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ACR Appropriateness Criteria® Recurrent Hodgkin Lymphoma:

Expert Panel on Radiation Oncology—Hodgkin Lymphoma:

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Abstract

This topic addresses the management of recurrent Hodgkin lymphoma. While autologous stem cell transplantation may be appropriate for select cases of recurrent disease following comprehensive combined-modality therapy, other options exist for patients treated with lower-dose therapy for early-stage disease. Additionally, innovative targeted therapies provide newer salvage options to

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consider. The American College of Radiology Appropriateness Criteria® are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer-reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation, or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment. By combining the most recent medical literature and expert opinion, this revised guideline can aid clinicians in the complex decisionmaking associated with the management of recurrent Hodgkin lymphoma.

Summary of Literature Review

Introduction/Background

Classical Hodgkin lymphoma is a highly curable cancer, even in advanced stages. Although radiation therapy (RT) alone improved disease-free survival (DFS) for many years, the management of classical Hodgkin lymphoma has changed dramatically over the past 2 decades with the use of highly effective systemic therapies and the subsequent reduction in the use of radiation. [1] Even with combined-modality therapy (CMT), rates of relapse can vary from 5% for early-stage disease to 35% for more advanced stages.[2,3] Approximately 10% of patients will have disease that is refractory to initial therapy.[4] Even in the setting of relapsed or refractory disease, classical Hodgkin lymphoma remains salvageable. The standard of care for relapsed/refractory disease is either conventional chemotherapy or high-dose chemotherapy with autologous stem cell transplantation (HDCT + ASCT). The role of RT in relapsed/refractory disease remains controversial and is reviewed in these guidelines.

Definitions and Determination of Relapsed/Refractory Disease

Relapse or recurrence can be defined as the reappearance of disease after initial therapy and complete response (CR) in the site of prior disease and/or in new sites. Progression refers to evidence of increasing disease after achievement of stable disease, partial remission (PR), or CR, whereas refractory disease is a failure to achieve either a CR or PR and may represent a more significant degree of radiation or drug resistance.[5,6]

Current National Comprehensive Cancer Network guidelines recommend biopsy to document relapse, progression, or refractory disease.[7] Until recently, guidelines as to how to document progression of disease in the setting of incomplete remission remained unclear. [8] Therefore, it is uncertain whether in practice biopsies are routinely performed according to this standard. However, biologic confirmation of disease is recommended. A biopsy may also be warranted in patients whose disease is refractory to therapy to confirm the initial diagnosis of classical Hodgkin lymphoma.

The majority of relapses following a CR in patients treated for classical Hodgkin lymphoma occur within 3 years of therapy, so routine surveillance by clinical examination is an essential component of a survivorship plan (see the ACR Appropriateness Criteria® Follow-

up of Hodgkin Lymphoma[9]). The use of routine imaging after a CR is being challenged by recent studies,[10] so decisions regarding use can be made on an individual basis. A clear plan for surveillance is crucial, as timing of relapse has important prognostic significance and may impact treatment options.[3] Early relapse (< 12 months) is a poor prognostic factor and warrants more aggressive therapy. Other prognostic factors include localized vs disseminated disease and disease that has relapsed in previously irradiated areas.[11]

Management of Relapse Following Chemotherapy or CMT

HDCT + ASCT is the standard of care for relapsed/refractory classical Hodgkin lymphoma and can induce durable remissions in > 50% of patients.[12] No randomized trials have compared the effectiveness of salvage regimens for classical Hodgkin lymphoma, so selecting the appropriate regimen may be a challenge when considering both efficacy and toxicities. Because the goal of salvage chemotherapy is to achieve a second CR, usually a regimen different from that used for the initial course of therapy is administered.[13]

Some institutions favor platinum-based multidrug regimens, such as ICE (ifosfamide, carboplatin, and etoposide) or DHAP (dexamethasone, cytarabine, and cisplatin).[14,15] More recently, gemcitabine-based regimens[16,17] and the use of bendamustine[18] have been explored; these regimens are effective and well tolerated even in heavily pretreated patients. Gemcitabine-based regimens have been used both as primary salvage and for secondary salvage after ASCT.[16,18,19] Few studies have been done comparing the efficacy of different multidrug regimens. A small prospective study of 44 patients compared GDP (gemcitabine, dexamethasone, and cisplatin) with ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine); no difference was found in the response rate for relapsed/refractory Hodgkin lymphoma.[20]

