

American College of Radiology ACR Appropriateness Criteria®

HODGKIN'S LYMPHOMA — STAGE III AND IV

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Summary of Literature Review

This review for Hodgkin's lymphoma addresses the treatment of patients who are newly diagnosed with clinical stage (CS) III or IV Hodgkin's lymphoma. Since there is only low-level evidence on the treatment of stage III or IV nodular lymphocyte predominant Hodgkin's lymphoma, this review is limited to advanced-stage classical Hodgkin's lymphoma. It is the result of a comprehensive review of the literature and expert opinion. Currently, a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is the most widely used chemotherapy regimen for Hodgkin's lymphoma. Alternatives to ABVD have been developed for patients with locally extensive or advanced-stage disease, including BEACOPP (a combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and its variants and the Stanford V regimen. Dose-escalated BEACOPP and its variants have been shown to be superior to standard-dose chemotherapy, although at the expense of increased toxicity, including infertility and leukemia risks. Stanford V, when given with radiotherapy as specified by the original protocol (involved-field radiotherapy [IFRT] to initial sites ≥ 5 cm and/or macroscopic splenic disease), yields results comparable to those of ABVD. Most randomized trials showed no significant benefit with the addition of consolidative radiation therapy after a complete response (CR) to chemotherapy based on computed tomography (CT) scans. There are data to

suggest, however, that there may be a role for radiation therapy in patients with initially bulky disease or in patients with a partial response (PR) to chemotherapy. Given the strong prognostic value of early positron emission tomography (PET) findings showing the disease's response to chemotherapy in patients with advanced-stage Hodgkin's lymphoma, investigators are exploring response-adapted therapy, including changing the chemotherapy regimen or omitting radiation therapy based on early PET-detected response.

Diagnosis of Advanced-Stage Hodgkin's Lymphoma

The diagnosis of Hodgkin's lymphoma should be confirmed pathologically by biopsy. According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition), stage III is defined as involvement of lymph nodes on both sides of the diaphragm, which also may be accompanied by extralymphatic extension or by involvement of the spleen. Stage IV disease is defined as diffuse or disseminated involvement of one or more extralymphatic organs, or isolated extralymphatic organ involvement in conjunction with disease in distant sites, or any involvement of the liver or bone marrow, or nodular involvement of the lung(s). Bulky disease is commonly defined in North America as a mediastinal mass that has a width greater than one-third the maximum intrathoracic diameter on a standing posteroanterior chest radiograph or a mass >10 cm on a CT scan [1]. It is important to note that clinical trials have defined bulky disease differently with the smallest dimensions used being 5 cm or the presence of focal splenic nodules (macroscopic splenic disease) [2-5].

Prognostic Factors

The International Prognostic Project [6] identified risk factors that, when added together, give a score (IPS) that indicates the likelihood of freedom from disease progression. This study was devised using patients treated with chemotherapy with or without radiation. Seven adverse prognostic factors had similar independent prognostic effects. The seven factors are: male sex, age 45 years or older, stage IV disease, albumin <4 g per deciliter, a hemoglobin level <10.5 g per deciliter, a leukocytosis count of at least 15,000 per cubic millimeter, and a lymphocyte count of <600 per cubic millimeter or $<8\%$ of the white cell count, or both. Five-year freedom-from-progression rates based on the number of factors ranged from 84% for those with zero factors to 42% for those with five or more factors.

The IPS itself does not include all potentially important adverse prognostic features on presentation. For example, it does not include bulky disease. Other prognostic factors that may be important include B symptoms, histologic subtype, number of nodal sites of disease, number of organs involved, bone marrow involvement, erythrocyte

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sedimentation rate, platelet count, serum alkaline phosphatase, serum lactate dehydrogenase, and comorbidities [7-12].

With the increasing use of PET for the staging and restaging for lymphoma patients, PET-detected early response to chemotherapy has been identified as a powerful prognostic tool in Hodgkin's lymphoma. In a study by Gallamini et al [13] that included 260 patients with stage II-IVB disease, the 2-year progression-free survival rates for patients with positive versus negative PET results after 2 cycles of chemotherapy (PET-2) were 12.8% and 95.0%, respectively (P<0.0001). In multivariable regression analysis that included PET-2 status and IPS as a continuous variable, IPS lost its prognostic value, and only PET-2 status had significant independent prognostic value for progression-free survival (HR, 38.3, P<0.0001). As such, trials have been designed investigating the role of response-adapted therapy based on early PET findings (discussed below).

