National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 1.2012

NCCN.org

Continue

NCCN Guidelines Version 1.2012 Panel Members
Hodgkin Lymphoma

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

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

Ranjana Hira Advani, MD †
Stanford Comprehensive Cancer Center

Weiyun Z. Ai, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

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

Patricia Aoun, MD, MPH ≠
UNMC Eppley Cancer Center at The Nebraska Medical Center

Celeste M. Bello, MD, MSPH †
H. Lee Moffitt Cancer Center & Research Institute

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

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

Robert Chen, MD ‡ ξ
City of Hope Comprehensive Cancer Center

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

Ysabel Duron ¥
Latinas Contra Cancer

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

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

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

Ephraim P. Hochberg, MD †
Massachusetts General Hospital Cancer Center

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

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

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

Monika Metzger, MD €
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute

Joseph O. Moore, MD †
Duke Cancer Institute

David Morgan, MD † ‡ ξ
Vanderbilt-Ingram Cancer Center

Craig H. Moskowitz, MD † Þ
Memorial Sloan-Kettering Cancer Center

Matthew Poppe, MD §
Huntsman Cancer Institute at the University of Utah

Barbara Pro, MD † Þ
Fox Chase Cancer Center

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

Joachim Yahalom, MD §
Memorial Sloan-Kettering Cancer Center

NCCN
Kristina Gregory, RN, MSN, OCN
Hema Sundar, PhD

§ Radiation oncology
† Medical oncology
‡ Hematology/Hematology oncology
ξ Bone Marrow Transplantation
€ Pediatric oncology
≠ Pathology
Þ Internal medicine
¥ Patient Advocacy

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2012 Table of Contents Hodgkin Lymphoma

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

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

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

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

See NCCN Categories of Evidence and Consensus

NCCN Guidelines Version 1.2012 Updates
Hodgkin Lymphoma

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

Summary of the changes in the 1.2012 version of the Hodgkin Lymphoma Guidelines from the 3.2011 version include:

HODG-1

Diagnosis

- **"FNA alone is generally insufficient" deleted.**
- **Footnote "a" is new to the page: "FNA alone is to be avoided and only considered to be adequate if called diagnostic of HL by a hematopathologist or cytopathologist."**

Workup

- **HIV test moved to essential from useful in selected cases.**
- **The following added to Useful in Select Cases: "Oophoropexy in premenopausal women if pelvic RT is contemplated."**
- **Neck CT - "if neck RT planned" deleted.**

HODG-2

- **Footnote "k" clarified by adding "of the GHSG" to the strict criteria.**
- **Footnote "m" is new to the page: "Patients with elevated ESR or > 3 sites of disease may be managed with Stanford V per this algorithm."**
- **Initial restaging modified by changing PET-CT to CT and adding "through regions of initial disease." (also applies to HODG-3)**
- **CR after primary treatment: restaging with PET-CT added after IFRT with further treatment options based on PET results.**
- **PR after primary treatment: biopsy removed as a treatment option.**

HODG-3

- **Response criteria after initial restaging based on CT results. Previous footnote "r" removed: "Patients who have no residual evidence of disease on the diagnostic CT asa well as a negative PET.".**
- **Recommendation for PFTs after 4 cycles of ABVD moved to footnote "r". (also applies to HODG-4)**
- **PR or SD; PET positive after restaging: IFRT added as a treatment option.**

HODG-4

- **Primary treatment: ABVD changed from 2 cycles to 4 cycles.**
- **PR or SD restaging: modified footnote "s": "The value of interim PET *imaging* scan ~~after 2-4 cycles~~ is unclear ~~but may have a role in management and prognosis~~ *for many clinical scenarios. All measures of response should be considered in the context of management decisions.* (also applies for HODG-6, HODG-7)**
- **PR or SD after primary treatment; CR after restaging: ABVD deleted as a treatment option, recommendation to proceed to IFRT.**
- **PR or SD after primary treatment; PR or SD after restaging: ABVD deleted as a treatment option, IFRT added as a treatment option.**
- **PR or SD after primary treatment; PR or SD after restaging; IFRT; PR or SD after further restaging: IFRT deleted as a treatment option, observe added as a treatment option.**

HODG-5

- **PR after primary treatment: Biopsy added as a treatment option; negative biopsy proceeds to RT, positive biopsy proceeds to HODG-12.**

HODG-6

- **Primary treatment: ABVD changed from 2 cycles to 4 cycles.**
- **PR or SD after primary treatment; CR after restaging: ABVD deleted as a treatment option, recommendation to proceed to IFRT or observe.**
- **PR or SD after primary treatment; PR or SD after restaging: ABVD deleted as a treatment option, IFRT added as a treatment option.**
- **PR or SD after primary treatment; PR or SD after restaging; Biopsy negative: observe added as a treatment option.**
- **PR or SD after primary treatment; PR or SD after restaging; IFRT; CR, PR, SD after further restaging: All previous treatment recommendation deleted and replaced with observe. PD after further restaging: Biopsy added.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2012 Updates Hodgkin Lymphoma

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

Summary of the changes in the 1.2012 version of the Hodgkin Lymphoma Guidelines from the 3.2011 version include:

HODG-7
- Footnote "w" is new to the page: "If being used for relapsed LPHL, consider the addition of rituximab."
- Response criteria after initial staging: SD removed from PR and added to PD.
- Footnote "y" new to the page: "If stable disease after 2 cycles of ABVD, consider a total of 4 cycles of ABVD before proceeding to biopsy."
- CR after primary treatment and PR after primary treatment; CR after restaging: RT recommendation clarified as "selectively to initially bulky disease."
- PR after primary treatment; PR or SD after restaging: IFRT changed to RT to regions with residual disease ± initially bulky sites.
- Stanford V regimen recommendations are now on page HODG-8.

HODG-10
- Footnote "aa" is new to the page: "In some patients treated with rituximab alone, maintenance rituximab may be considered for 5 years."

HODG-12
- Page revised to only address progressive disease.
- Footnote "ff" modified: There are no data to support a superior outcome with any *of the treatment modalities. Individualized treatment is recommended*. (also applies to HODG-12)
- Recommendations clarified and expanded to address the timing of HDT/ASCR and additional therapy after progression.

HODG-13
- Page added to address suspected relapse (previously on page HODG-11).
- Recommendations clarified and expanded to address the timing of HDT/ASCR and additional therapy after suspected relapse.

HODG-A
- The following footnote added: The GHSG definition of nodal sites differs from the Ann Arbor system in that the infraclavicular region is included with the ipsilateral cervical/supraclavicular, the bilateral hila are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.

HODG-C
- The following statement added: "Therapy with either photons or protons is acceptable."
- Footnote "*" clarified: See HODG-A for definition of nodal sites.

HODG-E 1 of 2
- The following bullet added: Rituximab should be considered with all regimens for relapsed LPHL.

HODG-E 2 of 2
- Regimens and references moved to page HODG-E 2 of 2.
- Brentuximab added as a second-line chemotherapy option prior to transplant.

ST-1
- The following clarification added to B symptoms "(within 6 months prior to diagnosis)."

NCCN Guidelines Version 1.2012
Hodgkin Lymphoma

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

DIAGNOSIS

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic[a]
- Immunohisto-chemistry highly recommended for Hodgkin lymphoma[b]

WORKUP

Essential:

- H&P including: B symptoms, alcohol intolerance, pruritus, fatigue, performance status, exam lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- LDH, LFT, albumin
- BUN, creatinine
- Pregnancy test: women of childbearing age
- Chest x-ray
- Diagnostic chest/abdominal/pelvic CT[c]
- PET-CT scan[d]
- Adequate bone marrow biopsy in stage IB, IIB and stage III-IV
- Evaluation of ejection fraction for doxorubicin-containing regimens
- HIV test
- Counseling: Fertility, smoking cessation, psychosocial (see Distress Management Guidelines)

Useful in selected cases:

- Semen cryopreservation, if chemotherapy or pelvic RT contemplated
- IVF or ovarian tissue or oocyte cryopreservation
- Oophoropexy in pre-menopausal women if pelvic RT is contemplated
- Neck CT
- Pulmonary functions tests (PFTs incl. DLCO) if ABVD or BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated

CLINICAL STAGING

- Classical Hodgkin lymphoma[e]
  - Stage IA, IIA Favorable[g] → See Primary Treatment (HODG-2)[h]
  - Stage I-II Unfavorable[g] (Bulky disease) → See Primary Treatment (HODG-4)[h]
  - Stage I-II Unfavorable[g] (Non-bulky disease) → See Primary Treatment (HODG-6)[h]
  - Stage III-IV → See Primary Treatment (HODG-7)[h]
- Lymphocyte-predominant Hodgkin lymphoma (LPHL)[f] → See Primary Treatment (HODG-10)[h]

[a] FNA alone is to be avoided and only considered to be adequate if called diagnostic of HL by a hematopathologist or cytopathologist.

[b] Typical immunophenotype for Classical Hodgkin lymphoma: CD30+, CD15+ (majority); CD3-, CD45-; CD20+ (<40%). Lymphocyte-predominant Hodgkin lymphoma: CD20+, CD45+; CD3-, CD15-, CD30-. An expanded panel of markers may be required especially if equivocal diagnosis. See NHL Guidelines.

[c] A separate diagnostic CT does not need to be done if it was part of the integrated PET-CT scan.

[d] 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 upstage patient. See (ST-1).

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

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

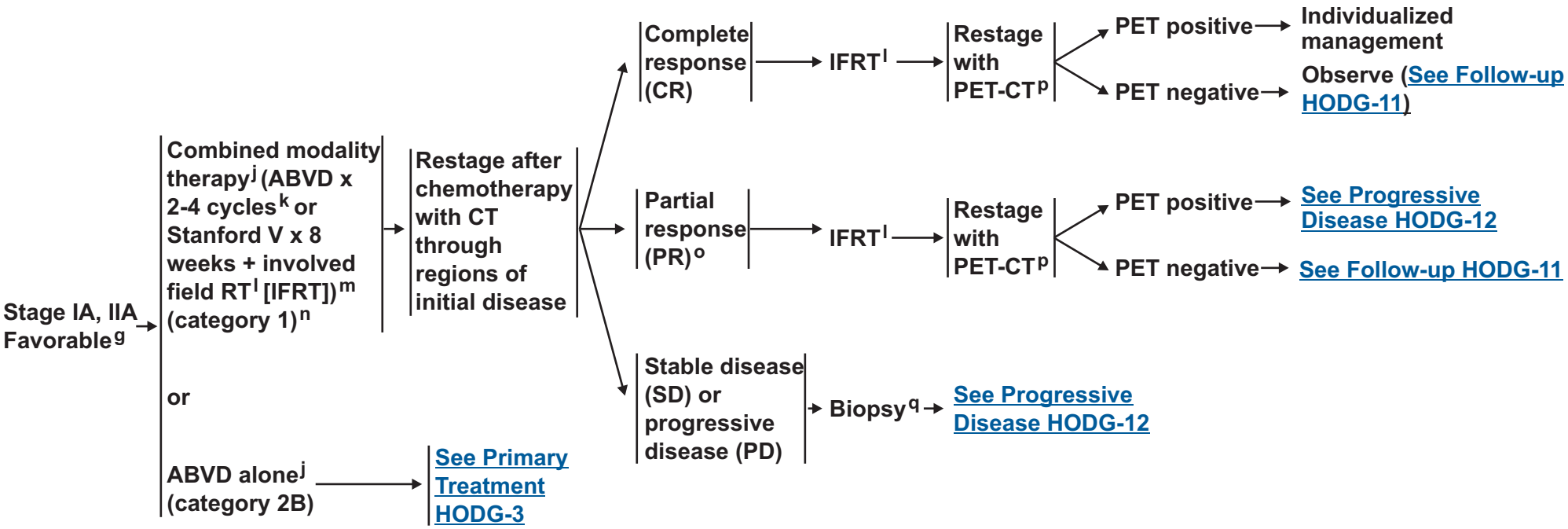
[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).

[h] Treatment recommendations for postadolescent Hodgkin lymphoma.

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]

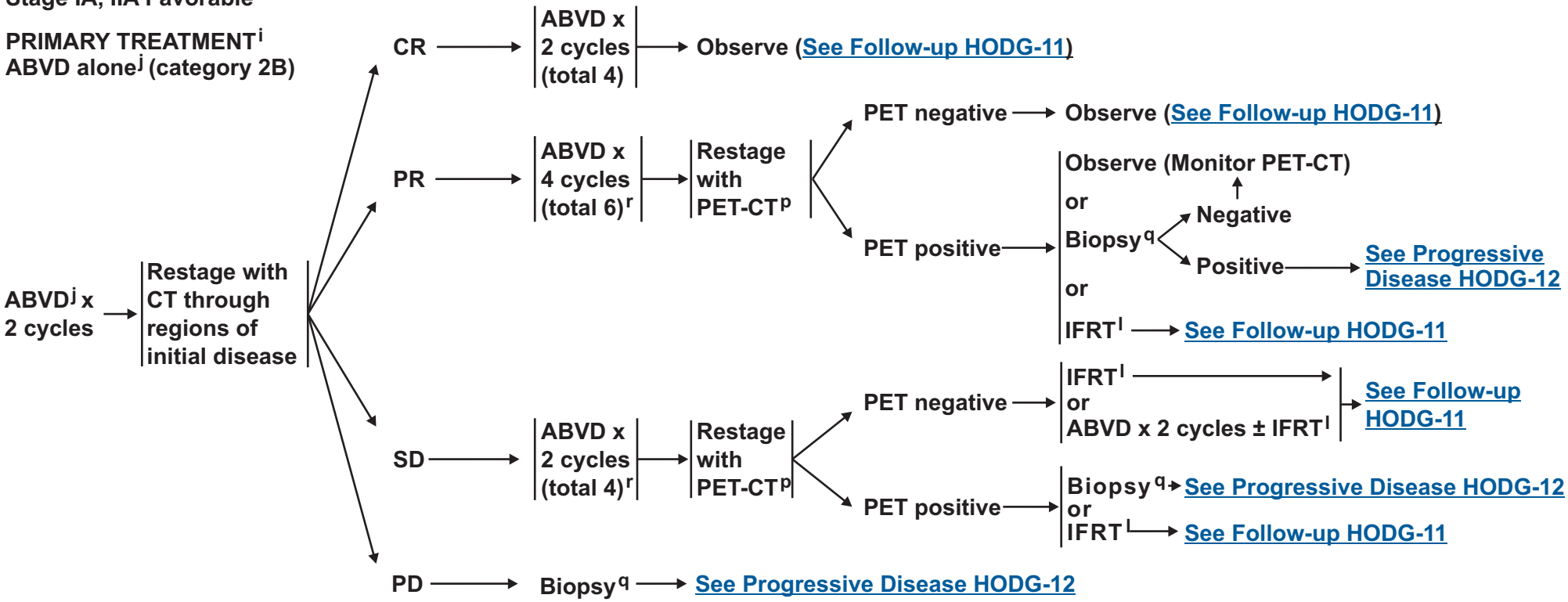
PRIMARY TREATMENT[i]



