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blood advances

Impact of event-free survival status after stem cell transplantation on subsequent survival of patients with lymphoma

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Key Points

- EFS status was a useful end point among lymphoma patients after HSCT.
- The SMR was higher in patients with HL, DLBCL, or FL after allo-HSCT than in the general population even after achieving EFS24 or EFS60.

We evaluated the impact of event-free survival (EFS) status at 24 months (EFS24) and 60 months (EFS60) after hematopoietic stem cell transplantation (HSCT) using registry data. Patients who underwent their first autologous HSCT (auto-HSCT) or allogeneic HSCT (allo-HSCT) for lymphoma between 1981 and 2018 were included. Overall survival was compared with that of the age-, sex, and calendar period–matched general population. A total of 14 977 patients, including 10 964 and 4013 who underwent auto-HSCT and allo-HSCT, respectively, were analyzed. Although patients who achieved EFS24 and EFS60 had favorable outcomes, most had significantly poorer survival rates than the general population. The standardized mortality ratios (SMRs) of patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) were significantly higher than that of the general population even after achieving EFS24 or EFS60. The SMRs of those after auto-HSCT were 2.5 to 3.5 and 2.7 to 3.7, respectively. The SMR was consistently highest in Hodgkin lymphoma (HL) patients after HSCT. By contrast, subsequent survival of patients with primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, or peripheral T-cell lymphoma, not otherwise specified, who achieved EFS60 after auto-HSCT, and those with extranodal natural killer/T-cell lymphoma who achieved EFS60 after allo-HSCT did not significantly differ from that of the general population, with SMRs of 1.6, 1.2, 1.8, and 1.3, respectively. Our results suggest that EFS24 and EFS60 were clinically useful end points after HSCT for lymphoma patients. Furthermore, patients with certain lymphoma subtypes who achieved EFS had a comparable prognosis with that of the general population and were potentially cured after HSCT.

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The full-text version of this article contains a data supplement.

Introduction

The number of patients diagnosed with lymphoma has gradually increased over the past few decades.[1] The prognosis of patients with B-cell non-Hodgkin lymphoma was improved by the introduction of rituximab in the early 2000s.[2,3] Thereafter, the development of several new agents, including anti-CD20 antibodies, molecular-targeted agents, small molecular inhibitors, and novel combination chemotherapies, improved the survival of lymphoma patients over time.

Recent studies have reported the impact of the event-free survival (EFS) status at 24 months (EFS24) after initial diagnosis on stratification of the subsequent overall survival (OS) in patients with different lymphoma subtypes, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), classic Hodgkin lymphoma (HL), and peripheral T-cell lymphoma (PTCL).[4-7] Lymphoma patients who achieve EFS24 generally have better outcomes than those who do not. In particular, the OS of patients with DLBCL and FL who achieve EFS24 is good, and does not significantly differ from that of the age- and sex-matched general population.[4,5] By contrast, the OS of patients with PTCL who achieved EFS24 is poorer than that of the age- and sex-matched general population.[7]

Despite recently introduced new anticancer agents, hematopoietic stem cell transplantation (HSCT) is still a potentially curative treatment, particularly for refractory and relapsed lymphoma patients. Although the prognosis of these patients is generally poor, those who maintain a disease response for certain period after HSCT may have a better outcome, similar to that of the general population, than those who do not. The impact of the EFS status of lymphoma patients after HSCT on their subsequent OS was evaluated in several studies.[8,9] However, these studies were restricted to patients who underwent autologous HSCT (auto-HSCT) for relapsed/refractory DLBCL. Therefore, the present study was conducted to evaluate the utility of EFS status as a clinical end point after autologous or allogeneic HSCT (allo-HSCT) for all lymphoma subtypes using a large transplant registry database in comparison with general population data in Japan.

Methods

Data source

This multicenter retrospective study was conducted using consecutively collected patient data from the Japanese nationwide transplant registry database. All HSCT data in Japan are electronically collected and survival data are renewed annually by the Japanese Data Center for Hematopoietic Cell Transplantation (www.jdchct.or.jp/en/outline/) using a web-based program and are provided to the Working Group members of the Japan Society for Hematopoietic Cell Transplantation.[10,11] The general Japanese population database used as a reference group was provided by the National Cancer Center Japan (https://ganjoho.jp/reg_stat/statistics/qa_words/cohort01.html).

Patient selection and study overview

Patients with all subtypes of lymphoma who received their first auto- or allo-HSCT between January 1980 and December 2018 were analyzed. The data originally included 15 686 or 7367 lymphoma patients who underwent their first auto- or allo-HSCT, respectively, during the defined period. Of the patients who received auto- and allo-HSCT, we excluded those lacking information on the histological subtypes of lymphoma according to World Health Organization (WHO) classification (N = 4047 and 2268), previous transplant (N = 0 and 107), and survival data (N = 337 and 115), respectively. Finally, data were analyzed from 15 715 lymphoma patients, including 11 302 and 4413 who underwent auto- and allo-HSCT, respectively. Each lymphoma subtype was diagnosed by a primary physician and a hematopathologist at each institution. At least 100 or more patients per lymphoma subtype were analyzed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Japan Society for Hematopoietic Cell Transplantation Ethical Committee and the Institutional Review Board of Shimane University Hospital, as described previously.[12]

Outcome definitions

The treatment response at HSCT was evaluated according to the relevant criteria by a primary physician at each institution.[13,14] The patient's general condition at the time of HSCT was evaluated using the Eastern Cooperative Oncology Group Performance Status. OS was defined as the time from the date of HSCT to the date of death by any cause. Surviving patients were censored at the last follow-up. EFS was defined as the time from the date of HSCT to relapse, progression, or death by any cause. EFS24 and EFS status at 60 months (EFS60) were selected as end points of evaluation for subsequent OS based on previous studies,[4-8] and were defined as EFS24 and EFS60 after HSCT, respectively, as described previously.[4] When calculating the proportion of patients who achieved EFS, those who were lost to follow-up within the defined period were excluded.[15] When evaluating OS according to EFS status, OS was calculated as the time from the date of EFS failure to death for patients who failed to achieve EFS24 or EFS60, or as the time from 24 or 60 months after HSCT to death for patients who achieved EFS at each defined point.[4,5,7]

Statistical analysis

Survival data were analyzed using the Kaplan-Meier method and compared using the log-rank test. The OS of patients who achieved EFS24 or EFS60 from each defined time point was compared with that of the age-, sex-, and calendar period–matched general population. The expected survival curve was created using a conditional approach using the "survexp.fr" and "relsurv" packages in R. The standardized mortality ratios (SMRs) of observed to expected deaths with 95% confidence intervals (CIs) were also calculated. Two-sided P values of $<.05$ were considered as statistically significant. Analyses using the general Japanese population were performed using R package version 4.0.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). Other analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX).

