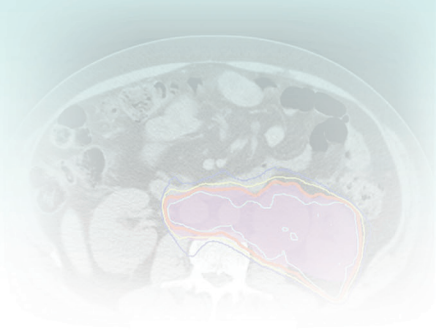
CHAPTER

74 Pediatric Hodgkin's Lymphoma



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EPIDEMIOLOGY AND BIOLOGIC CHARACTERISTICS

Relative to adult Hodgkin's lymphoma (HL), pediatric Hodgkin's lymphoma has:

- Distinct features in relation to geographic distribution, gender, association with Epstein-Barr virus (EBV), and histological subtype;
- Relatively higher incidence in developing countries and in males;
- Nodular lymphocyte predominant subtype is more frequent.

STAGING EVALUATION

- All patients: history and physical examination; complete blood count; blood chemistries; upright posteroanterior and lateral thoracic radiographs; computed tomography (CT) of the neck, chest, abdomen, and pelvis; functional nuclear imaging studies with ^{18}fluoro-2-deoxyglucose [FDG] positron emission tomography [PET]);
- Bone marrow biopsies in selected patients with clinical stages III and IV disease or B symptoms;
- Staging laparotomy is rarely appropriate, but biopsy of specific sites with equivocal findings by clinical staging should be considered where results will alter therapy;
- Two thirds of children are stage I or II, and one third have B symptoms.

PRIMARY THERAPY

- Risk-adapted therapy based on some of the following presenting features at diagnosis:
  - B symptoms, mediastinal and peripheral lymph-node bulk, extranodal extension of disease to contiguous tissues, number of involved nodal regions, Ann Arbor stage, and gender;
- Response to chemotherapy:
  - Profound prognostic factor;
  - Reduction in therapy may be based on rapidity and the degree of response to chemotherapy;
  - Augmentation of therapy may be based on lack of or insufficient response to chemotherapy;
- Toxicity
  - Children have a relatively increased risk, compared with adults, for long-term cardiopulmonary compromise, musculoskeletal growth impairment, and subsequent malignant neoplasms;
  - Late effects experience (e.g., second cancers, cardiopulmonary effects) from the legacy of archaic extended field high-dose radiotherapy technique have limited bearing on modern clinical practice;
- Chemotherapy:
  - Common regimens:
    - doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)
    - vincristine, doxorubicin, methotrexate, prednisone (VAMP)
    - vincristine, etoposide in boys, procarbazine in girls, predinsone, doxorubicin (OEPA/OPPA)
    - mechlorethamine, vincristine, procarbazine, prednisone (MOPP)
    - MOPP substituting cyclophosphamide for mechlorethamine (COPP)
    - bleomycin, etoposide, doxorubicin added to COPP (BEACOPP)
    - mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone (Stanford V)
    - doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC)
  - Early stage favorable disease most commonly uses ABVD or derivative chemotherapy; VAMP and OEPA/OPPA are alternatives
  - Intermediate- or high-risk disease use dose dense combinations derived from both ABVD and MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) along with the addition of etoposide; ABVE-PC, OEPA/OPPA with COPP are examples of this.
- Radiotherapy:
  - Use of low-dose radiation therapy (RT) following chemotherapy is response based. RT used for slowly responding, bulk, residual, or recurrent disease is the emerging standard across all stages;
  - Ongoing concerns about the incremental toxicity of RT, particular secondary cancers, remain a stimulus for investigations of chemotherapy alone;
  - Shift to involved-node or involved-site RT from traditional involved field volumes
- Results
  - Chemotherapy alone: long-term event-free survival (EFS) ranges from 85% to 100% in patients with localized favorable disease and 70% to 90% in those with advanced or unfavorable disease;
  - Incremental improvements in EFS with addition of involved field RT are in range of 5% to 10%. Rapid response to chemotherapy predicts for negligible benefit from RT.
  - The subset of patients who relapse after initial therapy have a high chance for long-term disease remission with second-line therapies.

INTRODUCTION

Given the high cure rates in treating children with HL, the ongoing challenge has been the development of less toxic therapy. In this regard, the progress in HL management in children has often presaged that in adult patients. Although many similarities between pediatric and adult HL exist, there are a number of distinctions that suggest different biologic processes, though this remains controversial. Differences associated with age include gender ratio, the proportion of patients with the most common histologic subtypes, the underlying biology (e.g., the role of EBV), and the potential for cure.[1] Pediatric HL has an excellent prognosis with high survival rates.[1,2] Given the high cure rates, HL, particularly in children, has provided much of the knowledge base we have about late toxicities of RT and cytotoxic chemotherapy. Because of the increased vulnerability of children to the adverse effects of therapy, the management of pediatric HL has led the way in the evolution of treatment strategies that consider both the toxicity and efficacy of therapy.

Historically, the desire to avoid the musculoskeletal hypoplasia that occurred following high-dose extended field RT, and leukemogenesis and infertility associated with certain alkylating agents led to a more rational combined modality therapy. Subsequent observations of cardiovascular dysfunction and increased risk of secondary cancers have played additional roles in modifying therapeutic approaches. The first generation of combined-modality therapy regimens used cycles of chemotherapy to replace a portion of the RT in children staged with laparotomy.[3-8] Second-generation regimens used doxorubicin-containing combinations to replace or reduce offending alklylating agents. Concurrent with advances in diagnostic imaging, investigators eventually abandoned surgical staging after demonstrating efficacy of the combined-modality treatment approach.

In time, risk-adapted trials evolved that prescribed fewer cycles of multiagent chemotherapy and lower radiation doses and treatment volumes for patients with favorable clinical presentations.[9,10] The definition of risk groups for disease stratification can vary in different trials and has changed with therapeutic advances. In some trials, gender-related predispositions also influence the treatment algorithm. For example, following cumulative doses of alkylating agent chemotherapy used in primary treatment regimens, boys exhibit a greater sensitivity to gonadal toxicity compared to girls, who generally maintain ovarian function unless chemotherapy is combined with abdomino-pelvic radiotherapy.[11] Conversely, young women treated with thoracic RT have a markedly increased risk of a breast cancer that is not observed in their male counterparts; however, current approaches with more restricted RT volumes are decreasing this risk.[12-14]

Because of the spectrum of prognostic factors in pediatric HL, and the unique developmental and gender-related predispositions to therapy effects, no single treatment method is ideal for all patients. Contemporary treatment for children and adolescents with HL uses a risk-adapted approach that considers presenting risk features at diagnosis. Therapy duration and intensity are selected to maintain long-term remission with minimal treatment-related morbidity. Moreover, the response to initial chemotherapy is itself an important prognostic factor and now a trigger to reduce or augment therapy.[7,15,16] The Children's Oncology Group (COG) intermediate-risk group Phase III trial AHOD0031 was the first HL trial to demonstrate that a rapid interim response to chemotherapy would allow for the elimination of involved field RT.[17]

Consequently, the evolution of therapy for pediatric HL has served as a model for other cancers. Pediatric HL management has also been early to adopt improved risk stratification and more recently response-based strategies that titrate the aggressiveness of therapy to improve the therapeutic ratio. Ongoing investigations aim to identify subgroups of HL that may be treated with reduced volume and dose of irradiation or with chemotherapy alone. The concerns about RT are to a certain extent the legacy of the significant late complications (second malignancies, cardiopulmonary dysfunction, and musculoskeletal hypoplasia) observed following archaic extended field high-dose RT techniques that have limited bearing on modern clinical practice. Nevertheless, children are more susceptible to late effects of therapy, and the trends in clinical trials have been to strive to reduce adjuvant RT despite many individual trials showing a small improvement in disease-free survival (DFS) from involved field RT and even a meta-analysis showing a small survival advantage in patients who are in early-stage disease.[18] With better risk- and response-adapted therapies, there is a general decline in RT for the upfront management of pediatric HL. RT remains important, however, to (1) complement chemotherapy when there is slowly responding, residual, or possibly initial bulky disease; (2) reduce chemotherapy intensity in selected patients where the predicted late toxicity risk for RT is small; and (3) help manage relapsed disease.

ETIOLOGY AND EPIDEMIOLOGY

Pediatric HL, accounts for 5% to 6% of childhood cancers and exhibits distinctive epidemiologic features. The childhood form, which presents in patients younger than 15 years of age, is associated with a marked male predominance, increasing family size, and decreasing socioeconomic status.[19-21] In developed countries, HL is rarely diagnosed in children younger than 5 years of age. The young adult form, which presents in patients ages 15 years to 34 years, is associated with a higher socioeconomic status in industrialized countries. Overall, the incidence is highest in developed countries (North America and Europe) and rare in Asian populations; in childhood, however, some developing regions have relatively higher incidences.[22] In adolescents, the incidence between males and females is roughly equal, and most older adolescent patients are white.[21] The risk for young adult HL decreases significantly with increased sibship size and birth order.[23,24] Specifically, the risk of HL in young adults is lower in individuals with multiple older, but not younger, siblings. Histologic subtypes also vary by age at presentation. Mixed cellularity subtype (more commonly associated with EBV) is more common in HL of childhood and the elderly, whereas nodular sclerosing subtype is more frequently observed in adolescents and young adults.

Although underappreciated because of the rarity of HL, there is a genetic predisposition that may be important to better advise families as well to help elucidate the underlying etiology of this disease. First-degree siblings of HL patients younger than 40 years of age have a 3-fold increased risk for HL.[25] Other studies report that siblings have as high as a increased incidence that may be a 9-fold increased risk in same-sex siblings.[26] Parent-child dyads have been observed. Moreover, a 99-fold increase risk in identical twins, but not in dizygotic twins has been reported.[27] More recent genetic correlative studies and exon sequencing has linked the genetic susceptibility for HL with various chromosomal loci, human leukocyte antigen (HLA) subtypes, and single nucleotide polymorphisms.[28-31] In this regard, there may be interactions with specific HLA loci and viral pathogenesis. The nodular lymphocyte predominant variant—thought to be more akin to a low-grade B cell non-HL with a lengthy time to diagnosis and time to relapse—also has a familial pattern of inheritance in some instances, linked to mutation in the ataxia

telangiectasia gene.[32,33] Increased risk for nodular lymphocyte predominant HL has also been observed in individuals with autoimmune lymphoproliferative syndrome (ALPS), a disorder associated with defects in fas-mediated apoptosis.[34]

Pediatric HL exhibits epidemiologic features similar to that seen with paralytic poliomyelitis. Delayed exposure to an infectious agent might increase the risk of the young adult form of HL, whereas early and intense exposure to an infectious agent might increase the risk for the childhood form of HL.[23] Data also indicate an association between nursery school or daycare attendance and reduced risk of HL among young adults, supporting a model in which childhood exposure to common infections promotes maturation of cellular immunity.[35] The presence of high-antibody titers to EBV, in situ hybridization evidence of EBV genomes in Reed-Sternberg cells, and EBV early RNA1 and RNA2 (EBER1 and EBER2-Epstein-Barr Early Ribonucleoprotein 1) sequences provide evidence that enhanced activation of EBV may play a role in the development of HL.[36,37] The incidence of EBV-associated HL varies by age, sex, ethnicity, histologic subtype, regional economic level, and underlying immune function.[38,39] Approximately 30% to 40% of patients with HL have associated EBV.[38] In one series of childhood HL, EBV early RNA1 was expressed in the malignant Reed-Sternberg cells in 58% of cases.[40] More specifically, an association with EBV is greater in populations of lower socioeconomic status, cases of mixed cellularity HL, and cases occurring in both young children and in the elderly.[36] Finally, there is an increased incidence of EBV-associated HL in patients with primary immunodeficiency disorders such as common variable immunodeficiency as well as with secondary immunodeficiency (e.g., HIV infection and immunosuppression for solid organ transplantation).[41]

PATHOLOGY AND PATHWAYS OF SPREAD

The pathologic features of HL are similar in adults and children; however, the distribution of the histological subtypes defined by the World Health Organization may vary by age at presentation.[42,43] Nodular lymphocyte-predominant Hodgkin's lymphoma (nLPHL) makes up almost 10% of pediatric cases. This histological subtype usually presents as clinically localized disease and is more common among male and younger patients. In contrast to classical HL, which is CD-15 and CD-30 positive, nLPHL is an indolent B cell neoplasm with histopathology notable for lacunar or Reed-Sternberg–like giant cells that are CD-20 positive and usually CD-15 and CD-30 negative.

Nodular sclerosing HL represents the most common histologic subtype in pediatric cases under the rubric of classical HL, affecting approximately 70% of adolescents and children.[44] Nodular sclerosing HL most commonly involves the lower cervical, supraclavicular, and mediastinal lymph nodes. The bulky growth of some involved nodal regions (particularly in the mediastinum) may be associated with persistent radiographic abnormalities even when the patient has fully responded to therapy. The other classical form, mixed-cellularity HL is observed in approximately 15% of patients, is more common in children aged 10 years or younger, and more frequently presents as advanced disease with extranodal involvement.[44] Lymphocyte-depleted HL is rare in children but relatively more common in patients infected with human immunodeficiency virus (HIV).[45] Lymphocyte-depleted disease in patients who are HIV-positive is often associated with EBV. Lymphocyte-rich classical Hodgkin lymphoma (LRHL) makes up approximately 5% of all HL and closely overlaps with the nodular lymphocyte-predominant subtype in presenting clinical features and prognosis.[46] The median age at presentation for LRHL (32 years) is, however, higher than for NLPHL, and there is a slightly higher incidence of mediastinal involvement and stage III disease at presentation.[47]

STAGING, CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND PROGNOSTIC FACTORS

Staging

Physical examination and diagnostic imaging evaluations are used in pediatric patients to designate a clinical stage according to the Ann Arbor staging system.[48] This historical staging system is based on anatomical groups of regional lymph nodes as delineated at the 1970 Ann Arbor symposium. It was subsequently revised at the Cotswolds meeting in 1989, although not all recommendations are in current usage.[49] This staging system persists to date with stage I identifying disease confined to one nodal region. Stage II signifies disease confined to two or more regions, but on one side of the diaphragm. Stage III indicates nodal disease that is on both sides of the diaphragm, whereas stage IV is diffuse or disseminated disease that includes extranodal sites. A special subset of stages I and II disease may be designated as extralymphatic or extranodal with the "E" suffix, which historically had been interpreted to be a disease distribution that could be encompassed within a reasonable radiation treatment portal; this operational definition has current difficulties because the role of RT is being curtailed but still is needed for prognostic purposes to designate early stage. Largely ignored from the Cotswold recommendations in current practice is the suffix "X" to designate bulky disease (greater than 10 cm maximum dimension) and a category of response to therapy, unconfirmed/uncertain complete remission (CR[u]), introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance before the current use of metabolic imaging.

