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HODGKIN LYMPHOMA — UNFAVORABLE CLINICAL STAGE I AND II

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Summary of Literature Review

Historical Overview

A brief historical view of the management of Hodgkin lymphoma is necessary to place current management concepts and treatment controversies in proper context. Early in the empiric development of radiation oncology many decades ago, Hodgkin lymphoma was found to ostensibly spread to contiguous lymph node sites in its natural history and to be very radiation sensitive [1,2]. The use of extended-field radiation therapy (EFRT) (to encompass grossly evident lymphoma and adjacent microscopic disease) and appropriate radiation dosing led to the first cures of this disease [3]. With the development of megavoltage radiation therapy (RT) and with improved staging of Hodgkin lymphoma by staging laparotomy, cure rates for early-stage Hodgkin lymphoma steadily improved [4]. Patients with more advanced stages and relapses were found to benefit from the introduction of multiagent chemotherapy. MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and its variants constituted the first generation of successful therapy, although ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and its variants have been a second generation having improved efficacy and toxicity profiles [5,6]. With identification of risk factors for relapse, chemotherapy was often added to subtotal or total nodal irradiation for patients deemed to have unfavorable early-stage Hodgkin lymphoma. Although there were early theoretical considerations that radiation dose and volumes could be reduced when effective chemotherapy was given [7], decades of clinical trials have led to current standards of care using combined-modality therapy (CMT) for stage I and II Hodgkin lymphoma in which radiation doses and fields have been substantially reduced to minimize toxicity while maintaining high cure rates. Radiation techniques are still in evolution while there are ongoing efforts to see which patients can be treated with chemotherapy alone.

Driving the current debates on optimizing therapy of Hodgkin lymphoma has been the desire to minimize the risk of secondary malignant neoplasms (SMN) and cardiovascular effects of therapy [8]. With highly successful cure rates of Hodgkin lymphoma, these long-term toxicities of therapy seen over many years and decades of follow-up have provided an impetus for risk-adapted combined chemotherapy and reduced-intensity RT. Moreover, modern imaging with computed tomography (CT) scanning, positron emission tomography (PET) imaging (which has supplanted the use of Gallium scanning), and, to a lesser degree, magnetic resonance imaging (MRI) has eliminated the need for staging laparotomy. In the modern diagnostic workup after a pathologic diagnosis using modern immunohistochemistry, PET/CT scanning has become increasingly standard, along with selected biopsy of bone marrow and other disease sites only when results would change therapy.

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Definition of Early-Stage Unfavorable Hodgkin Lymphoma

In addition to staging, the identification of prognostic factors has taken on importance as a determinant of treatment algorithms. Complicating this matter are 3 concepts. First, prognostic factors are in flux as more effective or higher-intensity therapy may negate adverse risk factors previously demonstrated. 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. Thus, there is some variability in classification of Hodgkin patients into favorable and unfavorable groupings. Lastly, there is an evolving understanding that early response to systemic therapy may be an important prognostic factor that can be used to guide further treatment decisions [9]. Although this concept is under investigation in adults with Hodgkin lymphoma, one may acknowledge that response-based therapy has recently developed firm roots in pediatric Hodgkin lymphoma treatment paradigms [10,11].

Dating from the time that early-stage Hodgkin lymphoma was treated with subtotal or total nodal irradiation including splenic irradiation, often termed EFRT, numerous adverse prognostic factors in stage I–II disease have identified those patients who benefit from CMT [12-15]. As a result, the concept of risk-adapted therapy, in which the presence of poor prognostic factors drives more intensive therapy, has been developed; 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.

There has been general consensus that 2 of these factors in stage I–II Hodgkin lymphomas should most influence management decisions. The first is constitutional B symptoms: unexplained fevers >38ºC, drenching night sweats, or significant weight loss >10% in 6 months, as clearly defined in the Ann Arbor staging classification system [16]. The presence of B symptoms is 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 [17].

The second prognostic factor that should influence treatment selection is the presence of large mediastinal adenopathy or bulky disease in nonmediastinal sites. A variety of definitions of large mediastinal adenopathy have been reported in the literature [18]. The most commonly used definition is based on measurement of the maximum width of the mediastinal mass on a standing posteroanterior chest radiograph, compared with the maximum intrathoracic diameter. A ratio greater than 1:3 is defined as “bulky.” Other reports have used a ratio with the intrathoracic width at T5–6 as the denominator [19], and still others use absolute measurements [20], surface area calculations, or volume measurements. Bulky disease in nonmediastinal sites has similarly been classified by varying definitions. Some protocols define bulky as ≥10 cm, and others use ≥5 cm or ≥6 cm.

In interpreting results of trials, it is important to note that the definition of unfavorable-prognosis, early-stage disease varies among cooperative groups. 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 [21]. 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 a bulky mediastinal mass [22]. Many of the North American cooperative groups, however, have classified stage I and II patients with either bulky disease or B symptoms under the rubric of advanced-stage disease for purposes of protocol eligibility, despite the potential for overtreatment. For instance, stage I/II patients with bulky mediastinal adenopathy accounted for a third of patients in the Eastern Cooperative Oncology Group (ECOG) E2496 Intergroup trial of locally extensive and advanced Hodgkin lymphoma [23]. Table 2 summarizes some of these prognostic groupings. There is also an ongoing research effort to identify biologically based prognostic factors. The density of macrophages as measured by CD68-positive infiltrating cells was found to be one such prognostic factor by one group of investigators [24]. Within the context of the E2496 study, this finding was confirmed, but a 23-gene expression panel proved to be a better determinant of prognosis [25]. Recent pediatric experience within the Children’s Oncology Group has led to a simplified prognostic score based on just 4 factors (stage IV, large mediastinal mass, fever, and albumin level) [26].

Treatment Principles

The understanding that an unacceptably high rate of late complications stems from external beam RT has led to the abandonment of primary RT [8]. Although cardiovascular complications from mediastinal RT increase as a function of radiation dose and volume, anthracylines also cause heart disease—both cardiomyopathy with age-dependent thresholds and by potentiating the effects of RT on risk of congestive heart failure, coronary artery disease, and valvular heart disease. However, the chief impetus to changing treatment philosophies has been the risk of SMN. Although beyond the scope of this brief review, the risk of secondary malignancies is dependent on patient age, gender, and specifics of treatment exposure to normal tissues. Conceptions that alkylating agents independently cause leukemias and that RT causes solid tumors are overly simplistic and probably inaccurate.

