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HODGKIN LYMPHOMA — FAVORABLE PROGNOSIS STAGE I AND II

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Summary of Literature Review

Introduction/Background

This topic addresses the treatment of newly diagnosed patients with favorable-prognosis stage I and II Hodgkin lymphoma (HL). For most cases of favorable-prognosis stage I and II HL, combined-modality therapy (chemotherapy followed by involved-site radiation therapy [ISRT]) constitutes the current standard of care. Increasing information about the late effects of treatment has led to attempts to decrease toxicity by using less chemotherapy (decreased duration and/or intensity or different agents) and less radiation therapy (RT) (reduced volume and/or dose) while maintaining excellent efficacy.

Prognostic Factors

The definition of favorable-prognosis stage I and II HL varies somewhat among major cooperative groups, as outlined in Table 1. All 3 cooperative groups exclude patients with large mediastinal masses; however, the definitions vary slightly. The German Hodgkin Study Group (GHSG) and National Comprehensive Cancer Network (NCCN) divide the maximum width of the mass on an upright posteroanterior chest radiograph by the maximum intrathoracic diameter to determine the mediastinal mass ratio (MMR). The European Organisation for Research and Treatment of Cancer (EORTC) uses the intrathoracic diameter at the T5-6 vertebral body level as the denominator to determine the mediastinal tumor ratio (MTR). The NCCN guidelines also define nonmediastinal bulk as disease ≥10 cm on an axial computed tomography (CT) scan [1]. All 3 groups consider the erythrocyte sedimentation rate (ESR) value and systemic symptoms, but defining criteria differ. Both the GHSG and the EORTC define favorable disease using an ESR of <50 mm/h in the absence of "B" symptoms (significant unexplained fever, night sweats, or unexplained weight loss exceeding 10% of body weight during the previous 6 months) and an ESR of <30 mm/h in the presence of B symptoms. The NCCN definition sets the ESR limit at 50 for all and excludes patients with B symptoms. Regarding the number of involved sites, the groups differ in that the GHSG criteria allow up to 2 sites of involvement and the EORTC and NCCN criteria allow for up to 3 sites. In addition, the GHSG criteria exclude patients with extranodal disease, the EORTC has an age requirement (age ≤50 years), and the NCCN further excludes patients with bulky disease >10 cm [1-3]. In interpreting trial results, it is important to pay attention to the risk group definition, as the results are applicable only to patients who fit the strict and specific inclusion criteria.

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Table 1: Criteria for Favorable-Prognosis Hodgkin Lymphoma

Risk Factor	EORTC	GHSG	NCCN
Mediastinal mass	MTR <0.35	MMR <0.33	MMR <0.33
ESR and B symptoms	ESR <50 mm/h if A; ESR <30 mm/h if B	ESR <50 mm/h if A; ESR <30 mm/h if B	ESR <50 mm/h and no B symptoms
# Nodal sites	≤3 sites of involvement	≤2 sites of involvement	≤3 sites of involvement
Extranodal involvement	—	Not permitted	—
Age	<50 y	—	—
Bulk	—	—	≤10 cm

Historic Trials That Established Combined-Modality Therapy as Standard of Care

Large, single-institutional studies of patients treated in the 1960s and 1970s demonstrated >80% actuarial 10- to 15-year freedom from relapse and <10% mortality rates from HL following mantle and para-aortic irradiation for pathologically staged IA-IIA patients [4-6]. Increasing concern for the long-term consequences of treatment [7-15] prompted many investigators to evaluate new approaches for early-stage HL. As outlined below, this ultimately established a combined-modality approach using involved-field radiation therapy (IFRT) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as the standard of care, with the Stanford V regimen (nitrogen mustard, doxorubicin, vincristine, vinblastine, etoposide, bleomycin, prednisone, and radiation) as an acceptable alternative.

In the GHSG HD7 trial, patients with early-stage favorable HL were randomized to receive either extended-field radiation therapy (EFRT) or 2 cycles of ABVD followed by EFRT. Patients in the combined-modality arm had a significantly higher rate of freedom from treatment failure than those in the EFRT-alone arm (7-year rates, 88% versus 67%, $P<0.0001$). There was no significant difference in overall survival (OS) between the 2 arms (7-year rates, 94% versus 92%, $P=0.43$) [16]. The Southwest Oncology Group and Cancer and Leukemia Group B conducted a similar study and found that the combined-modality arm had a significantly higher failure-free survival rate than patients in the subtotal lymphoid irradiation arm (3-year rate, 94% versus 81%, $P<0.001$) [17]. These 2 trials showed that the addition of chemotherapy improves early-disease-control outcomes in patients treated with EFRT or subtotal lymphoid RT.

