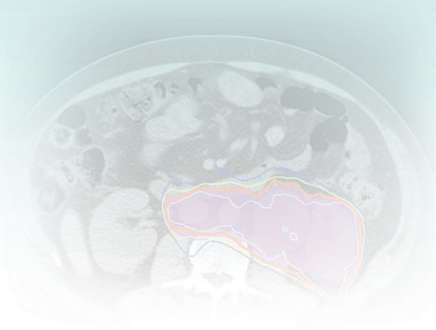
CHAPTER

76 Hodgkin's Lymphoma



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INCIDENCE

There are approximately 8,500 new cases in the United States each year.

BIOLOGIC CHARACTERISTICS

Hodgkin's/Reed-Sternberg (HRS) cells are the malignant cells in Hodgkin's lymphoma.

Increasing epidemiologic and molecular evidence support that a combination of genetic susceptibility, immune response impairment, and exposure to specific infectious agents may play a central role in the pathogenesis of the disease.

PATHOLOGY

Classical Hodgkin's lymphoma (HL; CD15+, CD30+, CD45–), four subtypes: nodular sclerosis, lymphocyte rich, mixed cellularity and lymphocyte depleted.

Nodular lymphocyte predominant HL (CD45+, CD20+, CD 15–, CD 30–).

STAGING EVALUATION

History and physical examination, focusing on constitutional symptoms, nodal involvement, and organomegaly.

Complete blood count, erythrocyte sedimentation rate (ESR), and serum albumin.

Computed tomography (CT) of chest, abdomen, and pelvis; positron emission tomography (PET).

Bone marrow biopsy if constitutional symptoms present or advanced-stage disease is.

THERAPY IN EARLY-STAGE DISEASE

Standard therapy is combined-modality therapy with two to four cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved-site radiation therapy in favorable patients and four to six cycles of ABVD followed by involved-site radiation therapy in patients with unfavorable disease, with 5-year disease-free survival (DFS) of about 90%.

Abbreviated regimens in patients with unfavorable prognostic features (bulky disease, four or more sites of disease, presence of constitutional symptoms) should be avoided.

Clinical trials are evaluating the role of PET response to chemotherapy in guiding the use of adjuvant radiotherapy.

THERAPY IN ADVANCED-STAGE DISEASE

Standard therapy is chemotherapy alone with ABVD, with 5-year DFS of 70% to 80%.

Dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and its variants may yield superior freedom-from-treatment failure but is associated with increased toxicity.

There is no difference between Stanford V and ABVD as shown in the ECOG 2496 randomized trial on advanced HL.

There may be a role for consolidative radiation therapy in selected cases, including initial bulky disease or lack of complete response to chemotherapy.

SALVAGE THERAPY

High-dose therapy with autologous bone marrow or stem-cell transplantation is the salvage therapy of choice in patients who are refractory to, or relapsed after, a short initial remission to chemotherapy.

Selected patients may be candidates for conventional dose salvage therapy, namely, patients with limited nodal relapse, absence of constitutional symptoms, and long remission duration.

INTRODUCTION

HL was first described by the British physician Thomas Hodgkin in 1832, when he reported six patients with pathologic enlargement of lymph nodes and spleen at Guy's Hospital.[1] Attempts to treat the disease using various chemical or surgical means were unsuccessful until around the turn of the century, when the effectiveness of x-ray in shrinking the disease was first demonstrated. Only crude, low energy x-ray equipment was available at the time, which merely allowed the temporary reduction of the enlarged lymph nodes. The development of kilovoltage equipment in the 1920s and the subsequent pioneering work of Gilbert, a Swiss radiotherapist, paved the way for the definitive treatment of patients with HL.[2] Vera Peters at Ontario Institute of Radiotherapy first reported the curability of early-stage HL in 1950 using high doses of fractionated radiation therapy.[3] The availability of modern, high-energy radiation therapy equipment in the late 1950s and early 1960s allowed the delivery of higher doses of radiation to deep-seated tumor with less limitations by reactions in the superficial tissues. The introduction of effective combination chemotherapy further improved the treatment outcome of HL, especially in patients with unfavorable prognostic features or advanced-stage disease.[4] Over the last three decades, continued improvements in radiation therapy techniques allowing more uniform and better targeted dose delivery, development of more effective and less toxic multiagent chemotherapy regimens, advances in radiographic imaging technology, and the refinement of prognostic factors that allow better tailoring of treatments, HL, a previously fatal illness, has now become one of the most curable forms of malignancy.

ETIOLOGY AND EPIDEMIOLOGY

HL is a relatively uncommon neoplasm, with approximately 8,500 new cases in the United States each year, representing less than 1% of all cancer diagnosis.[5] The incidence, age, and gender distribution of HL vary depending on the geographic

location. The age-incidence curve in developed countries is characterized by a bimodal distribution.[6,7] There is an initial peak in young adults at around age 25, and a second peak occurring at ages 60 to 70, in which a male predominance is observed. The majority of the cases seen in young adulthood are of nodular sclerosis (NS) histology, and many of the factors that have been associated with the development of HL in these patients appear to be a reflection of delayed exposure to infectious agents or higher socioeconomic status. These include early birth order, small sibship size, growing up in single-family houses, few playmates, and high parental education.[8-10] In contrast, in economically disadvantaged parts of the world, HL is relatively rare among young adults.[7] Mixed cellularity (MC) is the predominant histologic subtype in developing countries, with an initial peak in childhood for boys and a late peak in older patients.

The etiology of HL is an unresolved issue but is likely complex and may vary depending on the different subtypes. A combination of genetic susceptibility, immune response impairment, and environmental exposures, especially specific infectious agents, are likely to play a central role in the pathogenesis of the disease.

Several of the epidemiological and clinical features of the disease are suggestive of infectious causes, and there have been increasing evidence that Epstein Barr Virus (EBV) may be involved in the pathogenesis of HL in at least a subset of cases. Patients with history of infectious mononucleosis, in which EBV is the causative agent, are at an approximately threefold increased risk for HL, and particularly EBV-associated HL.[7,11,12] Elevated levels of the IgG and IgA immunoglobulins against the EBV capsid antigen have been demonstrated months to years before clinical HL development.[13,14] In about one third to one half of cases of classical HL occurring in Western populations, monoclonal EBV genome can be detected in the Reed-Sternberg cells.[15,16] EBV positivity is predominantly associated with the MC subtype,[17] which is more common among young children and older adults, and is less frequently associated with NS cases seen mostly in the young adults in the developed world.

The observation of familial aggregation of cases of HL suggests that genetic susceptibility as well as environmental exposure may contribute to the development of HL. A 5-fold increased risk has been demonstrated in first-degree relatives, and siblings of young adults with HL have a 7-fold increased risk.[18] The excess risk appears to be more pronounced in same-sex siblings, which may be related to more shared environmental exposure.[19] In a twin study of young adults with HL, monozygotic twins of patients had an almost 100-fold increased risk,[20] whereas no increased risk for dizygotic twins was observed, supporting the contribution of heritable factors to the development of the disease. In particular, follow-up twin studies have suggested that persons with genetically determined lower IL-6 levels may be less susceptible to young adult HL.[21] In addition, a genome screen of families at high risk for HL has provided evidence for a susceptibility gene on several chromosomes, particularly chromosome 4.[22] Finally, a number of specific human leukocyte antigen (HLA) haplotypes, as well as specific polymorphisms within chromosome 6p21.32 (an area which includes genes involved in immune function, including *HLA-DRB$_1$ and HLA-DOB$_1$*) have been identified to be associated with an increased risk of HL.[22-25] Because immune response is genetically determined by the HLA type, patients with these HLA haplotypes may have increased susceptibility to certain infections, which in turn may lead to the increased HL risk as well as increased susceptibility to autoimmune conditions. In fact, an elevated risk of HL has been found in patients with personal histories of several autoimmune conditions.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The malignant cells in classical HL, the HRS cells, are large, uni- or multinucleated cells, which usually comprise only 1% of the cells present in the tissue sample, with the majority of the tumor consisting of a variety of nonneoplastic inflammatory cells and fibrosis. Results of molecular single-cell studies have shown that in more than 90% of cases, HRS cells have monoclonal immunoglobulin gene rearrangements that are characteristic of mature B lymphocytes, and somatically mutated VH genes that are specific markers for germinal center B cells and their descendants, supporting a germinal center or postgerminal center B-cell origin.[26,27] However, unlike normal B cells that have undergone successful maturation through the germinal cells, HRS cells characteristically show absence of immunoglobulin gene expression. This has been attributed to mutations in the coding or regulatory regions,[28] lack of expression of transcription factors that are responsible for activation of the promoters and enhancers,[28] epigenetic silencing of the immunoglobulin heavy-chain transcription,[29] and constitutive expression of master regulators such as Notch1, ID2, activated B-cell factor 1, and STAT5.[29] Despite their inability to express immunoglobulin receptors, HRS cells are resistant to apoptosis, which normally removes immunoglobulin negative B cells that have traversed the germinal center.

There is increasing evidence connecting the prevention of apoptosis and survival of HRS cells to the activation of the nuclear factor kappa B (NF-κB) transcription factor-signaling pathway. Constitutive NF-κB is required for proliferation and survival of HL tumor cells.[30] The cause of the constitutive activation of NF-κB is probably multifactorial and may include amplification of the REL gene,[31] mutations in NF-κB inhibitors, and somatic mutations in the novel tumor suppressor gene *TNFAIP3*.[32] There is an inverse relationship between EBV infection and inactivation of A20, the protein encoded by the *TNFAIP3* gene, suggesting that they may represent alternative pathways of pathogenesis.[29]

Molecular profiling experiments using HL-derived cell lines with suppressed and unsuppressed NF-κB activity have been performed to better understand the NF-κB signaling pathway and to identify its target genes. One of the regulators of apoptosis that is expressed in dependence of NF-κB is cIAP2, a direct inhibitor of caspase 3, suggesting that HRS cells are protected from caspase 3–induced apoptosis by cIAP2.[33] Another NF-κB dependent regulator of apoptosis is CD95, which has been shown to be upregulated in HRS cells. However, unlike the other NF-κB-dependent regulators, CD95 is known to trigger apoptosis rather than prevent it. The resistance of HRS cells to CD95-mediated apoptotic cell death may be because of functional inhibition of death receptor pathways by cellular FADD-like IL1B-converting enzyme inhibitory proteins (c-FLIP), which is one of the most strongly NF-κB-regulated genes.[34] The contribution of NF-κB signaling to the development of HL is further supported by epidemiological data showing that regular aspirin use is associated with a reduced risk of developing HL, presumably through inhibition of NF-κB transcription.[35] Continued efforts in the elucidation of the NF-κB pathway in the pathogenesis of HL may have important therapeutic implications through pharmacological downregulation of NF-κB activity and its target genes, and increasing the susceptibility of HRS to apoptosis. However, bortezomib, a proteasome inhibitor that inhibits NF-κB activity, does not appear to be clinically active against HL.

The JAK/STAT pathway may also be important in the pathogenesis of HL with chromosomal gains in JAK2 found in about 20% of cases and, in rare cases, a translocation

involving JAK2 may be found.[36] JAK2 may be an activator of STAT signaling. Other signaling pathways possibly deregulated in HL include the PI3K/AKT, MAPK/ERK, and various receptor tyrosine kinase pathways.

Finally, translocations involving the MHC class II transactivator gene CIITA have been found in a subset of classical HL cases, and may contribute to the pathogenesis of HL by inhibiting MHC class II expression.[37]

PATHOLOGY

Since the 1930s, a number of pathological classification systems for HL have been developed. The Rye classification system, introduced at a conference in Rye, New York, in 1966, divided cases of HL into lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depletion (LD).[38] This system was widely adopted in the next 25 years and was subsequently modified in the revised European-American classification of malignant lymphomas (REAL) and later in the World Health Organization (WHO) classification (Table 76-1).[39,40] In the current classification system, HL is specifically recognized as a lymphoma. Based on morphological, immunophenotypic, and clinical characteristics, it is divided into two distinct entities: classical HL and nodular lymphocyte predominant Hodgkin's lymphoma (NLPHD). Table 76-2 compares the morphological and immunophenotypic features of the malignant cells of these two entities. The diagnosis of HL is based on morphological assessment with identification of HRS cells or their variants, along with immunohistochemical studies.

