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A Multi-Institutional Analysis of Peritransplantation Radiotherapy in Patients With Relapsed/Refractory Hodgkin Lymphoma Undergoing Autologous Stem Cell Transplantation

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Abstract

BACKGROUND—No consensus exists regarding the use of radiotherapy (RT) in conjunction with high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) for patients with relapsed/refractory classical Hodgkin lymphoma (HL). The objectives of the current study

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AUTHOR CONTRIBUTIONS

Sarah A. Milgrom: Conceptualization, methodology, formal analysis, investigation, data curation, original draft preparation, visualization, supervision, and project administration. **Shekeab Jauhari:** Conceptualization, methodology, formal analysis, investigation, data curation, original draft preparation, supervision, and project administration. **John P. Plastaras:** Conceptualization, methodology, reviewing and editing, and supervision. **Yago Nieto:** Conceptualization and reviewing and editing. **Bouthaina S. Dabaja:** Conceptualization, methodology, reviewing and editing, and supervision. **Chelsea C. Pinnix:** Conceptualization, methodology, and reviewing and editing. **Grace L. Smith:** Conceptualization, methodology, and reviewing and editing. **Pamela K. Allen:** Methodology, formal analysis, and reviewing and editing. **J. Nicholas Lukens:** Conceptualization, methodology, and reviewing and editing. **Amit Maity:** Conceptualization and reviewing and editing. **Yasuhiro Oki:** Conceptualization and reviewing and editing. **Michelle A. Fanale:** Conceptualization and reviewing and editing. **Sunita D. Nasta:** Conceptualization, methodology, reviewing and editing, and supervision.

were to characterize practice patterns and assess the efficacy and toxicity of RT at 2 major transplantation centers.

METHODS—Eligible patients underwent HDC/ASCT from 2006 through 2015 using the combination of either carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM) or cyclophosphamide, BCNU, and etoposide (CBV).

RESULTS—For the cohort of 189 patients, the 4-year overall survival rate was 80%, the progression-free survival rate was 67%, and the local control (LC) rate was 68%. RT was used within 4 months of ASCT for 22 patients (12%) and was given more often for disease that was early stage, primary refractory, or [¹⁸F]fluorodeoxyglucose (FDG)-avid at the time of HDC/ASCT. Disease recurrence occurring after HDC/ASCT was associated with primary refractory disease and FDG-avidity at the time of HDC/ASCT. RT was not found to be associated with LC, progression-free survival, or overall survival on univariate analysis. In a model incorporating primary refractory HL and FDG-avid disease at the time of HDC/ASCT, RT was found to be associated with a decreased risk of local disease recurrence (hazard ratio, 0.3; $P=.02$). In patients with primary refractory HL and/or FDG-avid disease at the time of HDC/ASCT, the 4-year LC rate was 81% with RT versus 49% without RT ($P=.03$). There was one case of Common Terminology Criteria for Adverse Events grade 3 RT-related toxicity (acute grade 3 pancytopenia).

CONCLUSIONS—In patients undergoing ASCT for relapsed/refractory HL, peritransplantation RT was used more often for disease that was early stage, primary refractory, or FDG-avid after salvage conventional-dose chemotherapy. RT was associated with improved LC of high-risk localized disease and was well tolerated with modern techniques.

Keywords

Hodgkin lymphoma; lymphoma; radiotherapy (RT); stem cell transplantation (SCT)

INTRODUCTION

Classical Hodgkin lymphoma (HL) is highly curable in the modern era. Greater than 90% of patients with early stage disease maintain a complete remission after frontline combined modality therapy.^{1,2} However, 25% to 30% of patients with advanced stage HL develop relapsed or refractory disease.^{1,2} The treatment of choice for patients with relapsed/refractory HL is salvage conventional-dose chemotherapy, followed by high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT).² Carmustine (BCNU)-containing HDC regimens used commonly during ASCT include BEAM (BCNU, etoposide, cytarabine, and melphalan) and CBV (cyclophosphamide, BCNU, and etoposide).^{2,3} ASCT with these regimens yields 5-year progression-free survival (PFS) rates of 50% to 60%.⁴ Thus, up to one-half of patients with relapsed/refractory HL may experience disease recurrence after ASCT with these agents.

