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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 2.2022 — February 23, 2022

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Hodgkin Lymphoma

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‡ Hematology/ Hematology oncology	¶ Patient advocacy
¶ Internal medicine	€ Pediatric oncology
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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

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

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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

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Updates in Version 2.2022 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2022 include:

MS-1

- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2022 of the NCCN Guidelines for Hodgkin Lymphoma from Version 4.2021 include:

General

- Footnote h remains on HODG-1 but has been removed from HODG-3 through HODG-7.

HODG-1

- Workup, essential
 - Second bullet modified: CBC, differential; platelets
 - Sixth bullet modified: Pregnancy test for women of childbearing age *prior to cytotoxic chemotherapy or RT*
- Footnote b modified: ...EBER-ISH is recommended at initial diagnosis (*CHL: EBER±; NLPHL: EBER-*). An expanded panel of markers (eg, MUM-1, BOB-1, OCT-2) may be required, especially if equivocal diagnosis. See NCCN Guidelines for B-Cell Lymphomas. For NLPHL, immunoarchitectural pattern should be specified as *A or B* (typical) vs. *C–F* (variant).
- Footnote c modified: See Principles of FDG-PET/CT (HODG-A). ~~PET/CT should be done with patient on a flat table with arms up, if possible. In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1).~~
- Footnote e added: See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology for more details on fertility/fertility preservation, and psychosocial assessments in AYA patients.

HODG-2

- Column added to table for "ESR >50 or # Sites >3"
- Column added to table for "Type"

HODG-3

- Deauville 3, additional therapy, first combined modality therapy option modified: "ISRT 20 Gy (per GHSG HD40/16..."
- Footnote moved to HODG-A: An integrated PET/CT or a PET with a diagnostic CT is recommended. [See Principles of FDG-PET/CT \(HODG-A\). \(Also on HODG-4 through HODG-7\)](#)
- ~~Footnote q modified: ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D). (Also on HODG-4, HODG-8, and HODG-11 through HODG-13)~~

HODG-4

- Box added with "Special considerations for Deauville 4–5 after ABVD x 2 cycles" (Also on HODG-5)
- Deauville 4–5 after ABVD x 2 cycles
 - After therapy with Escalated BEACOPP x 2 cycles, if Deauville 1–3, added "(adapted from RATHL)" to the chemotherapy alone option of escalated BEACOPP x 2 cycles
 - ◊ Modified combined modality therapy option: ISRT 30 Gy (adapted from HD44, HD44, H10U)
- Footnote s added to this page: Escalated BEACOPP is only an option for those aged <60 y.

HODG-5

- Primary treatment
 - Option modified: Brentuximab vedotin + AVD (category 2B) (category 2A in select patients; eg, no known neuropathy, IPS ≥4v or bleomycin contraindicated) *(Use with caution in patients aged >60 y; contraindicated in those with neuropathy)* (Also on HODG-6)
 - Brentuximab vedotin + AVD has been moved from "Useful in certain circumstances" to "Other recommended regimen"
- Following primary treatment with ABVD x 2 cycles, Deauville 4–5 at restaging, and then escalated BEACOPP x 3 cycles:
 - Option modified for those with Deauville 1–3 after restaging: Escalated BEACOPP x 1 cycle ± ISRT (Also on HODG-7)

[Continued](#)

UPDATES



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Updates in Version 1.2022 of the NCCN Guidelines for Hodgkin Lymphoma from Version 4.2021 include:

HODG-6

- Footnote o modified: A Deauville 5 score *may should* prompt re-biopsy... (Also on HODG-7)

HODG-7A

- References updated.

HODG-8

- CS III-IV, primary treatment, option was moved from the last option to the first option: Observe, if asymptomatic
- Modified: ~~Re-evaluation~~ *Restage* with PET/CT
- Footnote removed: ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).
- Footnote ff modified: Generally a brief course of chemotherapy (3–4 2–4 months) would be given with radiation therapy.

HODG-9

- Follow-up After Completion of Treatment Up to 5 Years:
 - ▶ Bullet modified: *Consider* neck/chest/abdomen/pelvis CT scan with contrast no more often than every 6 mo for the first 2 y following completion of therapy, or as clinically indicated *after 2 y, especially in NLP HL where late relapse may occur.*

HODG-11

- Additional therapy, Deauville 4
 - ▶ Arrow added from RT to "If response, consider transplant (autologous or allogeneic)"
 - ▶ Arrow added from subsequent systemic therapy ± RT to "if response, consider transplant (autologous or allogeneic)"

HODG-13

- After "Biopsy negative," option added: Observe with short-interval follow-up (see HODG-9).
- NLP HL, after second-line therapy, modified: ~~Reevaluation~~ *Restage* with PET/CT after treatment
- Footnote uu modified: At relapse, ~~patient should be considered for re-biopsy should be considered~~ because of risk for transformation...

HODG-A

- Bullet added (previously footnote on HODG-3): An integrated PET/CT or a PET with a diagnostic CT is recommended for initial diagnosis and restaging.
- Bullet added (previously footnote on HODG-1): PET/CT should be *done performed* with patient on a flat table with arms up, if possible. In cases of PET positivity where ~~disease 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 the patient. See (ST-1).

HODG-B (1 of 2)

- Heading modified: ~~PRINCIPLES OF UNFAVORABLE RISK FACTORS~~
- Table heading modified: Unfavorable Risk Factors for Stage I–II ~~Classic~~ Hodgkin Lymphoma

HODG-C (1 of 5)

- Reference updated for brentuximab vedotin + AVD: Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol* 2021;8:e410–e421.

HODG-C (3 of 5)

- Table headings modified:
 - ▶ *Second-Line and Subsequent Therapy*
 - ▶ *Third-Line and Subsequent Therapy*
- Second-line and subsequent therapy for relapsed/refractory CHL
 - ▶ Option added: GVD + pembrolizumab
- Third-line and subsequent therapy for relapsed/refractory CHL
 - ▶ Option modified: GCD (gemcitabine, ~~carboplatin~~ *cisplatin*, dexamethasone)

HODG-C (4 of 5)

- References have been updated.

HODG-E (1 of 2)

- Relapsed or refractory disease
 - ▶ Last bullet modified for consistency with changes on HODG-C (3 of 5): Second-line, *third-line* and subsequent therapy options (only for CHL) as listed on Principles of Systemic Therapy for Relapsed or Refractory Disease HODG-C (3 of 5).



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DIAGNOSIS/WORKUP

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

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, examination of lymphoid regions, spleen, liver
- CBC, differential
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for women of childbearing age prior to cytotoxic chemotherapy or RT
- PET/CT scan (skull base to mid-thigh or vertex to feet in selected cases)^c
- Counseling: Fertility/psychosocial^d and smoking cessation ([See NCCN Guidelines for Smoking Cessation](#))

Useful in selected cases:

- Fertility preservation^{d,e}
- Pulmonary function tests ([PFTs] including diffusing capacity [DLCO])^f if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV and hepatitis B/C testing (encouraged)
- Diagnostic CT^g (contrast-enhanced)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- Adequate bone marrow biopsy if there are unexplained cytopenias other than anemia (eg, thrombocytopenia or neutropenia) and negative PET^h
- Evaluation of ejection fraction if anthracycline-based chemotherapy is indicated
- MRI of select sites, with contrast unless contraindicated
- PET/MRI (skull base to mid-thigh) without contrast

CLINICAL PRESENTATION

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

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) → [See HODG-8](#)

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

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

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

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

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

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

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

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

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

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

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



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Hodgkin Lymphoma (Age ≥18 years)

CLINICAL STAGING/RISK CLASSIFICATION OF CLASSIC HODGKIN LYMPHOMA (CHL)^j

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

- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- Most patients will benefit from multidisciplinary input prior to final treatment decisions.

^j For definitions of bulky disease and lymph node regions, [see HODG-B](#).

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Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION: Stage IA/IIA Favorable (Non-Bulky) Classic Hodgkin Lymphoma^k

Important Considerations:

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

PRIMARY TREATMENT

Stage IA/IIA
Favorable
(Non-bulky)
CHL

ABVD x
2 cycles^l
(category 1)

Restage
with
PET/CT^c

Deauville
1–2^m

Deauville
3^m

Deauville
4^{m,n}

Deauville
5^{m,o}

ADDITIONAL THERAPY

Chemotherapy alone

ABVD x 2 cycles (per H10F, CALGB)^{p,1,2}

or
ABVD x 1 cycle (per RAPID)³

Combined modality therapy

Involved-site radiation therapy (ISRT) 20 Gy^q (per GHSG HD16; if ESR <50, no e-lesions, <3 nodal sites per GHSG favorable criteria)⁴

or
ABVD x 1 cycle + ISRT 30 Gy^q (per RAPID, H10F)^{2,3}

Chemotherapy alone

AVD x 4 cycles (per RATHL)⁵

Deauville
1–3^m

ISRT 30 Gy^q (adapted
from RAPID, H10)^{2,3}

Deauville
4–5^{m,o}

Biopsy^o

Negative

Positive

Biopsy^o

Negative

Positive

[See
Follow-up
\(HODG-9\)](#)

[See
Refractory
Disease
\(HODG-11\)](#)

[See Refractory Disease \(HODG-11\)](#)

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

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

^l See Principles of Systemic Therapy (HODG-C).

^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).

ⁿ The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy. (eg, If only focally positive, it may be feasible to continue with 2 more cycles of ABVD and then repeat the PET scan.) For a scan that remains positive throughout the area(s) of initial disease the consensus is to escalate therapy (with consideration of biopsy, especially if an easily accessible site).

^o A Deauville 5 score should prompt re-biopsy, especially if a readily accessible site, which would then inform subsequent therapy. If a biopsy is not performed, treatment should be escalated.

^p Consider PFTs after 4 cycles of ABVD.

^q See Principles of Radiation Therapy (HODG-D).

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

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For references 1–5,
[see HODG-7A](#)



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Hodgkin Lymphoma (Age ≥18 years)

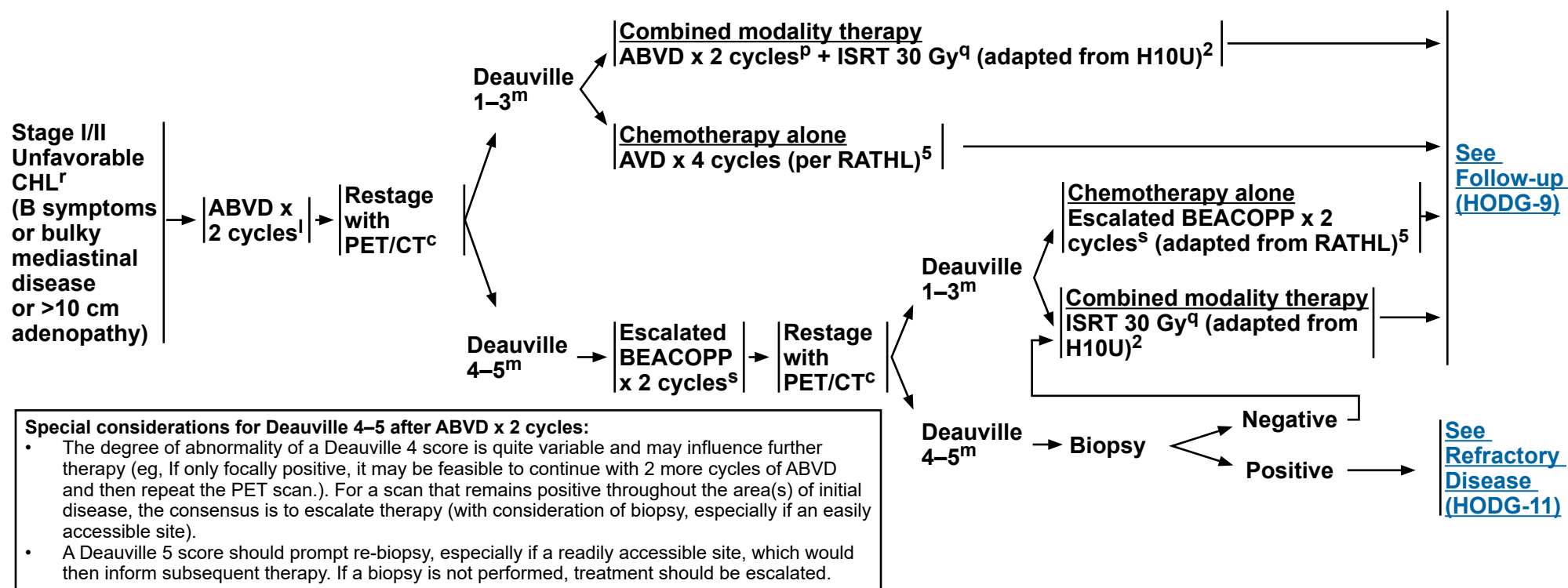
CLINICAL PRESENTATION: Stage I/II Unfavorable Classic Hodgkin Lymphoma^k (B symptoms or bulky mediastinal disease or >10 cm adenopathy)

Important Considerations:

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

PRIMARY TREATMENT^k

ADDITIONAL THERAPY



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

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

^l See Principles of Systemic Therapy (HODG-C).

^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).

^p Consider PFTs after 4 cycles of ABVD.

^q See Principles of Radiation Therapy (HODG-D).

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

^s Escalated BEACOPP is only an option for those aged <60 y.

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

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**For references 2, and 5
see HODG-7A**



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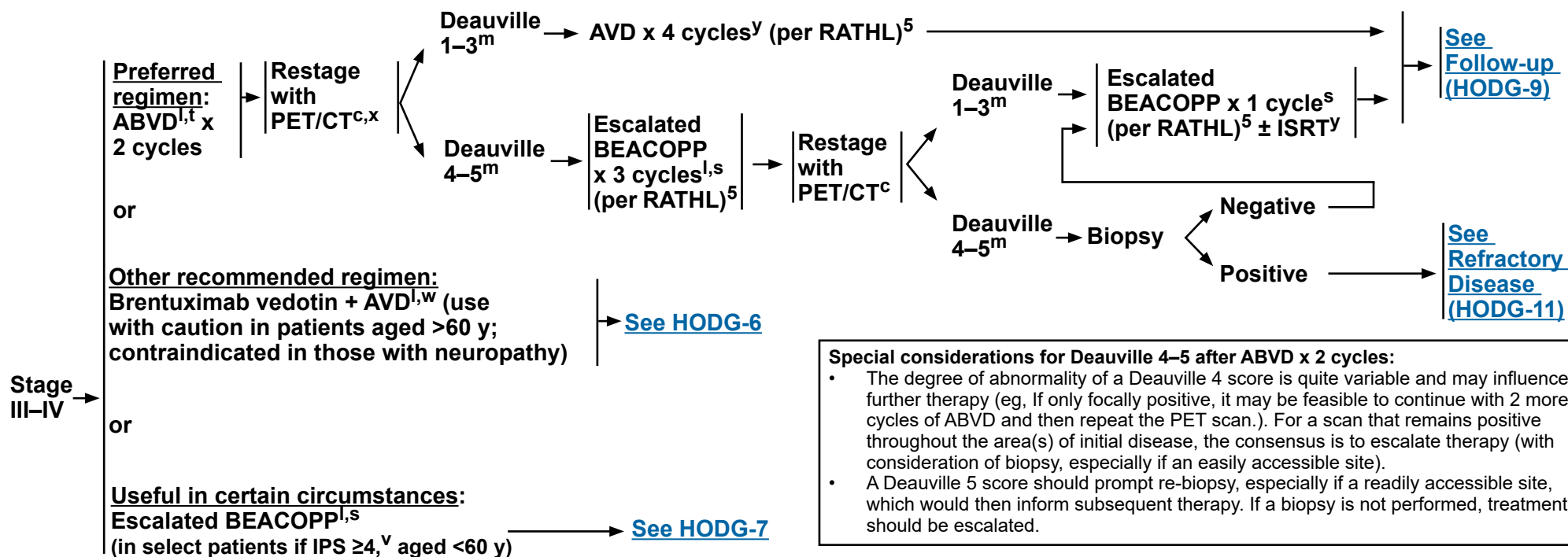
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CLINICAL PRESENTATION: Stage III–IV Classic Hodgkin Lymphoma^k

PRIMARY TREATMENT^k



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

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

^l See Principles of Systemic Therapy (HODG-C).

^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).

^s Escalated BEACOPP is only an option for those aged <60 y.

^t ABVD is preferred based on the toxicity profile and quality of data.

^v See International Prognostic Score (IPS) (HODG-B).

^w All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.

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

^y Consider ISRT to initially bulky or PET-positive sites. See Principles of Radiation Therapy (HODG-D).