Results

Patient characteristics

In total, 10 964 and 4013 patients after auto- and allo-HSCT, respectively, were used for the analyses. Of the patients treated with auto-HSCT, 5817 were diagnosed with DLBCL, 1294 with HL, 1139 with FL, 659 with mantle cell lymphoma (MCL), 213 with primary mediastinal large B-cell lymphoma (PMBL), 192 with

intravascular large B-cell lymphoma (IVL), 160 with primary DLBCL of the central nervous system (PCNSL), 111 with Burkitt lymphoma (BL), 530 with PTCL, not otherwise specified (PTCL-NOS), 382 with angioimmunoblastic T-cell lymphoma (AITL), 272 with anaplastic large cell lymphoma (ALCL), and 195 with extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL). The patients after allo-HSCT analyzed included 1220 with DLBCL, 896 with FL, 342 with HL, 154 with MCL, 124 with BL, 457 with PTCL-NOS, 209 with AITL, 176 with ALCL, 100 with mycosis fungoides/Sézary syndrome (MF/SS), and 335 with ENKTL. The baseline characteristics of the patients who underwent auto- or allo-HSCT are shown in Tables 1 and 2, respectively. The median age of patients with HL, PMBL, BL, or ALCL ranged from 30 to 40 years, which was lower than that of other lymphoma subtypes. The response status at HSCT varied widely depending on the lymphoma subtype. The complete response (CR) rate at HSCT was generally lower among patients who underwent allo-HSCT (11.0% to 44.2%) than those who underwent auto-HSCT (47.7% to 83.0%). Among the patients who underwent auto-HSCT, the CR rate at HSCT was highest in those with MCL and IVL (>80% at HSCT), and lowest in patients with HL (<50%). Among the patients who underwent allo-HSCT, the CR rate was highest among those with ENKTL (44.2%).

Outcomes according to EFS status

The median follow-up time of survivors was 53 months (range, 0-378 months) and 59 months (range, 0-348 months) among the patients who underwent auto- and allo-HSCT, respectively. The 2-year and 5-year OS and EFS of the patients are listed in supplemental Table 1. The patients had significantly worse survival than the general population at the time of auto- or allo-HSCT. The OS compared with the expected survival of patients with major lymphoma subtypes is shown in supplemental Figures 1-5. The OS improved as patients survived longer without relapse or progression after HSCT. The rate of patients who achieved EFS24 and EFS60 after auto-HSCT in each lymphoma subtype ranged from 36.9% to 73.1% and from 22.8% to 54.0%, respectively. (Table 3). Patients who achieved EFS24 or EFS60 after auto-HSCT had significantly better subsequent outcomes than those who failed to achieve EFS irrespective of lymphoma subtypes. The 5-year OS for patients who achieved EFS24 and EFS60 after auto-HSCT was 76.2% to 97.8% and 80.0% to 96.4%, respectively (Table 3; supplemental Figures 6 and 7). The rate of patients who achieved EFS24 and EFS60 after allo-HSCT in each lymphoma subtype ranged from 16.3% to 50.4% and from 11.4% to 39.0%, respectively (Table 3). Patients who achieved EFS24 or EFS60 after allo-HSCT had significantly better outcomes than those who failed to achieve EFS irrespective of lymphoma subtype. The 5-year OS for patients who achieved EFS24 and EFS60 after allo-HSCT was 82.4% to 100% and 84.2% to 100%, respectively (Table 3; supplemental Figures 8 and 9).

Outcomes after achieving EFS status following auto-HSCT

Patients who achieved EFS24 or EFS60 had a better OS than those who did not in all subtypes (supplemental Figures 6 and 7). However, the OS of patients who achieved EFS24 after auto-HSCT was significantly poorer than that of the general population, except for those with PMBL (PMBL [SMR, 3.6; 95% CI, 0.97-9.28; P = .054]) (Figures 1 and 2). The SMRs of patients with HL, DLBCL, or

Table 1. Baseline characteristics of patients who underwent auto-HSCT

	DLBCL, n = 5817	HL, n = 1294	FL, n = 1139	MCL, n = 659	PMBL, n = 213	IVL, n = 192	PCNSL, n = 160	BL, n = 111	PTCL-NOS, n = 530	AITL, n = 382	ALCL, n = 272	ENKTL, n = 195
Median age (range), y	58 (7-82)	34 (4-80)	56 (24-81)	59 (24-74)	32 (15-66)	60 (31-74)	55.5 (18-74)	34 (1-70)	56 (2-77)	59 (22-76)	40 (2-69)	51 (12-70)
>60 y, n	2154	136	305	278	7	92	57	9	175	154	26	43
Sex, male, n	3354	804	608	530	94	112	99	82	371	252	181	139
Stage, III or IV, n	4491	765	986	610	123	187	74	87	419	355	193	83
Extranodal sites, >1, n	2009	NA	248	279	43	111	6	35	135	112	77	56
IPI, high-int or high, n	2695	NA	253	263	68	156	25	42	202	196	80	51
Stage at HSCT, CR or Cru, n	3532	617	629	543	110	160	97	58	290	249	177	130
ECOG-PS at HSCT, 0-1, n	5179	1058	1058	638	200	173	138	73	468	355	225	180

CRu, unconfirmed complete response; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; int, intermediate; IPI, International Prognostic Index; NA, not available.

Table 2. Baseline characteristics of patients who underwent allo-HSCT

	DLBCL, n = 1220	FL, n = 896	HL, n = 342	MCL, n = 154	BL, n = 124	PTCL-NOS, n = 457	AITL, n = 209	ALCL, n = 176	MF/SS, n = 100	ENKTL, n = 335
Median age (range), y	52 (2-73)	53 (2-76)	30.5 (1-68)	57.5 (23-73)	30 (3-68)	49 (3-73)	55 (17-72)	35 (3-73)	44 (23-68)	45 (1-70)
>60 y, n	230	142	8	52	4	85	48	15	12	27
Sex, male, n	703	470	220	121	93	303	134	129	57	216
Stage, III or IV, n	954	793	218	141	105	390	198	139	76	186
Extranodal sites, >1, n	421	208	NA	54	57	168	64	63	36	137
IPI, high-int or high, n	483	174	NA	48	74	189	95	54	27	117
Stage at HSCT, CR or Cru, n	319	217	73	50	42	108	51	52	11	148
ECOG-PS at HSCT, 0-1, n	912	776	283	131	71	365	159	121	82	279

