National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Hodgkin Lymphoma

V.2.2010

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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

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Summary of the Guidelines updates

The 2.2010 version of the Hodgkin Lymphoma Guidelines represents the addition of the Discussion section correspondent to the changes in the algorithm (MS-1). Footnote "r" was added to page HODG-6 to clarify treatment for stage I-II unfavorable, non-bulky disease.

Summary of changes in the 1.2010 version of the Hodgkin Disease/Lymphoma guidelines from the 2.2009 version include:

Global Changes

- **Title of Guidelines was changed from Hodgkin Disease/Lymphoma to Hodgkin Lymphoma.**

HODG-1

- **The typical immunophenotype for Hodgkin Lymphoma is now described in footnote "a".**
- **Pulmonary function tests were moved from the "Useful in selected case" to "Essential" and clarified for "if ABVD or BEACOPP are being used."**
- **Evaluation of ejection fraction was clarified for "doxorubicin-containing regimens."**

HODG-3

- **This is a new page detailing the treatment and restaging for treatment with ABVD alone for stage IA-IIA (favorable).**

HODG-4

- **Stage I-II (unfavorable) divided into "bulky disease" (HODG-4) and "non-bulky disease" (HODG-6).**
- **Primary treatment now includes restaging after ABVD x 2 cycles, treatment and restaging detailed on HODG-5.**

HODG-6

- **Primary treatment now includes restaging after ABVD x 2 cycles, treatment and restaging detailed on HODG-7.**

HODG-8

- **"Restage after chemotherapy with PET-CT" was changed to "Restage with PET-CT or diagnostic CT, repeat PFTs."**
- **"Selected cases" was added to "Escalated BEACOPP."**
- **For patients with a PR after 4 cycles of ABVD, "biopsy" was added as an alternative to 2 additional cycles of ABVD.**
- **For patients that are PET negative after 6 cycles of ABVD, "2 more cycles of ABVD" was removed as a treatment option.**
- **"Observe in selected circumstances" was added as a recommendation for patients that are PET positive after treatment for a PR.**

HODG-9

- **"Selected cases" was added to "Escalated BEACOPP."**

HODG-9

- **For patients with a PR after 4 cycles of escalated BEACOPP, "biopsy" was added as an alternative to 4 additional cycles of BEACOPP.**
- **For patients with a CR after 4 cycles of escalated BEACOPP, RT was changed to optional after 4 additional cycles of baseline BEACOPP.**

HODG-10

- **For stage I-IIB, "chemotherapy followed by IFRT" was changed to "Chemotherapy ± IFRT." "Rituximab ± chemotherapy ± IFRT" was added as a treatment option.**
- **For stage III-IVA, "Rituximab ± chemotherapy" was added as a treatment option.**
- **For stage III-IVB, "Rituximab ± chemotherapy ± RT" was added as a treatment option.**

HODG-11

- **The text of previous footnote "z" was moved to the top of the page.**
- **"Consider" was removed from "Consider baseline stress test/echocardiogram at 10 y."**
- **"Pneumococcal revaccination every 5-7 y, was replaced with "after 5 y".**

HODG-12

- **"Non-cross resistant" was replaced with "salvage."**
- **"± RT" was added to HDT/ASCR and salvage chemotherapy.**

HODG-A

- **"≥ 2 extranodal sites" was changed to "> 1 extranodal site."**

HODG-B 1 of 3

- **For stage IA-IIA favorable, a description of the course for chemotherapy alone was added.**
- **For Stage I-II unfavorable, the number of ABVD cycles was changed from 4 to 4-6 cycles.**
- **For Stage III-IV, the number of cycles of ABVD was changed from 6-8 to 6 cycles.**
- **PFTs were added after 4 cycles of ABVD.**

HODG-C

- **Nonbulky disease (stage I-II), radiation dose was changed from 30 Gy to 20-30 Gy for patients treated with ABVD.**

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Hodgkin Lymphoma

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Hodgkin Lymphoma TOC
Staging, Discussion, References

DIAGNOSIS

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic
- FNA alone is insufficient
- Immunohistochemistry highly recommended for Hodgkin lymphoma[a]

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[b]
- PET-CT scan[c]
- Adequate bone marrow biopsy in stage IB-IIB and stage III-IV
- Counseling: Fertility, smoking cessation, psychosocial (see Distress Management Guidelines)
- Pulmonary functions tests (PFTs incl. DLCO) if ABVD or BEACOPP are being used

Useful in selected cases:

- Semen cryopreservation, if chemotherapy or pelvic RT contemplated
- IVF or ovarian tissue or oocyte cryopreservation
- Neck CT, if neck RT planned
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV, if risk factors, unusual disease presentations
- Evaluation of ejection fraction for doxorubicin-containing regimens

CLINICAL STAGING

- Classical Hodgkin lymphoma[d]
  - Stage IA-IIA Favorable[f] → 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-8)[h]
- Lymphocyte-predominant Hodgkin lymphoma (LPHL)[e] → See Primary Treatment (HODG-10)[h]

[a] 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 Non-Hodgkin's Lymphoma guidelines.

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

[c] 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).

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

[e] 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.

[f] No unfavorable factors present (See Unfavorable Factors HODG-A).

[g] Bulky disease, B symptoms, ESR >50, >3 sites of disease, >1 extranodal site (see Unfavorable Factors HODG-A).

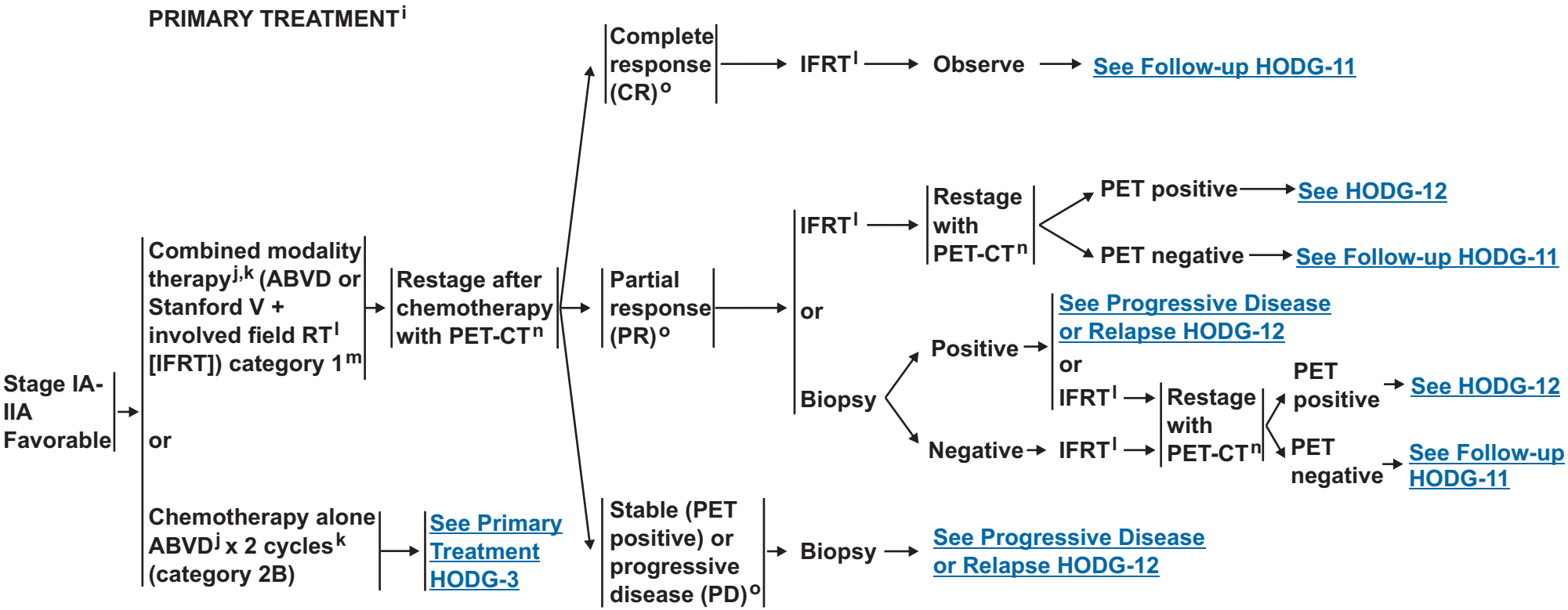
[h] Treatment recommendations for postadolescent Hodgkin lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
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CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[d]



[d] 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).

[k] Interim PET scan after 2-4 cycles has increasingly shown to have a role in management and prognosis. Further management may include IFRT, biopsy, or change in chemotherapy.

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

[m] Depending upon co-morbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able tolerate chemotherapy.

