National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 4.2021 — April 20, 2021

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ф Diagnostic radiology
‡ Hematology/ Hematology oncology
Þ Internal medicine
† Medical oncology
ϕ Nuclear medicine
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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.

Updates in Version 4.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 3.2021 include:

HODG-8
- **Footnote added: An FDA-approved biosimilar is an acceptable substitute for rituximab. (Also on HODG-13, and HODG-C)**

MS-1
- **Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 3.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2021 include:

HODG-D (3 of 11)
- **New section added: RT Dose Constraints for Lymphoma**

HODG-D (9 of 11)
- **References have been updated.**

Continued

Updates in Version 2.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 1.2021 include:

HODG-5

- **Footnote o added: 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).**

Updates in Version 1.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2020 include:

General

- **Algorithms for early-stage classic HL have been combined and significantly revised:**
  - **CS I-II *Favorable* (*I/IIA,* non-bulky)**
  - **CS I-II *Unfavorable (I/IIB or bulky mediastinal disease or >10 cm adenopathy)***
- **Important considerations added:**
  - **Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon 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.**

HODG-1

- **Diagnostic CT (contrast-enhanced) moved from "essential" to "useful in selected cases"**
- **Useful in selected cases**
  - **7th bullet modified: Adequate bone marrow biopsy if there are *unexplained cytopenias other than anemia (eg, thrombocytopenia or neutropenia)* ~~cytopenias~~ and negative PET**
  - **8th bullet modified: Evaluation of ejection fraction if ~~doxorubicin~~ *anthracycline*-based chemotherapy is indicated**
  - **9th bullet modified: MR*I to select sites, with contrast unless contraindicated***
- **Footnotes modified:**
  - **a: Fine-needle aspiration (FNA) alone, in distinction from a core biopsy, is *generally* insufficient for diagnosis. ~~except in unusual circumstances when in combination with immunohistochemistry it is judged adequate by a hematopathologist or cytopathologist.~~**
  - **b: "... *EBER is recommedned at initial diagnosis.* An expanded panel of markers (eg, ~~EBER~~ *MUM-1,BOB-1, OCT-2*) may be required. See NCCN Guidelines for B-Cell Lymphomas. *For NLPHL, immunoarchitectural pattern should be specified as typical vs. variant.***
  - **c: *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.**
  - **d: See Principles of FDG-PET/CT (HODG-A). ~~PET/CT should be obtained in accordance with American College of Radiology (ACR) practice guidelines.~~ PET/CT should be done...**

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Updates in Version 1.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2020 include:

HODG-2
- Table significantly modified.
- Columns removed: Number of Nodal Sites; Erythrocyte Sedimentation Rate (ESR) (at diagnosis)
- Footnote removed: E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation. (Engert A, et al. N Engl J Med 2010;363:640-652.)

HODG-3 and **HODG-4**
- References have been added throughout the algorithms. See HODG-7A for references. (Also applies to HODG-5/6/7)
- Footnote added: 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). (Also on HODG-4)
- Footnote added: 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. (Also on HODG-4/5/6/7)
- Footnotes removed:
  - Other recommended primary therapy regimens include: Stanford V x 8 weeks + 30 Gy ISRT (Advani RH, et al. Ann Oncol 2013;24:1044-1048.)
  - Other recommended primary therapy regimens include: Stanford V x 12 weeks + 30 Gy ISRT (Gordon LI, et al. J Clin Oncol 2013;31:684-691.); If GHSG HD14 unfavorable (see HODG-B): Escalated BEACOPP x 2 cycles followed by ABVD x 2 cycles + 30 Gy ISRT (von Tresckow B, et al. J Clin Oncol 2012;30:907-913.)
  - Other recommended regimens: Stanford V x 12 weeks + ISRT in select patients where reduced cumulative doses of doxorubicin and/or bleomycin are desired. (Gordon LI, et al. J Clin Oncol 2013;31:684-691.); or Escalated BEACOPP x 2 cycles followed by ABVD x 2 cycles + 30 Gy ISRT (if GHSG HD14 unfavorable, see HODG-B. Patients with B symptoms in combination with bulky or extranodal disease were excluded and treated according to the algorithm for stage III–IV disease (HODG-9).)(von Tresckow B, et al. J Clin Oncol 2012;30:907-913)

HODG-5
- Top pathway, following AVD x 4 cycles: Removed "observe or ISRT to initially bulky or selected PET+ sites"
- Deauville 4–5: Pathways combined and significantly modified.
- Footnote added: Consider ISRT to initially bulky or PET+ sites. See Principles of Radiation Therapy (HODG-D). (Also on HODG-6/7)
- Footnote removed: ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).

HODG-6
- Deauville 4–5: Pathways combined.

HODG-7
- Footnote added: 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.

HODG-7A
- Primary treatment reference page added.

HODG-8
- Footnote added: See Principles of Radiation Therapy (HODG-D).
- Footnote modified: ~~Consider biopsy of persistent or new subdiaphragmatic sites to rule out transformation.~~ ***Recommend biopsy for sites of progressive disease, especially subdiaphragmatic sites, to rule out transformation.***

HODG-9
- Follow-up After Completion of Treatment Up to 5 Years
  - 4th bullet modified: ~~Acceptable to obtain a~~ Neck/chest/abdomen/pelvis CT scan with contrast *no more often than every 6 months for the first 2 y* ~~at 6, 12, and 24 mo~~ following completion of therapy, or as clinically indicated. PET/CT only if last PET was Deauville 4–5, to confirm complete response.
  - Footnote added: 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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Updates in Version 1.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2020 include:

HODG-10
- Bullet removed: Screening for secondary cancers as clinically indicated (See NCCN Guidelines for Survivorship).

HODG-11
- Deauville 5, modified maintenance therapy: *If response, consider transplant* (autologous or allogeneic) ~~stem cell transplant if response to secondary therapy~~
- Footnote removed: Allotransplant is an option in select patients as a category 3 recommendation.
- Footnote added: The role of maintenance brentuximab vedotin has not been well-defined in patients who received brentuximab vedotin prior to maintenance therapy.
- Footnote removed: ~~Moskowitz CH, Nademanee A, Masszi T, et al. 1. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;385:1853-1862.~~

HODG-12
- Initial stage IA-IIA (no prior RT with failure in initial sites)
  - Second-line therapy modified for patients who received abbreviated chemotherapy (3–4 cycles) without RT:
    - ◊ Option removed: RT alone in highly selected cases.
    - ◊ Option modified: *Second-line systemic therapy followed by* HDT/ASCR ± ISRT
  - Second-line therapy modified for patients who received full-course chemotherapy: Second-line systemic therapy ~~+ RT or~~ *followed by* HDT/ASCR ± ISRT
- All others
  - Second-line therapy modified: Second-line systemic therapy *followed by HDT/ASCR ± ISRT*
- Footnote modified: Strongly consider radiation therapy for selected sites that have not been previously irradiated. ~~In a radiation-naive patient, TLI may be an appropriate component of HDT.~~
- Footnote removed: For patients not considered suitable for more aggressive therapy, radiation therapy can be used alone as a second-line therapy and conventional involved-field or extended-field treatment is indicated.

HODG-A
- Interpretation
  - 4th bullet modified: The final report for any PET/CT examination to define response should include the Deauville 5-point scale score*, which is a visual score*.
  - 5th bullet modified: 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 when no appropriate Deauville score has been provided.*

HODG-A (2 of 2)
- Table moved from former HODG-E.
- Added column to define negative and positive scores.
- 4 modified: Uptake moderately higher than liver *and visually above adjacent background activity*
- Footnote added: 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

HODG-B (2 of 2)
- Table expanded to include infradiaphragmatic nodal regions.

HODG-C (1 of 5)
- Bullet modified: The most common variants of chemotherapy used at NCCN Member Institutions include ABVD ~~and Stanford V~~.
- Stanford V reference removed.
- Escalated BEACOPP reference added: 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.

HODG-C (3 of 5)
- CHL, second-line option added: Pembrolizumab (for patients not candidates for transplant)
- NLPHL, second-line options added:
  - R-Bendamustine
  - R-CHOP (if not previously used)
  - R-ABVD (if not previously used)
  - R-CVP (if not previously used)

Continued

Updates in Version 1.2021 of the NCCN Guidelines for Hodgkin Lymphoma from Version 2.2020 include:

HODG-C (5 of 5)
- **References added.**

HODG-E (1 of 2)
- **Stage I–II Favorable Disease**
  - **Option removed: VEPEMB ± ISRT**
- **Stage I–II Unfavorable or Stage III–IV Disease**
  - **Option removed: PVAG ± ISRT**
  - **Option removed: VEPEMB ± ISRT**
- **Footnote modified: Bleomycin should be used with caution as it may not be tolerated in older adults, *and it should not be used beyond two cycles.***
- **ISRT doses have been removed, and a replaced with a footnote: See Principles of Radiation Therapy (HODG-E).**

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DIAGNOSIS/WORKUP

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic[a]
- Immunohisto-chemistry 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, platelets
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for women of childbearing age
- PET/CT scan[c] (skull base to mid-thigh or vertex to feet in selected cases)
- Counseling: Fertility, smoking cessation, psychosocial (See NCCN Guidelines for Supportive Care)

Useful in selected cases:
- Fertility preservation[d]
- Pulmonary function tests (PFTs incl. diffusing capacity [DLCO])[e] 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[f] (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[g]
- Evaluation of ejection fraction if anthracycline-based chemotherapy is indicated
- MRI to select sites, with contrast unless contraindicated
- PET/MRI (skull base to mid-thigh) without contrast

CLINICAL PRESENTATION

- Classic Hodgkin lymphoma (CHL)[h] → 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 is recommedned at initial diagnosis. 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 typical vs. variant.