Nevertheless, CMT consisting of chemotherapy followed by lower-dose RT represents the standard of care for most patients with unfavorable stage I–II Hodgkin lymphoma. Anthracycline-containing regimens are the most widely accepted systemic therapy as part of CMT, with ABVD being the prototype. Various hybrid regimens, such as MOPP/ABV, have been used. Stanford V, a 12-week, 7-drug regimen that is administered on a weekly basis, includes the topoisomerase II inhibitor etoposide but contains lower cumulative doses of mechlorethamine, adriamycin, and bleomycin than do MOPP and ABVD, respectively. BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) is another active and efficacious regimen developed by the GHSG originally for advanced-stage Hodgkin lymphoma.

In most trials of CMT, RT has evolved from EFRT to involved-field radiation therapy (IFRT) directed at all regions of initial involvement at diagnosis. The definition of IFRT has been detailed elsewhere [27]. In a continuous effort to limit the toxicity of radiation in the presence of effective chemotherapy, involved-site radiation therapy (ISRT) has been introduced as the new standard of care. The International Lymphoma Radiation Oncology Group (ILROG) recently published the guidelines of ISRT. The main differences compared to IFRT are 1) use of the modern definition of treatment volume as defined by the International Commission on Radiation Units and Measurements Report and 2) the extended fields in IFRT are now replaced by limited volumes based solely on detectable disease at presentation using contrast-enhanced CT and PET/CT [28]. Suffice it to say, following chemotherapy, lymphatic regions initially involved at diagnosis are targeted. The superior-inferior extent of the radiation field typically encompasses the prechemotherapy extent of disease, although the lateral or radial extent can be limited to the postchemotherapy extent of disease in the mediastinum. The initial lateral extent of mediastinal disease should not be treated unless there is known extranodal disease extension into bone or chest wall. The dose fractionation is variable from one trial to another, but dose per fraction has varied from 1.5 to 2.0 Gy; whether or not there are any significant radiobiological differences in this fractional dose range is unclear. Also unclear is the use of shrinking field technique, where bulky or slowly responding disease is differentially dosed higher than other areas. Often, simple anterior-posterior fields have been used. Limiting excess radiation to critical structures in the vicinity of involved sites is essential in today's radiation treatment. Technical advances represented by computer planning have been introduced, as represented by the use of intensity-modulated radiation therapy (IMRT), breath-hold techniques, image-guided therapy, and 4-D CT treatment planning. Along the same lines, proton beam RT is sometimes an appropriate consideration.

Important Clinical Trials

In the GHSG HD8 trial, 1204 unfavorable-prognosis patients were treated with 2 cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) and ABVD, followed by either EFRT or IFRT [29]. Radiation doses were 30 Gy, with bulky disease boosted to 40 Gy. There was no difference in 5-year freedom from treatment failure (FFTF) at 86% versus 84%, respectively. Notably, acute side effects were less frequent in the IFRT group. A subset analysis of elderly patients >60 years of age showed that age is an important poor prognostic factor [30]. Moreover, elderly patients did worse with EFRT compared to IFRT in terms of both 5-year FFTF (58% versus 70%, P=0.034) and overall survival (OS) (59% versus 81%, P=0.008). A preliminary update of the HD8 trial shows that there continues to be no difference in the EFRT and IFRT arms at 10 years of follow-up with respect to FFTF (79.8% versus 79.7%) and OS (86.4% versus 87.3%) [31]. Deaths due to secondary malignancies were higher in the EFRT arm (5.3% versus 3.4%), in part explained by a higher number of cases of acute myeloid leukemia in those receiving EFRT (11 cases versus 4 cases out of 533 eligible patients randomized in each group).

In the EORTC-H8U trial, patients were randomized to 6 cycles of MOPP/ABV followed by IFRT, 4 cycles of MOPP/ABV followed by IFRT, or 4 cycles of MOPP/ABV followed by EFRT [32]. Radiation doses were in the 36 to 40 Gy range. At a median follow-up of 92 months, there was no significant difference in 5-year event-free

survival (EFS) rates among the 3 treatment groups (84%, 88%, and 87%, respectively), specifically showing no benefit to the EFRT arm [32]. With this dose of radiation, now deemed high by today's standards, 6 cycles of chemotherapy were no better than 4 cycles. Even with dropping the radiation dose to 30 Gy in the EORTC-H9-U trial, there was also no significant difference between 4 and 6 cycles of ABVD plus IFRT at a median follow-up of 57 months [33]. Similarly, an Italian study with favorable- and unfavorable-prognosis patients showed no difference in freedom from progression (FFP) or OS rates between patients treated with EFRT or IFRT following 4 cycles of ABVD [34]. Based on such international randomized trials, IFRT is considered the standard radiation treatment field after chemotherapy for early-stage Hodgkin lymphoma, for the time being.

When the Stanford V program was developed for "advanced" Hodgkin lymphoma, adjuvant RT was no longer directed at all sites of initial disease but specifically targeted only sites of initial bulky disease, defined as masses at initial diagnosis measuring ≥5 cm, large mediastinal masses, and/or macroscopic splenic disease. However, subsequent trials in early-stage, nonbulky disease have had RT target all initial sites of disease [35,36]. Most published experiences in adults with Stanford V have used a prescription dose of 36 Gy starting 2 weeks after the chemotherapy completion. In a report on 142 patients with stage III or IV or locally extensive mediastinal stage I or II Hodgkin lymphoma, a 5-year FFP and OS of 89% and 96%, respectively, were achieved [37]. There have been several randomized trials comparing Stanford V to ABVD, but germane to this review of unfavorable early-stage Hodgkin lymphoma is the aforementioned E2496 trial randomizing patients to ABVD × 6–8 cycles with RT to 36 Gy directed at only the mediastinal bulky disease, if present at diagnosis, versus Standard V with RT as originally conceived to 36 Gy to pretreatment bulky sites >5 cm and the spleen if macroscopic nodules were seen on baseline CT scanning. There were no statistically significant differences between the 2 groups at 5 years, with a failure-free survival (FFS) of 74% for ABVD and 71% for Stanford V (P=0.32 [23]. With "localized disease" a stratification factor in the trial design, the early-stage patients with bulky mediastinal adenopathy had a 5-year FFS of 82% and a 5-year OS of 94%. Within this subgroup, there were no differences in 5-year FFS for ABVD + RT versus Stanford V, at 85% compared to 77% (P=0.13) [38]. In Stanford's G4 trial for stage I–II nonbulky Hodgkin lymphoma using abbreviated Stanford V chemotherapy with 30-Gy IFRT, the 8-year FFP rate was 94%. Of this patient cohort, 42% and 33% met criteria for unfavorable prognosis by GHSG and EORTC definitions, respectively [35].

