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Characteristics and outcomes of children, adolescents and young adults with relapsed/refractory non-hodgkin lymphoma undergoing autologous stem cell transplant

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Abstract

Background There is paucity of data regarding outcomes of children, adolescents and young adults (CAYA) patients with non-Hodgkin lymphoma (NHL) undergoing autologous stem cell transplantation (ASCT).

Methods Patients aged 0–39 years undergoing first ASCT for NHL at MD Anderson Cancer Center between 2000 and 2020 were analyzed.

Results Two hundred twenty-one patients were included in the analysis, 129 (58%) were male and the median age was 32 (range 6–39) years. The most common histological subtypes were diffuse large B cell lymphoma (DLBCL) (44%), T-NHL (19%) and primary mediastinal B-Cell lymphoma (PMBCL) (19%). Younger patients (age ≤ 25) had lower incidence of DLBCL and higher incidence of PMBCL and T-NHL compared to older patients (age > 25) ($P=0.02$). None of the younger patients had double hit (DH)/double expressor (DE) DLBCL, compared to 14 patients in the older age group (18%, $P=0.07$). Considering the three main aggressive NHL subtypes (DLBCL, PMBCL and T-NHL), younger patients had numerically better 15-year post-transplant progression free survival (PFS) (67% vs. 54%) and overall survival (OS) (71% vs. 62%) compared to older patients, yet these differences did not reach statistical significance ($P=0.19$ and $P=0.24$, respectively). In multivariate analysis, not achieving a CR prior to ASCT was independently predictive of worse PFS [partial remission (PR) (HR, 3.9); stable disease (SD) (HR, 18.0), $P=0.03$] and of worse OS [PR (HR, 4.2), SD (HR, 6.5) and progressive disease (HR, 4.7), $P<0.0001$]. DH/DE status was an independent adverse predictor of PFS in multivariate analysis (HR 5.8, $p=0.03$).

Ten patients (4.5%) (all aged > 25 years) developed second primary malignancies (SPM), at a median of 34.4 (range, 1.0–196.6) months after ASCT, and SPM was the cause of death in five (50%) of them.

Conclusions CAYA NHL patients aged ≤ 25 years who received ASCT presented a distinct NHL histology as compared to older CAYA patients, and none in this younger age group had DH/DE DLBCL. We observed a trend towards improved PFS and OS in younger patients. Disease status at ASCT was predictive of both PFS and OS. DH/DE status was an adverse predictor of PFS.

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Keywords Non hodgkin lymphoma, Children, Adolescents, Young adults, Autologous transplant

Introduction

There is growing recognition of the unique characteristics and challenges facing children, adolescents and young adults (CAYA) with cancer [1]. NHL accounts for approximately 8% of reported malignancies in the AYA population. AYA with NHL have distinct clinical presentations, biological characteristics and outcomes compared to children or older adults [2]. The most common NHL subtypes in this age group include diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma and primary mediastinal large B-cell lymphoma (PMBCL). Compared to older adults, DLBCL in children and AYA is more likely to have a germinal center B-like (GCB) immunophenotype, *MYC* translocation or overexpression, high proliferative index and absence of *BCL2* translocation [3–5].

Burkitt lymphoma and DLBCL are the most common subtypes of NHL in children, and most patients have a favorable outcome with standard of care first line treatment, with over 90% 5-year event-free survival [6]. However, prognosis remains poor for patients with relapsed/refractory disease [7], and early prognostic parameters are being studied to enable early identification of CAYA patients with high-risk disease. Minimal disseminated disease (MDD), a PCR-based test to detect translocation (8;14) or patient-specific immunoglobulin gene rearrangements, represents one such tool for molecular prognostication and for treatment response monitoring [8]. Particularly in this age group, efforts to integrate novel agents into NHL therapies instead of conventional chemotherapy, could reduce the burden of therapy and its long-term consequences in the future [9].

CAYA patients undergoing hematopoietic stem cell transplantation face unique difficulties, including social and psychological challenges [10, 11], yet there is paucity of data focusing on outcomes of autologous stem cell transplantation (ASCT) in CAYA patients with NHL.

In the present study we aimed to examine the characteristics and outcomes of contemporaneous CAYA patients who received their first ASCT due to NHL at MD Anderson Cancer Center. We evaluated potential impact of patient and disease-related variables on outcomes and compared the younger and older age groups within our cohort.