FL were significantly higher than those of the general population (HL [SMR, 9.0; 95% CI, 7.08-11.36; $P < .0001$]; DLBCL [SMR, 3.5; 95% CI, 3.10-3.88; $P < .0001$]; FL [SMR, 3.7; 95% CI, 2.91-4.63; $P < .0001$]). These results were consistent independent of the year of HSCT, including whether the year was before or after the advent of rituximab (supplemental Tables 2 and 3). The results were also consistent for most lymphoma subtypes when analyzing those achieving CR at the time of HSCT (supplemental Table 4). Even though patients achieved EFS60 after auto-HSCT, the OS of patients with major lymphoma subtypes, including HL, DLBCL, and FL, was still significantly worse than that of the general population (HL [SMR, 6.0; 95% CI, 4.00-8.71; $P < .0001$]; DLBCL [SMR, 2.5; 95% CI, 2.03-2.96; $P < .0001$]; FL [SMR, 2.7; 95% CI, 1.78-3.99; $P < .0001$]) (Figure 1). By contrast, subsequent survival did not significantly differ between patients with PMBL, IVL, PCNSL, BL, PTCL-NOS, or ENKTL and the general population (PMBL [SMR, 1.6; 95% CI, 0.02-9.13; $P = .9$]; IVL [SMR, 1.2; 95% CI, 0.24-3.52; $P = .9$]; PCNSL [SMR, 2.3; 95% CI, 0.03-12.96; $P = .7$]; BL [SMR, 2.9; 95% CI, 0.32-10.42; $P = .3$]; PTCL-NOS [SMR, 1.8; 95% CI, 0.66-3.93; $P = .2$]; ENKTL [SMR, 3.6; 95% CI, 0.96-9.14; $P = .06$]) (Figure 1; supplemental Figure 10).

Outcomes after achieving EFS status following allo-HSCT

Patients who achieved EFS24 or EFS60 had a better OS than those who did not in all subtypes (supplemental Figures 8 and 9). However, the OS of patients who achieved EFS24 after allo-HSCT was significantly poorer than that of the general population, except for those with BL or MF/SS (BL [SMR, 3.1; 95% CI, 0.04-17.1; $P = .6$]; MF/SS [SMR, 5.7; 95% CI, 0.07-31.77; $P = .3$]) (Figures 1 and 3). The SMR of patients with DLBCL or FL was significantly higher than that of the general population (DLBCL [SMR, 9.7; 95% CI, 6.97-13.08; $P < .0001$]; FL [SMR, 4.7; 95% CI, 3.53-6.20; $P < .0001$]). These results were consistent independent of the year of HSCT, including whether the year was before or after the advent of rituximab (supplemental Tables 5 and 6). These results were also similar for most subtypes independent of disease status at the time of HSCT, or of conditioning regimen with or without total-body irradiation (supplemental Tables 7-9). In general, the SMR was significantly higher in patients treated with allo-HSCT compared with the general population, independent of whether a myeloablative or reduced-intensity regimen was used. However, the SMR of patients with ENKTL who underwent allo-HSCT using a reduced-intensity conditioning regimen did not differ significantly compared with the general population (supplemental Tables 10 and 11). Although ~30% of patients who underwent allo-HSCT had a previous history of auto-HSCT, the results were similar (supplemental Tables 11 and 12). The OS of those with DLBCL and FL was still significantly worse than that of the general population even though those achieved EFS60 after allo-HSCT (DLBCL [SMR, 8.2; 95% CI, 4.77-13.12; $P < .0001$]; FL [SMR, 3.5; 95% CI, 2.26-5.26; $P < .0001$]). However, the OS of patients with AITL and ENKTL did not significantly differ from the general population (AITL [SMR, 2.6; 95% CI, 0.29-9.36; $P = .4$]; ENKTL [SMR, 1.3; 95% CI, 0.02-6.98; $P = .9$]) (Figure 1; supplemental Figure 11) The SMR of patients with MF/SS who achieved EFS60 could not to be estimated because no events were observed from 5 years after HSCT.

Table 3. The numbers and survival rates of patients who achieved EFS status after auto- or allo-HSCT

	DLBCL	HL	FL	MCL	PMBL	IVL	PCNSL	BL	PTCL-NOS	AITL	ALCL	MF/SS	ENKTL
Auto-HSCT													
Median follow-up time of survivors (range), mo	53 (0-323)	53 (0-348)	67 (1-299)	47 (1-240)	63 (1-271)	49 (1-237)	35 (1-147)	105 (1-378)	45 (1-275)	41 (1-316)	67 (0-295)	—	51 (1-184)
EFS24-achieved patients, n (%)	2754 (47.3)	657 (50.8)	594 (52.2)	391 (59.3)	127 (59.6)	102 (53.1)	55 (34.4)	58 (52.3)	171 (32.3)	154 (40.3)	135 (49.6)	—	87 (44.6)
5-y OS from 24 mo, %	89.0	90.7	89.1	86.9	97.8	85.4	88.7	94.8	84.6	76.2	91.6	—	89.9
5-y expected OS from 24 mo, %	96.9	99.0	97.3	95.8	99.3	95.8	97.6	99.1	96.9	96.5	98.6	—	97.7
EFS60-achieved patients, n (%)	1568 (27.0)	384 (29.7)	355 (31.2)	169 (25.6)	81 (38.0)	55 (28.6)	25 (15.6)	50 (45.0)	93 (17.5)	71 (18.6)	91 (33.5)	—	54 (27.7)
5-y OS from 60 mo, %	90.1	95.5	93.8	82.9	96.4	95.3	87.5	94.0	94.5	80.0	94.2	—	93.8
5-y expected OS from 60 mo, %	96.2	98.6	97.2	95.2	99.1	94.6	97.1	99.0	96.2	95.4	98.4	—	97.0
Allo-HSCT													
Median follow-up time of survivors (range), mo	51 (0-310)	55 (1-278)	81 (1-244)	82 (3-224)	—	—	—	95 (2-348)	58 (0-184)	52 (2-169)	57 (2-313)	49 (2-166)	55 (2-215)
EFS24-achieved patients, n (%)	264 (21.6)	112 (32.7)	421 (47.0)	68 (44.2)	—	—	—	34 (27.4)	152 (33.3)	86 (41.1)	71 (40.3)	15 (15.0)	114 (34.0)
5-y OS from 24 mo, %	84.1	82.4	90.7	84.2	—	—	—	100.0	86.2	83.5	83.3	92.3	91.4
5-y expected OS from 24 mo, %	98.2	99.5	98.1	95.7	—	—	—	99.3	98.4	97.5	99.0	98.8	98.8
EFS60-achieved patients, n (%)	138 (11.3)	59 (17.3)	287 (32.0)	44 (28.6)	—	—	—	28 (22.6)	90 (19.7)	41 (19.6)	42 (23.9)	10 (10.0)	66 (19.7)
5-y OS from 60 mo, %	84.2	90.3	93.4	87.1	—	—	—	95.2	86.5	94.4	91.2	100.0	98.4
5-y expected OS from 60 mo, %	98.0	99.4	97.8	94.7	—	—	—	99.2	98.0	97.1	99.1	99.0	98.4

—, no data.