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**For reference 5,
see HODG-7A**



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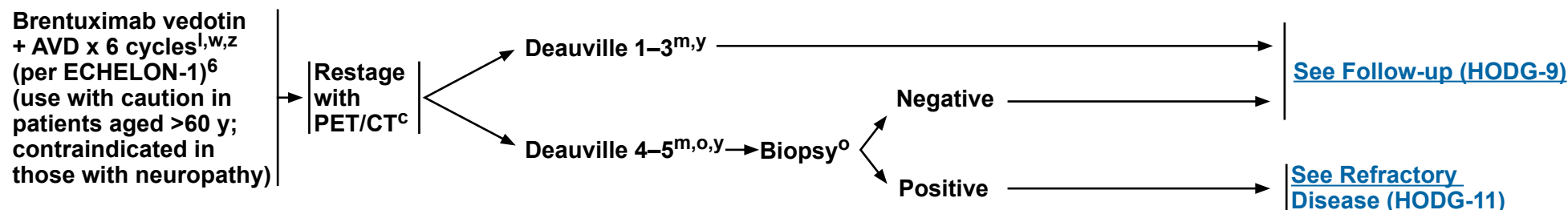
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CLINICAL PRESENTATION: Stage III–IV Classic Hodgkin Lymphoma

PRIMARY TREATMENT^k (continued from [HODG-5](#))



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

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

^l See Principles of Systemic Therapy (HODG-C).

^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).

^o A Deauville 5 score should prompt re-biopsy, especially if a readily accessible site, which would then inform subsequent therapy. If a biopsy is not performed, treatment should be escalated.

^w All cycles include growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.

^y Consider ISRT to initially bulky or PET-positive sites. See Principles of Radiation Therapy (HODG-D).

^z If performing an interim PET/CT before completion of 6 cycles, and PET is positive (Deauville 5), conduct a biopsy; if biopsy positive, change therapy.

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

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**For reference 6,
see [HODG-7A](#)**

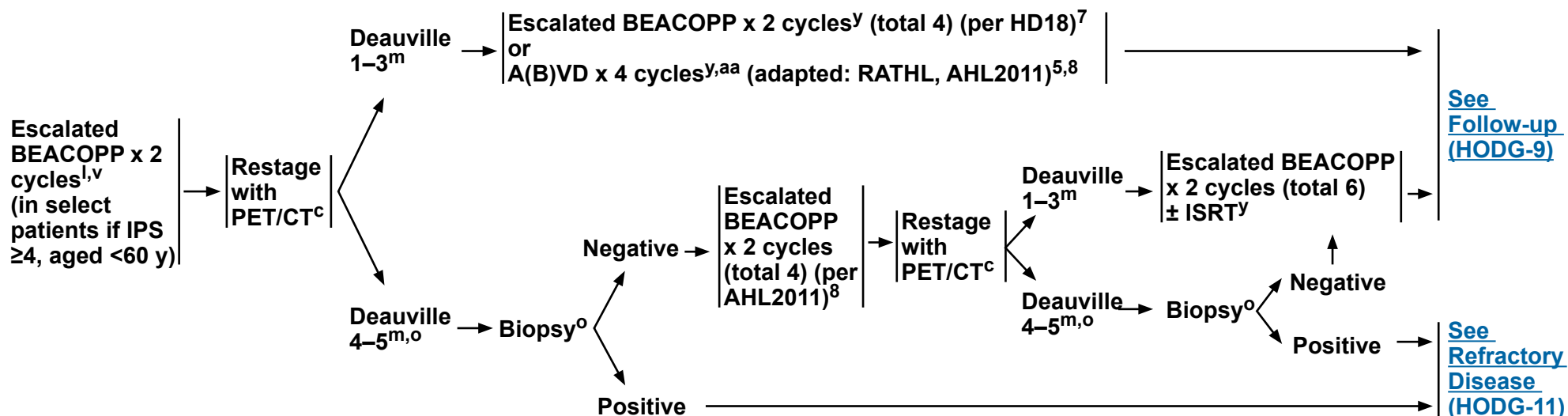


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CLINICAL PRESENTATION: Stage III–IV Classic Hodgkin Lymphoma

PRIMARY TREATMENT^k (continued from [HODG-5](#))



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

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

^l See Principles of Systemic Therapy (HODG-C).

^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).

^o A Deauville 5 score should prompt re-biopsy, especially if a readily accessible site, which would then inform subsequent therapy. If a biopsy is not performed, treatment should be escalated.

^v See International Prognostic Score (IPS) (HODG-B).

^y Consider ISRT to initially bulky or PET-positive sites. See Principles of Radiation Therapy (HODG-D).

^{aa} Bleomycin is optional.

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For references 5, 7, and 8, see [HODG-7A](#)



NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

CLASSIC HODGKIN LYMPHOMA PRIMARY TREATMENT REFERENCES

- ¹ CALGB 50604: Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. *Blood* 2018;132:1013-1021.
- ² EORTC/LYSA/FIL H10: André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2017;35:1786-1794.
- ³ RAPID study: Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015;372:1598-1607.
- ⁴ GHSG H16: Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol* 2019;37:2835-2845.
- ⁵ RATHL study: Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 2016;374:2419-2429.
- ⁶ ECHELON-1: Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol* 2021;8:e410-e421.
- ⁷ GHSG HD18: Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 2018;390:2790-2802.
- ⁸ AHL2011: Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol* 2019;20:202-215.

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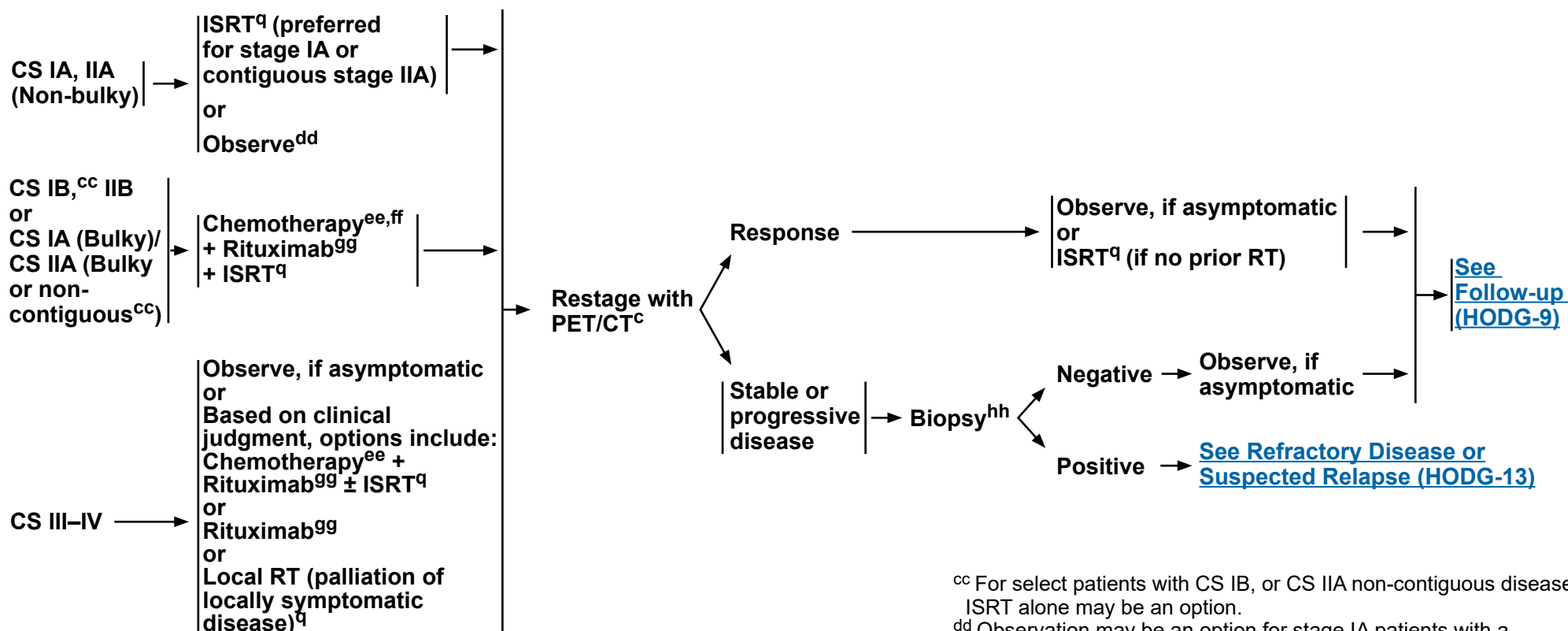


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Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION: Nodular Lymphocyte-Predominant Hodgkin Lymphoma^{bb}

PRIMARY TREATMENT



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

^q See Principles of Radiation Therapy (HODG-D).

^{bb} NLPHL has a different natural history and response to therapy than CHL, especially stages I–II.

For that reason, separate guidelines are presented for NLPHL. Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma. Data suggest outcomes differ for typical immunoarchitectural patterns (A/B) versus variant patterns (C/D/E/F). (Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2017).

^{cc} For select patients with CS IB, or CS IIA non-contiguous disease, ISRT alone may be an option.

^{dd} Observation may be an option for stage IA patients with a completely excised solitary lymph node. See Follow-up (HODG-9).

^{ee} See Principles of Systemic Therapy (HODG-C, 2 of 5).

^{ff} Generally, a brief course of chemotherapy (2–4 mo) would be given with radiation therapy (RT).

^{gg} An FDA-approved biosimilar is an acceptable substitute for rituximab.

^{hh} Biopsy is recommended for sites of progressive disease, especially subdiaphragmatic sites, to rule out transformation.

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Hodgkin Lymphoma (Age ≥18 years)

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

- Complete response 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 therapy, including details of radiation therapy (RT), organs at risk (OARs), and cumulative anthracycline dosage given.
- Follow-up with an oncologist is recommended and should be coordinated with the primary care physician (PCP), especially during the first 5 y after treatment to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease ([see NCCN Guidelines for Survivorship](#)).^{ii,jj} 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 and other vaccines as clinically indicated ([see NCCN Guidelines for Survivorship](#)).
- Laboratory studies^{kk}:
 - ▶ 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.
- Consider neck/chest/abdomen/pelvis CT scan with contrast no more often than every 6 mo for the first 2 y following completion of therapy, or as clinically indicated after 2 y, especially in NLPHL where late relapse may occur. PET/CT only if last PET was Deauville 4–5, to confirm complete response.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-examination, 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-12](#)) or NLPHL ([HODG-13](#))

[Follow-Up and Monitoring After 5 Years \(HODG-10\)](#)

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

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

^{kk} Lynch RC, Sundaram V, Desai M, et al. Utility of routine surveillance laboratory testing in detecting relapse in patients with classic Hodgkin lymphoma in first remission: Results from a large single-institution study. JCO Oncol Pract 2020;16:e902-e911.

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NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

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

Follow-up and Monitoring After 5 Years^{ii,jj}

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

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

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

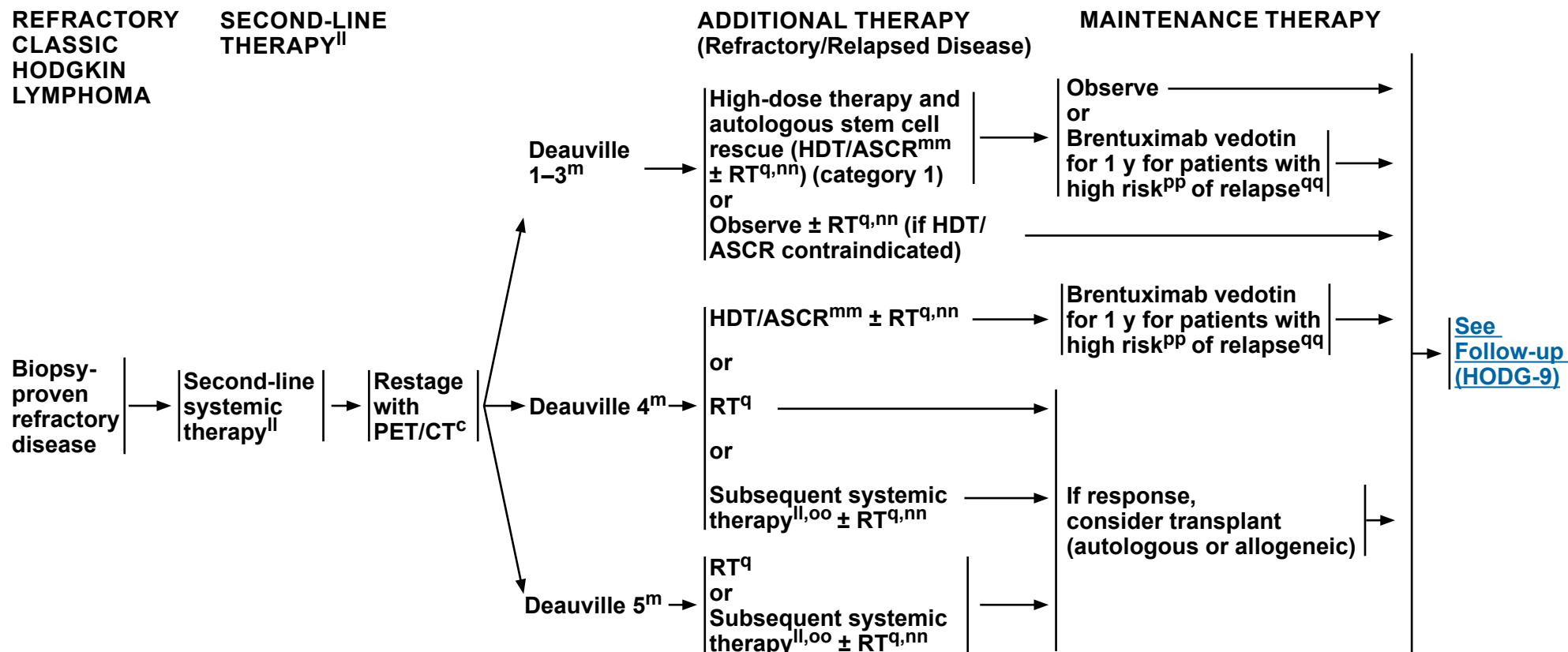
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Hodgkin Lymphoma (Age ≥18 years)

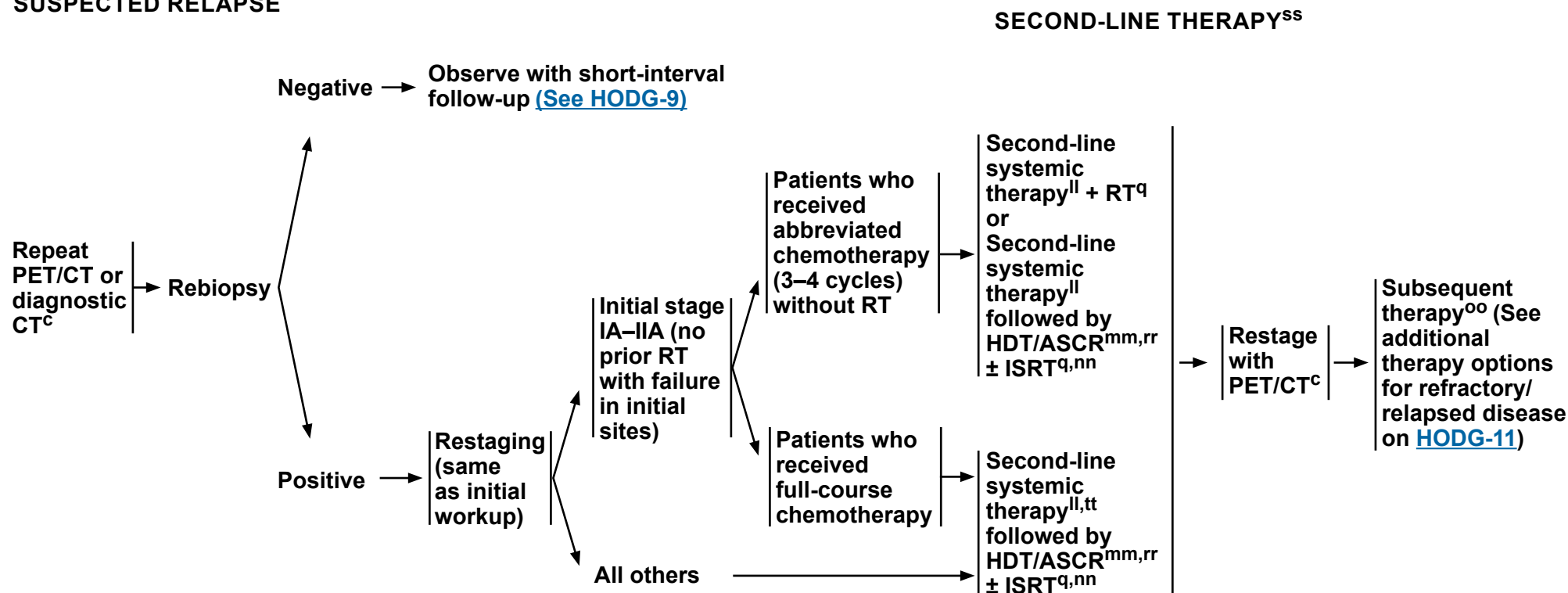
^c See Principles of FDG-PET/CT (HODG-A).^m See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).^q See Principles of Radiation Therapy (HODG-D).^{II} See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C, 3 of 5).^{mm} Strongly consider RT for selected sites that have not been previously irradiated. In a radiation-naïve patient, total lymphoid irradiation (TLI) may be an appropriate component of HDT.ⁿⁿ Conventional-dose chemotherapy may precede HDT. Timing of RT may vary.^{oo} Subsequent systemic therapy options include second-line therapy options that were not previously used (See HODG-C, 3 of 5).^{pp} Patients with 2 or more of the following risk factors are considered high risk: Remission duration <1 year, extranodal involvement, PET+ response at time of transplant, B symptoms, and/or >1 salvage/subsequent therapy regimen.^{qq} The role of maintenance brentuximab vedotin has not been well-defined in patients who received brentuximab vedotin prior to maintenance therapy.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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Hodgkin Lymphoma (Age ≥18 years)

CLASSIC HODGKIN LYMPHOMA SUSPECTED RELAPSE



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

^q See Principles of Radiation Therapy (HODG-D).

