Late Relapses Following High-Dose Autologous Stem Cell Transplantation (HD-ASCT) for Hodgkin Lymphoma (HL) in the ABVD Therapeutic era

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Abstract

Salvage chemotherapy followed by high dose autologous stem cell transplantation (HD-ASCT) is the standard of care for patients who have relapsed or refractory Hodgkin Lymphoma (HL). Few trials have had long-term follow-up post HD-ASCT in the ABVD era of treatment. We reviewed 95 consecutive patients who received HD-ASCT for relapsed or refractory HL following ABVD failure between 1990 and 2006 at the University of Rochester. Median follow-up for survivors was 8.2 years. All patients received HD-ASCT following up-front ABVD (or equivalent) failure. At 5 years, overall survival (OS) and event-free survival (EFS) were 54% and 37%, respectively. In total, 54 patients have died; 37 of these patients died directly of HL. Notably, there were 19 deaths > 3 years post HD-ASCT and 13 of these late deaths are directly attributable to HL. Furthermore, there were 51 documented relapses, 9 of which occurred >3 years post HD-ASCT. In contrast to other studies, we did not observe a plateau in EFS following transplantation. Patients appear to be at continuous risk of recurrence beyond 3 years after HD-ASCT. Our results emphasize the importance of long-term follow-up for both toxicity and recurrence, and have important implications in defining success of post-transplant maintenance strategies.

Keywords

Hodgkin lymphoma; hematopoietic stem cells; late effects of therapy; relapsed and refractory disease; HD–ASCT

Introduction

Approximately 80% of patients with advanced stage Hodgkin Lymphoma (HL) achieve a complete remission (CR) when treated with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine), the current gold-standard up-front HL therapy in the United States, or ABVD/ MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) hybrid therapy [1]. Thus, 20% of patients fail primary induction and an additional 20% will relapse within one year of initial therapy [1]. High-dose chemotherapy followed by autologous stem cell

transplantation (HD-ASCT) post salvage therapy is the standard of care for patients with relapsed or primary refractory HL [2–12].

Early relapses following HD-ASCT in the pre-ABVD era are well-defined in the literature. Indeed, the majority of HL relapses occur within the first two years following HD-ASCT [13–15]. Poor prognostic factors have been identified, including: systemic symptoms, extra-nodal disease at relapse, increased age, increased cycles of pre-transplant regimens, bulky disease, and poor performance status at transplant [7, 15–20]. Several studies, however, have called for systematic examination of long-term effects and, specifically, relapse following HD-ASCT [10, 17]. Long term complications have been identified, including mortality associated with infections, cardiac problems, including myocardial infarction and cardiomyopathy, and secondary malignancies [6, 14, 21–23]. However, very few studies have exclusively examined late relapses following autologous transplant. While relapse itself does not necessarily pose an immediate threat to survival, only a small number of patients who relapse after HD-ASCT will achieve long-term disease-free survival [4, 12]. The median time to progression (TTP) following HD-ASCT is approximately 6 months [24]. Several studies conducted at large transplant centers have clearly identified a plateau in OS beginning at 2 years post HD-ASCT in the pre-ABVD therapeutic era, implying that HL mortality after this point is negligible. The Vancouver group's landmark 2005 study on the first 100 patients to undergo HD-ASCT at their center, universally viewed as the paradigm of long-term surveillance post-transplant, defines a plateau in OS beginning at 2 years post HD-ASCT [14].

There is therefore a lack of studies which examine the long-term outcomes and late relapses of HD-ASCT following first-line therapy in the modern ABVD era; additional studies that characterize the late effects associated with ABVD failure rescued by HD-ASCT are valuable as ABVD is the current standard of care for advanced stage HL in the United States [25]. We analyzed all consecutive patients who underwent HD-ASCT following ABVD failure at the University of Rochester from 1990–2006 to characterize the long-term outcomes and late effects of relapsed and refractory HL treated with HD-ASCT in the ABVD therapeutic era.