Patients with relapsed or refractory disease after initial salvage have a median survival of < 3 years with standard therapies. [21] Newer biologics and targeted therapies, such as brentuximab vedotin and nivolumab, may further improve survival. Brentuximab vedotin (SGN-35) is a CD30-directed antibody linked to monomethyl auristatin E, an antitubulin agent.[21] In a phase I trial, this potent antibody-drug conjugate was able to induce a CR or PR in 17 of 45 patients with relapsed or refractory disease who had been treated with multiple prior therapies.[22] The other 19 cases had stable disease after treatment. In a more recent multicenter, prospective, phase II study, the use of brentuximab enabled 86% of patients with relapsed/refractory Hodgkin lymphoma to proceed to ASCT.[23] The conjugate has also been shown to be effective in patients with relapsed/refractory disease after prior autologous or allogeneic stem cell transplantation, with overall response rates of 75% and 50%, respectively.[24,25] Nivolumab is a programmed death 1 (PD-1)-blocking antibody that has considerable activity even in patients heavily pretreated for relapsed/refractory Hodgkin lymphoma who had previously failed brentuximab vedotin.[26] Other targeted agents currently in development may also impact outcomes in the setting of relapsed/refractory classical Hodgkin lymphoma.[27]

Role of RT in Hodgkin Lymphoma Salvage Programs

Poen et al[28] reported the results of a prospective trial evaluating the efficacy of involved-field radiation therapy (IFRT) as part of the salvage regimen in patients selected for ASCT. Of 100 patients with relapsed/refractory classical Hodgkin lymphoma planning to proceed to ASCT, 24 received IFRT either before (n = 18) or after (n = 6) transplant. In patients with relapsed stage I-III classical Hodgkin lymphoma, the use of IFRT was associated with an improved 3-year freedom from relapse (100% vs 67%; $P = .04$) and a trend toward improved overall survival (OS) (85% vs 60%; $P = .16$).

Two additional contemporary retrospective studies also showed that IFRT following HDCT + ASCT improves local control and survival in refractory disease, particularly in patients who have bulky disease at the time of relapse. [29,30] In one analysis, IFRT conferred benefits with respect to both 3-year OS (69.6% vs 40%) and disease-specific survival (82.1% vs 57.6%). [29] The timing of when to administer IFRT, either before or after ASCT, has been debated. When radiation is administered prior to ASCT, patients are more likely to receive the radiation as planned. Any marrow that may be in the field will be replaced once the patient's transfused stem cells engraft, and there is a greater chance that the patient will enter ASCT with no residual disease. Some may prefer delivering radiation after ASCT to minimize the interval between the last dose of chemotherapy and ASCT, although several centers are accelerating the course of radiation to accommodate a quicker transition to ASCT. There is also a concern that radiation before ASCT may delay treatment plans because of increased toxicity; however, in the modern era, involved-site radiation therapy (ISRT) is the preferred method used in the management of both Hodgkin lymphoma and non- Hodgkin lymphoma,[31] and the smaller fields may reduce risk of acute treatment-related toxicities.

Total lymphoid irradiation (TLI) can be utilized as part of conditioning regimens prior to ASCT. A recent study evaluated the use of positron emission tomography (PET)/computed tomography (CT) to predict outcomes of 51 patients treated for relapsed/refractory disease with TLI followed by HDCT + ASCT.[32] The 10-year progression-free survival (PFS) and OS rates were 56% and 54%, respectively. There are several ongoing clinical trials utilizing TLI as part of nonmyeloablative, reduced-intensity conditioning regimens for several hematologic disorders, including Hodgkin lymphoma (www.ClinicalTrials.gov). Some institutions have included total body irradiation (TBI) as part of the pretransplant conditioning regimen.[28,33,34] A feasibility study of tandem ASCT for relapsed/refractory classical Hodgkin lymphoma compared myeloablative regimens containing either busulfan or 12 Gy of TBI for patients making it to the second transplant.[33] Of the 43 patients enrolled, 32 received the second ASCT, with half receiving TBI. An additional 20 Gy of IFRT was included for 5 of these patients. In this particular study, the use of TBI did not increase risk of acute or late toxicities when compared with the group receiving chemotherapy alone.