Other trials also tested the use of combined-modality therapy versus radiation alone. For example, EORTC H7 randomized early-stage favorable patients to receive either subtotal nodal irradiation alone (36–40 Gy) or 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) followed by IFRT (36–40 Gy). Patients in the combined-modality arm had a significantly higher rate of event-free survival compared to the RT-alone arm (10-year rates, 88% versus 78%, $P=0.01$). Again, there was no significant difference in OS between the 2 arms (10-year rates, 92% versus 92%, $P=0.79$). This trial demonstrated that the previous standard of EFRT alone could be replaced by combined-modality therapy with IFRT in favorable-prognosis stage I or II HL patients, resulting in improved event-free survival and similar OS [18]. In a subsequent trial, EORTC H8F, 543 patients with supradiaphragmatic stage I or II HL and favorable prognostic features were randomized to receive either subtotal nodal irradiation or 3 cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) combined with doxorubicin, bleomycin, and vinblastine (ABV) followed by IFRT [19]. Patients in the combined-modality arm had a significantly higher event-free survival rate than did patients in the subtotal nodal irradiation arm (98% versus 74%, $P<0.001$).

Few randomized trials have compared different chemotherapy regimens in combination with RT for the treatment of patients with favorable-prognosis early-stage HL. The ABVD regimen has been used most commonly, based in large part upon the extrapolation of trials that compared ABVD with other regimens in patients with more advanced HL. Specifically, ABVD has demonstrated superior efficacy and less toxicity when compared with MOPP in patients with both unfavorable-prognosis early-stage and advanced-stage HL [20,21].

The Stanford V regimen is a highly effective and well-tolerated alternative to ABVD. It was initially developed for patients with locally extensive and advanced HL [22]. However, an abbreviated 8-week regimen followed by 30-Gy IFRT was studied in the phase II Stanford G4 trial of early-stage IA/IIA nonbulky HL patients. The

therapy was well tolerated and at a median follow-up of 10 years the freedom from progression and OS rates were 94% and 94%, respectively [23].

As noted above, in most of the modern trials combined-modality therapy has resulted in higher rates of freedom from recurrence but no difference in OS. Given the effectiveness of salvage with chemotherapy after failure of RT, this lack of apparent survival advantage may be due in large part to the relatively short follow-up of those studies. Long-term follow-up of the EORTC H8F trial does demonstrate that although patients in both arms had similar response rates and cumulative risk for second cancers, patients who received combined-modality therapy had a significant 10-year OS benefit when compared with those who received RT alone (10-year rates, 97% versus 92%, P=0.001) [19]. A recent meta-analysis comparing chemotherapy alone to combined chemotherapy and RT for early-stage HL patients likewise demonstrated both a recurrence-free and OS advantage to combined-modality therapy [24].

Contemporary Approaches

The cumulative experience as outlined above established a combined-modality approach of 4 cycles of ABVD with 30 Gy of IFRT as the standard of care for favorable early-stage HL, with long-term follow-up confirming excellent outcomes [25]. Nonetheless, increasing information about the late effects of treatment has led to attempts to further decrease toxicity by using even more highly refined chemotherapy (decreased duration and/or intensity or different agents) and RT (reduced volume and/or dose) while maintaining excellent efficacy.

It is important to note that the data on late effects after HL are largely based on studies of patients treated decades ago with outdated RT techniques, using much larger treatment fields and higher doses. There is ample evidence that the risks of late complications are directly related to radiation dose [26-31] and field size [8,32]. Similarly, modern chemotherapy regimens that exclude alkylators are expected to further reduce the risk of late effects, specifically leukemia and infertility [33,34]. Certainly 4 cycles of ABVD followed by 30 Gy of IFRT would be expected to decrease late effects in the years following treatment, relative to antiquated regimens. While long-term toxicity data from this regimen mature, contemporary approaches are aimed at reducing the late effects from therapy even further while maintaining excellent efficacy.

