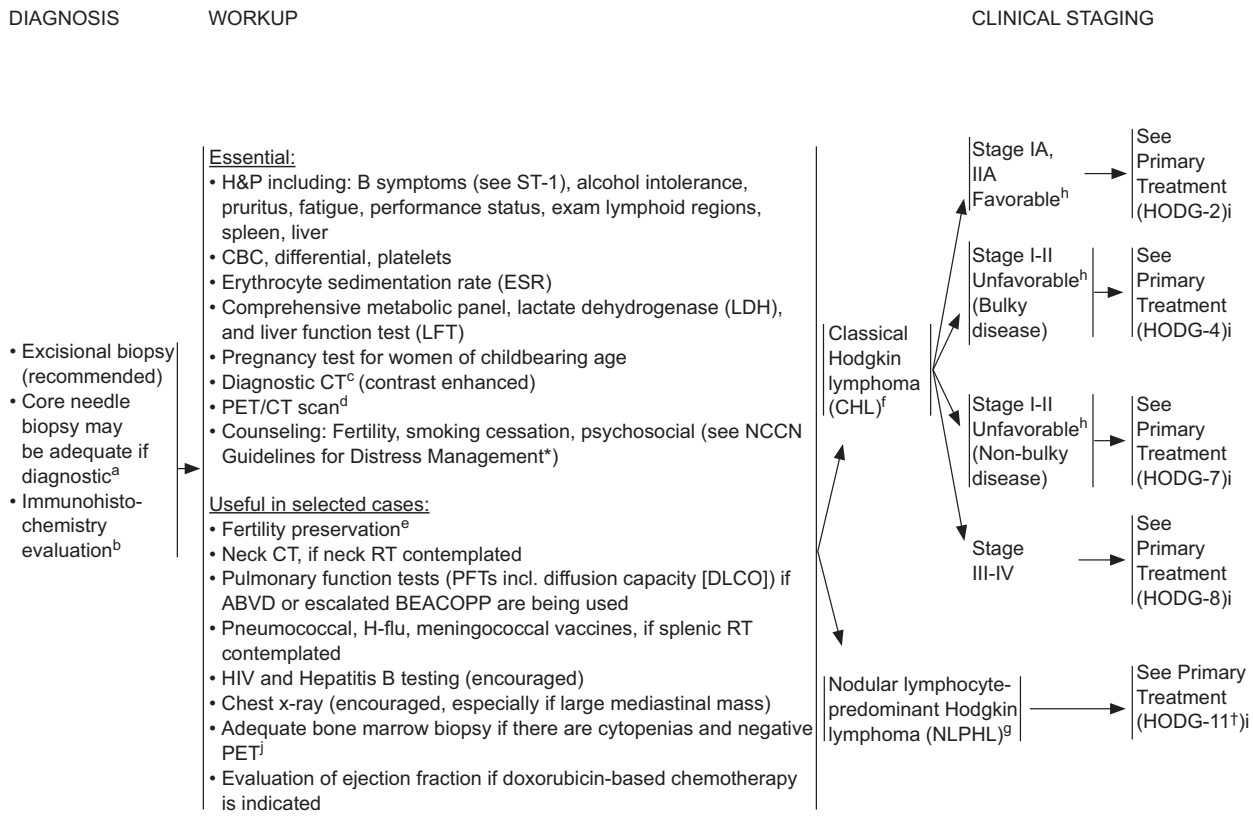


*To view the most recent version of these guidelines, visit NCCN.org.
†Available online, in these guidelines, at NCCN.org.

[a]Fine-needle aspiration biopsy (FNAB) alone is to be avoided and only considered to be adequate along with immunohistochemistry if called diagnostic of Hodgkin lymphoma by a hematopathologist or cytopathologist.

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

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

[d]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).

[e]Fertility preservation options include: Semen cryopreservation, if chemotherapy or pelvic RT contemplated; IVF or ovarian tissue or oocyte cryopreservation and oophoropexy in pre-menopausal women if pelvic RT is contemplated.

