Hodgkin Lymphoma

Clinical Practice Guidelines in Oncology

Richard T. Hoppe, MD; Ranjana H. Advani, MD; Weiyun Z. Ai, MD; Richard F. Ambinder, MD, PhD; Celeste M. Bello, MD, MSPh; Philip J. Bierman, MD; Kristie A. Blum, MD; Bouthaina Darbaja, MD; Ysabel Duron; Andres Forero, MD; Leo I. Gordon, MD; Francisco J. Hernandez-Illizaliturri, MD; Ephraim P. Hochberg, MD; David G. Maloney, MD, PhD; David Mansur, MD; Peter M. Mauch, MD; Monika Metzger, MD; Joseph O. Moore, MD; David Morgan, MD; Craig H. Moskowitz, MD; Matthew Poppe, MD; Barbara Pro, MD; Lawrence Weiss, MD; Jane N. Winter, MD; and Joachim Yahalom, MD

Overview

Hodgkin disease/lymphoma (HD/HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. In 2010, an estimated 8490 new diagnoses of HD/HL and 1320 deaths from the disease occurred in the United States. 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. 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 WHO classification divides HL into 2 main types: classical and lymphocyte-predominant Hodgkin lymphoma (CHL and LPHL, respectively).\(^3\) CHL is divided into 4 subtypes: nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich. In Western countries, LPHL accounts for 5% and CHL for 95% of all HL cases.

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

These NCCN Guidelines discuss the clinical management of CHL and LPHL, focusing exclusively on patients from postadolescence 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.
Hodgkin Lymphoma Version 2:2011

**DIAGNOSIS**

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

**WORKUP**

**Essential:**
- H&P including: B symptoms, alcohol intolerance, pruritus, fatigue, performance status, and examination of lymphoid regions, spleen, and 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^a^
- Adequate bone marrow biopsy in stage IB, IIB and stage III-IV
- Evaluation of ejection fraction for doxorubicin-containing regimens
- Counseling: fertility, smoking cessation, psychosocial (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Distress Management^[b]^)

**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
- Pulmonary functions tests (PFTs including DLCO) if ABVD or BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV, if risk factors, unusual disease presentations

**CLINICAL STAGING**

- **Stage IA, IIA**
  - See Primary Treatment (facing page^[1]^)
- **Stage I-II unfavorable (bulky disease)**
  - See Primary Treatment (page 1025^[2]^)
- **Stage I-II favorable (nonbulky disease)**
  - See Primary Treatment (page 1027^[3]^)
- **Stage III-IV**
  - See Primary Treatment (page 1028^[4]^)

- **Lymphocyte-predominant Hodgkin lymphoma** ([LPHL]^[5]^)
  - See Primary Treatment (page 1030^[6]^)

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.*

---


^b^A separate diagnostic CT is not necessary 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 in the presence of an unusual disease presentation (i.e., HIV), additional clinical evaluation may be required to upstage patient. See the staging table, available online, in these guidelines, at www.NCCN.org (ST-1).

^d^Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

^e^LPHL has a different natural history and response to therapy than classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for LPHL.

^f^NCCN unfavorable factors for stage I-II disease include bulky mediastinal or > 10-cm disease, B symptoms, ESR > 50, > 3 sites of disease (see Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033).

^g^Treatment recommendations for postadolescent Hodgkin lymphoma.
Hodgkin Lymphoma Version 2:2011

CLASSICAL PRESENTATION:
Classical Hodgkin lymphoma

PRIMARY TREATMENT

Stage IA, IIA favorable

Combined modality therapy (ABVD x 2-4 cycles) or Stanford V x 8 weeks + involved-field RT (IFRT) (category 1)

or

ABVD alone (category 2B)

See See Primary Treatment (page 1024)

Complete response (CR)

IFRT → Observe → See Follow-up (page 1031)

Restage after chemotherapy with PET/CT

Partial response (PR)

or

Positive

PET-positive

See Progressive Disease (page 1032)

Negative

IFRT

Restage with PET/CT

PET-negative

See Follow-up (page 1031)

Biopsy

Negative

IFRT

Restage with PET/CT

PET-negative

See Follow-up (page 1031)

Biopsy

See Progressive Disease (page 1032)

Stable disease (SD) or progressive disease (PD)

Biopsy

See Progressive Disease (page 1032)


4Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

NCCN unfavorable factors for stage I-II disease include bulky mediastinal or > 10-cm disease, B symptoms, ESR > 50, > 3 sites of disease (see Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033).

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

2See Principles of Systemic Therapy (page 1034).

4Cycles of ABVD unless patient fulfills strict criteria of only 2 sites of disease and no extralymphatic lesions in which case 2 cycles is sufficient.

7See Principles of Radiation Therapy (page 1035).

1Depending on comorbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able to tolerate chemotherapy.

3An integrated PET/CT or a PET with a diagnostic CT is recommended.

6See Revised Response Criteria for Lymphoma (page 1036).

8Recommend ABVD x 4 cycles (total) before proceeding to IFRT or biopsy.

9Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.
Hodgkin Lymphoma Version 2:2011

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

© JNCCN–Journal of the National Comprehensive Cancer Network | Volume 9 Number 9 | September 2011

---

**CLINICAL PRESENTATION:**
Classical Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Stage IA, IIA favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD alone x 2 cycles (category 2B)</td>
</tr>
<tr>
<td>Restage with PET/CT</td>
</tr>
<tr>
<td>CR (with CR on CT)</td>
</tr>
<tr>
<td>ABVD x 2 cycles (total 4)</td>
</tr>
<tr>
<td>Observe (See Follow-up, page 1031)</td>
</tr>
<tr>
<td>PR or CR with PR on CT</td>
</tr>
<tr>
<td>• ABVD x 4 cycles (total 8)</td>
</tr>
<tr>
<td>• Repeat PFTs after 4 cycles</td>
</tr>
<tr>
<td>Restage with PET/CT</td>
</tr>
<tr>
<td>PET-positive</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Observe (monitor PET/CT)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>See Progressive Disease (page 1032)</td>
</tr>
<tr>
<td>PET-negative</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>IFRT</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>ABVD x 2 cycles ± IFRT</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>ABVD x 2 cycles (total 4)</td>
</tr>
<tr>
<td>Repeat PFTs</td>
</tr>
<tr>
<td>PET-positive</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>See Progressive Disease (page 1032)</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>See Progressive Disease (page 1032)</td>
</tr>
</tbody>
</table>

---

Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

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

Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033.

See Principles of Systemic Therapy (page 1034).

See Principles of Radiation Therapy (page 1035).

See Revised Response Criteria for Lymphoma (page 1036).
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma\(^d\)
Stage I-II unfavorable\(^f\) (bulky)

PRIMARY TREATMENT\(^h\)

- ABVD x 2 cycles (total 4)
- Repeat PFTs

CR\(^n\) → ABVD x 2 cycles (total 6)
- IFRT\(^k\)
- See Follow-up (page 1031)

CR\(^n\) → IFRT\(^k\)
- See Follow-up (page 1031)

Restage with PET/CT\(^m\)

- ABVD x 2 cycles (total 6)
- Repeat PFTs

CR\(^n\) → ABVD x 2 cycles (total 6)
- IFRT\(^k\)
- See Follow-up (page 1031)

CR\(^n\) → IFRT\(^k\)
- See Follow-up (page 1031)

OR

OR

BVD alone x 2 cycles (category 2B)

- Restage with PET/CT\(^m,q\)

CR (with CR on CT)

- ABVD x 2 cycles
- Total 4

Observe (See Follow-up, page 1031)

- ABVD x 4 cycles (total 6)
- Repeat PFTs after 4 cycles

PR or CR with PR on CT

SD

PD

- ABVD x 2 cycles
- Total 4

Restage with PET/CT

- Repeat PFTs

m PET-positive

n PET-negative

Biopsy

IFRT or ABVD x 2 cycles ± IFRT

k See Revised Response Criteria for Lymphoma (page 1036).

PDn → Biopsy\(^p\)

See Progressive Disease (page 1032)

CR, PR, SD

Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

NCCN unfavorable factors for stage I-II disease include bulky mediastinal or > 10-cm disease, B symptoms, ESR > 50, > 3 sites of disease (see Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033).

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

See Principles of Systemic Therapy (page 1034).

See Principles of Radiation Therapy (page 1035).

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

See Revised Response Criteria for Lymphoma (page 1036).

Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.