Trials Evaluating Optimal Number of Cycles of Chemotherapy and Combinations of Agents

The use of fewer cycles of chemotherapy could potentially reduce long-term toxicity from combined-modality therapy. Results were published recently from the GHSG HD10 trial [35]. In this trial 1371 stage I or II favorable-prognosis HL patients were randomized to 1 of 4 arms: 1) 4 cycles of ABVD followed by 30 Gy of IFRT, 2) 4 cycles of ABVD followed by 20 Gy of IFRT, 3) 2 cycles of ABVD followed by 30 Gy of IFRT, and 4) 2 cycles of ABVD followed by 20 Gy of IFRT. At a median follow-up of 7.5 years, there were no significant differences in 5-year progression-free survival (PFS) or OS. However, there were significant differences in World Health Organization (WHO) grade III or IV toxicity between 4 and 2 cycles of ABVD in the overall number of events (52% versus 33%), including leukopenia (24% versus 15%), infections (5.1% versus 1.7%), and hair loss (28% versus 15%). It is certainly possible that late cardiac disease rates will increase in the 4-cycle versus 2-cycle ABVD arms as well.

The GHSG 13 trial investigated whether certain agents could be omitted from the ABVD regimen in patients treated with combined-modality therapy. In this 4-arm randomized study, patients with stage I or II HL were treated with either ABVD, ABV, AVD, or AV, all followed by 30 Gy of IFRT. The 5-year freedom from treatment failure was 93.1%, 81.4%, 89.2%, and 77.1% with ABVD, ABV, AVD, and AV, respectively. Compared with ABVD, inferiority of the dacarbazine-deleted variants was detected, with 5-year differences of −11.5% (95% confidence interval [CI], 18.3 to −4.7) for ABV and −15.2% (−23.0 to −7.4) for AV. Noninferiority of AVD compared with ABVD could also not be detected, with a 5-year difference of −3.9% (−7.7 to −0.1). The study concluded that dacarbazine cannot be omitted from ABVD without substantial loss of efficacy and bleomycin cannot be safely omitted either [36].

The previously mentioned Stanford G4 trial demonstrated that an abbreviated 8-week course of the Stanford V regimen results in efficacy comparable to that seen in the GHSG HD10 trial. This is particularly impressive given that a significant proportion of patients on the Stanford G4 trial had unfavorable risk factors that would have excluded them from inclusion in the GHSG HD10 trial. It is possible that the subset of favorable patients in the G4 trial would do well with further reduction of therapy, and so the G5 trial is evaluating a modified 8-week version in which nitrogen mustard is replaced by cyclophosphamide and the RT dose is reduced from 30 Gy to 20 Gy while the volume is reduced to involved-node radiation therapy (INRT) [37]. While data from G5 mature, it is

worthwhile to note that although the cumulative doses of doxorubicin are similar between the abbreviated Stanford V regimen used in the G4 trial and 2 cycles of ABVD, the bleomycin dose was 50% lower in the Stanford regimen. Therefore, in situations where is it desirable to limit exposure to bleomycin, this regimen may be particularly attractive.

Trials Evaluating Optimal Radiation Dose

Two randomized trials have investigated the optimal radiation dose in favorable-prognosis stage I or II HL patients treated with combined-modality therapy.

In the GHSG HD10 trial discussed above there was no significant difference in freedom from treatment failure (P=1.00), PFS (P=0.98) or OS (P=0.61) between the groups treated with 20 Gy and 30 Gy of IFRT. The 5-year rate of freedom from treatment failure was 93% with 20 Gy or 30 Gy of IFRT. However, there were significant differences in WHO grade III or IV between 30 Gy and 20 Gy IFRT in overall events (8.7% versus 2.9%), including dysphagia (3% versus 2%) and mucositis (3.4% versus 0.7%) [35].

In the EORTC H9F trial, patients were treated with 6 cycles of EBVP and those attaining a complete response were randomized to 1 of 3 arms: 1) no radiation, 2) 20-Gy IFRT, and 3) 36-Gy IFRT [38]. The no-radiation arm was closed early, as discussed in the section "Trials Evaluating Chemotherapy Alone." The event-free survival rates of the 20-Gy and 36-Gy arms were 84% and 87%, respectively. Mature results of this trial will determine whether the lower dose of 20 Gy can be used in patients with favorable disease as per the EORTC criteria.

Preliminary data suggest that 20 Gy may be adequate in well-selected patients treated with the abbreviated Stanford V regimen as well [37].

Trials Evaluating Optimal Radiation Field Size, Volume, and Technique

Over the past few decades, with advances in systemic therapy and radiation treatment planning and delivery, as well as an improved understanding of the late effects of therapy, there has been a successful effort to decrease the radiation field while maintaining efficacy.

The original total nodal and extended radiation fields were based on bony anatomy and 2-D RT planning. These radiation fields were replaced by IFRT, which substantially reduced the treatment volumes. Although no randomized trial has compared IFRT and EFRT in favorable-prognosis patients, multiple trials have addressed this issue in unfavorable-prognosis patients [19,25,39].