Classical Hodgkin Lymphoma

In the majority of cases of the HRS of classical HL, most markers for B cells or T cells, as well as leukocyte common antigen (CD45) are absent, whereas a number of antigens including CD30 and CD15, which are not usually expressed by normal B cells or T cells, can be detected. The immunophenotypic and genetic features of the malignant cells of the four histological subtypes of classical HL are similar. However, the four subtypes vary in the morphology of the HRS cells, nature of the surrounding reactive cells, association with EBV, and clinical characteristics.

TABLE 76-1 The WHO Histological Classification of Hodgkin Lymphoma[40]

Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL)
Classical Hodgkin's lymphoma (CHL):
Nodular sclerosis classical Hodgkin's lymphoma (NSHL)
Mixed cellularity classical Hodgkin's lymphoma (MCHL)
Lymphocyte rich classical Hodgkin's lymphoma (LRCHL)
Lymphocyte-depleted classical Hodgkin's lymphoma (LDHL)

TABLE 76-2 Comparison of Morphological and Immunophenotypical Characteristics of the Malignant Cells of Classical HD and NLPHD

	Classical HD (HRS cells)	NLPHD (L&H cells)
Nuclei	Mono- and multinucleated, mono- and multilobulated	Mononucleated, multilobulated
Nucleoli	Large	Multiple, small
CD30	+	—
CD15	+ in majority of cases	—
CD45	—	+
CD20	— in majority of cases	+
CD79a	— in majority of cases	+

HD, *Hodgkin's disease;* HRS, *Hodgkin and Reed/Sternberg;* L&H, *lymphocytic and histiocytic;* NLPHD, *nodular lymphocyte predominant Hodgkin's disease.*

The NS subtype accounts for approximately 70% of classical HL, affecting predominantly young adults. Morphologically, it is characterized by the presence of one or more sclerotic bands radiating from a thickened lymph node capsule. The British National Lymphomas Investigation subclassified NS HL into two grades based on the percentage of nodules showing lymphocyte depletion or increased number of anaplastic-appearing HRS cells.[41,42] However, the prognostic value of this grading system with modern therapy is unclear.

The MC subtype is more frequently seen in developing countries, accounting for more than half of the cases, whereas in the more developed parts of the world, it comprises approximately 25% of classical HL. Morphologically, HRS cells are seen scattered in a diffuse inflammatory background with the absence of nodular sclerosing fibrosis. In contrast to the NS and lymphocyte rich classical Hodgkin's lymphoma (LRCHD), EBV positivity is much more frequent in the MC subtype.[43]

LRCHD accounts for approximately 5% of classical HL, has a male predominance and older median age at presentation.[44] It is characterized by a background infiltrate of small, mature, predominantly B-lymphocytes with rare HRS and variants. It can resemble NLPHD morphologically, and immunohistochemical studies of the malignant cells are essential to make the distinction. The prognosis may be slightly better than other subtypes of classical HD.[44]

The LD subtype has increased number of HRS and is depleted in lymphocytes. Many cases that were previously classified as LD HL are now determined to be anaplastic or large-cell non-Hodgkin's lymphoma based on immunohistochemical studies.[45] Reliable clinical data on this subtype is limited given its rarity and uncertainty concerning its diagnosis.

Adverse pathologic prognostic factors include macrophage gene expression signature and higher numbers of CD163+ or CD68+ macrophages; expression of BCL2, the T-cell antigens CD2 and CD4, galectin-1, ABCC1 by HRS cells; a characteristic mRNA signature; and a characteristic miRNA signature.[46]

Nodular Lymphocyte Predominant Hodgkin's Lymphoma

NLPHD comprises 5% of HL. The malignant cells of NLPHD are the LP cells, which are also known as popcorn cells because of their characteristic appearance. The pathogenesis of LP cells is probably distinct from that of HRS but probably shares constitutive NF-κB activity; recurrent translocations involving BCL6 are present in about one half of cases. Unlike classical HL, the neoplastic cells of NLPHD typically lack the expression of CD15 and CD30 markers but are consistently CD20 and CD45 positive.[47] A nodular pattern is seen usually completely or partially replacing the lymph node. The nodules tend to be large and closely packed, and the LP cells are typically seen within or around the nodules. There are usually large numbers of CD57 positive small lymphocytes in the nodules, often with ringing around the lymphocytic and histiocytic (L&H) cells. In about 3% to 5% of cases, transformation to diffuse large B-cell lymphoma may occur.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Presentation

The most common clinical presentation of HL is nontender lymphadenopathy, mostly in the cervical nodal chain,

occurring in about 70% of cases. Axillary or inguinal adenopathy are less frequently reported, found in about 15% and 10% of patients, respectively. Another common presentation is mediastinal adenopathy detected on radiographic imaging. In cases of large mediastinal adenopathy, patients may occasionally present with local symptoms including shortness of breath, chest pain, cough, or superior vena cava syndrome. Rarely, patients may present with an enlarging anterior chest wall mass because of local extension.

Patients may also present exclusively with constitutional symptoms in the absence of any physical findings. These symptoms, also known as B symptoms, include fever, unexplained weight loss, and drenching night sweats. Severe, generalized pruritus, not classified as a B symptom, is noted in about 10% to 15% of patients, and has been associated with a poorer prognosis.[48] Alcohol-induced pain, typically at the site of lymphadenopathy or bony involvement, can be a presenting symptom in some patients.[49]

Staging System

The Ann Arbor staging classification (Table 76-3), developed in 1971, is a four-stage system formulated to provide prognostic information and to guide therapeutic decisions. However, it does not reflect other important prognostic factors such as bulky disease or multiple sites of involvement.[50] The availability of improved imaging techniques has also changed its applicability. In 1988, revisions to the Ann Arbor staging system were made based on a meeting in Coltswolds, England (Table 76-4).[51] Main changes include the following: (1) Allowed the use of CT scanning to assess disease involvement below the diaphragm. (2) For stage II disease, the number of anatomic nodal sites were indicated by a subscript (e.g., stage II_3). (3) For stage III disease, upper and lower abdominal involvement were subdivided as III_1 and III_2, respectively. (4) Bulky disease was denoted by *X*, defined as more than one third widening of the mediastinum at T5-6 level or >10 cm maximum dimension of the nodal mass. (5) Unconfirmed/uncertain complete remission (CRu) was introduced to denote presence of residual imaging abnormality but absence of pathologically confirmed residual disease.

TABLE 76-3 Ann Arbor Staging Classification

Stage	Definitions
Stage I	Involvement of single lymph node region (I) or of single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S), or limited, contiguous extralymphatic organ or site (III_E) or both (III_{SE})
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

The absence or presence of fever, night sweats or unexplained weight loss of 10% or more of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively. The clinical stage (CS) denotes the stage as determined by all diagnostic examinations and a single biopsy only. If a second biopsy of any kind has been obtained, whether negative or positive, the term pathologic stage (PS) is used.

Patient Evaluation and Staging Workup

An adequate surgical biopsy for pathological assessment by an experienced hematopathologist is essential in the initial diagnosis of HL. All patients need to undergo a careful history and physical examination. Particular attention should be placed on the presence and duration of constitutional symptoms, as well as other symptoms that may be indicative of extent and bulkiness of local disease. On physical examination, all nodal groups should be thoroughly palpated with clear documentation of the extent of disease involvement. Baseline blood work, some of which have been shown to be of prognostic value in patients with HL, should be obtained. These include complete blood count with differential, sedimentation rate, and serum albumin.[52] Fluorine-18-fluorodeoxyglucose positron emission tomographic (FDG-PET) scan, which has been shown to be more sensitive then CT scanning, and results in upstaging of 15% to 25% of patients, is now considered part of standard staging work-up for HL.[53-59] A separate diagnostic CT is not necessary if it was done as part of an integrated PET-CT scan. The performance of bone

TABLE 76-4 The Coltswolds Staging Classification for Hodgkin's Lymphoma

Stage	Definitions
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a suffix (e.g., II_3)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both III SE) III_1: With or without involvement of splenic, hilar, celiac or portal nodes III_2: With involvement of paraaortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
DESIGNATIONS APPLICABLE TO ANY DISEASE STAGE	
A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained weight loss >10% of body weight within the prior 6 months
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension greater than 10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathological stage (as determined by staging laparotomy)

TABLE 76-5 Patient Evaluation and Staging

HISTORY
Constitutional symptoms
Symptoms that may be indicative of extent and bulk of local disease (e.g., pulmonary symptoms, swelling, pain)
PHYSICAL EXAMINATION
Careful palpation of all nodal groups
Palpate for organomegaly
RADIOGRAPHIC STAGING
PET/CT scan
PATHOLOGICAL EVALUATION
Excisional biopsy depending on location of disease
Bone marrow biopsy only in patients with advanced stage disease or constitutional symptoms
BLOOD WORK
CBC with differential
ESR
Serum albumin
PRETREATMENT BASELINE EVALUATION
Patients to be receiving Adriamycin: baseline MUGA scan
Patients to be receiving bleomycin: baseline pulmonary function tests

CBC, *Complete blood count;* ESR, *erythrocyte sedimentation rate;* MUGA, *multigated acquisition scan;* PET/CT, *positron emission tomography/computed tomography.*

marrow biopsy should be limited to patients with advanced-stage disease or in those with constitutional symptoms given the low yield in patients with early-stage, favorable-prognosis disease of less than 1%.[60,61] The recommended patient evaluation and staging studies for newly diagnosed HL are listed in Table 76-5.

Prognostic Factors

For patients with early-stage HL, several prognostic factors, largely based on patients treated with radiation therapy alone, have been identified. These include B symptoms, sedimentation rates, disease bulk, number of sites of disease, age, and histology. Cooperative groups have used varying combination of these factors to stratify patients into favorable versus unfavorable disease in clinical trials. Examples of various prognostic classification systems used by cooperative groups are shown in Table 76-6.

For patients with advanced-stage disease, Hasenclever et al developed the International Prognostic Score (IPS), using data from more than 5000 patients with advanced-stage HL, mostly treated with doxorubicin-based combination chemotherapy.[52] Seven factors were found to have similar independent prognostic value in predicting freedom-from progression (FFP) and overall survival (OS). These included hypoalbuminemia (<4 g per deciliter), anemia (<10.5 g per deciliter), male sex, age 45 years or older, stage IV disease, leukocytosis (>15,000 per cubic millimeter), and lymphocytopenia (<600 per cubic millimeter, <8 percent of the white-cell count, or both). The 5-year FFP ranged from 42% in patients with an IPS score of ≥5% to 84% in patients with a score of 0 (Table 76-7). However, patients with five or more of the adverse factors account for only 7% of the study population. The IPS has been used in trials for patient selection and patient stratification, and it may also have a role in guiding tailored therapy based on relapse risk in advanced-stage patients.

An early response to PET has been identified as a powerful prognostic tool in HL.[62] In a joint Italian-Danish study,[53] PET response after two cycles of chemotherapy overshadowed the prognostic value of IPS and emerged as the single most important prognostic factor in advanced-stage HL. Several PET-adaptive clinical trials are testing the hypothesis that interim PET results can guide decisions regarding treatment escalation or deescalation.

TABLE 76-6 The Prognostic Classification Systems for CS I-II Hodgkin's Lymphoma

Institution	Prognostic Classification
EORTC	***Unfavorable Prognosis***: Presence of *any* one of the following: Age >50 years No B symptoms with ESR ≥50 B symptoms with ESR ≥30 ≥4 sites of involvement Bulky mediastinal involvement ***Favorable Prognosis***: Absence of *all* of the factors in the unfavorable prognosis group
GHSG	***Unfavorable Prognosis***: Presence of *any* one of the following: Elevated erythrocyte sedimentation rate (≥50 mm without or ≥30 mm with B symptoms) ≥3 sites of involvement Extranodal involvement Large mediastinal mass ***Favorable Prognosis***: Absence of *all* of the factors in the unfavorable prognosis group
NCI-C (excluded patients with bulky disease)	***Low risk***: Presence of *all* of the following: LP/ NS Age <40 ESR <50 <3 sites of involvement ***High risk***: All other patients

CS, *Clinical stage;* EORTC, *European Organisation for Research and Treatment of Cancer;* ESR, *erythrocyte sedimentation rate;* GHSG, *German Hodgkin Study Group;* LP, *lymphocyte predominant;* NCI-C, *National Cancer Institute-Canada;* NS, *nodular sclerosis.*

TABLE 76-7 The International Prognostic Scoring System for Advanced-Stage Hodgkin's Lymphoma

Prognostic Score	5-Year Freedom-From-Progression (%)	5-Year Overall Survival (%)
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
>5	42	56

Note: Each of the following factors carries a score of one: hypoalbuminemia, anemia, male sex, age ≥45, stage IV disease, leukocytosis, and lymphocytopenia.

