 88.3%, respectively; *P* = .13; OS, 97.3% vs. 98.4%, respectively; *P* = .534). Five-year PFS and OS rates were also similar among patients with HL who were pregnant versus not pregnant with advanced-stage disease (PFS, 90.9% vs. 74.0%, respectively; *P* = .334; OS, 100% vs. 96.2%, respectively; *P* = .146).

NCCN Recommendations for CHL During Pregnancy

For patients with CHL in the first trimester of pregnancy who are asymptomatic or minimally symptomatic, the panel recommends delaying treatment with close observation until the second or third trimester. For those in the first trimester of pregnancy with severe symptoms or organ compromise, referral to a center with expertise should be considered. Pregnancy termination or treatment with single-agent vinblastine followed by ABVD after the end of the first trimester may also be considered for those with severe symptoms or organ compromise.

For patients with CHL in the second or third trimester of pregnancy who are asymptomatic or minimally symptomatic, the panel recommends delaying treatment with close observation until after delivery. For those in the second or third trimester of pregnancy with severe symptoms or organ compromise, the panel recommends treatment with ABVD, with involvement of high-risk obstetrics to avoid delivery during the nadir period.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

NLPHL is characterized by an indolent course and occasional late relapse. It has a different natural history and response to therapy compared with CHL.[146] The majority of patients present with early-stage disease and rarely with B symptoms, mediastinal or extranodal involvement, or bulky disease.[147-149] Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma.[3,150] Data suggest outcomes differ for typical immunoarchitectural patterns (A/B) versus variant patterns (C/D/E/F), with the variant patterns being associated with advanced-stage disease and a higher risk of relapse.[3,151-153] In the retrospective analysis from the GHSG that included 394 patients with NLPHL, 63% had early-stage favorable, 16% had early-stage unfavorable, and 21% had advanced-stage disease. At a median follow-up of 50 months, FFTF (88% vs. 82%) and OS (96% vs. 92%) were better for NLPHL compared with CHL.[148] Among patients with NLPHL, FFTF was better for early-stage favorable disease (93%) compared with early-stage unfavorable (87%) and advanced-stage disease (77%). The European Task Force on Lymphoma also reported favorable FFTF for early-stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or stage IV (24%) disease.[147] Advanced stage at presentation, age (≥45 years), low hemoglobin, and the presence of B symptoms are associated with worse OS.[148,149]

Several retrospective studies have reported favorable clinical outcomes for patients with stage I to II disease treated with RT alone[154-158] or in combination with chemotherapy.[149,159,160] RT alone is an effective treatment option for patients with stage IA–IIA disease.[154,156,161] In a retrospective analysis, the Australasian Radiation Oncology Lymphoma Group reported follow-up of 202 patients with stage I–II NLPHL treated with RT alone, including mantle and total lymphoid irradiation (TLI).[156] At 15 years, FFP was 84% for patients with stage I disease and 73% for those with stage II disease. An additional retrospective analysis from the GHSG clinical trials reported favorable PFS and OS rates (91.9% and 99.0%, respectively) at 8 years in patients with stage IA disease treated with IFRT.[161] Among the studies that have evaluated the outcomes of patients treated with RT alone or CMT, the subgroup analysis of 64 patients with NLPHL included in the GHSG HD7 trial showed a non-significant trend toward better 7-year FFTF for the combined modality group (96%) compared with the extended-field RT (EFRT) group (83%; $P = .07$).[160] However, other retrospective studies have shown no difference in outcome between patients treated with RT alone or in combination with chemotherapy.[155,157,158] The GHSG retrospectively compared 3 treatment options, including EFRT, IFRT, and CMT in patients with stage IA NLPHL.[157] Median follow-up was 78 months for EFRT, 40 months for CMT, and 17 months for IFRT. CRs were observed in 98% after EFRT,

95% after CMT, and 100% after IFRT, and no significant differences were seen in FFTF, suggesting that IFRT is equally as effective as EFRT and CMT.

A report from the French Adult Lymphoma Study Group that analyzed the long-term outcomes of 164 patients with NLPHL (82% of patients had stage IA–IIA disease) included 58 patients who were observed following diagnosis and lymph node biopsy.[162] The 10-year PFS rate for this group of patients was 41% compared to 66% for patients who received specific treatment. However, the 10-year OS rate was not different between the two groups (91% and 93%, respectively), and 50% of patients treated with a watch-and-wait approach had achieved a CR at a median follow-up of 3 years. Watchful waiting has also been shown to be an appropriate treatment option in pediatric patients with early-stage NLPHL who are in CR following lymph node excision.[163,164]

Binkley et al reported an international retrospective review of 559 adult patients with stage I–II NLPHL treated with RT alone (n = 257), CMT (n = 184), chemotherapy alone (n = 47), observation (n = 37), rituximab plus RT (n = 19), or rituximab monotherapy (n = 15). The 5-year PFS and OS for the entire cohort were 87.1% and 98.3%, respectively.[165] The 5-year PFS rates were 91.1% after RT, 90.5% after CMT, 77.8% after chemotherapy alone, 73.5% after observation, 80.8% after rituximab plus RT, and 38.5% after rituximab monotherapy.[165] The variant immunoarchitectural pattern was associated with a worse PFS. Three point eight percent of patients developed large cell transformation.