[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

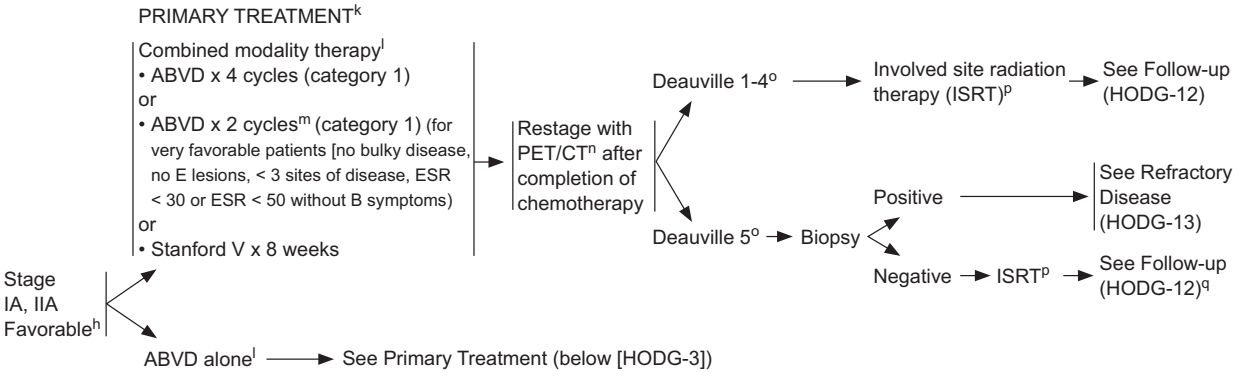
[g]Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL.

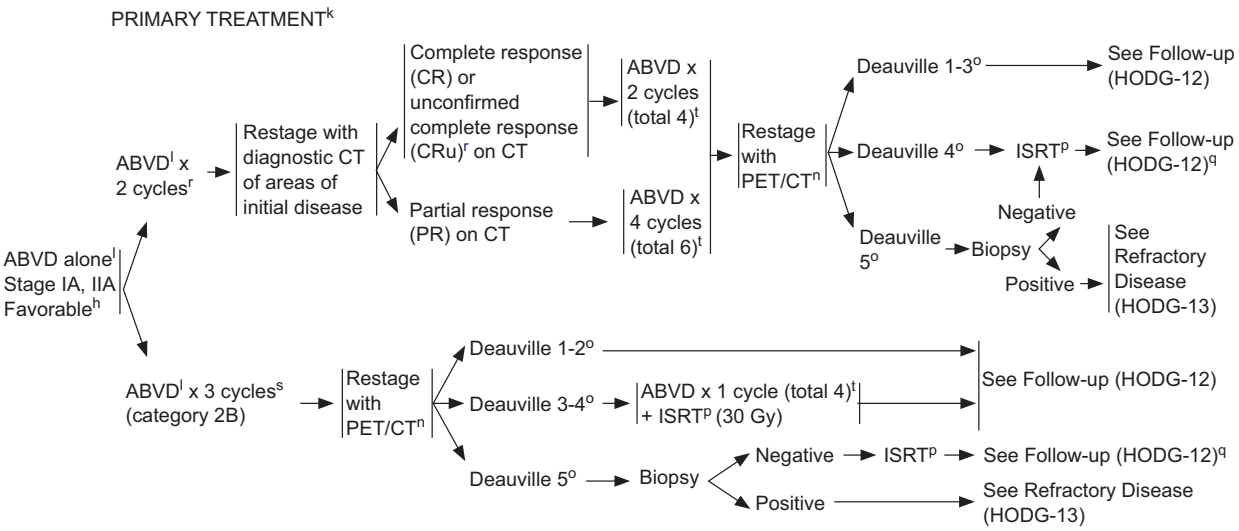
[h]For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

[i]Treatment recommendations for postadolescent Hodgkin lymphoma.

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

CLINICAL PRESENTATION:
CLASSICAL HODGKIN LYMPHOMA[f]
STAGE IA, IIA FAVORABLE





[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[h]For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[m]Two cycles of ABVD only if patient fulfills strict criteria of the GHSG with no bulky disease, no extralymphatic (E) lesions, <3 sites of disease, ESR <30 or ESR <50 without B symptoms.

