Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2016 September 01; 96(1): 110–118. doi:10.1016/j.ijrobp.2016.03.052.

Treatment of Early-Stage Unfavorable Hodgkin Lymphoma: Efficacy and Toxicity of 4 Versus 6 Cycles of ABVD Chemotherapy With Radiation

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Abstract

Purpose—The German Hodgkin Study Group HD11 trial validated 4 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy followed by involved field radiation therapy (IFRT) for early unfavorable Hodgkin lymphoma (HL) patients. However, practitioners often recommend 6 cycles followed by RT, especially for bulky disease. We compared patient outcomes after treatment with 4 or 6 cycles of ABVD followed by RT (IFRT and involved site RT [ISRT]).

Methods and Materials—We identified 128 patients treated for early unfavorable HL (GHSG criteria) between 2000 and 2013. Clinical outcomes (overall survival [OS] and freedom from relapse [FFR]) were estimated using Kaplan-Meier analysis. Toxicities were evaluated.

Results—The median follow-up time was 5.0 years. Patients received 4 (70 patients, 55%) or 6 (58 patients, 45%) cycles of chemotherapy. Bulky disease was present in 22 patients (31%; 0 stage IA, 3 stage IB, 19 stage IIA) of the 4-cycle group and 42 patients (72%; 5 stage IA, 3 stage IB, 34 stage IIA) of the 6-cycle group. For patients receiving 4 and 6 cycles, the 6-year OS was 100% and 97% ($P=.35$), respectively, and the 6 year FFR was 100% and 98% ($P=.28$), respectively. More patients received 6 cycles if they were treated before 2010 (HD11 report) ($P=.01$) and if they had bulky disease ($P<.01$). Sixty-eight percent of patients received ISRT. The 6-year FFR was 99% and

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Conflict of interest: none.

100% for patients receiving ISRT and IFRT, respectively ($P=.58$). More patients experienced bleomycin pulmonary toxicity in the 6-cycle group (20% vs 31%, $P=.16$). For patients with bulky disease, the 4-year FFR was similar with receipt of 4 (100%) or 6 (98%) cycles ($P=.48$) and IFRT (100%) or ISRT (98%) ($P=.52$). There were no deaths among patients with bulky disease.

Conclusions—Patients with early unfavorable HL have excellent outcomes with 4 cycles of ABVD chemotherapy followed by ISRT. Six cycles of chemotherapy does not appear superior for disease control, even for bulky disease.

Introduction

Over the past several decades, the treatment of Hodgkin lymphoma has improved considerably, resulting in excellent outcomes and survival rates of 95% to 100% for early-stage disease (1–5). For this reason, de-escalation of therapy has become the goal, with intent to spare patients treatment toxicities that often manifest decades later (6–10). Both chemotherapy and radiation therapy (RT) regimens have been deintensified and optimized in attempts to provide only the minimum treatment necessary to maintain excellent outcomes (11, 12).

A large, randomized trial from the German Hodgkin Study Group (GHSG) sought to identify the optimum treatment for patients with early-stage disease and higher-risk features, a group termed “early unfavorable” (4). This trial compared 2 chemotherapy regimens: doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) and 2 radiation doses (20 and 30 Gy) in a 2×2 factorial design and concluded that BEACOPP did not improve outcomes for early unfavorable HL patients (4). Therefore, early unfavorable patients were recommended to receive treatment with 4 cycles of ABVD followed by 30 Gy of involved field radiation therapy (IFRT). This recommendation was not widely adopted, reflected by practice variation, and many providers have continued to prescribe 6 cycles with RT for this patient group, especially for those with high-risk features such as bulky disease, aggressive pathologic features, or large disease burden (multiple nodal stations) (13, 14).

