Hodgkin Lymphoma
Version 1.2017

Clinical Practice Guidelines in Oncology

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Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged ≥55 years. In 2017, an estimated 8,260 people will be diagnosed with HL in the United States and 1,070 will die of the disease. The WHO classification

Abstract

This portion of the NCCN Guidelines for Hodgkin lymphoma (HL) focuses on the management of classical HL. Current management of classical HL involves initial treatment with chemotherapy or combined modality therapy followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5-point scale). The introduction of less toxic and more effective regimens has significantly advanced HL cure rates. However, long-term follow-up after completion of treatment is essential to determine potential long-term effects.


NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

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Disclosures for the NCCN Hodgkin Lymphoma Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Hodgkin Lymphoma Panel members can be found on page 638. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
divides HL into 2 main types: classical HL (CHL) and nodular lymphocyte-predominant HL (NLPHL). CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed popcorn cells.

The past few decades have seen significant progress in the management of patients with HL; it is now curable in at least 80% of patients. The advent of more effective treatment options has improved the 5-year survival rates that are unmatched in any other cancer over the past 4 decades. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HL discuss the clinical management of patients with CHL and NLPHL, focusing on adult patients aged ≥18 years who do not have serious intercurrent disease.

This portion of the guidelines discusses recommendations outlined in the NCCN guidelines for the management of CHL. For the complete and most updated version of these guidelines, visit NCCN.org.

### Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system. Each stage is subdivided into A and B categories; “A” indicates that no systemic symptoms are present and “B” is assigned to patients with unexplained fevers >38°C, drenching night sweats, or weight loss of >10% of their body weight within 6 months of diagnosis. 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 of the

Text cont. on page 624.
### DIAGNOSIS

<table>
<thead>
<tr>
<th>Essential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- H&amp;P including: B symptoms (unexplained fever &gt;38°C; drenching night sweats; or weight loss &gt;10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examine lymphoid regions, spleen, liver</td>
</tr>
<tr>
<td>- CBC, differential, platelets</td>
</tr>
<tr>
<td>- Erythrocyte sedimentation rate (ESR)</td>
</tr>
<tr>
<td>- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)</td>
</tr>
<tr>
<td>- Pregnancy test for women of childbearing age</td>
</tr>
<tr>
<td>- Diagnostic CT* (contrast enhanced)</td>
</tr>
<tr>
<td>- PET/CT scan** (skull base to mid-thigh)</td>
</tr>
<tr>
<td>- Counseling: Fertility, smoking cessation, psychosocial (See NCCN Guidelines for Supportive Care)</td>
</tr>
</tbody>
</table>

Useful in selected cases:

- Fertility preservation*
- Diagnostic neck CT with contrast, if neck is PET/CT+ or if neck RT contemplated
- Pulmonary function tests (PFTs incl. diffusing capacity [DLCO]) if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV and hepatitis B/C testing (encouraged)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- Adequate bone marrow biopsy if there are cytopenas and negative PET
- Evaluation of ejection fraction if doxorubicin-based chemotherapy is indicated
- MRI or PET/MRI with contrast (skull base to mid-thigh)

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

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### WORKUP

- **Excisional biopsy** (recommended)
- **Core needle biopsy** may be adequate if diagnostic
- Immunohistochemistry evaluation

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### CLINICAL PRESENTATION

- **Classical Hodgkin lymphoma (CHL)**
  - See HODG-2
- **Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)**
  - See HODG-13*

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### TREATMENT ALGORITHMS FOR CLASSICAL HODGKIN LYMPHOMA (CHL)

<table>
<thead>
<tr>
<th>Number of Nodal Sites</th>
<th>Sites (E)</th>
<th>Sites (L)</th>
<th>Nodal Total</th>
<th>Erythrocyte Sedimentation Rate (ESR) Guidelines Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA ± extralymphatic</td>
<td>No &lt;3</td>
<td>&lt;50</td>
<td>1 IIA, no extralymphatic</td>
<td>No &lt;3 &lt;50 HODG-4 or HODG-6</td>
</tr>
<tr>
<td>IIB ± extralymphatic</td>
<td>No &lt;4</td>
<td>&lt;50</td>
<td>2 IIB ± extralymphatic</td>
<td>No &lt;4 &lt;50 HODG-4</td>
</tr>
<tr>
<td>III-IV</td>
<td>Yes/No</td>
<td>Any</td>
<td>3 III-IV</td>
<td>Any</td>
</tr>
</tbody>
</table>

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### HODG-1

*Fine-needle aspiration (FNA) alone is insufficient for diagnosis except in unusual circumstances when in combination with immunohistochemistry it is judged adequate by a hematopathologist or cytopathologist.

Typical immunophenotype for nodular lymphocyte-predominant Hodgkin lymphoma: CD20+, CD45+, CD79a+, BCL6+, P AX-5+; CD3-, CD15-, CD30+, P AX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-

Typical immunophenotype for classical Hodgkin lymphoma: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-

Typical immunophenotype for nodular lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

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

PET/CT should be done with patient on a flat table with arms up, if possible. In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1).

Fertility preservation options include: Semen cryopreservation, IVF or ovarian tissue or oocyte cryopreservation and oophoropexy.

CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

NLPHL has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL.

In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake, a bone marrow biopsy is not required and if there is multifocal (three or more) skeletal PET/CT lesions, marrow may be assumed to be involved.
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TREATMENT ALGORITHMS FOR CLASSICAL HODGKIN LYMPHOMA (CHL)¹

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Bulky Disease¹ (mediastinal or peripheral)</th>
<th>Number of Nodal Sites¹</th>
<th>Erythrocyte Sedimentation Rate (ESR)</th>
<th>Guidelines Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No</td>
<td>1</td>
<td>&lt;50</td>
<td>HODG-3 or HODG-4</td>
</tr>
<tr>
<td>IB</td>
<td>No</td>
<td>1</td>
<td>Any</td>
<td>HODG-6</td>
</tr>
<tr>
<td>IIA, no extralymphatic (E) lesions</td>
<td>No</td>
<td>&lt;3</td>
<td>&lt;50</td>
<td>HODG-3 or HODG-4</td>
</tr>
<tr>
<td>IIA ± extralymphatic (E) lesions²</td>
<td>No</td>
<td>&lt;4</td>
<td>&lt;50</td>
<td>HODG-4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>≥4 or ≥50</td>
<td>Any</td>
<td>HODG-4 or HODG-6</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>HODG-7</td>
</tr>
<tr>
<td>IIB ± extralymphatic (E) lesions²</td>
<td>No</td>
<td>Any</td>
<td>Any</td>
<td>HODG-6</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>HODG-7</td>
</tr>
<tr>
<td>III-IV</td>
<td>Yes/No</td>
<td>Any</td>
<td>Any</td>
<td>HODG-10</td>
</tr>
</tbody>
</table>

¹For definitions of bulky disease and lymph node regions, see HODG-A.
²E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation. (Engert A, et al. N Engl J Med 2010;363:640-652.)
### Hodgkin Lymphoma, Version 1.2017

#### PRIMARY TREATMENT: Modified from GHSG HD10 Trial

<table>
<thead>
<tr>
<th>Stage IA, IIA (no bulky disease, &lt;3 sites of disease, ESR &lt;50, and no E-lesions)</th>
<th>ABVD x 2 cycles (category 1) or See HODG-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA, IIA (no bulky disease)</td>
<td>ABVD x 3 cycles (Preference to treat with chemotherapy alone) or ABVD x 2 cycles (Preference to treat with combined modality therapy)</td>
</tr>
<tr>
<td>Stage IA-IIA (no bulky disease)</td>
<td>Stanford V x 8 weeks (Combined modality therapy)</td>
</tr>
</tbody>
</table>