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

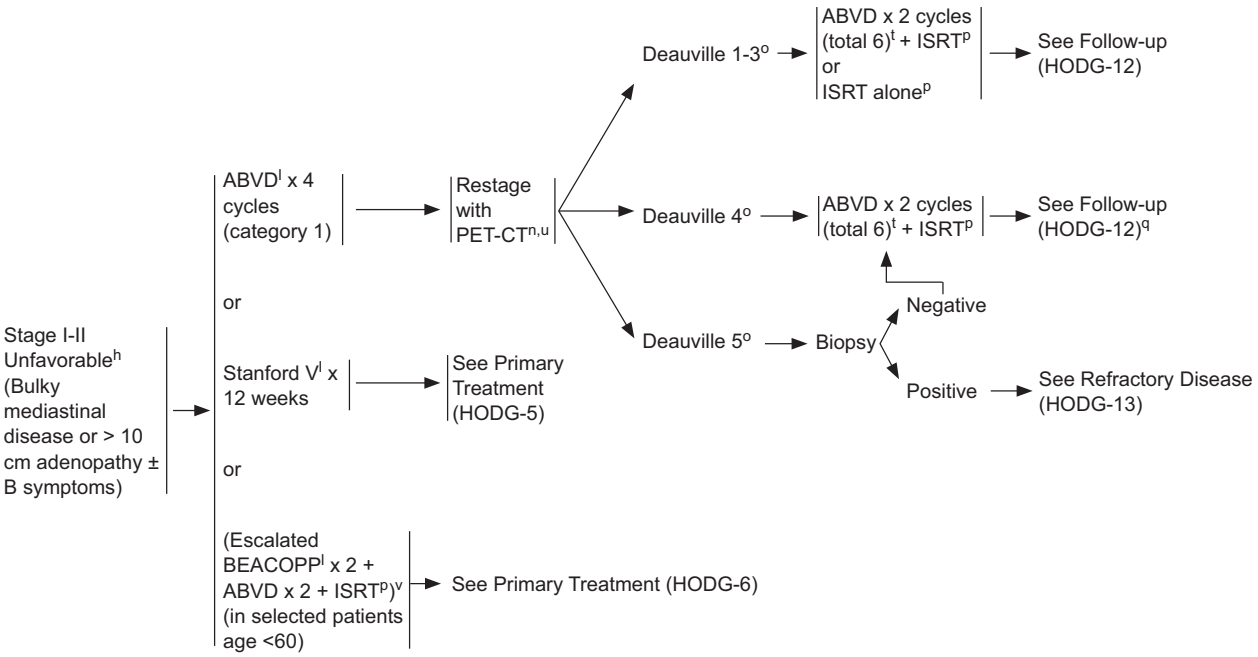
[r]Meyer R, Gospodarowicz M, Connors J, et al. ABVD Alone versus radiation based therapy in limited stage Hodgkin's lymphoma. N Engl J Med 2012;366:399-408. Criteria for CRu as described in Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636.

[s]Radford J, Barrington S, Counsell N, et al. Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin Lymphoma and a negative PET scan after 3 cycles of ABVD. Results of the UK NCRI RAPID Trial (abstract). Blood 2012;120:Abstract 547.

[t]Consider PFTs after 4 cycles of ABVD.

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage I-II Unfavorable[t] (Bulky mediastinal disease or > 10 cm adenopathy ± B symptoms)
Planned Combined Modality Therapy

PRIMARY TREATMENT[k]



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[h]For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[t]Consider PFTs after 4 cycles of ABVD.

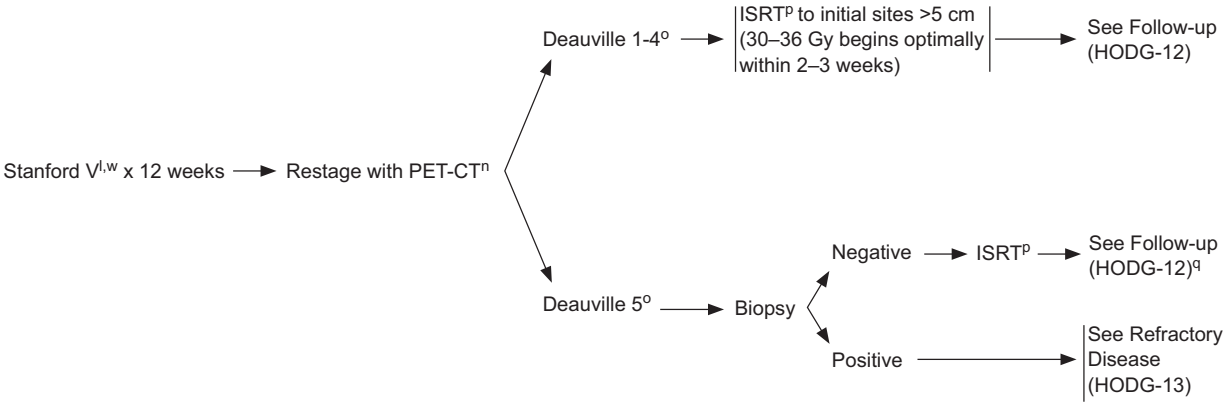
[u]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

[v]In the GHSG trial on which this therapy is based, patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-10).