Cause of death in patients who achieved EFS after auto-HSCT

A total of 632 patients (12.0%) who achieved EFS24 after auto-HSCT died during follow-up. The death rate across lymphoma subtypes ranged from 9% to 27% (supplemental Figure 12). The cumulative incidence of death in patients who achieved EFS24 after auto-HSCT is demonstrated according to the cause of death in Figure 4 and supplemental Figure 13. Patients with AITL had the highest rate of death after EFS24 achievement after auto-HSCT. The main causes of death were primary disease and secondary malignancy. By contrast, there were few deaths (<10%) among patients with PMBL or BL who had achieved EFS24. A total of 230 patients (7.7%) who achieved EFS60 after auto-HSCT eventually died during follow-up. The death rate across lymphoma subtypes ranged from 1.2% to 22.5% (supplemental Figure 12). Late mortality from 5 years after auto-HSCT was highest among patients with AITL.

Cause of death in patients who achieved EFS after allo-HSCT

A total of 177 patients (13.2%) who achieved EFS24 after allo-HSCT died during follow-up. The death rate across lymphoma subtypes ranged from 2.9% to 20.6% (supplemental Figure 12) The cumulative incidence of death in patients who achieved EFS24 after allo-HSCT is demonstrated according to the cause of death in Figure 5 and supplemental Figure 14. Mortality by primary disease was highest in patients with MCL. A total of 71 patients (8.8%) who achieved EFS60 after allo-HSCT died during follow-up. The death rate across lymphoma subtypes ranged from 0% to 13.6% (supplemental Figure 7). The late mortality rate 5 years after allo-HSCT was highest in patients with HL, DLBCL, or MCL. The mortality rate was lowest among patients with BL, MF/SS, or ENKTL, and none of these patients died due to primary disease.

Discussion

This study reveals the clinical value of EFS status in lymphoma patients after receiving HSCT. To our knowledge, this is the first study to examine the impact of EFS status after HSCT on subsequent OS across all subtypes of lymphoma. Achievement of EFS24 and EFS60, irrespective of HSCT type or lymphoma subtype, was favorable to OS outcome. More than 80% of the patients who achieved EFS60 were alive at 120 months after HSCT across all lymphoma subtypes. Although patients who achieved EFS status survived long-term, those requiring HSCT for lymphoma generally have a greater risk of a poor prognosis due to disease relapse or treatment-related mortality, especially those who underwent allo-HSCT, and secondary malignancy than the general population. Therefore, the SMRs of most lymphoma patients, including those with DLBCL or FL, were significantly higher than that of the general population even though those achieved EFS24 or EFS60. Among these, the patients with HL had the highest SMR. By contrast, a proportion of patients who achieved EFS had a comparable prognosis with that of the general population and were potentially cured after HSCT. Although the impact of EFS achievement varied depending on the lymphoma subtype, our study provides useful information for the management of lymphoma patients, survival prediction, treatment strategies, and future clinical trials.

