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# Role of Consolidative Radiation Therapy After Autologous Hematopoietic Cell Transplantation for the Treatment of Relapsed or Refractory Hodgkin Lymphoma

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## Abstract

**Purpose—**To evaluate the role of the addition of consolidative radiation therapy after high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT) for relapsed or refractory Hodgkin lymphoma (HL).

**Methods and Materials—**Medical records were reviewed from a total of 80 consecutive patients who underwent high-dose chemotherapy with AHCT treated under a single protocol at University of Minnesota between November 2005 and January 2014. Of these, 32 patients received radiation therapy after AHCT as planned consolidation.

**Results—**At a median follow-up of 25 months, the 2-year overall survival (OS) and progression-free survival (PFS) for the entire cohort was 96% and 52%, respectively. Consolidative radiation therapy was found to significantly improve the 2-year PFS (67% vs 42%, $P<.01$) without a significant change in OS (100% vs 93%, $P=.15$). On subgroup analysis, consolidative radiation therapy was shown to improve PFS in patients with bulky disease (62% vs 39%, $P=.02$), B-symptoms (48% vs 28%, $P=.05$), primary refractory disease (47% vs 32%, $P=.02$), and those with a partial response on pretransplant imaging (47% vs 32%, $P=.02$). The improvement seen on 2-year PFS with consolidative radiation therapy remained significant on multivariate analysis (hazard ratio 4.64, 95% confidence interval 1.98–10.88). Minimal toxicity was observed among the patients receiving radiation therapy.



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Conflict of interest: none.

**Conclusions—**The addition of consolidative radiation therapy after high-dose chemo-therapy and AHCT demonstrated a significant improvement in 2-year PFS and no impact on OS. Radiation therapy was well tolerated, with minimal toxicity. Our study supports a role of consolidative radiation therapy in patients with HL treated with AHCT.

## Introduction

The past several decades have witnessed significant advances and refinements in the treatment of Hodgkin lymphoma (HL). Currently the majority of patients with HL, including those with advanced disease, can be cured by means of conventional chemotherapy and/or radiation (1–5). Yet patients with relapsed or refractory disease require subsequent salvage options.

High-dose chemotherapy with autologous hematopoetic cell transplantation (AHCT) has been shown to be superior to conventional chemotherapy regimens in the setting of recurrent disease (6, 7). The areas involved at the time of recurrence are typically the most common sites for treatment failure after AHCT, which has prompted interest in the use of consolidative radiation therapy in this setting (8–10). However, the widespread use of consolidative radiation therapy remains controversial (11, 12), in part owing to concern for increased treatment-related toxicity and secondary malignancies (13, 14). Although there are no large, randomized prospective studies that have explicitly addressed the role of consolidation radiation therapy, several retrospective series have demonstrated a potential benefit in terms of disease control and/or overall survival with the use of radiation therapy in the transplant setting (10, 15–24).

The purpose of this study was to further clarify the role of radiation therapy in patients undergoing AHCT for the treatment of relapsed or refractory HL. To this end, we retrospectively examined a cohort of HL patients treated uniformly at University of Minnesota on a single institutional protocol and analyzed the impact of consolidation radiation therapy on disease control and survival.

## Methods and Materials

### Patients

Using prospectively collected data from University of Minnesota Blood and Marrow Transplantation Database, we analyzed 80 consecutive patients (40 male/40 female) with HL who underwent AHCT using uniform conditioning between November 2005 and January 2014. This study was approved by the institutional review board at University of Minnesota, and all patients signed institutional review board–approved informed consent forms and were treated according to the Declaration of Helsinki.

Eligibility criteria for transplant included age <75 years, Karnofsky performance status >80%, and no evidence of serious end-organ dysfunction. Patients with early-stage disease initially treated with primary radiation therapy were required to have failed at least one salvage chemotherapy regimen, whereas those with advanced disease needed to have failed an adriamycin-containing regimen or an alternative non–cross-resistant regimen.

We defined bulky disease as any adenopathy or tumor mass measuring ≥5 cm in greatest dimension before the initiation of pretransplant salvage chemotherapy (10, 17, 20). The number of discrete disease relapses before AHCT was also recorded for each patient, with those who never achieved a remission to initial therapy before transplant evaluation characterized as having primary refractory disease.

## Transplant protocol

Pretransplant salvage therapy with non–cross-resistant chemotherapy was administered before transplantation. Patients without an objective response after completion of 3 cycles of chemotherapy (ie, those with stable or progressive disease) were deemed ineligible for autotransplantation.

Patients with a complete response to pretransplant chemotherapy underwent stem cell mobilization by granulocyte colony-stimulating factor alone. Those with a partial response requiring additional disease reduction received chemomobilization with ifosfamide, carboplatin, and etoposide. Transplant conditioning consisted of cyclophosphamide 1.5 g/m$^2$ daily × 4 days, carmustine 300 mg/m$^2$ 1 × day, and etoposide 150 mg/m$^2$ every 12 hours × 6 doses, followed by infusion of autologous hematopoietic cells. We used standard supportive care as previously described (25).