Materials and Methods

Patients

This study was reviewed and approved by the Institutional Review Board (IRB) at URMC. All consecutive patients over the age of 17 with documented HL who received HD-ASCT at the University of Rochester Medical Center James P. Wilmot Cancer Center (URMC) between the years 1990 and 2006 following up-front ABVD therapy or equivalent and who were registered in the URMC Bone Marrow Transplant (BMT) Registry were examined in this study. All patients who underwent HD-ASCT after either a failure to achieve complete remission or disease relapse following initial ABVD chemotherapy or equivalent were eligible for inclusion. All HL diagnoses were confirmed by hematopathology review at URMC. Disease status was established prior to HD-ASCT by the treating physician and was not re-evaluated at the time of transplant. Relapsed and primary refractory disease prior to HD-ASCT was confirmed by biopsy or imaging. In the event that both CT +/− PET and biopsy confirmed relapsed disease, the date of biopsy was taken as date of relapse. Patients were categorized as: primary refractory or induction failure if they had relapsed less than one year after initial HL diagnosis; first relapse if they had one relapse ≥ 1 year after initial diagnosis; and advanced disease if they had experienced 2 or more HL relapses at the time of HD-ASCT.

Data Collection

The first day of follow-up was defined as the day after HD-ASCT; follow-up continued until date of most recent medical contact or date of confirmed death. All data were abstracted through extensive review of URMC medical records (including clinical, histological, laboratory and diagnostic imaging records), URMC BMT records, outside clinic charts, physician correspondence, death certificates, and autopsy reports when available. Data collected included: disease characteristics and staging; pre-HD-ASCT treatment history; salvage, conditioning, and HD-ASCT regimens; progression of disease; treatments following post HD-ASCT relapse; secondary malignancies; vital status; and cause of death.

Information regarding cause of death (COD) and vital status of patients with a prolonged follow-up time was confirmed via the National Death Index (NDI). Records were matched according to NDI's published recommendations [26–27]. At the time of data collection, NDI records extended through the year 2006; thus date and cause of death for patients with a date of last contact beyond 2006 was determined solely by our URMC chart review process. In cases where there was no URMC cause of death, the NDI search results were used exclusively. Cause of death was classified according to a modified version of the three-tiered system described by Lavoie et al in 2005: progressive HL (including treatment related death from recurrent HL after HD-ASCT), treatment-related mortality (TRM) (including organ failure or second malignancy), or other (death unrelated to HL disease progression or treatment) [14].

Statistical Analysis

Demographic characteristics of the study cohort were summarized and reported as median values (and range) for continuous variables, and proportions for categorical variables. Event Free Survival (EFS) was defined as time from HD-ASCT date to relapse or death from any cause, and patients without an event were censored at their most recent medical contact. Overall Survival (OS) was defined as time from HD-ASCT date to death from any cause; patients who were still alive at the end of follow-up were censored as either December 31, 2006 (end of NDI record availability) or their most recent medical contact if after January 1, 2007. Both EFS and OS were estimated by standard Kaplan-Meier survival techniques. We compared OS from time of first documented relapse post HD-ASCT by timing of relapse (<6 months post HD-ASCT, excluding TRM; 6–12 months post HD-ASCT, and >12 months post HD-ASCT) using the log-rank test. Expecting that those patients that relapsed within the first year post HD-ASCT were going to have an inferior prognosis, we further evaluated whether or not there was a difference in OS post HD-ASCT relapse for those relapsing 1–3 years post HD-ASCT and those that relapsed late (defined arbitrarily as >3 years post HD-ASCT), though we acknowledge that this comparison is exploratory due to limited power to formally test this comparison. Median follow-up was calculated both based on median time from HD-ASCT to censoring date among the living patients, and using the reverse Kaplan-Meier estimator [28]. Statistical analysis was conducted using SAS statistical software (SAS, Cary, NC).

Results

Patient Characteristics

Ninety-five patients were eligible and are included in this analysis. Demographic attributes of patients and therapy details are included in Table 1. The majority of patients were white (88%) and female (51%). Median age was 34 years (19–66). Patients predominantly presented with stage III-IV (53%), nodular sclerosing HL (70%), and B symptoms (62%) at the time of diagnosis. All patients underwent ABVD or ABVD equivalent therapy. The majority of patients in this study had chemosensitive disease (78%). Median time to HD-

ASCT from diagnosis was 1.9 years (0.7 – 19.6 years). A greater proportion of patients (60%) was transplanted in the first relapse.