[c] 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).

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

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

[f] 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 neck/chest/abdomen/pelvis, at minimum include the areas identified as abnormal on PET/CT.

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

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

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.

CLINICAL STAGING/RISK CLASSIFICATION OF CLASSIC HODGKIN LYMPHOMA (CHL)[i]

Clinical Stage	Bulky Mediastinal Disease[i] or >10 cm Adenopathy	Guidelines Page
I/IIA	No	Favorable Disease (HODG-3)
	Yes	Unfavorable Disease (HODG-4)
IB/IIB	Yes/No	Unfavorable Disease (HODG-4)
III–IV	Yes/No	HODG-5

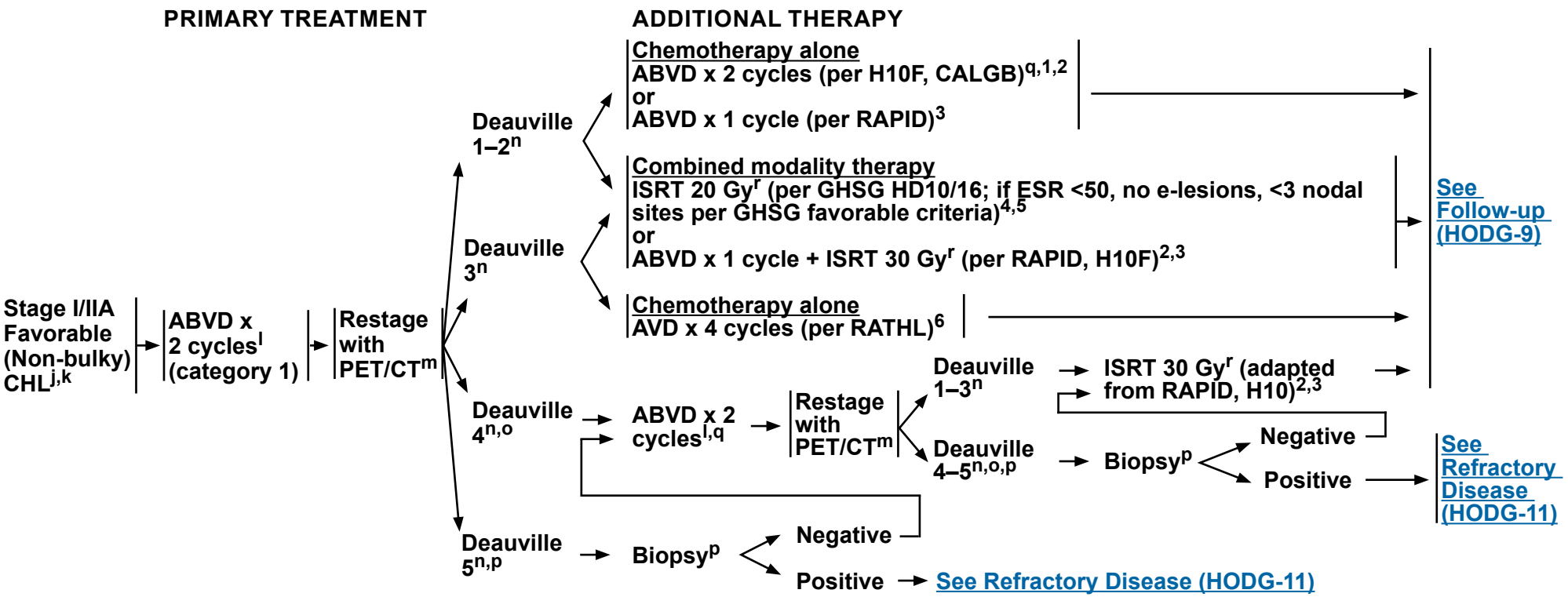
- **Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).**
- **Most patients will benefit from multidisciplinary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

[i]For definitions of bulky disease and lymph node regions, see HODG-B.

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.

CLINICAL PRESENTATION:
Stage I/IIA Favorable (Non-Bulky) CHL[h,k]

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon 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.



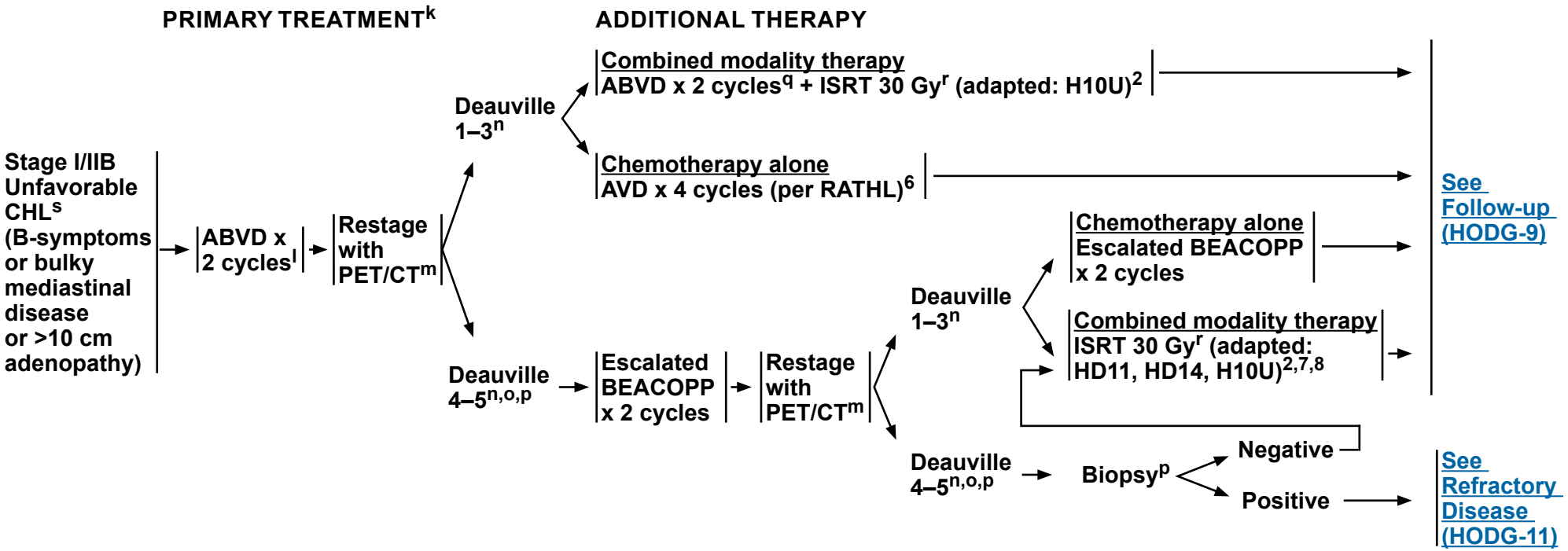
[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[k] Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[o] 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).
[p] 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.
[q] Consider PFTs after 4 cycles of ABVD.
[r] ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).

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

CLINICAL PRESENTATION:
Stage I/IIB Unfavorable CHL[h,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 upon 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.



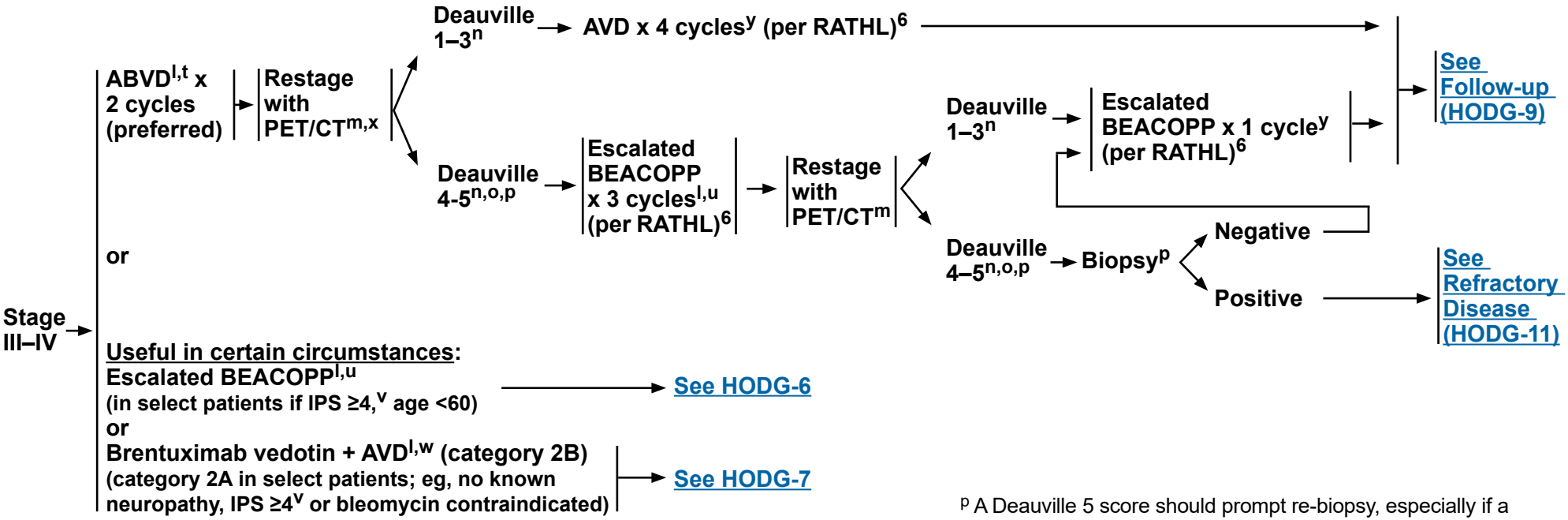
[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[k] Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[o] 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).
[p] 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.
[q] Consider PFTs after 4 cycles of ABVD.
[r] ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).
[s] NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-B).