Role of RT in Advanced-Stage Chemorefractory Hodgkin Lymphoma

Limited data are available on the role of consolidative RT in the setting of residual fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) avidity following combination

chemotherapy for patients with advanced classical Hodgkin lymphoma. Sher et al[35] performed a retrospective analysis of 73 patients who received consolidative IFRT following systemic therapy to evaluate the prognostic significance of residual FDG avidity. The majority of patients (n = 60) were PET-negative at the end of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) therapy; the actuarial 2-year failure-free survival rate was 97% for this group, with 100% salvage for patients who relapsed. The 2-year failure-free survival rate was 69% for the PET-positive group with IFRT doses of ≥ 30 Gy, generating the hypothesis that the addition of RT may successfully sterilize local residual disease, thereby precluding the need to proceed immediately to salvage therapy in this setting.

In the European Organisation for Research and Treatment of Cancer (EORTC) 20884 trial, patients with stage III/IV classical Hodgkin lymphoma were treated with 6 to 8 cycles of MOPPABV (mechlorethamine, vincristine, procarbazine, and prednisone with doxorubicin, bleomycin, and vinblastine); patients who achieved a PR received 30-Gy IFRT.[36] The freedom from treatment failure (FFTF) and OS for this group were similar to patients who had achieved a CR in this study (5-year event-free survival, 79%; 5-year OS, 87%), suggesting that IFRT following a PR to systemic therapy improves outcomes.

Similarly, the German Hodgkin Study Group (GHSG) HD15 trial for patients with advanced-stage classical Hodgkin lymphoma administered 30-Gy IFRT to patients with PET-positive disease that measured ≥ 2.5 cm on CT scan after BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). [37] Of 311 patients who met criteria for enrollment, PET was positive in 66 patients; RT was recommended for 63. The PFS rate at 18 months was 96% for PET-negative patients and 85% for PET-positive patients, indicating that IFRT for patients with persistently FDG-avid disease can successfully sterilize residual disease and may be a viable alternative to HDCT + ASCT.

Salvage Without Stem Cell Transplantation

Although HDCT + ASCT is the standard of care for relapsed/refractory classical Hodgkin lymphoma, several scenarios exist where alternative treatment strategies could be considered. These include patients with late relapse (> 1 year), patients who received limited frontline therapies such as RT or chemotherapy alone, or patients with early-stage disease treated with reduced-intensity therapy (eg, 2 cycles of ABVD followed by 20-Gy RT).

Relapse following RT alone—Historical series suggest that approximately 20% to 35% of patients with early-stage Hodgkin lymphoma treated with RT alone will relapse. [38,39] Yet there were many variables across studies, including staging with or without laparotomy, inclusion of patients with different prognostic factors, and differences in radiation field size, which may have impacted DFS and therefore make comparing studies a challenge. Ng et al[40] described out-comes of a single-institution prospective trial evaluating the use of mantle irradiation alone in patients with early-stage classical Hodgkin lymphoma. Patients with stage I-IIA classical Hodgkin lymphoma were enrolled in the study; patients with B symptoms, bulky disease, or subcarinal or hilar involvement were excluded. Mantle

radiation with doses ranging from 30 to 40 Gy was delivered from 1988 to 2000 in a cohort of patients with a median age of 30 years. Of the 87 patients enrolled, 13 (15%) relapsed, with most sites of relapse outside of the original treatment field. Half of the patients were salvaged with ABVD alone; the other half had CMT with IFRT. Only 1 patient experienced a second relapse and underwent salvage with HDCT followed by stem cell transplantation (SCT).[40]

An earlier retrospective study from MD Anderson Cancer Center enrolling patients beginning in 1967 included patients with unfavorable disease, including bulky tumor, > 4 sites of disease, and/or B symptoms.[41] The 10-year PFS rate following mantle irradiation for this cohort that included patients with higher-risk disease was 75.3%. However, 10- and 20-year actuarial OS rates were 87.6% and 65.3%, respectively, confirming highly successful salvage rates after treatment with radiation alone.

