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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 2.2016

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Hodgkin Lymphoma

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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](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2016.



NCCN Guidelines Version 2.2016 Updates

Hodgkin Lymphoma

Updates in Version 2.2016 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2016 include:

[HODG-B \(2 of 2\)](#)

- The CVP regimen for NPLHL has been revised as follows: CVP (cyclophosphamide, ~~vincristine~~ *vinblastine*, ~~prednisone~~ *prednisolone*) ± rituximab.

Updates in Version 1.2016 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2015 include:

[General](#)

- "Age ≥18 Years" has been added to each page and the following footnote has been removed: "Treatment recommendations for postadolescent Hodgkin lymphoma."
- Footnote "j" has been revised: "Individualized treatment may be necessary for older patients and patients with concomitant disease. See *Management of Classical Hodgkin Lymphoma for Older Adults (HODG-F)*."
- Footnote "z" has been revised: ~~"For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A)."~~

[HODG-1](#)

- Under essential workup, B symptoms have been defined in the first bullet: "Unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis."
- Footnote "a" has been revised: "Fine-needle aspiration biopsy (FNAB) alone is ~~to be avoided~~ *strongly discouraged* and only considered to be adequate..."
- Footnote "e" has been revised: "Fertility preservation options include: Semen cryopreservation, ~~if chemotherapy or pelvic RT is contemplated~~ IVF or ovarian tissue or oocyte cryopreservation and oophorectomy ~~in premenopausal women if pelvic RT is contemplated.~~"

[HODG-2](#)

- This page has been added with a new clinical staging table for classical hodgkin lymphoma.

[HODG-3](#)

- This page has been significantly revised to include a new algorithm for stage IA, IIA favorable disease (no bulky disease, <3 sites of disease, ESR <50, and no E-lesions).
- Footnote "k" has been added: "This group of patients may also be treated as per the algorithms for stage IIA (favorable) disease on HODG-4."
- As indicated in footnote "m," the recommendations have been modified from GHSG HD10 study: Engert A, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640-652.

[HODG-4](#)

- The options for stage IIA disease (no bulky disease, <4 sites of disease, ESR <50, ± E-lesions) have been significantly revised. They include options for "intent to treat with chemotherapy alone," "intent to treat with combined modality therapy," or "Stanford V."
- As indicated in footnotes "r-t", the recommendations have been modified from the following references:
 - ▶ RAPID Study: Radford J, et al. *N Engl J Med* 2015;372:1598-1607.
 - ▶ EORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. *J Clin Oncol* 2014;32:1188-1194.
 - ▶ Stanford G4 Trial: Advani RH, et al. *Ann Oncol* 2013;24:1044-1048.
- Footnote "v" has been added: "Consider imaging after additional 2 cycles of chemotherapy."

[HODG-5](#)

- The following has been added for clarification: "Stanford V x 8 weeks (*Combined modality therapy*)."
- For deauville 1-4, 30 Gy has been added as the recommended ISRT dose.
- For deauville 5, biopsy negative, an arrow has been added to ISRT option above.
- The following footnote has been removed: "For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A)."

[HODG-6](#)

- Footnote "y" has been added: "For this algorithm, unfavorable factors include B symptoms, ESR >50, and >3 sites of disease."

[HODG-7](#)

- "± B symptoms" has been removed from unfavorable definition.
- The following reference has been added to footnote "aa": von Tresckow B, et al. *J Clin Oncol* 2012;30:907-913. (Also on HODG-9)

[HODG-10](#)

- For deauville 1-3, "AVD x 4 cycles" has been added as a primary treatment option with the following footnote: "Adapted from the RATHL study: Johnson PW, et al. *Hematol Oncol* 2015;33(suppl 1):102 (Abstract 008)."

[Continued on next page](#)



NCCN Guidelines Version 2.2016 Updates

Hodgkin Lymphoma

Updates in Version 1.2016 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2015 include:

[HODG-11](#)

- The primary treatment recommendation has been revised: "Stanford V x 12 weeks (*in selected patients if IPS <3*)."

[HODG-13](#)

- From CS IIIA,IVA, "palliation only" has been removed beside local RT.
- "Reevaluation" has been revised: "Reevaluation *with PET-CT*."
- The following footnote has been removed: "In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years."

[HODG-14](#)

- Follow-up after completion of treatment up to 5 years, fourth bullet has been revised: "Acceptable to obtain a CT scan ~~once during the first~~ at 6, 12, and 24 mo following the completion of therapy, ~~then~~ or as clinically indicated."
- Follow-up and monitoring after 5 years, "Annual fasting glucose" has been added to the list of recommended laboratory studies.
- Footnote "mm" has been revised: "Low-dose chest CT is optional ~~after 5 y~~ if for current smokers (age 55–75) and former smokers who quit in the past 15 years with a history of smoking >30 packs/year; patients who received chest RT or alkylating agent therapy may also be at risk. ~~treated with a non-alkylating agent, no RT to the chest, and no other risk factors are present.~~"

[HODG-15](#)

- Recommended indications for use of maintenance therapy have been revised: "...if primary refractory or extranodal disease or relapse <12 months following primary therapy."
- Footnote "ww" has been revised: "The value of brentuximab maintenance for a patient who previously received brentuximab vedotin is not known. *It does not provide a survival benefit.*"

[HODG-17](#)

- For NLPHL, the division for "asymptomatic" versus "symptomatic" has been removed and all proceed to one list of second-line therapy options.
- "Observe" has been added to the second-line therapy options.
- "Re-evaluation" has been revised: "Re-evaluation *with PET-CT*."
- After progressive disease, an option has been added to go back through the second-line therapy pathway.
- Footnote "bbb" added: "Consider rebiopsy to rule out transformation."

[HODG-A](#)

- NCIC criteria have been removed from the table of "Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma."

[HODG-B \(1 of 2\)](#)

- References have been updated. (Also on HODG-B 2 of 2, HODG-C 3 of 3, and HODG-E 2 of 2)

[HODG-E](#)

- Regimens have been moved to HODG-E (1 of 2). References have been moved to HODG-E (2 of 2)
- The second bullet has been added: "Patients in complete response to second-line therapy have improved outcomes following HDT/ASCR."
- The last sub-bullet has been added: "In selected patients, brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy."
- The following bullets have been removed:
 - ▶ "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. However, patients tend to have an improved outcome when transplanted in a minimal disease state. Thus, cytoreduction with chemotherapy 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."
 - ▶ "Rituximab should be considered with all second-line chemotherapy regimens for relapsed or refractory NLPHL."
- The following regimens have been added as "additional therapy options" including appropriate references:
 - ▶ Nivolumab
 - ◇ Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 Blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015;372:311-9.
 - ◇ Timmerman J, Armand P, Lesokhin AM, et al. Nivolumab in patients with relapsed/refractory lymphoid malignancies and classical Hodgkin lymphoma: updated results of a phase 1 study (CA 209-039) [abstract] *Hematol Oncol* 2015; 33:Abstract 010.
 - ▶ Pembrolizumab
 - ◇ Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013) [abstract]. *Blood* 2014;124:Abstract 290.

[HODG-F](#)

- This newly added section outlines recommendations for the management of classical Hodgkin lymphoma in older adults (age >60).



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Hodgkin Lymphoma (Age ≥18 years)

DIAGNOSIS

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

WORKUP

Essential:

- H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, exam lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for women of childbearing age
- Diagnostic CT^c (contrast enhanced)
- PET/CT scan^d
- Counseling: Fertility, smoking cessation, psychosocial ([see NCCN Guidelines for Distress Management](#))

Useful in selected cases:

- Fertility preservation^e
- Neck CT, if neck RT contemplated
- Pulmonary function tests (PFTs incl. diffusion capacity [DLCO]) if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV and Hepatitis B testing (encouraged)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- Adequate bone marrow biopsy if there are cytopenias and negative PET^h
- Evaluation of ejection fraction if doxorubicin-based chemotherapy is indicated

CLINICAL PRESENTATION

Classical Hodgkin lymphoma (CHL)^f → [See HODG-2](#)

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)^g → [See HODG-13](#)

^aFine-needle aspiration (FNA) alone is strongly discouraged and only considered to be adequate along with immunohistochemistry if called diagnostic of Hodgkin lymphoma by a hematopathologist or cytopathologist.

^bTypical immunophenotype for classical Hodgkin lymphoma: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-. Typical immunophenotype for nodular lymphocyte-predominant Hodgkin lymphoma: CD20+, CD45+, CD79a+, BCL6+, PAX-5+; CD3-, CD15-, CD30- (Swerdlow SH, Campo E, Harris NL, et al; WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2008). An expanded panel of markers may be required especially if equivocal diagnosis. [See NCCN Guidelines for NHL.](#)

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

^dPET/CT should be done with patient on a flat table with arms up, if possible.

In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. [See \(ST-1\).](#)

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

^fCHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

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

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

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.



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Hodgkin Lymphoma (Age ≥18 years)

CLINICAL STAGING FOR CLASSICAL HODGKIN LYMPHOMA (CHL)ⁱ

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

ⁱFor definitions of bulky disease and lymph node regions, [see HODG-A](#).

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

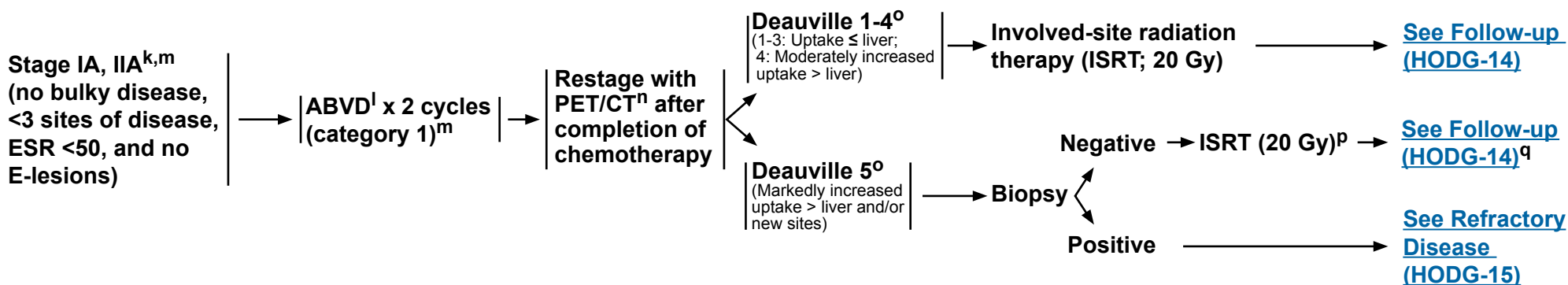
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Hodgkin Lymphoma (Age ≥18 years)

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



^fCHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

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

^kThis group of patients may also be treated as per the algorithms for stage IIA (favorable) disease on [HODG-4](#).

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

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

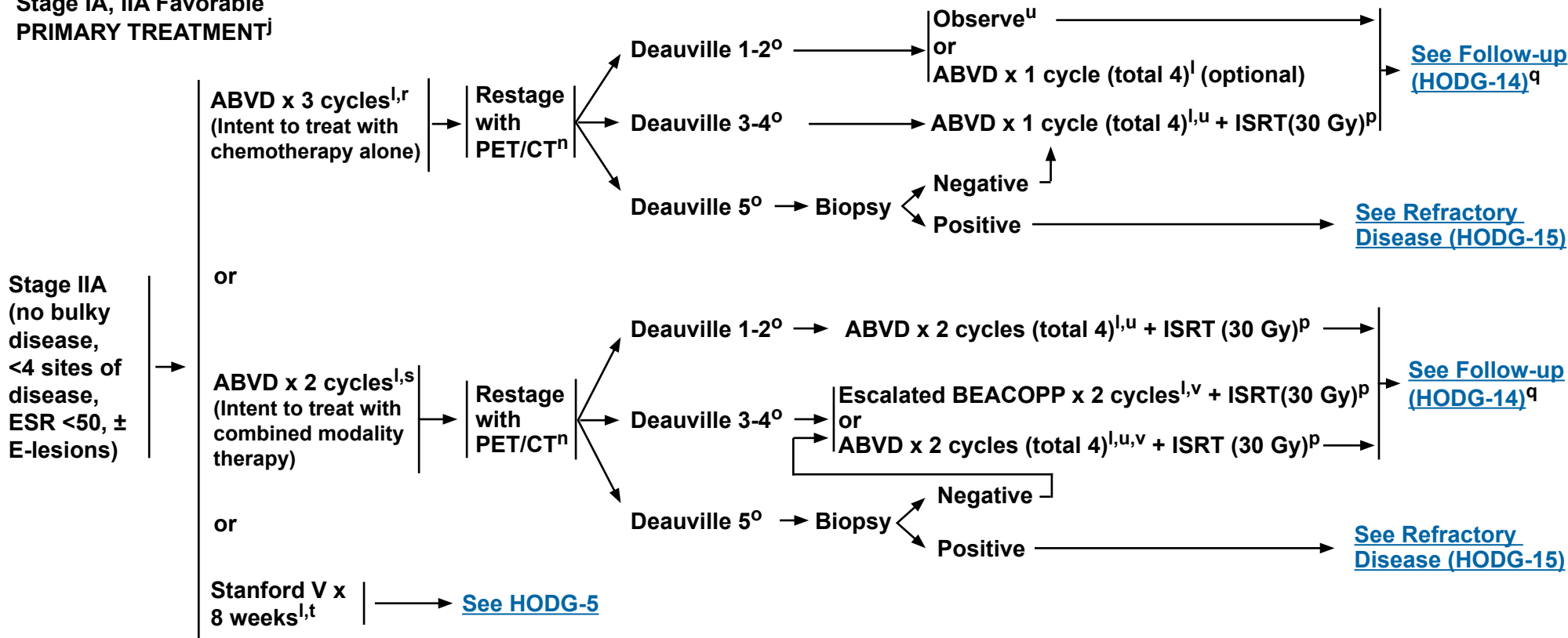
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Hodgkin Lymphoma (Age ≥18 years)

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



^fCHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

^jIndividualized treatment may be necessary for older patients and patients with concomitant disease. [See Management of Classical Hodgkin Lymphoma in Older Adults \(HODG-F\)](#).
[See Principles of Systemic Therapy \(HODG-B\)](#).

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

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^uModified from RAPID Study: Radford J et al. N Engl J Med 2015;372:1598-1607.

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

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

^uConsider PFTs after 4 cycles of ABVD.

^vConsider imaging after additional 2 cycles of chemotherapy.

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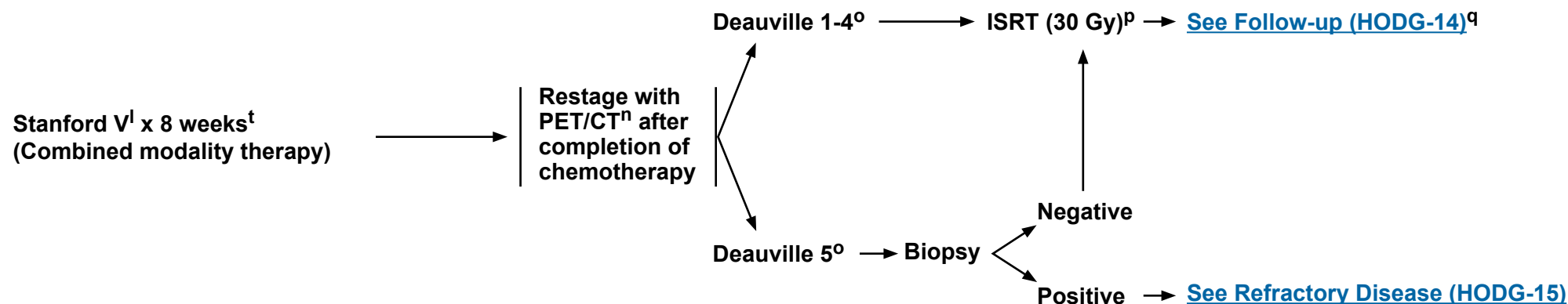


NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage IA, IIA Favorable
(Continued from HODG-4)

PRIMARY TREATMENT^j



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

^tModified from Stanford G4 Trial: Advani RH, et al. *Ann Oncol* 2013;24:1044-1048.