^{ll} See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C, 3 of 5).

^{mm} Strongly consider RT for selected sites that have not been previously irradiated. In a radiation-naïve patient, TLI may be an appropriate component of HDT.

ⁿⁿ Conventional-dose chemotherapy may precede HDT. Timing of RT may vary.

^{oo} Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 5).

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

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

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

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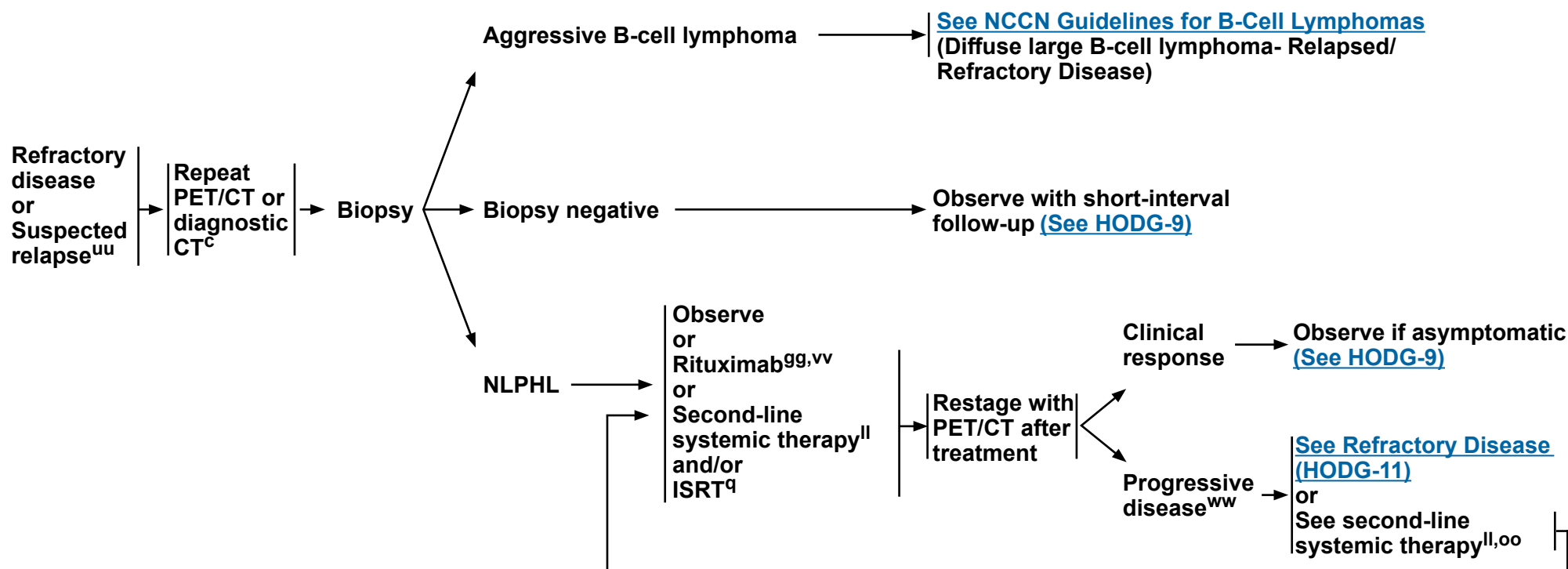


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Hodgkin Lymphoma (Age ≥18 years)

NLPHL REFRACTORY OR SUSPECTED RELAPSE

SECOND-LINE THERAPY^{ss}



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

^q See Principles of Radiation Therapy (HODG-D).

^{gg} An FDA-approved biosimilar is an acceptable substitute for rituximab.

^{ll} See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C, 3 of 5).

^{oo} Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 5).

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

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

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

^{ww} Consider rebiopsy to rule out transformation.

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NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF FDG-PET/CT

Technique

- An integrated PET/CT or a PET with a diagnostic CT is recommended for initial diagnosis and restaging.
- For FDG-PET/CT performed in the staging or response assessment in Hodgkin lymphoma (HL), image acquisition should be obtained in accordance with the American College of Radiology (ACR) practice parameter guidelines¹ or the Society of Nuclear Medicine and Molecular Imaging (SNMMI), which adopted the European Association of Nuclear Medicine (EANM) procedure guidelines for tumor imaging: version 2.0 (with the exception that the "SUV max" is used in the United States as the quantitative measurement).²
 - ▶ PET/CT should be performed with the patient on a flat table with arms up, if possible. In cases of PET positivity where disease sites are inconsistent with usual presentation of HL or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage the patient. [See \(ST-1\)](#).
- FDG-PET/CT scans obtained outside of these parameters (eg, in outdated mobile tomographs) can result in both false-negative and false-positive tests, and lead to inappropriate patient management. In these cases, consideration should be made for repeating the study on an acceptable PET/CT tomograph.

Timing

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

Interpretation

- The panel supports the ACR¹ and SNMMI² recommendation for PET/CT interpretation, including the requirement that PET/CT examinations should be performed under the supervision of and interpreted by a physician with the following qualifications:
 - ▶ Board certification in radiology or diagnostic radiology, nuclear radiology, or nuclear medicine
 - OR
 - ▶ Completion of a formal Accreditation Council for Graduate Medical Education (ACGME)-approved general nuclear medicine program in addition to 1000 hours of clinical training in general nuclear medicine, 20 hours of continuing medical education (CME) in PET, and at least 150 oncologic PET/CT examinations interpreted or multi-read during the previous 3 years.¹
- Continuing experience/education should include interpretation of a minimum of 150 PET/CT examinations in 3 years (multi-read is acceptable) and completion of 150 hours (including 75 hours of Category 1 CME) during the preceding 3 years pertinent to the physician's practice patterns, including PET imaging.¹
- The interpreting radiology or nuclear medicine physician should have adequate training and CME/experience in interpreting PET/CT for patients with lymphoma, including use of the Deauville 5-point scoring system.
- The final report for any PET/CT examination to define response should include the Deauville 5-point scale score, which is a visual score.
- A second opinion/overread is encouraged of scans that are not initially interpreted by qualified individuals, when there is a discrepancy between the clinical presentation and radiology report, and/or when no appropriate Deauville score has been provided.

¹ American College of Radiology. ACR-SPR Practice Parameters for Performing FDG-PET/CT in Oncology. 2016. Available at: <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/FDG-PET-CT.pdf?la=en>. Accessed November 19, 2021.

² Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42:328-354.

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Hodgkin Lymphoma (Age ≥18 years)

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

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

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

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

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Hodgkin Lymphoma (Age ≥18 years)

UNFAVORABLE RISK FACTORS

Unfavorable Risk Factors for Stage I–II Hodgkin Lymphoma

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

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

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

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

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

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

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NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

UNFAVORABLE RISK FACTORS

Definitions of Lymph Node Regions*

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

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

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY

Primary Systemic Therapy Regimens

Classic Hodgkin Lymphoma

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

Regimens and References (listed in alphabetical order)

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

Engert A, Plütschow 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.

André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2017;35:1786-1794.

Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 2010;28:4199-4206.

Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. *Blood* 2018;132:1013-1021.

ABVD followed by escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) ± ISRT

Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. *Blood* 2018;132:1013-1021.

Escalated BEACOPP

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

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

Escalated BEACOPP followed by ABVD with ISRT

von Tresckow B, Plütschow 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.

Brentuximab vedotin + AVD (doxorubicin, vinblastine, and dacarbazine)

Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol* 2021;8:e410-e421.

[See Principles of Systemic Therapy for NLP HL \(HODG-C, 2 of 5\)](#)

[See Principles of Systemic Therapy for Relapsed or Refractory Disease \(HODG-C, 3 of 5\)](#)

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NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY

Primary Systemic Therapy Regimens

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

• The most common chemotherapy regimens used at NCCN Member Institutions for NLPHL are listed below.^a

Regimens and References (listed in alphabetical order)

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab^b

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^b

Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. *Blood* 2017;130:472-477.

CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab^b

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^b

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;111:109-111.

Eichenauer DA, Fuchs M, Plütschow 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, Plütschow A, Fuchs M, et al. Long-term course of patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma: A report from the German Hodgkin Study Group. *J Clin Oncol* 2015;33:2857-2862.

^a 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.

^b An FDA-approved biosimilar is an acceptable substitute for rituximab.

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY RELAPSED OR REFRACTORY DISEASE

Relapsed/Refractory Disease		
	Second-Line and Subsequent Therapy ^{c,d} (in alphabetical order)	Third-Line and Subsequent Therapy ^{c,d} (in alphabetical order)
CHL	<ul style="list-style-type: none"> • Brentuximab vedotin¹ • Brentuximab vedotin + bendamustine² • Brentuximab vedotin + nivolumab³ • DHAP (dexamethasone, cisplatin, high-dose cytarabine)^{4,5} • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)^{6,7,8} • Gemcitabine/bendamustine/vinorelbine⁹ • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)¹⁰ • GVD + pembrolizumab¹¹ • ICE (ifosfamide, carboplatin, etoposide)^{5,12,13} • IGEV (ifosfamide, gemcitabine, vinorelbine)¹⁴ • Pembrolizumab^{15,16} (for patients not candidates for transplant) 	<ul style="list-style-type: none"> • Bendamustine¹⁷ • Bendamustine + carboplatin + etoposide¹⁸ • C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone)^{19,20} • Everolimus²¹ • GCD (gemcitabine, cisplatin, dexamethasone)²² • GEMOX (gemcitabine, oxaliplatin)²³ • Lenalidomide²⁴ • MINE (etoposide, ifosfamide, mesna, mitoxantrone)²⁵ • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)^{26,27} • Nivolumab^{28,29} (see indications below) • Pembrolizumab^{15,16} (see indications below)
NLPHL^d	<ul style="list-style-type: none"> • R (rituximab)^b + Bendamustine³⁰ • R^b + DHAP^{4,5} • R^b + ESHAP^{6,7,8} • R^b + ICE^{5,12} • R^b + IGEV¹⁴ • If not previously used: <ul style="list-style-type: none"> ▶ R^b-ABVD³¹ ▶ R^b-CHOP³² ▶ R^b-CVbP³³ 	

General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed/Refractory CHL^{e,f}

- CPI are recommended for any patients with CHL that has relapsed or progressed after HDT/ASCR ± brentuximab vedotin.³⁴
- CPI are also an option for patients with relapsed/refractory CHL who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy.
- Post-allogeneic transplant, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic transplantation; CPI should be used with caution before allogeneic transplantation due to increased risk of GVHD (graft-versus-host disease) and other immunologic complications.

^b An FDA-approved biosimilar is an acceptable substitute for rituximab.

^c Choice depends on prior therapies and prior toxicities. There are no preferred second-line or subsequent therapy options.

^d Subsequent systemic therapy options include second-line therapy options that were not previously used.

^e National Institutes of Health. Nivolumab package insert. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f570b9c4-6846-4de2-abfa-4d0a4ae4e394>. Accessed November 19, 2021.

^f National Institutes of Health. Pembrolizumab package insert. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287>. Accessed November 19, 2021.

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE

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NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY¹⁻¹⁷

General Principles

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced RT technologies such as intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), breath hold or respiratory gating, and/or image-guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important 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. For optimal mediastinal treatment planning, organs/tissues to be contoured should include the lungs, heart, coronary arteries, and left ventricle.
- The demonstration of significant dose-sparing for these OARs reflects best clinical practice, as it reduces the risk of late complications from normal tissue damage. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- In mediastinal HL, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion and minimize dose to OARs are essential, especially deep inspiration breath-hold techniques, respiratory gating, and image-guided RT during treatment delivery. Breath-hold techniques have been shown to decrease incidental dose to the heart and lungs in many disease presentations.
- Although the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, the "low-dose bath" to normal structures such as the breasts must be considered in choosing the final RT technique. In any case, 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^a–30 Gy (if treated with ABVD); 1.5–2.0 Gy per fraction
 - ▶ Non-bulky disease (stage IB–IIB): 30 Gy; 1.5–2.0 Gy per fraction
 - ▶ Bulky disease sites (all stages): 30–36 Gy; 1.5–2.0 Gy per fraction
 - ▶ Sites of partial response to chemotherapy: 36–45 Gy
- ISRT Alone (uncommon, except for NLPHL)
 - ▶ Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5–2.0 Gy per fraction
 - ▶ Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT for NLPHL includes extension to clinically relevant initially uninvolved nodes.
- Palliative RT: 4–30 Gy

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

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References



NCCN Guidelines Version 2.2022

Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY¹⁻¹⁷

Volumes

- ISRT is recommended as the appropriate field for HL.
 - Planning for ISRT requires modern CT-based simulation and treatment 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 or suspected extent of disease prior to chemotherapy or surgery. However, it spares adjacent uninvolved organs (eg, lungs, bone, muscle, 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, treatment should extend beyond the PET-positive or CT-enlarged nodes.
 - The CTV definition for treating NLPHL with RT alone will be greater than that used 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 can be designed using conventional, 3-D conformal, proton therapy, or IMRT techniques using clinical treatment planning considerations of coverage and normal tissue avoidance.
- The treatment of extranodal disease is individualized, but similar principles of GTV/CTV/PTV definition should be applied as for nodal disease.
 - Chest wall extension – Effort should be made to include regions of initial chest wall extension to definitive doses.
 - Lung involvement – Areas of extension into the lung from mediastinal or hilar disease may be treated with lower doses (~15 Gy) unless the relative volume is small, in which case higher doses may be utilized. Careful consideration of partial lung tolerance is essential. Pulmonary nodular disease is usually not treated following chemotherapy unless residual disease is present.
 - Pleural or pericardial effusions are not included in the GTV. Nodular pericardial involvement may be included with consideration of cardiac tolerance.
 - Bone – Areas of osseous disease may be treated with a CTV expansion beyond the GTV defined by imaging. In vertebral body disease, the entire vertebra is generally treated.

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA^b

Organ at Risk		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA ^c	Xerostomia ^{18,19}
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA ^c	Xerostomia ²⁰
	Oral cavity (surrogate for minor salivary glands)	Mean <11 Gy	Xerostomia, dysgeusia, oral mucositis ²⁰
	Thyroid	V25 Gy <63.5% Minimize V30 Gy	Hypothyroidism ²¹
	Lacrimal glands	V20 Gy <80%	Dry eye syndrome ²²
	Larynx/Pharyngeal constrictors	Mean <25 Gy	Laryngeal edema, dysphagia ²³
	Carotids	Ipsilateral: Avoid hotspots Contralateral: ALARA ^c	Carotid artery atherosclerosis
Thorax	Heart	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Major adverse cardiac events ^{d,24-27}
	Aortic and mitral valves	Dmax <25 Gy	Valvular heart disease ^{25,28,29}
	Tricuspid and pulmonic valves	Dmax <30 Gy	
	Left ventricle	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Heart failure ^{25,30}
	Pericardium	D100 (heart) <5 Gy	Pericarditis ³¹
	Coronary vessels	Avoid hotspots	
	Lungs	Mean dose <13.5 Gy V20 <30% V5 <55%	Pneumonitis ³²

^b General Principles of RT Dose Constraints, [see HODG-D \(5 of 11\)](#).^c ALARA - as low as reasonably achievable.^d As cardiac toxicity is likely related to dose to specific substructures, it is recommended that these are contoured, constraints are applied, and doses are recorded. Contouring atlases are available.^{33,34}**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References



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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA^b

Organ at Risk		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Abdomen	Liver	Mean <15 Gy V20 <30% V30 <20%	Hepatic toxicity ^{35,36}
	Stomach	Dmax <45 Gy	Ulceration ³⁷
	Spleen	Mean <10 Gy V5 ≤30% V15 ≤20%	Late infections ³⁸ Lymphopenia ³⁹
	Pancreas	Minimize volume >36 Gy (especially to pancreatic tail)	Diabetes ⁴⁰
	Small bowel	V15 <120 cc Dmax <45 Gy	Diarrhea ³⁷ Obstruction, ulceration, fistula ³⁷
	Kidneys	Mean <8 Gy V10 <30% V20 <15% (recommended); <25% (acceptable)	Renal insufficiency ^{41,42}
Other	Bone marrow ^e	V5: ALARA ^c V10 <50% V25 <25%	Acute cytopenias ^{43,44} Chronic cytopenias ⁴⁵
	Long bone	V40 <64%	Fracture ⁴⁶

SECONDARY MALIGNANCIES^f

Organ at Risk	Dose Recommendation (1.8–2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy	Breast cancer (adenocarcinoma) ⁵⁰
Esophagus	Minimize volume >30 Gy	Esophageal cancer ⁵¹
Stomach	Minimize volume >25 Gy	Gastric cancer ⁵²
Pancreas	Minimize volume >5–10 Gy	Pancreatic cancer ⁵³

^b General Principles of RT Dose Constraints, [see HODG-D \(5 of 11\)](#).