The National Cancer Institute of Canada (NCIC) led Intergroup trial HD.6, which enrolled 405 patients with nonbulky stage I–IIA Hodgkin lymphoma [39]. Although designed in conjunction with the E2496 trial to not have overlapping eligibility criteria, it is remarkably anomalous, based on our current knowledge, that a control group getting RT would receive EFRT rather than IFRT. Regardless, favorable-risk prognosis patients were randomized to receive 4–6 cycles of ABVD versus EFRT. Unfavorable-risk prognosis patients (age ≥40 years, ESR ≥50 mm/h, mixed cellularity, lymphocyte-depleted histology, or ≥4 sites of disease) were randomized to receive either 4–6 cycles of ABVD or CMT with 2 cycles of ABVD followed by EFRT. The radiation prescription for both the favorable and unfavorable RT arms was 35 Gy in 20 fractions. Among the unfavorable-risk prognosis patients, the rate of FFP at 5 years was significantly higher in the CMT arm than in the chemotherapy-alone arm (95% versus 88%, P=0.004). At 12 years of follow-up, this finding remained stable, with FFP rates of 94% versus 86% (hazard ratio [HR] for disease progression, 3.23; 95% confidence interval [CI], 1.28–8.13; P=0.006). The major finding of this trial was that with a median follow-up of 11.3 years, those who received EFRT had a worse OS related to the development of SMN, negating any benefit of lymphoma control from the antiquated RT as performed in this trial. Specifically, at 12 years, the rate of OS was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal RT (HR for death with ABVD alone, 0.50; 95% CI, 0.25–0.99; P=0.04); the rates of FFP were 87% and 92% in the 2 groups, respectively (HR for disease progression, 1.91; 95% CI, 0.99–3.69; P=0.05); and the rates of EFS were 85% and 80%, respectively (HR for event, 0.88; 95% CI, 0.54–1.43; P=0.60).This finding is not surprising since a large body of evidence for EFRT alone for early-stage Hodgkin lymphoma is associated with an increasing risk for late complications and associated mortality, especially related to SMN. Lost on many commentators of this trial is the fact that use of reduced radiation doses and fields, particularly in adult patients, has a significantly lower risk of late complications [40,41]. Regardless, for this NCIC HD.6 trial, there was a nonsignificant trend toward a lower rate of OS among patients with an unfavorable risk profile than among those with a favorable risk profile (12-year estimates, 92% versus 98%; HR for death with an unfavorable risk profile, 4.96; 95% CI, 0.64–38.40; P=0.09).

Related to the risk of complications from RT, there has been much debate as to the efficacy of chemotherapy alone for early-stage Hodgkin lymphoma. A meta-analysis that looked at chemotherapy with or without adjuvant

RT included 1245 patients from 5 randomized trials after an exhaustive literature review, confining the analysis to adult phase III trials of 6 cycles of the same chemotherapy in both treatment arms, randomized after a good response to chemotherapy, and at least 80% of patients with stage I–II disease [42]. These included the Mexico B2H031 trial [43], the Cancer and Leukemia Group B 7751 trial [44], the EORTC-GELA H9-F trial [45], the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) 9-H-77 trial [46], and the Memorial Sloan Kettering Cancer Center (MSKCC) 90-44 trial [47]. Thus, this meta-analysis did not primarily include the above-mentioned NCIC HD.6 trial [39,48]; the Mumbai, India (Tata Hospital) trial [49]; 2 pediatric trials (pediatric Children's Cancer Group (CCG) 5942 trial [50,51] and Pediatric Oncology Group 8625 trial [52]); an Italian trial testing consolidative RT for bulky mediastinal adenopathy [53]; or a small MOPP-era trial [54]. Preliminary results of the NCIC HD.6 trial, as well as these other aforementioned trials, were part of a sensitivity analysis that did not change the meta-analysis results. Although this meta-analysis is open to some methodological criticism, the salient finding was that IFRT added to chemotherapy (6 cycles, mostly anthracycline containing) significantly improved disease-free survival (DFS), as well as OS. The HR for survival of CMT over chemotherapy alone was 0.4 (95% CI, 0.27–0.59). Except for the EORTC-GELA H9-F trial, all trials included in the meta-analysis had enrolled varying proportions of unfavorable-risk, early-stage Hodgkin patients. Several of these trials testing the addition of IFRT to chemotherapy are worth highlighting.

The results of the EORTC-GELA H9-F trial [45] have only been presented in abstract form at meetings in 2005. Although this trial is not directly germane to a review of unfavorable Hodgkin lymphoma, it does highlight that the deletion of adjuvant RT in early-stage patients can be deleterious in terms of relapse risk. Moreover, the H9-F trial showed that in the absence of risk factors, the radiation dose can be reduced to 20 Gy, which will hopefully translate into a lower risk for late effects related to radiation. This trial enrolled 783 patients, of which 619 patients (79%) achieved a complete response after 6 cycles of EBVP (epirubicin, bleomycin, vinblastine, and prednisone), followed by a randomized comparison of 36-Gy IFRT versus 20-Gy IFRT versus no RT. The 4-year EFS rates for 36 Gy, 20 Gy, and 0 Gy were 87%, 84%, and 70%, respectively ($P<0.001$). The chemotherapy-alone arm had to be closed early due to clinical trial stopping rules. Four-year OS, however, was equivalent in all 3 groups at 98%.

The Mexican B2H031 trial [43] enrolled 307 patients with early-stage Hodgkin lymphoma with bulky disease, mainly large mediastinal masses. Patients were randomized to EFRT alone, to ABVD × 6 cycles, or to ABVD × 6 with EFRT sandwiched in the midst of chemotherapy. Patients mostly received mantle fields (supradiaphragmatic regions) to 35 Gy when RT was given. With a median follow-up of 11.4 months, DFS and OS were best in the CMT group. The 12-year DFS rates for RT alone, chemotherapy alone, and CMT were 42%, 48%, and 76%, respectively ($P<0.01$). Correspondingly, 12-year OS rates were 53%, 59%, and 88%, respectively, tending to favor CMT. This trial is not comparable to the NCIC-ECOG trial, which did not include patients with bulky disease.

The MSKCC 90-44 [47] trial has been interpreted by some as a negative trial for adjuvant RT in early-stage disease. In fact, it is an underpowered trial showing trends in favor of CMT in terms of DFS. One hundred fifty-two patients with clinical stages IA, IB, IIA, IIB, and IIIA without bulky disease were prospectively randomized to ABVD × 6 alone versus ABVD × 6 followed by 36 Gy to modified extended fields in most patients, although a minority were treated to involved fields. Roughly 30%–50% of patients had unfavorable risk factors, including 13% who had stage IIIA disease. Of 76 patients randomized to receive RT, 65 actually received it, and 11 did not (4 progressed, 1 had bleomycin toxicity, 6 refused). At 5 years, the FFP and OS for ABVD + RT versus ABVD alone were 86% versus 81% ($P=0.61$) and 97% versus 90% ($P=0.08$), respectively (log-rank). The 95% CIs for FFP and OS differences at 5 years were −8% to 18% and −4% to 12%, respectively.