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

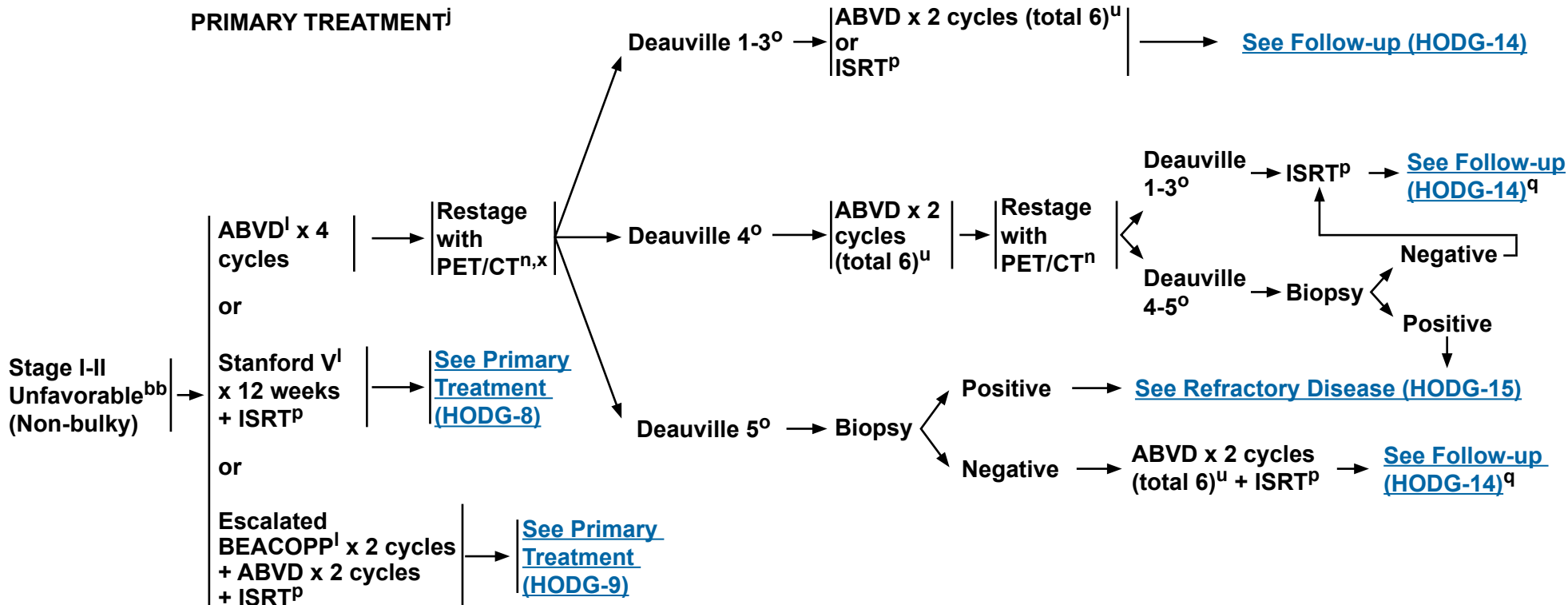
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Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION: Classical Hodgkin Lymphoma^f Stage I-II Unfavorable^y (Non-bulky)



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

^uConsider PFTs after 4 cycles of ABVD.

^xThe value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

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

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

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Hodgkin Lymphoma (Age ≥18 years)

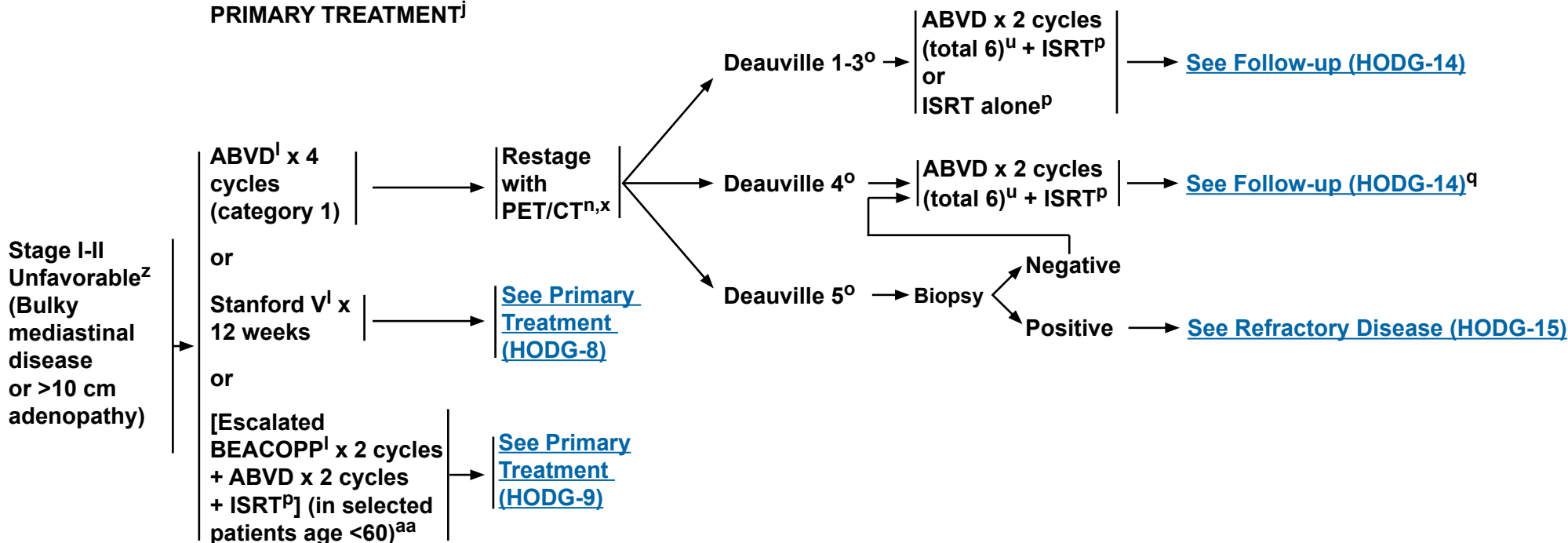
CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^f

Stage I-II Unfavorable^z (Bulky mediastinal disease or >10 cm adenopathy)

Planned Combined Modality Therapy

PRIMARY TREATMENT^j



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

^uConsider PFTs after 4 cycles of ABVD.

^xThe value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

^zNCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease ([see HODG-A](#)).

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

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

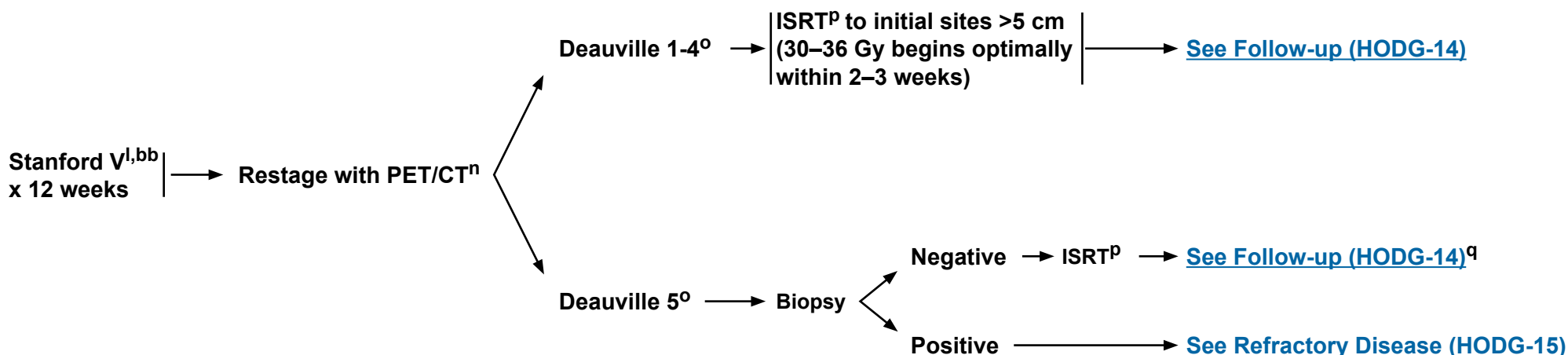
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage I-II Unfavorable^z (Bulky or non-bulky)
PRIMARY TREATMENT^j
(continued from HODG-7)



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

^zNCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease ([see HODG-A](#)).

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

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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

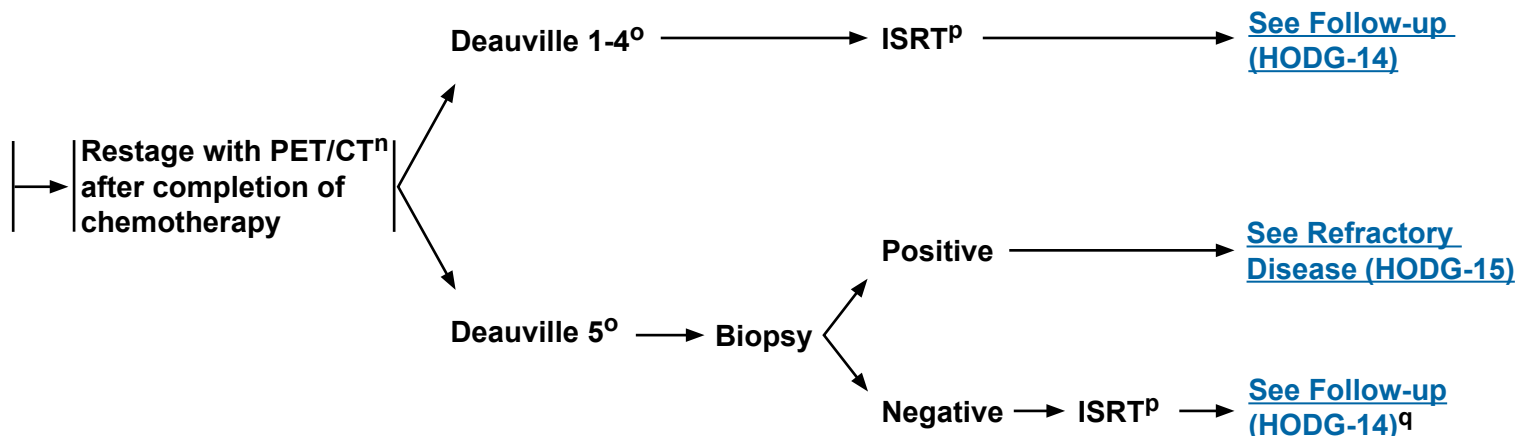
CLINICAL PRESENTATION:

Classical Hodgkin Lymphoma^f
Stage I-II Unfavorable^{z,aa} (Bulky or Non-bulky)

PRIMARY TREATMENT^j

(continued from HODG-7)

Escalated BEACOPP^{l,aa} x 2 cycles
+ ABVD x 2 cycles
(in selected patients age <60)



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

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

^l[See Principles of Systemic Therapy \(HODG-B\).](#)

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\).](#)

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

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

^zNCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease ([see HODG-A](#)).

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

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

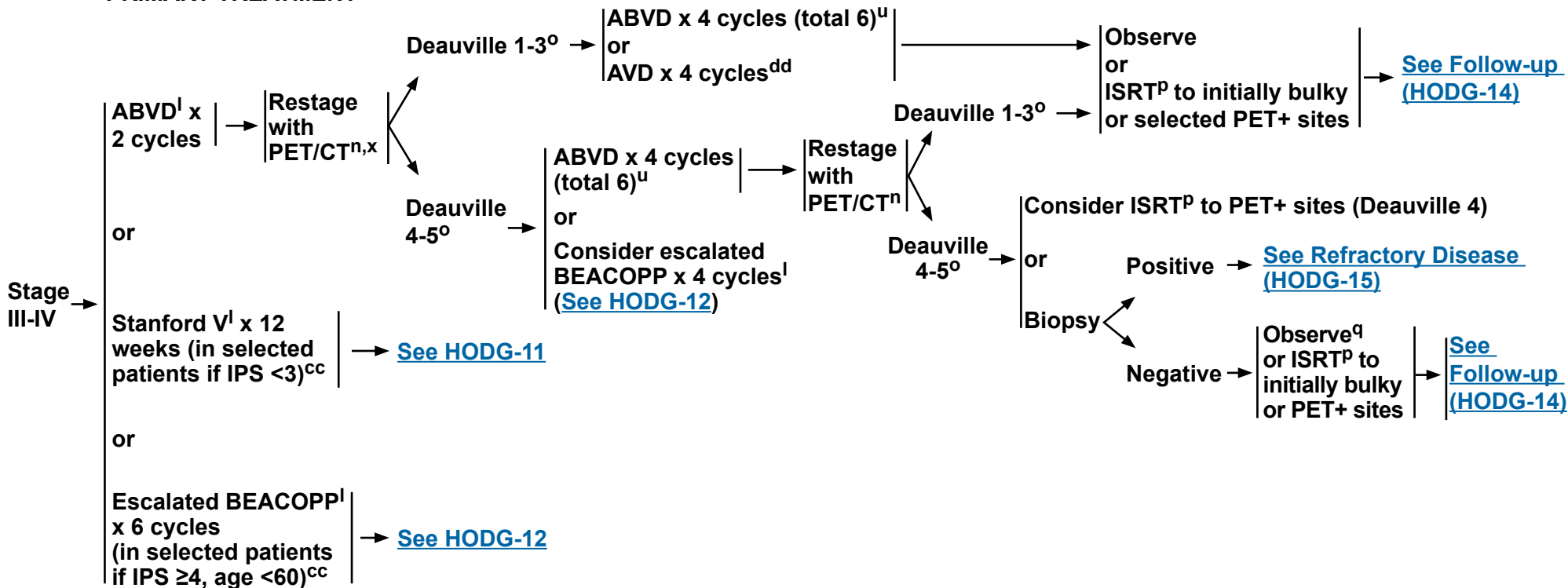
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2016 Hodgkin Lymphoma (Age ≥18 years)

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

PRIMARY TREATMENT^j



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

^uConsider PFTs after 4 cycles of ABVD.

^xThe value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

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

^{dd}Adapted from the RATHL study: Johnson PW, et al. *Hematol Oncol.* 2015;33(suppl 1):102 (Abstract 008).

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

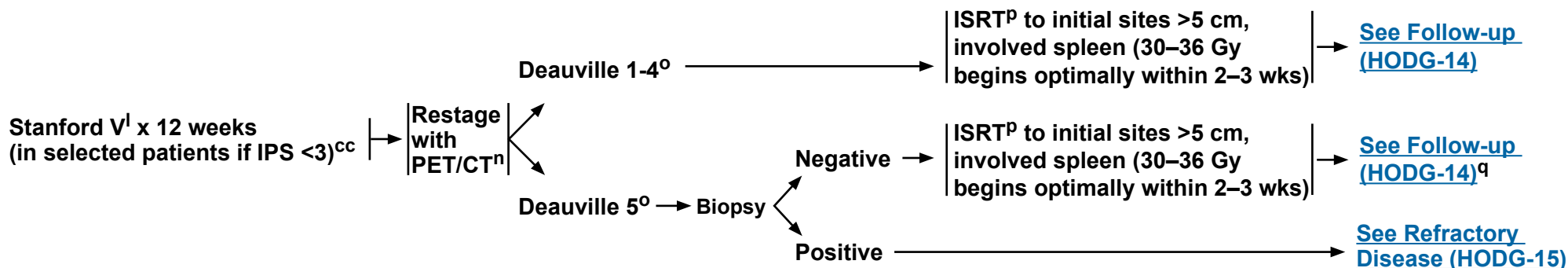
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage III-IV
PRIMARY TREATMENT^j
(continued from HODG-10)



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

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

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

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

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

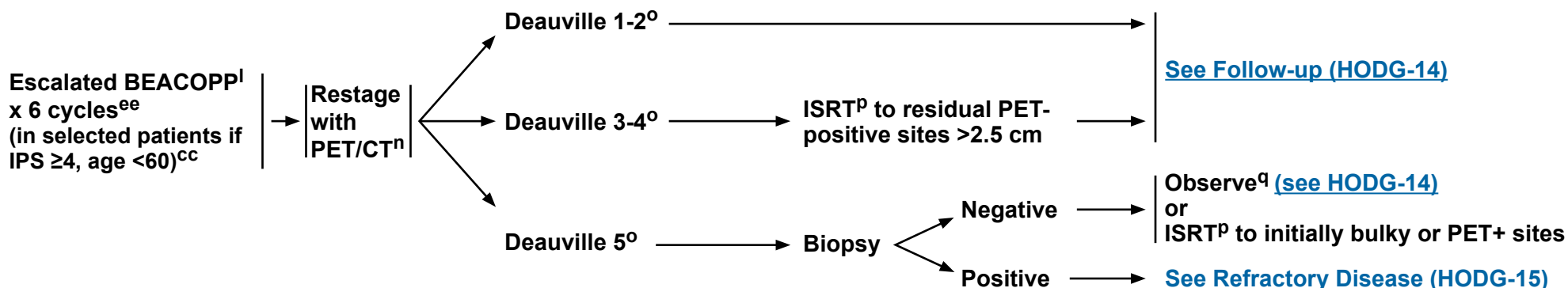
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma^f
Stage III-IV
PRIMARY TREATMENT^j
(continued from HODG-10)



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

^jIndividualized treatment may be necessary for older patients and patients with concomitant disease. [See Management of Classical Hodgkin Lymphoma for Older Adults \(HODG-F\)](#).