**CLINICAL PRESENTATION:**
- Classical Hodgkin Lymphoma
- Stage IA, IIA Favorable

**PRIMARY TREATMENT**

<table>
<thead>
<tr>
<th>Deauville 1-2°</th>
<th>Observe or ABVD x 1 cycle (total 4) (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deauville 3-4°</td>
<td>ABVD x 1 cycle (total 4) + ISRT (30 Gy)</td>
</tr>
<tr>
<td>Deauville 5°</td>
<td>Biopsy Positive → See Refractory Disease (HODG-15*)</td>
</tr>
</tbody>
</table>

- Involved-site radiation therapy (ISRT; 20 Gy) See Follow-up (HODG-14)³

- Escalated BEACOPP x 2 cycles + ISRT (30 Gy) or ABVD x 2 cycles + ISRT (30 Gy) or Positive → See Follow-up (HODG-14)³

- Negative or Positive → See Refractory Disease (HODG-15*)

**CLINICAL PRESENTATION:**
- Classical Hodgkin Lymphoma
- Stage IA, IIA Favorable

**PRIMARY TREATMENT**

<table>
<thead>
<tr>
<th>Deauville 1-2°</th>
<th>ABVD x 1 cycle (total 3) + ISRT (30 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deauville 3-4°</td>
<td>Escalated BEACOPP x 2 cycles + ISRT (30 Gy)</td>
</tr>
<tr>
<td>Deauville 5°</td>
<td>Biopsy Positive → See Refractory Disease (HODG-15*)</td>
</tr>
</tbody>
</table>

- Involved-site radiation therapy (ISRT; 20 Gy) See Follow-up (HODG-14)³

- Escalated BEACOPP x 2 cycles + ISRT (30 Gy) or ABVD x 2 cycles + ISRT (30 Gy) or Positive → See Follow-up (HODG-14)³

- Negative or Positive → See Refractory Disease (HODG-15*)

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

1. CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDNL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.
2. Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F).
3. See Principles of Systemic Therapy (HODG-B).
5. See PET 5-Point Scale (Deauville Criteria) (HODG-D).

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CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma
Stage I-II Unfavorable\(^a\) (Non-bulky)

PRIMARY TREATMENT\(^k\)
(Modified from GHSG-HD10 and HD14, RATHL, and EORTC H10 Trials)\(^k,y,za\)

<table>
<thead>
<tr>
<th>Stage I-II Unfavorable(^a) (Non-bulky)</th>
<th>See Primary Treatment (HODG-8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD(^1) x 2 cycles</td>
<td>Restage with PET/CT(^n,\text{2b})</td>
</tr>
<tr>
<td>or</td>
<td>Escalated BEACOPP(^1) x 2 cycles</td>
</tr>
<tr>
<td>or</td>
<td>ABVD x 2 cycles + ISRT(^p)</td>
</tr>
<tr>
<td>or</td>
<td>Positive</td>
</tr>
<tr>
<td>or</td>
<td>Negative</td>
</tr>
<tr>
<td>or</td>
<td>Biopsy</td>
</tr>
<tr>
<td>or</td>
<td>Stanford V(^\text{1}\text{x}12) weeks</td>
</tr>
</tbody>
</table>

\(^1\)Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

\(^a\)Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F; available online, in these guidelines, at NCCN.org).

\(^k\)See Principles of Systemic Therapy (HODG-B).

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

\(^za\)See PET 5-Point Scale (Deauville Criteria) (HODG-D).

\(^2\)PIRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
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CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma
Stage I-II Unfavorable (Bulky mediastinal disease or >10 cm adenopathy) - Planned Combined Modality Therapy

PRIMARY TREATMENT (continued from HODG-7)
(Modified from ECOG-2496 Trial)

Stage I-II Unfavorable (Bulky mediastinal disease or >10 cm adenopathy)

- ABVD x 2 cycles (category 1)
- Escalated BEACOPP x 2 cycles

or

- Stanford V x 12 weeks
- Escalated BEACOPP x 2 cycles + ABVD x 2 cycles + ISRT
in selected patients age <60)

See Refractory Disease (HODG-15)

See Follow-up (HODG-14)

See Primary Treatment (HODG-8)

See Primary Treatment (HODG-9)

See Refractory Disease (HODG-15, available online, in these guidelines, at NCCN.org)

See Follow-up (HODG-14)

- ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
- Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

HODG-7

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.
Classical Hodgkin Lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F, available online, in these guidelines, at NCCN.org).

See Principles of Systemic Therapy (HODG-B).

An integrated PET/CT or a PET with a diagnostic CT is recommended. See PET 5-Point Scale (Deauville Criteria) (HODG-D).

ISRT fields are generally smaller than IFR T fields. See Principles of Radiation Therapy (HODG-C).

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

NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).


Deauville 1-4o

Deauville 5o

Biopsy

ISRTp to initial sites >5 cm (30–36 Gy begins optimally within 2–3 weeks)

See Follow-up (HODG-14)q

Restage with PET/CTp

Restage with PET/CTp after completion of chemotherapy

Positive

See Refractory Disease (HODG-15, available online, in these guidelines, at NCCN.org)

Escalated BEACOPPl,ee x 2 cycles + ABVD x 2 cycles (in selected patients age <60)

Stanford Vl,x 12 weeks

Biopsy

Deauville 5o

Despite lower risk factors, patients with bulky mediastinal disease or >10 cm disease and/or B symptoms, and elevated ESR, and/or >3 sites in absence of bulky disease are treated for stage III-V disease (HODG-12).

The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-5.

In the GHSG HD14 trial (von Tr esckow B, et al. J Clin Oncol 2012;30:907-913), patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-V disease (HODG-12).

The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-5.

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CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma
Stage III-IV

PRIMARY TREATMENT*
(Modified from RATHL, ECOG-2496, GHSG HD15 trials)

Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

*Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-G).

See Principles of Systemic Therapy (HODG-B).

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

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

ISRRT fields are generally smaller than IFRRT fields. See Principles of Radiation Therapy (HODG-C).

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

Consider PFTs after 4 cycles of ABVD.

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

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

HODG-10

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.
Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for NHL, available at NCCN.org.

Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F).

See Principles of Systemic Therapy (HODG-B).

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

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

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

Complete response should be documented including reversion of PET to “negative” within 3 months following completion of therapy.


See International Prognostic Score (IPS) (HODG-A).

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

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

**Follow-up After Completion of Treatment up to 5 Years**

- Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually
- Annual influenza vaccine
- Laboratory studies:
  - CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated
  - Thyroid-stimulating hormone (TSH) at least annually if RT to neck.
- Acceptable to obtain a neck/chest/abdomen/pelvis CT scan with contrast, at 6, 12, and 24 mo following completion of therapy, or as clinically indicated. PET/CT only if last PET was Deauville 4-5, to confirm complete response.

**Follow-up and Monitoring After 5 Years**

- Interim H&P: Annually
  - Annual blood pressure, aggressive management of cardiovascular risk factors
  - Pneumococcal, meningococcal, and H-flu revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to CDC recommendations)
  - Annual influenza vaccine
  - Cardiovascular symptoms may emerge at a young age.
    - Consider stress test/echocardiogram at 10-y intervals after treatment is completed.
    - Consider carotid ultrasound at 10-y intervals if neck irradiation.
  - Laboratory studies:
    - CBC, platelets, chemistry profile annually
    - TSH at least annually if RT to neck
    - Biannual lipids
    - Annual fasting glucose
  - Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.