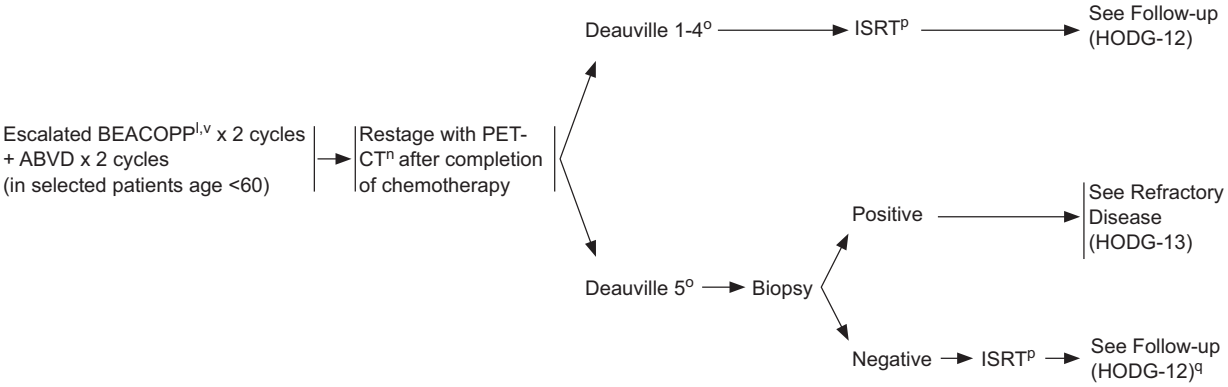
Hodgkin Lymphoma, Version 2.2015

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage I-II Unfavorable[h] (Bulky or Non-bulky)

PRIMARY TREATMENT[k]
(continued from HODG-4)



PRIMARY TREATMENT[k]
(continued from HODG-4)



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[h]For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

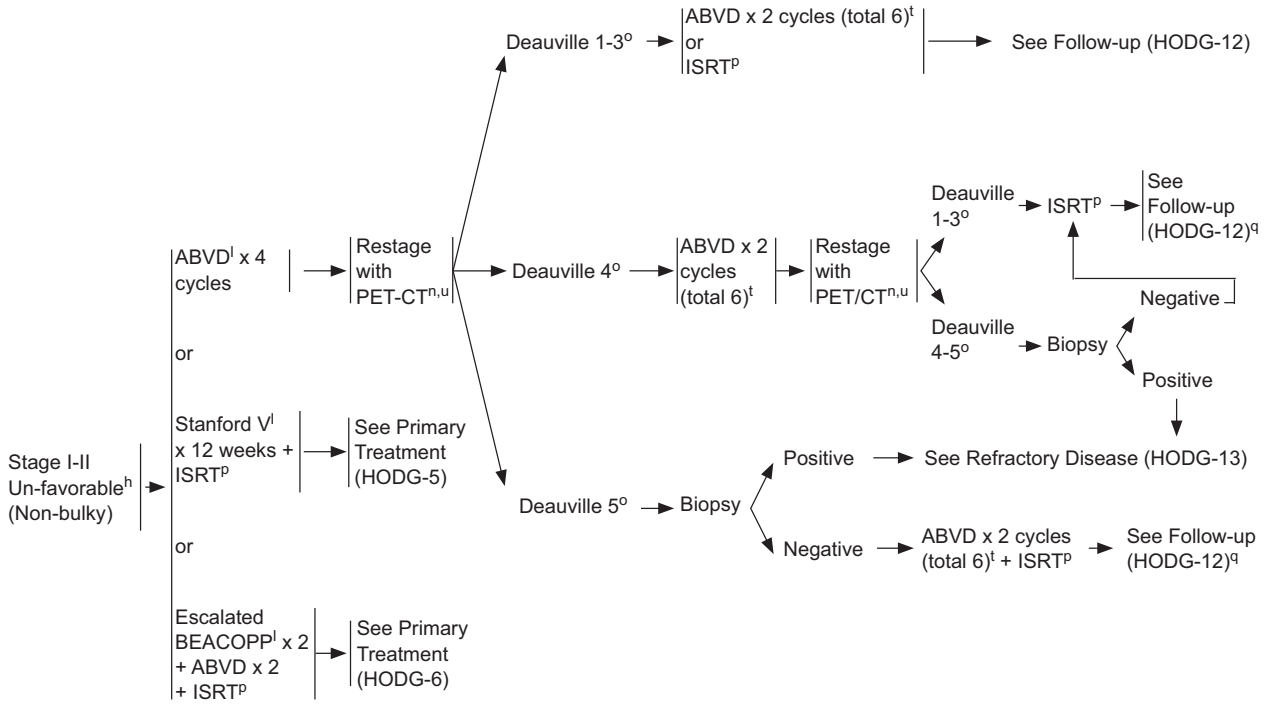
[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[v]In the GHSG trial on which this therapy is based, patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-10).

