Hodgkin Lymphoma, Version 2.2020

Richard T. Hoppe, MD[1,*]; Ranjana H. Advani, MD[1,*]; Weiyun Z. Ai, MD, PhD[2]; Richard F. Ambinder, MD, PhD[3]; Philippe Armand, MD, PhD[4]; Celeste M. Bello, MD, MSPH[5]; Cecil M. Benitez, PhD[1]; Philip J. Bierman, MD[6]; Kirsten M. Boughan, MD[7]; Bouthaina Dabaja, MD[8]; Leo I. Gordon, MD[9]; Francisco J. Hernandez-Ilizaliturri, MD[10]; Alex F. Herrera, MD[11]; Ephraim P. Hochberg, MD[12]; Jiayi Huang, MD[13]; Patrick B. Johnston, MD, PhD[14]; Mark S. Kaminski, MD[15]; Vaishalee P. Kenkre, MD[16]; Nadia Khan, MD[17]; Ryan C. Lynch, MD[18]; Kami Maddocks, MD[19]; Jonathan McConathy, MD, PhD[20]; Matthew McKinney, MD[21]; Monika Metzger, MD[22]; David Morgan, MD[23]; Carolyn Mulroney, MD[24]; Rachel Rabinovitch, MD[25]; Karen C. Rosenspire, MD, PhD[26]; Stuart Seropian, MD[27]; Randa Tao, MD[28]; Jane N. Winter, MD[9]; Joachim Yahalom, MD[29]; Jennifer L. Burns[30,*]; and Ndiya Ogba, PhD[30,*]

ABSTRACT

The NCCN Clinical Practice Guidelines in Oncology for Hodgkin Lymphoma (HL) provide recommendations for the management of adult patients with HL. The NCCN panel meets at least annually to review comments from reviewers within their institutions, examine relevant data, and reevaluate and update their recommendations. Current management of classic HL involves initial treatment with chemotherapy alone or combined modality therapy followed by restaging with PET/CT to assess treatment response. Overall, the introduction of less toxic and more effective regimens has significantly advanced HL cure rates. This portion of the NCCN Guidelines focuses on the management of classic HL.

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[1]Stanford Cancer Institute; [2]UCSF Helen Diller Family Comprehensive Cancer Center; [3]The Sidney Kimmel Comprehensive Cancer Center at John Hopkins; [4]Dana-Farber/Brigham and Women's Cancer Center; [5]Moffitt Cancer Center; [6]Fred & Pamela Buffett Cancer Center; [7]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [8]The University of Texas MD Anderson Cancer Center; [9]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [10]Roswell Park Comprehensive Cancer Center; [11]City of Hope National Medical Center; [12]Massachusetts General Hospital Cancer Center; [13]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [14]Mayo Clinic Cancer Center; [15]University of Michigan Rogel Cancer Center; [16]University of Wisconsin Carbone Cancer Center; [17]Fox Chase Cancer Center; [18]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [19]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [20]O'Neal Comprehensive Cancer Center at UAB; [21]Duke Cancer Institute; [22]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [23]Vanderbilt-Ingram Cancer Center; [24]UC San Diego Moores Cancer Center; [25]University of Colorado Cancer Center; [26]Abramson Cancer Center at the University of Pennsylvania; [27]Yale Cancer Center/Smilow Cancer Hospital; [28]Huntsman Cancer Institute at the University of Utah; [29]Memorial Sloan Kettering Cancer Center; and [30]National Comprehensive Cancer Network.

*Discussion Writing Committee Member.

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 noted.

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.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

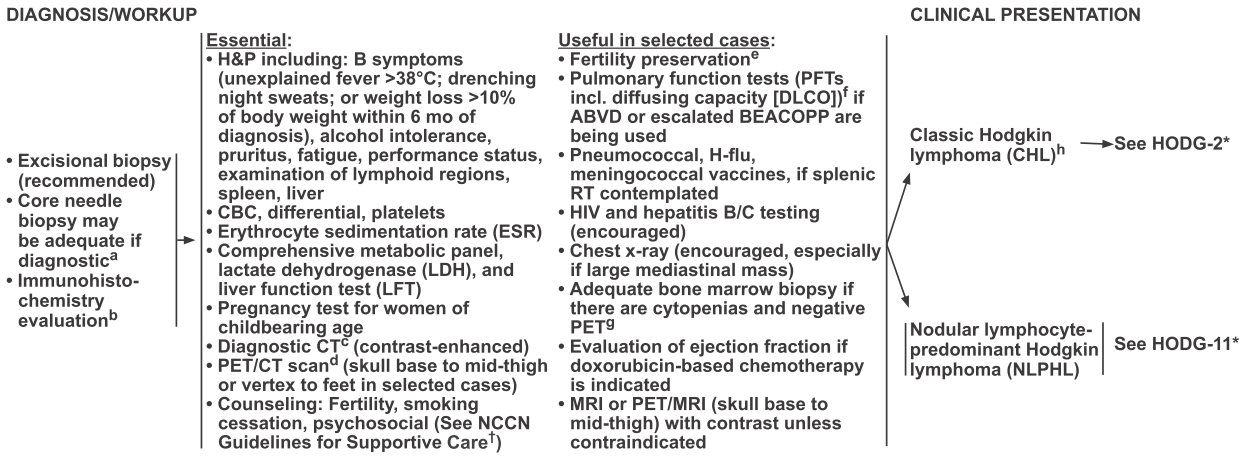
The complete NCCN Guidelines for Hodgkin Lymphoma are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Hodgkin Lymphoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Hodgkin Lymphoma Panel members can be found on page 781. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[a]Fine-needle aspiration (FNA) alone, in distinction from a core biopsy, is insufficient for diagnosis except in unusual circumstances when in combination with immunohistochemistry it is judged adequate by a hematopathologist or cytopathologist.

[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; 2008). An expanded panel of markers may be required, especially if equivocal diagnosis. See NCCN Guidelines for B-Cell Lymphomas[†].

[c]CT is considered diagnostic if it is IV contrast-enhanced. CT component of a conventional PET/CT is often not IV contrast-enhanced. Although the diagnostic CT will often be neck/chest/abdomen/pelvis, at minimum include the areas identified as abnormal on PET/CT.

[d]See Principles of FDG-PET/CT (HODG-A*). PET/CT should be obtained in accordance with American College of Radiology (ACR) practice guidelines. PET/CT should be done with patient on a flat table with arms up, if possible. In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1*).

[e]Fertility preservation options include: semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

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

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

[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas[†].

*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.

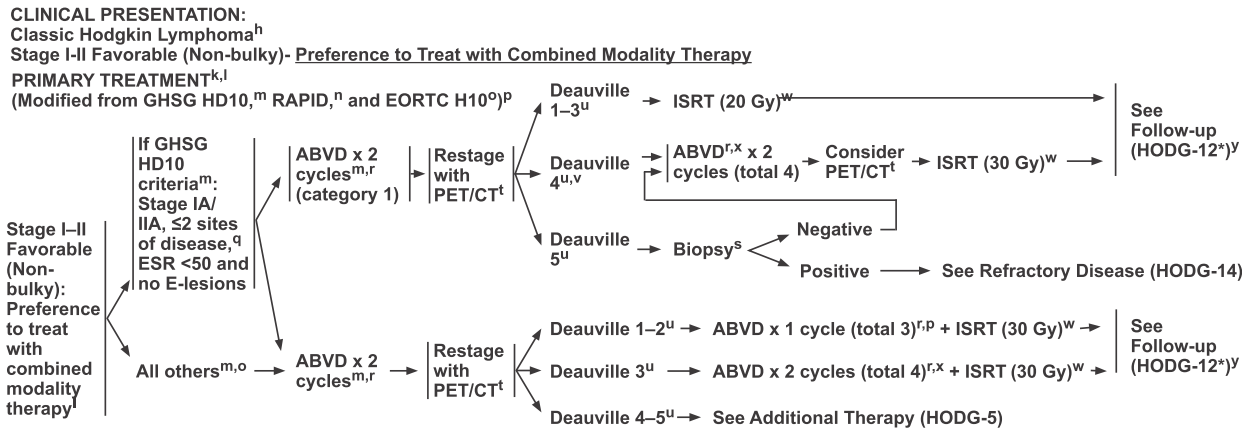
HODG-1

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. In 2020, an estimated 8,480 people will be diagnosed with HL in the United States and 970 people will die of the disease.[1] The WHO classification divides HL into 2 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. CHL is divided into 4 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 patients with HL; it is now curable in at least 80% of patients. The advent of more effective treatment options has improved 5-year survival rates, which have been unmatched in any other cancer over the past 4 decades. Every patient with newly diagnosed HL has an overwhelming likelihood of being cured with the appropriate treatment. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease. 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 Guidelines for HL discuss the clinical management of patients with CHL and NLPHL, focusing on adult patients 18 years and older who do not have serious intercurrent disease. The guidelines do not address HL in pediatric patients or those with unusual situations, such as HIV positivity or pregnancy. Individualized treatment may be necessary for older patients and those with concomitant disease. Consistent with NCCN philosophy, participation in clinical trials is always encouraged. This portion of the guidelines



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas†.
[k]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).
[l]Other recommended primary therapy regimens include: Stanford V x 8 weeks + 30 Gy ISRT (Advani RH, et al. Ann Oncol 2013;24:1044-1048.)
[m]The GHSG HD10 trial did not use PET after ABVD x 2 cycles to define eligibility for ISRT. GHSG HD10 study: Engert A, et al. N Engl J Med 2010;363:640-652.
[n]RAPID study: Radford J et al. N Engl J Med 2015;372:1598-1607.
[o]EORTC/LYSA/FIL H10 Trial: Andre MPE, et al. J Clin Oncol 2017;35:1786-1794.
[p]In general these studies show an improvement in PFS for combined modality therapy, but no difference in overall survival.
[q]See Definitions of Lymph Node Regions (HODG-B*).
[r]See Principles of Systemic Therapy (HODG-C).
[s]Biopsy recommended to differentiate refractory Hodgkin lymphoma from discordant histology with appropriate action based upon results. If no biopsy is done, clinical judgment should define management.
[t]An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A*).
[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
[v]Deauville 4 is often difficult to assess and treatment decisions will require clinical judgment (See Discussion).
[w]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D*).
[x]Consider PFTs after 4 cycles of ABVD.
[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

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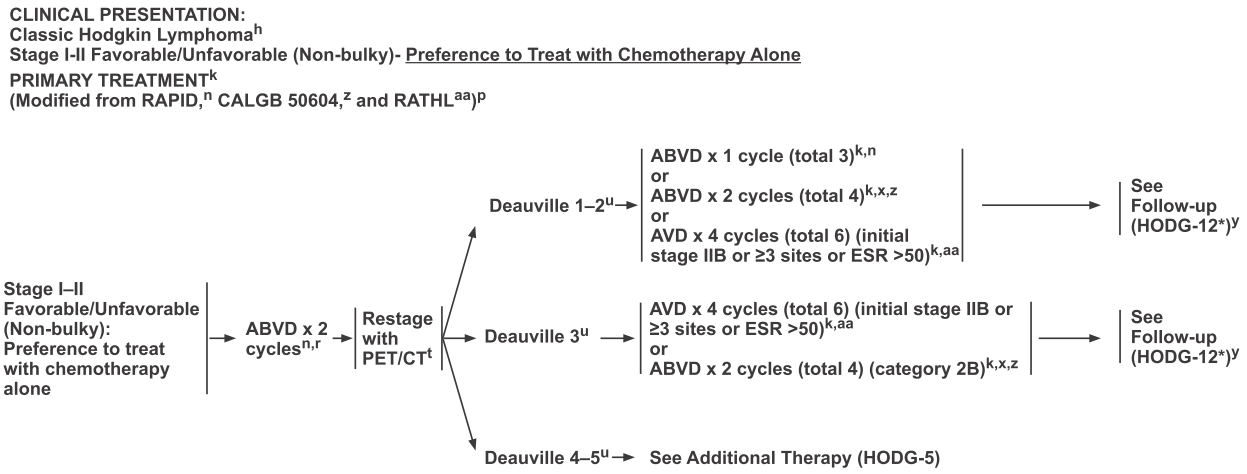
HODG-3

discusses recommendations for the workup, diagnosis, and management of CHL. According to NCCN categories of evidence and consensus, all outlined NCCN recommendations are considered to be category 2A, unless otherwise noted. For the complete and most updated version of these guidelines and for additional guidelines and recommendations for NLPHL, visit NCCN.org.