Treatment Options Overview

Chemotherapy Regimens

Combination chemotherapy has been the mainstay of treatment since the 1970s after the National Cancer Institute reported results with the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen [14]. Since that seminal report, several approaches have been attempted, including: 1) substitution of some of the chemotherapeutic agents while maintaining a similar regimen; 2) use of an entirely new regimen, most notably ABVD; 3) use of non-cross-resistant agents in combination with MOPP, such as the MOPP/doxorubicin, bleomycin, and vinblastine (ABV) hybrid; 4) use of a dose-dense regimen with or without radiation such as dose-escalated BEACOPP or Stanford V; and 5) use of a time-condensed regimen such as BEACOPP-14 where baseline-dose BEACOPP is given every 2 weeks rather than every 3 weeks with granulocyte colony-stimulating factor support for advanced-stage Hodgkin's lymphoma.

Unlike with most other advanced-stage malignancies, chemotherapy cures the majority of Hodgkin's lymphoma patients. Following the seminal paper by DeVita et al [14], several randomized trials showed that ABVD or ABVD-containing regimens were significantly superior to MOPP [7,10,15]. The MOPP/ABV hybrid was subsequently found to be more toxic and to offer no significant improvement in outcomes compared to ABVD [16]. As a result, ABVD has become the most widely used regimen in the United States.

The dose-escalated BEACOPP regimen, developed by the German Hodgkin's Study Group (GHSG), yielded significantly better survival compared with conventional-dose regimens in the GHSG HD9 study [17]. In this three-arm trial, patients with stage IIB-IV Hodgkin's lymphoma were randomized to 8 cycles of cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP-ABVD), baseline-dose BEACOPP, or dose-

escalated BEACOPP. In the most recent update of the study with 1,196 evaluable patients and a median follow-up of 111 months, the 10-year freedom-from-relapse rate was significantly higher in the dose-escalated BEACOPP arm than in the baseline BEACOPP and COPP-ABVD arms (82%, 70%, and 64%, respectively, P<0.0001) [18]. The corresponding 10-year overall survival rates were 86%, 80%, and 75%, respectively (P=0.0005). However, in the standard arm of this trial, COPP-ABVD rather than modern ABVD was used. Also, patients on the dose-escalated BEACOPP arm had a significantly higher 10-year cumulative incidence of acute myelogenous leukemia/myelodysplasia (3.2%, 2.2%, and 0.4%, respectively, P=0.03).

To reduce treatment-related toxicity, the GHSG explored the efficacy of modified versions of the BEACOPP regimen. The GHSG HD12 trial was a four-arm study for patients with bulky stage IIB and stages III-IV disease comparing 8 cycles of dose-escalated BEACOPP with or without radiation therapy versus 4 cycles of escalated and 4 cycles of baseline BEACOPP with or without radiation therapy [19]. In the most recent update that included 1,571 eligible patients and a median follow-up of 78 months, the 5-year freedom from treatment failure, progression-free survival, and overall survival rates of the entire cohort were 85.5%, 86.2% and 91%, respectively. There were no significant differences in these endpoints between the two chemotherapy regimens, but less hematologic toxicities were observed in the arm that contained baseline BEACOPP.

The BEACOPP-14 regimen, a time-intensified variant of standard-dose BEACOPP wherein chemotherapy is administered every 2 weeks rather than 3 weeks for 8 cycles with growth factor support, showed no acute leukemia or myelodysplasia based on a median follow-up of 34 months [20]. The GHSG HD15 trial compared 8 cycles versus 6 cycles of dose-escalated BEACOPP versus 8 cycles of BEACOPP-14 [21]. This study also evaluated the use of PET response to select patients for chemotherapy alone, the preliminary findings of which are discussed below. Comparison results of the three systemic therapy arms, however, are not yet available.

The GHSG HD18 trial, which recently started recruitment, is designed to evaluate the role of intensifying or reducing systemic therapy based on early PET results. The standard arm consists of 8 cycles of dose-escalated BEACOPP. On the experimental arm, patients receive 2 cycles of dose-escalated BEACOPP followed by a PET scan. PET-positive patients receive 6 additional cycles of dose-escalated BEACOPP with rituximab, while PET-negative patients receive only two additional cycles of dose-escalated BEACOPP.

Variations of the BEACOPP regimen have also been investigated by groups other than the GHSG. Federico et al [22] in Italy reported that four escalated and two standard doses of BEACOPP resulted in superior progression-free survival compared with ABVD for patients with an IPS ≥ 4 (5-year rates, 81% and 68%,

respectively, $P=0.038$). However, BEACOPP did not significantly improve overall survival and resulted in higher rates of acute grade 3-4 neutropenia and severe infections than ABVD. The Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) and Intergruppo Italiano Linfomi (IIL) cooperative groups compared 6-8 cycles of ABVD versus 4 cycles of dose-escalated followed by 4 cycles of baseline BEACOPP as first-line therapy, with preplanned high-dose therapy as salvage [23]. BEACOPP was associated with a significantly higher 3-year freedom-from-progression rate (87% vs 71%, $P=0.01$) than ABVD, though differences in freedom from second progression and overall survival were not observed.