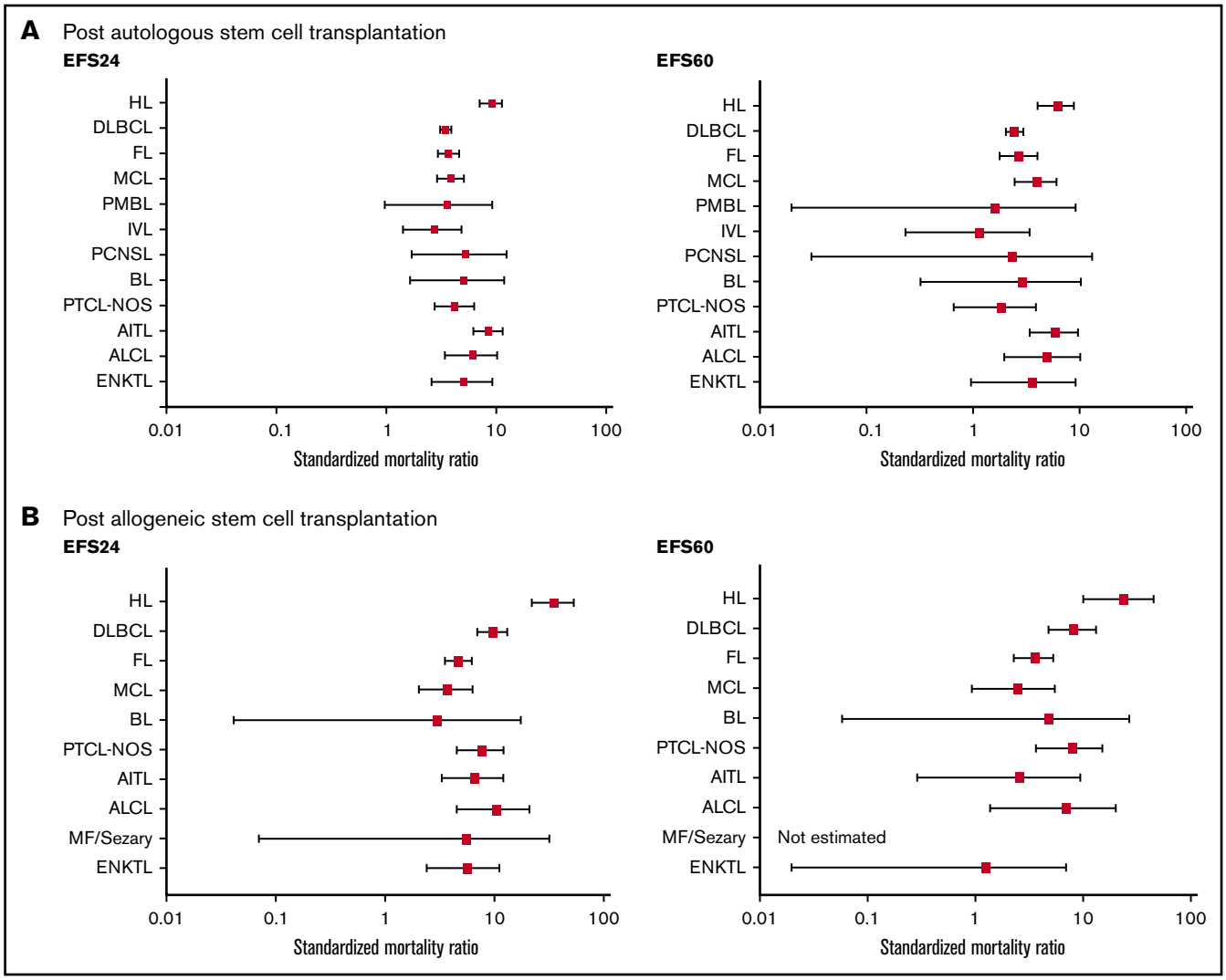

Figure 1. Forest plots of the SMR with 95% CIs for patients with each lymphoma subtype who achieved EFS24 and EFS60, respectively, after HSCT compared with the general population. (A) Post–autologous stem cell transplantation. (B) Post–allogeneic stem cell transplantation. NA, not available.

There are a few studies evaluating the impact of EFS on the subsequent survival of patients after auto-HSCT. Regarding patients with DLBCL after auto-HSCT, the impact of EFS achievement was evaluated in 2 previous studies.[8,9] Both studies demonstrated that the OS of patients who achieved EFS24 after auto-HSCT was inferior to that of the general population, which was consistent with our results for DLBCL patients who achieved both EFS24 and EFS60. However, 1 study reported that the SMR of patients with DLBCL who achieved EFS60 after auto-HSCT did not significantly differ from that of the general population.[9] This study was a subgroup analysis of the LY.12 and CORAL studies, which were prospectively conducted to examine salvage treatments for relapsed or refractory DLBCL patients. It is possible that the patient condition in the study cohort might be better than that in the general practice. Therefore, the results of our study more precisely reflect the actual prognosis of lymphoma patients.

Only patients with PMBL who achieved EFS24 after auto-HSCT had an outcome that did not significantly differ from that of the general population in terms of the SMR. This result was consistent across all subgroup analyses. Although there has been marked improvement in the survival of PMBL patients,[16] 10% to 30% of them still progress with disease or relapse.[17] In the previous study, the survival curve plateaued at 70% after ~2 years. This result is comparable with our results concerning the subsequent survival and the low mortality of PMBL patients who achieved EFS24.[17] Therefore, achievement of EFS24 after auto-HSCT is an important end point for patients with PMBL.

The SMR of patients with certain lymphoma subtypes who achieved EFS60 after auto-HSCT did not significantly differ from that of the general population. Among them, the SMRs of patients with IVL or PTCL-NOS were 1.2 (95% CI, 0.24-3.52) and 1.8 (95% CI, 0.66-3.93), respectively, suggesting that these populations were more likely to be potentially cured. The impact of EFS status on the OS of patients with PTCL-NOS from the initial diagnosis was evaluated in previous studies.[7,18] In the cohorts of newly diagnosed PTCL-NOS patients, the OS of those who achieved EFS24 after diagnosis was

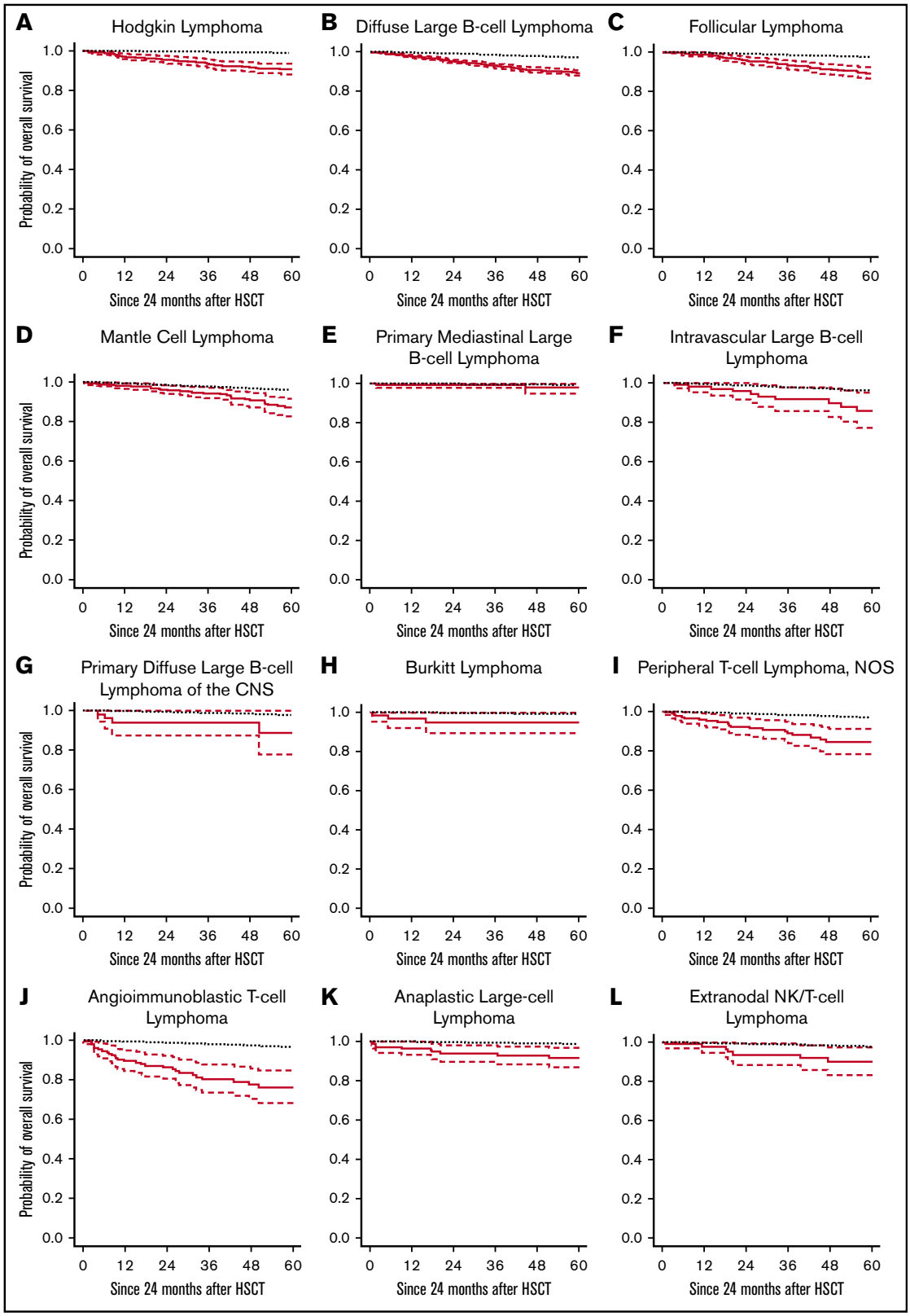

Figure 2. OS of patients who achieved EFS24 after auto-HSCT. OS of these patients after auto-HSCT (solid red line) with 95% CIs (dotted red lines) compared with that of the age-, sex-, and calendar period–matched general population (dotted black line). (A) HL. (B) DLBCL. (C) FL. (D) MCL. (E) PMBL. (F) IVL. (G) PCNSL. (H) BL. (I) PTCL-NOS. (J) AITL. (K) ALCL. (L) ENKTL.