^l[See Principles of Systemic Therapy \(HODG-B\)](#).

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

^o[See PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

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

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

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

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.

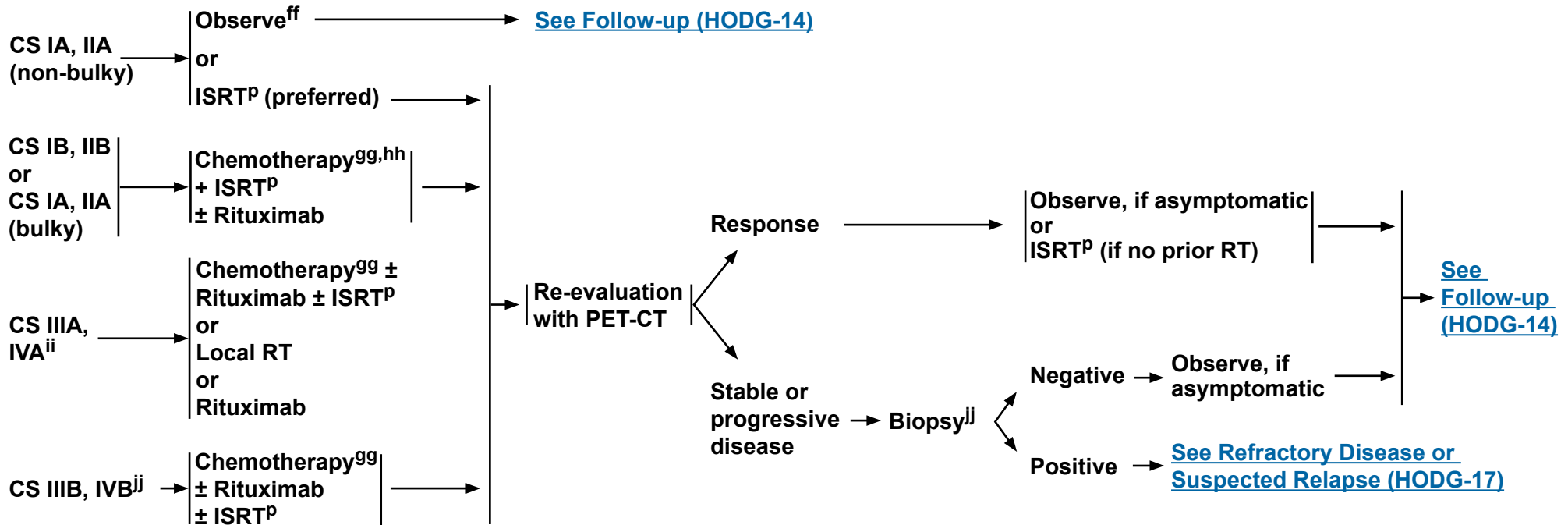


NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION: Nodular Lymphocyte-Predominant Hodgkin Lymphoma^g

PRIMARY TREATMENT



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

^PISRT fields are generally smaller than IFRT fields. [See Principles of Radiation Therapy \(HODG-C\)](#).

^{ff}Observation may be an option for stage IA patients with a completely excised solitary lymph node.

^{gg}[See Principles of Systemic Therapy \(HODG-B 2 of 2\)](#).

^{hh}Generally a brief course of chemotherapy (3–4 months) would be given with radiation therapy.

ⁱⁱFor stage CS IIIA, IVA, observation may be an option in selected cases (category 2B).

^{jj}Consider biopsy of persistent or new subdiaphragmatic sites to rule out transformation.

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.



NCCN Guidelines Version 2.2016 Hodgkin Lymphoma (Age ≥18 years)

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

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

Follow-up After Completion of Treatment up to 5 Years

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

Suspected Relapse CHL ([HODG-16](#)) or NLPHL ([HODG-17](#))

Follow-up and Monitoring After 5 Years^{kk, ll}

- Interim H&P: Annually
 - ▶ Annual blood pressure, aggressive management of cardiovascular risk factors
 - ▶ Pneumococcal, meningococcal, and H-flu revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to CDC recommendations)
 - ▶ Annual influenza vaccine
- Cardiovascular symptoms may emerge at a young age.
 - ▶ Consider stress test/echocardiogram at 10-y intervals after treatment is completed.
 - ▶ Consider carotid ultrasound at 10-y intervals if neck irradiation.
- Laboratory studies:
 - ▶ CBC, platelets, chemistry profile annually
 - ▶ TSH at least annually if RT to neck
 - ▶ Biannual lipids
 - ▶ Annual fasting glucose
- Consider low-dose chest CT for patients at increased risk for lung cancer.^{mmm}
- Annual breast screening: Initiate 8–10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Colonoscopy every 10 years for patients age ≥50, if high risk begin at age 40, which is consistent with ACS Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.

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

^{ll}Appropriate medical management should be instituted for any abnormalities.
^{mmm}Low-dose chest CT is optional for current smokers (age 55–75) and former smokers who quit in the past 15 years with a history of smoking >30 packs/year; patients who received chest RT or alkylating agent therapy may also be at risk.

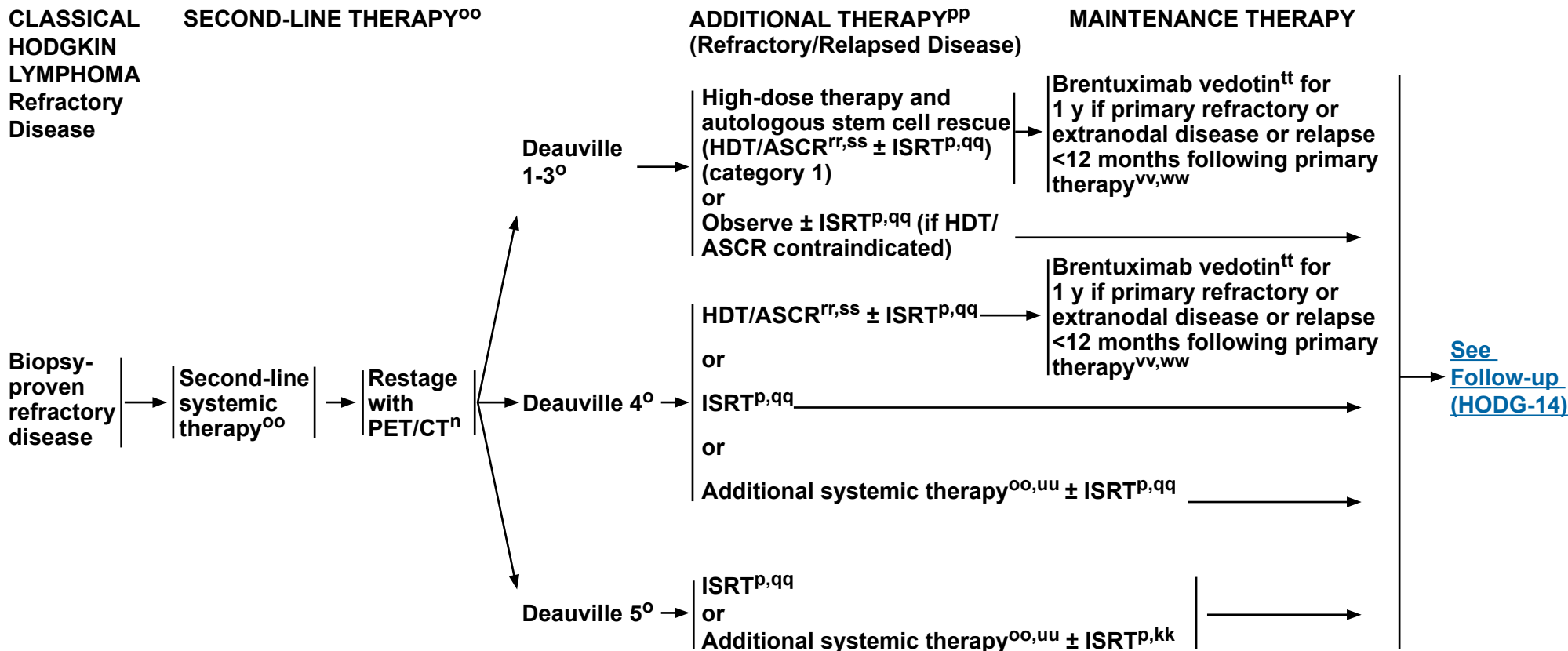
Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)



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

^oSee [PET 5-Point Scale \(Deauville Criteria\) \(HODG-D\)](#).

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

^{oo}See [Principles of Systemic Therapy for Relapsed or Refractory Disease \(HODG-E\)](#).

^{pp}There are no data to support a superior with any of the treatment modalities. Individualized treatment is recommended.

^{qq}Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.

^{rr}Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naïve patient, TLI may be an appropriate component of HDT.

^{ss}Allotransplant is an option in select patients as a category 3 recommendation.

^{tt}Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.

^{uu}Additional systemic therapy options include second-line therapy options that were not previously used (See [HODG-E](#)).

^{vv}Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;385:1853-1862.

^{ww}The value of brentuximab maintenance for a patient who previously received brentuximab vedotin is not known. It does not provide a survival benefit.

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.

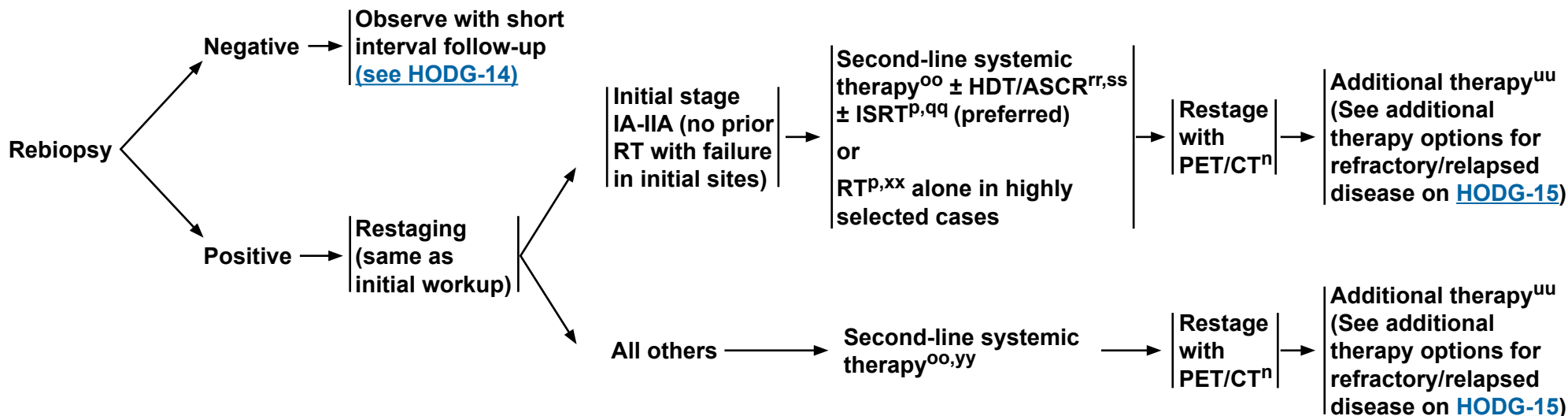


NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

CLASSICAL HODGKIN LYMPHOMA SUSPECTED RELAPSE

SECOND-LINE THERAPY^{PP}



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

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

^{oo}[See Principles of Systemic Therapy for Relapsed or Refractory Disease \(HODG-E\)](#).

^{pp}There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

^{qq}Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.

^{rr}Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naïve patient, TLI may be an appropriate component of HDT.

^{ss}Allotransplant is an option in select patients as a category 3 recommendation.

^{uu}Additional systemic therapy options include second-line therapy options that were not previously used. [\(See HODG-E\)](#).

^{xx}If radiation therapy is being used alone as a second-line therapy, conventional involved-field or extended-field treatment is indicated.

^{yy}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.

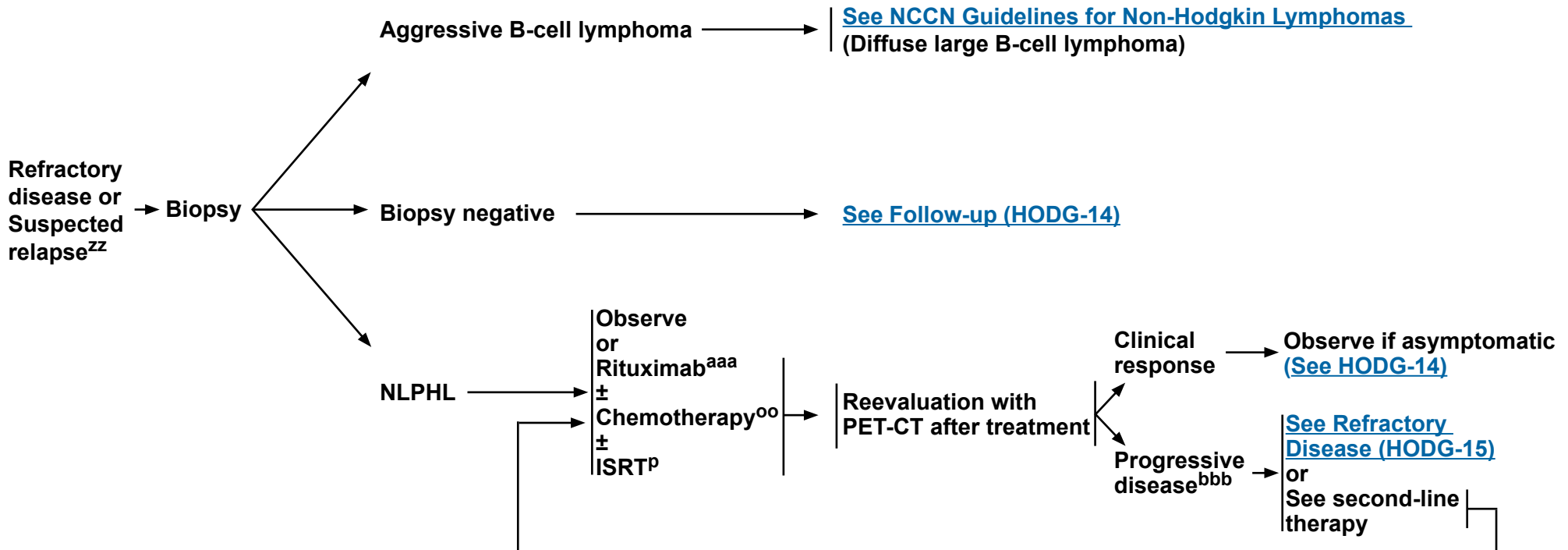


NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA REFRACTORY OR SUSPECTED RELAPSE

SECOND-LINE THERAPY^{PP}



^PISRT fields are generally smaller than IFRT fields. [See Principles of Radiation Therapy \(HODG-C\)](#).

^{oo}[See Principles of Systemic Therapy for Relapsed or Refractory Disease \(HODG-E\)](#).

^{PP}There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

^{ZZ}At relapse, patient should be considered for re-biopsy because of risk for transformation, especially if intraabdominal or splenic disease. Some patients with NLPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed.

^{aaa}In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years.

^{bbb}Consider rebiopsy to rule out transformation.

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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

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

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

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

Definitions of Lymph Node Regions*

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

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

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

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

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

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

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NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY (1 of 2)

Classical Hodgkin Lymphoma

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

Regimens and References

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

Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640-652.
Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015;372:1598-1607.
Raemaekers JM, André MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography–negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014;32:1188-1194.
Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD 11 trial. *J Clin Oncol* 2010;28:4199-4206.

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

Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. *Ann Oncol* 2013;24:1044-1048.
Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2013;31:684-691.
Advani RH, Hong F, Fisher RI, et al. Randomized phase III trial comparing ABVD plus radiotherapy with the Stanford V regimen in patients with stages I or II locally extensive, bulky mediastinal Hodgkin lymphoma: a subset analysis of the north american Intergroup E2496 trial. *J Clin Oncol* 2015;33:1936-1942.
Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol* 2010;21:574-581.

