



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology™

Hodgkin Disease/ Lymphoma

V.2.2008

Continue

www.nccn.org

NCCN Hodgkin Disease/Lymphoma Panel Members

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

Ranjana Hira Advani, MD †
Stanford Comprehensive Cancer
Center

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

Philip J. Bierman, MD † ‡ ξ
UNMC Eppley Cancer Center at The
Nebraska Medical Center

Clara D. Bloomfield, MD †
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute at
The Ohio State University

Kristie Blum, MD ‡
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute at
The Ohio State University

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

Benjamin Djulbegovic, MD, PhD † ‡
H. Lee Moffitt Cancer Center & Research
Institute

Andres Forero, MD † ‡
University of Alabama at Birmingham
Comprehensive Cancer Center

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

Francisco J. Hernandez-Ilizaliturri, MD †
Roswell Park Cancer Institute

Melissa M. Hudson, MD ‡
St. Jude Children's Research
Hospital/University of Tennessee Cancer
Institute

Mark S. Kaminski, MD †
University of Michigan Comprehensive
Cancer Center

Gena Love ¥
New Mexico Department of Health
Comprehensive Cancer Programs

David G. Maloney, MD † ‡
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

David Mansur, MD
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Peter M. Mauch, MD §
Dana-Farber/Brigham and Women's
Cancer Center | Massachusetts General
Hospital Cancer Center

Joseph O. Moore, MD †
Duke Comprehensive Cancer Center

Russell J. Schilder, MD † ‡
Fox Chase Cancer Center

Lawrence M. Weiss, MD ≠
City of Hope

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

Joachim Yahalom, MD §
Memorial Sloan-Kettering Cancer Center

Andrew D. Zelenetz, MD, PhD † ‡
Memorial Sloan-Kettering Cancer Center

§ Radiation oncology
† Medical Oncology
‡ Hematology/Hematology oncology
ξ Bone Marrow Transplantation
≠ Pathology
‡ Internal medicine
¥ Patient Advocacy
* Writing Committee Member

Continue

Table of Contents

[NCCN Hodgkin Disease/Lymphoma Panel Members](#)

[Summary of Guidelines Updates](#)

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

Primary Treatment

- Classical Hodgkin Lymphoma:

[CS IA-IIA Nonbulky \(HODG-2\)](#)

[CS I-II Bulky \(HODG-3\)](#)

[CS IB-IIB Nonbulky and Stage III-IV \(Nonbulky and Bulky\) \(HODG-4\)](#)

- Lymphocyte-predominant Hodgkin Lymphoma:

[CS IA-IIA \(HODG-6\)](#)

[CS IB-IIB \(HODG-6\)](#)

[CS IIIA-IVA \(HODG-6\)](#)

[CS IIIB-IVB \(HODG-6\)](#)

[Follow-up After Completion of Treatment and Monitoring For Late Effects \(HODG-7\)](#)

[Relapse \(HODG-8\)](#)

[Unfavorable Factors \(localized and advanced disease\) \(HODG-A\)](#)

[Principles of Chemotherapy \(HODG-B\)](#)

[Principles of Radiation Therapy \(HODG-C\)](#)

[Revised Response Criteria \(HODG-D\)](#)

[Principles of Second-line Chemotherapy \(HODG-E\)](#)

[Guideline Index](#)

[Print the Hodgkin Disease/Lymphoma Guidelines](#)

[For help using these documents, please click here](#)

[Staging](#)

[Manuscript](#)

[References](#)

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

To find clinical trials online at NCCN member institutions, [click here:
nccn.org/clinical_trials/physician.html](#)

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#)

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these 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 makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.

Summary of the Guidelines updates

The addition of the manuscript represents the version change to 2.2008

Summary of changes in the 1.2008 version of the Hodgkin Disease/Lymphoma guidelines from the 1.2007 version include:

Global change

The terminology for stem cell transplant was changed throughout to high dose therapy with autologous stem cell rescue.

HODG-1

- The category 2B recommendation was removed from PET scan
- Footnotes b, c, d and g are new to the page.
- The therapy recommendations for stage I-II bulky were moved to HODG-3.

HODG-2

- Flow diagrams were revised including rewording for the restaging and response categories.
- ABVD was added as a treatment option with a category 2B designation.
- Footnote l is new to the page.
- The therapy recommendations for Stage IB-IIB nonbulky and stage IIIA, IIIB and IV nonbulky and bulky were moved to HODG-4.

HODG-3

- Flow diagrams were revised including rewording for the restaging and response categories.
- Footnotes l, n, o and p are new to the page.

HODG-4

- Escalated BEACOPP was added as an option for treatment and the detailed recommendations are on page HODG-5.
- "Initial sites of bulky disease" was added an indication for IFRT.
- Footnotes l, p, r and s are new to the page.
- The recommendations for Lymphocyte-predominant Hodgkin lymphoma were moved to HODG-6.

HODG-5

- New page with treatment recommendations for BEACOPP.
- The Follow-up section moved to page HODG-7.

HODG-6

- Footnotes l and t are new to the page.
- The recommendations for Progressive disease or relapse have moved to page HODG-8.

HODG-7

- The recommendation for chest imaging and abdominal/pelvic CT was changed to every 6-12 m.
- PET scan was clarified as "should not be done routinely".

HODG-8

- The treatment recommendations for patients who had RT alone for primary therapy was changed to be consistent with the recommendations listed on page HODG-4.
- The Individualized treatment recommendation was clarified as the following options: RT, non-cross resistant chemotherapy, or HDT/ASCR.
- Footnotes r and dd are new to the page.

HODG-A

- The title for the Unfavorable factors for advanced disease was changed to the "International Prognostic Score".

HODG-B 1 of 3

- For stage IA-IIA non-bulky disease, the recommendation for ABVD for 2 cycles followed by 20 Gy was added for patients with favorable factors. Footnote 2 is new to the page.
- For Stanford V regimen, the RT recommendation was expanded to include "residual PET positive sites".

HODG-B 2 of 3

- All regimen references are new to the page.

HODG-B 3 of 3

- All regimens and references are new to the page.

HODG-C

- RT doses were added for treatment with BEACOPP.

HODG-E

- The GVD and IGEV regimens were added as options for second-line therapy with references.

ST-1

- Footnote 1 is new to the page.

DIAGNOSIS^a

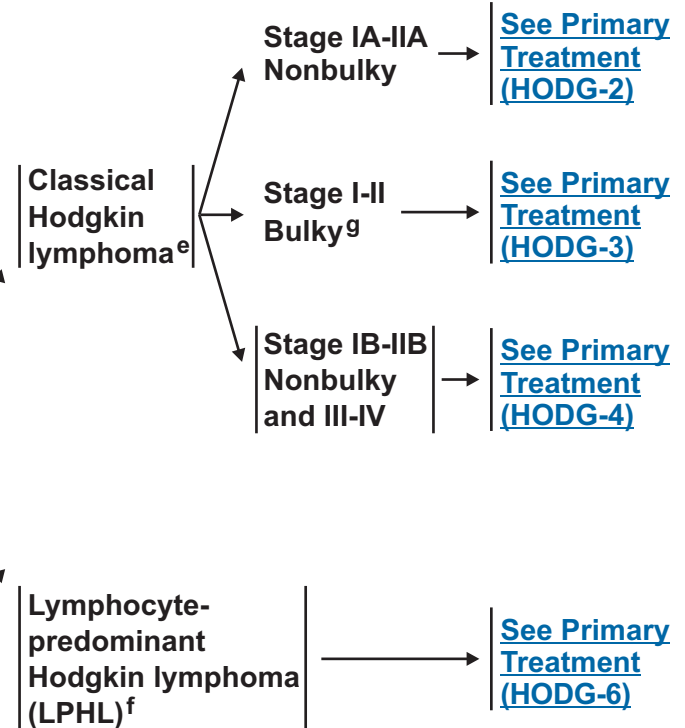
WORKUP

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic
- FNA alone is insufficient
- Immunohistochemistry highly recommended for classical Hodgkin lymphoma
- For lymphocyte-predominant Hodgkin lymphoma, recommend CD3, CD15, CD20, CD21, CD30, CD57^b
- For typical classical Hodgkin lymphoma, recommend CD3, CD15, CD20, CD30, CD45^b

- H&P including:
 - B symptoms
 - Alcohol intolerance
 - Pruritus
 - Fatigue
 - Performance status
 - Exam lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- LDH, LFT, albumin
- BUN, creatinine
- Pregnancy test: women of childbearing age
- Chest x-ray
- Chest/abdominal/pelvic CT
- PET scan^{c,d}
- Adequate bone marrow biopsy in stage IB-IIB and stage III-IV
- Counseling: Fertility, smoking cessation, psychosocial ([see NCCN Distress Management Guidelines](#))

- Useful in selected cases:**
- Semen cryopreservation, if chemotherapy or pelvic RT contemplated
 - Neck CT, if neck RT planned
 - Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
 - HIV, if risk factors, unusual disease presentations
 - Evaluation of ejection fraction
 - Pulmonary functions tests (PFTs), Diffusion capacity of the lungs for carbon monoxide (DLCO)

CLINICAL STAGING



^aTreatment recommendations for postadolescent Hodgkin lymphoma.

^bAn expanded panel of markers may be required especially if equivocal diagnosis. [See Non-Hodgkin's Lymphoma guidelines.](#)

^cIn 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 upstage patient. [See Table 1 \(ST-1\).](#)

^dPET/CT always preferred.

^eClassical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).

^fLymphocyte-predominant Hodgkin lymphoma (LPHL) has a different natural history and response to therapy than does classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for LPHL.

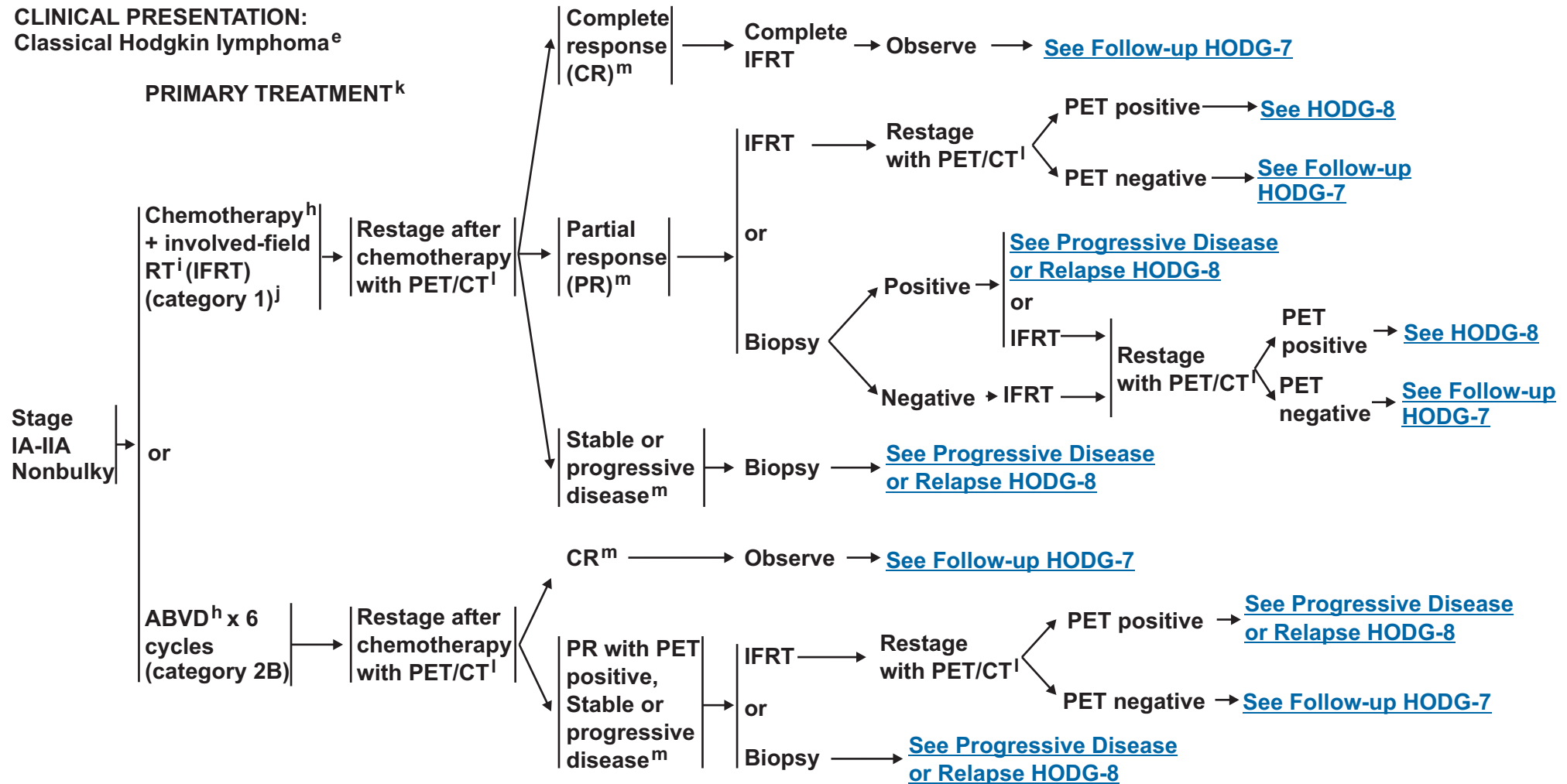
^gBulky disease with or without B symptoms ([see Unfavorable Factors, HODG-A](#)).

