

## American College of Radiology ACR Appropriateness Criteria®

### HODGKIN'S LYMPHOMA — UNFAVORABLE CLINICAL STAGE I AND II

Expert Panel on Radiation Oncology–Hodgkin's Lymphoma: Prajnan Das, MD, MPH<sup>1</sup>; Andrea Ng, MD<sup>2</sup>; Louis S. Constone, MD<sup>3</sup>; Ranjana Advani, MD<sup>4</sup>; Christopher Flowers, MD, MS<sup>5</sup>; Jonathan Friedberg, MD<sup>6</sup>; David C. Hodgson, MD<sup>7</sup>; Cindy L. Schwartz, MD<sup>8</sup>; Richard B. Wilder, MD<sup>9</sup>; Lynn D. Wilson, MD, MPH<sup>10</sup>; Michael J. Yunes MD.<sup>11</sup>

#### **Summary of Literature Review**

Numerous studies have evaluated the impact of prognostic factors in stage I–II Hodgkin's lymphoma in order to identify patients who benefit from more intensive therapy [1–4]. 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.

In the United States there has been general consensus that two of these factors in stage I–II Hodgkin's lymphoma should influence management decisions. The first is constitutional (B) symptoms — unexplained fevers, drenching night sweats, or significant weight loss as clearly defined in the Ann Arbor staging classification system [5]. The presence of B symptoms is correlated with a higher likelihood of systemic disease, including occult subdiaphragmatic disease. Evidence suggests that fevers and weight loss have more prognostic significance than night sweats alone [6].

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 [7]. The most commonly used definition is based on a measurement of

the maximum width of the mediastinal mass on standing posteroanterior (PA) chest radiograph, compared with the maximum intrathoracic diameter. A ratio  $>1/3$  is defined as “bulky.” Other reports have used a ratio with the intrathoracic width at T5–6 as the denominator [8], while still others use absolute measurements [9], surface area calculations, or volume measurements. Bulky disease in nonmediastinal sites has similarly been classified with varying definitions. Some protocols define bulky as  $\geq 10$  cm, while others use  $\geq 5$  cm or  $\geq 6$  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  $\geq 50$  in the absence of B symptoms, ESR  $\geq 30$  with B symptoms,  $\geq 4$  sites of involvement or bulky mediastinal involvement [10]. For the German Hodgkin's Lymphoma Study Group (GHSG), the following are considered unfavorable factors: ESR  $\geq 50$  in the absence of B symptoms, ESR  $\geq 30$  with B symptoms,  $\geq 3$  sites of involvement, extranodal involvement, or bulky mediastinal mass [11].

Combined modality therapy, consisting of chemotherapy followed by radiation therapy (RT), represents the standard of care for most patients with unfavorable stage I–II Hodgkin's lymphoma. In the United States, the most widely accepted systemic therapy as part of combined modality therapy is ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). Stanford V, a 12-week, 7-drug regimen that is administered on a weekly basis, contains lower cumulative doses of mechlorethamine, adriamycin, and bleomycin than MOPP (mechlorethamine, vincristine, procarbazine and prednisone) and ABVD, respectively. Patients with initial disease of  $\geq 5$  cm and/or macroscopic splenic disease, receive 36 Gy of involved-field radiation therapy (IFRT) 2 weeks after the chemotherapy. In a report on 142 patients with stage III or IV or locally extensive mediastinal stage I or II Hodgkin's lymphoma, a 5-year freedom from progression and overall survival of 89% and 96%, respectively, were achieved [12]. The EORTC H7U trial explored the use of a less intensive regimen, EBVP II (epirubicin, bleomycin, vinblastine, and prednisone) in unfavorable-prognosis early-stage patients, and found that it was significantly inferior to MOPP/ABV (10-year event-free survival (EFS) rate 68% vs 88%,  $P < 0.0001$ ) [10]. Other trials examined whether unfavorable-prognosis patients may benefit from the regimen, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), originally developed for patients with advanced-stage disease. Both the EORTC H9U and