[w]The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-2.

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage I-II Unfavorable[h] (Non-bulky)

PRIMARY TREATMENT[k]



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[h]For stage I-II: NCCN Favorable implies absence of all unfavorable risk factors. NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

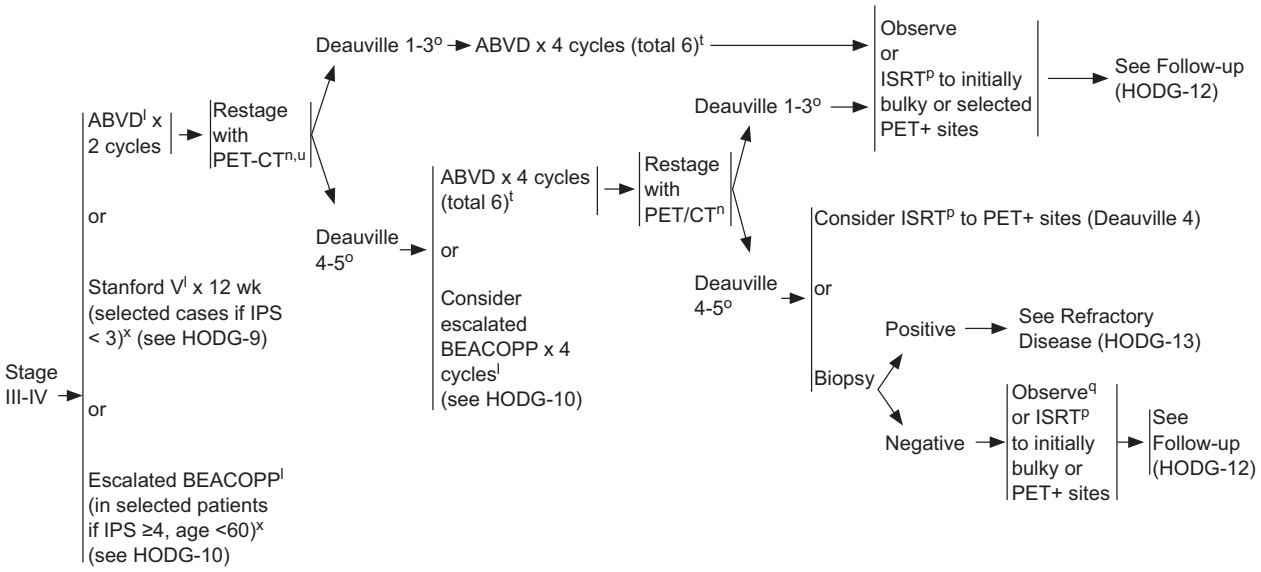
[t]Consider PFTs after 4 cycles of ABVD.

[u]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.

Hodgkin Lymphoma, Version 2.2015

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage III-IV

PRIMARY TREATMENT[k]



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

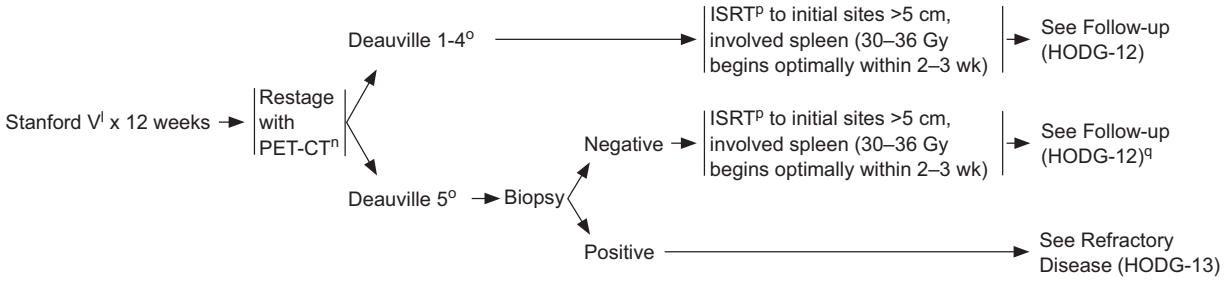
[t]Consider PFTs after 4 cycles of ABVD.

[u]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.