Although the use of RT as a primary treatment of classical Hodgkin lymphoma is no longer the standard of care, for the small cohort of patients previously treated with RT alone, it is still important to bear in mind that chemotherapy alone or with RT may be sufficient for salvage. However, limited data exist to provide definitive treatment recommendations.

Relapse following reduced-intensity therapy for early-stage disease—Reduced-intensity therapy with 2 cycles of ABVD followed by 20-Gy IFRT for patients with favorable early-stage classical Hodgkin lymphoma provides favorable outcomes, with a FFTF rate of 91.1% at 5 years.[2] Since relapse in this very favorable group is uncommon, decisions must be made regarding the appropriate salvage therapies. Little data exist regarding the best salvage options in this setting.

The GHSG assessed results of salvage therapy in 42 patients out of 1,129 who were enrolled in 3 different prospective trials evaluating the use of 2 cycles of ABVD followed by IFRT.[11] About 50% of these patients experienced an infield relapse, and a variety of salvage regimens were employed, including chemotherapy, HDCT + ASCT, and RT alone. In this small cohort, which had a median follow-up of 3 years, the OS rate was 67% following salvage therapy. Although this small report provides some insight into salvage following reduced-intensity therapy, additional prospective studies are needed to define the optimal salvage regimen in this cohort. In the meantime, extrapolation from these data regarding treatment of relapses with either chemotherapy or RT alone should help make informed decisions.

Relapse following chemotherapy alone—In the modern era, most patients diagnosed with Hodgkin lymphoma receive chemotherapy as part of initial therapy, either with or without consolidative RT. Treatment options at the time of relapse will vary based on a variety of prognostic features, the most significant of which are the presence of refractory disease and early and advanced relapses.[42]

Despite evidence suggesting that the addition of RT to systemic therapy improves tumor control and OS in patients with early-stage classical Hodgkin lymphoma,[34,43] efforts are still underway to validate the use of chemotherapy alone as a means to decrease late

treatment-related toxicities. One retrospective study reports the results of patients with early-stage classical Hodgkin lymphoma who were treated with chemotherapy alone from 1992 to 2008.[44] Bulky disease was excluded and eligible patients received 6 cycles of ABVD. All 71 of the patients included in the study achieved a CR. At a median follow-up of 60 months, there were 6 relapses (8%), all at the site of presenting disease. Five of the relapses occurred within the first 2 years after a CR, and salvage consisted of CMT followed by ASCT.

It bears mentioning that salvage RT alone may be sufficient in these patients with local recurrence. Josting et al[45] reported the results of salvage RT for patients enrolled in GHSG trials from 1988 to 1999 who relapsed; most had been treated with COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/ABVD-like regimens. Salvage RT was used to treat patients at the time of initial relapse; the treatment field varied but mantle or IFRT was most often applied. Of the 100 patients, 77 achieved a CR. Sixty-eight of these patients (88%) had stage I/II disease. [45] In this largest series evaluating use of salvage RT, the 5-year FFTF and OS rates were 28% and 51%, respectively, highlighting the need for appropriate patient selection.

Likewise, the management of patients who initially received chemotherapy alone for early-stage disease and then relapsed locally must be carefully considered when outlining a treatment plan. Although ASCT has been shown to improve OS in relapsed classical Hodgkin lymphoma, it may not be necessary in this particular cohort of patients. [42] For each case, the long-term toxicity of additional chemotherapy must be weighed against that of modern RT (see Variants 1-6).