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

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

Escalated BEACOPP followed by ABVD with ISRT

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

[See Principles of Systemic Therapy for NLPHL \(HODG-B 2 of 2\)](#)

[See Principles of Systemic Therapy for Relapsed or Refractory Disease \(HODG-E\)](#)

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

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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY (2 of 2)

Nodular Lymphocyte-Predominant Hodgkin Lymphoma**

• The most common chemotherapies used at NCCN Member Institutions for NLPHL are listed below.

Regimens and References

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± rituximab

Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. *Blood* 2011;118:4585-4590.

Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's Lymphoma? *J Clin Oncol* 2010;28:e8.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab

Fanale MA, Lai C-M, McLaughlin P, et al. Outcomes of nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) patients treated with R-CHOP. *ASH Annual Meeting Abstracts* 2010;116:2812.

CVP (cyclophosphamide, vinblastine, prednisolone) ± rituximab

Shankar A, Hall GW, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma - an Anglo-French collaborative report. *Eur J Cancer* 2012;48:1700-1706.

Rituximab

Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. *Blood* 2013;122:4182-4188.

Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol* 2014;32:912-918.

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(1):109-111.

Eichenauer DA, Fuchs M, Plutschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood* 2011;118:4363-4365.

Eichenauer DA, Plutschow A, Fuchs M, et al. Long-Term Course of Patients With Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group. *J Clin Oncol* 2015;33:2857-2862.

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

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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY (1 of 3)

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

Involved-site Radiation Therapy (ISRT)

Dose:

- Combined Modality Therapy
 - ▶ Non-bulky disease (stage I-II): 20*–30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)
 - ▶ Non-bulky disease (stage IB-IIB): 30 Gy
 - ▶ Bulky disease sites (all stages): 30–36 Gy
 - ▶ PET scan Deauville 3-4 following chemotherapy: 30–45 Gy
- ISRT Alone (uncommon, except for NLPHL):
 - ▶ Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL)
 - ▶ Uninvolved regions: 25–30 Gy

[Continued on next page](#)

[See References \(HODG-C 3 of 3\)](#)

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

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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY (2 of 3)

Volumes:

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

[See References \(HODG-C 3 of 3\)](#)

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY (3 of 3)

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Hodgkin Lymphoma (Age ≥18 years)

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

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

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

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (1 OF 2) Regimens

- The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.
- Patients in complete response to second-line therapy have improved outcomes following HDT/ASCR.
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.
 - ▶ In selected patients, brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy.

Second-Line or Subsequent Therapy Options (listed in alphabetical order):

- Brentuximab vedotin (only for CHL)¹
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)^{2,3}
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)^{4,5,6}
- GCD (gemcitabine, carboplatin, dexamethasone)^{7,8}
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)⁹
- ICE (ifosfamide, carboplatin, etoposide)^{10,11}
- IGEV (ifosfamide, gemcitabine, vinorelbine)¹²
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)¹³
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)^{14,15}

Additional Therapy Options* (only for CHL) (listed in alphabetical order):

- Bendamustine¹⁶
- Everolimus¹⁷
- Lenalidomide¹⁸
- Nivolumab^{19,20}
- Pembrolizumab²¹

[See References \(HODG-E 2 of 2\)](#)

*Additional systemic therapy options include second-line therapy options that were not previously used.

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

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NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (2 OF 2)

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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.



NCCN Guidelines Version 2.2016

Hodgkin Lymphoma (Older Adults)

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

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

SUGGESTED TREATMENT REGIMENS (Listed in alphabetical order)

Stage I-II Favorable disease

- A(B)VD* (2 cycles) ± AVD (2 cycles) + 20–30 Gy ISRT (preferred)^{7,8,9}
- CHOP (4 cycles) + ISRT¹⁰
- VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin) ± ISRT¹¹

Stage I-II Unfavorable or Stage III-IV disease

- A(B)VD* (2 cycles) followed by AVD (4 cycles)**, if PET scan is negative after 2 cycles of ABVD.¹²
 - Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment.
- CHOP (6 cycles) ± ISRT¹⁰
- PVAG (6–8 cycles) (prednisone, vinblastine, doxorubicin, and gemcitabine)¹⁴
- VEPEMB (6 cycles) ± ISRT^{11,13}

Relapsed or Refractory Disease

- Outcomes are uniformly poor for patients with relapsed or refractory disease.¹⁵
- No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended.
- Individualized treatment is necessary.

Palliative Therapy Options

- Bendamustine
- Brentuximab vedotin
- Additional therapy options (only for CHL) as listed on [Principles of Systemic Therapy for Relapsed or Refractory Disease HODG-E \(1 of 2\)](#)
- ISRT

*Bleomycin should be used with caution as it may not be tolerated in older adults.

**If stage I-II unfavorable, consider a total of 4 cycles.

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[References on next page](#)



NCCN Guidelines Version 2.2016 Hodgkin Lymphoma (Older Adults)

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

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HODGKIN LYMPHOMA STAGING¹

Table 1

Definitions of Stages in Hodgkin's Disease²

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

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

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

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

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

A No systemic symptoms present

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

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

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/20/15.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. In 2015, an estimated 9,050 people will be diagnosed with HL in the United States and 1,150 people will die from the disease.¹ The WHO classification divides HL into 2 main types: classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).² In Western countries, CHL accounts for 95% and NLPHL accounts for 5% of all HL.

CHL is divided into 4 subtypes: nodular sclerosis CHL; mixed cellularity; lymphocyte-depleted CHL; and lymphocyte-rich CHL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed *popcorn cells*.

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

The NCCN Guidelines discuss the clinical management of patients with CHL and NLPHL, focusing exclusively on patients from post adolescence through the seventh decade of life who do not have serious intercurrent disease. The guidelines do not address HL in pediatric or older 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Hodgkin Lymphoma, an electronic search of the PubMed database was performed to obtain key literature in Hodgkin Lymphoma published between August 2013 and August 2014, using the following search terms: Hodgkin lymphoma, classical Hodgkin lymphoma, nodular lymphocyte predominant, early stage, advanced stage, imaging, PET, positron emission tomography, response assessment, Deauville, treatment, late effects, follow-up, and surveillance. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.³

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 70 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as

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

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.^{4,5} Each stage is subdivided into A and B categories. "A" indicates that no systemic symptoms are present and "B" is assigned to patients with unexplained weight loss of >10% of their body weight, unexplained fevers, or drenching night sweats.

Patients with HL are usually classified into 3 groups: early-stage favorable (stage I-II with no unfavorable factors); early-stage unfavorable (stage I-II with any of the unfavorable factors such as large mediastinal adenopathy; >2–3 nodal sites of disease; B symptoms; extranodal involvement; or significantly elevated erythrocyte sedimentation rate [ESR] ≥ 50) and advanced-stage disease (stage III-IV).

Mediastinal bulk, an unfavorable prognostic factor in patients with early-stage HL, is measured most commonly using the mediastinal mass ratio (MMR).⁶ The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR greater than 0.33 is defined as bulky disease. Another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter. According to the Cotswolds modification of the Ann Arbor staging system, bulky disease is defined as a mediastinal mass exceeding one

third of the internal transverse diameter of the thorax at the T5-T6 interspace on a posteroanterior chest radiograph.⁷

The early-stage unfavorable factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, German Hodgkin Study Group (GHSG), and the National Cancer Institute of Canada (NCIC).^{8,9} The NCCN unfavorable factors for stage I-II disease include bulky mediastinal disease (MMR greater than 0.33) or bulky disease greater than 10 cm, B symptoms, ESR greater than 50, and >3 nodal sites of disease.

An international collaborative effort evaluating more than 5000 patients with advanced CHL (stage III-IV) identified 7 adverse prognostic factors, each of which reduced survival rates by 7% to 8% per year:¹⁰

- 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 >15,000/mm³)
- Lymphocytopenia (lymphocyte count <8% of the white blood count and/or lymphocyte count <600/mm³)

The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.¹⁰ The IPS helps to determine the clinical management and predict prognosis for patients with stage III-IV disease.¹⁰ For instance, selected patients with IPS <3 and advanced disease could be treated with Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) while escalated-dose BEACOPP (bleomycin, etoposide,

doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) may be more appropriate for all other patients with stage III-IV disease.

Response Criteria

Clinical management of patients with CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging at the completion of chemotherapy to assess treatment response.

Assessment of response to initial treatment is essential because the need for additional treatment is based on the treatment response.

The original Cotswolds response criteria included the response category, CR (complete response) unconfirmed/uncertain (CRu), which denoted patients in whom the remission status was unclear. There was “no clinical evidence of Hodgkin’s disease but some radiological abnormality, not consistent with the effects of therapy, persists at the site of previous disease”.⁷ This designation indicated that it was not possible to determine whether residual masses identified on CT scan represented residual HL, scarring, or some other nonmalignant process. The International Working Group (IWG) published the guidelines for response criteria in 1999.¹¹ These criteria are based on the size reduction of enlarged lymph nodes as measured on CT scan, and the extent of bone marrow involvement determined using bone marrow aspirate and biopsy.

In 2007, the IWG guidelines were revised by the International Harmonization Project (IHP) to incorporate immunohistochemistry (IHC), flow cytometry, and PET scans in the definition of response.^{12,13} The revised guidelines eliminated CRu based partly on the ability of PET scans to further characterize residual masses detected with CT. Using the revised system, response is categorized as complete response (CR), partial response (PR), stable disease, relapsed

disease, or progressive disease.¹² The IHP response criteria were initially developed for the interpretation of PET scans at the completion of treatment. In recent years, these criteria have also been used for interim response assessment.¹⁴

In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of FDG uptake in the involved sites. These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.¹⁵⁻¹⁷ In the 5-PS (Deauville criteria), scores 1 to 4 refer to initially involved sites and score 5 refers to an initially involved site and/or new lesions related to lymphoma.^{15,16} PET scans with a score of 1 or 2 are considered “negative” and PET scans with a score of 4 and 5 are considered “positive.”¹⁸ In some situations, a score of 3 may be considered negative; however, for de-escalation of therapy based on interim PET scans, a threshold for positivity that includes a score of 3 using the mediastinal blood pool uptake as the reference is appropriate (PET scans with a score of 1–2 are considered negative and PET scans with a score of 3–5 are considered positive).¹⁹ The 5-PS (Deauville criteria) has been validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.²⁰⁻²⁴

Role of PET Scans

PET imaging and, more recently, integrated PET and CT (PET/CT, hereafter referred to as PET) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.^{14,17} In a recent meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.²⁵ PET positivity at the end of treatment has been shown to

be a significant adverse risk factor in patients with early-stage as well as advanced-stage disease.²⁶⁻²⁸ In a study of 73 patients (the majority of whom had stage I-IIA disease), Sher et al reported that the actuarial 2-year failure-free survival (FFS) rate was 95% for those who were PET-negative at the end of chemotherapy, and 69% for the PET-positive group.²⁸ In the HD15 trial, positive PET after chemotherapy with BEACOPP was associated with a higher risk of subsequent treatment failure. The progression-free survival (PFS) at 48 months was 92.6% and 82.6%, respectively, for PET-negative and PET-positive patients ($P = .022$).²⁹ In this study, PET-positive patients received radiation therapy (RT) to the PET-positive sites.

The NCCN PET Task Force and the NCCN Guidelines recommend PET scans for initial staging and for evaluating residual masses at the end of treatment.³⁰ An integrated PET scan plus a diagnostic CT is recommended for initial staging, although a separate diagnostic CT is not needed if it was part of the integrated PET scan.

The role of PET in post-therapy surveillance remains controversial, and further studies are needed to determine its role. Until those studies are completed, PET scans are not recommended for routine surveillance due to the risk of false-positive findings and unnecessary diagnostic interventions and/or radiation exposure.³¹⁻³³

Interim PET Scans

PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone.²¹ The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios and all measures of response should be considered in the context of management decisions.

The guidelines recommend biopsy for all patients with a score of Deauville 5 (markedly increased uptake compared to liver at any initially involved site and/or new lesions). In general, patients with a positive biopsy should be managed as described for refractory disease and for those with a negative biopsy, CR should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

Stage IA-IIA (Favorable Disease)

Available evidence, primarily from retrospective studies, suggests only a limited value for interim PET imaging among patients with early-stage disease.

Hutchings et al reported that five of seven (71%) patients with stage I-II disease who had a positive interim PET scan remained in remission at a median follow-up of 3 years, whereas all patients with advanced disease (stage III-IV) with a positive PET scan had relapsed within 2 years.³⁴

In another study that included a majority of patients with stage I-IIA disease (43 out of 73), the actuarial 2-year FFS rate was 95% for those who were PET-negative at the end of chemotherapy, and was 69% for the PET-positive group.²⁸ However, among the 46 patients who underwent interim PET imaging after 2 or 3 cycles of chemotherapy, 20 patients had positive interim PET scans and 13 of these 20 patients (65%) had negative PET scans at the completion of chemotherapy. The actuarial 2-year FFS rate was 92% for this group compared to 96% for patients with negative PET scans during and after completion of chemotherapy.

Barnes et al also showed that interim PET scans did not predict outcome in patients with non-bulky stage I-II disease. The 4-year PFS

rate was 91% for those with a negative interim PET scan and 87% for those with a positive interim PET scan ($P = .57$).³⁵

More recent reports have confirmed the prognostic significance of interim PET scans after 2 or 3 cycles of chemotherapy in patients with early-stage disease.³⁶⁻³⁸ In a retrospective analysis that included 147 patients with early-stage disease, Zinzani et al recently reported the best predictive value for interim PET scans after 2 cycles of ABVD (PET-2) in patients with early-stage favorable disease.³⁶ At a median follow-up of 45 months, 97.6% of patients with a negative PET-2 scan remained in CR, whereas only 21% of patients with a positive PET-2 scan remained in CR at a median follow-up of 28 months. The 9-year PFS rate was also significantly higher for patients with a negative PET-2 scan than for those with a positive PET-2 scan (94.7% and 31.3%, respectively). The corresponding 9-year overall survival (OS) rates were 100% and 85.2%, respectively ($P = .0001$) for the 2 groups.

NCCN Recommendations

Initial results from retrospective analyses failed to demonstrate the prognostic significance of interim PET scans in patients with stage I-II favorable disease.^{28,34,35,39} More recent reports suggest that interim response assessment with PET/CT after 2 or 3 cycles of chemotherapy based on the 5-PS (Deauville criteria) is a good prognostic indicator in patients with early-stage disease.³⁶⁻³⁸

Based on these recent findings, the panel consensus was to incorporate the Deauville criteria (5-PS) for interim response assessment with PET scans after 2 to 4 cycles of ABVD for patients receiving combined modality therapy and after 2 cycles of ABVD for patients receiving chemotherapy alone. In patients receiving the Stanford V regimen, interim response assessment is usually performed

after completion of chemotherapy (8 weeks) prior to the initiation of involved-site RT (ISRT).

Stage I-II (Unfavorable Disease) and Stage III-IV Disease

Early interim PET imaging after chemotherapy has been shown to be a sensitive prognostic indicator of treatment outcome in patients with advanced-stage disease (stage II disease with unfavorable risk factors [with or without bulky disease] or stage III-IV disease).^{40,41}

In two prospective studies, the PET scan after 2 cycles of standard ABVD chemotherapy was a strong and independent prognostic factor of PFS in patients with advanced-stage and extranodal disease.^{42,43} In a combined report from these two prospective studies (190 patients with stage IIB-IVB; 70 patients with stage IIA with adverse prognostic factors), the 2-year PFS was significantly better for patients with negative PET after 2 cycles of ABVD than for those with positive PET (95% vs.13%).⁴⁴

Cerci et al reported similar findings in a recent prospective study of 102 patients with stage II-IV disease (35% had stage IV disease; 58% had bulky disease; and 63.5% had B symptoms). The 3-year event-free survival (EFS) rate was 53% for patients with positive PET after 2 cycles of ABVD and 90.5% for those with negative PET ($P < .001$).⁴⁵

A retrospective international multicenter study confirmed that interim response assessment (based on the 5-PS [Deauville criteria]) after 2 cycles of ABVD was predictive of FFS in patients with stage IIB-IVB disease (207 patients) or stage IIA disease with adverse prognostic factors (53 patients).^{22,24} After a median follow up of 37 months, the 3-year PFS rate was 83% for the entire study population (95% for patients with a negative PET scan [score 1-3]) and 28% for those with a positive PET scan [score 4-5]; $P < .0001$).²⁴ The 3-year OS rate was

97% for the entire study population (99% for patients with a negative PET scan and 87% for those with a positive PET scan).²⁴

In a retrospective analysis of 81 patients with stage I/II (non-bulky or bulky mediastinal disease) and stage III/IV disease treated with the Stanford V regimen, Advani and colleagues showed that PET positivity after 8 and 12 weeks of chemotherapy was a significant predictor of PFS even after controlling for bulky disease and IPS > 2. At a median follow-up of 4 years, the freedom from progression (FFP) was 96% in those with negative PET scans compared with 33% in those with positive PET scans at the completion of chemotherapy.⁴⁶

Markova and colleagues demonstrated that interim PET scans after 4 cycles of BEACOPP (PET-4) is a strong prognostic marker for PFS in patients with early-stage unfavorable (stages IIB with large mediastinal mass or extranodal disease) or advanced-stage (stages III and IV) disease.⁴⁷ At a median follow-up of 55 months, the 4-year PFS for PET-4 negative (n = 51) and PET-4 positive (n = 18) patients was 96% and 78%, respectively (P = .016). PET scans at 3 months after the completion of chemotherapy was of limited value when the interim PET-4 was negative.