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

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma^e

PRIMARY TREATMENT^k



^eClassical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).

^h[See Principles of Chemotherapy \(HODG-B\).](#)

ⁱ[See Principles of Radiation Therapy \(HODG-C\).](#)

^jDepending upon co-morbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able tolerate chemotherapy.

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease.

^lAn integrated PET/CT or a PET with a diagnostic CT is recommended.

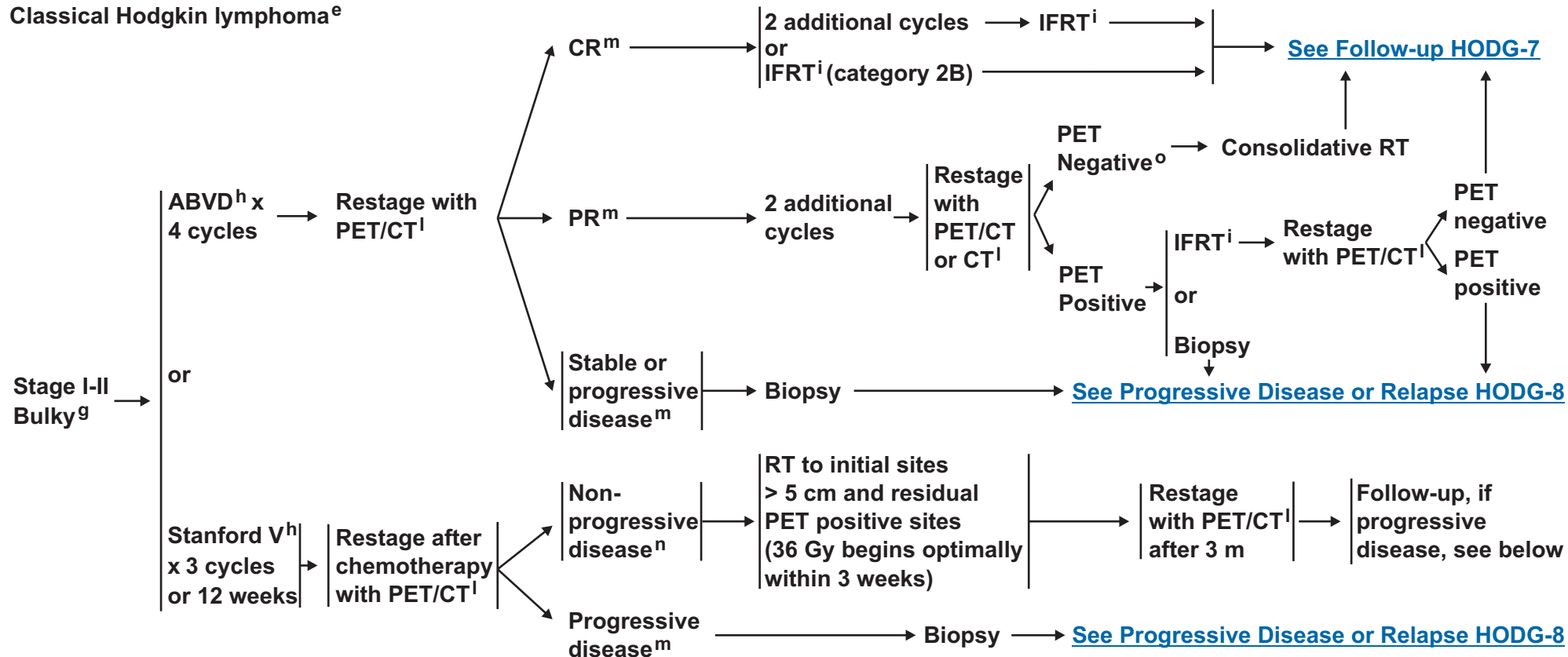
^m[See Revised Response Criteria for Lymphoma \(HODG-D\).](#)

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

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma^e

PRIMARY TREATMENT^k



^eClassical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).

^gBulky mediastinal disease with or without B symptoms ([see Unfavorable Factors, HODG-A](#)).

^h[See Principles of Chemotherapy \(HODG-B\)](#).

ⁱ[See Principles of Radiation Therapy \(HODG-C\)](#).

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease.

^lAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^m[See Revised Response Criteria for Lymphoma \(HODG-D\)](#).

ⁿMay include patients with residual PET positive sites.

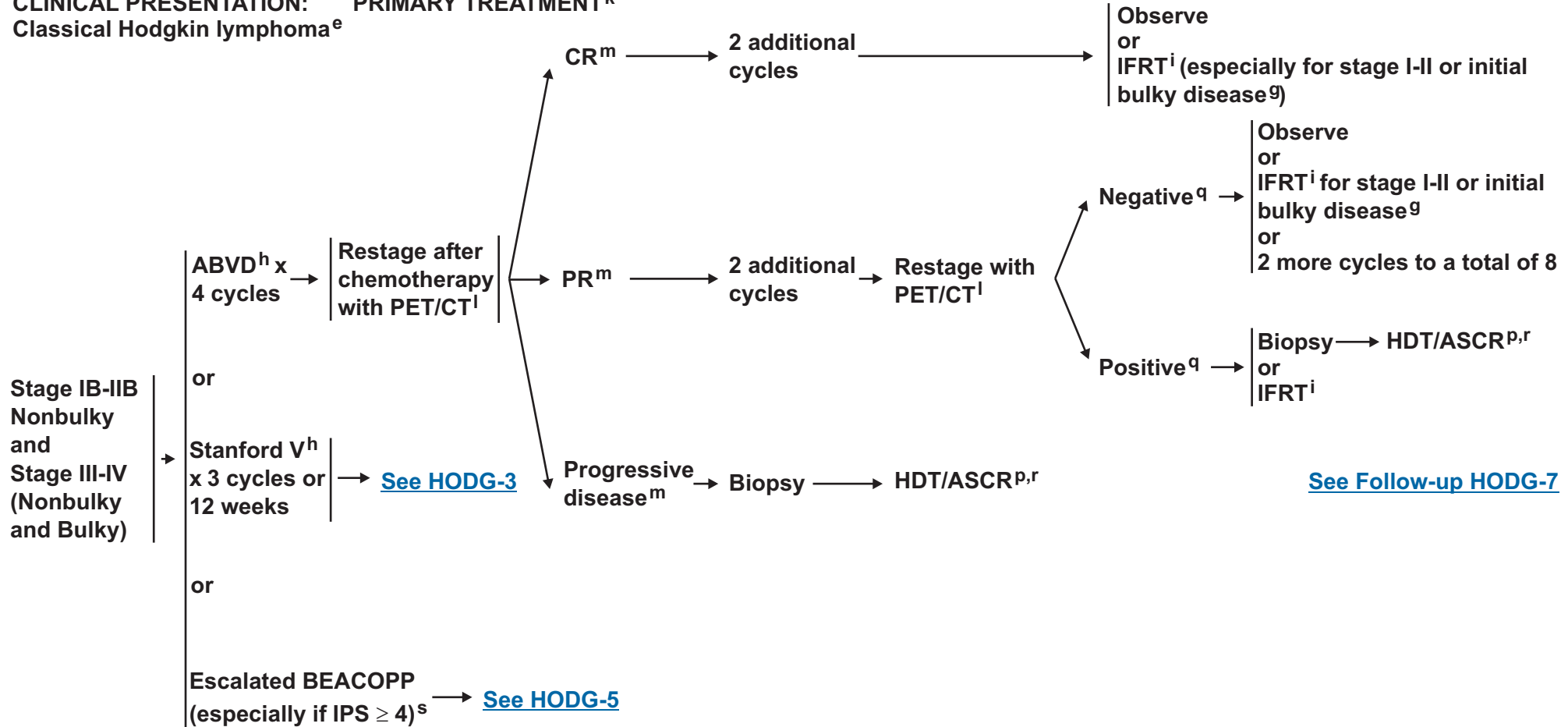
^oDo not add two additional cycles of ABVD.

^pRT to residual disease pre or posttransplant.

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

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

CLINICAL PRESENTATION: PRIMARY TREATMENT^k
Classical Hodgkin lymphoma^e



[See Follow-up HODG-7](#)

^eClassical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).

^gBulky disease with or without B symptoms ([see Unfavorable Factors, HODG-A](#)).

^h[See Principles of Chemotherapy \(HODG-B\)](#).

ⁱ[See Principles of Radiation Therapy \(HODG-C\)](#).

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease.

^lAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^m[See Revised Response Criteria for Lymphoma \(HODG-D\)](#).

^pRT to residual disease pre or posttransplant.

^qIf there is bulky mediastinal disease on CT after 6 cycles of ABVD, consolidative RT to mediastinum recommended. It is not known in the context of PET negative whether the outcomes will be altered.

^rAllotransplant is an option in select patients as a category 3.

^s[See International Prognostic Score \(IPS\) \(HODG-A\)](#).