The value of interim PET scan after 2-4 cycles is unclear but may have a role in management and prognosis.
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma\textsuperscript{d}
Stage I-II unfavorable\textsuperscript{f} (bulky or nonbulky)

PRIMARY TREATMENT\textsuperscript{h}
(continued from page 1025)

\begin{itemize}
\item Stanford \textsuperscript{v,s} x 12 weeks
\item Restage with PET/CT\textsuperscript{m}
\item CR\textsuperscript{n} or PR\textsuperscript{n} \rightarrow RT\textsuperscript{h} to initial sites > 5 cm and residual PET-positive sites (36 Gy begins optimally within 3 wk)
\item Restage with CT (or PET/CT if last PET scan was still positive) after 3 mo
\item Follow-up (see page 1031)
\end{itemize}

Progressive disease (see page 1032)

\begin{itemize}
\item SD\textsuperscript{n} or PD\textsuperscript{n} \rightarrow Biopsy\textsuperscript{p}
\item See Progressive Disease (page 1032)
\end{itemize}

\textsuperscript{d}Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.
\textsuperscript{f}NCCN unfavorable factors for stage I-II disease include bulky mediastinal or > 10-cm disease, B symptoms, ESR > 50, > 3 sites of disease (see Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033).
\textsuperscript{h}Individualized treatment may be necessary for older patients and patients with concomitant disease.
\textsuperscript{v}See Principles of Systemic Therapy (page 1034).
\textsuperscript{w}See Principles of Radiation Therapy (page 1035).
\textsuperscript{v}An integrated PET/CT or a PET with a diagnostic CT is recommended.
\textsuperscript{h}See Revised Response Criteria for Lymphoma (page 1036).
\textsuperscript{p}Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.
\textsuperscript{s}The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or > 10-cm disease and/or B symptoms. Patients with elevated ESR, or > 3 sites are treated according to the Stanford V algorithm on page 1023.
Hodgkin Lymphoma Version 2:2011

**CLINICAL PRESENTATION:**
Classical Hodgkin lymphoma<sup>d</sup>

**PRIMARY TREATMENT**<sup>h</sup>

- ABVD x 2 cycles (total 4)
- Repeat PFTs
- Observe or IFRT<sup>k</sup>
- See Follow-up (page 1031)

- ABVD x 2 cycles (total 6)
- Observe or IFRT<sup>k</sup>
- See Follow-up (page 1031)

- ABVD x 2 cycles (total 6)
- Restage with PET/CT<sup>m</sup>
- CR<sup>n</sup>
- Observe or IFRT<sup>k</sup>
- See Follow-up (page 1031)

- ABVD x 2 cycles (total 6)
- Restage with PET/CT<sup>m</sup>
- PR or SD<sup>n</sup>
- Observe or IFRT<sup>k</sup>
- See Follow-up (page 1031)

- ABVD x 2 cycles (total 6)
- Restage with PET/CT<sup>m</sup>
- PD<sup>n</sup>
- Observe or IFRT<sup>k</sup>
- See Progressive Disease (page 1032)

- ABVD x 2 cycles (total 6)
- Restage with PET/CT<sup>m</sup>
- Negative
- Biopsy<sup>p</sup>
- PD<sup>n</sup>
- Biopsy<sup>p</sup>
- See Progressive Disease (page 1032)

- ABVD x 2 cycles (total 6)
- Restage with PET/CT<sup>m</sup>
- Positive
- Biopsy<sup>p</sup>
- PD<sup>n</sup>
- Biopsy<sup>p</sup>
- See Progressive Disease (page 1032)

<sup>d</sup>Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

<sup>e</sup>NCCN unfavorable factors for stage I-II disease include bulky mediastinal or > 10-cm disease, B symptoms, ESR > 50, > 3 sites of disease (see Examples of Unfavorable Factors for Stage I-II Hodgkin Disease, page 1033).

<sup>f</sup>Individualized treatment may be necessary for older patients and patients with concomitant disease.

<sup>g</sup>See Principles of Systemic Therapy (page 1034).

<sup>h</sup>See Principles of Radiation Therapy (page 1035).

<sup>i</sup>An integrated PET/CT or a PET with a diagnostic CT is recommended.

<sup>j</sup>See Revised Response Criteria for Lymphoma (page 1036).

<sup>k</sup>Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.

<sup>l</sup>The value of interim PET scan after 2-4 cycles is unclear but may have a role in management and prognosis.
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma

PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Stage III-IV</th>
<th>ABVD i x 2-4 cycles</th>
<th>Restage with PET/CT m</th>
<th>PR n or SD n</th>
<th>CR n</th>
<th>ABVD x 2-4 cycles (total 6)</th>
<th>Repeat PFTs after 4 total cycles</th>
<th>Observe or RT k/h to initial bulky or PET-positive sites (especially for initial bulky disease) u</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABVD x 2-4 cycles (total 6)</td>
<td>Repeat PFTs after 4 total cycles</td>
<td>Observe or RT k/h to initial bulky or PET-positive sites (especially for initial bulky disease) u</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>ABVD x 2-4 cycles (total 6)</td>
<td>Repeat PFTs after 4 total cycles</td>
<td>Observe or RT k/h to initial bulky disease u</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>ABVD x 2-4 cycles (total 6)</td>
<td>Repeat PFTs after 4 total cycles</td>
<td>Observe or RT k/h to initial bulky disease u</td>
</tr>
<tr>
<td></td>
<td>Biopsy p</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>ABVD x 2-4 cycles (total 6)</td>
<td>Repeat PFTs after 4 total cycles</td>
<td>Observe or RT k/h to initial bulky disease u</td>
</tr>
<tr>
<td></td>
<td>PD n</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>Biopsy p</td>
<td>or</td>
<td>Biopsy p</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>PD n</td>
<td>or</td>
<td>PD n</td>
</tr>
<tr>
<td></td>
<td>See Progressive Disease (page 1032)</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>See Progressive Disease (page 1032)</td>
<td>or</td>
<td>See Progressive Disease (page 1032)</td>
</tr>
<tr>
<td></td>
<td>See page 1026</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>See page 1026</td>
<td>or</td>
<td>See page 1026</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>See facing page</td>
<td>or</td>
<td>See facing page</td>
</tr>
</tbody>
</table>

- Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.
- Individualized treatment may be necessary for older patients and patients with concomitant disease.
- See Principles of Systemic Therapy (page 1034).
- See Principles of Radiation Therapy (page 1035).
- An integrated PET/CT or a PET with a diagnostic CT is recommended.
- See Revised Response Criteria for Lymphoma (page 1036).
- Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.
- See International Prognostic Score (IPS; page 1033).
- If initial bulky mediastinal disease is seen on CT, consolidative RT to the mediastinum is recommended after completion of chemotherapy.
**Hodgkin Lymphoma Version 2:2011**

**CLINICAL PRESENTATION:**
Classical Hodgkin lymphoma
Stage III-IV

**PRIMARY TREATMENT**
(continued from opposite page)

- **Es escalated BEACOPP**\(\times 4\) cycles (selected cases if IPS \(\geq 4\))
  - Restage with PET/CT\(^{m}\)
  - 4 cycles of baseline BEACOPP
  - CR\(^{n}\) or SD\(^{n}\)
  - CR\(^{n}\) to initial sites > 5 cm
  - Observe
  - See Follow-up (page 1031)
  - Negative
  - See Follow-up (page 1031)
  - Positive
  - See Progressive Disease or Relapse (page 1032)

- **PD\(^{n}\)**
  - Biopsy\(^{p}\)
  - See Progressive Disease (page 1032)

---

\(^{a}\)Classical Hodgkin lymphomas include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich.

\(^{b}\)Individualized treatment may be necessary for older patients and patients with concomitant disease.

\(^{c}\)See Principles of Systemic Therapy (page 1034).

\(^{d}\)See Principles of Radiation Therapy (page 1035).

\(^{e}\)An integrated PET/CT or a PET with a diagnostic CT is recommended.

\(^{f}\)See Revised Response Criteria for Lymphoma (page 1036).

\(^{g}\)Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.