Patients with advanced-stage NLPHL have a worse prognosis than those with early-stage favorable disease and can be treated with chemotherapy. In the European Task Force on Lymphoma study, the 8-year disease-specific survival and FFTF were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.[147] Most of these patients (80%–95%) were treated with chemotherapy (MOPP- or ABVD-like regimens), with or without RT.

In the absence of randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for NLPHL, although ABVD is often used based on the data for patients with CHL. Savage et al have reported that ABVD chemotherapy with (n = 89) or without (n = 11) RT was associated with superior outcomes compared to a historical cohort of patients treated with RT alone for stage IA, IB, or IIA NLPHL.[166] With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without RT had a superior 10-year time to progression (TTP) (98% vs. 76%), PFS (91% vs. 65%), and OS (93% vs. 84%) compared to those treated with RT alone. However, an analysis of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III–IV NLPHL treated with chemotherapy alone, showed that 75% of the 12 patients treated with ABVD or EVA (etoposide, vinblastine, and doxorubicin) and 32% of the 25 patients treated with alkylating agent-containing regimens (MOPP or MOPP/ABVD) had inferior outcomes.[167] Some investigators have also reported good response rates with CHOP plus rituximab[168-170] or CVbP (cyclophosphamide, vinblastine, and prednisolone) in patients with early-stage or advanced disease.[171]

Because NLPHL cells consistently express CD20 antigen, several clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody, for patients with newly diagnosed and relapsed or refractory NLPHL.[172-176]

In a prospective phase II trial conducted by the Stanford Group, patients with previously treated (n = 10) and untreated (n = 12) stage I–IV NLPHL received 4 weekly doses of rituximab at 375 mg/m^2. The ORR was 100% (41% CR, 54% partial response [PR], and 5% CR unconfirmed [CRu]). At a median follow-up of 13 months, 9 patients experienced relapse and the estimated median FFP was 10.2 months.[172] The estimated probability of

disease progression at 10.2 months was 52%. Rituximab was well tolerated, with few adverse side effects.

In a GHSG phase II study that investigated rituximab in patients with newly diagnosed stage IA NLPHL (n = 28), the ORR was 100% (CR and PR were achieved in 86% and 14% of patients, respectively). At a median follow-up of 43 months, the OS rate was 100%; the PFS rate at 12, 24, and 36 months was 96%, 85%, and 81%, respectively.[174] However, the relapse rate was 25%. In the GHSG phase II study that evaluated rituximab in patients with relapsed or refractory CD20-positive NLPHL (n = 15), the ORR was 94% (8 patients with CR and 6 patients with PR). At a median follow-up of 63 months, median TTP was 33 months and the median OS was not reached.[173]

Rituximab followed by rituximab maintenance has also been evaluated in patients with newly diagnosed and relapsed or refractory NLPHL. In a study conducted by the Stanford Group, patients with newly diagnosed or previously treated NLPHL (n = 39) were treated with rituximab (4 weekly doses of rituximab at 375 mg/m^2) or rituximab followed by rituximab maintenance (once every 6 months for 2 years).[176] The ORR was 100% (67% CR and 33% PR) at the end of initial therapy with rituximab alone. The median follow-up was 9.8 years for rituximab and 5 years for rituximab plus maintenance rituximab. The estimated 5-year PFS rate was 39.1% and 58.9%, respectively, for patients treated with rituximab and rituximab followed by maintenance rituximab. The corresponding 5-year OS rates were 95.7% and 85.7%, respectively. Rituximab as initial treatment was also associated with a pattern of relapse with evidence of transformation to aggressive B-cell lymphoma, primarily in patients with intra-abdominal disease. This underscores the importance of biopsy of intra-abdominal sites of disease at initial presentation or relapse. Rituximab maintenance for 2 years was associated with a non-significant increase in median PFS compared to rituximab alone (5.6 years and 3 years, respectively; *P* = .26).

Collectively, the above data suggest that rituximab alone or in combination with chemotherapy has activity in the management of newly diagnosed and relapsed NLPHL.[172,174,176]

NCCN Recommendations for NLPHL

Available evidence from retrospective studies supports the use of ISRT alone as a treatment option for patients with early-stage disease.[154-158]

The panel recommends that ISRT (30–36 Gy) be the preferred treatment for all patients with stage IA or contiguous stage IIA non-bulky disease. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky or non-contiguous disease. For select patients with stage IB or stage IIA non-contiguous disease, ISRT alone may be considered. Rituximab monotherapy can be used for palliation in select patients with stage IB, IIB, IA, or IIA bulky or non-contiguous disease.