The European Organization for Research and Treatment of Cancer (EORTC) protocol 20012 is comparing 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP to 8 cycles of ABVD in stage III-IV patients with an IPS ≥ 3 . Recruitment is currently ongoing.

Stanford V is a 12-week, seven-drug regimen that is administered on a weekly basis. Promising phase II results have been reported, with a low risk of pulmonary toxicity, infertility, leukemia, or myelodysplasia [2,4-5]. Patients with initial disease measuring ≥ 5 cm and/or macroscopic splenic disease, receive 36 Gy of IFRT starting 2 weeks after the chemotherapy. The importance of radiation therapy as part of Stanford V was highlighted by a multi-institutional randomized trial from Italy [24] comparing modified Stanford V, mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin and vindesine (MEC hybrid), and ABVD. In this study, radiation therapy was limited to patients with initially bulky disease (>6 cm) or with PR to chemotherapy, and those with only up to two sites of disease. The 5-year relapse-free survival (RFS) rates of patients on the modified Stanford V arm were significantly lower than those of patients treated with MEC hybrid and ABVD (73%, 92%, and 88%, $P<0.01$). The inferior outcome with the modified Stanford V was attributed to the fact that radiation therapy was not given according to the Stanford V guidelines, such that only 76% of patients with a CR to chemotherapy received radiation therapy. In addition, the results were difficult to interpret because the response evaluations that determined if patients would continue on a study arm were performed at different times: after 8 and 12 weeks of modified Stanford V, 16 weeks of ABVD, and 24 weeks of MEC hybrid.

A phase III study from the United Kingdom National Cancer Research Institute Lymphoma Group [25] suggests that Stanford V is as effective as ABVD when radiotherapy is given as specified by the Stanford group. Similar results were reported by The Eastern Cooperative Oncology Group (ECOG) E2496 Intergroup phase III trial which compared 6-8 cycles of ABVD with the Stanford V regimen [26]. RT in the latter trial was administered in the ABVD arm only to patients with bulky mediastinal disease ($>1/3$ mediastinal mass ratio (MMR) or 10 cm), whereas on Stanford V, RT was administered to nodal

sites ≥ 5 cm and macroscopic splenic disease if present. At a median follow-up of 5.5 years, there was no significant difference in response, 5-year failure-free survival, 5-year overall survival, or grade 3 + 4 neutropenia rates between the two study arms. There was a significantly higher rate of grade 3 + 4 sensory neuropathy (10% vs 3%, $P<0.0001$) on Stanford V. Thus, ABVD for 6-8 cycles plus 36 Gy RT to bulky mediastinal disease remains the standard of care. (See [Variant 1](#) and [Variant 2](#).)

Assessment of Response

Response assessment in Hodgkin's lymphoma can be challenging. It is common to note a residual mass on a CT scan, especially in a patient who presents with bulky disease. It is important to note that the definition of response can vary from trial to trial. The most recent response criteria for malignant lymphomas apply to Hodgkin's lymphoma as well [27]. The key changes involve incorporating PET imaging into the response criteria and eliminating the complete response/unconfirmed (CRu) category. For a CR, residual masses of any size are permitted if the PET scan is negative. While the CRu category has been removed from response criteria, only moderate reproducibility of PET scan interpretation among nuclear medicine experts suggests that uncertainty regarding response has not been eliminated, but rather has shifted from one modality (CT) to another (PET) [28]. After the completion of radiation therapy, PET scans should not be obtained for at least 8 to 12 weeks because of the difficulty in distinguishing residual tumor from post-therapy inflammatory changes.

The Role of Radiation

The role of radiation therapy in advanced-stage Hodgkin's lymphoma is controversial because most early reports used chemotherapeutic regimens such as MOPP and relatively large radiotherapy fields such as mantle fields or subtotal nodal irradiation. In addition, high radiation doses were sometimes delivered. These factors most likely contributed to the excess morbidity such as second cancers and cardiac disease and mortality. Early approaches involved the use of radiotherapy to treat all initially involved areas to high doses (>30 Gy) after a CR to chemotherapy. Later approaches used radiotherapy to treat all involved areas to low doses (~ 10 -24 Gy) after a CR. More recent approaches have used IFRT to doses of 30-36 Gy to only treat sites of disease initially measuring ≥ 5 cm, macroscopic splenic disease, or PET-positive residual sites of disease after chemotherapy [17,19,21,29-34].