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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 overall survival rate were observed between BEACOPP and ABVD in the EORTC H9U trial [13]. Recently updated results of the GHSg HD11 showed a significantly higher 5-year freedom-from treatment failure (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%]) [11]. 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 in this population. This trial randomized patients with unfavorable CS I-II disease to 4 cycles of ABVD versus 2 cycles of dose-escalated BEACOPP and 2 cycles of ABVD, followed by involved-field irradiation to 30 Gy. Preliminary results showed a significantly superior 3-year FFTF in the dose-escalated BEACOPP containing arm (96% vs 90%), but no differences in overall survival [14]. Of note, these different chemotherapy regimens could be associated with different rates of acute and late toxicity, such as higher rates of infertility with BEACOPP. Hence, long-term follow-up will be required to evaluate the rates of late toxicity, such as cardiovascular effects and second malignancies, with these chemotherapy regimens.

Two trials addressed the optimal number of cycles of chemotherapy in patients with unfavorable, early-stage Hodgkin's lymphoma. In the EORTC-H8U trial, patients were randomized to 6 cycles of MOPP/ABV followed by involved-field irradiation, 4 cycles of MOPP/ABV followed by IFRT or 4 cycles of MOPP/ABV followed by extended-field irradiation [15]. At a median follow-up of 92 months, there was no significant difference in 5-year EFS rates among the three treatment groups (84%, 88% and 87%, respectively). The overall survival rates at 10 years were also not significantly different (88%, 85%, and 84%, respectively). In the EORTC-H9U trial described above, there was also no significant difference between 4 versus 6 cycles of ABVD at a median follow-up of 57 months [13].

The role of consolidative RT after chemotherapy has been explored by variety of randomized trials using different criteria for risk stratification. These studies consistently demonstrated a benefit for freedom from disease progression with the addition of consolidative irradiation.

The Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) conducted a trial with 277 stage I-II favorable- or unfavorable-prognosis Hodgkin lymphoma patients who were randomized to receive either 6 cycles of cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP), or CVPP followed by IFRT [16]. Overall, the disease-free survival rate was significantly higher in the combined-modality arm compared with the chemotherapy alone arm (7-year rates, 71% vs 62%,  $P=0.01$ ). Among the unfavorable-prognosis patients, the disease-free survival rate (75% vs 34%,  $P=0.001$ ) and the overall survival rate (84% vs 66%) were higher in the combined-modality arm compared with the chemotherapy

alone arm. The use of the CVPP regimen and the inclusion of pediatric patients (45% of subjects) 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 six cycles of ABVD, were randomized to receive either IFRT or no radiotherapy [17]. 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 overall survival rate was significantly higher in the RT arm than in the no-RT arm (8-year rates, 100% vs 89%,  $P=0.002$ ). The EFS rate was also significantly higher in the RT arm (8-year rates, 88% vs 76%,  $P=0.01$ ). However, the high proportion of pediatric, stage III-IV and mixed cellularity patients in this trial limit the generalizability of this trial as well.

The National Cancer Institute of Canada (NCIC) Eastern Cooperative Oncology Group (ECOG) trial enrolled 405 patients with nonbulky stage I-IIA Hodgkin lymphoma [18]. Favorable risk-prognosis patients were randomized to receive either 4-6 cycles of ABVD or subtotal nodal irradiation. Unfavorable risk-prognosis patients (age  $\geq 40$  years, or ESR  $\geq 50$  mm/hour, mixed cellularity, lymphocyte-depleted histology, or  $\geq 4$  sites of disease) were randomized to receive either 4-6 cycles of ABVD, or combined-modality therapy with 2 cycles of ABVD followed by subtotal nodal irradiation. Among the unfavorable-risk prognosis patients, the rate of freedom from disease progression was significantly higher in the combined-modality arm compared with the chemotherapy alone arm (95% vs 88%,  $P=0.004$ ), but there was no significant difference in overall survival. Of note, the use of subtotal nodal irradiation in this trial may eventually lead to an increased rate of late effects from RT, thereby diminishing the benefits from RT. While the NCIC-ECOG trial and the other trials discussed above have various limitations, it can still be concluded that the addition of RT to chemotherapy improves freedom from disease progression in patients with unfavorable prognosis Hodgkin's lymphoma. (See [Variant 1](#).)