^c ALARA - as low as reasonably achievable.

^e Active bone marrow can be delineated using various imaging modalities and is most abundant in the pelvic bones, thoracic-lumbar spine, and sacrum.⁴⁷⁻⁴⁹

^f The linear no-threshold model supports limiting radiation dose to susceptible organs as low as reasonably achievable. The following dose guidelines, based on published data, may further guide treatment decisions.

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[References](#)



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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

General Principles of RT Dose Constraints

- Patients with hematologic malignancies typically receive far lower doses than patients with epithelial or mesenchymal malignancies and generally have more favorable long-term outcomes. Therefore, more stringent dose constraints, often proportionally reduced from acceptable thresholds in other malignancies, are recommended. Doses to OARs should follow principles of ALARA (as low as reasonably achievable). In some scenarios, target coverage may require dose constraints to be exceeded if the OAR is within the PTV.
- A relatively rare but serious complication of RT is induction of secondary malignancies. Most studies have shown that increasing dose is associated with increasing risk without a safe threshold dose (linear no-threshold model).⁵⁴ Therefore, limiting radiation dose to susceptible organs as much as possible is vital. Disease- and patient-related factors are also contributory (eg, age, tobacco exposure).
- In addition to secondary malignancies, cardiac and pulmonary complications after RT are most concerning and are reviewed further in the following sections.

Heart

- Multiple cardiac complications can develop from mediastinal RT, including pericarditis, arrhythmias, coronary artery disease (CAD), valvular disease, and cardiomyopathy/congestive heart failure.^{27,55} In addition to radiation factors, the risk of cardiac events is also influenced by chemotherapy administration (eg, doxorubicin), pre-existing cardiovascular disease, age, and other cardiac risk factors (eg, diabetes, hypertension, hyperlipidemia).^{27,56-58} While global heart metrics such as mean heart dose are most commonly used to assess risk, there is an increasing recognition that radiation dose-fractionation to cardiac substructures must be accounted for. Atlases for radiation oncologists to assist with contouring cardiac substructures are available.⁵⁹⁻⁶¹
- Because of the long-term survival of thousands of patients with breast cancer and HL, many large cohort studies have been able to explore the relationship of heart radiotherapy dose with cardiac toxicity and death. Mediastinal radiotherapy of lymphomas, relative to breast cancer and other thoracic malignancies, is characterized by radiation exposures to larger volumes of the heart and substructures, albeit to lower doses (20–40 Gy). Common for both breast and lymphoma RT, there is typically a latency of >20 years for secondary cardiac disease.^{27,62-64}
- As mentioned previously, most studies have associated cardiac events with either prescribed mediastinal radiation dose or mean heart dose. In both the breast cancer and lymphoma radiotherapy literature, mean heart dose has been related to the risk of cardiac events despite the variable volume of whole heart exposed in these two diseases. The risk appears to be linear, without a clear safe threshold dose, with the risk of heart disease increasing by 4.1–7.4% per 1 Gy of cardiac radiation dose administered.^{27,62-64} One of the best data sets relating radiation dose to cardiac disease risk in adult patients is an HL case-control study from the Netherlands.²⁷ Patients were treated prior to 1996 mainly using AP/PA fields. Using the metric of mean heart dose as a measure of cardiac toxicity risk, Van Nimwegen et al demonstrated an excess relative risk of 7.4% per Gy mean heart dose. A statistically significant increased risk of coronary heart disease was demonstrated among patients getting a mean heart dose as low as 5–14 Gy (RR, 2.31) compared with a mean heart dose of 0 Gy. This risk was even higher for a mean heart dose of 15 Gy or higher (RR, 2.83 for 15–19 Gy; RR, 2.9 for 20–24 Gy; and RR, 3.35 for 25–34 Gy). This study also explored different age-of-diagnosis cohorts and generally showed the same radiation dose-response relationships.

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PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Heart (continued)

- The number of studies evaluating specific dose constraints for cardiac substructures is rather limited. Dutch investigators demonstrated a relationship between heart failure and mean dose to the left ventricle.²⁷ Chemotherapy was a clear confounder in regards to the risk of heart failure. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean LV dose <15 Gy, 15.9% for 16–20 Gy, and 32.9% for ≥21 Gy.
- In regards to valvular heart disease (VHD), increasing mediastinal radiation dose, especially >30 Gy, has been associated with an elevated risk of valvular dysfunction.^{27,28} Using a large Dutch cohort of adult patients treated with radiation to the mediastinum, Cutter et al demonstrated 30-year cumulative risks of VHD of 3%, 6.4%, 9.3%, and 12.4% for mean valvular doses of <30, 31–35, 36–40, and >40 Gy.²⁸ VHD was related to aortic valve abnormalities in 71% of patients. Mitral valvular abnormalities, which can also be related to ischemic heart disease due to papillary muscle dysfunction after myocardial infarction, occurred in 50% of patients (some patients had multiple dysfunctional valves). Tricuspid valvular disease was uncommon and pulmonic valve dysfunction was not reported—perhaps due to right heart dysfunction tending to be less clinically problematic. There was no confounding effect of anthracycline chemotherapy on VHD risk in this study. In agreement with this Dutch study, the previously mentioned German-Austrian pediatric cohort showed that prescribed mediastinal radiation dose was the only independent risk factor for VHD.²⁹ No cases of VHD were observed for individuals with doses of 20 Gy, while the 25-year cumulative risks among individuals with prescribed doses of 25 Gy, 30 Gy, and 36 Gy were 2%, 1%, and 16%, respectively.
- Radiation dose constraints for coronary arteries is a work in progress. Standard CT-simulation imaging, even with contrast, does not identify the entire coronary tree very well. There are resolution issues, acquisition time issues, and cardiac motion issues. Coronary anatomy is variable along with some individual variation with collateral blood flow. Proximal coronary arteries and the mid-trunk of the left anterior descending (LAD) are often visible, since the latter is located in the epicardial fat of the left anterolateral aspect of the global heart structure, apparently with minimal motion artifact. Even with research techniques to merge coronary CT angiograms,^{65,66} the important branch vessels (diagonals off the LAD; obtuse marginals off the left circumflex (LCx), posterior descending branch of the right coronary artery [RCA]) are not well demonstrated. Nevertheless, there have been studies in breast and lymphoma radiotherapeutic management to contour the major coronary arteries and try to relate coronary dosimetry to risk of CAD. Moignier et al analyzed 33 irradiated HL patients—21 without coronary stenosis (controls) and 12 patients with critical coronary stenosis (cases) seen on CT angiography.⁶⁶ Radiation dose to stenotic coronary segments and normal coronary segments was compared using a logistic regression. In this manner, the risk of stenosis was found to be increased by 4.9% per Gy over the median dose to the control segments. This data set is too small to be a basis of radiation dose constraints, but does support the general notion of a dose-response effect in the clinical range of lymphoma radiation prescriptions. Another study by Hahn et al used a sample of 125 HL patients treated with mediastinal RT and analyzed various dosimetry parameters of whole heart and coronary segments, looking for a relationship to cardiac events.⁶⁷ Multivariable competing risk regression models found that when any adverse cardiac event was the outcome, models using coronary artery variables did not perform better than models using whole heart variables. However, in a subanalysis of ischemic cardiac events only, the model using coronary artery variables was superior to the whole heart. Major findings for this study were that the V5 Gy for the LAD and the V20 Gy for the LCx had predictive value when looking at ischemic endpoints such as need for coronary revascularization, myocardial infarction, or cardiac death. The modeling analysis was not robust enough to yield specific guidance on dose constraints to specific coronary arteries.

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[References](#)

HODG-D
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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Heart (continued)

- From the historical use of extended-field radiotherapy for HL, whole heart irradiation increases the risk of constrictive pericarditis, especially with doses >15 Gy. Modern radiotherapy for lymphomas rarely requires whole heart irradiation.
- Patients who survived childhood cancers represent a unique high-risk group. In a French cohort study of pediatric HL survivors, the relative risk of severe cardiac disease at age 40 y is 1.9 at a cardiac radiation dose of 1–5 Gy and increases to 19.5–75.2 at a dose >15 Gy for survivors of childhood cancer.²⁴ There are at least two other notable pediatric survivorship study cohorts that provide insights to radiation dose relationship with subsequent cardiovascular disease. Schellong et al reported on 1132 HL survivors treated on the German-Austrian pediatric cooperative group studies from 1978–1995.²⁹ Patients could be binned into mediastinal radiation dose exposures of 36 Gy, 30 Gy, 25 Gy, 20 Gy, and 0 Gy. Cardiac valvular defects were the most frequent late cardiac disease, followed by CAD, cardiomyopathy, conduction disorders, and pericardial abnormalities. The cumulative incidence of cardiac disease after 25 years correlated with radiation dose with incidence of 21% for 36 Gy, decreasing to 10%, 6%, 5%, and 3% for the lower dose groups, respectively ($P < .001$). Multivariate analysis of several putative risk factors showed that mediastinal radiation dose was the only significant variable predicting for cardiac disease-free survival ($P = .0025$). Mulrooney et al published the Childhood Cancer Survivor Study (CCSS) analysis of cardiovascular disease risk in pediatric cancer survivors (not just HL) and analyzed the confounding and independent effects of anthracycline and mediastinal radiation prescribed dose showing a dose-response effect for both chemotherapy and radiotherapy.²⁵ In this study of 14,358 patients, doses between 15 Gy and 35 Gy were not well distinguished, but there was a suggestion that 15 Gy might be a threshold dose associated with not only future VHD but also congestive heart failure and myocardial infarction. Bates et al recently updated the CCSS experience in a 2019 publication of 24,214 5-year survivors, providing further insights into the relationships between radiation and risk of long-term cardiac disease.²⁶ Mean heart doses >10 Gy were associated with increasing cardiac disease risk in a dose-response manner. Volumes of the heart receiving radiation also were correlated with cardiac risk. Children receiving a heart V5 of >50% had a 1.6-fold increased risk of late cardiac disease. Those receiving at least 20 Gy to any part of the heart also were at increased risk.
- While the data regarding cardiac constraints for modern RT of lymphomas is imperfect, we recommend that the mean heart dose be kept as low as possible, ideally <8 Gy, although in some patients a higher dose will be necessary given lymphoma extent. This also recognizes that patients with lymphoma tend to also receive anthracycline chemotherapy, although cumulative chemotherapy doses in modern practice tend to be lower than historical cohorts. Rarely should mean heart dose exceed 15 Gy, unless patients are being treated in the salvage setting with curative intent where larger RT doses are necessary.²⁶ Ideally, mean left ventricular dose should be kept lower than 8 Gy, although up to 15 Gy may be necessary in some circumstances. Aortic and mitral valve doses should be kept below 25 Gy, and ideally even lower. Tricuspid and pulmonic valves may be less critical OARs and it is recommended that doses be kept below 30 Gy. Constraints to coronary arteries are less well defined but should be as low as possible in terms of dose and volume/length.

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Hodgkin Lymphoma (Age ≥18 years)

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA

Lungs

- The primary pulmonary toxicity related to mediastinal RT is radiation pneumonitis. Other complications, such as symptomatic fibrosis or bronchopleural fistula, are rarely encountered given the lower doses used for lymphoma management. Radiation pneumonitis is a clinical diagnosis consisting of dry cough, dyspnea, and occasionally low-grade fevers. Radiation pneumonitis must be distinguished from other entities including infectious pneumonia, acute bronchitis, pulmonary embolism, etc. Pulmonary complications, including pneumonitis, can arise from systemic modalities also, including bleomycin and immunotherapy.
- The most important risk factor for radiation pneumonitis is lung dose–volume metrics including mean lung dose (MLD), V20, and V5. Such metrics have been associated with pneumonitis risk in both epithelial⁶⁸ and hematologic malignancies.³² For epithelial malignancies, such as non-small cell lung cancer, guidelines generally recommend MLD <20 Gy and V20 <35%. In most circumstances, given the lower doses used in lymphoma management, much lower doses are generally achievable with careful planning.
- We recommend limiting MLD <13.5 Gy and V20 <30%, although dose to the lungs in most lymphoma patients can be kept below these thresholds. More pertinent to IMRT or volumetric arc techniques, we recommend limiting the V5 <55%.

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Hodgkin Lymphoma (Age ≥18 years)

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Hodgkin Lymphoma (Age ≥18 years)

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Hodgkin Lymphoma (Age ≥18 years)

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Hodgkin Lymphoma (Older Adults)

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

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

SUGGESTED TREATMENT REGIMENS (Listed in alphabetical order)

Stage I–II Favorable Disease

- A(B)VD^a (2 cycles) ± AVD (2 cycles) + ISRT^b (preferred)^{7,8,9}
- CHOP (4 cycles) + ISRT^{b,10}

Stage I–II Unfavorable or Stage III–IV Disease

- A(B)VD^a (2 cycles) followed by AVD (4 cycles),^c if PET scan is negative after 2 cycles of ABVD.¹¹
 - ▶ Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment.
- Brentuximab vedotin followed by AVD, conditionally followed by brentuximab vedotin in responding patients with CR or PR¹²
- Brentuximab vedotin + DTIC (dacarbazine)^{13,14}
- CHOP (6 cycles) ± ISRT^{b,10}

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 include:
 - ▶ Bendamustine
 - ▶ Brentuximab vedotin
 - ▶ ISRT
 - ▶ Nivolumab [See Checkpoint Inhibitors \(CPI\) HODG-C \(3 of 5\)](#)
 - ▶ Pembrolizumab [See Checkpoint Inhibitors \(CPI\) HODG-C \(3 of 5\)](#)
 - ▶ Second-line, third-line and subsequent therapy options (only for CHL) as listed on [Principles of Systemic Therapy for Relapsed or Refractory Disease HODG-C \(3 of 5\)](#)

^a Bleomycin should be used with caution as it may not be tolerated in older adults, and it should not be used beyond 2 cycles.

^b [See Principles of Radiation Therapy \(HODG-E\).](#)

^c If stage I–II is unfavorable, consider a total of 4 cycles.

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[References](#)



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Hodgkin Lymphoma (Older Adults)

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

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- ¹⁰ Kolstad A, Nome O, Delabie J, et al. Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. *Leuk Lymphoma* 2007;48:570-576.
- ¹¹ Johnson P, Federico M, Fossa A, et al. Response-adapted therapy based on interim FDG-PET scans in advanced Hodgkin lymphoma: first analysis of the safety of de-escalation and efficacy of escalation in the international RATHL study (CRUK/07/033) [abstract]. *Hematol Oncol* 2015;33 (Suppl S1):Abstract 008.
- ¹² Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. *J Clin Oncol* 2018;36:3015-3022.
- ¹³ Friedberg JW, Forero-Torres A, Bordon RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL. *Blood* 2017;130:2829-2837.
- ¹⁴ Friedberg JW, Forero-Torres A, Holkova B, et al. Long-term follow-up of brentuximab vedotin ± dacarbazine as first line therapy in elderly patients with Hodgkin lymphoma [abstract]. *J Clin Oncol* 2018;36 (Suppl 15): Abstract 7542.
- ¹⁵ Böll B, Goergen H, Arndt N, et al. Relapsed hodgkin lymphoma in older patients: a comprehensive analysis from the German hodgkin study group. *J Clin Oncol* 2013;31:4431-4437.

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

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

**HODGKIN LYMPHOMA STAGING¹****Table 1****Definitions of Stages in Hodgkin Lymphoma²**

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;31:1860-1861.

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

² PET 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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NCCN Categories of Evidence and Consensus

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

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

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

All recommendations are considered appropriate.



Discussion

This discussion corresponds to the NCCN Guidelines for Hodgkin lymphoma. Last updated: February 23, 2022.