The majority of HL recurrences after ASCT occur at sites of prior disease involvement.^{5–7} This finding has lent support to the use of local, consolidative therapies around the time of ASCT to improve outcomes. An important example of such a modality is radiotherapy (RT). For decades, RT has been used for salvage treatment, yielding durable responses in patients with relapsed/refractory HL.⁸ RT has been used before and after ASCT at multiple

transplantation centers.^{7,9,10} Peritransplantation RT has been associated with improved local control (LC), although its influence on survival measures is unclear.^{11–14} Historically, concerns about toxicity, including pneumonitis, limited the adoption of peritransplantation RT as standard practice.^{14,15} However, modern RT dosing, techniques, and timing of administration may be associated with substantially less toxicity.

Peritransplantation RT is an important treatment option for patients undergoing ASCT for relapsed/refractory HL, but the optimal patient selection, dose, and timing of administration are unclear. In this multi-institutional retrospective analysis, we identified patients with relapsed/refractory HL who were treated with ASCT using BEAM or CBV as HDC. The purpose was to characterize patients for whom RT was recommended, to assess its influence on LC and survival measures, and to evaluate the incidence of early toxicities.

MATERIALS AND METHODS

After Institutional Review Board approval was obtained, all patients aged >17 years who underwent ASCT for relapsed/refractory HL from 2006 to 2015 at The University of Texas MD Anderson Cancer Center (MDACC) or the University of Pennsylvania were identified retrospectively. To be eligible for analysis, patients must have received HDC consisting of BEAM or CBV. Clinical data were obtained from the electronic medical record.

Bulky disease was defined as that measuring ≥10 cm in maximal diameter at the time of initial diagnosis or ≥5 cm at the time of disease recurrence.^{16,17} Disease was categorized as primary refractory if progression was noted during or within 3 months of upfront chemotherapy and was defined as relapsed if disease progression occurred >3 months after the completion of initial therapy.

All patients received salvage conventional-dose chemotherapy before HDC/ASCT. The most commonly used regimens were ifosfamide, carboplatin, and etoposide (ICE); cytarabine, cisplatin, and dexamethasone (DHAP); and etoposide, cytarabine, cisplatin, and methylprednisolone (ESHAP). A positron emission tomography (PET) scan was performed after the completion of salvage conventional-dose chemotherapy and before HDC/ASCT in all patients to establish disease chemosensitivity. Only patients with at least a partial response to conventional-dose chemotherapy proceeded to HDC/ASCT. Patients were defined as having residual active disease at the time of HDC/ASCT if the pretransplantation PET demonstrated residual [¹⁸F]fluorodeoxyglucose (FDG) avidity. For patients treated later during the study period, a 5-point Deauville score was reported; in these patients, a Deauville score of 4 to 5 was interpreted to represent residual active disease. However, the majority of patients were treated before the 5-point Deauville score was used routinely. In these patients, disease response was based on the radiologists' impression and the International Working Group response criteria.¹⁸

All patients received HDC with BEAM or CBV, followed by ASCT. Peritransplantation RT, defined as RT given within 4 months of HDC/ASCT, was used for selected patients, at the discretion of the multidisciplinary team. The recommendation for RT was made on a case-

by-case basis; however, factors that influenced practitioners to recommend RT included localized disease and incomplete response to salvage conventional-dose chemotherapy.

The treating radiation oncologist chose the RT dose and technique, and treatment volumes were delineated according to an involved site technique.¹⁹ The area to be irradiated was chosen on a case-by-case basis to balance the benefits of RT with its potential toxicity. Typically, in patients who had Ann Arbor stage I or II disease at the time of diagnosis with HL, the clinical target volume encompassed all sites of initial involvement, with the relapsed/refractory sites treated to a higher dose. For example, if a patient had cervical lymph node disease that responded completely to upfront chemotherapy and mediastinal disease that was refractory, then the site of involvement in the neck might be treated to 36 Gray (Gy) and the mediastinum to 40 Gy. Conversely, in patients with advanced stage disease, only the highest-risk relapsed or refractory sites were irradiated. For example, if a patient had adenopathy above and below the diaphragm, all of which responded to conventional-dose chemotherapy, with the exception of mediastinal adenopathy, then the site of refractory mediastinal disease was irradiated.