PRIMARY THERAPY FOR EARLY-STAGE HODGKIN'S LYMPHOMA

Early-stage HL comprises about 60% of all cases of HL. Historically, the primary therapy for early-stage HL had been

extended-field radiation therapy alone, with addition of chemotherapy in the presence of unfavorable prognostic factors. Since the introduction of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), a more effective and less toxic combination chemotherapy regimen than mechlorethamine, vincristine, procarbazine, prednisone (MOPP), there has been a shift to the use of combined-modality therapy in patients with early-stage disease, which yields long-term cure rates of approximately 90% or higher. Randomized studies have shown a significantly higher FFTF with combined-modality therapy than with radiation therapy alone.[63-65]

Because of the excellent survival in this relatively young group of patients, late effects of therapy have been increasingly recognized.[66-73] Most of the current trials on early-stage HL focus on treatment reduction and modification. The key questions addressed by the trials on the use of combined-modality therapy for early-stage HL include the following: (1) What is the optimal combination chemotherapy regimen? (2) How many cycles of chemotherapy are needed? (3) What are the appropriate radiation field size and dose? (4) Can radiation therapy be eliminated?

Optimal Combination Chemotherapy Regimen

Investigators have explored alternatives or modification of the ABVD regimen to limit toxicity in favorable patients or to improve efficacy in unfavorable patients. Examples include vinblastine, bleomycin, and methotrexate (VBM)[74-77]; methotrexate, vinblastine, and prednisone (MVP)[75]; doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone (VAPEC-B)[78]; doxorubicin, vinblastine (AV)[63]; mitoxantrone, vincristine, vinblastine, and prednisone (NOVP)[79]; and epirubicin, bleomycin, vinblastine, and prednisone (EBVP II, administered monthly).[80] Most of these regimens showed promising results at least in patients with favorable-prognosis disease, with relapse-free survival (RFS) rates of about 90%. The Stanford V regimen (nitrogen mustard, Adriamycin, vincristine, vinblastine, etoposide, bleomycin, and prednisone, followed by radiation therapy to initial nodal involvement in selected cases), a short but intensive 12-week regimen, was originally developed for patients with advanced-stage disease or bulky, early-stage disease.[81,82] The Stanford group reported the results on 87 patients with nonbulky, stages I to IIA disease treated with an abbreviated, 8-week course of Stanford V followed by involved-field radiotherapy (IFRT) to 30 Gy.[83] At a median follow-up of 10 years, the FFP, DFS, and OS were 94%, 99%, and 94%, respectively. The German Hodgkin's Study Group (GHSG) HD13 trial compared two cycles of ABVD, AVD, ABV, and AV, all followed by 30 Gy of involved-field irradiation in clinical stage (CS) I to CS II patients without risk factors. The two arms without dacarbazine (AV and ABV) were closed early because of higher than expected relapse rates. In the most recent update, the AVD arm was significantly inferior to the ABVD arm mainly as a result of late relapses.

Attempts to deescalate chemotherapy in patients with unfavorable-prognosis disease have been disappointing.[84] To improve the treatment outcome in patients with unfavorable features, trials had been conducted to determine whether these patients may benefit from the regimen BEACOPP, originally developed for patients with advanced-stage disease. Both the European Organization for Research and Treatment of Cancer (EORTC) H9U and the GHSG HD11 studies compared four to six cycles of ABVD with four cycles of BEACOPP-baseline, followed by involved-field irradiation to 20 Gy to 30 Gy. No significant differences in 4-year EFS or OS were observed between BEACOPP and ABVD in the EORTC H9U trial. In the GHSG HD11, at a median follow-up of 82 months, a significantly higher 5-year freedom-from-treatment failure (FFTF) in the four cycles of baseline BEACOPP arm over the four cycles ABVD arm, if followed by 20 Gy of involved-field radiation therapy (86.8% versus 81.1%; 95% confidence interval [CI] of difference, 0.1% to 11.3%). However, there was no significant difference between BEACOPP and ABVD if followed by 30 Gy of involved-field radiation therapy.[85] Patients treated with baseline BEACOPP had a higher rate of severe toxicity than patients treated with ABVD (73.8% versus 51.5%, $p < 0.001$). The GHSG HD 14 trial tested increasing dose intensity using dose-escalated BEACOPP in patients with unfavorable CSs I-II disease, randomizing patients to four cycles of ABVD versus two cycles of dose-escalated BEACOPP and two cycles of ABVD (two-plus-two regimen), followed by involved field irradiation to 30 Gy. At a median follow up of 43 months, the two-plus-two regimen had a significantly improved 5-year FFTF by 7.2% (hazard ratio [HR], 0.44, $p < 0.001$), though it was associated with more acute toxicity. There was no difference in overall survival between the two arms.[86]

Optimal Duration of Chemotherapy

Whether the number of cycles of chemotherapy can be shortened in patients with favorable-prognosis disease was by addressed by the GHSG HD10 trial, in which CSs I-II patients without risk factors were randomized to four cycles or two cycles of ABVD, followed by 30 Gy or 20 Gy involved-field irradiation. At a median follow-up of 7.5 years, there were no significant differences between four versus two cycles of chemotherapy in 8-year FFTF (88.4% versus 85.7%), 8-year OS (94.6% versus 94.4%).[87] In patients with unfavorable-prognosis disease, the optimal number of cycles of chemotherapy was one of the study questions in two successive EORTC trials using different chemotherapy regimens. In the EORTC-H8U trial, patients were randomized to six cycles of MOPP/ABV followed by involved-field irradiation, four cycles of MOPP/ABV followed by involved-field irradiation or four cycles of MOPP/ABV followed by extended-field irradiation.[88] At a median follow-up of 92 months, there was no significant difference in 5-year EFS rates among the three treatment groups (84%, 88%, and 87%). The OS rates at 10 years were also not significantly different (88%, 85%, and 84%).[64] In the previously described EORTC-H9U trial, randomizing patients to six cycles of ABVD, four cycles of ABVD, or four cycles of BEACOPP, all followed by involved-field irradiation, at a median follow up of 57 months, there was no difference in 4-year EFS among the three arms (91%, 87%, and 90%, $p = 0.38$).[89]

Optimal Radiation Field Size

Historical Radiation Fields

Historically, extended field radiation therapy (EFRT) alone was standard treatment for early-stage HL, and later administered as part of combined-modality therapy. However, mature results from several randomized trials have since become available, showing no difference in FFTF and OS between EFRT versus IFRT after chemotherapy for early-stage HL.[64,90,91] As expected, more second malignancy cases were seen in the EFRT arm than the IFRT arm.

In most clinical trials conducted in the past decade, IFRT was employed. An involved field encompasses not only the involved nodes but also the other lymph nodes within the same lymph node region, as denoted by the Rye classification for staging. It was developed in the two-dimensional treatment planning era, in which the field design is largely based on bony landmark, with inclusion of a considerable volume of normal tissue in the irradiated field.[92] However, there are data suggesting that relapse sites in HL after chemotherapy

alone are largely limited to the initially involved node.[93] This has led to the concept of involved-node radiotherapy (INRT), first described by the European Organization for Research and Treatment of Cancer/Groupe d'Etudes des Lymphomes de l'Adulte (EORTC/GELA) and later the GHSG.[94,95]

Modern Radiation Fields: ISRT and INRT

Availability of cross-sectional imaging for radiation planning, accurate dosimetry using modern algorithms that adjust for tissue inhomogeneities, complex beam shaping with multileaf collimation, and intensity-modulated beam delivery in selected cases have made it possible to better define and further decrease radiation fields. Guidelines for INRT and involved-site radiation therapy (ISRT), based on best available evidence and consensus of expert opinion, were recently published by the International Lymphoma Radiation Oncology Group (ILROG).[96] The key difference between INRT and ISRT is whether an optimal prechemotherapy PET-CT scan is available to guide the treatment planning. For INRT, ideally, the prechemotherapy PET/CT is acquired in the treatment position, using the same breathing instructions and immobilization device. However, prechemotherapy PET/CT scan with patient in an approximate position suitable for later radiation treatment is also considered sufficient. ISRT accommodates cases in which optimal prechemotherapy imaging is not available. In such cases, allowance should be made in the clinical target volume (CTV) for uncertainties resulting from differences in positioning of the prechemotherapy scan and planning CT.

For volume definitions, the guidelines recommend that the CTV be determined by fusion of planning CT with with prechemotherapy PET-CT. The original disease volume is first contoured, and then uninvolved normal structures (e.g., lungs, muscles, major vessels) are excluded. Figure 76-1 illustrates case examples of CTV determination based on prechemotherapy PET-CT results. The determination of the CTV is the most important and challenging step because it heavily relies on the availability of optimal prechemotherapy imaging.

In selected sites, there may also be a need to determine an internal target volume (ITV), with expansion of the CTV to account for uncertainties in size, shape, and position of the CTV because of motion. Margins for extension from CTV to ITV may be obtained from four-dimensional CT or fluoroscopy. This may be most relevant where target motion is expected, including chest and upper abdominal sites, and where breath-hold techniques are not available. The EORTC/GELA group defines the planning target volume (PTV) as 1-cm isotropic expansion of the CTV to allow for organ motion and set-up variations.[94] The GHSG defines the PTV as 2-cm axial and 3-cm cranial caudal expansion of the CTV (if necessary, can be reduced to 1 cm to 1.5 cm if close proximity to critical structures) and for mediastinal disease, 1-cm axial and 2-cm cranial caudal expansion.[95] Unlike the European guidelines, the ILROG guidelines do not specify the extent of the PTV expansion. Instead, the recommendation is to use standard margins per institution, depending on immobilization device, body site, and patient cooperation.

Several studies have addressed the safety of radiation field reduction from IFRT. Investigators from the British Columbia reported results of their experience on INRT for patients with early-stage HL. At a median follow up of 50 months, no local recurrences were observed. However, the INRT employed in this study encompassed the initially involved lymph nodes with a margin ranging from 1.5 cm to 5 cm to the field edge and therefore included a larger volume than that of the INRT as defined by the European groups.[97] In addition, two-dimensional planning was performed in some of the patients. In a study from the Institut Gustave Roussy, results of 50 patients with early-stage HL treated with ABVD followed by INRT as per the EORTC/GELA definition was reported. With a median follow-up time of 53 months, the 5-year progression-free survival (PFS) rate was 92%. A total of four relapses were observed, including two distant and two infield relapses. Maraldo et al reported on treatment outcome of 97 patients with early-stage HL treated with ABVD followed by INRT according to the EORTC/GELA guidelines. A 4-year FFP rate of 96% was reported at a median follow up of 50 months. There were three relapses, two of which were infield and one was in the contralateral neck. Results thus far therefore suggest that the use of a much more limited field than the traditional IFRT does not appear to be associated with marginal misses and may indeed be safe in the presence of effective chemotherapy.

In the EORTC/Lymphoma Study Association (LYSA)/the Italian Lymphoma Foundation (FIL) H10 trial (which will be discussed later) for early-stage favorable and unfavorable HL, INRT was adopted in both the standard and experimental arms. In the ongoing GHSG HD17 trial for early-stage HL with risk factors (which will be discussed later), addressing the use of PET response to guide radiotherapy use, INRT is used in the experimental arm in patients with PET-positive disease after chemotherapy.