- Annual breast screening: Initiate 8–10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Perform other routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per the ACS Cancer Screening Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.

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

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**Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EOR TC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33</td>
</tr>
<tr>
<td>Bulky &gt;10 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E lesion any</td>
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<td></td>
<td></td>
</tr>
<tr>
<td># Nodal sites &gt;2*</td>
<td>&gt;3*</td>
<td>&gt;3</td>
<td></td>
</tr>
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<tr>
<td>Hemoglobin &lt;10.5 g/dL</td>
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</tr>
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<td>Albumin &lt;4 g/dL</td>
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<td>C</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B symptoms &gt;50 if A; &gt;30 if B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR &gt;50 if A; &gt;30 if B</td>
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</tr>
<tr>
<td>Any B symptoms</td>
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</table>

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**Definitions of Lymph Node Regions**

- **L Hilum**
- **R Hilum**
- **CL/Subpectoral**
- **Axilla**
- **Cervical**

---

**Notes**

- *Note that the EOR TC includes the infraclavicular/subpectoral area

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**References**

- Appropriate medical management should be instituted for any abnormalities.

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HODG-14
Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCCN</th>
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<tr>
<td>Age</td>
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<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33</td>
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<tr>
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<td>&gt;2*</td>
<td>&gt;3*</td>
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<td></td>
</tr>
<tr>
<td>Bulky</td>
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<td>&gt;10 cm</td>
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GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

Definitions of Lymph Node Regions

<table>
<thead>
<tr>
<th></th>
<th>Ann Arbor</th>
<th>EORTC</th>
<th>GHSG</th>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>R Axilla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Axilla</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>R Hilum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Hilum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
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</table>

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

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

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

Hodgkin Lymphoma, Version 1.2017

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 with ABVD.
- Leukopenia is not a factor for delay of treatment or reduction of dose intensity (except for escalated BEACOPP).

Regimens and References

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

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

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

Escalated BEACOPP followed by ABVD with ISRT

See Principles of Systemic Therapy for NLPHL (HODG-B 2 of 2, available online, in these guidelines, at NCCN.org)

See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E, available online, in these guidelines, at NCCN.org)

*Cyclophosphamide may be used as an alternate to nitrogen mustard.
**PRINCIPLES OF RADIATION THERAPY**

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

**Involved-site Radiation Therapy (ISR T)**

**Dose:**
- Combined Modality Therapy
  - Non-bulky disease (stage I-II): 20–30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V); 1.5-2.0 Gy per fraction
  - Non-bulky disease (stage IB-IIB): 30 Gy; 1.5-2.0 Gy per fraction
  - Bulky disease sites (all stages): 30–36 Gy; 1.5-2.0 Gy per fraction
  - ISR T Alone (uncommon, except for NLPHL):
    - Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5-2.0 Gy per fraction
    - Uninvolved regions: 25–30 Gy; 1.5-2.0 Gy per fraction

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

See References (HODG-C 3 of 3)

*A dose of 20 Gy following ABVD x 2 is sufficient if the patient has non-bulky stage I-IIA disease with an ESR <50, no extralymphatic lesions, and only one or two lymph node regions involved. See HODG-A for definition of nodal sites according to GHSG.*
Hodgkin Lymphoma, Version 1.2017

PRINCIPLES OF RADIATION THERAPY

References


Hodgkin Lymphoma, Version 1.2017

Table 1
Definitions of Stages in Hodgkin’s Disease

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

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

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (III_E), by involvement of the spleen (III_S), or by both (III_E+S).

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

A No systemic symptoms present
B Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)


PET 5-POINT SCALE (DEAUVILLE CRITERIA)

<table>
<thead>
<tr>
<th>Score</th>
<th>PET/CT scan result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum but ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately higher than liver</td>
</tr>
<tr>
<td>5</td>
<td>Uptake markedly higher than liver and/or new lesions</td>
</tr>
<tr>
<td>X</td>
<td>New areas of uptake unlikely to be related to lymphoma</td>
</tr>
</tbody>
</table>


PET scans are useful for upstaging in stage I-II disease. If there is PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.
unfavorable factors such as large mediastinal adenopathy; >3 nodal sites of disease; B symptoms; extranodal involvement; or significantly elevated erythrocyte sedimentation rate [ESR] ≥50; and advanced-stage disease (stage III–IV).

The early-stage unfavorable factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, German Hodgkin Study Group (GHSG), and National Cancer Institute of Canada. NCCN unfavorable factors for stage I–II disease include bulky mediastinal disease (mediastinal mass ratio >0.33) or bulky disease >10 cm; B symptoms; ESR ≥50; and >3 nodal sites of disease (see HODG-A; page 619). The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis and helps determine the clinical management and predict prognosis for patients with stage III–IV disease.7

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

The International Working Group (IWG) published the guidelines for response criteria in 1999.8 In 2007, the IWG guidelines were revised by the International Harmonization Project (IHP) to incorporate immunohistochemistry, flow cytometry, and PET scans into the definition of response.9,10 The IHP response criteria were initially developed for the interpretation of PET scans at treatment completion. In recent years, these criteria have also been used for interim response assessment.11

In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of 18F-fluorodeoxyglucose (FDG) uptake in the involved sites. These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and liver.12–14 In the 5-PS (Deauville criteria), scores of 1 to 4 refer to initially involved sites and a score of 5 refers to an initially involved site and/or new lesions related to lymphoma.12,13 PET scans with a score of 1 or 2 are considered “negative” and those with a score of 4 and 5 are considered “positive.”15 In some situations, a score of 3 may be considered negative; however, for deescalation of therapy based on interim PET scans, a threshold for positivity that includes a score of 3 using the mediastinal blood pool uptake as the reference is appropriate (PET scans with a score of 1–2 are considered negative and those with a score of 3–5 are considered positive).16 The 5-PS (Deauville criteria) has been validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.17–21

Role of PET Scans
PET imaging including integrated PET and CT (PET/CT) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.11,14 In a meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.22 PET positivity at the end of treatment has been shown to be a significant adverse risk factor in patients with early-stage and advanced-stage disease.23–25 PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone.21

The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios and that all measures of response should be considered in the context of management decisions. It is important that the Deauville score be incorporated into the nuclear medicine PET scan report, because subsequent management often depends on that score.

The guidelines recommend biopsy for all patients with a score of Deauville 5. In general, patients with a positive biopsy result should be managed as described for refractory disease. For those with a negative biopsy, complete response (CR) should be documented, including reversion of PET to “negative” within 3 months after therapy completion.

Principles of Radiation Therapy
Radiation therapy (RT) can be delivered with photons, electrons, or protons, depending on clinical circumstances. Advanced RT techniques emphasize...
tightly conformal doses and steep gradients adjacent to normal tissues; therefore, target definition, delineation, and treatment delivery verification require careful monitoring (see HODG-1; page 610). Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound, and other imaging modalities facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OARs; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue, and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4-dimensional CT simulation, intensity-modulated RT, image-guided RT, respiratory gating, or deep inspiration breathhold.26,27 These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and decrease the risk of normal tissue damage and late effects without compromising the primary goal of local tumor control.28–34

Randomized prospective studies to test these concepts are unlikely to be conducted because these techniques are designed to decrease late effects, which usually develop ≥10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OARs in a clinically meaningful manner without compromising target coverage should be considered in these patients, who are likely to have long life expectancies after treatment.