The Israeli Study Group has evaluated the utility of interim PET scans to develop risk-adapted and/or response-adapted treatment in small cohorts of patients with early-stage unfavorable and advanced-stage disease.⁴⁸⁻⁵⁰ Avigdor and colleagues evaluated response-adapted de-escalation of therapy (escalated-dose BEACOPP followed by ABVD) in patients with advanced-stage disease and IPS ≥ 3.⁴⁹ Forty-five patients were initially treated with 2 cycles of escalated-dose BEACOPP followed by interim PET scan. Patients with a negative interim PET scan received 4 cycles of ABVD, and those with a positive interim PET scan were removed from the study and considered for

second-line therapy followed by high-dose chemotherapy and autologous stem-cell transplantation. After a median follow-up of 48 months, the PFS and OS rates were 78% and 95%, respectively, for patients who completed 4 cycles of ABVD. The 4-year PFS for PET-negative patients (n = 31) and PET-positive patients (n = 13) were 87% and 53%, respectively (P = .01). Long-term follow-up of this study also confirmed that patients with advanced-stage disease with an IPS ≥ 3 who achieved CR after 2 cycles of escalated BEACOPP (as determined by interim PET scan using the revised response criteria) had a favorable outcome after de-escalation of therapy to 4 cycles of ABVD.⁵¹ The 5-year OS rate was significantly higher for patients in CR after early interim PET scan than those with PR (98% vs. 79%; P = .015). The Israeli H2 study also showed that de-escalation of therapy is feasible in patients with advanced stage disease with negative PET scan after 2 cycles of escalated BEACOPP.⁵²

Dann and colleagues evaluated a risk-adapted approach with BEACOPP based on the results of interim PET scans for patients with early-stage unfavorable and advanced-stage disease (n = 124).^{48,50} Patients with advanced disease (stage I-II bulky with B symptoms and stage III-IV) with an IPS ≥ 3 were treated with 2 cycles of escalated-dose BEACOPP, and those with an IPS ≤ 2 received 2 cycles of standard-dose BEACOPP followed by restaging. Those with a positive interim PET scan received 4 additional cycles of escalated-dose BEACOPP, whereas 4 cycles of standard-dose BEACOPP were given to patients with a negative interim PET scan. The 10-year PFS rate was 83% for patients with a positive interim PET scan and 93% for those with a negative interim PET scan.⁵⁰

NCCN Recommendations

Although the prognostic significance of interim PET scans has been established in patients with advanced disease, the timing of the interim

PET scans is still unclear. In one of the prospective studies, there was no significant difference between the prognostic value of interim PET scans after 2 and 4 cycles of chemotherapy.⁴³ In a recent prospective study, interim PET imaging after 2 cycles of ABVD was highly predictive of treatment success in patients with stage I-II unfavorable disease and stage III-IV disease; the difference in 3-year EFS was significant for patients with stage III-IV disease ($P < .001$) and for those with stage I-II disease ($P = .002$).⁴⁵

Based on the recent findings, the panel consensus was to incorporate the Deauville criteria (5-PS) for interim response assessment with PET scans for patients with stage I-II (unfavorable, bulky, or non-bulky disease) and patients with stage III-IV disease. The guidelines recommend interim response assessment with PET after 2 or 4 cycles of ABVD or after 4 cycles of escalated-dose BEACOPP. In patients receiving Stanford V regimen, interim response assessment is usually performed after completion of chemotherapy (8 or 12 weeks) prior to the initiation of RT.

Principles of Radiation Therapy

RT can be delivered with photons, electrons or protons, depending upon clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues so target definition and delineation and treatment delivery verification require careful monitoring. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound (US) and other imaging modalities facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and

delivery techniques such as 4D-CT simulation, intensity-modulated RT (IMRT), image-guided RT, respiratory gating or deep inspiration breath hold.^{53,54} These techniques offer significant and clinically relevant advantages in specific instances to spare OAR and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control.⁵⁵⁻⁶¹

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

ISRT and involved-node RT are being used as alternatives to involved-field RT (IFRT) in an effort to restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long-term toxicities associated with radiation exposure.⁶²⁻⁶⁴ ISRT targets the originally involved nodal sites and possible extranodal extensions, which generally defines a smaller field than the classical IFRT.⁶⁵

ISRT targets the initially involved nodal and extra-nodal sites as defined by the pre-treatment evaluation (physical examination, CT and PET imaging). However, it is intended to spare the adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The optimized treatment plan

for ISRT is designed using conventional, 3-D conformal RT or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR. The gross tumor volume defined by PET-CT imaging prior to chemotherapy or surgery provides the basis for determining the clinical target volume (CTV). The planning target volume (PTV) is an additional expansion of the CTV to account for any setup variations and internal organ motion.⁶⁶ PTV margins should be defined individually for each disease site.

In the setting of combined modality therapy, the panel recommends an RT dose of 30 to 36 Gy when combined with ABVD or 36 Gy with Stanford V for patients with bulky disease (all stages).^{67,68} In patients with stage I-II non-bulky disease, the recommended RT dose is 20 to 30 Gy following ABVD and 30 Gy after Stanford V.^{69,68} The recommended RT dose with BEACOPP is 30 to 36 Gy. For patients treated with RT alone (uncommon, except for NLPHL) the recommended dose is 30 to 36 Gy for the involved regions and 25 to 30 Gy for uninvolved regions. The panel recommends that high cervical regions in all patients and axillae in women always be excluded from RT fields, if those regions are uninvolved.

Treatment Guidelines

Diagnosis

Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy generally be performed. Although fine-needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, its role in the diagnosis of lymphoma is still controversial and a diagnosis of lymphoma cannot be ruled out by a negative FNA biopsy.⁷⁰⁻⁷² FNA biopsy should be avoided and is considered to be adequate along with IHC only when it is called diagnostic of HL by an expert hematopathologist or cytopathologist.

IHC evaluation is recommended. The Reed-Sternberg cells of CHL express CD15 and CD30 in the majority of patients and are usually negative for CD3 and CD45. CD20 may be detectable in less than 40% of patients. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended for CHL. NLPHL cells are usually CD45+ and CD20+, do not express CD3 or CD15, and rarely express CD30. In addition, NLPHL cells also express epithelial membrane antigen, which is usually not present in CHL. For NLPHL, 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 tests (complete blood count, differential, platelets, ESR, serum lactate dehydrogenase, albumin, and liver and renal function tests); PET/CT; and diagnostic contrast-enhanced CT. Chest x-ray is encouraged for patients with large mediastinal mass. Although diagnostic CT scans will often include neck, chest, abdomen, or pelvis, it should at minimum include involved areas identified as abnormal on PET scan. The NCCN Guidelines recommend using PET scans to define the extent of disease. However, it should be noted that PET scans may be positive in sites of infection or inflammation, even in the absence of HL. In patients with PET-positive sites outside of the disease already identified, or if the PET-positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. In patients with newly diagnosed HL undergoing pretreatment staging with PET/CT, routine bone marrow biopsy is not required if the PET scan is negative or displays a homogenous pattern of bone marrow uptake.⁷³

An adequate bone marrow biopsy should be performed if the PET scan displays multifocal (three or more) skeletal lesions or if cytopenias are present.

Evaluation of ejection fraction is recommended for most patients undergoing doxorubicin-based chemotherapy. HIV and hepatitis B testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. Pulmonary function tests including the test of the diffusion capacity of the lungs for carbon monoxide (DLCO) are recommended for patients receiving bleomycin-based chemotherapy. H-flu, pneumococcal, and meningococcal vaccines are recommended if splenic RT is contemplated. A neck CT scan is also recommended for patients in whom RT to the neck is planned.

A pregnancy test should be performed before women of childbearing age undergo treatment. Alkylating agent-based chemotherapy is associated with a higher risk of premature ovarian failure than chemotherapy with non-alkylating agent-based chemotherapy.⁷⁴ The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) prior to the initiation of chemotherapy with alkylating agents or pelvic RT.^{75,76} Oophoropexy should be considered to preserve ovarian function in pre-menopausal women if pelvic RT is contemplated.⁷⁷

Classical Hodgkin Lymphoma

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

- Stage I-II
- Stage III-IV

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

- Stage IA-IIA (favorable)
- Stage I-II (unfavorable with bulky disease)
- Stage I-II (unfavorable with non-bulky disease)

Stage I-II Favorable Disease

RT alone was a standard treatment option for patients with early-stage HL for many decades.⁷⁸ However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.⁷⁹ With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD and Stanford V) into the management of patients with early-stage disease, combined modality therapy (chemotherapy and RT) has replaced RT alone as the treatment of choice for patients with early-stage, favorable disease.

The ABVD regimen was developed as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia.⁶⁷ The Stanford V regimen is a brief but dose-intensive regimen with significantly fewer cumulative doses of doxorubicin and bleomycin than those used in ABVD, alternating MOPP/ABVD, BEACOPP, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.^{80,81} RT is an integral part of the Stanford V regimen.⁸²

Bonadonna and colleagues initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy IFRT as the standard treatment for patients with early-stage disease.⁶⁷ The HD10 trial from the GHSG

investigated the reduction of the number of cycles of ABVD as well as the IFRT dose in patients with stage I-II disease with no risk factors.⁶⁹ Patients were not eligible if they had 3 or more sites of disease, any E-lesions, bulky mediastinal adenopathy, ESR > 50, or ESR > 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to one of the 4 treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT or 2 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT.⁶⁹ The final analysis of this trial showed that (with a median follow-up of 79–91 months), there were no significant differences between 4 and 2 cycles of ABVD in terms of 5-year OS (97.1% and 96.6%), freedom from treatment failure (FFTF) (93.0% vs. 91.1%), and PFS (93.5% vs. 91.2%). With respect to the dose of IFRT, the OS (97.7% vs. 97.5%), FFTF (93.4% vs. 92.9%), and PFS (93.7% vs. 93.2%) were also not significantly different between 30 Gy and 20 Gy IFRT.⁶⁹ More importantly there were also no significant differences in OS, PFS, and FFTF among the four treatment arms. The results of the HD10 study confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment for patients with a very favorable presentation of early-stage disease with no risk factors, thereby minimizing the risk of late effects.

The G4 study conducted by the Stanford and Kaiser hospitals evaluated the efficacy of the abbreviated Stanford V chemotherapy (8 weeks or 2 cycles) followed by IFRT (30 Gy) in patients with non-bulky stage IA or IIA disease.⁶⁸ Among the 87 patients included in the study, unfavorable risk factors according to GHSG criteria (>2 nodal sites, ESR ≥ 50, or extranodal involvement) were present in 42 patients (48%), and 33 patients (38%) had unfavorable characters defined by EORTC criteria (>3 nodal sites, ESR ≥ 50, mixed cellularity, and age 50 years or older). At a median follow-up of 10.6 years, the estimated 10-year FFP, disease-specific survival, and OS rates were 94%, 99%,

and 94%, respectively. Among patients with GHSG criteria, FFP was 100% for patients with favorable disease and 88% for those with unfavorable non-bulky disease. The FFP was 98% and 88%, respectively, for patients with favorable and unfavorable disease according to EORTC criteria. No patient developed secondary acute myeloid leukemia or myelodysplastic syndrome (MDS). No late cardiac or pulmonary toxicities have been observed.

Chemotherapy with ABVD alone has also been investigated as a treatment option for patients with early-stage non-bulky disease (stage I-II or IIIA).⁸³⁻⁸⁶

In the Memorial Sloan Kettering Cancer Center (MSKCC) study, 152 patients with stages I, II, and IIIA non-bulky disease were prospectively randomized to ABVD (6 cycles) followed by IFRT or extended-field RT (36 Gy) or ABVD (6 cycles) alone. At 60-month follow-up, there were no significant differences in CR duration (91% vs. 87%, respectively; $P = .61$), FFP (86% vs. 81%, respectively; $P = .61$), and OS (97% vs. 90%, respectively, $P = .08$) among patients treated with ABVD plus radiation and those treated with ABVD alone.⁸⁴

In the multicenter study conducted by the NCIC Clinical Trials Group (HD.6), 405 patients with stage IA or IIA HL were randomized to receive ABVD (4–6 cycles) or subtotal nodal RT with or without ABVD.⁸⁵ In patients assigned to RT, those who had a favorable risk profile received subtotal nodal RT alone, and those with any of the adverse prognostic factors (high ESR, age >39, mixed cellularity or lymphocyte depleted histology, or ≥ 4 nodal sites) were treated with 2 cycles of ABVD followed by subtotal nodal RT. At a median follow-up of 12 years, OS rate was higher among patients treated with ABVD alone than those treated with subtotal nodal RT with or without ABVD (94% vs. 87%; $P = .04$).⁸⁶ However, ABVD alone was associated with a lower rate of FFP

than subtotal nodal RT with or without ABVD (87% vs. 92%; $P = .05$), and there were no significant differences in the EFS rates between the two groups (85% and 80%, respectively; $P = .60$). In the subset analysis of patients with favorable disease, there were no significant differences between any outcome for patients randomly assigned to subtotal nodal RT alone and those assigned to ABVD alone.⁸⁶ Among patients with unfavorable risk factors, the 12-year estimated OS rate was higher among patients in the ABVD-only group than among the patients who received subtotal nodal RT plus ABVD (92% vs. 81%, respectively; $P = .04$), whereas the rate of FFP was lower in the ABVD-only group (86% vs. 94%; $P = .006$) and there was no significant difference in the 12-year EFS rate (83% vs. 78%; $P = .74$) between the groups.⁸⁶ Among patients randomized to ABVD alone the FFP was significantly higher among those who achieved a CR or Cru (based on CT) after 2 cycles of ABVD than among those who did not achieve CR (12-year estimated rate of FFP 94% and 81%, respectively, $P = .02$). This study, however, was closed prematurely since the results of the EORTC H8-F study demonstrated excellent outcomes for patients with stage I-II favorable disease treated with chemotherapy and more limited RT (IFRT).⁸⁷

The results of a recent exploratory subset analysis involving patients treated in the HD10 and HD.6 trials showed that combined modality therapy provides better disease control than ABVD alone in patients with stage IA-IIA disease not achieving CR after 2 cycles of ABVD.⁸⁸

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

on PET scan after 2 to 4 cycles of ABVD, in order to avoid the long-term risks of RT.

NCCN Recommendations

Combined modality therapy (ABVD plus ISRT [category 1]⁶⁹ or Stanford V chemotherapy)⁶⁸ or chemotherapy (ABVD alone)^{21,85,86} are included as treatment options for patients with stage IA to IIA favorable disease (absence of all NCCN unfavorable risk factors: bulky mediastinal or >10 cm disease, B symptoms, ESR ≥ 50 and >3 nodal sites of disease).

In combined modality therapy, ABVD is generally administered for 4 cycles followed by 30 Gy ISRT. In patients who fulfill the GHSG criteria for favorable disease (ESR < 30 or ESR < 50 without B symptoms, no bulky disease or extralymphatic lesions, and < 3 sites of nodal disease), 2 cycles of ABVD followed by 20 Gy ISRT may be sufficient.⁶⁹ Stanford V regimen is administered for 8 weeks followed by 30 Gy ISRT which is optimally instituted within 3 weeks of completion of chemotherapy.⁶⁸ Interim restaging with PET is recommended after 4 cycles of ABVD (after 2 cycles for patients who fulfill the GHSG criteria for favorable disease) or after 8 weeks of Stanford V chemotherapy. Completion of planned course of ISRT followed by observation is recommended for patients with a Deauville score 1 to 4. Biopsy is recommended for all patients with a score of Deauville 5 after completion of chemotherapy. ISRT followed by observation is recommended for patients with a negative biopsy and patients with a positive biopsy should be managed as described for refractory disease.