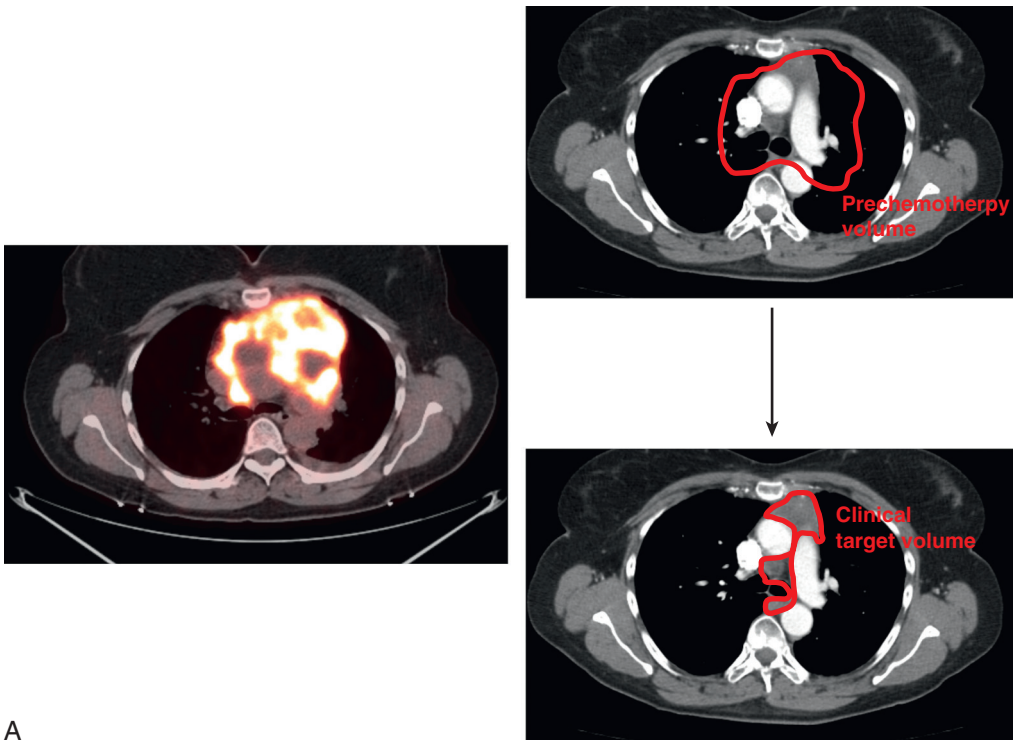
Optimal Radiation Dose

The appropriate radiation dose after chemotherapy in early-stage HL has been explored by three trials.[80,85,87,98,99] The EORTC H9F trial is a three-arm trial in which all patients receive six cycles of EBVP II.[80] After a complete response, patients were randomized to receive no further treatment, 36 Gy, or 20 Gy of IFRT. Patients with a partial response all received 36 Gy of IFRT with or without a 4-Gy boost. A complete response or complete response unconfirmed was achieved in 619 patients. At a median follow-up of 33 months, the 4-year EFS in the three arms of 36 Gy, 20 Gy, and no radiotherapy were 87%, 84%, and 70%, respectively. The difference in treatment results between the two doses of radiotherapy was not significant. However, the no-radiotherapy arm was closed early because stopping rules were met (>20% of events, which will be discussed).

The GHSG HD10 trial is a four-arm trial for low risk (no bulky mediastinal mass or extranodal disease, 3 or less nodal sites, low sedimentation rate) patients at CSs I to II, in which involved-field radiotherapy to 30 Gy versus 20 Gy after four or two cycles of ABVD were compared.[87] At a median follow-up of 7.5 years, there were no significant differences between 30 Gy versus 20 Gy of involved-field radiotherapy in 8-year OS (94.9% versus 95.6%), 8-year FFTF (87.8% versus 88.6%) and 8-year PFS (88.1% versus 88.9%). The question of optimal radiation dose in unfavorable patients was addressed by the GHSG HD11 trial,[85] a four-arm trial comparing 20 Gy versus 30 Gy after four cycles of ABVD or baseline BEACOPP. At a median follow-up of 82 months, the 5-year FFTF rates were 81.1%, 85.3%, 86.8%, and 87.0%, respectively. Baseline BEACOPP was more effective than ABVD when followed by 20 Gy of IFRT, but the two regimens yielded similar outcome when followed by 30 Gy of IFRT. There was no significant difference in 5-year FFTF rate between baseline BEACOPP and ABVD when followed by 30 Gy of IFRT; however, inferiority of 20 Gy cannot be excluded after four cycles of ABVD, leading to the authors' conclusion of four cycles of ABVD followed by 30 Gy of IFRT as optimal therapy for early-stage, unfavorable HL.

Chemotherapy Alone

There are well-documented late effects of radiotherapy for HL, based largely on patients treated with radiation therapy



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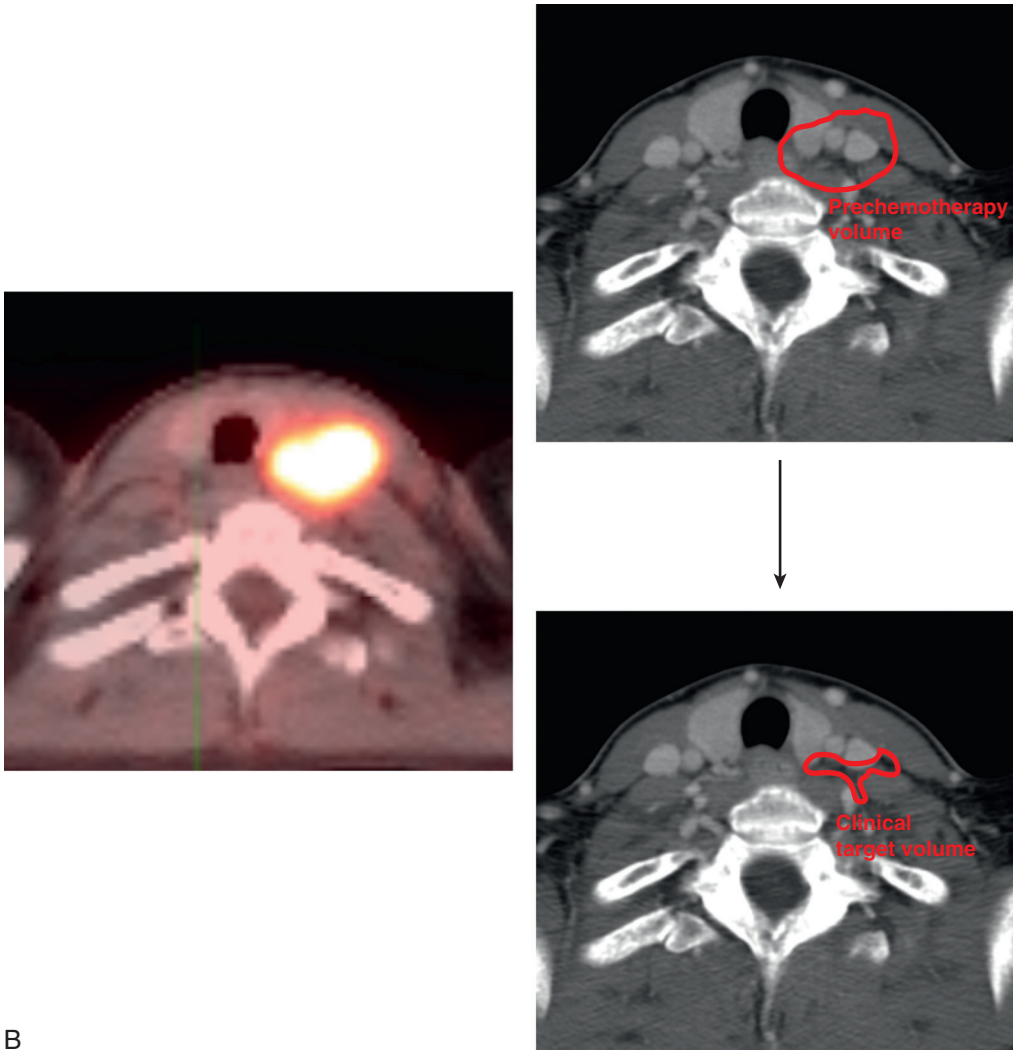

B

Figure 76-1 Determination of clinical target volume (CTV) based on prechemotherapy volume with disease involvement of the mediastinum **(A),** neck **(B),** and axilla **(C).**

Continued

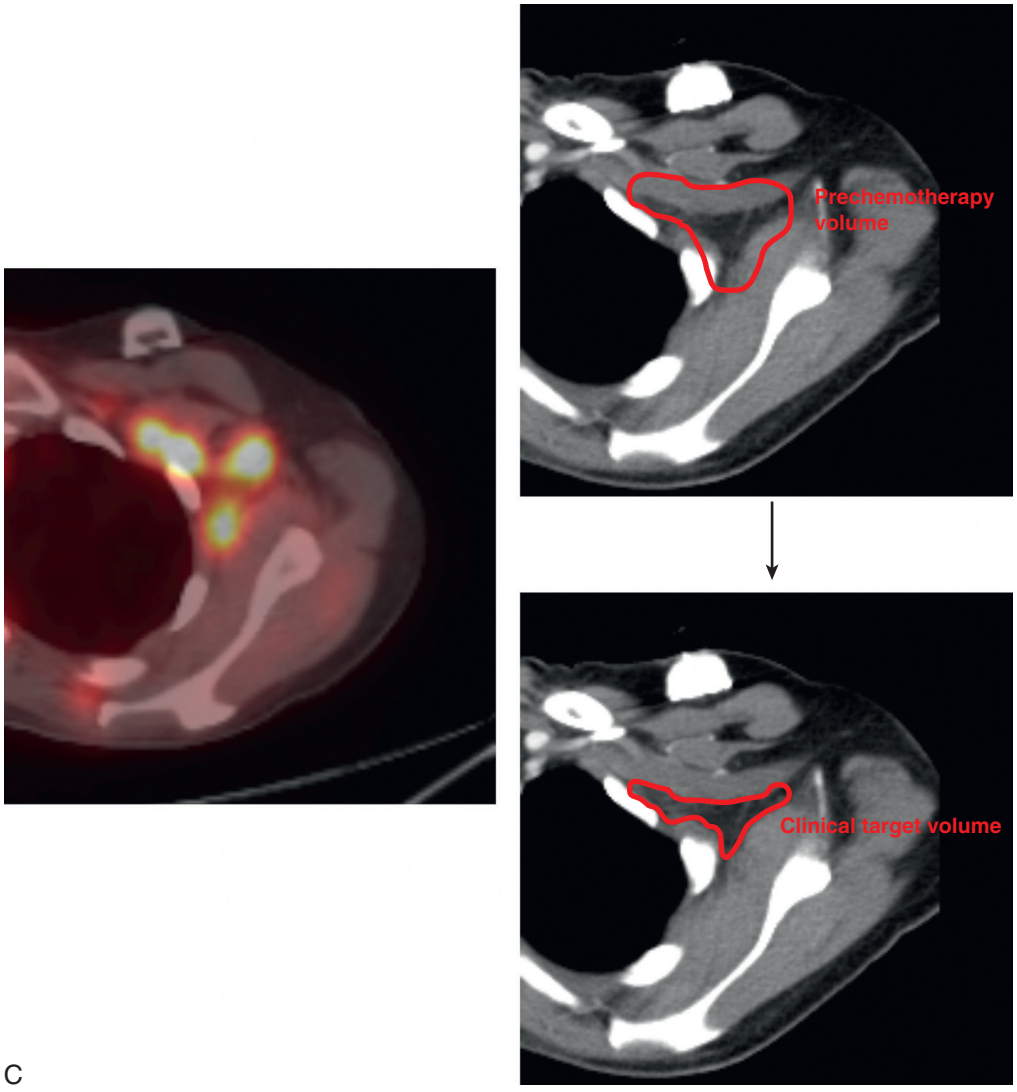

Figure 76-1, cont'd

alone with larger treatment fields and higher doses of radiation than currently employed. These include risks of second malignancies,[100-103] in particular, the risk of breast cancer in women irradiated at a young age,[104,105] and lung cancer among smokers,[106-108] and risks of cardiovascular disease.[109] Because of these concerns, investigators have explored the option of eliminating radiation therapy and treating patients with early-stage disease with chemotherapy alone. Table 76-8 summarizes randomized trials that had compared combined modality therapy with chemotherapy alone.[110-117] These trials varied in the study design, patient population, types of chemotherapy, and radiation fields employed. All but one trial showed a significant DFS, EFS, or freedom-from-progression benefit with the addition of radiation therapy.[110-114] This included the recently reported National Cancer Institute Canadian (NCIC) HD6 trial,[117] which showed that the radiotherapy-containing arms were associated with an improved 10-year failure-free survival rate (92% versus 87%, $p = 0.05$). This is despite the fact that extended-field radiation therapy alone, an approach that has been shown to significantly inferior to combined-modality therapy, was used in patients with low-risk disease. In the same trial, however, despite the improved failure-free survival, the radiotherapy-containing arm was associated with a significantly reduced 10-year OS (87% versus 92%, $p = 0.04$). Ten of the 24 deaths on the radiotherapy-containing arm were from second malignancy, which is likely related to the use of extended-field radiation therapy in patients with both low- and high-risk disease in this trial.