Patients were followed according to standard institutional practice. After ASCT, they met routinely with a multidisciplinary team to monitor for disease recurrence and treatment-related morbidity. In addition, patients who received RT were seen weekly during treatment by the radiation oncologist for the evaluation of side effects. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.03.

Statistical analyses were performed using SPSS statistical software (version 22.0; IBM Corporation, Armonk, NY) and Stata/MP 14.2 statistical software (Release 14; StataCorp LP, College Station, TX). Categorical variables were compared using the Fisher exact test, and continuous variables were compared using the Student *t* test. Survival outcomes were assessed using Kaplan-Meier methods and were compared using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to determine the effect of covariates on survival outcomes. Variable selection for the multivariate models was based on statistically significant associations with peritransplantation RT administration and patient outcome. Covariates were selected that were not collinear, minimized overfitting, and were appropriately parsimonious based on the number of events.²⁰ There was no missing covariate information in the multivariate analysis, and therefore no patients were excluded from the models due to missing data. The proportional hazards assumption was tested for all models. The overall likelihood ratio was determined for each multivariate model, relative to the model including RT alone. Two-sided tests were performed. Differences associated with *P* values $\leq .05$ were considered to be statistically significant.

RESULTS

Patient Characteristics

A total of 189 patients underwent ASCT for relapsed/refractory HL with the BEAM or CBV regimen used for HDC. Patient, disease, and treatment characteristics for the complete cohort are summarized in Table 1. The median age at ASCT was 39 years. Sixty patients (32%) received RT as a part of upfront management. Disease was primary refractory in 51

patients (27%) and relapsed in 138 patients (73%). Patients received a median of 2 lines of conventional-dose chemotherapy as part of upfront and salvage therapy. The HDC regimen for ASCT was BEAM for 129 patients (68%) and CBV for 60 (32%).

Peritransplantation RT Information

A total of 22 patients (12%) received RT within 4 months of ASCT (median, 3 months). In 21 of these patients (95%), RT was delivered after ASCT. The median dose was 36 Gy (range, 25.2–41.4 Gy). Irradiated sites encompassed the mediastinum in 7 patients (32%); the mediastinum and neck in 11 patients (50%); the mediastinum, neck, and axilla in 3 patients (14%); and the neck in 1 patient (4%). The technique for RT delivery was intensitymodulated RT in 7 patients (32%), proton therapy in 5 patients (23%), 3-dimensional conformal RT in 8 patients (36%), and unknown in 2 patients (9%).

Table 2 compares the characteristics of patients based on RT administration. Patients treated with RT were more likely to have primary refractory disease ($P<.001$), active (FDG-avid) HL at the time of HDC/ASCT ($P=.002$), and disease limited to one side of the diaphragm at the time of initial diagnosis ($P=.001$) and disease recurrence ($P=.001$). These patients also were less likely to have extranodal disease ($P=.001$).

Clinical Outcomes

At a median follow-up of 44 months after ASCT (range, 1–108 months), there were a total of 59 disease recurrences at any site (local and/or distant), 56 local recurrences, and 41 deaths, as summarized in Figure 1. At 4 years after ASCT, the overall survival (OS) rate was 80% (95% confidence interval [95% CI], 72%–85%), the progression-free survival (PFS) rate was 67% (95% CI, 59%–73%), and the LC rate was 68% (95% CI, 60%–75%). Survival curves for the total cohort are shown in Figure 2.

In the subset of 22 patients who received RT, a total of 7 disease recurrences occurred. Of these, 3 were distant recurrences (ie, outside of the irradiated area). One patient experienced an isolated local recurrence within the RT field after treatment to a total dose of 30 Gy. The remaining 3 patients experienced a concurrent local and distant disease recurrence after treatment to 33 Gy (1 patient) or 36 Gy (2 patients). Of the 4 local recurrences, 1 occurred within a site that was bulky, both at the time of initial diagnosis and disease recurrence, and 3 occurred within nonbulky sites. Of the local recurrences, 1 occurred within a site that was PET-positive at HDC/ASCT, and 3 were within sites that responded completely to salvage conventional-dose chemotherapy.