The GATLA conducted a trial [46] with 277 stage I–II favorable- or unfavorable-prognosis Hodgkin lymphoma patients who were randomized to receive either 6 cycles of CVPP (cyclophosphamide, vinblastine, procarbazine, and prednisone) or CVPP followed by IFRT to 30 Gy. Overall, the DFS rate was significantly higher in the CMT arm than in the chemotherapy-alone arm (7-year rates, 71% versus 62%, $P=0.01$). Among the unfavorable-prognosis patients, the DFS rate (75% versus 34%, $P=0.001$) and the OS rate (84% versus 66%) were higher in the CMT arm than in the chemotherapy-alone arm. The use of the CVPP regimen and the inclusion of pediatric patients (45% of patients) limit the generalizability of this trial. Moreover, the outcomes in this trial were poorer compared with other studies with similar patients.

In a trial from the Tata Memorial Hospital, India, 179 patients who achieved a complete response to 6 cycles of ABVD were randomized to receive either IFRT or no RT [49]. Mean radiation dose was 30 Gy, with a protocol

specifying a 10-Gy boost to sites of bulky disease. In this trial, 55% of patients had stage I–II disease, 15% had bulky disease, and 54% had B symptoms; hence, a large proportion had early-stage unfavorable disease. The OS rate was significantly higher in the RT arm than in the no-RT arm (8-year rates, 100% versus 89%; P=0.002). The EFS rate was also significantly higher in the RT arm (8-year rates, 88% versus 76%; P=0.01). However, the high proportions of pediatric, stage III–IV, and mixed-cellularity patients in this trial limit the generalizability of this trial as well.

The pediatric CCG 5942 trial [50] has been recently updated and randomized all stages of pediatric Hodgkin patients to chemotherapy alone versus CMT. Four hundred ninety-eight patients achieving an initial complete response to chemotherapy were randomly assigned to receive IFRT or no further therapy. Ten-year EFS and OS rates were 91.2% versus 82.9% (P=0.004) and 97.1% and 95.9% (P=0.50) for IFRT and no further therapy, respectively. Bulky disease, B symptoms, and nodular sclerosis histology were risk factors for inferior EFS. The subgroup corresponding to unfavorable early-stage patients numbered 225 patients and included those who had at least 1 adverse feature including hilar adenopathy, involvement of 4 or more nodal regions, a mediastinal tumor with a diameter greater than or equal to one-third of the chest diameter, and node or nodal aggregate with a diameter >10 cm. Those patients received COPP/ABV chemotherapy for 6 cycles, plus or minus IFRT to 21 Gy in 12 fractions. For this subgroup, the difference in 10-year EFS was 84% versus 78% in favor of IFRT; however, this difference did not reach statistical significance.

Two trials addressed the optimal number of cycles of chemotherapy in patients with unfavorable early-stage Hodgkin lymphoma. In the EORTC-H8U trial, patients were randomized to 6 cycles of MOPP/ABV followed by IFRT, 4 cycles of MOPP/ABV followed by IFRT, or 4 cycles of MOPP/ABV followed by EFRT [32]. At a median follow-up of 92 months, there was no significant difference in 5-year EFS rates among the 3 treatment groups (84%, 88%, and 87%, respectively). The OS rates at 10 years were also not significantly different (88%, 85%, and 84%, respectively). In the EORTC-H9-U trial described above, there was also no significant difference between 4 versus 6 cycles of ABVD at a median follow-up of 57 months [33].

Several phase III trials (other than E2496) have compared different chemotherapy regimens followed by standard IFRT. The EORTC H7 trial explored the use of a less intensive regimen, EBVP, in unfavorable-prognosis, early-stage patients and found that it was significantly inferior to MOPP/ABV (10-year EFS rate, 68% versus 88%; P<0.0001) [21]. Other trials examined whether unfavorable-prognosis patients can benefit from the intensified BEACOPP regimen. Both the EORTC H9-U and the GHSG HD11 studies compared 4–6 cycles of ABVD with 4 cycles of BEACOPP as baseline, followed by IFRT to 20–30 Gy. No significant differences in 4-year EFS rate or OS rate were observed between BEACOPP and ABVD in the EORTC H9-U trial [33]. Recently updated results of the GHSG HD11 showed a significantly higher 5-year FFTF in the BEACOPP arm over the ABVD arm, if followed by 20 Gy of IFRT (5-year FFTF difference, 5.7%; 95% CI, 0.1%–11.3%) [22]. However, there was no significant difference between BEACOPP and ABVD with 30 Gy of IFRT. The GHSG HD14 trial tested increasing dose intensity using dose-escalated BEACOPP (BEACOPPesc) in this population. This trial randomized patients with unfavorable CS I–II disease to 4 cycles of ABVD versus 2 cycles of BEACOPPesc and 2 cycles of ABVD ("2 + 2"), followed by IFRT to 30 Gy. There was a significantly superior 5-year FFTF in the BEACOPPesc-containing 2 + 2 arm, with a difference of 7.2% (95% CI, 3.8%–10.5%; 94.8% versus 87.7%), but no differences in OS [55]. A subgroup analysis suggested that a bulky mediastinal mass and an elevated ESR continued to predict a higher relapse rate. The use of BEACOPPesc was associated with higher acute toxicity, particularly with myelosuppression and a related 0.52% acute death rate; the ABVD × 4 arm had no acute deaths. A higher rate of infertility with BEACOPP might also be expected, but in the context of this H14 trial with a substitution of 2 cycles of BEACOPPesc for 2 cycles of ABVD, observed rates of motherhood in female premenopausal patients were better in the 2 + 2 arm [56]. Biochemical assays in follow-up, however, did show lower levels of anti-Müllerian hormone and follicle-stimulating hormone in the 2 + 2 arm, suggesting a lower ovarian reserve and potential for earlier menopause in those women getting BEACOPP. However, an intriguing observation was that the use of gonadotropin-releasing hormone during chemotherapy significantly augmented the probability of subsequent pregnancies, regardless of what chemotherapy regimen was used. Longer follow-up will be required to evaluate toxicity rates, but at a median follow-up of 43 months, rates of secondary malignancy were similar (2.0% versus 2.2%). The GHSG has adopted BEACOPPesc × 2 + ABVD × 2 followed by IFRT to 30 Gy as their current standard for unfavorable early-stage Hodgkin lymphoma (see Variant 1).

