NCCN

Hodgkin Lymphoma

Version 1.2017

Clinical Practice Guidelines in Oncology

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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. In 2017, an estimated 8,260 people will be diagnosed with HL in the United States and 1,070 will die of the disease.¹ The WHO classification

Abstract

This portion of the NCCN Guidelines for Hodgkin lymphoma (HL) focuses on the management of classical HL. Current management of classical HL involves initial treatment with chemotherapy or combined modality therapy followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5-point scale). The introduction of less toxic and more effective regimens has significantly advanced HL cure rates. However, long-term follow-up after completion of treatment is essential to determine potential long-term effects.

J Natl Compr Canc Netw 2017;15(5):608–638

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 for any cancer patient 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 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 representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Hodgkin Lymphoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

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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 638. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

Journal of the National Comprehensive Cancer Network

divides HL into 2 main types: classical HL (CHL) and nodular lymphocyte-predominant HL (NLPHL).² 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 the 5-year survival rates that are unmatched in any other cancer over the past 4 decades. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HL discuss the clinical management of patients with CHL and NLPHL, focusing on adult patients aged ≥18 years who do not have serious intercurrent disease.

This portion of the guidelines discusses recommendations outlined in the NCCN Guidelines for the management of CHL. For the complete and most updated version of these guidelines, visit NCCN.org.

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.^{3,4} Each stage is subdivided into A and B categories; “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

Text cont. on page 624.

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DIAGNOSIS	WORKUP	CLINICAL PRESENTATION
<ul style="list-style-type: none"> Excisional biopsy (recommended) Core needle biopsy may be adequate if diagnostic^a Immunohistochemistry evaluation^b 	<p><u>Essential:</u></p> <ul style="list-style-type: none"> H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examine lymphoid regions, spleen, liver CBC, differential, platelets Erythrocyte sedimentation rate (ESR) Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT) Pregnancy test for women of childbearing age Diagnostic CT^c (contrast enhanced) PET/CT scan^d (skull base to mid-thigh) Counseling: Fertility, smoking cessation, psychosocial (See NCCN Guidelines for Supportive Care) <p><u>Useful in selected cases:</u></p> <ul style="list-style-type: none"> Fertility preservation^e Diagnostic neck CT with contrast, if neck is PET/CT+ or if neck RT contemplated Pulmonary function tests (PFTs incl. diffusing capacity [DLCO]) if ABVD or escalated BEACOPP are being used Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated HIV and hepatitis B/C testing (encouraged) Chest x-ray (encouraged, especially if large mediastinal mass) Adequate bone marrow biopsy if there are cytopenias and negative PET^h Evaluation of ejection fraction if doxorubicin-based chemotherapy is indicated MRI or PET/MRI with contrast (skull base to mid-thigh) 	<p>Classical Hodgkin lymphoma (CHL)^f → See HODG-2</p> <p>Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)^g → See HODG-13*</p>

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

^aFine-needle aspiration (FNA) alone is insufficient for diagnosis except in unusual circumstances when in combination with immunohistochemistry it is judged adequate by a hematopathologist or cytopathologist.

^bTypical immunophenotype for classical Hodgkin lymphoma: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-. Typical immunophenotype for nodular lymphocyte-predominant Hodgkin lymphoma: 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 NHL, available at NCCN.org.

^cA CT is considered diagnostic if it is IV contrast-enhanced. The 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 it should include the areas identified as abnormal on PET/CT.

^dPET/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).

^eFertility preservation options include: Semen cryopreservation, IVF or ovarian tissue or oocyte cryopreservation and oophorectomy.

^fCHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^gNLPHL has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL.

^hIn most instances, if the PET/CT displays a homogeneous pattern of marrow uptake, a bone marrow biopsy is not required and if there is multifocal (three or more) skeletal PET/CT lesions, marrow may be assumed to be involved.

HODG-1

Hodgkin Lymphoma, Version 1.2017

TREATMENT ALGORITHMS FOR CLASSICAL HODGKIN LYMPHOMA (CHL)ⁱ

Clinical Stage	Bulky Disease ^j (mediastinal or peripheral)	Number of Nodal Sites ⁱ	Erythrocyte Sedimentation Rate (ESR)	Guidelines Page
IA	No	1	<50	HODG-3 or HODG-4
IB	No	1	Any	HODG-6
IIA, no extralymphatic (E) lesions	No	<3	<50	HODG-3 or HODG-4
IIA ± extralymphatic (E) lesions ^j	No	<4	<50	HODG-4
	No	≥4 or	≥50	HODG-4 or HODG-6
	Yes	Any	Any	HODG-7
IIB ± extralymphatic (E) lesions ^j	No	Any	Any	HODG-6
	Yes	Any	Any	HODG-7
III-IV	Yes/No	Any	Any	HODG-10

ⁱFor definitions of bulky disease and lymph node regions, see HODG-A.

^jE-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation. (Engert A, et al. N Engl J Med 2010;363:640-652.)

HODG-2

Hodgkin Lymphoma, Version 1.2017

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage IA, IIA Favorable

PRIMARY TREATMENT^k (Modified from GHSG HD10^m Trial)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage IA, IIA Favorable

PRIMARY TREATMENT^k (Modified from RAPID^r, EORTC H10^s, and Stanford G4^t Trials)

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

^fCHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F*).

^lSee Principles of Systemic Therapy (HODG-B).

^mGHSG HD10 study: Engert A, et al. N Engl J Med 2010;363:640-652.

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^pISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^rRAPID Trial: Radford J et al. N Engl J Med 2015;372:1598-1607.

^sEORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.

^tStanford G4 Trial: Advani RH, et al. Ann Oncol 2013;24:1044-1048.

^uConsider PETs after 4 cycles of ABVD.

^vConsider PET/CT after additional 2 cycles of chemotherapy.

HODG-3
HODG-4
HODG-5

Hodgkin Lymphoma, Version 1.2017

CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^f
Stage I-II Unfavorable^x (Non-bulky)

PRIMARY TREATMENT^k

(Modified from GHSG-HD11 and HD14, RATHL, and EORTC H10 Trials)^{s,y,z,aa}

^fClassical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F, available online, in these guidelines, at NCCN.org).

^lSee Principles of Systemic Therapy (HODG-B).

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^pISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^sEORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.

^uConsider PFTs after 4 cycles of ABVD.

^xFor this algorithm, NCCN unfavorable factors include B symptoms, ESR >50, and >3 sites of disease.

^yGHSG HD11 trial: Eich HT, et al. J Clin Oncol 2010;28:4199-4206.

^zGHSG trial HD14: von Tresckow B, et al. J Clin Oncol 2012;30:907-913.

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

^{bb}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.

HODG-6

CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^fStage I-II Unfavorable^{cc} (Bulky mediastinal disease or >10 cm adenopathy)- Planned Combined Modality TherapyPRIMARY TREATMENT^k(Modified from GHSG-HD11, EORTC H10, RATHL, ECOG-2496 Trials)^{s,y,aa,dd}

^fClassical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F, available online, in these guidelines, at NCCN.org).

^lSee Principles of Systemic Therapy (HODG-B).

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^pISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^sEORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.

^uConsider PFTs after 4 cycles of ABVD.

^yGHSG HD11 trial: Eich HT, et al. J Clin Oncol 2010;28:4199-4206.

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

^{bb}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.

^{cc}NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

^{dd}ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.

^{ee}In the GHSG HD14 trial (von Tresckow B, et al. J Clin Oncol 2012;30:907-913) patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-12).

HODG-7

Hodgkin Lymphoma, Version 1.2017

CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^fStage I-II Unfavorable^{cc} (Bulky or non-bulky)PRIMARY TREATMENT^k (continued from HODG-7)(Modified from ECOG-2496 Trial)^{dd}

CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^fStage I-II Unfavorable^{cc} (Bulky or Non-bulky)PRIMARY TREATMENT^k

(continued from HODG-7)

(Modified from GHSG HD14 Trial)^{ee}

^fClassical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F, available online, in these guidelines, at NCCN.org).

^lSee Principles of Systemic Therapy (HODG-B).

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^pISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^{cc}NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

^{dd}ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.

^{ee}In the GHSG HD14 trial (von Tresckow B, et al. J Clin Oncol 2012;30:907-913), patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-12).

^{ff}The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-5.

HODG-8
HODG-9

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage III-IV

PRIMARY TREATMENT^k
(Modified from RATHL, ECOG-2496, GHSG HD15 trials)^{aa,dd,gg}

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

^fClassical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F).

^lSee Principles of Systemic Therapy (HODG-B).

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^pISRT fields are generally smaller than IFRT fields. See Principles of

Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^uConsider PFTs after 4 cycles of ABVD.

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

^{bb}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.

^{dd}ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.

^{gg}HD15 trial: Engert A, et al. Lancet 2012; 379(9828):1791-1799.