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

CLINICAL PRESENTATION:
Stage III–IV CHL[h,k]

PRIMARY TREATMENT[k]



[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[k] Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[o] 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).
[p] 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.
[t] ABVD is preferred based on the toxicity profile and quality of data.
[u] Escalated BEACOPP is only an option for those aged <60 years.
[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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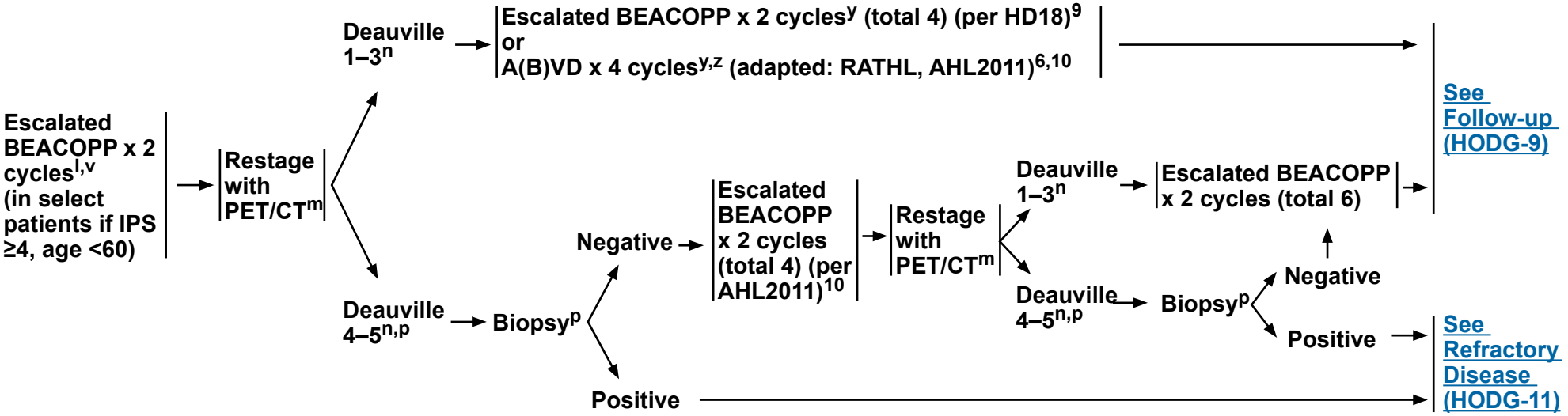
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

REFERENCES

CLINICAL PRESENTATION:
Stage III–IV CHL[h]

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



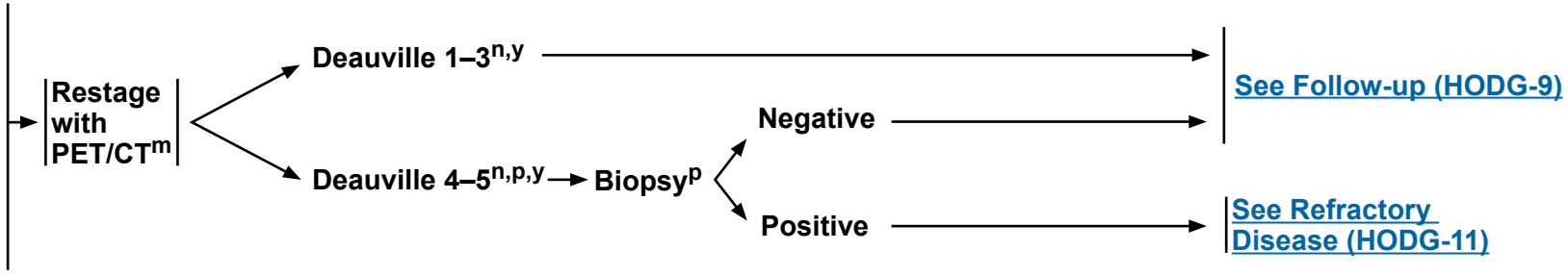
[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[k] Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[p] A Deauville 5 score may 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).
[z] Bleomycin is optional.

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

CLINICAL PRESENTATION:
Stage III–IV CHL[h]

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



[h] CHL includes NSHL, MCHL, LDHL, and LRHL subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[k] Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[p] A Deauville 5 score may 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.
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[v] See International Prognostic Score (IPS) (HODG-B).
[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).
[aa] 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.
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

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(10):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(16):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(17):1598-1607.

[4] GHSG HD10: 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(7):640-652.

[5] 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(31):2835-2845.

[6] 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(25):2419-2429.

[7] HD11: Eich HT, Diehl V, Görgen 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(27):4199-4206.

[8] HD14: 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(9):907-913.

[9] 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(10114):2790-2802.

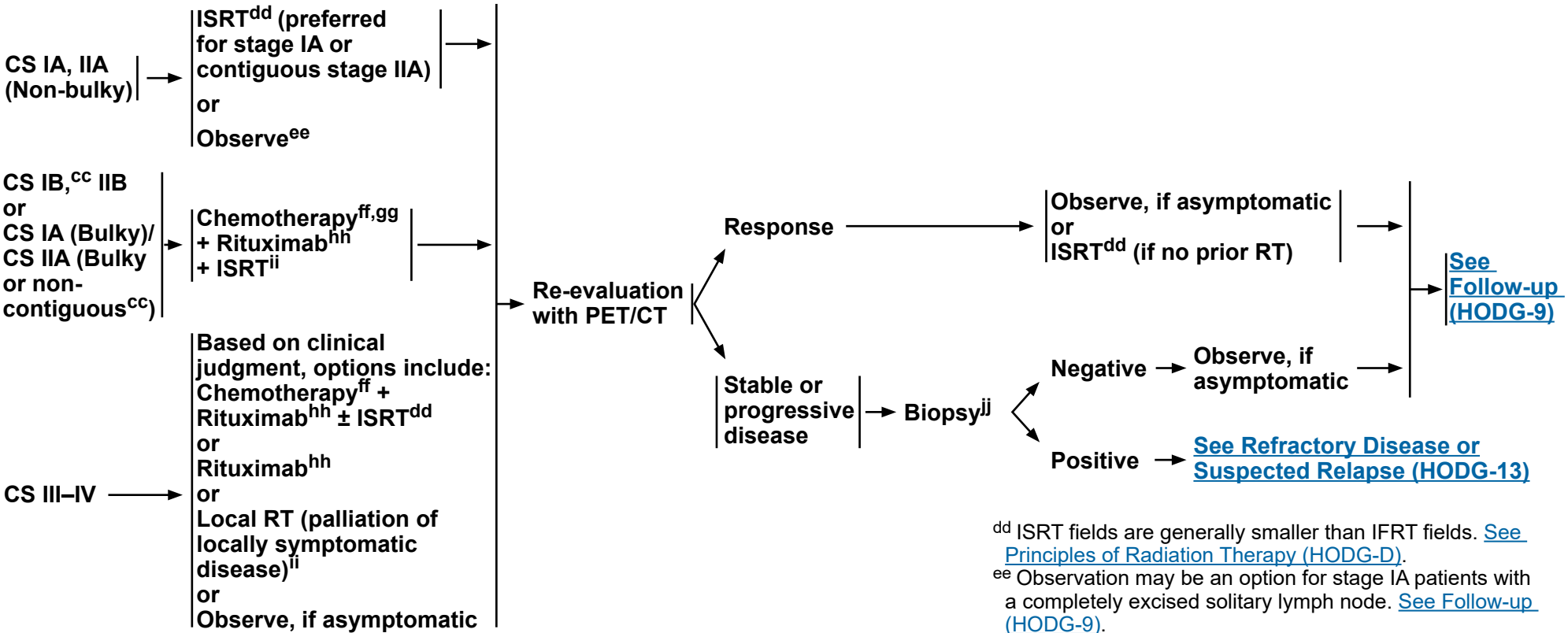
[10] AHL2011: Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol 2019;20:202-215.

[11] ECHELON-1: Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma [published correction appears in N Engl J Med 2018 Mar 1;378(9):878] N Engl J Med 2018;378(4):331-344.

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.

CLINICAL PRESENTATION:
Nodular Lymphocyte-Predominant Hodgkin Lymphoma[bb]

PRIMARY TREATMENT



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

[ee] Observation may be an option for stage IA patients with a completely excised solitary lymph node. See Follow-up (HODG-9).

[ff] See Principles of Systemic Therapy (HODG-C 2 of 4).

[gg] Generally a brief course of chemotherapy (3–4 months) would be given with radiation therapy.

[hh] An FDA-approved biosimilar is an acceptable substitute for rituximab.

