Hodgkin Disease/ Lymphoma

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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 Consensus:

All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Summary of Guidelines Updates

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of changes in the 1.2007 version of the Hodgkin Disease/Lymphoma guidelines from the 1.2006 version include:

- In the workup of a patient with Hodgkin disease, category 2B was added to PET scan. Fertility counseling was also added (HODG-1).
- New treatment algorithms were developed for the management of classical Hodgkin Disease based upon type of chemotherapy to be administered. The previous "Interim Restaging" pages have been removed. Footnotes g, i, and j are new to these algorithms (HODG-2 and HODG-3).
- Footnote l is new to the page describing chemotherapy for NLPHD (HODG-4).
- The following was added to the "Follow-up after Completion of Treatment" - Surveillance PET is not encouraged due to the risk for false positives. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed (HODG-5).
- Chest imaging for Monitoring for Late Effects after 5 Years was clarified to "Consider spiral chest CT for patients at increased risk for lung cancer." The mammography recommendation was modified to "5"-8 years after initial therapy. The American Cancer Society recommendation for breast MRI was added (HODG-5).
- Consider RT was added as an option after salvage therapy for Initial stage IA-IIA (HODG-6).
- Extranodal sites was added as an unfavorable factor for localized presentations. Footnotes 1 and 4 are new to the page (HODG-A).
- The recommended RT dose to bulky sites was changed from 20 to 30 Gy (HODG-C).
- Revised Response Criteria for Lymphoma (HODG-D).
**DIAGNOSIS**

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic
- FNA alone is insufficient
- Immunohistochemistry recommended but not necessary for classical Hodgkin disease.
- For nodular lymphocyte-predominant Hodgkin disease, recommend CD3, CD15, CD20, CD21, CD30, CD57
- For typical classical Hodgkin disease, recommend CD3, CD15, CD20, CD30, CD45

**WORKUP**

- H&P including:
  - B symptoms
  - ETOH intolerance
  - Pruritus
  - Fatigue
  - Performance status
  - Exam lymphoid regions
  - Spleen, liver
  - CBC, differential, platelets
  - Erythrocyte sedimentation rate (ESR)
  - LDH, LFT, albumin
  - BUN, creatinine
  - Chest x-ray
  - Chest/abdominal/pelvic CT
  - PET scan, especially if equivocal CT (category 2B)
  - Adequate bone marrow biopsy in stage IB-II and stage III-IV
  - Counseling: Fertility, smoking cessation, psychosocial
    (see NCCN Distress Management Guidelines)

**CLINICAL STAGING**

- Useful in selected cases:
  - Pregnancy test: women of childbearing age
  - Fertility Counseling
  - Oophoropexy, if premenopausal and pelvic RT contemplated
  - Semen cryopreservation, if chemotherapy or pelvic RT contemplated
  - Neck CT
  - Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
  - HIV, if risk factors, unusual disease presentations
  - Evaluation of ejection fraction (eg, if ABVD or BEACOPP planned)
  - Pulmonary functions tests (PFTs), Diffusion capacity of the lungs for carbon monoxide (DLCO) (eg, ABVD or BEACOPP planned)

**Notes**

- Treatment recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Classical Hodgkin disease (HD) includes nodular sclerosis (NSHD), mixed cellularity (MCHD), lymphocyte-depleted (LDHD) and lymphocyte-rich (LRHD).

Bulky mediastinal disease (see Unfavorable Factors, HODG-A) or mass > 10 cm.

See Principles of Chemotherapy (HODG-B).

See Principles of Radiation Therapy (HODG-C).

Depending upon co-morbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able tolerate chemotherapy and chemotherapy alone may be considered for patients who are not candidates for radiation (category 2B).

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

A corresponding CT scan is always recommended with PET scan.

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

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Classical Hodgkin disease (HD) includes nodular sclerosis (NSHD), mixed cellularity (MCHD), lymphocyte-depleted (LDHD) and lymphocyte-rich (LRHD). Individualized treatment may be necessary for older patients and patients with concomitant disease.

A corresponding CT scan is always recommended with PET scan.