The Cochrane Haematological Malignancies Group recently conducted a meta-analysis,[118] in which five randomized controlled trials that compared chemotherapy alone with identical chemotherapy combined with radiotherapy for patients with stages I to II HL were included. The results showed that, in addition to a significant disease-control benefit favoring the combined-modality therapy approach, there was a highly significant overall survival benefit with the addition of radiation therapy (HR, 0.4; $p < 0.00001$). However, one main criticism of this analysis was the inclusion of trials that used inadequate chemotherapy. It therefore appears that less effective or abbreviated chemotherapy, or alternatives to ABVD designed to limit chemotherapy-related toxicity, is not acceptable when radiation therapy is omitted, and the addition of radiation therapy may allow the use of lower cumulative doses of doxorubicin or less toxic regimens. Toxicities associated with full course ABVD can be nontrivial, and these include myelosuppression, peripheral neuropathy, bleomycin lung toxicity, and cardiac toxicity.[119-121] A significantly increased excess cardiac

TABLE 76-8 Randomized Trials Comparing Combined Modality Therapy and Chemotherapy Alone in Early-Stage Hodgkin's Lymphoma

Institution	No.	Patient Population	Treatment Arms		MED F/U	Results	
						CMT	Chemo Alone
GATLA[114]	277	CS I-II (Included patients with unfavorable factors: age >45, >2 sites or bulky disease) 45% <16 years	CVPP × 6	30 Gy IFRT No RT	84 months	DFS: 71% OS: 89% *Favorable group:* DFS: 77% OS: 92% *Unfavorable group:* DFS: 75% OS: 84%	62% (p = 0.01) 82% 70% 91% 34% (p = 0.001) 66%
CCG[116]	829	Group 1: CS I-II without adverse factors* and without B Sx in CS II Group 2: CS I-II with adverse factors and CS III Group 3: CS IV	Group 1: COPP/ABV × 4 Group 2: COPP/ABV × 6 Group 3: intensive multidrug chemotherapy with GCSF support If CR If PR	 21 Gy IFRT No RT 21 Gy IFRT	92 months	*As-treated:* 10-yr EFS: 91.2% 3-yr OS: 97.1%	82.9% (p = 0.004) 95.9% (p = 0.5) ARM CLOSED
Tata Memorial Hospital[110]	251	CS I-IV (55% CS I-II 46% age <15 years 71% MC histology 15% bulky disease)	ABVD × 6 If CR	 RT† No RT	63 months	8-yr EFS: 88% 8-yr OS: 100%	76% (p = 0.01) 89% (p = 0.002)
MSKCC[115]	152	CS IA-IIB, CS IIIA (bulky disease excluded)	ABVD × 6	RT‡ No RT	60 months	5-yr FFP: 86% 5-yr OS: 97%	81% (p = 0.61) 90% (p = 0.08)
NCIC/ECOG[117]	405	CS I-IIA (bulky disease excluded) Low risk: LP/NS, age <40, ESR <50 and <3 sites High risk: all other	Low risk: High risk:	STNI ABVD × 4-6 ABVD × 2 + STNI ABVD × 4-6	11.3 years	(*Low risk:* STNI; *High risk:* CMT) 10-yr FFS: 92% 10-yr OS: 87%	 87% (p = 0.05) 92% (p = 0.04)
EORTC H9F[80]	771	CS I-II, favorable-prognosis	EBVP II × 6 If CR If PR	 36 Gy IFRT 20 Gy IFRT No RT 36 Gy IFRT ± 4 Gy	33 months	(36 Gy) 4-yr EFS: 87% (20 Gy) 4-yr EFS: 84%	(0 Gy) 70% ARM CLOSED

CCG, *Childhood Cancer Group;* CMT, *combined modality therapy;* CR, *complete response;* CS, *clinical stage;* CVPP, *cyclophosphamide, vinblastine, procarbazine, and prednisone;* DFS, *disease-free survival;* EBVP, *epiribicin, bleomycin, inblastine, prednisone;* EFS, *event-free survival;* EORTC, *European Organisation for Research and Treatment of Cancer;* ESR, *erthryocyte sedimentation rate;* GATLA, *El grupo argentino de tratamiento de la leucemia aguda;* Gy, *gray;* FFP, *freedom-from-prorgression;* IFRT, *involved-field radiation therapy;* LP/NS, *lymphocyte predominant/nodular sclerosis;* MC, *mixed cellularity;* MSKCC, *Memorial Sloan Kettering Cancer Center;* NCIC/ECOG, *National Cancer Institute-Canada/East Coast Oncology Group;* OS, *overall survival;* PR, *partial response;* STNI, *subtotal nodal irradiation;* yr, *year.*

**Adverse factors: hilar disease, >4 sites, LMA or bulky disease >10 cm.*

†IFRT 30 + 10 Gy boost for early-stage and EFRT 25 + 10 Gy boost for advanced-stage.

‡Modified extended-field RT in 83% of patients (91% received 36 Gy).

mortality has been demonstrated after ABVD without mediastinal irradiation.[120,121]

Elimination of Radiation Therapy Based on PET-Response

Convincing data on the high prognostic value of response to chemotherapy based on PET findings, especially for patients with advanced-stage disease,[53,122] has led to an increasing interest in the use of PET response (either early in the course of chemotherapy or at the end of chemotherapy) to identify patients in whom radiation therapy can be eliminated. Picardi et al conducted a randomized trial designed to evaluate whether radiation therapy can be safely eliminated if a complete response by PET scan is achieved after chemotherapy.[123] A total of 260 patients with stages I to IV HL with tumor mass greater than 5 cm were included in the study. One hundred and sixty patients became PET negative and had a more than 75% reduction in the tumor mass at the completion of six cycles of etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone (VEBEP). These patients were randomized to 32 Gy of IFRT versus no further treatment. At a median follow-up of 40 months, there was a significant DFS benefit with the addition of consolidative radiation therapy (96% versus 86%, $p = 0.03$), suggesting that even in carefully selected patients based on optimal functional imaging response to chemotherapy, the omission of radiation therapy is associated with a higher relapse rate. However, this study is limited by the use of suboptimal chemotherapy.

In recent years, several randomized trials were designed to specifically address the elimination of radiation therapy in patients with early-stage HL based on PET response to modern chemotherapy.[87,124] In the EORTC/LYSA/FIL H10 trial, patients with favorable early-stage disease were randomized to the standard arm of three cycles of ABVD followed by INRT, versus the experimental arm of two cycles of ABVD followed by PET scan. If the scan was negative, patients received two additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received two cycles of dose-escalated BEACOPP, followed by INRT. For patients with unfavorable early-stage disease, the standard arm consisted of four cycles of ABVD followed by INRT, whereas patients on the experimental arm received two cycles of ABVD followed by PET scan. If the scan was negative, patients received four additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received two cycles of dose-escalated BEACOPP, followed by INRT. In the most recent interim analysis, for patients with PET-negative disease after ABVD, there were 9 events in the no radiotherapy arm versus 1 event in the radiotherapy arm (HR, 9.36) in the favorable group, and 16 events in the no radiotherapy arm versus 7 events in the radiotherapy arm (HR, 2.42) in the unfavorable groups. This led to the conclusion that the objective of non-inferiority of chemotherapy alone as compared with combined-modality therapy has not been met, and at the recommendation of an independent data monitoring committee, the experimental arms of no radiotherapy in both groups of patients were closed.

In United Kingdom RAPID trial,[125] patients with CS IA and IIA non-bulky HL underwent PET scan after three cycles of ABVD. If the scan was negative, patients were randomized to IFRT versus no further treatment. In the most recent update of this trial,[124] 571 patients had a PET scan following three cycles of ABVD. The Deauville Criteria was used to determine PET response: A score of 1 or 2 was considered negative (uptake less than or equal to mediastinal blood pool). A total of 426 patients (74%) were scored as PET-negative, and the remaining were scored as PET-positive and went on to receive IFRT. Among the 420 patients who were PET-negative randomized, 209 were randomized to the radiotherapy arm, though 26 of the patients did not receive radiotherapy. At a median follow-up time of 48.6 months, by intent-to-treat analysis, there was no difference between the radiotherapy versus no radiotherapy arm (3-year PFS 94.5% versus 90.8%, $p = 0.23$). By per-treatment analysis, however, there is a significant benefit in the radiotherapy arm (3-year PFS 97% versus 90.7%, $p = 0.03$). There was a nonsignificant trend toward lower survival in the radiotherapy arm (97.1% versus 99.5%, $p = 0.07$). However, among the seven deaths in patients randomized to the radiotherapy arm, five occurred prior to initiation of the radiotherapy.

Two ongoing trials conducted by the GHSG are exploring omission of radiotherapy by PET-response. The HD16 trial randomizes patients with low-risk early-stage disease to two cycles ABVD followed by 30 Gy IFRT irrespective of PET results after chemotherapy, versus two cycles ABVD followed by 30 Gy IFRT for only patients with positive PET after chemotherapy and no further therapy if PET is negative after chemotherapy. The HD17 trial randomizes patients with high-risk early-stage disease to two cycles of dose-escalated BEACOPP followed by two cycles ABVD (two-by-two regimen), followed by 30 Gy IFRT irrespective of PET results after chemotherapy, versus the same two-by-two regimen, followed by 30 Gy INRT only for patients with positive PET after chemotherapy and no further therapy if PET is negative.

Recommendation on Treatment for Early-Stage Hodgkin's Lymphoma

The optimal treatment for early-stage HL is in evolution. At this time, in patients with early-stage disease with favorable prognosis based on GHSH criteria (no bulky mediastinal mass or extranodal disease, 3 or fewer nodal sites, low sedimentation rate), two cycles of ABVD chemotherapy followed by ISRT to 20 Gy may be adequate.[87] In patients with unfavorable early-stage disease, four cycles of ABVD may be adequate, but 30 Gy of ISRT is needed after ABVD.[85]

Based on early results, there appears to be an approximately 7% gain in PFS with the addition of radiotherapy in patients who achieved PET-negative disease (less than or equal to mediastinal blood pool uptake) after chemotherapy. Preliminarily, the lower cure rate and toxicity of salvage therapy in the small proportion of patients with relapse disease needs to be weighed against the toxicity of INRT (which will be discussed later). However, longer follow-up of these recently completed or ongoing trials will be needed to account for late relapses in both arms.

PRIMARY TREATMENT FOR ADVANCED-STAGE HODGKIN'S LYMPHOMA

The introduction of the combination chemotherapy regimen, MOPP, in the mid-1960s substantially improved the curability of patients with advanced-stage HL.[4] The ABVD regimen was initially introduced as a second-line therapy in patients who had a poor response to, or relapse after MOPP chemotherapy.[126] Its role as primary treatment in newly diagnosed patients was subsequently substantiated by several randomized trials in patients with advanced-stage disease, showing that ABVD-containing regimens are associated with a higher failure-free survival than MOPP.[127-130] Results of an intergroup randomized trial comparing MOPP/ABV hybrid versus ABVD in advanced-stage HL showed that the addition of MOPP to ABVD did not confer any therapeutic benefit but did add to treatment-related toxicity.[131] ABVD is significantly less myelosuppressive, and it also does not carry the risk of

gonadal dysfunction and leukemogenesis. Currently, in the United States, ABVD is accepted by most as the standard systemic therapy for advanced-stage HL, which yields long-term failure-free survival of 60% to 65% and OS of 70% to 75%. To further improve treatment results, dose-escalated or dose-dense regimens for advanced-stage HL have been developed. The two major regimens, BEACOPP and its variants, and Stanford V, are discussed here.