## Imaging

Disease status was evaluated by positron emission tomography (PET)/computerized tomography (CT) before transplant and at day +100 after transplant and by CT at day +28, every 3 months for 1 year, and at 18 and 24 months thereafter using standard response criteria for HL. A complete remission by PET was denoted if fluorodeoxyglucose uptake was equal to or less than mediastinal uptake (26, 27). A partial remission was defined as residual fluorodeoxyglucose uptake greater than mediastinal uptake, provided it had decreased in comparison with baseline pretreatment PET/CT imaging (28).

## Consolidation radiation therapy

Per protocol, patients with persistent nodal masses ≥2 cm or sites suspicious for residual disease involvement on day +28 posttransplant CT were referred for consideration of consolidative radiation therapy after adequate recovery of their blood counts (absolute neutrophil counts >1500/μL and platelets >100,000/μL). Consolidative radiation therapy was administered at the discretion of the treating radiation oncologist.

## Statistical analysis

Data on patient characteristics, posttransplantation outcomes, and complications were prospectively collected by the Biostatistical Support Group at University of Minnesota using standardized collection procedures. Patients and disease characteristics were summarized using descriptive statistics. Statistical comparisons of these variables between groups were completed by nonparametric Wilcoxon test for continuous factors and Pearson $\chi^2$ test for categorical factors. All patients were followed longitudinally until death or censored at last follow-up. The end points included overall survival (OS) and progression-free survival (PFS). Progression-free survival was defined as the time until the first clinical or

radiographic evidence of disease recurrence/progression or death from any cause. Both OS and PFS were measured from the time of transplant. The Kaplan-Meier method was used to estimate OS and PFS. Statistical comparisons of OS and PFS between groups were completed by the log-rank test. Nine factors were considered in the univariate analysis: consolidation RT (yes/no), bulky disease (yes/no), B-symptoms (yes/no), disease status (first or second relapse vs primary refractory), stage at relapse (I/II vs III/IV), prior radiation therapy (yes/no), posttransplant tumor size (<2 cm vs ≥2 cm), age (<30 years vs ≥30 years), and response to pretransplant therapy (complete remission vs partial remission). Only factors with clinical meaning or with a univariable *P* value <.20 were used for multivariable analysis. Although response to pretransplant therapy showed a significant association with PFS, it was not included in the multivariable analysis because of its strong correlation with bulky disease, disease status, and posttransplant tumor size.

All statistical analyses were performed with Statistical Analysis System statistical software, version 9.3 (SAS Institute, Cary, NC).

## Results

### Patient, disease, and transplant characteristics

Characteristics of the 80 consecutive patients studied are summarized in Table 1. Of these, a total of 32 patients received consolidative radiation therapy, whereas 48 did not. The median radiation therapy dose was 30.6 Gy (range, 16–44 Gy), and all radiation therapy was delivered within 6 months of transplantation (median 84 days; range, 36–181 days). The patients who received consolidative radiation therapy tended to be younger (median age 27 vs 34 years, $P=.03$) and were more likely to have bulky disease (81.3% vs 50%, $P<.01$) and persistent nodal masses ≥2 cm after AHCT (59.4% vs 46.3%, $P=.05$) compared with the control group. There was otherwise no difference between the 2 groups in terms of stage at relapse, the presence of B-symptoms, the proportion with primary refractory disease, the use of prior radiation therapy, or the response to pretransplant chemotherapy (Table 1).

Radiation was generally administered to localized fields and limited to the areas of disease involvement before transplant or those that were radiographically suspicious for residual disease burden. Of the 32 patients who received consolidative radiation therapy, 16 received treatment to a single site, 13 to 2 sites, and 3 to 3 sites. The mediastinum was the most frequently treated site (81% of patients), followed by the head and neck (44%), axilla (13%), and abdominal and pelvic regions (13%).

### Posttransplant outcomes

After a median follow-up of 25 months (range, 1–96 months), there were a total of 36 disease relapses and 3 deaths due to relapsed disease within the entire cohort. Two-year PFS and OS were 52% and 96%, respectively.

Patients who had received consolidative radiation therapy had a significantly improved 2-year PFS compared with the control group (67% vs 42%, $P<.01$; Fig. 1, Table 2). There was no significant difference in the 2-year OS between the groups (radiation therapy 100% vs control 93%, $P=.15$; Fig. 1, Table 2). Improved 2-year PFS was also observed in patients

without B-symptoms (72% vs 36%, $P<.01$), those with relapsed versus refractory disease (65% vs 29%, $P<.01$), and those who achieved a complete remission to pretransplant chemotherapy (64% vs 41%, $P=.03$). Overall survival was not affected by any of these factors. None of these groups were found to significantly affect 2-year OS (Table 2).

When stratified by the use of consolidative radiation therapy, 2-year PFS was improved in patients with bulky disease (62% radiation therapy vs 39% no radiation therapy, $P=.02$), B-symptoms (48% radiation therapy vs 28% no radiation therapy, $P=.05$), those with primary refractory disease (47% radiation therapy vs 32% no radiation therapy, $P=.02$), and patients with a partial remission on pretransplant imaging (47% radiation therapy vs 32% no radiation therapy, $P=.02$) (Fig. 2).

On multivariate analysis, after adjusting for other factors, the use of consolidative radiation therapy was associated with 4.6-fold lower risk of treatment failure when controlling for the presence of B-symptoms, refractory versus relapsed disease, stage at relapse, tumor size, and age. In addition to radiation therapy, the presence of B-symptoms (hazard ratio 3.2, $P<.01$) and refractory disease (hazard ratio 3.5, $P<.01$) was also independently associated with a higher risk of disease progression after AHCT (Table 3).