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.
CLINICAL PRESENTATION: Nodular lymphocyte-predominant Hodgkin Disease

Nodular lymphocyte-predominant has a different natural history and response to therapy than does classical Hodgkin disease, especially stages I-II. For that reason, separate guidelines are presented for NLPHD.

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

See Principles of Radiation Therapy (HODG-C).

A corresponding CT scan is always recommended with PET scan.

CR or PET/CT negative

Restage PET/CT

< CR

Observe, if asymptomatic or Chemotherapy or RT

(See also HODG-6

CS IIA

Involved-field or regional RTf or
Chemotherapyl,m + involved-field RTf (category 2B) or
Observation (if patient cannot tolerate RT)

CRj or PET/CT negative

Restage with PET/CTi

< CRj

Observe, if asymptomatic or Chemotherapy or RT

(See also HODG-6

CS I-IIB

Chemotherapym + involved-field RTf (category 2B)

CS III-IVA

Chemotherapym ± RTf or
Observation (category 2B) or
Local RT (palliation only) or
Rituximab (in selected symptomatic patients who are not candidates for chemotherapy or observation) (category 2B)

CS III-IVB

Chemotherapym ± RTf or
Rituximab (in selected symptomatic patients who are not candidates for chemotherapy) (category 2B)

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS**

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.\(^n\)\(^o\)\(^p\)

**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, 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 (category 2B for CT) every 3-6 mo during first 2-3 y, then annually thereafter depending on clinical circumstances\(^q\)

- **Abdominal/pelvic CT (category 2B):**
  - Every 3-12 mo for first 2-3 y, then annually up to 5 y
- **Annual mammographic screening:**
  - Initiate 5-8 y post-therapy, or at age 40, whichever comes first, if RT above diaphragm
- **Counseling:**
  - Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
  - Surveillance PET is not encouraged due to risk for false positives. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed.

**Monitoring for Late Effects after 5 Years**\(^o\)\(^p\)

- **Interim H&P:** Annually
  - Annual blood pressure, serum glucose and lipid screening
  - Baseline stress test/echocardiogram at 10 y
  - Pneumococcal revaccination every 5-7 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, ESR, chemistry profile annually
  - TSH at least annually if RT to neck

- **Chest imaging:**
  - Consider spiral chest CT for patients at increased risk for lung cancer\(^q\)
- **Annual mammographic/breast MRI screening:**
  - Initiate 5-8 y post-therapy, or at age 40, whichever comes first, if RT above diaphragm. The American Cancer Society recommends breast MRI in addition to mammography.
- **Counseling:**
  - Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.

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\(^n\)The frequency and types of tests may vary depending on clinical circumstances; age and stage at diagnosis, social habits, treatment modality, etc.


\(^p\)Appropriate medical management should be instituted for any abnormalities.

\(^q\)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.
### Hodgkin Disease/Lymphoma

**Classical Hodgkin Disease**

**Progressive Disease or Relapse**
- Rebiopsy
- Restaging (same as initial work-up, including bone marrow biopsy)
- Consider cytogenetics prior to transplant

**Salvage Therapy**
- If primary therapy was chemotherapy alone or combination chemotherapy/RT
  - If initial stage was IA-IIA:  
    - No prior RT and failure in initial sites only
    - Appropriate treatment in this setting has not been identified, individualized treatment is recommended
  - Consider RT
- AHSCT (category 1) ± locoregional RT or Combined modality therapy
- Chemotherapy: ABVD
  - Treat to complete response + 2 cycles (6-8 cycles) ± involved-field RT (category 2B for RT), if relapse is outside original field
- Complete response
  - Follow-up
- Less than complete response
  - AHSCT

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

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

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1. Patients with NLPHD may be managed according to the same algorithm; however, some patients with NLPHD have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed.

2. There are no data to support a superior outcome with any modalities.

3. This applies to patients with relapse, not those with progressive disease.

4. See Principles of Salvage Chemotherapy (HODG-E).

5. Biopsy especially if plan to treat with high-dose therapy.

6. Conventional-dose chemotherapy may precede high-dose therapy. Response is not essential to proceed to AHSCT. Timing of RT may vary.