Methods

Study design and participants

We conducted a retrospective chart review of patients aged 0–39 years who received their first ASCT for NHL

treated at MD Anderson Cancer Center between January 2000 and January 2020. We excluded patients who received a previous allogeneic or autologous transplant. We divided this cohort into two age groups: younger (≤ 25 years) and older (> 25 years) patients. This division was based on developmental stage: ≤ 25 years to include pediatric, adolescents and emerging adults, and > 25 years to include young adulthood patients [12]. This retrospective chart review was approved by the Institutional Review Board.

We used standard criteria for staging, response and outcomes according to guidelines from the Lymphoma Imaging Working Group [13] and Harmonization Project in Lymphoma [14]. As per these criteria, complete remission (CR) was defined as the disappearance of any evidence of disease on positron emission tomography/computed tomography (PET/CT); partial remission (PR) was defined as regression of measurable disease and no new sites on PET/CT; stable disease (SD) was defined as failure to attain either CR/PR or progressive disease (PD); PD was defined as any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir on PET/CT.

Double/triple hit lymphoma and double expressor lymphoma were defined according to the WHO classification of lymphoid neoplasms [15].

Statistical methods

Wilcoxon rank-sum tests were used to compare the distribution of continuous variables between age groups. Fisher's exact tests were used to compare the distribution of categorical variables between groups. The method of Kaplan and Meier was used to estimate the distribution of overall survival (OS) and progression-free survival (PFS) from the date of transplant. Patients who remained alive (OS) or alive and progression-free (PFS) were censored at the last follow-up date. Distributions were compared using the log-rank test. Cox proportional hazards regression models were fit to each survival endpoint. In some cases, Firth's penalized likelihood method was used to fit models when the number of patients in one or more categories was small. Univariate and multivariate Cox regression models were also fit to each survival endpoint using factors specified by the investigator. Because there was substantial missing data in the second-line international prognostic index (sIPI) variable, two models were fit for each: one considering sIPI and one without it.

All statistical analyses were performed using R version 4.1.1. All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

Results

Patients and disease characteristics

We included 221 consecutive patients in the analysis, 129 (58%) were male and 92 (42%) female. The median age was 32 (range 6–39) years. The most common histological subtypes in the entire cohort were DLBCL ($N=98$, 44%), T-NHL ($N=43$, 19%) and PMBCL ($N=41$, 19%) (Table 1). Within the subset of DLBCL patients, 14 patients (14%) had either double/triple hit or double expressor lymphoma. Most patients received 2 (37%) or 3 (31%) lines of treatment prior to ASCT, and the majority achieved a pre-transplant response of either CR (59%) or PR (32%).

Younger patients (age ≤ 25) had a lower incidence of DLBCL (34% vs. 48%) and higher incidence of PMBCL (25% vs. 17%) and T-NHL (32% vs. 16%) compared to older patients ($P=0.02$), within the main aggressive NHL subtypes. None of the younger patients had double hit (DH)/double expressor (DE) DLBCL, compared to 14 patients in the older group (18%, $P=0.07$). The age range for patients with DH/DE NHL was 31–39 years. Number of treatment lines and responses prior to ASCT were similar in both age groups ($p=0.93$ and $p=0.71$, respectively) (Table 1).

Outcomes

After a median follow up of 5.5 (range 0.1–21.1) years, the median PFS for the entire cohort was 19.1 (95% CI 14.5 – NR) years (Fig. 1A) and the median OS was 19.1 (95% CI 19.1 – NR) years (Fig. 1B). When considering the three main aggressive NHL subtypes (DLBCL, PMBCL and T-NHL), younger patients had numerically better 15-year post-transplant PFS (67% vs. 54%, Fig. 2A) and OS (71% vs. 62%, Fig. 2B), as compared to older patients, yet these differences did not reach statistical significance ($P=0.19$ and $P=0.24$, respectively). The most common cause of death in both age groups was progression of lymphoma, that accounted for 43 deaths (72% of all deaths) (Supplementary Table 1).