Diagnosis/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 (see HODG-1, page 756). A diagnostic assessment based solely on fine-needle aspiration biopsy is insufficient except in unusual circumstances when in combination with immunohistochemistry it is judged to be diagnostic of HL by an expert hematopathologist or cytopathologist. Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, and PAX5 is recommended for CHL. The Reed-Sternberg cells of CHL express CD30 in all patients and CD15 in most patients; they are usually negative for CD3 and CD45. CD20 may be detectable in fewer than 40% of patients.

Workup should include a thorough history and physical examination, including determination of B symptoms (unexplained fevers >38°C, drenching night sweats, or 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, differential, platelets, erythrocyte sedimentation rate [ESR], serum lactate dehydrogenase, albumin, and liver and renal function tests); PET/CT scan (skull base to midthigh or vertex to feet in selected cases); and diagnostic contrast-enhanced CT (neck, chest, abdomen, and pelvis). At minimum, diagnostic CT scans should include involved areas identified as abnormal on PET scan. Posterior-anterior and lateral chest X-rays are encouraged in selected cases for patients with large mediastinal mass.



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[p]In general these studies show an improvement in PFS for combined modality therapy, but no difference in overall survival.
[r]See Principles of Systemic Therapy (HODG-C).
[t]An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A*).
[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
[x]Consider PFTs after 4 cycles of ABVD.
[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[z]CALGB 50604: Straus DJ, et al. Blood 2018;132:1013-1021.
[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.

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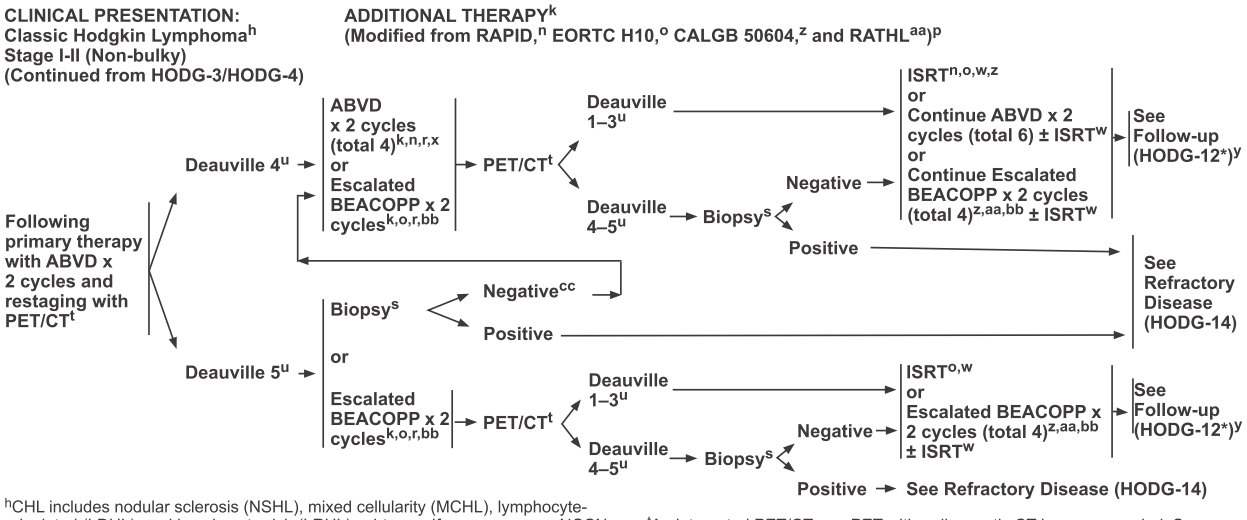
HODG-4

The NCCN PET Task Force and the NCCN Guidelines consider PET scans essential for initial staging and for evaluating residual masses at the end of treatment.[3] An integrated PET scan plus a diagnostic CT is recommended for initial staging and should be obtained no longer than 1 month before the start of therapy. A separate contrast-enhanced diagnostic CT is not needed if it was part of the integrated PET scan. The panel supports the American College of Radiology (ACR)[4] and Society of Nuclear Medicine and Molecular Imaging[5] recommendations for PET/CT interpretation (see "Principles of FDG-PET/CT," HODG-A, available at NCCN.org).[6–9] However, it should be noted that PET scans may be positive in sites of infection or inflammation, even in the absence of HL. In patients with PET-positive sites outside of the disease already identified, or if the 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 PET/CT, routine bone marrow biopsy is not required if the PET scan is negative or displays a homogenous pattern of bone marrow uptake, which may be secondary to cytokine release.[10,11] The bone marrow may be assumed to be involved if the PET scan displays multifocal (≥3) skeletal lesions.[10,12] However, a bone marrow biopsy may be performed if cytopenias are present. In select cases, MRI and PET/MRI with contrast (skull base to midthigh) may also be considered for anatomic imaging, unless contraindicated.

Evaluation of ejection fraction is recommended, as all patients will receive anthracycline-based therapy. HIV and hepatitis B or C testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. 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.[13,14] A seasonal flu shot is recommended. Pneumococcal, H-flu, and meningococcal vaccines are recommended if splenic radiation therapy (RT) is contemplated.



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[o]EORTC/LYSA/FIL H10 Trial: Andre MPE, et al. J Clin Oncol 2017;35:1786-1794.
[p]In general these studies show an improvement in PFS for combined modality therapy, but no difference in overall survival.
[r]See Principles of Systemic Therapy (HODG-C).
[s]Biopsy recommended to differentiate refractory Hodgkin lymphoma from discordant histology with appropriate action based upon results. If no biopsy is done, clinical judgment should define management.
[t]An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A*).
[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
[w]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D*).
[x]Consider PFTs after 4 cycles of ABVD.
[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[z]CALGB 50604: Straus DJ, et al. Blood 2018;132:1013-1021.
[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.
[bb]Escalated BEACOPP is only an option for those aged <60 years.
[cc]Use clinical judgment to determine if tissue specimen is adequate for accurate biopsy results. Confirm clinically that patient is not progressing symptomatically.

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HODG-5

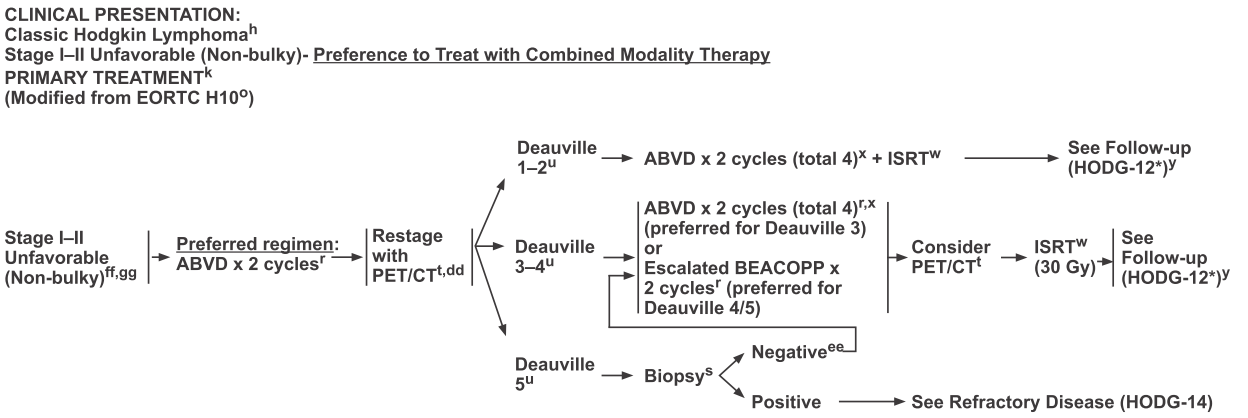
A pregnancy test should be performed before women of childbearing age undergo treatment. Alkylating agent-based chemotherapy is associated with a higher risk of premature ovarian failure than chemotherapy with nonalkylating agent-based chemotherapy.[15] In select cases and if the patients are interested, the guidelines recommend consideration of fertility preservation (ie, semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) before the start of chemotherapy with alkylating agents or pelvic RT.[16,17]

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.[18,19] 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 >38°C, drenching night sweats, or weight loss of >10% of their body weight within 6 months of diagnosis.

Patients with HL are usually classified into 3 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 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).[20] The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR >0.33 is defined as bulky disease. This is the definition used most commonly 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 10 cm or greater 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 chest radiograph.[21] In this context, any



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[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
[w]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D*).

Preference to treat with chemotherapy alone (HODG-4)

[x]Consider PFTs after 4 cycles of ABVD.
[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[dd]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[ee]Use clinical judgment to determine if tissue specimen is adequate for accurate biopsy results. Confirm clinically that patient is not progressing symptomatically.
[ff]Other recommended primary therapy regimens include:
- Stanford V x 12 weeks + 30 Gy ISRT (Gordon LI, et al. J Clin Oncol 2013;31:684-691.)
- If GHSG HD14 unfavorable (see HODG-B*): Escalated BEACOPP x 2 cycles followed by ABVD x 2 cycles + 30 Gy ISRT (von Tresckow B, et al. J Clin Oncol 2012;30:907-913.)

[gg]For this algorithm, NCCN unfavorable factors include B symptoms, ESR ≥50, and >3 sites of disease.