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

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

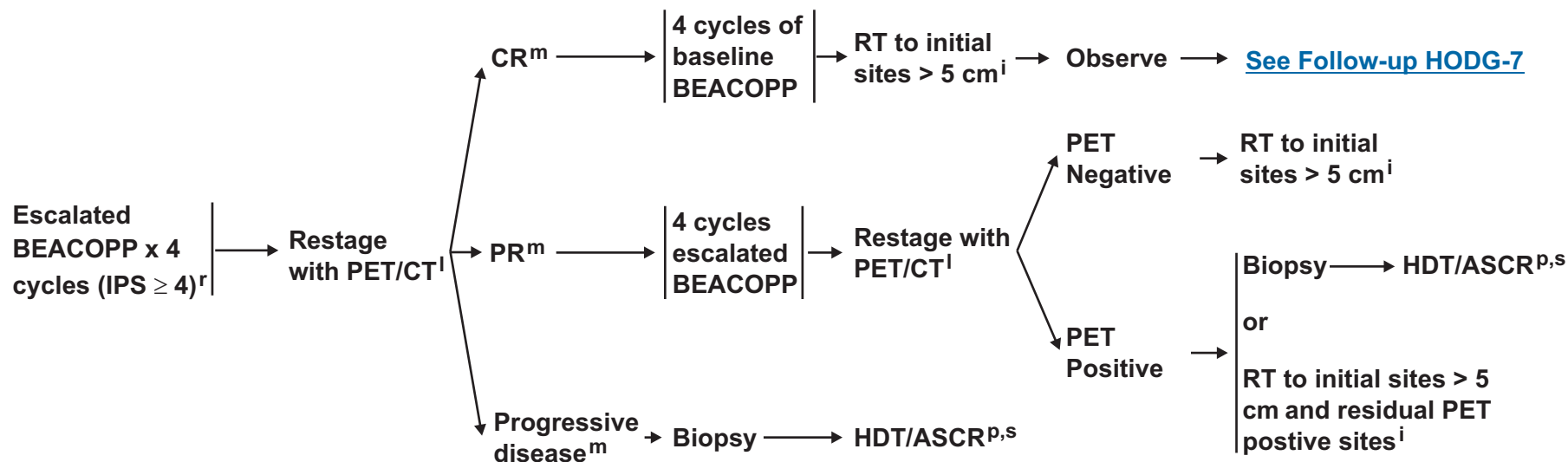
CLINICAL PRESENTATION:

Classical Hodgkin lymphoma^e

Stage IB-IIIB Nonbulky and Stage III-IV (Nonbulky and Bulky)

PRIMARY TREATMENT^k

(continued from HODG-4)



[See Follow-up HODG-7](#)

^eClassical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).

^h[See Principles of Chemotherapy \(HODG-B\).](#)

ⁱ[See Principles of Radiation Therapy \(HODG-C\).](#)

^kIndividualized treatment may be necessary for older patients and patients with concomitant disease.

^lAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^m[See Revised Response Criteria for Lymphoma \(HODG-D\).](#)

^pRT to residual disease pre or posttransplant.

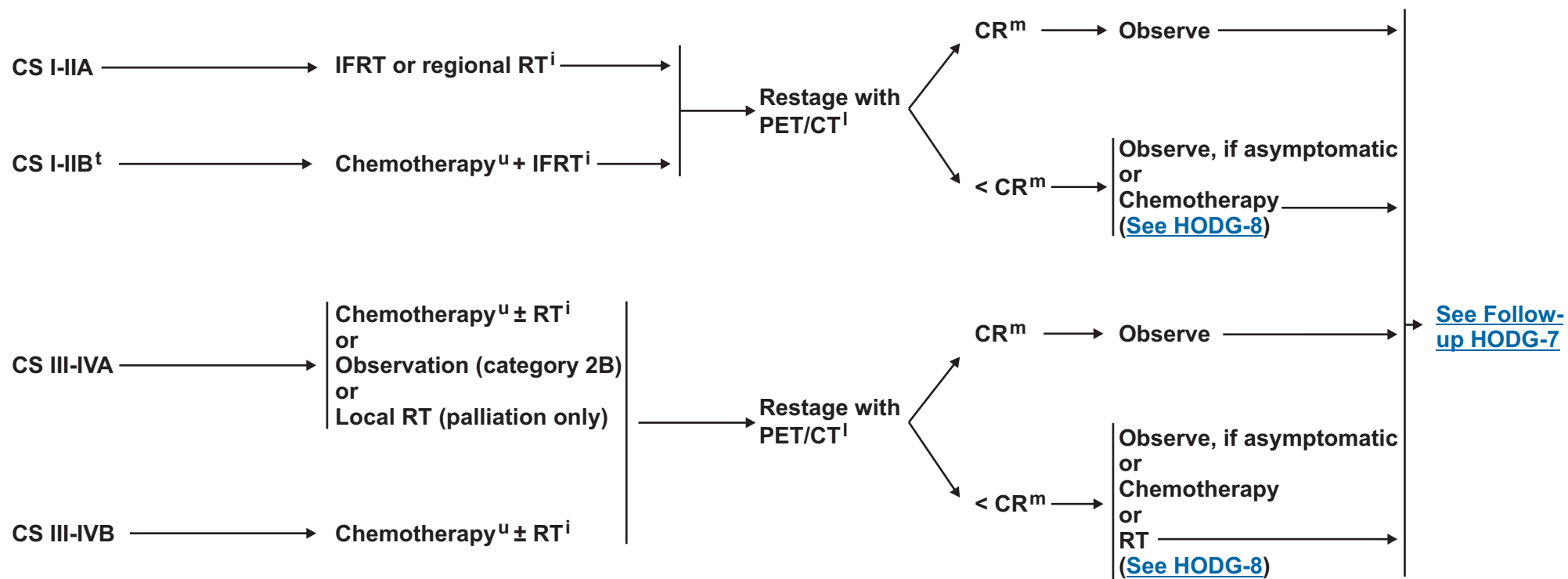
^r[See International Prognostic Score \(IPS\) \(HODG-A\).](#)

^sAllotransplant is an option in select patients as a category 3.

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

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

CLINICAL PRESENTATION: PRIMARY TREATMENT
Lymphocyte-predominant
Hodgkin lymphoma^f



^fLymphocyte-predominant has a different natural history and response to therapy than does classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for LPHL.

ⁱ[See Principles of Radiation Therapy \(HODG-C\).](#)

^lAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^m[See Revised Response Criteria for Lymphoma \(HODG-D\).](#)

^tThe presence of unequivocal B symptoms for Stage I-II disease is highly unusual, referral should be made to a center with expertise in lymphoma.

^uChemotherapy may be different for LPHL than for Classical HL. Alkylating agent based regimens may be preferred. [See Principles of Chemotherapy \(HODG-B\).](#)

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

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

FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS^w
Follow-up with an oncologist is recommended especially during the first 5 y interval to detect recurrence, then annually due to the risk of late complications including second cancers and cardiovascular disease.^{x,y}

Follow-up after completion of treatment

- **Interim H&P:**
Every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
 - ▶ Consider annual influenza vaccine especially in high risk patients (eg, treated with chest RT, bleomycin)
- **Laboratory studies:**
 - ▶ CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
 - ▶ TSH at least annually if RT to neck
- **Chest imaging:**
Chest x-ray or CT every 6-12 mo during first 2-5 y
- **Abdominal/pelvic CT (category 2B):**
Every 6-12 mo for first 2-3 y
- **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 pathological correlation is needed.**

[See Recurrence \(HODG-8\)](#)

Monitoring for Late Effects after 5 Years^{x,y}

- **Interim H&P: Annually**
 - ▶ Annual blood pressure, serum glucose and lipid screening
 - ▶ Consider baseline stress test/echocardiogram at 10 y
 - ▶ Pneumococcal revaccination every 5-7 y, if patient treated with splenic RT or previous splenectomy
 - ▶ Meningococcal + H-flu in selected cases
 - ▶ Consider annual influenza vaccine especially in high risk patients (eg, treated with chest RT, bleomycin)
- **Laboratory studies:**
 - ▶ CBC, platelets, ESR, chemistry profile annually
 - ▶ TSH at least annually if RT to neck
- **Annual chest imaging for patients at increased risk for lung cancer^z**
- **Annual mammographic/breast MRI screening:**
Initiate 8-10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The American Cancer Society recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10 and 30 y.
- **Counseling:**
Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk.

^wThe frequency and types of tests may vary depending on clinical circumstances; age and stage at diagnosis, social habits, treatment modality, etc.

^xMauch 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).

^yAppropriate medical management should be instituted for any abnormalities.

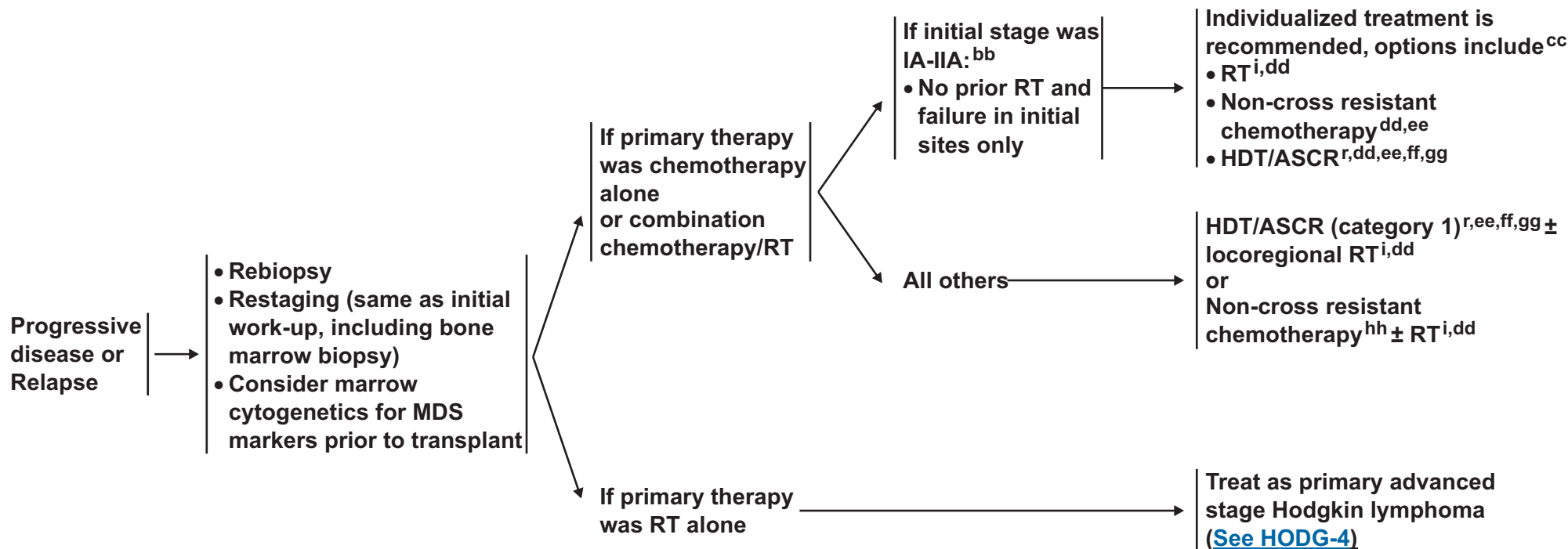
^zChest imaging optional after 5 y if patient treated with a non-alkylating agent, no RT to the chest and no other risk factors are present.

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

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

**CLASSICAL HODGKIN LYMPHOMA^{aa}
PROGRESSIVE DISEASE OR RELAPSE**

SECONDARY THERAPY



ⁱSee Principles of Radiation Therapy (HODG-C).

^rAllotransplant is an option in select patients as a category 3.

^{aa}Patients with LPHL may be managed according to the same algorithm; however, some patients with LPHL have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed.

^{bb}This applies to patients with relapse, not those with progressive disease.

^{cc}There are no data to support a superior outcome with any modalities.

^{dd}Radiation therapy recommended when sites of relapse have not been previously irradiated.

^{ee}See Principles of Second-Line Chemotherapy (HODG-E).

^{ff}Biopsy to confirm relapse especially if plan to treat with high-dose therapy.

^{gg}Conventional-dose chemotherapy may precede high-dose therapy. Response is not essential to proceed to HDT/ASCR. Timing of RT may vary.

^{hh}For select patients with long disease-free interval and other favorable features; selection of chemotherapy should be individualized.