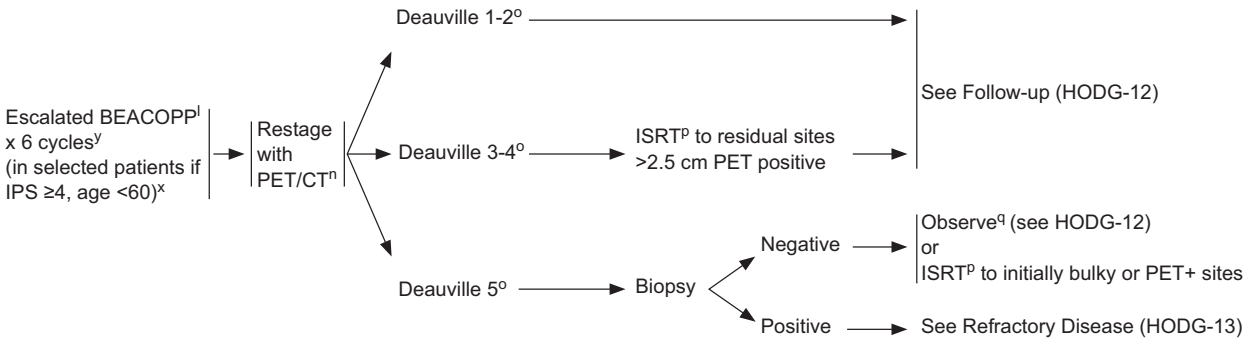
[x]See International Prognostic Score (IPS) (HODG-A).

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage III-IV

PRIMARY TREATMENT[k]
(continued from HODG-8)



PRIMARY TREATMENT[k]
(continued from HODG-8)



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

[k]Individualized treatment may be necessary for older patients and patients with concomitant disease.

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

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[x]See International Prognostic Score (IPS) (HODG-A).

[y]Interim restaging with PET/CT may be considered after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy (4 cycles of ABVD) in patients with a negative interim PET/CT. (Avigdor A, Bulvik S, Levi I, et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma. Ann Oncol 2010;21:126-132.)

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

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

Follow-up After Completion of Treatment up to 5 Years

- Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually.
  - Annual influenza vaccine
- Laboratory studies:
  - CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated
  - Thyroid-stimulating hormone (TSH) at least annually if RT to neck
- Acceptable to obtain a CT scan once during the first 12 mo, then as clinically indicated. PET/CT should only be obtained if last previous PET was Deauville 4-5, to confirm CR.
- 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-14)
or NLPHL (HODG-15)

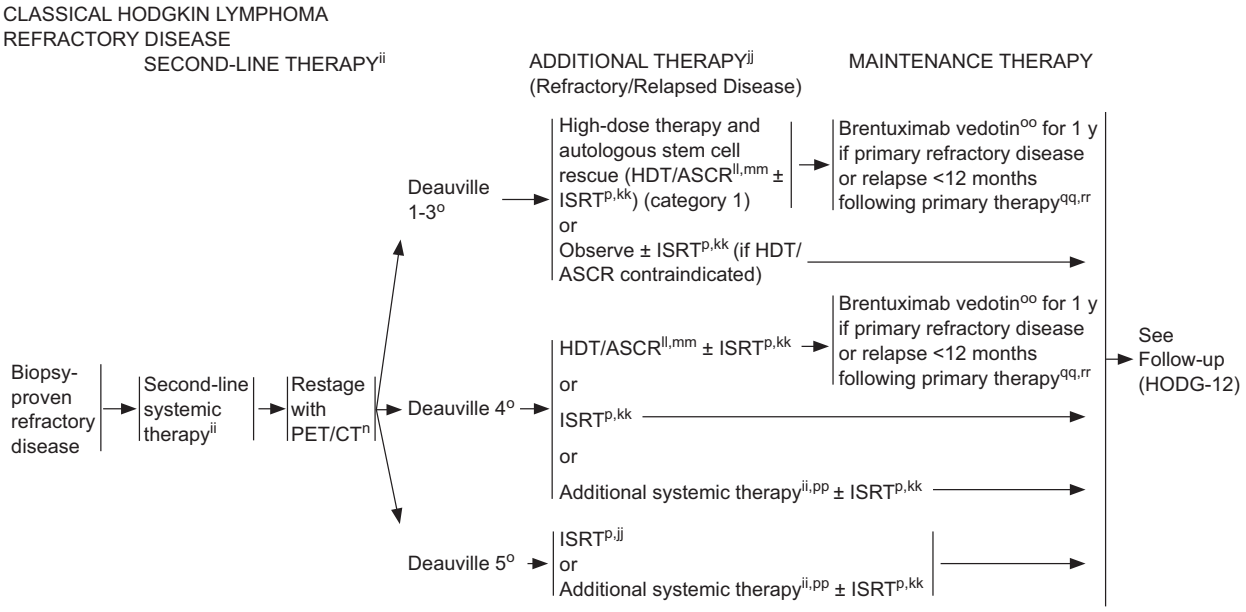
Follow-up and Monitoring After 5 Years[ff,gg]