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HODG-6

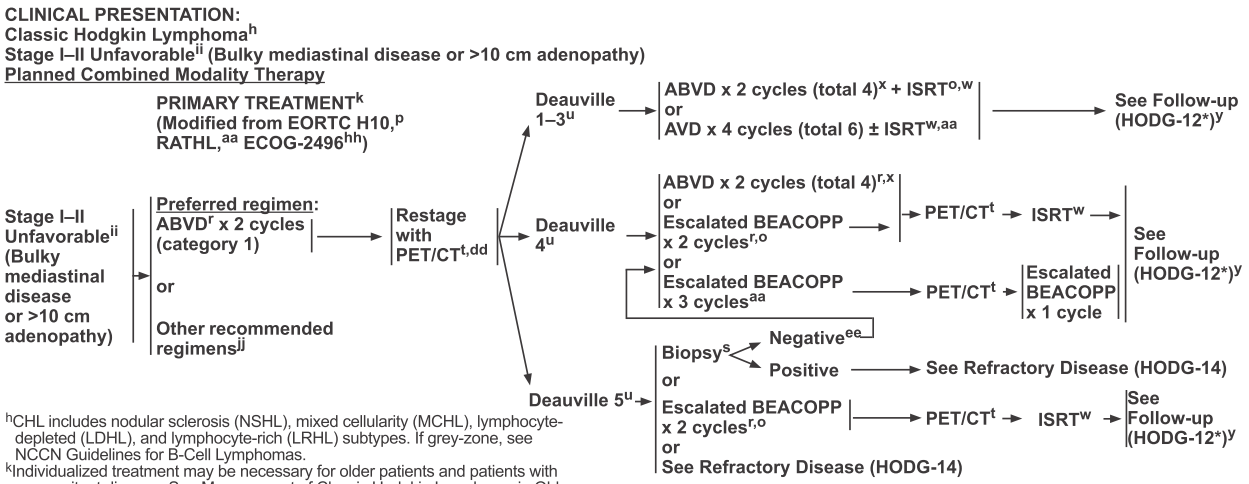
mass with MTR >0.35 is defined as bulky disease. This is the definition used by the European Organization for Research and Treatment of Cancer (EORTC).

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.[22,23] 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. The GHSG combines subpectoral with supraclavicular or cervical, and 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 >10 cm, B symptoms, ESR ≥50, and >3 involved nodal regions. In contrast, the GHSG considers patients with >2 nodal regions as having unfavorable disease.

An international collaborative effort evaluating more than 5,000 patients with advanced CHL (stage III–IV) identified 7 adverse prognostic factors, each of which reduced survival rates by 7%–8% per year,[24] including: age 45 years or older; male gender; stage IV disease; albumin level below 4 g/dL; hemoglobin level below 10.5 g/dL; leukocytosis (white blood cell count >15,000/mm^3); and lymphocytopenia (lymphocyte count <8% of the white blood cell and/or lymphocyte count <600/mm^3). The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.[24,25] The IPS helps to determine the clinical management and predict prognosis for patients with stage III–IV disease.[24,25]

The Role of PET Imaging in Patient Management

Clinical management of patients with CHL involves initial treatment with chemotherapy or combined modality therapy, 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



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[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
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[dd]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[ee]Use clinical judgment to determine if tissue specimen is adequate for accurate biopsy results. Confirm clinically that patient is not progressing symptomatically.
[hh]ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.
[ii]NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-B*).
[jj]Other recommended regimens:
- Stanford V x 12 weeks + ISRT in select patients where reduced cumulative doses of doxorubicin and/or bleomycin are desired. (Gordon LI, et al. J Clin Oncol 2013;31:684-691.); or
- Escalated BEACOPP x 2 cycles followed by ABVD x 2 cycles + 30 Gy ISRT (if GHSG HD14 unfavorable, see HODG-B. Patients with B symptoms in combination with bulky or extranodal disease were excluded and treated according to the algorithm for stage III–IV disease (HODG-9).)(von Tresckow B, et al. J Clin Oncol 2012;30:907-913)

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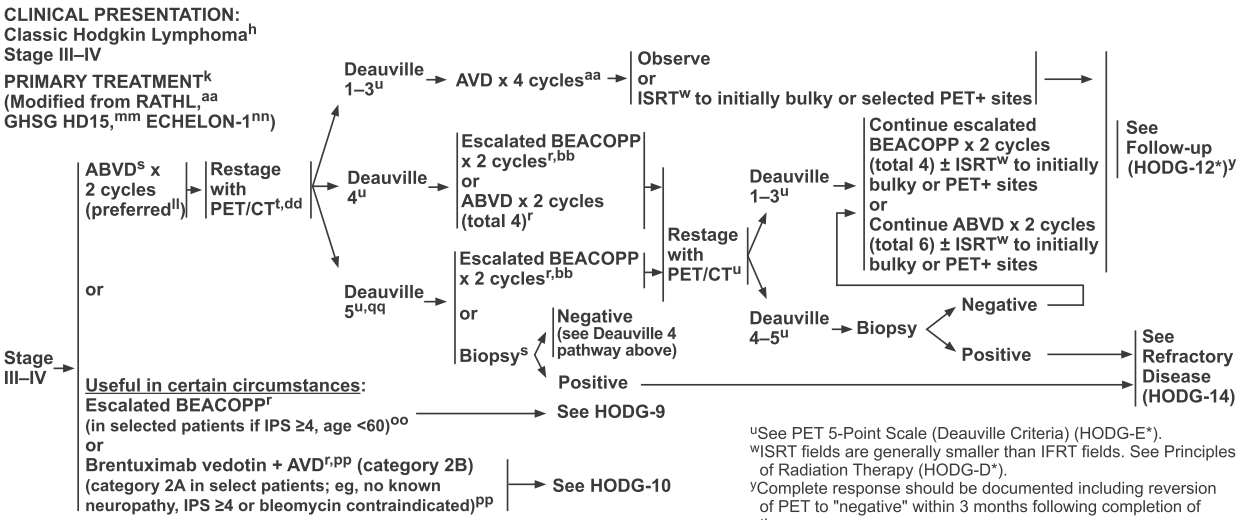
HODG-7

response. PET should not be used for routine surveillance following completion of therapy.

PET imaging including integrated PET and CT (PET/CT) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.[26,27] In a meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.[28] 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.[29–31] In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of ^{18}F-fluorodeoxyglucose (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.[27,32,33] 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.[32,33] Interim or end-of-treatment PET scans with a score of 1, 2, or 3 are considered "negative" and PET scans with a score of 4 and 5 are considered "positive."[34] A score of 4 can be difficult to assess when FDG uptake in mediastinal masses cannot clearly be differentiated from thymic uptake or inflammatory reactions,[27,35,36] and treatment decisions in these cases will require clinical judgment. In addition, Deauville 4 may represent just a single area of persistent disease or failure to respond in any site. The 5-PS (Deauville criteria) has been validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.[37–41]

Interim PET Imaging

Interim PET scans can be prognostic and are increasingly being used to assess treatment response during therapy[42,43] as they can inform treatment adaptation, including treatment escalation and de-escalation.[44,45] Early interim 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



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas†.

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).

[r]See Principles of Systemic Therapy (HODG-C).

[s]Biopsy recommended to differentiate refractory Hodgkin lymphoma from discordant histology with appropriate action based upon results. If no biopsy is done, clinical judgment should define management.

[t]An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A*).

[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).

[w]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D*).

[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.

[bb]Escalated BEACOPP is only an option for those aged <60 years.

[dd]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

[ll]ABVD is preferred based on the toxicity profile and quality of data.

[mm]GHSG HD15 trial: Engert A, et al. Lancet 2012;379(9828):1791-1799.

[nn]ECHELON-1: Connors JM, et al. NEJM 2018;374(4):331-344.

[oo]See International Prognostic Score (IPS) (HODG-B*).

[pp]All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors†.

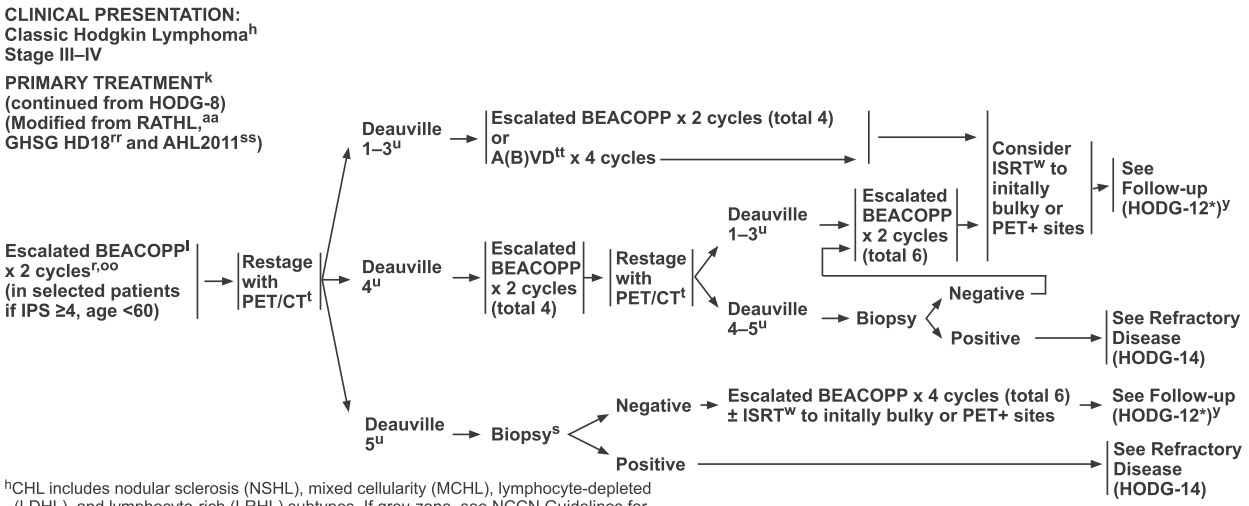
*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

HODG-8

bulky disease] or stage III–IV disease).[46,47] Interim 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.[41,48] The NCCN Guidelines emphasize that the value of interim 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 PET scan report, since subsequent management is often dependent on that score. Individual prospective trials that use interim PET imaging are discussed subsequently in the treatment management section.

Principles of RT

RT can be delivered with photons, electrons, or protons, depending on clinical circumstances.[49] Although advanced RT techniques emphasize tightly conformal doses and steep gradients adjacent to normal tissues, the "low-dose bath" to normal structures such as the breasts must be considered in choosing the final RT technique. Therefore, target definition, delineation, and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound, and other imaging modalities facilitate target definition. 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, and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4-dimensional CT simulation, intensity-modulated RT/volumetric modulated arc therapy, image-guided RT, respiratory gating, or deep inspiration breath hold.[50,51] 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.[49,52–58] For optimal mediastinal treatment planning, organs or tissues to be contoured should include



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[o]EORTC/LYSA/FIL H10 Trial: Andre MPE, et al. J Clin Oncol 2017;35:1786-1794.