[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[k] 4 cycles of ABVD unless patient fulfills strict criteria of the GHSG with only 2 sites of disease and no extralymphatic lesions in which case 2 cycles is sufficient.
[l] See Principles of Radiation Therapy (HODG-C).
[m] Patients with elevated ESR or > 3 sites of disease may be managed with Stanford V per this algorithm.
[n] Depending upon co-morbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able to tolerate chemotherapy.
[o] Recommend ABVD x 4 cycles (total) before proceeding to IFRT or biopsy.
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

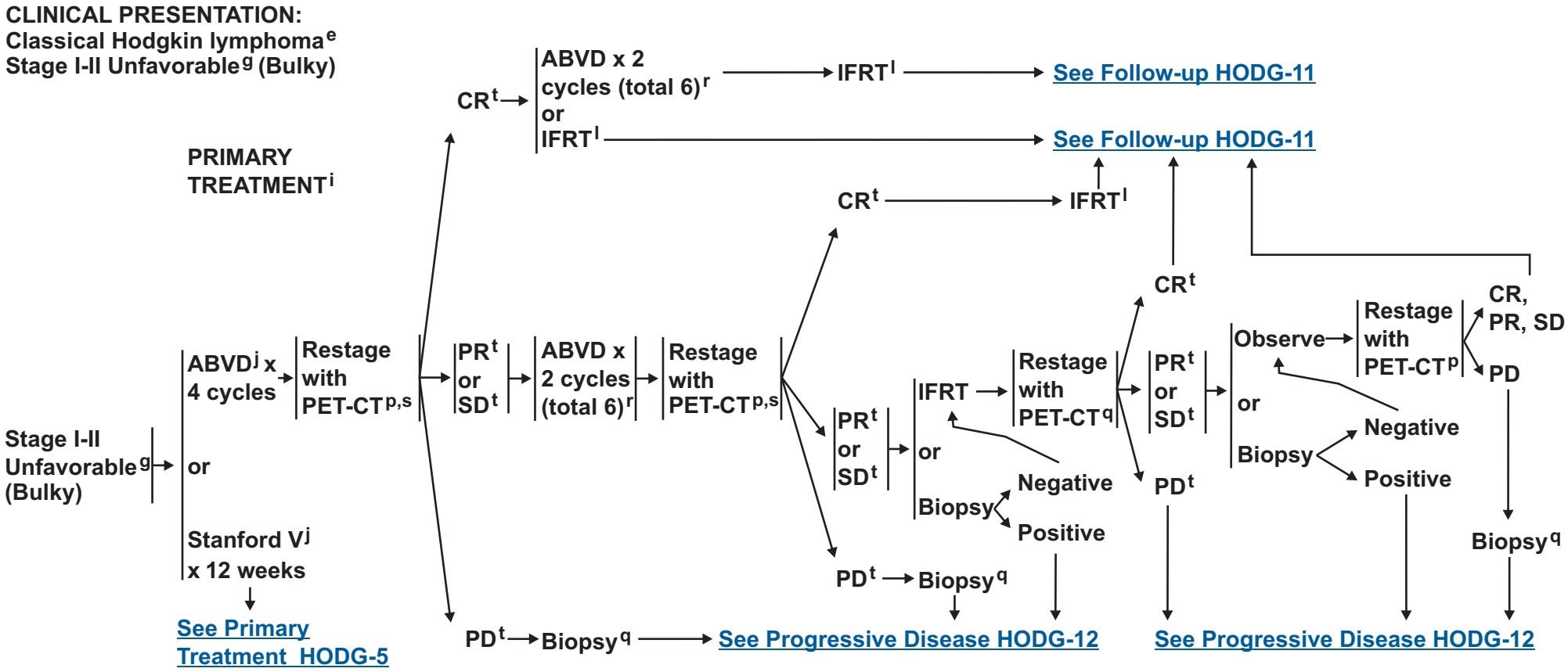
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]
Stage IA, IIA Favorable



[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[l] See Principles of Radiation Therapy (HODG-C).
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[r] Consider PFTs after 4 cycles of ABVD.

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



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

[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).

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

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

[l] See Principles of Radiation Therapy (HODG-C).

[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.

[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[r] Consider PFTs after 4 cycles of ABVD.

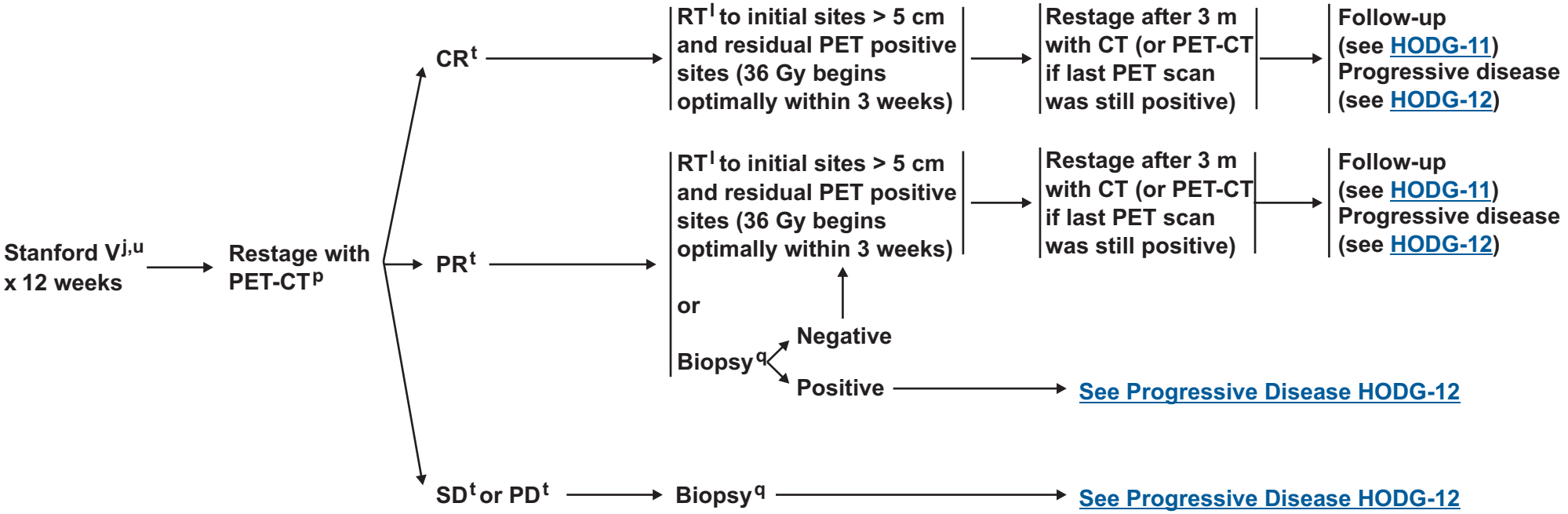
[s] The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

[t] See Revised Response Criteria for Lymphoma (HODG-D).

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]
Stage I-II Unfavorable[g] (Bulky or Nonbulky)

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



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

[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).

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

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

[l] See Principles of Radiation Therapy (HODG-C).

[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.

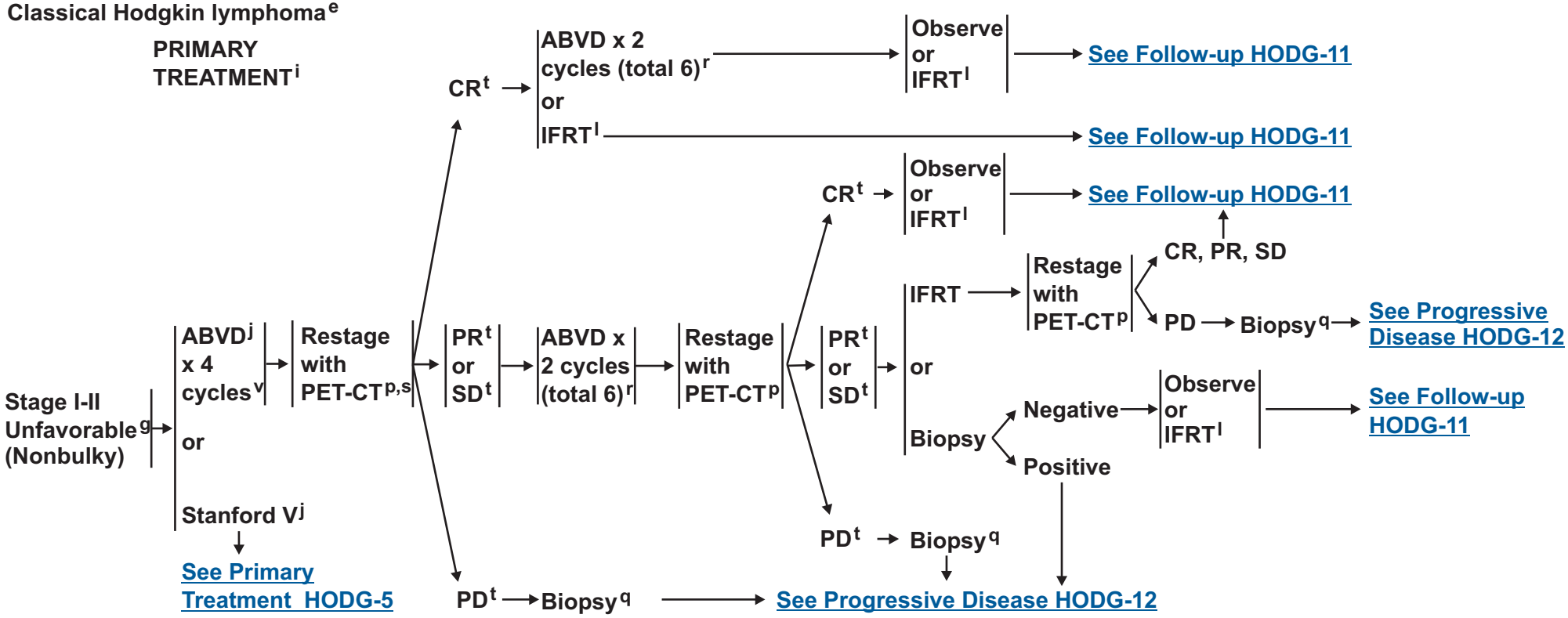
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[t] See Revised Response Criteria for Lymphoma (HODG-D).

[u] 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, or > 3 sites are treated according to the Stanford V algorithm on HODG-2.

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]



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

[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).

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

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

[l] See Principles of Radiation Therapy (HODG-C).

[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.

[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[r] Consider PFTs after 4 cycles of ABVD.

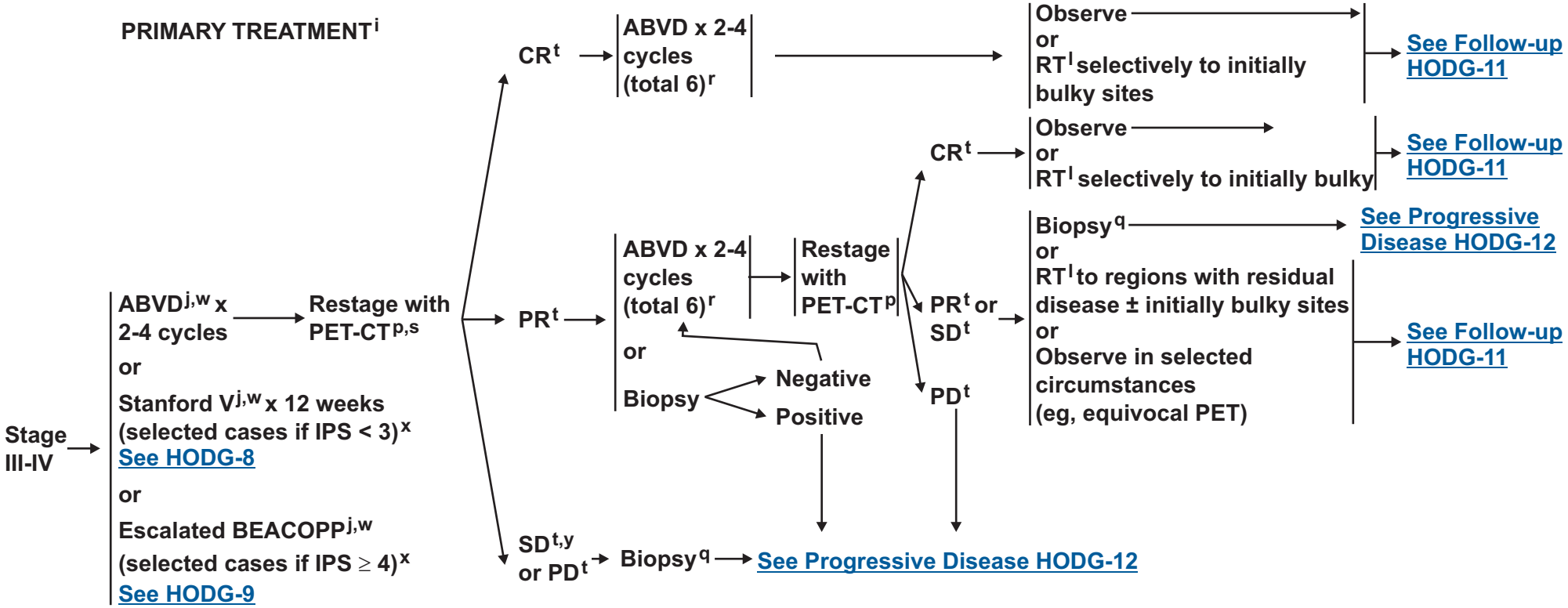
[s] The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

[t] See Revised Response Criteria for Lymphoma (HODG-D).

[v] If clinical circumstances warrant, initial PET-CT may be performed after just 2-3 cycles of ABVD.

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]

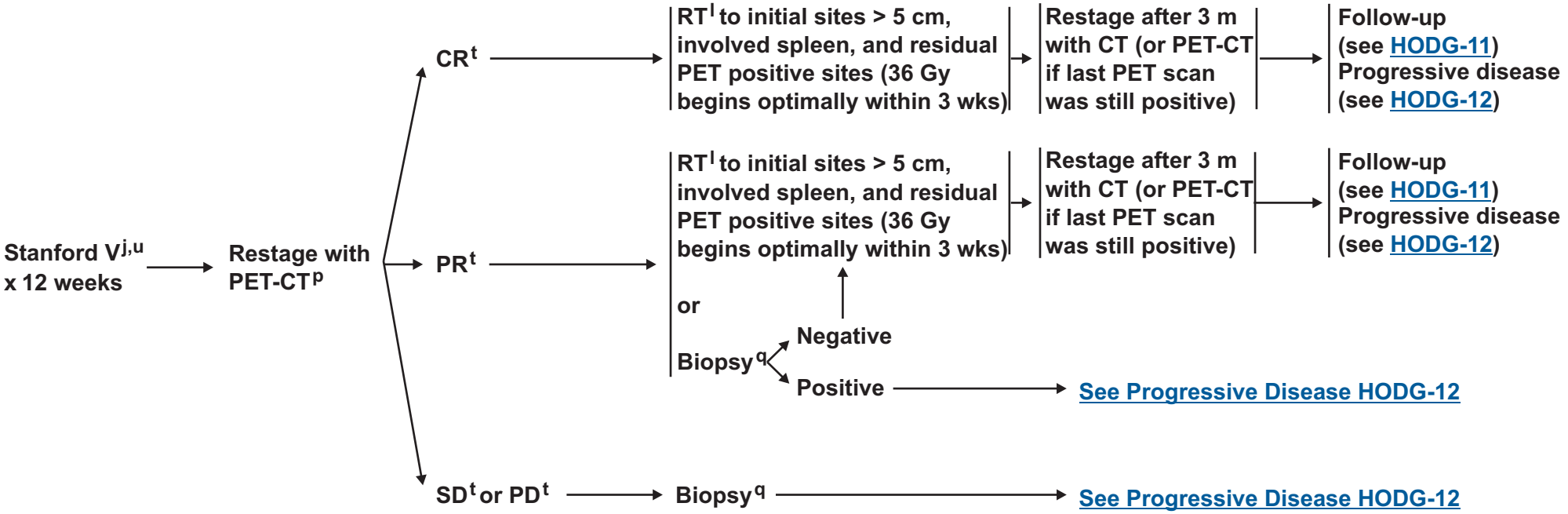


[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[l] See Principles of Radiation Therapy (HODG-C).
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[r] Consider PFTs after 4 cycles of ABVD.
[s] 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.
[t] See Revised Response Criteria for Lymphoma (HODG-D).
[w] If being used for relapsed LPHL, consider the addition of rituximab.
[x] See International Prognostic Score (IPS) (HODG-A).
[y] If stable disease after 2 cycles of ABVD, consider a total of 4 cycles of ABVD before proceeding to biopsy.