Among patients treated with chemotherapy alone, ABVD is initially administered for 2 or 3 cycles followed by interim restaging. In the NCIC study (HD.6), patients assigned to ABVD alone were restaged with CT after 2 cycles.^{85,86} The FFP was superior for patients who

achieved a CR or CRu after 2 cycles of ABVD (compared to those who did not, based on CT criteria) and these patients went on to receive 2 more cycles of ABVD alone (4 total); patients who did not achieve a CR or CRu received a total of 6 cycles of ABVD. Consistent with the results of the NCIC study (HD.6), the guidelines recommend restaging with diagnostic CT of areas of initial disease after 2 cycles of ABVD. Two additional cycles of ABVD (total of 4) is recommended for patients with a CR or CRu on CT and 4 additional cycles of ABVD (total of 6) is recommended for those with a PR on CT. Restaging with PET is recommended for all patients after completion of 4 or 6 cycles of ABVD. Observation is recommended for those with a Deauville score of 1 to 3 on end of treatment PET. ISRT is recommended for patients with a Deauville score of 4 on end-of-treatment PET scan.

Two studies from Europe have evaluated the value of interim PET scans in defining the need for IFRT in patients with stage I-II favorable disease (the UK RAPID trial and the EORTC H10 trial).^{21,89} However, these trials come to somewhat different conclusions. The interim analysis of the EORTC H10 trial (n = 1137; 444 patients with stage I-II favorable disease; 693 patients with stage I-II unfavorable disease) showed that combined modality therapy (ABVD + involved-node RT) resulted in fewer early progressions compared to treatment with ABVD alone, even in patients with early stage favorable disease and a negative PET scan after 2 cycles of ABVD.⁸⁹ The RAPID trial showed that patients with stages IA-IIA disease with a negative PET scan after 3 cycles of ABVD have an excellent outcome.²¹ In this study (n = 602; 426 patients had a negative PET scan after 3 cycles of ABVD), patients with stage IA-IIA favorable disease (no B symptoms or mediastinal bulky disease) and a Deauville score of 1 to 2 on interim PET scan after 3 cycles ABVD were randomized to either IFRT (n = 209) or observation (n = 211). After a median follow-up of 45.7 months, the

estimated 3-year PFS rate was 93.8% for those treated with IFRT compared to 90.7% for those who received no further treatment. The corresponding 3-year OS rates were 97% and 99.5% respectively. The results of the RAPID trial have been published only in abstract and additional follow-up data are required to establish the impact of this approach on long-term survival.

At the present time, the panel has included the option of ABVD (3 cycles) followed by interim restaging with PET with a category 2B recommendation. Consistent with the results of the RAPID trial, no further treatment is recommended for patients with a Deauville score of 1 or 2.²¹ An additional cycle of ABVD (total of 4) plus ISRT is recommended for those with a Deauville score of 3 or 4.

Biopsy is recommended for all patients with a Deauville score of 5 after completion of treatment with ABVD (3 or 6 cycles). ISRT is recommended for patients with a negative biopsy and patients with a positive biopsy should be managed as described for refractory disease.

Stage I-II Unfavorable Disease

The HD8 trial from the GHSG investigated the efficacy of IFRT vs. extended-field RT (EFRT) in the context of combined modality therapy for patients with early-stage unfavorable HL with one or more risk factors (large mediastinal mass; extranodal disease; splenic involvement; elevated ESR with or without B symptoms; and >2 lymph node areas of involvement).⁹⁰ This trial randomized 1204 patients to 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone] plus ABVD) followed by EFRT or IFRT. RT (30 Gy plus 10 Gy to bulky sites in both arms) was initiated after chemotherapy for all patients without progressive disease. At 5 years of follow-up, FTF (85.8% for EFRT and 84.2% for IFRT) and OS (90.8% vs. 92.4%) were similar for the two groups. In contrast, acute side

effects, including thrombocytopenia, leukopenias, and gastrointestinal toxicity, were more frequent in the EFRT group. The 10-year follow-up results confirmed the non-inferiority of IFRT in terms of FTF (79.8% vs. 79.7%), PFS (79.8% vs. 80.0%), and OS (86.4% vs. 87.3%).⁹¹ IFRT was also associated with less acute toxicity and fewer secondary malignancies.

The HD11 trial from the GHSG demonstrated that 4 cycles of ABVD followed by 30 Gy IFRT is an effective treatment option for patients with early-stage unfavorable disease.⁹² In this study, 1395 patients with stage I-II unfavorable disease (stage IA, IB, or IIA with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR \geq 50 or ESR \geq 30 with B symptoms; or 3 or more involved lymph nodes and stage IIB disease with no bulky mediastinal mass or extranodal involvement) were randomized to either ABVD (4 cycles followed by 30 Gy or 20 Gy IFRT) or standard-dose BEACOPP (4 cycles followed by 30 Gy or 20 Gy IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FTF and PFS rates were 86.8% and 87%, respectively, for BEACOPP. The corresponding rates were 81% and 82%, respectively, for ABVD). However, there was no difference between the 2 regimens when followed by 30 Gy of IFRT (5-year FTF and PFS were 87% and 88%, respectively, for BEACOPP. The corresponding rates were 85% and 87%, respectively, for ABVD). BEACOPP was also associated with more toxicity than ABVD.

The results of the prospective study conducted by the Stanford group demonstrated the efficacy of Stanford V regimen followed by RT to initially bulky sites for patients with locally extensive and advanced-stage disease.⁹³ In this study, 142 patients with locally extensive mediastinal stage I or II disease or stage III or IV disease were treated with Stanford V chemotherapy (12 weeks) followed by RT

(36 Gy) to initial bulky sites (\geq 5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year FFP and OS rates were 89% and 96%, respectively. No patient progressed during treatment and there were no treatment-related deaths or secondary leukemia. Among 16 patients who relapsed, the freedom from second relapse was 69% at 5 years.

A randomized Italian study reported that ABVD and MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) were superior to the Stanford V regimen in response rate, FFS, and PFS in patients with intermediate-stage and advanced-stage HL.⁹⁴ However, interpretation of these results was difficult because the timing of response evaluation was different among the arms (8 and 12 weeks for Stanford V, 16 weeks for ABVD, and 24 weeks for MOPPEBVCAD). In addition, modifications of the RT protocol in the Stanford V arm were substantial, including limitation of the number of sites irradiated (no more than 2) and a different definition of bulky disease.

Other investigators, however, have confirmed that the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile, when RT is administered according to Stanford V protocol guidelines.⁹⁵⁻⁹⁷ In the MSKCC study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36 Gy IFRT to bulky sites (5 cm or larger) and/or to macroscopic splenic disease.⁹⁶ The 5- and 7-year OS rates were 90% and 88%, respectively. Fifty-eight percent 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). Aversa and colleagues from another Italian study group also reported similar findings in patients with

bulky or advanced disease.⁹⁵ The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (Study ISRCTN 64141244) also showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rate (ORR), the 5-year PFS and OS rates in patients with stage I to IIA with bulky disease, or other adverse features, stage IIB, III, or IV disease. RT was administered in both arms to sites of previous bulky sites (> 5 cm) and to splenic deposits.⁹⁷ At the median follow-up of 4.3 years, the ORR, 5-year PFS, and 5-year OS rates were 91%, 76%, and 90%, respectively, for ABVD. The corresponding rates were 92%, 74%, and 92%, respectively, for Stanford V.

The phase III intergroup trial (E2496) also confirmed that there were no significant differences between ABVD and Stanford V in terms of response rates, FFS, OS, and toxicity in patients with locally extensive (stage I-IIA/B and bulky mediastinal disease) and stage III-IV disease.⁹⁸ In this trial, 854 patients were randomized to ABVD (n = 428; 6–8 cycles plus 36 Gy RT only for patients with bulky mediastinal disease) or Stanford V (n = 426; 12 weeks of chemotherapy plus 36 Gy RT for sites > 5 cm or for macroscopic splenic disease). The primary endpoint was FFS, defined as the time from randomization to progression, relapse, or death, whichever occurred first. With a median follow-up of 6.4 years, there was no difference in ORR (clinical CR rates were 72.7% for ABVD and 68.7% for Stanford V), OS (88% at 5 years for both ABVD and Stanford V; $P = .86$), or FFS (74% for ABVD and 71% for Stanford V at 5 years; $P = .32$) between the two arms. Toxicity was also similar in both groups. The planned subgroup analysis showed that the outcome of patients with locally extensive disease was significantly better than that of patients with stage III-IV disease.⁹⁸ The 3-year and 5-year FFS rates were 82% for patients with locally extensive disease. The corresponding survival rates were 71% and 67%, respectively, for

patients with stage III-IV disease ($P = .001$). The 5-year OS rates were 94% and 85%, respectively ($P < .001$).

The HD14 trial of the GHSG demonstrated that BEACOPP followed by ABVD and IFRT significantly improved tumor control and PFS in patients with early-stage unfavorable disease (stage IA, IB, or IIA HL with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥ 50 [without B symptoms] or ESR ≥ 30 [with B symptoms]; or ≥ 3 involved lymph nodes) and stage IIB disease with either of the latter two risk factors).⁹⁹ In this trial, 1528 patients were randomized to 4 cycles of ABVD (n = 765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD (n = 763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FFS rate was 94.8% compared to 87.7% for ABVD ($P < .001$). The 5-year PFS rate was 95.4% and 89.1%, respectively ($P < .001$). The 5-year OS rate was not significantly different between the 2 arms (97.2% and 96.8%, respectively; $P = .731$). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs. 8.4%; $P < .001$).

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

NCCN Recommendations

Stage I-II (Unfavorable Bulky Mediastinal Disease or Adenopathy > 10 cm with or without B symptoms)

ABVD followed by ISRT (category 1)⁹² or Stanford V^{93,98} or escalated BEACOPP (2 cycles) followed by ABVD (2 cycles) and ISRT for

selected patients < 60 years⁹⁹ are included as options for patients with stage I-II unfavorable bulky disease.

In the HD14 trial that evaluated escalated BEACOPP followed by ABVD and ISRT, patients with bulky disease in combination with either B symptoms or extranodal disease were excluded.⁹⁹ These patients are managed as described for stage III-IV disease.

ABVD is initially administered for 4 cycles followed by interim restaging with PET. Patients with a Deauville score of 1 to 3 are treated with ISRT alone or in combination with 2 additional cycles of ABVD (total of 6), and those with a Deauville score of 4 are treated with 2 additional cycles of ABVD (total of 6) with ISRT. Biopsy is recommended for all patients with a Deauville score of 5 after 4 cycles of ABVD. If the biopsy is negative, patients should receive 2 additional cycles of ABVD (total of 6) with ISRT. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30 to 36 Gy) to patients with stage I-II bulky mediastinal disease or bulky disease >10 cm and/or B symptoms.^{93,98} Patients are restaged with PET at the completion of chemotherapy. ISRT to initial sites > 5 cm is recommended for all patients with a Deauville score of 1 to 4. ISRT should be instituted within 2 to 3 weeks of completion of chemotherapy. Biopsy is recommended for all patients with a Deauville score of 5 after completion of therapy. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Patients receiving escalated BEACOPP (2 cycles) and ABVD (2 cycles) are restaged after completion of chemotherapy. ISRT is recommended for those with a Deauville score of 1 to 4 and biopsy is recommended

for patients with a Deauville score of 5. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stage I-II (Unfavorable Non-bulky Disease)

ABVD is initially administered for 4 cycles followed by interim restaging with PET. ISRT or 2 additional cycles of ABVD (total of 6) is recommended for patients with a Deauville score of 1 to 3 and those with a Deauville score of 4 are treated with 2 additional cycles of ABVD alone (total of 6) followed by restaging. ISRT is recommended for those with a Deauville score of 1 to 3 or a Deauville score 4 or 5 with a negative biopsy after completion of 6 cycles of ABVD. Biopsy is recommended for patients with a Deauville score of 5 after initial treatment with 4 cycles of ABVD. Two additional cycles of ABVD (total of 6) with ISRT is recommended, if the biopsy is negative. All patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30 Gy) for patients with stage I-II unfavorable non-bulky disease based upon presence of B symptoms.⁹⁸ Patients are restaged with PET at the completion of chemotherapy as described above for patients with stage I to II unfavorable bulky disease. Patients with other unfavorable factors (elevated ESR or > 3 sites of disease) are treated with 8 weeks of Stanford V plus 30 Gy ISRT followed by restaging as described for stage IA-IIA favorable disease.⁶⁸

Restaging and additional treatment for patients treated with BEACOPP followed by ABVD are similar to that described above for patients with stage I to II (unfavorable bulky disease).

Stage III-IV

While chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.^{29,93,98}

MOPP was the first successful regimen for patients with advanced HL, with a response rate of 84% and a 66% disease-free survival of >10 years from end of treatment.¹⁰⁰ 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 CALGB showed that ABVD alone or alternating with MOPP was superior to MOPP alone in patients with newly diagnosed advanced HL (stage III-IV).¹⁰¹ 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.¹⁰² The rates of complete remission (76% vs. 80%), 5-year FFS (63% vs. 66%), and OS (82% vs. 81%) rates were similar for ABVD and MOPP/ABV, respectively. However, MOPP/ABV was associated with a greater risk for acute pulmonary and hematologic toxicity, MDS, and leukemia.

Another randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) also confirmed that there was no significant difference in EFS and OS between ABVD and other multidrug regimens in patients with advanced HL. The other multidrug regimens were more toxic than ABVD and were associated with poorer outcomes in older patients.¹⁰³ Updated results with a median follow-up of 83 months were consistent with the early results.¹⁰⁴

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

The results from prospective studies conducted by the Stanford group and other investigators have demonstrated the efficacy of Stanford V and IFRT in patients with advanced-stage disease.^{93,95-97} The recently completed phase III intergroup trial (E2496) also showed that there was no significant difference between ABVD and Stanford V (with RT, when indicated, according to Stanford V protocol guidelines) in ORR, FFS, OS, and toxicity in patients with stage III-IV disease.⁹⁸ However, among patients with high-risk disease (IPS ≥ 3), the 5-year FFS rate was significantly better for ABVD than Stanford V (67% vs. 57%; $P = .02$), but there was no significant difference in 5-year OS rate (84% vs. 77%; $P = .15$).

The efficacy of BEACOPP in patients with advanced disease was demonstrated in two phase III randomized trials conducted by the GHSG.^{105,106} In the HD9 study, 1196 patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP-ABVD, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP.¹⁰⁵ Each regimen was followed by RT to initial sites of disease greater than 5 cm. The majority of patients in each treatment arm had stage III-IV disease. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP-ABVD and significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP. The 10-year analysis confirmed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP-ABVD in terms of FFS (82%, 70%, and 64%, respectively) and OS rates (86%, 80%, and 75%, respectively). Escalated-dose BEACOPP was

significantly better than standard-dose BEACOPP in terms of FFTF ($P < .0001$) and OS ($P = .0053$).¹⁰⁶

The final results of the HD12 study ($n = 1670$) that compared 8 cycles of escalated-dose BEACOPP with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP, with or without RT, also confirmed the efficiency of escalated-dose BEACOPP for patients with advanced-stage HL who have risk factors, as reported in the HD9 trial.¹⁰⁷ In this study, at 5 years, the FFTF (86.4% and 84.8%, respectively) and PFS (87.5% and 85%, respectively) were better (although the difference was not significant) for 8 cycles of escalated-dose BEACOPP compared to 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP. The 5-year OS rate, however, was not different (92% and 90.3%, respectively).¹⁰⁷

The final analysis of the HD15 trial recently reported by Engert et al showed that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT resulted in significantly superior OS and tumor control than 8 cycles of escalated-dose BEACOPP in patients with advanced-stage disease (stage IIB with large mediastinal mass or stage III-IV).²⁹ In this study, 2182 patients were randomly assigned to one of the 3 treatment groups: 8 cycles of escalated-dose BEACOPP ($n = 728$), 6 cycles of escalated-dose BEACOPP ($n = 726$), or 8 cycles of a time-intensified standard-dose BEACOPP ($n = 728$). RT (30 Gy) was restricted to patients with PET-positive residual sites (2.5 cm or more) after chemotherapy. The 5-year FFTF rates were 84.4%, 89.3%, and 85.4%, respectively, for the 3 groups. The corresponding OS rates were 91.9%, 95.3%, and 94.5%, respectively, and were significantly better with 6 cycles of escalated-dose BEACOPP than with 8 cycles of escalated-dose BEACOPP ($P = .019$). Escalated-dose BEACOPP was also associated with less treatment-related mortality (TRM) (4.6% vs.