**Treatment Guidelines**

**Diagnosis and Workup**

Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy generally be performed (see HODG-1; page 610). The role of fine-needle aspiration (FNA) biopsy in the diagnosis of lymphoma is still controversial.35–37 A diagnostic assessment based solely on FNA biopsy is insufficient except in unusual circumstances when, in combination with immunohistochemistry, it is judged to be diagnostic of HL by an expert hematopathologist or cytopathologist. Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, and PAX5 is recommended for CHL.

Workup should include a thorough history and physical examination; standard laboratory tests; PET/CT (skull base to mid-thigh); and diagnostic contrast-enhanced CT. A chest radiograph is encouraged for patients with a large mediastinal mass. In patients with newly diagnosed HL undergoing pretreatment staging with PET/CT, routine bone marrow biopsy is not required if the PET scan is negative or displays a homogenous pattern of bone marrow uptake.38 The bone marrow may be assumed to be involved if the PET scan displays multifocal (≥3) skeletal lesions.38,39 However, a bone marrow biopsy may be performed if cytopenias are present. In select cases, MRI and PET/MRI with contrast (skull base to mid-thigh) may also be considered for anatomic imaging.

Evaluation of ejection fraction is recommended for most patients undergoing doxorubicin-based chemotherapy. HIV and hepatitis B or C testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. Pulmonary function tests, including the test of the diffusing capacity of the lungs for carbon monoxide, are recommended for patients receiving bleomycin-based chemotherapy. Haemophilus influenzae (H-flu), pneumococcal, and meningococcal vaccines are recommended for patients receiving bleomycin-based chemotherapy.40 The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) before the initiation of chemotherapy with alkylating agent–based chemotherapy.41–43 Oophoropexy should be considered to preserve ovarian function in premenopausal women if pelvic RT is contemplated.44 A pregnancy test should be performed before women of childbearing age undergo treatment. Alkylating agent–based chemotherapy is associated with a higher risk of premature ovarian failure compared with chemotherapy with non–alkylating agent–based chemotherapy.40 The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) before the initiation of chemotherapy with alkylating agents or pelvic RT.41,42 Oophoropexy should be considered to preserve ovarian function in premenopausal women if pelvic RT is contemplated.41

**Stage I–II Favorable Disease:** RT alone was a standard treatment option for patients with early-stage HL for many decades.44 However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.45 With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] and Stanford V) into the management of patients with early-stage disease,
combined modality therapy (chemotherapy and RT) has replaced RT alone as the preferred treatment for patients with early-stage, favorable disease.

The ABVD regimen was developed 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 a brief but dose-intensive regimen with significantly fewer cumulative doses of doxorubicin and bleomycin than those used in ABVD, alternating MOPP/ABVD, BEACOPP, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity. RT is an integral part of the Stanford V regimen.

Bonadonna et al initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy of involved-field RT (IFRT) as the standard treatment for patients with early-stage disease. The HD10 trial from the GHSG investigated the reduction of the number of cycles of ABVD and the IFRT dose in patients with stage I–II disease with no risk factors. The definitions of unfavorable risk factors and lymph node sites used to determine clinical disease staging are outlined on HODG-A (page 619). It is worth noting that the GHSG and EORTC do not define the lymph node regions strictly according to the Ann Arbor criteria. Patients were not eligible if they had ≥3 sites of disease, any E-lesions, bulky mediastinal adenopathy, ESR >50, or ESR >30 in conjunction with B symptoms. In this trial, 1,370 patients were randomized to 1 of 4 treatment groups: 4 cycles of ABVD followed by 30 or 20 Gy of IFRT, or 2 cycles of ABVD followed by 30 or 20 Gy of IFRT. The final analysis of this trial showed that (with a median follow-up of 79–91 months) there were no significant differences between 4 and 2 cycles of ABVD in terms of 5-year overall survival (OS; 97.1% and 96.6%), freedom from treatment failure (FFTF; 93.0% vs 91.1%), and progression-free survival (PFS; 93.5% vs 91.2%). With respect to the dose of IFRT, the OS (97.7% vs 97.5%), FFTF (93.4% vs 92.9%), and PFS (93.7% vs 93.2%) were also not significantly different between 30 and 20 Gy IFRT. More importantly, no significant differences were seen in OS, PFS, and FFTF among the 4 treatment arms. The results of the HD10 study 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.

The G4 study conducted by the Stanford and Kaiser hospitals evaluated the efficacy of the abbreviated Stanford V chemotherapy (8 weeks or 2 cycles) followed by IFRT (30 Gy) in patients with nonbulky stage IA or IIA disease. Among the 87 patients included in the study, unfavorable risk factors according to GHSG criteria (>2 nodal sites, ESR ≥50, or extranodal involvement) were present in 42 patients (48%), and 33 patients (38%) had unfavorable characters defined by EORTC criteria (>3 nodal sites, ESR ≥50, mixed cellularity, and ≥50 years of age). At a median follow-up of 10.6 years, the estimated 10-year freedom from progression (FFP), disease-specific survival, and OS rates were 94%, 99%, and 94%, respectively. Among patients with GHSG criteria, FFP was 100% for patients with favorable disease and 88% for those with unfavorable nonbulky disease. The FFP was 98% and 88%, respectively, for patients with favorable and unfavorable disease according to EORTC criteria. No late cardiac or pulmonary toxicities were observed. No patient developed secondary acute myeloid leukemia or a myelodysplastic syndromes (MDS).

Two studies from Europe have evaluated the value of interim PET scans in defining the need for IFRT in patients with stage I–II favorable disease (the UK RAPID trial and the EORTC H10 trial). The interim analysis of the EORTC H10 trial (n=1,137; 444 patients with stage I–II favorable disease; 693 patients with stage I–II unfavorable disease) showed that combined modality therapy (ABVD + involved-node RT [INRT]) resulted in fewer early progressions compared with treatment with ABVD alone, even in patients with early-stage favorable disease and a negative PET scan after 2 cycles of ABVD.

Chemotherapy with ABVD alone has also been investigated as a treatment option for patients with early-stage nonbulky disease (stage I–II). The RAPID trial showed that patients with stages IA–IIB disease with a negative PET scan after 3 cycles of ABVD have an excellent outcome with or without IFRT. In this study (n=602; 426 patients had a negative PET scan after 3 cycles of ABVD), patients with stage IA–IIB favorable disease (no B symptoms or mediastinal bulky disease) and a Deauville score of 1 to 2 on interim PET scan after 3 cycles ABVD were randomized to either IFRT (n=209) or
observation (n=211). After a median follow-up of 60 months, the estimated 3-year PFS rate was 94.6% for those treated with IFRT compared with 90.8% for those who received no further treatment. The corresponding 3-year OS rates were 97.1% and 99.0%, respectively, suggesting a benefit for combined modality therapy but not necessarily superiority over chemotherapy alone with this regimen.

Combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment for patients with stage I–II favorable disease.34 However, ABVD alone could be a reasonable choice of treatment, especially for younger patients who are in CR after 2 cycles (as documented by CT scan) or for those with a Deauville score of 1 to 3 on PET scan after 2 to 4 cycles of ABVD, in order to avoid the long-term risks of RT.

**NCCN Recommendations:** Combined modality therapy (ABVD plus involved site RT [ISRT]50 [category 1] or Stanford V chemotherapy51) or chemotherapy (ABVD alone21) are included as treatment options for patients with stage IA to IIA favorable disease (absence of all NCCN unfavorable risk factors: bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 nodal sites of disease) (see HODG-3 and HODG-4; page 612).