7. For select patients with long disease-free interval and other favorable features; selection of chemotherapy should be individualized.
**UNFAVORABLE FACTORS**

### (localized presentations)

- **Bulky disease:**
  - Mediastinal mass (chest x-ray):
    - Maximum mass width
    - Maximum intrathoracic diameter
  - Mediastinal mass greater than 35% of the thoracic diameter at T5-6
  - Any other mass > 10 cm (CT)
- Erythrocyte sedimentation rate ≥ 50, if asymptomatic
- > 3 sites
- B symptoms
- Extranodal sites

### (advanced disease)

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

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1. Only bulky disease is incorporated into the guideline algorithm for localized presentations, however the other factors are considered for assignment into some clinical trials.
3. Consider use of dose-escalated BEACOPP if patient has 4 or more risk factors.
4. The unfavorable factors for advanced disease are not incorporated into the guideline algorithm for stage III-IV, however these factors are considered for assignment into some clinical trials.

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

- 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.

- Stage IA-IIA non-bulky disease
  - ABVD is generally administered for 4 cycles. Complete restaging takes place at completion of chemotherapy. Consolidative irradiation follows. If no irradiation is given, but the patient has achieved a CR, two additional cycles of chemotherapy should be administered.
  - 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 bulky disease (See HODG-A)
  - ABVD is generally administered for 4-6 cycles. Complete restaging takes place either after 4 cycles or at the completion of chemotherapy. Consolidative irradiation follows the completion of chemotherapy.
  - Stanford V chemotherapy is administered for 12 weeks (3 cycles). Complete restaging takes place at the completion of chemotherapy. Consolidative irradiation is optimally instituted within 3 wks (36 Gy to initial sites > 5 cm).
  - BEACOPP (escalated dose) is administered every 3 weeks. Complete restaging takes place at the end of 4 cycles and at the end of 8 cycles (completion of chemotherapy). This is followed by 30-40 Gy irradiation to initial sites > 5 cm.

See Principles of Salvage Chemotherapy page HODG-E

**PRINCIPLES OF RADIATION THERAPY**

<table>
<thead>
<tr>
<th><strong>COMBINED MODALITY-RT DOSES:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>● Bulky disease sites (all stages)</td>
</tr>
<tr>
<td>If treated with ABVD: 30-36 Gy</td>
</tr>
<tr>
<td>If treated with Stanford V: 36 Gy</td>
</tr>
<tr>
<td>● Nonbulky disease (stage I-II)</td>
</tr>
<tr>
<td>If treated with ABVD: 20-30 Gy</td>
</tr>
<tr>
<td>If treated with Stanford V: 30 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>RT-ALONE DOSES (uncommon scenario):</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>● Involved regions: 30-44 Gy(^1)</td>
</tr>
<tr>
<td>● Uninvolved regions: 30-36 Gy</td>
</tr>
</tbody>
</table>

**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 NLPHD.
## REVISED RESPONSE CRITERIA FOR LYMPHOMA (including PET)

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


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

- The selection of salvage chemotherapy regimens depends on the pattern of relapse and the agents previously used.
  - Examples of salvage chemotherapy prior to transplant include ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cisplatin, high-dose cytarabine), ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin).
  - Some studies suggest that late relapses (selected patients) can be successfully treated with the same regimen used for initial remission induction with favorable results if a second CR is achieved.\(^1\)\(^2\)
  - Induction failures and early relapses will require chemotherapy regimens composed of agents not previously used before treatment with high-dose chemotherapy with stem-cell rescue. Some of the regimens previously evaluated are: Mini-Beam,\(^3\) MINE,\(^4\) VIM-D,\(^5\) and EVA.\(^6\)
- 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.\(^7\)\(^8\)\(^9\) However, patients tend to have an improved outcome when transplanted in a minimal disease state.\(^10\) Thus, cytoreduction with chemotherapy (see above) before high-dose chemotherapy with stem-cell rescue may be beneficial. In addition, salvage chemotherapy serves as a test for drug sensitivity and to facilitate the harvest of stem cells.
- Some studies suggest that nitrogen mustard, procarbazine, carmustine, and melphalan may adversely affect both quality and quantity of stem-cell collection.

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Table 1
Definitions of Stages in Hodgkin's Disease

**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. I\(_I\)).

**Stage III** Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (III\(_E\)), by involvement of the spleen (III\(_S\)), or by both (III\(_{E+S}\)).