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Summary of Recommendations

- Hodgkin lymphoma is a highly curable disease, even in the relapsed setting.
- Although the standard of care for relapsed disease remains salvage therapy followed by ASCT, other alternatives exist in the modern era.
- Biologics and targeted agents such as brentuximab vedotin and nivolumab offer alternative systemic therapies that may get patients to ASCT faster and with less toxicity.
- The role of RT in the relapsed setting remains controversial, but prognostic factors such as timing and extent of relapse may help guide clinical decision making.
- In selected patients with small isolated relapses that occur > 3 years after initial presentation, consideration may also be given to a course of RT alone or CMT without transplant.
- RT is particularly indicated as part of CMT for patients with local relapse after treatment with chemotherapy alone or for relapses outside of the original site of disease; in this setting, ASCT may be deferred.
- ASCT should be considered for all patients with early relapsed or progressive disease while on therapy. If there is a PR to salvage chemotherapy, RT may be given pretransplant to achieve a CR.
- If a patient has a CR and the timing of RT is not dictated by a clinical trial, consolidative RT after ASCT allows the patient to proceed with therapy that is proven to improve OS.
- Modern radiation techniques, smaller treatment field, and lower overall doses help improve the therapeutic ratio of RT.
- Decisions regarding the best options in the relapsed setting should be made in the multidisciplinary setting.

VARIANT 1.

25-year-old woman with CS IA (right neck) NSHL was treated with 2 cycles of ABVD + 20-Gy IFRT and achieved a CR. Two years after completion of treatment, a new 3-cm node was palpated in left neck. (Late nodal relapse after reduced-intensity therapy.)

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	9	
Recommended treatment		
RT alone	4	
Salvage chemotherapy alone	6	
Salvage chemotherapy + RT	7	
Salvage chemotherapy + SCT	6	SCT has treatment-related morbidity but may be appropriate in this clinical scenario.
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	5	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to site of relapse	8	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	2	
Timing of RT		
Primary therapy	4	
Following salvage chemotherapy, if no SCT	8	
RT dose (CR to salvage chemotherapy)		
< 30 Gy	4	There are limited data on low dose in this setting.
30–36 Gy	7	
> 36 Gy	4	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; IFRT = involved-field radiation therapy; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; RT = radiation therapy; SCT = stem cell transplantation; TLI = total lymphoid irradiation.

VARIANT 2.

25-year-old woman with CS IIA (bilateral neck) NSHL was treated with 4 cycles of ABVD alone and achieved a CR. Two years after completion of treatment, a new 3-cm node was palpated in left neck. (Late nodal relapse after chemotherapy alone.)

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	9	
Recommended treatment		
RT alone	4	
Salvage chemotherapy alone	4	
Salvage chemotherapy + RT	7	
Salvage chemotherapy + SCT	5	
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	5	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to site of relapse	8	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	3	
Timing of RT		
Primary therapy	3	There are limited data to address this question.
Following salvage chemotherapy, if no SCT	7	
After salvage chemotherapy, before SCT (CR to salvage chemotherapy)	6	
After SCT	7	Some clinical trials dictate timing of RT
RT dose (CR to salvage chemotherapy)		
< 30 Gy	4	
30–36 Gy	8	
> 36 Gy	4	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; RT = radiation therapy; SCT = stem cell transplantation; TLI = total lymphoid irradiation.

VARIANT 3.

25-year-old woman with CS IIIA (neck, mediastinum, and para-aortic) NSHL was treated with 6 cycles of ABVD alone and achieved a CR. Six months after completion of treatment, a new 3-cm node was palpated in left neck. (Early nodal relapse after chemotherapy alone.)

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	9	
Recommended treatment		
RT alone	2	
Salvage chemotherapy alone	3	
Salvage chemotherapy + RT	5	
Salvage chemotherapy + SCT	7	
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	8	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to site of relapse	8	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	3	In this scenario, TLI is not referring to conditioning for SCT Consider whether it is appropriate to use TLI as adjuvant therapy.
Timing of RT		
Primary therapy	2	
Following salvage chemotherapy, if no SCT	7	
After salvage chemotherapy, before SCT (CR to salvage chemotherapy)	7	
After SCT	7	
RT dose (CR to salvage chemotherapy)		
< 30 Gy	4	
30–36 Gy	8	
> 36 Gy	5	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; RT = radiation therapy; SCT = stem cell transplantation; TLI = total lymphoid irradiation.