Number of previous lines of treatment was predictive of PFS in univariate analysis (UVA) (HR 1.35, $p=0.02$), but not multivariate analyses (MVA). In MVA, not achieving a CR prior to ASCT was independently predictive of worse PFS [PR (hazard ratio (HR), 3.9); SD (HR, 18.0), $P=0.03$] and of worse OS [PR (HR, 4.2), SD (HR, 6.5) and PD (HR, 4.7), $P<0.0001$]. DH/DE status was an independent adverse predictor of PFS in MVA (HR 5.8, $p=0.03$), but not of OS (HR=1.8, $p=0.26$). Complete MVA for PFS and OS are provided in Table 2. UVA for PFS and OS are provided in Supplementary Tables 2 and 3, respectively.

Ten patients in the cohort (4.5%), all aged >25 years, developed second primary malignancies (SPM), at a

median of 34.4 (range, 1.0–196.6) months after ASCT: 6 hematological malignancies (myelodysplastic syndrome (MDS) $n=4$, acute myeloid leukemia $n=2$) and 4 solid tumors (sarcoma, squamous cell carcinoma, thyroid cancer and lung cancer $n=1$ each). SPM was the cause of death in five (50%) of them. Three patients with t-MDS received an allogeneic HCT. For all patients with a SPM, median PFS and OS times were both 161.2 (10.2 – NR) months following ASCT.

Discussion

In the present study we describe patient characteristics and long-term outcomes of a large cohort of CAYA who received ASCT for NHL at a large tertiary transplant center. The three most common histological subtypes of NHL in the entire cohort were DLBCL, T-NHL and PMBCL. More than 90% achieved \geq PR prior to transplant. We found that patients aged ≤ 25 years presented a distinct NHL histology as compared to older CAYA patients, and none in this younger age group had DH/DE DLBCL. Disease status at ASCT was predictive of both PFS and OS, whereas DH/DE status was an adverse predictor of PFS.

Considering the three main aggressive NHL subtypes, we observed numerically better survival outcomes in younger patients, yet there was no statistically significant difference between the two age groups. A report by Berkman et al. examined long-term survivors of DLBCL AYA patients (defined as age of 15–39 years) using the Surveillance Epidemiology and End Results (SEER) database [16] found that each additional year of age at diagnosis was associated with a decrease of 6% in overall survival ($p<0.0001$). On the other hand, in the Japanese AYA registry study [17], age was not associated with survival outcomes. In the subset of patients who received ASCT, younger patients (<16 years) had similar OS and EFS compared to older patients (≥ 16 years) [(45.7% vs. 44.8%, $p=0.547$) and (42.3% vs. 38.9%, $p=0.775$), respectively]. However, younger patients in that study did have a higher rate of transplant related mortality (TRM) (5.1% vs. 0.8%, $p=0.0043$). We observed higher rates of PFS and OS in our cohort, compared to the Japanese registry study: The 5-year PFS in our study was 76.5% for the younger age group and 63.8% in the older age group, and the 5-year OS were 86.4% and 72.5%, respectively. There are several methodological differences that can partially explain these differences in outcomes. First, we included a broader range of ages in our study, so that our study cohort comprised both pediatric patients as well as the most commonly used definitions of AYA, up to the age of 39 [10]. Furthermore, the two studies also had different proportions of the various NHL histological subtypes and used a different age