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Hodgkin Lymphoma

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy of B-cell origin. Most patients are diagnosed between ages 15 and 30 years, followed by another peak in adults aged 55 years or older. In 2022, an estimated 8540 people will be diagnosed with HL in the United States and 920 people will die from the disease.¹ The World Health Organization (WHO) classification divides HL into two main types: classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).² In Western countries, CHL accounts for 95% and NLPHL accounts for 5% of all HL.

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

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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hodgkin Lymphoma discuss the clinical management of patients with CHL

and NLPHL, focusing on adult patients 18 years and older who do not have serious intercurrent disease. The Guidelines do not address HL in pediatric patients or those with unusual situations, such as HIV positivity or pregnancy. Individualized treatment may be necessary for older patients and those with concomitant disease. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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 since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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 data from key PubMed articles 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 at www.NCCN.org.



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Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.^{4,5} The system divides each stage into subcategories A and B, the latter for presence of B symptoms. “A” indicates that no systemic symptoms are present and “B” is assigned to patients with unexplained fevers greater than 38°C, drenching night sweats, or unexplained weight loss of greater than 10% of their body weight within 6 months of diagnosis.

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

Mediastinal bulk, an unfavorable prognostic factor in patients with early-stage HL, is measured most commonly using the mediastinal mass ratio (MMR).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. This is the definition used most commonly in North America and also by the German Hodgkin Study Group (GHSG). Another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter. According to the Cotswolds modification of the Ann Arbor staging system, bulky disease is defined as the mediastinal thoracic ratio (MTR), which is the ratio of the maximum width of the mediastinal mass and the internal transverse diameter of the thorax at the T5–T6 interspace on a posteroanterior chest radiograph.⁷ In this context, any mass with MTR greater than 0.35 is defined as bulky disease. This is the definition used by the European Organization for Research and Treatment of Cancer (EORTC).

The early-stage unfavorable factors are based largely on a composite of factors derived from the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, GHSG, and the National Cancer Institute of Canada (NCIC).^{8,9} Of note, the nodal *regions* as defined by the GHSG and EORTC are not the same as the Ann Arbor *sites*. Both research groups bundle the mediastinum and bilateral hila as a single region. In addition, the GHSG combines subpectoral with supraclavicular or cervical, while the EORTC combines subpectoral with axilla as one region. The NCCN and EORTC unfavorable factors for stage I–II disease include bulky mediastinal disease (MMR >0.33 and MTR >0.35 , respectively) or bulky disease greater than 10 cm, B symptoms, ESR 50 or greater, and greater than three involved nodal regions. In contrast, the GHSG considers patients with greater than two nodal regions as having unfavorable disease.

An international collaborative effort evaluating more than 5000 patients with advanced CHL (stage III–IV) identified seven adverse prognostic factors, each of which reduced survival rates by 7% to 8% per year,¹⁰ including: age 45 years or older; male gender; stage IV disease; albumin level below 4 g/dL; hemoglobin level below 10.5 g/dL; leukocytosis (white blood cell [WBC] count $>15,000/\text{mm}^3$); and lymphocytopenia (lymphocyte count $<8\%$ of the WBC and/or lymphocyte count $<600/\text{mm}^3$). The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.^{10,11} The IPS helps to determine the clinical management and predict prognosis for patients with stage III–IV disease.^{10,11}

The Role of PET Imaging in Patient Management

Clinical management of patients with CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging at the completion of chemotherapy to assess treatment response. Assessment of response to initial treatment is essential because the need for additional



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treatment is based on the treatment response. PET should not be used for routine surveillance following the completion of therapy.

PET imaging including integrated PET and CT (PET/CT) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.^{12,13} In a meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.¹⁴ 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.¹⁵⁻¹⁷ In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of ¹⁸F-fluorodeoxyglucose (FDG) uptake in the involved sites. These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.^{13,18,19} In the 5-PS (Deauville criteria), scores of 1 to 4 refer to initially involved sites and a score of 5 refers to an initially involved site and/or new lesions related to lymphoma.^{18,19} Interim or end-of-treatment PET scans with a score of 1, 2, or 3 are considered “negative” and PET scans with a score of 4 and 5 are considered “positive.”²⁰ A score of 4 can be difficult to assess when FDG uptake in mediastinal masses cannot clearly be differentiated from thymic uptake or inflammatory reactions,^{13,21,22} and treatment decisions in these cases will require clinical judgment. In addition, Deauville 4 may represent just a single area of persistent disease or failure to respond in any site. The 5-PS (Deauville criteria) has been validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.²³⁻²⁷ The NCCN Hodgkin Lymphoma Panel encourages a second opinion of scans when there is a discrepancy between the clinical presentation and radiology report of a scan that was not originally interpreted by a qualified individual, and/or when no Deauville score is provided.

Interim PET Imaging

Interim PET scans can be prognostic and are increasingly being used to assess treatment response during therapy^{28,29} as they can inform treatment adaptation, including treatment escalation and de-escalation.^{30,31} 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).^{32,33} Interim PET scans may also be useful to identify a subgroup of patients with early- and advanced-stage disease that can be treated with chemotherapy alone.^{27,34} The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for some clinical scenarios, and all measures of response should be considered in the context of management decisions. It is important that the Deauville score be incorporated into the nuclear medicine PET scan report, since subsequent management is often dependent on that score. Individual prospective trials that use interim PET imaging are discussed below in the treatment management section.

Principles of Radiation Therapy

RT can be delivered with photons, electrons, or protons, depending on clinical circumstances.³⁵ Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OARs; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue, salivary glands) can be achieved with advanced radiation therapy (RT) planning and delivery techniques such as four-dimensional CT (4D-CT) simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), respiratory gating, or deep inspiration breath hold.^{36,37} These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control.^{35,38-44} Although advanced RT



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techniques emphasize tightly conformal doses and steep gradients adjacent to normal tissues, the “low-dose bath” to normal structures such as the breasts must be considered in choosing the final RT technique. Therefore, target definition, delineation, and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound (US), and other imaging modalities facilitate target definition.

For optimal mediastinal treatment planning, organs or tissues to be contoured should include the lungs, heart, and the cardiac subunits, including the coronary arteries (the left main, circumflex, left anterior descending, and right coronary arteries, with priority placed on sparing the proximal over distal portions of the arteries), the valves, and left ventricle.

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

Involved-site RT (ISRT) and involved-node RT (INRT) are being used as alternatives to involved-field RT (IFRT) in an effort to further restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long-term toxicities associated with radiation exposure.⁴⁵⁻⁴⁷ ISRT targets the originally involved nodal sites and possible extranodal extensions, which generally defines a smaller field than the classical IFRT that encompassed entire lymph node regions, without a demonstrable attendant decrease in efficacy.⁴⁸

ISRT targets the initially involved nodal and extranodal 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, proton therapy,³⁵ or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OARs. The gross tumor volume (GTV) 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.⁴⁹ 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 (doxorubicin, bleomycin, vinblastine, dacarbazine) for most patients.⁵⁰ In patients with stage I–II non-bulky disease, the recommended RT dose is 20 to 30 Gy following ABVD.^{51,52} 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.

Principles of RT Dose Constraints

Patients with hematologic malignancies typically receive far lower doses of RT than patients with epithelial or mesenchymal malignancies, while generally achieving more favorable long-term outcomes. More stringent dose constraints, often proportionally reduced from acceptable thresholds



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in other malignancies, are recommended. Doses to OARs should follow principles of ALARA (as low as reasonably achievable). In some scenarios, target coverage may require dose constraints to be exceeded if the OAR is within the PTV.

A late side effect of RT is the development of radiation-induced secondary cancers. Studies have reported that increasing RT dose without a safe threshold dose (linear no-threshold model) is associated with an increased risk for secondary cancers, although the pattern of risk is less well understood than those after low-dose exposure.⁵³ Other contributing factors include age, environmental exposure, genetic risk factors, and radiation technique, among others.⁵⁴

RT dose constraints recommended for OAR especially heart and lung are described below.

Heart

Multiple cardiac complications can develop from mediastinal RT including pericarditis, arrhythmias, coronary artery disease (CAD), valvular heart disease (VHD), and cardiomyopathy/congestive heart failure.^{55,56} In addition to factors related to RT, the risk of cardiac events is also influenced by chemotherapy administration (eg, doxorubicin), pre-existing cardiovascular disease, age, and other cardiac risk factors (eg, diabetes, hypertension, hyperlipidemia).^{55,57-59} While global heart metrics such as mean heart dose (MHD) are most commonly used to assess risk, there is an increasing recognition that radiation dose-fractionation to cardiac substructures must be accounted for.

Mediastinal RT for lymphomas, relative to breast cancer and other thoracic malignancies, is characterized by radiation exposures to larger volumes of the heart and substructures, albeit to lower doses (20–40 Gy). The MHD has been related to the risk of cardiac events, although the volume of the whole heart exposed to RT is variable.^{60,61} In a case-control study of HL

survivors who were treated mainly with AP/PA fields, using MHD as a measure of cardiac toxicity risk, van Nimwegen et al demonstrated an excess relative risk (RR) of 7.4% per Gy MHD.⁶¹ A significantly increased risk of coronary heart disease was reported among patients who received an MHD as low as 5 to 14 Gy (RR, 2.31) compared to a MHD of 0 Gy.⁶¹ This risk was increased for an MHD of greater than or equal to 15 Gy (RR, 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy).⁶¹

The number of studies evaluating specific dose constraints for cardiac substructures is limited.^{55,62,63} The prescribed mediastinal RT dose was the only independent risk factor for VHD in a pediatric cohort study and increasing mediastinal RT dose (especially >30 Gy), has been associated with an elevated risk of valvular dysfunction.^{62,63} In a large Dutch cohort of adult patients treated with mediastinal RT, the 30-year cumulative risks of VHD increased with increasing mean valvular RT doses (3% for <30 Gy, 6.4% for 31–35 Gy, 9.3% for 36–40 Gy, and 12.4% for >40 Gy) and there was no confounding effect of anthracycline chemotherapy on the risk of VHD.⁶³ van Nimwegen et al demonstrated a relationship between heart failure and mean left ventricular dose.⁵⁵ Chemotherapy was a clear confounder in regards to the risk of heart failure. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean leucovorin (LV) dose less than 15 Gy, 15.9% for 16 to 20 Gy, and 32.9% for greater than or equal to 21 Gy.

RT dose constraints for coronary arteries is a work in progress and only a few studies have evaluated the effect of coronary RT dose on the risk of coronary artery disease.⁶⁴⁻⁶⁷ In a large retrospective study of patients with non-small cell lung cancer (NSCLC) treated with thoracic RT, major adverse cardiac events were found to be associated with the volume of the left anterior descending coronary artery receiving 15 Gy (V15 Gy ≥10%).⁶⁷ Although there is no robust evidence to recommend specific guidance on dose constraints to specific coronary arteries in patients with



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lymphomas, limited available evidence support the general notion of a dose-response effect in the clinical range of lymphoma RT prescriptions.

NCCN Recommendations

While the data regarding cardiac constraints for modern RT for lymphomas are imperfect, the panel recommends that the MHD be kept as low as possible, ideally less than 8 Gy, although in some patients a higher dose will be necessary given lymphoma extent. The panel recognizes that nearly all patients with lymphoma receive anthracycline-based chemotherapy, although cumulative chemotherapy doses in modern practice tend to be lower than historical cohorts. Whole heart irradiation increases the risk of constrictive pericarditis, especially with whole heart RT doses greater than 15 Gy⁶⁸; therefore, it is recommended that MHD should rarely exceed 15 Gy. This may be reconsidered if patients are being treated in the second-line setting with curative intent where larger RT doses are necessary. Mean left ventricular dose should not exceed 8 Gy, although in some circumstances up to 15 Gy may be necessary. Aortic and mitral valve doses should be less than 25 Gy, although lower doses would be optimal. Given that tricuspid and pulmonic valves may be less affected OARs, it is recommended that doses less than 30 Gy be administered. Constraints to coronary arteries are less well defined,⁶⁹ but should be as low as possible in terms of dose and volume and length.

Lungs

Mediastinal RT-related pulmonary toxicity is primarily radiation pneumonitis, although complications including symptomatic fibrosis or bronchopleural fistula have been encountered rarely. Radiation pneumonitis is a clinical diagnosis consisting of dry cough, dyspnea, and occasionally low-grade fevers, and must be distinguished from other entities including drug-induced (especially bleomycin) pneumonitis, infectious pneumonia, acute bronchitis, and pulmonary embolism.

Pulmonary complications can also arise from systemic modalities such as brentuximab vedotin and immunotherapy.

The most important risk factors for radiation pneumonitis are lung dose-volume metrics, including mean lung dose (MLD), V20 Gy, and V5 Gy. Such metrics have been associated with pneumonitis risk in both epithelial⁷⁰ and hematologic malignancies.⁷¹ For epithelial malignancies such as non-small cell lung cancer, it is generally recommended that MLD be less than 20 Gy and V20 Gy be less than 35%. In most circumstances, given the lower doses used in lymphoma management, much lower doses are generally achievable with careful planning.

NCCN Recommendations

The panel recommends limiting MLD less than 13.5 Gy and V20 Gy less than 30%, although RT to the lungs in most patients with lymphoma can be maintained below these thresholds. In cases where IMRT or volumetric arc techniques are appropriate, limiting the V5 to less than 55% is recommended.

Treatment Guidelines

Diagnosis and Workup

For evaluation and initial workup of HL the panel recommends that an excisional lymph node biopsy generally be performed, although a core needle biopsy may be adequate if diagnostic. A diagnostic assessment based solely on fine-needle aspiration (FNA) biopsy is generally insufficient except in unusual circumstances when in combination with immunohistochemistry (IHC) it is judged to be diagnostic of HL by an expert hematopathologist or cytopathologist. Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, PAX5, and EBER is recommended for CHL. The Reed-Sternberg cells of CHL express CD30 in all patients, express CD15 in the majority of patients, and are usually negative for CD3 and CD45. CD20 may be detectable in less than 40% of patients. An



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extended panel of markers (ie, MUM-1, BOB-1, OCT-2) may be required, especially if there is an equivocal diagnosis. For NLPHL, the immunoarchitectural pattern should be specified as typical (subtypes A or B) or variant (subtypes C, D, E, or F).

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

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

The NCCN PET Task Force and the NCCN Guidelines consider PET scans essential for initial staging and for evaluating residual masses at the end of treatment.⁷² An integrated PET scan plus a diagnostic CT is recommended for initial staging and should be obtained no longer than 1 month prior to the initiation of therapy. A separate contrast-enhanced diagnostic CT is not needed if it was part of the integrated PET scan. The panel supports the ACR⁷³ and Society of Nuclear Medicine and Molecular Imaging (SNMMI)⁷⁴ recommendations for PET/CT interpretation (see *Principles of FDG-PET/CT* in the algorithm).⁷⁵⁻⁷⁸ However, it should be

noted that PET scans may be positive in sites of infection or inflammation, even in the absence of HL. In patients with PET-positive sites outside of the disease already identified, or if the PET-positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. In patients with newly diagnosed HL undergoing pretreatment staging with PET/CT, routine bone marrow biopsy is not required if the PET scan is negative or displays a homogenous pattern of bone marrow uptake, which may be secondary to cytokine release.^{79,80} The bone marrow may be assumed to be involved if the PET scan displays multifocal (three or more) skeletal lesions.^{79,81} However, a bone marrow biopsy may be performed if the PET scan is negative, but unexplained cytopenias other than anemias are present (eg, thrombocytopenia, neutropenia). In select cases, MRI with contrast to select sites may be considered, unless contraindicated. PET/MRI without contrast (skull base to mid-thigh) may also be considered for anatomical imaging.

Evaluation of ejection fraction is recommended if anthracycline-based therapy is indicated. HIV and hepatitis B or C testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. Pulmonary function tests, including diffusing capacity of the lungs for carbon monoxide (DLCO), are recommended for patients receiving bleomycin-based chemotherapy. In general, a DLCO threshold of at least 60% is acceptable for bleomycin use.^{82,83} A seasonal flu shot is recommended. Pneumococcal, H-flu, and meningococcal vaccines are recommended if splenic RT is contemplated.

A pregnancy test should be performed before patients 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.⁸⁴ In select cases and if the patients are interested, the Guidelines recommend consideration of fertility



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preservation (ie, 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.^{85,86}

Classic 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 with non-bulky disease)
- Stage IA–IIA (unfavorable with bulky mediastinal disease or >10 cm adenopathy)
- Stage IB–IIB (unfavorable disease)

RT alone was a standard treatment option for patients with early-stage HL for many decades.⁸⁷ However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.⁸⁸ With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD is the most commonly used systemic therapy based on a balance of efficacy and toxicity) into the management of patients with early-stage disease, combined modality therapy (chemotherapy and RT) has replaced RT alone as the treatment of choice for patients with early-stage, favorable disease. Bonadonna 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.⁵⁰ The NCIRC HD.6 trial established ABVD alone as a potential treatment for patients with stage I–II disease.⁸⁹ Selection of combined modality therapy

or chemotherapy alone should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement. Generally, combined modality therapy provides for a better progression-free survival (PFS)/freedom from progression (FFP); however, it presents no difference in overall survival (OS). Most patients will benefit from multidisciplinary input prior to final treatment decisions.