7.5% for 8 cycles of escalated-dose BEACOPP and 5.2% for 8 cycles of time-intensified standard-dose BEACOPP) and fewer secondary cancers (2.4% compared to 4.7% and 3.1%, respectively, for 8 cycles of escalated-dose BEACOPP and 8 cycles of time-intensified standard-dose BEACOPP). These results confirm that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT is an acceptable treatment for patients with advanced-stage disease.

Results from studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although it resulted in better tumor control in patients with advanced disease.¹⁰⁸⁻¹¹¹ However, these studies were not sufficiently powered to determine differences in OS due to small patient numbers. The long-term follow-up analysis of the HD2000 trial also showed that the risk of secondary malignancy at 10 years was significantly higher with BEACOPP than with ABVD (6.7 vs. 0.9; $P = .027$).¹¹² The ongoing EORTC 20012 trial is evaluating BEACOPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III-IV disease and IPS ≥ 3 (274 patients in the BEACOPP arm and 275 patients in the ABVD arm).¹¹⁰ The preliminary results showed that there was no improvement in OS (86.7% and 90.3, respectively, at 4 years; $P = .208$) or EFS (63.7% and 69.3%, respectively, at 4 years; $P = .312$), although the PFS was significantly better with BEACOPP (83.4% vs. 72.8% for ABVD; $P = .005$). Early discontinuations were also more frequent with BEACOPP. The median follow-up was 3.8 years.¹¹⁰ Long-term follow-up is necessary to confirm these preliminary findings.

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

The Southwest Oncology Group multicenter study showed no improvement in OS rates for patients who underwent low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, procarbazine plus bleomycin, doxorubicin, and prednisone), but the remission duration was prolonged in several subgroups, especially in patients with bulky nodular sclerosis CHL.¹¹³ In the randomized trial (EORTC 20884 trial) that assessed the role of consolidation RT following MOPP-ABV chemotherapy in patients with advanced disease, 739 patients with untreated stage III to IV disease received 6 to 8 cycles of MOPP-ABV. Patients with a CR on CT imaging after chemotherapy were randomized to no further treatment or IFRT, and those with a PR received IFRT to involved nodal areas and extranodal sites.¹¹⁴ The 8-year OS and EFS rates in the PR group were 76% and 84%, respectively. These outcomes were not significantly different in patients with a CR (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing PR after chemotherapy.

In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) that compared ABVD with two other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation.¹⁰⁴ PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was also seen for OS. The final results of the HD12 trial also showed that consolidation RT was beneficial for patients with residual disease after escalated-dose BEACOPP (FFTF was 90.4% and 87%, respectively), whereas this effect was not seen in patients with initial bulk disease who were in CR after chemotherapy.¹⁰⁷ In contrast, Laskar and colleagues reported a survival advantage for consolidative RT in patients experiencing CR after initial chemotherapy, particularly in patients younger than 15 years and in patients with B symptoms and bulky and advanced disease.¹¹⁵

However, this study included patients with a different distribution of histologic subtypes of HL than those included in Western studies, and most patients had early-stage HL. Of note, none of these studies incorporated PET scan for the evaluation of response.

In the HD15 trial, RT (30 Gy) after BEACOPP chemotherapy was restricted to those patients in PR with PET-positive residual disease (2.5 cm or more). PET-negative patients received no additional RT.²⁹ Of the 739 qualified patients with residual disease (2.5 cm or more) after 6 to 8 cycles of BEACOPP, 548 patients (74%) were PET-negative; 191 patients (26%) were PET-positive and received consolidative RT. The final analysis showed that the prognosis of patients in PR with a PET-negative persistent residual disease after chemotherapy was similar to those who were in CR as measured by conventional CT (4-year PFS was 92.1%), suggesting that consolidative RT could be omitted in patients with a PET-negative PR.²⁹ However, the use of consolidative RT was effective for patients with PET-positive PR, since the 4-year PFS in this group was 86.2%.

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.^{116,117} Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after an initial course of doxorubicin-based chemotherapy. Instead, additional courses of the same conventional chemotherapy used as initial treatment produced equivalent or better outcomes than HDT/ASCR.

NCCN Recommendations

ABVD, Stanford V (selected patients with IPS < 3), or escalated-dose BEACOPP (in selected patients < 60 years with an IPS of ≥ 4) are

included as options for primary treatment for patients with stage III-IV disease.^{29,96,98,102}

ABVD is initially administered for 2 cycles followed by restaging with PET. Patients with a Deauville score of 1 to 3 are treated with an additional 4 cycles (total of 6). Four additional cycles of ABVD (total of 6) followed by restaging are recommended for patients with a Deauville score of 4 or 5. Several ongoing studies have reported that early intensification to escalated BEACOPP in patients with a positive interim PET scan (based on the 5-PS) after 2 cycles of ABVD is associated with favorable outcomes.^{23,118,119} Based on these findings, the guidelines recommend consideration of escalated BEACOPP (4 cycles) as an alternative option for patients with a Deauville score of 4 or 5 after 2 cycles of ABVD.

Consistent with the results of the E2496 study, observation or ISRT to initially bulky or selected PET-positive sites are included as options for patients with a Deauville score of 1 to 3 after 6 cycles of ABVD.⁹⁸ Biopsy is recommended for all patients with a Deauville score of 4 to 5 after 6 cycles of ABVD. Observation or ISRT to the mediastinum (if bulky mediastinal disease was initially present) are included as options for patients with a negative biopsy. Patients with a positive biopsy should be managed as described for refractory disease. Alternatively, ISRT to PET-positive sites could be considered for patients with a Deauville score of 4.

Stanford V is administered for 12 weeks (3 cycles) followed by restaging after chemotherapy. ISRT (30–36 Gy; within 2–3 weeks after completion of chemotherapy) to initial sites > 5 cm and involved spleen is recommended for patients with a Deauville score of 1 to 4 and for those with a Deauville score of 5 with a negative biopsy.^{96,97} Patients

with a positive biopsy should be managed as described for refractory disease.

Escalated-dose BEACOPP is administered for 6 cycles followed by restaging with PET. No further treatment is necessary for patients with a Deauville score of 1 or 2. Based on the final results of the HD 12 and HD 15 trials, ISRT to residual PET-positive sites > 2.5 cm is recommended for patients with a Deauville score of 3 or 4 after 6 cycles of BEACOPP.^{29,107} Biopsy is recommended for all patients with a Deauville score of 5 after 6 cycles of BEACOPP. Observation or ISRT to the initially bulky or PET-positive sites are included as options for patients with a negative biopsy. Patients with a positive biopsy should be managed as described for refractory disease.

The feasibility of de-escalation of therapy to ABVD in patients with advanced-stage disease (IPS ≥ 3) who achieved CR after 2 cycles of escalated BEACOPP has been demonstrated in studies conducted by the Israeli Study Group.⁴⁹ Interim restaging with PET after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy to 4 cycles of ABVD may be considered in patients with a negative interim PET.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

NLPHL is characterized by an indolent course and occasional late relapse. It has a different natural history and response to therapy compared with CHL.¹²⁰ The majority of patients present with early-stage disease and rarely with B symptoms, mediastinal or extranodal involvement, and bulky disease.¹²¹⁻¹²³ In the retrospective analysis from the GHSG that included 394 patients with NLPHL, 63% had early-stage favorable, 16% had early-stage unfavorable, and 21% had advanced-stage disease. At a median follow-up of 50 months, FTF (88% vs. 82%) and OS (96% vs. 92%) were better for NLPHL

compared with CHL.¹²² Among patients with NLPHL, FFTF was better for early-stage favorable disease (93%) compared with early-stage unfavorable (87%) and advanced-stage disease (77%). The European Task Force on Lymphoma also reported favorable FFTF for early-stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or stage IV (24%) disease.¹²¹ Advanced stage at presentation, age (≥ 45 years), low hemoglobin, and the presence of B symptoms are associated with worse OS.^{122,123}

Several retrospective studies have reported favorable clinical outcomes for patients with stage I to II disease treated with RT alone¹²⁴⁻¹²⁸ or in combination with chemotherapy.^{123,129,130} RT alone is an effective treatment option for patients with stage IA-IIA disease.^{124,126} In a retrospective analysis, Schlembach and colleagues reported favorable 5-year relapse-free survival (RFS; 95%) and OS (100%) for patients with stage IA disease treated with IFRT and regional RT alone.¹²⁴ There was no evidence of secondary solid tumors even after long-term follow-up (11.6 years for IFRT and 5.5 years for regional RT). Longer follow-up is needed to define the risks for cardiac toxicity; however, mediastinal treatment is infrequently required for patients with NLPHL. Another retrospective study from the Australasian Radiation Oncology Lymphoma Group reported longer follow-up of 202 patients with stage I to II NLPHL treated with RT alone, including mantle and total lymphoid irradiation (TLI).¹²⁶ At 15 years, FFP was 84% for patients with stage I disease and 73% for those with stage II disease.

Among the studies that have evaluated the outcomes of patients treated with RT alone or combined modality treatment, the subgroup analysis of 64 patients with NLPHL included in the GHSG HD7 trial, showed a non-significant trend toward better 7-year FFTF for the combined modality group (96%) compared with the EFRT group (83%; $P = .07$).¹³⁰ However, other retrospective studies have shown no

difference in outcome between patients treated with RT alone or in combination with chemotherapy.^{125,127,128} The MD Anderson study that evaluated RFS, OS, and patterns of first recurrence in patients with stage I-II NLPHL treated with RT alone or with chemotherapy followed by RT showed that the RFS (77% and 68%, respectively) and OS (90% and 100%, respectively) were similar in the 2 treatment groups at 9.3 years and that chemotherapy did not reduce the recurrence outside the RT field.¹²⁵ The GHSG retrospectively compared 3 treatment options, including EFRT, IFRT, and combined modality treatment in patients with stage IA NLPHL.¹²⁷ 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 FFTF, suggesting that IFRT is equally as effective as EFRT and combined modality treatment. Recently, Chen and colleagues reported the long-term outcome of 113 patients with NLPHL treated at the author's institution with a median follow-up of 136 months.¹²⁸ Ninety-three patients received RT alone, 13 received RT with chemotherapy, and 7 received chemotherapy alone. The 10-year PFS rates were 85% (stage I) and 61% (stage II); OS rates were 94% and 97% for stages I and II, respectively. The addition of chemotherapy to RT did not improve PFS or OS compared with RT alone and six of seven patients who received chemotherapy alone developed early disease progression.

A recent report from the French Adult Lymphoma Study Group that analyzed the long-term outcome of 164 patients with NLPHL (82% of patients had stage IA-IIA disease) included 58 patients who were observed following diagnosis and lymph node biopsy.¹³¹ The 10-year PFS rate for this group of patients was 41% compared to 66% for patients who received specific treatment. However, the 10-year OS rate

was not different between the two groups (91% and 93% respectively) and 50% of patients treated with a watch and wait approach were in CR at a median follow-up of 3 years. Watchful waiting has also been shown to be an appropriate treatment options in pediatric patients with early-stage NLPHL who are in CR following lymph node excision.^{132,133}

Patients with advanced-stage NLPHL have a worse prognosis than those with early-stage favorable disease, and can be treated with chemotherapy. In the European Task Force on Lymphomas 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.¹²¹ Most of these patients (80%–95%) were treated with chemotherapy (MOPP- or ABVD-like regimens) with or without RT.

In the absence of randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for NLPHL, although ABVD is often used based on the data for patients with CHL. Savage et al have reported that ABVD chemotherapy with (n = 89) or without (n = 11) RT was associated with superior outcomes compared to a historical cohort of patients treated with RT alone for stage IA, IB or IIA NLPHL.¹³⁴ With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without RT had a superior 10-year TTP (98% vs. 76%), PFS (91% vs. 65%), and OS (93% vs. 84%) compared to those treated with RT alone. On the other hand, an analysis of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III-IV NLPHL treated with chemotherapy alone, showed that the failure rate was 75% for the 12 patients treated with ABVD or EVA (etoposide, vinblastine, and doxorubicin) and 32% for the 25 patients treated with alkylating agent-containing regimens (MOPP or MOPP/ABVD).¹³⁵ Some investigators have also reported good response rates with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus

rituximab^{136,137} or CVP (cyclophosphamide, vincristine, and prednisone) in patients with early-stage or advanced disease.¹³⁸

Because NLPHL cells consistently express CD20 antigen, several clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody for patients with newly diagnosed and relapsed or refractory NLPHL.¹³⁹⁻¹⁴³

In a prospective phase II trial conducted by the Stanford group, previously treated (n = 10) and untreated (n = 12) patients with stage I to IV NLPHL received 4 weekly doses of rituximab at 375 mg/m². The ORR was 100% (41% CR, 54% PR, and 5% CRu). At a median follow-up of 13 months, 9 patients had relapsed and the estimated median FFP was 10.2 months.¹³⁹ The estimated probability of disease progression at 10.2 months was 52%. Rituximab was well tolerated, with few adverse side effects.

In a GHSG phase II study that investigated rituximab in patients with newly diagnosed stage IA NLPHL (n = 28), the ORR was 100% (complete and partial remission were achieved in 86% and 14% of patients, respectively). At a median follow-up of 43 months, the OS rate was 100%; the PFS rate at 12, 24, and 36 months was 96%, 85%, and 81%, respectively.¹⁴¹ However, the relapse rate was 25%. In the GHSG phase II study that evaluated rituximab in patients with relapsed or refractory CD20-positive NLPHL (n = 15), the ORR was 94% (8 patients with CR and 6 patients with PR). At a median follow-up of 63 months, median time to progression was 33 months and the median OS was not reached.¹⁴⁰

Rituximab followed by rituximab maintenance has also been evaluated in patients with newly diagnosed and relapsed or refractory NLPHL. In a study conducted by The Stanford Group, newly diagnosed or

previously treated patients with NLPHL (n = 39) were treated with rituximab (4 weekly doses of rituximab at 375 mg/m²) or rituximab followed by rituximab maintenance (once every 6 months for 2 years).¹⁴³ The ORR was 100% (67% CR and 33% PR) at the end of initial therapy with rituximab alone. The median follow-up was 9.8 years for rituximab and 5 years for rituximab plus maintenance rituximab. The estimated 5-year PFS rate was 39.1% and 58.9%, respectively for patients treated with rituximab and rituximab followed by maintenance rituximab. The corresponding 5-year OS rates were 95.7% and 85.7%, respectively. Rituximab as initial treatment was also associated with a pattern of relapse with evidence of transformation to aggressive B-cell lymphoma, primarily in patients with intra-abdominal disease. This underscores the importance of biopsy of intra-abdominal sites of disease at initial presentation or relapse. Rituximab maintenance for 2 years was associated with a non-significant increase in median PFS compared to rituximab alone (5.6 years and 3 years, respectively; *P* = .26).

Collectively, the above data suggest that rituximab alone or in combination with chemotherapy has activity in the management of patients with newly diagnosed and relapsed NLPHL.^{139,141,143}

NCCN Recommendations

Available evidence from retrospective studies supports the use of ISRT alone as a treatment option for patients with early-stage disease.¹²⁴⁻¹²⁸

The panel recommends that ISRT (30–36 Gy) be the preferred treatment for all patients with stage IA or IIA non-bulky disease. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with or without rituximab is recommended for patients with stage IB or IIB disease and for very rare patients

presenting with stage IA or IIA bulky disease. Chemotherapy with or without rituximab with or without ISRT is recommended for all patients with stage III-IV disease. Alternatively, selected patients with stage IIIA-IVA disease can either be observed (category 2B) or treated with local RT for palliation or rituximab. Maintenance therapy with rituximab may be considered for 2 years in some patients treated with rituximab alone.¹⁴³ Abdominal involvement has been associated with the risk of transformation to an aggressive B-cell lymphoma.¹⁴³ Biopsy of persistent or new subdiaphragmatic sites should be considered to rule out transformation for patients with stage III or IV disease.