Lymphoma staging continues to be unique with the inclusion of prognostically significant constitutional symptoms. The absence of symptoms is labeled with the suffix "A," whereas "B" symptoms included in the staging assignment are unexplained fever with temperatures taken orally that are higher than 38°C, unexplained weight loss of 10% within 6 months preceding diagnosis, and drenching night sweats. At one time pruritus had been included as a B symptom but was dropped many decades ago.

In the past, pathologic staging, based on the findings of a staging laparotomy, including splenectomy, was routinely used to assess infradiaphragmatic disease. The increasing use of systemic therapy in children and the development of more accurate diagnostic imaging modalities led to the routine use of clinical staging and abandonment of surgical staging except to assess equivocal findings. Currently, surgical staging—most typically nodal sampling without splenectomy—is pursued only if the anticipated findings will significantly alter the treatment plan.

Clinical Manifestations

Pediatric patients most commonly present with painless cervical or supraclavicular lymphadenopathy. Mediastinal lymphadenopathy occurs in up to 66% of patients and may be associated with a nonproductive cough or other symptoms of tracheal or bronchial compression. Axillary or inguinal lymphadenopathy is less frequently seen as the first presenting sign. Primary infradiaphragmatic disease is rare in pediatric patients and occurs in fewer than 5% of cases. Splenic involvement occurs in 30% to 40% of pediatric patients with HL, whereas hepatic involvement is exceedingly rare. The pulmonary parenchyma, chest wall, pleura, and pericardium are the most

TABLE 74-1 Pediatric Hodgkin's Lymphoma: Demographic and Clinical Characteristics at Presentation

	Children*,† (%) *N* = 1985	Children‡ (%) *N* = 2836	Adults‡ (%) *N* = 18,898	Adults† (%) *N* = 1912
TOTAL PATIENTS				
<10 y	360 (18)	312 (11)		
≥10 y	1625 (82)	2524 (89)	18,898 (100)	1912 (100)
GENDER				
Male	1100 (55)	1455 (51)	10,330 (55)	1147 (60)
Female	885 (45)	1381 (49)	8568 (45)	765 (40)
HISTOLOGY				
Lymphocyte predominant	192 (10)	177 (6.3)	1224 (6.5)	96 (5.0)
Lymphocyte depleted	—	8 (0.3)	321 (1.7)	115 (6.0)
Mixed cellularity	307 (16)	284 (10)	3176 (17)	325 (17)
Nodular sclerosing	1431 (72)	2142 (76)	11,583 (61)	1377 (72)
Not classified	55 (2.8)	225 (7.9)	2594 (14)	
B SYMPTOMS				
Present	564 (28)	863 (39)	6477 (48)	612 (32)
Absent	1421 (72)	1337 (61)	7012 (52)	1300 (68)
STAGE§				
I	229 (12)	522 (19)	4208 (23)	210 (11)
II	1078 (54)	1337 (49)	7021 (39)	899 (47)
III	391 (20)	518 (19)	3569 (20)	593 (31)
IV	287 (15)	366 (13)	3156 (18)	210 (11)

y, *Year.*

**Data taken from Ruhl U, Albrecht M, Dieckmann K, et al: Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: An interim report at 5 years of the German GPOH-HD 95 trial. Int J Radiat Oncol Biol Phys 51(5):1209–1218, 2001[50] and Nachman JB, Sposto R, Herzog P, et al: Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 20(18):3765–3771, 2002.[51]*

†*Data taken from Cleary SF, Link MP, Donaldson SS: Hodgkin's disease in the very young. Int J Radiat Oncol Biol Phys 28(1):77–83, 1994.*

‡*Data taken from Bazzeh F, Rihani R, Howard S, et al: Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988-2005: An analysis of 21 734 cases. Leuk Lymphoma 51(12):2198–2207, 2010[52]; breakdown by age <10 versus ≥10 years estimated from chart.*

§*Data derived from both pathologically and clinically staged patients.*

commonly involved extranodal sites of disease. Bone marrow involvement at the time of initial presentation of HL is also uncommon in children. Approximately 65% of children have stages I and II disease and 35% have stages III and IV disease (Table 74-1).

Nonspecific systemic symptoms are often associated with lymphadenopathy and may include fatigue, anorexia, mild weight loss, and pruritus. The prognostically significant B symptoms have already been defined and occur in approximately 33% of patients (see Table 74-1). Laboratory changes observed at presentation are nonspecific but may provide clues about the extent of disease. Hematological abnormalities may include anemia, neutrophilic leukocytosis, lymphopenia, eosinophilia, and monocytosis. Anemia may be associated with the presence of advanced disease and may result from impaired mobilization of iron stores or less commonly from hemolysis. Several autoimmune disorders have been reported in patients with HL including nephrotic syndrome, autoimmune hemolytic anemia, autoimmune neutropenia, immune thrombocytopenia, and autoimmune lymphoproliferative disorder.[53] These conditions typically remit as the lymphoma is responding to therapy. Several acute phase reactants including erythrocyte sedimentation rate, serum copper, ferritin, and C-reactive protein levels may be elevated at diagnosis and useful in follow-up evaluations.

Patient Evaluation

Posteroanterior and lateral thoracic radiographs should be performed as soon as HL becomes part of the differential diagnosis to assess mediastinal involvement, airway patency, and other intrathoracic structures. This is particularly important if sedation is planned for diagnostic procedures. An excisional lymph node biopsy is the preferred diagnostic procedure because it permits evaluation of the malignant Hodgkin Reed-Sternberg cells within the background of characteristic architectural changes of the specific histological subtypes. All nodal regions, including Waldeyer's ring, should be assessed by careful physical examination. Historically, an upright chest radiograph was also important to assess mediastinal bulk that is defined by mediastinal lymphadenopathy measuring 33% or more of the maximum intrathoracic cavity. Whether or not this definition for bulk mediastinal adenopathy may be replaced by CT-based mass dimensions or volumes is currently under debate. CT is most frequently used to evaluate the nodal regions in the neck, axilla, thoracic and abdominal cavities, and pelvis. Administration of both oral and intravenous contrast agents is required for CT to accurately distinguish lymphadenopathy from other infradiaphragmatic structures. Organ size is an unreliable indicator of lymphomatous involvement in the liver or spleen because tumor deposits may be less than 1 cm in diameter and not visualized by diagnostic imaging modalities. Increased size of either organ can, of course, be caused by nonmalignant causes. The presence of hypodense lesions by CT or abnormal functional avidity PET scanning provides stronger evidence of tumor infiltration in these organs.

Functional nuclear-imaging studies are appropriately used in patients with HL as a diagnostic and monitoring modality. FDG-PET scanning has become a standard part of the staging

TABLE 74-2 Risk Stratification in Pediatric Hodgkin's Lymphoma Cooperative Group Clinical Trials

Trial	Low Risk	Intermediate Risk	High Risk
Children's Oncology Group			
AHOD0431 (low risk); AHOD0031 (intermediate risk); AHOD0831 (high risk)[17,65]	IA, IIA with no bulk	IA bulk or E; IB; IIA bulk or E; IIB; IIIA, IVA	IIIB, IVB
C5942[51,66]	IA, IB, IIA with no bulk, no hilar nodes and <4 sites	IA, IB, IIA with bulk, hilar nodes or ≥4 sites; III	IV
C59704 (high risk)[67]			IIB/IIIB with bulk, IV
P9425/P9426[68]	IA, IIA with no bulk	IB, IIA, $IIIA_1$ with bulk; $IIIA_2$	IIB, IIIB, IV
German Multicenter/Euronet			
GPOH-HD 95; GPOH-HD 2002; PHL-C1*[,69-71]	1A/B, IIA	I_EA/B; II_EA; IIB; IIIA	II_EB; III_EA/B; IIIB; IV
Stanford/St. Jude/Dana-Farber Cancer Institute Consortium			
HOD08† (low risk); HOD05‡ (intermediate risk); HOD99§ (high risk)	IA, IIA with no bulk, E and <3 sites	IB, IIIA, IA/IIA with E, ≥3 sites or bulk	IIB, IIIB, IV

Adapted from Kelly KM: Management of children with high-risk Hodgkin lymphoma. Br J Haematol 157(1): 3–13, 2012.[72]
E, *Extralymphatic stage;* $IIIA_1$, *minimal splenic, splenic hilar, or celiac involvement stage;* $IIIA_2$, *massive splenic or lower abdominal node involvement.*
**ClinicalTrials.gov identifier: NCT00433459.*
†*ClinicalTrials.gov identifier: NCT00846742.*
‡*ClinicalTrials.gov identifier: NCT00352027.*
§*ClinicalTrials.gov identifier: NCT00846742.*

work-up and assessment of response to therapy. Fused positron emission tomography/computed tomography (PET-CT) offers the advantage of integrating functional and anatomic tumor characteristics. Residual or persistent FDG avidity appears to be useful in predicting prognosis and the need for additional therapy in posttreatment evaluation.[54-58] Moreover, PET may be useful in evaluating abnormalities that become clinically manifest or appear on imaging to assess recurrence.[59] The utility of PET for follow-up is being studied because other reports suggest low rates of diagnosing relapsed disease and problems with a high degree of false-positive findings.[60-62] Because extranodal disease involving the bones and bone marrow is relatively uncommon in children, these staging evaluations can be omitted in patients presenting with localized and asymptomatic disease. Bone pain should be evaluated with plain radiographs; magnetic resonance (MR) may also be necessary in this situation for questions about focal bone involvement. PET scanning is supplanting technetium-99 bone scans for skeletal evaluation, which historically have also been performed when there was an elevated serum alkaline-phosphatase concentration beyond that expected for age, or extranodal disease identified by other staging evaluations. A bone marrow biopsy should be performed in any patient with clinical stage III or IV disease or B symptoms, although this standard recommendation is being reconsidered when PET imaging shows no bone or bone marrow involvement.[63] Because the pattern of infiltration in the bone marrow may be diffuse or focal and is often accompanied by reversible marrow fibrosis, a bone marrow aspirate alone is inadequate to assess the marrow for disease.

Prognostic Factors

The identification of prognostic factors has taken on importance as a determinant of risk- and response-adapted treatment algorithms. Many prognostic factors have been identified from adult trials. Regardless, this effort is complicated by several concepts. First, prognostic factors are in flux as more effective or higher intensity therapy may negate adverse risk factors previously demonstrated.[64] Second, various risk-stratification schemes have been used by different institutions and cooperative groups to allocate patients to various treatments regimens making comparisons of patient populations challenging. Most data are based on reports that primarily include adults. Although there is overlap in the biology and response to therapy of pediatric and adult forms of HL, there is divergence in prognostic groupings just as there are differences in treatment regimens. Even among pediatric protocols and cooperative groups there is a lack of standardization in prognostic factors. See Table 74-2. Third, there is an evolving understanding that early response to systemic therapy may be an important prognostic factor that may be used to guide further treatment decisions.[57] While this concept is under investigation in adults with HL, response-based therapy has recently developed firm roots in pediatric HL treatment paradigms.[17] Thus, there is much variability in classifications of patients with HL into favorable, intermediate, and unfavorable/advanced strata.

Dating from the time that early-stage HL was treated with subtotal or total nodal irradiation including splenic irradiation—often termed extended field radiotherapy (EFRT)—numerous adverse prognostic factors in stages I to II disease have identified those patients who benefit from combined-modality therapy.[73-76] In pediatric management, EFRT was abandoned in favor of primary chemotherapy and reduced dose involved field RT in the 1970s and 1980s to reduce late effects of full dose EFRT. This switch in adult management of early-stage disease did not occur until the mid-1990s. Regardless, the concept of risk-adapted therapy was first developed in which the presence of poor prognostic factors drive more intensive therapy; at the same time, favorable factors identify a population appropriately treated with less intensive therapy designed to maintain high cure rates with fewer acute and late side effects. Prognostic factors identified in these analyses include the number of involved lymphoid regions, the size of individual nodes, the extent of mediastinal disease, patient gender and age, the presence of B symptoms or pruritus, histology, erythrocyte sedimentation rate (ESR), and overall tumor burden as measured by number of sites and disease bulk.