Chemotherapy and rituximab with or without ISRT is recommended for all patients with stage III–IV disease. Alternatively, patients can be observed if asymptomatic, or treated with rituximab or with local RT for palliation of locally symptomatic disease. Abdominal involvement, especially involvement of the spleen, has been associated with the risk of transformation to an aggressive B-cell lymphoma.[176] Biopsy of persistent or new subdiaphragmatic sites should be considered to rule out transformation for patients with stage III or IV disease.

Restaging with FDG-PET should be done for all patients after completion of initial therapy. Observation is recommended for all patients who are

asymptomatic with a clinical response. ISRT is recommended if not received previously. Biopsy is recommended for patients with stable or progressive disease, especially of subdiaphragmatic sites. Patients who are asymptomatic with a negative biopsy can be observed. For those with a positive biopsy, treatment is as described for relapsed or refractory disease.

Rituximab may be used in combination with chemotherapy regimens that are most commonly used at NCCN Member Institutions (ABVD, CHOP, or CVbP).[166,167,169,171,177] Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for patients with NLPHL. The results of two large randomized trials have demonstrated the non-inferiority of subcutaneous rituximab (rituximab and hyaluronidase human injection for subcutaneous use) compared to IV rituximab when used in combination with chemotherapy in patients with certain subtypes of NHL.[178,179] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by IV infusion. An FDA-approved biosimilar is an acceptable substitute for rituximab after patients have received the first full dose of rituximab by IV infusion.

Follow-up After Completion of Treatment

Recommendations included in the Guidelines are based largely on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, since there are very few data available on the follow-up and monitoring of late effects in patients with HL, after completion of treatment.[180]

The panel overwhelmingly agrees that, given the long-term risks of the therapies for HL, patients should follow up with an oncologist who is aware of these risks and complications, and care should be coordinated with the primary care provider, especially during the first 5 years after treatment to detect recurrence and then annually due to the risk for late complications, including secondary cancers and cardiovascular disease.[180] The follow-up schedule should be individualized, depending on clinical circumstances such as patient's age, stage of disease, and initial treatment modality. Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects (secondary cancers, cardiac disease, and reproduction), health habits, and psychosocial issues (see the NCCN Guidelines for Survivorship). It is recommended that the patient be provided with a treatment summary at the completion of therapy, including details of RT, the dose to the OARs, and cumulative anthracycline dosage given.

Interim physical examinations and blood tests (CBC, platelets, chemistry profile, and ESR if elevated at initial diagnosis) should be performed every 3 to 6 months for 1 to 2 years, then every 6 to 12 months for the next 3 years, and then annually.[181] Patients who have had neck or superior mediastinal irradiation should have their thyroid function tested at least annually. Annual fasting glucose levels may also be monitored. An annual influenza vaccination and other vaccines as clinically indicated are recommended for all patients (see the NCCN Guidelines for Survivorship). In addition, patients treated with splenic RT or splenectomy should receive pneumococcal, meningococcal, and H-flu type b revaccination after 5 to 7 years (according to the current Centers for Disease Control and Prevention [CDC] recommendations).

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen.[182] Imaging should be obtained if there is significant clinical concern for relapse, or as mandated if enrolled in an active clinical trial protocol. Otherwise, diagnostic CT imaging should be obtained no more frequently than at 3-to-6-month intervals for up to 2 years as clinically indicated, or after 2 years if relapse is suspected. However, PET scans are not recommended for routine

surveillance due to the risk of false positives.[82,83,85] FDG-PET/CT should only be done if evaluating for potential relapse.

Monitoring for Late Effects

Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most significant late effects in long-term survivors of HL. The incidence of these late effects increases with longer follow-up time. The risk may be less with current treatment programs compared to those used >10 years ago.

Secondary Cancers

Solid tumors are the most common secondary cancers and most develop >10 years after the completion of treatment. The risk of developing secondary cancers is highest when RT is used as a component of first-line treatment. Meta-analysis by Franklin and colleagues showed that the risk of developing secondary cancers was lower with CMT than with RT alone as the initial treatment.[183] The risk was marginally higher with CMT when compared with chemotherapy alone as initial treatment. No significant differences in the risk of developing secondary cancers were seen with IFRT versus EFRT, although the risk of developing breast cancer was substantially higher for EFRT and was likely related to the extent of mediastinal and axillary irradiation. Risks for secondary lung cancer, NHL, and leukemia were increased after treatment with chemotherapy alone, whereas CMT was associated with an increased risk for these and several other cancers.[184] Lung cancer and breast cancer are the most common secondary cancers in patients treated for HL.