For patients who fulfill the GHSG criteria for favorable stage IA to IIA disease, 2 cycles of ABVD followed by interim restaging with PET is recommended. For patients with a Deauville score of 1 to 4, a planned course of ISRT (20 Gy) is recommended, whereas biopsy is recommended for those with a score of Deauville 5 after completion of chemotherapy. ISRT followed by observation is recommended for patients with a negative biopsy, and those with a positive biopsy should be managed as described for refractory disease.

Three treatment regimens are also recommended as suitable options for all patients with nonbulky, favorable stage IA to IIA disease. The first option is used when there is a preference to treat patients with chemotherapy alone and involves an initial administration of 3 cycles of ABVD followed by interim restaging with PET. After interim restaging, and consistent with the results of the RAPID trial, no further treatment is recommended for patients with a Deauville score of 1 or 2.21 However, these patients may receive an optional additional cycle of ABVD (total of 4). For patients with a Deauville score of 3 to 4, an additional cycle of ABVD (total of 4) and ISRT (30 Gy) is recommended. Biopsy is recommended for patients with a Deauville score of 5, and patients with a negative biopsy should be managed with an additional cycle of ABVD (total of 4) and ISRT (30 Gy). If biopsy is positive, patients should be managed as described for refractory disease.

If there is a preference to treat patients with combined modality therapy, patients are administered 2 cycles of ABVD and restaged with PET. An additional cycle of ABVD (total of 3) and ISRT (30 Gy) is recommended for patients with a Deauville score of 1 to 2. Patients with a Deauville score of 3 to 4 can either be treated with 2 additional cycles of ABVD (total of 4) and ISRT (30 Gy) or 2 cycles of escalated BEACOPP and ISRT (30 Gy). A Deauville score of 5 warrants a biopsy. If the results are negative, patients can be managed as described for those with a Deauville score of 3 to 4, and if results are positive, they should be managed as described for refractory disease.

The third option is treatment with the Stanford V regimen for 8 weeks followed by interim PET restaging. Patients with a Deauville score of 1 to 4 are treated with 30 Gy ISRT, which is optimally instituted within 3 weeks of completion of chemotherapy.51 A Deauville score of 5 warrants a biopsy. If the results are negative, patients are treated with 30 Gy ISRT, and if positive, they should be managed as described for refractory disease. The combined modality treatment regimen with Stanford V offers an alternative when it is desirable to limit the patient’s exposure to bleomycin.51

**Stage I–II Unfavorable Disease:** The HD8 trial from the GHSG investigated the efficacy of IFRT versus extended-field RT in the context of combined modality therapy for patients with early-stage unfavorable HL with ≥1 risk factors (large mediastinal mass, extranodal disease, splenic involvement, elevated ESR with or without B symptoms, and >2 lymph node areas of involvement).52 No significant differences in FFTF or OS were seen when larger radiation fields were used. IFRT was also associated with less acute toxicity and fewer secondary malignancies. This established combined modality therapy with IFRT as the standard of care for these patients.52,55

To investigate the number of cycles of chemotherapy required for maximal efficacy in combined modality therapy, the EORTC-H9U trial randomized
808 patients with stage I–II unfavorable disease to 3 treatment arms and compared 6 cycles of ABVD, 4 cycles of ABVD, and 4 cycles of BEACOPP, followed by IFRT (30 Gy) in all arms. At 4 years of follow-up, when the number of ABVD cycles was reduced from 6 to 4, the trial showed similar event-free survival (EFS; 94% vs 89%) and OS (96% vs 95%) rates, but increased toxicity was observed in the BEACOPP arm.

The HD11 trial from the GHSG demonstrated that 4 cycles of ABVD followed by 30 Gy IFRT is an effective treatment option for patients with early-stage unfavorable disease. In this study, 1,395 patients with stage I–II unfavorable disease (stage IA, IB, or IIA with ≥1 of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥50 or ESR ≥30 with B symptoms; or ≥3 involved lymph nodes and stage IIB disease with no bulky mediastinal mass or extranodal involvement) were randomized to either ABVD (4 cycles followed by 30 or 20 Gy IFRT) or standard-dose BEACOPP (4 cycles followed by 30 or 20 Gy IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FFTF and PFS rates were 86.8% and 87%, respectively, for BEACOPP; the corresponding rates were 81% and 82%, respectively, for ABVD). However, no difference was seen between the 2 regimens when followed by 30 Gy of IFRT. BEACOPP was also associated with more toxicity than ABVD.

The EORTC H10 trial (n=1,137; 444 patients with stage I–II favorable disease; 693 patients with stage I–II unfavorable disease) aimed to demonstrate prognostic significance of early interim PET after 2 cycles of chemotherapy. The H10U trial within this study randomized patients into 2 treatment arms. In the standard arm, patients were treated with 2 cycles of ABVD, underwent interim PET, and were treated with 2 additional cycles of ABVD with INRT (30–36 Gy). In the experimental arm, patients were treated with 2 cycles of ABVD, underwent interim PET scans, and, if found to be PET-negative, were treated with an additional 4 cycles of ABVD. If patients were found to be PET-positive after the initial 2 cycles of ABVD, chemotherapy was intensified with 2 cycles of escalated BEACOPP with INRT (30–36 Gy). Although interim analysis demonstrated that chemotherapy alone is a viable treatment option, PET scans showed that combined modality therapy (ABVD + INRT) resulted in fewer early progressions compared with treatment with ABVD alone.

The results of the prospective study conducted by the Stanford group demonstrated the efficacy of the Stanford V regimen followed by RT to initially bulky sites for patients with locally extensive and advanced-stage disease. In this study, 142 patients with locally extensive mediastinal stage I or II disease or stage III or IV disease were treated with Stanford V chemotherapy (12 weeks) followed by RT (36 Gy) to initial bulky sites (≥5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year FFT and OS rates were 89% and 96%, respectively. No patients progressed during treatment and there were no treatment-related deaths or secondary leukemia. Among 16 patients who experienced relapse, the freedom from second relapse was 69% at 5 years.

A randomized Italian study reported that ABVD and MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) were superior to the Stanford V regimen in response rate, failure-free survival (FFS), and PFS in patients with intermediate-stage and advanced-stage HL. However, interpretation of these results was difficult because the timing of response evaluation was different among the arms (8 and 12 weeks for Stanford V, 16 weeks for ABVD, and 24 weeks for MOPPEBVCAD). In addition, modifications of the RT protocol in 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 the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile when RT is administered according to Stanford V protocol guidelines. In the Memorial Sloan Kettering Cancer Center 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, with 5- and 7-year OS rates of 90% and 88%, respectively. Of 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 an 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 (study ISRCTN 64141244) also showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rate (ORR) and 3-year PFS and OS rates in patients with stage IIB, III, or IV disease or stage I–IIA HL with bulky disease or other adverse features. RT was administered in both arms to sites of previous bulky sites (>5 cm) and to splenic deposits. At the median follow-up of 4.3 years, the ORR, 5-year PFS, and 5-year OS rates were 91%, 76%, and 90%, respectively, for ABVD and 92%, 74%, and 92%, respectively, for Stanford V.