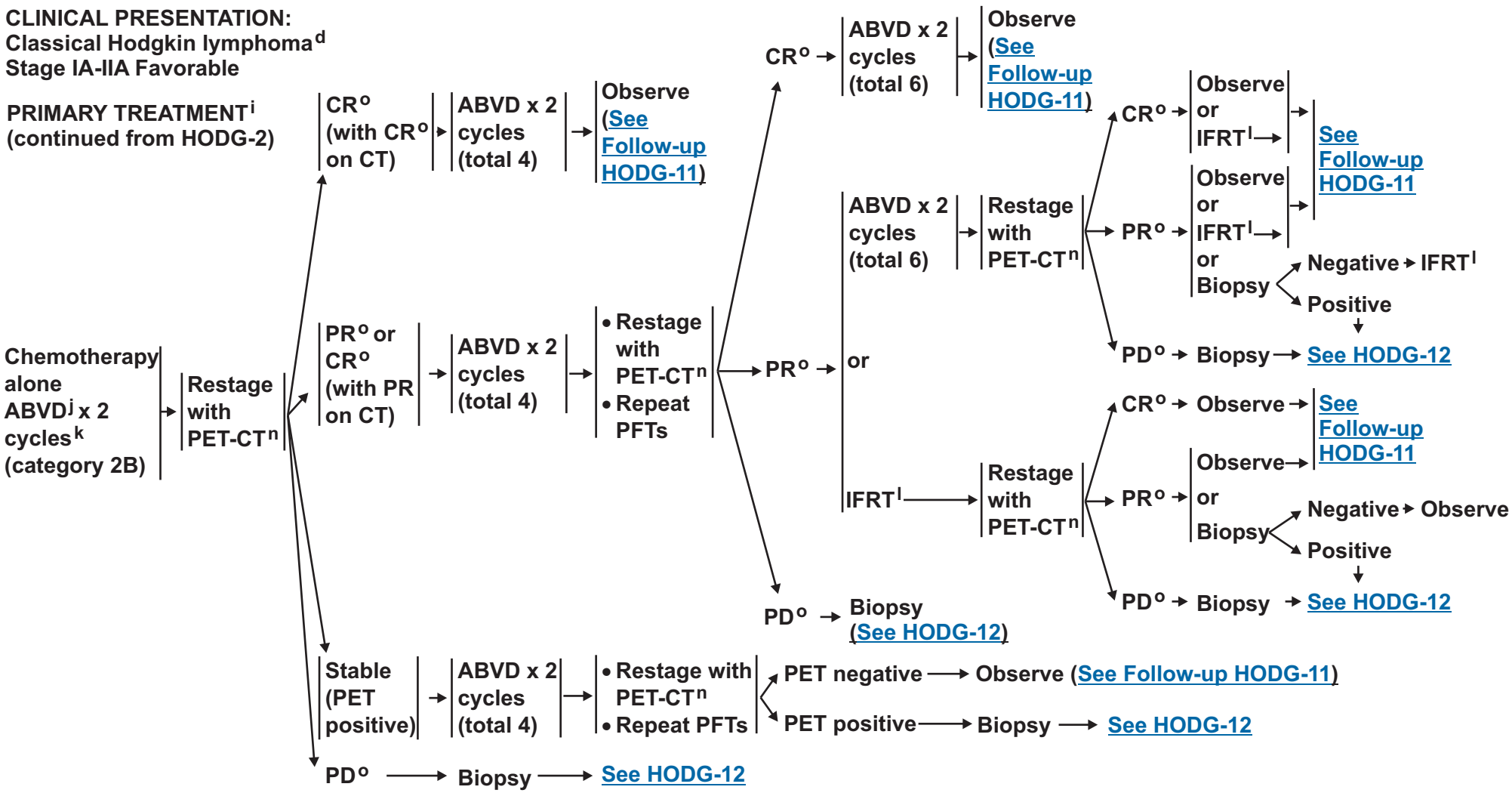
[n] An integrated PET-CT or a PET with a diagnostic CT is recommended.

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

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[k] Interim PET scan after 2-4 cycles has increasingly shown to have a role in management and prognosis. Further management may include IFRT, biopsy, or change in chemotherapy.
[l] See Principles of Radiation Therapy (HODG-C).
[n] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[o] See Revised Response Criteria for Lymphoma (HODG-D).

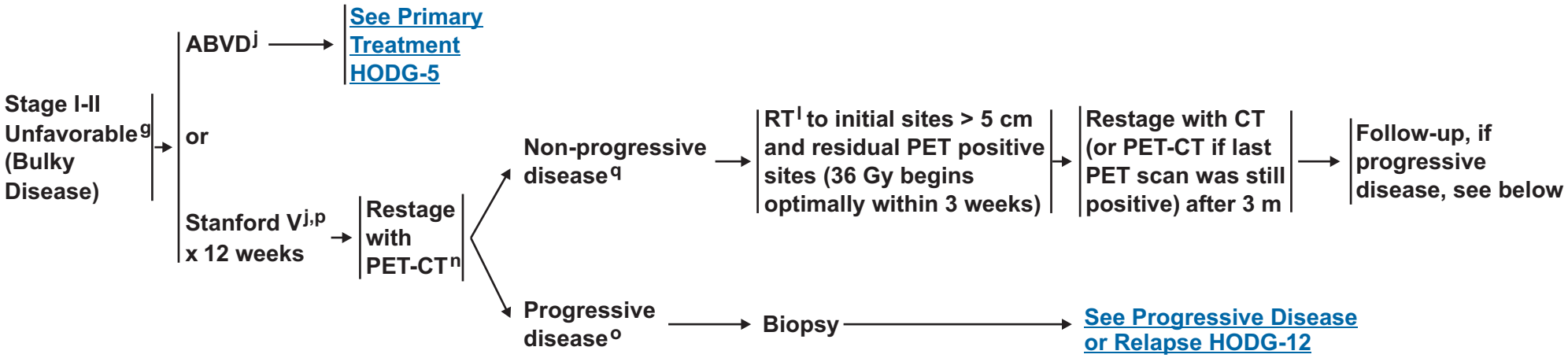
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CLINICAL PRESENTATION: Classical Hodgkin lymphoma[d]

PRIMARY TREATMENT[i]



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

[g] Bulky disease, B symptoms, ESR >50, >3 sites of disease, >1 extranodal site (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).

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

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

[p] The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or B symptoms. Patients with other "unfavorable" factors are not treated on this protocol.

[q] May include patients with residual PET positive sites.

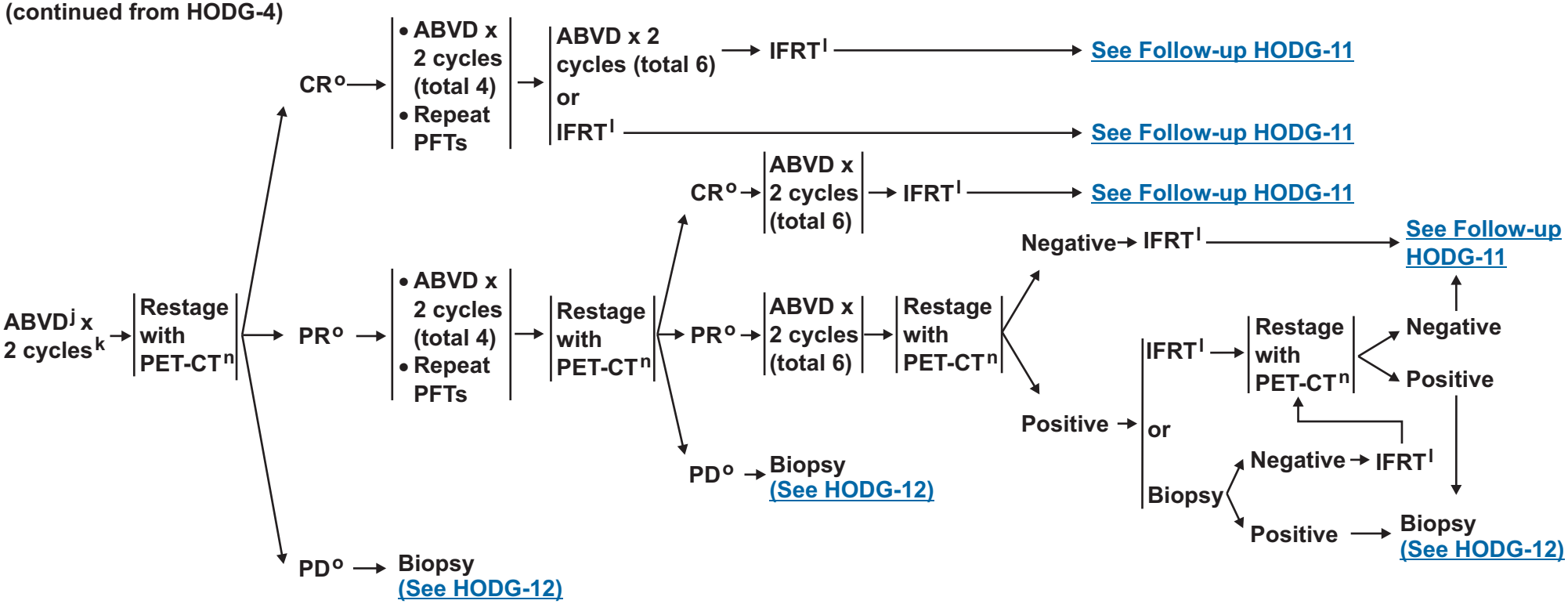
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CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[d]
Stage I-II Unfavorable (bulky)