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

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

UNFAVORABLE FACTORS¹
(localized presentations)

- Bulky disease:
 - ▶ Mediastinal mass (chest x-ray):
$$\frac{\text{Maximum mass width}}{\text{Maximum intrathoracic diameter}} > \frac{1}{3}$$
 - ▶ Mediastinal mass greater than 35% of the thoracic diameter at T5-6
 - ▶ Any other mass > 10 cm (CT)
- Erythrocyte sedimentation rate ≥ 50 , if asymptomatic
- > 3 sites
- B symptoms
- Extranodal sites

International Prognostic Score (IPS)
1 point per factor
(advanced disease)²

- 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)

¹Only bulky disease is incorporated into the guideline algorithm for localized presentations, however the other factors are considered for assignment into some clinical trials.

²Derived 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.

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

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

PRINCIPLES OF CHEMOTHERAPY¹ (1 of 3)

Classical Hodgkin Lymphoma

- The most common variants of chemotherapy used at NCCN member institutions include ABVD and Stanford V. Some institutions will use dose-escalated BEACOPP as an alternative regimen in selected cases for highly unfavorable, high-risk patients, usually with an International Prognostic Score (IPS) ≥ 4 .
- Stage IA-IIA non-bulky disease
 - ▶ ABVD is generally administered for 4 cycles. Complete restaging takes place at completion of chemotherapy. Consolidative irradiation follows. In favorable patients,² 2 cycles of ABVD followed by 30 Gy RT may be sufficient.
 - ▶ Stanford V chemotherapy for Stage I-II non-bulky disease is administered for 8 weeks (2 cycles). Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (30 Gy to all involved fields).
- Stage I-II bulky disease ([See HODG-A](#))
 - ▶ ABVD is generally administered for 4-6 cycles. Complete restaging takes place either after 4 cycles or at the completion of chemotherapy. If the patient has achieved a CR or PR, two additional cycles of chemotherapy may be administered (maximum 6). Consolidative irradiation follows the completion of chemotherapy.
 - ▶ Stanford V chemotherapy is administered for 12 wks (3 cycles). Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (36 Gy to initial sites > 5 cm and residual PET positive sites after chemotherapy).
- Stage IB-IIB non-bulky, Stage III-IV
 - ▶ ABVD is generally administered for 6-8 cycles. Complete restaging takes place after 4 cycles of chemotherapy following which two additional cycles of chemotherapy are administered to patients who have achieved a CR or PR. Patients with bulky disease may have consolidative RT.
 - ▶ Stanford V chemotherapy is administered for 12 wks (3 cycles). Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (For stage I-IIB, 30 Gy to initial sites; for Stage II-IV, 36 Gy to initial sites > 5 cm and spleen if focal nodules are present initially or residual PET positive sites).
 - ▶ BEACOPP (escalated dose) is administered every 3 wks. Complete restaging takes place at the end of 4 cycles and at the end of 8 cycles (completion of chemotherapy). This is followed by 30 Gy irradiation to initial sites > 5 cm and 40 Gy to residual PET positive sites.

[See Regimens and References page HODG-B 2 of 3](#)

[See Principles of Chemotherapy for LPHL page HODG-B 3 of 3](#)

[See Principles of Second-line Chemotherapy page HODG-E](#)

¹Diehl 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(24):2386-2395.

²Favorable patients are defined as without the following clinical risk factors: Large mediastinal mass \geq one-third of the maximum thorax diameter, extranodal disease, massive splenic involvement, high erythrocyte sedimentation rate (≥ 50 mm/h in asymptomatic patients or ≥ 30 mm/h in symptomatic patients, > 2 sites of disease) Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: Final results of the GHSG HD7 Trial. J Clin Oncol 2007;25(23):3495-3502.

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

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

PRINCIPLES OF CHEMOTHERAPY (2 of 3)
Regimens and References**ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) plus radiation therapy**

Engert A, Franklin J, Eich HT, et al. Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy Is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial. *J Clin Oncol.* 2007;25(23):3495-3502.

Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized Comparison of ABVD Chemotherapy With a Strategy That Includes Radiation Therapy in Patients With Limited-Stage Hodgkin's Lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2005;23(21):4634-4642.

Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD Plus Subtotal Nodal Versus Involved-Field Radiotherapy in Early-Stage Hodgkin's Disease: Long-Term Results. *J Clin Oncol.* 2004;22(14):2835-2841.

ABVD

Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood.* 2004;104(12):3483-3489.

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(4):607-614.

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

Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol.* 2002;20(3):630-637.

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(3):141-147.

Horning SJ, Hoppe RT, Advani R, et al. Efficacy and Late Effects of Stanford V Chemotherapy and Radiotherapy in Untreated Hodgkin's Disease: Mature Data in Early and Advanced Stage Patients. *ASH Annual Meeting Abstracts.* 2004;104(11):308.

Horning SJ, Williams J, Bartlett NL, et al. Assessment of the Stanford V Regimen and Consolidative Radiotherapy for Bulky and Advanced Hodgkin's Disease: Eastern Cooperative Oncology Group Pilot Study E1492. *J Clin Oncol.* 2000;18(5):972.

BEACOPP (Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone)

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(24):2386-2395.

Diehl V, Franklin J, Pfistner B, Engert A, German Hodgkin Study Group. Ten-year results of a German Hodgkin Study Group randomized trial of standard and increased dose BEACOPP chemotherapy for advanced Hodgkin lymphoma (HD9). *J Clin Oncol (Meeting Abstracts).* 2007;25(18_suppl):LBA8015.

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

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

PRINCIPLES OF CHEMOTHERAPY (3 of 3)

Lymphocyte-predominant Hodgkin Lymphoma¹**• The most common chemotherapies used at NCCN member institutions for LPHL include:**

- ▶ ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± rituximab
- ▶ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab
- ▶ EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) ± rituximab
- ▶ CVP (cyclophosphamide, vincristine, prednisone) ± rituximab
- ▶ Single agent rituximab^{2,3}

¹Ongoing clinical trials will help to clarify the role of a watch-and-wait strategy or systemic therapy, including anthracycline (epirubicin or doxorubicin), bleomycin, and vinblastine-based chemotherapy or antibody-based approaches, in the treatment of these patients.

²Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. *Blood*. 2003;101(11):4285-4289.

³Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood*. 2008;111(1):109-111.

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

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

PRINCIPLES OF RADIATION THERAPY

COMBINED MODALITY-RT DOSES:

- Bulky disease sites (all stages)
If treated with ABVD: 30-36 Gy
If treated with Stanford V: 36 Gy
- Nonbulky disease (stage I-II)
If treated with ABVD: 30 Gy
If treated with Stanford V: 30 Gy
- Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV)
If treated with BEACOPP: 30-40 Gy

RT-ALONE DOSES (uncommon, except for LPHL):

- Involved regions: 30-36 Gy¹
- Uninvolved regions: 25-30 Gy

RADIATION FIELDS

- When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.
Involved-field: involved lymphoid region(s) only
Regional-field: involved and immediately adjacent lymphoid regions

¹The dose of 30 Gy is mainly used for excised LPHL.

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

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

REVISED RESPONSE CRITERIA FOR LYMPHOMA
(including PET)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Source: Table 2 from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J of Clin Oncol 2007;25(5):579-586. Reprinted with permission from the American Society of Clinical Oncology.

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

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY

- The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.
 - ▶ Examples of second-line chemotherapy prior to transplant include ICE (ifosfamide, carboplatin, etoposide)¹, DHAP (dexamethasone, cisplatin, high-dose cytarabine)², ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)³, GVD (gemcitabine, vinorelbine, doxorubicin)⁴, IGEV (ifosfamide, gemcitabine, vinorelbine)⁵, Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)⁶, MINE (etoposide, ifosfamide, mesna, mitoxantrone)⁷, and VIM-D (etoposide, ifosfamide, mitoxantrone and dexamethasone)⁸.
 - ▶ Some studies have suggested that patients with minimal disease burden at relapse (not refractory) may not need additional treatment prior to high-dose chemotherapy with stem-cell rescue.^{9,10,11} However, patients tend to have an improved outcome when transplanted in a minimal disease state.¹² Thus, cytoreduction with chemotherapy (see above) before high-dose chemotherapy with stem-cell rescue may be beneficial. In addition, second-line chemotherapy serves as a test for drug sensitivity and to facilitate the harvest of stem cells.
 - ▶ Nitrogen mustard, procarbazine, carmustine, and melphalan may adversely affect both quality and quantity of stem-cell collection.

¹ Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood* 2001;97(3):616-623.

² Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol* 2002;13(10):1628-1635.

³ Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. *Ann Oncol* 1999;10(5):593-595.

⁴ Bartlett N, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007;18(6):1071-1079.

⁵ Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* 2007;92(1):35-41.

⁶ Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. *J Clin Oncol* 1995;13:396-402.

⁷ Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed or refractory Hodgkin's disease. *Ann Oncol* 1995;6(6):543-9.

⁸ Phillips JK, Spearing RL, Davies JM, et al. VIM-D salvage chemotherapy in Hodgkin's disease. *Cancer Chemother Pharmacol* 1990;27(2):161-3.

⁹ Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. *Lymphoma Working Party of the European Group for Blood and Marrow Transplantation*. 1997;20(9):745-52.

¹⁰ Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. *Ann Oncol* 1996;7(2):151-6.

¹¹ Chopra R, McMillan AK, Linch DC, et al. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. *Blood* 1993;81:1137-45.

¹² Stewart DA, Guo D, Gluck S, et al. Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. *Bone Marrow Transplant* 2000;26(4):383-8.

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

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

Staging

Table 1

Definitions of Stages in Hodgkin's Disease¹

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 (e.g. 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 C; drenching night sweats; or weight loss >10% of body weight

Adapted from 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.

¹PET 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.

Manuscript

NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence and uniform consensus.

Category 2A: Based on lower-level evidence including clinical experience and uniform consensus.

Category 2B: Based on lower-level evidence including clinical experience and nonuniform consensus (but no major disagreement).

Category 3: Based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Hodgkin disease/lymphoma (HD/HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. In 2008, an estimated 8,220 new diagnoses and 1,350 deaths will occur in the United States.¹ Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older.

The past few decades have seen significant progress in the management of HL; it is now curable in at least 80% of patients. Since the advent of more effective treatment options, national statistics have shown an improvement in the 5-year survival rates of these patients that is unmatched in any other cancer over the past 4 decades. When appropriate treatment is selected, every patient with newly diagnosed HL has an overwhelming likelihood of being cured. In fact, cure rates for HL have increased so extensively that the overriding treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease. For advanced disease, clinical trials still emphasize improvement in cure rates, but the potential long-term effect of treatments remain an important consideration.

The World Health Organization (WHO) classification divides HL into 2 main types: classical and lymphocyte-predominant Hodgkin lymphoma (CHL and LPHL, respectively).² In Western countries, LPHL accounts for 5% and CHL for 95% of all HL cases. CHL is divided into 4 subtypes: nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas LPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells, also termed *popcorn cells*. LPHL can have nodular or diffuse pattern. The nodular subtype has lymphocytic and histiocytic cells embedded in a background predominantly composed of B lymphocytes, whereas the diffuse subtype has a background consisting mainly of T cells.

These guidelines discuss the clinical management of CHL and LPHL, focusing exclusively on patients from postadolescence through the seventh decade of life who do not have serious intercurrent disease. The guidelines do not address HL in pediatric or elderly patients or those with unusual situations, such as HIV positivity or pregnancy. Individualized treatment may be necessary for older patients and those with concomitant disease. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

Staging and Prognosis

Staging for HD is based on Ann Arbor staging system ([Table 1](#)). Each stage (I-IV) is subdivided into A and B categories. "A" indicates that no systemic symptoms are present and "B" is assigned to patients with unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.³ Patients with HL are usually classified into 3 groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal adenopathy), early-stage unfavorable

(stage I-II with large mediastinal mass, with or without B symptoms; stage IB-IIB with bulky disease), and advanced-stage disease (stage III-IV).