Univariate analyses were performed to assess for an association between the outcomes and covariates (see Supporting Information Table 1). The risk of death after ASCT was found to be associated with advanced stage disease at the time of disease recurrence (hazard ratio [HR], 2.1; $P=.02$), receipt of RT as part of upfront therapy (HR, 0.3; $P=.004$), receipt of >1 line of salvage conventional-dose chemotherapy (HR, 2.7; $P=.002$), and primary refractory HL (HR, 1.8; $P=.08$). Disease recurrence (local or distant) after ASCT was associated with advanced stage relapsed/refractory disease (HR, 1.9; $P=.02$), receipt of RT as part of upfront therapy (HR, 0.5; $P=.02$), primary refractory HL (HR, 1.9; $P=.02$), and active HL at the time of HDC/ASCT (HR, 1.7; $P=.07$). Local recurrence was associated with receipt of RT as part

of upfront therapy (HR, 0.5; $P=.03$) and advanced stage relapsed/refractory disease (HR, 2.1; $P=.005$). Peritransplantation RT was not found to be associated with LC, PFS, or OS on univariate analysis.

We hypothesized that peritransplantation RT was not an independent protective factor due to selection bias. Patients who received RT were more likely to have risk factors associated with adverse outcomes, such as primary refractory HL and active (FDG-avid) disease at the time of HDC/ASCT. We performed a multivariate analysis to control for these confounders. In a model incorporating primary refractory disease and active disease at the time of HDC/ASCT, peritransplantation RT was found to be associated with a statistically significant reduction in the risk of local disease recurrence (HR, 0.3; $P=.02$). The HRs associated with RT in all multivariate models are summarized in Table 3. The proportional hazards assumption was not violated for any model.

The overall likelihood ratio (LR) was calculated for each multivariate model compared with model 1 (RT alone). The variables included in each model are listed in Table 3. For LC, the LR was 5.12 for model 2 ($P=.02$), 4.09 for model 3 ($P=.04$), 8.78 for model 4 ($P=.01$), and 14.3 for model 5 ($P=.003$). For PFS, the LR was 6.26 for model 2 ($P=.01$), 3.28 for model 3 ($P=.07$), 9.02 for model 4 ($P=.01$), and 14.3 for model 5 ($P=.003$). For OS, the LR was 2.69 for model 2 ($P=.10$), 1.51 for model 3 ($P=.22$), 3.69 for model 4 ($P=.16$), and 9.36 for model 5 ($P=.03$).

A separate analysis was performed of the subgroup of patients with primary refractory HL and/or active disease at the time of HDC/ASCT (72 patients). In this group, the 4-year OS rate was 70%, the PFS rate was 53%, and the LC rate was 57%. Peritransplantation RT was associated with significantly better LC in this subset of patients (Fig. 3). At 4 years, the LC rate was 81% in patients who received RT versus 49% in patients who did not ($P=.03$). The 4-year PFS rate was 67% in patients who received RT versus 49% in patients who did not ($P=.4$), and the 4-year OS rate was 82% versus 65%, respectively ($P=.9$).

Radiation-Related Toxicity

One case of grade >2 RT-related toxicity was observed. This patient had acute grade 3 pancytopenia. Notably, this patient was found to have significant disease progression and suspected bone marrow involvement soon after RT, which may have contributed to the decreased blood counts. There was no instance of late grade >2 toxicity reported. No case of pneumonitis was observed.

DISCUSSION

The current multi-institutional, retrospective analysis characterized patients with relapsed/refractory HL who were treated with peritransplantation RT and assessed the efficacy and toxicity of this treatment. Of 189 patients in the study, 22 received RT. On univariate analysis, peritransplantation RT was not found to be associated with LC, PFS, or OS. We hypothesized that RT was not an independent protective factor due to confounding variables, because RT was used more frequently for patients with primary refractory HL or persistent active (FDG-avid) disease at the time of HDC/ASCT, and each of these covariates was

associated with adverse outcomes. To control for imbalanced covariates, multivariate and subset analyses were performed. In a multivariate model controlling for primary refractory HL and persistent active disease at the time of HDC/ASCT, RT was found to be associated with a significant reduction in the risk of local disease recurrence (HR, 0.3; $P=.02$). In the subset of patients with primary refractory disease and/or residual PET-positive disease at the time of HDC/ASCT, the 4-year LC rate was 81% in patients who received RT versus 49% in patients who did not ($P=.03$). These findings suggest that peritransplantation RT improves LC in patients at high risk of disease recurrence. In the same subset of patients, the 4-year PFS rate was 67% and the 4-year OS rate was 82% in patients receiving RT. No significant improvement in PFS or OS was found to be associated with RT, possibly due to insufficient statistical power. However, these PFS and OS rates compare favorably with outcomes reported in the literature for all patients with relapsed/refractory HL, suggesting that peritransplantation RT might partially overcome these adverse prognostic factors.