^{hh}See International Prognostic Score (IPS) (HODG-A).

HODG-10

Hodgkin Lymphoma, Version 1.2017

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage III-IV

PRIMARY TREATMENT^k (continued from HODG-10)
(Modified from ECOG-2496 Trial)^{dd}

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage III-IV

PRIMARY TREATMENT^k (continued from HODG-10)
(Modified from HD15 Trial)^{gg}

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

Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F, available online, in these guidelines, at NCCN.org).

^lSee Principles of Systemic Therapy (HODG-B).

ⁿAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^oSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^qComplete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

^{dd}ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.

^{gg}HD15 trial: Engert A, et al. Lancet 2012; 379(9828):1791-1799.

^{hh}See International Prognostic Score (IPS) (HODG-A).

ⁱⁱInterim restaging with PET/CT may be considered after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy (4 cycles of ABVD) in patients with a negative interim PET/CT. (Avigdor A, et al. Ann Oncol 2010;21:126-132.)

HODG-11
HODG-12

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

- CR should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
- It is recommended that the patient be provided with a treatment summary at the completion of his/her therapy, including details of radiation therapy, organs at risk, and cumulative anthracycline dosage given.
- Follow-up with an oncologist is recommended, especially during the first 5 years after treatment to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease.^{oo,pp} Late relapse or transformation to large cell lymphoma may occur in NLPHL.
- The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.

Follow-up After Completion of Treatment up to 5 Years

- Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually
- Annual influenza vaccine
- Laboratory studies:
 - ▶ CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated
 - ▶ Thyroid-stimulating hormone (TSH) at least annually if RT to neck.
- Acceptable to obtain a neck/chest/abdomen/pelvis CT scan with contrast, at 6, 12, and 24 mo following completion of therapy, or as clinically indicated. PET/CT only if last PET was Deauville 4–5, to confirm complete response.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
- Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.

Suspected Relapse CHL (HODG-16*) or
NLPHL (HODG-17*)

Follow-up and Monitoring After 5 Years^{pp,qq}

- Interim H&P: Annually
 - ▶ Annual blood pressure, aggressive management of cardiovascular risk factors
 - ▶ Pneumococcal, meningococcal, and H-flu revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to CDC recommendations)
 - ▶ Annual influenza vaccine
- Cardiovascular symptoms may emerge at a young age.
 - ▶ Consider stress test/echocardiogram at 10-y intervals after treatment is completed.
 - ▶ Consider carotid ultrasound at 10-y intervals if neck irradiation.
- Laboratory studies:
 - ▶ CBC, platelets, chemistry profile annually
 - ▶ TSH at least annually if RT to neck
 - ▶ Biannual lipids
 - ▶ Annual fasting glucose
- Annual breast screening: Initiate 8–10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Perform other routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per the ACS Cancer Screening Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.

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

^{oo}Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation-sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9–16, 2003, Bellagio, Italy. Eur J Haematol 2005;75(s66).

^{pp}Appropriate medical management should be instituted for any abnormalities.

HODG-14

Hodgkin Lymphoma, Version 1.2017

Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

GHSG = German Hodgkin Study Group

EORTC = European Organization for the

Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter

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

Definitions of Lymph Node Regions*

	Ann Arbor	EORTC	GHSG
R Cervical/SCL			
R ICL/Subpec			
R Axilla			
L Cervical/SCL			
L ICL/Subpec			
L Axilla			
Mediastinum			
R Hilum			
L Hilum			
Total	9	5	5

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

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

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

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

HODG-A

PRINCIPLES OF SYSTEMIC THERAPY

Classical Hodgkin Lymphoma

- The most common variants of chemotherapy used at NCCN Member Institutions include ABVD and Stanford V.
- Routine use of growth factors is not recommended with ABVD.
- Leukopenia is not a factor for delay of treatment or reduction of dose intensity (except for escalated BEACOPP).

Regimens and References

ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± ISRT

Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640-652.

Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015;372:1598-1607.

Raemaekers JM, André MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography–negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014;32:1188-1194.

Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD 11 trial. *J Clin Oncol* 2010;28:4199-4206.

Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone)*

Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. *Ann Oncol* 2013;24:1044-1048.

Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2013;31:684-691.

Advani RH, Hong F, Fisher RI, et al. Randomized phase III trial comparing ABVD plus radiotherapy with the Stanford V regimen in patients with stages I or II locally extensive, bulky mediastinal Hodgkin lymphoma: a subset analysis of the north american Intergroup E2496 trial. *J Clin Oncol* 2015;33:1936-1942.

Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol* 2010;21:574-581.

Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)

Engert A, Haverkamp H, Cobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012; 379(9828):1791-1799.

Escalated BEACOPP followed by ABVD with ISRT

von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol* 2012;30:907-913.

See Principles of Systemic Therapy for NLPHL (HODG-B 2 of 2, available online, in these guidelines, at NCCN.org)

See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E, available online, in these guidelines, at NCCN.org)

*Cyclophosphamide may be used as an alternate to nitrogen mustard.

Hodgkin Lymphoma, Version 1.2017

PRINCIPLES OF RADIATION THERAPY

- Treatment with photons, electrons, or protons may all be appropriate, depending upon clinical circumstances.
- Advanced radiation therapy (RT) technologies such as IMRT, breath hold or respiratory gating, image-guided RT, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk (OARs) such as the heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.
- The demonstration of significant dose-sparing for these OARs reflects best clinical practice. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- In mediastinal Hodgkin lymphoma, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion such as respiratory gating, inspiration breath-hold techniques, and image-guided RT during treatment delivery may be necessary.
- Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound, and other imaging modalities facilitate target definition. Image guidance may be required to provide assurance of accurate daily delivery.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to develop. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

Involved-site Radiation Therapy (ISRT)

Dose:

- Combined Modality Therapy
 - ▶ Non-bulky disease (stage I-II): 20*–30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V); 1.5-2.0 Gy per fraction
 - ▶ Non-bulky disease (stage IB-IIB): 30 Gy; 1.5-2.0 Gy per fraction
 - ▶ Bulky disease sites (all stages): 30–36 Gy; 1.5-2.0 Gy per fraction
- ISRT Alone (uncommon, except for NLPHL):
 - ▶ Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5-2.0 Gy per fraction
 - ▶ Uninvolved regions: 25–30 Gy; 1.5-2.0 Gy per fraction

Volumes:

- ISRT is recommended as the appropriate field for HL. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging such as PET and MRI often enhances treatment volume determination.
- ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.
- The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment.
- For NLPHL, often treated with RT alone, larger fields should be considered. For example, the CTV definition for treating NLPHL with RT alone will be greater than that employed for CHL with similar disease distribution being treated with combined modality therapy.
- Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume, ITV) should also influence the final CTV.
- The planning target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations and may differ by site and immobilization technique. See ICRU definitions: Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559.
- OARs should be outlined for optimizing treatment plan decisions.
- The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.
- The treatment of extranodal disease is individualized, but similar principles of GTV/CTV/PTV definition should be applied as for nodal disease.
 - ▶ Chest wall extension – effort should be made to include regions of initial chest wall extension to definitive doses.
 - ▶ Lung involvement – areas of extension into the lung from mediastinal or hilar disease may be treated with lower doses (~15 Gy) unless the relative volume is small, in which case higher doses may be utilized. Careful consideration of partial lung tolerance is essential. Pulmonary nodular disease is usually not treated following chemotherapy unless residual disease is present.
 - ▶ Pleural or pericardial effusions are not included in the GTV. Nodular pericardial involvement may be included with consideration of cardiac tolerance.
 - ▶ Bone – Areas of osseous disease may be treated with a CTV expansion beyond the GTV defined by imaging. In the presence of vertebral body disease, the entire vertebra is generally treated.

See References (HODG-C 3 of 3)

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

HODG-C
1 and 2 OF 3

PRINCIPLES OF RADIATION THERAPY

References

- ¹Cella L, Conson M, Caterino M, et al. Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2012;82(5):1802-1808.
- ²Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. *Pract Radiat Oncol* 2014;4:174-180.
- ³Filippi AR, Ciammella P, Piva C, et al. Involved-site image-guided intensity modulated versus 3D conformal radiation therapy in early stage supradiaphragmatic Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2014;89(2):370-375.
- ⁴Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. *Pract Radiat Oncol* 2013;3:216-222.
- ⁵Fox AM, Dosoretz AP, Mauch PM, et al. Predictive factors for radiation pneumonitis in Hodgkin lymphoma patients receiving combined-modality therapy. *Int J Radiat Oncol Biol Phys* 2012;83(1):277-283.
- ⁶Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy in patients with early Hodgkin lymphoma: concepts and guidelines. *Radiother Oncol* 2006;79:270-277.
- ⁷Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? *Int J Radiat Oncol Biol Phys* 2006;64:218-226.
- ⁸Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer Radiother* 2011;15:555-559.
- ⁹Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2012;84:449-455.
- ¹⁰Hoskin PJ, Diez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. *Clin Oncol (R Coll Radiol)* 2013;25:49-58.
- ¹¹Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys* 2011;81(1):167-174.
- ¹²Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. *Radiat Oncol* 2007;2:20.
- ¹³Paumier A, Ghalibafian M, Beaudre A, et al. Involved node radiotherapy and Modern radiation treatment techniques in patients with Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2011;80(1):199-205.
- ¹⁴Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of IMRT combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2012;82(4):1522-1527.
- ¹⁵Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys* 2014;89(4):854-862.
- ¹⁶van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol* 2016;34:235-243.
- ¹⁷Voong KR, McSpadden, Pinnix CC, et al. Dosimetric advantages of a "butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin lymphoma. *Radiat Oncol* 2014;9:94.