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



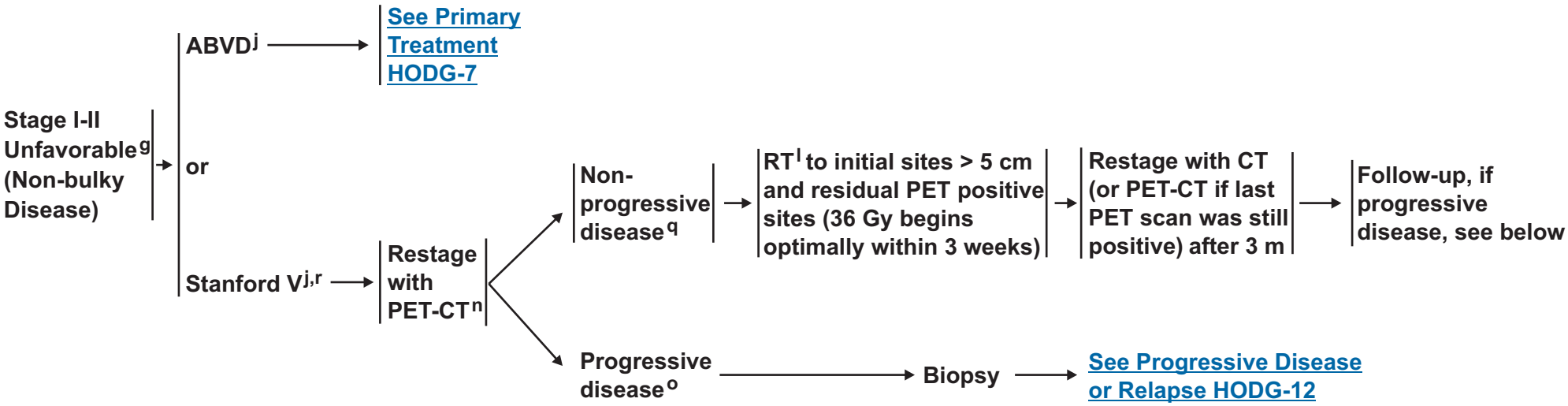
[d] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[k] Interim PET scan after 2-4 cycles has increasingly shown to have a role in management and prognosis. Further management may include IFRT, biopsy, or change in chemotherapy.
[l] See Principles of Radiation Therapy (HODG-C).
[n] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[o] See Revised Response Criteria for Lymphoma (HODG-D).

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CLINICAL PRESENTATION: Classical Hodgkin lymphoma[d]

PRIMARY TREATMENT[i]



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

[g] Bulky disease, B symptoms, ESR >50, >3 sites of disease, >1 extranodal site (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).

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

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

[q] May include patients with residual PET positive sites.

[r] Patients with unfavorable stage I-II disease based upon presence of B symptoms are treated with 12 weeks of Stanford V + 30 Gy IFRT. Patients with other criteria for unfavorable disease are treated with 8 weeks of Stanford V + 30 Gy IFRT.

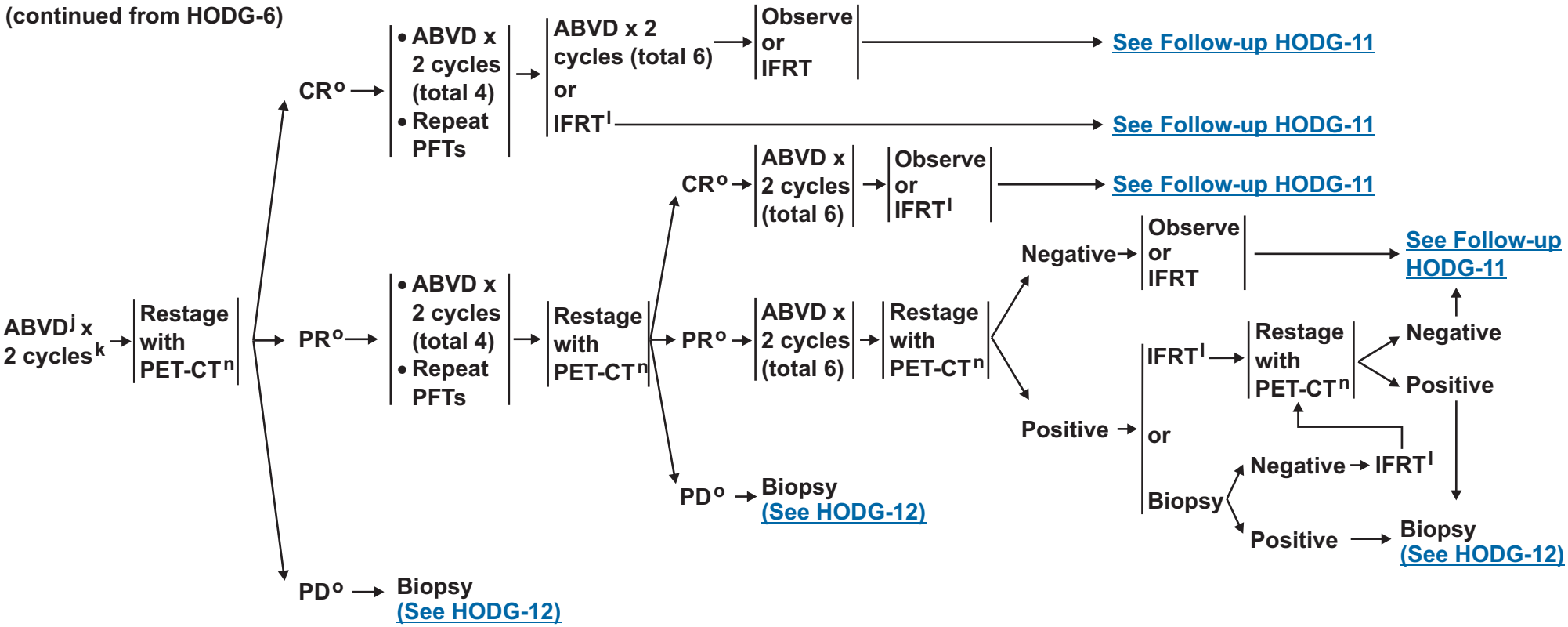
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CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[d]
Stage I-II Unfavorable (non-bulky)