[r]See Principles of Systemic Therapy (HODG-C).

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[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.

[mm]GHSG HD15 trial: Engert A, et al. Lancet 2012; 379(9828):1791-1799.

[oo]See International Prognostic Score (IPS) (HODG-B*).

[rr]GHSG HD18: Borchmann P, et al. Lancet 2018;390(10114):2790-2802.

[ss]Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol 2019;20:202-215.

[tt]Bleomycin is optional.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

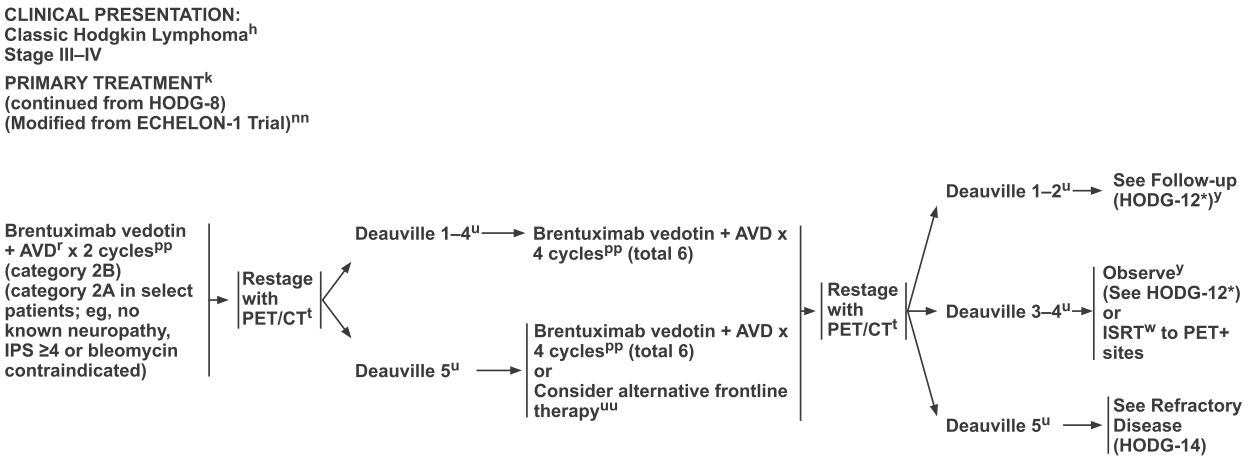
HODG-9

the lungs, heart, coronary arteries (including the left main, circumflex, left anterior descending, and right coronary arteries, with priority placed on sparing the proximal over distal portions of the arteries), and left ventricle.

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

Involved-site RT (ISRT) and involved-node RT (INRT) are being used as alternatives to involved-field RT (IFRT) in an effort to 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.[59–61] ISRT targets the originally involved nodal sites and possible extranodal extensions, which generally defines a smaller field than the classic IFRT.[62]

ISRT targets the initially involved nodal and extranodal sites as defined by the pretreatment evaluation (physical examination, CT and PET imaging). However, it is intended to spare the adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses after chemotherapy. Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The optimized treatment plan for ISRT is designed using conventional 3-D conformal RT, proton therapy,[49] or intensity-modulated RT techniques using clinical treatment planning considerations of coverage and dose reductions for OARs. The gross tumor volume defined by PET/CT imaging before chemotherapy or surgery provides the basis for determining the clinical target volume. The planning target volume is an additional expansion of the clinical target volume to account for any setup variations and internal organ



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[w]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D*).
[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[nn]ECHELON-1: Connors JM, et al. NEJM 2018;374(4):331-344.
[pp]All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors[†].
[uu]Options may include escalated BEACOPP (category 2B) or therapy for refractory disease (see HODG-14).

*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.

HODG-10

motion.[63] Planning target volume margins should be defined individually for each disease site.

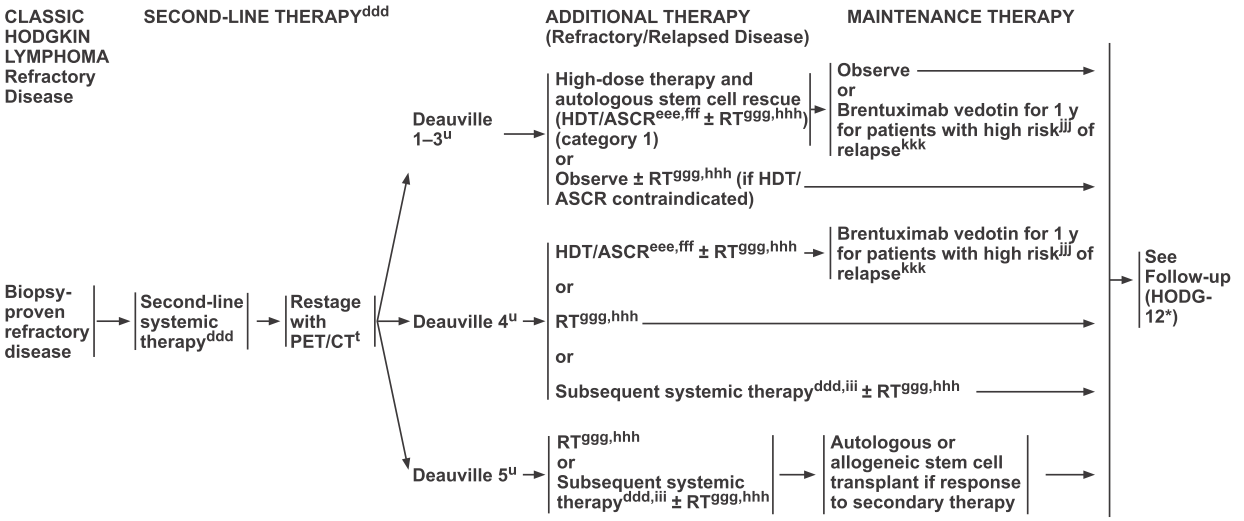
In the setting of combined modality therapy, the panel recommends an RT dose of 30 to 36 Gy when combined with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or Stanford V regimens for patients with bulky disease (all stages).[64,65] In patients with stage I–II nonbulky disease, the recommended RT dose is 20 to 30 Gy following ABVD.[65,66] 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 women always be excluded from RT fields, if those regions are uninvolved.

Management of CHL

RT alone was a standard treatment option for patients with early-stage HL for many decades.[67] However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.[68] With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD is the most commonly used systemic therapy based on a balance of efficacy and toxicity) into the management of patients with early-stage disease, combined modality therapy (chemotherapy and RT) has replaced RT alone as the treatment of choice for patients with early-stage, favorable disease. Bonadonna et al[64] initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy IFRT as the standard treatment of patients with early-stage disease.

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.[66] The definition of favorable disease implies the absence of unfavorable risk factors outlined in HODG-A in the NCCN Guidelines (available at NCCN.org). It is worth noting that for purposes of stratification the GHSG and EORTC do not define the



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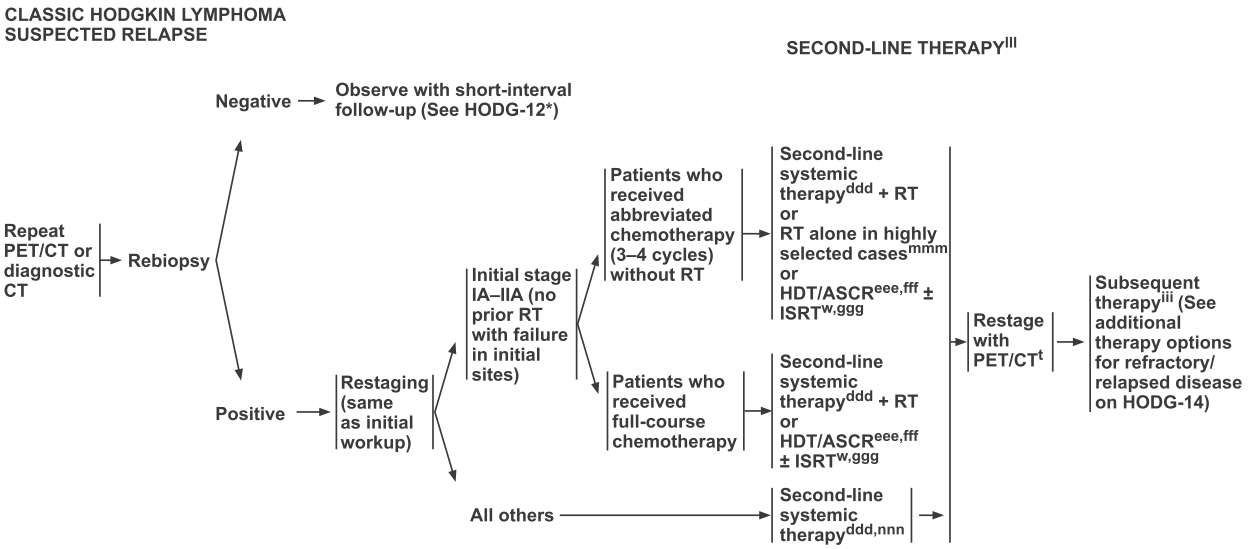
[u]See PET 5-Point Scale (Deauville Criteria) (HODG-E*).
[ddd]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4).
[eee]Strongly consider radiation therapy for selected sites that have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.
[fff]Allotransplant is an option in select patients as a category 3 recommendation.
[ggg]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[hhh]See Principles of Radiation Therapy (HODG-D*).
*Available online, in these guidelines, at NCCN.org.

[iii]Subsequent systemic therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 4).
[jjj]Patients with 2 or more of the following risk factors are considered high risk: Remission duration less than 1 year, extranodal involvement, PET+ response at time of transplant, B symptoms, and/or >1 salvage/subsequent therapy regimen.
[kkk]Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;385:1853-1862.

HODG-14

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, 1,370 patients were randomized to one of the 4 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.[66] The final analysis of this trial showed that (with a median follow-up of 79–91 months) no significant differences were seen between 4 and 2 cycles of ABVD in terms of 5-year overall survival (OS) (97.1% and 96.6%), freedom from treatment failure (FFTF) (93.0% vs 91.1%), and progression-free survival (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.[66] More importantly, there were also no significant differences in OS, PFS, and FFTF among the 4 treatment arms. The results of the HD10 study confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment of 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 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 PET scan after 3 cycles of ABVD have an excellent outcome with or without IFRT.[41] In this study (n=602; 426 patients had a negative 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 PET scan after 3 cycles 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 with 90.8% for those who received no further treatment. The corresponding 3-year OS rates were 97.1% and 99.0%, respectively.[41] In the "per protocol" (as treated) analysis, the 3-year PFS rates were 97.1% and 90.8%, respectively, favoring the use of combined modality therapy.