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]
Stage III-IV

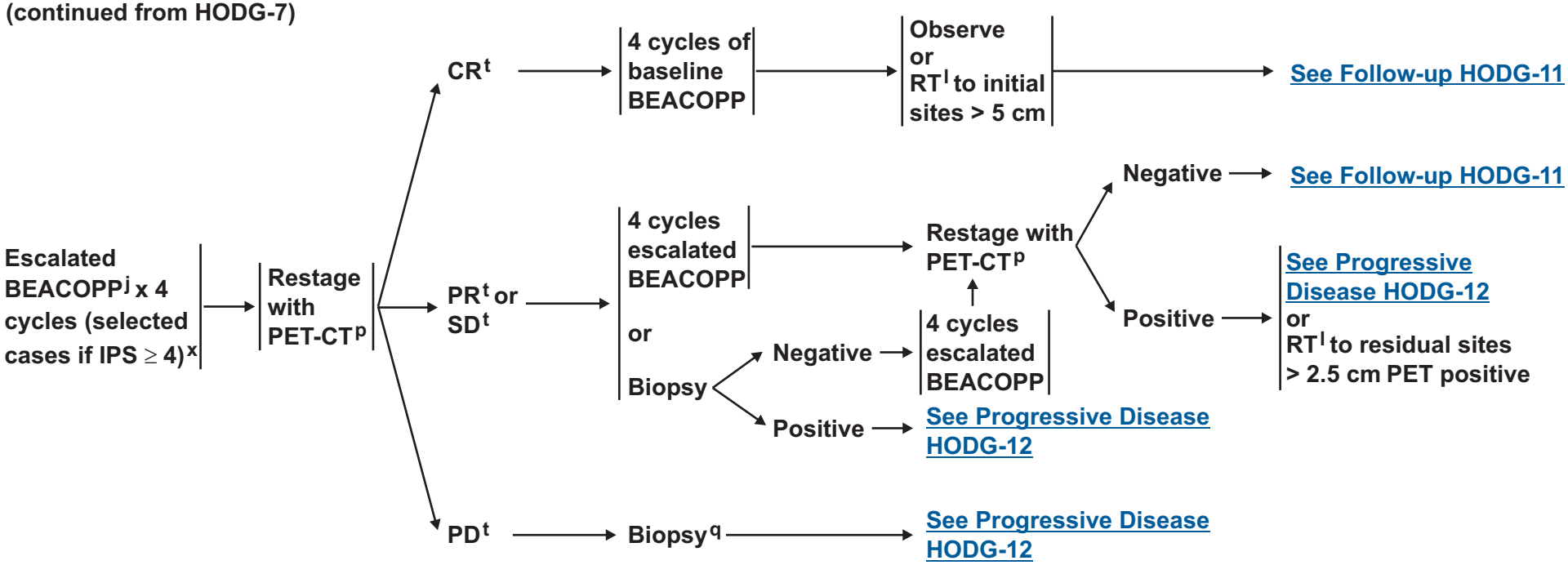
PRIMARY TREATMENT[i]
(continued from HODG-7)



[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[l] See Principles of Radiation Therapy (HODG-C).
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[t] See Revised Response Criteria for Lymphoma (HODG-D).
[u] 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, or > 3 sites are treated according to the Stanford V algorithm on HODG-2.

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

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[e]
Stage III-IV
PRIMARY TREATMENT[i]
(continued from HODG-7)

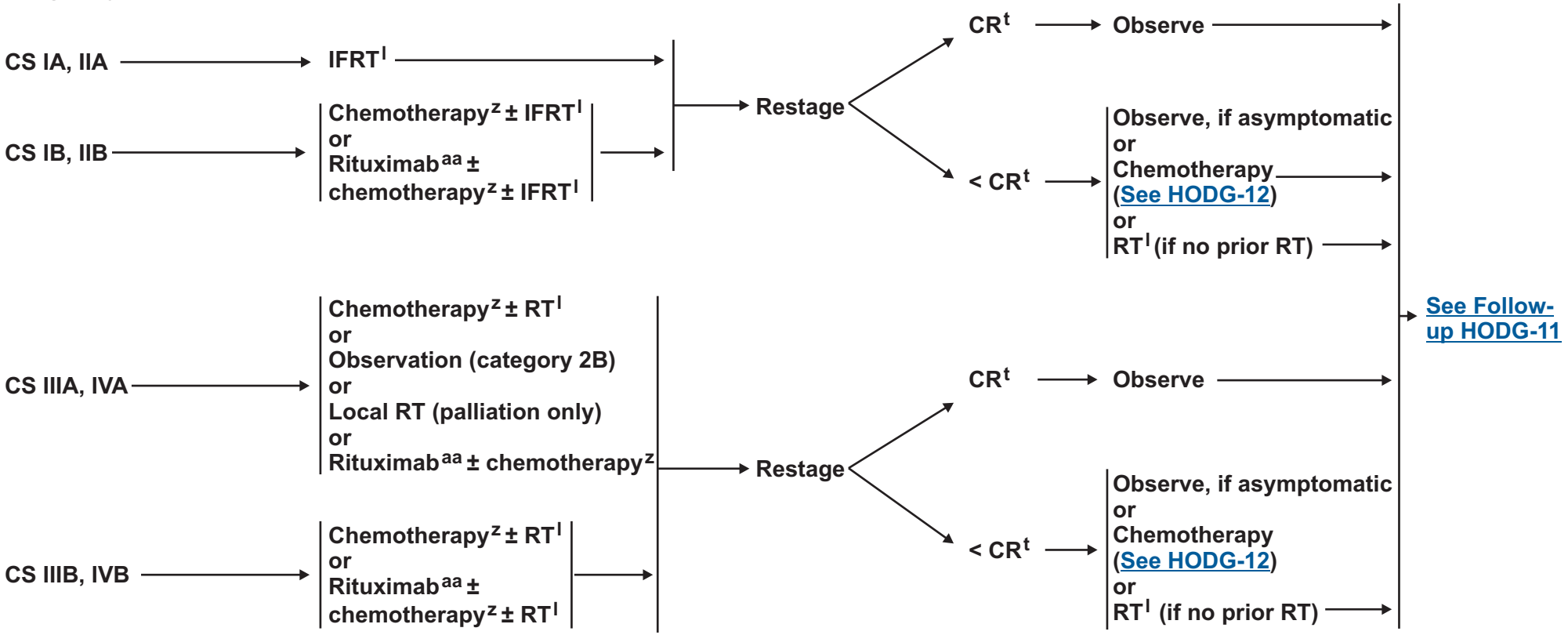


[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[l] See Principles of Radiation Therapy (HODG-C).
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[t] See Revised Response Criteria for Lymphoma (HODG-D).
[x] See International Prognostic Score (IPS) (HODG-A).

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

CLINICAL PRESENTATION: **PRIMARY TREATMENT**

Lymphocyte-predominant Hodgkin lymphoma[f]



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

[l]See Principles of Radiation Therapy (HODG-C).

[t]See Revised Response Criteria for Lymphoma (HODG-D).

[z]See Principles of Systemic Therapy (HODG-B 2 of 2).

[aa]In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years.

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

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

- **It is recommended that the patient be provided with a treatment summary at the completion of his/her therapy.**
- **Follow-up with an oncologist is recommended especially during the first 5 y interval to detect recurrence, then annually due to the risk of late complications including second cancers and cardiovascular disease.[bb,cc] Late relapse or transformation to large cell lymphoma may occur in LPHL.**
- **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 institutions.**

Follow-up after completion of treatment

- **Interim H&P:**
  Every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
  - **Annual influenza vaccine**
- **Laboratory studies:**
  - **CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y**
  - **TSH at least annually if RT to neck**
- **Chest imaging:**
  Chest x-ray or CT every 6-12 mo during first 2-5 y
- **Abdominal/pelvic CT (category 2B):**
  Every 6-12 mo for first 2-3 y
- **Counseling:**
  Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
- **Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed.**

Suspected Relapse HODG-13

Monitoring for Late Effects after 5 Years[bb,cc]

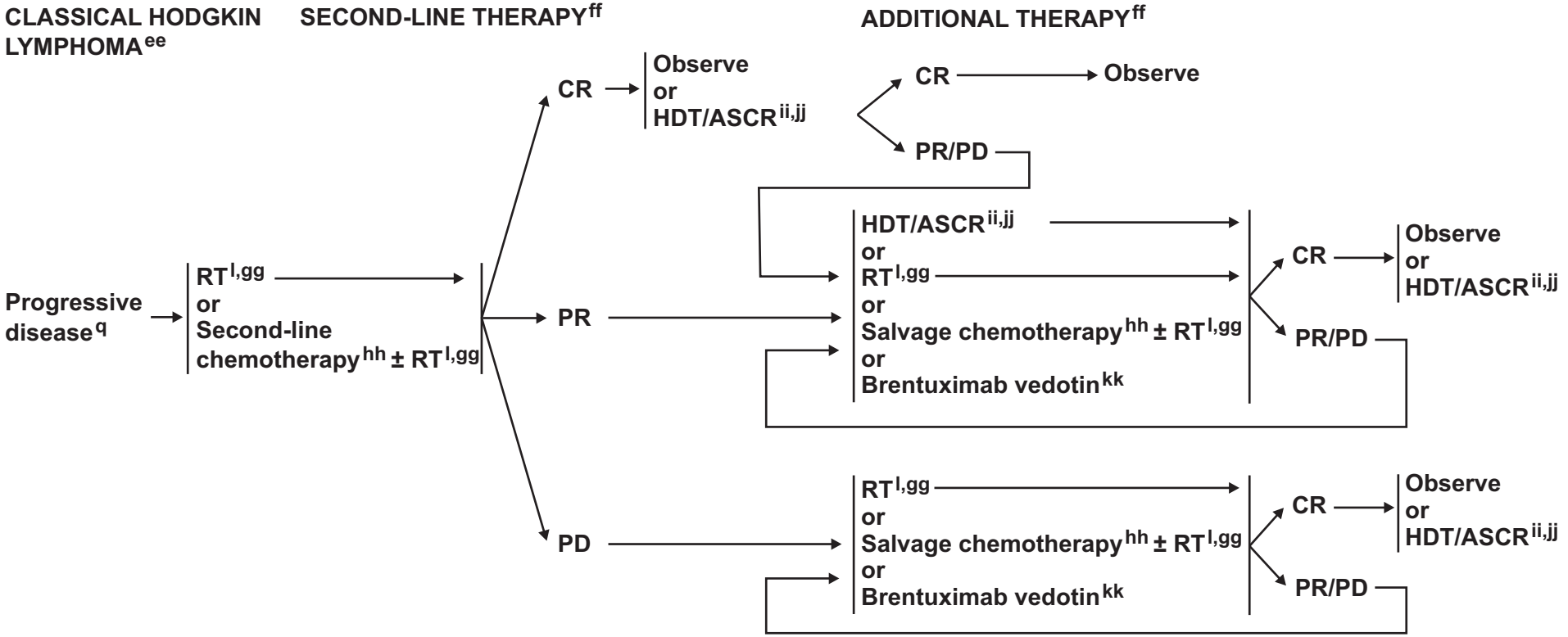
- **Interim H&P: Annually**
  - **Annual blood pressure, aggressive management of cardiovascular risk factors**
  - **Baseline stress test/echocardiogram at 10 y**
  - **Pneumococcal, meningococcal, and H-flu revaccination after 5 y, if patient treated with splenic RT or previous splenectomy**
  - **Annual influenza vaccine**
- **Laboratory studies:**
  - **CBC, platelets, chemistry profile annually**
  - **TSH at least annually if RT to neck**
  - **Annual lipids**
- **Annual chest imaging (chest x-ray or chest CT) for patients at increased risk for lung cancer[dd]**
- **Annual breast screening:**
  Initiate 8-10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The American Cancer Society recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10 and 30 y.
- **Counseling:**
  Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk.
- **Cardiovascular symptoms may emerge at a young age.**
- **Treatment summary and consideration of transfer to PCP.**

[bb] 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).

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

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

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



[l] See Principles of Radiation Therapy (HODG-C).

[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[ee] Patients with LPHL may be managed according to the same algorithm; however, some patients with LPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed. At relapse, patient should be considered for re-biopsy because of risk for transformation.

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

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

[hh] See Principles of Second-Line Chemotherapy (HODG-E).

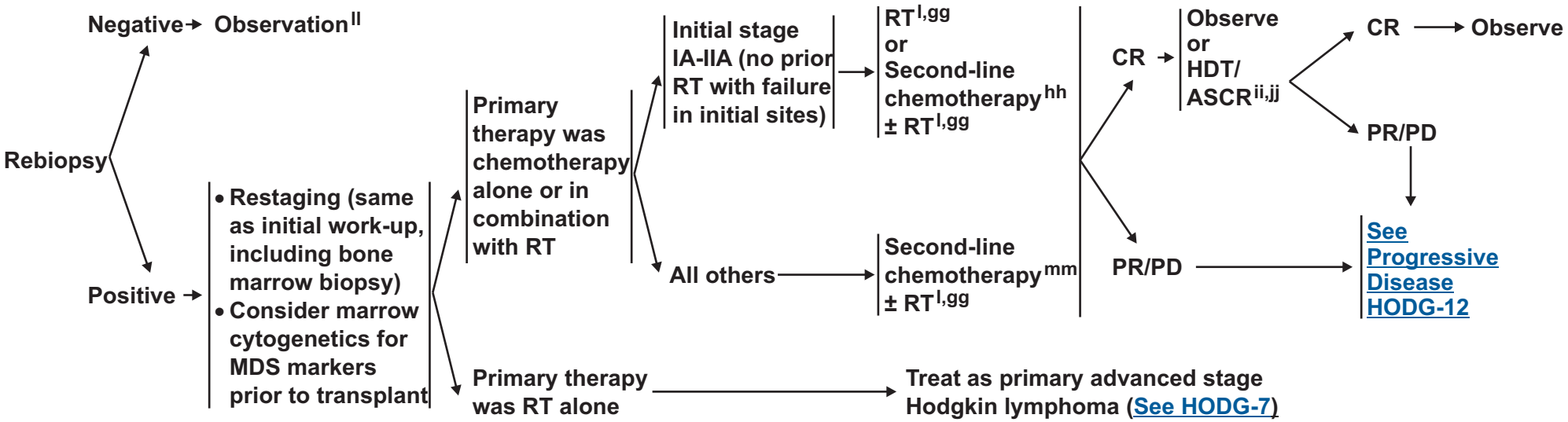
[ii] Radiation therapy recommended when sites have not been previously irradiated. In a radiation naive patient, TLI may be an appropriate component of HDT.