Reevaluation with PET should be done for all patients after completion of initial therapy. Observation is recommended for all asymptomatic patients with a clinical response. ISRT is recommended if not received previously. Biopsy is recommended for patients with a stable or progressive disease. Asymptomatic patients with a negative biopsy can be observed and those with a positive biopsy should be managed as described for relapsed or refractory disease.

Rituximab may be used in combination with chemotherapy regimens (ABVD, CHOP or CVP) that are most commonly used at NCCN Member Institutions. Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for patients with NLPHL.

Follow-up after Completion of Treatment

Recommendations included in the guidelines are based largely on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, since there are very few data available on the follow-up and monitoring of late effects in patients with HL, after completion of treatment.¹⁴⁴

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

Interim physical examinations and blood tests (CBC, platelets, ESR if elevated at initial diagnosis and chemistry profile) are performed every 3 to 6 months for 1 to 2 years and then every 6 to 12 months for the next 3 years and then annually. An annual influenza vaccination is recommended for all patients. In addition, patients treated with splenic RT or splenectomy should receive pneumococcal, meningococcal, and H-flu revaccination after 5 to 7 years (according to the current CDC recommendations).

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen.¹⁴⁵ In a randomized trial that compared the use of PET/CT with the combination of ultrasonography (US) and chest radiography for systematic follow-up of 300 patients with advanced stage disease, the sensitivity for the detection of relapse was similar for both procedures.¹⁴⁶ The specificity (96% vs 86%, respectively; $P = .02$) and positive predictive value (91% vs 73% respectively; $P = .01$) were significantly higher for the

combination of US and chest radiography. It is acceptable to obtain a CT scan once during the first 12 months and then as clinically indicated. However, PET scans are not recommended for routine surveillance due to the risk of false positives.³¹⁻³³

Monitoring for Late Effects

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

Secondary Cancers

Solid tumors are the most common secondary cancers and most develop more than 10 years after the completion of treatment. The risk of developing secondary cancers is highest when RT is used as a component of first-line treatment. Recent meta-analysis by Franklin and colleagues showed that the risk of developing secondary cancers was lower with combined modality treatment than with RT alone as the initial treatment.¹⁴⁷ The risk was marginally higher with combined modality treatment when compared with chemotherapy alone as initial treatment. No significant differences in the risk of developing secondary cancers were seen with IFRT vs. EFRT, although the risk of developing breast cancer was substantially higher for EFRT. Risks for secondary lung cancer, non-Hodgkin's lymphoma (NHL), and leukemia were significantly higher after treatment with chemotherapy alone, whereas combined modality therapy was associated with a higher risk for these and several other cancers.¹⁴⁸ Lung cancer and breast cancer are the most common secondary cancers in patients with HL.

Low-dose chest CT should be considered for patients at increased risk for lung cancer (patients treated with chest irradiation or alkylating

agent chemotherapy, and those with a smoking history).¹⁴⁵ Low dose chest CT is optional after 5 years for patients who were treated with nonalkylating agent chemotherapy, did not undergo RT, and have no other risk factors.

Annual breast screening [mammography and MRI] beginning no later than 8 to 10 years after completion of therapy or at age 40 (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation.¹⁴⁵ They should also be encouraged to perform monthly breast self-examination and undergo yearly breast examination by a health care professional. In a prospective study that evaluated the sensitivity and specificity of breast MRI with that of mammography in women who received chest irradiation for HL, the sensitivity of the combined MRI and mammography as a combined screening modality was higher than that of MRI or mammography alone (94% for combined MRI and mammography; 67% and 68% respectively, for MRI and mammography).¹⁴⁹ The guidelines recommend breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age, which is consistent with the recommendation of the American Cancer Society Guidelines.¹⁵⁰

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.¹⁵¹⁻¹⁵³ RT-induced cardiotoxicity is observed usually more than 5–10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Coronary CT angiography abnormalities have been detected in nearly 15% of the patients within the first 5 years after treatment and their incidence significantly increases 10 years after treatment.¹⁵⁴ In a multivariate analysis patient's age at treatment, hypercholesterolemia, hypertension, and RT dose to

the coronary artery origins, were identified as independent prognostic factors.

Based on data regarding increased long-term risk of cardiac disease, annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors is recommended.¹⁴⁵ A baseline stress test or echocardiogram and carotid US (for patients treated with neck RT) should be considered at 10 year intervals after completion of treatment.

Hypothyroidism

Abnormal thyroid function, mostly hypothyroidism, is reported in about 50% of long-term survivors who received neck or upper mediastinal irradiation.¹⁴⁴ A careful thyroid examination should be a part of the physical exam. Thyroid function tests should be done at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression

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

Pulmonary Toxicity

Bleomycin-induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose,

pulmonary irradiation, and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity. Martin and colleagues reported that BPT significantly decreases the 5-year OS rate, especially in patients 40 years or older.¹⁵⁵ They also showed that the use of growth factor with chemotherapy significantly increases the incidence of BPT (26% vs. 9%). Recently, two separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.^{156,157} Five-year EFS (87.4% vs. 80%, respectively) and OS (94.1% vs. 91.3%, respectively) rates in patients who received ABVD with no growth factors were comparable to those in patients who received prophylactic growth factor support with the ABVD regimen.¹⁵⁷

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

Refractory or Relapsed Disease

Classical Hodgkin Lymphoma

Two randomized phase III studies performed by the British National Lymphoma Investigation¹⁵⁸ and the GHSG/European Group for Blood and Marrow Transplantation¹⁵⁹ have compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvement in EFS and PFS and FTF (with no difference in OS) 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 not cured with primary treatment, even though it does not improve OS.

Some studies have suggested that patients with CR to second-line therapy prior to HDT/ASCR or those with chemosensitive disease to

second-line chemotherapy have improved outcomes following HDT/ASCR compared to those with resistant disease.^{160,161} Moskowitz et al reported that the EFS, PFS, and OS were significantly better for patients with disease responding to second-line chemotherapy (60%, 62%, and 66%, respectively) compared to those who had a poor response (19%, 23%, and 17%, respectively) ($P < .001$).¹⁶⁰ More recently Sirohi et al also reported similar findings; the 5-year OS rate was 79%, 59%, and 17%, respectively, for patients who were in CR, PR, or those with resistant disease at the time of HDT/ASCR ($P < .0001$), and the 5-year PFS rate was 69%, 44%, and 14%, respectively ($P < .001$).¹⁶¹

Several investigators have developed prognostic models to predict the outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice and colleagues used end-of-treatment to relapse interval (12 months or less) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR.¹⁶² The PFS rates were 93%, 59%, and 43%, respectively, for patients with 0, 1, or 2 of these risk factors. In a prospective study, Moskowitz and colleagues identified extranodal sites, CR duration of less than 1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR.¹⁶³ In patients with none or one factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of treatment for relapsed or refractory disease to improve EFS in poorer risk patients.¹⁶⁴ In a retrospective analysis of 422 patients with relapsed disease, Josting and colleagues from the GHSG identified time to relapse, clinical stage at relapse, and anemia at relapse as independent risk factors to develop a prognostic score that classified patients into four subgroups

with significantly different freedom from second failure and OS.¹⁶⁵ More recently, investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first CR (less than one year), detectable disease at transplant, and the presence of >1 extranodal site as adverse factors for OS.¹⁶⁶ Other groups have identified extent of prior chemotherapy,¹⁶⁷ short time from diagnosis to transplant,¹⁶⁸ and disease status at transplantation¹⁶⁹ as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome in patients with recurrent/refractory HL.¹⁷⁰⁻¹⁷³ The main potential of these prognostic factor studies is to facilitate comparison of outcomes at different centers, where the preparatory regimens may vary.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.^{163,174-181} Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),¹⁸² IGEV (ifosfamide, gemcitabine, and vinorelbine),¹⁸³ and GCD (gemcitabine, carboplatin and dexamethasone)¹⁸⁴ have also been effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials.

Bendamustine, lenalidomide, and everolimus have also shown activity in patients with relapsed or refractory HL.¹⁸⁵⁻¹⁸⁷ In an ongoing phase II trial, bendamustine was well tolerated and highly active in heavily pre-treated patients (including those who had failed HDT/ASCR) with relapsed or refractory disease, resulting in an ORR of 56% among evaluable patients (34 out of 36 patients enrolled).¹⁸⁵ The ORR by intent-to-treat analysis was 53% (33% CR and 19% PR). The median response duration was 5 months. Lenalidomide and everolimus have also shown single-agent activity in a small cohort of patients with relapsed or refractory HL, resulting in ORR of 19% and 47%, respectively.^{186,187}

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.¹⁸⁸ In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective responses and complete remissions in 75% and 34% of patients, respectively, with a median follow-up of more than 1.5 years. The median PFS for all patients and the median duration of response for those in CR were 5.6 months and 20.5 months, respectively.¹⁸⁹ Based on the results of this study, the FDA approved brentuximab vedotin for the treatment of patients with HL after failure of HDT/ASCR or at least two prior chemotherapy regimens in patients who are not candidates for HDT/ASCR. The 3-year follow-up data confirmed durable remissions in patients with disease responding to brentuximab vedotin.¹⁹⁰ After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 months and 9.3 months. In patients who achieved a complete remission on brentuximab vedotin, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.¹⁹⁰

The efficacy of brentuximab vedotin in patients with relapsed or refractory HL (prior to HDT/ASCR) was also confirmed in a recent prospective phase II study (n = 36).¹⁹¹ The best ORR was 69% (33% CR). The ORR was 75% for primary refractory disease and 66% for relapsed disease. Among 30 patients evaluable for HDT/ASCR, 27 patients (90%) successfully proceeded to HDT/ASCR.

Josting and colleagues from the GHSG reported that second-line RT may be effective in a select subset of patients with relapsed or refractory disease.¹⁹² The 5-year FFTF and OS rates were 28% and 51%, respectively. B symptoms and stage at the time of disease progression or relapse were identified as significant prognostic factors for OS. Moskowitz and colleagues have demonstrated the efficacy and

feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease.¹⁶³ At a median follow-up of 43 months, the response rate to ICE (ifosfamide, carboplatin, and etoposide) and IFRT was 88% and the EFS rate for patients who underwent HDT/ASCR was 68%. Second-line RT may be effective in patients who are in good performance status with limited-stage late relapses and without B symptoms. It may be a very effective treatment for patients with initial favorable stage I-II disease who are treated with chemotherapy alone and relapse in initially involved sites.

NCCN Recommendations for Refractory Disease

Individualized treatment is recommended since there are no data to support a superior outcome with any of the treatment modalities.

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cytoreduction and HDT/ASCR (with ISRT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of ISRT or systemic therapy with or without ISRT. Conventional-dose second-line systemic therapy may precede HDT/ASCR. ISRT is recommended when the sites of relapse have not been previously irradiated. In radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR.¹⁹³

Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should be treated with HDT/ASCR with or without ISRT or observation with or without ISRT, if HDT/ASCR is contraindicated. Additional second-line therapy (ISRT or second-line systemic therapy with or without ISRT) is recommended for patients with a Deauville score of 4 or 5. Alternatively, those with a Deauville score of 4 can be treated with HDT/ASCR with or without ISRT. Among patients with

relapsed or refractory disease, those with a CR to second-line therapy prior to HDT/ASCR have better outcomes following HDT/ASCR compared to those with resistant disease.^{160,161}

Everolimus and brentuximab vedotin are included as options for second-line systemic therapy for patients with relapsed or refractory CHL.^{187,191} Bendamustine and lenalidomide are included as options for third-line therapy for patients with relapsed or refractory CHL.^{185,186}

The use of brentuximab vedotin as consolidation therapy following HDT/ASCR was evaluated in the AETHERA trial. In this trial, 329 patients who were at high risk of progression (patients with disease refractory to front-line therapy, relapsed disease <12 months after frontline therapy, and relapsed disease ≥12 months after frontline therapy with extranodal disease) were randomized (following HDT/ASCR) to brentuximab vedotin (n = 165) or placebo (n = 164).¹⁹⁴ Patients were required to have obtained a CR, PR, or stable disease to second-line therapy prior to ASCT. The interim analysis (after a median follow-up of 30 months) showed that early consolidation with brentuximab vedotin following HDT/ASCR was associated with improved PFS and the survival benefit was demonstrated across all risk groups. The median PFS was 42.9 months in the brentuximab vedotin group and 24.1 months in the placebo group. The estimated 2-year PFS rates were 65% and 45%, respectively, for the brentuximab vedotin and placebo arms ($P = .0013$). At the time of this interim analysis, there was no statistically significant difference in OS between the two groups (HR 1.15; $P = .6204$). Brentuximab vedotin was also well tolerated. Peripheral sensory neuropathy (36%), upper respiratory tract infection (25%), neutropenia (24%) and fatigue (21%) were the most common adverse events.

Based on the results of this study, the panel has included maintenance therapy with brentuximab vedotin (for one year) following HDT/ASCR for patients with primary refractory disease or for those with disease relapse less than 12 months following primary treatment. However, the value of this approach in patients who have received prior treatment with brentuximab vedotin is not known.

Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was >50%. Allogeneic HSCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.^{195,196} However, this approach remains investigational. The panel has included allogeneic HSCT with a category 3 recommendation for patients with refractory or relapsed disease.

NCCN Recommendations for Relapsed Disease

While second-line systemic therapy is an appropriate treatment for any patient with relapsed disease, regardless of the length of initial remission,¹⁹⁷ some studies have also suggested that it may not be essential before proceeding to HDT/ASCR for patients with minimal residual disease at relapse.¹⁹⁸ In selected patients with long disease-free intervals and other favorable features, the selection of second-line therapy should be individualized.

Suspected relapse should be confirmed with biopsy. Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative. Restaging is recommended for patients with positive biopsy. Second-line systemic therapy with or without ISRT or HDT/ASCR is the preferred treatment option for patients with stage IA to IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites. RT alone (conventional or extended field treatment) may be appropriate for selected patients. All other patients

experiencing disease relapse after initial treatment with chemotherapy or combined modality therapy should be treated with second line systemic therapy.

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

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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

NCCN Recommendations

Late relapse or transformation to DLBCL has been reported in patients with NLPHL.¹⁹⁹⁻²⁰¹ In a study of 95 patients diagnosed with NLPHL, with a median follow-up of 6.5 years, transformation to aggressive lymphoma was seen in 13 (14%) patients and the actuarial risk at 10 and 20 years was 7% and 30%, respectively.²⁰¹

Re-biopsy should be considered to rule out transformation to aggressive lymphoma prior to initiation of treatment for refractory disease or suspected disease relapse. Patients with a negative biopsy can be observed. Among patients with biopsy-proven relapsed NLPHL, asymptomatic patients should be observed whereas symptomatic patients should be treated with second-line therapy (rituximab with or without chemotherapy or ISRT) followed by reevaluation. No further treatment is necessary for patients with clinical response. Biopsy is

recommended for patients with progressive disease. Maintenance rituximab for 2 years may be considered for patients treated with rituximab alone.¹⁴³ Patients with disease transformation to DLBCL should be managed as discussed in the NCCN Guidelines for Non-Hodgkin Lymphomas.

Summary

HL is an uncommon malignancy involving lymph nodes and the lymphatic system. CHL and NLPHL are the two main types of HL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL is characterized by the presence of lymphocytic and histiocytic cells.

Current management of CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5-PS). Combined modality therapy (ABVD plus ISRT or Stanford V) or ABVD alone are included as treatment options for patients with stage IA or IIA favorable CHL. Chemotherapy (ABVD or Stanford V or BEACOPP plus ABVD) followed by consolidative ISRT is recommended for patients with stage I-II unfavorable disease. Chemotherapy with ABVD or Stanford V or escalated-dose BEACOPP is recommended for patients with stage III-IV disease.

HDT/ASCR is the best treatment option for patients with refractory or relapsed CHL, although it does not improve OS. Second-line therapy (RT or second-line systemic therapy with or without RT) may be given prior to HDT/ASCR. Maintenance therapy with brentuximab vedotin (for one year) following HDT/ASCR is included as an option for patients with primary refractory disease or for those with disease relapse less than 12 months following primary treatment.

ISRT is the preferred treatment for patients with stage IA or IIA non-bulky NLPHL. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with or without rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky disease. Chemotherapy with or without rituximab with or without ISRT is recommended for all patients with stage III-IV disease. Alternatively, selected patients with stage IIIA-IVA disease can either be observed or treated with local RT or rituximab. Maintenance rituximab for 2 years may be considered for patients treated with rituximab alone.

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

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

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Discussion
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