\(^{h}\)See International Prognostic Score (IPS; page 1033).
Hodgkin Lymphoma Version 2:2011

Clinical presentation: Lymphocyte-predominant Hodgkin lymphoma

Primary treatment:

- CS IA, IIA: IFRT
- CS IB, IIB: Chemotherapy ± IFRT or Rituximab ± chemotherapy ± IFRT
- CS IIIA, IVA: Chemotherapy ± RT or Observation (category 2B) or Local RT (palliation only) or Rituximab ± chemotherapy
- CS IIIB, IVB: Chemotherapy ± RT or Rituximab ± chemotherapy ± RT

CR

- Observe
- Restage
- < CR

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 therapy.
- Follow-up with an oncologist is recommended, especially during the first 5 y interval to detect recurrence, then annually because of risk of late complications, including second cancers and cardiovascular disease. Late relapse or transformation to large cell lymphoma may occur in LPHL.
- The frequency and types of tests may vary depending on clinical circumstances, such as age and stage at diagnosis, social habits, and treatment modality. Few data support specific recommendations; these represent the range of practice at NCCN Member Institutions.

Interim H&P:
- Every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
- Annual influenza vaccine
- Laboratory studies:
  - CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
  - Thyroid-stimulating hormone (TSH) at least annually if RT to neck
- Chest imaging:
  - Chest radiograph or CT every 6-12 mo during first 2-5 y
- Pneumococcal, m revaccination after 5 y, if patient treated with splenic RT or previous splenectomy
- Annual influenza vaccine
- Annual blood pressure, aggressive management of cardiovascular risk factors
- Baseline stress test/echocardiogram at 10 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,
- Cardiovascular symptoms may emerge at a young age.
- Treatment summary and consideration of transfer to primary care practitioner.

Monitoring for late effects after 5 years:

- Abdominal/pelvic CT (category 2B):
  - Every 6-12 mo for first 2-3 y
- Surveillance PET should not be performed routinely because of risk for false-positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.
- Annual breast screening:
  - Initiate 8-10 y posttherapy, 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,
- End-of-treatment discussion.

*Note:
- LPHL has a different natural history and response to therapy compared with classical Hodgkin lymphoma, especially stages I-II. Therefore, separate guidelines are presented for LPHL.
- See Revised Response Criteria for Lymphoma (page 1036).
- See Principles of Systemic Therapy (page 1034).
- See Principles of Radiation Therapy (page 1035).
Hodgkin Lymphoma Version 2:2011

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 therapy.
• Follow-up with an oncologist is recommended, especially during the first 5-y interval to detect recurrence, then annually because of risk of late complications, including second cancers and cardiovascular disease. Late relapse or transformation to large cell lymphoma may occur in LPHL.
• The frequency and types of tests may vary depending on clinical circumstances, such as age and stage at diagnosis, social habits, and treatment modality. Few data support specific recommendations; these represent the range of practice at NCCN Member Institutions.

Follow-Up After Completion of Treatment

• Interim H&P: Every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
  • Annual influenza vaccine
• Laboratory studies:
  > CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
  > Thyroid-stimulating hormone (TSH) at least annually if RT to neck
• Chest imaging:
  > Chest radiograph 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 performed routinely because of risk for false-positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.
  
Monitoring for Late Effects After 5 Years

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

---


*x Appropriate medical management should be instituted for any abnormalities.

y Chest imaging optional after 5 y if patient treated with a nonalkylating agent, no RT to the chest, and no other risk factors are present.
**CLASSICAL HODGKIN LYMPHOMA**

Progressive disease

- Negative → Observation
- Positive
  - Restaging (same as initial workup, including bone marrow biopsy)
  - Consider marrow cytogenetics for MDS markers before transplant

Suspected relapse → Re-biopsy

Individualized treatment is recommended, options include:

- RT
- Salvage chemotherapy ± RT
- HDT/ASCR ± RT

**SECOND-LINE THERAPY**

If initial stage was IA-IIA:
- No prior RT and failure in initial sites only
- HDT/ASCR (category 1) ± RT or Salvage chemotherapy ± RT
- Treat as primary advanced stage Hodgkin lymphoma (See page 1028)

If primary therapy was chemotherapy alone or combination chemotherapy/RT

- If primary therapy was RT alone

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCIC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50 y</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Histology MC or LD</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ESR and B symptoms &gt; 50 if A; &gt; 30 if B sx</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal mass &gt; 10 cm</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td># Nodal sites &gt; 3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bulky &gt; 10 cm</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LD, lymphocyte-depleted; MC, mixed cellularity; 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); NCIC, National Cancer Institute, Canada; Sx, symptoms.

*See Principles of Radiation Therapy (page 1035).
*Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.
*Clinical circumstances may warrant additional treatment even in the presence of a negative biopsy.
*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.
*No data support a superior outcome with any modalities.

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

See Principles of Second-Line Chemotherapy (page 1037).

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

Biopsy to confirm relapse, especially if plan to treat with high-dose therapy.

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

For select patients with a long disease-free interval and other favorable features; selection of chemotherapy should be individualized.
Hodgkin Lymphoma Version 2:2011

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCIC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 50</td>
<td>≥ 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>MC or LD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms</td>
<td>&gt; 50 if A; &gt; 30 if B sx</td>
<td>&gt; 50 if A; &gt; 30 if B sx</td>
<td>&gt; 50 or any B sx</td>
<td>&gt; 50 or any B sx</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33 or &gt; 10 cm</td>
<td>MMR &gt; .33</td>
</tr>
<tr>
<td># Nodal sites</td>
<td>&gt; 2</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>E lesion</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td></td>
<td>&gt; 10 cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LD, lymphocyte-depleted; MC, mixed cellularity; 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; NCIC, National Cancer Institute, Canada; Sx, symptoms.

International Prognostic Score (IPS)

1 point per factor (advanced disease)

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 y
- Stage IV disease
- Leukocytosis (WBC count ≥ 15,000/mm³)
- Lymphocytopenia (lymphocyte count < 8% of WBC count, and/or lymphocyte count < 600/mm³)

PRINCIPLES OF SYSTEMIC THERAPY

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

Regimens and References
• ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± RT
  • Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone)
  • BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)

Lymphocyte-Predominant Hodgkin Lymphoma
• The most common chemotherapies used at NCCN Member Institutions for LPHL include:
  • ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± rituximab
  • CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) ± rituximab
  • CVP (cyclophosphamide, vincristine, and prednisone) ± rituximab
  • EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) ± rituximab
  • Single-agent rituximab

See Principles of Second-line Chemotherapy, page 1037

1Ongoing 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.
PRINCIPLES OF RADIATION THERAPY

COMBINED MODALITY-RT DOSES:
- Nonbulky disease (stage I-II): 20-30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)
- Nonbulky disease (stage IB-IIIB) and bulky and nonbulky disease (stage III-IV): 30-36 Gy (if treated with BEACOPP)
- Bulky disease sites (all stages): 30-36 Gy (if treated with ABVD), 36 Gy (if treated with Stanford V)

RT-ALONE DOSES (uncommon, except for LPHL):
- Involved regions: 30-36 Gy (the dose of 30 Gy is mainly used for LPHL)
- Uninvolved regions: 25-30 Gy

RADIATION FIELDS

- When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.
- Consider oophoropexy to preserve ovarian function in premenopausal women.
  - Involved-field: involved lymphoid region(s) only, modified as above

\[^1\text{A dose of 20 Gy after ABVD x 2 is sufficient if the patient has nonbulky stage I-IIA disease with an ESR < 50, no extralymphatic lesions, and only 1 or 2 lymph node regions involved.}\]
### REVISED RESPONSE CRITERIA FOR HODGKIN 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>FDG-avid or PET-positive before 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>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 before therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR, or progressive disease</td>
<td>FDG-avid or PET-positive before therapy; PET-positive at prior sites of disease and no new sites on CT or PET</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Relapsed disease or progressive disease

| 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 before therapy | > 50% increase from nadir in the SPD of any previous lesions | New or recurrent involvement |

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; SPD, sum of the product of the diameters.

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY

- 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/1,2 (ifosfamide, carboplatin, and etoposide)
  - C-MOPP/3,4 (cyclophosphamide, vincristine, procarbazine, and prednisone)
  - CHVP/5 (Chlorambucil, vinblastine, procarbazine, and prednisone)
  - DHAP/6 (dexamethasone, cisplatin, and high-dose cytarabine)
  - ESHAP/7-9 (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin)
  - GVD/10 (gemcitabine, vinorelbine, and liposomal doxorubicin)
  - IGEV/11 (ifosfamide, gemcitabine, and vinorelbine)
  - Mini-BEAM/12-15 (carmustine, cytarabine, etoposide, and melphalan)
  - MINE/14 (etoposide, ifosfamide, mesna, and mitoxantrone)
  - VIM-D/16 (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. 17-19 However, patients tend to have an improved outcome when transplanted in a minimal disease state. 20 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.


Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1]). Each stage (I–IV) is subdivided into A and B categories. “A” indicates that no systemic symptoms are present, and “B” is assigned to patients with unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.2 Patients with HL are usually classified into 3 groups: early-stage favorable (stage I–II with no unfavorable factors), early-stage unfavorable (stage I–II with any unfavorable factors, such as large mediastinal adenopathy, B symptoms; numerous sites of disease; or significantly elevated erythrocyte sedimentation rate [ESR]), and advanced-stage disease (stage III–IV).

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

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

In addition to these unfavorable factors for stage I to II disease, an international collaborative effort evaluating more than 5000 cases of advanced (stage III–IV) HL identified 7 adverse prognostic factors, each of which reduced survival rates by 7% to 8% per year9:

- Age ≥ 45 years
- Male gender
- Stage IV disease
- Albumin level < 4 g/dL
- Hemoglobin level < 10.5 g/dL
- Leucocytosis (WBC count > 15,000/mm³)
- Lymphocytopenia (lymphocyte count < 8% of the white blood count and/or lymphocyte count < 600/mm³)

The number of unfavorable factors (International Prognostic Score [IPS]) helps to determine clinical management and predict prognosis for patients with stage III to IV disease. 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 this.

The International Working Group (IWG) published guidelines for lymphoma response criteria in 1999.10 These criteria are based on the size reduction of enlarged lymph nodes as measured on CT scan, and the extent of bone marrow involvement determined using bone marrow aspirate and biopsy. The original response criteria included complete response uncertain (CRU), 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 PET scans in the definition of response for lymphoma. 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 generally insufficient for initial diagnosis. Although it is widely used to diagnose malignant neoplasms, its role in diagnosing lymphoma is still controversial. 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 most cases and are usually negative for CD3 and CD45. CD20 may be detectable in fewer than 40% of the cases. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended. LPHL cells are usually CD45+ and CD20+, do not express CD15, and rarely express CD30. In addition, LPHL cells also express epithelial membrane antigen, which is usually not present in CHL. For LPHL, the guidelines recommend staining for CD3, CD15, CD20, CD21, CD30, and CD57. An expanded panel of markers may be required, especially for equivocal diagnosis.

**Workup**

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

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

The NCCN Guidelines recommend fertility preservation (sperm cryopreservation in men; ovarian tissue or oocyte cryopreservation in women) before the initiation of chemotherapy with alkylating agents or pelvic radiotherapy. 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, are recommended for patients receiving bleomycin-based chemotherapy. H-flu, pneumococcal, and meningococcal vaccines are recommended if splenic radiotherapy is contemplated.

PET/CT (hereafter referred to as “PET”) scanning has been used for initial staging, restaging, and follow-up of patients with lymphoma. 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 most cases and are usually negative for CD3 and CD45. CD20 may be detectable in fewer 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.

In prospective studies, the PET scan after 2 cycles of standard ABVD chemotherapy was a strong and independent prognostic factor of progression-free survival in patients with advanced-stage disease. The 2-year progression-free survival was significantly better for patients with negative PET after 2 cycles of ABVD than those with positive PET (95% vs. 13%). Advani et al. 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. Markova et al. recently reported that PET scan after 4 cycles of BEACOPP chemotherapy is predictive of treatment outcome in patients with advanced-stage disease. At a median follow-up of 25 months, 2 of 14 patients with
a positive PET after 4 cycles had experienced progression or relapse, whereas no patients with a negative PET experienced progression or relapse. Dann et al.29 from an Israeli Study group reported on the usefulness of interim PET/CT scan after 2 cycles of BEACOPP therapy in standard- and high-risk patients. Relapse or progression occurred in 27% of patients with a positive PET/CT compared with 2.3% of patients with a negative PET/CT. The role of PET in posttherapy surveillance remains controversial, and further studies are needed to determine its role.

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

The NCCN PET/CT Task Force recommends using PET scans for initial staging of patients with lymphomas, including HL, and evaluating residual masses at the end of treatment.31 The panel recommends using PET scans to define the extent of disease, especially if the CT scan is equivocal. An integrated PET/CT scan plus a diagnostic CT is recommended, although a separate diagnostic CT is not needed if it was part of the integrated PET/CT scan. However, caution should always be taken and common sense used in applying PET findings to patient management. For example, PET scans are often positive in sites of infection or inflammation, even in the absence of HL. In cases of PET positivity outside of the disease already identified, or if the PET-positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended. PET scans should not be used for routine surveillance because of the risk for false-positives.

Principles of Radiation Therapy
Involved-field radiation therapy (IFRT) refers to treatment of the involved lymphoid regions only. The NCCN Guidelines Panel recommends that high cervical regions in all patients and axillae in women be excluded from radiation fields, if those regions are uninvolved. Oophoropexy should be considered to preserve ovarian function in premenopausal women if pelvic radiotherapy is contemplated.

In combined modality therapy, the panel recommends a radiotherapy dose of 30 to 36 Gy when combined with ABVD or 36 Gy with Stanford V for patients with bulky disease (all stages). In patients with stage I to II nonbulky disease, the recommended radiotherapy dose is 20 to 30 Gy after ABVD and 30 Gy after Stanford V. This recommendation is based on experience and practice across NCCN Member Institutions. The recommended radiotherapy dose with BEACOPP is 30 to 36 Gy.

CHL
Patients are divided into the following groups after initial diagnosis and workup:
- Stage I–II
- Stage III–IV

Patients with stage I to II CHL are further classified into the following subgroups depending on the presence or absence of unfavorable factors:
- Stage IA–IIB (favorable)
- Stage I–II (unfavorable with bulky disease)
- Stage I–II (unfavorable with nonbulky disease)

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

The ABVD regimen was first introduced by Santoro et al.36 as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia. 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. Radiotherapy is an integral part of the Stanford V regimen. Although the regimen is dose-intensive, the cumulative doses of these drugs are significantly less than those in MOPP, ABVD, alternating MOPP/ABVD, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.

The ground-breaking study to show the value of combined modality therapy with ABVD and limited radiation was the trial reported by Bonadonna et al. Patients with stage I to II disease were treated with 4 cycles of ABVD and were then randomized to treatment with IFRT or extended field radiotherapy (EFRT). No difference was seen in outcome between the radiation arms.

The HD8 trial from the GHSG is the largest that investigated the efficacy of IFRT versus EFRT in early-stage unfavorable HL. This trial randomized 1204 patients to undergo 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone] plus ABVD) followed by EFRT or IFRT. At 5 years of follow-up, freedom from treatment failure (85.8% for EFRT and 84.2% for IFRT) and overall survival (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 GHSG HD10 trial investigated reduction in the number of ABVD cycles and the IFRT dose in patients with stage I to II disease with no risk factors. Patients were not eligible if they had 3 or more sites of disease, any E-lesions, bulky mediastinal adenopathy, ESR greater than 50, or ESR greater than 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to 1 of the 4 treatment groups: 4 cycles of ABVD followed by 30 or 20 Gy of IFRT; 2 cycles of ABVD followed by 30 or 20 Gy of IFRT. The final analysis of this trial showed (with a median follow-up of 79–91 months) no significant differences between 4 and 2 cycles of ABVD in terms of 5-year overall survival (97.1% vs. 96.6%), freedom from treatment failure (93.0% vs. 91.1%), and progression-free survival rates (93.5% vs. 91.2%). With respect to the dose of IFRT, the overall survival (97.7% vs. 97.5%), freedom from treatment failure (93.4% vs. 92.9%), and progression-free survival rates (93.7% vs. 93.2%) were also not significantly different between 30 and 20 Gy of IFRT. More importantly, no significant differences were seen in overall survival, progression-free survival, and freedom from treatment failure rates among the 4 treatment arms. Results from the HD10 trial confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment for patients with a very favorable presentation of early-stage disease with no risk factors, thereby minimizing the risk of late effects.