Various unfavorable prognostic factors have been identified. Mediastinal bulk is an unfavorable prognostic factor in patients with early-stage HD. Mediastinal bulk on chest radiograph is measured most commonly using mediastinal mass ratio or mediastinal tumor ratio.⁴ Mediastinal mass ratio is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Mediastinal tumor ratio is the ratio of the maximum width of the mass and the intrathoracic diameter at the T5-T6 interspace. Any mass with mediastinal mass ratio greater than 0.33 or mediastinal tumor ratio greater than 0.35 is defined as bulky disease. Another definition of bulk is any single abdominal node or nodal mass that is 10 cm or greater in diameter. According to the Cotswold modification of the Ann Arbor staging system, bulky disease is defined as a mediastinal mass exceeding one third of the internal transverse diameter of the thorax on a posteroanterior chest radiograph.⁵

Other unfavorable prognostic factors for patients with stage I to II disease include the presence of B symptoms, more than 3 sites of disease, or an erythrocyte sedimentation rate (ESR) of 50 or more. These factors are based largely on data from the European Organization for Research and Treatment of Cancer (EORTC) and the definition of unfavorable prognostic groups for their trials.^{6,7}

Mauch et al.⁴ first reported the impact of mediastinal bulk on the prognosis of patients treated with radiation therapy alone. They found that patients with mediastinal bulk greater than one third of the chest diameter had a significantly higher risk for developing relapse (40%-50%) than those with lesser or no mediastinal disease (5%).

Only bulky disease is incorporated into the guidelines for localized disease; the other factors are used to refine selection criteria for clinical trials. In addition to the unfavorable factors listed earlier, an international collaborative effort evaluating more than 5000 cases of advanced HL identified 7 adverse prognostic factors that each reduce survival rates by 7% to 8% per year.⁸

- Age 45 years or older
- Male gender
- Stage IV disease
- Albumin level below 4 g/dL
- Hemoglobin level below 10.5 g/dL
- Leucocytosis (white blood cell count more than 15,000/mm³)
- Lymphocytopenia (lymphocyte count less than 8% of the white blood count and/or lymphocyte count less than 600/mm³)

The number of unfavorable factors (International Prognostic Score [IPS]) helps to determine clinical management and predict prognosis. For instance, if the patient has more than 4 unfavorable factors (IPS \geq 4) and advanced disease, treatment with a dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen may be a more appropriate option.

Response Criteria

Clinical management of patients with HL 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 lymphoma response criteria in 1999.⁹ These criteria are based on the

size reduction of the enlarged lymph node as measured with CT scan, and the extent of bone marrow involvement determined using bone marrow aspirate and biopsy. The original response criteria included CRu (complete response uncertain), indicating that it was not possible to determine whether residual masses identified on CT scan represented residual HD, scarring or some other nonmalignant process.

In 2007, the IWG guidelines were revised by the International Harmonization Project to incorporate immunohistochemistry, flow cytometry and PET scans, in the definition of response for lymphoma.¹⁰ The revised guidelines eliminated CRu based partly on the ability of FDG-PET scan to further characterize residual masses detected with CT. Using the revised system, response is categorized as complete response, partial response, stable disease, relapsed disease, or progressive disease.

Diagnosis

Fine needle aspiration alone is insufficient for diagnosis. Although it is widely used to diagnose malignant neoplasms, its role in diagnosing lymphoma is still controversial.^{11,12,13} Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy.

Immunohistochemistry is recommended but not necessary for CHL. CHL cells usually express CD15 and CD30 but lack CD20 and CD45. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended.² LPHL cells are usually CD45+ and CD20+, do not express CD15, and rarely express CD30. In addition, LPHL cells also express epithelial membrane antigen, which is usually not present in CHL. For LPHL, the guidelines recommend staining for CD3, CD15, CD20, CD21, CD30, and CD57. An expanded panel of markers may be required, especially for equivocal diagnosis.

Workup

Workup should include a thorough history and physical examination, including determination of B symptoms, alcohol intolerance, pruritus, fatigue, and performance status, and examination of the lymphoid regions, spleen, and liver. Standard laboratory testing should include a CBC, differential, platelets, ESR, serum lactate dehydrogenase level, albumin, and liver and renal function tests. Adequate bone marrow biopsy should be performed for patients with stage IB to IIB disease or higher. Chest radiograph and chest/abdominopelvic CT scans are appropriate imaging studies.

FDG-PET scan has been used for initial staging, restaging, and follow-up of patients with lymphoma.¹⁴ In a recent meta-analysis, FDG-PET showed high positivity and specificity when used to stage and restage patients with lymphoma.¹⁵ PET is widely used after completion of therapy to assess response and, to a lesser extent, during therapy for pretreatment staging and assessment of response, as reviewed by Juweid.¹⁶

Recent studies have reported the predictive value of PET scans after chemotherapy in patients with advanced-stage or extranodal HL.^{17,18,19} In patients treated with the Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin and prednisone), freedom from progression (FFP) was 96% in those with negative PET scans compared with 33% in those whose scans were positive.¹⁹ The role of PET in post therapy surveillance remains controversial, and further studies are needed to determine their role.

Integrated PET/CT is a new imaging technology that has higher diagnostic accuracy than CT alone in staging HL. Hutchings et al. investigated the value of PET and combined PET/CT scans for staging HL, and their impact on treatment selection.²⁰ PET scans would have upstaged 19% and downstaged 5% of patients, leading to a different

treatment in 9%. The corresponding figures for combined PET/CT scans were 17%, 5%, and 7%. PET and PET/CT scans had higher sensitivity than CT in evaluating nodal regions (92% for PET and PET/CT vs. 83% for CT) and organ involvement (86% for PET and 73% for PET/CT vs. 37% for CT). PET was associated with more false-positive nodal sites than CT and PET/CT. However, the authors emphasize that PET and PET/CT should be used very cautiously in patients with excellent prognosis to avoid overtreatment.

In another retrospective study, PET/CT performed with low-dose nonenhanced CT was found to be more sensitive and specific than routine contrast-enhanced CT in evaluating lymph node and organ involvement in patients with HD or high-grade non-Hodgkin's lymphoma.²¹

The NCCN PET/CT Task Force recommends using PET scans for initial staging of patients with lymphomas, including HL, and evaluating residual masses at the end of treatment.²² The panel recommends using PET scans to define the extent of disease, especially if the CT scan is equivocal. PET scans may upstage patients with stage I to II disease.

An integrated PET/CT or PET scan with a diagnostic CT is recommended, although PET/CT is always preferred. However, management decisions should not be based on PET scan alone. PET scans are always positive in patients with HIV infection, even in the absence of HL. In cases of PET positivity outside of the disease already identified, or if the PET positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. PET scans should not be used for routine surveillance because of the risk for false-positives.

A pregnancy test should be performed before women of childbearing age undergo treatment. Patients with risk factors for HIV or unusual

disease presentations should be given an HIV test. If chemotherapy or pelvic RT is contemplated in male patients, semen cryopreservation should be performed. If pelvic RT is planned for premenopausal patients, oophorectomy should be performed.

A neck CT scan is also recommended in selected patients if radiation therapy is planned. Evaluation of ejection fraction is recommended for patients undergoing doxorubicin-based chemotherapy. Other optional procedures include pulmonary functions tests and a test of the diffusion capacity of the lungs for carbon monoxide. H-flu, pneumococcal, and meningococcal vaccines are recommended if splenic radiation therapy is contemplated.

Principles of Radiation Therapy

Extended-field irradiation (EFRT) refers to involved and immediately adjacent lymphoid regions. Involved-field irradiation (IFRT) refers to the involved lymphoid regions only. Radiation therapy alone is not used for CHL but is more common in LPHL. For radiation therapy alone, the recommended range of dosages is 30 to 36 Gy to involved regions and 25 to 30 Gy to uninvolved sites. The panel recommends that high cervical regions in all patients and axillae in women be excluded from radiation fields, if possible.

In combined modality therapy, the panel recommends 30 to 36 Gy when used with ABVD (doxorubicin bleomycin, vinblastine, and dacarbazine) or 36 Gy when used with Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin and prednisone) for patients with stages I through IV bulky disease. In the absence of bulky disease, the radiation dose could be reduced to 30 Gy (with both ABVD and Stanford V) for patients with stage I to II disease. This recommendation is based on experience and practice across NCCN institutions. When used with BEACOPP for stage IB to IIB (nonbulky) and stage III to IV disease, 30 to 40 Gy is recommended.

Classical Hodgkin Lymphoma

Stage I to II

Radiation therapy alone has been a standard treatment option for patients with favorable early-stage HL for many decades.²³ However, long-term toxicity of large radiation fields can increase the risk for heart disease, pulmonary dysfunction, and secondary malignancies.²⁴ Chemotherapy regimens (ABVD and Stanford V) routinely used to treat advanced disease were recently explored for the management of early-stage CHL, with or without radiation therapy.^{25,26}

The ABVD regimen was first introduced by Santoro et al. as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia.²⁷ The Stanford V regimen is one of the new regimens developed by the Stanford group for patients with early-stage bulky and advanced-stage HL.^{28,29} Radiation therapy is an integral part of the Stanford V regimen. Although the regimen is dose-intensive, the cumulative doses of these drugs are significantly less than those in MOPP, ABVD, alternating, or other hybrid regimens, thereby reducing the risks for infertility, secondary neoplasms, and cardiac and pulmonary toxicity.

Clinical trials have evaluated a short course of chemotherapy combined with radiation therapy for patients with early-stage disease. In a phase III randomized Intergroup trial, Press et al. showed that 3 cycles of doxorubicin and vinblastine followed by subtotal lymphoid irradiation (STLI) had a superior failure-free survival rate (94%) compared with STLI alone (81%).³⁰

In a recent report from the German Hodgkin Study Group (GHSG HD 7 trial), 2 cycles of ABVD followed by EFRT (30 Gy plus 10 Gy to the involved field) were more effective than the same dose of EFRT alone in patients with newly diagnosed early-stage favorable HL (stage IA to

IIB without risk factors such as large mediastinal mass, extranodal disease, massive splenic involvement, or high ESR).³¹ At median follow-up of 7 years, no differences were seen in overall survival between the treatment groups. However, patients in the combined modality treatment group had significantly better FFTF (88%) compared with those who underwent EFRT alone (67%), mainly because relapses were more frequent. Relapses occurred mostly within a year in patients who underwent EFRT alone, whereas no relapses occurred in the combined modality arm within the first 2 years.

Several studies have investigated the reduction of chemotherapy and radiation field size to overcome the potential overlapping toxicity of doxorubicin and bleomycin with radiation. IFRT was as effective as EFRT in patients with early-stage disease.³²⁻³⁵

The HD8 trial from the GHSG is the largest that investigated the efficacy of IFRT versus EFRT in early-stage unfavorable HL.³³ This trial randomized 1204 patients to undergo 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone] plus ABVD) followed by EFRT or IFRT. At 5-years of follow-up, FFTF (85.8% for EFRT and 84.2% for IFRT) and overall survival (90.8% vs. 92.4%) were similar for the groups. In contrast, acute side effects, including leukopenia, thrombocytopenias, and gastrointestinal toxicity, were more frequent in the EFRT group.

The EORTC-GELA H8 trials (H8-F and H8-U) investigated the reduction of chemotherapy and radiation therapy fields in the treatment of patients with early-stage HL.³⁴ The H8-F trial compared 3 cycles of MOPP-ABV plus IFRT with subtotal nodal irradiation (STNI) alone in patients with favorable stage I to II disease. The H8-U trial used 3 different regimens (6 cycles of MOPP-ABV plus IFRT, 4 cycles of MOPP-ABV plus IFRT, and 4 cycles of MOPP-ABV plus STNI) in patients with unfavorable stage I to II disease. Median follow-up was 92 months.