There has been growing interest in further refining the radiation treatment technique by using volume-based, 3-D treatment planning to treat only the initially involved nodes [40]. Initial results are promising. A retrospective study from Canada compared 96 patients treated with IFRT and 102 patients treated with INRT, all of whom received combined-modality therapy [41]. In this study, INRT was defined as prechemotherapy nodal volumes with margins $\leq$5 cm. Five relapses occurred in the IFRT group and 3 in the INRT group. There were no locoregional or marginal relapses in the INRT group. Moreover, there was no significant difference in OS or PFS between the IFRT and INRT groups. An additional retrospective analysis of 97 patients with stage I-II HL treated with ABVD plus INRT and followed for a median of 50 months reported an estimated 4-year freedom from disease progression of 96.4% (95% CI, 92.4%–100%) [42].

Of note, the method by which the treatment volume used in INRT is defined varies between different groups. For example, the EORTC recommends the use of prechemotherapy positron emission tomography (PET)/CT in the radiation treatment planning position as well as a post-treatment scan to determine the clinical target volume. The expansion from clinical target volume to planning target volume is 1 cm isotropically [40]. In contrast, the GHSG does not require the use of pretreatment PET/CT. Their expansion is from the clinical target volume to the planning target volume by 1–3 cm, depending on the anatomic location [43].

Clearly, INRT is technically very challenging and for many practitioners the above requirements would preclude its use. The International Lymphoma Radiation Oncology Group (ILROG) of experts has recently published guidelines that propose a new RT technique, termed ISRT, that is similar to INRT but uses more conservative parameters for determination of the volume at risk [44]. This technique allows for uncertainties due to a lack of ideal imaging (for example, lack of prechemotherapy PET and simulation prior to chemotherapy as noted above). It is important to note that INRT is essentially a form of ISRT with more stringent requirements for prechemotherapy imaging studies in addition to postchemotherapy imaging, including simulation for treatment planning. Therefore, disease control following ISRT is expected to be at least as good as that obtained with INRT.

Additionally, these reduced treatment volumes can be safely and efficiently combined with modern radiation treatment techniques such as intensity-modulated RT [45,46] or proton therapy [47,48], as well as respiratory gating [35,40], which should further reduce late radiation toxicity [49].

Additional studies are needed to establish the role of INRT for favorable-prognosis HL. The ongoing EORTC H10F trial, discussed later, has already incorporated INRT in both the standard and experimental arms, and INRT is the volume used in the Stanford G5 trial as well [37]. A new trial by the GHSG HD17 is comparing IFRT versus INRT in early-stage patients. In the meantime, the ISRT guidelines published by the ILROG should be followed.

Trials Evaluating Chemotherapy Alone

Since RT has been associated with long-term side effects such as second malignancies and cardiac toxicity, some studies have evaluated whether early-stage HL patients could be treated with chemotherapy alone, thereby excluding RT. This remains highly controversial, and although several trials have been conducted, the results are difficult to interpret because of issues related to trial design and patient accrual and characteristics, as well as highly variable chemotherapy regimens and RT fields and volumes.

In a randomized trial at the Memorial Sloan Kettering Cancer Center, 152 patients with stage IA to IIIA nonbulky HL were treated with either 6 cycles of ABVD or 6 cycles of ABVD followed by RT to a dose of 36 Gy (IFRT in 14%, modified extended-field in the rest) [50]. This trial did not detect any significant difference between the chemotherapy and combined-modality arms for the 5-year rates of freedom from progression (81% versus 86%, P=0.61) or OS (90% versus 97%, P=0.08). However, this trial closed early because of poor accrual and was not powered to detect any difference <20%.

More recently, the National Cancer Institute of Canada and the Eastern Cooperative Oncology Group conducted a randomized trial on 405 patients with nonbulky stage I or IIA HL [51]. Favorable-risk patients were randomized to receive either subtotal nodal irradiation or 2 cycles of ABVD followed by CT-based restaging and an additional 2 or 4 cycles of chemotherapy based on response. Among the favorable-risk patients, there was no difference between the 2 arms in either disease-free survival (DFS) or OS, which was estimated at 94% after 12 years. Of note, this trial compared chemotherapy alone to RT alone, not chemotherapy versus combined-modality therapy, which has clearly been shown to be superior to RT alone. More importantly, the subtotal nodal irradiation field used in this trial was replaced decades ago by smaller fields precisely because of concerns regarding the potentially fatal late effects that were seen in this trial. Moreover, the radiation dose was higher (35 Gy) than the current standard. Furthermore, this trial was conducted before the widespread availability of PET, so both initial staging and subsequent treatment response evaluations were CT based. Therefore, the results of this trial are difficult to extrapolate to contemporary approaches because it compared an experimental chemotherapy-only arm to an antiquated RT-only "control" arm. Nonetheless, the excellent DFS and OS achieved by chemotherapy alone are certainly impressive and noteworthy in their own right. Risk-adapted chemotherapy-only–based approaches are an active area of investigation, as noted in the section "Response-Adapted Therapy Based on Early PET Results."