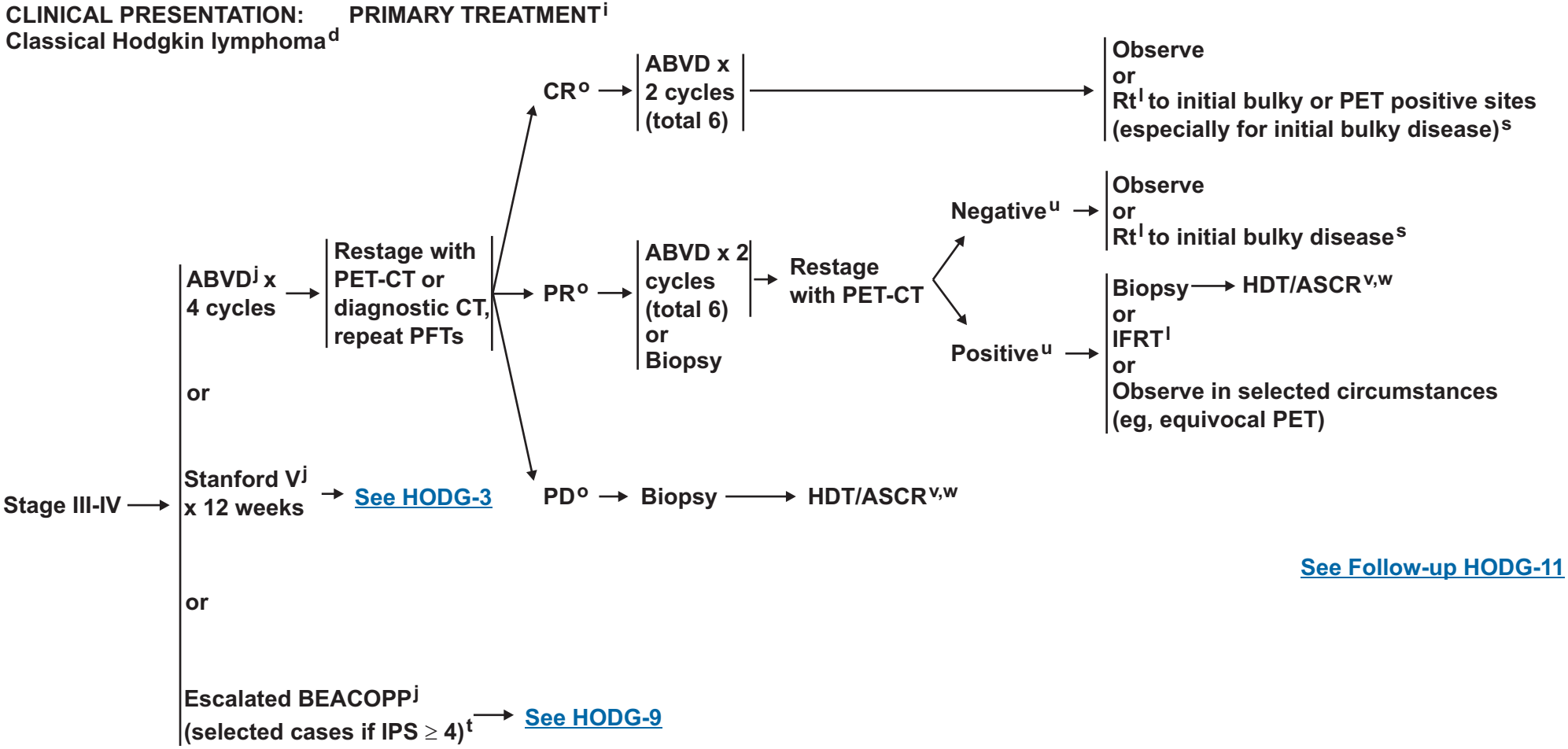
PRIMARY TREATMENT[i]
(continued from HODG-6)



[d] 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).
[k] Interim PET scan after 2-4 cycles has increasingly shown to have a role in management and prognosis. Further management may include IFRT, biopsy, or change in chemotherapy.
[l] See Principles of Radiation Therapy (HODG-C).
[n] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[o] See Revised Response Criteria for Lymphoma (HODG-D).

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See Follow-up HODG-11

[d] 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).
[o] See Revised Response Criteria for Lymphoma (HODG-D).
[s] See Unfavorable Factors HODG-A.
[t] See International Prognostic Score (IPS) (HODG-A).
[u] If there is bulky mediastinal disease on CT after 6 cycles of ABVD, consolidative RT to mediastinum recommended. It is not known in the context of PET negative whether the outcomes will be altered.
[v] RT to residual disease pre or posttransplant.
[w] Allotransplant is an option in select patients as a category 3.

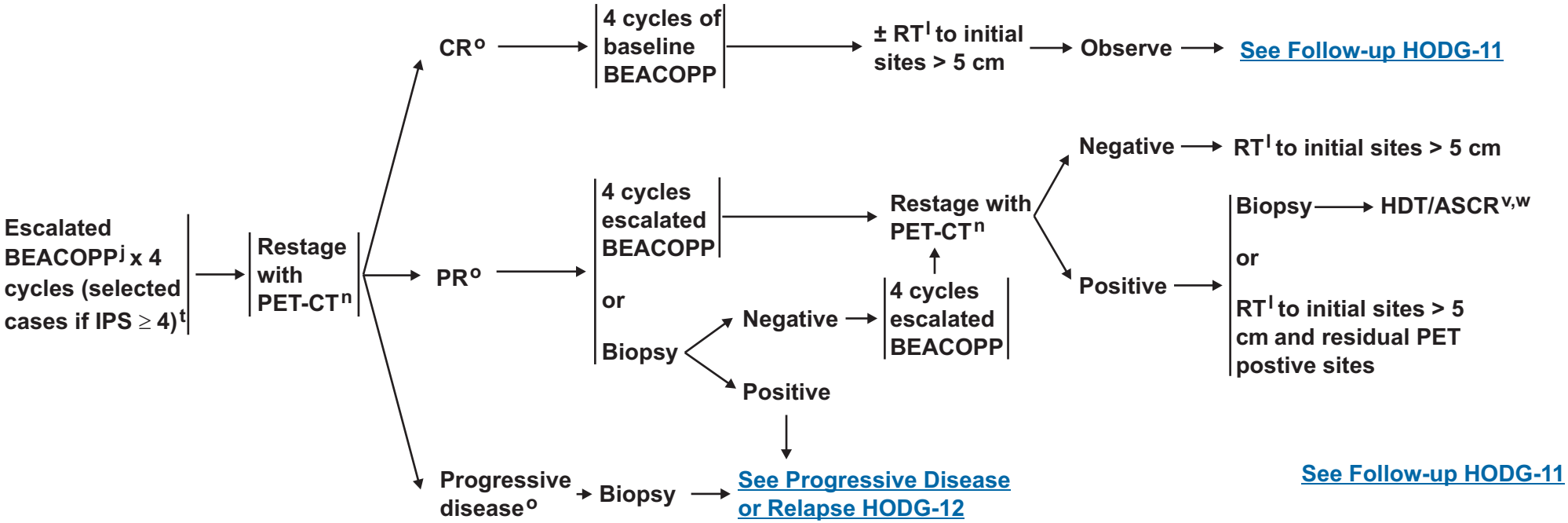
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CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[d]
Stage III-IV

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



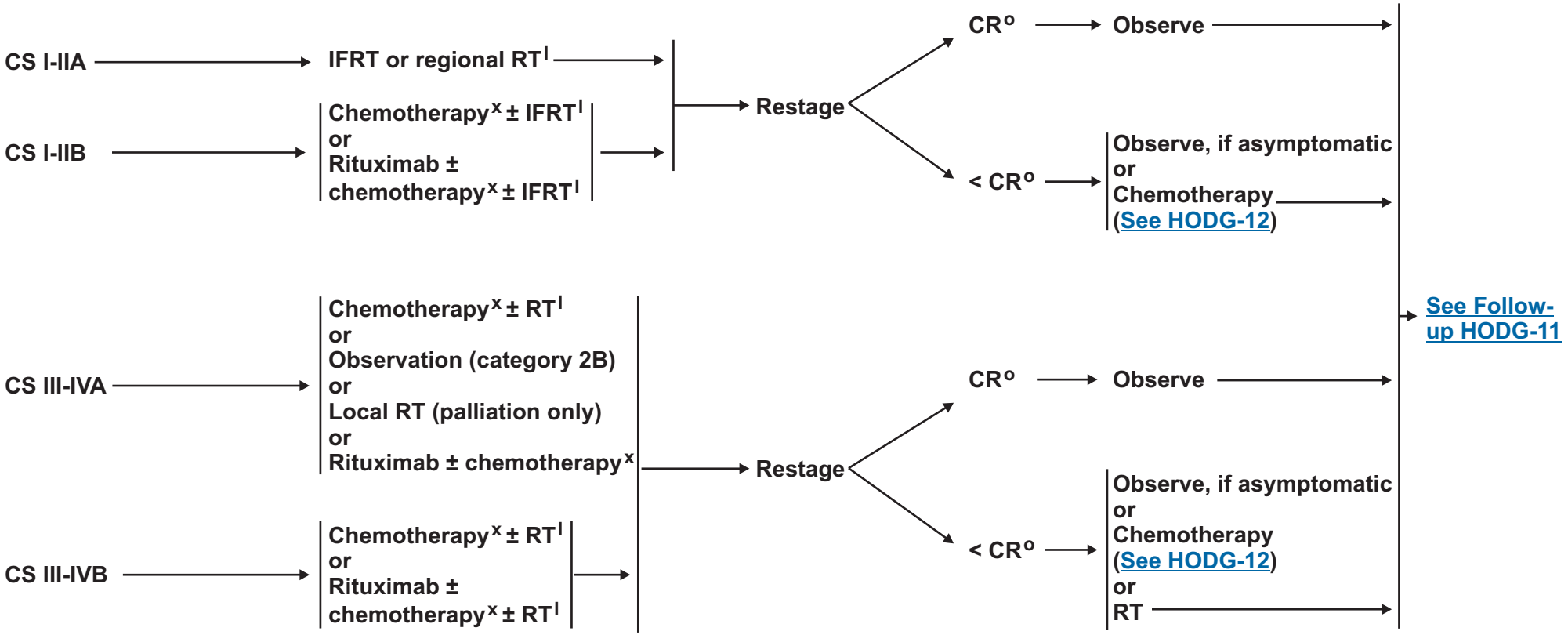
[d] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[l] See Principles of Radiation Therapy (HODG-C).
[n] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[o] See Revised Response Criteria for Lymphoma (HODG-D).
[t] See International Prognostic Score (IPS) (HODG-A).
[v] RT to residual disease pre or posttransplant.
[w] Allotransplant is an option in select patients as a category 3.