HODG-C
3 OF 3

Hodgkin Lymphoma, Version 1.2017

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

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

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

HODGKIN LYMPHOMA STAGING¹

Table 1

Definitions of Stages in Hodgkin's Disease²

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

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

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II₃).

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

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

A No systemic symptoms present

B Unexplained fevers $>38^{\circ}\text{C}$; drenching night sweats; or weight loss $>10\%$ of body weight (within 6 months prior to diagnosis)

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1.

¹For additional information regarding the staging of Hodgkin lymphoma, refer to: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification. J Clin Oncol 2014;32:3059-3068.

²PET scans are useful for upstaging in stage I-II disease. If there is PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.

HODG-D
ST-1

Cont. from page 609.

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unfavorable factors such as large mediastinal adenopathy; >3 nodal sites of disease; B symptoms; extranodal involvement; or significantly elevated erythrocyte sedimentation rate [ESR] ≥ 50); and advanced-stage disease (stage III–IV).

The early-stage unfavorable factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, German Hodgkin Study Group (GHSg), and National Cancer Institute of Canada.^{5,6} NCCN unfavorable factors for stage I–II disease include bulky mediastinal disease (mediastinal mass ratio >0.33) or bulky disease >10 cm; B symptoms; ESR ≥ 50 ; and >3 nodal sites of disease (see HODG-A; page 619). The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis and helps determine the clinical management and predict prognosis for patients with stage III–IV disease.⁷

Response Criteria

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 response.

The International Working Group (IWG) published the guidelines for response criteria in 1999.⁸ In 2007, the IWG guidelines were revised by the International Harmonization Project (IHP) to incorporate immunohistochemistry, flow cytometry, and PET scans into the definition of response.^{9,10} The IHP response criteria were initially developed for the interpretation of PET scans at treatment completion. In recent years, these criteria have also been used for interim response assessment.¹¹

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 liver.^{12–14} 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.^{12,13} PET scans with a score of 1 or 2 are considered

“negative” and those with a score of 4 and 5 are considered “positive.”¹⁵ In some situations, a score of 3 may be considered negative; however, for deescalation of therapy based on interim PET scans, a threshold for positivity that includes a score of 3 using the mediastinal blood pool uptake as the reference is appropriate (PET scans with a score of 1–2 are considered negative and those with a score of 3–5 are considered positive).¹⁶ 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.^{17–21}

Role of PET Scans

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.^{11,14} In a meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.²² PET positivity at the end of treatment has been shown to be a significant adverse risk factor in patients with early-stage and advanced-stage disease.^{23–25} PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone.²¹

The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios and that 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, because subsequent management often depends on that score.

The guidelines recommend biopsy for all patients with a score of Deauville 5. In general, patients with a positive biopsy result should be managed as described for refractory disease. For those with a negative biopsy, complete response (CR) should be documented, including reversion of PET to “negative” within 3 months after therapy completion.

Principles of Radiation Therapy

Radiation therapy (RT) can be delivered with photons, electrons, or protons, depending on clinical circumstances. Advanced RT techniques emphasize

tightly conformal doses and steep gradients adjacent to normal tissues; therefore, target definition, delineation, and treatment delivery verification require careful monitoring (see HODG-C; page 621). 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, image-guided RT, respiratory gating, or deep inspiration breath-hold.^{26,27} These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and decrease the risk of normal tissue damage and late effects without compromising the primary goal of local tumor control.^{28–34}

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

Treatment Guidelines

Diagnosis and Workup

Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy generally be performed (see HODG-1; page 610). The role of fine-needle aspiration (FNA) biopsy in the diagnosis of lymphoma is still controversial.^{35–37} A diagnostic assessment based solely on FNA 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.

Workup should include a thorough history and physical examination; standard laboratory tests; PET/CT (skull base to mid-thigh); and diagnostic contrast-

enhanced CT. A chest radiograph is encouraged for patients with a large mediastinal mass. 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.³⁸ The bone marrow may be assumed to be involved if the PET scan displays multifocal (≥ 3) skeletal lesions.^{38,39} However, a bone marrow biopsy may be performed if cytopenias are present. In select cases, MRI and PET/MRI with contrast (skull base to mid-thigh) may also be considered for anatomic imaging.

Evaluation of ejection fraction is recommended for most patients undergoing doxorubicin-based chemotherapy. 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 the test of the diffusing capacity of the lungs for carbon monoxide, are recommended for patients receiving bleomycin-based chemotherapy. Haemophilus influenzae (H-flu), pneumococcal, and meningococcal vaccines are recommended if splenic RT is contemplated. A diagnostic neck CT scan with contrast is useful in select cases of patients if the neck is positive on PET/CT or in whom RT to the neck is planned.

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 compared with chemotherapy with non-alkylating agent-based chemotherapy.⁴⁰ The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) before the initiation of chemotherapy with alkylating agents or pelvic RT.^{41,42} Oophoropexy should be considered to preserve ovarian function in premenopausal women if pelvic RT is contemplated.⁴³

Stage I–II Favorable Disease: RT alone was a standard treatment option for patients with early-stage HL for many decades.⁴⁴ However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.⁴⁵ With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] and Stanford V) into the management of patients with early-stage disease,

combined modality therapy (chemotherapy and RT) has replaced RT alone as the preferred treatment for patients with early-stage, favorable disease.

The ABVD regimen was developed as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia.⁴⁶ The Stanford V regimen is a brief but dose-intensive regimen with significantly fewer cumulative doses of doxorubicin and bleomycin than those used in ABVD, alternating MOPP/ABVD, BEACOPP, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.^{47,48} RT is an integral part of the Stanford V regimen.⁴⁹

Bonadonna et al⁴⁶ initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy of involved-field RT (IFRT) as the standard treatment for patients with early-stage disease. The HD10 trial from the GHSG investigated the reduction of the number of cycles of ABVD and the IFRT dose in patients with stage I–II disease with no risk factors.⁵⁰ The definitions of unfavorable risk factors and lymph node sites used to determine clinical disease staging are outlined on HODG-A (page 619). It is worth noting that the GHSG and EORTC do not define the lymph node regions strictly according to the Ann Arbor criteria. Patients were not eligible if they had ≥ 3 sites of disease, 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 1 of 4 treatment groups: 4 cycles of ABVD followed by 30 or 20 Gy of IFRT, or 2 cycles of ABVD followed by 30 or 20 Gy of IFRT.⁵⁰ The final analysis of this trial showed that (with a median follow-up of 79–91 months) there were no significant differences between 4 and 2 cycles of ABVD in terms of 5-year 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 and 20 Gy IFRT.⁵⁰ More importantly, no significant differences were seen 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 for patients with a very favorable presentation of early-

stage disease with no risk factors, thereby minimizing the risk of late effects.

The G4 study conducted by the Stanford and Kaiser hospitals evaluated the efficacy of the abbreviated Stanford V chemotherapy (8 weeks or 2 cycles) followed by IFRT (30 Gy) in patients with nonbulky stage IA or IIA disease.⁵¹ Among the 87 patients included in the study, unfavorable risk factors according to GHSG criteria (>2 nodal sites, ESR ≥ 50 , or extranodal involvement) were present in 42 patients (48%), and 33 patients (38%) had unfavorable characters defined by EORTC criteria (>3 nodal sites, ESR ≥ 50 , mixed cellularity, and ≥ 50 years of age). At a median follow-up of 10.6 years, the estimated 10-year freedom from progression (FFP), disease-specific survival, and OS rates were 94%, 99%, and 94%, respectively. Among patients with GHSG criteria, FFP was 100% for patients with favorable disease and 88% for those with unfavorable nonbulky disease. The FFP was 98% and 88%, respectively, for patients with favorable and unfavorable disease according to EORTC criteria. No late cardiac or pulmonary toxicities were observed. No patient developed secondary acute myeloid leukemia or a myelodysplastic syndromes (MDS).