Stage I–II

The HD10 trial from the GHSG investigated the reduction of the number of cycles of ABVD as well as the IFRT dose in patients with stage I–II disease with no risk factors.⁵² The definition of favorable disease implies the absence of unfavorable risk factors outlined in *Principles of Unfavorable Risk Factors* in the algorithm. It is worth noting that for purposes of stratification the GHSG and EORTC do not define the lymph node regions strictly according to the Ann Arbor criteria. In this trial, patients were not eligible if they had three or more involved lymph node regions, any E-lesions, bulky mediastinal adenopathy, ESR greater than 50, or ESR greater than 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to one of the four treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT or 2 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT.⁵² 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.⁵² 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



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

Subsequent studies have assessed the value of interim PET scans in defining the need for RT in patients with stage I–II disease. The UK RAPID trial showed that patients with stages IA–IIA disease with a negative PET scan after 3 cycles of ABVD have an excellent outcome with or without IFRT.²⁷ In this study (n = 602; 426 patients had a negative PET scan after 3 cycles of ABVD), patients with stage IA–IIA favorable disease (no B symptoms or mediastinal bulky disease) and a Deauville score of 1 to 2 on interim PET scan after 3 cycles ABVD were randomized to either IFRT (n = 209) or observation (n = 211). After a median follow-up of 60 months, in an intent-to-treat analysis, the estimated 3-year PFS rate was 94.6% for those treated with IFRT compared to 90.8% for those who received no further treatment. The corresponding 3-year OS rates were 97.1% and 99.0%, respectively.²⁷ In the “per protocol” (as treated) analysis, the 3-year PFS rates were 97.1% and 90.8%, respectively, favoring the use of combined modality therapy.

In the EORTC H10 trial, which included 754 patients in the favorable group (H10F), PET response after 2 cycles of ABVD facilitated early treatment adaptation.³⁰ In this study, mediastinal blood pool activity was used as the reference background activity for PE-positivity of residual masses greater than or equal to 2 cm in greatest transverse diameter, regardless of location. A smaller residual mass or a normal-sized lymph node was considered positive if its activity was above that of the surrounding background. Patients who were PET negative after receiving 2 cycles of ABVD received 1 additional cycle of ABVD (total of 3 cycles) followed by INRT in the standard arm, or 2 additional cycles of ABVD (total of 4 cycles) only in the experimental arm.³⁰ After a median follow up of 5 years, the intent-to-treat PFS rates were 99.0% and 87.1% in the ABVD + RT and ABVD only arms, respectively.³⁰ If the interim PET was positive,

patients in both the H10F and H10U (unfavorable group) were continued on ABVD for a total of 4 cycles on the standard arm or treatment was intensified to 2 cycles of escalated-BEACOPP + INRT in the experimental arm.³⁰

In the H10U group (n = 1196), patients were randomized into two treatment arms.³⁰ In the standard arm, patients were treated with 2 cycles of ABVD, underwent interim PET, and were treated with 2 additional cycles of ABVD + INRT (30–36 Gy). In the experimental arm, patients were treated with 2 cycles of ABVD, underwent interim PET scans, and if found to be PET negative, were treated with an additional 4 cycles of ABVD. For the interim PET-negative patients, the 5-year PFS was 92.1% following 4 cycles of ABVD + INRT versus 89.6% following 6 cycles of ABVD.³⁰ If patients were found to be PET positive after the initial 2 cycles of ABVD, chemotherapy was intensified with 2 cycles of escalated BEACOPP + INRT (30–36 Gy) as in the H10F group. The final results of this trial demonstrated that in patients with stage I–II (favorable or unfavorable disease), a PET-positive response after 2 cycles of ABVD facilitates early treatment adaptation to 2 cycles of escalated BEACOPP + INRT, with improved 5-year PFS when compared to 2 additional cycles of ABVD and INRT (90.6% vs. 77.4%, respectively).³⁰

The GHSG HD16 trial (n = 1150) included patients with stage I–II favorable disease according to GHSG criteria.⁹⁰ Patients randomized to the standard arm received 2 cycles of ABVD followed by an interim PET and IFRT (20 Gy), regardless of the PET result. On the experimental arm, following 2 cycles of ABVD, patients with a negative PET (Deauville score <3) received no further therapy, while those with a positive PET received IFRT (20 Gy). Among the 628 patients in the combined arms who had a negative interim PET, the 5-year PFS was 93.4% following combined modality therapy and 86.1% following ABVD alone ($P = .04$).⁹⁰



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The CALGB 50604 trial examined the use of interim PET to guide treatment of patients with stage I–II HL (excluding only patients with bulky disease).⁹¹ Patients received 2 cycles of ABVD followed by PET. Patients with a PET-negative response (Deauville score of 1–3, which is different from the H10 and RAPID trials that used a score of 1–2) were given 2 more cycles of ABVD, whereas patients with a PET-positive response were treated with escalated BEACOPP + IFRT.⁹¹ With a median follow-up time of 3.8 years, the estimated 3-year PFS for the PET-negative and PET-positive groups were 91% and 66%, respectively.⁹¹ The 3-year PFS was 94% for patients with Deauville 1–2 response on interim PET compared to only 77% for patients with Deauville 3 response.

The HD14 trial of the GHSG evaluated patients with stage I–II unfavorable disease.⁹² 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 FFTF rate was 94.8% compared to 87.7% for ABVD ($P < .001$). The 5-year PFS rate was 95.4% and 89.1%, respectively ($P < .001$).⁹² The 5-year OS rate was not significantly different between the two arms (97.2% and 96.8%, respectively; $P = .731$). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs. 8.4%; $P < .001$). However, the acute toxicity was greater in the BEACOPP/ABVD arm compared to the ABVD arm.⁹² The risk for WHO grade 3–4 events was 87.1% and 50.7%, respectively. Grade 4 toxicity was reported in 56.6% and 5.9%, respectively.

The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial examined the use of interim PET to guide treatment for patients with advanced disease, which included 500 patients (41.6%) who had stage II with various risk factors (B symptoms, bulky disease, or at least 3 involved sites).^{23,31} In the randomized trial, 1119 patients with stage

II–IV disease received 2 cycles of ABVD and underwent interim PET scans. Patients with a Deauville score of 1 to 3 were assigned in a 1:1 ratio to continue treatment with 4 cycles of either ABVD or AVD. At a median of 41 months, the 3-year PFS and OS rates between the ABVD and AVD groups did not differ significantly (85.7% vs. 84.4% and 97.2% vs. 97.6%, respectively). However, the omission of bleomycin from the ABVD regimen after negative PET results (ie, Deauville score of 1–3) led to a decrease in the incidence of pulmonary toxic effects when compared to continued ABVD.³¹ The potential value of added RT was not tested in this trial.

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

The recommended primary treatment for stage I–IIA with favorable non-bulky disease is 2 cycles of ABVD (category 1), followed by restaging with PET/CT. If there is a preference to treat patients with combined modality therapy, treatment options for patients with a Deauville score of 1 to 3 include ISRT (20 Gy) if ESR less than 50, no e-lesions present, and less than 3 nodal sites^{52,90} or 1 cycle of ABVD plus ISRT (30 Gy).^{27,30}

If there is a preference to treat with chemotherapy alone, patients with a Deauville score of 1 to 2 are recommended to be treated with 1^{30,91} or 2²⁷ cycles of ABVD according to the RAPID or H10F trials. Per the RATHL trial, a Deauville score of 3 should be treated with 4 cycles of AVD.

For patients with a Deauville score of 4, if only focally positive, patients may continue with 2 additional cycles of ABVD before repeat scan. Following restaging, a biopsy is recommended for all patients with a score of Deauville 4 to 5. The panel recommends escalating therapy for patients whose scan remains positive throughout the area(s) of initial disease. ISRT (30 Gy) is recommended for patients with a Deauville score of 1 to 3, or 4 to 5 with a negative biopsy.^{27,30} A Deauville score of 5 after interim restaging should be managed as described for refractory disease. Biopsy is recommended for all patients with a score of Deauville 5. If the biopsy is



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negative, patients may follow treatment course of patients with a Deauville score of 4. If the biopsy is positive, patients should be managed as described for refractory disease.

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

For stage I–II unfavorable CHL with B symptoms, bulky mediastinal disease, or greater than 10 cm adenopathy, the preferred regimen, ABVD, is initially administered for 2 cycles followed by restaging with PET. If there is a preference to treat patients with combined modality therapy, patients with a Deauville score of 1 to 3 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT (30 Gy).³⁰ If there is a preference to treat with chemotherapy alone, patients with a Deauville score of 1 to 3 are recommended to receive 4 cycles of AVD.³¹

Patients with a Deauville score of 4 to 5 are treated with 2 cycles of escalated BEACOPP followed by interim PET restaging. A Deauville score of 5 should prompt re-biopsy to inform subsequent therapy. If a biopsy is not performed, treatment should be escalated. Patients with a Deauville score of 1 to 3 who prefer combined modality therapy are followed up with ISRT (30 Gy).^{30,92,93} Two cycles of escalated BEACOPP is recommended for those who prefer chemotherapy alone. Biopsy is recommended for patients with a Deauville score of 4 to 5 after restaging. If the biopsy is negative, patients are treated as described for patients with a Deauville score of 1 to 3. All patients with a positive biopsy should be managed as described for refractory disease.

Stage III–IV

While chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach in some instances, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.^{94,95}

ABVD is the preferred chemotherapy regimen based on several randomized clinical trials that have failed to show a survival benefit for more intensive regimens.⁹⁵⁻⁹⁸ The potential role for RT in stage III–IV disease has not been demonstrated in contemporary randomized clinical trials; however, it may be useful in selected clinical situations, such as described in the HD15 trial, below.

The results of the important RATHL trial demonstrated that the omission of bleomycin from the ABVD regimen in patients with negative interim PET scan (Deauville score 1–3) after 2 cycles of ABVD, resulted in a lower incidence of pulmonary toxicity than with continued ABVD without impacting efficacy (3-year PFS 81.6% and OS 97%).³¹ In this trial, patients who had a positive interim PET (Deauville 4–5) had treatment intensified to escalated BEACOPP. With a median follow-up of 5 years, the 3-year PFS and OS were 71% and 85%, respectively. Similar PET-adapted escalation has been evaluated in the U.S. Intergroup trial S0186^{99,100} and the Italian GITIL/FIL HD 0607 trial.¹⁰¹ For the U.S. Intergroup trial, the 5-year PFS and OS for patients who had a positive interim PET were 65% and 97%, respectively.^{99,100} Similar results were also seen in the 0607 trial for patients who had a positive interim PET, with a 3-year PFS and OS of 60% and 89%, respectively.¹⁰¹

Other options for advanced stage disease include brentuximab vedotin-AVD x 6 cycles or escalated BEACOPP x 2 cycles followed by restaging with PET (and additional cycles of escalated BEACOPP [total of 4 or 6 cycles] or A(B)VD x 4 cycles depending on the Deauville score at interim restaging) for select patients younger than 60 years with IPS greater than or equal to 4.¹⁰²⁻¹⁰⁵

The efficacy of escalated BEACOPP has been demonstrated in several sequential studies by the GHSG.^{106,107} The final analysis of the HD15 trial that included patients with stage III–IV and IIB with large mediastinal adenopathy or extranodal disease established 6 cycles of escalated



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BEACOPP followed by PET-guided RT (to sites >2.5 cm that were PET positive) as the standard of care within the GHSG. The 5-year FFTF and OS rates were 89.3% and 95.3%, respectively.⁴⁴ One hundred ninety-one patients were PET positive, received consolidative RT, and achieved a 4-year PFS of 86.2% with outcomes similar to those who achieved a complete response (CR).¹⁰⁸

The subsequent HD18 trial investigated an interim PET-adapted design.¹⁰⁴ After 2 cycles of escalated BEACOPP, PET-negative (Deauville 1–2) patients were randomized to receive an additional 2 or 6 cycles of escalated BEACOPP, and PET-positive patients were randomized to receive an additional 6 cycles of escalated BEACOPP alone or with rituximab. The final results showed non-inferiority of 4 cycles of escalated BEACOPP (n = 501) compared to 6 or 8 cycles, with a 5-year PFS of 92.2% versus 90.8%, respectively.¹⁰⁴ These results suggest that 4 cycles of escalated BEACOPP is adequate therapy in patients with a negative interim PET.

The AHL2011 trial investigated whether PET monitoring during treatment could allow dose de-escalation by switching regimens from escalated BEACOPP to ABVD in early responders with newly diagnosed advanced-stage HL (stage IIB with large mediastinal mass or stage III–IV).¹⁰⁵ In this study, all patients (n = 823) were randomized to receive standard treatment (6 cycles of escalated BEACOPP; n = 413) or PET-adapted treatment (n = 410). In the PET-adapted group, after 2 cycles of escalated BEACOPP, patients with positive PET2 scans (Deauville score 4 or 5) received 2 additional cycles of escalated BEACOPP, whereas patients with negative PET2 scans (Deauville score 1–3) were switched to 2 cycles of ABVD for the remaining induction therapy.¹⁰⁵ With a median follow-up of 50.4 months (interquartile range [IQR], 42.9–59.3), the 5-year PFS by intention to treat in the standard treatment and PET-adapted treatment groups were 86.2% and 85.7% ($P =$

.65), respectively.¹⁰⁵ The PET-adapted treatment arm was also associated with significantly less treatment-related toxicities.¹⁰⁵

Results from studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although in some studies it resulted in better tumor control.^{98,109–111} However, some of these studies were not sufficiently powered to determine differences in OS due to small patient numbers. The EORTC 20012 trial evaluated BEACOPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III–IV disease and IPS greater than or equal to 3 (274 patients in the BEACOPP arm and 275 patients in the ABVD arm).¹⁰⁹ The results showed that there was no improvement in OS (86.7% and 90.3, respectively, at 4 years; $P = .208$) or event-free survival (EFS) (63.7% and 69.3%, respectively, at 4 years; $P = .312$), although the PFS was significantly better with BEACOPP (83.4% vs. 72.8% for ABVD; $P = .005$). Early discontinuations were also more frequent with BEACOPP. The median follow-up was 3.6 years.¹⁰⁹ Interestingly, long-term follow-up analysis of the HD2000 trial failed to show a PFS advantage of escalated BEACOPP over ABVD, largely due to the risk of secondary malignancy at 10 years, which was significantly higher with escalated BEACOPP than with ABVD (6.6 vs. 0.9; $P = .027$).⁹⁷

The results of the ECHELON-1 trial showed that brentuximab vedotin -AVD had superior progression-free survival (PFS) compared to ABVD in the treatment of patients with stage III–IV disease.^{102,103} In this trial patients with previously untreated stage III or IV CHL were randomized to receive ABVD (n = 670) or brentuximab vedotin - AVD (n = 664).¹⁰² Patients received 6 cycles of chemotherapy without treatment adaptation based on interim restaging. The 5-year follow-up data confirmed that PFS benefit for brentuximab vedotin - AVD compared to ABVD was consistent in all patient subgroups independent of disease



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stage, age and IPS.¹⁰³ At a median follow-up of 61 months, the 5-year PFS rates in the BV - AVD and ABVD groups were 82% and 75%, respectively ($P = .0017$).¹⁰³

A prespecified subgroup analysis confirmed that brentuximab vedotin -AVD was associated with consistent improvement in PFS at 3 years among patients in high-risk subgroups as assessed by the investigator hazard ratio (HR, 0.723 for patients with stage IV disease; $P = .032$; HR, 0.588 for patients with IPS 4–7; $P = .012$).¹¹² The 3-year PFS rate in patients with an IPS of 4–7 was 79.6% in the brentuximab vedotin - AVD group compared to 65.7% for the ABVD group. Patients in the high-risk subgroups did not experience greater incidences of treatment-related adverse events (TEAE) than the total population. However, to date there is no clear benefit of brentuximab vedotin - AVD over ABVD in patients older than 60 years as confirmed by the pre-specified sub-group analyses with extended follow-up for the overall population. The 5-year PFS rates for brentuximab vedotin - AVD were similar to that of ABVD among older patients with stage III disease (HR, 1.051; $P = .917$) or stage IV disease (HR, 0.722; $P = .291$).¹¹³

While the incidence of pulmonary toxicity was lower in the brentuximab vedotin - AVD arm due to the elimination of bleomycin, there was a higher rate of peripheral neuropathy (19% compared to 9% for patients in the ABVD group) and febrile neutropenia (19% compared to 11% for patients in the ABVD group) mandating the use of growth factor support with this regimen.^{102,103} Furthermore, the rate of pulmonary toxicity in the control group does not reflect that of modern management, as bleomycin may be omitted in the vast majority of patients after the first 2 cycles (see RATHL trial discussion above). Upon longer follow-up, continued resolution or improvement of peripheral neuropathy was seen in both groups (85% of patients in the brentuximab vedotin - AVD group compared with 86% on ABVD).¹⁰³

NCCN Recommendations for Stage III–IV Disease

ABVD, the preferred regimen, is initially administered for 2 cycles followed by restaging with PET. Patients with a Deauville score of 1 to 3 are treated with 4 cycles of AVD based on results from the RATHL trial.³¹ After 4 cycles of AVD, patients should be followed and monitored for late effects as described.