RT, and possibly some chemotherapy drugs such as alkylating agents, increase the risk of developing lung cancer, and the risk increases linearly with dose to the lung.[185,186] The increased risk is most apparent in people who smoke, particularly those who continue to use tobacco after diagnosis.[187]

In fact, continuing to smoke after thoracic RT multiplies the risk of developing lung cancer. Therefore, a concerted effort should be made to help patients who currently smoke and require thoracic RT to stop smoking. Lung cancer screening with low-dose CT may also be appropriate depending upon clinical circumstances including age and pack-year tobacco exposure history. See NCCN Guidelines for Lung Cancer Screening.

Breast cancer is the most common malignancy in individuals AFAB and the risk is increased with doses as low as 4 Gy. Annual breast screening (mammography and MRI) beginning 8 years after completion of therapy or at age 40 years (whichever occurs earlier) is recommended for patients who have received chest or axillary irradiation.[182] They should also be encouraged to be familiar with their breasts and any changes to them (breast awareness) and undergo breast examination by a health care professional 1 to 2 times per year. In a prospective study that evaluated the sensitivity and specificity of breast MRI with that of mammography in females who received chest irradiation for HL, the sensitivity of the combined MRI and mammography as a combined screening modality was higher than that of MRI or mammography alone (94% for combined MRI and mammography; 67% and 68%, respectively, for MRI and mammography).[188] NCCN Guidelines recommend breast MRI in addition to mammography, often alternated every 6 months, for patients who received irradiation to the chest between ages 10 and 30 years, which is consistent with the recommendation of the American Cancer Society Guidelines.[189] Neither MRI nor mammography should be pursued until a patient is at least 25 years of age. See NCCN Guidelines for Breast Cancer Screening and Diagnosis (BSCR-3). There are limited data on screening in individuals assigned male at birth at increased risk.

Chemoprevention with selective estrogen receptor modulators and aromatase inhibitors have been shown to reduce the risk of breast cancer

by 50% to 60% in high-risk populations. These trials, however, did not include individuals with prior breast RT for non-epithelial breast cancers. Patients should consider discussion of chemoprevention with their oncologist or breast specialist. See NCCN Guidelines for Breast Cancer Risk Reduction.

NCCN Guidelines recommend that routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer be performed as per the NCCN Guidelines for Detection, Prevention, and Risk Reduction and the American Cancer Society Guidelines.[190]

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.[191-193] RT-induced cardiotoxicity is usually observed >5 to 10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Coronary CT angiography abnormalities have been detected in nearly 15% of patients within the first 5 years after treatment, and their incidence significantly increases 10 years after treatment.[194] In a multivariate analysis, patient's age at treatment, hypercholesterolemia, hypertension, and RT dose to the coronary artery origins were identified as independent prognostic factors.

Based on data regarding increased long-term risk of cardiac disease, annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors is recommended.[182] A baseline stress test, echocardiogram, or coronary artery calcium (CAC) score and carotid US (for patients treated with neck RT) should be considered at 10-year intervals after completion of treatment.[182,195]

Hypothyroidism

Abnormal thyroid function, mostly hypothyroidism, is reported in approximately 50% of long-term survivors who received neck or upper mediastinal irradiation.[180] A careful thyroid examination should be a part of the physical examination. Thyroid function tests should be done at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression

Myelosuppression is the most common side effect of chemotherapy and is associated with increased risk of infections. It is uncommon for myelosuppression to continue for very long beyond completion of the primary treatment program. However, patients who undergo high-dose therapy (HDT)/autologous stem cell rescue (ASCR) or allogeneic hematopoietic cell transplant (HCT) may be at continued risk for infection. Pneumococcal, meningococcal, and H-flu revaccinations are recommended every 5 years for patients treated with splenic RT or splenectomy.[196]

Infertility

Certain chemotherapy combinations (eg, escalated BEACOPP) may cause immediate and permanent infertility.[197,198] Other combinations (eg, ABVD) are only rarely associated with infertility.[93,199] Since patients with ovaries who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause,[91] this should be taken into consideration with respect to family planning.

Pulmonary Toxicity

BPT is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation, and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity. Martin and colleagues reported that BPT significantly decreases the 5-year OS rate, especially in patients ≥40 years.[200] They also showed that the use of growth factors with chemotherapy significantly increases the incidence of BPT (26% vs.

9%). Two separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.[201,202] Five-year EFS (87.4% vs. 80%, respectively) and OS (94.1% vs. 91.3%, respectively) rates in patients who received ABVD with no growth factors were comparable to those in patients who received prophylactic growth factor support with the ABVD regimen.[202]

Neutropenia is not a risk factor for reduction of dose intensity with ABVD. The NCCN Guidelines do not recommend the routine use of growth factors with ABVD regimens.

Relapsed or Refractory Disease

Classic Hodgkin Lymphoma

Two randomized phase III studies performed by the British National Lymphoma Investigation[203] and the GHSG/European Group for Blood and Marrow Transplantation[204] have compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvements in EFS, PFS, and FFTF (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone.