Treatment and Conditioning Regimens

Patients received one of several salvage therapies, including: DHAP (dexamethasone, cytarabine, and cisplatin), ESHAP (etoposide, methylprednisone, cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, and etoposide), ABVD, EVA (etoposide, vinblastine, and doxorubicin), bortezomib and gemcitabine on a clinical trial [29], cyclophosphamide, local radiotherapy, and surgical debulking. A minimum of 2×10^8 mononuclear cells/kg body weight from the bone marrow, or 2×10^6 CD34$^+$ cells/kg body weight from the peripheral blood were required in order to proceed to autologous transplantation. Conditioning regimens were: BEAM (carmustine, etoposide, cytarabine, and melphalan) (38%), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) (53%), or TBI + cyclophosphamide (9%). Forty-seven patients (49%) also received consolidative radiotherapy following HD-ASCT.

Post HD-ASCT

Twenty-nine patients were alive without relapse as of August 5, 2011. The median follow-up time for survivors was 8.2 years (1.5–21.2.1 years), and the KM estimated median follow-up was 10.3 years (95% CI: 6.5–11.1 years). Patient outcomes are summarized in Figure 1, and causes of death for the 54 observed deaths to date are summarized in Table 2. Kaplan-Meier estimated EFS and OS at 5 years was 37% and 54%, respectively (Figure 2). Our central findings is that 19 of the 54 deaths (35%) occurred more than 3 years after HD-ASCT, and 13 (68% of all late deaths) are directly attributable to HL.

Post HD-ASCT Treatment Related Mortality

In total, 10 deaths of 54 total deaths were attributed to complications of therapy (TRM defined previously). Included in this category are 6 deaths within 101 days of transplant, 2 deaths beyond 101 days due to post-transplant complications, and 2 deaths due to secondary malignancy without evidence of HL progression.

Progression of HL post HD-ASCT

We observed documented relapses in 51 patients. Forty-two relapses occurred within 3 years post-transplant. However, we observed 9 relapses (18% of all relapses) beyond 3 years; the disease characteristics of these late relapsed patients are provided in Table 3. Out of all 51 patients who relapsed, 39 patients have expired: 37 deaths are due to HL (including TRM for recurrent HL), 1 death is unrelated to HL, and 1 death is due to unknown causes. Twelve of the 51 relapsed patients remain alive and many have received multiple treatment regimens since relapse post HD-ASCT: 7 patients were treated with localized radiotherapy; 5 received additional chemotherapy; 4 received allogeneic transplants (3 have relapsed; 1 is in remission); 3 were treated with monoclonal antibodies, 2 with Brentuximab vedotin (SGN 35) [30], and 1 with SGN 30; and 1 patient had a second autologous transplant. Four of these 12 patients achieved complete remission: 1 following a second autologous stem cell transplant; 1 following an allogeneic transplant; 1 following radiation therapy; and 1 following SGN 30.

Death from Progression of HL post HD-ASCT

Thirty-seven patients (39%) have died of progressive HL. Included in progressive HL deaths are patients who died of treatment related complications for recurrent HL. We do observe inferior OS for those that relapse early in the first year post HD-ASCT, as expected (Figure 3, Panel A). However, among those who relapse more than 1 year post HD-ASCT, the

survival experience past relapse appears similar for those relapsing later (defined as >3 years post HD-ASCT for this study) as compared to those patients that relapse earlier (1–3 years post HD-ASCT) (Figure 3, Panel B).

Discussion

This study examined the long-term outcomes of patients with relapsed or refractory HL who underwent HD-ASCT in the ABVD era. We reported a median follow-up time of 8.2 years. Similar to comparable studies [13–15, 31–34] the majority of our patients remain alive at 5 years and over one-third is disease free, emphasizing the continued utility of HD-ASCT. In contrast to these studies, however, we observed a noticeably higher number of late relapses. In particular, we observed 9 late relapses ≥3 years post HD-ASCT (18% of total relapses) without a plateau in either OS or EFS. We also observed 19 late deaths occurring 3 years post HD-ASCT; 13 of these late deaths are directly attributed to HL. While the 3 year post HD-ASCT threshold for defining late relapses and late deaths is somewhat arbitrary, our experience demonstrates a clear, continual risk of late relapse and HL-related mortality following HD-ASCT. Most notably our threshold is even later than the 2-year OS plateau identified in large cohort series, such as the Vancouver study and the CCTCI/MSKCC study, underscoring the finding that there is no plateau in OS. We did observe, however, a similar survival experience following HD-ASCT relapse when comparing those who we designated as late relapse (>3 years post HD-ASCT) to those who relapsed earlier (1–3 years post HD-ASCT).