Involved-Site Radiation Therapy

In recent years, there has been growing interest in further limiting the radiation treatment volume to involved-node radiation therapy (INRT) [57]. The definition of INRT varies from group to group. In the EORTC/GELA H11 trial for early-stage, unfavorable-prognosis Hodgkin lymphoma (discussed below), INRT was adopted in both the standard and experimental arms. The GHSG is enrolling patients with unfavorable-prognosis, early-stage disease in a randomized trial (HD17) comparing IFRT versus INRT. Results of these trials, including details on patterns of failure, will clarify the role of INRT in early-stage patients. Recently, a new set of field designs, the ISRT, have been developed and endorsed by the steering committee of ILROG. Led by experienced radiation oncologists specializing in lymphoma who initially organized the standardization of IFRT fields in the 2-D era a decade ago [27], 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, 3-D and 4-D treatment planning with CT scanners, conformal treatment techniques, and the use of image guidance, to replace the antiquated IFRT that was based on 2-D treatment planning and bony anatomy. These treatment volumes 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 detailed description of the ISRT concept has been published and has been recommended in the 2013 National Comprehensive Cancer Network guidelines for Hodgkin lymphoma [28,58].

The appropriate radiation dose in patients with unfavorable-prognosis, early-stage disease after chemotherapy was addressed by the GHSG HD11 trial described above [22]. After 4 cycles of BEACOPP, a significant difference in 5-year FFTF between 20 Gy and 30 Gy was not observed. However, after 4 cycles of ABVD, an inferiority of the 20-Gy arm could not be excluded, with a 4.7% lower absolute difference in 5-year FFTF in the 20-Gy arm not reaching the 7% threshold margin in the trial design. This led to the conclusion that a reduction of radiation dose from 30 Gy to 20 Gy of IFRT in unfavorable-prognosis patients may be justified after BEACOPP but not clearly after ABVD when 4 cycles of chemotherapy are administered. At present, there is no reported subgroup analysis of patients from the GHSG HD11 or HD14 trials of bulky mediastinal adenopathy to compare to the results from the E2496. Consequently, there is a range of chemotherapy cycles and radiation doses that are deemed acceptable but may have significantly different late effects. Additional follow-up data will be required for further elucidation. In addition, retrospective data from Duke, Yale, and Tata Memorial Hospital in India suggest that after 4–6 cycles of anthracycline-based chemotherapy with a complete response at chemotherapy completion (emphasizing 6 cycles for bulky disease), radiation doses in the 20–25 Gy range may yield good results [10,59,60] (see Variant 2 and Variant 3).

Response-Based Treatment Paradigm

PET has emerged as a useful tool in the staging and follow-up of patients with Hodgkin lymphoma. Additionally, PET response of chemotherapy has been shown to be a powerful prognostic factor [9]. There is an increasing interest to see if response to chemotherapy by PET assessment will help select patients who may not benefit from RT. A recent randomized trial evaluated whether RT can be omitted in patients with bulky masses at diagnosis who show a complete response by PET following chemotherapy [53]. One hundred sixty patients who had a complete response to induction chemotherapy with 6 cycles of VEBEP (vinblastine, etoposide, bleomycin, epirubicin, and prednisone), but with a residual mass and a PET-negative scan, were randomized to undergo either observation or consolidative RT to 32 Gy in 20 fractions. The EFS rate was significantly lower in the observation arm than in the RT arm (86% versus 96%, P=0.03).

Whether an early response to chemotherapy as judged by PET imaging after the initial 2 cycles of chemotherapy might better distinguish which patients require RT is being tested in several clinical trials. The Children's Oncology Group has completed a large trial (COG AHOD0031) in "intermediate-risk" patients, defined as stage I–II with either bulk or extranodal involvement through stage IIIA–IVA without bulk, in which rapidly responding patients treated with ABVE-PC (adriamycin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone) were randomized to chemotherapy alone for total of 4 cycles versus the same chemotherapy with IFRT to 21 Gy in 14 fractions [11]. Results show a nonstatistical difference in 4-year DFS of 87.9% (95% CI, 83.7%–91.1%) for patients randomized to receive IFRT versus 84.3% (95% CI, 79.8%–87.9%) for those randomized to no IFRT (P=0.11).

The ongoing EORTC/GELA H10U trial also explored the use of PET response to identify patients with unfavorable-prognosis, early-stage disease in whom RT can be omitted. The standard arm of this trial consisted of 4 cycles of ABVD followed by INRT to 30 Gy, although patients on the experimental arm received 2 cycles of

ABVD followed by a PET scan. If the scan was negative, patients received 4 additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received 2 cycles of BEACOPPesc, followed by INRT to 30 Gy. Interim results published show an excess of relapses in the patients who had INRT omitted [61]. Stopping rules resulted in this experimental arm of this trial to be closed [62]. Thus, on this EORTC/GELA H10U trial, patients with a rapid early response are still getting INRT. Several other trials are testing the concept that early response assessed by PET scan will be a predictor of who can avoid RT if abnormal fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) uptake has completely resolved after cycle 2. Conversely if PET after cycle 2 is positive, augmentation of chemotherapy is being tested. Thus for the time being, in adults with early-stage Hodgkin lymphoma there is insufficient evidence to support the omission of RT based on PET response or early PET response; such an approach should be pursued in the context of a clinical trial (see Variant 4).

An international consensus panel has evaluated the growing evidence using PET/CT imaging to grade response to systemic therapy and now recommends the use of a visual analog score for interim and end-of-therapy assessments using the 5-point Deauville scale (see Table 1) [63,64]. This 5-point scale uses the FDG uptake of the mediastinal blood pool and the liver for comparison. A score of 1 or 2 (in midtherapy or end-of-therapy PET/CT) is considered to represent a complete response, and a score of 3 is considered to predict a favorable outcome. However, a score of 4 or 5 at the end of therapy is considered to be treatment failure; these patients should be considered for a biopsy to confirm the presence of residual disease before salvage therapy.

Table 1. Five-Point Deauville Scale

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than (eg, >2–3 times) liver and/or new lesions

X. New areas of uptake unlikely to be related to lymphoma

Management of Refractory Hodgkin Lymphoma

Recurrence or persistence of disease occurs in approximately 10%–15% of early-stage patients, although it is higher in advanced-stage patients, approaching 30%–40% [65,66]. Although precise data are difficult to find, perhaps a third of this category of poor-prognosis patients includes high-risk primary refractory disease. In the GHSG, 3807 patients with intermediate or advanced Hodgkin lymphoma enrolled in their various trials from 1988 to 1998. Of these, 239 patients (6.3%) were found to have primary refractory disease [67]. With the clinical adoption of PET/CT imaging to assess chemotherapy response, primary refractoriness may have a higher incidence and is currently defined either by progression at any time during chemotherapy or RT and up to 3 months after the end of treatment, and/or by persistence of a PET-positive residual mass. Thus, a Deauville score of 4 or 5 at the completion of chemotherapy defines refractory disease, but only if correlated with an enlarged mass or node on CT scanning (to mitigate the problem of false-positive scans) [68] (see Variant 5).