[ii] See Principles of Radiation Therapy (HODG-D).

[jj] Recommend biopsy for sites of progressive disease, especially subdiaphragmatic sites, to rule out transformation.

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

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 his/her 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 years 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).[kk,ll] Late relapse or transformation to large cell lymphoma may occur in NLPHL.**
- **The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.**

Follow-up After Completion of Treatment Up to 5 Years

- **Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually**
- **Annual influenza vaccine and other vaccines as clinically indicated (see NCCN Guidelines for Survivorship)**
- **Laboratory studies:[mm]**
  - **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.**
- **Neck/chest/abdomen/pelvis CT scan with contrast no more often than every 6 months for the first 2 y following completion of therapy, or as clinically indicated. PET/CT only if last PET was Deauville 4–5, to confirm complete response.**
- **Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.**
- **Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.**

Suspected Relapse CHL (HODG-12) or NLPHL (HODG-13)

Follow-Up and Monitoring After 5 Years (HODG-10)

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

[ll] Appropriate medical management should be instituted for any abnormalities.

[mm] 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.

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.

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

Follow-up and Monitoring After 5 Years[kk,ll]

- **Interim H&P: Annually**
  - **Annual blood pressure, aggressive management of cardiovascular risk factors.**
  - **Pneumococcal, meningococcal, and 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, 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-exam, and skin cancer risk.**
- **Treatment summary and consideration of transfer to PCP.**
- **Consider a referral to a survivorship clinic.**

[kk]Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation-Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol Suppl 2005;(66):68-76.
[ll]Appropriate medical management should be instituted for any abnormalities.

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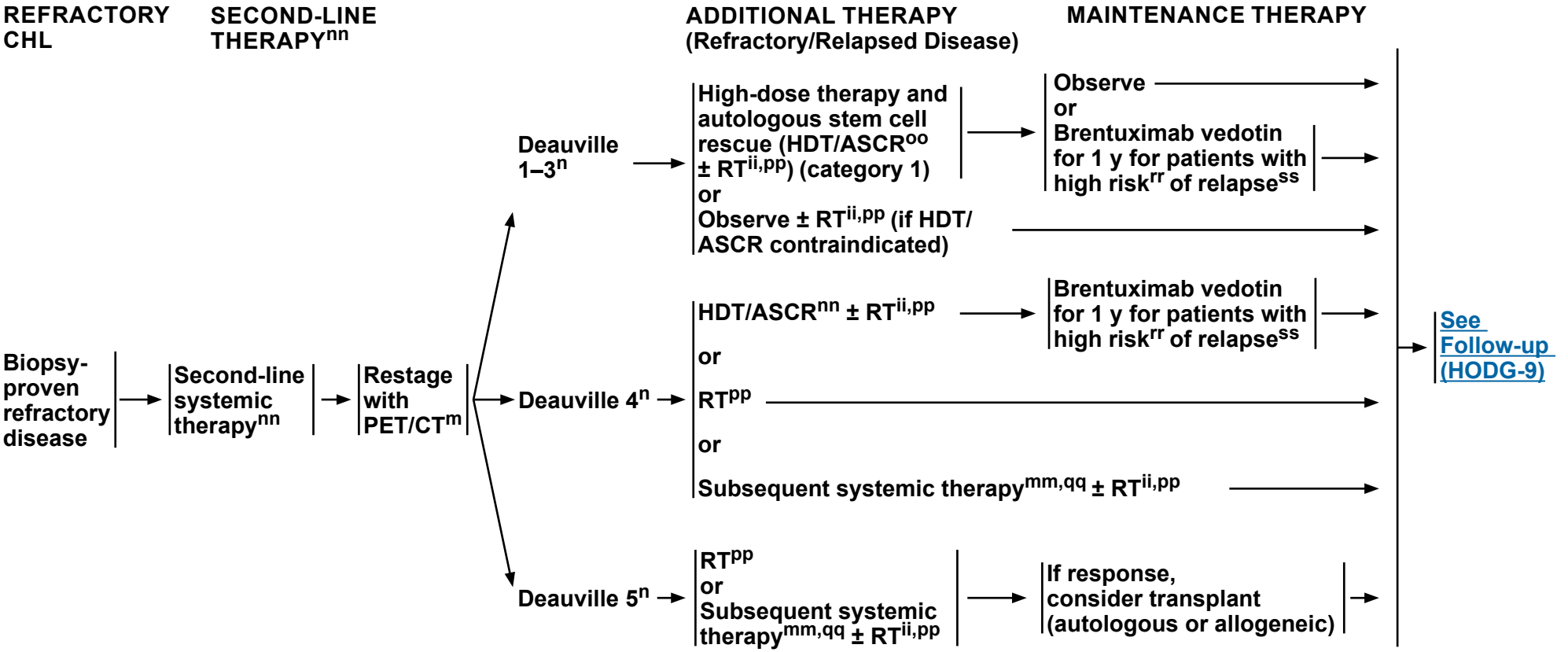

[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[n] See PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[ii] See Principles of Radiation Therapy (HODG-D).
[nn] See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4).
[oo] Strongly consider radiation therapy for selected sites that have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.
[pp] Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[qq] Subsequent systemic therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 4).
[rr] Patients with 2 or more of the following risk factors are considered high risk: Remission duration less than 1 year, extranodal involvement, PET+ response at time of transplant, B symptoms, and/or >1 salvage/subsequent therapy regimen.
[ss] The role of maintenance brentuximab vedotin has not been well-defined in patients who received brentuximab vedotin prior to maintenance therapy.

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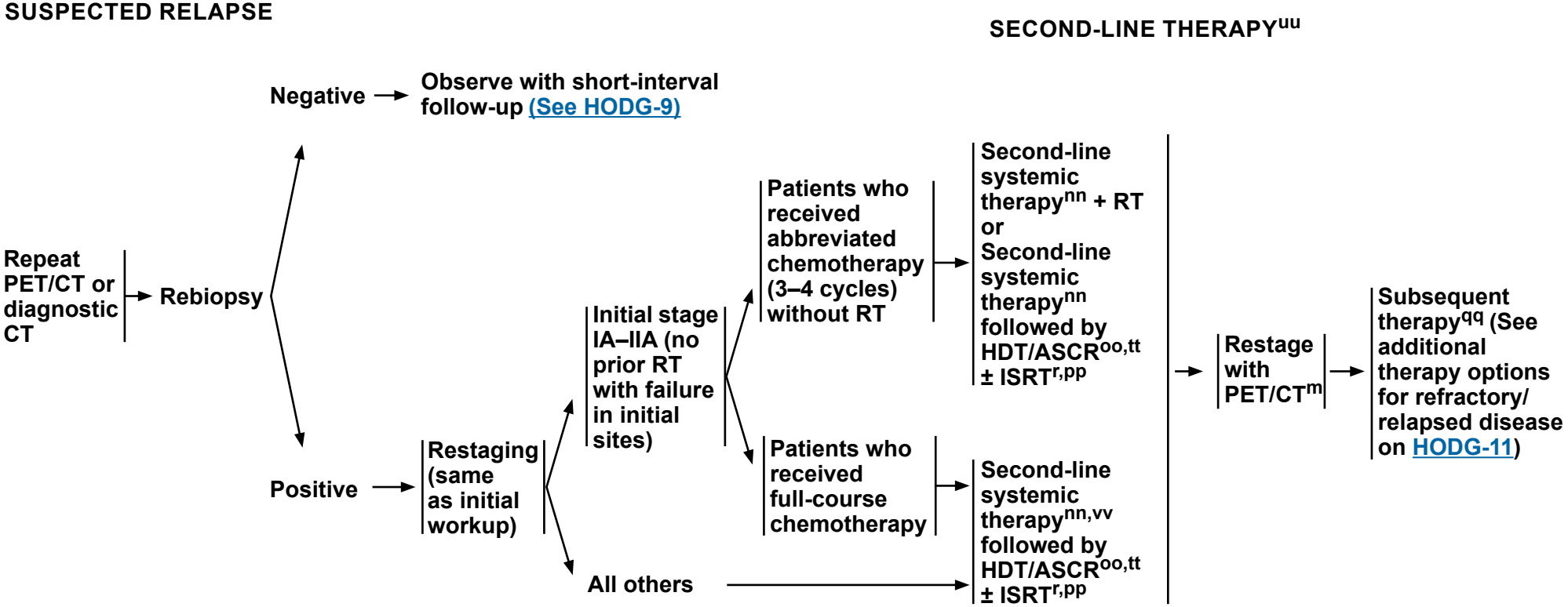
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CHL
SUSPECTED RELAPSE