There are several potential explanations for the late relapses observed in this study. We have examined long-term HD-ASCT in the post-ABVD therapeutic era, and suggest that the use of ABVD has important ramifications for our observed results. The majority of studies that have examined HD-ASCT outcomes in relapsed HL (summarized in Table 4) did so drawing heavily on data from the early 1990s before up-front ABVD therapy or equivalent was established unequivocally as standard of care treatment for advanced HL in the United States [1, 15, 25, 35–38]. Our data differs substantially from previous experiences in the pre-ABVD therapeutic era and potentially suggests that the natural history of HL after HD-ASCT following upfront ABVD therapy may differ from the historical experience of MOPP. This finding may have further implications when even more aggressive induction therapies, such as BEACOPP escalated, are utilized [39–40]. Additionally, our findings might be explained by the rigorous methods used to track patients following HD-ASCT. Larger clinical investigations might not employ such aggressive follow-up to patients more than three years removed from autologous transplant. This explanation would suggest that late relapses occur, but are not captured by the majority of studies; thus the current body of literature might be under-reporting the true incidence of late relapses following HD-ASCT. Lastly, it is possible that we observed an increased number of late relapses because our "real world" patient population was not selected for favorable prognostic features. The majority of the clinical trial literature examines HD-ASCT outcomes of a selected group of relatively young patients with favorable prognostic features. Many of the patients in our series had prognostically unfavorable characteristics at diagnosis, including B symptoms (62%), and advanced stage (III/IV) HL (53%). In addition, 33 patients in our series (35%) were primary induction failures, and 5 patients (5%) had advanced disease. Interestingly, the majority of our patients had chemosensitive disease (78%), and only one of our late relapses had documented chemoresistance. Comparable studies often include a highly selected patient population, with additional cardiac, pulmonary, renal, and hepatic function inclusion criteria. We submit that late events and relapses detailed in our series might be more applicable to the average HL patient with relapsed or refractory disease requiring aggressive treatment encountered in a clinic setting.

With a median follow-up time of 8.2 years, we demonstrated a substantial number of relapses and deaths ≥ 3 years post HD-ASCT. Clinicians need to be aware that HL patients remain at a continued risk of relapse, in addition to the well-documented risk of late therapy-related toxicity. Based on our results, HL patients may benefit from close monitoring post-transplant, perhaps for at least 5–10 years after HD-ASCT. Furthermore, our results emphasize the potential role for novel therapeutic approaches currently under evaluation to improve HD-ASCT outcomes, including maintenance approaches with therapeutic agents such as Brentuximab vedotin, anticipated to receive FDA approval, as well as with intensive, double HD-ASCT [30, 41–44]. Reduced-intensity allogeneic transplant might yield lasting remission in those patients who fail HD-ASCT, while limiting toxic exposure. Additionally, consolidative radiotherapy following autologous transplant was shown in the 2003 SWOG study to improve outcomes following HD-ASCT and should be considered as a potential strategy to maximize response in high-risk patients or those with refractory disease [34]. Moreover, given that late relapse is a reality following HD-ASCT in the ABVD era, the long natural history of HL has significant implications on endpoints for clinical trials of novel conditioning regiments prior to autologous transplantation, as well as maintenance strategies post HD-ASCT.

Acknowledgments

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ASCT at URMC 1990 – 2006
N=95 Patients

No evidence of HL relapse
N=44 Patients

15 Expired
≤ 3 years post HD-ASCT
 n=6 TRM < 101 days post HD-ASCT
 n=1 Second malignancies
 n=1TRM >101 days post HD=ASCT
 n=3 unrelated to HL

> 3 years post HD-ASCT
 n=1 Second malignancies
 n=1 TRM >101 days post HD=ASCT
 n=1 unknown
 n=1 unrelated to HL