Studies have suggested that patients with a CR or with chemosensitive disease to second-line therapy have improved outcomes following HDT/ASCR compared to those with resistant disease.[205,206] Moskowitz et al reported that the EFS, PFS, and OS were significantly better for patients with disease responding to second-line chemotherapy (60%, 62%, and 66%, respectively) compared to those whose disease had a poor response (19%, 23%, and 17%, respectively) ($P < .001$).[205] Sirohi et al also reported similar findings; the 5-year OS rate was 79%, 59%, and 17%, respectively, for patients who were in CR, PR, or those with resistant disease at the time of HDT/ASCR ($P < .0001$), and the 5-year PFS rates were 69%, 44%, and 14%, respectively ($P < .001$).[206]

Several investigators have developed prognostic models to predict the outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice and colleagues used end-of-treatment to relapse interval (≤12 months) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR.[207] The PFS rates were 93%, 59%, and 43%, respectively, for patients with 0, 1, or 2 of these risk factors. In a prospective study, Moskowitz and colleagues identified extranodal sites, CR duration of <1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR.[208] In patients with 0 to 1 risk factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of treatment for relapsed or refractory disease to improve EFS in patients with poor-risk disease.[209] In a retrospective analysis of 422 patients with relapsed disease, Josting and colleagues from the GHSG identified time to relapse, clinical stage at relapse, and anemia at relapse as independent risk factors to develop a prognostic score that classified patients into four subgroups with significantly different freedom from second failure and OS.[210] Investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first CR (<1 year), detectable disease at transplant, and the presence of more than 1 extranodal site as adverse factors for OS.[211] Other groups have identified extent of prior chemotherapy,[212] short time from diagnosis to transplant,[213] and disease status at transplantation[214] as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome and it may be the most important factor in patients with recurrent/refractory HL.[215-218] The main potential of these prognostic factor studies is to facilitate comparison of outcomes at different centers, where the preparatory regimens may vary.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.[208,219-227] ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, cisplatin, and high-dose cytarabine) are the most commonly used regimens. Gemcitabine-based combination regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),[228] IGEV (ifosfamide, gemcitabine, and vinorelbine),[229] GCD (gemcitabine, cisplatin, and dexamethasone),[230,231] and GEMOX (gemcitabine and oxaliplatin)[232] have also been effective for relapsed or refractory HL. However, none of these regimens have been studied in randomized trials.

Bendamustine, lenalidomide, and everolimus as single agents have also shown activity in patients with relapsed or refractory HL.[233-235] In a phase II trial, bendamustine was well tolerated and highly active in patients with heavily pretreated relapsed or refractory disease (including those with HL whose disease did not to respond to HDT/ASCR treatment), resulting in an ORR of 56% among patients with evaluable data (34 out of 36 patients enrolled).[233] The ORR by intent-to-treat analysis was 53% (33% CR and 19% PR). The median response duration was 5 months. Lenalidomide and everolimus have also shown single-agent activity in a small cohort of patients with relapsed or refractory HL, resulting in ORRs of 19% and 47%, respectively.[234,235] In a phase II study, bendamustine in combination with gemcitabine and vinorelbine (BeGEV) was used as induction therapy before HDT/ASCR in patients with relapsed or refractory HL, resulting in an ORR of 83% (73% CR and 10% PR).[236] In a phase I/II study, bendamustine with carboplatin and etoposide also demonstrated 85% response rates (70% CR) in patients with relapsed or refractory HL.[237]

BV, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[238,239] In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, BV induced objective responses and CRs in 75% and 34% of patients, respectively, with a median follow-up of more than 1.5 years. The median PFS for all patients and the median duration of response for those in CR were 5.6 months and 20.5 months, respectively.[238] Based on the results of this study, the FDA approved BV for the treatment of patients with HL after failure of HDT/ASCR or at least two prior chemotherapy regimens in patients who are not candidates for HDT/ASCR. The 3-year follow-up data confirmed durable remissions in patients with disease responding to BV.[239] After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 months and 9.3 months, respectively. In patients who achieved a CR on BV, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.[239] A systematic review and meta-analysis of effectiveness outcomes for BV revealed similar results to the pivotal phase II trial, with pooled ORR estimates of 62.6% after 4 cycles, 66.7 after 4 to 6 cycles, and 72% after more than 6 cycles. Pooled CR rates were similar between all cycle subgroups, at 33.4% after more than 6 cycles.[240]

Several studies are investigating the utility of BV in combination with other regimens, as second-line therapy for relapsed or refractory disease prior to HDT/ASCR. Preliminary data from studies that have evaluated BV in combination with ICE or bendamustine have reported PET-negative responses ranging from approximately 75% to 90%.[241-243] A trial from Memorial Sloan Kettering Cancer Center (MSKCC) used a PET-adapted design in which 45 patients received 2 cycles of BV followed by a PET scan.[241] Patients who achieved a CR after BV (27%) proceeded directly to HDT/ASCR, while patients with residual disease received 2 cycles of augmented ICE. Overall, 76% of patients achieved a CR prior to HDT/ASCR using this PET-adapted approach.[241] A similar approach was used by investigators at City of Hope National Medical Center in which 37 patients received 4 cycles of BV followed by a PET scan.[244] Patients who achieved a CR after BV (35%) proceeded directly to HDT/ASCR, while those with residual disease received platinum-based chemotherapy.