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

A. No systemic symptoms present
B. Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight

The NCCN guidelines for HD focus exclusively on patients from post-adolescence through the seventh decade of life who do not have serious intercurrent disease. These guidelines do not address HD in pediatric or elderly patients or in patients with unusual situations, such as HIV-positive or pregnant patients. Individualized treatment may be necessary for these patients, older patients, and patients with concomitant disease.

The guidelines begin with the diagnosis and workup of HD. The WHO classification divides HD into two main types: classical HD and nodular lymphocyte-predominant HD (NLPHD). Classical HD includes nodular sclerosis (NSHD), mixed cellularity (MCHD), lymphocyte-depleted (LDHD), and lymphocyte-rich (LRHD).

The discussion of clinical management issues starts with classical HD (stages I-IV, nonbulky and bulky). Next, the guidelines discuss nodular lymphocyte-predominant disease (stages I-IV). The discussion then considers interim and end of treatment restaging, follow-up strategies, and management of disease relapse.

In general, these guidelines emphasize the use of combined modality therapy (abbreviated chemotherapy and limited irradiation) in early stage nonbulky disease; combined modality therapy for the intermediate-prognosis patients (bulky mediastinal stage II disease); and systemic treatment with or without local field irradiation for patients with stage III-IV disease. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

**Radiation Therapy Doses**

Radiation oncologists who participated in the development of the HD guidelines have somewhat divergent views, which are reflected in a broad range of radiation doses for specific clinical situations and combined modality therapy. For radiation therapy (RT) alone, which
is not commonly used, the range of recommended doses is 30 to 44 Gy to involved regions and 30 to 36 Gy to uninvolved sites. The dose of 30 Gy is primarily used for excised NLPHD.

In combined modality therapy dose ranges are determined by whether the disease is bulky or nonbulky. For patients with stages I-IV bulky disease, a radiation dose of 20 to 36 Gy is recommended even after they have received a full course of chemotherapy. This recommendation reflects limited experience with the use of lower doses in this setting. In the absence of bulky disease in patients with stage I-IV the radiation dose could be reduced to 20 to 30 Gy. This recommendation is based on the range of experience and practice across NCCN institutions.

**Unfavorable Factors**

Unfavorable prognostic factors in early stage disease influence the management guidelines. The mediastinal mass ratio identifies patients who have a poor prognosis when treated with single-modality therapy. A recommended measurement of mediastinal bulk is the ratio of the maximum width of the mediastinal mass on chest x-ray to the maximum intrathoracic diameter. A ratio exceeding one third is unfavorable. Alternatively, mediastinal bulky disease may be defined as greater than 35% of the thoracic diameter at the T5-T6 interspace. Another measurement of bulk is any mass greater than 10 cm, which occurs only rarely outside the mediastinum.

An erythrocyte sedimentation rate (ESR) of 50 or more is also considered unfavorable. This is based largely on European Organization for Research and Treatment of Cancer (EORTC) data and the definition of unfavorable prognostic groups for their trials. Another EORTC report analyzing prognostic factors in early stage HD identified a poor prognostic group as having more than three sites of disease. “B” symptoms are also considered an unfavorable factor in patients with localized HD. The guidelines include flexibility with respect to how the ESR or number of disease sites impacts management.

An international collaborative effort evaluating more than 5,000 cases of advanced HD identified seven adverse prognostic factors, each of which reduces survival rates by 7% to 8% per year. These factors are 1) age of 45 years or older, 2) male gender, 3) stage IV disease, 4) albumin level below 4 g/dL, 5) hemoglobin level below 10.5 g/dL, 6) white blood cell count above 15,000/mm³, and 7) lymphocytopenia (lymphocyte count below 600/mm³ or less than 8% of the total white count). The number of unfavorable factors helps to determine clinical management and predict prognosis. For instance, if the patient has more than four unfavorable factors and advanced disease, the use of dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen may be considered as a treatment option.