Just as chemotherapy regimens and radiation doses have been progressively reduced, radiation treatment fields have also become smaller and more targeted. Imaging and technologic advances such as respiratory gating have allowed more accurate and precise RT delivery, which provides greater confidence when treatment field sizes are reduced (15–21). Therefore, current recommendations advocate involved site radiation therapy (ISRT) (22), a technique based on treating disease identified at presentation using a combination of imaging techniques, including computed tomography (CT) with contrast medium, positron emission tomography (PET), and magnetic resonance imaging. These changes have the potential to ameliorate the side effect profile of treatment with RT (18, 23). However, the large randomized controlled studies that validated the current treatment regimens were performed with older RT techniques, specifically IFRT (24). There are, currently, limited data available to provide guidance on the adequacy of this treatment in the era of ISRT (25).

The current National Comprehensive Cancer Network (NCCN) guidelines for early unfavorable patients recommend 4 cycles of ABVD followed by assessment with PET-CT.

For patients responding to chemotherapy, either ISRT or an additional 2 cycles of chemotherapy followed by ISRT is recommended. Our study included a population of early-stage unfavorable patients treated at our institution who fit the criteria for the HD11 trial and also reflect the common practice of using either 4 or 6 cycles of chemotherapy at the discretion of the treating physician. We hope to provide evidence that patients receiving 4 cycles of chemotherapy followed by RT also achieve excellent outcomes and benefit from decreased toxicity of treatment. We also attempt to show that de-escalated chemotherapy regimens and radiation doses still apply in the setting of smaller, modern ISRT fields.

Methods and Materials

Patient identification

After institutional review board approval, patients with pathologically proven HL treated at our institution were reviewed. We identified 128 consecutive patients with stage I or II HL treated between 2000 and 2013 who fit the classification of early unfavorable based on GHSG HD 11 trial criteria (bulky disease, extranodal sites, ≥ 3 involved sites, or erythrocyte sedimentation rate elevation [≥ 50 mm/h without B symptoms or ≥ 30 mm/h with B symptoms]) (1). Patients with stage IIB and bulky disease or stage IIB and extranodal involvement were excluded (as per HD11). All patients were treated with the goal of consolidation after chemotherapy; no patients who had experienced relapse were included.

Patient characteristics

Patient stage, including extranodal sites and bulky disease, was abstracted from clinical documentation and verified by review of initial imaging (contrast-enhanced CT and PET/CT scan). Bulky disease was defined as >10 cm in greatest diameter on CT axial slices within the mediastinum or ≥ 5 cm outside the mediastinum. Disease was staged by the Ann Arbor system, and patients were defined as early favorable/unfavorable per HD11 criteria (GHSG risk group classifications). Number of disease sites (per Ann Arbor and GHSG systems) was determined by review of initial PET/CT scans. B symptoms were recorded from clinical documentation. All cases had pathologic review at our institution confirmed by histologic and immunophenotypic examination of excisional or core needle biopsy specimens (including flow cytometry and immunohistochemical analysis of fixed, paraffin-embedded tissue).

Restaging evaluations

Patients underwent interim PET/CT evaluations at the discretion of the treating oncologist. The scans were read by a radiologist specializing in nuclear medicine. Deauville criteria were not routinely assigned. A PET/CT scan was considered negative if complete resolution of hypermetabolism was noted.

Chemotherapy treatment

Patients were required to complete all cycles of intended chemotherapy (4 or 6) to be included in the study. Patients whose bleomycin was discontinued because of toxicity or preparation for radiation finished the remaining cycles as AVD only (ABVD with bleomycin omitted).

Radiation treatment

Radiation therapy plans were classified as ISRT, IFRT, or other (eg, mantle fields, EFRT). These designations were made using clinical documentation in the medical record and review of the RT plan by 2 radiation oncologists (B.S.D., C.C.P.). If plans were not available for review because a patient had been treated at an outside facility, terminology used in clinical documentation was used. We defined ISRT according to the International Lymphoma Radiation Oncology Group (ILROG) guidelines (22). IFRT was defined according to the HD11 study (1).