Two studies from Europe have evaluated the value of interim PET scans in defining the need for IFRT in patients with stage I–II favorable disease (the UK RAPID trial and the EORTC H10 trial).^{21,52,53} The interim analysis of the EORTC H10 trial ($n=1,137$; 444 patients with stage I–II favorable disease; 693 patients with stage I–II unfavorable disease) showed that combined modality therapy (ABVD + involved-node RT [INRT]) resulted in fewer early progressions compared with treatment with ABVD alone, even in patients with early-stage favorable disease and a negative PET scan after 2 cycles of ABVD.⁵³

Chemotherapy with ABVD alone has also been investigated as a treatment option for patients with early-stage nonbulky disease (stage I–II). The 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.²¹ 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, 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,²¹ suggesting a benefit for combined modality therapy but not necessarily superiority over chemotherapy alone with this regimen.

Combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment for patients with stage I–II favorable disease.⁵⁴ However, ABVD alone could be a reasonable choice of treatment, especially for younger patients who are in CR after 2 cycles (as documented by CT scan) or for those with a Deauville score of 1 to 3 on PET scan after 2 to 4 cycles of ABVD, in order to avoid the long-term risks of RT.

NCCN Recommendations: Combined modality therapy (ABVD plus involved site RT [ISRT]⁵⁰ [category 1] or Stanford V chemotherapy⁵¹) or chemotherapy (ABVD alone²¹) are included as treatment options for patients with stage IA to IIA favorable disease (absence of all NCCN unfavorable risk factors: bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 nodal sites of disease) (see HODG-3 and HODG-4; page 612).

For patients who fulfill the GHSG criteria for favorable stage IA to IIA disease, 2 cycles of ABVD followed by interim restaging with PET is recommended. For patients with a Deauville score of 1 to 4, a planned course of ISRT (20 Gy) is recommended,⁵⁰ whereas biopsy is recommended for those with a score of Deauville 5 after completion of chemotherapy. ISRT followed by observation is recommended for patients with a negative biopsy, and those with a positive biopsy should be managed as described for refractory disease.

Three treatment regimens are also recommended as suitable options for all patients with nonbulky, favorable stage IA to IIA disease. The first option is used when there is a preference to treat patients with chemotherapy alone and involves an initial administration of 3 cycles of ABVD followed by interim restaging with PET. After interim restaging, and consistent with the results of the RAPID trial, no further treatment is recommended for patients with a Deauville score of 1 or 2.²¹ However, these patients may receive an optional additional cycle of ABVD (total of 4). For patients with a Deauville score of 3 to 4, an

additional cycle of ABVD (total of 4) and ISRT (30 Gy) is recommended. Biopsy is recommended for patients with a Deauville score of 5, and patients with a negative biopsy should be managed with an additional cycle of ABVD (total of 4) and ISRT (30 Gy). If biopsy is positive, patients should be managed as described for refractory disease.

If there is a preference to treat patients with combined modality therapy, patients are administered 2 cycles of ABVD and restaged with PET. 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 to 4 can either be treated with 2 additional cycles of ABVD (total of 4) and ISRT (30 Gy) or 2 cycles of escalated BEACOPP and ISRT (30 Gy). A Deauville score of 5 warrants a biopsy. If the results are negative, patients can be managed as described for those with a Deauville score of 3 to 4, and if results are positive, they should be managed as described for refractory disease.

The third option is treatment with the Stanford V regimen for 8 weeks followed by interim PET restaging. Patients with a Deauville score of 1 to 4 are treated with 30 Gy ISRT, which is optimally instituted within 3 weeks of completion of chemotherapy.⁵¹ A Deauville score of 5 warrants a biopsy. If the results are negative, patients are treated with 30 Gy ISRT, and if positive, they should be managed as described for refractory disease. The combined modality treatment regimen with Stanford V offers an alternative when it is desirable to limit the patient's exposure to bleomycin.⁵¹

Stage I–II Unfavorable Disease: The HD8 trial from the GHSG investigated the efficacy of IFRT versus extended-field RT in the context of combined modality therapy for patients with early-stage unfavorable HL with ≥1 risk factors (large mediastinal mass, extranodal disease, splenic involvement, elevated ESR with or without B symptoms, and >2 lymph node areas of involvement).⁵² No significant differences in FFTR or OS were seen when larger radiation fields were used. IFRT was also associated with less acute toxicity and fewer secondary malignancies. This established combined modality therapy with IFRT as the standard of care for these patients.^{52,55}

To investigate the number of cycles of chemotherapy required for maximal efficacy in combined modality therapy, the EORTC-H9U trial randomized

808 patients with stage I–II unfavorable disease to 3 treatment arms and compared 6 cycles of ABVD, 4 cycles of ABVD, and 4 cycles of BEACOPP, followed by IFRT (30 Gy) in all arms.⁵⁶ At 4 years of follow-up, when the number of ABVD cycles was reduced from 6 to 4, the trial showed similar event-free survival (EFS; 94% vs 89%) and OS (96% vs 95%) rates, but increased toxicity was observed in the BEACOPP arm.⁵⁶

The HD11 trial from the GHSG demonstrated that 4 cycles of ABVD followed by 30 Gy IFRT is an effective treatment option for patients with early-stage unfavorable disease.⁵⁷ In this study, 1,395 patients with stage I–II unfavorable disease (stage IA, IB, or IIA with ≥ 1 of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥ 50 or ESR ≥ 30 with B symptoms; or ≥ 3 involved lymph nodes and stage IIB disease with no bulky mediastinal mass or extranodal involvement) were randomized to either ABVD (4 cycles followed by 30 or 20 Gy IFRT) or standard-dose BEACOPP (4 cycles followed by 30 or 20 Gy IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FTF and PFS rates were 86.8% and 87%, respectively, for BEACOPP; the corresponding rates were 81% and 82%, respectively, for ABVD). However, no difference was seen between the 2 regimens when followed by 30 Gy of IFRT. BEACOPP was also associated with more toxicity than ABVD.

The EORTC H10 trial (n=1,137; 444 patients with stage I–II favorable disease; 693 patients with stage I–II unfavorable disease) aimed to demonstrate prognostic significance of early interim PET after 2 cycles of chemotherapy.⁵³ The H10U trial within this study randomized patients into 2 treatment arms. In the standard arm, patients were treated with 2 cycles of ABVD, underwent interim PET, and were treated with 2 additional cycles of ABVD with 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. If patients were found to be PET-positive after the initial 2 cycles of ABVD, chemotherapy was intensified with 2 cycles of escalated BEACOPP with INRT (30–36 Gy). Although interim analysis demonstrated that chemotherapy alone is a viable treatment option, PET scans showed that combined modality therapy (ABVD + INRT) resulted in fewer

early progressions compared with treatment with ABVD alone.⁵³

The results of the prospective study conducted by the Stanford group demonstrated the efficacy of the Stanford V regimen followed by RT to initially bulky sites for patients with locally extensive and advanced-stage disease.⁵⁸ In this study, 142 patients with locally extensive mediastinal stage I or II disease or stage III or IV disease were treated with Stanford V chemotherapy (12 weeks) followed by RT (36 Gy) to initial bulky sites (≥ 5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year FTF and OS rates were 89% and 96%, respectively. No patients progressed during treatment and there were no treatment-related deaths or secondary leukemia. Among 16 patients who experienced relapse, the freedom from second relapse was 69% at 5 years.

A randomized Italian study reported that ABVD and MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) were superior to the Stanford V regimen in response rate, failure-free survival (FFS), and PFS in patients with intermediate-stage and advanced-stage HL.⁵⁹ However, interpretation of these results was difficult because the timing of response evaluation was different among the arms (8 and 12 weeks for Stanford V, 16 weeks for ABVD, and 24 weeks for MOPPEBVCAD). In addition, modifications of the RT protocol in the Stanford V arm were substantial, including limitation of the number of sites irradiated (no more than 2) and a different definition of bulky disease.

Other investigators have confirmed that the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile when RT is administered according to Stanford V protocol guidelines.^{60–62} In the Memorial Sloan Kettering Cancer Center study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36 Gy of IFRT to bulky sites (≥ 5 cm) and/or to macroscopic splenic disease,⁶¹ with 5- and 7-year OS rates of 90% and 88%, respectively. Of the patients for whom the Stanford V regimen failed, 58% underwent successful second-line therapy with high-dose therapy and autologous stem cell rescue (HDT/ASCR). Aversa et al⁶⁰ from an Italian study group also reported similar findings in patients

with bulky or advanced disease. The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (study ISRCTN 64141244) also showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rate (ORR) and 5-year PFS and OS rates in patients with stage IIB, III, or IV disease or stage I–IIA HL with bulky disease or other adverse features. RT was administered in both arms to sites of previous bulky sites (>5 cm) and to splenic deposits.⁶² At the median follow-up of 4.3 years, the ORR, 5-year PFS, and 5-year OS rates were 91%, 76%, and 90%, respectively, for ABVD and 92%, 74%, and 92%, respectively, for Stanford V.