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[ddd]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4).
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[fff]Allotransplant is an option in select patients as a category 3 recommendation.
[ggg]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
*Available online, in these guidelines, at NCCN.org.
[iii]Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 4).
[III]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[mmm]For patients not considered suitable for more aggressive therapy, radiation therapy can be used alone as a second-line therapy and conventional involved-field or extended-field treatment is indicated.
[nnn]For select patients with long disease-free interval and other favorable features, selection of chemotherapy should be individualized.

HODG-15

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.[44] In this study, mediastinal blood pool activity was used as the reference background activity for PET positivity of residual masses ≥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 who were PET negative after receiving 2 cycles of ABVD received one 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.[44] After a median follow up of 5 years, the intent-to-treat PFS rates were 99.0% and 87.1% in the ABVD + RT and ABVD only arms, respectively.[44] 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.[44]

In the H10U group (n=1,196), patients were randomized into 2 treatment arms.[44] 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 interim PET-negative patients, the 5-year PFS was 92.1% following 4 cycles of ABVD + INRT versus 89.6% following 6 cycles of ABVD.[44] 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. The final results of this trial showed 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 with 2 additional cycles of ABVD and INRT (90.6% vs 77.4%, respectively).[44]

PRINCIPLES OF SYSTEMIC THERAPY
RELAPSED OR REFRACTORY DISEASE

Relapsed/Refractory Disease

	Second-Line Options[c] (in alphabetical order)	Subsequent Options[c,d] (in alphabetical order)
CHL	• Brentuximab vedotin[1] • Brentuximab vedotin + bendamustine[2] • Brentuximab vedotin + nivolumab[3] • DHAP (dexamethasone, cisplatin, high-dose cytarabine)[4,5] • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)[6,7,8] • Gemcitabine/bendamustine/vinorelbine[9] • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[10] • ICE (ifosfamide, carboplatin, etoposide)[5,11] • IGEV (ifosfamide, gemcitabine, vinorelbine)[12]	• Bendamustine[13] • Bendamustine + carboplatin + etoposide[14] • C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) • Everolimus[15] • GCD (gemcitabine, carboplatin, dexamethasone)[16,17] • GEMOX (gemcitabine, oxaliplatin)[18] • Lenalidomide[19] • MINE (etoposide, ifosfamide, mesna, mitoxantrone)[20] • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)[21,22] • Nivolumab[23,24] (see indications below) • Pembrolizumab[25] (see indications below)
NLPHL[c]	• R (rituximab) + DHAP[4,5] • R + ESHAP[6,7,8] • R + ICE[5,11] • R + IGEV[12]	

General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed/Refractory CHL[e,f]
- **CPI are recommended for any patients with CHL that has relapsed or progressed after autologous HSCT ± brentuximab vedotin.**
- **CPI are also an option for patients with relapsed/refractory CHL who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy.**
- **Post-allogeneic transplant, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic transplantation; CPI should be used with caution before allogeneic transplantation due to increased risk of GVHD (graft-versus-host disease) and other immunologic complications.**

[c]Choice depends on prior therapies and prior toxicities. There are no preferred second-line or subsequent therapy options.
[d]Subsequent systemic therapy options include second-line therapy options that were not previously used.
[e]National Institutes of Health. Nivolumab package insert. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f570b9c4-6846-4de2-abfa-4d0a4ae4e394. Accessed December 20, 2017.
[f]National Institutes of Health. Pembrolizumab package insert. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287. Accessed December 20, 2017.

The GHSG HD16 trial (n=1150) included patients with stage I–II favorable disease according to GHSG criteria.[69] 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 93.4% following combined modality therapy and 86.1% following ABVD alone (P=.04).[69]

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).[70] 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.[70] 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.[70] The 3-year PFS was 94% for patients with Deauville 1–2 response on interim PET and 77% for patients with Deauville 3 response.

The phase III intergroup trial (E2496) confirmed that there were no significant differences between ABVD and Stanford V in terms of response rates, failure-free survival, OS, and toxicity in patients with locally extensive (stage I–IIA/B and bulky mediastinal disease) and stage III–IV disease.[71,72] A planned subgroup analysis in patients with stage I–II locally extensive disease comparing both ABVD (n=135) and Stanford V (n=129) showed that there were no significant differences in complete response (CR) rates (75% for ABVD and 81% for Stanford V; P=.30) and overall response rate (ORR) (83% for ABVD and 88% for Stanford V; P=.40).[71]

The HD14 trial of the GHSG evaluated patients with stage I–II unfavorable disease.[73] In this trial, 1528 patients were randomized to 4 cycles of ABVD (n=765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD

MANAGEMENT OF CLASSIC HODGKIN LYMPHOMA IN OLDER ADULTS (AGE >60)

- CHL in older adult patients 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 older patients.[3-6]
- There are limited prospective data evaluating alternatives to standard therapies for older patients. Selection of standard versus alternate first-line therapy for an older patient should be based on clinical judgment, with the goal of minimizing toxicity while maximizing efficacy.
- The regimens listed below should be considered in older patients to lessen/minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in the older patients.
- Clinical trial is recommended when available.
- ISRT alone is an option when systemic therapy is not considered feasible or safe.

SUGGESTED TREATMENT REGIMENS
(Listed in alphabetical order)

Stage I–II Favorable Disease
- A(B)VD[a] (2 cycles) ± AVD (2 cycles) + 20–30 Gy ISRT (preferred)[7,8,9]
- CHOP (4 cycles) + 30 Gy ISRT[10]
- VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin) ± 30 Gy ISRT[11]

Stage I–II Unfavorable or Stage III–IV Disease
- A(B)VD[a] (2 cycles) followed by AVD (4 cycles),[b] if PET scan is negative after 2 cycles of ABVD.[12]
  - Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment.
- Brentixumab vedotin followed by AVD, conditionally followed by brentuximab vedotin in responding patients with CR or PR[13]
- Brentuximab vedotin + DTIC (dacarbazine)[14,15]
- CHOP (6 cycles) ± 30 Gy ISRT[10]
- PVAG (6 cycles) (prednisone, vinblastine, doxorubicin, and gemcitabine)[16] ± 30 Gy ISRT
- VEPEMB (6 cycles) ± 30 Gy ISRT[11,17]

Relapsed or Refractory Disease
- Outcomes are uniformly poor for patients with relapsed or refractory disease.[18]
- 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
  - Brentuximab vedotin
  - ISRT
  - Nivolumab See Checkpoint Inhibitors (CPI) HODG-C (3 of 4)
  - Pembrolizumab See Checkpoint Inhibitors (CPI) HODG-B* (3 of 4)
  - Second-line and subsequent therapy options (only for CHL) as listed on Principles of Systemic Therapy for Relapsed or Refractory Disease HODG-C (3 of 4)

[a]Bleomycin should be used with caution as it may not be tolerated in older adults.
[b]If stage I–II unfavorable, consider a total of 4 cycles.

*Available online, in these guidelines, at NCCN.org.

HODG-F
1 OF 2

(n=763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FFTF rate was 94.8% compared with 87.7% for ABVD ($P<.001$). The 5-year PFS rate was 95.4% and 89.1%, respectively ($P<.001$).[73] The 5-year OS rate was not significantly different between the 2 arms (97.2% and 96.8%, respectively; $P=.731$). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs 8.4%; $P<.001$). However, the acute toxicity was greater in the BEACOPP/ABVD arm compared with the ABVD arm.[73] The risk for WHO grade 3–4 events was 87.1% and 50.7%, respectively. Grade 4 toxicity was reported in 56.6% and 5.9%, respectively.

The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial examined the use of interim PET to guide treatment of patients with advanced disease, which included 500 patients (41.6%) who had stage II with various risk factors (B symptoms, bulky disease, or at least 3 involved sites).[37,45] In the randomized trial, 1,119 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 41 months, the 3-year PFS and OS rates between the ABVD and AVD groups did not differ significantly (85.7% vs 84.4% and 97.2% vs 97.6%, 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 with continued ABVD.[45] The potential value of added RT was not tested in this trial.

NCCN Recommendations for Stage I–II Favorable, Non-Bulky Disease

Preference to Treat With Combined Modality Therapy

If there is a preference to treat patients with combined modality therapy, for patients who fulfill the GHSG HD10 criteria for favorable stage IA–IIA disease (no bulky disease or extralymphatic lesions, ≤2 involved regions, and an ESR <50 without E-lesions), 2 cycles of ABVD followed by interim restaging with PET is recommended (category 1) (see HODG-3, page 757). For patients with a

Deauville score of 1 to 3, a planned course of ISRT (20 Gy) is recommended.[66] For patients with a Deauville score of 4, 2 additional cycles of ABVD followed by interim PET/CT may be considered prior to ISRT (30 Gy). Biopsy is recommended for all patients with a score of Deauville 5 after completion of chemotherapy. If the biopsy is negative, patients may be treated with 2 additional cycles of ABVD and ISRT (30 Gy). A repeat PET/CT could be considered before initiation of RT. If the biopsy is positive, patients should be managed as described for refractory disease.

In another approach using combined modality therapy for favorable stage I–II disease, patients are administered 2 cycles of ABVD and restaged with PET (see HODG-3, page 757). An additional cycle of ABVD (total of 3) and ISRT (30 Gy) is recommended for patients with a Deauville score of 1 to 2. Patients with a Deauville score of 3 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT (30 Gy).

For patients with an interim PET Deauville score of 4, options include: 2 additional cycles of ABVD (total of 4) or switching therapy to 2 cycles of escalated BEACOPP followed by restaging with PET.[41,44] (see HODG-5, page 759) If the Deauville score is 1 to 3, the treatment options include ISRT (30 Gy) alone or 2 additional cycles of ABVD (if previously given, for a total of 6 cycles) with or without RT, or an additional 2 cycles of escalated BEACOPP (if previously given, for a total of 4 cycles) with or without RT.[41,44,45,70] For patients with a Deauville score is 4 to 5 and a negative biopsy, management should be as described above for a Deauville score of 1 to 3. If the biopsy is positive, patients should be managed as described for refractory disease.

Preference to Treat With Chemotherapy Alone

If there is a preference to treat patients with chemotherapy alone, an initial administration of 2 cycles of ABVD is followed by interim restaging with PET (see HODG-4, page 758). After interim restaging patients with a Deauville score of 1 or 2 may receive an additional 1 to 2 cycles of ABVD (total of 3 or 4)[41,70] or 4 cycles of AVD (for initial stage IIB or ≥3 sites).[45] For patients with a Deauville score of 3, an additional 2 cycles of ABVD (total of 4 [category 2B])[70] or 4 cycles of AVD (for initial stage IIB or ≥3 sites)[45] is recommended.

In patients with a Deauville score of 4, the recommended treatment options include 2 additional cycles of ABVD (total of 4) or 2 cycles of escalated BEACOPP followed by restaging with PET.[41,44] (see HODG-5, page 759) If the Deauville score is 1 to 3, the treatment options include an additional 2 cycles of ABVD (if previously given, for a total of 6 cycles), or an additional 2 cycles of escalated BEACOPP (if previously given, for a total of 4 cycles).[41,44,45,70] A Deauville score of 5 warrants a biopsy (see HODG-5). If the biopsy is negative, patients should be managed as described above for Deauville 1 to 3. If the biopsy is positive, patients should be managed as described for refractory disease.