Data on the optimal management of this situation are complex, particularly as the literature has lumped refractory lymphoma with relapsed disease. Some studies of hematopoietic stem cell transplantation even combine Hodgkin and non-Hodgkin patients. There are no good comparisons of different salvage regimens for refractory Hodgkin lymphoma, such that individual judgment is required. Some dogma exists that chemotherapy failures cannot be managed with RT [69]. However, limited sites of persistent disease can anecdotally be controlled with RT to 30–45 Gy. In the pre-PET era within the GHSG experience, a subset of 47 patients with primary refractory Hodgkin lymphoma with limited sites of disease were able to be managed with salvage RT with curative intent using a broad mix of radiation treatment volumes from total nodal to involved fields [67]. With a median radiation dose of 40 Gy, the complete response rate was 62%, although the 4-year actuarial freedom from second relapse rate was a disappointing 22%. Nevertheless, a renewed interest and basis for RT to manage limited refractory disease now derives from the GHSG HD15 trial for advanced disease. In the context of aggressive backbone systemic therapy with BEACOPPesc × 6, consolidative RT to sites of persistent PET activity for 30 Gy contributed to an excellent DFS. With 11% of enrolled patients requiring consolidative RT, the 5-year FFTF was 89.4% [70]. How this might translate to earlier-stage patients receiving less intensive systemic therapy needs further study.

Alternatively, there is extensive experience with second-line systemic therapy for refractory disease using platinum-containing regimens such as DHAP (dexamethasone, high-dose cytarabine [Ara-C], and cisplatin) or ICE (ifosfamide, carboplatin, and etoposide). These and other second-line combinations have not been compared

directly in a randomized trial. Choice is based on side effects, experience, and expert consensus. Remission rates are in the 30% to 40% range, as reviewed by Kuruvilla et al [66]. After adequate cytoreduction, autologous stem cell harvesting can be performed to facilitate high-dose chemotherapy and autologous hematopoietic stem cell transplantation. BEAM (carmustine [BCNU], etoposide, cytarabine, and melphalan) and CBV (cyclophosphamide, carmustine, and etoposide) are common regimens prior to an autotransplant. Patients who are able to undergo this therapeutic sequence have 8- to 10-year OS rates of 21% to 27%, with FFTF on the order of 16% [67,71]. However, if patients are PET negative going into an autotransplant, results are improved. One study showed that progression-free survival of the PET-negative group of lymphoma patients after conventional-dose chemotherapy followed by high-dose chemotherapy salvage was 72% versus 23% for the PET-positive group [72]. Primary refractory disease has been generally categorized as high risk relative to patients relapsing >12 months after first remission; as such, some investigators have concluded that such patients may be best treated with a tandem transplant [68,73]. A multicenter European transplant trial for Hodgkin lymphoma, for instance, showed that poor-risk patients, including those with primary refractory disease, had a 5-year freedom from second failure and OS of 46% and 57%, respectively, using a tandem autotransplant [74]. The first transplant used BEAM or CBV, and the second transplant was either TBI (total body irradiation) and melphalan or busulfan-melphalan, depending on prior RT exposures. TBI-based treatment was favored when feasible and used 12 Gy in 6 fractions over 3 days. Concerns regarding the toxicity of TBI have led some investigators to incorporate total or subtotal lymphoid irradiation into some autotransplant regimens instead of TBI, especially when there is a nodal pattern of failure for a given patient [75]. Needless to say, for early-stage patients with refractory disease this form of tandem transplant may seem to be excessive therapy as second-line treatment by some experts.

The recent development of new agents such as brentuximab vedotin (an anti-CD30 antibody conjugated with a microtubule toxin) in phase II trials shows durably good response rates over historical experience with third-line cytotoxic chemotherapy in patients recurring after an autotransplant [76]. Brentuximab is now under investigation as first- and second-line therapy in combination with chemotherapy (albeit with the avoidance of bleomycin to avoid undue risk for pneumonitis) [77].

For patients who complete salvage chemotherapy with a good response, which may often include high-dose chemotherapy with autotransplantation, there may be consideration of consolidation RT to sites of resistant disease. Several retrospective studies suggest an improvement in progression-free survival from such RT. A group at Emory performed a matched case-control study and showed a significant improvement in DFS with RT in this setting, but not OS [78]. Even so, sites of initial bulky disease that remain resistant or sluggish to respond to chemotherapy were associated with sites of additional recurrence despite application of consolidation RT. Investigators from Chicago reported that IFRT reduced local relapse rates in sites of prior Hodgkin involvement from 43% to 26%, thus improving 5-year local control rates in all sites, nodal sites, and sites that were resistant to high-dose chemotherapy [79]. Another group at Stanford reported only 4 local failures out of 67 irradiated sites [80]. Moderate-dose RT as part of salvage therapy is commonly practiced, although radiation treatment volumes need to be highly individualized to balance toxicity and disease-control concerns. Whether all sites of initial involvement at diagnosis need to be irradiated in this scenario is not well understood or worked out. Too small a treatment volume may defeat the benefit to RT [81]. Timing of consolidative RT is controversial. Some concern exists for chest RT prior to autotransplant having an undue risk of pneumonitis, as initially reported by a Toronto group [82]. Other investigators, such as at Memorial Sloan Kettering Cancer Center, dispute this and prefer to give RT prior to high-dose therapy and transplant [83]. The recommended radiation dose is at least 30 Gy with a potential boost of 6–10 Gy, particularly for sites of disease not in metabolic complete response on PET imaging prior to transplant [68].

Summary of Recommendations

Core Concept:

- The standard of care for unfavorable stage I–II Hodgkin lymphoma is CMT, consisting of chemotherapy followed by low dose RT (generally 30 Gy, but certain circumstances justify lower doses).

Chemotherapy:

- The most widely accepted chemotherapy regimen is ABVD.
- ABVD × 4–6, BEACOPP × 2 + ABVD × 2 (“2 + 2”), Stanford V, or ABVE-PC (pediatric regimen) are well documented, with variable radiation dose prescriptions and volumes based on specific regimens and responses to chemotherapy.