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

[kk] Brentuximab vedotin is a treatment option for patients who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens.

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

CLASSICAL HODGKIN LYMPHOMA[ee] SUSPECTED RELAPSE



[l] See Principles of Radiation Therapy (HODG-C).

[ee] Patients with LPHL may be managed according to the same algorithm; however, some patients with LPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed. At relapse, patient should be considered for re-biopsy because of risk for transformation.

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

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

[hh] See Principles of Second-Line Chemotherapy (HODG-E).

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

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

[ll] Clinical circumstances may warrant additional treatment even in face of negative biopsy.

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

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

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, 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

*The GHSG definition of nodal sites differs from the Ann Arbor system in that the infraclavicular region is included with the ipsilateral cervical/supraclavicular, the bilateral hila are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.

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

- **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)**

[1] Derived from Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339:1506-1514.

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

PRINCIPLES OF 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) ± RT

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 RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005;23(21):4634-4642.

Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-Term Results. J Clin Oncol. 2004;22(14):2835-2841.

Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an Intergroup Trial. J Clin Oncol. 2003;21(4):607-614.

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

Gordon LI, Hong F, Fisher RI, et al. A Randomized Phase III Trial of ABVD Vs. Stanford V +/- Radiation Therapy In Locally Extensive and Advanced Stage Hodgkin's Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496). ASH Annual Meeting Abstracts 2010;116:415-.

Advani RH, Hoppe RT, Baer DM, et al. Efficacy of abbreviated Stanford V chemotherapy and involved field radiotherapy in early stage Hodgkin's Disease: Mature results of the G4 trial. Blood (ASH Annual Meeting Abstracts) 2009;114:Abstract 1670.

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.

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

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

Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol 2009;27:4548-4554.

See Principles of Chemotherapy for LPHL page HODG-B 2 of 2

See Principles of Second-line Chemotherapy page HODG-E

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

PRINCIPLES OF SYSTEMIC THERAPY (2 of 2)

Lymphocyte-predominant Hodgkin Lymphoma[1]

- **The most common chemotherapies used at NCCN member institutions for LPHL are listed below.**

Regimens and References

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

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

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

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

Fanale MA, Lai C-M, McLaughlin P, et al. Outcomes of Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL) Patients Treated with R-CHOP. ASH Annual Meeting Abstracts 2010;116:2812-.

CVP (cyclophosphamide, vincristine, prednisone) ± rituximab

EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) ± rituximab

Single agent rituximab

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

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

Horning SJ, Bartlett NL, Breslin S, et al. Results of a Prospective Phase II Trial of Limited and Extended Rituximab Treatment in Nodular Lymphocyte Predominant Hodgkin's Disease (NLPHD). ASH Annual Meeting Abstracts. 2007;110:644.

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

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

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

PRINCIPLES OF RADIATION THERAPY

Therapy with either photons or protons is acceptable.

COMBINED MODALITY-RT DOSES:

- **Nonbulky disease (stage I-II): 20*-30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)**
- **Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV): 30-36 Gy (if treated with BEACOPP)**
- **Bulky disease sites (all stages): 30-36 Gy (if treated with ABVD), 36 Gy (if treated with Stanford V)**

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

- **Involved regions: 30-36 Gy (the dose of 30 Gy is mainly used for LPHL)**
- **Uninvolved regions: 25-30 Gy**

RADIATION FIELDS

- **When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.**
- **Consider oophoropexy to preserve ovarian function in pre-menopausal women.**

Involved-field: involved lymphoid region(s) only, modified as above

***A dose of 20 Gy following ABVD x 2 is sufficient if the patient has nonbulky 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.**

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

REVISED RESPONSE CRITERIA FOR HODGKIN LYMPHOMA (including PET)

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

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

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

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY (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.[1-3] However, patients tend to have an improved outcome when transplanted in a minimal disease state.[4] 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 regimens for relapsed LPHL.**

See Regimens and References, HODG-E 2 of 2

[1] Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. 1997;20(9):745-52.
[2] Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. Ann Oncol 1996;7(2):151-6.
[3] Chopra R, McMillan AK, Linch DC, et al. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. Blood 1993;81:1137-45.
[4] Stewart DA, Guo D, Gluck S, et al. Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant 2000;26(4):383-8.

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

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY (2 of 2)
Regimens and References
(listed in alphabetical order)

Bendamustine
Moskowitz AJ, Hamlin PA, Jr., Gerecitano J, et al. Bendamustine Is Highly Active in Heavily Pre-Treated Relapsed and Refractory Hodgkin Lymphoma and Serves as a Bridge to Allogeneic Stem Cell Transplant. ASH Annual Meeting Abstracts 2009;114:720-. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/720.

Brentuximab
Younes A, Bartlett NL, Leonard JP, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas. New England Journal of Medicine 2010;363:1812-1821.
Chen RW, Gopal AK, Smith SE, et al. Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL). ASCO Meeting Abstracts 2011;29:8031.

ChlVPP (Chlorambucil, vinblastine, procarbazine, prednisone)
The International ChlVPP Treatment Group. ChlVPP therapy for Hodgkin's disease: Experience of 960 patients. Ann Oncol. 1995;6(2):167-172.

C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone)
Takenaka T, Mikuni C, Miura A, et al. Alternating Combination Chemotherapy C-MOPP (Cyclophosphamide, Vincristine, Procarbazine, Prednisone) and ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) in Clinical Stage II-IV Hodgkin's Disease: a Multicenter Phase II Study (JCOG 8905). Jpn. J Clin Oncol. 2000;30(3):146-152.
Montoto S, Camos M, Lopez-Guillermo A, et al. Hybrid chemotherapy consisting of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (C-MOPP/ABV) as first-line treatment Hodgkin disease. Cancer. 2000;88(9):2142-2148.

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.
Akhtar S, Abdelsalam M, El Weshi A, et al. High-dose chemotherapy and autologous stem cell transplantation for Hodgkin's lymphoma in the kingdom of Saudi Arabia: King Faisal specialist hospital and research center experience. Bone Marrow Transplant 2008;42 Suppl 1:S37-S40.
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.

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.

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

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

Table 1

Definitions of Stages in Hodgkin's Disease[1]

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

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

Note: The number of lymph node regions involved may be indicated by a subscript (e.g. 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 from **Carbone PP, Kaplan HS, Musshoff K et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1.**

[1] 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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/16/11

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Hodgkin disease/lymphoma (HD/HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. In 2010, an estimated 8,490 new diagnoses and 1,320 deaths will occur in the United States.[1] Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older.

The past few decades have seen significant progress in the management of HL; it is now curable in at least 80% of patients.[2] With the advent of more effective treatment options, national statistics have shown an improvement in the 5-year survival rates of these patients that is unmatched in any other cancer over the past 4 decades. When appropriate treatment is selected, every patient with newly diagnosed HL has an overwhelming likelihood of being cured. In fact, cure rates for HL have increased so markedly that the overriding treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease. For advanced disease, clinical trials still emphasize improvement in cure rates, but the potential long-term effects of treatment remain an important consideration.

The World Health Organization (WHO) classification divides HL into 2 main types: lymphocyte-predominant Hodgkin lymphoma (LPHL) and classical Hodgkin lymphoma (CHL).[3] CHL is divided into 4 subtypes: nodular sclerosis CHL (NSCHL), mixed cellularity CHL (MCCHL), lymphocyte-depleted CHL (LDCHL), and lymphocyte-rich CHL (LRCHL). In Western countries, LPHL accounts for 5% and CHL for 95% of all HL cases.

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

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

Staging and Prognosis

Staging for HL is based on Ann Arbor staging system (Table 1). Each stage (I-IV) is subdivided into A and B categories. “A” indicates that no systemic symptoms are present and “B” is assigned to patients with unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.[4] Patients with HL are usually classified into 3 groups: early stage favorable (stage I-II with no unfavorable factors), early stage unfavorable (stage I-II with any unfavorable factor such as large mediastinal adenopathy, B symptoms; numerous sites of disease; or significantly elevated ESR), and advanced stage disease (stage III-IV).

Various unfavorable prognostic factors have been identified. Mediastinal bulk is an unfavorable prognostic factor in patients with early stage HL. Mediastinal bulk on chest radiograph is measured most commonly using the mediastinal mass ratio.[5] The mediastinal mass ratio (MMR) is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR greater than 0.33 is defined as bulky disease. Another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter. According to the Cotsworld modification of the Ann Arbor staging system, bulky disease is defined as a mediastinal mass exceeding one third of the internal transverse diameter of the thorax at the T5-T6 interspace on a posteroanterior chest radiograph.[6]

Other unfavorable prognostic factors for patients with stage I to II disease include the presence of B symptoms, more than 3 nodal sites of disease, or an erythrocyte sedimentation rate (ESR) of 50 or more. These factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by European Organization for Research and Treatment of Cancer (EORTC), German Hodgkin Study Group (GHSG) and National Cancer Institute of Canada (NCIC).[7, 8] NCCN unfavorable factors for stage I-II disease include bulky mediastinal disease (MMR greater than 0.33) or bulky disease greater than 10 cm, B symptoms, ESR greater than 50 and more than 3 nodal sites of disease.

In addition to these unfavorable factors for stage I-II disease, an international collaborative effort evaluating more than 5000 cases of advanced (stage III-IV) HL identified 7 adverse prognostic factors , each of which reduced survival rates by 7% to 8% per year:[9]

- Age 45 years or older
- Male gender
- Stage IV disease
- Albumin level below 4 g/dL
- Hemoglobin level below 10.5 g/dL
- Leucocytosis (white blood cell count more than 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of the white blood count and/or lymphocyte count less than 600/mm^3

The number of unfavorable factors (International Prognostic Score [IPS]) helps to determine clinical management and predict prognosis for patients with stage III-IV disease. For instance, if the patient has more than 4 unfavorable factors (IPS $\geq$ 4) and advanced disease, treatment with a dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen may be a more appropriate option than ABVD (doxorubicin bleomycin, vinblastine, and dacarbazine) chemotherapy or Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin and prednisone).

Response Criteria

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

The International Working Group (IWG) published the guidelines for lymphoma response criteria in 1999.[10] These criteria are based on the size reduction of enlarged lymph nodes as measured on computed tomography (CT) scan, and the extent of bone marrow involvement determined using bone marrow aspirate and biopsy. The original response criteria included CRu (complete response uncertain), indicating that it was not possible to determine whether residual masses identified on CT scan represented residual HL, scarring or some other nonmalignant process.

In 2007, the IWG guidelines were revised by the International Harmonization Project to incorporate immunohistochemistry, flow cytometry and positron emission tomography (PET) scans, in the definition of response for lymphoma.[11] The revised guidelines eliminated CRu based partly on the ability of PET scan to further characterize residual masses detected with CT. Using the revised system, response is categorized as complete response (CR), partial response (PR), stable disease, relapsed disease, or progressive disease.

Diagnosis

Fine needle aspiration alone is generally insufficient for initial diagnosis. Although it is widely used to diagnose malignant neoplasms, its role in diagnosing lymphoma is still controversial.[12-14] Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy generally be performed.

Immunohistochemistry is recommended but not necessary for CHL. The Reed-Sternberg cells of CHL express CD15 and CD30 in majority of cases and are usually negative for CD3 and CD45. CD20 may be detectable in less than 40% of the cases. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended. LPHL cells are usually CD45+ and CD20+, do not express CD15, and rarely express CD30. In addition, LPHL cells also express epithelial membrane antigen, which is usually not present in CHL. For LPHL, the guidelines recommend staining for CD3, CD15, CD20, CD21, CD30, and CD57. An expanded panel of markers may be required, especially for equivocal diagnosis.

Workup

Workup should include a thorough history and physical examination, including determination of B symptoms, alcohol intolerance, pruritus, fatigue, and performance status, and examination of the lymphoid regions, spleen, and liver. Standard laboratory testing should include a CBC, differential, platelets, ESR, serum lactate dehydrogenase level, albumin, and liver and renal function tests. Patients with risk factors for HIV or unusual disease presentations should be given an HIV test. Pregnancy test should be performed before women of childbearing age undergo treatment.

Chest radiograph and diagnostic CT scans of chest, abdomen and pelvis are appropriate imaging studies. A neck CT scan is also recommended for patients in whom RT is planned. PET scanning (or more commonly, integrated PET-CT scanning) is an integral part of initial staging. An adequate bone marrow biopsy should be performed for patients with B symptoms or stage III-IV disease.

The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) prior to the initiation of chemotherapy with alkylating agents or pelvic RT.[15, 16] Evaluation of ejection fraction is recommended for patients undergoing doxorubicin-based chemotherapy. Pulmonary function tests (PFTs) including the test of the diffusion capacity of the lungs for carbon monoxide (DLCO) are recommended for patients receiving bleomycin-based chemotherapy. H-flu, pneumococcal, and meningococcal vaccines are recommended if splenic RT is contemplated.

PET-CT (hereafter referred to as PET) scanning has been used for initial staging, restaging, and follow-up of patients with lymphoma.[17] In a recent meta-analysis, PET showed high positivity and specificity when used to stage and restage patients with lymphoma.[18] PET is widely used after completion of therapy to assess response and also during therapy for assessment of response, as reviewed by Juweid.[19] 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.[20, 21]

Early interim PET scan after 2-4 cycles of standard dose chemotherapy has also been shown to be a sensitive prognostic indicator in patients with advanced stage disease.[22-24] In prospective studies, the PET scan after 2 cycles of standard ABVD chemotherapy was a strong and independent prognostic factor of progression-free survival (PFS) in patients with advanced stage and extranodal disease.[25, 26] The 2-year PFS was significantly better for patients with negative PET after 2 cycles of ABVD than those with positive PET (95% vs.13%).[25] Advani and colleagues recently showed that in patients treated with the Stanford V regimen, freedom from progression was 96% in those with negative PET scans compared with 33% in those whose scans were positive at the completion of 12 weeks of chemotherapy.[27] Markova and colleagues recently reported that PET scan after four cycles of BEACOPP chemotherapy is predictive of treatment outcome in patients with advanced stage disease.[28] At a median follow-up of 25 months, 2 out of 14 patients with a positive PET after 4 cycles had progressed or relapsed, while no patients with a negative PET experienced progression or relapse. Dann and colleagues from an Israeli Study group reported the usefulness of interim PET-CT scan after 2 cycles of BEACOPP therapy in standard and high-risk patients.[29] Relapse or progression occurred in 27% of patients with positive PET-CT compared to 2.3% of patients with negative PET-CT. The role of PET in post therapy surveillance remains controversial, and further studies are needed to determine its role.