For patients with a Deauville score of 4 to 5, recommended treatment is 3 cycles of escalated BEACOPP per RATHL trial results,³¹ followed by reassessment of response with PET. For patients with a Deauville score of 1 to 3, the recommended options are to continue on therapy with 1 additional cycle of escalated BEACOPP alone or combined with ISRT to initially bulky or selected PET-positive sites. A biopsy is recommended for patients with a Deauville score of 4 or 5. If the biopsy is negative, treatment is as described for patients with a Deauville score of 1 to 3. Patients with a positive biopsy should be managed as described for refractory disease.

In select patients younger than 60 years with IPS greater than or equal to 4, escalated BEACOPP is initially administered for 2 cycles followed by restaging with PET. Treatment options for patients with a Deauville score of 1 to 3 include an additional 2 cycles of escalated BEACOPP (total of 4 cycles) or 4 cycles of ABVD. If reduced exposure to bleomycin is desired, the panel recommends omitting bleomycin from ABVD per the RATHL trial.³¹ Following an end-of-treatment PET, ISRT may be considered to initially bulky or PET-positive sites. For patients with a Deauville score of 4 to 5, a biopsy is recommended. Patients with a positive biopsy should be managed as described for refractory disease. Two cycles of escalated BEACOPP (total of 4 cycles)¹⁰⁵ is recommended for negative biopsies, followed by restaging with PET. For patients with a Deauville score of 4 to 5, an additional biopsy is recommended. If the resulting Deauville score is 1 to 3, or 4 to 5 with a negative biopsy, an additional 2 cycles of escalated



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BEACOPP (total of 6 cycles) with or without ISRT is recommended. Patients with a Deauville score of 4 to 5 with a positive biopsy should be managed as described for refractory disease.

Based on the updated safety and efficacy data from ECHELON-1 trial (discussed above), brentuximab vedotin - AVD is now included with a category 2A recommendation for all patients with stage III or IV disease but needs to be used with caution in patients with neuropathy.¹⁰³ Furthermore, its benefit is not clear in patients older than 60 years and its toxicity in this age group should be considered. Long-term results of this trial, especially with respect to potential differences in survival, are awaited. Brentuximab vedotin - AVD is initially administered for 6 cycles followed by restaging with PET.¹⁰³ If performing a PET/CT before completion of 6 cycles, a biopsy is recommended in patients with a Deauville score of 5. Therapy should be re-evaluated for positive biopsies. At the completion of therapy, patients with a Deauville score of 1 to 3 should be managed as described for follow-up and monitored for relapse/late effects. ISRT to initially bulky or PET-positive sites may be considered for patients with a Deauville score of 4 to 5. Alternatively, a biopsy may be considered for patients with a Deauville score of 5 and, if positive, alternative therapy for refractory disease should be pursued.

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

Management of Classic Hodgkin Lymphoma in Older Adults (>60 years)

CHL in older adult patients (>60 years) is associated with worse disease outcomes.¹¹⁴ B symptoms, poor performance status, mixed cellularity,

histologic subtype, Epstein-Barr virus-positive (EBV+) disease, and medical comorbidities are more frequent in this population.¹¹⁵ Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and transplant-related mortality (TRM) in older patients.¹¹⁶⁻¹¹⁹ However, there are limited prospective data evaluating alternatives to standard therapies for older patients. Selection of standard versus alternate first-line regimens should be based on clinical judgment and patient's performance status, with the goal of minimizing toxicity while maximizing efficacy.

In the HD10 and HD13 trials led by the GHSG, the impact of bleomycin in the ABVD regimen in older (≥60 years) patients with stage I–II favorable HL was evaluated. Two hundred eighty-seven patients were randomized to receive: 2 cycles of ABVD or 2 cycles of AVD followed by 20 or 30 Gy IFRT (HD13 study) and 2 cycles of ABVD or 4 cycles of ABVD followed by 20 or 30 Gy IFRT (HD10 study).¹²⁰ Overall grade III–IV toxicity and grade III–IV leukopenia and infection rates were higher in patients receiving 4 cycles of ABVD. The results of the study suggested limited benefit in older patients receiving more than 2 cycles of bleomycin.¹²⁰

Due to pulmonary toxicity, bleomycin should be used with caution, as it may not be tolerated in elderly patients. In a retrospective analysis, 147 patients with stage I–IV HL aged at least 60 years were treated with ABVD and evaluated for toxicity and survival.¹²¹ All patients received at least 1 full course of ABVD and 50 patients received additional RT (30–40 Gy). Bleomycin was removed or reduced in 53 patients due to pulmonary toxicity. CR was observed in 117 patients (80%) with a 5-year OS rate estimated at 67% (95% CI, 58–74).¹²¹ Other risk factors that may be associated with bleomycin-induced pulmonary toxicity (BPT) include a history of smoking and use of granulocyte-colony stimulating factor (G-CSF) during treatment.^{122,123}



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In a phase II multicenter study, the impact of sequential brentuximab vedotin given before and after AVD was examined in untreated older patients with stage II–IV HL (n = 48).¹²⁴ After two lead-in doses of brentuximab vedotin, 37 of 48 patients (77%) completed 6 cycles of AVD, and 35 patients (73%) received at least one brentuximab vedotin consolidation.¹²⁴ Among 42 response-evaluable patients, the overall response and CR rates after 6 cycles of AVD were 95% and 90%, respectively.¹²⁴ By intent-to-treat, the 2-year EFS, PFS, and OS rates were 80%, 84%, and 93%, respectively.¹²⁴

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

- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)¹²⁵
- Brentuximab vedotin plus dacarbazine (DTIC)^{126,127}
- VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin)^{128,129}
- BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)¹¹⁹
- PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine)¹³⁰

NCCN Recommendations

The regimens listed below should be considered in older patients to lessen or minimize toxicity. These regimens have not been proven to overcome the poorer disease outcomes observed in older patients. Clinical trial is recommended when available.

Stage I–II Favorable Disease

ABVD and CHOP are included as primary treatment options for patients older than 60 years with stage I–II favorable disease.^{52,120,121,125,129} In this

setting, 2 cycles of ABVD or AVD followed by ISRT is the preferred option. The other treatment regimen includes 4 cycles of CHOP with ISRT.

Stage I–II Unfavorable or Stage III–IV Disease

ABVD, brentuximab vedotin lead in followed by AVD and brentuximab vedotin maintenance, brentuximab vedotin plus DTIC, and CHOP with or without ISRT are included as primary treatment options for elderly patients with stage I–II unfavorable or stage III–IV disease.^{31,124–127,130} For the ABVD regimen, a PET scan follows treatment with 2 cycles of ABVD. Bleomycin should not be used beyond 2 cycles if included in the regimen. If the PET scan is negative (Deauville score 1–3), patients can be treated with 4 cycles of AVD (total of 6 cycles), although 2 cycles of AVD (total of 4 cycles) followed by ISRT may be considered for stage I–II unfavorable disease. If the PET scan is positive (Deauville score 4–5) after 2 cycles of ABVD, an individualized treatment plan should be developed.

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.¹³¹ The majority of patients present with early-stage disease and rarely with B symptoms, mediastinal or extranodal involvement, or bulky disease.^{132–134} Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma.^{2,135} Data suggest outcomes differ for typical immunoarchitectural patterns (A/B) versus variant patterns (C/D/E/F), with the variant patterns being associated with advanced-stage disease and a higher risk of relapse.^{2,136–138} In the retrospective analysis from the GHSG that included 394 patients with NLPHL, 63% had early-stage favorable, 16% had early-stage unfavorable, and 21% had advanced-stage disease. At a median follow-up of 50 months, FFTF (88%



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vs. 82%) and OS (96% vs. 92%) were better for NLP HL compared with CHL.¹³³ Among patients with NLP HL, 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.¹³² Advanced stage at presentation, age (≥ 45 years), low hemoglobin, and the presence of B symptoms are associated with worse OS.^{133,134}

Several retrospective studies have reported favorable clinical outcomes for patients with stage I to II disease treated with RT alone¹³⁹⁻¹⁴³ or in combination with chemotherapy.^{134,144,145} RT alone is an effective treatment option for patients with stage IA–IIA disease.^{139,141,146} In a retrospective analysis, the Australasian Radiation Oncology Lymphoma Group reported follow-up of 202 patients with stage I–II NLP HL treated with RT alone, including mantle and total lymphoid irradiation (TLI).¹⁴¹ At 15 years, FFP was 84% for patients with stage I disease and 73% for those with stage II disease. An additional retrospective analysis from the GHSG clinical trials reported favorable PFS and OS rates (91.9% and 99.0%, respectively) at 8 years in patients with stage IA disease treated with IFRT.¹⁴⁶

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 NLP HL included in the GHSG HD7 trial showed a non-significant trend toward better 7-year FFTF for the combined modality group (96%) compared with the extended-field radiation therapy (EFRT) group (83%; $P = .07$).¹⁴⁵ However, other retrospective studies have shown no difference in outcome between patients treated with RT alone or in combination with chemotherapy.^{140,142,143} The GHSG retrospectively compared 3 treatment options, including EFRT, IFRT, and combined

modality treatment in patients with stage IA NLP HL.¹⁴² Median follow-up was 78 months for EFRT, 40 months for combined modality, and 17 months for IFRT. CRs 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.

A report from the French Adult Lymphoma Study Group that analyzed the long-term outcomes of 164 patients with NLP HL (82% of patients had stage IA–IIA disease) included 58 patients who were observed following diagnosis and lymph node biopsy.¹⁴⁷ The 10-year PFS rate for this group of patients was 41% compared to 66% for patients who received specific treatment. However, the 10-year OS rate was not different between the two groups (91% and 93%, respectively), and 50% of patients treated with a watch-and-wait approach had achieved a CR at a median follow-up of 3 years. Watchful waiting has also been shown to be an appropriate treatment option in pediatric patients with early-stage NLP HL who are in complete remission following lymph node excision.^{148,149}

Binkley et al reported an international retrospective review of 559 adult patients with stage I–II NLP HL treated with RT alone ($n = 257$), combined modality therapy ($n = 184$), chemotherapy alone ($n = 47$), observation ($n = 37$), rituximab plus RT ($n = 19$), or rituximab monotherapy ($n = 15$). The 5-year PFS and OS for the entire cohort were 87.1% and 98.3%, respectively.¹⁵⁰ The 5-year PFS rates were 91.1% after RT, 90.5% after combined modality therapy, 77.8% after chemotherapy alone, 73.5% after observation, 80.8% after rituximab plus RT, and 38.5% after rituximab monotherapy.¹⁵⁰ The variant immunoarchitectural pattern was associated with a worse PFS. 3.8% of patients developed large-cell transformation.

Patients with advanced-stage NLP HL have a worse prognosis than those with early-stage favorable disease, and can be treated with chemotherapy. In the European Task Force on Lymphoma study, the 8-year



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disease-specific survival and FFTF were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.¹³² 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.¹⁵¹ With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without RT had a superior 10-year time to progression (TTP) (98% vs. 76%), PFS (91% vs. 65%), and OS (93% vs. 84%) compared to those treated with RT alone. However, an analysis of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III–IV NLPHL treated with chemotherapy alone, showed that 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).¹⁵² Some investigators have also reported good response rates with CHOP plus rituximab¹⁵³⁻¹⁵⁵ or CVbP (cyclophosphamide, vinblastine, and prednisolone) in patients with early-stage or advanced disease.¹⁵⁶

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.¹⁵⁷⁻¹⁶¹

In a prospective phase II trial conducted by the Stanford group, previously treated (n = 10) and untreated (n = 12) patients with stage I–IV NLPHL received 4 weekly doses of rituximab at 375 mg/m². The overall response rate (ORR) was 100% (41% CR, 54% partial response [PR], and 5% CR

unconfirmed [CRu]). At a median follow-up of 13 months, 9 patients had relapsed and the estimated median FFP was 10.2 months.¹⁵⁷ The estimated probability of disease progression at 10.2 months was 52%. Rituximab was well tolerated, with few adverse side effects.

In a GHSG phase II study that investigated rituximab in patients with newly diagnosed stage IA NLPHL (n = 28), the ORR was 100% (CR and PR were achieved in 86% and 14% of patients, respectively). At a median follow-up of 43 months, the OS rate was 100%; the PFS rate at 12, 24, and 36 months was 96%, 85%, and 81%, respectively.¹⁵⁹ However, the relapse rate was 25%. In the GHSG phase II study that evaluated rituximab in patients with relapsed or refractory CD20-positive NLPHL (n = 15), the ORR was 94% (8 patients with CR and 6 patients with PR). At a median follow-up of 63 months, median TTP was 33 months and the median OS was not reached.¹⁵⁸

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).¹⁶¹ 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.



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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.^{157,159,161}

NCCN Recommendations for NLPHL

Available evidence from retrospective studies supports the use of ISRT alone as a treatment option for patients with early-stage disease.¹³⁹⁻¹⁴³

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

Chemotherapy and rituximab with or without ISRT is recommended for all patients with stage III–IV disease. Alternatively, patients can be observed if asymptomatic, or treated with local RT for palliation of locally symptomatic disease or rituximab. Abdominal involvement, especially involvement of the spleen, has been associated with the risk of transformation to an aggressive B-cell lymphoma.¹⁶¹ Biopsy of persistent or new subdiaphragmatic sites should be considered to rule out transformation for patients with stage III or IV disease.

Restaging with PET should be done for all patients after completion of initial therapy. Observation is recommended for all patients who are asymptomatic with a clinical response. ISRT is recommended if not

received previously. Biopsy is recommended for patients with stable or progressive disease, especially of subdiaphragmatic sites. 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 that are most commonly used at NCCN Member Institutions.(ABVD, CHOP, or CVbP)^{151,152,154,156} 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.¹⁶²

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, and coordinated with the primary care provider, especially during the first 5 years after treatment to detect recurrence and then annually due to the risk for late complications, including secondary cancers and cardiovascular disease.¹⁶² 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, the dose to the OARs, and cumulative anthracycline dosage given.



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Interim physical examinations and blood tests (CBC, platelets, and ESR if elevated at initial diagnosis and chemistry profile) are performed every 3 to 6 months for 1 to 2 years, then every 6 to 12 months for the next 3 years, and then annually.¹⁶³ Patients who have had neck or superior mediastinal irradiation should have their thyroid function tested at least annually. Annual fasting glucose levels may also be monitored. An annual influenza vaccination and other vaccines as clinically indicated is recommended for all patients (see the [NCCN Guidelines for Survivorship](#)). In addition, patients treated with splenic RT or splenectomy should receive pneumococcal, meningococcal, and Haemophilus influenzae type b revaccination after 5 to 7 years (according to the current Centers for Disease Control and Prevention [CDC] recommendations).

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen.¹⁶⁴ In a randomized trial that compared the use of PET/CT with the combination of 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.¹⁶⁵ 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. A neck/chest/abdominal/pelvis CT scan with contrast should not be obtained more often than every 6 months for the first 2 years following completion of therapy, or as clinically indicated after 2 years, especially in NLPHL where late relapse can occur. However, PET scans are not recommended for routine surveillance due to the risk of false positives.^{75,76,78}

Monitoring for Late Effects

Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most significant late effects in long-term survivors of HL. The incidence of these late effects increases with longer follow-up time.

The risk may be less with current treatment programs compared to those used 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. 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.¹⁶⁶ 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 versus EFRT, although the risk of developing breast cancer was substantially higher for EFRT and was likely related to the extent of mediastinal and axillary irradiation. Risks for secondary lung cancer, non-Hodgkin 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.¹⁶⁷ Lung cancer and breast cancer are the most common secondary cancers in patients treated for HL.

Annual breast screening [mammography and MRI] beginning no later than 8 to 10 years after completion of therapy or at age 40 years (whichever occurs earlier) is recommended for females who have received chest or axillary irradiation.¹⁶⁴ 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 females who received chest irradiation for HL, the sensitivity of the combined MRI and mammography as a combined screening modality was higher than that of MRI or mammography alone (94% for combined MRI



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and mammography; 67% and 68%, respectively, for MRI and mammography).¹⁶⁸ The Guidelines recommend breast MRI in addition to mammography for females who received irradiation to the chest between ages 10 and 30 years, which is consistent with the recommendation of the American Cancer Society Guidelines¹⁶⁹ and the NCCN Guidelines for Detection, Prevention, and Risk Reduction.