The phase III intergroup trial (E2496) also confirmed no significant differences between ABVD and Stanford V in terms of response rates, FFS, OS, and toxicity in patients with locally extensive (stage I–IIA/B and bulky mediastinal disease) and stage III–IV disease.^{63,64} In this trial, 854 patients were randomized to ABVD (n=428; 6–8 cycles plus 36 Gy RT only for patients with bulky mediastinal disease) or Stanford V (n=426; 12 weeks of chemotherapy plus 36 Gy RT for sites ≥5 cm or for macroscopic splenic disease). The primary end point was FFS, defined as the time from randomization to progression, relapse, or death, whichever occurred first. With a median follow-up of 6.4 years, no difference between the arms was seen for ORR (clinical CR rates were 72.7% for ABVD and 68.7% for Stanford V), OS (88% at 5 years for both ABVD and Stanford V; $P=.86$), or FFS (74% for ABVD and 71% for Stanford V at 5 years; $P=.32$). Toxicity was also similar in both groups. The planned subgroup analysis showed that the outcome of patients with locally extensive disease was significantly better than that of patients with stage III–IV disease.⁶⁴ The 3- and 5-year FFS rates were 82% for patients with locally extensive disease and 71% and 67%, respectively, for patients with stage III–IV disease ($P=.001$). The 5-year OS rates were 94% and 85%, respectively ($P<.001$).

The GHSG HD14 trial showed that BEACOPP followed by ABVD and IFRT significantly improved tumor control and PFS in patients with early-stage unfavorable disease (stage IA, IB, or IIA HL with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥50 [without B symptoms] or ESR ≥30 [with B symptoms]; or ≥3 involved lymph nodes) and stage

IIB disease with either of the latter 2 risk factors.⁶⁵ In this trial, 1,528 patients were randomized to 4 cycles of ABVD (n=765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD (n=763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FFS rate was 94.8% compared with 87.7% for ABVD ($P<.001$). The 5-year PFS rate was 95.4% and 89.1%, respectively ($P<.001$). 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%; $P<.001$).

The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial has also examined the use of interim PET to guide treatment for patients with advanced disease, which included 500 patients (41.6%) who had stage II HL with various risk factors (B symptoms, bulky disease, or at least 3 involved sites).^{17,66} 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 compared with continued ABVD.⁶⁶

Overall, these results suggest that ABVD plus 30 Gy of IFRT remains the standard of care for patients with early-stage unfavorable disease. Stanford V (when given as described with RT) or BEACOPP followed by ABVD are acceptable alternatives for some patients.

NCCN Recommendations: ABVD followed by ISRT⁵⁷ or AVD,⁶⁶ ABVD followed by escalated BEACOPP and ISRT,⁵³ Stanford V plus ISRT,^{58,64} or escalated BEACOPP (2 cycles) followed by ABVD (2 cycles) and ISRT for selected patients aged <60 years⁶⁵ are included as options for patients with stage I–II unfavorable disease (see HODG-6 and HODG-7; pages 613 and 614). In the HD14 trial that evaluated escalated BEACOPP followed by ABVD and ISRT, patients with bulky disease in combination with either

B symptoms or extranodal disease were excluded.⁶⁵ These patients are managed as described for stage III–IV disease.

Stage I–II (Unfavorable Nonbulky Disease): ABVD is initially administered for 2 cycles followed by interim restaging with PET. Patients with a Deauville score of 1 to 2 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT, or 4 cycles of AVD (total of 6) with or without ISRT. Patients with a Deauville score of 3 to 4 are treated with either 2 additional cycles of ABVD alone (total of 4) or 2 cycles of escalated BEACOPP. PET restaging may be considered at this point and patients are followed up with ISRT. 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 with 4 cycles of AVD (total of 6) with ISRT. All patients with a positive biopsy should be managed as described for refractory disease.

Stage I–II (Unfavorable Bulky Mediastinal Disease or Adenopathy >10 cm With or Without B Symptoms): ABVD is initially administered for 2 cycles followed by interim restaging with PET. This is a category 1 recommendation. 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. Patients with a Deauville score of 4 are treated with 2 additional cycles of ABVD (total of 4) and ISRT or 2 cycles of escalated BEACOPP and ISRT (30 Gy). 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 either receive 2 additional cycles of ABVD (total of 4) and ISRT or 2 cycles of escalated BEACOPP and ISRT. Patients with a positive biopsy should be managed as described for refractory disease.

Stage I–II (Unfavorable Nonbulky Disease and Unfavorable Bulky Mediastinal Disease or Adenopathy >10 cm With or Without B Symptoms): Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30–36 Gy) to patients with stage I–II nonbulky and bulky disease and/or B symptoms (see HODG-8; page 615).^{58,64} 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. If the patients present with unfavorable nonbulky disease and other unfavorable factors (elevated ESR or >3 sites of disease), they are treated with 8 weeks of Stanford V followed by restaging and treated with ISRT (30 Gy) as described for stage IA–IIA favorable disease.⁵¹

Patients receiving escalated BEACOPP (2 cycles) and ABVD (2 cycles) are restaged after completion of chemotherapy (see HODG-9; page 615). 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: Although 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.^{58,64,67}

The landmark randomized trial by the CALBG showed that ABVD alone or alternating with MOPP was superior to MOPP alone in patients with newly diagnosed advanced HL (stage III–IV).⁶⁸ ABVD also was less myelotoxic than MOPP or ABVD alternating with MOPP, and has since been the standard treatment for patients with stage III–IV disease. Stanford V and BEACOPP are the other 2 regimens developed to improve the outcome of patients with advanced disease.

The results from prospective studies conducted by the Stanford group and other investigators have demonstrated the efficacy of Stanford V and IFRT in patients with advanced-stage disease.^{58,60–62} The recently completed phase III intergroup trial (E2496) also showed no significant difference in ORR, FFS, OS, and toxicity between ABVD and Stanford V (with RT, when indicated, according to Stanford V protocol guidelines) in patients with stage III–IV disease.⁶⁴ However, among patients with high-risk disease (IPS ≥3), the 5-year FFS rate was significantly better for ABVD than Stanford V (67% vs

57%; $P=.02$), but no significant difference was seen in 5-year OS rate (84% vs 77%; $P=.15$).

The efficacy of BEACOPP in patients with advanced disease was demonstrated in 2 phase III randomized trials conducted by the GHSG.^{69,70} In the HD9 study, 1,196 patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP-ABVD, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP.⁶⁹ Each regimen was followed by RT to initial sites of disease >5 cm. Most patients in each treatment arm had stage III–IV disease. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP-ABVD and significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP. The 10-year analysis confirmed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP-ABVD in terms of FFTF (82%, 70%, and 64%, respectively) and OS rates (86%, 80%, and 75%, respectively). Escalated-dose BEACOPP was significantly better than standard-dose BEACOPP in terms of FFTF ($P<.0001$) and OS ($P=.0053$).⁷⁰

The final results of the HD12 study ($n=1,670$) that compared 8 cycles of escalated-dose BEACOPP with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP, with or without RT, also confirmed the efficiency of escalated-dose BEACOPP for patients with advanced-stage HL who have risk factors, as reported in the HD9 trial.⁷¹ In this study, at 5 years, the FFTF (86.4% and 84.8%, respectively) and PFS (87.5% and 85%, respectively) were better (although the difference was not significant) for 8 cycles of escalated-dose BEACOPP compared with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP. The 5-year OS rate, however, was not different (92% and 90.3%, respectively).⁷¹

The final analysis of the HD15 trial reported by Engert et al⁶⁷ showed that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT resulted in significantly superior OS and tumor control than 8 cycles of escalated-dose BEACOPP in patients with advanced-stage disease (stage IIB with large mediastinal mass or stage III–IV). In this study, 2,182 patients were randomly assigned to 1 of the 3 treatment groups: 8 cycles of escalated-dose BEACOPP ($n=728$), 6 cycles of escalated-dose BEACOPP

($n=726$), or 8 cycles of a time-intensified standard-dose BEACOPP ($n=728$). RT (30 Gy) was restricted to patients with PET-positive residual sites (≥ 2.5 cm) after chemotherapy. The 5-year FFTF rates were 84.4%, 89.3%, and 85.4%, respectively, for the 3 groups. The corresponding OS rates were 91.9%, 95.3%, and 94.5%, respectively, and were significantly better with 6 cycles of escalated-dose BEACOPP than with 8 cycles of escalated-dose BEACOPP ($P=.019$). Escalated-dose BEACOPP was also associated with less treatment-related mortality (TRM; 4.6% vs 7.5% for 8 cycles of escalated-dose BEACOPP and 5.2% for 8 cycles of time-intensified standard-dose BEACOPP) and fewer secondary cancers (2.4% vs 4.7% and 3.1%, respectively, for 8 cycles of escalated-dose BEACOPP and 8 cycles of time-intensified standard-dose BEACOPP). These results confirm that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT is an acceptable treatment for patients with advanced-stage disease.