The significance of interim PET scan in patients with early stage disease is unclear, but may have a role in the management or prognosis. In a study of 73 patients (majority of whom had stage I-II disease), the actuarial 2-year FFS rate was 95% for those who were PET-negative at the end of chemotherapy, and 69% for the PET-positive group.[30] However, among the 46 patients who underwent interim PET scan after 2-3 cycles of chemotherapy, 20 patients had positive interim scans and 13 of these 20 patients had negative scans at the completion of chemotherapy. The actuarial 2-year FFS was 92% for patients with interim PET-positive and postchemotherapy PET-negative disease; 96% for those with interim PET-negative and postchemotherapy PET-negative disease.

The NCCN PET-CT Task Force recommends using PET scans for initial staging of patients with lymphomas, including HL, and evaluating residual masses at the end of treatment.[31] The panel recommends using PET scans to define the extent of disease, especially if the CT

scan is equivocal. An integrated PET-CT scan plus a diagnostic CT is recommended, although a separate diagnostic CT is not needed if it was part of the integrated PET-CT scan. However, caution should always be taken and common sense applied in the application of PET findings to patient management. For example, PET scans are often positive in sites of infection or inflammation, even in the absence of HL. In cases of PET positivity outside of the disease already identified, or if the PET positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. PET scans should not be used for routine surveillance because of the risk for false positives.

Principles of Radiation Therapy

Involved-field radiation therapy (IFRT) refers to treatment of the involved lymphoid regions only. The panel recommends that high cervical regions in all patients and axillae in women be excluded from radiation fields, if those regions are uninvolved. Oophoropexy should be considered to preserve ovarian function in pre-menopausal women if pelvic RT is contemplated.

In combined modality therapy, the panel recommends RT dose of 30-36 Gy when combined with ABVD or 36 Gy with Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin and prednisone) for patients with bulky disease (all stages). In patients with stage I-II non-bulky disease, the recommended RT dose is 20-30 Gy following ABVD and 30 Gy after Stanford V. This recommendation is based on experience and practice across NCCN institutions. The recommended RT dose with BEACOPP is 30-36 Gy.

Classical Hodgkin Lymphoma

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

- Stage I-II
- Stage III-IV

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

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

Stage I to II

RT alone was a standard treatment option for patients with favorable early stage HL for many decades.[32] However, the potential long-term toxicity of high dose, large field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary malignancies.[33] Chemotherapy regimens (ABVD and Stanford V) routinely used in advanced disease have also been incorporated into the management of early stage CHL.[34, 35]

The ABVD regimen was first introduced by Santoro and colleagues as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia.[36] The Stanford V regimen is one of the new regimens initially developed by the Stanford group for patients with early stage bulky and advanced stage HL.[37, 38] RT is an integral part of the Stanford V regimen.[39] Although the regimen is dose-intensive, the cumulative doses of these drugs are significantly less than those in MOPP, ABVD,

alternating MOPP/ABVD, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.

The ground-breaking study to demonstrate the value of combined modality therapy with ABVD and limited radiation was the trial reported by Bonadonna and colleagues.[40] Patients with stage I-II disease were treated with 4 cycles of ABVD and were then randomized to treatment with involved field or extended field RT. There was no difference in outcome between the two radiation arms.

The HD8 trial from the GHSG is the largest that investigated the efficacy of IFRT versus EFRT in early stage unfavorable HL.[41] This trial randomized 1204 patients to undergo 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone) plus ABVD) followed by EFRT or IFRT. At 5-years of follow-up, freedom from treatment failure (85.8% for EFRT and 84.2% for IFRT) and OS (90.8% vs. 92.4%) were similar for the groups. In contrast, acute side effects, including leukopenia, thrombocytopenias, and gastrointestinal toxicity, were more frequent in the EFRT group.

The HD10 trial from the GHSG investigated the reduction of the number of cycles ABVD as well as the IFRT dose in patients with stage I-II disease with no risk factors. Patients were not eligible if they had 3 or more sites of disease, any E-lesions, bulky mediastinal adenopathy, ESR >50, or ESR > 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to one of the 4 treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT; 2 of ABVD followed by 30 Gy or 20 Gy of IFRT.[42] The final analysis of this trial showed that (with a median follow-up of 79-91 months), there was 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 (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%), freedom from treatment failure (93.4% vs. 92.9%) and PFS (93.7% vs. 93.2%) were also not significantly different between 30 Gy and 20 Gy IFRT.[42] More importantly there were also no significant differences in OS, PFS and freedom from treatment failure among the four treatment arms. The results of the HD10 study confirms 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.

In studies conducted by the Stanford Group, the Stanford V regimen and IFRT was also shown to be effective in early stage favorable or unfavorable disease. In the G4 study, 87 patients with non-bulky stage IA or IIA disease received 8 weeks (2 cycles) of Stanford V plus 30 Gy IFRT, and 61 patients with bulky stage I-II disease were treated with 12 weeks of Stanford V plus 36 Gy of IFRT to bulky sites. At the median follow- up of 6 years, the actuarial 8-year freedom from progression was 96% in patients with stage I-II non-bulky disease and 92% for those with stage I-II bulky disease.[43] Posttreatment conceptions occurred in 25% of patients. Advani and colleagues recently reported the updated results for the 87 patients with non-bulky stage IA or IIA disease treated in the G4 study.[38] Among the 87 patients, unfavorable risk factors according to GHSG criteria (more than 2 nodal sites, ESR > 50 or extranodal involvement) were present in 47 patients (54%). At a median follow-up of 9 years, freedom from progression and OS rates were 94% and 96% respectively. Freedom from progression was 100% for patients with favorable disease and 89% for those with unfavorable non-bulky disease with no differences in OS (96.9% versus 95.7%). No secondary AML and no late cardiac or pulmonary toxicities have been observed. The updated results confirm that Stanford V chemotherapy (8

weeks; 2 cycles) and IFRT (30 Gy) is a safe and highly effective regimen for patients with unfavorable stage I-II disease without bulky or symptomatic disease.

In a randomized Italian study which compared a modified Stanford V regimen with MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) and ABVD in intermediate- and advanced stage HL, ABVD and MOPPEBVCAD were superior to the Stanford V regimen in response rate, FFS, and PFS.[44] However, interpretation of these results was difficult because the timing of response evaluation was different among the arms, (8 and 12 weeks for Stanford V, 16 weeks for ABVD, and 24 weeks for MOPPEBVCAD). In addition, modifications of the RT protocol for the Stanford V arm were substantial, including limitation of the number of sites irradiated (no more than 2) and a different definition of bulky disease.

Other investigators have confirmed that when RT is administered according to Stanford guidelines, the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile.[45-47] In the MSKCC study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36Gy IFRT to bulky sites (5 cm or larger) and/or to macroscopic splenic disease.[46] The 5- and 7-year OS were 90% and 88%, respectively. Fifty eight percent of the patients for whom the Stanford V regimen failed underwent successful second-line therapy with high-dose therapy with autologous stem cell rescue (HDT/ASCR). Aversa and colleagues from another Italian study group also reported similar findings in patients with bulky or advanced disease.[45] The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (Study ISRCTN 64141244) compared Stanford V and ABVD in patients with stage IIB, III, or IV disease or stage I to IIA with bulky disease or other adverse features.[47] RT was administered in both arms to sites of previous bulky sites (> 5 cm) and to splenic deposits. The results of this study showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rates (91% and 92%) respectively. At the median follow-up of 4.3 years, there was no evidence of a difference in the projected 5-year PFS and OS rates (76% and 90%, respectively, for ABVD; 74% and 92%, respectively, for Stanford V).

The recently completed phase III Intergroup trial (E2496) compared the Stanford V regimen with ABVD plus RT for the management of patients with stage I-IIA/B and bulky mediastinal disease and stage III-IV disease.[48] In this study, 812 patients were randomized to ABVD (6-8 cycles) plus 36 Gy RT (only for patients with bulky mediastinal disease) or Stanford V (12 weeks) plus 36 Gy RT (for sites larger than 5 cm or for macroscopic splenic disease). With a median follow-up of 5 years, there was no difference in response rates between the two arms (72% CR, 7.7% PR and 7.9% SD for ABVD; 69% CR, 7% PR and 10 % SD for Stanford V).[48] Toxicity was also similar in both groups. There were also no significant differences in either FFS or OS between the 2 treatment groups. The 5-year FFS and OS rates were was 73% and 88% respectively for ABVD. The corresponding survival rates were 71% and 87% respectively, for Stanford V. In a subset analysis of patients with stage I-II bulky mediastinal disease, the overall response rate was 82% for ABVD and 86% for Stanford V.[49] At a median follow-up of 5.5 years, there were no significant differences between ABVD and Stanford V in terms of either FFS (85% versus 77% p=0.13) or OS (95% versus 92% p=0.31). ABVD (6 - 8 cycles) plus 36 Gy RT remains the standard of care for patients with bulky stage I-II and stage III-IV disease. Stanford V, when given as described with RT, remains an acceptable alternative for some patients.

The results of the HD11 multicenter trial from the GHSG showed that intensified chemotherapy with BEACOPP did not significantly improve outcome of patients with early stage unfavorable disease compared to ABVD.[50] In this study, 1395 patients were randomized to either ABVD (4 cycles followed by 30 Gy or 20 Gy IFRT) or baseline BEACOPP (4 cycles followed by 30 Gy or 20 Gy IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FFTF and PFS were 86.8% and 87% respectively for BEACOPP. The corresponding rates were 81% and 82% respectively for ABVD). However, there was no difference between the 2 regimens when followed by 30 Gy of IFRT (5-year FFTF and PFS were 87% and 88% respectively for BEACOPP. The corresponding rates were 85% and 87% respectively for ABVD). Since the toxicity of the BEACOPP regimen was greater, ABVD plus 30 Gy IFRT was considered the better treatment.

Chemotherapy alone has also been investigated as a treatment option for patients with early stage non-bulky disease (stage I-II or IIIA).[51-54] In the multicenter study conducted by the NCIC Clinical Trials Group and ECOG, patients with stage IA or IIA HL were randomized to receive ABVD (4-6 cycles) or subtotal lymphoid radiation therapy (STLI).[52] In patients assigned to RT, those with any of the adverse prognostic factors (high ESR or ≥ 4 nodal sites) were treated with 2 cycles of ABVD before RT. At a median follow-up of 4.2 years, patients assigned to ABVD plus RT or RT alone had better freedom from progression (93% vs. 87%, respectively) and EFS (88% vs. 86%, respectively) compared with those treated with ABVD alone, with no significant difference in OS (94% vs. 96%, respectively). In a subset analysis of patients with unfavorable prognostic factors, freedom from progression was superior for those treated with ABVD plus RT (95% vs. 88%), but no differences were seen in 5-year OS or EFS rates. In the MSKCC study, there were no significant differences in complete response duration (91% vs. 87%, respectively), freedom from progression (86% vs. 81%, respectively), and OS (97% vs. 90%, respectively, p=0.08), among patients treated with ABVD plus radiation and those treated with ABVD alone.[54]

In a recent retrospective study, Canellos and colleagues reported that 6 cycles of ABVD is an effective and safe treatment for selected patients with limited-stage, non-bulky disease.[55] The majority (69%) of patients had stage IIA disease, 13% had stage IA and 15% had stage IIB disease. Fifty-five (76%) of 75 patients received 6 of ABVD. Two patients (2.6%) received four cycles of ABVD. In 16 (21%) of 75 patients, bleomycin was discontinued after a median of four cycles because of concern for pulmonary dysfunction. All patients included in this series achieved a clinical complete remission to chemotherapy alone. The FFS rate was 92% and the median follow-up was at least 60 months.

Results of these trials suggest that ABVD alone could be a reasonable choice of treatment for younger patients with favorable presentations of stage I-II non-bulky disease, especially if they experience prompt and CR to the first 2 cycles of ABVD (as documented by CT scan), in order to avoid the long-term risks of RT.

NCCN Recommendations

Stage IA to IIA (Favorable Disease)

Combined modality therapy (ABVD plus 20-30 Gy IFRT or Stanford V chemotherapy plus 30 Gy IFRT) is the preferred treatment (category 1) for patients with favorable disease. The panel has also included ABVD alone as an alternative treatment option with a category 2B recommendation.[52, 54, 55] Highly selected patients who are unable to tolerate chemotherapy because of the presence of comorbidities may

be treated with RT alone (category 1 recommendation for STLI and category 2A for mantle field irradiation).

In combined modality therapy, ABVD is generally administered for 2-4 cycles with 30 Gy IFRT (involved lymphoid regions only) and Stanford V regimen is administered for 8 weeks (2 cycles) with 30 Gy IFRT. Consolidative RT is optimally instituted within 3 weeks. In patients who fulfill the criteria for favorable disease (ESR less than 50, no extralymphatic lesions and only one or two lymph node regions involved), 2 cycles of ABVD followed by 20 Gy IFRT may be sufficient.[42] Restaging occurs at the completion of chemotherapy. Completion of IFRT is recommended for all patients who have achieved a CR or PR. Alternatively, patients with a PR can undergo biopsy prior to receiving IFRT. After completion of IFRT, no further treatment is necessary for patients with CR whereas further restaging is required for patients with a partial response. Histological confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Follow-up is recommended for patients with negative PET scan at the completion of therapy, and those with positive PET scans are treated as described for progressive disease. All patients with stable (PET positive) or progressive disease are managed as described for progressive disease. Biopsy is recommended strongly before initiating treatment for progressive disease.

Among patients eligible for treatment with chemotherapy alone, ABVD is initially administered for 2 cycles followed by restaging. If a patient has achieved a CR (no evidence of residual disease on the diagnostic CT scan as well as PET negative), 2 additional (total of 4) cycles are administered. No further treatment is necessary. Patients with a PR are treated with 4 additional cycles (total of 6) followed by restaging. Histological confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Additional treatment may be warranted under certain clinical circumstances even in the case of a negative biopsy. No further treatment is necessary if they are responding to additional therapy (PET-negative CR or PET-positive PR and biopsy negative). Patients with residual disease on PET scan as well as biopsy should be managed as described for progressive disease. Patients with stable (PET-positive) disease after 2 cycles of ABVD, receive an additional 2 cycles (total of 4) followed by restaging. Consolidation with IFRT or ABVD (2 cycles) with or without IFRT is recommended for PET negative patients. All patients with PET positive or progressive disease are managed as described for progressive disease. Biopsy is recommended before initiating treatment.