Early HL Relapses
(≤ 3 years post HD-ASCT)
N=42 Patients

33 Expired
≤ 3 years post HD-ASCT
 n=24 Progressive HL
 n=1 unrelated to HL

> 3 years post HD-ASCT
 n=8 Progressive HL

Late HL Relapses
(> 3 years post HD-ASCT)
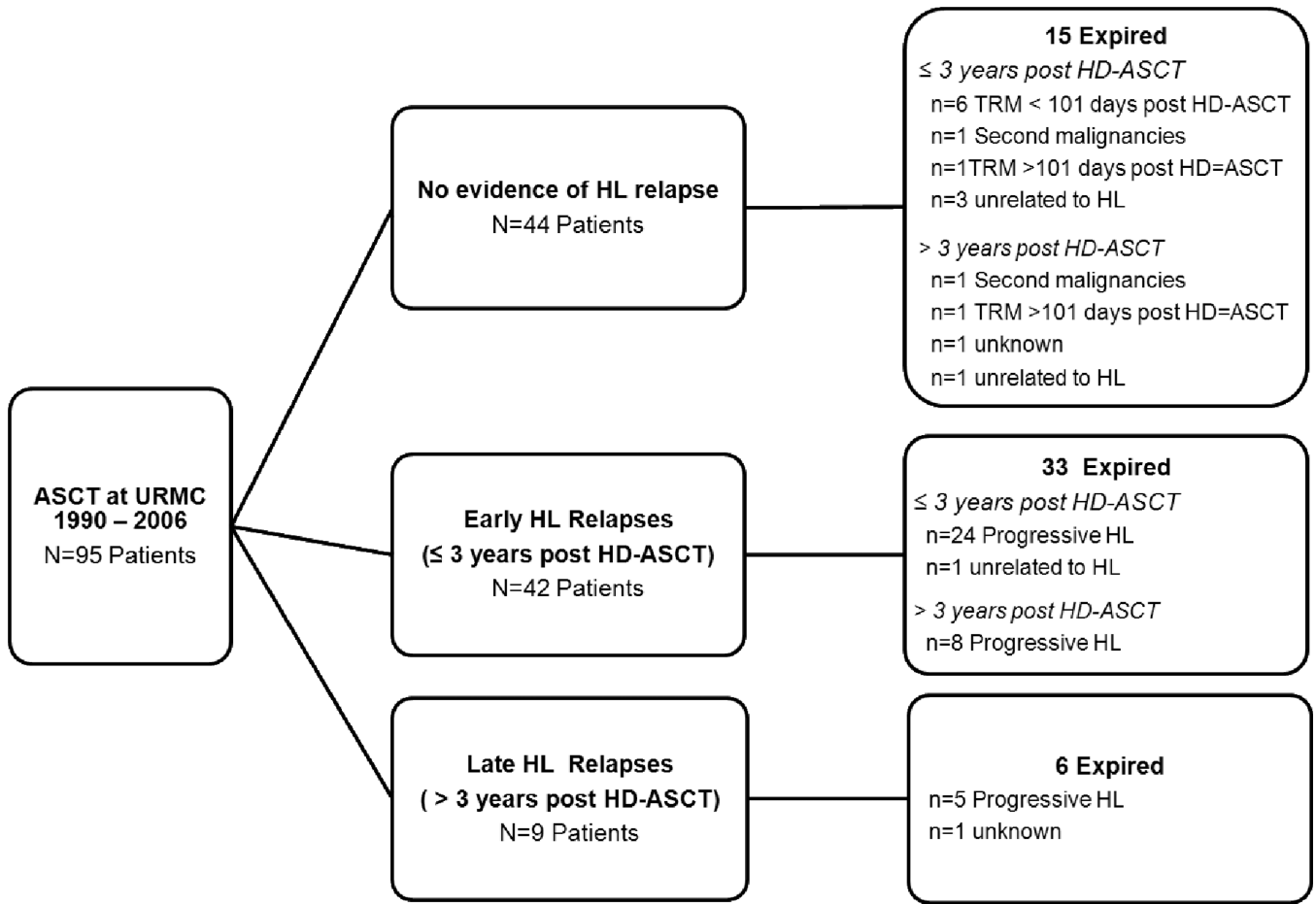N=9 Patients

6 Expired
n=5 Progressive HL
n=1 unknown

Figure 1.
Summary of patient outcomes following HD-ASCT

A.

Product-Limit Survival Estimate
with Number of Subjects at Risk

B.