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 it resulted in better tumor control in patients with advanced disease.^{72–75} 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).⁷² The results showed that there was no improvement in OS (86.7% and 90.3%, respectively, at 4 years; $P=.208$) or 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.⁷² The long-term follow-up analysis of the HD2000 trial also showed that the risk of secondary malignancy at 10 years was significantly higher with BEACOPP than with ABVD (6.6 vs 0.9; $P=.027$).⁷⁶

Several trials have addressed the role of consolidative RT after completion of chemotherapy in patients with stage III–IV disease.

The SWOG multicenter study showed no improvement in OS rates for patients who underwent

low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, procarbazine plus bleomycin, doxorubicin, and prednisone), but the remission duration was prolonged in several subgroups, especially in patients with bulky nodular sclerosis CHL.⁷⁷ In the randomized trial (EORTC 20884 trial) that assessed the role of consolidation RT following MOPP-ABV chemotherapy in patients with advanced disease, 739 patients with untreated stage III to IV disease received 6 to 8 cycles of MOPP-ABV. Patients with CR on CT imaging after chemotherapy were randomized to no further treatment or IFRT, and those with a partial response (PR) received IFRT to involved nodal areas and extranodal sites.⁷⁸ The 8-year OS and EFS rates in the PR group were 76% and 84%, respectively. These outcomes were not significantly different in patients with CR (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing PR after chemotherapy.

In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) that compared ABVD with 2 other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation.⁷⁹ PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was seen for OS. The final results of the HD12 trial also showed that consolidation RT was beneficial for patients with residual disease after escalated-dose BEACOPP (FFTF was 90.4% and 87%, respectively), whereas this effect was not seen in patients with initial bulk disease who were in CR after chemotherapy.⁷¹ In contrast, Laskar et al⁸⁰ reported a survival advantage for consolidative RT in patients experiencing CR after initial chemotherapy, particularly in patients aged <15 years and those with B symptoms and bulky and advanced disease. However, this study included patients with a different distribution of histologic subtypes of HL compared with those included in Western studies, and most patients had early-stage HL. Of note, none of these studies incorporated PET scan for the evaluation of response.

In the HD15 trial, RT (30 Gy) after BEACOPP chemotherapy was restricted to those patients in PR with PET-positive residual disease (≥ 2.5 cm). PET-negative patients received no additional RT.⁶⁷ Of the 739 qualified patients with residual disease (≥ 2.5 cm) after 6 to 8 cycles of BEACOPP, 548 (74%) were

PET-negative; 191 patients (26%) were PET-positive and received consolidative RT. The final analysis showed that the prognosis of patients in PR with PET-negative persistent residual disease after chemotherapy was similar to that of those who were in CR as measured by conventional CT (4-year PFS was 92.1%), suggesting that consolidative RT could be omitted in patients with a PET-negative PR.⁶⁷ However, the use of consolidative RT was effective for patients with PET-positive PR, because the 4-year PFS in this group was 86.2%. In relapse analysis of the HD15 trial, of 225 patients with PET-positive disease after BEACOPP chemotherapy and RT, 197 (89%) were relapse-free for the duration of their follow-up (median 42 months).⁸¹

Two European trials evaluated the role of HDT/ASCR as a consolidative therapy for patients with advanced-stage and unfavorable HL that responded to initial chemotherapy.^{82,83} Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing CR or PR after an initial course of doxorubicin-based chemotherapy. Instead, additional courses of the same conventional chemotherapy used as initial treatment produced equivalent or better outcomes than HDT/ASCR.

NCCN Recommendations: ABVD, Stanford V (selected patients with IPS <3), or escalated-dose BEACOPP (in selected patients aged <60 years with an IPS of ≥ 4) are included as options for primary treatment for patients with stage III–IV disease (see HODG-10; page 616).^{61,64,66,67,84} In this setting, the ABVD regimen is preferred.

ABVD is initially administered for 2 cycles followed by restaging with PET. Patients with a Deauville score of 1 to 3 are treated with 4 cycles of AVD based on results from the RATHL trial.⁶⁶ Consistent with the results of the E2496 study, observation or ISRT to initially bulky or selected PET-positive sites are included as options for patients with a Deauville score of 1 to 3 after 2 cycles of ABVD and 4 cycles of AVD.⁶⁴ In patients with a positive PET scan (Deauville score of 4 to 5), treatment with 2 additional cycles of ABVD (total of 4) is recommended. Patients are then restaged with PET, and 2 additional cycles of ABVD (total of 6) administered with or without ISRT is an option for those with a negative interim PET scan (Deauville score of 1 to 3). A biopsy is recommended for patients with a Deauville score of 4

or 5. If the biopsy is negative, treatment with 2 additional cycles of ABVD (total of 6) administered with or without ISRT is an option. Patients with a positive biopsy should be managed as described for refractory disease.

Several studies have reported that early intensification to escalated BEACOPP in patients with a positive interim PET scan (based on the 5-PS) after 2 cycles of ABVD is associated with favorable outcomes.^{66,85,86} Based on these findings, the guidelines recommend escalated BEACOPP (4 cycles) as an option for patients with a Deauville score of 4 or 5 after 2 cycles of ABVD. Patients are then restaged with PET, with observation or ISRT to initially bulky or selected PET-positive sites included as options for patients with a Deauville score of 1 to 3, and biopsy recommended for patients with a Deauville score of 4 or 5. If the biopsy is negative, treatment with ISRT directed to PET-positive sites is an option. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by restaging after chemotherapy (see HODG-11; page 617). ISRT (30–36 Gy; within 2–3 weeks after completion of chemotherapy) to initial sites >5 cm and involved spleen is recommended for patients with a Deauville score of 1 to 4 and for those with a Deauville score of 5 with a negative biopsy.^{61,62} Patients with a positive biopsy should be managed as described for refractory disease.

Escalated-dose BEACOPP is administered for 6 cycles followed by restaging with PET (see HODG-12; page 617). No further treatment is necessary for patients with a Deauville score of 1 or 2. Based on the final results of the HD12 and HD15 trials, ISRT to residual PET-positive sites >2.5 cm is recommended for patients with a Deauville score of 3 or 4 after 6 cycles of BEACOPP.^{67,71} Biopsy is recommended for all patients with a Deauville score of 5 after 6 cycles of BEACOPP. Observation or ISRT to the initially bulky or PET-positive sites are included as options for patients with a negative biopsy. Patients with a positive biopsy should be managed as described for refractory disease.

The feasibility of de-escalation of therapy to ABVD in patients with advanced-stage disease (IPS ≥3) who experienced CR after 2 cycles of escalated BEACOPP has been demonstrated in studies conducted by the Israeli Study Group.⁸⁷ Interim restaging

with PET after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy (4 cycles of ABVD) may be considered in patients with a negative interim PET.

Follow-up After Completion of Treatment

Recommendations included in the guidelines are largely based on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, because there are very few data available on the follow-up and monitoring of late effects in patients with HL after completion of treatment.⁸⁸

The panel agrees that given the long-term risks of the therapies for HL, patients should be followed up with an oncologist who is aware of these risks and complications, especially during the first 5 years after treatment to detect recurrence and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease (see HODG-14; page 618). The follow-up schedule should be individualized, depending on clinical circumstances such as patient's age, stage of disease, and initial treatment modality. Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects, health habits, and psychosocial issues. It is recommended that the patient be provided with a treatment summary at the completion of therapy, including details of RT, OARs, and cumulative anthracycline dosage given.

Monitoring for Late Effects

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

Secondary Cancers: Solid tumors are the most common secondary cancers and most develop >10 years after treatment completion. The risk of developing secondary cancers is highest when RT is used as a component of first-line treatment. A meta-analysis by Franklin et al⁸⁹ showed that the risk of developing secondary cancers was lower with combined modality treatment than with RT alone as the initial treatment. The risk was marginally higher with combined modality treatment compared with chemotherapy alone as initial treatment. Lung and breast cancers

are the most common secondary cancers in patients with HL. Annual breast screening [mammography and MRI] beginning no later than 8 to 10 years after completion of therapy or at age 40 years (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation.⁹⁰ The NCCN Guidelines recommend breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age, which is consistent with the recommendation of the American Cancer Society guidelines.⁹¹ The NCCN Guidelines recommend that routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancers be performed as per the American Cancer Society guidelines.