**Diagnosis and Workup**

Fine needle aspiration (FNA) alone is insufficient for diagnosis. Core needle biopsy may be adequate, but the panel recommends excisional nodal biopsy. Immunohistochemistry is recommended but not necessary for classical HD. Immunostaining for CD15, CD30, CD3, CD20, and CD45 is recommended for classical HD. For nodular lymphocyte-predominant HD, the guidelines recommend staining for CD20, CD57, CD15, CD30, CD3, and CD21.

The workup should include a thorough history and physical examination such as “B” symptoms, EtOH intolerance, pruritus, fatigue, patient performance status, and examination of the lymphoid regions, spleen and liver. Standard laboratory testing
should include a complete blood count (CBC), differential, platelets, erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH) level, albumin, and liver and renal function tests. Chest x-ray and chest/abdominopelvic computerized tomographic (CT) scans are appropriate imaging studies. If the CT scan is equivocal, positron emission tomography (PET) imaging is helpful in defining the extent of disease. Data show that PET imaging has a high sensitivity compared to CT in detection of both nodal disease and organ involvement. Adequate bone marrow biopsy should be performed on patients who have stage IB-IIB disease or higher. Other tests should be based on specific symptoms or abnormalities on the standard staging studies.

Additional information is useful in selected cases. Pregnancy test should be done for women of childbearing age before treatment. For patients with risk factors for HIV or unusual disease presentations, an HIV test is needed. If chemotherapy or pelvic RT is contemplated in male patients, semen cryopreservation should be done. For premenopausal female patients, if pelvic RT is planned, oophoropexy should be performed. In addition, a neck CT scan is recommended in selected patients. Pulmonary functions tests (PFTs), diffusion capacity of the lungs for carbon monoxide (DLCO), and evaluation of ejection fraction are also useful if patients are going to get ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP therapy.

If splenic RT is contemplated, pneumococcal vaccine, H-flu vaccine, and meningococcal vaccine are recommended.

### Clinical Management

The guidelines begin with consideration of classical HD. Nodular lymphocyte predominant HD (NLPHD) has a different natural history and response to therapy than does classical HD, especially stages I-II. For that reason, NLPHD is addressed separately.

### Classical Hodgkin Disease/Lymphoma

#### Stage I-IIA

The guidelines stratify classical HD according to the presence of bulky disease. For patients with nonbulky disease, the preferred treatment is combined modality therapy. An example is chemotherapy such as four cycles of ABVD with involved-field irradiation (20-30 Gy) (category 1). Highly selected patients who cannot tolerate chemotherapy may be treated with RT alone, which should include sequential treatment to the mantle and paraaortic-spleen fields (category 1) or Mantle field irradiation alone (category 2B). For highly selected patients where RT is contraindicated, chemotherapy alone is also a treatment option (category 2B).

For patients who have bulky disease, which is almost always mediastinal, the panel recommends routine combined modality therapy, beginning with chemotherapy, and followed by limited radiation. Generally, irradiation of the mediastinum, including contiguous sites of bulky involvement and bilateral supraclavicular areas, is sufficient. The usual dose is 30 to 36 Gy. Minimal disease (less than 5 cm) outside that field may be left unirradiated if a full course of chemotherapy has been administered.

The chemotherapy that NCCN panelists recommend for early stage disease is ABVD for 4 cycles or Stanford V (mechloretamine,
doxorubicin, etoposide, vincristine, vinblastine, bleomycin, and prednisone) regimen for 8 weeks (2 cycles).

Complete restaging takes place at completion of chemotherapy if 4 cycles of ABVD are planned and after 4 cycles if 6 cycles are planned. Consolidative irradiation follows. If no irradiation is given, but the patient has achieved a complete remission (CR) or CRu (complete remission uncertain), 2 additional cycles of chemotherapy should be administered.

If Stanford V regimen is being used, complete restaging takes place at the completion of chemotherapy (2 cycles). Consolidative irradiation is optimally instituted within 3 weeks (30 Gy to all involved fields).

Stage I-IIIB

Clinical stage IB HD is uncommon, but occasional patients present with stage IIB disease. The treatment recommended for patients with nonbulky stage I-IIIB disease is combined chemotherapy plus RT to the involved nodal regions (category 1). Some panel members feel that chemotherapy alone is an appropriate management option for highly selected patients where RT is contraindicated; however, differences of opinion exist among the panelists regarding its suitability (category 2B).