Even for pediatric management, it is relevant to note that the adult cooperative groups have refined favorable versus unfavorable groupings. For instance, the European Organization for Research and Treatment of Cancer (EORTC) and

Groupe d'Etudes des Lymphomes de l'Adulte (GELA) specify the following as unfavorable factors: age >50 years, ESR ≥ 50 in the absence of B symptoms, ESR ≥ 30 with B symptoms, ≥4 sites of involvement or bulky mediastinal involvement.[77] For the German Hodgkin Lymphoma Study Group (GHSG), the following are considered unfavorable factors: ESR ≥50 in the absence of B symptoms, ESR ≥ 30 with B symptoms, ≥3 sites of involvement, extranodal involvement, or bulky mediastinal mass.[78]

For pediatric practice, adverse prognostic features have included advanced stage, B symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, and three or more involved nodal regions. Based on the most recent intermediate risk COG protocol AHOD0031, a preliminary prognostic scoring system has been proposed, with the acronym CHIPS for Childhood Hodgkin International Prognostic Score. Based on a multivariate analysis, four predictors—stage IV, large mediastinal adenopathy, albumin <3.5, and fever—were identified as predictive of adverse EFS.[79] This simple scoring system needs further validation, particularly as treatment algorithms change, prognostic factors may change and become more difficult to identify. But for the present, several prognostic factors continue to influence the success and choice of therapy for pediatric practice:

1. *Stage of disease:* Stage persists as the most important prognostic variable. Patients with advanced stage disease, especially stage IV, have a poorer outcome than patients with early-stage disease.[80]
2. *B symptoms:* These constitutional symptoms likely result from cytokine secretion, and correlate with biologic aggressiveness. Thus, unexplained fevers, drenching night sweats, or significant weight loss with definitions noted in the Ann Arbor staging classification system[48] continue to have prognostic importance and in turn influence management decisions. The presence of B symptoms has correlated with a higher likelihood of systemic disease, including occult subdiaphragmatic disease when staging laparotomies were once performed. Evidence suggests that fevers and weight loss have more prognostic significance than night sweats alone.[81]
3. *Bulk:* The bulk of disease combines the number of disease sites and the volume of involvement at each site. Patients with several sites of involvement, defined variably as either three or four or more sites of disease, fare less well.[82] This prognostic factor may also influence treatment selection as to the reduction or elimination of RT after primary chemotherapy for patients with early-stage HL.[83,84] Moreover, the presence of large mediastinal adenopathy or bulky disease in nonmediastinal sites has been another consistent risk factor. A variety of definitions of large mediastinal adenopathy have been reported in the literature.[85] The most commonly used definition is based on a measurement of the maximum width of the mediastinal mass on standing posteroanterior (PA) chest radiograph, compared with the maximum intrathoracic diameter. A ratio greater than one third is defined as "bulky." Other reports have used a ratio with the intrathoracic width at T5-6 as the denominator,[86] whereas still others use absolute measurements,[87] surface area calculations, or volume measurements. In the absence of a chest x-ray, CT-based measurements of mediastinal masses have not reached a consensus recommendation, but some commentators have suggested that 10-cm maximal diameter may be reasonable. Bulky disease in nonmediastinal sites has similarly been classified with varying definitions. Some protocols define bulky as ≥10 cm, while others use ≥5 cm[88] or ≥6 cm.[17,89,90] In Europe, the EuroNet Pediatric Hodgkin Lymphoma Group uses a volumetric definition of bulk. This was initially assessed by a definition of 50 mL,[64] but subsequent experience has found a 200-mL volume definition to be more prognostically discriminatory and is now used in their EuroNet PHL C2 trial to stratify patients.[91] Moreover, volume of a given site of disease is estimated by a simple formula estimating an ellipsoid where $V = (xyz)/2$ where x, y, and z are the diameters of the mass in three dimensions. This becomes much more complex when measuring mediastinal masses where adding multiple ellipsoids of disease to avoid counting normal structures is the procedure.
4. *Laboratory studies*, including the ESR, hemoglobin level, and serum albumin, have been reported to predict worse outcomes.[76] This could reflect disease biology or bulk. In adult cooperative group trials, ESR has been an important stratification factor in treatment protocols. Low hemoglobin and albumin levels have been found to be important factors in an International Prognostic Score.[92]
5. *Histologic subtype* has importance. As already noted, patients with NLPHL are biologically different and generally have improved DFS and overall survival (OS) relative to classical HL; separate protocols with minimal therapy are under way for patients with early-stage NLPHL. Patients with lymphocyte depleted Hodgkin's lymphoma (LDHL) fare poorly. Mixed reports suggest better or poorer outcome of other histologies that may be related to other prognostic factors as well. Some reports suggest that the mixed cellularity subtype of classical HL may have better prognosis than nodular sclerosis subtype in the pediatric age group.[93]
6. *Age* is a significant factor with survival rates for children with HL approaching 85% to 95%, and higher than adults stage for stage. In a report from Stanford, the 5-year and 10-year survival rates for children with HL ≤ 10 years of age was 94% and 92%, respectively, compared with 93% and 86% for adolescents (aged 11-years to 16-years old) and 84% and 73% for adults.[21]
7. *Rapidity of response to initial chemotherapy* is an important prognostic variable. Early-response to therapy was initially observed in patients with advanced stage HL treated on Pediatric Oncology Group (POG) 8725, where 93% of patients who attained a complete response (CR) after three cycles of chemotherapy remained disease free.[7] This was also confirmed for lower stage patients[16] and afterward incorporated in the latest COG front-line trials. Early CR to therapy has also been successfully incorporated into the German trials with low-risk patients who achieve CR after two cycles of oncovin, etoposide, prednisone, and Adriamycin (OPEA)) not requiring further RT.[69,94] Response-based therapy is currently the paradigm on which modern pediatric trials are based.

PRIMARY THERAPY

Risk-Adapted Treatment Approach

Contemporary treatment for children and adolescents with HL involves a risk-adapted and now a response-adapted approach based on the patient's presenting features at diagnosis[50,51,70,71,95-98] and re-evaluation after one or two cycles of chemotherapy. Factors included in the risk assessment may vary across studies; but they most often include the presence of B symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease to contiguous structures, number of involved nodal regions, Ann Arbor stage, and gender. A favorable clinical presentation is typically characterized as localized (stages I and II) nodal involvement in the absence of B symptoms and bulky disease. Although the historical definition of mediastinal bulk has been based on the ratio greater than one third between the transverse dimension

of the mediastinal mass to the intrathoracic cavity on an upright chest radiograph, some trials have moved to use a simple size criteria on cross-sectional imaging as used for peripheral lymph node bulk. That definition, however, is highly variable across studies ranging from 4 cm to 10 cm as a minimal threshold. Moreover, there is additional subjectivity in the definition of bulk when there are multiple matted or adjacent nodes, contributing to confusion on such risk stratification in practice. Fewer than three or four involved nodal regions are considered favorable. In some risk-adapted treatment protocols, patients with localized disease presenting with unfavorable features are designated intermediate in risk and treated similarly to those with advanced-stage disease; whereas in others a therapy intermediate in intensity is prescribed. The criteria for unfavorable clinical presentations has also differed among studies, but most often it is comprised of the presence of B symptoms, bulky lymphadenopathy, hilar lymphadenopathy, more than three to four involved nodal regions, extranodal extension to contiguous structures, or advanced-stage (IIIB-IV) disease. The results of contemporary trials indicate that children and adolescents with early-stage or favorable presentations of HL are excellent candidates for reduced therapy.[50,51,96,98] Ongoing trials are evaluating whether intensification of therapy improves outcomes in patients with intermediate- and high-risk presentations.

Although not widely used to guide therapy assignment in pediatric trials, other factors such as gender, age at diagnosis, and histology are most definitely considered in individual patients. The trials organized by the German-Austrian Pediatric Oncology Group (GPOH) and one trial by the Children's Cancer Group (now integrated in the Children's Oncology Group [COG]) have been unique in their aims to prospectively evaluate gender-based therapy.[50,99] Long-term follow-up of the GPOH 90 and 95 studies demonstrate that the substitution of etoposide for procarbazine in the OPPA regimen does not compromise DFS and provides less potential risk for gonadal toxicity.[50,70] Although age at presentation has not been used as a criterion to assign therapy in prospective trials, reports describing outcomes after treatment with chemotherapy alone stress the benefits of this approach in younger children at higher risk of radiation-related toxicity.[51,97]

Prognostic groupings now dictate the intensity of therapy with the goal of matching up just enough cytotoxic therapy to yield a high chance for cure while minimizing those exposures responsible for late complications. Within the last cycle of COG trials, patients were allocated into a favorable group if they had stage IA or IIA disease without bulk. Unfavorable patients were those with stage IIIB or IVB disease. The heterogeneous group of patients in between were deemed intermediate risk. See Table 74-2. The upcoming cycle of COG trials beginning in 2014 will categorize patients either into low- or high-risk strata; high risk will include those patients with stage IIB disease with bulk, IIIB, IVA, and IVB disease. In Europe, the GPOH has merged into a geographically broader EuroNet cooperative group in which patients will be categorized as follows[91]:

1. TG-1: patients of stages I A/B and II A without bulk ≥200 mL and without ESR ≥ 30 mm/hr
2. TG-2: patients of stages IEA/B, IIEA, II B, or III A and patients of stages I A/B and II A with bulk ≥200 mL or ESR ≥ 30 mm/hr
3. TG-3: patients of stages IIEB, IIIEA/B, III B, or IV A/B

Finally, a collaborative group of investigators from St Jude's, Stanford, and Harvard have defined a favorable early-stage cohort that may be treated with minimal therapy; patients with stages I to IIA disease without mediastinal bulk, no extranodal disease, and less than three sites of disease.[83]

A summary of trials in children with early- and intermediate- and advanced-stage HL is provided in Tables 74-3 and 74-4.

Response-Based Therapy

The response to chemotherapy, either early in its course or at its completion, is known to be an important prognostic factor in HL.[15] This has led to a hypothesis that modifications in therapy may be based on the initial response to chemotherapy in a similar fashion to the management of acute lymphoblastic leukemia. Based on rapidity of a complete response to chemotherapy, a reduction or augmentation of therapy may be possible, a concept under cautious investigation in clinical trials. Response-based approaches titrate the overall duration of chemotherapy or the need for RT by assessing the early response to chemotherapy. Two Pediatric Oncology Group trials from the USA (POG 8725 and 8625) comparing chemotherapy alone versus chemo-radiotherapy supported this idea that a rapid early response (RER) to chemotherapy reflects the chemosensitivity of a patient's HL and is a predictor of good long-term control.[7,16] The implication is that treatment can be reduced in intensity or duration for those with RER to mitigate toxicity or increased for those with a slow early response (SER) to improve disease control.

The augmentation in therapy for SER can be either an increased RT dose, additional chemotherapy, or both. The French Society of Pediatric Oncology MDH90 treated 202 children with stage I or II HL with four cycles of vinblastine, bleomycin, etoposide, and prednisone (VBVP). Good responders received 20 Gy IFRT alone, whereas poor responders were given an additional one to two cycles of OPPA and then either 20 Gy IFRT (good responders at second evaluation) or 40 Gy IFRT (poor responders). The 5-year OS and EFS were 97.5% and 91.1%, respectively.[98] In the German trial, GPOH HD-95, patients with early-stage disease who had a complete response to chemotherapy (two cycles OPPA for girls or two cycles OEPA for boys) did not receive adjuvant RT. OPPA/OEPA chemotherapy alone produced a 5-year DFS of 88%, which was not significantly different from that observed in patients who received RT (92%).[70] In this German trial, higher-risk patients who received RT were prescribed radiation doses of up to 35 Gy if complete response was not achieved. The use of higher-dose RT with simple anterior-posterior beams is certainly known to cause undesirable musculoskeletal toxicities and the potential for increased cardiopulmonary injury and secondary cancers, such that augmentation of chemotherapy or more conformal RT may be better approaches for nonresponders. POG 9425 administered three versus five cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy and 21-Gy regional RT for rapid and slow responders, respectively.[68] Two-year EFS was 88.2%, with no statistical difference between early and slow responders. These studies suggest that interim or early response-adapted therapy may be useful in identifying patients with favorable disease, who can be treated with lower RT doses or abbreviated chemotherapy.

The recent COG intermediate-risk HL study AHOD0031 was a response-based paradigm in which chemotherapy was intensified enough to safely eliminate RT for some patients. Although the results are detailed, children with stages IA and IIA with bulky disease, IB, IIB, IIIA, or IVA disease received two cycles of ABVE-PC prior to response evaluation with CT imaging. Those with RER defined as at least a 60% reduction in the sum of the product of the perpendicular diameters of up to six target lesions, and who proceed to a complete response with at least an 80% reduction in disease

TABLE 74-3 Published Treatment Results for Low-Risk Pediatric Hodgkin Lymphoma

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
COMBINED MODALITY TRIALS								
Gehan, 1990[5]	Intergroup Hodgkin (SWOG/POG)	97	PS I-II	6 MOPP	35, IF	97	93	5
Schellong, 1992[100]	GPOH-HD 82	100	IA/IB-IIA	2 OPPA	35, IF	98	100	9
		53	IIB-IIIA	2 OPPA/2 COPP	30, IF	94	96	9
	GPOH-HD 85	53	IA/IB-IIA	2 OPA	35, IF	85	95	6
		21	IIB-IIIA	2 OPA/2 COMP	30, IF	55	95	6
Schellong, 1999[10,71,101]	GPOH-HD 90	275	IA/IB-IIA	2 OEPA/OPPA	25, IF	94/95	99	5
		124	IIB-IIIA	2 OEPA/OPPA + 2 COPP	25, IF	90/96	97	5
Dörffel, 2003, 2010[69,70]	GPOH-HD 95	328	I-IIA	2 OPPA/OEPA	20-35, IF for PR; no rt if CR	93.2	98.8	10
		256	II_EA, IIB, IIIA	2 OPPA/OEPA + 2 COPP		86.7	97.3	10
Shankar, 1997[102]	Royal Marsden	125	II	6-10 ChlVPP	35, IF	85.0	92.0	10.0
Shankar, 1998[103]	Royal Marsden	46	I-III	8 VEEP	30-35, IF	82.0	93.0	5.0
Cramer, 1985[104]	Hôpital St. Louis, Paris	72	CS IA-II2A	3 MOPP	35-40, IF	87.6	91.6	6.8
			CS II3A-IIB	6 MOPP or 3 MOPP + 3 CVPP	35-40, IF for pathologic residual dz			
Oberlin, 1992[105]	SFOP MDH-82	79	CS I-IIA	4 ABVD	20-40, IF	90		6
		67	CS I-IIA	2 MOPP/2 ABVD	20-40, IF	87		6
		31	CS IB-IIB	3 MOPP/3 ABVD	20-40, IF		92	6
Landman-Parker, 2000[98]	SFOP MDH-90	171	I-II	4 VBVP, good responders	20, IF	91.0	97.5	5.0
		27	I-II	4 VBVP + 1-2 OPPA, poor responders	20, IF	78.0		5.0
Hudson, 1993[106]	St. Jude	58	CS II/III	4-5 COP(P)/3-4 ABVD	20, IF	96.0/97.0	96.0/100.0	5.0
Hunger, 1997[107]	Stanford	44	CS/PSI-III	3 MOPP/3 ABVD	15-25.5, IF	100.0	100.0	10.0
Donaldson, 2007[96,108]	Stanford/St. Jude/Dana Farber Consortium	110	CS I/II†	4 VAMP	15-25.5, IF	92.7	99.1	5.0
						89.4	96.1	10.0
Hudson, 2004[109]	Stanford/St. Jude/Dana Farber Consortium	77	I	3 VAMP/3 COP (2 cycles/RT/2 cycles/RT/2 cycles/RT)	15, IF for CR; 25.5, IF for PR	100.0	92.7 (all)	5.8
			II			78.4		
Vecchi, 1993[110]	AEIOP MH-83	58	IA-IIA nonbulk	3 ABVD	20-25 IF	94.6	85.7	7
		56	IIA bulk - IIIA	3 MOPP/3 ABVD	20-25 EF	81.4		7