Cardiovascular Disease: Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.⁹²⁻⁹⁴ RT-induced cardiotoxicity is usually observed more than 5 to 10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Coronary CT angiography abnormalities have been detected in nearly 15% of patients within the first 5 years after treatment, and the incidence significantly increases 10 years after treatment.⁹⁵ In a multivariate analysis, patient's age at treatment, hypercholesterolemia, hypertension, and RT dose to the coronary artery origins were identified as independent prognostic factors.

Based on data regarding increased long-term risk of cardiac disease, annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors is recommended.⁹⁰ A baseline stress test or echocardiogram and carotid ultrasound (for patients treated with neck RT) should be considered at 10-year intervals after treatment completion.

Hypothyroidism: Abnormal thyroid function, mostly hypothyroidism, is reported in approximately 50% of long-term survivors who received neck or upper mediastinal irradiation.⁸⁸ A careful thyroid examination should be a part of the physical examination. Thyroid function tests should be performed at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression: Myelosuppression is the most common side effect of chemotherapy and is associated with increased risk of infections. It is uncommon

for myelosuppression to continue for very long beyond completion of the primary treatment program. However, patients who undergo HDT/ASCR or allogeneic hematopoietic stem cell transplant may be at continued risk for infection. Pneumococcal, meningococcal, and H-flu revaccinations are recommended every 5 years for patients treated with splenic RT or splenectomy.

Infertility: Certain chemotherapy combinations (eg, BEACOPP) may cause immediate and permanent infertility in both men and women.^{96,97} Other combinations (eg, ABVD) are only rarely associated with infertility.^{42,98} Because women who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause,⁴⁰ this should be taken into consideration with respect to family planning.

Pulmonary Toxicity: Bleomycin-induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation, and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity, and their concurrent use with chemotherapy significantly decreases OS rate.⁹⁹ Recently, 2 separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.^{100,101} The NCCN Guidelines do not recommend the routine use of growth factors with ABVD regimens.

Summary

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 (ABVD, ABVD followed by escalated BEACOPP, or Stanford V plus ISRT) or ABVD alone are included as treatment options for patients with stage IA or IIA favorable CHL. Chemotherapy (ABVD or Stanford V or BEACOPP plus ABVD) followed by consolidative ISRT is recommended for patients with stage I-II unfavorable disease. Chemotherapy with ABVD or Stanford V or escalated-dose BEACOPP is recommended for patients with stage III-IV disease.

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HL is now curable in most patients because of the introduction of more effective and less toxic regimens. However, survivors may experience late treatment-related side effects. For this reason, long-term follow-up by an oncologist 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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed. Lyon, France: IARC; 2008.
3. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971;31:1860–1861.
4. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:3059–3068.
5. Henry-Amar M, Friedman S, Hayat M, et al. Erythrocyte sedimentation rate predicts early relapse and survival in early-stage Hodgkin disease. The EORTC Lymphoma Cooperative Group. *Ann Intern Med* 1991;114:361–365.
6. Tubiana M, Henry-Amar M, Hayat M, et al. Prognostic significance of the number of involved areas in the early stages of Hodgkin's disease. *Cancer* 1984;54:885–894.
7. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998;339:1506–1514.
8. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;17:1244–1244.
9. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–586.
10. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007;25:571–578.
11. Cheson BD. Role of functional imaging in the management of lymphoma. *J Clin Oncol* 2011;29:1844–1854.
12. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8–9 April 2010. *Leuk Lymphoma* 2010;51:2171–2180.
13. Meignan M, Gallamini A, Itti E, et al. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26–27 September 2011 and Menton 2011 consensus. *Leuk Lymphoma* 2012;53:1876–1881.
14. Barrington SF, Mikhael NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol* 2014;32:3048–3058.
15. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging* 2010;37:1824–1833.
16. Dann EJ. PET/CT adapted therapy in Hodgkin disease: current state of the art and future directions. *Curr Oncol Rep* 2012;14:403–410.
17. Barrington SF, Kirkwood AA, Franceschetto A, et al. PET-CT for staging and early response: results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study. *Blood* 2016;127:1531–1538.
18. Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nucl Med* 2013;54:683–690.
19. Gallamini A, Barrington SF, Biggi A, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. *Haematologica* 2014;99:1107–1113.
20. Gallamini A, Kostakoglu L. Interim FDG-PET in Hodgkin lymphoma: a compass for a safe navigation in clinical trials? *Blood* 2012;120:4913–4920.
21. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015;372:1598–1607.
22. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. *Cancer* 2005;104:1066–1074.
23. de Wit M, Bohuslavizki KH, Buchert R, et al. 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. *Ann Oncol* 2001;12:29–37.
24. Guay C, Lepine M, Verreault J, Benard F. Prognostic value of PET using 18F-FDG in Hodgkin's disease for posttreatment evaluation. *J Nucl Med* 2003;44:1225–1231.
25. Sher DJ, Mauch PM, Van Den Abbeele A, et al. Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. *Ann Oncol* 2009;20:1848–1853.
26. Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys* 2011;81:167–174.
27. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2012;84:449–455.
28. Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? *Int J Radiat Oncol Biol Phys* 2006;64:218–226.
29. Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. *Radiat Oncol* 2007;2:20–20.
30. Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2012;82:1522–1527.
31. Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. *Pract Radiat Oncol* 2013;3:216–222.
32. Charpentier A-M, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: impact on normal tissue dose. *Pract Radiat Oncol* 2014;4:174–180.
33. Filippi AR, Ciammella P, Piva C, et al. Involved-site image-guided intensity modulated versus 3D conformal radiation therapy in early stage supradiaphragmatic Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2014;89:370–375.
34. Voong KR, McSpadden K, Pinnix CC, et al. Dosimetric advantages of a "butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma. *Radiat Oncol* 2014;9:94–94.
35. Caraway NP. Strategies to diagnose lymphoproliferative disorders by fine-needle aspiration by using ancillary studies. *Cancer* 2005;105:432–442.
36. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. *J Clin Oncol* 2004;22:3046–3052.
37. Meda BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytology and flow cytometry. *Am J Clin Pathol* 2000;113:688–699.
38. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naïve patients with Hodgkin lymphoma. *J Clin Oncol* 2012;30:4508–4514.

Hodgkin Lymphoma, Version 1.2017

39. Moulin-Romsee G, Hindie E, Cuenca X, et al. (18)F-FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging. *Eur J Nucl Med Mol Imaging* 2010;37:1095–1105.
40. van der Kaaij MA, Heutte N, Meijnders P, et al. Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Etude des Lymphomes de l'Adulte Cohort Study. *J Clin Oncol* 2012;30:291–299.
41. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSg). *Blood* 2008;111:71–76.
42. van der Kaaij MA, van Echten-Arends J, Simons AH, Kluin-Nelemans HC. Fertility preservation after chemotherapy for Hodgkin lymphoma. *Hematol Oncol* 2010;28:168–179.
43. Terenziani M, Piva L, Meazza C, et al. Oophorectomy: a relevant role in preservation of ovarian function after pelvic irradiation. *Fertil Steril* 2009;91:935 e915–936.
44. Duhmke E, Franklin J, Pfreundschuh M, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. *J Clin Oncol* 2001;19:2905–2914.
45. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta Oncol* 2003;42:589–604.
46. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol* 2004;22:2835–2841.
47. Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol* 1995;13:1080–1088.
48. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J Clin Oncol* 2013;31:592–598.
49. Abuzetun JY, Loberiza F, Vose J, et al. The Stanford V regimen is effective in patients with good risk Hodgkin lymphoma but radiotherapy is a necessary component. *Br J Haematol* 2009;144:531–537.
50. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640–652.
51. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. *Ann Oncol* 2013;24:1044–1048.
52. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003;21:3601–3608.
53. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014;32:1188–1194.
54. Olszewski AJ, Shrestha R, Castillo JJ. Treatment selection and outcomes in early-stage classical Hodgkin lymphoma: analysis of the National Cancer Data Base. *J Clin Oncol* 2015;33:625–633.
55. Sasse S, Klimm B, Gorgen H, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. *Ann Oncol* 2012;23:2953–2959.
56. Noordijk EM, Thomas J, Ferme C, et al. First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma (HL) [abstract]. *J Clin Oncol* 2005;23(Suppl):Abstract 6505.
57. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 2010;28:4199–4206.
58. Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol* 2002;20:630–637.
59. Chisesi T, Bellei M, Luminari S, et al. Long-term follow-up analysis of HD9601 trial comparing ABVD versus Stanford V versus MOPP/EBV/CAD in patients with newly diagnosed advanced-stage Hodgkin's lymphoma: a study from the Intergruppo Italiano Linfomi. *J Clin Oncol* 2011;29:4227–4233.
60. Aversa SM, Salvagno L, Soraru M, et al. Stanford V regimen plus consolidative radiotherapy is an effective therapeutic program for bulky or advanced-stage Hodgkin's disease. *Acta Haematol* 2004;112:141–147.
61. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol* 2010;21:574–581.
62. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *J Clin Oncol* 2009;27:5390–5396.
63. Advani RH, Hong F, Fisher RI, et al. Randomized phase III trial comparing ABVD plus radiotherapy with the Stanford V regimen in patients with stages I or II locally extensive, bulky mediastinal Hodgkin lymphoma: a subset analysis of the North American Intergroup E2496 trial. *J Clin Oncol* 2015;33:1936–1942.
64. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an Intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2013;31:684–691.
65. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol* 2012;30:907–913.
66. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 2016;374:2419–2429.
67. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012;379:1791–1799.
68. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478–1484.
69. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003;348:2386–2395.
70. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSg HD9 study. *J Clin Oncol* 2009;27:4548–4554.
71. Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol* 2011;29:4234–4242.
72. Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in stage III to IV, International Prognostic Score ≥ 3 , high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup trial. *J Clin Oncol* 2016;34:2028–2036.
73. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* 2009;27:805–811.
74. Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles $\geq$ 4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol* 2014;25:1622–1628.
75. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* 2011;365:203–212.
76. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *J Clin Oncol* 2016;34:1175–1181.
77. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. *Ann Intern Med* 1994;120:903–912.
78. Aleman BM, Raemaekers JM, Tomisic R, et al. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2007;67:19–30.