Stage I to II (Unfavorable Disease)

For patients with unfavorable bulky disease the panel recommends chemotherapy (ABVD or Stanford V) followed by IFRT. ABVD is initially administered for 2 cycles followed by restaging. PFTs should be repeated after 4 cycles. If there is CR, 2-4 additional cycles (total of 4 or 6) are administered followed by IFRT (30-36 Gy). Patients with PR or stable disease are treated with 2 additional cycles (total of 4) followed by restaging. If there is CR or PR, 2 additional cycles (total of 6) are administered followed by consolidative IFRT for patients with a CR. Patients with a PR are restaged at the completion of chemotherapy. Consolidative IFRT is recommended if they have achieved a CR. Patients with PR or stable disease (after 6 cycles) are treated with IFRT (30-36 Gy) followed by end-of-treatment restaging. Histological confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Additional treatment may be warranted under certain clinical circumstances even in the case of a negative biopsy. All patients with residual disease on PET scan as well as biopsy and those with progressive disease are managed as described for progressive disease. Biopsy is recommended before initiating treatment for progressive disease. Patients with stage I-II

unfavorable non-bulky disease are managed in the same manner as described above. The guidelines have included observation as an option for patients with CR after a total of 6 cycles of ABVD.

Stanford V is administered for 12 weeks (3 cycles) plus IFRT (36 Gy for bulky disease and 30 Gy for non-bulky disease) to patients with stage I-II bulky mediastinal disease or bulky disease more than 10 cm and/or B symptoms and for patients with stage I-II unfavorable non-bulky disease based upon presence of B symptoms. Patients are restaged when they complete chemotherapy. If there is CR or PR (including those with residual PET positive sites), RT (36 Gy) is recommended not only for initial sites larger than 5 cm but also to residual PET-positive sites. Generally, this includes the mediastinum and bilateral supraclavicular areas. Consolidative RT should be instituted within 3 weeks of completion of chemotherapy. All patients with stable or progressive disease are managed as described for progressive disease. Biopsy is recommended before initiating treatment for progressive disease. Patients with other criteria for unfavorable disease (elevated ESR or more than 3 sites of disease) are treated with 8 weeks of Stanford V plus 30 Gy IFRT followed by restaging as described for stage IA-IIA favorable disease.[38]

Stage III to IV (Advanced Disease)

While chemotherapy is always used for patients with advanced stage HL, combined modality therapy is an effective treatment for patients with large mediastinal masses.[56, 57] MOPP was the first successful regimen for HL, with a response rate of 84% and a 66% disease-free survival (DFS) of more than 10 years from end of treatment.[58] However, in addition to other long-term toxicities, MOPP is associated with loss of fertility (mostly in men) and myelodysplasia.

The landmark randomized trial by the Cancer and Leukemia Group B (CALGB) showed that ABVD alone or alternating with MOPP was superior to MOPP alone in PFS and 5-year OS.[59] ABVD also was less myelotoxic than MOPP, or ABVD alternating with MOPP. These results were confirmed in a large Intergroup study, which compared ABVD with a MOPP/ABV hybrid regimen in 856 patients with advanced HL.[60] The rates of complete remission (76% vs. 80%), 5-year FFS (63% vs. 66%), and OS (82% vs. 81%) were similar for ABVD and MOPP/ABV, respectively. However, MOPP/ABV was associated with acute pulmonary and hematologic toxicity, myelodysplastic syndrome, and leukemia.

Another randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) also confirmed that there was no significant difference in EFS and OS between ABVD and other multidrug regimens in patients with advanced HL. Multidrug regimens were more toxic than ABVD and were associated with poorer outcomes in older patients.[61] Updated results with a median follow-up of 83 months were consistent with the early results.[62]

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

In prospective studies conducted by the Stanford group, 108 patients with stage III to IV disease were treated with 12 weeks of Stanford V regimen plus 36 Gy of RT to initially bulky sites larger than 5 cm. In the most recent update of the mature results from these studies, 8- and 12-year freedom from progression rates were 86% and 83%, respectively, and 8- and 12-year OS rates were 95%.[43] No instances of secondary myelodysplasia or leukemia occurred. Fertility was

maintained, with 72 posttreatment conceptions. Similar outcomes were reported in other studies for patients with advanced stage HL treated with the Stanford V regimen.[45-47] The recently completed phase III intergroup trial (E2496) showed that there was no significant difference between ABVD and Stanford V in response rates, FFS, OS, and toxicity in patients with stage III-IV disease.[48]

The BEACOPP regimen was developed by the GHSG to improve treatment results through dose escalation and time intensification.[63] In a phase III randomized trial (HD9), patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP-ABVD (cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine), 8 cycles of standard-dose BEACOPP, or 8 cycles of dose-escalated BEACOPP.[64] Each regimen was followed by RT to initial sites of disease greater than 5 cm. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP-ABVD. It also showed significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP, and 10-year analysis showed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP-ABVD in terms of freedom from treatment failure (82%, 70% and 64% respectively) and OS rates (86%, 80% and 75% respectively).[65] These results confirm the efficiency of dose-escalated BEACOPP for patients with advanced stage HL who have risk factors.

The standard and escalated dose BEACOPP has also been evaluated in another randomized trial (HD2000) by the Italian Lymphoma Study group. In this study, 307 patients with advanced disease (stage IIB, III, and IV) were randomly assigned to receive 6 courses of ABVD, 4 escalated plus 2 standard courses of BEACOPP, or 6 courses of COPPEBVCAD [CEC] (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin), plus a limited radiation therapy program.[66] After a median follow-up of 41 months, BEACOPP was associated with a superior PFS with a significant reduction in the risk of progression. No differences were observed between BEACOPP and CEC or CEC and ABVD. The 5-year PFS rates were 68%, 81% and 78% for ABVD, BEACOPP and CEC respectively. BEACOPP and CEC also had higher rates of grade 3-4 neutropenia than ABVD. The ongoing EORTC 20012 trial is comparing BEACOPP and ABVD in patients with stage III or IV HL.

A study group from Israel reported the results of a risk-adapted approach using BEACOPP to treat patients with standard- and high-risk HL.[29] Patients with advanced disease (stage I-II bulky with B symptoms and stage III-IV) and IPS of 3 or higher were treated with 2 cycles of escalated BEACOPP, and all others underwent 2 cycles of standard-dose BEACOPP followed by restaging. Those with a positive PET scan received 4 additional cycles of escalated-dose BEACOPP, whereas 4 cycles of standard-dose BEACOPP were given to patients with a negative PET scan. The complete remission, 5-year EFS, and OS rates were 97%, 85%, and 90%, respectively. EFS and OS rates were similar in both risk groups.

Two recent European trials evaluated the role of HDT/ASCR as a consolidative therapy for patients with advanced stage and unfavorable HL that responded to initial chemotherapy.[67, 68] Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after initial course of doxorubicin-based chemotherapy. Instead, additional courses of the same conventional chemotherapy used as initial treatment produced equivalent or better outcomes than HDT/ASCR.

Several trials have addressed the role of consolidative RT in patients with stage III to IV HL who completed chemotherapy.[62, 69-71] The EORTC 20884 trial is the only randomized trial that assessed the role of consolidation RT following MOPP-ABV chemotherapy in patients with advanced disease.[69, 70] In this trial, patients with untreated stage III to IV disease underwent 6 to 8 cycles of MOPP-ABV. Those experiencing CR after chemotherapy were randomized to no further treatment or IFRT, and those with a PR received IFRT to involved nodal areas and extranodal sites. The 8-year OS and EFS rates in the partial response group were 76% and 84%, respectively. These outcomes were not significantly different in the complete response group (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing PR after chemotherapy. In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) which compared ABVD with two other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation.[62] PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was also seen for OS. The Southwest Oncology Group multicenter study showed no improvement in OS rates for patients who underwent low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, prednisone plus bleomycin, doxorubicin, and procarbazine), but the remission duration was prolonged in several subgroups, especially patients with bulky nodular sclerosis.[71]

In contrast, Laskar and colleagues reported a survival advantage for consolidative RT in patients experiencing CR after initial chemotherapy particularly in patients younger than 15 years.[72] However, this study included patients with a different distribution of histologic subtypes of HL than those included in Western studies, and most had early stage HL.

The role of consolidative RT for bulky or residual sites after chemotherapy for stage III to IV disease is being addressed in an ongoing GHSG randomized trial (HD15) in patients with advanced stage HL treated with BEACOPP.[73] Of the 728 qualified patients with residual disease (2.5 cm or more) after 6-8 cycles of BEACOPP, 74% were PET-negative and 26% were PET-positive. Only patients with positive PET scans at the end of chemotherapy received consolidative RT. Preliminary results of this trial showed that with a follow-up period of 12 months, PFS was 96% in the PET-negative patients and 86% for the PET-positive patients, suggesting that consolidative RT can be omitted in PET-negative patients who have been treated with BEACOPP without increasing the risk of relapse or progression. At the same time, consolidative RT appeared to be sufficient for the management of most patients who remained PET-positive after BEACOPP chemotherapy. Longer follow-up data also confirmed these preliminary results.[74] With a median follow-up of 38 months, the time-to-progression after PET at 3 years was 92% and 86% respectively for PET-negative and PET-positive patients.

NCCN Recommendations

ABVD or Stanford V is recommended for primary treatment for patients with advanced disease. Escalated-dose BEACOPP (4 cycles) should be considered for high-risk patients with an IPS score of four or more.

ABVD is initially administered for 2-4 cycles followed by restaging. PFTs should be repeated after 4 cycles. Patients with CR, PR or stable disease are treated with additional 2-4 cycles (total of 6). Patients with PR or stable disease are restaged at the completion of therapy. No further treatment is necessary for patients with CR after a total of 6 cycles. Consolidative RT to the mediastinum or residual PET-positive sites is recommended, especially if bulky mediastinal disease was present initially. Patients with PR or stable disease after 6 cycles can

be treated with IFRT. In the absence of bulky mediastinal disease, observation is an option in selected circumstances when the PET scan findings are equivocal. Histological confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Additional treatment may be warranted under certain clinical circumstances even in the case of a negative biopsy. In the case of positive biopsy, patients should be managed as described for progressive disease.

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

Escalated-dose BEACOPP is administered every 3 weeks, and restaging occurs at the end of 4 cycles. Four additional cycles of baseline BEACOPP [with or without consolidative RT(30-40 Gy to initial bulky sites > 5 cm, and 40 Gy of RT to residual PET-positive sites] are administered for patients who have experienced CR, whereas 4 cycles of escalated-dose BEACOPP followed by end-of-treatment restaging are recommended for those with PR or stable disease. Biopsy can be considered before initiating additional cycles of BEACOPP. All patients who are PET-positive and biopsy positive should be managed as described for progressive disease. RT is recommended for those with residual PET-positive sites that are greater than 2.5 cm. Patients with progressive disease are managed as described for progressive disease or else with RT to residual PET-positive sites. Biopsy is recommended before initiating treatment.

Lymphocyte-Predominant Hodgkin lymphoma

LPHL is characterized by an indolent course and occasional late relapse. It has a different natural history and response to therapy compared with CHL.[75] The GHSG has reported a comprehensive description of natural history, clinical presentation, and outcomes for LPHL.[76] In a retrospective analysis that included 394 patients with LPHL, 63% had early stage favorable, 16% had early stage unfavorable, and 21% had advanced stage disease. At a median follow-up of 50 months, freedom from treatment failure (88% vs. 82%) and OS (96% vs. 92%) were better for LPHL compared with CHL.[76] Among patients with LPHL, freedom from treatment failure was better for early favorable disease (93%) compared with early unfavorable (87%) and advanced stage disease (77%).

The European Task Force on Lymphoma (ETFL) also reported favorable freedom from treatment failure for early stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or IV (24%) disease.[77] In the GHSG study, adverse prognostic factors for freedom from treatment failure included advanced stage, low hemoglobin, and lymphopenia; age (≥ 45 years), advanced stage, and low hemoglobin were the negative prognostic factors for OS.

Early stage favorable LPHL has a better prognosis than CHL and its management is different. RT alone or in combination with chemotherapy has been an efficient treatment for patients with stage I to II LPHL.[78-85] In a retrospective analysis, Schlembach and colleagues reported favorable 5-year relapse-free (95%) and OS (100%) for patients with stage IA LPHL treated with IFRT and regional RT alone.[79] There was no evidence of secondary solid tumors even after long-term follow-up (11.6 years for IFRT and 5.5 years for regional RT). Longer follow-up is needed to define the risks for cardiac toxicity; however,

mediastinal treatment is infrequently required in LPHL. Another retrospective study from the Australasian Radiation Oncology Lymphoma Group reported longer follow-up in patients with stage I to II LPHL treated with RT alone, including mantle and total lymphoid irradiation.[82] At 15 years, freedom from progression was 84% for patients with stage I disease and 73% for those with stage II disease. Recently, Chen and colleagues reported the long-term outcome of 113 patients with LPHL treated at the author's institution with a median follow-up of 136 months.[83] Ninety-three patients received RT alone, 13 received RT with chemotherapy, and seven received chemotherapy alone. The 10-year PFS rates were 85% (stage I) and 61% (stage II); OS rates were 94% and 97% for stages I and II, respectively. The addition of chemotherapy to RT did not improve PFS or OS compared with RT alone and six of seven patients who received chemotherapy alone developed early disease progression.

The GHSG compared 3 treatment options, including EFRT, IFRT, and combined modality treatment in patients with stage IA LPHL.[78]Median follow-up was 78 months for EFRT, 40 months for combined modality, and 17 months for IFRT. Complete remissions were observed in 98% after EFRT, 95% after combined modality, and 100% after IFRT, and no significant differences were seen in freedom from treatment failure, suggesting that IFRT is equally effective as EFRT and combined modality treatment. However, in a subgroup analysis of 64 patients with LPHL included in the GHSG HD 7 trial, a trend was seen toward better 7-year freedom from treatment failure for the combined modality group (96%) compared with the EFRT group (83%). An M.D. Anderson study also showed that patients with early stage (I-II) disease treated with RT alone, or chemotherapy followed by RT, had similar relapse-free (77% and 68%, respectively) and OS (90% and 100%, respectively) at 9.3 years.[81] Additional data and longer-term follow-up are required to define the best treatment for early stage favorable LPHL.

Patients with advanced stage LPHL have a worse prognosis than those with early stage favorable disease, and can be treated with chemotherapy. In the European Task Force on Lymphomas (ETFL) study, the 8-year disease-specific survival and freedom from treatment failure were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.[77] Most of these patients (80%-95%) were treated with chemotherapy (MOPP- or ABVD-like regimens) with or without RT.

Because LPHL cells consistently express CD20 antigen, clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody.[86] In a Stanford study, previously treated (10) and untreated (12) patients with stage I to IV LPHL received 4 weekly doses of rituximab at 375 mg/m^2. The overall response rate was 100% (41% CR, 54% PR, and 5% CRu).[87] The estimated probability of progressive disease at 10.2 months was 52%. The protocol was later modified to repeat 4 weekly 375 mg/m^2 doses at 6-month intervals for 2 years.[88] Median follow-up was 72 months for limited and 30 months for extended treatment. The overall response rate was 97% (69% CR or CRu, 28% PR). Among patients undergoing limited treatment with rituximab, 56% experienced CR or CRu, compared with 88% of those treated with extended rituximab. The estimated freedom from progression at 30 months was 52% for limited rituximab and 88% for extended rituximab. Rituximab was well tolerated, with few adverse side effects. Additional follow-up is needed to assess benefit duration.