Table 1 Patient and disease characteristics

Parameter	All (N=221) n (%)	Age ≤ 25 years (N=53) n (%)	Age > 25 years (N=168) n (%)	p-value
Gender				1.0
Male	129 (58)	31 (58)	98 (58)	
Female	92 (42)	22 (42)	70 (42)	
Histology (all)				0.05
DLBCL	98 (44)	18 (34)	80 (48)	
T-NHL ^a	43 (19)	17 (32)	26 (16)	
PMBCL	41 (19)	13 (25)	28 (17)	
Low-grade B-Cell lymphoma	10 (5)	0 (0)	10 (6)	
Hepatosplenic gamma-delta T-cell lymphoma	7 (3)	2 (4)	5 (3)	
Burkitt lymphoma	8 (4)	3 (6)	5 (3)	
Primary CNS Lymphoma	4 (2)	0 (0)	4 (2)	
Plasmablastic lymphoma	3 (1)	0 (0)	3 (2)	
Lymphoblastic lymphoma ^b	3 (1)	0 (0)	3 (2)	
Mantle Cell Lymphoma	2 (1)	0 (0)	2 (1)	
Waldenstrom's macroglobulinemia / lymphoplasmacytic lymphoma	1 (0)	0 (0)	1 (1)	
Cutaneous T-cell lymphoma/Sezary	1 (0)	0 (0)	1 (1)	
Histology (main aggressive NHL)				0.02
DLBCL	98 (54)	18 (38)	80 (60)	
T-NHL	43 (24)	17 (35)	26 (19)	
PMBCL	41 (23)	13 (27)	28 (21)	
Double or Triple Hit / Double Expressor status^c				0.07
Positive	14 (14)	0 (0)	14 (18)	
Negative	84 (86)	18 (100)	66 (83)	
No. treatment lines before ASCT				0.93
1	42 (19)	9 (17)	33 (20)	
2	82 (37)	21 (40)	61 (36)	
3	69 (31)	19 (36)	50 (30)	
4	21 (10)	3 (6)	18 (11)	
5	7 (3)	1 (2)	6 (4)	
Response prior to ASCT				0.71
CR	131 (59)	36 (68)	95 (57)	
PR	71 (32)	14 (26)	57 (34)	
SD	9 (4)	1 (2)	8 (5)	
PD	9 (4)	2 (4)	7 (4)	
Untreated	1 (0)	0 (0)	1 (1)	
siPI				0.55
0/1	84 (82)	22 (88)	62 (81)	
2/3	18 (18)	3 (12)	15 (20)	
Conditioning regimen				0.55
BEAM ± rituximab	138 (62)	37 (69)	101 (60)	
GemBuMel—based	71 (32)	14 (26)	57 (34)	
KPS/LPS prior to transplant				0.62
100	63 (33)	15 (33)	48 (33)	
90	89 (46)	21 (46)	68 (47)	
80	32 (17)	8 (17)	24 (16)	
70	7 (4)	1 (2)	6 (4)	
60	1 (1)	1 (2)	0 (0)	

DLBCL diffuse large B-cell lymphoma, T-NHL T-cell non-hodgkin lymphoma, PMBCL primary mediastinal B-cell lymphoma, CNS central nervous system, ASCT autologous hematopoietic stem cell transplantation, CR complete remission, PR partial remission, SD stable disease, PD progressive disease, siPI secondary international prognostic index, BEAM BCNU, etoposide, cytarabine and melphalan, GemBuMel gemcitabine, busulfan and melphalan, KPS/LPS karnofsky/lansky performance scale

^a Includes: Large cell anaplastic lymphoma, ALK positive, *n* = 24; Large cell anaplastic lymphoma, ALK negative, *n* = 1; Extranodal NK / T-cell lymphoma, nasal type, *n* = 3; Peripheral T-cell Lymphoma, *n* = 15

^b Includes: T lymphoblastic lymphoma, *n* = 2; B lymphoblastic lymphoma, *n* = 1

^c Considered positive if either of the following positive: double hit / triple hit / double expressor. Calculated for patients with DLBCL histology only

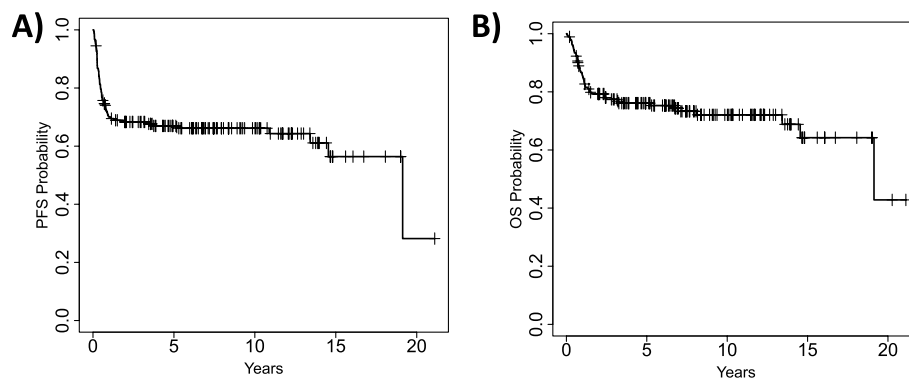


Fig. 1 Progression free survival (A) and overall survival (B) for the entire cohort