Data do exist to support caution in excluding RT in the treatment of early-stage HL. In the EORTC H9F trial, patients with favorable-prognosis stage I or II HL were treated with 6 cycles of EBVP, and those attaining a complete response were randomized to 1 of 3 arms: 1) no RT, 2) 20 Gy of IFRT, and 3) 36 Gy of IFRT [38]. The no-RT arm of the trial was forced to close early after predefined stopping rules were met. The event-free survival rate was significantly lower in the no-RT arm (4-year rate, 70%) compared to the 20-Gy (84%) and 36-Gy (87%) arms (P<0.001). In addition, several studies with predominately pediatric patients and a significant proportion of later-stage disease have also demonstrated inferior outcomes when IFRT was omitted [52,53]. In a recent meta-analysis that included randomized trials in early-stage patients comparing chemotherapy alone versus the same chemotherapy and RT, combined-modality therapy was associated with a significantly improved tumor control rate (hazard ratio [HR] =0.41, P=0.0003), which translated into a significant OS benefit (HR =0.4, P<0.00001) [24]. Lastly, an analysis of the National Cancer Data Base of 20,600 patients with early-stage HL found that a combined-modality approach was associated with an improved OS (HR =0.61; 95% CI, 0.53–0.70) compared with chemotherapy alone. Of particular concern, the proportion of patients who were treated with chemotherapy alone steadily increased from 2003 (40.6%) to 2011 (54.8%) and treatment selection was significantly influenced by gender, race, and socioeconomic factors [54].

Response-Adapted Therapy Based on Early PET Results

PET scans have become well established as standard of care in the initial staging and post-therapy evaluation of patients with HL. In addition, multiple studies have shown that interim PET results are highly predictive of treatment outcome [55-58]. Naturally, this has led to investigations of the use of PET/CT data for early response-adapted therapy, with therapeutic stratification, often the omission of RT following chemotherapy, based on interim results. Picardi et al [59] conducted one of the earlier randomized trials addressing the question of whether RT can be omitted if a complete response by PET is achieved after chemotherapy in patients with HL. Patients with disease size of ≥5 cm were included in this trial. One hundred sixty patients who had a complete response to induction chemotherapy but residual mass and PET-negative scan were randomized to undergo either observation or consolidative RT. Patients in the observation arm had a significantly inferior event-free survival rate (86%) compared to those in the RT arm (96%, P=0.03). These results suggest that negative PET scans cannot be reliably used to exclude patients from RT.

Three prospective PET-adapted clinical trials on early-stage HL are exploring the possibility of omitting RT in patients with negative interim PET results. It is important to note that these trials use standardized criteria for PET/CT scan interpretation (Deauville criteria) that grade uptake relative to internal structures (thereby minimizing inter-reader subjectivity and interdevice inconsistency because the patient serves as his or her own control) as follows: 1) no uptake; 2) uptake ≤ mediastinum; 3) uptake > mediastinum but ≤ liver; 4) uptake > liver; and 5) uptake > liver and new sites of disease. However, the study inclusion criteria vary.

In the EORTC H10F trial, all early-stage favorable HL patients are treated initially with 2 cycles of ABVD followed by a PET scan. Regardless of PET scan results, all patients randomized to the standard arm receive a third cycle of ABVD and INRT. Patients on the experimental arm receive response-adapted therapy based on the PET scan results as follows: those with a negative PET scan (as defined by a score of 1 or 2 using the Deauville criteria) receive an additional 2 cycles of ABVD, and those who had a positive PET scan receive 2 cycles of dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) followed by INRT. Based on recent interim analysis, it was determined that the experimental arm of omitting RT in the setting of negative PET after 2 cycles of ABVD was unlikely to be noninferior to the standard arm of combined-modality therapy. At the recommendation of an independent data-safety monitoring board, the experimental arm of no RT was closed and all patients on the trial are to receive INRT [60]. The portion of the experimental arm using dose-escalated BEACOPP in patients with PET-positive disease after 2 cycles of ABVD is still ongoing.