Alternatives to ABVD

BEACOPP

The dose-escalated BEACOPP regimen (eTable 76-1), developed by the GHSG, yielded significantly higher survival outcome compared with conventional-dose regimens in the GHSG HD9 study.[132] In this three-armed trial, patients with stages IIB, IIIA, IIIB, and IV were randomized to eight cycles of COPP-ABVD, baseline-dose BEACOPP, or dose-escalated BEACOPP. In the most recent update of the study on 1196 evaluable patients, at a median follow-up of 111 months, the 10-year freedom-from-relapse rate was significantly higher in the dose-escalated BEACOPP arm than the baseline BEACOPP and COPP-ABVD arms (82%, 70%, and 64%, respectively, $p < 0.0001$).[133] The corresponding 10-year OS rates were 86%, 80%, and 75%, respectively ($p = 0.0005$). However, in the standard arm of this trial, COPP-ABVD, rather than modern ABVD, was used. Also, it was noted that patients on the dose-escalated BEACOPP arm had significantly higher 10-year cumulative incidence of acute myelogenous leukemia and myelodysplasia (3.2%, 2.2%, and 0.4%, respectively, $p = 0.03$).

In an attempt to reduce treatment-related toxicity, the GHSG explored the efficacy of modified versions of the BEACOPP regimen. The GHSG HD12 trial is a four-arm study for patients with bulky stage IIB and stages III to IV disease comparing eight cycles of dose-escalated BEACOPP with or without radiation therapy, versus four cycles of escalated and four cycles of baseline BEACOPP with or without radiation therapy. In the most recent update that included 1571 eligible patients, at a median follow-up of 69 months,[134] the 5-year FFTF, PFS, and OS of the entire cohort were 85.5%, 86.2%, and 91%, respectively. There were no significant differences in outcome between the two chemotherapy regimens, but less hematologic toxicities were observed in the arm that contained baseline BEACOPP.

The GHSG HD 15 trial compared right cycles of dose-escalated BEACOPP ($8B_{esc}$), six cycles of dose-escalated BEACOPP ($6B_{esc}$), or eight cycles of $BEACOPP_{14}$ ($8B_{14}$) a time-intensified variant of baseline BEACOPP baseline.[135] This study also evaluated the use of PET to select patients for chemotherapy alone (which will be discussed). At a median follow up of 48 months, the 5-year FFTF rates were 84.4%, 89.3%, and 85.4% in the $8B_{esc}$ $6B_{esc}$ $8B_{14}$ arms, respectively, and the 5-year OS rates were 91.9%, 95.3%, and 94.5%, respectively. There were more deaths from acute toxicity and more second malignancies in the $8B_{esc}$ arm. This led to the authors' conclusion that six cycles of dose-escalated BEACOPP is more effective and less toxic than eight cycles of the chemotherapy.

Variations of the BEACOPP regimen have also been investigated by other groups. The Gruppo Italiano per lo Studio dei Linfomi conducted a randomized trial comparing four cycles of dose-escalated BEACOPP followed by two cycles of baseline BEACOPP, ABVD, and the CEC hybrid regimen (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) for patients with stages IIB to IV HL.[136] Radiotherapy was administered to sites of bulky disease to 25.2 Gy, or to slowly or partially responding sites to 30.6 Gy. Among 295 evaluated patients, at a median follow-up of 41 months, those assigned to the BEACOPP arm had a significantly higher 5-year FFS and PFS compared with patients on the ABVD arm (65% versus 78%, $p = 0.036$ and 68% versus 81%, $p = 0.038$). Unlike the GHSG HD9 trial, however, a significant difference in OS was not observed, and this may be related to the relatively small size of the study, the limited follow-up time, and the different chemotherapy used in the standard arms of the two trials. It was noted, however, that the 5-year FFS of 65% in patients treated with ABVD on this trial was inferior to the outcome of a previous trial that included similar patients receiving ABVD, where a 5-year FFS of 78% was observed.[136] The Michelangelo, Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) and Intergruppo Italiano Linfomi (IIL) cooperative groups conducted a randomized trial comparing six to eight cycles of ABVD versus four cycles of dose-escalated followed by four cycles of baseline BEACOPP as first-line therapy, with preplanned high-dose therapy as salvage.[137] At a median follow up of 61 months, BEACOPP was associated with a significantly higher 7-year FFP (85 versus 73%, $p = 0.004$) than ABVD, though differences in EFS (78% versus 71%, $p = 0.15$) and OS (89% versus 84%, $p = 0.39$) were not observed. Finally, the EORTC 20012 trial, an international multicenter study, compares four cycles of dose-escalated followed by four cycles of baseline-dose BEACOPP versus right cycles of ABVD in patients with stages III to IV disease. At a median follow up of 3.8 years, there was a significantly higher PFS rate in the BEACOPP versus the ABVD arms (83.4% versus 72.8%, $p = .005$). However, there were no EFS (69.3% versus63.7%, $p = 0.03$) or OS (90.3% versus 86.7%, $p = 0.2$) differences between the two arms.[138]

A number of ongoing or recently completed trials are addressing treatment deescalation in patients who achieved negative interim PET results.[139] For patients with early PET complete response, the GHSG HD18 is comparing six cycles versus four cycles escalated BEACOPP, the RATHL study compares ABVD with AVD, and the GELA AHL trials compares BEACOPP with standard ABVD. The HD0607 and HD0801 trials conducted by the GITIL and FIL are investigating radiation therapy versus no radiation therapy after six cycles of ABVD in patients with interim and final PET-negative results.

Stanford V

The Stanford V regimen is a 12-week, seven-drug regimen that is administered on a weekly basis (eTable 76-2).[140] It contains lower cumulative doses of mechlorethamine, Adriamycin, and bleomycin than MOPP and ABVD, respectively, to limit leukemogenesis, sterility, cardiac, and pulmonary toxicity. Patients with initial disease of 5 cm or larger or macroscopic splenic disease, which account for about 90% of the patients, receive 36 Gy of involved-field radiation therapy 2 weeks after the chemotherapy. In a report on 142 patients with stage III or IV or locally extensive mediastinal stage I or II HL, a 5-year FFP and overall survival of 89% and 96%, respectively, were achieved.[140] No secondary leukemia was observed at a median follow-up of 5.4 years, although one case of acute leukemia was reported in an earlier Eastern Cooperative Oncology Group (ECOG) pilot study using the same regimen on 45 patients.[82]

The importance of radiation therapy as part of Stanford V was highlighted by a multiinstitutional randomized trial from Italy.[141] In this study, 355 patients with bulky stage II or advanced-stage HL were randomized to receive ABVD, MEC hybrid, and Stanford V. In this study, radiation therapy was limited to patients with initially bulky disease (>6 cm) or with partial response to chemotherapy, and those with only two or more sites of disease. In the most recent update, at a median follow up time of 86 months, the 10-year failure-free survival

eTABLE 76-1 Schedule for the Dose-Escalated BEACOPP

		Days													
Drug	**Dose (mg/m²)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Bleomycin	10	—	—	—	—	—	—	—	X	—	—	—	—	—	—
Etoposide	100	X	X	X	—	—	—	—	—	—	—	—	—	—	—
Doxorubicin	35	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Cyclophosphamide	1200	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Vincristine	1.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Procarbazine	100	X	X	X	X	X	X	X	—	—	—	—	—	—	—
Prednisone	40	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: The regimen repeated on day 22 for a total of eight cycles; filgrastim from day 8 of each cycle until the leukocyte count returned to normal; radiation therapy given for bulky disease of >5 cm.

eTABLE 76-2 Schedule of the Stanford V regimen

		Week											
Drug	**Dose (mg/m²)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Mechlorethamine	6	X	—	—	—	X	—	—	—	X	—	—	—
Doxorubicin	25	X	—	X	—	X	—	X	—	X	—	X	—
Vinblastine	6	X	—	X	—	X	—	X	—	X	—	X	—
Vincristine	1.4	—	X	—	X	—	X	—	X	—	X	—	X
Bleomycin	5	—	X	—	X	—	X	—	X	—	X	—	X
Etoposide	60	—	—	XX	—	—	—	XX	—	—	—	XX	—
Prednisone qod	40	X	X	X	X	X	X	X	X	X	X	X	X

Note: Patients with initial bulky disease (≥5 cm) received involved-field radiation therapy to 36 Gy.

in the ABVD, MEC hybrid, and Stanford V arms were 75%, 74%, and 49%, respectively ($p < 0.001$). Among patients randomized to receive Stanford V, the 10-year DFS rates were significantly higher in patients who received radiation therapy versus those who did not (76% versus 33%, $p = 0.004$).

Another multicenter trial, conducted by the United Kingdom National Cancer Research Institute, randomized 520 patients with poor risk early-stage and advanced-stage HL to six to eight cycles of ABVD versus Stanford V.[142] In this trial, specified indications for radiotherapy in the Stanford V arm was the same as the original regimen, although the decision on whether to irradiate was left up to teams in the individual centers. Overall, 73% of patients in the Stanford V arm received radiotherapy, which is lower than that in the original Stanford study (91%). The proportion of patients not receiving radiotherapy as specified was not reported. At a median follow-up of 52 months, there were no significant differences in 5-year PFS (76% versus 74%) and OS (90% versus 92%) between ABVD versus Stanford V.

Results of the ECOG 2496 comparing ABVD and Stanford V in patients with locally extensive and advanced-stage HL were recently reported by Gordon et al.[143] At a median follow up of 6.2 years, there was no difference in 5-year FFS between the ABVD versus Stanford V arms (74% versus 71%, $p = 0.32$) and no OS differences (88% versus 88%, $p = 0.86$). In this study, 75% of patients received radiotherapy in the Stanford V arm for disease >5 cm, whereas in the ABVD arm, 41% received radiation therapy for bulky mediastinal disease.

The Role of Radiation Therapy in Advanced-Stage Hodgkin's Lymphoma

The rationale for the addition of radiation therapy to combination chemotherapy in advanced-stage HL is based on the patterns of failure after chemotherapy, in which the majority of relapses are at the site of initial disease.[144,145] A number of randomized trials have been performed addressing the role of consolidative radiation therapy after chemotherapy in advanced-stage HL.[88,146-150] Summarized in Table 76-9 are some of the more recent randomized studies comparing combined-modality therapy versus chemotherapy alone, using the same chemotherapy regimens in both arms, for advanced-stage HL.[134,146,149-151] The results of these trials were largely negative for significant benefit with the addition of radiation therapy. The previously described study from Tata Memorial Hospital, which included patients of all stages, is the only study that showed a significant survival benefit of combined-modality therapy over chemotherapy alone.[110] On subgroup analysis, the survival benefit was limited to patients with advanced-stage disease. The 8-year overall survival for patients with stages III to IV disease was 80% in the chemotherapy alone arm versus 100% in the combined modality arm ($p = 0.006$). Other subgroups that appeared to especially benefit from radiation therapy in this trial included patients with B symptoms and younger age patients.

In the EORTC trial, patients with stages III to IV disease with a complete response to MOPP-ABV were randomized to receive either radiation therapy or no further treatment.[150] At a median follow-up of 79 months, there were no differences in 5-year EFS or OS. The 5-year cumulative risk of second malignancy was significantly higher in the 172 patients randomized to radiation therapy than the 161 patients randomized to no radiation therapy (7.8% and 4.0%, $p = 0.05$). However, among the patients with a partial response who received radiation therapy to a higher dose, the 5-year cumulative risk of second malignancy was only 3.2%, but the reason for the discrepancy is not entirely clear. The authors also separately reported results of the 227 patients with a partial response who went on to receive 30 Gy of consolidative radiation therapy with or without additional boost.[152] The 8-year EFS and OS rates were 76% and 84%, respectively, which were comparable to the treatment results of patients who had a complete response, leading to the conclusion that patients with a partial response after chemotherapy may benefit from radiation therapy.

