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PEDIATRIC HODGKIN LYMPHOMA

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Summary of Literature Review

Introduction

Historically children and adults were treated with the same chemotherapy regimens, radiation therapy fields, and doses. However, irradiation techniques suitable for adults produced significant morbidities in children, such as impaired musculoskeletal development, an increased risk for subsequent benign and malignant neoplasms, and cardiopulmonary toxicities that became unacceptable. A desire to reduce these morbidities has motivated the development of new treatment strategies for pediatric Hodgkin lymphoma (HL) [1,2].

Epidemiology

Childhood HL comprises 6% of childhood cancers and is epidemiologically distinct from adult HL. A striking male/female predominance is found among young children (ratio of 4:1 for 3- to 7-year-olds, and 3:1 for 7- to 9-year-olds) whereas, the ratio for older children is closer to that of adults (1.3:1) [3]. The disease is uncommon before age 5, and among children is most common in adolescence.

Evidence for a genetic predisposition exists and is relevant when counseling families. Siblings have a 2- to 5-fold increased incidence, and this rises 9-fold in same-sex siblings. Parent-child associations are reported [4]. Mack et al [5] reported a 99-fold increased risk in monozygotic twins of patients, but no increased risk in dizygotic twins. The role of Epstein-Barr virus (EBV) in the pathogenesis of HL is well established. In one report, EBV early RNA1 was expressed in R-S cells in 58% of childhood cases [6]. Of particular interest is that expression was age dependent — 75% of children under age 10 compared with 20% of older children. In addition, a history of infectious mononucleosis increases the risk for HL, and anti-EBV titers are elevated prior to diagnosis of HL.

Clinical Presentation

HL typically presents with a dominant nodal mass, with 90% of patients demonstrating contiguous lymphatic spread [7]. Most children are diagnosed on the basis of supradiaphragmatic lymph nodes, with painless cervical adenopathy in 80% of cases. Mediastinal involvement occurs in 76% of adolescents, but in only 33% of 1- to 10-year-olds. About one-third of patients will have systemic "B" symptoms of fever (temperature >38ºC), drenching night sweats, and/or unexplained loss of more than 10% of body weight within 6 months preceding diagnosis [7].

Pathologic Classification

The clinico-pathologic characteristics for children and adults are identical:

- *Nodular lymphocyte-predominant HL* (nLPHL): The characteristic lymphocyte and histiocytic cells are CD20+ (B-lymphocyte marker). nLPHL is reminiscent of indolent non-Hodgkin lymphomas, with a lengthy time to diagnosis and time to relapse. It is relatively more common in young children, where it commonly involves a single peripheral lymph node region and spares the mediastinum [8].

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- *Lymphocyte-rich (classic) HL*: Hodgkin Reed-Sternberg (R-S) cells (CD15+) are identifiable in a background predominantly of lymphocytes. Clinical behavior is similar to that of mixed-cellularity HL.
- *Mixed-cellularity (classic) HL (MCHL)*: R-S cells (CD15+) are frequent in a background of abundant normal reactive cells (lymphocytes, plasma cells, eosinophils, histiocytes).
- *Nodular sclerosis (classic) HL (NSHL):* Collagenous bands divide the lymph node into nodules which often contain an R-S cell variant called the lacunar cell. NSHL frequently occurs in children, involving supradiaphragmatic nodes and spreading along contiguous nodal chains.
- *Lymphocyte-depleted (classic) HL (LDHL)*: This subtype is rare and commonly confused with non-Hodgkin lymphoma, particularly of the anaplastic large-cell type. LDHL is often advanced at diagnosis and has a poor prognosis.

The distribution of the subtypes in younger children differs from that in adolescents and adults [3]. Although NSHL is the most common subtype in all age groups, it is more frequent in adolescents (77%) and adults (72%) than in younger children (44%). Conversely, MCHL is more common in younger children (33%) than in adolescents (11%) or adults (17%).

Staging

The 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, although not all suggestions are consistently used [9].

Diagnostic Evaluation

After pathologic confirmation, patients should undergo a clinical staging, beginning with a detailed history of systemic symptoms and physical examination. Laboratory studies include complete blood count and biochemical evaluation with liver function tests (including albumin). Acute-phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein, may be elevated at diagnosis. Patients with "B" symptoms or stage III and IV lymphoma should have a bone marrow biopsy.

Imaging studies of the neck and thorax should be performed to assess the extent of cervical and mediastinal disease. Bulky mediastinal lymphadenopathy is defined by the ratio of the mediastinal mass to the maximal measurement of the chest cavity on an upright chest radiograph; mediastinal ratios of 33% or higher are considered bulky. Computerized tomography (CT) scans are necessary to define disease involvement in the neck and chest [10]. Distinguishing normal (or hyperplastic) thymus from nodes in young children can be challenging.

An abdominal and pelvic CT should be used for infradiaphragmatic evaluation. If CT is used, oral and intravenous contrast is required to accurately define retroperitoneal and pelvic lymph nodes. HL involving the liver or spleen is suggested by CT findings of definite areas of abnormal density representing lymphomatous deposits. If the etiology of abnormalities seen in the liver on CT is not clear, then magnetic resonance imaging (MRI) and/or positron emission tomography (PET) can be useful to aid diagnosis.

PET is increasingly recognized as the most useful functional staging modality for lymphoma [11]. Uptake of the radioactive glucose analogue, fluorodeoxyglucose (FDG), correlates with metabolic activity in tumors undergoing anaerobic glycolysis. Areas of abnormal avidity have assisted in disease delineation and been correlated with outcome when assessed after initial cycles of chemotherapy and at completion of therapy. However, there are limitations in the pediatric setting (ie, false positives for a variety of reasons as well as false negatives in the presence of necrosis).