Hodgkin Lymphoma, Version 1.2017

79. Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). *J Clin Oncol* 2010;3352–3359.
80. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? *J Clin Oncol* 2004;22:62–68.
81. Kriz J, Reinartz G, Dietlein M, et al. Relapse analysis of irradiated patients within the HD15 trial of the German Hodgkin Study Group. *Int J Radiat Oncol Biol Phys* 2015;92:46–53.
82. Carella AM, Bellei M, Brice P, et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. *Haematologica* 2009;94:146–148.
83. Proctor SJ, Mackie M, Dawson A, et al. A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the Scotland and Newcastle Lymphoma Group (SNLG) prognostic index. A Scotland and Newcastle Lymphoma Group study (SNLG HD III). *Eur J Cancer* 2002;38:795–806.
84. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003;21:607–614.
85. Gallamini A, Rossi A, Patti C, et al. Early treatment intensification in advanced-stage high-risk Hodgkin lymphoma (HL) patients, with a positive FDG-PET scan after two ABVD courses—second interim analysis of the GITIL/FIL HD0607 clinical trial [abstract]. *Haematologica* 2013;98(Suppl 2):Abstract P006.
86. Press OW, Li H, Schoder H, et al. US Intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol* 2016;34:2020–2027.
87. Avigdor A, Bulvik S, Levi I, et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma. *Ann Oncol* 2010;21:126–132.
88. Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9–16, 2033, Bellagio, Italy. *Eur J Haematol Suppl* 2005:68–76.
89. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol* 2006;17:1749–1760.
90. Ng A, Constine LS, Advani R, et al. ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer* 2010;34:211–227.
91. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2005;57:75–89.
92. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743–749.
93. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 2004;22:3139–3148.
94. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878–1886.
95. Girinsky T, M'Kacher R, Lessard N, et al. Prospective coronary heart disease screening in asymptomatic Hodgkin lymphoma patients using coronary computed tomography angiography: results and risk factor analysis. *Int J Radiat Oncol Biol Phys* 2014;89:59–66.
96. Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2005;23:7555–7564.
97. van der Kaaij MA, Heutte N, Le Stang N, et al. Gonadal function in males after chemotherapy for early-stage Hodgkin's lymphoma treated in four subsequent trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2007;25:2825–2832.
98. Hodgson DC, Pintilie M, Gitterman L, et al. Fertility among female Hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. *Hematol Oncol* 2007;25:11–15.
99. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005;23:7614–7620.
100. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. *Ann Oncol* 2007;18:376–380.
101. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. *Br J Haematol* 2007;137:545–552.

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Individual Disclosures for the Non-Small Cell Lung Cancer Panel				
Panel Member	Clinical Research Support/ Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Ranjana H. Advani, MD	Agensys; Allos Therapeutics; Celgene Corporation; Genentech, Inc.; Infinity; Janssen Pharmaceutica Products, LP; Kura Oncology, Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Pharmacyclics; Regeneron Pharmaceuticals, Inc.; and Seattle Genetics	Bristol-Myers Squibb Company; Cell Medica; Forty Seven, Inc.; Genentech, Inc.; Juno; Spectrum; and Sutro	None	12/6/16
Weiyun Z. Ai, MD, PhD	None	Seattle Genetics	None	3/31/16
Richard F. Ambinder, MD, PhD	None	Chinese University Hong Kong	None	7/4/16
Patricia Aoun, MD, MPH	None	None	None	8/26/16
Celeste M. Bello, MD, MSPH	Seattle Genetics	None	Celgene Corporation; and Seattle Genetics	12/12/16
Cecil M. Benitez, PhD	None	None	None	12/21/16
Karl Bernat, MD	None	None	None	11/27/16
Philip J. Bierman, MD	None	None	None	7/14/16
Kristie A. Blum, MD	Celgene Corporation; Constellation Pharmaceuticals; Janssen Pharmaceutica Products, LP; Millennium Pharmaceuticals, Inc; Morphosys; Novartis Pharmaceuticals Corporation; and Pharmacyclics	Morphosys	None	11/28/16
Robert Chen, MD	Bristol-Myers Squibb Company; Pharmacyclics; and Seattle Genetics	Genentech, Inc.; Merck & Co., Inc.; and Seattle Genetics	Genentech, Inc.; and Seattle Genetics	11/15/16
Bouthaina Dabaja, MD	None	None	None	12/5/16
Andres Forero, MD	Abbott Laboratories; Celgene Corporation; Daiichi-Sankyo Co.; Genentech, Inc.; GlaxoSmithKline; Incyte; Novartis Pharmaceuticals Corporation; Oncothyreon; Pfizer Inc.; Pharmacyclics; Seattle Genetics; Synta Pharmaceuticals Corp.; and TRACON	Incyte; and Seattle Genetics	None	11/26/16
Leo I. Gordon, MD	None	None	None	1/17/17
Francisco J. Hernandez-Ilizaliturri, MD	None	Celgene Corporation; Novartis Pharmaceuticals Corporation; and Seattle Genetics	None	1/6/17
Ephraim P. Hochberg, MD	None	Flatiron; and Intervention Insights	None	7/4/16
Richard T. Hoppe, MD	None	None	None	11/14/16
Jiayi Huang, MD	None	None	Viewray Inc.	6/1/16
Patrick B. Johnston, MD, PhD	None	None	None	12/8/16
Mark S. Kaminski, MD	None	Gilead; Nordic Nanovector; and Pharmacyclics	None	1/3/17
Vaishalee P. Kenkre, MD	Abbott Laboratories; Celgene Corporation; MedImmune Inc.; MEI Pharma; and Seattle Genetics	None	None	11/23/16
Nadia Khan, MD	Fox Chase Cancer Center	Pharmacyclics	Genentech, Inc.	1/4/17
David G. Maloney, MD, PhD	GlaxoSmithKline; and Juno Therapeutics	Bristol-Myers Squibb Company; Celgene Corporation; F. Hoffmann LaRoche; and Gilead	None	4/10/17
Peter M. Mauch, MD	None	None	None	8/10/16
Monika Metzger, MD	Seattle Genetics	None	None	11/14/16
Joseph O. Moore, MD	ARIAD Pharmaceuticals, Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	None	None	3/13/17
David Morgan, MD	None	None	None	3/14/17
Craig H. Moskowitz, MD	Merck & Co., Inc.; Pharmacyclics; and Seattle Genetics	Celgene Corporation; Genentech, Inc.; Merck & Co., Inc.; and Seattle Genetics	Seattle Genetics	12/7/16
Carolyn Mulrone, MD	Amgen Inc.; Eli Lilly and Company; Merck & Co., Inc.; Pharmacyclics; Takeda Pharmaceuticals North America, Inc.; and TG therapeutics	None	None	1/5/17
Matthew Poppe, MD	None	Garlington Lohn Robinson law firm; and Kalkstein, Johnson & Dye, PC	None	5/27/16
Rachel Rabinovitch, MD	RTOG Data Safety and Monitoring Board	None	None	1/11/17
Stuart Seropian, MD	None	None	None	1/30/17
Mitchell Smith, MD, PhD	Infinity	Celgene Corporation	None	4/29/16
Jane N. Winter, MD*	GlaxoSmithKline; Merck & Co., Inc.; and Seattle Genetics	Celgene Corporation; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	2/5/17
Joachim Yahalom, MD	None	None	None	8/10/16

The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:

Jane Winter, MD: UpToDate