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CLINICAL PRESENTATION: Lymphocyte-predominant Hodgkin lymphoma[e]

PRIMARY TREATMENT



[e] 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.

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

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

[x] See Principles of Systemic Therapy (HODG-B 3 of 3).

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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.[y,z]
- 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
  - Consider annual influenza vaccine especially in high risk patients (eg, treated with chest RT, bleomycin)
- 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.

See Progressive Disease or Relapse (HODG-12)

Monitoring for Late Effects after 5 Years[y,z]

- Interim H&P: Annually
  - Annual blood pressure, aggressive management of cardiovascular risk factors
  - Baseline stress test/echocardiogram at 10 y
  - Pneumococcal revaccination after 5 y, if patient treated with splenic RT or previous splenectomy
  - Meningococcal + H-flu in selected cases
  - Consider annual influenza vaccine especially in high risk patients (eg, treated with chest RT, bleomycin)
- Laboratory studies:
  - CBC, platelets, chemistry profile annually
  - TSH at least annually if RT to neck
  - Lipids
- Annual chest imaging (chest x-ray or chest CT) for patients at increased risk for lung cancer[aa]
- 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 an earlier age.
- Treatment summary and consideration of transfer to PCP.

[y] 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: July 9-16, 2003, Bellagio, Italy. Eur J Haematol 2005;75(s66).

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

[aa] 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.

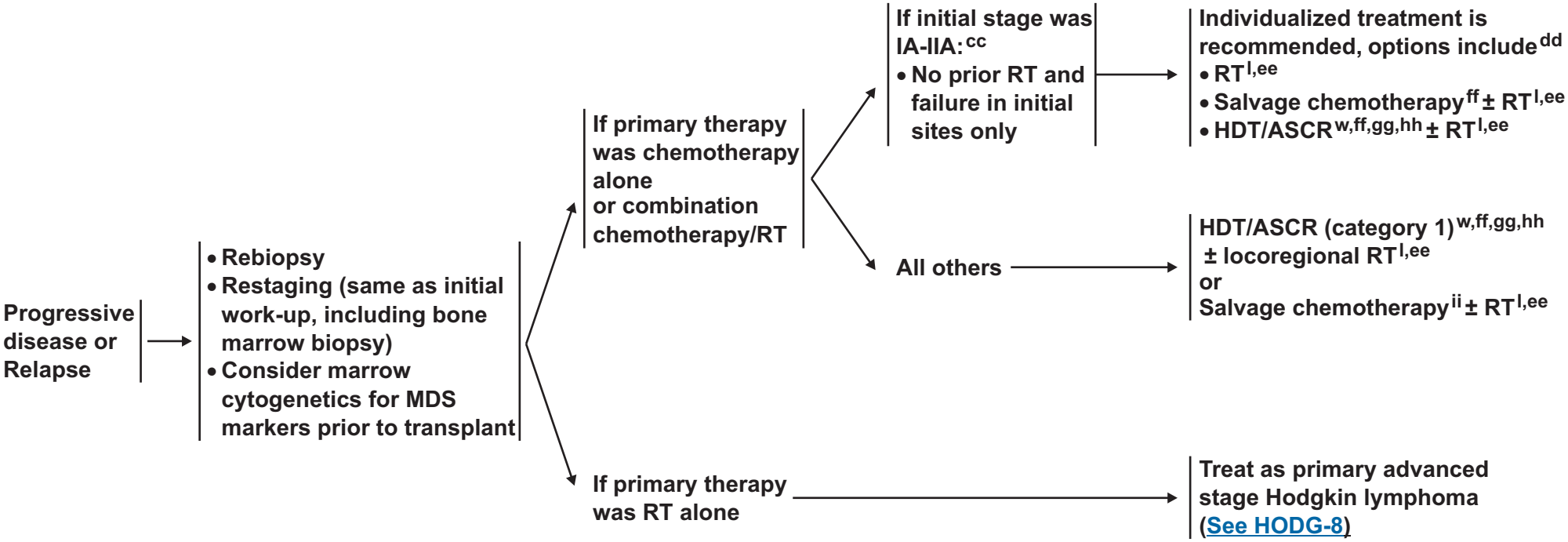
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CLASSICAL HODGKIN LYMPHOMA[bb]
PROGRESSIVE DISEASE OR RELAPSE

SECOND-LINE THERAPY



[l] See Principles of Radiation Therapy (HODG-C).
[w] Allotransplant is an option in select patients as a category 3.
[bb] 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.
[cc] This applies to patients with relapse, not those with progressive disease.
[dd] There are no data to support a superior outcome with any modalities.
[ee] Radiation therapy recommended when sites of relapse have not been previously irradiated. In a radiation naive patient, TLI may be an appropriate component of HDT.
[ff] See Principles of Second-Line Chemotherapy (HODG-E).
[gg] Biopsy to confirm relapse especially if plan to treat with high-dose therapy.
[hh] Conventional-dose chemotherapy may precede high-dose therapy. Response to conventional therapy is not essential to proceed to HDT/ASCR. Timing of RT may vary.
[ii] For select patients with long disease-free interval and other favorable features; selection of chemotherapy should be individualized.

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Hodgkin Lymphoma

Guidelines Index
Hodgkin Lymphoma TOC
Staging, Discussion, References

NCCN UNFAVORABLE FACTORS (localized presentations)

- **Bulky disease:**
  - **Mediastinal mass (chest x-ray):** $\frac{\text{Maximum mass width}}{\text{Maximum intrathoracic diameter}} > \frac{1}{3}$
  - **Any mass > 10 cm (CT)**
- **Erythrocyte sedimentation rate ≥ 50, if asymptomatic**
- **> 3 lymphoid regions**
- **B symptoms**
- **> 1 Extranodal site**

Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease according to major clinical trials groups

Risk Factor	GHSG	EORTC	NCIC
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
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33 or > 10 cm
# Nodal sites	> 2	> 3	> 3
E lesion	any		

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

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.

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PRINCIPLES OF SYSTEMIC THERAPY (1 of 3)

Classical Hodgkin Lymphoma

- The most common variants of chemotherapy used at NCCN member institutions include ABVD and Stanford V. Some institutions will use dose-escalated BEACOPP as an alternative regimen in selected cases for highly unfavorable, high-risk patients, usually with an International Prognostic Score (IPS) ≥ 4.
- Routine use of growth factors is not recommended. Leukopenia is not a factor for delay of treatment or reduction of dose intensity.
- Stage IA-IIA favorable
  - If combined modality therapy, ABVD is generally administered for 4 cycles. Complete restaging takes place at completion of chemotherapy. Consolidative irradiation follows. In favorable patients,[1] 2 cycles of ABVD followed by 30 Gy RT may be sufficient.
  - If chemotherapy alone, ABVD is generally administered for two cycles, followed by restaging. An additional 2-4 cycles of ABVD are administered, followed by complete restaging at the completion of chemotherapy.
  - Stanford V chemotherapy for Stage I-II non-bulky disease is administered for 8 weeks (2 cycles). Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (30 Gy to all involved fields).
- Stage I-II unfavorable (See HODG-A)
  - ABVD is generally administered for 4-6 cycles. Repeat PFT's after 4 cycles. Complete restaging takes place at the completion of chemotherapy. If the patient has achieved a CR or PR, two additional cycles of chemotherapy may be administered (maximum 6). Consolidative irradiation follows the completion of chemotherapy.
  - Stanford V chemotherapy
    Bulky disease - Stanford V is administered for 12 wks. Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (36 Gy to initial sites > 5 cm and residual PET positive sites after chemotherapy).
    Non-bulky disease - Patients with unfavorable stage I-II disease based upon presence of B symptoms are treated with 12 weeks of Stanford V + 30 Gy IFRT. Patients with other criteria for unfavorable disease are treated with 8 weeks of Stanford V + 30 Gy IFRT.
- Stage III-IV
  - ABVD is generally administered for 6 cycles. Repeat PFT's after 4 cycles. Complete restaging takes place after 4 cycles of chemotherapy. Two additional cycles of chemotherapy are administered to patients who have achieved a CR or PR. Patients with bulky disease may have consolidative RT.
  - Stanford V chemotherapy is administered for 12 wks. Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (For stage I-IIB, 30 Gy to initial sites; for Stage II-IV, 36 Gy to initial sites > 5 cm and spleen if focal nodules are present initially or residual PET positive sites).
  - BEACOPP (escalated dose) is administered every 3 wks. Complete restaging takes place at the end of 4 cycles and at the end of 8 cycles (completion of chemotherapy). This is followed by 30 Gy irradiation to initial sites > 5 cm and 40 Gy to residual PET positive sites.