Prognostic Factors

As the treatment of HL has improved, factors that are associated with outcome have become more difficult to identify. However, several prognostic factors continue to influence the success and choice of therapy: Also, most data are based on reports that primarily include adults.

- The *stage of disease* 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 [12].
- The *bulk of disease* combines the number of disease sites and the volume of involvement at each site. Patients with *several sites* of involvement, generally defined as four or more, fare less well [13].

- *Systemic ("B") symptoms* result from cytokine secretion, reflect biologic aggressiveness, and confer a worse prognosis.
- *Laboratory studies,* including the ESR, hemoglobin level, and serum albumin, have been reported to predict worse outcomes [14]. This could reflect disease biology or bulk.
- *Histologic subtype* is relevant. Patients with nLPHL are biologically different as demonstrated by improved disease-free survival (DFS) and overall survival (OS); separate protocols with minimal therapy are underway for early-stage patients. Patients with LDHL fare poorly. Mixed reports suggest better or poorer outcome of other histologies that may be related to other prognostic factors as well.
- *Age* is a significant prognostic factor, with survival rates for children with HL approaching 85%-95%. In a report from Stanford, the 5- and 10-year survival rates for children with HL ≤10 years of age are 94% and 92%, respectively, compared with 93% and 86% for adolescents (11 to 16 years of age) and 84% and 73% for adults [3].
- *Rapidity of response to initial therapy* is an important prognostic variable. Early response to therapy was initially observed in advanced-stage HL patients treated on Pediatric Oncology Group (POG) 8725, where 93% of patients who attained a complete response (CR) after 3 cycles of chemotherapy remained disease free [15]. This finding was also confirmed for lower-stage patients [16] and afterwards 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 2 cycles of OEPA (vincristine, etoposide, prednisone, and doxorubicin) not requiring further radiotherapy (RT) [17]. Response-based therapy is currently the paradigm on which modern pediatric trials are based.

Selection of Therapy

The desire to cure young children with minimal side effects has led to careful risk stratification, in an attempt to optimize reduced intensity and types of chemotherapy, as well as RT doses and volumes. Because of differences in the age-related developmental status of children, and the gender-related sensitivity to gonadal chemotherapy toxicity, no single treatment is ideal for all children. The use of RT and chemotherapy can broaden the spectrum of potential toxicities but reduce the severity of individual toxicities. Most current approaches entail chemotherapy in conjunction with reduced RT doses. The volume of RT and the intensity and duration of chemotherapy are risk- and response-adapted and determined by prognostic factors at presentation.

Chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisolone (MOPP) fell out of favor due to major toxicities, including risks of secondary acute myeloid leukemia, azoospermia in more than 90% of males treated at any age, and sterility in females, which increases with age [18]. Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) became front-line chemotherapy [19] in adults, as secondary leukemia and sterility are less common. The predominant adverse effects of ABVD are pulmonary toxicity related to bleomycin and cardiovascular toxicity secondary to doxorubicin. These side effects may be exacerbated by the addition of mediastinal or mantle irradiation [20]. Current pediatric regimens have evolved to further limit the risks of sterility, leukemia, and cardiopulmonary toxicity.

Risk-Adapted Therapy – Favorable-Risk Disease

Favorable-risk disease is defined differently by different clinical trial groups, and even among the same groups sometimes the concept evolves over time, so that protocols are not easily comparable. For the most part, favorable-risk disease encompasses patients with localized stage I and II disease without adverse prognostic features; however this definition will vary from group to group. Some of the unfavorable features considered are "B" symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, and 3 or more nodal regions. Treatment typically involves 2 to 4 cycles of chemotherapy and low-dose, involved-field radiation therapy (IFRT). In some regimens, the RT dose has been reduced based on a favorable response to chemotherapy [21]. (See Appendix 1.)

The German Paediatric Oncology and Haematology Society (GPOH) pioneered the use of risk- and gender-adapted therapy featuring the OEPA (vincristine, etoposide, prednisone, and doxorubicin) regimen for boys in order to limit the amount of alkylators, while girls received OPPA (vincristine, procarbazine, prednisone, and doxorubicin). The GPOH HD-95 trial investigated whether RT could be omitted in patients achieving a CR to chemotherapy. Early results (median follow-up time of 3 years) indicate a 97% event-free survival (EFS) rate for favorable-risk patients. There was no difference in outcome between favorable-risk patients treated with

chemotherapy alone and those treated with combined-modality therapy. Importantly, the criteria for CR were strict (CR defined as a volume reduction of ≥95% and ≤2 mL of the initial volume or unconfirmed CR if volume reduction was ≥75% or <2 mL) so that less than 30% of the favorable-risk patients fell into this category; the cohort consisted of classical HL and nLPHL [22]. These results were confirmed in the GPOH-HD 2002 study that excluded LPHL patients [17]. In this study, all patients received IFRT to 19.8 Gy except those 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 regions with <75% volume reduction, a boost to approximately 30 Gy was administered, and residual masses >100 mL were boosted to approximately 35 Gy. As in the previous study, less than one-third of all early-stage patients achieved a CR by these strict criteria.