In patients with early-stage favorable HL (H8-F trial), the estimated 5-year event-free survival rate was significantly higher after 3 cycles of MOPP-ABV plus IFRT compared with STNI alone (98% vs. 74%). In patients with unfavorable early-stage HL (H8-U trial), estimated 5-year event-free survival rates were similar for the 3 groups (84% after 6 cycles of MOPP-ABV plus IFRT, 88% after 4 cycles plus IFRT, and 87% after 4 cycles plus STNI). The H8 trial investigators concluded that chemotherapy plus IFRT should be standard treatment for early-stage HL.³⁴

In studies conducted by the Stanford Group, the Stanford V regimen and IFRT was equally effective and less toxic compared with EFRT alone in early-stage unfavorable HL. Patients with nonbulky stage I to IIA disease underwent 8 weeks of Stanford V plus 30 Gy IFRT, and those with bulky stage II disease were treated with 12 weeks of Stanford V plus 36 Gy of IFRT to bulky sites.³⁶

In the most recent update, the actuarial 8-year FFP was 96% for favorable stage I to II disease, 92% for stage I to II bulky disease.³⁶ The 8-year overall survival was 98% for patients with favorable stage I to II and 92% for those with stage I to II bulky disease. Posttreatment conception occurred in 25% of patients. A phase II study from Memorial Sloan-Kettering Cancer Center (MSKCC) and a multicenter study by the Italian group also showed similar outcomes in patients with locally extensive or advanced disease treated with the Stanford V regimen.^{37,38}

Recently, another Italian study group compared a modified Stanford V regimen with MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) and ABVD in intermediate- and advanced-stage HL.³⁹ ABVD and MOPPEBVCAD were superior to the Stanford V regimen in response rate, failure-free survival, and progression-free survival. 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). Modifications of the radiation therapy protocol for the Stanford V arm were substantial, including the limited number of sites (no more than 2) and different definition of bulky disease.

However, the results MSKCC study confirms that when radiation therapy is administered according to Stanford guidelines, the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile.³⁸ In this study, 58% of the patients for whom the Stanford V regimen failed underwent successful second-line therapy with high-dose therapy with autologous stem cell rescue (HDT/ASCR). The recently completed E2496 Intergroup trial compared the Stanford V regimen with ABVD plus radiation for the management of bulky stage II and stage III to IV disease.

Chemotherapy alone has also been investigated as a treatment option for patients with early-stage HL.^{40,41} In the MSKCC study, there were no significant differences in complete response duration (91% vs. 87%, respectively), FFP (86% vs. 81%, respectively), and overall survival (97% vs. 90%, respectively), among patients treated with ABVD plus radiation and those treated with ABVD alone.⁴⁰

In the multicenter study conducted by the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) and Eastern Cooperative Oncology Group, patients with stage I to IIA HL were randomized to receive ABVD (4-6 cycles) or subtotal lymphoid radiation therapy.⁴¹ In patients assigned to radiation therapy, those with any of the adverse prognostic factors (high ESR or ≥ 4 nodal sites) were treated with 2 cycles of ABVD before radiation therapy. At a median follow-up of 4.2 years, patients assigned to ABVD plus RT had better FFP (93% vs. 87%, respectively) and event-free survival (88% vs. 86%, respectively) compared with those treated with ABVD alone, with no significant difference in overall survival (94% vs. 96%, respectively). In a subset

analysis of patients with unfavorable prognostic factors, FFP was superior for those treated with ABVD plus RT (95% vs. 88%), but no differences were seen in 5-year overall or event-free survival rates.

Results of these trials suggest that ABVD alone could be a treatment option for patients with localized nonbulky disease, especially if they experience prompt and complete response to the first 2 cycles of ABVD. ABVD alone may be a reasonable choice of treatment in younger patients with favorable presentations of stage I to II disease, in whom the long-term toxic risks of radiation therapy must be avoided.⁴²

Stage IA to IIA (Nonbulky Disease)

In these guidelines, combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment (category 1) for patients with nonbulky disease ([HODG-2](#)). The panel has also included ABVD alone as an alternative treatment option with a category 2B recommendation. Highly selected patients who are unable to tolerate chemotherapy because of the presence of comorbidities may be treated with radiation therapy alone (STLI [category 1] or mantle field irradiation).

In combined modality treatment, ABVD is generally administered for 4 cycles. Restaging occurs at the completion of chemotherapy followed by consolidative irradiation. In patients with favorable outcomes and no risk factors (large mediastinal mass, massive splenic involvement, high ESR, and > 2 sites of disease), 2 cycles followed by IFRT may be sufficient.³¹ The Stanford V regimen is administered for 8 weeks (2 cycles). Restaging occurs at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 weeks. The panel recommends using 30 Gy of IFRT (involved lymphoid regions only) with ABVD and Stanford V regimens ([HODG-C](#)).

For patients undergoing combined modality treatment, IFRT is completed after they experience a complete response ([HODG-2](#)).

Patients experiencing a partial response are also treated with IFRT, but require further restaging after completion of radiation therapy. Follow-up is recommended for patients with negative PET scan at the completion of therapy, and those with positive PET scans are treated as described for relapsed or progressive disease ([HODG-8](#)).

Among patients treated with chemotherapy alone, ABVD is administered for 6 cycles followed by restaging. No further treatment is necessary for those experiencing complete response. Additional treatment options for patients experiencing partial response are similar to those for combined modality therapy.

Biopsy is recommended after restaging in patients experiencing a partial response after completing initial therapy. All patients with biopsy-confirmed progressive or relapsed disease are managed as described for relapsed or progressive disease.

Stage IB to IIB (Nonbulky Disease)

Clinical stage IB HL is uncommon, but occasionally patients present with stage IIB disease. Patients who have early-stage bulky disease with B symptoms (stage IB-IIB) are believed to have a clinical course similar to advanced-stage disease and are treated as described for stage III to IV disease ([HODG-4](#) and [HODG-5](#)).

Stage I to II (Bulky Disease)

For patients with bulky disease (with or without B symptoms), which is almost always mediastinal, the panel recommends chemotherapy (ABVD or Stanford V) followed by IFRT or similar radiation.^{43,44}

ABVD is administered for 4 to 6 cycles. Restaging occurs after completion of chemotherapy or after 4 cycles of ABVD when 6 are planned. Two additional cycles are administered for patients who have experienced complete or partial response, followed by IFRT (30-36 Gy) for patients experiencing complete response ([HODG-3](#)). Patients with

partial response are restaged after completing 2 additional cycles. Consolidative irradiation is recommended for patients with negative PET scans, and those with positive PET scans are treated with IFRT (30-36 Gy) followed by end-of-treatment restaging.

Stanford V is administered for 12 weeks (3 cycles). Consolidative irradiation (36 Gy) is instituted within 3 weeks. Generally, irradiation of the mediastinum, including contiguous sites of bulky involvement and bilateral supraclavicular areas, is sufficient. Patients are restaged when they complete chemotherapy. In patients with nonprogressive disease (including those with residual PET positive sites), radiation therapy (36 Gy) is recommended for initial sites larger than 5 cm and residual PET-positive sites.

For partial response with positive PET scan or progressive disease, biopsy is recommended before initiating treatment for progressive disease as described in [HODG-8](#).

Stage III to IV (Advanced-Stage Disease)

Chemotherapy is always used for patients with advanced-stage HL. MOPP was the first successful regimen for HL, with a response rate of 84% and a 66% disease-free survival of more than 10 years from end of treatment.⁴⁵ However, in addition to other long-term toxicities, MOPP is associated with loss of fertility (mostly in men) and myelodysplasia.

The landmark randomized trial by the Cancer and Leukemia Group B (CALGB) showed that ABVD alone or alternating with MOPP was superior to MOPP alone in progression-free and 5-year overall survival.⁴⁶ ABVD also was less myelotoxic than MOPP, or ABVD alternating with MOPP. These results were confirmed in a large Intergroup study, which compared ABVD with a MOPP/ABV hybrid regimen in 856 patients with advanced HL.⁴⁷ The rates of complete remission (76% vs. 80%), 5-year failure-free survival (63% vs. 66%), and overall survival (82% vs. 81%) were similar for ABVD and

MOPP/ABV, respectively. However, MOPP/ABV was associated with acute pulmonary and hematologic toxicities, myelodysplastic syndromes, and leukemia.

ABVD has since been the standard treatment for patients with advanced-stage HL. Stanford V and BEACOPP are the other 2 regimens developed to improve the outcome of patients with advanced disease.

In prospective studies conducted by the Stanford group, 108 patients with stage III to IV disease were treated with 12 weeks of Stanford V regimen plus 36 Gy of radiation therapy to initially bulky sites larger than 5 cm. In the most recent update of the mature results from these studies, 8- and 12-year FFP rates were 86% and 83%, respectively, and 8- and 12-year overall survival rates were 95%. No instances of secondary myelodysplasia or leukemia occurred.³⁶ Fertility was maintained, with 72 posttreatment conceptions. Similar outcomes were reported in other studies for patients with advanced-stage HL treated with the Stanford V regimen.^{37,38}

The BEACOPP regimen was developed by the GHSG to improve treatment results through dose escalation and time intensification.⁴⁸ In a phase III randomized trial (HD9), 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 (cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine), 8 cycles of standard-dose BEACOPP, or 8 cycles of dose-escalated BEACOPP.⁴⁸ Each regimen was followed by radiation therapy to initial sites of disease greater than 5 cm.

At 5-year analysis, escalated-dose BEACOPP showed better tumor control and overall survival than COPP-ABVD. It also showed significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP, and 10-year analysis showed that it

conferred superior FFTF (70% for standard-dose BEACOPP, 82% for escalated-dose BEACOPP, and 64% for COPP-ABVD) and overall survival rates (86% for escalated-dose BEACOPP, 80% for standard-dose BEACOPP, and 75% for COPP-ABVD).⁴⁹ These results confirm the efficiency of dose-escalated BEACOPP for patients with advanced-stage HL who have risk factors. The ongoing EORTC 20012 trial is comparing BEACOPP and ABVD in patients with stage III or IV HL.

Recently, a study group from Israel reported the results of a risk-adapted approach using BEACOPP to treat patients with standard- and high-risk HL.⁵⁰ Patients with advanced disease (stage I-II bulky with B symptoms and stage III-IV) and IPS of 3 or higher were treated with 2 cycles of escalated BEACOPP, and all others underwent 2 cycles of standard-dose BEACOPP followed by restaging. Those with a positive PET scan received 4 additional cycles of escalated-dose BEACOPP, whereas 4 cycles of standard-dose BEACOPP were given to patients with a negative PET scan. The complete remission, 5-year event-free survival, and overall survival rates were 97%, 85%, and 90%, respectively. Event-free and overall survival rates were similar in both risk groups. This study also showed the usefulness of interim PET scan in determining additional treatment options.

Two recent 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.^{51,52} Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after 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.