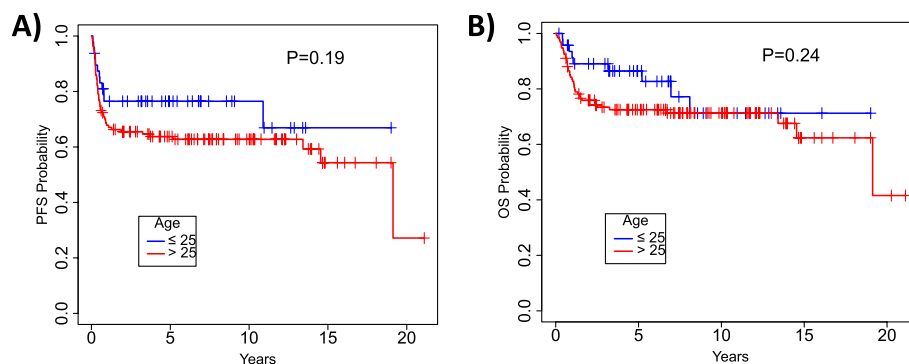


Fig. 2 Progression free survival (A) and overall survival (B) according to age at transplant: younger (≤ 25 years) versus older (> 25 years) patients

cutoff for the younger/older age subsets. In the Japanese registry study by Kobayashi et al., 28% of patients who received ASCT had T/B lymphoblastic lymphoma, and 6% had Burkitt Lymphoma. In the current study, only 5% of the cohort had either of these two highly aggressive sub-types of NHL. This discrepancy likely represents referral bias and differences in institutional practices pertaining to transplant.

Few previous reports have evaluated outcomes of ASCT in NHL with a varying range of ages within the CAYA spectrum [17–20], including a small single center study that included 36 pediatric NHL patients [19] and a Center for International Blood and Marrow Transplant Research (CIBMTR) registry study that included 182 children and adolescent NHL patients (aged 0–18 years; 90 received ASCT) that were transplanted between 1990 and 2005 [20]. A more recent analysis of the Japanese registry dataset compared outcomes of AYA patients (defined as aged 16–30, $n=387$) to pediatric patients (aged 0–15, $n=114$) undergoing ASCT for NHL [17]. TRM was significantly higher in children compared to AYA. A multi-national study included 639 patients with R/R NHL (mostly Burkitt lymphoma/leukemia

and DLBCL) aged 0–18 years. Only 23% of the entire cohort ($n=150$) received an ASCT, whereas 37% did not undergo any transplant. The 8-year OS of patients who underwent ASCT was superior to those who did not receive any transplant (55% vs. 8%, respectively; $p<0.0001$).

Our study focused only on first ASCT, and included both the pediatric and AYA populations. We were able to elucidate variables that impacted survival outcomes in this setting. We showed that achieving pre-transplant CR was associated with better PFS and OS in MVA. This finding complements previous studies that have shown the prognostic impact of responses prior to ASCT in adults with aggressive B-Cell [21] and T-Cell [22] NHL.

In our cohort none of the younger DLBCL patients had DH/DE lymphoma, whereas 14% of patients aged >25 years had either DH or DE disease. A previous study also observed that patients with DH/DL DLBCL were overall older than those without one of these high-risk features, and the youngest patients with DH and DE were 49 and 30 years of age, respectively [23]. Of note, patient age in that study ranged between 16–91 (median 64) years. In another series, only one of

Table 2 Multivariable Assessments for progression free survival (PFS) and overall survival (OS)

Parameter	Hazard Ratio (95% CI)	p-value
PFS		
Double or Triple Hit / Double Expressor status^a		
Negative	<i>ref</i>	
Positive	5.8 (1.2–23.3)	0.03
Response prior to ASCT		0.03
CR	<i>Ref</i>	
PR	3.9 (1.2–13.3)	
SD	18.0 (1.3–178.3)	
Number of treatment lines prior to ASCT	0.8 (0.4–1.6)	0.62
sIPI		
0/1	<i>Ref</i>	
2/3	0.7 (0.2–2.6)	0.63
Conditioning Regimen		
BEAM ± rituximab	<i>Ref</i>	
GemBuMel-based	0.5 (0.1–1.9)	0.31
OS		
Response prior to ASCT		< 0.0001
CR	<i>ref</i>	
PR	4.2 (2.2–8.7)	
SD	6.5 (1.9–18.5)	
PD	4.7 (0.9–17.2)	
Lines of treatment prior to ASCT	1.1 (0.8–1.5)	0.45
Conditioning Regimen		
BEAM ± rituximab	<i>ref</i>	
GemBuMel-based	1.0 (0.5–1.8)	0.93

Abbreviations: DH/DE double hit/double expressor, ASCT autologous hematopoietic stem cell transplantation, CR complete remission, PR partial remission, SD stable disease, PD progressive disease, sIPI secondary international prognostic index, BEAM BCNU, etoposide, cytarabine and melphalan, GemBuMel gemcitabine, busulfan and melphalan

^a Considered positive if either of the following positive: double hit / triple hit / double expressor. Calculated for patients with DLBCL histology only

16 pediatric DLBCL patients had DH DLBCL [3]. In the current study we confirmed the prognostic importance of DH/DE status in CAYA patients undergoing ASCT. A previous report demonstrated the prognostic impact of DH/DE status in adults (age range 30–76 years) [24].