Overall, 65% of patients achieved a CR prior to HDT/ASCR using this approach.[244]

The use of BV as consolidation therapy following HDT/ASCR was evaluated in the AETHERA trial.[245] For patients with high-risk disease, defined as having primary refractory disease, duration of first CR <1 year, or relapse with extranodal or advanced-stage disease, the phase 3 AETHERA trial randomized patients to receive up to 16 cycles of BV consolidation or placebo post-HDT/ASCR. Patients were required to have obtained a CR, PR, or stable disease to second-line therapy prior to HDT/ASCR. At 5-year follow-up, there was a sustained PFS benefit with BV consolidation compared to placebo (5-year PFS, 59% vs. 41%; HR, 0.52; 95% CI, 0.38–0.72) but no difference in OS. Peripheral sensory neuropathy was a common side effect of BV consolidation, but improved or resolved in the majority of patients after discontinuing therapy.[246]

Attempts to increase the CR rate prior to HDT/ASCR have led to numerous trials incorporating novel agents into initial second-line therapy. Checkpoint inhibitors (CPIs), including programmed cell death protein 1 (PD-1)-blocking monoclonal antibodies (eg, nivolumab or pembrolizumab), have also demonstrated activity in patients with relapsed or refractory PD-1–positive lymphomas (either as monotherapy or in combination regimens).[247-256]

In a phase II study (CheckMate 205 trial) of 80 patients with relapsed or refractory HL pretreated with both HDT/ASCR and BV, at a median follow-up of 8.9 months, nivolumab monotherapy induced an ORR of 66.3% (95% CI, 54.8–76.4) as determined by an independent radiologic review committee.[248] Extended follow-up of the CheckMate 205 trial analyzed the safety and efficacy of nivolumab in patients with relapsed or refractory HL according to treatment history: BV-naïve, BV after HDT/ASCR, or BV received before and/or after HDT/ASCR.[249] The ORR was 69% (95% CI, 63%–75%) overall and 65% to 73% in each cohort, with a median duration of response of 16.6 months (95% CI, 13.2–20 months).[249]

In a phase III trial (KEYNOTE-204), pembrolizumab monotherapy versus BV was evaluated on the parameters of safety and efficacy in adults with relapsed or refractory CHL (patients who were ineligible for transplant or those with relapse after autologous HCT); 151 patients were randomly assigned to pembrolizumab and 153 patients to BV.[254] At second interim analysis, primary endpoint PFS (OS not analyzed in interim analysis) was 13.2 months for pembrolizumab, and 8.3 months for BV (P = .0027).[254] Treatment-emergent adverse events (TEAEs) were observed in 74% of patients receiving pembrolizumab and 77% of patients receiving BV. The most common grade 3–5 TEAEs were pneumonitis (4% in the pembrolizumab group vs. 1% in the BV group), neutropenia (2% vs. 7%, respectively), decreased neutrophil count (1% vs. 5%, respectively), and peripheral neuropathy (1% vs. 3%, respectively).[254] Serious TEAEs were observed in 16% of patients receiving pembrolizumab and 11% of patients receiving BV.[254]

Nivolumab in combination with BV was evaluated as an option for relapsed or refractory HL prior to transplant.[251] In a phase I/II study of 91 patients with relapsed or refractory CHL, the combination of nivolumab with BV resulted in an ORR of 85% (67% CR). At a median follow-up of 34 months, the estimated 3-year PFS and OS rates were 77% (91% for patients who underwent HDT/ASCR directly after study treatment with BV + nivolumab) and 93%, respectively.[251] Nivolumab alone or in combination with ICE as second-line therapy and bridge to autologous HCT was studied in a phase II trial in patients with relapsed or refractory CHL.[256] In this study, patients received up to 6 cycles of nivolumab. Those in CR after cycle 6 went on to autologous HCT while those with progressive disease at any point or those not in CR after cycle 6 received 2 cycles of nivolumab plus ICE. Following nivolumab alone, ORR and CR rates were

81% and 71%, respectively. Following nivolumab/nivolumab plus ICE, ORR and CR rates were 93% and 91%, respectively. Two-year PFS and OS were 72% and 95%, respectively, in all patients, with 2-year PFS of 94% in those who bridged directly to autologous HCT.[256]

Pembrolizumab used in combination with GVD has also demonstrated activity as second-line treatment in transplant-eligible patients with relapsed or refractory CHL resulting in a CR rate of 95%.[255] At a median follow-up of 13.5 months, all patients who had undergone transplant had achieved remission.