Outcomes

Outcomes including overall survival (OS) and freedom from relapse (FFR) were calculated from date of pathologic diagnosis. Patients who survived were censored at the last date of follow-up.

Toxicity assessment

Cardiac toxicity was based on ejection fraction (EF) on echocardiogram or radionuclide ventriculography (EF estimations from these 2 modalities have excellent positive correlations) (26). Cardiac dysfunction was defined as a decrease in the left ventricular EF of >10% to a value <53% (2-dimensional echocardiography reference value) (27). Pulmonary function test reports were used to record carbon monoxide diffusion in the lung (DLCO) measurements. Bleomycin pulmonary toxicity was defined as clinical respiratory symptoms leading to discontinuation of bleomycin, bilateral opacities on CT imaging, drop in DLCO by 25%, or a combination of these events, in the absence of infection (ZA Yehia et al, unpublished data).

Data management and statistical analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at MD Anderson Cancer Center (28). REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources.

The OS and FFR curves were calculated using the Kaplan-Meier method. An exploratory subset analysis was performed for patients with bulky disease. Differences between patients receiving 4 versus 6 cycles were assessed using the χ^2 test (Fisher exact test for cell sizes ≤ 5). All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, NC) and Stata/MP 13.0 statistical software.

Results

Patient characteristics

The study included 128 patients with early unfavorable HL. Full information on patient characteristics is detailed in Table 1. Seventy patients (55%) received 4 cycles of

chemotherapy, and 58 patients (45%) received 6 cycles. Of those receiving 4 cycles, the median age was 29 years (range, 19–63 years). Thirty-one patients (44%) were male. Six patients (9%) had stage I disease, and 64 (91%) had stage II disease. Nearly all the patients (59, 84%) had nodular sclerosing histology. Eleven patients (16%) had B symptoms. A majority of patients were classified as early unfavorable because they had 3 or more nodal sites involved (53, 76%). All patients received ABVD chemotherapy. The median radiation dose was 30.6 Gy (range, 20–39.6 Gy), with 6 patients receiving 36 Gy. Fifty-three patients (76%) received ISRT, and 12 patients (17%) received IFRT. Most patients (54, 77%) had interim PET/CT evaluations, commonly after 2 cycles (median) of chemotherapy. One patient (2%) had positive disease (standard uptake value 7.6, decreased from initial SUV 9.9) at this time point, with final PET/CT negative.

For patients receiving 6 cycles of chemotherapy, the median age was 30 years (range, 18–70 years). Seventeen patients were male (29%). A majority of patients had stage II disease (51, 88%). Nearly all patients had nodular sclerosing histology. Eleven patients (19%) had B symptoms. A majority of the patients were classified as early unfavorable because of the presence of bulky disease (42, 77%), and 30 patients (52%) had 3 or more nodal sites involved. Nearly all patients (86%) received ABVD chemotherapy. Two patients received AVD with bleomycin omitted because of underlying lung disease. Six patients received an ABVD-based regimen with an additional agent, treated on institutional protocol. The median radiation dose for this group was 30.6 Gy (range, 27–41.4 Gy), with 16 patients receiving 36 Gy. Thirty-six patients (62%) received ISRT, and 16 patients (28%) received IFRT. Nearly all patients (51, 88%) had interim PET evaluations, most commonly after 2 cycles (median) of chemotherapy. Four patients (8%) had hypermetabolism on interim PET/CT evaluation and went on to complete the intended 6 cycles of chemotherapy. Two of these patients had residual hypermetabolism after all chemotherapy, and 1 patient received a higher radiation dose of 39.6 Gy.