Continued

TABLE 74-3 Published Treatment Results for Low-Risk Pediatric Hodgkin Lymphoma—cont'd

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	94	CS IA/B, HA*	4 COPP/ABV	21, IF	97.0 100	100.0	3 10
Kung, 2006[16]	USA POG 8625	81	PS IA-IIIA1	2 MOPP/2 ABVD	25.5 Gy, IF	91.1	96.8	8
Tebbi, 2006[111]	USA POG 9426	46	CS IA-IIIA1	4 DBVE	25.5 Gy, IF	91	98	6
Metzger, 2012[83]	Stanford/St. Jude/Dana Farber Consortium	41	CSIA-IIA, no extranodal, no mediastinal bulk, <3 sites	4 VAMP, partial response	25.5 Gy, IF	92.5	100	2
CHEMOTHERAPY ALONE TRIALS								
Lobo-Sanahuja, 1994[112]	Costa Rica	52	CS IA-IIIA	6 CVPP	None	90.0	100.0	5.0
Sackmann-Muriel, 1997[113]	GATLA	10 16	CS IA, IIA CS IB, IIB	3 CVPP 6 CVPP	None None	86.0 87.0		6.7 6.7
Behrendt, 1987[114]	Netherlands	21 16	CS I-II nonbulk CS I-II bulk	6 MOPP 6 MOPP	None None	87.5 86	100	5 5
Behrendt, 1996[115]	Netherlands	17	CS I-II (12 pts) CS III-IV (5 pts)	6 ABVD	None	71 (5 relapses, but only 2 with early stage)	92	8
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	106	CS IA/B, HA†	4 COPP/ABV	None	91.0 82.9	100.0	3.0 10.0
Baez, 1997[116]	Nicaragua	14	CS IA-IIA	6 COPP	None	100	100	3
Sripada, 1995[117]	Madras, India	10	CS IA-IIA	6 COPP/ABV	None	89		5
Olweny, 1978[118]	Uganda	18	CS IA-IIIA	6 MOPP	None	75	75	5
Kung, 2006[16]	POG 8625	78	PS IA-IIIA1	4 MOPP/4 ABVD	None	82.6	93.6	8
Ekert, 1993[119]	Australia/New Zealand	25	CS IA-IVA	2-3 EVAP + 0-4 EVAP/ABV	None	60	100	3
Metzger, 2012[83]	Stanford/St. Jude/Dana Farber Consortium	47	CSIA-IIA, no extranodal, no mediastinal bulk, <3 sites	4 VAMP, complete response	None	89.4	100	2

ABVD, *Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine;* CCG, *Children's Cancer Group;* ChlVPP, *chlorambucil, vinblastine, procarbazine, and prednisolone;* COP, *cyclophosphamide, Oncovin (vincristine), and procarbazine;* COPP, *cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine;* COPP/ABV, *cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone/Adriamycin (doxorubicin), bleomycin, and vinblastine;* CR, *complete response;* CS, *clinical stage;* DFS, *disease-free survival;* EFS, *event-free survival;* IF, *involved field;* GATLA, *Grupo Argentino de Tratamiento de Leucemia Aguda;* GPOH-HD, *German-Austrian Pediatric Oncology Group-Hodgkin's disease;* MOPP, *mechlorethamine, vincristine, procarbazine, and prednisone;* OEPA, *Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin);* OPPA, *Oncovin (vincristine), procarbazine, prednisolone, and Adriamycin (doxorubicin);* PR, *partial response;* PS, *pathologic stage;* R, *regional;* RFS, *relapse-free survival;* RT, *radiation therapy;* SFOP, *French Society of Pediatric Oncology;* VAMP, *vinblastine, doxorubicin, methotrexate, and prednisone;* VBVP, *vinblastine, bleomycin, etoposide, and prednisone;* VEEP, *vincristine, etoposide, epirubicin, and prednisolone;* y, *year.*

**Without adverse features.*

†With adverse features.

(Adverse disease features comprise one or more of the following: hilar adenopathy; involvement of >4 nodal regions; mediastinal tumor with diameter more than one third of the chest diameter; node or nodal aggregate with a diameter >10 cm.)

TABLE 74-4 Published Treatment Results for Intermediate- and High-Risk Pediatric Hodgkin Lymphoma

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
COMBINED MODALITY TRIALS								
Schellong, 1992[100]	GPOH-HD 82	50	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/4 COPP	25, IF	86	85	9
Schellong, 1996[100]	GPOH-HD 65	24	II_EB, III_EA/B, IIIB, IVA/B	2 OPA/4 COMP	25, IF	49	100	6
Schellong, 1999[10,71,101]	GPOH-HD 90	179	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/OEPA + 4 COPP	20-35, IF	86	94	5
Dörffel, 2003, 2013[69,70]	GPOH-HD 95	341	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/OEPA + 4 COPP	20-35, IF for PR; no RT if CR	84.5	93.2	10
Oberlin, 1992[105]	SFOP MDH-82	40 21	CS III CS IV	3 MOPP/3 ABVD 3 MOPP/3 ABVD	20-40, EF 20-40, EF	82 62		6 6
Vecchi, 1993[110]	AEIOP-83	49	IIIB-IV	5 MOPP/5 ABVD	20-40, EF		60	7
Sackmann-Muriel et al, 1997[113]	GATLA	43 21 24	Intermediate risk High risk	6 CVPP 6 AOPE CCOPP/CAPTe	30-40, IF	87 67 83		5 5 5
Mauch, 1983[120]	Joint Center/Harvard	83	IA-IIIB	6 MOPP	25-40	77	95	11
Shankar, 1997[102]	Royal Marsden	80 27	III IV	6-10 ChlVPP 6-10 ChlVPP	35, IF 35, IF	73 38	84 71	10 10
Hudson, 1993[106]	St. Jude	27	CS IV	4-5 COP(P)/3-4 ABVD	20 Gy, IF	85	86	5
Donaldson, 1987[3]	Stanford	28	III-IV	6 MOPP	15-25.5, IF	84	78	7.5
Hunger, 1997[107]	Stanford	13	III-IV	3 MOPP/3 ABVD	15-25.5, IF	69	85	10
Friedmann, 2002[97]	Stanford/St. Jude/Dana Farber Consortium	56	CS I/II bulky (n = 26), CS III/IV (n = 30)	6 VEPA	15-25.5, IF	67.8	81.9	5
Jenkin, 1990[121]	Toronto	57	CS IIA-IV	6 MOPP	25-30, EF	80	85	10
Hudson, 2004[109]	Stanford/St. Jude/Dana Farber Consortium	82	III IV	3 VAMP/3 COP (followed by consolidative RT)	15, IF for CR; 25.5, IF for PR/NR	68.9 68.5	92.7 (all)	5.8
Fryer, 1990[4]	USA-CCG	64	PS III-IV	12 ABVD	21, R	87	89	3
Hutchinson, 1993[122]	USA-CCG 521	54	PS III-IV	6 ABVD	21, EF	87	90	4
Weiner, 1991[8,56]	USA-POG 8426	62	CS/PS IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21, TLI	77	91	3
Weiner, 1997[7]	USA-POG 8725	80	CS/PS IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21, EF	80	87	5
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	103 36	CS I/II*, CS IIB, CS III CS IV	6 COPP/ABV COPP/ABV + CHOP + Ara-C/VP-16	21, IF 21, IF	87 84 90 88.5	95 100	3 10 3 10

Continued

TABLE 74-4 Published Treatment Results for Intermediate- and High-Risk Pediatric Hodgkin Lymphoma—cont'd

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
Kelly, 2002, 2011[67,99]	USA-CCG 59704	99	CS IIB/IIIB, bulky; IV	4 BEACOPP then if RR: 4 COPP/ABV (girls) or 4 ABVD (boys); if NRR: 4 BEACOPP	Female RR: no RT; Male RR: 21-35 Gy, IF NRR: 21, EF + boost to residual to 35 Gy	94	97	5
Schwartz, 2009[68]	USA-POG 9425	216	IB bulky-IV	RER: 3 ABVE-PC SER: 5 ABVE-PC	21 Gy, IF 21 Gy, IF	86 83	95 95	5 5
CHEMOTHERAPY ALONE TRIALS								
Atra, 2002[95]	UKCCSG	67	CS IV	6-8 ChlVPP	None	55.2	80.8	5
Ekert, 1988[123]	Australia/New Zealand	53	CS IV	6-8 MOPP or 6 ChlVPP	None	92	94	4
Ekert, 1999[124]	Australia/New Zealand	53	CS I-IV	5-6 VEEP	None	78	92	5
Olweny, 1978[118]	Uganda	10	CS IIIB-IV	6 MOPP	None	60		5
Baez, 1997[116]	Nicaragua	23	CS IIIB-IV	8-10 COPP/ABV	None	75		3
Lobo-Sanahuja, 1994[112]	Costa Rica	24	CS IIIB-IV	6 CVPP/6 EBO	None	60	81	5
Sripada, 1995[117]	Madras, India	43	CS IIB-IVB	6 COPP/ABV	None	90	5	
Van den Berg, 1997[125]	Netherlands	21 17 21	CS I-IV (<4 cm node) CS I-IV	6 MOPP 6 ABVD 3 MOPP/3 ABVD	None None None	91 70 91	100 94 91	5 5 5
Hutchinson, 1998[6]	USA-CCG	57	PS III/IV	6 MOPP/6 ABVD	None	77	84	4
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	122 30	CS I/II*, CSIIB, CS III CS IV	6 COPP/ABV COPP/ABV + CHOP + Ara-C/VP-16	None None	83 78 81 79.9	100 94	3 10 3 10
Weiner, 1997[7]	USA-POG	81	CS IIB, III_2A, IIIB, IV	4 MOPP/4 ABVD	None	79	96	5

ABVD, *Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine;* ABVE-PC, *Adriamycin (doxorubicin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide;* ara-C, *Arabinosylcytosine;* BEACOPP, *bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, vincristine, procarbazine, and prednisone;* CCG, *Children's Cancer Group;* ChlVPP, *chlorambucil, vinblastine, procarbazine, and prednisolone;* CHOP, *cyclophosphamide, Adriamycin (doxorubicin), Oncovin (vincristine), and prednisone;* COP, *cyclophosphamide, Oncovin (vincristine), and prednisone;* COP(P), *cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine;* COPP/ABV, *cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone/Adriamycin (doxorubicin), bleomycin, and vinblastine;* CR, *complete response;* CS, *clinical stage;* CVPP, *cyclophosphamide, vinblastine, procarbazine, and prednisone;* DFS, *disease-free survival;* EF, *extended field;* EFS, *event-free survival;* GPOH-HD, *German-Austrian Pediatric Oncology Group-Hodgkin's disease;* IF, *involved field;* MOPP, *mechlorethamine, vincristine, procarbazine, and prednisone;* NR, *no response;* OEPA, *Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin);* OPPA, *Oncovin (vincristine), procarbazine, prednisolone and Adriamycin (doxorubicin);* POG, *Pediatric Oncology Group;* PR, *partial response;* PS, *pathologic stage;* R, *regional;* RFS, *relapse-free survival;* RT, *radiation therapy;* UKCCSG, *United Kingdom Children Cancer Study Group;* VEEP, *vincristine, etoposide, epirubicin, and prednisolone;* VEPA, *vinblastine, etoposide, prednisone, and Adriamycin (doxorubicin);* y, *year.*

**With adverse features.*

(Adverse disease features comprise one or more of the following: hilar adenopathy; involvement of >4 nodal regions; mediastinal tumor with diameter ≥one-third of the chest diameter; node or nodal aggregate with a diameter >10 cm.)

cross-sectional area and normalization of metabolic abnormalities on gallium or FDG-PET after an additional two cycles of the same chemotherapy, were randomized to 21-Gy IFRT or no additional treatment. On the other hand, patients with SER to two cycles of chemotherapy are randomized to either standard therapy (an additional two cycles of ABVE-PC + 21 Gy IFRT) or intensified therapy (standard therapy plus two additional cycles of chemotherapy—dexamethasone, etoposide, cytarabine, and cis-platinum [DECA]—prior to IFRT). This trial showed that an excellent response to chemotherapy allowed for selection of patients who may avoid RT, but chemotherapy intensification among those with SER was not helpful in this instance. However, analysis is still under way to be confident that select subgroups, such as those who present with bulk mediastinal disease and hematologic abnormalities (e.g., anemia, elevated ESR), do not retain a benefit in EFS from IFRT. Two other pediatric trials have sorted out situations when favorable prognosis patients may have RT withheld after a good response to initial chemotherapy[69,83]; however, another COG trial, AHOD0431 (for the most favorable patients) found that AV-PC chemotherapy for three cycles was not sufficiently intensive to allow for RT to not be given when response was adjudicated by CT scan criteria only.[126]

Although most completed trials have used CT, with or without gallium or PET to determine response, it is becoming increasingly clear that PET scanning after the initial (one or two) chemotherapy cycles will better identify good-prognosis patients and facilitate treatment intensification.[15,57,127,128] When RT can be omitted among patients with a good response to chemotherapy, PET assessment appears to be important. The corollary problem is how to define a response by PET criteria as low levels of residual FDG activity after therapy are common. Another unresolved problem is the interpretation of splenic or hepatic involvement by HL given the physiologic uptake of FDG in these organs. A consensus panel has promulgated PET-based response criteria known as the International Harmonization Project, using mediastinal blood pool as a reference visual threshold to determine residual FDG uptake.[129,130] However, more recently a visual five-point score known as the Deauville criteria has been shown to improve prediction of outcome that is reproducible enough in adult advanced-stage HL to serve as a standard reporting criterion in clinical trials and practice.[131,132] Moreover, a preliminary analysis of this Deauville criteria in a pediatric cohort has suggested that more sensitive response criteria uses liver uptake rather than blood pool as a threshold indicator of interim response to chemotherapy.[133]

Chemotherapy Regimens and Radiation Therapy

MOPP and Derivative Chemotherapy

The prototype alkylator combination that provided the first effective systemic therapy for HL was MOPP.[134] Follow-up studies of MOPP-treated survivors confirmed that secondary acute myeloid leukemia (s-AML) and infertility resulted from the alkylating agents in the regimen and exhibited a dose-dependent relationship.[135] Subsequently, investigators developed a variety of MOPP-derivative regimens in an effort to reduce the risk of secondary leukemogenesis and gonadal toxicity.