There were a total of 9 relapses among the patients receiving radiation therapy. Three of these relapses occurred only within the treatment field, 3 occurred at sites distant from the treatment field, and 3 were simultaneous distant and local failures. There were a total of 27 relapses among the patients who did not receive radiation therapy. Nearly half (n=13) of the failures occurred within the sites of disease involvement before transplant, whereas 10 were simultaneous distant and local failures, with 4 distant-only failures.

### Toxicity

Consolidative radiation therapy was very well tolerated. Among the 32 patients who received radiation therapy, 11 developed grade 1 to 2 esophagitis, and 2 developed grade 1 to 2 mucositis. There was additionally a single case each of grade 3 pneumonitis and esophagitis reported within the radiation therapy cohort, both of which resolved with supportive management. There were otherwise no grade 4 or 5 acute toxicities observed within any of the patients reported in this study. Assessment of late toxicity is limited by the relatively short follow-up time.

## Discussion

We examined 80 patients with relapsed and refractory HL undergoing high-dose chemotherapy followed by AHCT and report a significant improvement in the 2-year PFS associated with the use of posttransplant consolidation radiation therapy to site(s) of prior HL involvement. The benefit of radiation was observed despite the fact that the RT group was enriched with higher-risk patients. Furthermore, improvement in PFS remained significant when accounting for the presence of B-symptoms, relapsed versus refractory disease, stage at relapse, posttransplant tumor size, and patient age.

The 2-year overall survival was quite favorable among our entire study population, with only 3 observed deaths, which were all due to disease progression. Given the limited number of events, relatively short follow-up, and new treatment of options for relapsed HL, we did not observe any differences in the overall survival of the compared groups. Nearly all of the patients with disease relapse after AHCT received additional therapy, and many subsequently received allogeneic transplantation. We anticipate that with further follow-up we could see additional lymphoma-related deaths and possibly a divergence in the survival curves with consolidation radiation therapy, as well as among other patient subgroups.

High-dose chemotherapy and AHCT is the current standard of care for patients with relapsed or refractory HL. More recently, the randomized AETHERA study demonstrated approximately 20% improvement in PFS using brentuximab vedotin (BV) consolidation after AHCT (29). Therapy with BV has been used between days 28 and 60 after AHCT, and in this trial selected patients were treated sequentially with posttransplant radiation therapy (29). Given that BV maintenance is recommended in all high-risk HL patients regardless of residual mass, our data suggest that consolidation with BV and radiation therapy may be synergistic to reduce locoregional recurrence. The role of consolidation radiation therapy in the posttransplant setting, though, remains controversial owing to a lack of prospective evidence from studies designed to address this issue. As a result there is significant institutional variability in the use of radiation therapy in this patient population.

In Table 4 we report several retrospective studies that examined the role of consolidation radiation in the peri-transplant setting. Most suggested a benefit with judicious application of radiation therapy (Table 4). Our results support other single-institutional series, including a study of 92 patients with relapsed/refractory HL by Kahn et al (17), which found a significant improvement in disease free survival with the use of pre- or posttransplant radiation therapy when stratified by disease bulk, as well as a study by Poen et al (20), which found an improvement in freedom from relapse associated with the use of consolidation radiation therapy in a group of 62 patients with stage I–III HL undergoing high-dose chemotherapy and AHCT.

The critical issue that continues to need to be addressed is the appropriate selection criteria of the patients who would achieve the largest benefit with consolidation radiation therapy. We found that the addition of consolidation radiation therapy resulted in an improved PFS in patients with high-risk factors, such as the presence of B-symptoms, those with a partial response on pretransplant PET imaging, and those with primary refractory disease. Of note, the majority of our patients received consolidative treatment to the mediastinum, which is the common site of persistent disease on posttransplant CT. As the treatment of patients with relapsed or refractory HL continues to evolve, such as the inclusion of brentuximab as a consolidation after AHCT (29), there is a heightened necessity to define the role of consolidative radiation therapy in this group.

We observed minimal acute toxicity associated with the use of consolidation radiation. In contrast to other institutional series, our patients received radiation therapy exclusively in the posttransplant setting, after adequate recovery of blood counts. Such a practice may have contributed to the limited peri-transplant morbidity in our series (14). Another contributing

factor was likely our use of limited radiation therapy fields. Because of concern for enhanced radiation-induced toxicity in the immediate posttransplant setting, the radiation fields typically encompassed only the sites concerning for residual disease/radiologic suspicious areas. Half of the patients receiving consolidative radiation therapy (16 of 32) had treatment to a single site, whereas the remainder received treatment to 2 (13 of 39) or 3 (3 of 39) sites. The most common side effect related to radiation therapy was mild to moderate esophagitis, which was not unexpected given the preponderance of mediastinal radiation therapy in the treated patients. We additionally did not observe any severe acute grade 4 or 5 toxicities related to therapy. There were no recorded severe radiation-induced late effects within our study population, although admittedly the follow-up interval was somewhat limited, and it is possible that we would witness additional treatment-related toxicities associated with a longer follow-up duration.