Clinical outcomes

The median follow-up time for all patients was 5.0 years. The 6-year OS was 100% and 97% for patients receiving 4 and 6 cycles of chemotherapy, respectively ($P=.35$; CI 79.8%–99.6%) (Fig. 1a). The 6-year FFR was 100% and 98% for patients receiving 4 and 6 cycles of chemotherapy, respectively ($P=.28$; CI 88.2%–99.8%) (Fig. 1b). One patient in the 6-cycle group died of unrelated chronic pulmonary issues, with no evidence of lymphoma at the time of death. One patient experienced relapse approximately 1 year after diagnosis (5 months after therapy completion). He initially presented with weight loss, shortness of breath, and fatigue. Imaging revealed a large mediastinal mass, biopsy positive for nodular sclerosing HL. He was staged as IB bulky and was dispositioned to 6 cycles of ABVD chemotherapy. His PET/CT scan showed complete metabolic response after cycle 4A of ABVD. He received 36 Gy in 20 fractions of ISRT to the mediastinum. Follow-up imaging 5 months after treatment identified diaphragmatic nodes that were biopsy positive for recurrent lymphoma. He underwent autologous stem cell transplantation after BEAM (BCNU, etoposide, ara-C, and melphalan) conditioning and was in remission at his most recent follow-up visit, approximately 5 years after transplantation.

The 6-year OS was 100% and 97% for patients receiving IFRT and ISRT, respectively ($P=.37$; CI 79.2%–99.5%) (Fig. 1c). The 6-year FFR was 100% and 99% for patients receiving IFRT and ISRT, respectively ($P=.58$; CI 92.1%–99.8%) (Fig. 1d). Patients with bulky disease had a median follow-up period of 4.7 years. Among these patients, there were no significant differences in 4-year FFR between the 4-cycle (100%) and 6-cycle (98%) groups ($P=.48$; CI 84.3%–99.7%). The 4-year FFR was 100% and 98% for patients receiving IFRT and ISRT, respectively ($P=.52$, CI 84.3%–99.7%) (Fig. 2). There were no deaths among the patients with bulky disease.

Treatment decisions

A greater proportion of patients were treated with 6 cycles of chemotherapy before 2010 ($P=.01$) and if bulky disease was present ($P<.01$). Although not significant, a greater percentage of patients had positive interim PET/CT evaluations in the 6-cycle group ($P=.11$). Otherwise, the clinical characteristics were fairly equal between the 2 groups (Table 2). Of those patients treated in 2010 and afterward, there was a higher proportion of patients with bulky disease in the 6-cycle group ($P<.01$). On chart review, a majority of the patients (40, 69%) had no reason documented in the medical record that clarified the decision to give 6 cycles of chemotherapy (Table 3). Other reasons that were documented included treatment on protocol (6, 10%), bulky disease (5, 9%), “standard of care” (4, 7%), residual disease on CT (non-PET/CT avid) after chemotherapy (1, 2%), or other aggressive risk factors (2, 3%) including, for example, aggressive pathologic features or increased number of nodal sites. Patients sometimes received higher, nonstandard RT doses, usually for residual mass with or without hypermetabolism.

Toxicity assessment

Forty-two patients (60%) in the 4-cycle group completed at least cycle 4A of the full ABVD regimen, including bleomycin. Twenty-one patients (30%) completed 3 cycles of bleomycin, and 7 patients (10%) completed 2 cycles of bleomycin. Fourteen patients (20%) experienced bleomycin pulmonary toxicity. Twenty-nine patients (50%) in the 6-cycle group completed at least cycle 6A of bleomycin. Nine patients (16%) completed 5 cycles, 10 patients (17%) completed 4 cycles, and 5 patients (9%) completed 3 cycles of bleomycin. Five patients did not receive bleomycin because of medical comorbidities. Eighteen patients (31%) experienced bleomycin pulmonary toxicity (Table 4).

Only 26 patients had cardiac assessment with EF evaluation both before and after chemotherapy. Of those with paired assessments, no patients (0%) in the 4-cycle group and 1 patient (10%) in the 6-cycle group had an EF decrease consistent with cardiac dysfunction at the completion of chemotherapy.