Several North American investigators have observed excellent treatment results in combined-modality trials for favorable-risk HL. Pediatric Hodgkin consortium investigators from Stanford, St. Jude, and Dana Farber reported treatment results using a nonalkylator regimen, VAMP (vinblastine, doxorubicin, methotrexate, and prednisone) for children with clinical I/II, nonbulky HL [23]. Patients received 4 cycles of VAMP chemotherapy and response-based IFRT after 2 cycles of chemotherapy. At a median follow-up of 9.6 years, 5- and 10-year EFS rates were 92.7% and 89.4%, respectively [23]. The Pediatric Oncology Group (POG) [24] evaluated the feasibility of combined-modality therapy using 4 courses of DBVE (doxorubicin, bleomycin, vincristine, and etoposide) followed by IFRT to 25.5 Gy to treat stage IA, IIA, and IIIA HL. At a median follow-up of 8.4 years, 6-year OS and EFS rates were 98% and 91%, respectively, with almost all patients (98%) achieving remission after completion of therapy. This DBVE regimen was used by the POG and the Children's Oncology Group (COG) to support reduction of chemotherapy via an early-response-based treatment algorithm. Patients received only 2 courses of ABVE if they achieved an early CR (45% of all patients) versus 4 courses of ABVE if they were slower responders. IFRT to 25.5 Gy was subsequently given to all, resulting in 5-year OS and EFS of 98% and 88%, respectively [25]. In the COG AHOD0431 single-arm study, 287 stage IA/IIA patients who achieved a CR after 3 cycles of doxorubicin, vincristine, prednisone and cyclophosphamide (AVPC) received no further therapy. Those with a partial response (PR) received 21 Gy IFRT. The 2-year EFS rate was 80% for those achieving CR after 3 cycles of AVPC (ie, no 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 who had 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) [26]. These preliminary results suggest that CT response alone is not adequate to identify patients who can be treated without RT after abbreviated chemotherapy. However, very early response as measured by PET1 may be useful for developing response-adapted therapy in favorable-risk patients.

In the Children's Cancer Group (CCG) trial reported by Nachman et al [21], chemotherapy alone using the COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine) hybrid regimen was compared to risk-adapted combined-modality therapy with low-dose IFRT. Patients achieving a CR to chemotherapy were eligible for randomization to receive low-dose IFRT or no further therapy. The trial was terminated early due to a significantly higher number of relapses among patients treated with chemotherapy alone. The 3-year EFS estimates were 92% for patients treated with combined-modality therapy and 87% for those treated with chemotherapy alone. The benefit of IFRT remained significant in the "as treated" analysis. Estimates of OS are not different between the randomized groups in early follow-up; however, salvage therapy after relapse is a known risk for neoplastic complications and early mortality [27]. In the GPOH-HD 95 trial, the relapse-free survival rate was better for patients treated with RT after PR (93%) than for those without RT after CR (89%) [22]. The difference was significant for patients treated for advanced-stage but not early-stage disease. These results were confirmed in the GPOH-HD2002 trial [17]. Patients with stage I, IIA, or IIIA HL were randomized in a POG 8625 study after a CR or PR to four courses of MOPP/ABVD to either two additional courses of alternating MOPP/ABVD or to IFRT to 25.5 Gy. At a median follow-up of 8.25 years, 8-year EFS rates were 83% for chemotherapy alone and 91% for combined-modality therapy while 8-year OS rates were 93.6% for chemotherapy alone and 96.8% for chemotherapy and RT [16]. This study was powered to detect a 15% difference in 3-year EFS rates with 80% power in comparison to the Nachman study which was powered to detect a 6% difference in postrandomization EFS rates with 83% power. Therefore, despite the larger difference in EFS between the two arms in the POG trial compared to the CCG 5942 trial; these differences were not statistically different. In the POG study, patients with early response to therapy had a significantly better outcome, which supports the paradigm of response-based treatment. (See Variant 1.)

Risk-Adapted Therapy – Intermediate-Risk Disease

In risk-adapted treatment regimens, patients presenting with localized (stage IA, IIA) disease with unfavorable features are often grouped into an intermediate-risk category that also includes those stage IIIA disease. The GPOH-HD84 was the first study to give this group of patients less intensive therapy than the unfavorable group, but more intense therapy compared to the favorable group. Building on this concept, the GPOH-HD 2002 study reported a 5-year EFS rate of 88% with 2 cycles of OEPA for boys and OPPA for girls. This was followed by 2 cycles of COPP for girls and cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC) for boys in order to spare fertility by reducing alkylator exposure. The COG has developed an approach of using dose density to support early-response-adapted therapy. A dose-dense regimen of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy was used for both intermediate and high-risk patients in the POG9425 study. This study provided encouraging clinical outcomes using response-based therapy. Patients with a rapid early response (RER) to 3 cycles of ABVE-PC received 21 Gy of regional field RT (mantle, para-aortic, or pelvis). Slow early responders (SER) received an additional 2 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% [28]. In the recently completed COG AHOD 0031 study, patients received 2 cycles of ABVE-PC followed by response assessment. Patients with RER received 2 additional cycles of ABVE-PC followed by a second response assessment. Those with a CR were randomized to 21 Gy IFRT or no further therapy. Patients with a RER who did not have a CR were all assigned to receive IFRT. SER patients were all randomized to either 2 additional cycles of ABVE-PC or dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional 2 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 2 cycles can be a powerful predictor of outcome and help optimize subsequent treatment. A secondary analysis of PET response after 2 cycles of ABVE-PC demonstrated that PET may further assist with treatment optimization. Analyses of the AHOD 0031 cohort are still ongoing, including an "as treated" analysis. This will yield further information on the influence of disease characteristics, such as bulk, and treatment-related factors on clinical outcomes [29]. (See Variant 2 and Variant 3.)

Risk-Adapted Therapy – Unfavorable-Risk Disease

The criteria for unfavorable clinical presentations vary, but typically include the presence of "B" symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of 3 or more nodal regions, extranodal extension to contiguous structures, or advanced-stage (IIIB-IV). RT for unfavorable and advanced HL is variable and protocol dependent. (See Appendix 2.) Although IFRT remains the standard in patients treated with combined-modality therapy, restriction of RT to areas of initial bulky disease or postchemotherapy residual disease is under investigation [17,21].