See Regimens and References page HODG-B 2 of 3

See Principles of Chemotherapy for LPHL page HODG-B 3 of 3

See Principles of Second-line Chemotherapy page HODG-E

[1]Favorable patients are defined as without the following clinical risk factors: Large mediastinal mass ≥ one-third of the maximum thorax diameter, extranodal disease, massive splenic involvement, high erythrocyte sedimentation rate (≥ 50 mm/h in asymptomatic patients or ≥ 30 mm/h in symptomatic patients, > 2 sites of disease) Diehl V, Brillant C, Engert A, et al. HD10: Investigating reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma. Interim analysis of a randomized trial of the German Hodgkin Study Group (GHSG). Proc Am Soc Clin Oncol. 2005;23:561s. Abstract 6506.

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PRINCIPLES OF SYSTEMIC THERAPY (2 of 3)
Regimens and References

ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) plus radiation therapy

Borchmann P, Diehl V, Goergen H, et al. Combined modality treatment with intensified chemotherapy and dose-reduced involved field radiotherapy in patients with early unfavorable Hodgkin Lymphoma (HL): Final analysis of the German Hodgkin Study Group (GHSG) HD11 Trial. Blood (ASH Annual Meeting Abstracts) 2009;114:Abstract 717.

Engert A, Diehl V, Pluetschow A, et al. Two cycles of ABVD followed by involved field radiotherapy with 20 Gray (Gy) is the new standard of care in the treatment of patients with early-stage Hodgkin Lymphoma: Final analysis of the randomized German Hodgkin Study Group (GHSG) HD10. Study supported by the Deutche Krebshilfe and in part by the Competence Network Malignant Lymphoma. Blood (ASH Annual Meeting Abstracts) 2009;114:Abstract 716.

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.

ABVD

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(12):3483-3489.

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)

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.

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(3):141-147.

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.

Horning SJ, Williams J, Bartlett NL, et al. Assessment of the Stanford V Regimen and Consolidative Radiotherapy for Bulky and Advanced Hodgkin's Disease: Eastern Cooperative Oncology Group Pilot Study E1492. J Clin Oncol. 2000;18(5):972.

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

Diehl V, Haverkamp H, Mueller R, et al. Eight cycles of BEACOPP escalated compared with 4 cycles of BEACOPP escalated followed by 4 cycles of BEACOPP baseline with or without radiotherapy in patients in advanced stage Hodgkin Lymphoma (HL): Final analysis of the HD12 trial of the German Hodgkin Study Group (GHSG). J Clin Oncol 2009;27:15s (suppl; abstr 8544).

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(24):2386-2395.

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PRINCIPLES OF SYSTEMIC THERAPY (3 of 3)

Lymphocyte-predominant Hodgkin Lymphoma[1]

- **The most common chemotherapies used at NCCN member institutions for LPHL include:**
  - **ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± rituximab**
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab**
  - **CVP (cyclophosphamide, vincristine, prednisone) ± rituximab**
  - **EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) ± rituximab**
  - **Single agent rituximab[2,3,4]**

[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.

[2] 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.

[3] 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.

[4] 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 .

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PRINCIPLES OF RADIATION THERAPY

COMBINED MODALITY-RT DOSES:

- **Bulky disease sites (all stages)**
  If treated with ABVD: 30-36 Gy
  If treated with Stanford V: 36 Gy
- **Nonbulky disease (stage I-II)**
  If treated with ABVD: 20-30 Gy
  If treated with Stanford V: 30 Gy
- **Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV)**
  If treated with BEACOPP: 30-40 Gy

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

- **Involved regions: 30-36 Gy[1]**
- **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.**

Involved-field: involved lymphoid region(s) only
Regional-field: involved and immediately adjacent lymphoid regions

[1] The dose of 30 Gy is mainly used for excised LPHL.

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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.

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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. Examples of second-line chemotherapy prior to transplant include:
  - ICE[1] (ifosfamide, carboplatin, etoposide)
  - C-MOPP[2,3] (cyclophosphamide, vincristine, procarbazine, prednisone)
  - ChlVPP[4] (Chlorambucil, vinblastine, procarbazine, prednisone)
  - DHAP[5] (dexamethasone, cisplatin, high-dose cytarabine)
  - ESHAP[6] (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
  - GVD[7] (gemcitabine, vinorelbine, liposomal doxorubicin)
  - IGEV[8] (ifosfamide, gemcitabine, vinorelbine)
  - Mini-BEAM[9] (carmustine, cytarabine, etoposide, melphalan)
  - MINE[10] (etoposide, ifosfamide, mesna, mitoxantrone)
  - VIM-D[11] (etoposide, ifosfamide, mitoxantrone and dexamethasone).
- 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.[12-14] However, patients tend to have an improved outcome when transplanted in a minimal disease state.[15] Thus, cytoreduction with chemotherapy (see above) 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.

See References page HODG-E 2 of 2

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PRINCIPLES OF SECOND-LINE CHEMOTHERAPY (2 of 2)
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[2]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.

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[9]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.

[10]Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed or refractory Hodgkin's disease. Ann Oncol 1995;6(6):543-9.

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

[12]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.

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Staging

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

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.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

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 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

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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 B symptoms or large mediastinal adenopathy), early stage unfavorable (stage I-II with large mediastinal mass, with or without B symptoms; stage I-II with 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 mediastinal mass ratio or mediastinal tumor ratio.[5] Mediastinal mass ratio is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Mediastinal tumor ratio is the ratio of the maximum width of the mass and the intrathoracic diameter at the T5-T6 interspace. Any mass with mediastinal mass ratio greater than 0.33 or mediastinal tumor ratio greater than 0.35 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 sites of disease, or an erythrocyte sedimentation rate (ESR) of 50 or more. These factors are based largely on data from the European Organization for Research and Treatment of Cancer (EORTC) and the definition of unfavorable prognostic groups for their trials.[7,8] Examples of unfavorable risk factors for stage I-II disease used by major clinical trial groups are listed in HODG-A.

In addition to these unfavorable factors, an international collaborative effort evaluating more than 5000 cases of advanced 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 instance, if the patient has more than 4 unfavorable factors (IPS ≥ 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

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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, partial response, stable disease, relapsed disease, or progressive disease.

Diagnosis

Fine needle aspiration alone is insufficient for 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.

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 (HODG-1). Standard laboratory testing should include a CBC, differential, platelets, ESR, serum lactate dehydrogenase level, albumin, and liver and renal function tests. Adequate bone marrow biopsy should be performed for patients with stage IB to IIB disease or higher. Chest radiograph and diagnostic CT scans of chest, abdomen and pelvis are appropriate imaging studies.

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. Semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients is recommended prior to the initiation of chemotherapy that might be sterilizing or pelvic RT.

A neck CT scan is also recommended in selected patients if RT is planned. 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 scanning (or more commonly, integrated PET-CT scanning) has been used for initial staging, restaging, and follow-up of patients with lymphoma.[15] In a recent meta-analysis, PET showed high positivity and specificity when used to stage and restage patients with lymphoma.[16]

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PET is widely used after completion of therapy to assess response and, to a lesser extent, during therapy for pretreatment staging and assessment of response, as reviewed by Juweid.[17] Early interim PET scan after 2-4 cycles of standard dose chemotherapy is a sensitive prognostic indicator in patients with advanced stage disease.[18-20] In prospective studies 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.[21,22] 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%).[21] 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.[23] 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.[24] 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.[25] 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 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.[26] 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 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. Extended-field radiation therapy (EFRT) refers to treatment of the involved and immediately adjacent lymphoid regions. RT alone is rarely used for CHL but is more commonly used in LPHL. For RT alone, the recommended range of dosages is 30-36 Gy to involved regions and 25-30 Gy to uninvolved sites. The panel recommends that high cervical regions in all patients and axillae in women be excluded from radiation fields, if those regions are uninvolved (HODG-C).

In combined modality therapy, the panel recommends 30-36 Gy 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 radiation dose is 20-30 Gy with ABVD and 30 Gy with Stanford V. This recommendation is based on experience and practice across NCCN institutions. The recommended radiation dose with BEACOPP is 30-40 Gy.

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Classical Hodgkin Lymphoma

Patients are divided into the following groups after initial diagnosis and workup (HODG-1):

- 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.[27] However, long-term toxicity of large radiation fields includes an increased risk for heart disease, pulmonary dysfunction, and secondary malignancies.[28] Chemotherapy regimens (ABVD and Stanford V) routinely used in advanced disease have more recently been incorporated into the management of early stage CHL.[29,30]

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.[31] 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.[32,33] RT is an integral part of the Stanford V regimen.[34] 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.