VARIANT 4.

25-year-old woman with CS IIIAX (neck, bulky mediastinum, upper para-aortic) NSHL was treated with ABVD × 6 and IFRT (30 Gy to the mediastinum).Three years after completion of therapy, chest CT showed new mediastinal adenopathy with bilateral lung nodules. (Possible late relapse after combined-modality therapy.)

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	9	
Recommended treatment		
RT alone	1	
Salvage chemotherapy alone	4	
Salvage chemotherapy + RT	3	
Salvage chemotherapy + SCT	8	
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	5	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to mediastinum	5	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	3	
Timing of RT		
Primary therapy	2	
Following salvage chemotherapy, if no SCT	5	This option is indicated if there is a CR to salvage chemotherapy.
After salvage chemotherapy, before SCT (CR to salvage chemotherapy)	6	
After SCT	7	
RT dose to mediastinum (CR to salvage chemotherapy)		
< 30 Gy	6	
30–36 Gy	6	
> 36 Gy	4	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; CT = computed tomography; IFRT = involved-field radiation therapy; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; RT = radiation therapy; SCT = stem cell transplantation; TLI = total lymphoid irradiation.

VARIANT 5.

25-year-old woman with CS IIIAX (neck, bulky mediastinum, upper para-aortic) NSHL was treated with ABVD. After 6 cycles of ABVD, no significant decrease in mediastinal abnormality was seen and a new axillary node was palpated. (Progression on chemotherapy.) PET Deauville 5.

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	8	Pathologic confirmation should help differentiate between relapse, follicular hyperplasia, infection, and transformation.
Recommended treatment		
RT alone	2	
Salvage chemotherapy alone	3	
Salvage chemotherapy + RT	3	
Salvage chemotherapy + SCT	7	
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	8	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to site of relapse	8	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	4	
Timing of RT		
Primary therapy	2	
Following salvage chemotherapy, if no SCT	5	
After salvage chemotherapy, before SCT (CR to salvage chemotherapy)	7	
After SCT	7	
RT dose to mediastinum (CR to salvage chemotherapy)		
< 30 Gy	4	
30–36 Gy	7	
> 36 Gy	6	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; PET = positron emission tomography; RT = radiation therapy; SCT = stem cell transplantation; TLI = total lymphoid irradiation.

VARIANT 6.

25-year-old woman with CS IIIAX (neck, bulky mediastinum, upper para-aortic) NSHL was treated with ABVD. After 6 cycles of ABVD, the mediastinal disease regressed by 33% and mass remained FDG avid [Deauville 4]. (Incomplete response to chemotherapy.)

Treatment	Rating	Comments
Evidence for relapse or refractory disease		
Requires pathologic confirmation	7	
Recommended treatment		
RT alone	5	
Salvage chemotherapy only	5	
Salvage chemotherapy + RT	5	
Salvage chemotherapy + SCT	7	
Salvage chemotherapy + RT + SCT (CR to salvage chemotherapy)	7	
Volume of RT (after CR to chemotherapy)		
RT (ISRT) to site of relapse	8	
Adjuvant RT to recurrent and all previously untreated nodal sites (TLI)	3	
Timing of RT		
Primary therapy	5	
Following salvage chemotherapy, if no SCT	5	
After salvage chemotherapy, before SCT (CR to salvage chemotherapy)	6	
After SCT	7	
RT dose to mediastinum (CR to salvage chemotherapy)		
< 30 Gy	3	
30–36 Gy	7	
> 36 Gy	7	

Rating Scale: 1,2,3 = usually not appropriate; 4,5,6 = may be appropriate; 7,8,9 = usually appropriate.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; CR = complete response; CS = clinical stage; FDG = 2-fluoro-2-deoxy-D-glucose; ISRT = involved-site radiation therapy; NSHL = nodular sclerosis Hodgkin lymphoma; RT = radiation therapy; SCT = stem cell transplantation;TLI = total lymphoid irradiation.