Discussion

In this study of early unfavorable HL patients (including those with bulky disease), we did not identify a significant difference in outcome for those treated with 4 or 6 cycles of ABVD followed by radiation. These favorable results apply even in the setting of modern radiation fields where IFRT has been refined to a much smaller ISRT field. This work provides

retrospective support for excellent treatment outcomes with both 4 and 6 cycles of chemotherapy.

The results of the GHSG HD11 support the use of 4 cycles of ABVD chemotherapy followed by IFRT to 30 Gy. With this treatment regimen, patients benefited from promising outcomes in terms of OS and FFR. Other prospective work has directly compared 4 versus 6 cycles of ABVD chemotherapy with IFRT for unfavorable (European Organization for Research and Treatment of Cancer definition) HL patients, and preliminary results show similar event-free and OS rates (29). Because these patients have long life expectancies, the focus has shifted from improvement of outcomes to de-escalation of therapy to spare these patients the potentially severe and permanent side effects of treatment (6, 23, 30).

Despite the data supporting this regimen for early-stage unfavorable HL patients, many providers continue to prescribe 6 cycles of chemotherapy followed by radiation. Some may believe that there is insufficient evidence to support only 4 cycles in patients with risk factors like bulky disease because these patients constituted only 19.5% of the HD11 study population (4). In our study, the proportion of patients with bulky disease in the 6-cycle group was strikingly higher than in the 4-cycle group, and many have documented bulky disease as reasoning for additional chemotherapy. We also recognize that treatment year played a role in the decision to give 6 cycles, given that the HD11 trial final report was published in 2010. It follows that many patients benefited from decreased treatment if their diagnoses were more recent, as the study conclusions were adopted more broadly. However, even for those treated after 2010, a large proportion of patients with bulky disease received 6 cycles. Interestingly, even a negative PET/CT result on interim analysis, achieved by nearly all patients receiving 6 cycles of chemotherapy, did not sway providers to abridge the chemotherapy regimen.

The NCCN guidelines allow a patient to receive 6 cycles of ABVD followed by RT, but our data provide evidence that this extra treatment is unnecessary and even potentially harmful. While recognizing our limited access to toxicity data, we found an increased rate of bleomycin pulmonary toxicity for patients receiving 6 cycles of chemotherapy. Treatment with a bleomycin-containing regimen carries known associated risks and necessitates regular pulmonary function tests. In fact, patients with toxicity from this agent have been found to have a decreased median OS compared with unaffected patients (31). This study also reported mortality from bleomycin pulmonary toxicity of 4.2% in all patients and 24% in those experiencing the pulmonary syndrome (31). Others have even attempted to validate the efficacy of the regimen with bleomycin omitted (31, 32), but the complete elimination of this agent was not found to be safe (33).

Similarly, cardiomyopathy and heart failure are known adverse events of prolonged anthracycline treatment, and more advanced monitoring techniques have demonstrated subclinical cardiac toxicity in a large fraction of patients (34). A landmark study on the cardiac toxicity of doxorubicin found that cumulative dose was the greatest determinant of heart failure development. Additional studies have shown subclinical, dose-dependent decreases in left ventricular EF, especially at doses greater than 350 mg/m² (34). Meta-analysis revealed that risk of cardiac death is increased 4.94-fold when anthracyclines are

used in a chemotherapy regimen (35). Unfortunately, our study cannot fully assess the cardiac toxicity associated with 6 cycles versus 4 cycles because few patients underwent paired cardiac evaluations before and after chemotherapy.

Because we were interested in assessing toxicity associated with additional chemotherapy only, we were not able to report long-term adverse events because all patients went on to receive RT. Given that both ABVD and RT can cause lung and cardiac adverse events, the cause of long-term toxicity could not be accurately attributed. Owing to the known risks of treatment and the strong evidence for excellent outcomes with only 4 cycles, we think that all early unfavorable HL patients can be safely treated with this regimen, regardless of risk factors such as bulky disease.