Previously published data support the conclusion that peritransplantation RT improves LC.^{7,11} For example, Mundt et al evaluated 54 patients who underwent HDC/ASCT for relapsed/refractory HL, 20 of whom received peritransplantation RT. The majority of recurrences after ASCT occurred at sites of previous disease involvement, and RT was found to be associated with a lower rate of disease recurrence at these sites ($P<.05$).⁷ However, the influence of peritransplantation RT on survival outcomes remains unclear. In the current study, RT was not found to be associated with PFS or OS on univariate or multivariate analysis. Conversely, other reports have suggested that peritransplantation RT may improve survival outcomes in subsets of patients.^{11–14} Poen et al reported on 100 patients with relapsed/refractory HL who underwent HDC/ASCT, 24 of whom received peritransplantation RT. In the subset with stage I to III disease, peritransplantation RT was associated with improved freedom from disease recurrence.¹² Biswas et al reported on 62 patients, 32 of whom received peritransplantation RT. RT was found to be associated with improved OS ($P=.05$), disease-specific survival ($P=.08$), and LC ($P=.03$).¹¹ Together, these results suggest that peritransplantation RT may benefit particular patient cohorts. Discrepant conclusions likely are due to differences in patient populations, selection criteria for RT, and endpoints of interest.

In the 22 patients who received peritransplantation RT in the current study, 4 instances of disease recurrence occurred within the irradiated area. Of these, 1 was an isolated local recurrence and 3 were combined local and distant recurrences. The small number of local recurrences after RT precludes the identification of a radiation dose response. However, all 4 recurrences occurred in patients who received the median dose (36 Gy) or below, suggesting that patients receiving peritransplantation RT for relapsed/refractory HL may benefit from dose escalation to >36 Gy. Researchers have demonstrated a PFS and OS benefit associated with dose escalation to 35 Gy in patients with relapsed/refractory HL who fail ASCT, thereby supporting the hypothesis that patients with chemotherapy-refractory disease may require higher RT doses.²¹

Peritransplantation RT was found to be well tolerated in the current study. One case of acute grade 3 pancytopenia was observed in a patient who developed a suspected bone marrow recurrence soon after RT, which may have contributed to the decreased blood counts. There

was no other case of acute grade 3 toxicity. Older studies have reported significantly higher rates of acute adverse events. In a cohort of patients treated with peritransplantation RT to a median dose of 30 Gy from 1995 through 2008, 13 of 46 patients (28%) experienced grade 4 to 5 toxicity.¹⁴ In the current study, rates of toxicity were considerably lower, despite treatment to a higher median dose. A major factor contributing to the decreased RT-associated toxicity observed in the current study cohort was likely the use of advanced RT techniques, including intensity modulated RT and proton therapy, which can deliver tightly conformal radiation dose and thus spare adjacent normal structures. In addition, at the study institutions, the use of deep inspiration breath-hold and image guidance further reduces the dose delivered to normal structures, thereby minimizing morbidity. Assessment of late adverse events in the current study was limited by the short follow-up time (median, 44 months); however, we hypothesize that the incidence of delayed toxicity would be reduced, as well, with modern techniques.

Additionally, the sequencing of RT after HDC/ASCT may contribute to lower toxicity rates. Historically, patients have received consolidative RT both before and after transplantation. In the current study, nearly all patients received RT after ASCT, reflecting institutional preferences. This may be advantageous for several reasons. When RT is given after ASCT, the patient has achieved maximal disease response, which may allow for reduced RT doses and treatment volumes, thereby limiting toxicity. In addition, delaying HDC for RT to be delivered first may allow for disease progression outside of the irradiated area before ASCT. Last, the administration of RT before ASCT may damage bone marrow in the irradiated area and thus may lengthen the period of aplasia.