There are several limitations to our study. Despite being one of the larger series, we had only 80 total patients. Given the small sample size and the emerging salvage options, only 3 deaths were observed during the study period, which limited the OS analysis. However, a total of 36 relapses occurred, therefore a meaningful assessment of the role of consolidative radiation therapy on PFS was still possible. As with any retrospective studies, selection bias exists. In particular, although protocol stipulates the referral of patients with persistent nodal disease on posttransplant CT scan, the decisions to refer as well as to treat were left to the discretion of the physicians. Our analysis was strengthened by taking into account multiple known risk factors. Furthermore, because patient information was collected into the transplant database in a prospective manner, there were relatively few missing data.

In summary, we have observed a significant improvement in the 2-year PFS with the addition of consolidation radiation therapy after high-dose chemotherapy and AHCT. This study represents one of the largest patient cohorts published to date, with the results supporting the observations of several other institutional series in the literature. The advantage of our study is that the examined patients were treated over a relatively compact time frame under a single-institutional protocol, which represents a more homogeneous treatment paradigm compared with other retrospective analyses. Altogether, this study adds to a growing body of literature supporting a beneficial role to consolidation radiation therapy in the transplant setting and highlights the need for prospective trials exploring this subject.

## References

1. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin’s lymphoma: Final results of the GHSG HD7 trial. J Clin Oncol. 2007; 25:3495–3502. [PubMed: 17606976]
2. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin’s lymphoma. N Engl J Med. 2010; 363:640–652. [PubMed: 20818855]
3. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin’s disease. N Engl J Med. 2007; 357:1916–1927. [PubMed: 17989384]
4. Specht L, Gray RG, Clarke MJ, et al. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin’s disease: A meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin’s Disease Collaborative Group. J Clin Oncol. 1998; 16:830–843. [PubMed: 9508163]

5. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med. 2003; 348:2396–2406. [PubMed: 12802025]
6. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: Results of a BNLI randomised trial. Lancet. 1993; 341:1051–1054. [PubMed: 8096958]
7. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. Lancet. 2002; 359:2065–2071. [PubMed: 12086759]
8. Dhakal S, Biswas T, Liesveld JL, et al. Patterns and timing of initial relapse in patients subsequently undergoing transplantation for Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2009; 75:188–192. [PubMed: 19250770]
9. Shamash J, Lee SM, Radford JA, et al. Patterns of relapse and subsequent management following high-dose chemotherapy with autologous haematopoietic support in relapsed or refractory Hodgkin's lymphoma: A two centre study. Ann Oncol. 2000; 11:715–719. [PubMed: 10942061]
10. Mundt AJ, Sibley G, Williams S, et al. Patterns of failure following high-dose chemotherapy and autologous bone marrow transplantation with involved field radiotherapy for relapsed/refractory Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1995; 33:261–270. [PubMed: 7673013]
11. Lazarus HM, Loberiza FR Jr, Zhang MJ, et al. Autotransplants for Hodgkin's disease in first relapse or second remission: A report from the Autologous Blood and Marrow Transplant Registry (ABMTR). Bone Marrow Transplant. 2001; 27:387–396. [PubMed: 11313668]
12. Isidori A, Piccaluga PP, Loscocco F, et al. High-dose therapy followed by stem cell transplantation in Hodgkin's lymphoma: Past and future. Expert Rev Hematol. 2013; 6:451–464. [PubMed: 23991931]
13. Dawson LA, Saito NG, Ratanatharathorn V, et al. Phase I study of involved-field radiotherapy preceding autologous stem cell transplantation for patients with high-risk lymphoma or Hodgkin's disease. Int J Radiat Oncol Biol Phys. 2004; 59:208–218. [PubMed: 15093918]
14. Tsang RW, Gospodarowicz MK, Sutcliffe SB, et al. Thoracic radiation therapy before autologous bone marrow transplantation in relapsed or refractory Hodgkin's disease PMH Lymphoma Group, and the Toronto Autologous BMT Group. Eur J Cancer. 1999; 35:73–78. [PubMed: 10211091]
15. Biswas T, Culakova E, Friedberg JW, et al. Involved field radiation therapy following high dose chemotherapy and autologous stem cell transplant benefits local control and survival in refractory or recurrent Hodgkin lymphoma. Radiother Oncol. 2012; 103:367–372. [PubMed: 22398312]
16. Eroglu C, Kaynar L, Orhan O, et al. Contribution of involved-field radiotherapy to survival in patients with relapsed or refractory Hodgkin lymphoma undergoing autologous stem cell transplantation. Am J Clin Oncol. 2015; 38:68–73. [PubMed: 23563207]
17. Kahn S, Flowers C, Xu Z, et al. Does the addition of involved field radiotherapy to high-dose chemotherapy and stem cell transplantation improve outcomes for patients with relapsed/refractory Hodgkin lymphoma? Int J Radiat Oncol Biol Phys. 2011; 81:175–180. [PubMed: 20732769]
18. Kahn ST, Flowers CR, Lechowicz MJ, et al. Refractory or relapsed Hodgkin's disease and non-Hodgkin's lymphoma: Optimizing involved-field radiotherapy in transplant patients. Cancer J. 2005; 11:425–431. [PubMed: 16259874]
19. Lancet JE, Rapoport AP, Brasacchio R, et al. Autotransplantation for relapsed or refractory Hodgkin's disease: Long-term follow-up and analysis of prognostic factors. Bone Marrow Transplant. 1998; 22:265–271. [PubMed: 9720740]
20. Poen JC, Hoppe RT, Horning SJ. High-dose therapy and autologous bone marrow transplantation for relapsed/refractory Hodgkin's disease: The impact of involved field radiotherapy on patterns of failure and survival. Int J Radiat Oncol Biol Phys. 1996; 36:3–12. [PubMed: 8823253]
21. Wadhwa P, Shina DC, Schenkein D, et al. Should involved-field radiation therapy be used as an adjunct to lymphoma autotransplantation? Bone Marrow Transplant. 2002; 29:183–189. [PubMed: 11859389]
22. Wendland MM, Asch JD, Pulsipher MA, et al. The impact of involved field radiation therapy for patients receiving high-dose chemotherapy followed by hematopoietic progenitor cell transplant