Studies conducted by the Stanford Group showed that the Stanford V regimen with IFRT was also effective in treating early-stage favorable or unfavorable disease. In the G4 study, 87 patients with nonbulky stage IA or IIA disease received 8 weeks (2 cycles) of Stanford V plus 30 Gy of IFRT, and 61 patients with bulky stage I to 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 to II nonbulky disease and 92% for those with stage I to II bulky disease. Post-treatment conceptions occurred in 25% of patients. Advani et al. recently reported the updated results for the 87 patients with nonbulky stage IA or IIA disease treated in the G4 study. Among the 87 patients, unfavorable risk factors according to GHSG criteria (>2 nodal sites, ESR >50, or extranodal involvement) were present in 47 patients (54%). At a median follow-up of 9 years, freedom from progression and overall survival rates were 94% and 96%, respectively. Freedom from progression was 100% for patients with favorable disease and 89% for those with unfavorable nonbulky disease with no differences in overall survival (96.9% vs. 95.7%). No secondary acute myeloid leukemia or late cardiac or pulmonary toxicities have been observed. The updated results confirm that Stanford V chemotherapy (8 weeks; 2 cycles) with IFRT (30 Gy) is a safe and highly effective regimen for patients with unfavorable stage I to II disease without bulky or symptomatic disease.

In a randomized Italian study comparing a modified Stanford V regimen with MOPP/EBV (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) and ABVD in intermediate- and advanced-stage HL, ABVD and MOPP/EBV were superior to the Stanford V regimen in response rate, failure-free survival, and...
Hodgkin Lymphoma

progression-free survival. 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 radiotherapy protocol for the Stanford V arm were substantial, including limitation of the number of sites irradiated (no more than 2) and a different definition of bulky disease.

Other investigators have confirmed that when radiotherapy is administered according to Stanford guidelines, the Stanford V regimen is highly effective for locally extensive and advanced HL, with a low toxicity profile. In the Memorial Sloan-Kettering Cancer Center (MSKCC) study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36 Gy of IFRT to bulky sites (≥ 5 cm) and/or to macroscopic splenic disease. The 5- and 7-year overall survival rates were 90% and 88%, respectively. Among the patients for whom the Stanford V regimen failed, 58% underwent successful second-line therapy with high-dose therapy and autologous stem cell rescue (HDT/ASCR). Aversa et al from another Italian study group also reported similar findings in patients with bulky or advanced disease. The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (ISRCTN 64141244) compared Stanford V and ABVD in patients with stage IIIB, III, or IV disease or stage I to IIA disease with bulky disease or other adverse features. Radiotherapy was administered in both arms to sites of previous bulky sites (≥ 5 cm) and to splenic deposits. 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, no difference was seen in the projected 5-year progression-free and overall survival rates (76% and 90%, respectively, for ABVD; 74% and 92%, respectively, for Stanford V).

The recently completed phase III Intergroup trial (E2496) compared the Stanford V regimen with ABVD plus radiotherapy for the management of patients with stage I to IIA/B and bulky mediastinal disease and those with stage III to IV disease. In this study, 812 patients were randomized to ABVD (6–8 cycles) plus 36 Gy of radiotherapy (only for patients with bulky mediastinal disease) or Stanford V (12 weeks) plus 36 Gy of radiotherapy (for sites > 5 cm or for macroscopic splenic disease). With a median follow-up of 5 years, no difference was seen in response rates between the arms (72% complete response, 7.7% partial response, and 7.9% stable disease for ABVD; 69% complete response, 7% partial response, and 10% stable disease for Stanford V). Toxicity was also similar in the groups. No significant differences were seen in either failure-free or overall survival between the treatment groups. The 5-year failure-free and overall survival rates were 73% and 88%, respectively, for ABVD, and 71% and 87%, respectively, for Stanford V. In a subset analysis of patients with stage I to II bulky mediastinal disease, the overall response rate was 82% for ABVD and 86% for Stanford V. At a median follow-up of 5.5 years, no significant differences were seen between ABVD and Stanford V in either failure-free survival rates (85% vs. 77%; P = .13) or overall survival rates (95% vs. 92%; P = .31). ABVD (6–8 cycles) plus 36 Gy of radiotherapy remains the standard of care for patients with bulky stage I to II and stage III to IV disease. Stanford V, when given as described with radiotherapy, remains an acceptable alternative for some patients.

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

Chemotherapy alone has also been investigated as a treatment option for patients with early-stage nonbulky disease (stage I–II or IIIA). In the multicenter study conducted by the NCIC Clinical
Trials Group and ECOG, patients with stage IA or IIA HL were randomized to receive ABVD (4–6 cycles) or subtotal lymphoid radiation therapy (STLI). \(^{52}\) In patients assigned to radiotherapy, those with any of the adverse prognostic factors (high ESR or ≥ 4 nodal sites) were treated with 2 cycles of ABVD before radiotherapy. At a median follow-up of 4.2 years, patients assigned to ABVD plus radiotherapy or radiotherapy alone had better freedom from progression (93% vs. 87%, respectively) and event-free survival rates (88% vs. 86%, respectively) than those treated with ABVD alone, with no significant difference in overall survival rates (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 radiotherapy (95% vs. 88%), but no differences were seen in 5-year overall or event-free survival rates. In the MSKCC study, no significant differences were seen in complete response duration (91% vs. 87%, respectively), freedom from progression (86% vs. 81%, respectively), and overall survival (97% vs. 90%, respectively; \(P = .08\)) among patients treated with ABVD plus radiation and those treated with ABVD alone. \(^{34}\)

In a recent retrospective study, Canellos et al. \(^{35}\) reported that 6 cycles of ABVD is an effective and safe treatment for selected patients with limited-stage, nonbulky disease. Most patients (69%) had stage IIA disease; 13% had stage IA and 15% had stage IIB disease. Of 75 patients, 55 (76%) received 6 cycles of ABVD; 2 patients (2.6%) received 4 cycles of ABVD. In 16 (21%) of 75 patients, bleomycin was discontinued after a median of 4 cycles because of concern for pulmonary dysfunction. All patients included in this series experienced a clinical complete remission with chemotherapy alone. The failure-free survival 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 to II nonbulky disease, especially if they experience prompt and complete response to the first 2 cycles of ABVD (as documented with CT scan), to avoid the long-term risks of radiotherapy.

**NCCN Recommendations**

**Stage IA to IIA (Favorable Disease):** Combined modality therapy (ABVD plus 20–30 Gy of IFRT or Stanford V chemotherapy plus 30 Gy of IFRT) is the preferred treatment (category 1) for patients with favorable disease. The panel has also included ABVD alone as an alternative treatment option with a category 2B recommendation. \(^{52,54,55}\) Highly selected patients who are unable to tolerate chemotherapy because of the presence of comorbidities may be treated with radiotherapy alone (category 1 recommendation for STLI and category 2A for mantle field irradiation).

In combined modality therapy, ABVD is generally administered for 2 to 4 cycles with 30 Gy of IFRT (involved lymphoid regions only) and Stanford V regimen is administered for 8 weeks (2 cycles) with 30 Gy IFRT. Consolidative radiotherapy is optimally instituted within 3 weeks. In patients who fulfill the criteria for favorable disease (ESR < 50, no extralymphatic lesions, and only 1 or 2 lymph node regions involved), 2 cycles of ABVD followed by 20 Gy IFRT may be sufficient. \(^{46}\) Restaging occurs at the completion of chemotherapy. Completion of IFRT is recommended for all patients who have experienced a complete or partial response. Alternatively, patients experiencing a partial response can undergo biopsy before receiving IFRT. After completion of IFRT, no further treatment is necessary for patients with complete response, whereas further restaging is required for patients with a partial response. Histologic confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Follow-up is recommended for patients with a negative PET scan at the completion of therapy, and those with positive PET scans are treated as described for progressive disease. All patients with stable (PET-positive) or progressive disease are managed as described for progressive disease. Biopsy is recommended strongly before initiating treatment for progressive disease.

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

**Stage I to II (Unfavorable Disease):** For patients with unfavorable bulky disease the panel recommends chemotherapy (ABVD or Stanford V) followed by IFRT. ABVD is initially administered for 2 cycles followed by restaging. PFTs should be repeated after 2 cycles. If a complete response occurs, 2 to 4 additional cycles (total of 4 or 6) are administered followed by IFRT (30–36 Gy). Patients with partial response or stable disease are treated with 2 additional cycles (total of 4) followed by restaging. If a complete or partial response occurs, 2 additional cycles (total of 6) are administered followed by consolidative IFRT for patients with a complete response. Patients with a partial response are restaged at the completion of chemotherapy. Consolidative IFRT is recommended if they have experienced a complete response. Patients with a partial response or stable disease (after 6 cycles) are treated with IFRT (30–36 Gy) followed by end-of-treatment restaging. Histologic confirmation with biopsy is recommended for those who are PET-positive after additional treatment. Additional treatment may be warranted under certain clinical circumstances even in the case of a negative biopsy. All patients with residual disease on PET scan and biopsy and those with progressive disease are managed as described for progressive disease. Biopsy is recommended before initiating treatment for progressive disease. Patients with stage I to II unfavorable nonbulky disease are managed in the same manner as described earlier. The guidelines have included observation as an option for patients experiencing complete response after a total of 6 cycles of ABVD.