Several trials have addressed the role of consolidative irradiation in patients with stage III to IV HL who completed chemotherapy. A Southwest Oncology Group multi-institutional study also showed no improvement in overall survival rates for patients who underwent low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, prednisone plus bleomycin, doxorubicin, and procarbazine), but the remission duration was prolonged in several subgroups, especially patients with bulky nodular sclerosis.⁵³

In the EORTC 20884 trial, patients with untreated stage III to IV disease underwent 6 to 8 cycles of MOPP-ABV. Those experiencing complete response after chemotherapy were randomized to no further treatment or IFRT, and those who showed partial response underwent IFRT. The 8-year overall and event-free survival rates in the partial response groups were 76% and 84%, respectively. These outcomes were similar to those observed in complete response groups with or without IFRT, suggesting that consolidative IFRT is beneficial for patients experiencing partial response after chemotherapy.⁵⁴

In contrast, Laskar et al. reported a survival advantage for consolidative radiation therapy in patients experiencing complete response after initial chemotherapy particularly in patients younger than 15 years.⁵⁵ However, this study included patients with a different distribution of histologic subtypes of HL than those included in Western studies, and most had early-stage HL.

The role of consolidative irradiation for bulky or residual sites after chemotherapy for stage III to IV disease is being addressed in an ongoing GHSG randomized trial (HD12).

Stage III to IV (Nonbulky and Bulky) and Stage IB to IIB (Nonbulky) ABVD (4 cycles) or Stanford V (3 cycles) is recommended for primary treatment for patients with advanced HL ([HODG-4](#)). Escalated-dose

BEACOPP (4 cycles) should be considered for high-risk patients with an IPS score of 4 or more ([HODG-5](#)).

ABVD is generally administered for 6 to 8 cycles, with restaging after 4. Two additional cycles are administered for patients who have experienced complete or partial response, followed by restaging for patients with initial partial response. No further treatment is necessary for patients who have experienced complete response or those with partial response and a negative PET scan. If bulky mediastinal disease was present initially, consolidative radiation therapy to the mediastinum is recommended after 6 cycles of ABVD. Patients with partial response and a negative PET scan can be treated with 2 more cycles of ABVD, to a total of 8. IFRT may be administered for initial sites of bulky disease (30-36 Gy) or for stage I to II disease (30 Gy).

Stanford V is administered for 12 weeks (3 cycles). Consolidative irradiation is instituted within 3 weeks (30 Gy to initial sites for stage IB-IIB; 36 Gy to initial bulky sites of 5 cm or larger and spleen if focal nodules are present initially). Restaging and additional treatment for patients treated with Stanford V regimen are similar to stage I to II bulky disease as outlined in [HODG-3](#).

Escalated-dose BEACOPP is administered every 3 weeks, and restaging occurs at the end of 4 cycles. Four additional cycles of baseline BEACOPP are administered for patients who have experienced complete response, whereas 4 cycles of escalated-dose BEACOPP are recommended for those with partial response, followed by end-of-treatment restaging. Consolidative irradiation (30-40 Gy to initial bulky sites > 5 cm, and 40 Gy of radiation therapy to residual PET-positive sites) is recommended for all patients.

For patients experiencing partial response with positive PET scans or progressive disease, a core needle biopsy is recommended before initiating treatment.

Lymphocyte-Predominant Hodgkin lymphoma

LPHL is characterized by an indolent course and occasional late relapse. It has a different natural history and response to therapy compared with CHL. The GHSG has reported a comprehensive description of natural history, clinical presentation, and outcomes for LPHL.⁵⁶ In a retrospective analysis that included 394 patients with LPHL, 63% had early-stage favorable, 16% had early-stage unfavorable, and 21% had advanced-stage disease. At a median follow-up of 50 months, FFTF (88% vs. 82%) and overall survival (96% vs. 92%) were better for LPHL compared with CHL. Among patients with LPHL, FFTF was better for early favorable disease (93%) compared with early unfavorable (87%) and advanced-stage disease (77%).

The European Task Force on Lymphoma (ETFL) also reported favorable FFTF for early-stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or IV (24%) disease.⁵⁷ In the GHSG study, adverse prognostic factors for FFTF included advanced stage, low hemoglobin, and lymphopenia; age (≥ 45 years), advanced stage, and low hemoglobin were the negative prognostic factors for overall survival.

Early-stage favorable LPHL has a better prognosis than CHL and its management is different.⁵⁸ IFRT (or slightly modified IFRT) or combined modality treatment are the treatment options for early stage LPHL. Radiation therapy alone was found to be an efficient treatment for patients with stage I to II LPHL. In a retrospective analysis, Schlembach et al. reported favorable 5-year relapse-free (95%) and overall survival (100%) for patients with stage IA LPHL treated with IFRT and regional radiation therapy alone.⁵⁹ No evidence showed secondary solid tumors even after long-term follow-up (11.6 years for IFRT and 5.5 years for regional radiation therapy). Longer follow-up is needed to define the risks for cardiac toxicity. Another retrospective study from the

Australasian Radiation Oncology Lymphoma Group reported longer follow-up in patients with stage I to II LPHL treated with radiation therapy alone, including mantle and total lymph node irradiation.⁶⁰ At 15 years, FFP was 84% for patients with stage I disease and 73% for those with stage II disease.

The GHSG compared 3 treatment options, including EFRT, IFRT, and combined modality treatment in patients with stage IA LPHL.⁶¹ Median follow-up was 78 months for EFRT, 40 months for combined modality, and 17 months for IFRT. Complete remissions were observed in 98% after EFRT, 95% after combined modality, and 100% after IFRT, and no significant differences were seen in FTF, suggesting that IFRT is equally effective as EFRT and combined modality treatment. However, in a subgroup analysis of 64 patients with LPHL included in the GHSG HD 7 trial, a trend was seen toward better 7-year FTF for the combined modality group (96%) compared with the EFRT group (83%).³¹

An EORTC-GELA study also showed that patients with early-stage (I-II) disease treated with radiation therapy alone, or chemotherapy followed by radiation therapy, had similar relapse-free (77% and 68%, respectively) and overall survival (90% and 100%, respectively) at 9.3 years.⁶² Additional data and longer-term follow-up are required to define the best treatment for early-stage favorable LPHL.

Patients with advanced-stage LPHL have a worse prognosis than those with early-stage favorable disease, and can be treated with aggressive chemotherapy. In the ETFL study, the 8-year disease-specific survival and FTF were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.⁵⁷ Most of these patients (80%-95%) were treated with chemotherapy (MOPP- or ABVD-like regimens) with or without radiation therapy.

Because LPHL cells consistently express CD20 antigen, clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody. GHSG evaluated rituximab for relapsed or refractory LPHL in a phase II trial.⁶³ Of 14 patients with CD20+ LPHL, 8 experienced complete and 6 partial remission. At a median follow-up of 63 months, median time to progression was 33 months.

In a Stanford study, previously treated (10) and untreated (12) patients with stage I to IV LPHL received 4 weekly doses of rituximab at 375 mg/m². The overall response rate was 100% (41% complete, 54% partial, and 5% unconfirmed complete responses).⁶⁴ The estimated probability of progressive disease at 10.2 months was 52%. The protocol was later modified to repeat 4 weekly 375 mg/m² doses at 6-month intervals for 2 years.⁶⁵ Median follow-up was 72 months for limited and 30 months for extended treatment. The overall response rate was 97% (69% complete or unconfirmed complete response, 28% partial response). Among patients undergoing limited treatment with rituximab, 56% experienced complete or unconfirmed complete response, compared with 88% of those treated with extended rituximab. The estimated FFP at 30 months was 52% for limited rituximab and 88% for extended rituximab. Rituximab was well tolerated, with few adverse side effects. Additional follow-up is needed to assess benefit duration.

Without randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for LPHL, although ABVD is often used based on data for CHL. Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for these patients. The most common regimens used at NCCN member institutions for LPHL include single-agent rituximab or any one of the following chemotherapy regimens (with or without rituximab): ABVD, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or EPOCH

(etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).

Stage I to II

NCCN guidelines recommend IFRT (30-36 Gy) or regional radiation therapy (25-30 Gy) alone for clinical stage IA to IIA disease ([HODG-6](#)). Chemotherapy followed by IFRT is recommended for patients with stage IB to IIB disease. However, the presence of "B" symptoms for stage I to II disease is highly unusual, and therefore treatment should be individualized for these patients at a center with expertise in lymphoma.

Stage III to IV

Chemotherapy with or without radiation therapy is an appropriate treatment option for stage III to IV disease ([HODG-6](#)). Alternatively, in asymptomatic patients (stage IIIA-IVA), disease can undergo either observation (category 2B) or treatment with local radiation therapy for palliative purposes.

End of Treatment Restaging

Restaging with PET or CT occurs after completion of initial therapy, and then observation is recommended for asymptomatic patients with unconfirmed complete response and all patients experiencing complete response.

Follow-up after Completion of Treatment

The guidelines for follow-up are based largely on the clinical practices of NCCN panelists and are not supported by high-level evidence. Interim physical examinations and blood work (including CBC, platelets, erythrocyte sedimentation rate if elevated at initial diagnosis, and chemistry profile) are performed less frequently as the length of time between follow-ups increases, but examinations and laboratory tests are continued annually after 5 years ([HODG-7](#)).

Interim evaluations should include consideration of pneumococcal revaccination every 5 to 7 years, especially for patients who have undergone splenic radiation therapy or splenectomy. High-risk patients (eg, treated with bleomycin, chest radiation therapy) should also be considered for annual influenza vaccinations. Meningococcal and H-flu revaccination can be considered in selected cases.

Patients who have had neck or upper mediastinal irradiation should undergo thyroid function studies at least annually to rule out hypothyroidism.⁶⁶

The panel overwhelmingly agrees that, given the long-term risks of the therapies for HL, patients should be followed up by oncologists who are aware of these risks and complications, especially during the first 5 years and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease.

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen. Chest radiograph or CT should be performed every 6 to 12 months during the first 2 to 5 years, then annually depending on clinical circumstances. Chest imaging is optional after 5 years for patients who were treated with nonalkylating agent chemotherapy, did not undergo radiation therapy, and have no other risk factors.

Abdominal/pelvic CT (category 2B) is monitored every 6 to 12 months for the first 2 to 3 years, then annually up to 5 years. The frequency and types of tests may vary depending on clinical circumstances, such as age and stage at diagnosis, social habits, and treatment modality.

Monitoring for Late Effects

Annual chest imaging is recommended for patients at increased risk for lung cancer. Because of the increased risk for breast cancer associated with radiation therapy, the panel recommends that women who have

received chest or axillary irradiation undergo routine annual mammography or breast MRI beginning no later than 8 to 10 years after completion of therapy, or at 40 years of age, whichever occurs earlier. They should also be counseled on breast self-examination ([HODG-7](#)).

Based on data regarding increased long-term risk of cardiac disease, the panel recommends a baseline resting and stress echocardiography 10 years after treatment, even in asymptomatic individuals.⁶⁷

In addition to the measures outlined earlier, the panel believes follow-up should include counseling on issues regarding survivorship; long-term treatment effects, including risks for second primary tumors, cardiac disease, and skin cancer; and reproduction. Health habits and psychosocial issues should also be discussed.

Progressive Disease or Relapse

Early studies exploring the use of HDT/ASCR in patients with relapsed or refractory HL produced complete response rates of 48% to 69%, as reviewed by Bryne and Gockerman.⁶⁸ Based on these promising results, 2 randomized phase III studies compared HDT/ASCR with conventional chemotherapy.^{69,70} Both studies showed significant improvement in event-free and progression-free survival and FFTF (with no difference in overall survival) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone. HDT/ASCR is the best option for patients with HL that is incurable with primary treatment, even though it does not improve overall survival. Moskowitz et al. identified the following as prognostic factors associated with event-free survival after HDT/ASCR: extranodal sites, complete response of less than 1 year, primary refractory disease, and B symptoms.⁷¹ In patients with none or one factor, 5-year event-free and overall survival were 83% and 90%,

respectively, which decreased to 10% and 25% if all factors were present.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.^{71,76} However, none of these regimens has been studied in randomized trials. Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) and IGEV (ifosfamide, gemcitabine, and vinorelbine), have also been effective for relapsed or refractory HL.^{77,78}

Some studies have also suggested that patients with minimal residual disease at relapse may not need conventional-dose chemotherapy before HDT.^{79,80} In select subset of patients who have early-stage disease with extranodal involvement, lack of B symptoms, and good response to primary treatment, second-line radiation therapy may be effective before HDT/ASCR.⁸¹

Patients with progressive CHL or disease relapse should undergo biopsy and restaging, including bone marrow biopsy. Bone marrow cytogenetics for markers of myelodysplastic syndromes may be considered if ASCR is planned. Management of progressive disease or relapse depends on whether primary treatment was radiation alone, chemotherapy, or combined modality therapy ([HODG-8](#)). Patients with LPHL may be managed according to the same algorithm. However, some have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed or treated with local irradiation.