For patients with unfavorable or advanced disease, two primary treatment approaches have been used. A conventional treatment approach involves chemotherapy on a twice-monthly schedule for 6–8 months. An alternative strategy condenses treatment into 3–5 months to enhance dose intensity and reduce the risk of developing resistant disease. Dose-intensified treatment regimens may also increase the risk of acute and late side effects. A recent assessment of a dose-intense, response-based regimen using BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in children with high-risk disease was reported by the COG. Females with a rapid response received 4 cycles of COPP/ABV following BEACOPP without IFRT, and males received 2 cycles of ABVD and IFRT. All patients with a slow response received 4 additional cycles of BEACOPP and IFRT. A high 5-year EFS rate of 94% was achieved, and the 5-year OS rate was 97% [30]. A summary of treatment results of published trials is provided in Appendix 2, which demonstrates EFS rates ranging from 70%-90%. (See Variant 4.)

The GPOH, building on its original experience with the OPPA/COPP regimen, showed that 6 cycles of OEPA/COPDAC together with 20-30 Gy IFRT also produced excellent results, with a 5-year EFS rate of approximately 87% [17].

In summary, early results have suggested that response-adapted therapy may identify favorable-risk pediatric HL patients 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 due to RT, including cardiopulmonary dysfunction and solid-tumor carcinogenesis. Current protocols have carefully balanced chemotherapy agents, treatment modalities, and doses to limit long-term risks. The data suggest that children with advanced or unfavorable symptomatic or bulky disease at presentation have better outcomes using a combined-modality approach. Identification of prognostic features requiring RT to optimize disease control is a focus of many ongoing pediatric trials.

Radiotherapeutic Management

Most newly diagnosed children will be treated with risk-adapted chemotherapy alone or with combined-modality therapy, including low-dose IFRT. In the past, fully grown adolescents with favorable early-stage disease were treated with full-dose extended-field radiation therapy (EFRT) using techniques that are standard for adults. However, this approach has been abandoned due to concerns of cardiac toxicity and second cancers.

Radiation fields must be meticulously and judiciously designed to maximize disease control and minimize normal tissue damage. Field definition depends on the anatomy of the region, including node distribution and patterns of disease extension. The traditional definitions of lymph node regions can be helpful but are not necessarily sufficient. As a result, field definitions are often protocol-specific.

Efforts to exclude unnecessary normal tissues (eg, breast tissue) are always important in a child with isolated mediastinal disease and no axillary involvement. Involved supradiaphragmatic fields can be simulated with the arms above 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, axillary lymph nodes then move into the vicinity of the humeral heads, which should be blocked in growing children. Breast tissue should be excluded or positioned under the lung/axillary blocking. When the decision is made to include some or all of a critical normal organ in the radiation field (eg, liver, kidney, or heart), normal tissue constraints are critical, particularly when boosting to doses >20 Gy. One should also take into account the chemotherapy protocol used.

Recently, a new set of field designs, the involved site (ISRT), has been developed and endorsed by the steering committee of the International Lymphoma Radiation Oncology Group (ILROG). Led by experienced radiation oncologists specializing in lymphoma, who initially organized the standardization of IFRT fields in the 2D era a decade ago, the ISRT fields are a "modernized" version of IFRT. These new field designs were developed to take into consideration modern technology, including the use of staging PET/CT scans, 3D and 4D treatment planning with CT scanners, conformal treatment techniques, and the use of image guidance to replace the antiquated IFRT that were based on 2D treatment planning and bony anatomy. These fields are expected to be somewhat smaller than the traditional IFRT, but larger than INRT for patients who do not have adequate imaging necessary for INRT treatment planning. A more detailed description of the ISRT field design are expected to be published in the near future and early descriptions can be found in the NCCN guidelines for Hodgkin lymphoma [31].

While CT-based planning and anterior-posterior opposed parallel pair beam arrangements remain common for radiation delivery in pediatric HL, three-dimensional conformal radiation therapy (3DCRT) using nonopposed beams, intensity-modulated radiation therapy (IMRT), or proton therapy may be considered in situations where more conformal techniques would reduce dose to surrounding normal critical structures. This is sometimes the case when treating the thorax to spare dose to the heart, lungs, and developing breast tissue, or when treating the abdomen and pelvis to minimize dose to the highly radiosensitive reproductive organs. Although data are accumulating in regard to the efficacy of IMRT and the decrease in median dose to normal surrounding tissues, some uncertainty exists about the potential for increased late effects from IMRT, particularly secondary malignancy, since IMRT results in a lower dose to a larger volume compared to conventional techniques. Therefore, keeping dosimetric parameters such as the V5 to breast and lung tissue to as low as reasonably achievable may be relevant as well for HL patients [32]. Data also suggest that use of a mean lung dose constraint <15 Gy results in low rates of radiation pneumonitis [33]. Proton therapy is currently being investigated and may further decrease the mean dose to normal surrounding tissue compared with IMRT or 3DCRT without increasing the volume of normal tissue receiving lower dose radiation. Although the efficacy of these more conformal techniques have been shown in other disease sites, the benefits of lower dose to critical organs are unlikely to be fully appreciated for a couple of decades.

Because patients with early-stage HL treated with chemotherapy alone most frequently relapse in the initially involved lymph node(s) [34], efforts have been made to reduce treatment fields to include only the initially

involved lymph node(s) and exclude surrounding normal tissues. The EORTC-GELA introduced the concept of involved-node radiation therapy (INRT) [35], which uses all available clinical information, including pre- and post-chemotherapy imaging with CT with the patient in the treatment position and FDG-PET scan to define the treatment field. The pre-chemotherapy PET/CT scan should be performed in the same treatment position as when the radiation will be delivered for accurate definition of the INRT field. Controversy still exists regarding the optimum margins for INRT [36,37], but initial clinical data are emerging. Campbell et al [38] reviewed clinical outcomes of patients with limited-stage HL treated with EFRT, IFRT, and INRT and found no marginal recurrences or locoregional failures with INRT. However, the INRT fields in this study employed margins ≤5 cm and used conventional treatment planning. These fields were thus significantly larger than the margins prescribed for INRT by the EORTC-GELA and GHSG guidelines. INRT requires that all available clinical information be used to appropriately reduce treatment field size without compromising the excellent clinical outcomes attainable with standard therapy.