The risk of secondary leukemia following alkylating agent chemotherapy peaks in frequency in the first 5 years to 10 years after treatment and plateaus to less than 2% after 10 years from diagnosis.[136] Older age at treatment, history of splenectomy, presentation with advanced disease, treatment with high cumulative doses of alkylating agents, and history of relapse have been reported to predispose to this complication.[136-141] Some alkylating agents are more potent leukemogens than others; the 15-year cumulative incidence of s-AML is 4% to 8% after MOPP-based therapy compared to less than 1% with cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone (COPP)-based therapy that substitutes cyclophosphamide for nitrogen mustard.[142] Pediatric protocols that limit the total dose of alkylating agents or substitute other less-leukemogenic drugs, such as cyclophosphamide, for mechlorethamine, have been associated with low incidence rates of s-AML.[142]

Gonadal injury is common in pediatric patients treated with MOPP and its derivative combinations. Azoospermia is typically irreversible in men treated with six or more cycles of MOPP-like therapy.[135,143] However, germ cell function may be preserved if treatment is limited to no more than three cycles of alkylator therapy.[144] In contrast, most young women will maintain or resume menses after a temporary period of amenorrhea following treatment including alkylating agents.[143] Ovarian transposition and shielding reduces the incidence of gonadal injury in young women requiring pelvic radiation, but these patients will experience a higher risk of premature menopause.[145] The radiation oncologist should also be aware of the age dependency in risk for ovarian failure.[146] Younger females tolerate a modestly higher radiation dose related to the gradual decline in oocyte numbers associated with aging.

ABVD and Derivative Chemotherapy

The ABVD combination provided a systemic therapy that produced superior DFS compared to MOPP and was not associated with an excess risk of secondary leukemia or infertility.[4,147] However, follow-up of patients treated with the ABVD regimen established its association with cardiopulmonary toxicity that was enhanced with the addition of thoracic radiation.[4] Many ABVD derivatives soon followed, aiming to reduce the risk of these sequelae.

Anthracycline agents are an important component of chemotherapy regimens for children with HL because of their significant lympholytic effects. In adults the cumulative incidence of cardiomyopathy increases significantly after anthracycline dose exceeds 550 mg/m^2; children are at increased risk of cardiac dysfunction at lower cumulative doses.[148-151] Other risk factors for anthracycline toxicity identified in studies of childhood leukemia survivors include younger age at treatment (especially younger than 5 years old) and female gender. Combination treatment with chest radiation or other cardiotoxic agents such as amsacrine or cyclophosphamide may also enhance risk of cardiac dysfunction.[150,152-155] Because treatment protocols for pediatric HL frequently include chest radiation or other chemotherapeutic agents with potential cardiotoxicity, most regimens limit cumulative doses of anthracycline agents to below 250 mg/m^2, particularly for patients with favorable-risk disease presentations.

Bleomycin in the ABVD regimen increases the risk of pulmonary toxicity that is most commonly manifested as pulmonary fibrosis and chronic pneumonitis.[156] Thoracic radiation may augment this risk. Patients at highest risk of pulmonary complications are those treated with cumulative bleomycin doses exceeding 400 U/m^2, that far exceed doses used in pediatric regimens for HL. Contemporary protocols use bleomycin doses in the range of 60 U/m^2 to 100 U/m^2; these cumulative exposures are usually associated with asymptomatic pulmonary restriction and diffusion deficits in long-term survivors, some of which will improve over time.[157,158] Serial monitoring of pulmonary function during therapy and withholding bleomycin doses in patients exhibiting significant declines in pulmonary function (20% or more from baseline) may reduce the risk of further pulmonary injury and does not appear to compromise disease control.[106]

Chemotherapy Combinations Including Etoposide

Etoposide has been increasingly incorporated into treatment regimens for pediatric HL over the last few decades. This agent is used in risk-adapted regimens for favorable patients as an effective alternative to alkylating agents in an effort to reduce gonadal toxicity.[68,71,97,98,103,113] Etoposide has been added to alkylating and anthracycline chemotherapy in regimens for advanced and unfavorable patients to enhance treatment response. For example, the previously mentioned dose-intensive ABVE-PC regimen used in recent U.S. cooperative groups yields excellent survival outcomes in intermediate- to high risk patients.[68] Balanced with this survival advantage is an excess risk of s-AML seen with topoisomerase-II inhibitors like etoposide and doxorubicin that differs in epidemiology and biology from alkylator-related s-AML.[159] Secondary AML that occurs in association with topoisomerase-II inhibitors is characterized by a brief time of onset from primary diagnosis, absence of a preceding myelodysplastic phase, monoblastic and myelomonoblastic histology, and translocations involving the *MLL* gene at chromosome band 11q23. Studies of childhood patients with leukemia suggest that intermittent weekly or twice weekly dosing schedules may result in transforming mutations of myeloid progenitor cells by epipodophyllotoxins.[160] A relationship between leukemogenic activity and cumulative epipodophyllotoxin dose could not be established in an evaluation of s-AML cases developing in patients treated with multiagent chemotherapy regimens including epipodophyllotoxins, alkylating agents, doxorubicin, and dactinomycin for pediatric solid tumors.[159] However, the risk of s-AML following treatment with regimens that restricted etoposide doses to 5.0 g/m^2 or less did not exceed that associated with other agents used in solid tumor regimens.[159] Pertinent to this discussion is the report of an increased incidence of second malignancies observed in children treated with ABVE or dose-intensified ABVE with prednisone and cyclophosphamide and the cardiopulmonary protectant dexrazoxane.[161] In these Pediatric Oncology Group trials, patients were randomly assigned to receive dexrazoxane to evaluate its potential to decrease cardiopulmonary toxicity. Unexpectedly, 10 patients developed SMN with AML/myelodysplastic syndrome (MDS) accounting for 8 of the 10 cases. Six of the 8 cases of AML/MDS and two solid tumors occurred in children randomized to receive dexrazoxane. The authors speculated that the use of multiple topoisomerase II inhibitors (dexrazoxane, etoposide, and doxorubicin) may have potentiated carcinogenesis. Collectively, most data support the relative safety of using limited doses of etoposide, but reports of s-AML in patients receiving etoposide for treatment of favorable pediatric HL raise concerns about whether this agent should be avoided in favorable disease presentations.[98]

Gender-Based Therapy

The German Paediatric Oncology and Haematology Society (GPOH) has explored the use of not only risk-adapted, but also gender-adapted therapy featuring the OEPA regimen for boys to limit the amount of alkylators, whereas girls received OPPA, substituting procarbazine for etoposide. Procarbazine is especially problematic in boys as a cause of infertility.[11,162] Although this has not caught on in North America as a strategy to limit late effects, the CCG 59704 high-risk study did include a successful gender-based consolidation phase. All patients received the escalated BEACOPP regimen pioneered by the GHSG as a backbone, having documented efficacy in adult trials with unfavorable features. All patients with a slow response received four additional cycles of BEACOPP and IFRT. But for rapidly responding males, two cycles of ABVD with IFRT were given while females received four cycles of COPP/ABV without radiotherapy particularly to avoid the risks for breast cancer and infertility with mantle and pelvic fields respectively. The concept of gender-based use of RT has been abandoned for now, though it remains quite reasonable as females seem to be particularly predisposed to secondary radiation-related cancers.[163-165]

Radiotherapy Considerations

The curability of pediatric HL and the vulnerability of the developing child to both RT and chemotherapy are critical issues in appropriately integrating radiation into the complex treatment algorithms currently used. Most newly diagnosed children will be treated with risk-adapted chemotherapy alone or combined-modality therapy including low-dose, involved-field RT. Full-dose, extended-field RT using techniques that were once standard for adults and even children has been long abandoned because of concerns primarily relating to growth inhibition, cardiovascular toxicity, and second malignant neoplasms. Historically, the results of treatment with RT alone for early-stage disease were superior at institutions that treated many patients with HL. Although different institutions and radiation oncologists may use slightly different treatment techniques, underlying principles, and in fact, most of the technical details remained constant.[166] However, currently in the United States, most adults with HL are treated in the community setting. Because most children are treated at academic or tertiary care hospitals often on institutional (or multiinstitutional) studies, the radiation oncologist should confirm all aspects of the diagnostic workup and staging; they must also understand study requirements to deliver appropriate RT. Supportive of this premise, up-front centralized review of patients entered into the GPOH-HD 90 study altered the treatment approach in a large number of children.[167] Similarly, prior Pediatric Oncology Group trials observed inferior outcomes related to major deviations in radiation protocol compliance.[168] These data support the need for prospective central review of RT in current COG HL protocols.

In contemporary trials, there is a considerable impetus to minimize RT when possible in children with HL to remove the associated late risks of therapy that include secondary malignancy, cardiovascular complications, and hypothyroidism among others. Secondary malignancy is the most compelling concern as children are more susceptible than adults for this problem despite the reduction in RT dose and volume relative to the historical use of extended field RT.[165] Moreover, young females getting low dose involved field RT to the chest are particularly at risk for breast cancer.[164,165] The risk for subsequent coronary artery disease, valvular heart disease, and heart failure after treatment for HL is multifactorial with both anthracycline and radiations exposures playing a role.[169] However, risk related to RT is radiation dose and volume dependent, and the risk is decreased with doses in the 20-Gy to 25-Gy range.[170] In turn, efforts within the Radiation Oncology community to make the use of low-dose RT safer include more conformal dose distributions with three-dimensional conformal techniques including intensity-modulated radiotherapy (IMRT) and proton RT, deep inspiration breath-hold techniques to improve radiation targeting, and a reduction in the volume of RT with involved-node radiotherapy (INRT) or involved-site radiotherapy (ISRT).

It is hoped that response-adapted therapy may identify patients with favorable-risk pediatric HL who can be treated with chemotherapy alone without significantly reducing DFS. In the past, chemotherapy-alone regimens for advanced-stage disease used higher cumulative doses, predisposing survivors to greater risks of acute and late toxicity associated with alkylating agents, anthracyclines, and bleomycin. These protocols

were designed with the hopes of avoiding toxicities because of RT. However, RT remains an effective agent in HL, and a danger continues to be engendered when systemic therapies are overemphasized and their own set of complications are underappreciated. Current protocols strive to carefully balance chemotherapy exposures along with RT details of dose and volume to limit long-term risks. Importantly, response-based paradigms now allow patients with a rapid response to systemic therapy to minimize the use of RT. The data suggest that children with HL may require RT for both early and advanced disease when the chosen chemotherapy program is insufficiently intensive, when there is a slow response to chemotherapy, when there is residual disease at completion of therapy, possibly when there is bulky disease at presentation, and selectively for relapsed lymphoma. Identification of prognostic features including response features that dictate integration of RT to optimize disease control is a focus of many ongoing pediatric trials.

There is considerable impetus to minimize RT exposures in HL because of late effects, particularly secondary malignancies. Some of the concern results from the historic use of extended field, high-dose radiotherapeutic practices that are no longer representative of modern RT. For example, the Late Effects Study Group analyzed patients treated from 1955 to 1986, before the widespread use of customized lung shielding, megavoltage linear accelerators, or CT-based image guided RT planning.[138] Both the RT doses and volumes are now significantly reduced in managing pediatric HL. As a result, the risk of late effects may be overestimated when analysis are based on past, antiquated techniques. As an example, several studies reveal a marked decrease in the risk for secondary breast cancer when RT volumes and doses are reduced.[14,163,171] But, an important confounding factor leading to reduction in breast cancer risk related to RT occurs from akylating agent chemotherapy or pelvic radiotherapy obstensibly because of ovarian failure and the consequential loss of hormonal influence on the neoplastic process. Nevertheless, the transition from extended-field RT to IFRT significantly reduces the dose to breast and lung tissue,[172] and has been predicted to result in a substantial reduction in secondary cancer risk.[13] Thyroid cancer may be one exception to the general concept that higher radiation doses correlate with higher risk for secondary cancers.[173] In this case, an update to the Late Effects Study Group has shown a nonlinear relationship of dose and cancer incidence with a maximum risk associated with radiation doses in the range of 15 Gy to 25 Gy and decreasing risk with higher doses greater than 29 Gy. Yet despite the use of lower radiation doses, children with HL still continue to harbor an increased risk for secondary solid-type malignancies relative to the general population risk from the use of RT, especially breast cancer in females.[164,165]

Volume

Treatment volumes are continuing to evolve with a current transition in progress from involved field to involved nodal or involved site RT.[174] When RT is indicated, meticulously and judiciously designed fields are necessary for maximum success in terms of both disease control and minimal tissue damage. Until recently, an anatomic region was targeted, designed in terms of lymph node distribution, patterns of disease extension into regional areas, and consideration for match-line problems should disease recur. An understanding of involved field principles remains important to understand the historical results of combined-modality therapy and potential side effects for follow-up purposes. Involved fields typically included not just the identifiably abnormal lymph nodes, but the entire lymph node region containing the involved nodes (Table 74-5). These traditional definitions of lymph node regions have operational details that date to a time when treatment planning technology required the use of simple parallel opposed fields with boundaries that dated to the use of lymphangiography rather than modern cross-sectional imaging. Successful outcomes had cemented field design concepts that have only recently been changed in response to the understanding of late effects.

TABLE 74-5 Historical Involved Field Radiation Guidelines

Involved Node(s)	Radiation Field
Cervical	Neck and infraclavicular/supraclavicular†
Supraclavicular	Neck and infraclavicular/supraclavicular with or without axilla
Axilla	Axilla with or without infraclavicular/supraclavicular
Mediastinum	Mediastinum, hila, infraclavicular/supraclavicular*†
Hila	Hila, mediastinum
Spleen	Spleen with or without para-aortics
Para-aortics	Para-aortics with or without spleen
Iliac	Iliacs, inguinal, femoral
Inguinal	External iliac, inguinal, femoral
Femoral	External iliac, inguinal, femoral

**Prechemotherapy volume is treated except for lateral borders of the mediastinal field, which is postchemotherapy.*
†Upper cervical region not treated if supraclavicular involvement is extension of the mediastinal disease.