With a median follow up period of 5.5 years, and some patients followed for more than 20 years, 4.5% of our CAYA cohort develop a SPM. This is lower than the 9% of SPM reported in a study that included 372 adult NHL patients who underwent ASCT [25], and slightly higher than the 2.6% reported in a large cohort of 1487 pediatric patients that were transplanted for a variety of indications (26% underwent ASCT due to lymphoma) [26]. A joint study from European and German study groups analyzed 189 cases of SPM in children and adolescents (aged 0–18) after treatment for NHL [27]. Half the SPM in that study were hematological malignancies (23% myeloid and 27% lymphoid neoplasms), and an additional 25% were carcinomas. This distribution was overall similar to the types of SPM observed in

our cohort. Of note, the aforementioned study did not report how many patients received ASCT.

The current study has several limitations inherent to its retrospective design, including heterogeneity in patient characteristics and treatments, as well as unidentified confounders that were not accounted for, despite the use of multivariable cox regression analysis. Furthermore, cohort size is rather modest, despite being one of the largest cohorts of CAYA NHL patients receiving ASCT in the published literature to date.

With the advent of novel therapeutic modalities, mainly chimeric antigen receptor (CAR) T-cell therapy, the role of ASCT needs additional clarification. Recently, two phase III trials have shown superiority of two anti-CD19 CAR T constructs for treatment of a subset of patients with R/R DLBCL [28, 29]. Both trials included only adult patients, and trials with autologous anti-CD19 CAR T in pediatric NHL patients are ongoing (NCT03610724, NCT02625480). Our data may serve as a benchmark for outcomes of future CAR T trial outcomes.

Conclusions

To the best of our knowledge, we report on the largest cohort to date of CAYA NHL patients receiving ASCT, including patient characteristics and long-term outcomes. Patients aged ≤ 25 years presented a distinct NHL histology as compared to older CAYA patients, and none in this younger age group had DH/DE DLBCL. We observed numerically better PFS and OS in younger patients with aggressive NHL compared to older CAYA patients, albeit without a statistically significant difference. Disease status at ASCT was predictive of both PFS and OS. DH/DE status was an adverse predictor of PFS.

Abbreviations

ASCT	Autologous stem cell transplantation
CIBMTR	Center for International Blood and Marrow Transplant Research
CAYA	Children, adolescents and young adults
CAR	Chimeric antigen receptor
CR	Complete remission
DLBCL	Diffuse large B-cell lymphoma
DE	Double expressor
DH	Double hit
GCB	Germinal center B-like
MVA	Multivariate analyses
MDS	Myelodysplastic syndrome
OS	Overall survival
PR	Partial remission
PET/CT	Positron emission tomography/computed tomography
PMBCL	Primary mediastinal large B-cell lymphoma
PFS	Progression-free survival
siPI	Second-line international prognostic index
SPM	Second primary malignancies
SD	Stable disease
SEER	Surveillance Epidemiology and End Results
TRM	Transplant related mortality

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-023-11712-6>.

Additional file 1: Supplementary Table 1. Causes of death.

Additional file 2: Supplementary Table 2. Univariate assessments for progression free survival (PFS).

Additional file 3: Supplementary Table 3. Univariate assessments for overall survival (OS).

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Not applicable

Authors' contributions

OP and YN conceived and designed the study. OP and SG collected and assembled the data. OP, RLB and YN analyzed and verified the data. BC, PT, CH, SS, JR, KMM, SK, DP, UP, MQ, PK, RC and EJS verified and interpreted the data. All authors wrote and approved of the article and are accountable for publication.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

This study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board.

We secured specific approval from the University of Texas MD Anderson Cancer Center Institutional Review Board to waive patient consent for this retrospective chart review study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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