Clinical trials have evaluated a short course of chemotherapy combined with RT for patients with early stage disease.[35] In a phase III randomized Intergroup trial, Press and colleagues. showed that 3 cycles of doxorubicin and vinblastine followed by subtotal lymphoid irradiation (STLI) had a superior failure-free survival (FFS) rate (94%) compared with STLI alone (81%).[36]

In a recent report from the German Hodgkin Study Group (GHSG HD 7 trial), two cycles of ABVD followed by EFRT (30 Gy plus 10 Gy to the involved field) was more effective than the same dose of EFRT alone in patients with newly diagnosed early stage favorable HL (stage IA to IIB without risk factors such as large mediastinal mass, extranodal disease, massive splenic involvement, or high ESR).[37] At median follow-up of 7 years, no differences were seen in overall survival (OS) between the treatment groups. However, patients in the combined modality treatment group had significantly better (88%) freedom from treatment failure compared with those who underwent EFRT alone (67%), mainly because relapses were more frequent. Relapses occurred mostly within a year in patients who underwent EFRT alone, whereas no relapses occurred in the combined modality arm within the first 2 years.

Several studies have investigated the reduction of chemotherapy and radiation field size to overcome the potential overlapping toxicity of doxorubicin and bleomycin with radiation. IFRT was as effective as EFRT in patients with early stage disease.[33,38-41]

The HD8 trial from the GHSG is the largest that investigated the efficacy of IFRT versus EFRT in early stage unfavorable HL.[39] 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

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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 EORTC-GELA H8 trials (H8-F and H8-U) investigated the reduction of chemotherapy and RT fields in the treatment of patients with early stage HL.[40] The H8-F trial compared 3 cycles of MOPP-ABV plus IFRT with subtotal nodal irradiation (STNI) alone in patients with favorable stage I to II disease. The H8-U trial used three different regimens (6 cycles of MOPP-ABV plus IFRT, 4 cycles of MOPP-ABV plus IFRT, and 4 cycles of MOPP-ABV plus STNI) in patients with unfavorable stage I to II disease. Median follow-up was 92 months.

In patients with early stage favorable HL (H8-F trial), the estimated 5-year event-free survival (EFS) rate was significantly higher after 3 cycles of MOPP-ABV and IFRT compared with STNI alone (98% vs. 74%). In patients with unfavorable early stage HL (H8-U trial), estimated 5-year EFS rates were similar for the 3 groups (84% after 6 cycles of MOPP-ABV plus IFRT, 88% after 4 cycles plus IFRT, and 87% after 4 cycles plus STNI). The H8 trial investigators concluded that chemotherapy plus IFRT should be standard treatment for early stage HL.[40]

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.[42] In this trial, patients were randomized between four vs. two cycles of ABVD and 30 Gy vs. 20 Gy of IFRT. At a median follow-up of 2 years, no statistical differences were seen in freedom from treatment failure (96.6%) and OS (98.5%) between the 4 groups. 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%).[43] With respect to the dose of IFRT, the OS (97.6% 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 20Gy IFRT. 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 a reduced dose (20 Gy) of IFRT is an effective primary treatment for patients with early stage disease with no risk factors, thereby minimizing the risk of late effects. Of note, in the GHSG HD10 Trial, patients were ineligible if they had more than two sites of disease.

In studies conducted by the Stanford Group, the Stanford V regimen and IFRT was equally effective and less toxic compared with EFRT alone in early stage unfavorable disease. In the G4 study, 87 patients with non-bulky stage I-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.[44] Posttreatment conceptions occurred in 25% of patients. Advani and colleagues recently reported the updated results for the 87 patients with non-bulky stage I-IIA disease treated in the G4 study.[33] Among the 87 patients, unfavorable risk factors were present in 47 patients (54%) according to GHSG criteria (more than 2 nodal sites, ESR > 50 or extranodal involvement). 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

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IFRT (30 Gy) is a safe and highly effective regimen for patients unfavorable stage I-IIA 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.[45] 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.

However, 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.[46-48] 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.[47] 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.[46] 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.[48] 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 E2496 Intergroup trial compared the Stanford V regimen with ABVD plus RT for the management of patients with bulky stage II and stage III to IV disease. Results of this trial are awaited.

Chemotherapy alone has also been investigated as a treatment option for patients with early stage non-bulky disease (stage I-II or IIIA).[49-52] In the multicenter study conducted by the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) and Eastern Cooperative Oncology Group, patients with stage I to IIA HL were randomized to receive ABVD (4-6 cycles) or subtotal lymphoid radiation therapy (STLI). [50] 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.[52]

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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.[53] 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 complete response 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)

In these guidelines, combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment (category 1) for patients with favorable disease (HODG-2). The panel has also included ABVD alone as an alternative treatment option with a category 2B recommendation. 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 4 cycles. Restaging occurs at the completion of chemotherapy. In patients with favorable outcomes and no risk factors according to the GHSG criteria (large mediastinal mass, massive splenic involvement, high ESR, and > 2 sites of disease),[42] 2 cycles of ABVD followed by IFRT may be sufficient. The Stanford V regimen is administered for 8 weeks (2 cycles). Restaging occurs at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 weeks. The panel recommends using 30 Gy of IFRT (involved lymphoid regions only) with ABVD and Stanford V regimens (except for patients who fulfill the GHSG criteria for favorable, in whom 20 Gy may be sufficient).

Completion of IFRT is recommended for all patients who have achieved a complete response. Patients experiencing a partial response either can be treated with IFRT or they can undergo biopsy prior to receiving IFRT. Further restaging is required after the completion of IFRT. 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 relapsed or progressive disease (HODG-12). All patients with stable (PET positive) or progressive disease are managed as described for relapsed or progressive disease (HODG-12). Biopsy is recommended 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 on CT, 2 additional (total of 4) cycles are administered (HODG-3). No further treatment is necessary for patients with a complete response on CT. Patients with a partial response are restaged after completion of chemotherapy. If there is complete response on CT, 2 additional cycles (total of 6) of ABVD are administered. Patients with partial response can be treated with IFRT or an additional 2 cycles (total of 6) of ABVD followed by restaging at the completion of therapy. No further treatment is necessary for patients responding to additional therapy. Alternatively, these patients can be treated with IFRT, if not previously given. Patients with stable (PET-positive) disease after 2 cycles of ABVD, receive an additional 2 cycles (total of 4) followed by restaging. No further treatment is

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necessary for PET negative patients. All patients with stable (PET positive) or progressive disease are managed as described for relapsed or progressive disease (HODG-12). Biopsy is recommended before initiating treatment.

Stage I to II (Unfavorable Disease)

For patients with unfavorable disease the panel recommends chemotherapy (ABVD or Stanford V) followed by IFRT or similar radiation. Stanford V is administered for 12 weeks (3 cycles) plus IFRT (36 Gy) to patients with stage I-II bulky mediastinal disease or B symptoms (HODG-4). Patients with unfavorable stage I-II non-bulky disease based upon presence of B symptoms are treated with 12 weeks of Stanford V plus 30 Gy IFRT whereas those with other criteria for unfavorable disease are treated with 8 weeks of Stanford V plus 30 Gy IFRT (HODG-6). Patients are restaged when they complete chemotherapy. In patients with non-progressive disease (including those with residual PET positive sites), RT (36 Gy) is recommended not only for initial sites larger than 5 cm but also residual PET-positive sites (HODG-4 and HODG-6). Generally, this includes the mediastinum and bilateral supraclavicular areas. Consolidative irradiation should be instituted within 3 weeks of completion of chemotherapy.

ABVD is generally administered initially for 4-6 cycles. Restaging takes place after 2 cycles. PFTs should be repeated after 4 cycles. If there is complete response, 2-4 additional cycles (total of 6) are administered followed by IFRT (30-36 Gy) (HODG-5 and HODG-7). Patients with partial response 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 for patients with negative PET scans, and those with positive PET scans are treated with IFRT (30-36 Gy) followed by end-of-treatment restaging. All patients with PET positive or progressive disease are managed as described for relapsed or progressive disease (HODG-12). Biopsy is recommended before initiating treatment for progressive disease.

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.[54,55] 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.[56] 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.[57] 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.[58] 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.[59] Updated results with a median follow-up of 83 months were consistent with the early results.[60]

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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%.[44] 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.[46-48]

The BEACOPP regimen was developed by the GHSG to improve treatment results through dose escalation and time intensification.[61] 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.[62] 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).[63] 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, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin), plus a limited radiation therapy program. [64] 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.[25] 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

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HL that responded to initial chemotherapy.[65,66] 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. [60,67-69] 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.[67,68] In this trial, patients with untreated stage III to IV disease underwent 6 to 8 cycles of MOPP-ABV. Those experiencing complete response after chemotherapy were randomized to no further treatment or IFRT, and those who showed partial response 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 partial response 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.[60] 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.[69].