An interesting result of the current study was that receipt of RT as part of upfront therapy was associated with improved salvage rates after HDC/ASCT. One possible explanation is that patients with primary refractory disease, who experienced worse outcomes after HDC/ASCT, were significantly less likely to receive RT as part of upfront therapy ($P<.001$) because they were directed immediately to salvage chemotherapy. In support of this hypothesis, when patients with primary refractory disease were excluded from the analysis, these associations lost statistical significance.

Another notable finding of the current study was the lack of standardized patient selection for peritransplantation RT. Patients were more likely to receive RT if they had stage I/II disease, refractory disease after frontline therapy, lymph node disease only at the time of disease recurrence, or active disease at the time of HDC/ASCT, thereby suggesting that patients with regionally limited, chemotherapy-refractory disease were preferentially selected for peritransplantation RT. However, not all patients with these characteristics were treated with RT, while; others with advanced-stage disease or a complete response before ASCT received peritransplantation RT. Overall, the findings of the current study suggest provider-specific biases and a lack of standardization in referrals for RT.

We attempted to select a homogeneous population across institutions, with patients treated during the same decade and receiving similar chemotherapy regimens. Nevertheless, differences remained between our institutional cohorts. One difference was the frequency of RT use. Of the 64 patients who underwent ASCT at the University of Pennsylvania, 15

(23%) received peritransplantation RT; conversely, of the 125 patients treated at MDACC, only 7 (6%) received RT. Another difference was the HDC regimen used before ASCT: CBV was used preferentially at the University of Pennsylvania, whereas BEAM was used at MDACC. Both regimens have significant antilymphoma activity and have demonstrated comparable efficacy.² Although it is unlikely that these differences influenced the conclusions of the current study, this possibility cannot be excluded.

The current study was limited by small numbers, the uneven distribution of patients by treatment arm, and a lack of standardization in referral for RT. Future prospective, multi-institutional study is warranted to evaluate the efficacy of RT among selected patients at high risk of local recurrence after ASCT, including those with primary refractory disease and active disease at the time of HDC/ASCT. Consideration should be given to evaluating the efficacy of posttransplantation RT, which may be associated with less toxicity than pretransplantation RT. The accurate selection of patients who are most likely to benefit from RT will be a crucial element of any future prospective study. An emerging question is the usefulness of peritransplantation RT in the era of novel treatments for relapsed/refractory HL, including brentuximab vedotin and programmed cell death protein 1 (PD-1) inhibitors. These therapies have been used in the post-ASCT setting,²² and can improve survival outcomes. The combined use of peritransplantation RT and these novel therapies is an area worthy of investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flow diagram summarizing the study cohort. ASCT indicates autologous stem cell transplantation; BEAM, carmustine (BCNU), etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine (BCNU), and etoposide; HDC, high-dose chemotherapy; HL, Hodgkin lymphoma; RT, radiotherapy.

Figure 2. (A) Local control, (B) progression-free survival, and (C) overall survival for the total cohort (189 patients). SCT indicates stem cell transplantation.

Figure 3.

(A) Local control, (B) progression-free survival, and (C) overall survival in the subset of patients with primary refractory Hodgkin lymphoma and/or active (FDG-avid) disease at the time of high-dose chemotherapy/autologous stem cell transplantation (72 patients). Dotted line indicates receipt of peritransplantation radiotherapy (RT); solid line, did not receive peritransplantation RT. SCT indicates stem cell transplantation.

TABLE 1**Patient, Disease, and Treatment Characteristics (n=189)**

Median age at ASCT (range), y	39 (20–73)
Male sex, no. (%)	101 (53%)
Stage I/II disease at time of initial diagnosis, no. (%)	82 (43%)
Bulky disease at time of initial diagnosis, no. (%)	45 (24%)
ABVD or ABVD-like chemotherapy at time of initial diagnosis, no. (%)	167 (88%)
RT at time of initial diagnosis, no. (%)	60 (32%)
Stage I/II relapsed/refractory disease, no. (%)	119 (63%)
Bulky disease at time of disease recurrence, no (%)	20 (11%)
B symptoms at time of disease recurrence, no. (%)	26 (14%)
Extranodal disease at time of disease recurrence, no. (%)	52 (28%)
Relapsed vs refractory disease, no. (%)	
Relapsed	138 (73%)
Primary refractory	51 (27%)
Median no. of disease recurrences prior to ASCT (range)	1 (1–4)
Median no. of lines of conventional-dose chemotherapy as part of upfront or salvage therapy (range)	2 (2–10)
Active disease at HDC/ASCT, no. (%)	36 (19%)
HDC regimen, no. (%)	
BEAM	129 (68%)
CBV	60 (32%)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem cell transplantation; BEAM, carmustine (BCNU), etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine (BCNU), and etoposide; HDC, high-dose chemotherapy; RT, radiotherapy.