The phase III intergroup trial (E2496) also confirmed no significant differences between ABVD and Stanford V in terms of response rates, FFS, OS, and toxicity in patients with locally extensive (stage I–IIA/B and bulky mediastinal disease) and stage III–IV disease. In this trial, 854 patients were randomized to ABVD (n=428; 6–8 cycles plus 36 Gy RT only for patients with bulky mediastinal disease) or Stanford V (n=426; 12 weeks of chemotherapy plus 36 Gy RT for sites ≥5 cm or for macroscopic splenic disease). The primary end point was FFS, defined as the time from randomization to progression, relapse, or death, whichever occurred first. With a median follow-up of 6.4 years, no difference between the arms was seen for ORR (clinical CR rates were 72.7% for ABVD and 68.7% for Stanford V), OS (88% at 5 years for both ABVD and Stanford V; P=.86), or FFS (74% for ABVD and 71% for Stanford V at 5 years; P=.32). Toxicity was also similar in both groups. The planned subgroup analysis showed that the outcome of patients with locally extensive disease was significantly better than that of patients with stage III–IV disease. The 3- and 5-year FFS rates were 82% for patients with locally extensive disease and 71% and 67%, respectively, for patients with stage III–IV disease (P=.001). The 5-year OS rates were 94% and 85%, respectively (P<.001).

The GHSG HD14 trial showed that BEACOPP followed by ABVD and IFRT significantly improved tumor control and PFS in patients with early-stage unfavorable disease (stage IA, IB, or IIA HL with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥50 [without B symptoms] or ESR ≥30 [with B symptoms]; or ≥3 involved lymph nodes) and stage IIB disease with either of the latter 2 risk factors. In this trial, 1,528 patients were randomized to 4 cycles of ABVD (n=765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD (n=763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FTF rate was 94.8% compared with 87.7% for ABVD (P<.001). The 5-year PFS rate was 95.4% and 89.1%, respectively (P<.001). The 5-year OS rate was not significantly different between the 2 arms (97.2% and 96.8%, respectively; P=.731). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs 8.4%; P<.001).

The Response-Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial has also examined the use of interim PET to guide treatment for patients with advanced disease, which included 500 patients (41.6%) who had stage II HL with various risk factors (B symptoms, bulky disease, or at least 3 involved sites). In the randomized trial, 1,119 patients with stage II–IV disease received 2 cycles of ABVD and underwent interim PET scans. Patients with a Deauville score of 1 to 3 were assigned in a 1:1 ratio to continue treatment with 4 cycles of either ABVD or AVD. At a median of 41 months, the 3-year PFS and OS rates between the ABVD and AVD groups did not differ significantly (85.7% vs 84.4% and 97.2% vs 97.6% respectively). However, the omission of bleomycin from the ABVD regimen after negative PET results (ie, Deauville score of 1–3) led to a decrease in the incidence of pulmonary toxic effects compared with continued ABVD.

Overall, these results suggest that ABVD plus 30 Gy of IFRT remains the standard of care for patients with early-stage unfavorable disease. Stanford V (when given as described with RT) or BEACOPP followed by ABVD are acceptable alternatives for some patients.

NCCN Recommendations: ABVD followed by ISRT or AVD, ABVD followed by escalated BEACOPP and ISRT, Stanford V plus ISRT, or escalated BEACOPP (2 cycles) followed by ABVD (2 cycles) and ISRT for selected patients aged <60 years are included as options for patients with stage I–II unfavorable disease (see HODG-6 and HODG-7; pages 613 and 614). In the HD14 trial that evaluated escalated BEACOPP followed by ABVD and ISRT, patients with bulky disease in combination with either
B symptoms or extranodal disease were excluded.55 These patients are managed as described for stage III–IV disease.

**Stage I–II (Unfavorable Nontuberculous Disease):** ABVD is initially administered for 2 cycles followed by interim restaging with PET. Patients with a Deauville score of 1 to 2 can be treated with 2 additional cycles of ABVD (total of 4) and ISRT, or 4 cycles of AVD (total of 6) with or without ISRT. Patients with a Deauville score of 3 to 4 are treated with either 2 additional cycles of ABVD alone (total of 4) or 2 cycles of escalated BEACOPP. PET restaging may be considered at this point and patients are followed up with ISRT. Biopsy is recommended for patients with a Deauville score of 5 after initial treatment with 2 cycles of ABVD. If the biopsy is negative, patients are treated with 4 cycles of AVD (total of 6) with ISRT. All patients with a positive biopsy should be managed as described for refractory disease.

**Stage I–II (Unfavorable Bulky Mediastinal Disease or Adenopathy >10 cm With or Without B Symptoms):** ABVD is initially administered for 2 cycles followed by interim restaging with PET. This is a category 1 recommendation. Patients with a Deauville score of 1 to 3 are treated with a combination of 2 additional cycles of ABVD (total of 4) and ISRT or with 4 cycles of AVD (total of 6) with or without ISRT. Patients with a Deauville score of 4 are treated with 2 additional cycles of ABVD (total of 4) and ISRT or 2 cycles of escalated BEACOPP and ISRT (30 Gy). Biopsy is recommended for all patients with a Deauville score of 5 after initial treatment with 2 cycles of ABVD. If the biopsy is negative, patients should either receive 2 additional cycles of ABVD (total of 4) and ISRT or 2 cycles of escalated BEACOPP and ISRT. Patients with a positive biopsy should be managed as described for refractory disease.

**Stage I–II (Unfavorable Nontuberculous Disease and Unfavorable Bulky Mediastinal Disease or Adenopathy >10 cm With or Without B Symptoms):** Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30–36 Gy) to patients with stage I–II nontuberculous and bulky disease and/or B symptoms (see HODG-8; page 615).58,64 Patients are restaged with PET at the completion of chemotherapy. ISRT to initial sites >5 cm is recommended for all patients with a Deauville score of 1 to 4. ISRT should be instituted within 2 to 3 weeks of completion of chemotherapy. Biopsy is recommended for all patients with a Deauville score of 5 after completion of therapy. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease. If the patients present with unfavorable nontuberculous disease and other unfavorable factors (elevated ESR or >3 sites of disease), they are treated with 8 weeks of Stanford V followed by restaging and treated with ISRT (30 Gy) as described for stage I–IIA favorable disease.51

Patients receiving escalated BEACOPP (2 cycles) and ABVD (2 cycles) are restaged after completion of chemotherapy (see HODG-9; page 615). ISRT is recommended for those with a Deauville score of 1 to 4 and biopsy is recommended for patients with a Deauville score of 5. ISRT should be given if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

**Stage III–IV:** Although chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.58,64

The landmark randomized trial by the CALGB showed that ABVD alone or alternating with MOPP was superior to MOPP alone in patients with newly diagnosed advanced HL (stage III–IV).68 ABVD also was less myelotoxic than MOPP or ABVD alternating with MOPP, and has since been the standard treatment for patients with stage III–IV disease. Stanford V and BEACOPP are the other 2 regimens developed to improve the outcome of patients with advanced disease.

The results from prospective studies conducted by the Stanford group and other investigators have demonstrated the efficacy of Stanford V and IFRT in patients with advanced-stage disease.58 Improved OS, and toxicity between ABVD and Stanford V (with RT, when indicated, according to Stanford V protocol guidelines) in patients with stage III–IV disease.64 However, among patients with high-risk disease (IPS ≥3), the 5-year FFS rate was significantly better for ABVD than Stanford V (67% vs...
57%; \( P = .02 \)), but no significant difference was seen in 5-year OS rate (84% vs 77%; \( P = .15 \)).