Product-Limit Survival Estimate
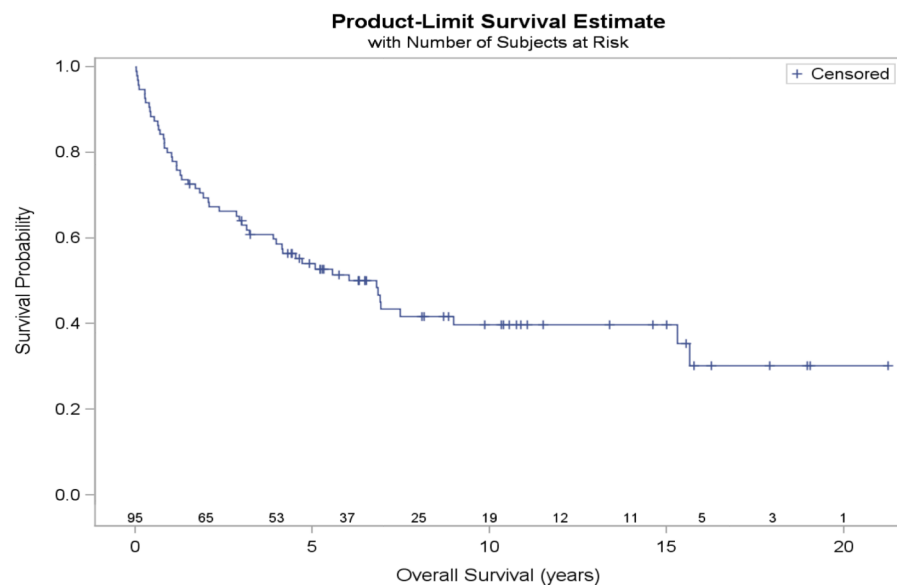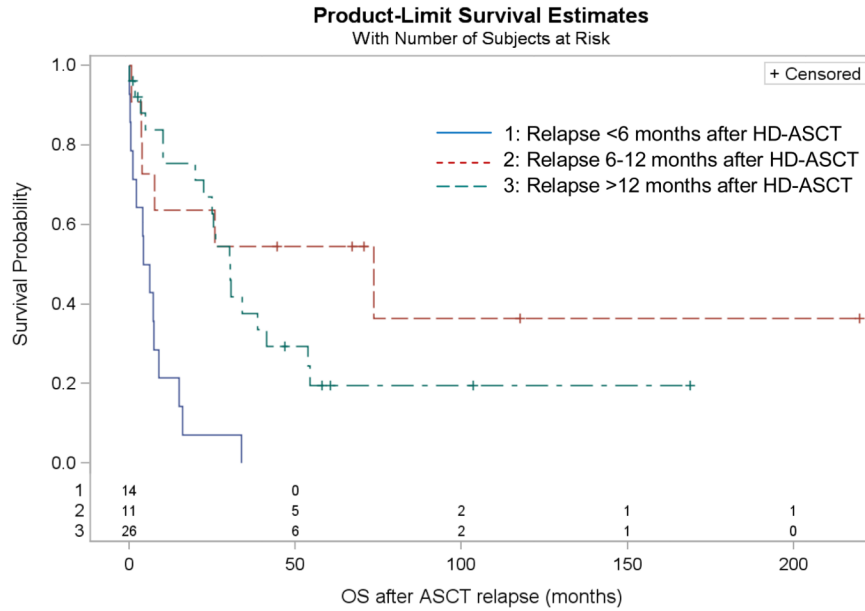with Number of Subjects at Risk
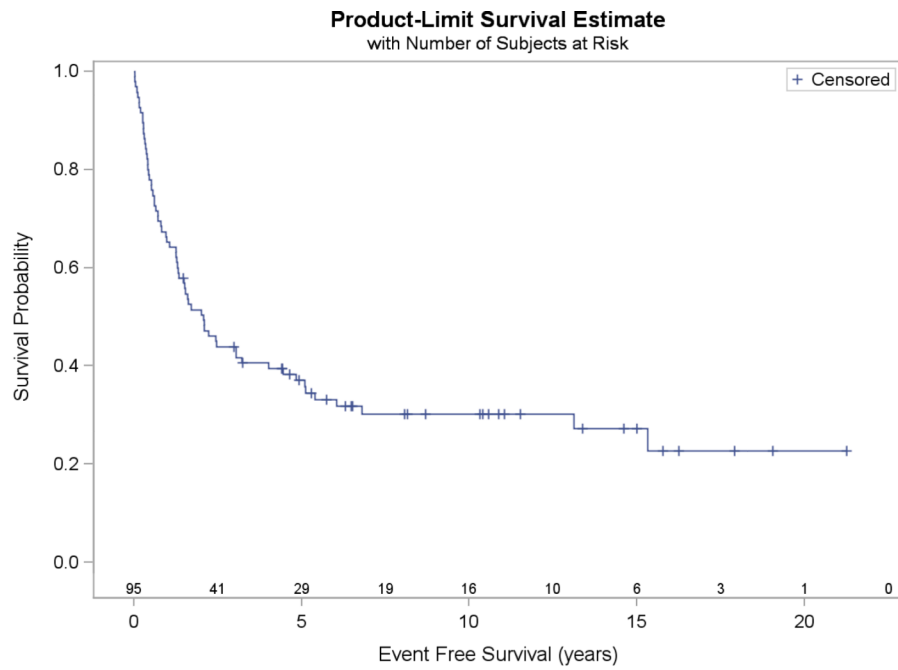
Figure 2.
Kaplan-Meier estimates of: A) Event Free survival, EFS (years; N=84); and B) Overall Survival, OS (years; N=84)