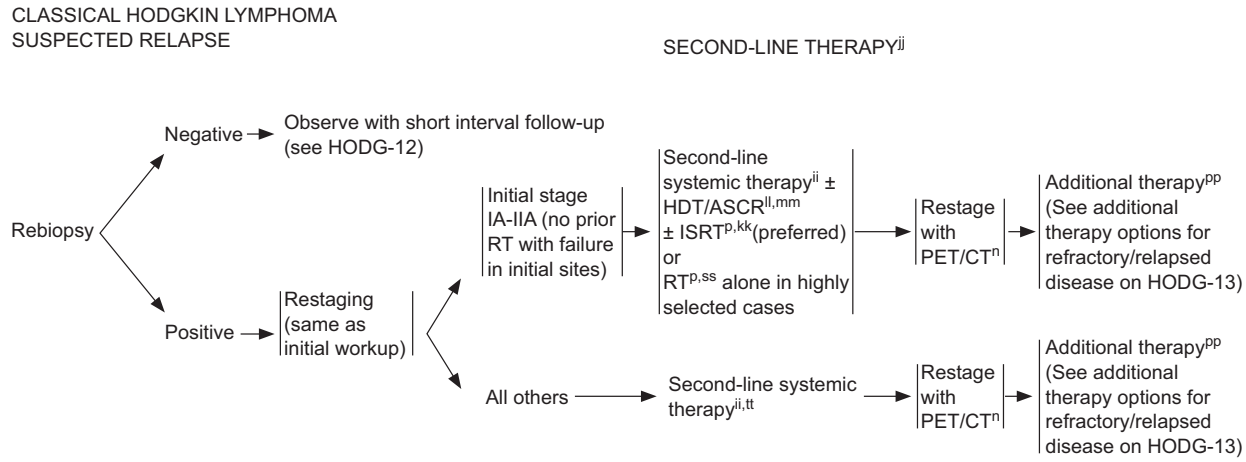
- Interim H&P: Annually
  - Annual blood pressure, aggressive management of cardiovascular risk factors
  - Pneumococcal, meningococcal, and H-flu revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to current CDC recommendations)
  - Annual influenza vaccine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

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

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

[hh]Low-dose chest CT is optional after 5 y if patient is treated with a non-alkylating agent, no RT to the chest, and no other risk factors are present.





[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.

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

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

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

[jj]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

[kk]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.

[ll]Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.

[mm]Allotransplant is an option in select patients as a category 3 recommendation.

[oo]Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.

[pp]Additional systemic therapy options include second-line therapy options that were not previously used. (See HODG-E).

[qq]The value of brentuximab maintenance for a patient who previously received brentuximab vedotin is not known.

[rr]Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015 [in press].

[ss]If radiation therapy is being used alone as a second-line therapy, conventional involved-field or extended-field treatment is indicated.

[tt]For select patients with long disease-free interval and other favorable features; selection of chemotherapy should be individualized.

HODG-13/14

Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease

Risk Factor	GHSG	EORTC	NCIC	NCCN
Age		≥50	≥40	
Histology			MC or LD	
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B sx	>50 or any B sx
Mediastinal mass	MMR >.33	MTR >.35	MMR >.33 or >10 cm	MMR >.33
# Nodal sites	>2*	>3*	>3	>3
E lesion	any			
Bulky				>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
NCIC = National Cancer Institute of Canada
MC = Mixed cellularity
LD = Lymphocyte-depleted
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

DEFINITIONS OF LYMPH NODE REGIONS*

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

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

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

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/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.

HODG-A

PRINCIPLES OF SYSTEMIC THERAPY (1 of 2)

Classical Hodgkin Lymphoma

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

Regimens and References

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

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.

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.

Meyer R, Gospodarowicz M, Connors J, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 2012;366:399-408.

Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol 2004;22:2835-2841.

Radford J, Barrington S, Counsell N, et al. Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin lymphoma and a negative PET scan after 3 cycles of ABVD. Results of the UK NCRI RAPID trial (abstract). Blood 2012;120:Abstract 547.