Some might argue that progressive decreases in RT fields could necessitate a larger contribution of treatment from chemotherapy. Radiation treatment fields have continued to decrease in size, with the current ILROG guidelines recommending ISRT as the standard conformal therapy when optimal imaging is not available (22). This technique uses upfront imaging to delineate the initial disease extent and treats only regions where disease was present. By contrast, the IFRT used in the HD11 trial included the entire involved nodal site regardless of disease location. With only 1 relapse and 1 unrelated death in our population of patients, there were no significant differences between the 2 arms, even for those patients who received only ISRT. With the current techniques available, including image guidance of treatment delivery, respiratory gating, and IMRT, smaller RT fields can be safely and effectively delivered without decreased treatment efficacy. This report should lend confidence to those treating HL patients in the modern era; additional chemotherapy is not necessary to compensate for decreased treatment fields.

Our report is limited by its retrospective nature and by the small number of patients with postchemotherapy pulmonary and cardiac evaluations. These data are necessary to enable stronger conclusions to be drawn regarding the possible toxicity of an additional 2 cycles of chemotherapy. In keeping with the trend of treatment de-escalation, involved nodal RT (36) may become more popular in the coming years, and future prospective studies could validate current chemotherapy and radiation dose regimens with this even more stringent RT technique.

Overall, this report is valuable because it further supports treatment de-escalation for early-stage HL patients. We have shown that patients who received the validated HD11 treatment regimen, 4 cycles of ABVD chemotherapy followed by 30 Gy RT, have excellent outcomes similar to the outcomes in patients who received 6 cycles of chemotherapy followed by RT. The potential for increased short-term and long-term treatment-related side effects should caution providers against prescribing longer chemotherapy regimens in the context of combined modality treatment, even for patients with risk factors such as bulky disease. Moreover, advances in the delivery of RT have allowed for accurate and precise delivery of radiation, and patients receiving ISRT also benefit from excellent outcomes with only 4 cycles of chemotherapy. Thus, physicians practicing in the modern era can continue to treat early unfavorable HL patients with this less-toxic regimen without concern for increased future failure.

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Summary

The German Hodgkin Study Group HD11 trial established treatment for patients with early-stage, unfavorable Hodgkin lymphoma as 4 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) with 30-Gy involved field radiation therapy (RT). However, patients often still receive 6 cycles of chemotherapy. We reviewed patients (including those with bulky disease) treated with 4 or 6 cycles of chemotherapy followed by RT and found that both regimens achieved excellent outcomes, even with involved site RT. Therefore, 4 cycles of ABVD with 30 Gy involved site RT is a reasonable and safe treatment paradigm.

Fig. 1. Kaplan-Meier plot of overall survival and freedom from relapse for patients receiving 4 versus 6 cycles of chemotherapy and involved site radiation therapy (ISRT) versus involved field radiation therapy (IFRT).

Fig. 2. Kaplan-Meier plot of freedom from relapse for patients with bulky disease receiving 4 versus 6 cycles of chemotherapy and involved site radiation therapy (ISRT) versus involved field radiation therapy (IFRT).