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

**Stage III to IV (Advanced Disease)**

Although chemotherapy is always used for patients with advanced-stage HL, combined modality therapy is an effective treatment for patients with large mediastinal masses. MOPP was the first successful regimen for HL, with a response rate of 84% and a 86% disease-free survival (DFS) of more than 10 years from end of treatment. 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 CALGB showed that ABVD alone or alternating with MOPP was superior to MOPP alone in progression-free survival and 5-year overall survival. 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. The rates of complete remission (76% vs. 80%), 5-year failure-free survival (63% vs. 66%), and overall survival (82% vs. 81%) were similar for ABVD and MOPP/ABV, respectively. However, MOPP/ABV was associated with acute pulmonary and hematologic toxicity, myelodysplastic syndromes, and leukemia.

Another randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) also confirmed that no significant difference in event-free
and overall survivals occurred 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.\textsuperscript{61} Updated results with a median follow-up of 83 months were consistent with the early results.\textsuperscript{62}

ABVD has since been the standard treatment for patients with advanced-stage HL. Stanford V and BEACOPP are the other 2 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 the Stanford V regimen plus 36 Gy of radiotherapy 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 overall survival rates were 95\%.\textsuperscript{43} No instances of secondary myelodysplasia or leukemia occurred. Fertility was maintained, with 72 posttreatment conceptions. Similar outcomes were reported in other studies for patients with advanced-stage HL treated with the Stanford V regimen.\textsuperscript{45-47} The recently completed phase III Intergroup trial (E2496) showed no significant difference between ABVD and Stanford V in response rates, failure-free survival, overall survival, and toxicity in patients with stage III to IV disease.\textsuperscript{48}

The BEACOPP regimen was developed by the GHSG to improve treatment results through dose escalation and time intensification.\textsuperscript{63} In a phase III randomized trial (HD9), patients with stage IIB and IIIA disease with risk factors or stage IIB 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.\textsuperscript{54} Each regimen was followed by radiotherapy to initial sites of disease greater than 5 cm. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and overall survival 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 overall survival rates (86\%, 80\%, and 75\%, respectively).\textsuperscript{65} These results confirm the efficiency of dose-escalated BEACOPP for patients with advanced-stage HL who have risk factors.

The standard- and escalated-dose BEACOPP has also been evaluated in another randomized trial (HD2000) by the Italian Lymphoma Study Group. In this study, 307 patients with advanced disease (stage IIB, III, and IV) were randomly assigned to receive 6 courses of ABVD, 4 escalated plus 2 standard courses of BEACOPP, or 6 courses of COPPEBVCAD (CEC; cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin), plus a limited radiation therapy program.\textsuperscript{66} After a median follow-up of 41 months, BEACOPP was associated with a superior PFS with a significant reduction in the risk of progression. No differences were observed between BEACOPP and CEC or CEC and ABVD. The 5-year progression-free survival rates were 68\%, 81\%, and 78\% for ABVD, BEACOPP, and CEC, respectively. BEACOPP and CEC also had higher rates of grade 3 to 4 neutopenia 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.\textsuperscript{29} Patients with advanced disease (stage I–II bulky with B symptoms and stage III–IV) and IPS of 3 or higher were treated with 2 cycles of escalated BEACOPP, and all others underwent 2 cycles of standard-dose BEACOPP followed by restaging. Those with a positive PET scan received 4 additional cycles of escalated-dose BEACOPP, whereas 4 cycles of standard-dose BEACOPP were given to patients with a negative PET scan. The complete remission, 5-year event-free survival, and overall survival rates were 97\%, 85\%, and 90\%, respectively. Event-free and overall survival rates were similar in both risk groups.

Two recent European trials evaluated the role of HDT/ASCR as a consolidative therapy for patients with advanced-stage and unfavorable HL that responded to initial chemotherapy.\textsuperscript{67,68} Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after an 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 radiotherapy in patients with stage III to IV HL who completed chemotherapy.\textsuperscript{52,69–71} The EORTC 20884 trial is the only randomized trial that assessed the role of consolidation radiotherapy after MOPP/ABV chemotherapy in patients with advanced disease.\textsuperscript{69,70} 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 with a partial response received IFRT to involved nodal areas and extranodal sites. The 8-year overall and event-free survival 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 a partial response after chemotherapy. In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial), which compared ABVD with 2 other multidrug regimens, IFRT was recommended for patients with an incomplete response to chemotherapy or bulky disease at presentation.\textsuperscript{62} Progression-free survival was superior for patients who received radiotherapy (5-year progression-free survival was 71% without radiotherapy and 86% with radiotherapy) and a similar advantage was also seen for overall survival. The SWOG multicenter study showed no improvement in overall survival rates for patients who underwent low-dose IFRT after MOP–BAP (mechlorethamine, vincristine, and prednisone plus bleomycin, doxorubicin, and procarbazine), but the remission duration was prolonged in several subgroups, especially patients with bulky nodular sclerosis.\textsuperscript{71}

In contrast, Laskar et al.\textsuperscript{72} reported a survival advantage for consolidative radiotherapy in patients experiencing a complete response after initial chemotherapy, particularly in patients younger than 15 years. However, this study included patients with a different distribution of histologic subtypes of HL compared with those included in Western studies, and most had early-stage HL.

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

**NCCN Recommendations**

ABVD or Stanford V is recommended for primary treatment for patients with advanced disease. Escalated-dose BEACOPP (4 cycles) should be considered for high-risk patients with an IPS score of 4 or more. ABVD is initially administered for 2 to 4 cycles followed by restaging. PFTs should be repeated after 4 cycles. Patients with a complete response, partial response, or stable disease are treated with additional 2 to 4 cycles (total of 6). Patients with a partial response or stable disease are restaged at the completion of therapy. No further treatment is necessary for patients with a complete response after a total of 6 cycles. Consolidative radiotherapy to the mediastinum or residual PET-positive sites is recommended, especially if bulky mediastinal disease was present initially. Patients with a partial response or stable disease after 6 cycles can be treated with IFRT. In the absence of bulky mediastinal disease, observation is an option in selected circumstances when the PET scan findings are equivocal. Histologic confirmation with biopsy is recommended for patients who are PET-positive after additional treatment. Additional treatment may be warranted under certain clinical circumstances even in the case of a negative biop-
sy. In the case of positive biopsy, patients should be managed as described for progressive disease.

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

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

LPHL

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

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

Early-stage favorable LPHL has a better prognosis than CHL and its management is different. Radiotherapy alone or in combination with chemotherapy has been an efficient treatment for patients with stage I to II LPHL.78–85 In a retrospective analysis, Schlembach et al.79 reported favorable 5-year relapse-free (95%) and overall survival rates (100%) for patients with stage IA LPHL treated with IFRT and regional radiotherapy. No evidence of secondary solid tumors was seen even after long-term follow-up (11.6 years for IFRT and 5.5 years for regional radiotherapy). 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 radiotherapy alone, including mantle and total lymphoid irradiation.82 At 15 years, freedom from progression was 84% for patients with stage I disease and 73% for those with stage II disease. Recently, Chen et al.83 reported the long-term outcome of 113 patients with LPHL treated at the author’s institution with a median follow-up of 136 months; 93 patients received radiotherapy alone, 13 received radiotherapy with chemotherapy, and 7 received chemotherapy alone. The 10-year progression-free survival rates were 85% and 61%, and the overall survival rates were 94% and 97% for stages I and II, respectively. The addition of chemotherapy to radiotherapy did not improve progression-free or overall survival compared with radiotherapy alone, and 6 of 7 patients who received chemotherapy alone developed early disease progression.