Radiation Dose, Volume, and Techniques:

- A range of radiation dose from 20–30 Gy is acceptable when there is a good response to initial chemotherapy. For patients meeting multiple criteria for unfavorable risk and receiving 4 cycles of chemotherapy, such as ABVD or BEACOPP × 2 + ABVD × 2, 30 Gy is strongly recommended. Some situations may justify doses <30 Gy, particularly when there is a strong rationale to reduce toxicity attributable to RT. This can be considered when there is a good response to 6 cycles of ABVD or similar chemotherapy, although this point requires further study. Patients who are young adults following pediatric-styled chemotherapy regimens can receive 20–25 Gy. Moreover, patients who have nonbulky disease and 3 sites of involvement may be considered either favorable or unfavorable under different criteria and may well have an improved therapeutic ratio with doses below 30 Gy.
- A dose per fraction in the range of 1.5–2.0 Gy is acceptable.
- Specific combined modality regimens have been well studied. For instance, the GHSG in particular has a well-described set of definitions for favorable versus unfavorable early-stage disease based on favorable patients having none of the following factors: >2 sites of disease, ESR ≥50 mm/h without B symptoms, ESR ≥30 mm/h in the presence of B symptoms, no bulky mediastinal disease, and no extranodal disease. In unfavorable patients with at least 1 risk factor, 4 cycles of chemotherapy and 30 Gy in 15–17 fractions have optimal results. However, other chemotherapy regimens of differing intensity and number of cycles may allow for lower radiation doses to reduce late effects.
- Higher radiation doses >30 Gy should be reserved for patients who have poor response to chemotherapy. The concept of using 36 Gy for bulky-disease consolidation in all patients is no longer reasonable as the risks for secondary malignancies and cardiovascular disease are well described.
- Anterior-posterior fields are often simple and efficacious. However, more conformal techniques using multiple fields, IMRT, volumetric modulated arc therapy, and proton RT may be useful to limit toxicities. Specific newer radiation techniques are beyond the scope of this review, but suffice it to say that 4-D treatment planning and deep inspiration breath-hold techniques are under investigation. Inherent with these techniques, the modern concept of ISRT is recommended [28]; margins of RT are expected to be smaller as part of volumetric 3-D treatment planning rather than the historic anatomic field definitions of IFRT.
- Differential dosing or a shrinking field technique to account for a variable burden of disease based on bulk at presentation or on response to chemotherapy is a reasonable method to balance toxicity and efficacy.

Chemotherapy Alone:

- Use of chemotherapy alone, such as 6 cycles of ABVD, is an acceptable option in selected patients, particularly in those without bulky disease at diagnosis, as this reduces the risk of late effects, especially when higher-dose RT is applied as adjuvant therapy. However, lower-dose radiation in the 21–25 Gy range is acceptable after ABVD × 6 when late toxicity concerns are deemed to be minimal, as low-dose RT may help prevent a relapse.
- If the decision to use ABVD × 6 alone is based on early response to chemotherapy, caution is advised until the results of the EORTC/GELA H10U and other trials are mature and published.
- The pediatric regimen ABVE-PC can be used in pediatric, adolescent, and young adult patients without RT when there is a rapid early response after 2 cycles, especially if defined by a negative PET scan and if at the end of chemotherapy there is a complete response by CT criteria.

Summary of Evidence

Of the 83 references cited in the *ACR Appropriateness Criteria® Hodgkin Lymphoma-Unfavorable Clinical Stage I and II* document, 73 are categorized as therapeutic references including 33 well designed studies and 23 good quality studies. Additionally, 10 references are categorized as diagnostic references including 5 well designed studies, 1 good quality study, and 2 quality studies that may have design limitations. There are 19 references that may not be useful as primary evidence.

The 83 references cited in the *ACR Appropriateness Criteria® Hodgkin Lymphoma-Unfavorable Clinical Stage I and II* document were published from 1950-2015.

While there are references that report on studies with design limitations, 62 well designed or good quality study provides good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Table 2: Clinical Risk Factors Used by Cooperative Groups to Categorize Favorable versus Unfavorable Early-Stage Hodgkin Lymphoma

	GHSG	EORTC/GELA	NCIC/ECOG	Stanford (Adult)
Risk factors	(a) Large mediastinal mass (b) Extranodal disease (c) ESR ≥50 without B symptoms or ≥30 with B symptoms (d) ≥3 nodal areas	(a) Large mediastinal mass (b) Age ≥50 years (c) ESR ≥50 without B symptoms or ≥30 with B symptoms (d) ≥4 nodal areas	(a) Histology other than lymphocyte-predominant or nodular sclerosing (b) Age ≥40 years (c) ESR ≥50 (d) ≥4 nodal areas	(a) B symptoms (b) Large mediastinal mass
Favorable early stage	CS I–II without risk factors	CS I–II (supradiaphragmatic) without risk factors	CS I–II without risk factors	CS I–II without risk factors
Unfavorable early stage	CS IA, IB, or IIA with ≥1 risk factor CS IIB with (c) or (d) but without (a) and (b)	CS I–II (supradiaphragmatic) with ≥1 risk factor	CS I–II with ≥1 risk factor	CS I–II with ≥1 risk factor
Advanced stage (treated as if stage III–IV)	CS IIB with (a) or (b)	Not applicable	CS I–II with bulky disease (large mediastinal mass or peripheral site >10 cm)	Not applicable

Clinical Condition: **Hodgkin Lymphoma — Unfavorable Clinical Stage I and II**

Variant 1: **45-year-old man with stage IIA nodular sclerosis Hodgkin lymphoma (NSHL); supradiaphragmatic (involving bilateral neck and mediastinum), no bulky disease; ESR, 55.**

Treatment	Rating	Comments
Overall plan		
Combined modality therapy	9	
Chemotherapy alone	6	Chemotherapy alone might be considered if there is high cardiovascular risk or contraindications to RT.
Radiation therapy alone	2	
Treatment options		
ABVD × 2, then RT	3	Two cycles are inadequate in an unfavorable patient, as is the case here.
ABVD × 4, then RT	8	
ABVD × 6, then RT	4	Six cycles are probably too much but might be a consideration if there was a partial response by PET criteria after 4 cycles.
ABVD × 6, no RT	6	
Stanford V over 8 weeks, then RT	7	Stanford V is a well-described program with published results documenting its use in unfavorable patients.
Stanford V over 8 weeks, no RT	3	
BEACOPP × 2, ABVD × 2, then RT	6	This procedure is not widely used in the United States but is commonly used in Europe because of concerns of toxicity. The risk of ovarian failure is mitigated by the use of luteinizing hormone–releasing hormone agonists.
MOPP × 6, then RT	2	
ABVD/MOPP × 4-6, then RT	3	
ABVE-PC × 4, then RT only if slow or incomplete response	3	There is no experience with this pediatric regimen in adults.