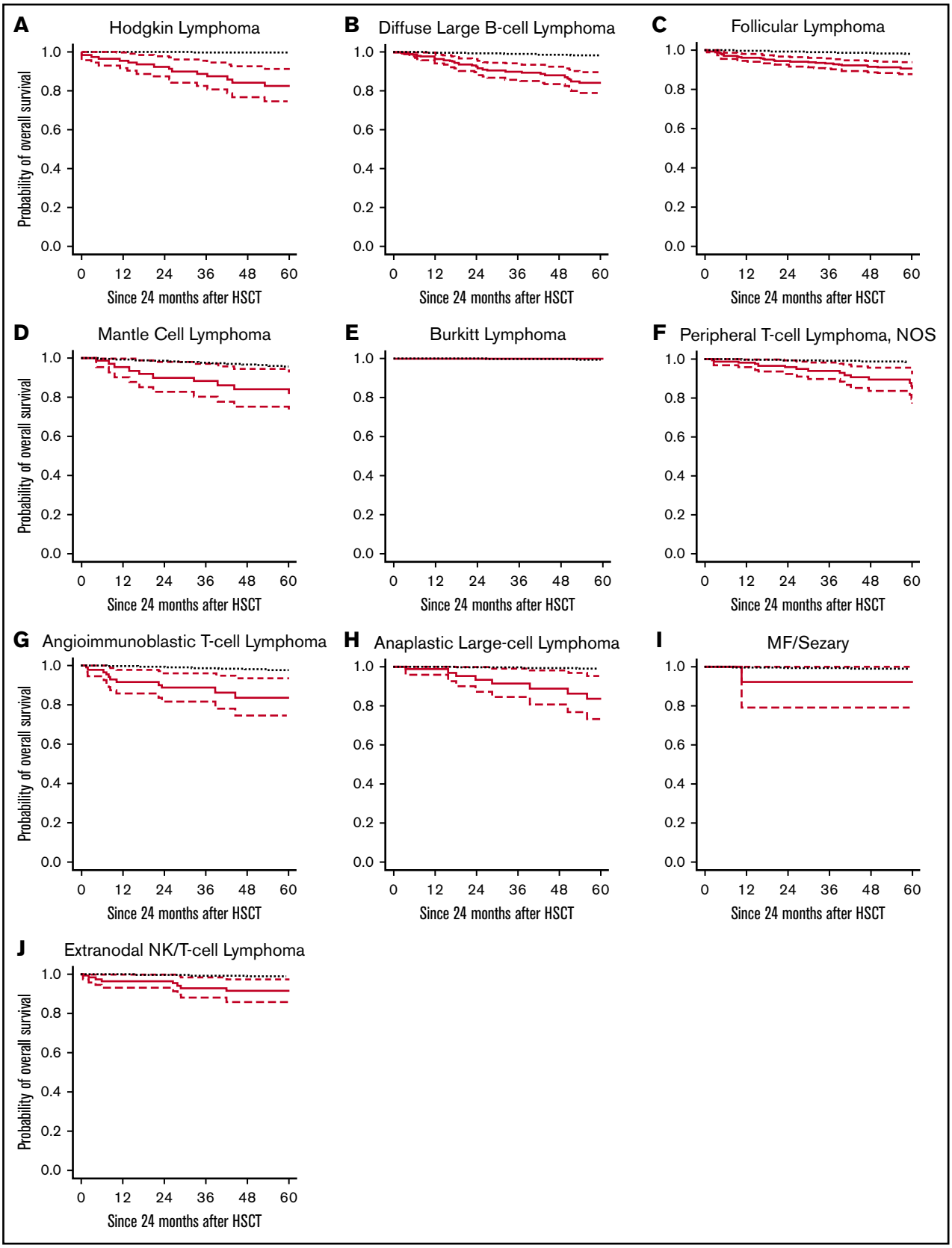

Figure 3. OS of patients who achieved EFS24 after allo-HSCT. OS of these patients after allo-HSCT (solid red line) with 95% CIs (dotted red lines) compared with that of the age-, sex-, and calendar period–matched general population (dotted black line). (A) HL. (B) DLBCL. (C) FL. (D) MCL. (E) BL. (F) PTCL-NOS. (G) AITL. (H) ALCL. (I) MF/SS. (J) ENKTL.