A.

B.
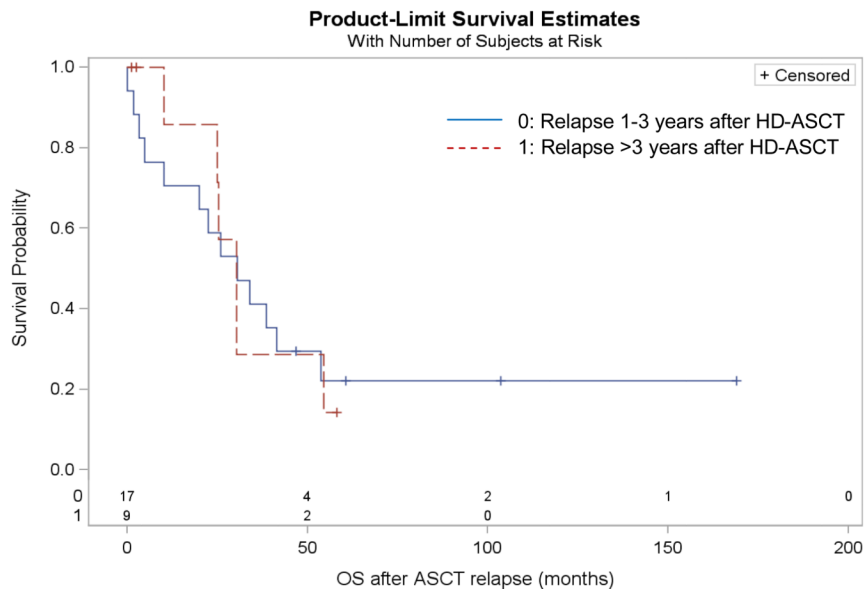
Figure 3.
Kaplan-Meier estimates of: A) Overall Survival from time of relapse, stratified by length of time between HD-ASCT and relapse (n=51 relapses, n=6 TRM excluded), log-rank p<0.001; and B) Overall Survival from time of relapse for those that relapsed 1–3 years post HD-ASCT versus those that relapsed >3 years post HD-ASCT (n=26), log-rank p=0.93, Hazard Ratio for OS with relapse >3 years post HD-ASCT vs. OS with relapse 1–3 years post HD-ASCT = 1.05 (95% CI: 0.39–2.77).

Table 1

Patient, Disease and Transplant Characteristics

Characteristic	N=95	%
Age (median, range)	34	(19–66)
Female	48	50.5%
Race		
White	84	88.4%
Black	7	7.4%
Other	4	4.2%
Hodgkin Lymphoma Histology		
Nodular Sclerosis	66	69.5%
Mixed cellularity	19	20.0%
Classical NOS	1	1.1%
Lymphocyte Predominant	4	4.2%
Lymphocyte Depleted	3	3.2%
Unknown	2	2.1%
Disease Stage at Diagnosis		
Early Stage (I/II)	43	45.3%
Advanced Stage (III/IV)	50	52.6%
B symptoms at Diagnosis	59	62.1%
Disease Status at Transplant		
First Relapse	57	60.0%
Primary Refractory or Induction Failure	33	34.7%
Advanced Disease	5	5.3%
Chemosensitivity		
Chemosensitive	74	77.9%
Conditioning Regimen		
BEAC	50	52.6%
BEAM	36	37.9%
TBI+cyclophosphamide	9	9.5%
Consolidative Radiation Therapy	47	49.5%
Graft Type		
Bone Marrow	17	17.9%
Peripheral Blood	66	69.5%
Bone Marrow + Peripheral Blood	12	12.6%