Summary Recommendations for Primary Disease

Optimal treatment planning involves a multidisciplinary approach beginning at diagnosis, with the pediatric and radiation oncologist meeting to review staging studies with a radiologist following examination of the patient. The treatment approach should consider patient factors such as age and gender that may enhance the risk of complications, as well as disease factors (eg, presence of "B" symptoms, bulky lymphadenopathy, and stage). Recommended treatment approaches for favorable localized, intermediate, and advanced unfavorable disease are summarized in Appendix 3. (See Variant 5.)

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Patients with nLPHL typically present with early-stage disease, peripheral lymph node (cervical, axillary, or inguinal) involvement, and a striking male predominance [39]. The disease is considered indolent with a favorable prognosis characterized by late recurrences [40]. The rare deaths are related to secondary malignancies, cardio-pulmonary treatment toxicity [8], or transformation to aggressive B-cell lymphoma [41]. Historically, patients with nLPHL have been treated on protocols for patients with classical HL; however, there are several reports in the adult and pediatric literature suggesting that they can be cured with less aggressive therapies. In adults, radiotherapy-only approaches are favored with reasonable outcomes [42,43]; however, the required doses of 30 to 40 Gy would be unacceptable in a pediatric setting except in very rare clinical circumstances.

In pediatrics, only small retrospective series have been published reviewing therapy (resection, radiotherapy, or chemotherapy alone, and combined-modality) and outcome of these patients, most of whom do well regardless of the modality chosen; however, toxicity remains the main concern for more involved treatment approaches [8,44,45]. The largest retrospective study evaluating resection alone in children looked at the outcome of 58 children from several European countries [46]. This study proved that a substantial proportion of patients with limited-stage nLPHL and completely resected disease could achieve a long-term remission without any further therapy. Based on these findings, the Euro-Net is conducting a clinical trial to prospectively validate this "watch and wait" approach for children with completely resected disease and low-dose chemotherapy for patients with residual disease after resection. The COG recently released the data of their AHOD03P1 study on 52 stage IA patients who were observed after surgery only. Nine relapses were observed among these patients and all were retrieved successfully with 3 cycles of AV-PC (doxorubicin, vincristine, prednisone and cyclophosphamide) and no radiotherapy. The current 2-year EFS estimate among these patients is 80.3% (95% CI: 65.3%-89.3%) [47].

Refractory and Relapsed Disease

HL may still be cured if initial treatment programs fail. Relapse occurs most often within 4 years, but late relapse is not rare, especially in nLPHL patients who can fail 10 years after initial diagnosis. The spectrum of treatment options include standard-dose chemotherapy (with or without RT), RT alone, or high-dose chemotherapy (with or without RT), followed by stem-cell support, clinical trials, or palliative therapy. RT may also be used pre- or post-transplant depending on the clinical scenario.

Factors that independently predict a more favorable outcome include the site of relapse (nodal better than extranodal), stage at relapse (early better than advanced), histology, and response to first-line salvage chemotherapy. The selection of the most appropriate salvage regimen is based on whether a complete remission was achieved, the durability of the remission, the extent of disease at relapse, and the intensity of the frontline therapy given. Three- to 5-year survival probabilities of 25%-80% have been reported (primarily in adults) following treatment with high-dose chemotherapy and hematopoietic stem cell rescue [48-50]. Data specific to

children with recurrent HL are limited. Claviez et al [51] reported probabilities of relapse at 2 and 5 years of 36% (+/-5%) and 44% (+/-6%), respectively. Progression-free survival (PFS) rates were 40% (+/-6%) and 30% (+/-6%) and OS rates were 54% (+/-6%) and 45% (+/-6%) at 2 and 5 years, respectively.

For higher risk relapses, a combination of ifosfamide and vinorelbine for pediatric patients in first relapse was studied by the COG (AHOD00P1). This regimen showed a very good overall response rate (CR/PR) of 78% and achieved good stem cell mobilization for future autologous stem cell transplant [52]. The goal in this group of patients is to proceed to autologous stem cell transplant once remission is achieved, since studies have shown that patients undergoing autologous stem cell transplant with active disease have a worse outcome. For patients who relapse after transplant or are upfront refractory, a combination of gemcitabine and vinorelbine was also studied by this group. It resulted in an overall response rate of 76% [53]. Patients who relapse after an autologous stem cell transplant are often considered for an allogeneic stem cell transplant.

Claviez et al [51] found an increased risk of relapse and lower PFS beyond 9 months when pediatric patients received reduced intensity conditioning compared to a myeloabalative conditioning regimen prior to undergoing allogeneic stem cell transplant. OS, however, was not different between the two groups.

Newer drugs promise great efficacy with less toxicity. Targeted therapy with brentuximab vedotin, an antibody-drug conjugate that targets CD30, has shown excellent results in early clinical trials [54]. Pediatric trials are underway to assess its efficacy and toxicity, and discussions about incorporating it into large clinical trials are under way. Furthermore, HDAC inhibitors like panobinostat are being investigated, as well as mTOR inhibitors.