TABLE 2

Characteristics of Patients Treated With Versus Without Peritransplantation RT

Characteristic	With Peritransplantation RT n = 22	Without Peritransplantation RT n = 167	P
Median age at ASCT (range), y	36 (20–64)	40 (20–73)	.07
Male sex, no. (%)	10 (45%)	91 (55%)	.5
Stage I/II disease at time of initial diagnosis, no. (%)	17 (77%)	65 (39%)	.001
Bulky disease at time of initial diagnosis, no. (%)	7 (32%)	38 (23%)	.4
RT at time of initial diagnosis, no. (%)	5 (23%)	55 (33%)	.5
Stage I/II relapsed/refractory disease, no. (%)	21 (95%)	98 (59%)	.001
Bulky disease at time of disease recurrence, no. (%)	4 (18%)	16 (10%)	.2
B symptoms at time of disease recurrence, no. (%)	4 (18%)	22 (13%)	.4
Extranodal disease at time of disease recurrence, no. (%)	0 (0%)	52 (31%)	.001
Relapsed vs refractory disease, no. (%)			
Relapsed	6 (27%)	132 (79%)	<.001
Primary refractory	16 (73%)	35 (21%)	
>1 recurrence prior to ASCT, no. (%)	1 (5%)	19 (11%)	.5
>1 line of salvage conventional dose chemotherapy prior to SCT, no. (%)	9 (41%)	43 (26%)	.2
Active disease at time of HDC/ASCT, no. (%)	10 (45%)	26 (16%)	.002

Abbreviations: ASCT, autologous stem cell transplantation; HDC, high-dose chemotherapy; SCT, stem cell transplantation; RT, radiotherapy.

TABLE 3

Multivariate Models Assessing the Effect of Peritransplantation RT

	Local Recurrence		Disease Progression		Death	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<i>Model 1</i>						
RT	0.5 (0.2–1.4)	.2	1.0 (0.4–2.2)	1	1.3 (0.5–3.0)	.6
<i>Model 2</i>						
RT	0.4 (0.1–1.0)	.06	0.7 (0.3–1.6)	.4	1.0 (0.4–2.4)	.9
Primary refractory	2.0 (1.1–3.6)	.02	2.1 (1.2–3.7)	.01	1.8 (0.9–3.7)	.09
<i>Model 3</i>						
RT	0.4 (0.1–1.1)	.09	0.8 (0.4–1.8)	.6	1.1 (0.5–2.8)	.8
Active disease at HDC/ASCT	1.9 (1.1–3.6)	.03	1.8 (1.0–3.2)	.06	1.6 (0.8–3.4)	.2
<i>Model 4</i>						
RT	0.3 (0.1–0.8)	.02	0.6 (0.2–1.3)	.2	0.9 (0.3–2.3)	.8
Primary refractory	2.0 (1.1–3.5)	.02	2.1 (1.2–3.6)	.01	1.7 (0.9–3.6)	.1
Active disease at HDC/ASCT	1.9 (1.0–3.4)	.05	1.7 (0.9–3.1)	.08	1.5 (0.7–3.2)	.3
<i>Model 5</i>						
RT	0.4 (0.1–1.2)	.09	0.8 (0.3–1.9)	.5	1.3 (0.5–3.6)	.6
Primary refractory	1.9 (1.1–3.4)	.03	2.0 (1.2–3.5)	.01	1.6 (0.8–3.3)	.2
Active disease at HDC/ASCT	1.8 (1.0–3.3)	.07	1.6 (0.9–2.9)	.1	1.4 (0.7–3.0)	.4
Advanced stage at time of disease recurrence	1.9 (1.1–3.3)	.02	1.9 (1.1–3.2)	.02	2.3 (1.2–4.4)	.02

Abbreviations: 95% CI, 95% confidence interval; ASCT, autologous stem cell transplantation; HDC, high-dose chemotherapy; HR, hazard ratio; RT, radiotherapy.