Patients who have stage IIB disease with bulky mediastinal involvement should be treated with chemotherapy plus involved-field RT. Whenever possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.

ABVD is generally administered for 4-6 cycles and the Stanford V chemotherapy is administered for 12 weeks (3 cycles). Complete restaging takes place at the completion of chemotherapy.

Consolidative irradiation is optimally instituted within 3 weeks (36 Gy to initial sites >5 cm).

Interim restaging of stage I-II patients should be conducted following 4 cycles of chemotherapy, or at the end of chemotherapy if less than 4 cycles of chemotherapy or combined modality therapy is planned. All previous positive imaging studies need to be repeated. If a CR or CRu is confirmed, completion of therapy is recommended.

Patients with response less than CRu should undergo a PET scan. Positive results with either CRu or response less than CRu indicate the need for additional chemotherapy, RT, or high-dose therapy individualized according to sites of disease. However, completion of planned therapy is recommended if the PET scan results are negative. If disease is progressive or there is no response to current therapy, a biopsy (may be a core needle biopsy) is strongly recommended to confirm the diagnosis, and a subsequent autologous hematopoietic stem cell transplant (AHSCT) with or without locoregional RT is recommended.

Choice of Chemotherapy in Advanced Disease

The gold standard of chemotherapy treatment for HD is ABVD. A randomized trial by the Cancer and Leukemia Group B (CALGB) showed that ABVD-containing regimens (ABVD alone or alternating MOPP/ABVD) were superior to MOPP alone. Some concern exists regarding using ABVD in combination with full-dose irradiation of the mediastinum because of potential overlapping toxicity of doxorubicin and bleomycin with radiation.

On the basis of experience at the NCCN institutions, the Stanford V regimen is also considered an acceptable drug combination for advanced disease. This is a brief (12 weeks) intensive chemotherapy regimen that includes mechlorethamine, doxorubicin, etoposide, vincristine, vinblastine, bleomycin, and prednisone. Although the regimen is dose intensive, the cumulative doses of such drugs as mechlorethamine, doxorubicin, and bleomycin are...
significantly less than those in MOPP, ABVD, alternating, or hybrid regimens, thereby reducing the risks of infertility, secondary neoplasms, and cardiac and pulmonary toxicity. An integral part of the treatment program is the incorporation of irradiation (36 Gy) to initial sites >5 cm and spleen, if involved, after completion of chemotherapy. This has been a very successful therapy and has been introduced in the management of advanced disease (stage III-IV and bulky stage II) in the E2496 intergroup trial.

Some NCCN institutions use dose-escalated BEACOPP regimen as an alternative in selected cases for high-risk patients with an International Prognostic Score (IPS≥4). This regimen was developed to improve treatment results by both dose and time intensification. Results suggest that BEACOPP is a promising treatment option for advanced HD.

Stage III-IV

Patients who present with stage III-IV disease may have any histologic subtype. The primary treatment is chemotherapy alone (eg, ABVD), as outlined above, or chemotherapy with RT (ie, Stanford V). The guidelines do not include an option for high-dose therapy "up front" for these patients. Two recent European trials failed to show an advantage for high-dose therapy for patients presenting with various combinations of unfavorable prognostic factors. Systemic symptoms, age ≥ 40 years old, bulky mediastinal involvement, elevated ESR, high serum LDH level, multiple extranodal sites, and low hematocrit were defined as unfavorable factors in this study.

The general concept is to restage patients whose studies are positive at the outset. This restaging should be completed at certain defined intervals, in keeping with the management philosophy of still giving additional chemotherapy beyond the point of restaging, even if the patient has a complete response.

Using ABVD or BEACOPP as an example, four cycles of chemotherapy would be administered, followed by restaging. If a complete response or CRu has occurred, two more cycles of ABVD would be administered followed by, in selected cases, RT (20-36 Gy) to bulky sites. If BEACOPP is being used, four additional cycles are recommended. A final restaging, to confirm the stability of any minor abnormalities, would follow the completion of chemotherapy. Treatment would then be discontinued after a total of six cycles of ABVD or 8 cycles of BEACOPP. For patients achieving response less than CRu or if CRu is associated with a positive PET scan, 2 additional cycles of ABVD (maximum total of 6 cycles) or 4 additional cycles of BEACOPP (total of 8 cycles), if BEACOPP is being used, may be considered.