The role of RT in the second-line therapy setting includes its use to cytoreduce prior to HDT/ASCR, its selective use to sites of relapse following HDT/ASCR, and occasionally its use as a primary component of second-line therapy. Moskowitz and colleagues have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed or refractory disease.[208] At a median follow-up of 43 months, the response rate to ICE and IFRT was 88% and the EFS rate for patients who underwent HDT/ASCR was 68%. Thus, RT may improve the chance of transitioning to HDT/ASCR in relapsed or refractory disease. Alternately, second-line RT may be effective in patients who are in good performance status with limited-stage late relapses and without B symptoms. It may be a very effective treatment for patients with initial favorable stage I–II disease who are treated with chemotherapy alone and relapse in initially involved sites. Josting and colleagues from the GHSG reported that second-line RT may be effective in a select subset of patients with relapsed or refractory disease.[257] The 5-year FFTF and OS rates were 28% and 51%, respectively. B symptoms and stage at the time of disease progression or relapse were identified as significant prognostic factors for OS. A comprehensive review and recommendations for incorporation of RT into treatment regimens for relapsed or refractory disease are provided by the International Lymphoma Radiation Oncology Group consensus guidelines.[258]

NCCN Recommendations for Refractory CHL

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. For biopsy-proven refractory disease, enrollment in a clinical trial is recommended, if available. Referral to or consultation with a center with expertise should be pursued. Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or systemic therapy with or without RT. Conventional-dose second-line systemic therapy may precede HDT/ASCR. RT should be strongly considered for selected sites of relapse that have not been previously irradiated. In patients who have not previously undergone radiation, TLI may be an appropriate component of HDT/ASCR.[259]

Second-line systemic therapy followed by response assessment with FDG-PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should proceed to HDT/ASCR with or without RT (category 1). Observation with or without RT can be considered, if HDT/ASCR is contraindicated. Maintenance therapy with BV can be considered for patients with high risk of relapse as defined by the AETHERA trial (defined as those having primary refractory disease, duration of first CR <1 year, or relapse with extranodal or advanced-stage disease).[245] An alternative regimen with or without RT or RT alone is recommended for patients with a Deauville score of 4 or 5 after second-line systemic therapy. Autologous or allogenic HCT following additional therapy may be considered in these patients. Another approach for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT, followed by maintenance therapy with BV for patients with a high risk of relapse. It is worth noting that the role of maintenance BV has not been well defined in patients who received BV earlier in the management of their disease. CPIs can be

continued despite progression on imaging if patients are deriving clinical benefit, as imaging progression may be indicative of immune flare rather than true progression.[260]

BV alone or in combination with bendamustine, nivolumab, or ICE[243,251,261,262]; DHAP[220,223]; GVD with or without pembrolizumab[228,255]; ICE alone or in combination with nivolumab[208,220,256] or pembrolizumab[263]; IGEV[229]; BeGEV[236]; and single agent pembrolizumab[253,254] regimens are included as options for second-line and subsequent therapy for patients with relapsed or refractory CHL. Bendamustine, bendamustine/carboplatin/etoposide, everolimus, GCD (gemcitabine, cisplatin, dexamethasone), GEMOX (gemcitabine, oxaliplatin), lenalidomide, and vinblastine are included as therapy options for patients with disease refractory to at least 3 prior lines of therapy.[230,232-235,237,264] Nivolumab alone [248,249] is also included as a therapy option for disease refractory to at least 3 prior lines of systemic therapy and also for patients with relapse or disease progression following HDT/ASCR.

Allogeneic HCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was greater than 50%. Allogeneic HCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.[265,266] However, this approach remains investigational. Nonmyeloablative allogeneic HCT and post-infusion cyclophosphamide have excellent outcomes even in patients undergoing haploidentical HCT with estimated OS and PFS rates of 63% and 59%, respectively, at 3 years.[267] The panel has included allogeneic HCT with a category 3 recommendation for select patients with relapsed or refractory disease. Autologous or allogeneic HCT is an option for patients with FDG-PET–positive refractory HL (Deauville 5) that is responsive to RT alone or to subsequent systemic therapy, with or without RT. If a CPI is used for relapsed or refractory disease prior to allogeneic HCT, the transplant regimen needs to be carefully considered by the transplant team due to potential increased risk of immune-related toxicities.