The efficacy of BEACOPP in patients with advanced disease was demonstrated in 2 phase III randomized trials conducted by the GHSG.\(^{69,70}\) In the HD9 study, 1,196 patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP-ABVD, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP.\(^{69}\) Each regimen was followed by RT to initial sites of disease ≥5 cm. Most patients in each treatment arm had stage III–IV disease. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP-ABVD and significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP. The 10-year analysis confirmed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP-ABVD in terms of FFTF (82%, 70%, and 64%, respectively) and OS rates (86%, 80%, and 75%, respectively). Escalated-dose BEACOPP was significantly better than standard-dose BEACOPP in terms of FFTF \((P < .0001)\) and OS \((P = .0053)\).\(^{70}\)

The final results of the HD12 study \((n = 1,670)\) that compared 8 cycles of escalated-dose BEACOPP with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP, with or without RT, also confirmed the efficiency of escalated-dose BEACOPP for patients with advanced-stage HL who have risk factors, as reported in the HD9 trial.\(^{71}\) In this study, at 5 years, the FFTF (86.4% and 84.8%, respectively) and PFS (87.5% and 85%, respectively) were better (although the difference was not significant) for 8 cycles of escalated-dose BEACOPP compared with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP. The 5-year OS rate, however, was not different (92% and 90.3%, respectively).\(^ {71}\)

The final analysis of the HD15 trial reported by Engert et al\(^ {67}\) showed that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT resulted in significantly superior OS and tumor control than 8 cycles of escalated-dose BEACOPP in patients with advanced-stage disease (stage IIIB with large mediastinal mass or stage III–IV). In this study, 2,182 patients were randomly assigned to 1 of the 3 treatment groups: 8 cycles of escalated-dose BEACOPP \((n = 726)\), 6 cycles of escalated-dose BEACOPP \((n = 726)\), or 8 cycles of a time-intensified standard-dose BEACOPP \((n = 728)\). RT (30 Gy) was restricted to patients with PET-positive residual sites (≥2.5 cm) after chemotherapy. The 5-year FFTF rates were 84.4%, 89.3%, and 85.4%, respectively, for the 3 groups. The corresponding OS rates were 91.9%, 95.3%, and 94.5%, respectively, and were significantly better with 6 cycles of escalated-dose BEACOPP than with 8 cycles of escalated-dose BEACOPP \((P = .019)\). Escalated-dose BEACOPP was also associated with less treatment-related mortality \((TRM; 4.6\% \text{ vs } 7.5\% \text{ for 8 cycles of escalated-dose BEACOPP and } 5.2\% \text{ for 8 cycles of time-intensified standard-dose BEACOPP and fewer secondary cancers (2.4\% vs 4.7\% and 3.1\%, respectively, for 8 cycles of escalated-dose BEACOPP and 8 cycles of time-intensified standard-dose BEACOPP). These results confirm that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT is an acceptable treatment for patients with advanced-stage disease.

Results from studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although it resulted in better tumor control in patients with advanced disease.\(^ {72–75}\) However, some of these studies were not sufficiently powered to determine differences in OS due to small patient numbers. The EORTC 20012 trial evaluated BEACOPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III–IV disease and IPS ≥3 (274 patients in the BEACOPP arm and 275 patients in the ABVD arm).\(^ {72}\) The results showed that there was no improvement in OS (86.7% and 90.3%, respectively, at 4 years; \( P = .208\)) or EFS (63.7% and 69.3%, respectively, at 4 years; \( P = .312\)), although the PFS was significantly better with BEACOPP (83.4% vs 72.8% for ABVD; \( P = .005\)). Early discontinuations were also more frequent with BEACOPP. The median follow-up was 3.6 years.\(^ {72}\) The long-term follow-up analysis of the HD2000 trial also showed that the risk of secondary malignancy at 10 years was significantly higher with BEACOPP than with ABVD (6.6 vs 0.9; \( P = .027\)).\(^ {76}\)

Several trials have addressed the role of consolidation RT after completion of chemotherapy in patients with stage III–IV disease.

The SWOG multicenter study showed no improvement in OS rates for patients who underwent
low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, procarbazine plus bleomycin, doxorubicin, and prednisone), but the remission duration was prolonged in several subgroups, especially in patients with bulky nodular sclerosis CHL. In the randomized trial (EORTC 20884 trial) that assessed the role of consolidation RT following MOPP-ABV chemotherapy in patients with advanced disease, 739 patients with untreated stage III to IV disease received 6 to 8 cycles of MOPP-ABV. Patients with CR on CT imaging after chemotherapy were randomized to no further treatment or IFRT, and those with a partial response (PR) received IFRT to involved nodal areas and extranodal sites. The 8-year OS and EFS rates in the PR group were 76% and 84%, respectively. These outcomes were not significantly different in patients with CR (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing PR after chemotherapy.

In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) that compared ABVD with 2 other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation. PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was seen for OS. The final results of the HD12 trial also showed that consolidation RT was beneficial for patients with residual disease after escalated-dose BEACOPP (FFTF was 90.4% and 87%, respectively), whereas this effect was not seen in patients with initial bulk disease who were in CR after chemotherapy. In contrast, Laskar et al. reported a survival advantage for consolidative RT in patients experiencing CR after initial chemotherapy, particularly in patients aged <15 years and those with B symptoms and bulky and advanced disease. However, this study included patients with a different distribution of histologic subtypes of HL compared with those included in Western studies, and most patients had early-stage HL. Of note, none of these studies incorporated PET scan for the evaluation of response.

In the HD15 trial, RT (30 Gy) after BEACOPP chemotherapy was restricted to those patients in PR with PET-positive residual disease (≥2.5 cm). PET-negative patients received no additional RT. Of the 739 qualified patients with residual disease (≥2.5 cm) after 6 to 8 cycles of BEACOPP, 548 (74%) were PET-negative; 191 patients (26%) were PET-positive and received consolidative RT. The final analysis showed that the prognosis of patients in PR with PET-negative persistent residual disease after chemotherapy was similar to that of those who were in CR as measured by conventional CT (4-year PFS was 92.1%), suggesting that consolidative RT could be omitted in patients with a PET-negative PR. However, the use of consolidative RT was effective for patients with PET-positive PR, because the 4-year PFS in this group was 86.2%. In relapse analysis of the HD15 trial, of 225 patients with PET-positive disease after BEACOPP chemotherapy and RT, 197 (89%) were relapse-free for the duration of their follow-up (median 42 months).

Two 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. Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing CR or PR 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.

NCCN Recommendations: ABVD, Stanford V (selected patients with IPS <3), or escalated-dose BEACOPP (in selected patients aged <60 years with an IPS of ≥4) are included as options for primary treatment for patients with stage III–IV disease (see HODG-10; page 616). In this setting, the ABVD regimen is preferred. ABVD is initially administered for 2 cycles followed by restaging with PET. Patients with a Deauville score of 1 to 3 are treated with 4 cycles of AVD based on results from the RATHL trial. Consistent with the results of the E2496 study, observation or ISRT to initially bulky or selected PET-positive sites are included as options for patients with a Deauville score of 1 to 3 after 2 cycles of ABVD and 4 cycles of AVD. In patients with a positive PET scan (Deauville score of 4 to 5), treatment with 2 additional cycles of ABVD (total of 4) is recommended. Patients are then restaged with PET, and 2 additional cycles of ABVD (total of 6) administered with or without ISRT is an option for those with a negative interim PET scan (Deauville score of 1 to 3). A biopsy is recommended for patients with a Deauville score of 4.
or 5. If the biopsy is negative, treatment with 2 additional cycles of ABVD (total of 6) administered with or without ISRT is an option. Patients with a positive biopsy should be managed as described for refractory disease.