If complete response or CRu is then achieved, an additional two cycles of ABVD chemotherapy (maximum total of 8 cycles) is completed. RT (20-36 Gy) to bulky sites may then be administered. If BEACOPP was administered, RT (30-40 Gy) is then delivered to initial sites of disease >5 cm. Both the Southwest Oncology Group (SWOG) study of MOPP-BAP (bleomycin, doxorubicin, and procarbazine) with or without radiation and the EORTC-GPMC trial of MOPP/ABV with or without radiation routinely irradiated patients who had achieved less than complete responses. A significant proportion of those patients then achieved complete responses.

For patients with response less than CRu or those who has CRu with a positive PET scan after interim restaging and no change after secondary restaging, additional therapy, that is individualized according to the sites of disease, is recommended. Therapy may include secondary chemotherapy, RT, or high-dose therapy. Biopsy
should be performed if a patient is to be treated with high-dose therapy.

If the Stanford V regimen is being used, restaging should be done after the completion of chemotherapy. Radiation therapy (36Gy) to initial sites (>5 cm) and macroscopic splenic disease should then be administered.

Another issue relates to the use of consolidative low-dose irradiation to all sites of disease following the completion of chemotherapy for patients with stage III-IV HD. The SWOG randomized trial showed no improvement in overall survival rates for those patients who received irradiation, but the disease-free interval was prolonged, especially for patients with bulky NSHD. The EORTC 20884 trial similarly showed no improvement in survival or freedom from relapse for patients treated with 25 Gy involved-field irradiation following completion of 8 cycles of MOPP-ABV. One remaining issue, the role of consolidative irradiation for stage III-IV disease with a “bulky” component, is being addressed in a randomized trial of the German Hodgkin’s Study Group (GHSG).

In the presence of truly progressive or no response disease, which is very uncommon, a core needle biopsy may be warranted (if only to confirm the diagnosis is truly HD), followed by high-dose salvage regimens with or without locoregional RT, and autologous hematopoietic stem cell transplant (AH SCT). Although the prognosis in such cases is poor, and the efficacy of high-dose therapy in this setting is not as good as in the setting of "minimal residual disease," this remains the best treatment option for these patients.

**Nodular Lymphocyte-Predominant Hodgkin Disease**

Nodular lymphocyte-predominant HD comprises about 4-5% of all HD. Treatment choices for NLPHD are based on clinical stage and presentation. For clinical stage IA, involved-field or regional RT alone is recommended. Patients with stage IIA disease may also be treated with involved-field or regional RT. However, some NCCN panelists believe that chemotherapy plus involved-field radiation is also appropriate in these cases (category 2B). For stage IA and IIA, observation may be considered if the patient cannot tolerate RT.

Observation (category 2B) or chemotherapy with or without RT is an appropriate option for asymptomatic patients with clinical stage III-IVA NLPHD disease. Local RT alone is also an appropriate treatment option for palliation purposes in this group of patients.

Rituximab is an option in selected symptomatic patients who are not candidates for chemotherapy in patients with clinical stage III-IV NLPHD (category 2B).

**End of Treatment Restaging**

The end-of-treatment restaging occurs after an earlier restaging process and should be performed 3 months after completion of treatment. The treatment options are similar to those at the time of initial restaging. Additional follow-up after completion of treatment is recommended for patients with complete response or CRu.

Patients with response less than CRu require a PET scan. For patients with either CRu or response less than CRu and a positive PET scan, biopsy is recommended if lymph node is easily accessible. In case of positive biopsy results, additional therapy (salvage CT, RT, or high-dose therapy) that is individualized according to the sites of disease and initial therapy, is recommended. If lymph node is not easily accessible for biopsy, observation is recommended until disease progression. If the PET scan is negative, the patient may be observed.
A patient with progressive disease that is confirmed by a positive biopsy will likely go on to AHSCT with or without locoregional RT.