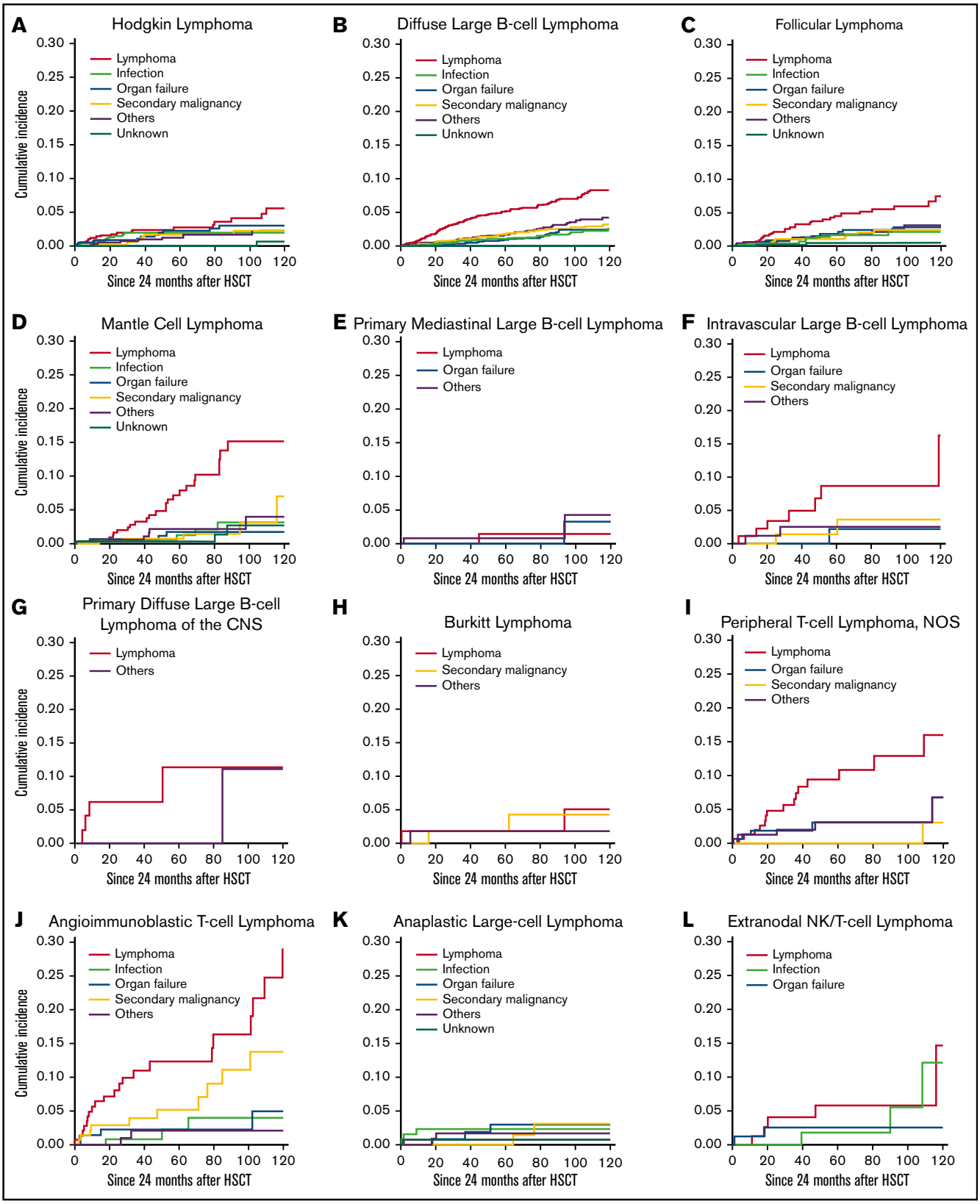

Figure 4. Cause of death of patients who achieved EFS24 after auto-HSCT. The cause of death was grouped into primary disease, infection, organ failure, secondary malignancy, other, and unknown. (A) HL. (B) DLBCL. (C) FL. (D) MCL. (E) PMBL. (F) IVL. (G) PCNSL. (H) BL. (I) PTCL-NOS. (J) AITL. (K) ALCL. (L) ENKTL.

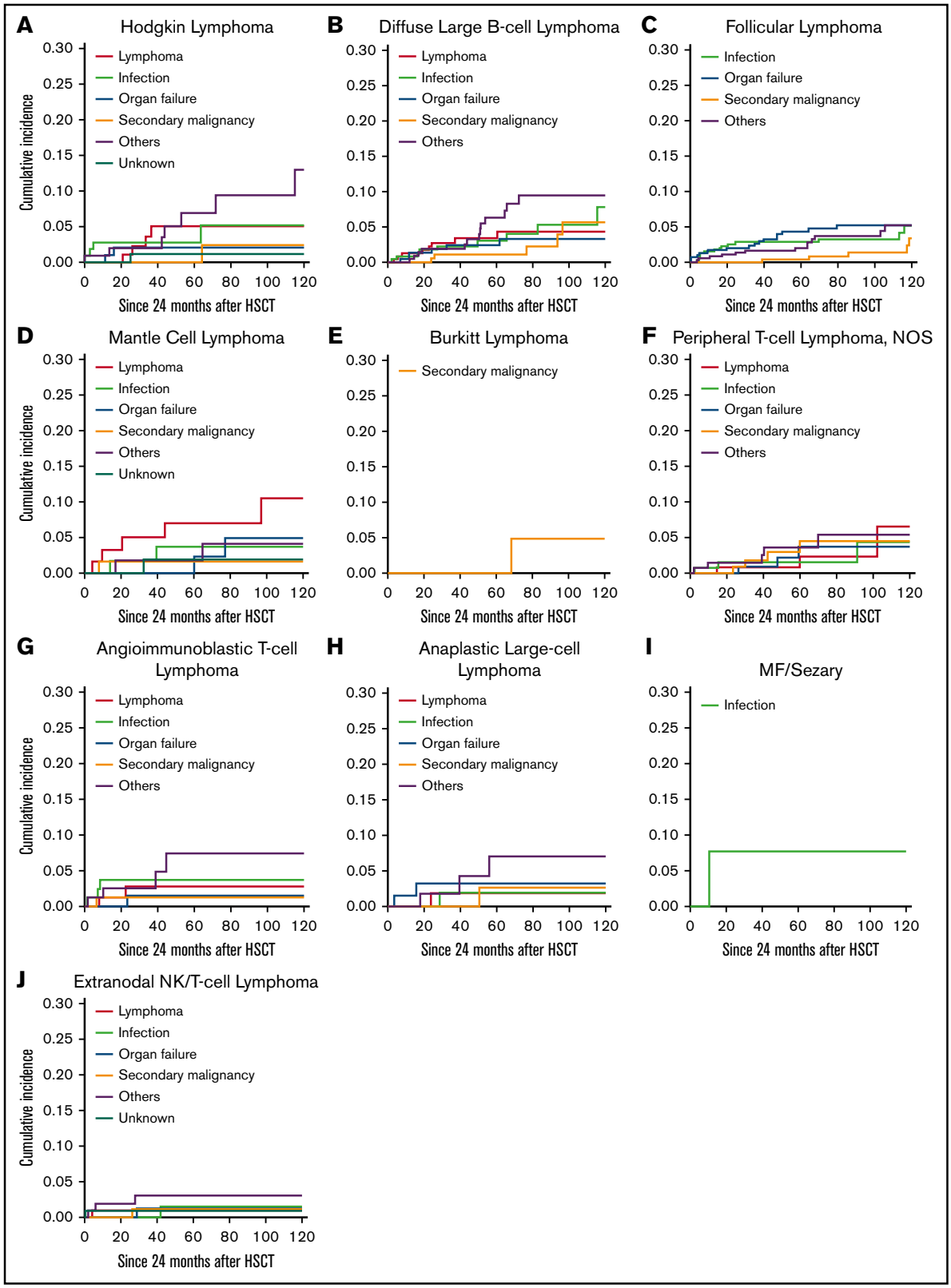

Figure 5. Cause of death of patients who achieved EFS24 after allo-HSCT. The cause of death was grouped into primary disease, infection, organ failure, secondary malignancy, other, and unknown. (A) HL. (B) DLBCL. (C) FL. (D) MCL. (E) BL. (F) PTCL-NOS. (G) AITL. (H) ALCL. (I) MF/SS. (J) ENKTL.

significantly better than that of those who failed to achieve EFS24, but it did not reach that of the general population.[7,18] A similar result was observed in the current study for PTCL-NOS patients who achieved EFS24 after auto-HSCT. Although patients who require auto-HSCT generally have a poorer prognosis than newly diagnosed patients, their prognosis after HSCT nearly reached that of the general population if they survived 60 months with no events. Our results are encouraging for lymphoma patients who achieve EFS60 after auto-HSCT.