Summary

- In an effort to cure children with minimal side effects, most current treatment approaches to pediatric HL entail combined-modality therapy with reduced dose radiation.
- Prognostic factors at presentation are used to risk stratify patients and determine treatment approach.
- A number of combined-modality therapy protocols exist, and the decision as to how to incorporate RT should be made within the context of the protocol followed.
- For favorable-risk disease, 2-4 cycles of non-cross-resistant chemotherapy are recommended, followed by response-based low-dose (eg, 15-25 Gy) IFRT depending on the protocol used.
- For intermediate-risk disease, 3-6 cycles of compacted, dose-intensive chemotherapy are recommended. Early response to therapy may be considered in determining the need for radiation in those achieving CR**.**
- For high-risk disease, 4-6 compacted, dose-intensive cycles of chemotherapy in addition to low-dose (eg, 15-25 Gy) IFRT to involved sites of disease are recommended.
- INRT in the pediatrics population remains investigational.
- Radiotherapy-alone approaches for pediatric nLPHL are discouraged due to the higher doses (eg, 30-40 Gy) required that may affect skeletal maturity. The approach of resection alone for limited-stage disease appears promising, although it is still under investigation. Chemotherapy-alone approaches remain standard.
- Advanced radiation techniques, such as IMRT and proton therapy, may be considered depending on the clinical scenario and if an improvement in the therapeutic ratio is expected.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Pediatric Hodgkin Lymphoma**

Variant 1: **12-year-old girl with CS IIA NSHL, three sites including nonbulky mediastinal and bilateral neck disease with rapid early response after initial chemotherapy and complete response at the end of chemotherapy.**

Treatment	Rating	Comments
Chemotherapy with or without Radiation Therapy		
4 cycles ABVD alone	6	Data for ABVD are sparse for pediatric patients.
6 cycles ABVD alone	3	This is typical therapy in adults, but probably more therapy than necessary for children.
2 cycles ABVD + 20-26 Gy IFRT	5	
4 cycles ABVD + 20-26 Gy IFRT	5	
6 cycles ABVD + 20-26 Gy IFRT	3	
4 cycles ABVE-PC alone	6	
3-4 cycles ABVE-PC + 20-26 Gy IFRT	5	More therapy than is necessary.
5 cycles ABVE-PC + 20-26 Gy IFRT	3	
2 cycles O(E/P)PA alone	8	
2 cycles O(E/P)PA + 20-26 Gy IFRT	5	
2 cycles O(E/P)PA + >26 Gy IFRT	3	
2 cycles O(E/P)PA + 2 COP(P/Dac) + 20-35 Gy IFRT	2	
2 cycles O(E/P)PA + 4 COP(P/Dac) + 20-35 Gy IFRT	1	
4 cycles VAMP alone	3	Should receive consolidated radiation.
4 cycles VAMP + 15-20 Gy IFRT	7	
4 cycles VAMP + 21-26 Gy IFRT	4	Too much radiation.
2 cycles DBVE + 20-26 Gy IFRT	6	
4 cycles DBVE alone	3	
4 cycles DBVE + 20-26 Gy IFRT	6	
4 cycles COPP/ABV hybrid alone	6	
6 cycles COPP/ABV hybrid alone	4	
4 cycles COPP/ABV hybrid + 20-26 Gy IFRT	6	
4 cycles BEACOPP + 4 COPP/ABV	2	
4 cycles BEACOPP + 2 ABVD + 20-26 Gy IFRT	2	
8 cycles BEACOPP + 20-26 Gy IFRT	1	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Pediatric Hodgkin Lymphoma**

Variant 2: **6-year-old girl with CS IIB NSHL with bulky mediastinal disease with rapid early response after initial chemotherapy and complete response at completion of chemotherapy.**

Treatment	Rating	Comments
Chemotherapy with or without Radiation Therapy		
4 cycles ABVD alone	3	
6 cycles ABVD alone	4	
2 cycles ABVD + 20-26 Gy IFRT	3	
4 cycles ABVD + 20-26 Gy IFRT	6	
6 cycles ABVD + 20-26 Gy IFRT	4	
4 cycles ABVE-PC alone	7	Based on data from recently completed COG study. Data still under analysis.
3-4 cycles ABVE-PC + 20-26 Gy IFRT	8	
5 cycles ABVE-PC + 20-26 Gy IFRT	6	
2 cycles O(E/P)PA alone	1	
2 cycles O(E/P)PA + 20-26 Gy IFRT	3	
2 cycles O(E/P)PA + >26 Gy IFRT	3	
2 cycles O(E/P)PA + 2 COP(P/Dac) + 20-35 Gy IFRT	7	
2 cycles O(E/P)PA + 4 COP(P/Dac) + 20-35 Gy IFRT	5	
4 cycles VAMP alone	3	
4 cycles VAMP + 15-20 Gy IFRT	3	
4 cycles VAMP + 21-26 Gy IFRT	3	
2 cycles DBVE + 20-26 Gy IFRT	2	
4 cycles DBVE alone	2	
4 cycles DBVE + 20-26 Gy IFRT	3	
4 cycles COPP/ABV hybrid alone	4	
6 cycles COPP/ABV hybrid alone	5	
4 cycles COPP/ABV hybrid + 20-26 Gy IFRT	5	
4 cycles BEACOPP + 4 COPP/ABV	4	
4 cycles BEACOPP + 2 ABVD + 20-26 Gy IFRT	4	
8 cycles BEACOPP + 20-26 Gy IFRT	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Pediatric Hodgkin Lymphoma**

Variant 3: **16-year-old boy with CS IIIA (neck, mediastinum, para-aortic) nonbulky NSHL with slow early response after initial chemotherapy and complete response at completion of chemotherapy.**