One study analyzed the outcomes of nonrandomized consolidative involved-field radiotherapy given after an objective response to chemotherapy in 702 patients with advanced-stage or early-stage unfavorable HL.[153] Consolidative radiation therapy of at least 30 Gy was recommended for patients with incomplete response to chemotherapy or bulky disease at presentation, and was received by 300 of the 702 patients. With a median follow-up of 6.9 years, a significantly higher PFS (71% versus 86%, $p < 0.0001$) and OS rates (87% versus 93%, $p = 0.014$) were found in patients who received radiation therapy, despite the fact that there were significantly more

TABLE 76-9 Randomized Trials Comparing Combined Modality Therapy and Chemotherapy Alone in Advanced-Stage Hodgkin's Lymphoma

Institution	No.	Patient Population	Treatment Arms		MED F/U	Results	
						CMT	Chemo Alone
SWOG[146]	278	Stages III-IV	MOP-BAP × 6		8 years	5 yr-RFS: 74% 5 yr OS: 86%	66% ($p > 0.2$) 79% ($p > 0.2$)
			If CR →	20 Gy RT No RT			
GATLA[149]	151	Stages III-IV	CVPP × 3 →	CVPP × 3 (total 6) 30 Gy RT CVPP × 3	7 years	7-yr FFS: 45% 7-yr OS: 71%	21% ($p = 0.0016$) 58 ($p = 0.15$)
EORTC[150]	421 (333 randomized)	Stages III-IV (excluded stage IIIAs)	MOPP-ABV × 6-8		79 months	5-yr EFS: 84% 5-yr OS: 79% If PR: 5-yr EFS: 79% 5-yr OS: 87%	91% ($p = 0.35$) 85% ($p = 0.07$)
			If CR →	24 Gy RT No RT			
			If PR →	30 Gy RT			
GHSG (Borchmann 2011, JCO)	1670	Bulky Stage II, Stage III-IV	bulky sites esc. BEA × 8 →	RT to No RT	69 months	5-yr FFTF: 90.4%	5-yr FFTF: 87%
			bulky sites esc. BEA × 4/ BE × 4 →	RT to No RT			

bulky patients and patients with partial response in the radiation therapy cohort.

As previously described, one of the study questions of the GHSG HD12 study is the role of radiation therapy in advanced-stage HL.[134] At a median follow-up of 69 months, there was no significant difference in 5-year FFTF between the radiotherapy or no-radiotherapy arms (90.4% versus 87%, $p = 0.08$) after either eight cycles of dose-escalated BEACOPP or four cycles escalated and four cycles of baseline BEACOPP. On subgroup analysis, among patients with residual CT abnormality of >1.5 cm, there was a significant 5.8% (95% CI 1.0% to 10.7%) higher 5-FFTF in the radiotherapy arm. However, among patients with <1.5-cm residual disease after chemotherapy, there was no significant benefit with the addition of radiotherapy even among patients with initial disease of 5 cm or greater.

In the GHSH HD15 trial comparing eight cycles of dose-escalated BEACOPP, six cycles of dose-escalated BEACOPP, versus eight cycles of BEACOPP-14, radiation therapy was limited to patients with residual disease of 2.5 cm and with residual PET avidity. Kobe et al reported results of 311 patients from this trial who had residual disease of 2.5 cm and underwent postchemotherapy PET scanning.[154] Sixty-six patients (21%) were found to have residual PET avidity, 63 of whom received 30-Gy radiation therapy to the residual mass as per protocol. Among patients with at least 12 months of follow-up, the 1-year PFS for PET-negative patients and PET-positive patients were 96% and 85%, respectively ($p = 0.011$). Although the treatment outcome of patients with residual PET avidity who received radiation therapy was inferior to those with negative PET in this study, the results are far superior to those reported in other series for patients with PET residual disease after chemotherapy, with PFS rates ranging from 0% to 33%.[122,155] In the most recent update, the 4-year PFS in patients with complete response or those with PET-negative disease and partial response after chemotherapy and did not receive radiation therapy were 92.6% and 92.1%, respectively.[135] As previously described, the HD0607 and HD0801 trials conducted by the Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) Fondazione Italiana Linfomi (FIL) randomized patients with interim and final PET-negative results to radiation therapy versus no radiation therapy, although final results are not yet available.

Optimal Radiation Dose and Field Size

There are limited data on the optimal dose and appropriate radiation treatment field after chemotherapy in advanced-stage HL. Randomized data are not available comparing radiation doses or fields as part of combined-modality therapy in advanced-stage HL. An earlier GHSG study combined data from two of the randomized trials on patients with stages I to III disease, with or without bulk, and found no differences in FFTF and OS between 20 Gy, 30 Gy, and 40 Gy of consolidative radiation therapy.[148] The radiation dose employed in several more recent trials on advanced-stage HL varied. In general, initially nonbulky sites, if treated, received to 20 Gy to 30 Gy, initially bulky sites received 30 Gy to 36 Gy and sites with partial response were treated to 30 Gy to 40 Gy.[132,136,142,150,153-155]

The treatment fields that have been used in trials are also variable. For instance, in the EORTC trial, the protocol mandated irradiating all initially involved areas (except for bone marrow) and that both the spleen and the paraaortic nodes be included in the treatment field even if only one of the sites were involved.[150] Patients also received low-dose whole lung or whole-liver irradiation if disease was initially present at these sites. Although referred to as "involved-field," patients can be treated to a large volume because of their disease extent. Other groups have restricted the radiation treatment field to initially bulky sites. In both the Stanford V and the original BEACOPP regimens in the GHSG HD9 trial, only sites that were initially 5 cm or greater were included in the radiation field.[132,140] With more effective systemic therapy, availability of functional imaging to assess response to systemic therapy, and concerns with toxicity associated with large field radiation therapy, there are further efforts to limit the field size if radiation therapy is to be given. In the HD15 trial, for patients receiving radiation therapy, the treatment field was limited to postchemotherapy residual masses. Patterns of failure were recently reported by Eich et al. Among the 175 patients who received radiotherapy to 30 Gy to the PET-positive site(s), 28 patients relapsed. Twelve (42%) patients had an "infield" relapse, 8 (29%) patients had a relapse outside of the irradiated site, and a further 8 (29%) patients had "in- and outfield" relapse.[156]

Recommendation on Treatment of Advanced-Stage Hodgkin's Lymphoma

In the United States, six to eight cycles of ABVD is still considered by most as the standard systemic therapy for advanced-stage HL. Dose-escalated BEACOPP has been shown to result in a significant survival advantage over conventional-dose regimens (although standard ABVD was not used in the GHSG HD9), but it is also associated with substantial toxicity. Dose-reduced variants of BEACOPP have been developed and tested against ABVD, showing an improved freedom-from-progression, but at the expense of increased toxicity and no difference in OS. Results of ECOG 2496 showed no difference between Stanford V and ABVD.[143] The use of early PET response in identifying patients for treatment escalation or deescalation in patients with advanced-stage disease is addressed by a number of ongoing trials.

Routine addition of radiation therapy after chemotherapy in patients with advanced-stage disease is not supported by available data. However, in selected cases, including initially bulky disease or lack of complete response to chemotherapy, there may be a role for consolidative radiation therapy. In the context of more effective, modern systemic therapy and the availability of functional imaging to assess response, if the decision is to proceed with radiation therapy, it is reasonable to limit the radiation treatment field to initially bulky sites and postchemotherapy residual disease. With the more restricted fields to high-risk areas, doses of 30 Gy to 36 Gy should be considered.

PRIMARY TREATMENT FOR NLPHD

In the REAL and WHO classification systems, NLPHD is classified as a distinct entity based on morphologic and immunophenotypic features.[39,40] Clinically, it is characterized by a male predominance, older age at diagnosis of 30 years to 50 years, peripheral nodal presentation with seldom mediastinal, liver, spleen, or bone marrow involvement, predominantly early-stage disease, an indolent clinical course, and late, multiple relapses.[47,157-161] Because of its rarity, comprising only about 5% of all cases of HL, there is a lack of randomized data in guiding its management, which range from watch and wait,[158] surgery alone,[162] radiation therapy with or without chemotherapy,[157-160,163-165] or immunotherapy.[166-168] Observations have been made that ABVD may not be as effective in patients with NLPHD, and alkylating-agent containing regimens may be a better choice when chemotherapy is indicated,[157,169] although data from British Columbia suggested that ABVD may be associated with a better outcome. Because NLPHD is rarely fatal, and the main cause of death in these patients is

treatment-related rather than disease-related,[157,158,161,168] it is sensible to choose a modality with well-established effectiveness while limiting the treatment exposure of these patients. Several series have reported on results of radiation therapy for early-stage NHLPD, with relapses occurring in 20% to 25% of patients, typically at sites outside of the irradiated field.[157,160,164,165,170] However, patients tend to remain responsive to further therapy despite multiple relapses.[158] The use of more limited treatment fields such as involved-field or regional-field radiation therapy to 30 Gy to 36 Gy did not appear to compromise treatment outcome compared with the use of more extensive fields.[160,165] In patients with neck or axillary involvement, the mediastinum, which is rarely involved, can be blocked, thereby avoiding exposure of the lungs and heart to radiation. For limited-stage NLPHD where radiation therapy is often the sole modality, the GTV should be readily visualized during simulation. The ILROG ISRT guidelines recommend that in this situation, the CTV should be more generous because microscopic or subclinical disease is more likely to be present without chemotherapy.[96]

REFRACTORY AND RECURRENT DISEASE

The standard salvage therapy for patients who are refractory, or relapsed, after a short initial remission to chemotherapy is high-dose therapy with autologous bone marrow or stem-cell transplantation. Two randomized trials compared high-dose therapy with bone marrow or hematopoietic stem cell rescue versus conventional-dose chemotherapy as salvage for patients with refractory to or relapsed HL after chemotherapy.[171,172] The British National Lymphoma Investigation group prospectively randomized 40 patients to either high-dose carmustine (BCNU), etoposide, cytarabine, melphalan (BEAM) followed by autologous bone marrow transplantation or mini-BEAM.[172] The inclusion criteria were lack of complete response after MOPP or similar regimen, or relapsed disease either within 1 year, or disease failure after two or more chemotherapy regimens. At a median follow-up of 34 months, 3-year actuarial eventful survival of the two arms were 53% and 10%, respectively ($p = 0.025$) and PFS were 88% and 35%, respectively ($p = 0.005$), favoring the high-dose therapy arm. The GHSG conducted a similar study comparing high-dose BEAM followed by autologous stem-cell transplantation and dexamethasone with conventional dose BEAM.[171] Only patients with chemosensitive disease were included in the trial. At a median follow-up of 39 months, the FFTF of the two arms were 55% and 34%, respectively ($p = 0.019$). Significant survival differences were not detected in either of the two trials, however.

One of key factors that influences outcome is chemosensitivity to second-line cytoreductive chemotherapy prior to the high-dose therapy and transplantation. Other factors that have been shown to be of prognostic significance include duration of complete response to initial treatment,[173] extranodal disease,[173,174] constitutional symptoms[74,173,175] or bulky disease[176] at the time of relapse, and Hasenclever index.[177]

In recent years, CD30, a cell surface protein expressed on the RS Hodgkin cells, has emerged as a therapeutic target for patients with relapsed or refractory HL. Brentuximab vedotin, an antibody-drug conjugate (ADC) that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells, was shown in a Phase I study to induce durable objective responses and result in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas.[178] In a subsequent Phase II study,[179] the efficacy and safety of brentuximab vedotin were evaluated in patients with relapsed or refractory HL after autologous stem-cell transplantation. A total of 102 patients were treated with brentuximab vedotin 1.8 mg/kg by intravenous infusion every 3 weeks to a maximum of 16 cycles. The overall response rate was 75% with a complete remission rate of 34%. Based on these results, brentuximab vedotin was approved by the Food and Drug Administration for patients who have relapsed after autologous stem cell transplantation (ASCT) or experiencing refractory or relapse disease after at least two prior multiagent chemotherapy regimens in patients who are deemed not to be ASCT candidates. Trials are also currently ongoing exploring brentuximab vedotin combined with second-line chemotherapeutic agents for salvage, as part of consolidation post-ASCT, and as part of frontline therapy in newly diagnosed patients.