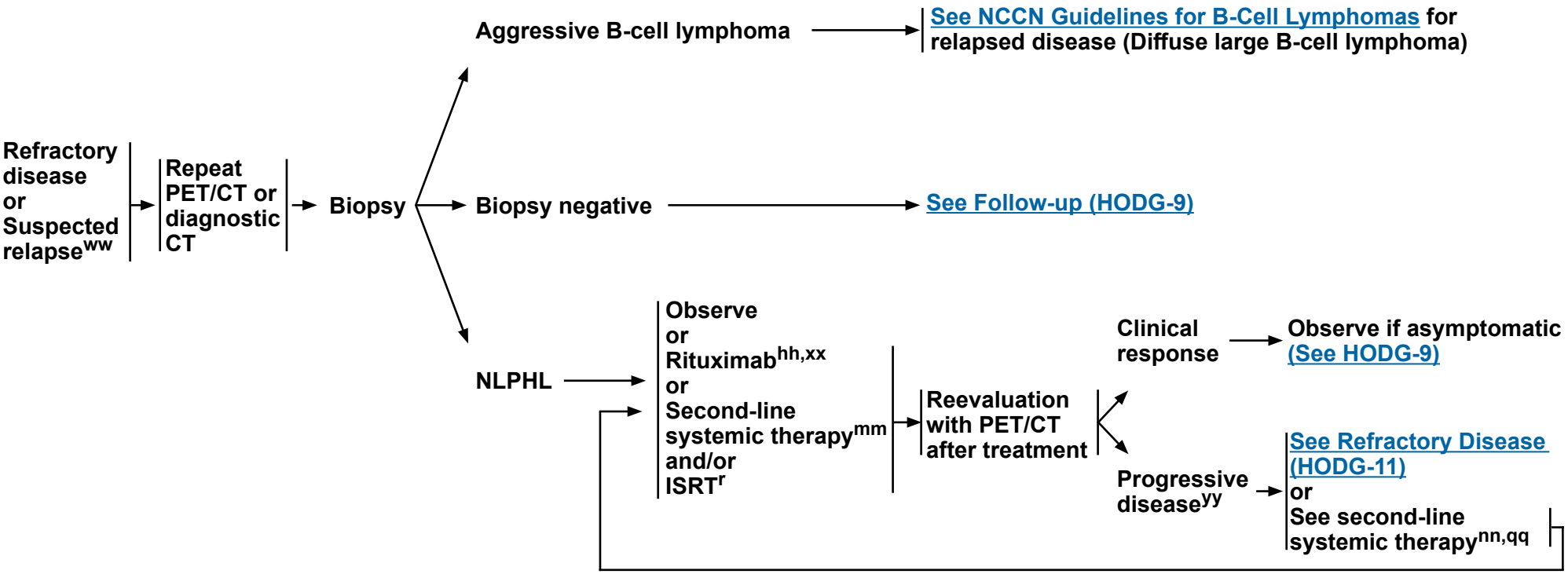


[m] An integrated PET/CT or a PET with a diagnostic CT is recommended. See Principles of FDG-PET/CT (HODG-A).
[r] ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).
[nn] See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4).
[oo] Strongly consider radiation therapy for selected sites that have not been previously irradiated.
[pp] Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[qq] Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 4).
[tt] Allotransplant is an option in select patients as a category 3 recommendation.
[uu] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[vv] For select patients with long disease-free interval and other favorable features, selection of chemotherapy should be individualized.

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

NLPHL
REFRACTORY OR SUSPECTED RELAPSE

SECOND-LINE THERAPY[uu]



[r] ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-D).
[hh] An FDA-approved biosimilar is an acceptable substitute for rituximab.
[nn] See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4).
[qq] Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-C, 3 of 4).
[uu] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[ww] At relapse, patient should be considered for re-biopsy because of risk for transformation, especially if intraabdominal or splenic disease. Some patients with NLPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed.
[xx] In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years.
[yy] Consider rebiopsy to rule out transformation.

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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.

PRINCIPLES OF FDG-PET/CT

Technique

- For FDG-PET/CT performed in the setting of staging or response assessment in Hodgkin lymphoma, image acquisition should be obtained in accordance with the American College of Radiology (ACR) practice parameter guidelines[1] 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]
- FDG-PET/CT scans obtained outside of these parameters (for example 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 one month prior to the initiation of therapy.
- The initial study should include a contrast-enhanced diagnostic CT if it is expected that radiation therapy may be a component of initial treatment.

Interpretation

- The panel supports the ACR[1] and SNMMI[2] 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 1,000 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 exams 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 the 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 January 24, 2020.
[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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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
	X[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(27):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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PRINCIPLES OF UNFAVORABLE RISK FACTORS

Unfavorable Risk Factors for Stage I–II Classic 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 the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

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

- **Albumin <4 g/dL**
- **Hemoglobin <10.5 g/dL**
- **Male**
- **Age ≥45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count at least 15,000/mm^3)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm^3)**

†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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PRINCIPLES OF 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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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

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

Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640-652.
Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598-1607.
Andre 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 HD 11 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, Cobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet 2012;379(9828):1791-1799.
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, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. J Clin Oncol 2012:30:907-913.

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

Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018;378(4):331-344.

See Principles of Systemic Therapy for NLPHL (HODG-C 2 of 4)
See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-C 3 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens

Nodular Lymphocyte-Predominant Hodgkin Lymphoma
• The most common chemotherapies used at NCCN Member Institutions for NLPHL are listed below.[a]

Regimens and References

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.

CVP (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]

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[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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PRINCIPLES OF SYSTEMIC THERAPY
RELAPSED OR REFRACTORY DISEASE

Relapsed/Refractory Disease

	Second-Line Options[c] (in alphabetical order)	Subsequent Options[c,d] (in alphabetical order)
CHL	• Brentuximab vedotin[1] • Brentuximab vedotin + bendamustine[2] • Brentuximab vedotin + nivolumab[3] • DHAP (dexamethasone, cisplatin, high-dose cytarabine)[4,5] • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)[6,7,8] • Gemcitabine/bendamustine/vinorelbine[9] • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[10] • ICE (ifosfamide, carboplatin, etoposide)[5,11] • IGEV (ifosfamide, gemcitabine, vinorelbine)[12] • Pembrolizumab[25,26] (for patients not candidates for transplant)	• Bendamustine[13] • Bendamustine + carboplatin + etoposide[14] • C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) • Everolimus[15] • GCD (gemcitabine, carboplatin, dexamethasone)[16,17] • GEMOX (gemcitabine, oxaliplatin)[18] • Lenalidomide[19] • MINE (etoposide, ifosfamide, mesna, mitoxantrone)[20] • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)[21,22] • Nivolumab[23,24] (see indications below) • Pembrolizumab[25,26] (see indications below)
NLPHL[d]	• R (rituximab)[b] + DHAP[4,5] • R[b] + ESHAP[6,7,8] • R[b] + ICE[5,11] • R[b] + IGEV[12] • R[b] + Bendamustine[27] • If not previously used: ▸ R[b]-CHOP[28] ▸ R[b]-ABVD[29] ▸ R[b]-CVP[30]	

General Guidelines for Checkpoint Inhibitors (CPI) for Relapsed/Refractory CHL[e,f]

- **CPI are recommended for any patients with CHL that has relapsed or progressed after autologous HSCT ± brentuximab vedotin.[31]**
- **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 December 20, 2017.
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References

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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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PRINCIPLES OF RADIATION THERAPY

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 Hodgkin lymphoma, 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 radiation therapy 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 one or two lymph node regions involved. See HODG-B for definition of nodal sites according to GHSG.

References

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PRINCIPLES OF RADIATION THERAPY

Volumes

- ISRT is recommended as the appropriate field for Hodgkin lymphoma.
  - 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 employed for CHL with similar disease distribution being treated with combined modality therapy.
- Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume, ITV) should also influence the final CTV.
- The planning target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations and may differ by site and immobilization technique.
  - See ICRU definitions: Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559.
- OARs should be outlined for optimizing treatment plan decisions.
- The treatment plan 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 the presence of vertebral body disease, the entire vertebra is generally treated.

References

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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 Contraints, 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 applied, and doses recorded. Contouring atlases are available.[33,34]

References

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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	Esophagus cancer[51]
Stomach	Minimize volume >25 Gy	Stomach cancer[52]
Pancreas	Minimize volume >5-10 Gy	Pancreas cancer[53]

[b] General Principles of RT Dose Contraints, 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

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 organs at risk should follow principles of ALARA (as low as reasonably achievable). In some scenarios, target coverage may require dose constraints to be exceeded if the organ at risk is within the planning target volume.
- A relatively rare but serious complication of radiation therapy 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 (e.g., age, tobacco exposure, etc.).
- In addition to secondary malignancies, cardiac and pulmonary complications after radiation therapy are most concerning and are reviewed further in the following sections.

Heart

- Multiple cardiac complications can develop from mediastinal radiation therapy 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 (e.g., doxorubicin), pre-existing cardiovascular disease, age, and other cardiac risk factors (e.g., diabetes, hypertension, hyperlipidemia).[27,56-58] While global heart metrics such mean heart dose are most commonly utilized 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 Hodgkin lymphoma (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 more than 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 datasets relating radiation dose to cardiac disease risk in adult patients is a 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 mean heart dose of 15 Gy or higher (RR 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy). This study also explored different age-of-diagnosis cohorts and generally showed the same radiation dose-response relationships.

References

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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 greater than or equal to 21 Gy.
- In regards to valvular disease, increasing mediastinal radiation dose, especially above 30 Gy, has been associated with an elevated risk of valvular dysfunction.[27,63] Using a large Dutch cohort of adult patients treated to the mediastinum, Cutter et al. demonstrated 30-year cumulative risks of valvular heart disease of 3%, 6.4%, 9.3%, and 12.4% for mean valvular dose of <30, 31–35, 36–40, and >40 Gy.[28] Valvular heart disease (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% (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 valvular heart disease 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 quite 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 dataset 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 sub-analysis 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.