Alternatively, patients with a Deauville score of 5 may receive 2 cycles of escalated BEACOPP followed by restaging with PET (see HODG-5, page 759). If the resulting Deauville score is 1 to 3, the recommended option is an additional 2 cycles of escalated BEACOPP (total of 4). If the Deauville score is 4 to 5, a biopsy is recommended and if negative, the recommended treatment is 2 additional cycles of escalated BEACOPP (total of 4). If positive, treat as refractory disease.

NCCN Recommendations for Stage I–II Unfavorable, Non-Bulky Disease

Preference to Treat With Combined Modality Therapy

If there is a preference to treat patients with combined modality therapy, the preferred regimen, ABVD, is initially administered for 2 cycles followed by interim restaging with PET (see HODG-6, page 760). Patients with a Deauville score of 1 to 2 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT. Patients with a Deauville score of 3 to 4 are treated with either 2 additional cycles of ABVD alone (total of 4; preferred if Deauville 3) or 2 cycles of escalated BEACOPP (preferred for Deauville 4 or 5). PET restaging may be considered at this point and patients are followed up with ISRT (30 Gy). Biopsy is recommended for patients with a Deauville score of 5 after initial treatment with 2 cycles of ABVD. If the biopsy is negative, patients are treated as described for patients with a Deauville score of 3 to 4. All patients with a positive biopsy should be managed as described for refractory disease.

In another approach, patients may start therapy with escalated BEACOPP (2 cycles) and ABVD (2 cycles) and are restaged after completion of chemotherapy.[73] ISRT is recommended for those with a Deauville score of 1 to 4 and biopsy is recommended for patients with a Deauville score of 5. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Preference to Treat With Chemotherapy Alone

If there is a preference to treat patients with chemotherapy alone, the treatment recommendations are as described earlier (See "NCCN Recommendations for Stage I–II Favorable, Non-Bulky Disease, Preference to Treat with Chemotherapy Alone," page 768).

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

The preferred regimen, ABVD (category 1), is initially administered for 2 cycles followed by interim restaging

with PET (see HODG-7, page 761). Patients with a Deauville score of 1 to 3 are treated with a combination of 2 additional cycles of ABVD (total of 4) and ISRT or with 4 cycles of AVD (total of 6) with or without ISRT.[44,45] The treatment options for patients with a Deauville score of 4 include 2 additional cycles of ABVD (total of 4), or 2 to 3 cycles of escalated BEACOPP followed by PET and ISRT or an additional cycle of escalated BEACOPP, if they were previously treated with 3 cycles of escalated BEACOPP.

A biopsy is recommended for all patients with a Deauville score of 5 after initial treatment with 2 cycles of ABVD. If the biopsy is negative, patients should be managed as described for patients with a Deauville score of 4. Patients with a positive biopsy should be managed as described for refractory disease. Alternatively, patients with a Deauville score of 5 can be treated with 2 cycles of escalated BEACOPP, followed by PET and ISRT.[44]

Another option for patients with stage I–II bulky mediastinal disease or adenopathy >10 cm is the Stanford V regimen, which is administered for 12 weeks (3 cycles) followed by ISRT (30–36 Gy).[71,72] Patients are restaged with PET at the completion of chemotherapy. ISRT to initial sites >5 cm is recommended for all patients with a Deauville score of 1 to 4. ISRT should be instituted within 2 to 3 weeks of completion of chemotherapy. Biopsy is recommended for all patients with a Deauville score of 5 after completion of therapy. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

In another option, patients may receive escalated BEACOPP (2 cycles) and ABVD (2 cycles) and are restaged after completion of chemotherapy. ISRT is recommended for those with a Deauville score of 1 to 4 and biopsy is recommended for patients with a Deauville score of 5. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stage III–IV

While chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.[72,74]

ABVD has continued to be the standard chemotherapy regimen for patients with stage III–IV disease based upon several randomized clinical trials that have failed to show a survival benefit for more intensive regimens.[72,75–77] 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, next column.

As noted previously in the RATHL trial, the omission of bleomycin from the ABVD regimen after a negative interim PET result (ie, Deauville score of 1–3) led to a decrease in the incidence of pulmonary toxic effects without any compromise in outcome compared with continued ABVD (3-year PFS 81.6% and OS 97%).[45] 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[78,79] and the Italian GITIL/FIL HD 0607 trial.[80] 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.[78,79] 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.[80]

The efficacy of escalated BEACOPP has been demonstrated in several sequential studies by the GHSG.[81,82] The final analysis of the HD15 trial that included patients with stage III–IV and IIB with large mediastinal adenopathy or extranodal disease established 6 cycles of escalated BEACOPP followed by PET-guided RT (to sites >2.5 cm that were PET positive) as the standard of care within the GHSG. The 5-year FFTF and OS rates were 89.3% and 95.3%, respectively.[44] One hundred ninety-one patients were PET-positive, received consolidative RT, and achieved a 4-year PFS of 86.2% with outcomes similar to those who achieved a CR.[83]

The subsequent HD18 trial investigated an interim PET-adapted design.[84] After 2 cycles of escalated BEACOPP, PET-negative (Deauville 1–2) patients were randomized to receive an additional 2 or 6 cycles of escalated BEACOPP, and PET-positive patients were randomized to receive an additional 6 cycles of escalated BEACOPP alone or with rituximab. The final results showed noninferiority of 4 cycles of escalated BEACOPP (n=501) compared with 6 or 8 cycles, with a 5-year PFS of 92.2% vs 90.8%, respectively.[84] These results suggest that 4 cycles of escalated BEACOPP is adequate therapy in patients with a negative interim PET.

The AHL2011 trial investigated whether PET monitoring during treatment could allow dose de-escalation by switching regimens from escalated BEACOPP to ABVD in early responders with newly diagnosed advanced-stage HL (stage IIB with large mediastinal mass or stage III–IV).[85] In this study, all patients (n=823) were randomized to receive standard treatment (6 cycles of escalated BEACOPP; n=413) or PET-adapted treatment (n=410). In the PET-adapted group, after 2 cycles of escalated BEACOPP, patients with positive PET2 scans (Deauville score 4 or 5) received 2 additional cycles of escalated BEACOPP, whereas patients with negative PET2 scans (Deauville score 1–3) were switched to 2

cycles of ABVD for the remaining induction therapy.[85] With a median follow-up of 50.4 months (interquartile range [IQR], 42.9–59.3), the 5-year PFS by intention to treat in the standard treatment and PET-adapted treatment groups were 86.2% and 85.7% (P=.65), respectively.[85] The PET-adapted treatment arm was also associated with significantly less treatment-related toxicities.[85]

Results from studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although in some studies it resulted in better tumor control.[77,86–88] However, some of these studies were not sufficiently powered to determine differences in OS due to small patient numbers. The EORTC 20012 trial evaluated BEACOPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III–IV disease and IPS ≥3 (274 patients in the BEACOPP arm and 275 patients in the ABVD arm).[86] The results showed that there was no improvement in OS (86.7% and 90.3, respectively, at 4 years; P=.208) or event-free survival (EFS) (63.7% and 69.3%, respectively, at 4 years; P=.312), although the PFS was significantly better with BEACOPP (83.4% vs 72.8% for ABVD; P=.005). Early discontinuations were also more frequent with BEACOPP. The median follow-up was 3.6 years.[86] Interestingly, long-term follow-up analysis of the HD2000 trial failed to show a PFS advantage of escalated BEACOPP over ABVD, largely due to the risk of secondary malignancy at 10 years, which was significantly higher with escalated BEACOPP than with ABVD (6.6 vs 0.9; P=.027).[76]

The ECHELON-1 trial compared the efficacy of ABVD (n=670) versus brentuximab vedotin + AVD (n=664) in previously untreated stage III or IV CHL.[89] Patients received 6 cycles of chemotherapy without treatment adaptation based upon interim imaging. While the incidence of pulmonary toxicity was lower in the brentuximab vedotin + AVD arm due to the elimination of bleomycin, there was more peripheral neuropathy and hematologic toxicity. At a median follow-up of 24.9 months, the 2-year *modified* PFS rates in the brentuximab vedotin + AVD and ABVD groups were 82.1% and 77.2%, respectively (P=.03).[89] For the subset of patients treated in North America at a median follow-up of 24.7 months, the 2-year modified PFS rates in the brentuximab vedotin + AVD and ABVD groups were 84.3% and 73.7%, respectively (P=.012).[90]

NCCN Recommendations for Stage III–IV Disease

ABVD, the preferred regimen, is initially administered for 2 cycles followed by restaging with PET (see HODG-8, page 762). Patients with a Deauville score of 1 to 3 are treated with 4 cycles of AVD based on results from the RATHL trial.[45] After 4 cycles of AVD, treatment strategies include observation or ISRT to initially bulky or selected PET-positive sites.[91]

For patients with a Deauville score of 4, options include 2 additional cycles of ABVD (total of 4) or 2 cycles of escalated BEACOPP followed by reassessment of response with PET. A biopsy is recommended for patients with a Deauville score of 5, but in select cases, 2 cycles of BEACOPP may be considered. If a biopsy is negative, treatment follows as outlined previously for patients with a Deauville score of 4. Patients with a positive biopsy should be managed as described for refractory disease.

Patients are then restaged with PET; for patients with a Deauville score of 1 to 3, the recommended options are to continue on therapy with 2 additional cycles of either escalated BEACOPP (total of 4) or ABVD (total of 6), alone or combined with ISRT to initially bulky or selected 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. Patients with a positive biopsy should be managed as described for refractory disease.

In selected patients <60 years of age with IPS ≥4, escalated BEACOPP is initially administered for 2 cycles followed by restaging with PET (see HODG-9, page 763). Based on the AHL2011 trial,[85] treatment options for patients with a Deauville score of 1 to 3 include an additional 2 cycles of escalated BEACOPP (total of 4 cycles) or 4 cycles of ABVD. If reduced exposure to bleomycin is desired, the panel recommends omitting bleomycin from ABVD per the RATHL trial.[45] Following an end-of-treatment PET, ISRT may be considered to initially bulky or PET-positive sites. For patients with a Deauville score of 4, an additional 2 cycles of escalated BEACOPP (total of 4 cycles) is recommended followed by restaging with PET. If the resulting Deauville score is 1 to 3, or 4 to 5 with a negative biopsy, an additional 2 cycles of escalated BEACOPP (total of 6 cycles) with ISRT to initially bulky or PET-positive sites is recommended. For patients with a Deauville score of 5, a biopsy is recommended. If the biopsy is negative, an additional 4 cycles of escalated BEACOPP (total of 6 cycles) with consideration of ISRT to PET-positive sites is recommended. Patients with a positive biopsy should be managed as described for refractory disease.