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

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

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

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

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

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

Escalated BEACOPP followed by ABVD with ISRT

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

See Principles of Systemic Therapy for NLPHL (HODG-B 2 of 2†)

See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E)

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

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

PRINCIPLES OF RADIATION THERAPY

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

Dose:

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

Volumes - Involved-site radiation therapy (ISRT)

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

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

PRINCIPLES OF RADIATION THERAPY (3 OF 3)

REFERENCES

[1]Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 2014;89:854-862.
[2]Cella L, Conson M, Caterino M, et al. Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1802-1808.
[3]Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. Pract Radiat Oncol 2014;4:174-180.
[4]Filippi AR, Ciammella P, Piva C, et al. Involved-site image-guided intensity modulated versus 3D conformal radiation therapy in early stage supradiaphragmatic Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2014;89:370-375.
[5]Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. Pract Radiat Oncol 2013;3:216-222.
[6]Fox AM, Dosoretz AP, Mauch PM, et al. Predictive factors for radiation pneumonitis in Hodgkin lymphoma patients receiving combined-modality therapy. Int J Radiat Oncol Biol Phys 2012;83:277-283.
[7]Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 2006;79:270-277.
[8]Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? Int J Radiat Oncol Biol Phys 2006;64:218-226.
[9]Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449-455.
[10]Hoskin PJ, Díez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol) 2013;25:49-58.
[11]Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. Int J Radiat Oncol Biol Phys 2011;81:167-174.
[12]Nieder C, Schill S, Kneschaurek P, Molls M. Inflence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007;2:20.
[13]Paumier A, Ghalibafian M, Beaudre A, et al. Involved node radiotherapy and Modern radiation treatment techniques in patients with Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2011;80:199-205.
[14]Paumier A, Ghalibafian M, Gilmore J, et al. Dosimetric benefits of IMRT combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1522-1527.
[15]Voong KR, McSpadden, Pinnix CC, et al. Dosimetric advantages of a "butterfly" technique for IMRT for young female patients with mediastinal Hodgkin lymphoma. Radiat Oncol 2014;9:94.
[16]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.

PET 5-POINT SCALE (DEAUVILLE CRITERIA)*

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

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

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

- The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.
- Some studies have suggested that patients with minimal disease burden at relapse (not refractory) may not need additional treatment prior to high-dose chemotherapy with stem-cell rescue. However, patients tend to have an improved outcome when transplanted in a minimal disease state. Thus, cytoreduction with chemotherapy before high-dose chemotherapy with stem-cell rescue may be beneficial. In addition, second-line chemotherapy serves as a test for drug sensitivity and to facilitate the harvest of stem cells.
  - Nitrogen mustard, procarbazine, carmustine, and melphalan may adversely affect both quality and quantity of stem-cell collection.
- Rituximab should be considered with all second-line chemotherapy regimens for relapsed or refractory NLPHL.
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (2 OF 2)
Regimens and References (listed in alphabetical order)

Second-Line or Subsequent* Therapy Options:

Brentuximab vedotin (only for CHL)**
Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012;30:2183-2189.

C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)

DHAP (dexamethasone, cisplatin, high-dose cytarabine)
Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13(10):1628-1635.
Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 2008;26(4):401-406.

ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncol 1999;10(5):593-595.
Fernández de Larrea C, Martínez C, et al. Salvage chemotherapy with alternating MINE-ESHAP regimen in relapsed or refractory Hodgkin's lymphoma followed by autologous stem cell transplantation. Ann Oncol 2010;21(6):1211-1216.

GCD (gemcitabine, carboplatin, dexamethasone)
Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemicitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.

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

ICE (ifosfamide, carboplatin, etoposide)
Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97(3):616-623.
Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 2008;26(4):401-406.

Second-Line/Subsequent* Therapy Options (continued):

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

Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. J Clin Oncol 1995;13:396-402.
Martín A, Fernández-Jiménez MC, Caballero MD, et al. Long-term follow-up in patients treated with Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. Br J Haematol 2001;113(1):161-171.

MINE (etoposide, ifosfamide, mesna, mitoxantrone)
Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphoms. Ann Oncol 1995;6(6):609-611.

Additional Therapy Options* (only for CHL):

Bendamustine
Moskowitz AJ, Hamlin PA, Perales M-A, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 2013;31:456-460.

Everolimus
Johnston PB, Inwards DJ, Colgan JP, et al; A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol. 2010;85(5):320-4.

Lenalidomide
Fehniger TA, Larson S, Trinkaus K, et al; A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood 2011;118(19):5119-25.

*Additional systemic therapy options include second-line therapy options that were not previously used.
**Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.

HODG-E
(1 & 2 of 2)

HODGKIN LYMPHOMA STAGING[1]

Table 1

Definitions of Stages in Hodgkin's Disease[2]

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

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 (IIE).

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

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or by both (IIIE+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 by permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1861.

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

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