Several studies have reported that early intensification to escalated BEACOPP in patients with a positive interim PET scan (based on the 5-PS) after 2 cycles of ABVD is associated with favorable outcomes. Based on these findings, the guidelines recommend escalated BEACOPP (4 cycles) as an option for patients with a Deauville score of 4 or 5 after 2 cycles of ABVD. Patients are then restaged with PET, with observation or ISRT to initially bulky or selected PET-positive sites included as options for patients with a Deauville score of 1 to 3, and biopsy recommended for patients with a Deauville score of 4 or 5. If the biopsy is negative, treatment with ISRT directed to PET-positive sites is an option. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by restaging after chemotherapy (see HODG-11; page 617). ISRT (30–36 Gy; within 2–3 weeks after completion of chemotherapy) to initial sites >5 cm and involved spleen is recommended for patients with a Deauville score of 1 to 4 and for those with a Deauville score of 5 with a negative biopsy. Patients with a positive biopsy should be managed as described for refractory disease.

Escalated-dose BEACOPP is administered for 6 cycles followed by restaging with PET (see HODG-12; page 617). No further treatment is necessary for patients with a Deauville score of 1 or 2. Based on the final results of the HD12 and HD15 trials, ISRT to residual PET-positive sites >2.5 cm is recommended for patients with a Deauville score of 3 or 4 after 6 cycles of BEACOPP. Biopsy is recommended for all patients with a Deauville score of 5 after 6 cycles of BEACOPP. Observation or ISRT to the initially bulky or PET-positive sites are included as options for patients with a negative biopsy. Patients with a positive biopsy should be managed as described for refractory disease.

The feasibility of de-escalation of therapy to ABVD in patients with advanced-stage disease (IPS ≥3) who experienced CR after 2 cycles of escalated BEACOPP has been demonstrated in studies conducted by the Israeli Study Group. Interim restaging with PET after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy (4 cycles of ABVD) may be considered in patients with a negative interim PET.

**Follow-up After Completion of Treatment**

Recommendations included in the guidelines are largely based on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, because there are very few data available on the follow-up and monitoring of late effects in patients with HL after completion of treatment.

The panel agrees that given the long-term risks of the therapies for HL, patients should be followed up with an oncologist who is aware of these risks and complications, especially during the first 5 years after treatment to detect recurrence and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease (see HODG-14; page 618). The follow-up schedule should be individualized, depending on clinical circumstances such as patient’s age, stage of disease, and initial treatment modality. Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects, health habits, and psychosocial issues. It is recommended that the patient be provided with a treatment summary at the completion of therapy, including details of RT, OARs, and cumulative anthracycline dosage given.

**Monitoring for Late Effects**

Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most serious late effects among 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 >10 years ago.

**Secondary Cancers:** Solid tumors are the most common secondary cancers and most develop >10 years after treatment completion. The risk of developing secondary cancers is highest when RT is used as a component of first-line treatment. A meta-analysis by Franklin et al. showed that the risk of developing secondary cancers was lower with combined modality treatment than with RT alone as the initial treatment. The risk was marginally higher with combined modality treatment compared with chemotherapy alone as initial treatment. Lung and breast cancers...
are the most common secondary cancers in patients with HL. Annual breast screening [mammography and MRI] beginning no later than 8 to 10 years after completion of therapy or at age 40 years (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation.90 The NCCN Guidelines recommend breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age, which is consistent with the recommendation of the American Cancer Society guidelines.91 The NCCN Guidelines recommend that routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancers be performed as per the American Cancer Society guidelines.

Cardiovascular Disease: Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.92–94 RT-induced cardiotoxicity is usually observed more than 5 to 10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Coronary CT angiography abnormalities have been detected in nearly 15% of patients within the first 5 years after treatment, and the incidence significantly increases 10 years after treatment.95 In a multivariate analysis, patient’s age at treatment, hypercholesterolemia, hypertension, and RT dose to the coronary artery origins were identified as independent prognostic factors.

Based on data regarding increased long-term risk of cardiac disease, annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors is recommended.96 A baseline stress test or echocardiogram and carotid ultrasound (for patients treated with neck RT) should be considered at 10-year intervals after treatment completion.

Hypothyroidism: Abnormal thyroid function, mostly hypothyroidism, is reported in approximately 50% of long-term survivors who received neck or upper mediastinal irradiation.96 A careful thyroid examination should be a part of the physical examination. Thyroid function tests should be performed at least annually to rule out hypothyroidism, especially in patients treated with RT 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 very long beyond completion of the primary treatment program. However, patients who undergo HDT/ASCR or allogeneic hematopoietic stem cell transplant may be at continued risk for infection. Pneumococcal, meningococcal, and H-flu revaccinations are recommended every 5 years for patients treated with splenic RT or splenectomy.

Infertility: Certain chemotherapy combinations (eg, BEACOPP) may cause immediate and permanent infertility in both men and women.96,97 Other combinations (eg, ABVD) are only rarely associated with infertility.92,98 Because women who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause,40 this should be taken into consideration with respect to family planning.

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, and their concurrent use with chemotherapy significantly decreases OS rate.99 Recently, 2 separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.100,101 The NCCN Guidelines do not recommend the routine use of growth factors with ABVD regimens.

Summary
Current management of CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5–PS). Combined modality therapy (ABVD, ABVD followed by escalated BEACOPP, or Stanford V plus ISRT) or ABVD alone are included as treatment options for patients with stage IA or IIA favorable CHL. Chemotherapy (ABVD or Stanford V or BEACOPP plus ABVD) followed by consolidative ISRT is recommended for patients with stage I–II unfavorable disease. Chemotherapy with ABVD or Stanford V or escalated-dose BEACOPP is recommended for patients with stage III–IV disease.
References


### Individual Disclosures for the Non–Small Cell Lung Cancer Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/ Data Safety Monitoring Board</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
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<td>Ranjana H. Advani, MD</td>
<td>Agenosy; Allos Therapeutics; Celgene Corporation; Genentech, Inc.; Infinity; Janssen Pharmaceutical Products, LP; Kura Oncology, Inc.; Merck &amp; Co., Inc.; Millennium Pharmaceuticals, Inc.; Pharmacyclics; Regeneron Pharmaceuticals, Inc.; and Seattle Genetics</td>
<td>Bristol-Myers Squibb Company; Cell Medica; Forty Seven, Inc.; Genentech, Inc.; Juno; Spectrum; and Sutro</td>
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<td>Weiyun Z. Ai, MD, PhD</td>
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<td>Richard F. Ambinder, MD, PhD</td>
<td>None</td>
<td>Chinese University Hong Kong</td>
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<td>Patricia Aoun, MD, MPH</td>
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<td>Celeste M. Bello, MD, MSPH</td>
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<td>Karl Bernat, MD</td>
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<td>Kristie A. Blum, MD</td>
<td>Celgene Corporation; Constellation Pharmaceuticals; Janssen Pharmaceutical Products, LP; Millennium Pharmaceuticals, Inc; Morphosys; Novartis Pharmaceuticals Corporation; and Pharmacies</td>
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<td>Andres Forero, MD</td>
<td>Abbott Laboratories; Celgene Corporation; Daiichi-Sankyo Co.; Genentech, Inc.; GlaxoSmithKline; Incyte; Novartis Pharmaceuticals Corporation; Oncosteryon; Pfizer Inc.; Pharmacyclics; Seattle Genetics; Synta Pharmaceuticals Corp.; and TRACON</td>
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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:

Jane Winter, MD: UptoDate