However as past is prologue, a discussion of involved field RT remains relevant despite the current move toward more restricted fields (See Table 74-5). For example, the cervical and supraclavicular lymph nodes have generally been treated when abnormal nodes are located anywhere within this area; this is consistent with the anatomic definition of lymph node regions used for staging purposes. However, the hila have usually been irradiated when the mediastinum is involved, despite the fact that the hila and mediastinum are separate lymph node regions. Similarly, the supraclavicular fossa (SCV) has typically been treated when the axilla or the mediastinum is involved, and the ipsilateral external iliac nodes have often been treated when the inguinal nodes are involved. However, in both situations care would have been taken to shield relevant normal tissues to the degree possible, such as the breast in the former situation and ovaries in the latter. Moreover, the decision to treat the axilla or mediastinum without the SCV, and the inguinal nodes without the iliacs, might have been appropriate depending on the size and distribution of involved nodes at presentation. In a young child (younger than age 5 years), consideration would be given to treating bilateral areas (e.g., both sides of the neck) to avoid growth asymmetry. However, this is less of a concern with low radiation doses, and unilateral fields are usually appropriate if the disease is unilateral. Efforts to exclude unnecessary normal tissues are always important, such as breast tissue in a child with isolated mediastinal disease and no axillary involvement.

Treatment of involved supradiaphragmatic fields or a mantle field has required precision because of the distribution of lymph nodes and the critical adjacent normal tissues. These fields could be simulated with the arms up over the head or down with hands on the hips. The former pulls the axillary lymph nodes away from the lungs, allowing greater lung shielding. However, the axillary lymph nodes then

move into the vicinity of the humeral heads, which should be blocked in growing children. Thus, the position chosen involves weighing concerns regarding lymph nodes, lung, and humeral heads. Attempts are consistently made to exclude or position breast tissue under the lung and axillary blocking.

When the decision is made to include some or all of a critical organ in the RT field, such as liver, kidney, or heart, normal tissue constraints, depending on the chemotherapy used and patient age, are critical. Thus, the width of a mediastinal field is generally based on the postchemotherapy residual disease, whereas the cephalad-caudad dimension respects the original disease extent. Humeral head blocks are appropriate unless bulky axillary adenopathy is thereby shielded. Laryngeal and occipital blocks have also been used unless disease is located in the vicinity of these structures; these blocks can be placed at the beginning of treatment or after some portion of it. Depending on the response of the disease to chemotherapy and the dose administered, field reductions might be considered. The entire heart or lungs are rarely treated above doses of 10 Gy to 16 Gy, depending on the distribution of disease and chemotherapy used.

When the subdiaphragmatic region has been treated, a treatment-planning CT is essential to devise the shielding. When treating the pelvis, special attention must be given to the ovaries and testes. The ovaries may be relocated or transposed and marked with surgical clips, laterally along the iliac wings or centrally behind the uterus. In this manner appropriate shielding may be used. The testes might still receive 5% to 10% of the administered pelvic dose, which is sufficient to cause transient or permanent azoospermia, depending on the total pelvic dose. The greatest shielding can be afforded to the testes if the patient is placed in a frog-legged position with an individually constructed testes shield. If multileaf collimation is available, the multileaf can be placed over the testes, additionally decreasing the transmitted dose.

Even though IFRT has been a standard treatment volume in recent studies, there is a clear shift to what is alternatively termed either INRT or ISRT. The rationale for this volume reduction derives from reconsideration of the anatomic definitions of lymph node regions and the patterns of recurrence in HL. Clinical definitions of lymph node regions are historic and based on anatomic or bony landmarks without the benefit of CT scanning to identify the location of nodes. The EORTC-GELA has introduced the concept of INRT.[175,176] This uses all available clinical information including pre- and postchemotherapy imaging with CT and FDG/PET scans to define the treatment field according to the prechemotherapy extent of disease. The concept is based on evidence that recurrence occurs most often in initially involved lymph nodes[177,178] suggesting that chemotherapy is adequate to treat disease contained within radiologically normal lymph nodes, while RT is needed only to treat sites of macroscopic enlargement. In a study of patients with early-stage HL, PET identified presumptively involved lymph nodes that were radiographically occult on CT scan. Therefore, evaluation with FDG/PET scan before chemotherapy may help to delineate the complete extent of clinical disease.[175] Initial clinical data with the use of INRT is only just emerging. Campbell et al reviewed clinical outcomes of patients with limited stage HL treated with EFRT, IFRT, and INRT ≤ 5 cm. No marginal recurrences or locoregional failures occurred with INRT.[179]

Various European trials are actively incorporating and testing INRT along with reported guidelines.[180] In the EORTC/GELA H11 trial for early-stage, unfavorable-prognosis HL, INRT was adopted in both the standard and experimental arms. Meanwhile, the German Hodgkin's Study Group (GHSG) is enrolling patients in a randomized trial with unfavorable-prognosis, early-stage disease (HD17) comparing IFRT versus INRT.

Recently, a new set of field designs, the involved site (ISRT), have been developed, published, and endorsed by the steering committee of the International Lymphoma Radiation Oncology Group (ILROG).[181] This represents the first effort by an expert group of radiation oncologists, having experience with lymphoma management, recognizing a need to promulgate a "modernized" version of IFRT. These new field designs take into account modern technology, including the use of staging PET/CT scans, three-dimensional and four-dimensional treatment planning with CT scanners, conformal treatment techniques, and the use of image guidance. These fields are expected to be somewhat smaller than the traditional IFRT, but larger than INRT especially recognizing the difficulty of staging PET-CT scans not being performed in the patient position used during eventual treatment planning and RT delivery. Regardless, in the years to come it is expected that these ISRT concepts will be applied to pediatric protocols and become more standardized in practice. Finally, as previously noted, RT for unfavorable and advanced HL is variable and protocol dependent. Although IFRT has been a standard when patients are treated with combined-modality therapy, restricting RT to areas of initial bulk disease (generally defined as 5 cm to 6 cm or more at the time of disease presentation), slowly responding sites, or postchemotherapy residual disease (generally defined as 2 cm to 2.5 cm or more, or residual PET avidity) is under investigation.

Dose

In the setting of combined therapy, certainly the intensity of the chemotherapy is important to consider in the choice of the RT dose and volume. In general, doses of 15 Gy to 25 Gy are typical with shrinking fields and boosts individualized. In the tables summarizing recent clinical trials (see Tables 74-3 and 74-4), the RT doses selected to complement the chemotherapy regimen are provided. Doses of more than 25 Gy are uncommon in the pediatric setting. Of interest are the results of the GPOH HD-90 trial, in which doses of 20 Gy to 25 Gy were administered in combination with OPPA or OEPA, with or without COPP. The radiation doses administered were 20 Gy to 25 Gy, with a local boost of 5 Gy to 10 Gy for insufficient remission following chemotherapy. Tumor burden, indicated by bulky disease or number of involved nodes, proved not to be prognostically significant because of the relatively high doses used for bulk disease.[64] In the GPOH-95 trial, the safety of lowering the standard radiation dose to 20 Gy was demonstrated, although boosts to residual large masses were still allowed.[69] Most current treatment approaches for children include radiation doses at the lower end of the 20-Gy to 25-Gy range. Indeed within the COG, radiation dose has been standardized to 21 Gy in 14 fractions.

Treatment Approaches

Chemotherapy Alone Versus Combined with Radiation Therapy

Noncross-resistant combination chemotherapy alone is well established as an effective modality for the treatment of pediatric HL.[7,8,95,112,113,115,116,123,125,182] This treatment approach eliminates the risk of radiation-induced growth complications, thyroid and cardiopulmonary dysfunction, and solid tumor carcinogenesis. However, the higher-cumulative doses of anthracyclines, alkylating agents, and bleomycin chemotherapy increase the risk of cardiopulmonary, toxicity infertility, and leukemogenesis and may be less effective as combined-modality therapy for treatment of bulky nodal disease. Chemotherapy alone trials have been limited by their small

numbers of patients, nonrandom treatment assignments, lack of long-term follow-up related to disease control, and late-treatment sequelae. Despite these deficiencies, identification of clinical factors predicting an optimal outcome following treatment with chemotherapy alone remains an important objective of many ongoing trials because of the desire to avoid late RT sequelae. As already noted, the early response to chemotherapy of sufficient intensity appears to be the one factor allowing for the elimination of RT.[17,83]

Investigators from North American pediatric cooperative groups have undertaken three longitudinal controlled trials to evaluate chemotherapy alone versus combined-modality therapy in pediatric HL.[6,7,51,66] The first two trials failed to show a statistically significant advantage in EFS or OS with the addition of RT to noncross-resistant chemotherapy. The Children's Cancer Group compared 12 cycles of alternating MOPP/ABVD to 6 cycles of ABVD plus low-dose (21 Gy) radiation.[6] EFS and OS suggested a survival advantage for the combined-modality group (90% 4-year EFS) over the chemotherapy-alone group (84% 4-year EFS), but this difference was statistically insignificant. In a Pediatric Oncology Group trial, adding low-dose radiation to four cycles of alternating MOPP and ABVD chemotherapy did not improve DFS or OS.[7] However, statistical and quality-assurance issues produced problems with interpretation of these data. Moreover, the findings of both studies are irrelevant to present-day practice because the treatments evaluated included the more leukemogenic MOPP-based therapy and an excessive number of treatment cycles.

Using an antiquated hybrid regimen, the Children's Cancer Group compared chemotherapy alone with COPP/ABV to combined-modality therapy including low-dose IFRT.[51,66] Clinical risk features including the presence of B symptoms, hilar lymphadenopathy, mediastinal and peripheral lymph node bulk, and the number of involved nodal regions determined treatment assignment. Patients who achieved a complete response to chemotherapy were eligible to be randomized to receive low-dose, IFRT or no further therapy. The trial was prematurely terminated because patients treated with chemotherapy alone had a significantly higher number of relapses. As updated with a median follow-up of 7.7 years, those patients receiving IFRT had a statistically improved EFS of 92.5% at 10 years compared to 83.5% for chemotherapy alone ($p = 0.004$).[66] OS was the same the result of effective retrieval therapies that often included high-dose chemotherapy with an autologous stem cell transplant. Risk factors for relapse included nodular sclerosis subtype, B symptoms, and bulk disease. Ten-year EFS was 83.5% for patients with nodular sclerosing histology compared with 96% for patients with other histologies. Patients with B symptoms at diagnosis had a 10-year EFS of 71.7% compared with 87.5% for patients without B symptoms ($p < 0.001$). And finally, patients with bulk disease had a 10-year EFS of 75.6% compared with 87.2% for patients with no bulk ($p < 0.001$).

European experience in pediatric HL with end of treatment assessment using CT or MRI scan criteria also suggests that elimination of RT may be detrimental in certain patient subsets. In a nonrandomized trial that omitted radiation for patients achieving a CR with chemotherapy, German-Austrian investigators reported a similar advantage for patients treated with radiation consolidation following combination chemotherapy in the GPOH-HD 95 trial.[69] In this study patients treated with RT after partial response to combination chemotherapy defined as more than 75% volume reduction received 20 Gy using a "reduced involved-field" along with an additional 10-Gy or 15-Gy boost to larger residual masses. In the early stage (TG1) patients, there was no detriment to omitting RT for those patients not in CR; the progression-free survival (PFS) at 10 years was 97% for CR patients not receiving RT compared to 92% for those receiving RT ($p = 0.21$). PFS was unsatisfactory for nonirradiated intermediate risk patients (TG2) at 68.5% compared to those who received RT who had a PFS of 91.4% ($p < 0.0001$). The TG3 advanced risk group patients had a nonsignificant trend favoring the receipt of RT with a 10 year PFS of 88.7% versus 82.6% without RT.

Contemporary practice now allows for interim assessment of response to chemotherapy incorporating both PET and anatomical criteria. RT may be reduced or eliminated after sufficiently intensive chemotherapy producing a rapid early response, even with initially bulky masses. The landmark COG AHOD0031 trial of intermediate-risk patients has already been mentioned. Final published results are eagerly awaited. Thus, the standard of care is shifting and no longer is involved field RT given across all stages of pediatric HL.

The results of chemotherapy-alone regimens in carefully selected patients document excellent efficacy of this treatment approach particularly in children with early-stage favorable HL and those with a rapid-early response to chemotherapy with intermediate-risk disease. Circumstances where RT may have particular toxicity, such as in young children, may warrant chemotherapy alone. The incremental value of adjuvant RT is small, but its importance lies in the avoidance of relapse therapy that often includes high-dose chemotherapy with an autologous stem-cell transplant. At the same time, there is an appreciation that safe radiation volume reductions using ISRT[181] are appropriate to reduce side effects and normal tissue exposures. As noted previously, European studies of adult HL are evaluating INRT as a shift away from targeting anatomic compartments.[175-178] PET imaging is proving particularly useful not only for response assessment but also RT planning.[183] By the same token conformal techniques such as IMRT or proton radiotherapy are also under investigation in HL.[175,184-190] Figures 74-1 and 74-2 are examples of the use of IMRT to ensure coverage of involved regions. In the first case, the mediastinal disease has extensive anterior chest wall extension, whereas the second case depicts splenic IMRT with AP-PA mantle fields. In these examples, radiation exposure to normal tissues (lung, heart, and kidney) was minimized to reduce toxicity, not readily accomplished by standard AP-PA beam arrangements.