Several randomized trials have evaluated the appropriate extent of RT field in unfavorable-prognosis Hodgkin's lymphoma patients after chemotherapy. In the GHSg HD8 trial, 1,204 unfavorable-prognosis patients were treated with 2 cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) and ABVD, followed by either extended-field RT or IFRT [19]. There were no significant differences in the rates of freedom from treatment failure or overall survival between the two groups, whereas acute side effects were less frequent in the IFRT group. In the EORTC H8U trial described above, there were no significant differences in the EFS or overall survival rates between the IFRT arms and extended-field arm [15].

Similarly, an Italian study with favorable- and unfavorable-prognosis patients showed no difference in

freedom from progression or overall survival rates between patients treated with subtotal nodal and splenic radiation, or IFRT, following 4 cycles of ABVD [20]. IFRT is therefore considered the standard radiation treatment field after chemotherapy. The definition of IFRT has been detailed elsewhere [21].

Following chemotherapy, the superior-inferior extent of the radiation field typically encompasses the prechemotherapy extent of disease, while the lateral extent can be limited to the postchemotherapy extent of disease. The initial lateral extent of mediastinal disease should not be treated, unless there is known extranodal disease extension into bone or chest wall.

In recent years, there is growing interest in further limiting the radiation treatment field to involved-node radiation therapy (INRT) [22]. The definition of INRT varies from group to group. In the EORTC/GELA H11 trial for early-stage, unfavorable-prognosis Hodgkin's lymphoma (discussed below), INRT was adopted in both the standard and experimental arms. The GHSG is planning a randomized trial in patients with unfavorable-prognosis, early-stage disease (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.

The appropriate radiation dose in patients with unfavorable-prognosis early-stage disease after chemotherapy was addressed by the GHSG HD11 trial described above [11]. After 4 cycles of BEACOPP, a significant difference in 5-year FTF 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% lower 5-year FTF in the 20 Gy arm. This led to the conclusion that a reduction of radiation dose from 30 Gy to 20 Gy of involved-field RT in unfavorable-prognosis patients may be justified only after BEACOPP, but not after ABVD. (See [Variant 2](#) and [Variant 3](#).)

Positron emission tomography (PET) has emerged as a useful tool in the staging and follow-up of patients with Hodgkin's lymphoma. Additionally, PET response during chemotherapy has been shown to be a powerful prognostic factor [23].

A recent randomized trial evaluated whether RT can be omitted in patients who show a complete response by PET following chemotherapy [24]. 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. The EFS rate was significantly lower in the observation arm compared with the RT arm (86% vs 96%, P=0.03). The ongoing EORTC/GELA H11 trial also explored the use of PET response to identify patients with unfavorable-prognosis early-stage disease in whom RT may be omitted. The standard arm of this trial consisted of 4 cycles of ABVD followed by INRT to 30 Gy while patients on the experimental arm received 2 cycles of ABVD followed by PET scan. If the scan was negative,

patients received four additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received 2 cycles of dose-escalated BEACOPP, followed by INRT to 30 Gy. The results of this trial are pending. It therefore appears that at the current time, there is no available data to support the omission of RT based on PET response or early PET response in patients with early-stage Hodgkin's lymphoma, an approach that should be reserved in the context of a clinical trial. (See [Variant 4](#).)

### Summary

- The standard of care for unfavorable stage I–II Hodgkin's lymphoma is combined-modality therapy, consisting of chemotherapy followed by radiation therapy.
- The most widely accepted chemotherapy regimen is ABVD. Other options, such as Stanford V and BEACOPP, may also be appropriate.
- The recommended radiation dose is 30–36 Gy after ABVD, and the recommended radiation field is IFRT.

### Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

**Clinical Condition:****Hodgkin's Lymphoma — Unfavorable Clinical Stage I and II****Variant 1:****26-year-old male with stage IIB nodular sclerosis Hodgkin's lymphoma (NSHL); supradiaphragmatic, no bulky disease; fevers >38°C and drenching night sweats.**

Treatment	Rating	Comments
<b>Overall Plan</b>		
Combined modality therapy	8	
Chemotherapy alone	5	Under investigation. Rapid response may predict for favorable outcome. See narrative.
Radiation therapy alone	1	
<b>Type of Chemotherapy</b>		
ABVD	8	
Stanford V	7	Includes IFRT to sites >5 cm or to spleen if macroscopic splenic involvement, to 36 Gy. Awaiting ECOG results.
BEACOPP (or variants)	6	Variants with supporting data include 2 cycles of dose-escalated BEACOPP followed by 2 cycles of ABVD followed by IFRT to 30 Gy, or 4 cycles of baseline BEACOPP followed by IFRT to 20 Gy. May be associated with increased toxicity; see narrative.
<b>Duration of Chemotherapy (Chemotherapy alone)</b>		
4 months	3	The addition of RT to chemotherapy improves freedom from disease progression.
6 months	8	
<b>Duration of Chemotherapy (Combined modality therapy)</b>		
4 months	8	If Stanford V is used, duration is 12 weeks (3 months).
6 months	7	
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

**Clinical Condition:**

Hodgkin's Lymphoma — Unfavorable Clinical Stage I and II

**Variant 2:**

26-year-old male with stage IIB NSHL; supradiaphragmatic, bulky disease 10 cm in the neck; fevers &gt;38°C and drenching night sweats; partial response by computed tomography (CT) (&gt;50% reduction) after 6 cycles of ABVD.

Treatment	Rating	Comments
<b>Radiation Field</b>		
IFRT to neck	8	
INRT to neck	5	Long-term data not available. INRT definition is still in evolution.
Mantle	3	
Subtotal nodal irradiation	1	
<b>Radiation Dose</b>		
20-<30 Gy IFRT	6	
30-36 Gy IFRT	8	
>36-40 Gy IFRT	4	
>40 Gy IFRT	2	
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

**Variant 3:**

26-year-old male, CS IIA NSHL with bulky mediastinal mass (11 cm) and bilateral neck disease; partial response by CT (&gt;50% reduction) after 6 cycles of ABVD.

Treatment	Rating	Comments
<b>Radiation Field</b>		
IFRT to mediastinum and bilateral neck	8	
INRT to mediastinum and bilateral neck	5	Long-term data not available. INRT definition is still in evolution.
Mantle	4	
Subtotal nodal irradiation	2	
<b>Radiation Dose</b>		
20-<30 Gy IFRT	6	
30-36 Gy IFRT	8	
>36-40 Gy IFRT	4	
Boost mediastinum dose to 36 Gy	7	
Boost mediastinum dose to 40 Gy	2	
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

**Clinical Condition:****Hodgkin's Lymphoma — Unfavorable Clinical Stage I and II****Variant 4:****26-year-old female, CS IIB NSHL with bulky mediastinal (13 cm) and left supraclavicular disease; >75% reduction of mass by CT and negative PET after 6 months of chemotherapy.**

Treatment	Rating	Comments
<b>Radiation Dose</b>		
No further RT	3	The addition of RT to chemotherapy improves freedom from disease progression.
20-<30 Gy IFRT	6	
30-36 Gy IFRT	8	
>36-40 Gy IFRT	4	
Boost mediastinum dose to 36 Gy	6	
Boost mediastinum dose to 40 Gy	2	
<b>Mediastinal Volume</b>		
Treat post-chemo volume only (laterally)	8	If there is no bone or chest-wall extension, the width of the postchemo RT field may correspond to the postchemo extent of disease.
Inferior margin 2 cm below pre-chemo volume	8	
Treat pre-chemo volume to 10-15 Gy, then shrink	2	
Inferior margin 2 cm below post-chemo volume	2	
Inferior margin 5 cm below post-chemo volume	2	
Inferior margin approximately at diaphragm	2	
Inferior margin 5 cm below pre-chemo volume	2	
<b>Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b>		