No reports have evaluated the impact of EFS status on subsequent survival after allo-HSCT. Our study showed that the prognosis of patients with DLBCL or FL, although achieving EFS60 after allo-HSCT, did not reach the level of the general population. These results were consistent across all subgroup analyses, suggesting that the value of allo-HSCT for these patients is limited. Although the number of patients who achieved EFS60 is small, the SMRs of the patients with certain lymphoma subtypes were comparable with that of the general population. Of note, the SMR of ENKTL patients who achieved EFS60 after allo-HSCT was 1.3 (95% CI, 0.02-6.98), which was not significantly different from that of the general population. In addition, this finding was consistent in patients who were treated with the reduced-intensity conditioning regimen, indicating that ENKTL patients could be cured if EFS60 was achieved after allo-HSCT.

One strength of our study is that the data were obtained from a sufficiently large number of patients with different lymphoma subtypes, enabling an evaluation of the impact of EFS status on subsequent survival across several lymphoma subtypes. In particular, our data contain a sufficient number of patients with NK/T-cell lymphoma, including ENKTL, which is more prevalent in Asian countries than in the United States.[19] However, there are several limitations. First, the sample size was small for some lymphoma subtypes, although their prevalence in the population is low. Therefore, a few lymphoma subtypes were unable to be evaluated with certainty. In addition, it is possible that the results of the SMR without significant difference from that of the general population could be affected by the small number of patients who achieved EFS status, particularly with rare lymphoma subtypes. Second, the differences between lymphoma subtypes might be affected by the multiple comparison. However, the conclusions were consistent in most lymphoma subtypes even after adjustments by the Bonferroni correction. Third, our results may have been affected by time-based changes. However, the calendar period was not a significant factor in our analyses. In addition, there is a risk of misclassification of lymphoma subtypes, particularly for patients who were diagnosed before 1996, prior to introduction of the WHO classification. However, those receiving auto- or allo-HSCT before 1996 were only 2.2% and 0.7%, respectively, of the whole cohort. Thus, the incidence of misclassification is presumed to be low.

Our results showed that EFS status at 24 months or 60 months could be an early end point after HSCT for patients with certain lymphoma subtypes. However, the prognosis of these patients did not reach the level of the general population even if they survived without relapse for a defined period after HSCT. This finding indicates that there is still room for improvement of the treatment of those patients. Novel targeted drugs, including the Bruton tyrosine kinase inhibitor, the programmed cell death protein-1 inhibitor, and CD30 antibody, can potentially improve survival when used in combination with HSCT. Moreover, chimeric antigen receptor T cells have been recently introduced as a promising immunotherapy and have demonstrated a durable response for a proportion of patients with refractory/relapsed B-cell lymphoma.[20] Therefore, comparisons between HSCT and novel therapies are waranted in the future to explore more effective strategies in each lymphoma subtype. Further analyses using a larger cohort are also warranted to confirm our results.

In conclusion, the importance of EFS status assessment as a clinical end point for lymphoma patients was confirmed in the HSCT setting. Our study will greatly encourage lymphoma patients who require HSCT by providing an early end point and hope for a disease cure.

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Authorship

Contribution: A.F. and R.S. designed the study; T.A. contributed to the technical support of data analyses; A.F. performed the analyses and wrote the manuscript; T.A. and R.S. revised the manuscript; and all authors discussed the results, interpreted the data, and reviewed the manuscript.

Conflict-of-interest disclosure: T.A. is an employee of EPS Corporation. N.U. received honoraria from Chugai Pharmaceutical Co Ltd, Astellas Pharma Inc, Otsuka Pharmaceutical Co Ltd, Sumitomo Dainippon Pharma Co Ltd, and Novartis Pharma Inc, outside of the submitted work. T. Mori received honoraria from Pfizer, Merck Sharp & Dohme (MSD), Janssen, Sumitomo Dainippon Pharma, Asahi Kasei Corporation, Astellas Pharma, Kyowa Hakko Kirin, Eisai, Japan Blood Product Organization, Novartis Pharma, Ono Pharmaceutical Co Ltd, Shire, Chugai Pharmaceutical Co Ltd, Takeda Pharmaceutical, Shionogi & Co, and Abbot Japan, and received research funding from MSD, Asahi Kasei Corporation, Kyowa Hakko Kirin, Japan Blood Product Organization, Chugai Pharmaceutical Co Ltd, LSI Medience Corporation, Medical & Biological Laboratories, and Otsuka Pharmaceutical Co Ltd, outside of the submitted work. M.S. received honoraria from Chugai, Pfizer, Astellas, Nippon-Shinyaku, Ono, MSD, Bristol Myers Squibb, Kyowa-Hakko Kirin, Asahi-Kasei, Novartis, Eisai, Otsuka, Sumitomo Dainippon, Sanofi, Takeda, Celgene, Mochida, Shire, and Mundi Pharma, outside of the submitted work. S.Y. received honoraria from Novartis, Ono Pharmaceutical Co Ltd, Takeda Pharmaceutical Co Ltd, Janssen, Eisai, Chugai Pharmaceutical Co Ltd, and Bristol Myers Squibb, and received consultant fees from Yakult, outside of the submitted work. T. Miyamoto received honoraria from Bristol Myers Squibb Co Ltd, Otsuka Pharmaceutical Co Ltd, MSD Co Ltd, Astellas Pharmaceutical Co Ltd, Astellas Amgen Pharmaceutical Co Ltd, Celgene Co Ltd, AbbVie Pharmaceutical Co Ltd, and Takeda Pharmaceutical Co, outside of the submitted work. K.-i.M. received honoraria from Kyowa Kirin Co Ltd, Astellas

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