for the treatment of relapsed or refractory Hodgkin disease. Am J Clin Oncol. 2006; 29:189–195. [PubMed: 16601441]

23. Milgrom SA, Jauhari S, Plastaras JP, et al. A multi-institutional analysis of peritransplantation radiotherapy in patients with relapsed/refractory Hodgkin lymphoma undergoing autologous stem cell transplantation. Cancer. 2016; 123:1363–1371. [PubMed: 27984652]
24. Levis M, Piva C, Filippi AR, et al. Potential benefit of involved-field radiotherapy for patients with relapsed-refractory Hodgkin's lymphoma with incomplete response before autologous stem cell transplantation. Clin Lymphoma Myeloma Leuk. 2016; 17:14–22. [PubMed: 27727134]
25. Lerner RE, Thomas W, Defor TE, et al. The international prognostic index assessed at relapse predicts outcomes of autologous transplantation for diffuse large-cell non-Hodgkin's lymphoma in second complete or partial remission. Biol Blood Marrow Transplant. 2007; 13:486–492. [PubMed: 17382255]
26. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25:579–586. [PubMed: 17242396]
27. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007; 25:571–578. [PubMed: 17242397]
28. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol. 2014; 32:3059–3068. [PubMed: 25113753]
29. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015; 385:1853–1862. [PubMed: 25796459]

## Summary

This was a retrospective analysis to evaluate the role of consolidation radiation therapy in the treatment of patients with relapsed or refractory Hodgkin lymphoma undergoing salvage therapy with high-dose chemotherapy and autologous hematopoietic cell transplantation. The results showed a significant improvement in 2-year progression-free survival among patients who received consolidation radiation therapy versus observation, although 2-year overall survival was similar in compared groups.