References

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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 the age of 40 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 coronary artery disease, 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<0.001). Multivariate analysis of several putative risk factors showed that mediastinal dose was the only significant variable predicting for cardiac disease-free survival (P=0.0025). 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 valvular heart disease 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 would recommend that one keep the mean heart dose as low as possible, ideally <8 Gy, though in some patients a higher dose will be necessary given lymphoma extent. This also recognizes that lymphoma patients tend to also receive anthracycline chemotherapy, even though 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, though 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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References

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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 utilized 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 epithelial[68] 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%, though dose to the lungs in most lymphoma patients can be kept below these thresholds. More pertinent to intensity modulated radiation therapy or volumetric arc techniques, we recommend limiting the V5 <55%.**

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hodgkin Lymphoma (Older Adults)

NCCN Guidelines Index
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Discussion

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

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

SUGGESTED TREATMENT REGIMENS
(Listed in alphabetical order)

Stage I–II Favorable Disease

- A(B)VD[a] (2 cycles) ± AVD (2 cycles) + 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 PR[12]
- 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 4)
  - Pembrolizumab See Checkpoint Inhibitors (CPI) HODG-C (3 of 4)
  - Second-line and subsequent therapy options (only for CHL) as listed on Principles of Systemic Therapy for Relapsed or Refractory Disease HODG-C (3 of 4)

[a] Bleomycin should be used with caution as it may not be tolerated in older adults, and it should not be used beyond two cycles.
[b] See Principles of Radiation Therapy (HODG-E).
[c] If stage I–II unfavorable, consider a total of 4 cycles.

References

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MANAGEMENT OF CLASSIC HODGKIN LYMPHOMA IN OLDER ADULTS (AGE >60)
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[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]Boll 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 STAGING[1]

Table 1

Definitions of Stages in Hodgkin Lymphoma[2]

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, II_3).

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 (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

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

A No systemic symptoms present

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

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1861.

[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.

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hodgkin Lymphoma

Discussion

This discussion corresponds to the NCCN Guidelines for Hodgkin lymphoma. Last updated: April 20, 2021.

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Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. In 2021, an estimated 8830 people will be diagnosed with HL in the United States and 960 people will die from the disease.[1] The 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; it is now curable in at least 80% of patients. 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. Every patient with newly diagnosed HL has an overwhelming likelihood of being cured with the appropriate treatment. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease. Clinical trials still emphasize improvement in cure rates for patients with advanced disease, but the potential long-term effects of treatment remain an important consideration.

The NCCN Guidelines discuss the clinical management of patients with CHL and NLPHL, focusing 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, using the following search terms: Hodgkin lymphoma, classic Hodgkin lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, early stage, advanced stage, imaging, PET, response assessment, late effects, and surveillance. 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 (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. According to the NCCN Categories of Evidence and Consensus, all outlined NCCN

recommendations are considered to be category 2A, unless otherwise noted.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

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 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 >10 cm, B symptoms, ESR ≥50, and >3 involved nodal regions. In contrast, the GHSG considers patients with >2 nodal regions as having unfavorable disease.

An international collaborative effort evaluating more than 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/mm^3); and lymphocytopenia (lymphocyte count <8% of the WBC and/or lymphocyte count <600/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 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 ^{18}F-fluorodeoxyglucose (FDG) uptake in the involved sites. These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.[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 upon that score. Individual prospective trials that utilize 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 upon clinical circumstances.[35] Although advanced RT techniques emphasize tightly conformal doses and steep gradients adjacent to normal tissues, the "low-dose bath" to normal structures such as the breasts must be considered in choosing the final radiation therapy (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. 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 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] For optimal mediastinal treatment planning, organs or tissues to be contoured should include the lungs, heart, coronary arteries (including the left main, circumflex, left anterior descending, and right coronary arteries, with priority placed on sparing the proximal over distal portions of the arteries), and left ventricle.

Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce 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 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.[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

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 second malignancies. Studies have reported that radiation exposure is associated with an increased risk for second cancers without a safe threshold dose (linear no-threshold model), although the pattern of risk is less understood than those after low-dose exposure.[53] Other contributing factors include age, environmental exposure, genetic risk factors, and radiation technique, among others.[54]

Heart

Multiple cardiac complications can develop from mediastinal RT including pericarditis, arrhythmias, coronary artery disease (CAD), valvular disease, and cardiomyopathy/congestive heart failure.[55,56] 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).[55,57-59] While global heart metrics such as mean heart dose (MHD) are most commonly utilized to assess risk, there is an increasing recognition that radiation dose-fractionation to cardiac substructures must be accounted for.

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). 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.[60] A significantly increased risk of coronary heart disease was reported among patients who received an MHD as low as 5–14 Gy (RR, 2.31) compared to a mean heart dose of 0 Gy.[60] This risk was increased for an MHD of 15 Gy or higher (RR, 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy).[60]

Although the number of studies evaluating specific dose constraints for cardiac substructures is rather limited, van Nimwegen et al demonstrated a relationship between heart failure and mean dose to the left ventricle.[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 LV dose less than 15 Gy, 15.9% for 16–20 Gy, and 32.9% for greater than or equal to 21 Gy.

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 infectious pneumonia, acute bronchitis, and pulmonary embolism, etc. Pulmonary complications, including pneumonitis, can arise from systemic modalities such as bleomycin and immunotherapy.

The most important risk factors for radiation pneumonitis are lung dose-volume metrics, including mean lung dose (MLD), V20, and V5. Such metrics have been associated with pneumonitis risk in both epithelial[61] and hematologic malignancies.[62] For epithelial malignancies such as non-small cell lung cancer, it is generally recommended that MLD be less than 20 Gy and V20 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 for RT Dose Constraints

While the data regarding cardiac constraints for modern RT of lymphomas is imperfect, the panel recommends that the MHD be kept as low as possible, ideally less than 8 Gy, though in some patients a higher dose will be necessary given lymphoma extent. The panel recognizes that patients with lymphoma also tend to receive anthracycline chemotherapy, even though 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 doses greater than 15 Gy;[63] therefore, it is recommended that MHD should rarely exceed 15 Gy. This may be reconsidered if patients are being treated in the salvage setting with curative intent where larger RT doses are necessary. Mean left ventricular dose should not exceed 8 Gy, though 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,[64] but should be as low as possible in terms of dose and volume and length.

The panel recommends limiting MLD less than 13.5 Gy and V20 less than 30%, though RT to the lungs in most lymphoma patients 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 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°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, platelets, 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 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. Posterior-anterior 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.[65] An integrated PET scan plus a diagnostic CT is recommended for initial staging and should be obtained no longer than one 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 ACR[66] and Society of Nuclear Medicine and Molecular Imaging (SNMMI)[67] recommendations for PET/CT interpretation (see *Principles of FDG-PET/CT* in the algorithm).[68-71] 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.[72,73] The bone marrow may be assumed to be involved if the PET scan displays multifocal (three or more) skeletal lesions.[72,74] 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.[75,76] 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 women of childbearing age undergo treatment. Alkylating agent-based chemotherapy is associated with a higher risk of premature ovarian failure than chemotherapy with non-alkylating agent-based chemotherapy.[77] In select cases and if the patients are interested, the guidelines recommend consideration of fertility preservation (ie, semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) prior to the initiation of chemotherapy with alkylating agents or pelvic RT.[78,79]

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 I–IIA (favorable with non-bulky disease)
- Stage I–IIA (unfavorable with bulky mediastinal disease or >10 cm adenopathy)
- Stage I–IIB (unfavorable disease)

RT alone was a standard treatment option for patients with early-stage HL for many decades.[80] However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.[81] 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.[82] Selection of combined modality therapy or chemotherapy alone should be based upon 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 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 ≥2 cm in greatest transverse diameter, regardless of location. A smaller residual mass or a normal-sized lymph node was considered

positive if its activity was above that of the surrounding background. Patients who were PET negative after receiving 2 cycles of ABVD received one additional cycle of ABVD (total of 3 cycles) followed by INRT in the standard arm, or 2 additional cycles of ABVD (total of 4 cycles) only in the experimental arm.[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.[83] 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).[83]

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).[84] 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.[84] 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.[84] 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.[85] 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).[85] The 5-year OS rate was not significantly different between the 2 arms (97.2% and 96.8%, respectively; P = .731). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs. 8.4%; P < .001). However, the acute toxicity was greater in the BEACOPP/ABVD arm compared to the ABVD arm.[85] 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 I–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[52,83] 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[30,84] or 2[27] 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 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–IIB Unfavorable, B Symptoms, Bulky Mediastinal Disease, or Adenopathy >10 cm

For stage I–IIB 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).[30,85,86] 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.[87,88]

ABVD has continued to be the standard chemotherapy regimen for patients with stage III–IV disease based upon several randomized clinical trials that have failed to show a survival benefit for more intensive regimens.[88-91] 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.