The RAPID trial, a multicenter trial in the United Kingdom, explored response-adapted therapy. It is important to note, however, that eligibility criteria differ in that the RAPID trial includes stage I (33%) and II (67%) patients without B symptoms or mediastinal bulk on presentation, but only 62% had favorable-prognosis disease as defined by the EORTC criteria. In this trial, all patients received 3 cycles of ABVD followed by a PET scan, which was negative in 74.7% of patients as defined by a score of 1 or 2 using the Deauville criteria. These PET-negative patients were then randomly assigned to IFRT to a dose of 30 Gy versus no further therapy. At a median of 60 months of follow-up after randomization, the 3-year PFS rate was 94.6% (95% CI, 91.5–97.7) in the RT group and 90.8% (95% CI, 86.9–94.8) in the group that received no further therapy, with an absolute risk difference of −3.8 percentage points (95% CI, −8.8 to 1.3) [61]. Despite the fact that early-stage HL patients on this study who had a negative PET after 3 cycles of ABVD had a very good prognosis either with or without consolidation RT, it should be noted that this was a statistically negative trial, as the study did not demonstrate the noninferiority of the strategy of no further treatment after chemotherapy with regard to PFS.

In the GHSG HD16 trial, all early favorable-prognosis HL patients are initially treated with 2 cycles of ABVD followed by a PET scan. Regardless of PET scan results, all patients randomized to the standard arm receive 2 additional cycles of ABVD followed by 20-Gy IFRT. Patients on the experimental arm receive response-adapted therapy based on the PET scan as follows: those with a negative PET scan receive 2 additional cycles of ABVD followed by observation and those with a positive PET scan receive 2 additional cycles of ABVD followed by 20-Gy IFRT. Preliminary results are pending.

These trials will further clarify whether PET response can be used to guide treatment for HL. It is important to note that although these studies were designed in an effort to decrease late effects and mortality associated with therapy, because the primary endpoint is PFS and the follow-up is limited, they directly address neither late effects nor survival. Therefore, changes in therapy (either changing chemotherapy or omitting RT) based on PET

response for early-stage patients should be recommended with caution after careful consideration and preferably as part of a clinical trial, at least until these preliminary data mature (see Variant 1, Variant 2, Variant 3, and Variant 4).

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare disease that represents only about 5% of all HLs. It has distinct histological features first described in the 1940s; however, it was not formally recognized as a separate disease entity until the 1994 Revised European-American Classification of Lymphoid Neoplasms. In any event, one must confirm the diagnosis of NLPHL given that up to one-half of patients who were initially diagnosed at 17 large academic centers in Europe and America with NLPHL were reclassified upon expert review as having classical HL (most frequently the lymphocyte-rich subtype) [62]. Due to the rarity of NLPHL, prospective clinical trial data in this subgroup are limited. However, based on retrospective series, small prospective studies, and more recently a comprehensive analysis from the GHSG based on HD4 and HD12 [63], it is apparent that the clinical presentation and natural history of NLPHL differ compared with its classical counterpart. Patients with NLPHL most frequently present with early-stage disease involving peripheral sites, as well as a significantly different natural history characterized by frequent relapses, but an overall very good prognosis. In addition, unlike in classical HL, the malignant cells of NLPHL universally express CD20.

Due to its rarity, there is no standardized treatment for NLPHL. However, the early presentation in over 80% of patients, its indolent, relapsing nature, and the recognition that a greater proportion of patients were dying from treatment-related complications rather than disease progression have led to the increasing use of less aggressive therapeutic approaches.

The GHSG recently published long-term results of an analysis of 256 patients with stage IA NLPHL who had been treated on one of their protocols between 1988 and 2009 [64]. Twenty-seven patients had been treated with 4 weekly standard doses of rituximab, 49 had been treated with EFRT, and 108 with IFRT; the remaining 72 patients had received combined-modality treatment. At 8 years, PFS and OS were 88.5% and 98.6% for combined-modality treatment, 84.3% and 95.7% for EFRT, and 91.9% and 99.0% for IFRT, respectively. Patients treated with rituximab had 4-year PFS and OS rates of 81.0% and 100%, respectively. Given that combined-modality treatment, EFRT, and IFRT resulted in equivalent PFS and OS, the authors recommended that IFRT be the standard of care as it would likely result in the least toxicity.