The GHSG compared EFRT, IFRT, and combined modality treatment in patients with stage IA LPHL.78 Median follow-up was 78 months for EFRT, 40 months for combined modality, and 17 months for IFRT. Complete remissions were observed in 98%
of patients 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 HD7 trial, a trend was seen toward better 7-year freedom from treatment failure for the combined modality group (96%) compared with the IFRT group (83%). An MD Anderson Cancer Center study also showed that patients with early-stage (I–II) disease treated with radiotherapy alone, or chemotherapy followed by radiotherapy, had similar relapse-free (77% and 68%, respectively) and overall survival rates (90% and 100%, respectively) at 9.3 years. 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 rates were 94% and 62%, respectively, for stage III disease, and 41% and 24%, respectively, for stage IV disease. Most of these patients (80%–95%) were treated with chemotherapy (MOPP- or ABVD-like regimens) with or without radiotherapy.

Because LPHL cells consistently express CD20 antigen, clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody. In a Stanford study, previously treated (n = 10) and untreated (n = 12) patients with stage I to IV LPHL received 4 weekly doses of rituximab at 375 mg/m². The overall response rate was 100% (41% complete response, 54% partial response, and 5% CRu). The estimated probability of progressive disease at 10.2 months was 52%. The protocol was later modified to repeat 4 weekly 375 mg/m² doses at 6-month intervals for 2 years. Median follow-up was 72 months for limited and 30 months for extended treatment. The overall response rate was 97% (69% complete response or CRu, 28% partial response). Among patients undergoing limited treatment with rituximab, 56% experienced complete response or CRu, compared with 88% of those treated with extended rituximab. The estimated freedom from progression at 30 months was 52% for limited rituximab and 88% for extended rituximab. Rituximab was well tolerated, with few adverse side effects. Additional follow-up is needed to assess benefit duration.

The GHSG evaluated rituximab for relapsed or refractory LPHL in a phase II trial. 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 et al. 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). The overall response rate was 100%, with 6 of the 7 patients experiencing a complete response. At a median follow-up of 2 years, the time to progression was 27 months. Collectively, these data suggest that rituximab alone or in combination with chemotherapy has activity in the management of patients with newly diagnosed and those with relapsed LPHL.

**NCCN Recommendations**

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

Without randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for LPHL, although ABVD is often used based on data for CHL. Savage et al. from British Columbia Cancer Agency reported that ABVD chemotherapy with (n = 89) or without (n = 11) radiotherapy was associated with superior outcomes compared to a historical cohort of patients treated with radiotherapy alone for stage IA, IB, or IIA nodular LPHL. With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without radiotherapy had a superior 10-year time to progression (97% vs. 77.5%) and progression-free survival (90% vs. 66.5%) compared with those treated with radiotherapy alone. However, in a review of the combined data from the CALGB and Dana-Farber Cancer Institute trials that included patients with stage III to IV LPHL treated with chemotherapy alone, Canellos and Mauch reported that among 12 patients treated with ABVD or EVA (etoposide,
vinblastine, and doxorubicin), the failure rate was 75%, whereas it was only 32% for the 25 patients treated with alkylating agent–containing regimens (MOPP or MOPP/ABVD).

Some investigators have also reported good response rates with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy with or without rituximab in patients with early-stage or advanced disease.93,94 Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for these patients. The following chemotherapy regimens are most commonly used at NCCN Member Institutions for patients with LPHL; they may be used in conjunction with rituximab, or rituximab may be used as a single agent:
- ABVD
- CHOP
- CVP
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)

Restaging occurs after completion of initial therapy, and then observation is recommended for all patients experiencing a complete response. Although some patients who do not experience a complete response may require additional therapy, some have a chronic indolent course that may not require aggressive retreatment. These asymptomatic patients may be observed or treated with local irradiation. Late relapse or transformation to diffuse large B-cell lymphoma has been reported in patients with LPHL; they may be used in conjunction with rituximab, or rituximab may be used as a single agent:

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, because very few data are available on the follow-up and monitoring of late effects in patients with HL after completion of treatment.98

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

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

Monitoring for Late Effects

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

Secondary Malignancies

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

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

Annual breast screening (mammography or MRI) beginning no later than 8 to 10 years after completion of therapy or at 40 years of age (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation. They should also be encouraged to perform monthly breast self-examination and have a yearly breast examination by a health care professional. The American Cancer Society (ACS) recommends breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age.

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

Hypothyroidism
Abnormal thyroid function, mostly hypothyroidism, is reported in approximately 50% of long-term survivors, especially those who received neck or upper mediastinal irradiation.98 A careful thyroid examination should be part of the physical examination. Thyroid function tests should be performed at least annually to rule out hypothyroidism, especially in patients treated with radiotherapy to the neck.

Myelosuppression
Myelosuppression is the most common side effect of chemotherapy and is associated with increased risk of infections. It is uncommon for myelosuppression to continue for long beyond completion of the primary treatment program. However, patients who undergo autologous or allogeneic hematopoietic cell transplantation as salvage therapy may be at continued risk for infection. Pneumococcal, meningococcal, and H-flu revaccination is recommended every 5 years for patients treated with splenic radiotherapy or splenectomy.

Pulmonary Toxicity
Bleomycin-induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation, and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity. Martin et al.104 reported that BPT significantly decreases the 5-year overall survival rate, especially in patients aged 40 years or older. They also showed that the use of growth factors with chemotherapy significantly increases the incidence of BPT (26% vs. 9%). Recently, 2 separate studies confirmed that ABVD chemotherapy can be safely administered at the full dose intensity without any growth factor support.105,106 Patients who received ABVD with no growth factors had comparable 5-year event-free survival (87.4% vs. 80%, respectively) and overall survival rates (94.1% vs. 91.3%, respectively) to patients who received prophylactic growth factor support with ABVD regimen.10

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 Investigation107 and the GHSG/European Bone Marrow Transplantation Group108 compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvement in
event-free and progression-free survivals and freedom from treatment failure (with no difference in overall survival) in 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 overall survival.

Several investigators have developed prognostic models to predict outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice et al.\textsuperscript{109} from the French cooperative group (GELA) used the end-of-treatment to relapse interval (≤ 12 months) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR. Progression-free survival rates were 93%, 59%, and 43%, respectively, for patients with 0, 1, or 2 of these risk factors. In a prospective study, Moskowitz et al.\textsuperscript{110} identified extranodal sites, complete response duration of less than 1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR. In patients with 0 or 1 factor, 5-year event-free and overall survival rates were 83% and 90%, respectively, which decreased to 10% and 25%, respectively, 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 event-free survival in poorer-risk patients.\textsuperscript{111} In a retrospective analysis of 422 patients with relapsed disease, Josting et al.\textsuperscript{112} from the GHSG identified time to relapse, clinical stage at relapse, and anemia at relapse as independent risk factors to develop a prognostic score that classified patients into 4 subgroups with significantly different freedom from second failure and overall survival. More recently, investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first complete response (< 1 year), detectable disease at transplant, and the presence of more than one extranodal site as adverse factors for overall survival.\textsuperscript{113} Other groups have identified extent of prior chemotherapy,\textsuperscript{114} short time from diagnosis to transplant,\textsuperscript{115} and disease status at transplantation\textsuperscript{116} as significant prognostic factors for overall survival and progression-free survival. Pretransplant functional imaging status has also been identified as an independent predictor of outcome in patients with recurrent/refractory HL.\textsuperscript{117,118}

The main potential of these prognostic factors 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.\textsuperscript{110,119–125} Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),\textsuperscript{126} IGEV (ifosfamide, gemcitabine, and vinorelbine),\textsuperscript{127} and GCD (gemcitabine, carboplatin, and dexamethasone),\textsuperscript{128} have also been effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials. Some studies have suggested that patients experiencing a complete response to second-line therapy before transplant or those with chemosensitive disease to second-line chemotherapy have improved outcomes after HDT/ASCR compared with those with resistant disease.\textsuperscript{129–131}

Although second-line chemotherapy is an appropriate treatment for any patient with relapsed Hodgkin’s disease, regardless of the length of initial remission,\textsuperscript{132} some studies have also suggested that patients with minimal residual disease at relapse may not need conventional-dose chemotherapy before HDT/ASCR.\textsuperscript{133}

**Radiotherapy**

Josting et al.\textsuperscript{134} from the GHSG reported that second-line radiotherapy may be effective in a select subset of patients with relapsed or refractory disease. The 5-year freedom from treatment failure and overall survival rates were 28% and 51%, respectively. B symptoms and stage at disease progression or relapse were identified as significant prognostic factors for overall survival. Moskowitz et al.\textsuperscript{110} showed the efficacy and feasibility of second-line radiotherapy with chemotherapy in patients with relapsed and refractory disease. At a median follow-up of 43 months, the response rate to ICE and IFRT was 88% and the event-free survival rate for patients who underwent HDT/ASCR was 68%.