As noted previously in the RATHL trial, the omission of bleomycin from the ABVD regimen after a negative interim PET result (ie, Deauville score of 1–3) led to a decrease in the incidence of pulmonary toxic effects without any compromise in outcome compared to continued ABVD (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[92,93] and the Italian GITIL/FIL HD 0607 trial.[94] 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.[92,93] 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.[94]

The efficacy of escalated BEACOPP has been demonstrated in several sequential studies by the GHSG.[95,96] The final analysis of the HD15 trial that included patients with stage III–IV and IIB with large mediastinal adenopathy or extranodal disease established 6 cycles of escalated BEACOPP followed by PET-guided RT (to sites >2.5 cm that were PET positive) as the standard of care within the GHSG. The 5-year FFTF and OS rates were 89.3% and 95.3%, respectively.[44.] One hundred ninety-one patients were PET positive, received consolidative RT, and achieved a 4-year PFS of 86.2% with outcomes similar to those who achieved a CR.[97]

The subsequent HD18 trial investigated an interim PET-adapted design.[98] 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.[98] 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).[99] 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.[99] 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.[99] The PET-adapted treatment arm was also associated with significantly less treatment-related toxicities.[99]

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.[91,100-102] 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).[100] 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.[100] 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).[90]

The ECHELON-1 trial compared the efficacy of ABVD (n = 670) versus brentuximab vedotin + AVD (n = 664) in previously untreated stage III or IV CHL.[103] Patients received 6 cycles of chemotherapy without treatment adaptation based upon interim imaging. While the incidence of pulmonary toxicity was lower in the brentuximab vedotin + AVD arm due to the elimination of bleomycin, there was more peripheral neuropathy and hematologic toxicity. At a median follow-up of 37 months, the 3-year PFS rates in the brentuximab vedotin + AVD and ABVD groups were 83.1% and 76%, respectively (*P* = .005)[103] Upon continued follow-up, 78% of patients with peripheral neuropathy on A+AVD had either complete resolution or improvement compared with 83% 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 less than 60 years of age 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)[99] 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 BEACOPP (total of 6 cycles) is recommended. Patients with a Deauville score of 4 to 5 with a positive biopsy should be managed as described for refractory disease.

Brentuximab vedotin + AVD is a category 2B recommendation, but it is a category 2A option in select patients with no known neuropathy, if IPS is greater than or equal to 4 or bleomycin is contraindicated. In patients with stage III or IV disease, brentuximab vedotin + AVD is initially administered for 6 cycles[104] followed by restaging with PET, based on results from the ECHELON-1 trial. 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. Patients with a Deauville score of 1 to 3 should be managed as described for follow-up and monitored for late effects. Consider ISRT to initially bulky or PET-positive sites for patients with a Deauville score of 4 to 5. A biopsy should be considered for these patients and, if positive, alternative therapy for refractory disease should be considered.

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

CHL in older adult patients (>60 years of age) is associated with worse disease outcomes.[105] B symptoms, poor performance status, mixed cellularity, histologic subtype, Epstein-Barr virus-positive (EBV+) disease, and medical comorbidities are more frequent in this population.[106] Standard chemotherapy regimens are associated with dose reductions, treatment toxicity, and transplant-related mortality (TRM) in older patients.[107-110] 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).[111] 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.[111]

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.[112] All patients received at least 1 full course of ABVD and 50 patients received additional RT (30–40 Gy). Bleomycin was removed or reduced in 53 patients due to pulmonary toxicity. Complete response (CR) was observed in 117 patients (80%) with a 5-year OS rate estimated at 67% (95% CI, 58–74).[112] 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.[113,114]

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).[115] 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.[115] Among 42 response-evaluable patients, the overall response and CR rates after 6 cycles of AVD were 95% and 90%,

respectively.[115] By intent-to-treat, the 2-year EFS, PFS, and OS rates were 80%, 84%, and 93%, respectively.[115]

Other regimens have been used as front-line chemotherapy in elderly patients with HL, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone);[116] brentuximab vedotin plus dacarbazine (DTIC);[117,118] VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin);[119,120] BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone);[110] and PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine).[121]

NCCN Recommendations for Older Adults (>60 years) with CHL

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 elderly patients (>60 years of age) with stage I–II favorable disease.[52,111,112,116,120] 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.[31,115-118,121] For the ABVD regimen, a PET scan follows treatment with 2 cycles of ABVD. Bleomycin should not be used beyond two 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.[122] The majority of patients present with early-stage disease and rarely with B symptoms, mediastinal or extranodal involvement, or bulky disease.[123-125] Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma.[2,126] 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.[2,127-129] 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% vs. 82%) and OS (96% vs. 92%) were better for NLPHL compared with CHL.[124] Among patients with NLPHL, FFTF was better for early-stage favorable disease (93%) compared with early-stage unfavorable (87%) and advanced-stage disease (77%). The European Task Force on Lymphoma also reported favorable FFTF for early-stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or stage IV (24%) disease.[123] Advanced stage at presentation, age (≥45 years), low hemoglobin, and the presence of B symptoms are associated with worse OS.[124,125]

Several retrospective studies have reported favorable clinical outcomes for patients with stage I to II disease treated with RT alone [130-134] or in

combination with chemotherapy.[125,135,136] RT alone is an effective treatment option for patients with stage IA–IIA disease.[130,132,137] In a retrospective analysis, the Australasian Radiation Oncology Lymphoma Group reported follow-up of 202 patients with stage I–II NLPHL treated with RT alone, including mantle and total lymphoid irradiation (TLI).[132] 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.[137]

Among the studies that have evaluated the outcomes of patients treated with RT alone or combined modality treatment, the subgroup analysis of 64 patients with NLPHL included in the GHSG HD7 trial showed a non-significant trend toward better 7-year FFTF for the combined modality group (96%) compared with the EFRT group (83%; *P* = .07).[136] However, other retrospective studies have shown no difference in outcome between patients treated with RT alone or in combination with chemotherapy.[131,133,134] The GHSG retrospectively compared 3 treatment options, including EFRT, IFRT, and combined modality treatment in patients with stage IA NLPHL.[133] 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 NLPHL (82% of patients had stage IA–IIA disease) included 58 patients who were observed following diagnosis and lymph node biopsy.[138] 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 NLPHL who are in complete remission following lymph node excision.[139,140]

Binkley et al. reported an international retrospective review of 559 adult patients with stage I-II NLPHL 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.[141] 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.[141] The variant immunoarchitectural pattern was associated with a worse PFS. 3.8% of patients developed large-cell transformation.

Patients with advanced-stage NLPHL have a worse prognosis than those with early-stage favorable disease, and can be treated with chemotherapy. In the European Task Force on Lymphoma study, the 8-year disease-specific survival and FFTF were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.[123] 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.[142] 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. On the other hand, an analysis of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III–IV NLPHL treated with chemotherapy alone, showed that the failure rate was 75% for the 12 patients treated with ABVD or EVA (etoposide, vinblastine, and doxorubicin) and 32% for the 25 patients treated with alkylating agent-containing regimens (MOPP or MOPP/ABVD).[143] Some investigators have also reported good response rates with CHOP plus rituximab[144-146] or CVP (cyclophosphamide, vincristine, and prednisone) in patients with early-stage or advanced disease.[147]

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.[148-152]

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/m^2. 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.[148] 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.[150] 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.[149]

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/m^2) or rituximab followed by rituximab maintenance (once every 6 months for 2 years).[152] The ORR was 100% (67% CR and 33% PR) at the end of initial therapy with rituximab alone. The median follow-up was 9.8 years for rituximab and 5 years for rituximab plus maintenance rituximab. The estimated 5-year PFS rate was 39.1% and 58.9%, respectively, for patients treated with rituximab and rituximab followed by maintenance rituximab. The corresponding 5-year OS rates were 95.7% and 85.7%, respectively. Rituximab as initial treatment was also associated with a pattern of relapse with evidence of transformation to aggressive B-cell lymphoma, primarily in patients with intra-abdominal disease. This underscores the importance of biopsy of intra-abdominal sites of disease at initial presentation or relapse. Rituximab maintenance for 2 years was associated with a non-significant increase in median PFS compared to rituximab alone (5.6 years and 3 years, respectively; P = .26).

Collectively, the above data suggest that rituximab alone or in combination with chemotherapy has activity in the management of patients with newly diagnosed and relapsed NLPHL.[148,150,152]

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.[130-134]

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.[152] Biopsy of persistent or new subdiaphragmatic sites should be considered to rule out transformation for patients with stage III or IV disease.

Reevaluation with PET should be done for all patients after completion of initial therapy. Observation is recommended for all asymptomatic patients with a clinical response. ISRT is recommended if not received previously. Biopsy is recommended for patients with 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 (ABVD, CHOP, or CVP) that are most commonly used at NCCN Member Institutions. Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for patients with NLPHL.

Follow-up After Completion of Treatment

Recommendations included in the guidelines are based largely on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, since there are very few data available on the follow-up and monitoring of late effects in patients with HL, after completion of treatment.[153]

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.[153] 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.

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.[154] 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 CDC recommendations).

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen.[155] 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.[156] 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. However, PET scans are not recommended for routine surveillance due to the risk of false positives.[68,69,71]

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.[157] 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.[158] 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 (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation.[155] They should also be encouraged to perform monthly breast self-examination and undergo yearly breast examination by a health care professional. In a prospective study that evaluated the sensitivity and specificity of breast MRI with that of mammography in women who received chest irradiation for HL, the sensitivity of the combined MRI and mammography as a combined screening modality was higher than that of MRI or mammography alone (94% for combined MRI and mammography; 67% and 68%, respectively, for MRI and mammography).[159] The guidelines recommend breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age, which is consistent with the recommendation of the American Cancer Society Guidelines[160] 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.[161-163] 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.[164] 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.[155] A baseline stress test or echocardiogram and carotid US (for patients treated with neck RT) should be considered at 10-year intervals after completion of treatment.