A number of randomized trials have addressed the role of radiotherapy after a CR to chemotherapy. The Southwest Oncology Group (SWOG) randomized 278 stage III-IV patients who achieved a CR to 6 cycles of nitrogen mustard, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine (MOP-BAP), to low-dose radiation, or without further treatment [32]. For the subgroup of patients with bulky disease, the 5-year remission-duration estimate was 75% for the low-dose radiation group and 57% for the no further treatment group ($P=0.05$). Laskar et al [35] in India randomized 179 Hodgkin's lymphoma

patients who achieved a CR to 6 cycles of ABVD to consolidative radiotherapy or no further therapy. The planned dose was typically 30 Gy with a 10 Gy boost to sites of bulky disease. Extended fields received 25 Gy with a boost of 10 Gy to bulky sites. The planned dose for total nodal irradiation was 21 Gy. Radiotherapy significantly improved event-free survival and overall survival in several subgroups of patients, including those with advanced-stage disease. However, most of the patients had mixed cellularity Hodgkin's lymphoma, and about half of the patients were younger than age 15 and had early-stage disease. The EORTC randomized trial reported by Aleman et al [29] failed to demonstrate a benefit to consolidative radiation therapy if a CR was obtained after 4 cycles of MOPP/ABV chemotherapy and a total of 6 cycles of chemotherapy were delivered. The authors separately reported results in 227 patients who failed to achieve a CR to 6 cycles of MOPP/ABV and received IFRT to 30 Gy to nodal areas and 18-24 Gy to extranodal sites with or without a boost [36]. The 8-year event-free and overall survival rates were 76% and 84%, respectively. These results were statistically no different than those for patients who achieved a CR to chemotherapy, suggesting a role for radiotherapy after a PR to 6 cycles of chemotherapy.

Ferne et al [33] addressed the use of additional chemotherapy versus radiation to 36 Gy after chemotherapy. In this trial, patients were randomized to 6 cycles of MOPP/ABV or ABVPP. If patients achieved a CR or a PR of at least 75% after 6 cycles, they were randomized to either consolidation with 2 additional cycles of chemotherapy or subtotal nodal irradiation to 36 Gy. No differences in 10-year DFS (73% vs 78%, $P=0.07$) or overall survival rate (84% vs. 79%, $P=0.29$) were detected. The GHSB HD12 trial [19,37] randomized adult patients to 30 Gy of radiotherapy to initial sites of disease >5 cm and residual disease versus observation after BEACOPP (8 cycles of escalated dose or 4 cycles of escalated dose plus 4 cycles of standard dose). With a median observation time of 48 months, there was no freedom-from-treatment failure or overall survival advantage to radiotherapy. However, 13% of patients who were not assigned to undergo radiation received it because of concerns regarding residual disease.

Johnson et al [38] analyzed the outcomes of nonrandomized consolidative IFRT given after chemotherapy in the initial treatment of advanced Hodgkin's lymphoma. At least 30 Gy of IFRT was delivered to residual masses or sites of originally bulky disease (more than one-third of the transthoracic ratio or 10 cm outside the chest). With a median follow-up of 6.9 years, significantly higher progression-free survival rates (71% vs 86%, $P<0.0001$) and overall survival rates (87% vs 93%, $P=0.014$) were found in patients who received radiation therapy. As in most other studies, PET was not used to assess response.

The GITIL is currently conducting a phase II trial involving PET-adapted chemotherapy in human immunodeficiency virus-negative patients between the

ages of 18 and 60 years with previously untreated stage IIB-IVB Hodgkin's lymphoma (GITIL-HD0607). On this trial, patients at first receive 2 cycles of ABVD chemotherapy. Individuals with PET-2-positive disease, as determined by a PET Reviewing Committee, are randomized to undergo 4 cycles of escalated-dose BEACOPP or rituximab-BEACOPP chemotherapy. In contrast, patients with PET-2 negative disease receive 4 additional cycles of ABVD. PET-2-negative patients with initially bulky disease are then randomized to IFRT to 30 Gy after 6 cycles of ABVD or no further treatment.

As part of the GHSB HD15 trial for advanced-stage Hodgkin's lymphoma [21], omission of radiation therapy in the setting of a PET-detected CR was evaluated in a nonrandomized fashion. At a median follow-up of 18 months, the 1-year progression-free survival rate was 96% in patients with a PET-detected CR to chemotherapy without radiation therapy. Among the 59 patients with PET-positive masses who underwent radiation therapy to 30 Gy, the 1-year progression-free survival rate was 85%. This result, while significantly inferior to the one in patients who achieved a PET-detected CR, is far more favorable than those reported in other series where treatment was not adjusted according to the PET findings [13], suggesting that the role of radiation in patients with PET-residual disease after chemotherapy deserves further study.