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

Clinical Condition: **Hodgkin Lymphoma — Unfavorable Clinical Stage I and II**

Variant 2: **26-year-old man with stage IB NSHL; supradiaphragmatic, bulky disease 10 cm in the neck; fevers >38ºC and drenching night sweats; complete resolution of FDG uptake on PET scan after 2 cycles (Deauville score 2); partial response by CT (>50% reduction) after 6 cycles of ABVD. Deauville score 2 after repeat PET scan at chemotherapy completion.**

Treatment	Rating	Comments
Radiation field		
IFRT to neck	6	There is overlap between IFRT and ISRT. The precise definition of ISRT is in evolution. IFRT is not wrong, but ISRT is preferred.
ISRT to neck	8	
Mantle	2	
Subtotal nodal irradiation	1	
Radiation dose		
20 to <30 Gy	4	There are limited data to use lower doses from Duke, India, and pediatric experiences after 6 cycles of chemotherapy. In addition, GHSG HD11 did not strictly show that 20 Gy was inferior to 30 Gy.
30–32 Gy	8	
>32–36 Gy	5	
>36–40 Gy	3	
>40 Gy	2	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Hodgkin Lymphoma — Unfavorable Clinical Stage I and II**

Variant 3: **26-year-old man, CS IIA NSHL with bulky mediastinal mass (11 cm) and nonbulky bilateral neck disease; complete resolution of FDG uptake on PET scan after 2 cycles (Deauville score 2); partial response by CT (>50% reduction) after 4 cycles of ABVD.**

Treatment	Rating	Comments
Additional chemotherapy	6	Bulky mediastinal adenopathy has been a criterion for advanced-stage disease in some studies in which 6 cycles of ABVD have been used and is considered more of a standard by some experts. The GHSG HD14 finding that more intensive chemotherapy is better is suggestive that more cycles of ABVD chemotherapy may be desirable as an alternative to the use of BEACOPP × 2 + ABVD × 2.
Radiation field (after chemotherapy)		
IFRT to mediastinum and bilateral neck	6	
ISRT to mediastinum and bilateral neck	9	
Mantle	2	
Subtotal nodal irradiation	1	
Radiation dose (after chemotherapy)		
20 to <30 Gy	3	
30–32 Gy	8	
>32–36 Gy	6	
>36–40 Gy	4	
20–21 Gy, then boost mediastinum dose to 30–32 Gy	5	Shrinking fields or differential dosing can be a good strategy to limit dose to the heart or lungs, especially if 6 cycles of ABVD are administered. Some limited data suggest bulky disease may be less well controlled with a lower dose, justifying this approach to improve the therapeutic ratio. Moreover, pediatric data suggest that using lower radiation doses appears to be effective in younger patients.
20–21 Gy, then boost mediastinum dose to 36–40 Gy	3	

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

Clinical Condition: **Hodgkin Lymphoma — Unfavorable Clinical Stage I and II**

Variant 4: **26-year-old woman, CS IIB NSHL with bulky mediastinal (13 cm) and left supraclavicular disease; >75% reduction of mass by CT (3 cm residual after chemotherapy) and negative PET after both 2 and 6 cycles of ABVD chemotherapy (both Deauville scores 2).**

Treatment	Rating	Comments
Radiation dose		
No further RT	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Despite evidence that omission of RT for bulky Hodgkin lymphoma is detrimental to disease control, there was concern that the risk of side effects such as secondary breast cancers and cardiopulmonary problems might outweigh the benefits.
If RT given, radiation dose		
20 to <30 Gy	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. There was no agreement that doses <30 Gy may be appropriate after 6 cycles of ABVD in this instance.
30–32 Gy	8	
>32–36 Gy	5	
>36–40 Gy	3	
Boost mediastinum dose to 36 Gy	4	This dose has been used in some recent trials but is generally felt to be too high.
Boost mediastinum dose to 40 Gy	3	
Mediastinal volume		
Treat postchemotherapy volume laterally	8	
Treat prechemotherapy volume laterally	3	
Inferior margin 1–2 cm below prechemotherapy volume	7	
Treat prechemotherapy volume to 15–20 Gy, then shrink	4	
Inferior margin 1–2 cm below postchemotherapy volume	4	
Inferior margin 5 cm below postchemotherapy volume	3	
Inferior margin approximately at diaphragm	3	
Inferior margin 5 cm below prechemotherapy volume	3	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Hodgkin Lymphoma — Unfavorable Clinical Stage I and II**

Variant 5: **26-year-old woman, CS IIB NSHL with bulky mediastinal (13 cm) and left supraclavicular disease treated with ABVD × 6; >75% reduction of mass by CT after 2 cycles (3 cm residual mass after chemotherapy) with good PET response (Deauville score 3); but after 6 cycles of ABVD chemotherapy residual mass is stable on CT but PET response looks worse (Deauville score 4). A needle biopsy of mediastinal mass shows CD30+ Reed-Sternberg cells.**

Treatment	Rating	Comments
RT alone	4	
If RT given alone, radiation dose should be:		
30–32 Gy	3	
>32–36 Gy	4	
>36–40 Gy	5	
30–32 Gy, boost mediastinum to 36 Gy	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
30–32 Gy, boost mediastinum to 40 Gy	7	
If RT given alone, radiation volume should be:		
Mediastinal site only	5	
Left neck and mediastinum	7	
Mantle field	3	
Extended field (subtotal nodal or total nodal)	2	
Salvage chemotherapy alone	4	
Salvage chemotherapy followed by consolidative RT	6	
If consolidative RT given, radiation dose should be:		
30–32 Gy	5	
>32–36 Gy	6	
>36–40 Gy	6	
30–32 Gy, boost mediastinum to 36 Gy	7	
30–32 Gy, boost mediastinum to 40 Gy	6	
If consolidative RT given, radiation volume should be:		
Mediastinal site only	5	
Left neck and mediastinum	8	
Mantle field	4	
Extended field (subtotal nodal or total nodal)	2	
Salvage chemotherapy with auto–stem cell transplantation (auto-SCT)	6	
Salvage chemotherapy with auto-SCT, followed by consolidative RT	8	

If consolidative RT given, radiation dose should be: 30–32 Gy	6	
>32–36 Gy	6	
>36–40 Gy	5	
30–32 Gy, boost mediastinum to 36 Gy	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
30–32 Gy, boost mediastinum to 40 Gy	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
If consolidative RT given, radiation volume should be: Mediastinal site only	5	This treatment may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Left neck and mediastinum	8	
Mantle field	3	
Extended field (subtotal nodal or total nodal)	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		