Brentuximab vedotin + AVD is a category 2B recommendation, but it is a category 2A option in select patients with no known neuropathy, if IPS ≥4 or bleomycin is contraindicated (see HODG-10, page 764). It should be noted that the ECHELON-1 trial, which evaluated brentuximab vedotin + AVD versus ABVD, did not use a PET-adapted strategy and all patients received 6 cycles of chemotherapy with imaging at the end of therapy.[89] In patients with stage III or IV disease,

brentuximab vedotin + AVD is initially administered for 2 cycles followed by restaging with PET, based on panel consensus. Patients with a Deauville score of 1 to 4 are treated with 4 additional cycles of brentuximab vedotin + AVD. If patients have a Deauville score of 5, a biopsy should be considered and, if positive, alternative therapy for refractory should be considered. If end-of-therapy PET results in a Deauville score of 3 or 4, patients may be observed or administered ISRT to PET-positive sites.

Management of CHL in Older Adults

CHL in older adult patients (>60 years of age) is associated with worse disease outcomes.[92] B symptoms, poor performance status, mixed cellularity, histologic subtype, Epstein-Barr virus-positive disease, and medical comorbidities are more frequent in this population.[93] Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and transplant-related mortality (TRM) in older patients.[94–97] However, there are limited prospective data evaluating alternatives to standard therapies for older patients. Selection of standard versus alternate first-line regimens 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 older (≥60 years) patients 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).[98] 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 older patients receiving more than 2 cycles of bleomycin.[98]

Due to pulmonary toxicity, bleomycin should be used with caution, as it may not be tolerated in elderly patients. In a retrospective analysis, 147 patients with stage I–IV HL aged at least 60 years were treated with ABVD and evaluated for toxicity and survival.[99] 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. Complete remission was observed in 117 patients (80%) with a 5-year OS rate estimated at 67% (95% CI, 58–74).[99] Other risk factors that may be associated with bleomycin-induced pulmonary toxicity include a history of smoking and use of granulocyte-colony stimulating factor during treatment.[100,101]

In a phase II multicenter study, the impact of sequential brentuximab vedotin given before and after AVD was examined in untreated older patients with stage II–IV HL (n=48).[102] After 2 lead-in doses of brentuximab vedotin, 37 of 48 patients (77%) completed 6 cycles of AVD, and 35 patients (73%) received at least one brentuximab vedotin consolidation.[102] Among 42 response-evaluable patients, the overall response and complete remission rates after 6 cycles of AVD were 95% and 90%, respectively.[102] By intent-to-treat, the 2-year EFS, PFS, and OS rates were 80%, 84%, and 93%, respectively.[102]

Other regimens have been used as front-line chemotherapy in elderly patients with HL, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)[103]; brentuximab vedotin plus dacarbazine (DTIC)[104,105]; VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin)[106,107]; BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)[97]; and PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine).[108]

NCCN Recommendations for Older Adults (Age >60 Years) With CHL

The regimens listed subsequently should be considered in older patients to lessen or minimize toxicity (see HODG-F 1 of 2, page 768). These regimens have not been proven to overcome the poorer disease outcomes observed in older patients. Clinical trial is recommended when available.

Stage I–II Favorable Disease

ABVD, CHOP, and VEPEMB are included as primary treatment options for elderly patients (>60 years of age) with stage I–II favorable disease.[66,98,99,103,107] In this setting, ABVD is the preferred option and 2 cycles of ABVD or AVD are administered followed by ISRT (20–30 Gy). The other treatment regimens include 4 cycles of CHOP with ISRT (30 Gy) and 3 cycles of VEPEMB with or without ISRT (30 Gy).

Stage I–II Unfavorable or Stage III–IV Disease

ABVD, brentuximab vedotin lead in followed by AVD and brentuximab vedotin maintenance, brentuximab vedotin plus DTIC, CHOP, PVAG, and VEPEMB with or without ISRT are included as primary treatment options for elderly patients with stage I–II unfavorable or stage III–IV disease.[45,102–108] For the ABVD regimen, a PET scan follows treatment with 2 cycles of ABVD. Bleomycin may be omitted from ABVD. If the 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 PET scan is positive (Deauville score 4–5) after 2 cycles of ABVD, an individualized treatment plan should be developed.

Relapsed or Refractory CHL

Two randomized phase III studies performed by the British National Lymphoma Investigation[109] and the GHSG/European Group for Blood and Marrow Transplantation[110] 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 high-dose therapy with autologous stem cell rescue (HDT/ASCR) compared with those with resistant disease.[111,112] Moskowitz et al[111] 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 with those who had a poor response (19%, 23%, and 17%, respectively) ($P<.001$). Sirohi et al[112] also reported similar findings; the 5-year OS rates were 79%, 59%, and 17%, respectively, for patients who were in CR, PR, and those with resistant disease at HDT/ASCR ($P<.0001$), and the 5-year PFS rates were 69%, 44%, and 14%, respectively ($P<.001$).

Several investigators have developed prognostic models to predict outcomes in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice et al[113] 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. 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 et al identified extranodal sites, CR duration of less than 1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR.[114] In patients with zero to one risk factors, 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 of relapsed or refractory disease to improve EFS in poorer-risk patients.[115] In a retrospective analysis of 422 patients with relapsed disease, Josting et al[116] 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 4 subgroups with significantly different freedom from second failure and OS. 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 >1 extranodal site as adverse factors for OS.[117] Other groups have identified extent of prior chemotherapy,[118] short time from diagnosis to transplant,[119] and disease status at transplantation[120] 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.[121–124] 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.[114,125–133] ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, cisplatin, and high-dose cytarabine) are the most commonly used regimens. Other regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),[134] IGEV (ifosfamide, gemcitabine, and vinorelbine),[135] GCD (gemcitabine, carboplatin, and dexamethasone),[136,137] and GEMOX (gemcitabine and oxaliplatin)[138] have also been effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials.

Bendamustine, lenalidomide, and everolimus have also shown activity in patients with relapsed or refractory HL.[139–141] In a phase II trial, bendamustine was well tolerated and highly active in heavily pretreated patients with relapsed or refractory disease (including those with HL that failed to respond to HDT/ASCR treatment), resulting in an ORR of 56% among evaluable patients (34 of 36 patients enrolled).[139] The ORR by intent-to-treat analysis was 53% (33% CR and 19% partial response [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.[140,141] In a phase II study, bendamustine in combination with gemcitabine and vinorelbine (BeGEV) was used as induction therapy before autologous stem cell transplant (ASCT) in patients with relapsed or refractory HL, resulting in an ORR of 83% (73% CR and 10% PR).[142] 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.[143]

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[144] In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective responses and complete remissions 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.[145] Based on the results of this study, the FDA approved brentuximab vedotin for the treatment of patients with HL after failure of HDT/ASCR or at least 2 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 brentuximab vedotin.[146] After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 and 9.3 months, respectively. In patients who experienced a complete remission on brentuximab vedotin, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.[146]

Attempts to increase the CR rate before ASCT have led to numerous trials incorporating the novel agents into initial salvage therapy. Several studies are investigating the utility of brentuximab vedotin as a second-line therapy for relapsed or refractory HL, either sequentially or in combination with other regimens, prior to HDT/ASCR. A trial from Memorial Sloan Kettering Cancer Center used a PET-adapted design in which 45 patients received 2 cycles of brentuximab vedotin followed by a PET scan.[147] Patients who achieved a CR after brentuximab vedotin (27%) proceeded directly to ASCT, while patients with residual disease received 2 cycles of augmented ICE. Overall, 76% of patients experienced a CR prior to ASCT using this PET-adapted approach.[147] A similar approach was used by investigators at City of Hope National Medical Center in which 37 patients received 4 cycles of brentuximab vedotin followed by a PET scan.[148] Patients who experienced CR after brentuximab vedotin (35%) proceeded directly to ASCT, while those with residual disease received platinum-based salvage chemotherapy. Overall, 65% of patients experienced CR prior to ASCT using this approach.[148]

Other studies have combined brentuximab vedotin with bendamustine, ICE, or ESHAP (etoposide, methylprednisolone, and high-dose cytarabine or cisplatin) with preliminary data demonstrating PET-negative responses ranging from approximately 75%–90%.[147,149–151] The combination of brentuximab vedotin and nivolumab has also been evaluated as initial salvage therapy prior to ASCT with a high CR rate of 61% after 4 cycles and no increase in toxicities compared with either agent alone.[152] For patients who underwent ASCT after the combination, the 2-year PFS was 91%.[153]

The use of brentuximab vedotin as consolidation therapy after HDT/ASCR was evaluated in the AETHERA trial.[154] For high-risk patients 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 after ASCT. Patients were required to have obtained a CR, PR, or stable disease to second-line therapy before ASCT. At 5-year follow-up, there was a sustained PFS benefit with BV consolidation compared with placebo (5-year PFS, 59% vs 41%; hazard ratio [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 most patients after discontinuing therapy.

Programmed death 1 (PD-1)-blocking monoclonal antibodies have also demonstrated activity in patients with relapsed or refractory PD-1–positive lymphomas.[155–159] In a phase I study of 23 patients with relapsed or refractory HL and pretreated with both HDT/ASCR and brentuximab vedotin, treatment with nivolumab, a human monoclonal PD-1–directed antibody, induced an ORR of 87% with a PFS rate of 86% at 24 weeks.[155] In a phase II study (CheckMate 205 trial) of 80 patients with relapsed or refractory HL and pretreated with both HDT/ASCR and brentuximab vedotin, treatment with nivolumab induced an objective response in 53 of 80 patients (66.3%; 95% CI, 54.8–76.4) as determined by an independent radiologic review committee and at a median follow-up of 8.9 months.[159] 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: brentuximab vedotin-naïve, brentuximab vedotin after HDT/ASCR, or brentuximab vedotin received before and/or after HDT/ASCR.[156] The overall ORR was 69% (95% CI, 63%–75%) and 65%–73% in each cohort, with a median duration of response of 16.6 months (95% CI, 13.2–20 months).[156] Armand et al[157] reported that pembrolizumab, another human monoclonal PD-1–directed antibody, may also be an option for patients with relapsed or refractory HL and pretreated with brentuximab vedotin. In a phase I study of 31 patients with relapsed or refractory HL and pretreated with brentuximab vedotin, pembrolizumab treatment induced a CR rate of 16% (90% CI, 7%–31%) and a PR rate of 48%, resulting in an ORR of 65% (90% CI, 48%–79%).[157] In a phase II study of 210 patients with relapsed or refractory HL, the efficacy of pembrolizumab was examined in 3 cohorts of patients with disease progression after: 1) ASCT and subsequent brentuximab vedotin; 2) salvage chemotherapy and brentuximab vedotin (ineligible for ASCT due to chemoresistant disease); and 3) ASCT without brentuximab vedotin[158]; the corresponding ORRs were 73.9%, 64.2%, and 70%, respectively.[158] Emerging data are investigating the combination of brentuximab vedotin and PD-1 or checkpoint inhibitors as an option for relapsed or refractory HL before transplant.[152]