HL, Hodgkin Lymphoma; HD-ASCT, high-dose autologous stem cell transplant

Table 2

Causes of death for N= 54 patients (Median follow-up = years)

Characteristic	N=54	%
Progressive HL (including TRM for recurrent HL)	37	68.5%
Treatment Related Mortality	10	18.5%
Early deaths (within 101 days of HD-ASCT)	6	
Second malignancies	2	
Deaths secondary to treatment (>101 days post HD-ASCT)[*]	2	
Deaths unrelated to HL	5	9.3%
Acute MI	2	
Acute cholecystitis	1	
Non-infective gastroenteritis/colitis	1	
COPD	1	
Unknown	2	

TRM, Treatment related mortality; HL, Hodgkin Lymphoma; HD-ASCT, high-dose autologous stem cell transplant; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease;

[*] pneumothorax (1), infection pneumonitis (1)

Table 3

Characteristics of Late Relapses (relapse >3 years postHD-ASCT, n=9)

Age[^]	Stage[*]	Histology	Conditioning Regimen	Disease Characteristics[†]	Post-transplant Radiation Consolidation	Event Free Survival (years)	Survival	COD
40	IV B	Lymphocyte Predominant	BEAC	Advanced disease; Chemosensitive	No	3.1	Expired	TRM
20	II B	Nodular Sclerosis	BEAC	PIF; Chemosensitive	Yes	3.1	Expired	Unknown
40	II	Indeterminate	BEAC	Chemosensitive	No	4.0	Alive	
33	IV	Mixed cellularity	BEAM	Chemosensitive	No	4.4	Alive	
40	III	Nodular Sclerosis	BEAC	Chemosensitive	No	4.8	Expired	HL
46	IV B	Nodular Sclerosis	TBI/Cy	Chemosensitive	Yes	5.1	Alive	
39	IV B	Nodular Sclerosis	BEAM	Chemoresistant	No	5.1	Alive	
44	III	Nodular Sclerosis	BEAM	PIF; Chemosensitive	No	5.4	Expired	HL
64	II	Nodular Sclerosis	BEAC	Unknown Chemosensitivity	Yes	13.1	Expired	HL

[^]
age at high-dose-autologous stem cell transplant;

[*]
stage at diagnosis;

[†]
all patients were transplanted after salvage following first relapse unless noted to be primary induction failures or have advanced disease (2 or more relapses before transplant); HD-ASCT, high-dose autologous stem cell transplant; PIF, primary induction failure; COD, cause of death; TRM, treatment related mortality; TBI, total body irradiation; Cy, cyclophosphamide

Table 4

Comparison of Studies Examining Long-Term Outcomes after HD-ASCT for Relapsed/Refractory HL

Author	Date	Study Duration	N	% ABVD	R/P	Median f/u time (yrs)	% EFS	%OS	Comment
Bierman	2002	1984–1999	379	NS^	R	5.1	24 (10y)	32 (10y)	
Stiff	2003	1990–1995	74	14	P	10	41 (5y)	54 (5y)	No late events in sensitive * pts; some late events in resistant † pts
Moskowitz	2004	1985–1998	75	81.3	P	10	45 (10y)	48 (10y)	OS, EFS plateau
Lavoie	2005	1985–1992	100	NS^	P	11.4	51(15y)	54 (15y)	OS plateau
Majhail	2006	1985–2003	141	63.8	R	6.3	48 (5y)	53 (5y)	OS plateau, some late events
Sirohi	2008	1985–2005	195	NS^	P	10.3	44 (5y)	55 (5y)	
Smith	2011	1995–2008	214	82.7	R	6	45	55	Study limited to early relapses; EFS plateau
URMC	2011	1990–2006	95	100	R	8.2	37 (5y)	54 (5y)	Notable late events

NS, not specified; R, retrospective study; P, prospective study; sensitive *, chemosensitive disease; resistant †, chemoresistant disease