Hypothyroidism

Abnormal thyroid function, mostly hypothyroidism, is reported in about 50% of long-term survivors who received neck or upper mediastinal irradiation.[153] A careful thyroid examination should be a part of the physical exam. Thyroid function tests should be done at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression

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

Infertility

Certain chemotherapy combinations (eg, BEACOPP) may cause immediate and permanent infertility in both men and women.[165,166] Other combinations (eg, ABVD) are only rarely associated with infertility.[79,167] Since women who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause,[77] 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.[168] They also showed that the 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.[169,170] 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.[170]

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

Relapsed or Refractory Classic Hodgkin Lymphoma

Two randomized phase III studies performed by the British National Lymphoma Investigation[171] and the GHSG/European Group for Blood and Marrow Transplantation[172] 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.[173,174] 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) ($P < .001$).[173] 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 ($P < .001$).[174]

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.[175] 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.[176] 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.[177] 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.[178] 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.[179] Other groups have identified extent of prior chemotherapy,[180] short time from diagnosis to transplant,[181] and disease status at transplantation[182] 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.[183-186] The main potential of these prognostic factor studies is to facilitate comparison of outcomes at different centers, where the preparatory regimens may vary.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.[176,187-195] ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, cisplatin, and high-dose cytarabine) are the most commonly used regimens. Other regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),[196] IGEV (ifosfamide, gemcitabine, and vinorelbine),[197] GCD (gemcitabine, carboplatin, and dexamethasone),[198,199] and GEMOX (gemcitabine and oxaliplatin)[200] 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.[201-203] 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).[201] 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.[202,203] In a phase II study, bendamustine in combination with gemcitabine and vinorelbine (BeGEV) was used as induction therapy before ASCT in patients with relapsed or refractory HL, resulting in an ORR of 83% (73% CR and 10% PR).[204] 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.[205]

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[206] 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.[207] 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.[208] 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.[208]

Attempts to increase the CR rate prior to ASCT have led to numerous trials incorporating the novel agents into initial salvage therapy. Several studies are investigating the utility of brentuximab vedotin as a second-line therapy for relapsed or refractory HL, either sequentially or in combination with other regimens, prior to HDT/ASCR. A trial from Memorial Sloan Kettering Cancer Center (MSKCC) used a PET-adapted design in which 45 patients received 2 cycles of brentuximab vedotin followed by a PET scan.[209] Patients who achieved a CR after brentuximab vedotin (27%) proceeded directly to ASCT, while patients with residual disease received 2 cycles of augmented ICE. Overall, 76% of patients achieved a CR prior to ASCT using this PET-adapted approach.[209] 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.[210] Patients who achieved a CR after brentuximab vedotin (35%) proceeded directly to ASCT, while those with residual disease received platinum-based salvage chemotherapy. Overall, 65% of patients achieved a CR prior to ASCT using this approach.[210]

Other studies have combined brentuximab vedotin with bendamustine, ICE, or ESHAP (etoposide, methylprednisolone, and high-dose cytarabine or cisplatin) with preliminary data demonstrating PET-negative responses ranging from approximately 75% to 90%.[209,211-213] The combination of brentuximab vedotin and nivolumab has also been evaluated as initial salvage therapy prior to ASCT with a high CR rate of 61% after 4 cycles and no increase in toxicities compared to either agent alone.[214] For patients who underwent ASCT after the combination, the 2-year PFS was 91%.[215]

The use of brentuximab vedotin as consolidation therapy following HDT/ASCR was evaluated in the AETHERA trial.[216] 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-ASCT. Patients were required to have obtained a CR, PR, or stable disease to second-line therapy prior to ASCT. 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. Programmed death 1 (PD-1)-blocking monoclonal antibodies have also demonstrated activity in patients with relapsed or refractory PD-1–positive lymphomas.[217-221] In a phase I study of 23 patients with relapsed or refractory HL and pretreated with both HDT/ASCR and brentuximab vedotin, treatment with nivolumab, a human monoclonal PD-1–directed antibody, induced an ORR of 87% with a PFS rate of 86% at 24 weeks.[217] In a phase II study (CheckMate 205 trial) of 80 patients with relapsed or refractory HL and pretreated with both HDT/ASCR and brentuximab vedotin, treatment with nivolumab induced an objective response in 53 of 80 patients (66.3%; 95% CI, 54.8–76.4) as determined by an independent radiologic review committee and at a median follow-up of 8.9 months.[221] 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.[218] 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).[218] Armand and colleagues reported that pembrolizumab, another human monoclonal PD-1–directed antibody, may also be an option for patients with relapsed or refractory HL and pretreated with brentuximab vedotin.[219] In a phase I study of 31 patients with relapsed or refractory HL and pretreated with brentuximab vedotin, pembrolizumab treatment induced a CR rate of 16% (90% CI, 7%–31%) and a PR rate of 48% resulting in an ORR of 65% (90% CI, 48%–79%).[219] In a phase II study of 210 patients with relapsed or refractory HL, the efficacy of pembrolizumab was examined in three cohorts of patients with disease progression after: 1) ASCT and subsequent brentuximab vedotin; 2) salvage chemotherapy and brentuximab vedotin (ineligible for ASCT due to chemoresistant disease); and 3) ASCT without brentuximab vedotin[220]; the corresponding ORRs were 73.9%, 64.2%, and 70%, respectively.[220] 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.[222] 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).[222] Treatment-related adverse events (TRAEs) were observed in 74% of patients receiving pembrolizumab and 77% of patients receiving brentuximab vedotin. The most common grade 3-5 TRAEs were pneumonitis (4% in the pembrolizumab group versus 1% in the brentuximab group), neutropenia (2% versus 7%, respectively), decreased neutrophil count (1% versus 5%, respectively) and peripheral neuropathy (1% versus 3%, respectively).[222] Serious TRAEs were observed in 16% of patients receiving pembrolizumab and 11% of patients receiving brentuximab vedotin.[222] Emerging data are investigating the combination of brentuximab vedotin and PD-1 or checkpoint inhibitors as an option for relapsed or refractory HL prior to transplant.[214]

The role of RT in salvage programs 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 salvage management. Moskowitz and colleagues have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease.[176] 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.[223] 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.[224]

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.[225]

Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should proceed to HDT/ASCR with or without RT (category 1 recommendation). If HDT/ASCR is contraindicated, then observation with or without RT can be considered. For patients with high risk of relapse as defined by the AETHERA trial, 1 year of brentuximab vedotin maintenance therapy can be considered.[216] For patients with a Deauville score of 4 or 5 after second-line systemic therapy, an alternative regimen with or without RT or RT alone is recommended, followed by repeat response assessment. Another approach for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT, followed by 1 year of brentuximab vedotin maintenance therapy for patients with a high risk of relapse. It is worth noting that the role of maintenance brentuximab vedotin has not been well defined in patients who received brentuximab vendotin earlier in the management of their disease.

Brentuximab vedotin alone or in combination with bendamustine[213] or nivolumab[214]; DHAP[188,191]; ESHAP[189,192,226]; GVD[196]; ICE[176,188]; IGEV[197]; and BeGEV[204] 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.[201-203] Nivolumab and pembrolizumab are included as subsequent therapy options for CHL patients who have relapsed or progressed following HDT/ASCR and post-transplant brentuximab vedotin, or after 3 or more lines of systemic therapy including autologous HSCT.[217-222]

Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was greater than 50%. Allogeneic HSCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.[227,228] However, this approach remains investigational. Nonmyeloablative allogeneic transplant 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.[229] The panel has included allogeneic HSCT with a category 3 recommendation for select patients with refractory or relapsed disease. For patients with PET-positive refractory HL (Deauville 5) that is

responsive to RT alone or to subsequent systemic therapy, with or without RT, use of ASCT or allogeneic SCT is an option.

NCCN Recommendations for Relapsed CHL

Suspected relapse at any point should be confirmed with biopsy. 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.[230] 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,[201] brentuximab vedotin,[201,231] everolimus,[203] lenalidomide,[202] nivolumab,[217,221] and pembrolizumab.[219] 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.

Relapsed or Refractory Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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

NCCN Recommendations for Refractory or Suspected Relapsed NLPHL

Late relapse or transformation to diffuse large B-cell lymphoma (DLBCL) has been reported in patients with NLPHL.[232-234] In a study of 95 patients diagnosed with NLPHL, with a median follow-up of 6.5 years, transformation to aggressive lymphoma was seen in 13 (14%) patients and the actuarial risk at 10 and 20 years was 7% and 30%, respectively.[234]

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. All patients with biopsy-proven relapsed NLPHL should be observed or treated with second-line therapy (rituximab and/or chemotherapy and/or ISRT) followed by reevaluation with PET. 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.[152] 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 involving lymph nodes and the lymphatic system. CHL and NLPHL are the two main types of HL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory

background, whereas NLPHL is characterized by the presence of lymphocytic and histiocytic (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. For patients with stage III–IV disease, chemotherapy alone is recommended.

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

ISRT is the preferred treatment for patients with stage IA or IIA non-bulky NLPHL. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with 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 NLPHL. In patients with suspected relapse, re-biopsy should be considered to rule out transformation to DLBCL. Patients with refractory or relapsed NLPHL can be managed with second-line therapy. However, some patients have a chronic indolent disease and may not require aggressive treatment, unless they are symptomatic.

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

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