A recent retrospective study reported outcomes in 113 patients with stage I-II lymphocyte-predominant HL, of whom 93 were treated with RT alone, 13 were treated with combined-modality therapy, and 7 were treated with chemotherapy alone [65]. The addition of chemotherapy to RT did not appear to improve OS or PFS. Most patients who received chemotherapy alone developed early relapse and required salvage. Among patients receiving RT alone, there was no difference in OS or PFS among those treated with limited-field RT such as IFRT (median dose, 32 Gy), regional RT such as mantle (median dose, 36 Gy), or EFRT (median dose, 38 Gy).

These retrospective studies indicate that IFRT to 30 Gy will likely provide excellent outcomes in patients with NLPHL, with less toxicity than EFRT or combined-modality therapy. Furthermore, rather than using antiquated involved fields based on bony anatomy, we recommend using the ILROG's volume-based ISRT guidelines with CT planning for NLPHL as well. Consistent with the guidelines, the volumes for NLPHL include a more generous margin (potentially including adjacent lymph nodes) compared to ISRT for classical HL.

Recently, because the malignant cells of NLPHL express CD20, targeted therapy with rituximab has been studied. The GHSG reported on 28 patients with favorable stage IA disease treated with 4 once-per-week standard doses (375 mg/m^2) of rituximab. As expected, toxicity was limited and after a median of 43 months OS was 100%; however, 25% of the patients had relapsed [66]. Another phase II trial that evaluated the same 4-week course of rituximab with and without the addition of maintenance therapy delivered every 6 months for 2 years reported similar findings in patients with previously untreated stage I to II disease; estimated 5-year PFS and OS were 56% and 87.5%, respectively [67]. Despite the fact that rituximab is clearly an active agent in NLPHL, these 2 studies suggest that rituximab responses are not durable, and results are clearly inferior to RT for patients with newly diagnosed early-stage disease (see Variant 5 and Variant 6).

Summary of Recommendations

- The standard of care for favorable stage I-II HL is combined-modality therapy consisting of 2–4 cycles of ABVD chemotherapy followed by 20–30 Gy of ISRT. For patients with early-stage favorable disease who fit

the GHSG favorable criteria, 2 cycles of ABVD followed by 20-Gy IFRT is adequate. For patients with early-stage favorable disease who fit the EORTC criteria but not the GHSG criteria, 3–4 cycles of ABVD followed by 30-Gy IFRT is recommended.

- The standard radiation treatment volume is ISRT. RT delivery with intensity-modulated RT, proton therapy, and techniques such as respiratory gating may further reduce the radiation dose to normal structures.
- Changing chemotherapy or omitting RT based on PET response for early-stage patients may be appropriate with caution after careful consideration and preferably as part of a clinical trial, at least until preliminary data mature.
- The standard of care for stage I-II lymphocyte-predominant HL is ISRT with more generous treatment volumes than classic HL according the ILROG guidelines to a dose of 30–36 Gy. Chemotherapy followed by ISRT may be appropriate in stage II disease.

Summary of Evidence

Of the 67 references cited in the *ACR Appropriateness Criteria® Hodgkin Lymphoma — Favorable Prognosis Stage I and II* document, 58 are categorized as therapeutic references including 17 well designed studies, 35 good quality studies, and 1 quality study that may have design limitations. Additionally, 7 references are categorized as diagnostic references including 6 well designed studies and 1 good quality study. There are 5 references that may not be useful as primary evidence. There are 2 references that are meta-analysis studies.

The 67 references cited in the *ACR Appropriateness Criteria® Hodgkin Lymphoma — Favorable Prognosis Stage I and II* document were published from 1982-2015.

Most of the references are well designed or good quality studies and provide good evidence.

Supporting Documents

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

References

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Clinical Condition: **Hodgkin Lymphoma — Favorable Prognosis Stage I and II**

Variant 1: **25-year-old woman with stage IIA nodular sclerosing HL (NSHL) with left supraclavicular and mediastinal (3 cm in widest diameter) involvement; normal ESR. Interim PET/CT is negative (Deauville 2).**

Treatment	Rating	Comments
Radiation alone	2	RT alone is appropriate only if there are significant contraindications to chemotherapy.
Chemotherapy and ISRT	8	
Chemotherapy and IFRT	5	IFRT is an antiquated technique but still within the current standard of care.
Chemotherapy alone	6	
Type of Chemotherapy		
ABVD	9	
Stanford V (8 week course)	7	
Stanford V (12 week course)	3	
Duration of ABVD (If Chemotherapy Given Alone)		
2 cycles	2	
3–4 cycles	5	
6 cycles	7	
Duration of ABVD (Combined-Modality)		
2 cycles	8	
4 cycles	6	
6 cycles	3	
Dose of Radiation Therapy (Combined-Modality)		
20 Gy (with ABVD)	8	
30 Gy (with ABVD)	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
30 Gy (with Stanford V)	7	