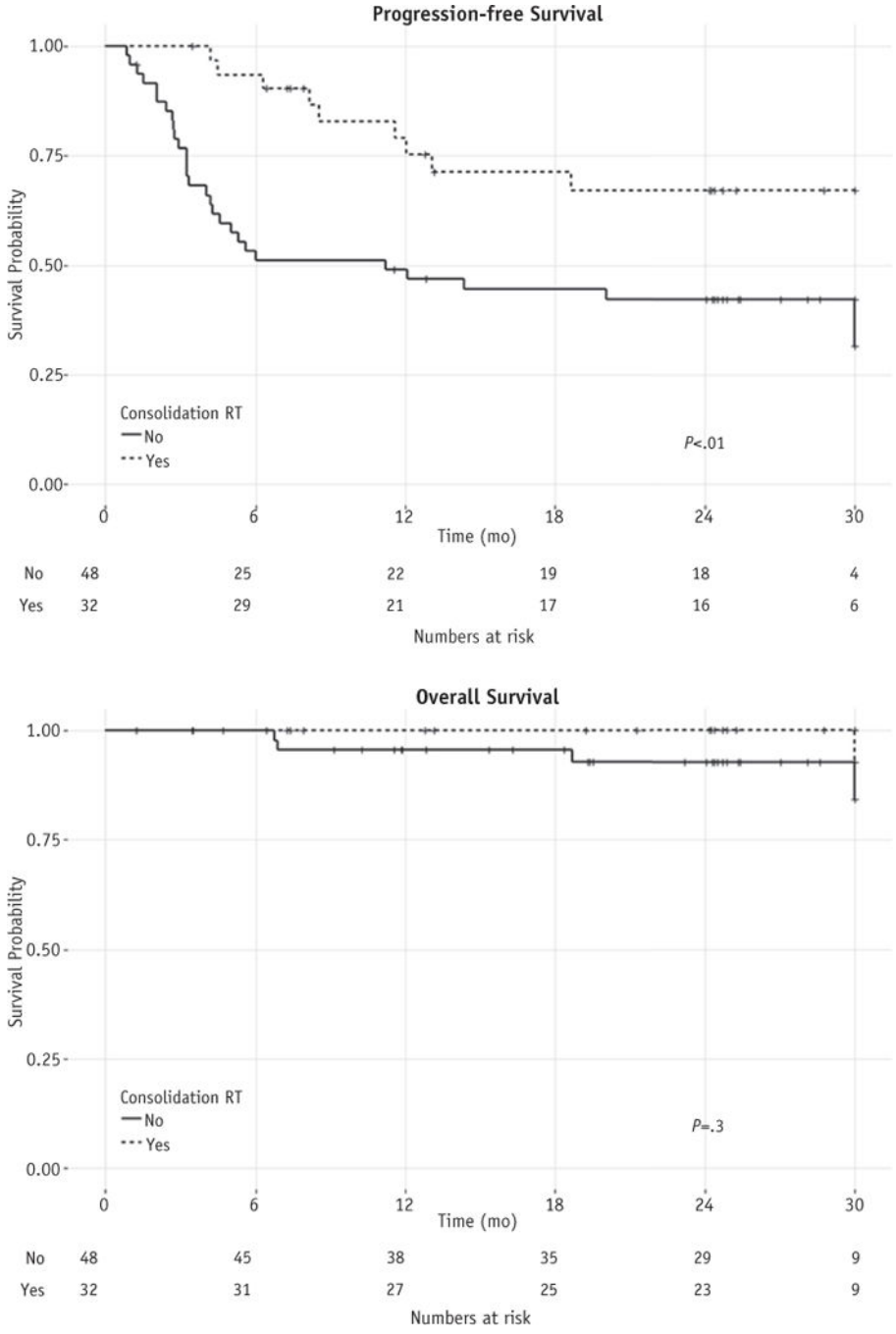


**Fig. 1.**

Kaplan-Meier plots of progression-free survival (top) and overall survival (bottom) of the entire cohort. *Abbreviation:* RT = radiation therapy.

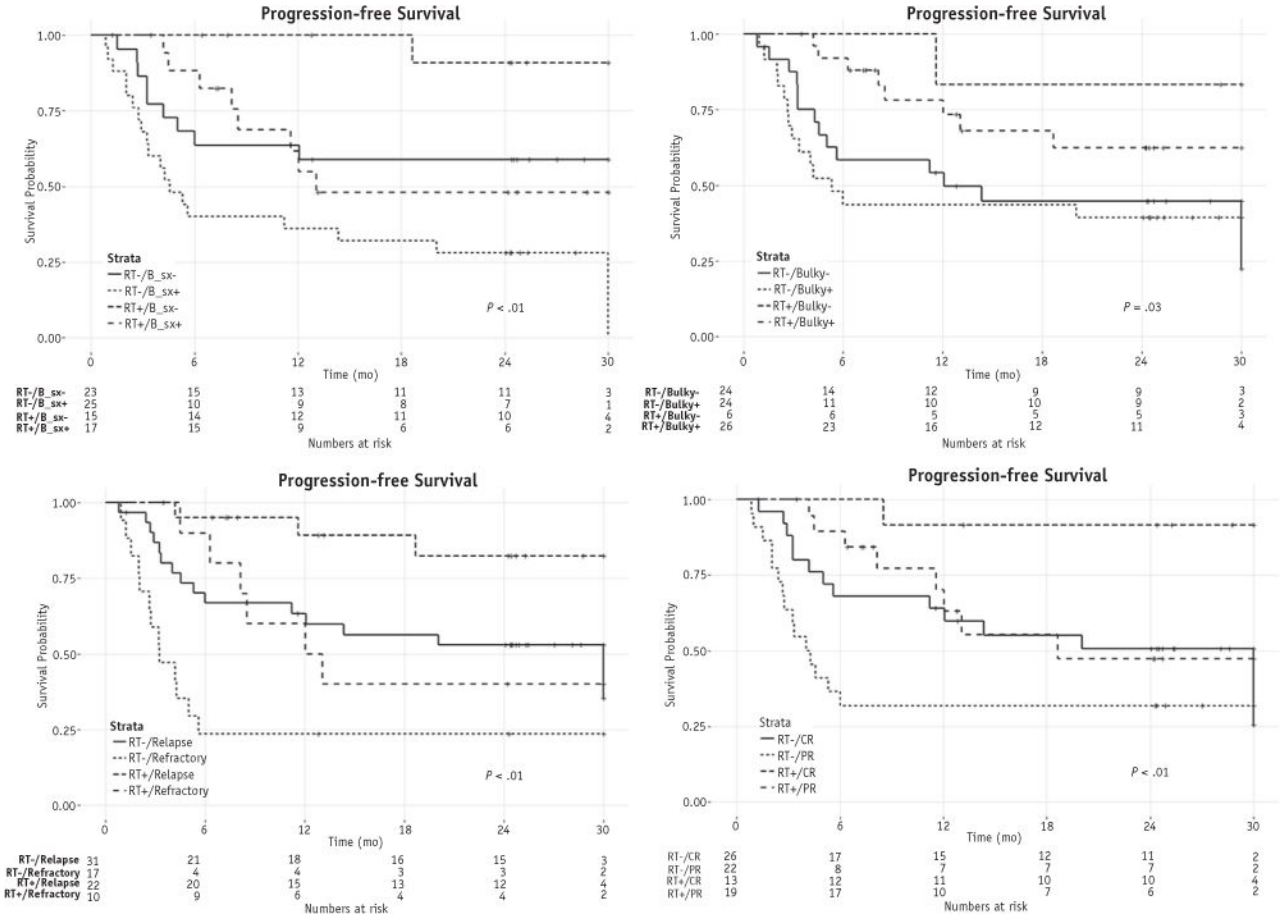


**Fig. 2.**

Kaplan-Meier plots of progression-free survival in patient subgroups stratified by consolidation radiation and B-symptoms (B_sx) (top left), bulky disease (top right), relapsed/refractory disease (bottom left), and response to pretransplant therapy (bottom right). *Abbreviations:* CR = complete remission; PR = partial remission; RT = radiation therapy.