Table 1

Patient and treatment characteristics

Characteristic	4 cycles (n=70)	6 cycles (n=58)
Age, y		
Median	29	30
Range	19–63	18–70
Sex		
Male	31 (44%)	17 (29%)
Female	39 (56%)	41 (71%)
Stage		
I	6 (9%)	7 (12%)
II	64 (91%)	51 (88%)
Histology		
Nodular sclerosing	59 (84%)	50 (86%)
Lymphocyte rich	2 (3%)	0
Lymphocyte depleted	1 (1%)	0
Mixed cellularity	3 (4%)	4 (7%)
Classic NOS	5 (7%)	4 (7%)
B symptoms	11 (16%)	11 (19%)
Risk factors		
3 sites	53 (76%)	30 (52%)
Bulky disease	22 (31%)	42 (72%)
IA	0 (0%)	5 (9%)
IB	3 (4%)	3 (5%)
IIA	19 (27%)	34 (57%)
Elevated ESR	10 (42 unknown) (14%)	6 (48 unknown) (10%)
Extranodal sites	2 (3%)	2 (3%)
Chemotherapy		
ABVD	70 (100%)	50 (86%)
AVD	0	2 (3%)
Other	0	6 (10%)
Radiation		
Dose	(3 unknown)	(9 unknown)
Median	30.6 Gy	30.6 Gy
Range	20–39.6 Gy	27–41.4 Gy
Dose ≥ 36 Gy	6 (9%)	16 (28%)
RT type	(2 unknown) (3%)	(6 unknown) (10%)
IFRT	12 (17%)	16 (28%)
ISRT	53 (76%)	36 (62%)
Other (eg, mantle)	3 (4%)	0 (0%)
PET		

Characteristic	4 cycles (n=70)	6 cycles (n=58)
Interim PET positive	1 of 54 pts (2%)	4 of 51 (8%)
Interim PET completed	54 (77%)	51 (88%)
After 2 cycles	48 (69%)	26 (45%)
After 3 cycles	6 (9%)	19 (33%)
After 4 cycles	n/a	5 (9%)
After 5 cycles	n/a	1 (2%)
Final PET positive	2 of 50 pts (4%)	2 of 45 pts (4%)

Abbreviations: AVD = doxorubicin, vinblastine, dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ESR = erythrocyte sedimentation rate; IFRT = involved field radiation therapy; ISRT = involved site radiation therapy; NOS = not otherwise specified; PET = positron emission tomography; RT = radiation therapy.

Table 2

Variables affecting decision for number of chemotherapy cycles

Variable	4 cycles (n=70)	6 cycles (n=60)	P value
Age, y			
<30	36	28	.72
30	34	30	
Diagnosis year			
Before 2010	35	42	.01
2010–2013	35	16	
Stage			
I	6	7	.51
II	64	51	
B symptoms			
Yes	11	11	.63
No	59	47	
Bulky			
Yes	22	42	<.01
No	48	16	
No. of sites (per Ann Arbor)			
<3	14	18	.15
3	56	40	
Extranodal sites			
Yes	2	2	1.0
No	68	56	
Interim PET			
Positive	1	5	.11
Negative	53	46	
Radiation type			
IFRT	12	16	.12
ISRT	53	36	
Patients treated 2010–2013			
Bulky	10	14	<.01
Nonbulky	25	2	

Abbreviations: IFRT = involved field radiation therapy; ISRT = involved site radiation therapy; PET = positron emission tomography.

Table 3

Documented reasoning for administration of 6 cycles of chemotherapy (58 patients)

Reason	n (%)
No reason given	40 (69)
On protocol	6 (10)
Bulky disease	5 (9)
“Standard of care”	4 (7)
CT disease after 4 cycles	1 (2)
Other aggressive risk factors (eg, pathology, no. of sites)	2 (3)

Abbreviation: CT = computed tomography.

Table 4

Assessment of toxicity related to chemotherapy

Toxicity assessment	4 cycles	6 cycles
Pulmonary toxicity		
Bleomycin cycles		
0	0	5 (9%)
2 (A ± B)	7 (10%)	0
3 (A ± B)	21 (30%)	5 (9%)
4 (A ± B)	42 (60%)	10 (17%)
5 (A ± B)	n/a	9 (16%)
6 (A ± B)	n/a	29 (50%)
Bleomycin pulmonary toxicity	14 (20%)	18 (31%) (<i>P</i> = .16)
Cardiac toxicity		
Patients with prechemotherapy and postchemotherapy evaluation	16	10
Decreased ejection fraction	0 (0%)	1 (10%)

Abbreviation: n/a = Not applicable.