GHSG evaluated rituximab for relapsed or refractory LPHL in a phase II trial.[89] Of 14 patients with CD20+ LPHL, 8 experienced complete and 6 partial remission. At a median follow-up of 63 months, median time to

progression was 33 months. Azim and colleagues recently reported a retrospective analysis of patients with LPHL who were treated with rituximab either as a single agent or in combination with chemotherapy [ABVD or ESHAP].[90] The overall response rate was 100% with 6 of the 7 patients achieving CR. At a median follow-up of 2 years, the time to progression was 27 months. Collectively, the above data suggest that rituximab alone or in combination with chemotherapy has activity in the management of patients with newly diagnosed as well those with relapsed LPHL.

NCCN Recommendations

IFRT (30-36 Gy) or regional RT is recommended for all patients with stage IA or IIA disease; chemotherapy with or without IFRT or RT, rituximab either as a single agent or in combination with chemotherapy (with or without RT) are the recommended treatment options for patients with stage IB or IIB or stage III-IV disease. Alternatively, asymptomatic patients with stage IIIA-IVA disease can either be observed (category 2B) or treated with local RT for palliation.

Without randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for LPHL, although ABVD is often used based on data for CHL. Savage et al from British Columbia Cancer Agency 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.[91] With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without RT had a superior 10 year TTP (97% vs. 77.5) and PFS (90% vs. 66.5%) compared to those treated with RT alone. On the other hand, in a review of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III-IV LPHL treated with chemotherapy alone, Canellos and Mauch reported that among 12 patients treated with ABVD or EVA (etoposide, vinblastine, and doxorubicin), the failure rate was 75%, while it was only 32% for the 25 patients treated with alkylating agent containing regimens (MOPP or MOPP/ABVD).[92]

Some investigators have also reported good response rates with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy with or without rituximab in patients with early stage or advanced disease.[93, 94]

Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for these patients. The following chemotherapy regimens are most commonly used at NCCN member institutions for patients with LPHL. They may be used in conjunction with rituximab, or rituximab may be used as a single agent:

- ABVD
- CHOP
- CVP
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)

Restaging occurs after completion of initial therapy, and then observation is recommended for all patients experiencing a CR. Although some patients who fail to achieve a CR may require additional therapy, some have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed or treated with local irradiation. Late relapse or transformation to diffuse large B-cell lymphoma has been reported in patients with NLPHL.[95-97] 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.[97] At relapse, re-biopsy should be considered because of the risk of transformation to aggressive lymphoma.

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 little data available on the follow-up and monitoring of late effects in patients with HL, after completion of treatment. [98]

The follow-up schedule should be individualized, depending on clinical circumstances such as patient's age, stage of the disease and initial treatment modality. Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects (secondary malignancies, cardiac disease and reproduction), health habits and psychosocial issues. The panel overwhelmingly agrees that, given the long-term risks of the therapies for HL, patients should be followed up by oncologists who are aware of these risks and complications, especially during the first 5 years and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease. Interim physical examinations and blood tests (CBC, platelets, ESR if elevated at initial diagnosis and chemistry profile) are performed every 2 to 4 months up to 2 years and then every 3 to 6 months for the next 3 to 5 years. An annual influenza vaccination is recommended for all patients.

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen. Chest radiograph or CT should be performed every 6 to 12 months during the first 2 to 5 years. Abdominal or pelvic CT (category 2B) is monitored every 6 to 12 months for the first 2 to 3 years. PET scans are not recommended for routine surveillance due to the risk of false positives.

Monitoring for Late Effects

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

Secondary Malignancies

Solid tumors are the most common secondary malignancies and most develop more than 10 years after the completion of treatment. The risk of developing secondary malignancies is highest when RT is used as a component of first-line treatment. Recent meta-analysis by Franklin and colleagues showed that the risk of developing secondary malignancies was lower with chemoradiation therapy than with RT alone as the initial treatment.[99] The risk was marginally higher with chemoradiation therapy when compared with chemotherapy alone as initial treatment. No significant differences in the risk of developing secondary malignancies were seen with IFRT vs. EFRT, although the risk of developing breast cancer was substantially higher for EFRT. The risk for developing lung cancer or colorectal cancer is increased after treatment with chemotherapy alone.[100]

Lung cancer and breast cancer are the most common secondary malignancies in patients with HL. Annual chest imaging (chest X-ray or chest CT) is recommended for patients at increased risk for lung cancer due to chest irradiation, alkylating agent therapy, or smoking history. Chest imaging is optional after 5 years for patients who were treated with nonalkylating agent chemotherapy, did not undergo RT, and have no other risk factors.

Annual breast screening [mammography or magnetic resonance imaging (MRI)] of breast beginning no later than 8 to 10 years after

completion of therapy or at the age of 40 (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation. They should also be encouraged to perform monthly self-breast examination and undergo yearly breast examination by a health care professional. The American Cancer Society (ACS) recommends breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age.

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.[101, 102,103] RT-induced cardiotoxicity is observed usually more than 5-10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Based on data regarding increased long-term risk of cardiac disease, the panel recommends a baseline stress test or echocardiogram at 10 years after treatment and annual blood pressure monitoring, even in asymptomatic individuals. Aggressive medical management of cardiovascular risk factors is recommended.

Hypothyroidism

Abnormal thyroid function, mostly hypothyroidism is reported in about 50% of long-term survivors, especially those patients who received neck or upper mediastinal irradiation.[98] A careful thyroid examination should be a part of physical exam. Thyroid function tests should be done at least annually to rule out hypothyroidism especially in patients treated with RT to 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 autologous or allogeneic hematopoietic cell transplantation as salvage therapy may be at continued risk for infection. Pneumococcal, meningiococcal and H-flu revaccination is recommended every 5 years for patients treated with splenic RT or splenectomy.

Pulmonary Toxicity

Bleomycin induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity. Martin and colleagues reported that BPT significantly decreases the 5-year OS rate, especially in patients 40 years or older.[104]They also showed that the use of growth factor with chemotherapy significantly increases the incidence of BPT (26% vs. 9%). Recently, two separate studies confirmed that ABVD chemotherapy can be safely administered at the full dose intensity without any growth factor support.[105, 106] 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 ABVD regimen.[106]

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

Progressive Disease or Relapse

HDT/ASCR

Two randomized phase III studies performed by the British National Lymphoma Investigation[107] and the GHSG/European Bone Marrow Transplantation Group[108] have compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvement in EFS and PFS and freedom from treatment failure (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone. HDT/ASCR is the best option for patients with HL that is not cured with primary treatment, even though it does not improve OS.

Several investigators have developed prognostic models to predict outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice and colleagues from the French cooperative group (GELA) used end-of-treatment to relapse interval (12 months or less) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR.[109] The PFS rates of 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.[110] In patients with none or one factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of salvage treatment in patients with relapsed or refractory disease to improve EFS in poorer risk patients.[111] 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.[112] More recently, investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first CR (less than one year), detectable disease at transplant and the presence of more than one extranodal site as adverse factors for OS.[113] Other groups have identified extent of prior chemotherapy,[114] short time from diagnosis to transplant[115] and disease status at transplantation[116] as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome in patients with recurrent/refractory HL.[117, 118]

The main potential of these prognostic factor studies is to facilitate comparison of outcomes at different centers, where the preparatory regimens may vary.

Second-Line Chemotherapy

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.[110,119-125] Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),[126] IGEV (ifosfamide, gemcitabine, and vinorelbine)[127] and GCD (gemcitabine, carboplatin and dexamethasone)[128] have also been effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials. Some studies have suggested that patients with CR to second-line therapy prior to transplant or those with chemosensitive disease to second-line chemotherapy have improved outcomes following HDT/ASCR compared to those with resistant disease.[129-131] While second-line chemotherapy is an appropriate treatment for any patient with relapsed Hodgkin's disease, regardless of the length of initial remission,[132] some studies have also suggested that patients with

minimal residual disease at relapse may not need conventional-dose chemotherapy before HDT/ASCR.[133]

Radiation Therapy

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.[134] The 5-year freedom from treatment failure 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. Moscowitz and colleagues have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease.[110] 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%.

Second-line RT may be effective in patients in good performance status with limited-stage late relapses and without B symptoms. It may be a very effective salvage regimen for patients with initial favorable stage I-II disease who are treated with chemotherapy alone and relapse in initially involved sites.

NCCN Recommendations

Individualized treatment is recommended for patients with progressive 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 second-line chemotherapy with or without RT. Brentuximab vedotin, a CD30-directed antibody-drug conjugate has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[135] In a phase II multicenter study of 102 patients with relapsed or refractory Hodgkin's lymphoma after HDT/ASCR, brentuximab vedotin induced objective responses and complete remissions in 75% and 34% of patients respectively, with a median follow-up of 9 months.[136] Based on the results of this study, the FDA approved brentuximab vedotin for the treatment of patients with Hodgkin's lymphoma after failure of HDT/ASCR or at least two prior chemotherapy regimens in patients who are not candidates for HDT/ASCR. The panel has included brentuximab vedotin as an option for patients with progressive disease after HDT/ASCR or at least two prior chemotherapy regimens for all patients regardless of their eligibility for HDT/ASCR.

Patients with suspected relapse should undergo biopsy and restaging, including bone marrow biopsy. Bone marrow cytogenetics for markers of myelodysplastic syndromes may be considered if ASCR is planned. Management of relapsed disease depends on whether primary treatment was RT alone, chemotherapy, or combined modality therapy. For patients treated initially with chemotherapy or combined modality therapy, the algorithm is a bit more complicated and therapy more likely to be individualized. Appropriate treatment has not been identified for disease relapse in patients with initial stage IA to IIA disease who underwent chemotherapy alone and experienced failure at the initial sites and therefore individualized treatment is recommended. Options include RT, second-line chemotherapy with or without RT or HDT/ASCR with or without RT. RT is recommended when the sites of relapse have not been previously irradiated. In radiation naïve patients, total lymphoid irradiation (TLI) may be an appropriate component of HDT/ASCR. For all other patients, the panel recommends HDT/ASCR (category 1) with or without locoregional RT or second-line chemotherapy with or without RT, but disease relapse should be confirmed with biopsy.

See Principles of second-line chemotherapy section of the guidelines for suggested second-line chemotherapy regimens. Conventional-dose

second-line chemotherapy may precede high-dose therapy. If there is minimal residual disease, second-line chemotherapy may not be essential before proceeding to HDT/ASCR. In selected patients with long disease-free intervals and other favorable features, salvage chemotherapy alone may be appropriate, with the selection of chemotherapy individualized.

The panel recommends that patients experiencing disease relapse after undergoing primary treatment with RT alone be treated as described for initial treatment of advanced disease. The extent of stage at relapse (relapse stage) after RT was the most important prognostic factor for freedom from second relapse.[137]

Allogeneic stem cell transplant (SCT) with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, treatment-related mortality (TRM) was more than 50%. Allogeneic SCT with reduced intensity conditioning has been reported to have decreased rates of TRM.[138, 139] However, this approach remains investigational. The panel has included allogeneic SCT with a category 3 recommendation for patients with progressive or relapsed disease.

LPHL patients with progressive or relapsed disease can be managed as described above. However, some patients have a chronic indolent course and may not require aggressive treatment.

Summary

HL is an uncommon malignancy involving lymph nodes and the lymphatic system. The WHO classification divides HL into 2 main types (CHL and LPHL). CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas LPHL is characterized by the presence of lymphocytic and histiocytic cells.

The management of HL continues to evolve. Major changes have been incorporated into these guidelines since inception. Current management of HL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging to assess treatment response. PET scans are recommended to evaluate initial staging and assess treatment response at restaging. Recent studies have shown the prognostic value of early interim PET scans in patients with advanced or extranodal disease. However, PET scans are not recommended for routine surveillance.

Combined modality therapy (ABVD or Stanford V and IFRT) is the preferred treatment for patients with stage IA or IIA favorable CHL. The panel has also included ABVD alone as an option with a category 2B recommendation. ABVD or Stanford V followed by consolidative IFRT is recommended for patients with stage I-II unfavorable disease. ABVD or Stanford V is recommended for patients with stage III-IV disease who have bulky mediastinal adenopathy. Escalated BEACOPP is an option for high-risk patients with an IPS score of 4 or more.

LPHL has a different natural history and response to therapy compared with CHL. IFRT alone is the treatment option for patients with stage IA or IIA disease whereas chemotherapy with or without RT is recommended for all other patients. In early phase clinical studies, rituximab has been effective either as a single agent or in combination with chemotherapy for patients with newly diagnosed as well those with relapsed LPHL. The guidelines have included rituximab either as a single agent or in combination with chemotherapy (with or without RT) as an option for patients with stage IB or IIB or stage III-IV disease. The role of chemotherapy or rituximab-based therapy is being explored in ongoing clinical trials for early stage and advanced stage LPHL.

HDT/ASCR is the best treatment option for patients with progressive disease and relapsed or refractory disease, although it does not improve OS. Conventional-dose second-line chemotherapy with or without RT may be given prior to high-dose therapy. The panel has included brentuximab vedotin as an option for patients with progressive disease after HDT/ASCR or at least two prior chemotherapy regimens for all patients regardless of their eligibility for HDT/ASCR. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610543.

2. Hoppe RT, Mauch PT, Armitage JO, et al. Hodgkin Lymphoma (ed 2). Philadelphia: Lippincott Williams and Wilkins; 2007.

3. WHO classification of tumours of haematopoietic and lymphoid tissues. In: Swerdlow SH, Campo E, Harris NL, et al., eds (ed 4). Lyon, France: IARC; 2008.

4. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on hodgkin's disease staging classification. Cancer Res 1971;31:1860-1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5121694.

5. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. Cancer 1978;42:1039-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/698907.

6. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2809679.

7. Henry-Amar M, Friedman S, Hayat M, et al. Erythrocyte sedimentation rate predicts early relapse and survival in early-stage Hodgkin disease. The EORTC Lymphoma Cooperative Group. Ann Intern Med 1991;114:361-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1992877.

8. Tubiana M, Henry-Amar M, Hayat M, et al. Prognostic significance of the number of involved areas in the early stages of Hodgkin's disease. Cancer 1984;54:885-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6378359.

9. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9819449.

10. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244-1244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561185.

11. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17242396.

12. Caraway NP. Strategies to diagnose lymphoproliferative disorders by fine-needle aspiration by using ancillary studies. Cancer 2005;105:432-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16222688.

13. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-3052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284254.

14. Meda BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. Am J Clin Pathol 2000;113:688-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10800402.

15. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). Blood 2008;111:71-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17890456.

16. van der Kaaij MA, van Echten-Arends J, Simons AH, Kluin-Nelemans HC. Fertility preservation after chemotherapy for Hodgkin

lymphoma. Hematol Oncol 2010;28:168-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20232475.

17. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110:3507-3516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709603.

18. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16047335.

19. Juweid ME. Utility of Positron Emission Tomography (PET) scanning in managing patients with Hodgkin Lymphoma. . Hematology 2006;2006:259-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124070.

20. de Wit M, Bohuslavizki KH, Buchert R, et al. 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. Ann Oncol 2001;12:29-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11249046.