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

Clinical Condition: **Hodgkin Lymphoma — Favorable Prognosis Stage I and II**

Variant 2: **25-year-old woman with stage IIA NSHL with left supraclavicular and mediastinal (3 cm in widest diameter) involvement; normal ESR. Interim PET/CT reveals response score as Deauville 3.**

Treatment	Rating	Comments
Radiation alone	2	
Chemotherapy and ISRT	8	
Chemotherapy and IFRT	6	
Chemotherapy alone	6	
Type of Chemotherapy		
ABVD	9	
Stanford V (8 week course)	7	
Stanford V (12 week course)	3	
Duration of ABVD (If Chemotherapy Given Alone)		
2 cycles	2	
3–4 cycles	4	
6 cycles	7	
Duration of ABVD (Combined-Modality)		
2 cycles	7	
4 cycles	7	
6 cycles	4	Six cycles of ABVD may be appropriate if the interim PET/CT was done after cycle 3 or 4.
Dose of Radiation Therapy (Combined-Modality)		
20 Gy (with ABVD)	7	
30 Gy (with ABVD)	6	
30 Gy (with Stanford V)	7	
30 Gy + 6 Gy boost to mediastinum	5	

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

Clinical Condition: **Hodgkin Lymphoma — Favorable Prognosis Stage I and II**

Variant 3: **25-year-old woman with stage IIA NSHL with bilateral supraclavicular and mediastinal (7 cm in widest diameter) involvement; normal ESR. Interim PET/CT is negative (Deauville 2).**

Treatment	Rating	Comments
Radiation alone	2	
Chemotherapy and ISRT	9	
Chemotherapy and IFRT	6	
Chemotherapy alone	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Type of Chemotherapy		
ABVD	9	
Stanford V (8 week course)	7	
Stanford V (12 week course)	5	
Duration of ABVD (If Chemotherapy Given Alone)		
2 cycles	1	
4 cycles	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
6 cycles	7	
Duration of ABVD (Combined-Modality)		
2 cycles	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
4 cycles	8	
6 cycles	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Dose of Radiation Therapy (Combined-Modality)		
20 Gy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
30 Gy	7	
30 Gy + 6 Gy boost to mediastinum	5	

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

Clinical Condition: **Hodgkin Lymphoma — Favorable Prognosis Stage I and II**

Variant 4: **25-year-old woman with stage IIA NSHL with bilateral supraclavicular and mediastinal (7 cm in widest diameter) involvement; normal ESR. Interim PET/CT scan demonstrates Deauville 3 in mediastinum.**

Treatment	Rating	Comments
Chemotherapy and ISRT	9	
Chemotherapy and IFRT	6	
Chemotherapy alone	6	
Duration of ABVD (If Chemotherapy Given Alone)		
2 cycles	2	
4 cycles	5	
6 cycles	7	This option assumes interim PET was negative after 4 cycles of chemotherapy.
Duration of ABVD (Combined-Modality)		
2 cycles	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
4 cycles	6	
6 cycles	4	
Dose of Radiation Therapy (Combined-Modality)		
20 Gy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
30 Gy	7	
30 Gy + 6 Gy boost to mediastinum	5	

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

Clinical Condition: **Hodgkin Lymphoma — Favorable Prognosis Stage I and II**

Variant 5: **30-year-old man with nonbulky stage IA NLPHL with right upper cervical involvement.**

Treatment	Rating	Comments
ISRT alone	7	
Chemotherapy and ISRT	6	
IFRT alone	7	
Chemotherapy and IFRT	4	
Mantle RT alone	1	
Chemotherapy alone	3	
Mantle-para-aortic and splenic RT alone	1	
Dose of Radiation Therapy (RT alone)		
20 Gy	3	
30–36 Gy	8	
>36 Gy	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 6: **30-year-old man with nonbulky stage IIA NLPHL with bilateral neck involvement.**

Treatment	Rating	Comments
ISRT alone	7	ISRT allows for a field that is very similar to IFRT in this situation.
Chemotherapy and ISRT	6	
IFRT alone	6	
Chemotherapy and IFRT	5	
Mantle RT alone	2	
Chemotherapy alone	3	This option is appropriate only if there are significant contraindications to RT.
Mantle-para-aortic and splenic RT alone	1	
Dose of Radiation Therapy (RT alone)		
20 Gy	3	
30–36 Gy	8	
>36 Gy	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		