The role of RT in salvage programs includes its use to cytoreduce prior to HDT/ASCR, its selective use to sites

of relapse after HDT/ASCR, and occasionally its use as a primary component of salvage management. Moskowitz et al[114] have shown the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease. 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 of patients with initial favorable stage I–II disease who are treated with chemotherapy alone and relapse in initially involved sites. Josting et al[160] from the GHSG reported that second-line RT may be effective in a select subset of patients with relapsed or refractory disease. The 5-year FFTF and OS rates were 28% and 51%, respectively. B symptoms and stage at disease progression or relapse were identified as significant prognostic factors for OS. A comprehensive review and recommendations for incorporation of RT into salvage treatment programs is provided by the International Lymphoma Radiation Oncology Group consensus guidelines.[161]

NCCN Recommendations for Refractory CHL

Histologic confirmation with biopsy is recommended before starting treatment of refractory disease (see HODG-14, page 765). 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 radiation-naïve patients, total lymphoid irradiation may be an appropriate component of HDT/ASCR.[162]

Second-line systemic therapy followed by response assessment with 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 recommendation). If HDT/ASCR is contraindicated, then observation with or without RT can be considered. For patients with high risk of relapse as defined by the AETHERA trial, 1 year of brentuximab vedotin maintenance therapy can be considered.[154] For patients with a Deauville score of 4 or 5 after second-line systemic therapy, an alternative regimen with or without RT or RT alone is recommended, followed by repeat response assessment. Another approach for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT, followed by 1 year of brentuximab vedotin maintenance therapy for patients with a high risk of relapse.

Brentuximab vedotin alone or in combination with bendamustine[151] or nivolumab[152]; DHAP[126,129]; ESHAP[127,130,163]; GVD[134]; ICE[114,126]; IGEV[135]; and BeGEV[142] regimens are included as options for second-line systemic therapy for patients with relapsed or refractory CHL (see HODG-C 3 of 4, page 767). Bendamustine, everolimus, and lenalidomide are included as subsequent therapy options for patients with relapsed or refractory CHL.[139–141] Nivolumab and pembrolizumab are included as subsequent therapy options for patients with CHL who have experienced relapse or progression after HDT/ASCR and posttransplant brentuximab vedotin, or after ≥3 lines of systemic therapy including autologous hematopoietic stem cell transplantation (HSCT).[155–159]

Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was >50%. Allogeneic HSCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.[164,165] However, this approach remains investigational. Nonmyeloablative allogeneic transplant using posttransplant cyclophosphamide has excellent outcomes even in haploidentical patients with estimated OS and PFS rates of 63% and 59%, respectively, at 3 years.[166] The panel has included allogeneic HSCT with a category 3 recommendation for select patients with refractory or relapsed disease. For patients with PET-positive refractory HL (Deauville 5) that is responsive to RT alone or to subsequent systemic therapy, with or without RT, use of ASCT or allogeneic SCT is an option.

NCCN Recommendations for Relapsed CHL

Suspected relapse at any point should be confirmed with biopsy (see HODG-15, page 766). Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative. Restaging is recommended for patients with positive biopsy. Most patients require second-line systemic therapy followed by HDT/ASCR with or without RT. 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 PET scan) are as described for patients with refractory disease.

NCCN Recommendations for the Management of Relapsed or Refractory CHL in Older Adults (Aged >60 Years)

Outcomes are uniformly poor for elderly patients with relapsed or refractory disease.[167] 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,[139] brentuximab vedotin,[139,168] everolimus,[141] lenalidomide,[140] nivolumab,[155,159] and pembrolizumab.[157] (see HODG-F 1 of 2, page 768) Nivolumab and pembrolizumab may be considered when patients have been previously treated with brentuximab vedotin or after 3 or more lines of systemic therapy, including HDT/ASCR. ISRT alone is an option when systemic therapy is not considered feasible or safe.

Summary of CHL Management

Current management of CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5-PS). Combined modality therapy or chemotherapy alone are included as treatment options for patients with stage I or II CHL. For patients with stage III–IV disease, chemotherapy alone is recommended.

Compared with conventional chemotherapy alone, HDT/ASCR is the best treatment option for patients with refractory or relapsed CHL that is not cured with primary treatment. Second-line therapy (RT or second-line systemic therapy with or without RT) may be given before HDT/ASCR. Maintenance therapy with brentuximab vedotin (for 1 year) after HDT/ASCR is included as an option for patients with primary refractory disease.

CHL is now curable in most patients because of the introduction of more effective and less toxic regimens. However, survivors may experience late treatment-related side effects. For this reason, long-term follow-up is essential after completion of treatment. Counseling about issues of survivorship and careful monitoring for late treatment-related side effects should be an integral part of follow-up. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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Individual Disclosures for the NCCN Hodgkin Lymphoma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Ranjana H. Advani, MD	Celgene Corporation; Forty Seven, Inc.; Genentech, Inc.; Roche Laboratories, Inc.; Janssen Pharmaceutica Products, LP; Kura Oncology, Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Pharmacyclics, Inc.; Regeneron Pharmaceuticals, Inc.; and Seattle Genetics, Inc.	Genentech, Inc.; Roche Laboratories, Inc.; Portola Pharmaceuticals, Inc.; Sanofi; Seattle Genetics, Inc.; and Takeda Pharmaceuticals North America, Inc.	None	Medical Oncology
Weiyun Z. Ai, MD, PhD	ADT Therapeutics; Nurix; and Rhizen Pharmaceuticals SA	Immune Design Corp.; Kyowa Hakko Kirin Co., Ltd.; and Seattle Genetics, Inc.	None	Hematology/Hematology Oncology, and Medical Oncology
Richard F. Ambinder, MD, PhD	None	None	None	Medical Oncology
Philippe Armand, MD, PhD	Adaptive; ADC Therapeutics; Affimed; Bristol-Myers Squibb Company; Genentech, Inc.; IGM Biosciences;Merck & Co., Inc.; and Tessa Therapeutics	Bristol-Myers Squibb Company; C4 Therapeutics; Celgene Corporation; Daiichi- Sankyo Co.; Enterome; GenMab; Merck & Co., Inc.; and MorphoSys AG	Bristol-Myers Squibb Company	Hematology/Hematology Oncology
Celeste M. Bello, MD, MSPH	None	Celgene Corporation, and Monsanto Corporation	Celgene Corporation	Medical Oncology
Cecil M. Benitez, PhD	None	None	None	Patient Advocacy
Philip J. Bierman, MD	None	None	None	Medical Oncology; Hematology/ Hematology Oncology; and Bone Marrow Transplantation
Kirsten M. Boughan, MD	None	None	None	Hematology/Hematology Oncology, and Bone Marrow Transplantation
Bouthaina Dabaja, MD	None	None	None	Radiation Oncology
Leo I. Gordon, MD	Zylem	Takeda Pharmaceuticals North America, Inc.	Gilead Sciences, Inc., and Juno Therapeutics, Inc.	Hematology/Hematology Oncology
Francisco J. Hernandez-Ilizaliturri, MD	None	Celgene Corporation; Karyopharm Therapeutics; Kite Pharma, Inc.; and Seattle Genetics, Inc.	Amgen Inc., and Pharmacyclics, Inc.	Medical Oncology
Alex F. Herrera, MD	None	Bristol-Myers Squibb Company; Genentech, Inc.; Gilead Sciences, Inc.; Kite Pharma, Inc.; and Merck & Co., Inc.	None	Hematology/Hematology Oncology
Ephraim P. Hochberg, MD	None	Intervention Insights	None	Medical Oncology
Richard T. Hoppe, MD	None	None	None	Radiation Oncology
Jiayi Huang, MD	Bristol-Myers Squibb Company, and Pfizer Inc.	None	None	Radiation Oncology
Patrick B. Johnston, MD, PhD	None	None	None	Radiation Oncology, and Internal Medicine
Mark S. Kaminski, MD	None	None	None	Medical Oncology
Vaishalee P. Kenkre, MD	None	None	None	Hematology/Hematology Oncology
Nadia Khan, MD	Bristol-Myers Squibb Company	Seattle Genetics, Inc.	Genentech, Inc.	Medical Oncology
Ryan C. Lynch, MD	Bayer HealthCare; Cyteir Therapeutics; Incyte Corporation; Juno Therapeutics, Inc.; Rhizen Pharmaceuticals SA; and TG Therapeutics, Inc.	None	None	Medical Oncology, and Hematology/ Hematology Oncology
Kami Maddocks, MD	None	Celgene Corporation; MorphoSys AG; Pharmacyclics, Inc.; and Seattle Genetics, Inc.	None	Hematology/Hematology Oncology
Jonathan McConathy, MD, PhD[a]	None	Blue Earth Diagnostics; Eli Lilly and Company; GE Healthcare; and ImaginAb	None	Nuclear Medicine
Matthew McKinney, MD	BeiGene; Bristol-Myers Squibb Company; Celgene Corporation; Incyte Corporation; Molecular Templates, Inc.; Pharmacyclics, Inc.; and Seattle Genetics, Inc.	Celgene Corporation; Pharmacyclics, Inc.; and Seattle Genetics, Inc.	Kite Pharma, Inc.	Hematology/Hematology Oncology
Monika Metzger, MD	Seattle Genetics, Inc.	None	None	Pediatric Oncology, and Hematology/ Hematology Oncology
David Morgan, MD	None	None	None	Medical Oncology; Hematology/ Hematology Oncology; and Bone Marrow Transplantation
Carolyn Mulroney, MD	Amgen Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Kiadis Pharma; Merck & Co., Inc.; Nicord; Novartis Pharmaceuticals Corporation; and Stemline Therapeutics	None	Bayer HealthCare	Medical Oncology; Hematology/ Hematology Oncology; and Bone Marrow Transplantation
Rachel Rabinovitch, MD	None	None	None	Radiation Oncology
Karen C. Rosenspire, MD, PhD	None	None	None	Diagnostic Radiology
Stuart Seropian, MD	None	None	None	Medical Oncology, and Internal Medicine
Randa Tao, MD	None	QED Therapeutics	None	Radiation Oncology
Jane N. Winter, MD	Astellas Pharma US, Inc.; Celgene Corporation; Daiichi- Sankyo Co.; Epizyme;Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Takeda Pharmaceuticals North America, Inc.	Amgen Inc.; Cardinal Health; CVS Caremark;Delta Fly Pharma; and Novartis Pharmaceuticals Corporation	None	Hematology/Hematology Oncology, and Medical Oncology
Joachim Yahalom, MD	None	None	None	Radiation Oncology

The NCCN Guidelines Staff have no conflicts to disclose.
[a]The following individuals have disclosed that they have anemployment/governing board, patent, equity, or royalty:
Jonathan McConathy, MD, PhD: AbbVie, Inc.