## Table 1

Patient, disease, and transplant characteristics

| Characteristic | All patients (N = 80) | Observation (n = 48) | Consolidation RT (n = 32) | *P* |
|---|---|---|---|---|
| Median age (y) | 30 | 34 | 27 | **.03** |
| Stage at relapse | | | | .70 |
| I | 4 (5.0) | 3 (6.3) | 1 (3.1) | |
| II | 32 (40.0) | 18 (37.5) | 14 (43.8) | |
| III | 17 (21.3) | 9 (18.8) | 8 (25.0) | |
| IV | 27 (33.8) | 18 (37.5) | 9 (28.1) | |
| B-symptoms | | | | .93 |
| Yes | 42 (52.5) | 25 (52.1) | 17 (53.1) | |
| No | 38 (47.5) | 23 (47.9) | 15 (46.9) | |
| Bulky disease | | | | **<.01** |
| Yes | 50 (62.5) | 24 (50.0) | 26 (81.3) | |
| No | 30 (37.5) | 24 (50.0) | 6 (18.8) | |
| Disease state | | | | .64 |
| First relapse | 52 (65.0) | 30 (62.5) | 22 (68.8) | |
| Second relapse | 1 (1.3) | 1 (2.1) | 0 | |
| Primary refractory | 27 (33.8) | 17 (35.4) | 10 (31.3) | |
| Prior radiation therapy | | | | .20 |
| Yes | 37 (46.3) | 25 (52.1) | 12 (37.5) | |
| No | 43 (53.8) | 23 (47.9) | 20 (62.5) | |
| Prior RT dose (Gy) | | | | |
| Median dose (range) | 30.6 (21.0–45.0) | 30.6 (21.0–45.0) | 30.0 (21.0–41.4) | |
| Response to pretransplant chemotherapy | | | | .24 |
| CR | 39 (48.8) | 26 (54.2) | 13 (40.6) | |
| PR | 41 (51.3) | 22 (45.8) | 19 (59.4) | |
| Posttransplant maximum nodal size (cm) | | | | **.05** |
| <2 | 43 (53.8) | 30 (62.5) | 13 (40.6) | |
| ≥2 | 37 (46.3) | 18 (37.5) | 19 (59.4) | |

*Abbreviations:* CR = complete remission; PR = partial remission.

Values are number (percentage) unless otherwise noted. B-symptoms include unexplained fever, drenching night sweats, and ≥10% weight loss over the previous 6 months.

*P* values ≤.05 are highlighted in bold.

## Table 2

Univariate analysis of 2-year progression-free survival and overall survival

| Factor | Total n | Relapses | PFS (%) | *P* |
|---|---|---|---|---|
| 2-y PFS by group | | | | |
| All patients | 80 | 36 | 52 | |
| Consolidation RT | | | | **<.01** |
| Yes | 32 | 9 | 67 | |
| No | 48 | 27 | 42 | |
| Bulky disease | | | | .99 |
| Yes | 50 | 22 | 52 | |
| No | 30 | 14 | 53 | |
| B-symptoms | | | | **< .01** |
| Yes | 42 | 26 | 36 | |
| No | 38 | 10 | 72 | |
| Disease status | | | | **< .01** |
| 1st or 2nd relapse | 53 | 17 | 65 | |
| Primary refractory | 27 | 19 | 29 | |
| Stage at relapse | | | | .10 |
| I/II | 36 | 13 | 61 | |
| III/IV | 44 | 23 | 45 | |
| Prior radiation therapy | | | | .10 |
| Yes | 37 | 13 | 63 | |
| No | 43 | 23 | 43 | |
| Posttransplant tumor size (cm) | | | | .63 |
| <2 | 43 | 19 | 54 | |
| ≥2 | 37 | 17 | 50 | |
| Response to pretransplant therapy | | | | **.03** |
| CR | 39 | 13 | 64 | |
| PR | 41 | 23 | 41 | |
| Age (y) | | | | .64 |
| <30 | 40 | 17 | 55 | |
| ≥30 | 40 | 19 | 50 | |
| 2-y overall survival by group | | | | |
| All patients | 80 | 3 | 96 | |
| Consolidation RT | | | | .15 |
| Yes | 32 | 0 | 100 | |
| No | 48 | 3 | 93 | |
| Bulky disease | | | | .28 |
| Yes | 50 | 1 | 97 | |
| No | 30 | 2 | 93 | |
| B-symptoms | | | | .12 |
| Yes | 42 | 3 | 92 | |

| Factor | Total n | Relapses | PFS (%) | *P* |
|---|---|---|---|---|
| No | 38 | 0 | 100 | |
| Disease status | | | | .98 |
| 1st or 2nd relapse | 53 | 2 | 95 | |
| Primary refractory | 27 | 1 | 96 | |
| Stage at relapse | | | | .11 |
| I/II | 36 | 0 | 100 | |
| III/IV | 44 | 3 | 92 | |
| Prior radiation therapy | | | | .49 |
| Yes | 37 | 2 | 94 | |
| No | 43 | 1 | 98 | |
| Posttransplant tumor size (cm) | | | | .47 |
| <2 | 43 | 1 | 98 | |
| ≥2 | 37 | 2 | 94 | |
| Response to pretransplant therapy | | | | .10 |
| CR | 39 | 0 | 100 | |
| PR | 41 | 3 | 92 | |
| Age (y) | | | | .56 |
| <30 | 40 | 1 | 97 | |
| ≥30 | 40 | 2 | 94 | |

*Abbreviation:* PFS = progression-free survival. Other abbreviations as in Table 1.