Follow-up after Completion of Treatment and Monitoring for Late Effects

The guidelines for follow-up are based largely on NCCN panelists’ own clinical practices and are not supported by high-level evidence. Interim physical examinations and blood work (including CBC, platelets, ESR, and chemistry profile) are performed less frequently as the length of time in between follow-ups increases, but the examinations and laboratory tests are continued annually after 5 years.

Interim evaluations should include consideration of pneumococcal revaccination every 5-7 years especially if the patient has been treated with splenic RT or had a splenectomy in the past. High-risk patients (eg, treated with bleomycin, chest RT) should also be considered for annual influenza vaccinations. Meningococcal and H-flu revaccination can be considered in selected cases.

Patients who have had neck or upper mediastinal irradiation should undergo thyroid function studies at least annually to rule out hypothyroidism.18

The panel overwhelmingly agrees that given the long-term risks of the therapies for HD, patients should be followed by oncologists who are aware of these risks and complications especially during the first 5-year interval then annually due to the risk of late complications including secondary cancers and cardiovascular disease.

Repeat imaging studies of initially involved sites are important, as are surveillance studies of both the chest and abdomen. Chest x-ray or CT (category 2B for CT) should be performed every 3-6 months during the first 2-3 years, then annually depending on clinical circumstances. Chest imaging is optional after 5 years if the patient was treated with a non-alkylating agent, did not have RT and no other risk factors (eg, smoking) are present.

Abdominal/pelvic CT (category 2B) is monitored every 3-12 months for the first 2-3 years, then annually up to 5 years. The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc.

The panel recommends that women who have been irradiated above the diaphragm undergo routine annual mammography beginning no later than 8 years after completion of therapy, or at age 40, whichever occurs earlier. Counseling regarding self-breast examination should also be provided.

The NCCN HD panel members agrees, based upon available data on increased long-term risk of cardiac disease, to recommend resting and stress echocardiography annually after 10 years from treatment.18,19

In addition to the follow-up measures outlined above, the panel believes counseling about the issues of the survivorship period, including long-term treatment effects, risks of second primary tumors, cardiac disease, skin cancer, and reproduction must be an integral part of follow-up for HD patients. Health habits and psychosocial issues should also be discussed with a patient.18

Relapse

Patients with classical HD that relapses should undergo biopsy and restaging. Restaging procedure should include bone marrow biopsy. Cytogenetics may be considered if bone marrow
transplantation is planned. Only in rare instances is relapse documented on clinical grounds alone. The management of relapse will depend on whether the primary treatment was radiation alone or included a systemic component, such as chemotherapy or combined modality therapy.

Patients with NLPHD may be managed according to the same algorithm. However, some patients with NLPHD have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed.

**Salvage Therapy**

Patients with classical HD whose initial treatment consisted of radiation alone have very effective salvage potential when a standard course of chemotherapy with or without RT is administered (category 2B for RT), especially if the failure is outside of the initial radiation field. Patients who achieve less than a complete response may be candidates for high-dose therapy.

For patients treated initially with chemotherapy or combined modality therapy, the algorithm is a bit more complicated and therapy is more likely to be individualized. Appropriate treatment has not been identified for patients with initial stage IA to IIA disease, who received chemotherapy alone, and experienced failure at the initial sites. The panel recommends an individualized approach in this situation. For all other settings the panel recommends AH SCT (category 1) with or without locoregional RT. Combined modality therapy, or chemotherapy may be used for selected patients with long disease-free interval and other favorable features.

Chemotherapy regimens should be individualized in this case. Examples of salvage chemotherapy regimens prior to transplant include ICE (ifosfamide, carboplatin, and etoposide), DHAP (dexamethasone, cisplatin, high-dose cytarabine), ESHAP (etoposide, methylprednisolone, high-dose cytarabine).

**Summary**

The management of HD continues to evolve. Major changes have been incorporated into the NCCN guidelines since their inception. Current management programs are based on comprehensive clinical staging followed by combined modality therapy for those patients with favorable and intermediate prognosis or chemotherapy alone for patients with advanced disease. Relapse is uncommon, but secondary management with peripheral stem cell transplant may be very effective. The excellent prognosis for these patients mandates careful long-term follow-up to detect late treatment effects.

**Disclosures for the NCCN Hodgkin Disease/Lymphoma Guidelines Panel**

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Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
References


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