The Guidelines recommend that routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer be performed as per the American Cancer Society Guidelines.

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.¹⁷⁰⁻¹⁷² RT-induced cardiotoxicity is usually observed more than 5 to 10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Coronary CT angiography abnormalities have been detected in nearly 15% of the patients within the first 5 years after treatment and their incidence significantly increases 10 years after treatment.¹⁷³ 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.¹⁶⁴ 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 approximately 50% of long-term survivors who received neck or upper

mediastinal irradiation.¹⁶² A careful thyroid examination should be a part of the physical examination. Thyroid function tests should be done at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression

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

Infertility

Certain chemotherapy combinations (eg, BEACOPP) may cause immediate and permanent infertility in both males and females.^{174,175} Other combinations (eg, ABVD) are only rarely associated with infertility.^{86,176} Since females who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause,⁸⁴ this should be taken into consideration with respect to family planning.

Pulmonary Toxicity

Bleomycin 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 aged 40 years or older.¹⁷⁷ They also showed that the



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use of growth factors with chemotherapy significantly increases the incidence of BPT (26% vs. 9%). Two separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.^{178,179} 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.¹⁷⁹

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

Refractory or Relapsed Disease

Classic Hodgkin Lymphoma

Two randomized phase III studies performed by the British National Lymphoma Investigation¹⁸⁰ and the GHSG/European Group for Blood and Marrow Transplantation¹⁸¹ have compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvements in EFS, PFS, and FFTF (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone.

Studies have suggested that patients with a CR or with chemosensitive disease to second-line therapy have improved outcomes following HDT/ASCR compared to those with resistant disease.^{182,183} 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) ($P < .001$).¹⁸² Sirohi et al also reported similar findings; the 5-year OS rate was 79%, 59%, and 17%, respectively, for patients who were in CR, PR, or those with resistant disease at the time of

HDT/ASCR ($P < .0001$), and the 5-year PFS rates were 69%, 44%, and 14%, respectively ($P < .001$).¹⁸³

Several investigators have developed prognostic models to predict the outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice and colleagues used end-of-treatment to relapse interval (≤ 12 months) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR.¹⁸⁴ 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.¹⁸⁵ In patients with zero to one risk factors, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of treatment for relapsed or refractory disease to improve EFS in poorer-risk patients.¹⁸⁶ 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.¹⁸⁷ Investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first CR (< 1 year), detectable disease at transplant, and the presence of > 1 extranodal site as adverse factors for OS.¹⁸⁸ Other groups have identified extent of prior chemotherapy,¹⁸⁹ short time from diagnosis to transplant,¹⁹⁰ and disease status at transplantation¹⁹¹ as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome and it may be the most important factor in patients with recurrent/refractory HL.¹⁹²⁻¹⁹⁵ The main potential of



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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.^{185,196-204} ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, cisplatin, and high-dose cytarabine) are the most commonly used regimens. Gemcitabine-based combination regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),²⁰⁵ IGEV (ifosfamide, gemcitabine, and vinorelbine),²⁰⁶ GCD (gemcitabine, cisplatin, and dexamethasone),^{207,208} and GEMOX (gemcitabine and oxaliplatin)²⁰⁹ have also been effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials.

Bendamustine, lenalidomide, and everolimus as single agents have also shown activity in patients with relapsed or refractory HL.²¹⁰⁻²¹² In a phase II trial, bendamustine was well tolerated and highly active in heavily pretreated patients with relapsed or refractory disease (including those with HL that failed to respond to HDT/ASCR treatment), resulting in an ORR of 56% among evaluable patients (34 out of 36 patients enrolled).²¹⁰ The ORR by intent-to-treat analysis was 53% (33% CR and 19% PR). The median response duration was 5 months. Lenalidomide and everolimus have also shown single-agent activity in a small cohort of patients with relapsed or refractory HL, resulting in ORRs of 19% and 47%, respectively.^{211,212} In a phase II study, bendamustine in combination with gemcitabine and vinorelbine (BeGEV) was used as induction therapy before HDT/ASCR in patients with relapsed or refractory HL, resulting in an ORR of 83% (73% CR and 10% PR).²¹³ In a phase I/II study, bendamustine with carboplatin and etoposide also demonstrated 85% response rates (70% CR) in patients with relapsed or refractory HL.²¹⁴

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive

lymphomas.^{215,216} In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective responses and CRs in 75% and 34% of patients, respectively, with a median follow-up of more than 1.5 years. The median PFS for all patients and the median duration of response for those in CR were 5.6 months and 20.5 months, respectively.²¹⁵ 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.²¹⁶ After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 months and 9.3 months, respectively. In patients who achieved a CR on brentuximab vedotin, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.²¹⁶

Several studies are investigating the utility of brentuximab vedotin in combination with other regimens, as second-line therapy for relapsed or refractory disease prior to HDT/ASCR. Preliminary data from studies have evaluated brentuximab vedotin in combination with ESHAP (etoposide, methylprednisolone, and high-dose cytarabine or cisplatin), ICE, or bendamustine have reported PET-negative responses ranging from approximately 75% to 90%.²¹⁷⁻²²⁰ A trial from Memorial Sloan Kettering Cancer Center (MSKCC) used a PET-adapted design in which 45 patients received 2 cycles of brentuximab vedotin followed by a PET scan.²¹⁸ Patients who achieved a CR after brentuximab vedotin (27%) proceeded directly to HDT/ASCR, while patients with residual disease received 2 cycles of augmented ICE. Overall, 76% of patients achieved a CR prior to HDT/ASCR using this PET-adapted approach.²¹⁸ A similar approach was used by investigators at City of Hope National Medical Center in which 37 patients received 4 cycles of brentuximab vedotin followed by a PET scan.²²¹ Patients who achieved a CR after brentuximab vedotin (35%)



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proceeded directly to HDT/ASCR, while those with residual disease received platinum-based salvage chemotherapy. Overall, 65% of patients achieved a CR prior to HDT/ASCR using this approach.²²¹

The use of brentuximab vedotin as consolidation therapy following HDT/ASCR was evaluated in the AETHERA trial.²²² For high-risk patients defined as having primary refractory disease, duration of first CR less than 1 year, or relapse with extranodal or advanced stage disease, the phase 3 AETHERA trial randomized patients to receive up to 16 cycles of BV consolidation or placebo post-HDT/ASCR. Patients were required to have obtained a CR, PR, or stable disease to second-line therapy prior to HDT/ASCR. At 5-year follow-up, there was a sustained PFS benefit with BV consolidation compared to placebo (5-year PFS, 59% vs. 41%; HR, 0.52; 95% CI, 0.38–0.72) but no difference in OS. Peripheral sensory neuropathy was a common side effect of BV consolidation, but improved or resolved in the majority of patients after discontinuing therapy.

Attempts to increase the CR rate prior to HDT/ASCR have led to numerous trials incorporating the novel agents into initial second-line therapy. Checkpoint inhibitors (CPIs) including programmed death 1 (PD-1)-blocking monoclonal antibodies (eg, nivolumab or pembrolizumab) have also demonstrated activity in patients with relapsed or refractory PD-1–positive lymphomas (either as monotherapy or in combination regimens).²²³⁻²³¹

In a phase II study (CheckMate 205 trial) of 80 patients with relapsed or refractory HL and pretreated with both HDT/ASCR and brentuximab vedotin, at a median follow-up of 8.9 months, nivolumab monotherapy induced an ORR of 66.3% (95% CI, 54.8–76.4) as determined by an independent radiologic review committee.²²⁴ Extended follow-up of the CheckMate 205 trial analyzed the safety and efficacy of nivolumab in patients with relapsed or refractory HL according to treatment history: brentuximab vedotin-naïve, brentuximab vedotin after HDT/ASCR, or

brentuximab vedotin received before and/or after HDT/ASCR.²²⁵ The ORR was 69% (95% CI, 63%–75%) overall and 65% to 73% in each cohort, with a median duration of response of 16.6 months (95% CI, 13.2–20 months).²²⁵

In a phase III trial (KEYNOTE-204), pembrolizumab monotherapy versus brentuximab vedotin was evaluated on the parameters of safety and efficacy in adults with R/R cHL (patients who were ineligible for transplant or those with relapse after autologous HCT; 151 patients were randomly assigned to pembrolizumab and 153 patients to brentuximab vedotin).²³⁰ At second interim analysis, primary endpoint PFS (OS not analyzed in interim analysis) was 13.2 months for pembrolizumab, and 8.3 months for brentuximab vedotin ($P = .0027$).²³⁰ TEAEs were observed in 74% of patients receiving pembrolizumab and 77% of patients receiving brentuximab vedotin. The most common grade 3–5 TEAEs were pneumonitis (4% in the pembrolizumab group vs. 1% in the brentuximab group), neutropenia (2% vs. 7%, respectively), decreased neutrophil count (1% vs. 5%, respectively) and peripheral neuropathy (1% vs. 3%, respectively).²³⁰ Serious TEAEs were observed in 16% of patients receiving pembrolizumab and 11% of patients receiving brentuximab vedotin.²³⁰

Nivolumab in combination of brentuximab vedotin was evaluated as an option for relapsed or refractory HL prior to transplant.²²⁷ In a phase I/II study of 91 patients with relapsed/refractory CHL, the combination of nivolumab with brentuximab vedotin resulted in an ORR of 85% (67% CR). At a median follow-up of 34 months, the estimated 3-year PFS and OS rates were 77% (91% for patients who underwent HDT/ASCR directly after study treatment with BV + nivolumab) and 93%, respectively.²²⁷ Pembrolizumab used in combination with GVD also has demonstrated activity as second-line treatment in transplant eligible patients with relapsed/refractory CHL resulting in a CR rate of 95%.²³¹ At a median



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follow-up of 13.5 months, all patients who had undergone transplant had achieved remission.

The role of RT in the second-line therapy settings includes its use to cytoreduce prior to HDT/ASCR, its selective use to sites of relapse following HDT/ASCR, and occasionally its use as a primary component of second-line therapy. Moskowitz and colleagues have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease.¹⁸⁵ At a median follow-up of 43 months, the response rate to ICE and IFRT was 88% and the EFS rate for patients who underwent HDT/ASCR was 68%. Thus, RT may improve the chance of transitioning to HDT/ASCR in relapsed or refractory disease. Alternately, second-line RT may be effective in patients who are in good performance status with limited-stage late relapses and without B symptoms. It may be a very effective treatment for patients with initial favorable stage I–II disease who are treated with chemotherapy alone and relapse in initially involved sites. Josting and colleagues from the GHSG reported that second-line RT may be effective in a select subset of patients with relapsed or refractory disease.²³² The 5-year FFTF and OS rates were 28% and 51%, respectively. B symptoms and stage at the time of disease progression or relapse were identified as significant prognostic factors for OS. A comprehensive review and recommendations for incorporation of RT into salvage treatment programs is provided by the International Lymphoma Radiation Oncology Group consensus guidelines.²³³

NCCN Recommendations for Refractory CHL

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or systemic therapy with or without RT. Conventional-dose second-line systemic

therapy may precede HDT/ASCR. RT should be strongly considered for selected sites of relapse that have not been previously irradiated. In radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR.²³⁴

Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should proceed to HDT/ASCR with or without RT (category 1). Observation with or without RT can be considered, if HDT/ASCR is contraindicated. Maintenance therapy with brentuximab vedotin (for one year) can be considered for patients with high risk of relapse as defined by the AETHERA trial (defined as those having primary refractory disease, duration of first CR less <1 year, or relapse with extranodal or advanced stage disease).²²² An alternative regimen with or without RT or RT alone is recommended for patients with a Deauville score of 4 or 5 after second-line systemic therapy. Autologous or allogeneic HCT following additional therapy may be considered in these patients. Another approach for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT, followed by maintenance therapy with brentuximab vedotin (for 1 year) for patients with a high risk of relapse. It is worth noting that the role of maintenance brentuximab vedotin has not been well defined in patients who received brentuximab vedotin earlier in the management of their disease.

Brentuximab vedotin alone or in combination with bendamustine or nivolumab^{220,235}; DHAP^{197,200}; ESHAP^{198,201,236}; GVD with or without pembrolizumab^{205,231}; ICE^{185,197}; IGEV²⁰⁶; and BeGEV²¹³ regimens are included as options for second-line systemic therapy for patients with relapsed or refractory CHL. Bendamustine, everolimus, and lenalidomide are included as subsequent therapy options for patients with relapsed or refractory CHL.^{210–212} Nivolumab^{224,225} and pembrolizumab^{229,230} are included as subsequent therapy options for patients with



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relapsed/refractory CHL after 2 or more line of systemic therapy and also for patients with relapse or disease progression following HDT/ASCR and post-transplant brentuximab vedotin. Pembrolizumab is also included as a second-line therapy option for relapsed/refractory disease in patients who are not eligible for transplant.^{229,230}

Allogeneic HCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was greater than 50%. Allogeneic HCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.^{237,238} However, this approach remains investigational. Nonmyeloablative allogeneic HCT and post-infusion cyclophosphamide has excellent outcomes even in haploidentical patients with estimated OS and PFS rates of 63% and 59%, respectively, at 3 years.²³⁹ The panel has included allogeneic HCT with a category 3 recommendation for select patients with refractory or relapsed disease. Autologous or allogeneic HCT is an option for patients with PET-positive refractory HL (Deauville 5) that is responsive to RT alone or to subsequent systemic therapy, with or without RT.

NCCN Recommendations for Relapsed CHL

Suspected relapse at any point 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. Most patients require second-line systemic therapy followed by RT or HDT/ASCR with or without ISRT. For patients with initial stage I–IIA disease treated initially with abbreviated chemotherapy alone (3–4 cycles) and relapsed in initial sites of disease RT alone may be appropriate.

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

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

Outcomes are uniformly poor for elderly patients with relapsed or refractory disease.²⁴⁰ No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended. Palliative therapy options include bendamustine,²¹⁰ brentuximab vedotin,²⁴¹ everolimus,²¹² lenalidomide,²¹¹ nivolumab,^{224,225} and pembrolizumab.²³⁰ Nivolumab and pembrolizumab may be considered when patients have been previously treated with brentuximab vedotin or after three or more lines of systemic therapy, including HDT/ASCR. ISRT alone is an option when systemic therapy is not considered feasible or safe.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Patients with refractory or relapsed NLP HL 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 NLP HL.

NCCN Recommendations for Refractory or Suspected Relapsed NLP HL

Late relapse or transformation to diffuse large B-cell lymphoma (DLBCL) has been reported in patients with NLP HL.^{242–244} In a study of 95 patients diagnosed with NLP HL, 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.²⁴⁴

Re-biopsy should be considered to rule out transformation to aggressive lymphoma prior to initiation of treatment for refractory disease or suspected disease relapse. Patients with a negative biopsy can be observed with short-interval follow-up. All patients with biopsy-proven



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relapsed NLP HL should be observed or treated with second-line therapy (rituximab and/or chemotherapy and/or ISRT) followed by restaging with PET/CT. No further treatment is necessary for patients with clinical response. Biopsy is recommended for patients with progressive disease to rule out transformation. At this stage, patients should be managed as described for refractory disease or treated with any second-line therapy that was not previously used (rituximab and/or chemotherapy and/or ISRT) followed by reevaluation with PET. Maintenance rituximab for 2 years may be considered for patients treated with rituximab alone.¹⁶¹ Patients with disease transformation to DLBCL should be managed as discussed in the [NCCN Guidelines for B-Cell Lymphomas](#).

Summary

HL is an uncommon malignancy of B-cell origin. CHL and NLP HL are the two main types of HL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLP HL is characterized by the presence of lymphocytic and histiocytic (LP or “popcorn”) 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 or chemotherapy alone are included as treatment options for patients with stage I or II CHL. Chemotherapy, followed by restaging with PET/CT to assess treatment response is recommended for patients with stage III-IV CHL.

Second-line systemic therapy followed by HDT/ASCR with or without RT is recommended for patients with relapsed or refractory CHL. Maintenance therapy with BV (for 1 year) following HDT/ASCR can be considered for patients with high risk of relapse. Nivolumab or pembrolizumab (as

monotherapy or in combination regimens) are also included as options for relapsed or refractory disease in appropriate patients.

ISRT is the preferred treatment for patients with stage IA or IIA non-bulky NLP HL. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky or non-contiguous disease. Chemotherapy with rituximab and with or without ISRT is recommended for all patients with stage III-IV disease. Alternatively, selected patients with stage III-IV disease can either be observed (if asymptomatic) or treated with local palliative RT or rituximab.

Late relapse or transformation to DLBCL has been reported in patients with NLP HL. In patients with suspected relapse, re-biopsy should be considered to rule out transformation to DLBCL. Patients with refractory or relapsed NLP HL 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.

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



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