Risk-Adapted Therapy: Favorable Risk Disease

Favorable risk has variable definitions across various studies as already noted, but generally includes patients with stages I and II disease without adverse prognostic features. These unfavorable features may be B symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, and three or more nodal regions involved. Treatment typically involves two to four cycles of chemotherapy and low-dose, IFRT. But in some instances, RT has been reduced or eliminated based on a favorable response to chemotherapy.[51]

The GPOH HD-95 trial used OEPA in boys and OPPA in girls, with RT successfully omitted in patients achieving a CR to chemotherapy, as already noted. The criteria for CR did not entail metabolic imaging, but rather volume reduction of ≥95% with ≤2 mL of the initial volume remaining. An unconfirmed CR that triggered low-dose RT occurred if volume reduction was ≥75% or <b2 mL, occurring in less than 30% of the favorable cohort. One caveat to note is that patients with nLPHL were included in this trial.[69,70] These results were confirmed in the GPOH-HD 2002 study that excluded nLPHL patients.[94] In the GPOH-HD2002 study, all patients received

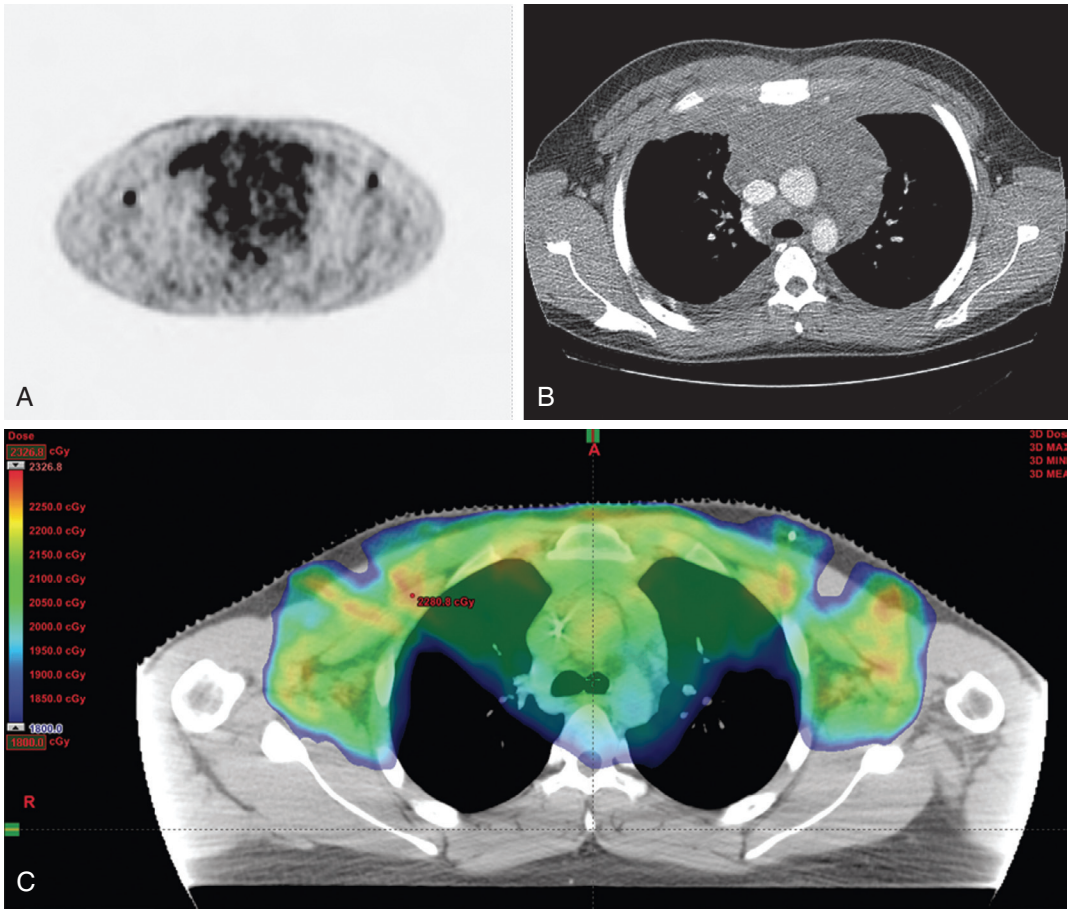

Figure 74-1 Use of intensity-modulated radiation therapy (IMRT) is not standard in Hodgkin's lymphoma but may be preferred in special circumstances. In this case, IMRT was used to treat extensive anterior chest wall involvement at diagnosis. This 18-year-old male with stage IVB nodular sclerosing Hodgkin's lymphoma presented with fevers, sweats, chest pain, purities, and right supraclavicular adenopathy. Staging showed neck, bilateral axillary, and bulky mediastinal adenopathy. Panel A and B shows extensive anterior chest wall involvement on positron emission tomography (PET) and computed tomography (CT) imaging, respectively. After a complete response to ABVE-PC chemotherapy for four cycles, the patient underwent involved field radiotherapy to 21 Gy in 14 fractions. Standard anteroposterior and posteroanterior (AP-PA) fields would have included too much lung. Instead, an IMRT plan yielded a better dose distribution with lower risk for pulmonary toxicity while insuring good coverage of initial sites of involvement. Panel C shows the IMRT dose distribution in a color wash superimposed on an axial CT scan postchemotherapy at the level of the carina. Two years following therapy, patient remains free of lymphoma and is a competitive swimmer in college.

IFRT to 19.8 Gy except patients in the early stage (IA/B and IIA without extranodal involvement) disease category who achieved a CR after induction therapy as defined in GPOH-HD 95. In contrast to North American practice, regions defined as a partial response by anatomic criteria (<75% volume reduction) received a boost to 30 Gy while residual masses greater than 100 mL were boosted even higher to 35 Gy.

Several North American investigators have observed excellent treatment results in combined modality trials for favorable risk HL. Investigators from St. Jude's, Stanford, and Harvard reported treatment results using a nonalkylator regimen, VAMP for children with clinical I/II, non-bulky HL.[108] Patients received four cycles of VAMP chemotherapy and response-based IFRT after two cycles of chemotherapy in which the radiation dose varied from 15 Gy to 25 Gy. At a median follow-up of 9.6 years, 5-year and 10-year EFS rates were 92.7% and 89.4%, respectively.[108] In a follow-up trial, the same investigators limited VAMP chemotherapy alone to a favorable group with less than three nodal sites of disease and no extranodal sites with a CR after one cycle of chemotherapy.[83] The 2-year EFS for patients who did not require RT was 89.4% compared with 92.5% for those who were not deemed in CR and received low-dose IFRT ($p = 0.61$). These results need to be contrasted with more mature adult experience with another minimal therapy approach that includes ABVD for two cycles and 20-Gy IFRT for similar favorable risk patients in which the PFS was 95.1% at 5 years and 86.5% at 8 years.[84]

In contrast to adult trials, there has been remarkably little study of ABVD in pediatric HL. The Pediatric Oncology Group (POG)[111] evaluated the feasibility of combined-modality therapy using four courses of DBVE followed by IFRT to 25.5 Gy to treat stages IA, IIA, and IIIA HL. At a median follow-up of 8.4 years, remarkably good 6-year OS and EFS rates were 98% and 91%, respectively, with almost (98%) all patients achieving remission after completion of therapy. This regimen (DBVE) was used by the POG/COG to support reduction of chemotherapy via an early-response–based treatment algorithm. Patients received only two courses of ABVE if they achieved an early CR, which occurred in 45% patients, whereas

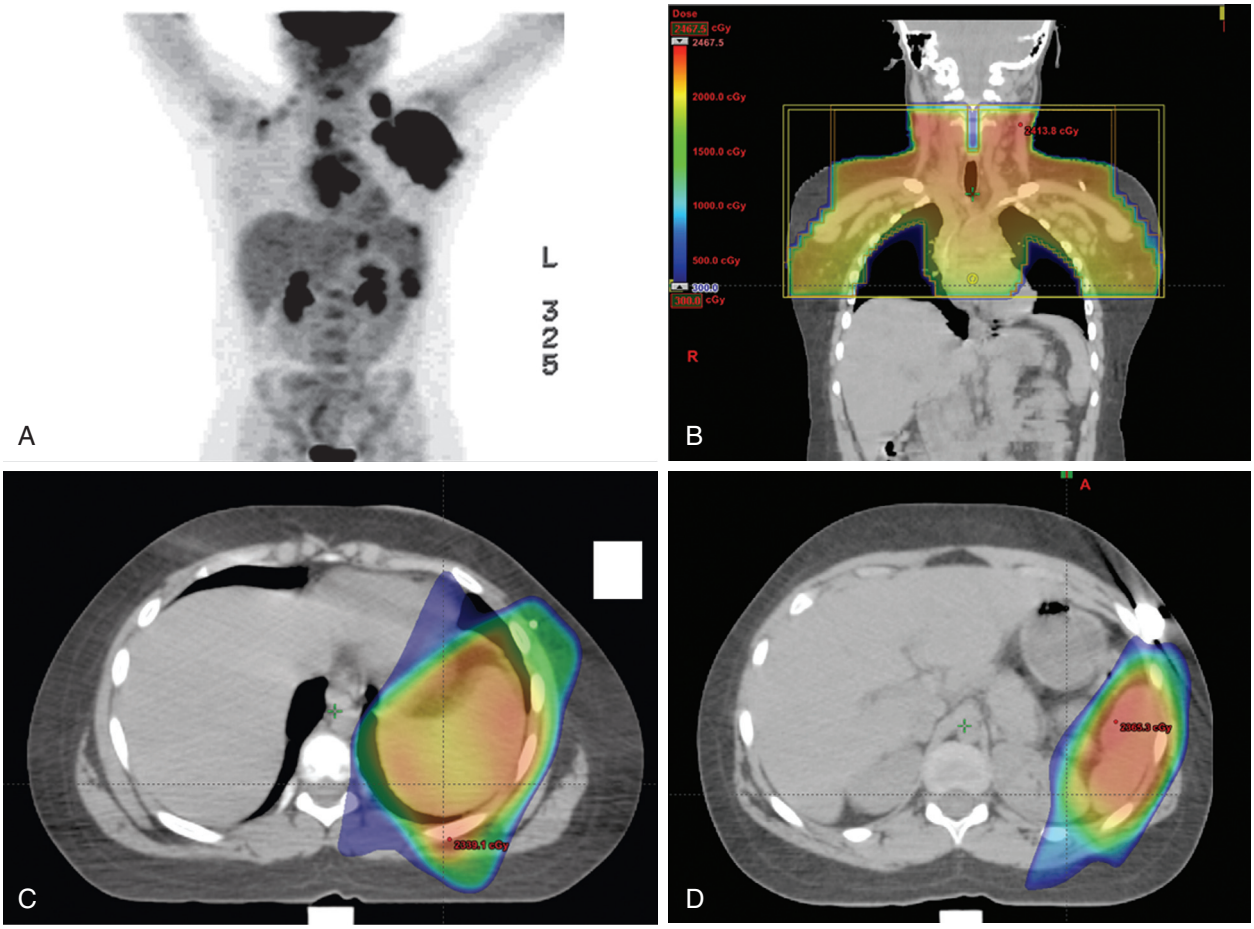

Figure 74-2 Use of non-standard IMRT to treat spleen along with anteroposterior and posteroanterior (AP-PA) mantle field. A 12-year old presented with stage IIIAS lymphocyte predominant Hodgkin's lymphoma with bulky right axillary adenopathy. On staging evaluation, PET scanning shown in Panel A showed bilateral neck and axillary adenopathy, bulky mediastinal disease, as well as multiple splenic nodules. After a complete response to ABVE-PC chemotherapy for four cycles, involved field radiotherapy to 21 Gy in 14 fractions was initiated. The supradiaphragmatic disease was well covered by standard APPA fields as shown in Panel B. APPA or oblique fields to the spleen would have treated too large a volume of the heart or kidney. Instead, a four-field IMRT field along with shallow breathing and appropriate margin for respiratory motion was devised. Panel C and D show superior and inferior aspects of the spleen treatment with the dose distribution shown with a color wash superimposed on the treatment planning CT scan. IMRT technique successfully minimized dose to the heart and left kidney.

four courses of ABVE were given to slow responders. All patients received 25.5 Gy IFRT, resulting in 5-year OS and EFS of 98% and 88%, respectively. With the desire to minimize the use of any RT, the COG AHOD0431 single-arm study already mentioned, stages IA and IIA patients who achieved a CR after three cycles of AVPC received no further therapy. Those with a partial response (PR) received 21-Gy IFRT. The 2-year EFS rate was 80% for those who did not receive RT versus 88% for patients achieving PR (and receiving IFRT) (p = 0.11). The 2-year OS rate was 100%. Of the evaluable patients with FDG-PET results after one cycle of chemotherapy (PET1), the 2-year EFS rates for CR patients who had a positive/equivocal PET1 versus a negative PET 1 were 65% versus 87%, respectively (p = 0.005). The 2-year EFS rates for PR patients who had a positive/equivocal PET1 versus a negative PET1 were 82% versus 96%, respectively (p = 0.047).[126,191] These preliminary results suggest that CT response alone is not adequate to identify patients who can be treated without RT after minimal therapy such as AVPC chemotherapy for three cycles.

Risk-Adapted Therapy: Intermediate-Risk Disease

In risk-adapted treatment regimens, localized disease presenting with unfavorable features are often grouped into an intermediate-risk category and includes those with localized (stages IA, IIA) disease with unfavorable features and those with stage IIIA disease. The GPOH-HD84 study was the first study to match this group of patients with chemotherapy whose intensity was midway between that of favorable and unfavorable/advanced patient cohorts. Building on this concept, the GPOH-HD 2002 study reported a 5-year EFS rate of 88% with two cycles of OEPA for boys and OPPA for girls. This was followed by two cycles of COPP for girls and cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC) for boys to spare fertility by reducing alkylator exposure. Deletion of RT appears to have been detrimental with reduced EFS for this group as already discussed.

The COG has developed an approach of using dose-dense chemotherapy to support response-adapted therapy.