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

Individualized treatment is recommended for patients with progressive disease. Although further cytoreduction and HDT/ASCR (with radiotherapy if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of radiotherapy or second-line chemotherapy with or without radiotherapy.

Patients with suspected relapse should undergo biopsy and restaging, including bone marrow biopsy. Bone marrow cytogenetics for markers of myelodysplastic syndromes may be considered if ASCR is planned. Management of relapsed disease depends on whether primary treatment was radiotherapy alone, chemotherapy, or combined modality therapy. For patients treated initially with chemotherapy or combined modality therapy, the algorithm is a bit more complicated and therapy is 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 radiotherapy, second-line chemotherapy with or without radiotherapy, or HDT/ASCR with or without radiotherapy. Radiotherapy is recommended when the sites of relapse have not been previously irradiated. In radiation-naïve patients, total lymphoid irradiation may be an appropriate component of HDT/ASCR. For all other patients, the panel recommends HDT/ASCR (category 1) with or without locoregional radiotherapy or second-line chemotherapy with or without radiotherapy, but disease relapse should be confirmed with biopsy.

See Principles of Second-Line Chemotherapy for suggested second-line chemotherapy regimens (page 1037). Conventional-dose second-line chemotherapy may precede high-dose therapy. If minimal residual disease is present, second-line chemotherapy may not be essential before proceeding to HDT/ASCR. In selected patients with long disease-free intervals and other favorable features, salvage chemotherapy alone may be appropriate, with the selection of chemotherapy individualized.

The panel recommends that patients experiencing disease relapse after undergoing primary treatment with radiotherapy alone be treated as described for initial treatment of advanced disease. The extent of stage at relapse (relapse stage) after radiotherapy was the most important prognostic factor for freedom from second relapse.\(^{135}\)

Allogeneic stem cell transplant (SCT) with myeloablative conditioning has been associated with lower relapse rates in patients with relapsed or refractory disease; however, treatment-related mortality was more than 50%. Allogeneic SCT with reduced-intensity conditioning has been reported to have decreased rates of treatment-related mortality.\(^{136,137}\) However, this approach remains investigational. The panel has included allogeneic SCT with a category 3 recommendation for patients with progressive or relapsed disease.

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

Summary

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

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

Combined modality therapy (ABVD or Stanford V and IFRT) is the preferred treatment for patients with stage IA or IIA favorable CHL. The panel has also included ABVD alone as an option with a category 2B recommendation. ABVD or Stanford V followed by consolidative IFRT is recommended for patients with stage I to II unfavorable disease. ABVD or Stanford V is recommended for patients with stage III to IV disease who have bulky mediastinal adenopathy. Escalated BEACOPP is an option for high-risk patients with an IPS score of 4 or more.
LPHL has a different natural history and response to therapy compared with CHL. IFRT alone is the treatment option for patients with stage IA or IIA disease, whereas chemotherapy with or without radiotherapy is recommended for all other patients. In early-phase clinical studies, rituximab has been effective either as a single agent or in combination with chemotherapy for patients with newly diagnosed and those with relapsed LPHL. The NCCN Guidelines have included rituximab either as a single agent or in combination with chemotherapy (with or without radiotherapy) as an option for patients with stage IB or IIB or stage III to IV disease. The role of chemotheraphy or rituximab-based therapy is being explored in ongoing clinical trials for early-stage and advanced-stage LPHL.

HDT/ASCR is the best treatment option for patients with relapsed or refractory disease, although it does not improve overall survival. Conventional-dose second-line chemotherapy with or without radiotherapy may be given before 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.

References

Hodgkin Lymphoma


Hodgkin Lymphoma


84. Feugier P, Laboury E, Djeridane M, et al. Comparison of initial characteristics and long-term outcome of patients with...
Hodgkin Lymphoma


## Individual Disclosures for the NCCN Guidelines Panel for Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
<th>Patent, Equity, or Royalty</th>
<th>Other</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranjana H. Advani, MD</td>
<td>Abbott Laboratories; Genentech, Inc.; Novartis Pharmaceuticals Corporation; Allos Therapeutics, Inc.; and Pharmacyclics, Inc.</td>
<td>Genentech, Inc.; Allos Therapeutics, Inc.; and Seattle Genetics</td>
<td>None</td>
<td>None</td>
<td>3/17/11</td>
</tr>
<tr>
<td>Weiyun Z. Ai, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/26/10</td>
</tr>
<tr>
<td>Richard F. Ambinder, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>12/16/09</td>
</tr>
<tr>
<td>Celeste M. Bello, MD, MSPH</td>
<td>None</td>
<td>Spectrum Pharmaceuticals</td>
<td>None</td>
<td>None</td>
<td>3/30/11</td>
</tr>
<tr>
<td>Philip J. Bierman, MD</td>
<td>Seattle Genetics</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/28/11</td>
</tr>
<tr>
<td>Kristie A. Blum, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Bouthaina Dabaja, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>11/10/10</td>
</tr>
<tr>
<td>Ysabel Duron</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1/13/10</td>
</tr>
<tr>
<td>Andres Forero, MD</td>
<td>Biogen Idec; Daiichi-Sankyo Co.; Eli Lilly and Company; Genentech, Inc.; BioCryst Pharmaceuticals, Inc.; Immunomedics, Inc.; and Seattle Genetics</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5/13/11</td>
</tr>
<tr>
<td>Leo I. Gordon, MD</td>
<td>CureTech Ltd.; Genentech, Inc.; Millennium Pharmaceuticals, Inc.; and Pharmacyclics, Inc.</td>
<td>CureTech Ltd.</td>
<td>None</td>
<td>CureTech Ltd.</td>
<td>7/21/09</td>
</tr>
<tr>
<td>Francisco J. Hernandez-Illizaliturri, MD</td>
<td>None</td>
<td>Amgen Inc.</td>
<td>None</td>
<td>None</td>
<td>6/11/10</td>
</tr>
<tr>
<td>Ephraim P. Hochberg, MD</td>
<td>None</td>
<td>Biogen Idec; and Proventys-NCCN</td>
<td>None</td>
<td>None</td>
<td>9/22/10</td>
</tr>
<tr>
<td>Richard T. Hoppe, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2/22/11</td>
</tr>
<tr>
<td>David G. Maloney, MD, PhD</td>
<td>None</td>
<td>Genentech, Inc.; F. Hoffmann-La Roche, Inc.; and Spectrum Pharmaceuticals, Inc</td>
<td>None</td>
<td>None</td>
<td>11/12/10</td>
</tr>
<tr>
<td>David Mansur, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/10/09</td>
</tr>
<tr>
<td>Peter M. Mauch, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>11/20/09</td>
</tr>
<tr>
<td>Monika Metzger, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/19/10</td>
</tr>
<tr>
<td>Joseph O. Moore, MD</td>
<td>ARIAD Pharmaceuticals, Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation</td>
<td>Amgen Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>1/14/11</td>
</tr>
<tr>
<td>David Morgan, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>12/17/10</td>
</tr>
<tr>
<td>Craig H. Moskowitz, MD</td>
<td>Cephalon, Inc.; Eli Lilly and Company; Genentech, Inc.; and Seattle Genetics</td>
<td>Seattle Genetics</td>
<td>None</td>
<td>None</td>
<td>9/7/10</td>
</tr>
<tr>
<td>Matthew Poppe, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9/17/10</td>
</tr>
<tr>
<td>Barbara Pro, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>8/20/10</td>
</tr>
<tr>
<td>Lawrence Weiss, MD</td>
<td>bioTheranostics, Inc.</td>
<td>Clarient, Inc.; and Pathwork Diagnostics, Inc.</td>
<td>None</td>
<td>None</td>
<td>2/10/11</td>
</tr>
<tr>
<td>Jane N. Winter, MD</td>
<td>Genentech, Inc.</td>
<td>Novartis Pharmaceuticals Corporation</td>
<td>None</td>
<td>None</td>
<td>12/23/09</td>
</tr>
<tr>
<td>Joachim Yahalom, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/21/11</td>
</tr>
</tbody>
</table>

The NCCN guidelines staff have no conflicts to disclose.