In conclusion, the use of radiation therapy is not recommended for patients with nonbulky (<5 cm) stage III-IV Hodgkin's lymphoma who achieve a CR to full-course chemotherapy [29,33]. For initially bulky sites [32,38] or if there are residual PET-positive site(s) after chemotherapy [36], IFRT is an option after 6 cycles of ABVD chemotherapy. Radiation doses of 30-36 Gy are usually appropriate after ABVD or BEACOPP [37-38]. IFRT to 36 Gy should be given to all sites that initially are ≥ 5 cm and to macroscopic splenic disease after chemotherapy with the Stanford V regimen [3]. (See [Variant 3](#) and [Variant 4](#).)

Summary

- ABVD x 6-8 cycles every 4 weeks is the most commonly accepted chemotherapy regimen for advanced-stage HL in North America.
- Other chemotherapy regimens including Stanford V (which incorporates IFRT to 36 Gy to initial sites of disease measuring ≥ 5 cm and macroscopic splenic disease) and dose-escalated BEACOPP and its variants (eg, four cycles of dose-escalated BEACOPP followed by four cycles of baseline BEACOPP) can be considered. Randomized trials comparing dose-escalated BEACOPP and its variants against ABVD are pending.
- IFRT to 30-36 Gy to initially bulky (>10 cm) site(s) of disease and/or site(s) with partial response to ABVD is appropriate.

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 — Stage III and IV

Variant 1:

25-year-old woman with classical Hodgkin's lymphoma: CS IIIA, with mediastinal, splenic, and para-aortic involvement, all sites nonbulky (<5 cm), and IPS <3.

Treatment	Rating	Comments
Type of Chemotherapy		
ABVD x 6-8 cycles (every 4 weeks)	8	
Stanford V	7	RT of 36 Gy to macroscopic splenic disease. If there had been nodal sites ≥ 5 cm, these would have been irradiated to 36 Gy as well.
Dose-escalated BEACOPP x 4 cycles and baseline BEACOPP x 4 cycles (every 3 weeks)	6	
Dose-escalated BEACOPP x 8 cycles (every 3 weeks)	5	
BEACOPP-14 x 8 cycles (every 2 weeks)	5	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2:

52-year-old man with classical Hodgkin's lymphoma: CS IVB, with bulky (>10 cm) mediastinal, splenic, para-aortic, and bone marrow involvement, albumin <4 g/dL, and hemoglobin <10.5 g/dL.

Treatment	Rating	Comments
Type of Chemotherapy		
ABVD x 6-8 cycles (every 4 weeks)	8	
Stanford V	7	RT of 36 Gy to sites ≥ 5 cm and macroscopic splenic disease.
Dose-escalated BEACOPP x 4 cycles and baseline BEACOPP x 4 cycles (every 3 weeks)	7	
Dose-escalated BEACOPP x 8 cycles (every 3 weeks)	6	
BEACOPP-14 x 8 cycles (every 2 weeks)	5	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Hodgkin's Lymphoma — Stage III and IV

Variant 3:

25-year-old woman with classical Hodgkin's lymphoma: CS IIIA, with mediastinal, splenic, and para-aortic involvement, all sites nonbulky (<5 cm), and IPS <3; completed 6 cycles of ABVD, followed by restaging PET/CT showing a complete response.

Treatment	Rating	Comments
Radiation Therapy		
No RT	8	
20-29 Gy IFRT	3	
30-36 Gy IFRT	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 4:

52-year-old man with classical Hodgkin's lymphoma: CS IVB, with bulky (>10 cm) mediastinal, splenic, para-aortic (<5 cm), and bone marrow involvement, albumin <4 g/dL, and hemoglobin <10.5 g/dL; 50% reduction in mediastinal mass with residual FDG avidity limited to the mediastinum after 2 cycles of ABVD; restaging PET/CT after 4 cycles of ABVD showed a complete response; completed 6 cycles of ABVD.

Treatment	Rating	Comments
Additional Therapy		
No further therapy	2	
Radiation therapy	7	
2 additional cycles of ABVD	5	
2 additional cycles of ABVD followed by RT	6	
Radiation Therapy (if given)		
20-29 Gy IFRT to all initial sites followed by a boost to the mediastinum to a total dose of 30-36 Gy	5	
30-36 Gy IFRT to mediastinum only	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		