NCCN Recommendations for Relapsed CHL

Suspected relapse at any point should be confirmed with biopsy. Observation (with short-interval follow-up with FDG-PET/CT) is appropriate if biopsy is negative. As for patients with refractory CHL, if biopsy is positive, enrollment in a clinical trial is recommended if available and referral to or consultation with a center with expertise should be pursued. Restaging is recommended for patients with positive biopsy. Most patients require second-line systemic therapy followed by RT or HDT/ASCR with or without ISRT. For patients with initial stage I–IIA disease treated initially with abbreviated chemotherapy alone (3–4 cycles) and relapsed in initial sites of disease, RT alone may be appropriate.

Restaging after completion of treatment is recommended for all patients. Subsequent treatment options (based on the score on interim FDG-PET scan) are as described for patients with refractory disease.

NCCN Recommendations for the Management of Relapsed or Refractory CHL in Adults Aged >60 Years or Adults with Poor Performance Status or Substantial Comorbidities

Outcomes are uniformly poor for patients who are older with relapsed or refractory disease.[268] No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended. Palliative therapy options include bendamustine,[233] BV,[269] nivolumab,[248,249] and pembrolizumab.[254] Nivolumab or pembrolizumab may be considered when patients have been previously treated with BV or after three or more lines of systemic therapy, including HDT/ASCR. ISRT alone is an option when systemic therapy is not considered feasible or safe. Use of everolimus,[235] or lenalidomide,[234] remains untested in the current era, where BV and CPIs are used in the relapsed setting.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Relapsed or refractory NLPHL can be managed with second-line therapy as described below. However, some patients have chronic indolent disease and may not require aggressive treatment. Individualized treatment is recommended since there are no data available to support a superior outcome with any of the treatment modalities. Rituximab should be considered with all second-line chemotherapy regimens for patients with relapsed or refractory NLPHL.

NCCN Recommendations for Refractory or Suspected Relapsed NLPHL

Late relapse or transformation to diffuse large B-cell lymphoma (DLBCL) has been reported in patients with NLPHL.[270-272] In a study of 95 patients diagnosed with NLPHL, with a median follow-up of 6.5 years, transformation to aggressive lymphoma was seen in 13 (14%) patients and the actuarial risk at 10 and 20 years was 7% and 30%, respectively.[272]

Re-biopsy should be considered to rule out transformation to aggressive lymphoma prior to initiation of treatment for refractory disease or suspected disease relapse. Patients with a negative biopsy can be observed with short-interval follow-up. All patients with biopsy-proven relapsed NLPHL should be observed or treated with second-line therapy (rituximab and/or chemotherapy and/or ISRT) followed by restaging with FDG-PET/CT. No further treatment is necessary for patients with clinical response. Biopsy is recommended for patients with progressive disease to rule out transformation. At this stage, treatment is as described for refractory disease or treatment with any second-line therapy that was not previously used (rituximab and/or chemotherapy and/or ISRT) can be pursued, followed by re-evaluation with FDG-PET. Maintenance rituximab for 2 years may be considered for patients treated with rituximab alone.[176] Disease transformation to DLBCL should be managed as discussed in the NCCN Guidelines for B-Cell Lymphomas.

Summary

HL is an uncommon malignancy of B-cell origin. CHL and NLPHL are the two main types of HL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL is characterized by the presence of lymphocytic and histiocytic (LP or “popcorn”) cells.

Current management of CHL involves initial treatment with chemotherapy or CMT, followed by restaging with FDG-PET/CT to assess treatment response using the Deauville criteria (5-PS). CMT or chemotherapy alone are included as treatment options for patients with stage I or II CHL. Systemic therapy (ABVD and BV-AVD are included as preferred treatment options) followed by restaging with FDG-PET/CT to assess treatment response is recommended for patients with stage III–IV CHL.

Second-line systemic therapy followed by HDT/ASCR with or without RT is recommended for patients with relapsed or refractory CHL. Maintenance therapy with BV following HDT/ASCR can be considered for patients with high risk of relapse. Nivolumab, pembrolizumab, or BV (as monotherapy or in combination regimens) are also included as options for relapsed or refractory disease in appropriate patients.

ISRT is the preferred treatment for patients with stage IA or IIA non-bulky NLPHL. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky or non-contiguous disease. Palliative rituximab can be considered for palliation in select patients with stage IA or IIA bulky or non-contiguous disease or stage IB or IIB disease. Chemotherapy with rituximab and with or without ISRT is recommended for all patients with stage III–IV disease. Alternatively, selected patients with stage III–IV

disease can either be observed (if asymptomatic) or treated with local palliative RT or rituximab.

Late relapse or transformation to DLBCL has been reported in patients with NLPHL. In patients with suspected relapse, re-biopsy should be considered to rule out transformation to DLBCL. Relapsed or refractory NLPHL can be treated with second-line therapy. However, some patients have chronic indolent disease and may not require aggressive treatment, unless they are symptomatic.

Long-term follow-up with careful monitoring for late treatment-related side effects and counseling about issues of survivorship should be an integral part of management of HL. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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