Treatment	Rating	Comments
Chemotherapy with or without Radiation Therapy		
4 cycles ABVD alone	3	
6 cycles ABVD alone	4	
2 cycles ABVD + 20-26 Gy IFRT	3	
4 cycles ABVD + 20-26 Gy IFRT	5	
6 cycles ABVD + 20-26 Gy IFRT	4	
4 cycles ABVE-PC alone	3	
3-4 cycles ABVE-PC + 20-26 Gy IFRT	8	
5 cycles ABVE-PC + 20-26 Gy IFRT	8	
2 cycles O(E/P)PA alone	1	
2 cycles O(E/P)PA + 20-26 Gy IFRT	2	
2 cycles O(E/P)PA + >26 Gy IFRT	2	
2 cycles O(E/P)PA + 2 COP(P/Dac) + 20-35 Gy IFRT	8	
2 cycles O(E/P)PA + 4 COP(P/Dac) + 20-35 Gy IFRT	4	
4 cycles VAMP alone	2	
4 cycles VAMP + 15-20 Gy IFRT	3	
4 cycles VAMP + 21-26 Gy IFRT	3	
2 cycles DBVE + 20-26 Gy IFRT	2	
4 cycles DBVE alone	3	
4 cycles DBVE + 20-26 Gy IFRT	4	
4 cycles COPP/ABV hybrid alone	3	
6 cycles COPP/ABV hybrid alone	5	
4 cycles COPP/ABV hybrid + 20-26 Gy IFRT	4	
4 cycles BEACOPP + 4 COPP/ABV	3	
4 cycles BEACOPP + 2 ABVD + 20-26 Gy IFRT	5	
8 cycles BEACOPP + 20-26 Gy IFRT	3	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Pediatric Hodgkin Lymphoma**

Variant 4: **14-year-old girl with CS IIIB (supraclavicular, mediastinum, para-aortic + splenomegaly) MCHL with partial response at completion of chemotherapy.**

Treatment	Rating	Comments
Chemotherapy with or without Radiation Therapy		
4 cycles ABVD alone	2	
6 cycles ABVD alone	3	
2 cycles ABVD + 20-26 Gy IFRT	2	
4 cycles ABVD + 20-26 Gy IFRT	3	
6 cycles ABVD + 20-26 Gy IFRT	7	
4 cycles ABVE-PC alone	3	
3-4 cycles ABVE-PC + 20-26 Gy IFRT	4	
5 cycles ABVE-PC + 20-26 Gy IFRT	8	
2 cycles O(E/P)PA alone	1	
2 cycles O(E/P)PA + 20-26 Gy IFRT	2	
2 cycles O(E/P)PA + >26 Gy IFRT	2	
2 cycles O(E/P)PA + 2 COP(P/Dac) + 20-35 Gy IFRT	3	
2 cycles O(E/P)PA + 4 COP(P/Dac) + 20-35 Gy IFRT	8	
4 cycles VAMP alone	2	
4 cycles VAMP + 15-20 Gy IFRT	2	
4 cycles VAMP + 21-26 Gy IFRT	2	
2 cycles DBVE + 20-26 Gy IFRT	2	
4 cycles DBVE alone	2	
4 cycles DBVE + 20-26 Gy IFRT	3	
4 cycles COPP/ABV hybrid alone	2	
6 cycles COPP/ABV hybrid alone	3	
4 cycles COPP/ABV hybrid + 20-26 Gy IFRT	5	
4 cycles BEACOPP + 4 COPP/ABV	6	
4 cycles BEACOPP + 2 ABVD + 20-26 Gy IFRT	5	
8 cycles BEACOPP + 20-26 Gy IFRT	7	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Pediatric Hodgkin Lymphoma**

Variant 5: **7-year-old boy with CS IIA nLPHL isolated to the right iliac and inguinal nodes.**

Treatment	Rating	Comments
Surgery alone	3	
Radiation Therapy Alone		
15-25 Gy IFRT	3	Inadequate data.
>25 Gy IFRT	3	Not recommended in this age group due to long-term side effects to the growing skeleton.
Chemotherapy with or without Radiation Therapy		
3 cycles AVPC alone	7	Data from recent COG study are promising.
3 cycles CVP alone	7	
4 cycles ABVD alone	5	
6 cycles ABVD alone	3	
2 cycles ABVD + 20-26 Gy IFRT	6	
4 cycles ABVD + 20-26 Gy IFRT	4	
6 cycles ABVD + 20-26 Gy IFRT	2	
4 cycles ABVE-PC alone	4	
3-4 cycles ABVE-PC + 20-26 Gy IFRT	3	
5 cycles ABVE-PC + 20-26 Gy IFRT	2	
2 cycles O(E/P)PA alone	7	Assuming CR.
2 cycles O(E/P)PA + 20-26 Gy IFRT	6	
2 cycles O(E/P)PA + >26 Gy IFRT	3	Too much radiation.
2 cycles O(E/P)PA + 2 COP(P/Dac) + 20-35 Gy IFRT	2	Overly toxic, unless newer techniques like IMRT are considered. Currently there are no data on these newer techniques.
2 cycles O(E/P)PA + 4 COP(P/Dac) + 20-35 Gy IFRT	1	
4 cycles VAMP alone	4	
4 cycles VAMP + 15-20 Gy IFRT	7	
4 cycles VAMP + 21-26 Gy IFRT	6	
2 cycles DBVE + 20-26 Gy IFRT	6	
4 cycles DBVE alone	4	Inadequate data.
4 cycles DBVE + 20-26 Gy IFRT	5	
4 cycles COPP/ABV hybrid alone	4	
6 cycles COPP/ABV hybrid alone	3	
4 cycles COPP/ABV hybrid + 20-26 Gy IFRT	3	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Appendix 1. Treatment Results for Favorable Pediatric Hodgkin Lymphoma

Group or Institution	*Patients (n)*	*Stage*	*Chemotherapy*	*Radiation (Gy), Field*	*Survival (%)*		*Follow-up Interval, (year)*
					Overall	**DFS, EFS, or RFS**	
Stanford* [55] St. Jude Dana Farber Consortium	49 61	I/II†	4 VAMP	If CR 15, IF < CR 25.5 IF	100 93	95.2 84.5	10
USA-CCG* [21]	109	IA/B, IIA	4 COPP/ABV	21 IF	100	97	3
	106	IA/B, IIA	4 COPP/ABV	None	100	91	3
GOPH- HD 2002 [17]	62 126	IA/B, IIA	2 OEPA/OPPA	If CR no RT < CR 20-35 IF	100 100	93.2 91.7	5
Florida-POG* [24]	51	I-IIIA	4 DBVE	25.5 IF	98	91	6
POG 8625* [16]	81	I-IIIA	4 MOPP/ABVD	25.5 IF	97	91	8
	78	I-IIIA	6 MOPP/ABVD	None	94	83	8