For patients treated initially with chemotherapy or combined modality therapy, the algorithm is a bit more complicated and therapy more likely to be individualized. Appropriate treatment has not been identified for disease relapse in patients with initial stage IA to IIA disease who underwent chemotherapy alone and experienced failure at the initial sites, and therefore individualized treatment is recommended. Options

include radiation therapy, non-cross resistant chemotherapy or HDT/ASCR. No data show a superior outcome with any of these options.

For all other patients, the panel recommends HDT/ASCR (category 1) with or without locoregional radiation therapy, but disease relapse should be confirmed with biopsy. Conventional-dose second-line chemotherapy may precede high-dose therapy. Suggested regimens are listed in [HODG-E](#). In select patients with long disease-free intervals and other favorable features, chemotherapy should be individualized.

The panel recommends that patients experiencing disease relapse after undergoing primary treatment with radiation therapy alone be treated as described for initial treatment of advanced disease as outlined in [HODG-4](#). The extent of stage at relapse (relapsed stage) after radiation therapy was the most important prognostic factor for freedom from second relapse.⁸²

Summary

The management of HL continues to evolve. Major changes have been incorporated into these guidelines since inception. Current management of HL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging to assess treatment response. PET scans are recommended to evaluate initial staging and assess treatment response at restaging. However, they are not recommended for routine surveillance.

Combined modality therapy (brief course of chemotherapy and limited irradiation) is the preferred treatment for early-stage favorable CHL (stage IA-IIA nonbulky) and early-stage unfavorable CHL (stage I-II bulky). Chemotherapy alone or combined modality therapy is recommended for advanced-stage CHL (stage IB-IIB nonbulky and stage III-IV).

Combined modality therapy or radiation alone is the option for early-stage LPHL. Patients with advanced-stage LPHL may be treated with more aggressive therapy. The role of chemotherapy or antibody-based therapy is being explored in ongoing clinical trials for early-stage and advanced-stage LPHL.

HDT/ASCR is the best treatment option for patients with relapsed or refractory HL, although it does not improve overall survival. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

HL is now curable in most patients because more effective and less toxic regimens have been introduced. 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 for these patients.

Disclosures for the NCCN Hodgkin Disease/Lymphoma Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Albuquerque Area Indian Health Board, Amgen, Biogen IDEC, Bristol-Myers Squibb, CALGB, Cancer Services of New Mexico, Clariant, Inc., Favril, Inc., Genentech, Genitope Corporation, GlaxoSmithKline, Lymphoma Research Foundation, Millennium, NCI, National Initiative for Lymphoma Education, NIH, Novartis, Oncomed, Ortho Biotech, Roche, Sankyo Pharma, Seattle Genetics, Inc. and Tibotec.

Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA Cancer J Clin* 2008;58:71-96.
2. Jaffe ES, Harris NL, Stein H, et al, eds. *Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press; 2001.
3. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M, et al. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31(11):1860-1861.
4. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. *Cancer* 1978;42:1039-1045.
5. Lister T, Crowther D, Sutcliffe S, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630-1636. Erratum in: *J Clin Oncol* 1990;8:1602.
6. 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.
7. 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.
8. 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.
9. 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;17:1244-1253. Erratum in: *J Clin Oncol* 2000;18:2351.
10. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579-586.
11. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. *J Clin Oncol* 2004;22:3046-3052.
12. 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 cytomorphology and flow cytometry. *Am J Clin Pathol* 2000;113:688-699.
13. Caraway NP. Strategies to diagnose lymphoproliferative disorders by fine-needle aspiration by using ancillary studies. *Cancer* 2005;105:432-442.
14. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. *Blood* 2007;110:3507-3516.
15. 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.
16. Juweid ME. Utility of positron emission tomography (PET) scanning in managing patients with Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 2006:259-265, 510-511.
17. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 2006;107:52-59.
18. Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. *Haematologica* 2006;91:475-481.
19. Advani R, Maeda L, Lavori P, et al. Impact of positive positron emission tomography on prediction of freedom from progression after Stanford V chemotherapy in Hodgkin's disease. *J Clin Oncol* 2007;25:3902-3907.

20. Hutchings M, Loft A, Hansen M, et al. Position emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. *Haematologica*. 2006;91(4):482-489.
21. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging-do we need contrast-enhanced CT? *Radiology* 2004;232:823-829.
22. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw* 2007;5(Suppl 1):S1-22.
23. 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.
24. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta Oncol* 2003;42:589-604.
25. Connors JM. State-of-the-art therapeutics: Hodgkin's lymphoma. *J Clin Oncol*. 2005;23(26):6400-6408.
26. Macdonald DA, Connors JM. New strategies for the treatment of early stages of Hodgkin's lymphoma. *Hematol Oncology Clin North Am*. 2007;21(5):871-880.
27. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *J Clin Oncol*.1987;5(1):27-37.
28. Horning SJ, Rosenberg SA, Hoppe RT. Brief chemotherapy (Stanford V) and adjuvant radiotherapy for bulky or advanced Hodgkin's disease. *Ann Oncol* 1996;7:105-108.
29. 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.
30. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized Intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. *J Clin Oncol* 2001;19:4238-4244.
31. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol* 2007;25:3495-3502.
32. 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.
33. 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.
34. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med* 2007;357:1916-1927.
35. Horning SJ, Hoppe RT, Advani RH, et al. A prospective trial of involved field radiation (IFRT) + chemotherapy compared to extended field (EFRT) radiation for favorable Hodgkin disease: survival differences and implications of mature follow-up for current combined modality therapy. *J Clin Oncol* 2007;25(18 Suppl 1): Abstract 8014.
36. Horning SJ, Hoppe RT, Advani R, et al. Efficacy and late effects of Stanford V chemotherapy and radiotherapy in untreated Hodgkin's disease: mature data in early and advanced stage patients [abstract]. *Blood* 2004;104:Abstract 308.
37. 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.

38. Edwards-Bennett SM, Moskowitz C, Jacobs J, et al. A non-Stanford mature experience with Stanford V ± RT regimen for locally extensive and advanced Hodgkin's lymphoma (HL). *Int J Radiat Oncol Biol Phys* 2007;69(2 Suppl 1):S18-19.

39. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. *J Clin Oncol* 2005;23:9198-9207.

40. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104:3483-3489.

41. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005;23:4634-4642.

42. Canellos GP. Chemotherapy alone for early Hodgkin's lymphoma: an emerging option. *J Clin Oncol* 2005;23:4574-4576.

43. Longo DL, Russo A, Duffey PL, et al. Treatment of advanced-stage massive mediastinal Hodgkin's disease: the case for combined modality treatment. *J Clin Oncol* 1991;9:227-235.

44. Behar RA, Horning SJ, Hoppe RT. Hodgkin's disease with bulky mediastinal involvement: effective management with combined modality therapy. *Int J Radiat Oncol Biol Phys* 1993;25:771-776.

45. DeVita VT Jr, Simon RM, Hubbard SM, et al. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of

MOPP-treated patients at the National Cancer Institute. *Ann Intern Med* 1980;92:587-595.

46. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced HD with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478-1484.

47. 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.

48. 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.

49. Diehl V, Franklin J, Pfistner B, Engert A, German Hodgkin Study Group. Ten-year results of a German Hodgkin Study Group randomized trial of standard and increased dose BEACOPP chemotherapy for advanced Hodgkin lymphoma (HD9). *J Clin Oncol (Meeting Abstracts)*. 2007;25(18_suppl):LBA8015.

50. Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. *Blood* 2007;109:905-909.

51. Federico M, 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. *J Clin Oncol* 2003;21:2320-2325.

52. 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.

53. 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.
54. 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(1):19-30.
55. 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(1):62-68.
56. Nogova L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol* 2008;26:434-439.
57. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol* 1999;17:776-783.
58. Tsai HK, Mauch PM. Nodular lymphocyte-predominant Hodgkin lymphoma. *Semin Radiat Oncol* 2007;17:184-189.
59. Schlembach PJ, Wilder RB, Jones D, et al. Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. *Cancer J*. 2002;8(5):377-383.
60. Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer* 2005;104:1221-1229.
61. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol* 2005;16:1683-1687.
62. Wilder RB, Schlembach PJ, Jones D, et al. European Organization for Research and Treatment of Cancer and Groupe d'Etude des Lymphomes de l'Adulte very favorable and favorable, lymphocyte-predominant Hodgkin disease. *Cancer* 2002;94:1731-1738.
63. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood* 2008;111:109-111.
64. Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. *Blood*. 2003;101(11):4285-4289.
65. Horning SJ, Bartlett NL, Breslin S, et al. Results of a prospective phase II trial of limited and extended rituximab treatment in nodular lymphocyte predominant Hodgkin's disease (NLPHD) [abstract]. *Blood* 2007;110:Abstract 644.
66. 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. *Eur J Haematol* 2005;75(Suppl 66):68-76.
67. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743-749.
68. Byrne BJ, Gockerman JP. Salvage therapy in Hodgkin's lymphoma. *Oncologist* 2007;12:156-167.
69. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993;341:1051-1054.

70. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002;359:2065-2071.

71. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97(3):616-623.

72. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol*. 2002;13(10):1628-1635.

73. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. *Ann Oncol*. 1999;10(5):593-595.

74. Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. *J Clin Oncol*. 1995;13(2):396-402.

75. Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. *Ann Oncol*. 1995;6(6):543-550.

76. Phillips JK, Spearing RL, Davies JM, et al. VIM-D salvage chemotherapy in Hodgkin's disease. *Cancer Chemother Pharmacol*. 1990;27(2):161-163.

77. Bartlett N, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007;18:1071-1079.

78. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* 2007;92:35-41.

79. Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. *Ann Oncol* 1996;7:151-156.

80. Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 1997;20(9):745-752.

81. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. *J Clin Oncol* 2005;23:1522-1529.

82. Roach M III, Brophy N, Cox R, et al. Prognostic factors for patients relapsing after radiotherapy for early-stage Hodgkin's disease. *J Clin Oncol* 1990;8:623-629.

Recommended Reading

Diehl V, Engert A, Re D. New strategies for the treatment of advanced-stage Hodgkin's lymphoma. *Hematol Oncology Clin North Am* 2007;21:897-914.

Hoppe RT, Mauch PT, Armitage JO, et al. Hodgkin Lymphoma. Philadelphia: Lippincott Williams & Wilkins; 2007.

Hoppe RT. Hodgkin's lymphoma: the role of radiation in the modern combined strategies of treatment. *Hematol Oncol Clin North Am* 2007;21:915-927.

Macdonald DA, Connors JM. New strategies for the treatment of early stages of Hodgkin's lymphoma. *Hematol Oncol Clin North Am* 2007;21:871-880.

Nogova L, Rudiger T, Engert A. Biology, clinical course and management of nodular lymphocyte-predominant Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*. 2006;266-272.