An intensive regimen of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC) chemotherapy was used for patients with both intermediate- and high-risk disease in the POG9425 study. Patients with a RER to three cycles of ABVE-PC received 21 Gy of regional field RT (mantle, para-aortic, or pelvis). Slow early responders (SER) received an additional two cycles of ABVE-PC and then received IFRT to 21 Gy. The 5-year EFS rates were 86% for RER patients and 83% for SER patients ($p = 0.85$) and the 5-year OS rate was 95%.[68]

In the recently completed COG AHOD 0031 study, patients received two cycles of ABVE-PC followed by response assessment. Patients with RER received two additional cycles of ABVE-PC followed by a second response assessment. Those with a CR as defined by an 80% reduction in cross-sectional area of disease and resolution of metabolic uptake on gallium or FDG-PET were randomized to 21-Gy IFRT or no further therapy. Patients who did not have a CR constituted a third of the RER cohort and all received IFRT—a subtlety in the results of this trial that may be underrecognized. All SER patients were randomized to either two additional cycles of ABVE-PC or dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional two cycles of ABVE-PC. All SER patients received 21-Gy IFRT after chemotherapy. Three-year EFS rates were 87.1% for RER patients versus 77.8% for SER patients ($p = 0.0001$). The 3-year OS rate for RER patients was 98.7% versus 96.9% for SER patients ($p = 0.02$). The 3-year EFS rate was 87.9% for RER/CR patients randomized to receive IFRT versus 85.4% for those randomized to no IFRT ($p = 0.07$). These results suggest that early response to chemotherapy defined by early reduction (60%) in tumor size—based on CT after two cycles can be a powerful predictor of outcome and help optimize subsequent treatment Moreover, the inclusion of a PET analysis after two cycles of ABVE-PC chemotherapy might more definitively help define a cohort of patients who do not benefit from IFRT, even in the presence of initial bulky disease.[192]

Risk-Adapted Therapy: Unfavorable Risk Disease

The criteria for the unfavorable prognostic group is also quite variable from one clinical trial to another, but typically include the presence of B symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of three or more nodal regions, extranodal extension to contiguous structures, or advanced stage (IIIB-IV). RT for unfavorable and advanced HL is also variable and protocol dependent. Suffice it to say, IFRT remains the standard in patients with advanced pediatric HL in good part because of the CCG 5942 results,[66] but restriction of RT volumes to regions of initial bulky disease or post-chemotherapy residual disease is under investigation.[51,94]

For patients with unfavorable or advanced disease, two primary treatment approaches have been used. First, a conventional treatment approach involves outpatient chemotherapy on a twice-monthly schedule for 6 months to 8 months. In adults the use of ABVD therapy for early unfavorable or high-stage HL has reported PFS in the range of 65% to 75% (which is low by pediatric standards).[193-195] In a limited Children's Cancer Study Group pilot trial, CCSG 521-P, ABVD for six cycles produced an 87% EFS and the same OS rate at 3 years. The principal problem, however, was a high serious pulmonary toxicity rate of 9%, predominantly occurring before RT was given.

An alternative strategy used dose-dense chemotherapy to reduce the theoretic risk of developing resistant disease but may also increase the risk for acute and late side effects. The C59704 trial, employing BEACOPP followed by gender-based consolidation, has some of the best disease control results for this high-risk group. A high 5-year EFS rate of 94% was achieved while the 5-year OS rate was 97%.[196] The GPOH, building up on their original experience with the OPPA/COPP regimen, showed that six cycles OEPA/COPDAC together with 20-Gy to 30-Gy IFRT also produced reasonably good results with a 5-year EFS rate of approximately 87%.[94]

Results of the COG AHOD0831 trial will be of interest, but none have yet been reported. This trial treated patients with stages IIIB and IVB disease with ABVE-PC for five cycles with higher doses of cyclophosphamide than the intermediate risk 0031 trial along with response assessment after cycles 1 and 2 with PET-CT imaging. Patients with SER received augmented chemotherapy of ifosfamide and vinorelbine for an additional two cycles. Radiation prescription rules were novel in which the goal was an incremental reduction in the volume of RT over past trials while the dose used was 21 Gy in 14 fractions. Regions of disease targeted were confined to initial sites of bulky disease that included any gross splenic involvement, slow responding sites, and residual masses at least 2.5 cm in diameter. Whole lung RT was discouraged.

Nodular Lymphocyte Predominant Hodgkin Lymphoma

In contrast to classical HL, nLPHL is considered a different disease that is more akin to a low-grade B-cell non-HL, having an indolent pattern of spread and growth with relapses that may occur after many years of follow-up.[197] Patients with nLPHL are characterized by early-stage disease, limited peripheral lymph node (cervical, axillary, or inguinal) presentations with rare involvement of the mediastinum, a male predominance, and an overall good prognosis.[198] Late complications of treatment such as secondary malignancies or cardiopulmonary toxicity,[199] or transformation to aggressive B-cell lymphoma[200] account for the majority of adverse fatal events. Historically, patients with nLPHL were treated like classical HL but more recent experience suggests that minimal therapy is often sufficient in both adults and children. In adults, IFRT alone is now favored with reports of good outcomes using 30 Gy to 36 Gy.[201,202] Because of concerns of growth abnormalities and secondary cancers from these radiation doses, this approach is not appropriate in most children. Because this is still an uncommon disease in children, much data derive from small retrospective series with a variety of treatment approaches that generally have acceptable short-term outcomes.[199,203,204] However, unique for lymphoma management is the excellent outcomes for excisional surgery alone with nLPHL.[205,206] Roughly half of such patients undergoing surgery only had good long-term disease control in one European trial of 58 children.[206] Relapses tend to be localized and limited, quite amenable to additional therapy with curative potential.

At the same time, early-stage nLPHD responds well to chemotherapy alone or combined modality therapy. One example of the former approach is a report entailing 55 pediatric patients with low-stage nLPHL treated with cyclophosphamide/vinblastine/prednisone (CVP), with 11 cases treated after initial surgical relapse. The 40-month freedom from treatment failure and OS for the entire cohort were 75.4% and 100%, respectively. On the other hand, excellent results with combined-modality therapy were reported with the VAMP combination plus LDRT in a series of 33 patients having a 100% 10-year survival and EFS.[108] The COG has validated this watchful waiting approach after surgery with its AHOD03P1 study. A total of 52 patients with stage IA disease underwent surgery only if disease was confined to a single lymph node. Twelve relapses have been localized and all were successfully salvaged with three cycles of AV-PC (Adriamycin, vincristine, prednisone, and cyclophosphamide) and no radiotherapy. The current 2-year EFS estimate among

these patients treated without chemotherapy is 81.6%.[207] A separate cohort of 127 patients with stage II or stage I with multiple nodes were treated upfront with AV-PC for three cycles. The vast majority of patients had a CR and were observed, whereas 12 patients with residual disease received low-dose IFRT. Nine additional patients with local relapse after surgery were also included in this scheme in which the 4-year EFS is estimated at 86.8%.[207]

TREATMENT OF RELAPSED AND REFRACTORY DISEASE

The generally excellent outcome in pediatric HL has limited opportunities to evaluate salvage therapy programs. Most relapses in patients with HL occur within the first 3 years, but some patients may relapse as long as 10 years after initial diagnosis.[208] Treatment and prognosis after relapse depends on the primary therapy, initial stage, and duration of remission (time of relapse). Harker-Murray et al have reviewed the literature on retrieval therapy for HL and have suggested a favorable to intermediate risk cohort of patients with early-stage disease without initial B symptoms and at least a 1 year remission duration to define a group for whom conventional chemotherapy with selective use of RT may be reasonable.[209] Indeed, such an approach may salvage 40% to 50% of children relapsing after a sustained remission (1 year or longer); however, adverse effects of treatment, including second malignancies, may reduce ultimate survival.[210-212] Patients who demonstrate refractory disease, or recurrence within 1 year after completing therapy, respond poorly to conventional salvage therapy, as do patients with multiple relapses. These high-risk patients have a better chance of achieving a durable remission if they are consolidated with myeloablative therapy followed by hematopoietic cell transplantation (HCT).

For higher risk relapses, a combination of ifosfamide/vinorelbine for pediatric patients in first relapse was studied by the COG (AHOD00P1 trial). This regimen showed a good overall complete or partial response rate of 78% and achieved good stem-cell mobilization for future autologous stem-cell transplant.[213] For patients who relapse after transplant or are upfront refractory to chemotherapy, a combination of a gemcitabine/vinorelbine has also studied by the COG, documenting a response rate of 76%.[214]

OS rates in children and adolescents with relapsed HL treated with high-dose chemotherapy and hematopoietic transplant range from 30% to 60%. Because of the higher transplant-related mortality associated with allogeneic transplantation, autologous HCT is preferred for patients with relapsed HL. However, recent investigations of reduced-intensity allogeneic transplantation have demonstrated acceptable rates of transplant-related mortality.[215-217] Nonmyeloablative conditioning regimens most often use fludarabine or low-dose total-body irradiation to provide a nontoxic immunosuppression and establish a graft-versus-lymphoma effect.

IFRT to sites of recurrent disease should be considered in the setting of HCT. In a Stanford report, patients with stages I to III disease at relapse who received autologous bone marrow transplantation and IFRT had a 3-year freedom from relapse of 100% and OS of 85%, compared with 67% and 60%, respectively, for patients not receiving IFRT.[218] For patients not previously irradiated, IFRT was associated with an improved freedom from relapse of 85% and OS of 93%, in contrast to 57% and 55%, respectively, for those previously irradiated. Morbidity was similar to those not irradiated, although RT may have contributed to the peritransplant death of two patients. Other reports on the use of consolidative RT suggest a benefit and low to moderate morbidity, although these are mostly adult data which suffer from inherent selection and publication biases.[219-224] Central issues relating to the use of IFRT are the dose, target volume, and timing with respect to the transplant. RT doses are generally 15 Gy to 25 Gy, in 1.5-Gy to 2.0-Gy fractions. This variation relates to potential normal tissue toxicity as well as the consideration for higher radiation doses in patients with an identifiable tumor that demonstrates radiation responsiveness. RT volume can vary and include treatment to all sites of initial disease, recurrent disease, persistent disease following salvage chemotherapy, persistent disease following the preparative regimen for transplant, or all nodal sites. Unless protocol-specific therapy is directed, individual considerations for such decision making are necessary at this time. IFRT can be administered before the high-dose chemotherapy program to place patients in a minimal disease state. Alternatively, RT can also be administered after the high-dose chemotherapy program to decrease the overall potential for disease progression and avoid RT-related peritransplant morbidity such as esophagitis, pneumonitis, cardiomyopathy, and veno-occlusive disease. Possible disadvantages of this approach include the loss of the pretransplant cytoreductive effect and the theoretical carcinogenic effect of RT on the newly proliferating hematopoietic system.

New agents for HL are being evaluated in the relapse setting. In particular there is great excitement with the anti-CD30-drug conjugate, Brentuximab Vedotin, that has shown excellent activity in early clinical trials.[225] This type of targeted therapy hold promise for greater efficacy with less toxicity as it is carefully combined with other agents. Clinical trials incorporating this agent in upfront therapy for both adults and children with HL are under way or being planned.

Treatment Algorithms

Table 74-6 summarizes recommendations for risk-adapted treatment approaches. Because patients with localized favorable disease presentations can achieve long-term disease-free survival using regimens that minimize alkylators, doxorubicin-based chemotherapy such as ABVD or ABVE is preferred for this group.[96,98,105,110] However, alkylating agents or etoposide can be added to the regimen without compromising disease outcome if the clinician prefers to restrict anthracycline chemotherapy exposure to preserve cardiac function.[50,51,101] Combined-modality treatment approaches including low-dose IFRT have historically produced excellent results in children with favorable localized disease and reduce cumulative chemotherapy doses. However, there is an increasing trend to try to use response-based programs to reduce or eliminate the use of radiotherapy in patients with a rapid early response with a goal of lessening the burden of late effects of therapy.

Combinations such as ABVE-PC or older ABVD/MOPP-type hybrid regimens with the addition of etoposide still provide the most effective chemotherapy strategies for children and adolescents with intermediate- or high-risk disease presentations.[50,51] In older regimens reporting good long-term outcomes, low-dose RT is administered following chemotherapy to areas of bulk disease, or nodes (usually the regions harboring the involved nodes) present at diagnosis. However, the use of dose-intensive regimens such as ABVE-PC allows rapid responders to significantly decrease their exposure to RT. This is rapidly evolving into a new standard for pediatric HL. At the same time this type of abbreviated, dose-dense regimen that induce rapid tumor response may permit reduction of cumulative chemotherapy doses below threshold levels associated with significant long-term toxicity.[68]

TABLE 74-6 Recommendations for Treatment Approach in Pediatric Hodgkin Lymphoma

Clinical Presentation	Stage	Recommended Treatment Approach
EARLY (low risk)		**RECOMMENDED THERAPY**
<3-4 nodal regions; no B symptoms, bulk, or extranodal extension from contiguous nodal disease	IA, IIA	2-4 cycles noncross-resistant chemotherapy without alkylators plus low-dose IFRT (15 Gy-21 Gy); in highly favorable patients with no extranodal disease and less then 3 sites, abbreviated chemotherapy with a CR on interim assessment or at completion of therapy may allow for deletion of RT **IN CLINICAL TRIAL SETTING ONLY** 2-4 cycles of chemotherapy alone if there is negative PET2; or such chemotherapy followed by ISRT or RT limited to initial bulky sites or residual disease sites (15 Gy-21 Gy)
INTERMEDIATE		**RECOMMENDED THERAPY**
≥3-4 nodal regions; bulky lymphadenopathy (mediastinal ratio ≥33%; peripheral lymph node mass ≥6-10 cm)	IA, IIA, IIB* IIIA, some IIIB	4-6 cycles (3-5 compacted, dose-intensive cycles) noncross-resistant chemotherapy. Low-dose RT (15 Gy -21 Gy) is reserved for patients with slow response, incomplete response, or residual disease or masses. **IN CLINICAL TRIAL SETTING ONLY** 4-6 cycles (3-5 compacted, dose-intensive cycles) noncross-resistant chemotherapy alone if there is negative PET2; or such chemotherapy followed by ISRT or RT limited to initial bulky sites or residual sites of disease (15 Gy-21 Gy)
ADVANCED (HIGH risk)		**RECOMMENDED THERAPY**
Stage II patients with fever or weight loss and/or bulk*; any patient with advanced stage (not all stage III would be high risk)	IIB* IIIB IV	6 cycles (4-6 compacted, dose-intensive cycles) of noncross-resistant chemotherapy plus low-dose IFRT (15 Gy-21 Gy) **IN CLINICAL TRIAL SETTING ONLY** 6 cycles (4-6 compacted, dose-intensive cycles) of noncross-resistant chemotherapy plus low-dose IFRT (15 Gy-25 Gy) restricted to (1) sites of initial bulky disease, (2) PET2 positive disease, or (3) residual masses

IFRT, *Involved-field radiotherapy;* INRT, *involved-nodal radiotherapy;* PET2, *PET scan after second cycle of chemotherapy used as indicator of rapid early response.*
**Patients with stage IIB disease have been variably treated as intermediate or unfavorable risk. Some studies use associated factors, e.g., weight loss, bulk disease, extranodal extension, for further risk stratification.*

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A full list of cited references is published online at www.expertconsult.com.

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