*Denotes study population results that include lymphocyte predominant HL (nLPHL) patients.
CCG, Children's Cancer Group; DFS, disease-free survival; EF, extended field; EFS, event-free survival; IF, involved field; RFS, relapse-free survival. **ABVD**, doxorubicin, bleomycin, vinblastine and dacarbazine; **COP(P)**, cyclophosphamide, vincristine, prednisone and procarbazine; **COPP/ABV,** cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; **MOPP**, nitrogen mustard, vincristine, procarbazine and prednisone; **OEPA**, vincristine, etoposide, prednisone, doxorubicin; **OPA,** vincristine, prednisone, Adriamycin; **OPPA**, vincristine, procarbazine, prednisolone and doxorubicin: **VAMP**, vinblastine, doxorubicin, methotrexate, and prednisone; **DBVE,** doxorubicin, bleomycin, vincristine, and etoposide.

Appendix 2. Treatment Results for Intermediate- and Advanced-Stage Pediatric Hodgkin Lymphoma

Group or Institution	*Patients (n)*	*Stage*	*Chemotherapy*	*Radiation (Gy), Field*	*Survival (%)*		*Follow-up Interval (year)*
					Overall	**DFS, EFS or RFS**	
GPOH-HD-2002 [17]	378	$I_{E,}$ IIB, II_EA/B, III_EA/B, IIIB, IV	2 OEPA/OPPA + 2 or 4 COPP/COPADC	20-35 IF	96	88	4
USA-POG* [15]	80	IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21 EF	87	80	5
	81	IIB/$IIIA_{2,}$ IIIB, IV	4 MOPP/4 ABVD	None	96	79	5
USA-CCG [56]	54 57	III/IV	6 ABVD 12 MOPP/ABVD	21 EF None	90 84	87 77	4
COG-P9425 [28]	216	IB, $IIA/IIIA_1$ with bulky mediastinum or $IIIA_{2,}$ IIB/IIIB/IVB	3 ABVE-PC for RER 5 ABVE-PC for SER	21 IF 21 IF	95 95	86 83	5
CCG 59704* [30]	99	IIB or IIIB with bulky dz or IV	All: 4 BEACOPP then (1) RER: Female: 4 COPP/ABV (2) RER: Male: 2 ABVD (3) SER: 4 BEACOPP	(1) None (2) 21 IF (3) 21 IF (<CR: boost 14 Gy)	97	94	5
USA-CCG* [21]	109	IIB, III	6 COPP/ABV	21 IF	95	87	3
	33	IV	COPP/ABV + CHOP + Ara-C/VP-16	21 IF	100	90	3
	110	IIB, III	6 COPP/ABV	None	100	83	3
	34	IV	COPP/ABV + CHOP + Ara-C/VP-16	None	94	81	3

*Denotes study population results that include lymphocyte predominant HL (nLPHL) patients.
CCG, Children's Cancer Group; CR, complete response; DFS, disease-free survival; EF, extended field; EFS, event-free survival; IF, involved field; POG, Pediatric Oncology Group; PR, partial response; RFS, relapse-free survival.
ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; **ABVE-PC**, doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide; **COP(P)**, cyclophosphamide, vincristine, prednisone and procarbazine; **COPP/ABV**, cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; **EVAP/ABV**, etoposide, vinblastine, cytarabine, cisplatin/doxorubicin, bleomycin, vincristine; **MOPP**, nitrogen mustard, vincristine, procarbazine and prednisone; **OEPA**, vincristine, etoposide, prednisone, doxorubicin; **OPA**, vincristine, prednisone, Adriamcyin; **OPPA**, vincristine, procarbazine, prednisolone and doxorubicin; **BEACOPP**, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

Appendix 3. Recommendations for Treatment Approach in Pediatric Hodgkin Lymphoma

Clinical presentation	Stage	Recommended treatment approach
Low Risk: Localized disease involving < 3-4 nodal regions in absence of "B" symptoms, bulky disease, or extranodal extension.	IA, IIA	**Recommended therapy:** 2-4 cycles non-cross-resistant chemotherapy (OEPA, VAMP, COPP-ABV, AV-PC). Response-based low-dose, IFRT (1500 cGy-2550 cGy). **Other considerations: Consider use of IFRT based on early response to chemotherapy.** If CR after 2 cycles of OEPA, no need for IFRT AV-PC without RT for RER.
Intermediate: Localized disease involving ≥3-4 nodal regions in presence of bulky lymphadenopathy (mediastinal ratio ≥33%; lymph node mass ≥6-10 cm), extranodal extension.	IA, IIA, IIB* IIIA	**Recommended therapy:** 3-6 cycles compacted, dose-intensive, non-cross-resistant chemotherapy (OEPA/COPP, ABVE-PC) plus low-dose, IFRT (1500 cGy-2550 cGy). **Other considerations: Early response to therapy may be considered in determining need for radiation in those achieving CR.**
High Risk: Stage II patients with constitutional symptoms of fevers or weight loss or any patient with advanced disease.	IIB* IIIB IV	**Recommended therapy:** 4-6 compacted, dose-intensive cycles of non-cross-resistant chemotherapy (COPP/OEPA, ABVE-PC) plus low-dose, IFRT (1500 cGy-2550 cGy). **Other considerations:** 8 cycles non-cross-resistant chemotherapy alone (BEACOPP) for high risk, poor early response.

*Stage IIB patients have been variably treated as intermediate or unfavorable risk. Some studies use associated factors, eg, weight loss, bulk disease, extranodal extension, for further risk stratification.