*P* values ≤.05 are highlighted in bold.

**Table 3**

Multivariate analysis of 2-year progression-free survival

| Factor | Hazard ratio (95% CI) | *P* |
|---|---|---|
| Consolidation RT | | **<.01** |
| Yes | 1 | |
| No | 4.64 (1.98–10.88) | |
| B-symptoms | | **<.01** |
| No | 1 | |
| Yes | 3.21 (1.52–6.77) | |
| Disease status | | **< .01** |
| 1st or 2nd relapse | 1 | |
| Primary refractory | 3.47 (1.75–6.90) | |
| Stage at relapse | | .09 |
| I/II | 1.00 | |
| III/IV | 2.07 | |
| Posttransplant tumor size (cm) | | .27 |
| <2 | 1 | |
| ≥2 | 1.49 (0.74–3.03) | |
| Age group (y) | | .73 |
| <30 | 1 | |
| ≥30 | 0.89 (0.45–1.75) | |

*Abbreviations:* CI = confidence interval; RT = radiation therapy.

*P* values ≤.05 are highlighted in bold.

**Table 4**

Review of previous retrospective studies evaluating consolidation radiation therapy after ASCT for HL

| Study (reference) | Year | N | No. receiving RT | HDCT regimen | Timing of RT | RT dose | PFS | OS |
|---|---|---|---|---|---|---|---|---|
| Mundt et al (10) | 1995 | 54 | 20 | BAC or CBV + thiotepa | 65% after AHCT | 20–40 Gy | 5-y 40% vs 12.1% (*P*=.04) for persistent dz | NR |
| Poen et al (20) | 1996 | 100 | 24 | CBV or TBI, etoposide and cyclophosphamide | 75% before AHCT | 12.5–45 Gy (median 30 Gy) | 3-y 63% vs 55% (*P*=.59) | 3-y 70% vs 61% (*P*=.41) |
| Lancet et al (19) | 1998 | 70 | 27 | BEAC | After AHCT | 20–40 Gy | 5-y 44% vs 26% (*P*=.006) | NR |
| Dawson et al (13) | 2004 | 13 | 13 | CBV | Before AHCT | 20–36 Gy | 2-y 50% | 2-y 84% |
| Wendland et al (22) | 2006 | 65 | 21 | CBV | 71% before AHCT | 21–43.2 Gy (median 28.8 Gy) | 5-y 68.8% vs 61.1% (*P*=.83) | 5-y 73.3% vs 55.6% (*P*=.16) |
| Kahn et al (17) | 2011 | 92 | 46 | BuCyE | 83% before AHCT | 21–45 Gy (median 30 Gy) | NS except for patients with bulky dz (HR 0.36, *P*=.03) | NS |
| Biswas et al (15) | 2012 | 62 | 32 | BEAC (8% with TBI) | After AHCT | 6.0–44.2 Gy (median 30.6 Gy) | 3-y DSS 82.1% vs 57.6% (*P*=.08) | 3-y 69.6% vs 40% (*P*=.05) |
| Eroglu et al (16) | 2015 | 45 | 20 | BEAM | 80% before AHCT | 25–44 Gy (median 30 Gy) | NR | 10-y 66% vs 24% (*P*=.05) (stage I and II only) |
| Levis et al (24) | 2016 | 73 | 21 | BEAM or FEAM | 71% after AHCT | 25.2–43.2 Gy (median 30 Gy) | 5-y 61.8% vs 59.6% (*P*=.39; all patients)<br>NS for limited stage and PET+ | 5-y 68.1% vs 66.3% (*P*=.45) |
| Milgrom et al (23) | 2016 | 189 | 22 | CBV or BEAM | 95% after AHCT | 25.2–41.4 Gy (median 36 Gy) | NS<br>(4-y LC 81% vs 49%, *P*=.03 for bulky dz and/or PET + at AHCT) | NS |
| Present study | 2017 | 80 | 32 | CBV | After AHCT | 16–44 Gy (median 30.6 Gy) | 2-y 67% vs 42% (*P*<.01) | 2-y 100% vs 93% (*P*=.15) |

*Abbreviations:* AHCT = autologous hematopoietic cell transplantation; BV = brentuximab vedotin; CBV = cyclophosphamide 1.5 g/m$^2$ daily × 4 days, carmustine 300 mg/m$^2$ × 1 day, and etoposide 150 mg/m$^2$ every 12 hours × 6 doses; dz = disease; HDCT = high-dose chemotherapy; HR = hazard ratio; LC = local control; NR = not reported; NS = not significant; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; RT = radiation therapy.