Role of Radiation Therapy Before or After High-Dose Therapy

Further relapses after high-dose therapy tend to occur at sites of initial relapsed disease.[180] The role of involved-field radiation therapy given either before or after high-dose therapy have not been addressed prospectively by randomized trials, but retrospective studies have indicated that the addition of radiation therapy may contribute to improved outcome. In one study from Stanford, subgroups of patients who significantly benefited from involved-field radiation therapy given either before or after the transplantation included patients with relapsed stages I to III disease and patients who did not receive prior radiation therapy.[81] In a study from University of Chicago, the use of involved-field radiation therapy in conjunction with high-dose therapy significantly improved local control of all sites of disease.[181] Patients with persistent disease following high-dose therapy had significantly improved PFS (40% versus 12.1%, $p = 0.04$). Wendland et al reviewed 65 patients with refractory or relapsed HL who underwent high-dose therapy and transplant.[182] Twenty-one patients received IFRT, whereas 44 patients did not receive radiation therapy. Half of the patients in the no IFRT group (22 of 44) died compared with 23.8% (5 of 21) of patients in the IFRT group, which was of borderline significance ($p = 0.06$). Kahn et al, in a study examining the role of IFRT in patients with HL and non-HL receiving transplant, found that patients who did not receive IFRT had a 2.09 relative risk of death, which was of borderline statistical significance on multivariable analysis ($p = 0.066$).[182] A study from the University of Rochester on 62 patients who underwent ASCT for relapsed or refractory HL found improved 3-year OS (69.6% versus 40%, $p = 0.05$), disease-specific survival (82.1% versus 57.6%, $p = 0.08$), and local control (94% versus 69%, $p = 0.03$) among patients who received IFRT posttransplant.[183] Results of these retrospective series, however, need to be interpreted with caution because of differences in characteristics of patients who did and did not receive radiation therapy. For example, patients who were offered radiation therapy tend to have bulkier disease or chemotherapy refractory disease, whereas patients who did not receive radiation therapy may have more disseminated disease.

The optimal temporal relationship between radiation therapy and high-dose therapy is unclear. In patients with persistent disease after cytoreductive chemotherapy, radiation therapy given before transplantation can allow further disease debulking. Furthermore, irradiation pretransplantation avoids exposure of newly engrafted stem cell to radiation, which may increase the risk of myelodysplasia and leukemia. This is especially relevant in patients with pelvic disease requiring radiation therapy to a large volume of bone marrow. In these patients, stem-cell mobilization or bone marrow harvest should be performed before initiation of pelvic irradiation. Delivery of radiation therapy before transplantation, however, can increase peritransplant morbidity such as pneumonitis and veno-occlusive disease. Also, there is a risk of systemic

disease progression during the time of the radiation therapy with the delay of the high-dose therapy.

Limited Relapse After Chemotherapy

A small proportion of patients who relapsed after chemotherapy can be successfully salvaged with conventional-dose salvage chemotherapy or radiation therapy. A number of series showed that in selected patients with favorable features, salvage rates as high as 80% can be achieved without exposing patients to high-dose therapy.[97,184-188] Potential candidates for conventional dose-salvage therapy include patients with initial remission duration of 1 year or longer, limited nodal relapse without extranodal disease, and absence of constitutional symptoms at relapse. In one series of 28 patients with limited nodal relapse after chemotherapy, the combination of salvage chemotherapy and radiation therapy yielded significantly superior outcome than radiation therapy alone.[186] In patients who received combined modality salvage therapy, the 7-year freedom from further relapse was 93% and the OS was 85%, whereas the corresponding actuarial estimates in patients treated with radiation therapy alone were significantly lower at 36% ($p = 0.002$) and 36% ($p = 0.03$), respectively. These data suggest that in carefully selected patients with favorable criteria at relapse, salvage with conventional-dose therapy can be considered, thereby sparing patients the toxicity of high-dose therapy.

TECHNIQUES OF RADIATION THERAPY

Radiation therapy is one of the most effective modality for the treatment of HL. Radiation therapy for HL has evolved from two-dimensional treatment planning, with field set-up mostly based on bony landmark to extensive treatment fields, to conformal therapy with improved image guidance to restricted treatment volumes.

Modern Conformal Therapy

Although three-dimensional conformal therapy is currently the most widely adopted radiation technique, there are emerging data on the use of newer, more sophisticated techniques, including IMRT and proton beam therapy for HL.

IMRT uses multiple beams over the targeted volume to provide a highly conformal radiation dose distribution. Dosimetric studies have shown IMRT plans to produce the most conformal high-dose distribution, significantly better PTV coverage and greater protection of the heart, coronary arteries, esophagus, and spinal cord, though at the expense of a greater volume of normal tissue receiving low radiation doses.[189-192] In a dosimetric study reported by Fiandra et al,[191] five different treatment techniques in a cohort of young women with HL were compared: three-dimensional conformal radiation therapy (3D-CRT), and four different IMRT solutions, including single-arc volumetric-modulated arc therapy (VMAT, single-arc), B-VMAT ("butterfly", multiple arcs), helical tomotherapy (HT) and Tomodirect (TD), a rapid, low-modulation solution of the tomotherapy. The B-VMAT technique, developed to reduce low doses radiation exposure to lungs and breasts, and consists of two coplanar arcs of 60 degrees (gantry starting angles 150 degrees and 330 degrees) and one non-coplanar arc of 60 degrees, was found to be associated with the lowest mean doses to the lungs and breasts. When INRT rather than IFRT was employed, there was no difference in cardiac structures sparing between three-dimensional conformal therapy and IMRT approaches. Paumier et al reported on outcome of 32 patients with early-stage HL treated with INRT with IMRT technique to a median dose of 40 Gy. Despite the high prescribed dose, the median heart V30 and lung V20 were 15.5% and 28.6%, respectively, and the median mean heart and lung doses were 4.8 Gy and 15.1 Gy, respectively. There was one in-field relapse and two out-of-field relapses at a median follow up of 60 months. One patient developed grade-3 radiation pneumonitis and there were no cardiac events at the time of last follow-up.

IMRT can play an especially important role in selected cases, including extensive chest wall involvement where conventional techniques would result in exposing large volumes of lungs in the irradiated field, or in the retreatment setting where there is significant dose limitation to vital structures such as the spinal cord. Goodman et al reported on their experience using IMRT for extremely large mediastinal masses or in patients with prior radiation therapy to the mediastinum.[193] In these special case scenarios, the use of IMRT resulted in not only improved PTV coverage, but also lower mean doses to the lungs.

Another modern conformal technique is proton therapy, in which charged particles deposit most of their energy at a proportional depth, resulting in a characteristic dose distribution known as the Bragg peak. With the addition of multiple energies, a spread-out Bragg peak can be created such that the target can be covered by a limited number of fields. Investigators from the University of Florida reported on dosimetric outcome of 10 patients with stages I to IIIB HL treated with INRT with proton beam technique.[194] Compared with 3D-CRT, proton therapy led to a median reduction of body V4 (total body exposed to 4 Gy or higher) by 51% ($p = 0.0098$), and compared with IMRT, a median reduction by 59% ($p = 0.002$). Proton therapy also provided the lowest mean doses to the heart, lungs, and breasts. Early results of 16 patients treated with involved-node proton therapy from the same institution were recently reported. At a median follow-up of 32 months, one patient with initial stage IIB disease relapsed both in and out-of-field, and one patient developed primary mediastinal large B-cell lymphoma. Proton beam therapy therefore appears to be associated with favorable dosimetric outcome and preliminary clinical outcome data are promising. However, major limitations of proton therapy at this time include the complexity and uncertainty of the treatment planning, costs, and access to photon facilities.

The Role of PET in Guiding Radiation Planning

Data from PET-CT are increasingly incorporated into radiation therapy decision making and in the radiation planning process. A number of studies have investigated the impact of PET-CT data in target volume definition for HL radiation therapy planning. Hutchings et al identified 30 patients with HL treated with involved field.[195] All patients had prechemotherapy PET-CT scan, although only the CT component was used for planning purposes. When the PET data was incorporated retrospectively in the planning, the involved field was increased in 7 patients (23%) and decreased in 2 patients (7%). Girinsky et al fused the prechemotherapy PET scan with the post-chemotherapy CT planning scan in 30 patients with HL treated with INRT.[196] In 11 of the 30 patients (36%), the PET scan identified involved nodal disease that was missed by the CT, resulting in changes of the radiation treatment field. It was also noted that on average only 25% of the lymphoma volume on CT showed FDG avidity on PET, leading to the conclusion that the target must include both CT-positive and PET-positive disease. Similarly, Terazakis et al found that the incorporation of PET data in the treatment planning of 29 patients with hematologic malignancies to 32 sites resulted in increase in PTV in 47% and reduced PTV in 40% of the planned sites.[197] These data suggest that PET/CT is the most accurate imaging

TABLE 76-10 Treatment Algorithm for Patients with Early-Stage Hodgkin's Lymphoma

CLASSICAL HODGKIN'S LYMPHOMA, FAVORABLE-PROGNOSIS
Two to four cycles of ABVD (restaging PET/CT scan after two to three cycles and at the end of chemotherapy)*
Involved-node or involved-site radiation therapy 3 to 4 weeks postchemotherapy to 20 Gy to 30 Gy*
CLASSICAL HODGKIN'S LYMPHOMA, UNFAVORABLE-PROGNOSIS
Four to six cycles of ABVD (restaging PET/CT after two to three cycles and at the end of chemotherapy)
Involved-node or involved-site radiation therapy 3 to 4 weeks postchemotherapy to 20 Gy to 30 Gy
NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA
Involved-node or involved-site radiation therapy alone to 30 Gy to 36 Gy

**The use of two cycles of ABVD and 20-Gy IFRT limited to patients with early-stage disease without risk factors as per GHSG criteria.*

TABLE 76-11 Treatment Algorithm for Patients with Advanced-Stage Hodgkin's Lymphoma

CLASSICAL HODGKIN'S LYMPHOMA
Six to eight cycles of ABVD (restaging PET/CT after two to three cycles and at the end of chemotherapy)
Other regimens, depending on institutional experience, include Stanford V and dose-escalated BEACOPP and its variants
Consolidative radiation therapy to 30 Gy to 36 Gy to sites of initial bulky disease (>5 cm) or without complete response to chemotherapy
NODULAR LYMPHOCYTE PREDOMINENT HODGKIN'S LYMPHOMA
Alkylating-agent based chemotherapy regimen (e.g., chlorambucil, vinblastine, procarbazine and prednisolone [ChlVPP] or rituximab, cyclophosphamide, vincristine, prednisone [R-CVP])

method for determining disease extent in HL, Thus, up-front PET/CT is considered mandatory for INRT design.[96]

Respiratory Motion Adaptation Techniques

As radiation treatment fields become more conformal, it is important to take into account respiratory motion, especially when treating sites that are subject to the effect of diaphragmatic motion, such as the mediastinum, lungs, pericardial nodes, or spleen. Breathing adaptation techniques, in the simplest form, involves covering the entire span of respiratory motion of the target on a four-dimensional CT scan. With respiratory gating, the radiation beam is turned on only during a prespecified period of the respiratory cycle, such that organ motion within the radiation field is limited to the motion taking place during the prespecified beam on time. Results of deep inspiration breath-hold (DIBH) techniques have been reported in patients with HL,[198-200] all demonstrating reduced doses to the heart and lungs. The ILROG ISRT/INRT guidelines encourage the use of four-dimensional imaging or DIBH technique for disease sites that are significantly affected by respiratory motion. In addition, when highly conformal techniques such as IMRT are used, adoption of strategies that account for respiratory motion is deemed especially important.

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE DIRECTIONS

The treatment algorithm for patients with early-stage and advanced-stage HL are outlined in Tables 76-10 and 76-11, respectively. In patients with favorable, early-stage disease, cure rates of more than 90% have been achieved. The key challenge in the management of these patients is to identify ways to limit late effects of HL therapy because multiple studies have demonstrated that over time, there is a significantly increased risk of mortality from causes other than HL, with second malignancies and cardiac disease being the two leading problems.[73]

There are increasing data available showing that these late effects are significantly related to radiation dose and volume.[103,105,107,201-204] A significant radiation dose-response relationship has been shown for the development of breast cancer,[104,105,202] lung cancer,[106,107] and gastric cancer[203] in HL survivors. Data are also available showing a significantly reduced risk of breast cancer with more restricted treatment fields.[103,204] These data justify current efforts of reducing radiation dose and field sizes in the treatment of early-stage HL. For patients with unfavorable prognosis disease or advanced-stage disease, the challenge remains further improving the cure of HL. More effective multiagent chemotherapy regimens are being developed and tested in clinical trials. In addition to traditional chemotherapy, new drugs and targeted immunotherapy, including brentuximab vedotin may benefit not only patients with chemotherapy refractory disease but also may serve as adjuncts to chemotherapy with curative intent.[205]

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