21. Guay C, Lepine M, Verreault J, Benard F. Prognostic value of PET using 18F-FDG in Hodgkin's disease for posttreatment evaluation. J Nucl Med 2003;44:1225-1231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902411.

22. Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. Haematologica 2006;91:475-481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16585014.

23. Gallamini A, Hutchings M, Avigdor A, Polliack A. Early interim PET scan in Hodgkin lymphoma: where do we stand? Leuk Lymphoma 2008;49:659-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18398732.

24. Terasawa T, Lau J, Bardet S, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. J Clin Oncol 2009;27:1906-1914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273713.

25. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 2007;25:3746-3752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646666.

26. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006;107:52-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16150944.

27. Advani R, Maeda L, Lavori P, et al. Impact of positive positron emission tomography on prediction of freedom from progression after Stanford V chemotherapy in Hodgkin's disease. J Clin Oncol 2007;25:3902-3907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664458.

28. Markova J, Kobe C, Skopalova M, et al. FDG-PET for assessment of early treatment response after four cycles of chemotherapy in patients with advanced-stage Hodgkin's lymphoma has a high negative predictive value. Ann Oncol 2009;20:1270-1274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19228806.

29. Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. Blood 2007;109:905-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17018856.

30. Sher DJ, Mauch PM, Van Den Abbeele A, et al. Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. Ann Oncol 2009;20:1848-1853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19541793.

31. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. J Natl Compr Canc Netw 2007;5 Suppl 1:S1-S22; quiz S23-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17509259.

32. Duhmke E, Franklin J, Pfreundschuh M, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. J Clin Oncol 2001;19:2905-2914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11387364.

33. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. Acta Oncol 2003;42:589-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14596517.

34. Connors JM. State-of-the-Art Therapeutics: Hodgkin's Lymphoma. J Clin Oncol 2005;23:6400-6408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16155026.

35. Macdonald DA, Connors JM. New strategies for the treatment of early stages of Hodgkin's lymphoma. Hematol Oncol Clin North Am 2007;21:871-880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17908625.

36. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 1987;5:27-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2433409.

37. Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol 2002;20:630-637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11821442.

38. Advani RH, Hoppe RT, Baer DM, et al. Efficacy of abbreviated Stanford V chemotherapy and involved field radiotherapy in early stage Hodgkin's disease: mature results of the G4 trial. Blood 2009;114:1670-. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1670.

39. Abuzetun JY, Loberiza F, Vose J, et al. The Stanford V regimen is effective in patients with good risk Hodgkin lymphoma but radiotherapy is a necessary component. Br J Haematol 2009;144:531-537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19055670.

40. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol 2004;22:2835-2841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15199092.

41. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003;21:3601-3608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12913100.

42. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20818855.

43. Horning SJ, Hoppe RT, Advani R, et al. Efficacy and late effects of Stanford V chemotherapy and radiotherapy in untreated Hodgkin's disease: mature data in early and advanced stage patients. Blood

2004;104:308. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/104/11/308.

44. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 2005;23:9198-9207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16172458.

45. Aversa SM, Salvagno L, Soraru M, et al. Stanford V regimen plus consolidative radiotherapy is an effective therapeutic program for bulky or advanced-stage Hodgkin's disease. Acta Haematol 2004;112:141-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15345896.

46. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19759185.

47. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol 2009;27:5390-5396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19738111.

48. Gordon LI, Hong F, Fisher RI, et al. A randomized phase III trial of ABVD vs. Stanford V +/- radiation therapy in locally extensive and advanced stage Hodgkin's Lymphoma: an Intergroup study coordinated by the Eastern Cooperatve Oncology Group (E2496) [abstract]. Blood 2010;116:Abstract 415. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/415.

49. Advani R, Hong F, Fisher RI, et al. Randomized phase III trial comparing ABVD + radiotherapy and the Stanford V regimen in patients with stage I/II bulky mediastinal Hodgkin Lymphoma: a subset analysis of the US Intergroup Trial E2496. Blood 2010;116:416-. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/416.

50. 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. Journal of Clinical Oncology 2010;28:4199-4206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20713848.

51. Longo D, Glatstein E, Duffey P, et al. Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. J Clin Oncol 1991;9:906-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2033427.

52. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:4634-4642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837968.

53. Rueda Dominguez A, Marquez A, Guma J, et al. Treatment of stage I and II Hodgkin's lymphoma with ABVD chemotherapy: results after 7 years of a prospective study. Ann Oncol 2004;15:1798-1804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15550585.

54. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood 2004;104:3483-3489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15315964.

55. Canellos GP, Abramson JS, Fisher DC, LaCasce AS. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. J Clin Oncol 2010;28:1611-1615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20159818.

56. Behar RA, Horning SJ, Hoppe RT. Hodgkin's disease with bulky mediastinal involvement: effective management with combined modality therapy. Int J Radiat Oncol Biol Phys 1993;25:771-776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7683016.

57. Longo DL, Russo A, Duffey PL, et al. Treatment of advanced-stage massive mediastinal Hodgkin's disease: the case for combined modality treatment. J Clin Oncol 1991;9:227-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1988570.

58. DeVita VT, Jr., Simon RM, Hubbard SM, et al. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. Ann Intern Med 1980;92:587-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6892984.

59. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327:1478-1484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1383821.

60. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003;21:607-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12586796.

61. Johnson PWM, Radford JA, Cullen MH, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol 2005;23:9208-9218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314615.

62. Johnson PWM, Sydes MR, Hancock BW, et al. Johnson PWM, Sydes MR, Hancock BW, Cullen M, Radford JA, Stenning SP. Consolidation radiotherapy in patients with advanced Hodgkin's Lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). . J Clin Oncol 2010:3352-3359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498402.

63. Diehl V, Sieber M, Ruffer U, et al. BEACOPP: an intensified chemotherapy regimen in advanced Hodgkin's disease. The German Hodgkin's Lymphoma Study Group. Ann Oncol 1997;8:143-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9093722.

64. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348:2386-2395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12802024.

65. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol 2009;27:4548-4554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704068.

66. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol 2009;27:805-811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19124807

67. Carella AM, Bellei M, Brice P, et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. Haematologica 2009;94:146-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19001284.

68. Proctor SJ, Mackie M, Dawson A, et al. A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the

Scotland and Newcastle Lymphoma Group (SNLG) prognostic index. A Scotland and Newcastle Lymphoma Group study (SNLG HD III). Eur J Cancer 2002;38:795-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11937314.

69. Aleman BM, Raemaekers JM, Tomisic R, et al. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2007;67:19-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17097834.

70. Aleman BMP, Raemaekers JMM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med 2003;348:2396-2406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12802025.

71. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. Ann Intern Med 1994;120:903-912. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8172436.

72. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol 2004;22:62-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14657226.

73. Kobe C, Dietlein M, Franklin J, et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. Blood 2008;112:3989-3994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757777.

74. Engert A, Kobe C, Markova J, et al. Assessment of Residual Bulky Tumor Using FDG-PET In Patients with Advanced-Stage Hodgkin Lymphoma After Completion of Chemotherapy: Final Report of the GHSG HD15 Trial. Blood 2010;116:764-. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/764.

75. Lee AI, LaCasce AS. Nodular lymphocyte predominant Hodgkin lymphoma. Oncologist 2009;14:739-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19605845.

76. Nogova L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol 2008;26:434-439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18086799.

77. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol 1999;17:776-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10071266.

78. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol 2005;16:1683-1687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16093276.

79. Schlembach PJ, Wilder RB, Jones D, et al. Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. Cancer J 2002;8:377-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12416895.

80. Tsai HK, Mauch PM. Nodular lymphocyte-predominant hodgkin lymphoma. Semin Radiat Oncol 2007;17:184-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17591565.

81. Wilder RB, Schlembach PJ, Jones D, et al. European Organization for Research and Treatment of Cancer and Groupe d'Etude des Lymphomes de l'Adulte very favorable and favorable,

lymphocyte-predominant Hodgkin disease. Cancer 2002;94:1731-1738. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920535.

82. Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. Cancer 2005;104:1221-1229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16094666.

83. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol 2010;28:136-141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933914.

84. Feugier P, Labouyrie E, Djeridane M, et al. Comparison of initial characteristics and long-term outcome of patients with lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma at clinical stages IA and IIA prospectively treated by brief anthracycline-based chemotherapies plus extended high-dose irradiation. Blood 2004;104:2675-2681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15231567.

85. Jackson C, Sirohi B, Cunningham D, et al. Lymphocyte-predominant Hodgkin lymphoma—clinical features and treatment outcomes from a 30-year experience. Annals of Oncology 2010;21:2061-2068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332141.

86. Maeda LS, Advani RH. The emerging role for rituximab in the treatment of nodular lymphocyte predominant Hodgkin lymphoma. Curr Opin Oncol 2009;21:397-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19606035.

87. Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood 2003;101:4285-4289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12586628.

88. Horning SJ, Bartlett NL, Breslin S, et al. Results of a prospective phase II Trial of limited and extended rituximab treatment in nodular lymphocyte predominant Hodgkin's disease (NLPHD) [abstract]. Blood 2007;110:Abstract 644. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/110/11/644.

89. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008;111:109-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17938252.

90. Azim HA, Jr., Pruneri G, Cocorocchio E, et al. Rituximab in lymphocyte-predominant Hodgkin disease. Oncology 2009;76:26-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19033694.

91. Savage KJ, Skinnider B, Al Mansour M, et al. Incorporation of ABVD increases cure rates of patients with limited stage nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) [abstract]. Blood 2010;116:Abstract 3887. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3887.

92. Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's Lymphoma? . Journal of Clinical Oncology 2010;28:e8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933898.

93. Unal A, Sari I, Deniz K, et al. Familial nodular lymphocyte predominant Hodgkin lymphoma: successful treatment with CHOP plus rituximab Leuk Lymphoma 2005;46:1613-1617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16236615.

94. Shankar AG, Daw S, Hall G, et al. Treatment of children & adolescents with early stage nodular lymphocyte predominant Hodgkin Lymphoma with a low intensity short duration chemotherapy regimen [CVP] - on behalf of the EuroNet-PHL group [abstract]. Blood 2006;108:Abstract 2471. Available at:

http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/2471.

95. Miettinen M, Franssila KO, Saxen E. Hodgkin's disease, lymphocytic predominance nodular. Increased risk for subsequent non-Hodgkin's lymphomas. Cancer 1983;51:2293-2300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6850508.

96. Huang JZ, Weisenburger DD, Vose JM, et al. Diffuse large B-cell lymphoma arising in nodular lymphocyte predominant Hodgkin lymphoma: a report of 21 cases from the Nebraska Lymphoma Study Group. Leuk Lymphoma 2004;45:1551-1557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15370206.

97. Al-Mansour M, Connors JM, Gascoyne RD, et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010;28:793-799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20048177.

98. Mauch P, Ng A, Aleman B, et al. Report from the Rockefellar Foundation sponsored international workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease. Eur J Haematol Suppl 2005:68-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16007872.

99. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol 2006;17:1749-1760. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16984979.

100. Mudie NY, Swerdlow AJ, Higgins CD, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. J Clin Oncol 2006;24:1568-1574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16520465.

101. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004;22:3139-3148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284266.

102. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109:1878-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17119114.

103. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 2003;42:743-749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12932613.

104. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol 2005;23:7614-7620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186594.

105. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 2007;18:376-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071938.

106. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 2007;137:545-552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17459049.

107. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993;341:1051-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8096958.

108. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed

chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002;359:2065-2071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12086759.

109. Brice P, Bouabdallah R, Moreau P, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. Societe Francaise de Greffe de Moelle. Bone Marrow Transplant 1997;20:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9232251.

110. 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;97:616-623. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157476.

111. Moskowitz CH, Yahalom J, Zelenetz AD, et al. High-dose chemo-radiotherapy for relapsed or refractory Hodgkin lymphoma and the significance of pre-transplant functional imaging. Br J Haematol 2010;148:890-897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20085577.

112. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol 2002;20:221-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773173.

113. Sureda A, Constans M, Iriondo A, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. Ann Oncol 2005;16:625-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15737986.

114. Stiff PJ, Unger JM, Forman SJ, et al. The value of augmented preparative regimens combined with an autologous bone marrow transplant for the management of relapsed or refractory Hodgkin disease: a Southwest Oncology Group phase II trial. Biol Blood Marrow Transplant 2003;9:529-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12931122.

115. Wheeler C, Eickhoff C, Elias A, et al. High-dose cyclophosphamide, carmustine, and etoposide with autologous transplantation in Hodgkin's disease: a prognostic model for treatment outcomes. Biol Blood Marrow Transplant 1997;3:98-9106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9267670.

116. Horning SJ, Chao NJ, Negrin RS, et al. High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: analysis of the Stanford University results and prognostic indices. Blood 1997;89:801-813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9028311.

117. Jabbour E, Hosing C, Ayers G, et al. Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. Cancer 2007;109:2481-2489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17497648.

118. Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pre-transplant functional imaging predicts outcome following autologous stem cell transplant for relapsed and refractory Hodgkin lymphoma. Blood 2010;116:4934-4937. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20733154.

119. ChlVPP therapy for Hodgkin's disease: experience of 960 patients. The International ChlVPP Treatment Group. Ann Oncol 1995;6:167-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7786824.

120. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncol 1999;10:593-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10416011.

121. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7844600.

122. 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;13:1628-1635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12377653.

123. Montoto S, Camos M, Lopez-Guillermo A, et al. Hybrid chemotherapy consisting of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (C-MOPP/ABV) as first-line treatment for patients with advanced Hodgkin disease. Cancer 2000;88:2142-2148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10813727.

124. Phillips JK, Spearing RL, Davies JM, et al. VIM-D salvage chemotherapy in Hodgkin's disease. Cancer Chemother Pharmacol 1990;27:161-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2249334.

125. Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. Ann Oncol 1995;6:543-549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8573532.

126. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol 2007;18:1071-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17426059.

127. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007;92:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229633.

128. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20578815.

129. Sirohi B, Cunningham D, Powles R, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. Ann Oncol 2008;19:1312-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18356139.

130. Gopal AK, Metcalfe TL, Gooley TA, et al. High-dose therapy and autologous stem cell transplantation for chemoresistant Hodgkin lymphoma: the Seattle experience. Cancer 2008;113:1344-1350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18623377.

131. Moskowitz CH, Kewalramani T, Nimer SD, et al. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. Br J Haematol 2004;124:645-652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14871252.

132. Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1997;20:745-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9384476.

133. Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. Ann Oncol 1996;7:151-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8777171.

134. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol 2005;23:1522-1529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15632410.

135. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas. New England Journal of Medicine 2010;363:1812-1821. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21047225.

136. Chen RW, Gopal AK, Smith SE, et al. Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL). ASCO Meeting Abstracts 2011;29:8031. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8031.

137. Roach M, 3rd, Brophy N, Cox R, et al. Prognostic factors for patients relapsing after radiotherapy for early-stage Hodgkin's disease. J Clin Oncol 1990;8:623-629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2313331.

138. Alvarez I, Sureda A, Caballero MD, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed hodgkin lymphoma: results of a spanish prospective cooperative protocol. Biol Blood Marrow Transplant 2006;12:172-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16443515.

139. Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26:455-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18086796.