In contrast, Laskar and colleagues reported a survival advantage for consolidative RT in patients experiencing complete response after initial chemotherapy particularly in patients younger than 15 years.[70] 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 6-8 cycles of BEACOPP-14.[71] Only patients who had positive PET scans at the end of chemotherapy received consolidative irradiation. Preliminary results of this trial showed that 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. Longer follow-up is necessary to confirm these preliminary results.

NCCN Recommendations

ABVD or Stanford V is recommended for primary treatment for patients with advanced disease (HODG-8). Escalated-dose BEACOPP (4 cycles) should be considered for high-risk patients with an IPS score of four or more (HODG-9).

ABVD is generally administered initially for 6 cycles. Restaging takes place after 4 cycles. PFTs should be repeated after 4 cycles. Two additional cycles (total of 6) are administered for patients who have experienced complete or partial response, followed by restaging for patients with initial partial response. No further treatment is necessary for patients who have experienced complete response or those with partial response and a negative PET scan. If bulky mediastinal disease was present initially, consolidative RT to the mediastinum is

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recommended after 6 cycles of ABVD. Patients with partial response and a positive PET scan 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.

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 bulky disease as outlined in HODG-4.

Escalated-dose BEACOPP is administered every 3 weeks, and restaging occurs at the end of 4 cycles. Four additional cycles of baseline BEACOPP are administered for patients who have experienced complete response, whereas 4 cycles of escalated-dose BEACOPP are recommended for those with partial response, followed by end-of-treatment restaging (HODG-9). Biopsy can be considered before initiating additional cycles of BEACOPP. Consolidative irradiation (30-40 Gy to initial bulky sites > 5 cm, and 40 Gy of RT to residual PET-positive sites) is recommended for all patients. Patients experiencing partial response with positive PET scans or progressive disease are managed as described for relapsed or progressive disease (HODG-12). 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.[72] The GHSG has reported a comprehensive description of natural history, clinical presentation, and outcomes for LPHL.[73] 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. 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.[74] 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.[75-82] 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.[76] 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.[79] 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.[80] Ninety-three patients received RT alone, 13 received RT with chemotherapy, and seven received chemotherapy

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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.[75]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.[78] 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 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.[74] 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.[83] 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% complete, 54% partial, and 5% unconfirmed complete responses).[84] 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.[85] Median follow-up was 72 months for limited and 30 months for extended treatment. The overall response rate was 97% (69% complete or unconfirmed complete response, 28% partial response). Among patients undergoing limited treatment with rituximab, 56% experienced complete or unconfirmed complete response, 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.[86] 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].[87] The overall response rate was 100% with 6 of the 7 patients achieving complete response. 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 newly diagnosed as well those with relapsed LPHL.

NCCN Recommendations

IFRT (30-36 Gy) or regional RT is recommended for all patients with stage I-IIA disease; chemotherapy with or without IFRT or RT, rituximab

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either as a single agent or in combination with chemotherapy (with or without RT) are the recommended treatment options for patients with stage IB-IIB or stage III-IV disease (HODG-10). 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. The French GOELAMS group has reported that anthracycline-based chemotherapy [ABVD or EBVM (epirubicin, bleomycin, vinblastine and methotrexate) or 7-drug epirubicin containing regimen] with extended RT may be suitable for patients with early stage disease based on the high 15-year freedom from progression and OS rates.[81] Some investigators have also reported good response rates with CVP or CHOP chemotherapy with or without rituximab in patients with early stage or advanced disease.[88,89] 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:

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

Restaging occurs after completion of initial therapy, and then observation is recommended for asymptomatic patients with unconfirmed complete response and all patients experiencing complete response. Patients with unconfirmed complete response or progressive disease may be managed according to the algorithm for relapsed or progressive CHL (HODG-12) . However, some have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed or treated with local irradiation.

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. [90]

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 (HODG-11).

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. Annual influenza vaccinations should be considered for high-risk patients (those who were treated with bleomycin-based chemotherapy or chest RT).

Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen. Chest radiograph or CT

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should be performed every 6 to 12 months during the first 2 to 5 years, then annually depending on clinical circumstances. Abdominal/pelvic CT (category 2B) is monitored every 6 to 12 months for the first 2 to 3 years, then annually up to 5 years. PET scans are not recommended for routine surveillance due to the risk of false positives.

Monitoring for Late Effects

Several modifications such as limiting the number of cycles of chemotherapy, reduction in radiation dose and irradiation fields have been investigated in clinical trials in an effort to improve treatment outcome with reduced toxicity and late effects. IFRT was equally effective and less toxic compared to EFRT in patients with early stage HL treated with combined modality therapy. A brief course of chemotherapy in combination with IFRT is associated with a reduced relapse risk compared to chemotherapy alone in patients with early stage HL. RT is also associated with survival benefits in a subset of patients with relapsed or refractory disease. RT has also been used as part of conditioning regimen in radiation naïve patients prior to ASCR. However, RT remains a significant risk factor for many of the long-term 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.

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.[91] 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.[92]

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. 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 (HODG-11).

Annual mammogram 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 (HODG-11). They should also be encouraged to perform monthly self-breast examination and undergo yearly breast examination by a health care professional. Women who received chest irradiation prior to age 30 should have screening with MRI, in addition to conventional mammography.

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease.[93,94] RT-induced cardiotoxicity is observed usually more than 5-10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Asymptomatic cardiac disease is also prevalent in patients who were treated with mantle field irradiation.[95]

Based on data regarding increased long-term risk of cardiac disease, the panel recommends a baseline stress test or echocardiogram at 10

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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.[90] A careful thyroid examination should be a part of physical exam. Thyroid function tests should be done at least annually to rule out hypothyroidism.

Myelosuppression

Myelosuppression is the most common side effect of chemotherapy and is associated with increased risk of infections. There are no data on the types of infections in long-term survivors of HL in different parts of the world.[90]

Pneumococcal revaccination is recommended every 5 to 7 years, especially for patients treated with splenic RT or splenectomy. Meningococcal and H-flu revaccination can be considered in selected cases (HODG-11).

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.[96]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.[97,98] 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.[98]

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 [99] and the German Hodgkin's Study Group (GHSG)/European Bone Marrow Transplantation Group (EBMT) [100] 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.[101] 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, complete response of less than 1 year, primary refractory disease, and B symptoms as adverse prognostic

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factors associated with poor survival after HDT/ASCR.[102] 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.[103] In a retrospective analysis of 422 patients with relapsed disease, Josting and colleagues from the German Hodgkin's Lymphoma Study Group (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.[104] More recently, investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first complete response (less than one year), detectable disease at transplant and the presence of more than one extranodal site as adverse factors for OS.[105] Other groups have identified extent of prior chemotherapy,[106] short time from diagnosis to transplant[107] and disease status at transplantation[108] as significant prognostic factors for OS and PFS.

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.[102,109-115] Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) [116] and IGEV (ifosfamide, gemcitabine, and vinorelbine) [117] 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 complete response 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.[118-120] While second-line chemotherapy is an appropriate treatment for any patient with relapsed Hodgkin's disease, regardless of the length of initial remission,[121] some studies have also suggested that patients with minimal residual disease at relapse may not need conventional-dose chemotherapy before HDT/ASCR.[122]

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.[123] 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.[102] 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

Patients with progressive CHL or disease 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 progressive disease or

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relapse depends on whether primary treatment was RT alone, chemotherapy, or combined modality therapy (HODG-12).

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.

Suggested second-line chemotherapy regimens are listed in HODG-E. Conventional-dose second-line chemotherapy may precede high-dose therapy. Response to conventional therapy is not essential to proceed to HDT/ASCR. In selected patients with long disease-free intervals and other favorable features, chemotherapy should be 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 as outlined in HODG-4. The extent of stage at relapse (relapse stage) after RT was the most important prognostic factor for freedom from second relapse.[124]

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 (brief course of chemotherapy and IFRT) is the preferred treatment for patients with stage IA-IIA favorable CHL. Chemotherapy followed by consolidative irradiation with IFRT is recommended for patients with stage I-II unfavorable disease and patients with stage III-IV disease who have bulky mediastinal adenopathy.

LPHL has a different natural history and response to therapy compared with CHL. IFRT alone is the treatment option for patients with stage IA-IIA disease whereas chemotherapy with or without RT is recommended for all other patients. In early phase clinical studies, rituximab (anti CD20 monoclonal antibody) 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 I-IIB or stage III-IV disease. The role of chemotherapy or antibody-based therapy is being explored in ongoing clinical trials for early stage and advanced stage LPHL.

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HDT/ASCR is the best treatment option for patients with relapsed or refractory HL, although it does not improve OS. Conventional-dose second-line chemotherapy with or without RT may be given prior to high-dose therapy. 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.

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