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Original Article

Predictive Factors of Event-Free Survival at 24 Months in Patients with Peripheral T-Cell Lymphoma: A Retrospective Study

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Purpose Event-free survival at 24 months (EFS24) is known to be a surrogate marker for overall survival (OS) for patients with peripheral T-cell lymphoma (PTCL). We examined the role of EFS24 in PTCL compared to diffuse large B-cell lymphoma (DLBCL), and then assessed the clinical predictive factors of achieving EFS24.

Materials and Methods Patients with newly diagnosed PTCL treated with anthracycline-based chemotherapy were included. Subsequent OS was defined as the time elapsed from 24 months after diagnosis until death from any cause in those who achieved EFS24.

Results Overall, 153 patients were evaluated, and 51 patients (33.3%) achieved EFS24. Patients who achieved EFS24 showed superior OS compared to patients who did not ($p < 0.001$). EFS24 could stratify the subsequent OS although it did not reach to that of the general population. After matching the PTCL group to the DLBCL group based on the international prognostic index, the subsequent OS in patients who achieved EFS24 was similar between the two groups ($p=0.094$). Advanced stage was a significant factor to predict the failing EFS24 by multivariable analysis ($p < 0.001$).

Conclusion Patients with PTCL who achieve EFS24 could have a favorable subsequent OS. Since advanced disease stage is a predictor of EFS24 failure, future efforts should focus on developing novel therapeutic strategies for PTCL patients presenting with advanced disease.

Key words Progression-free survival, Overall survival, Peripheral T-cell lymphoma, Stage

Introduction

Peripheral T-cell lymphoma (PTCL) consists of a heterogeneous group of lymphomas that develop from mature lymphocytes and represents approximately 6% to 10% of all non-Hodgkin's lymphoma (NHL) cases [1]. Most patients with PTCL display a highly aggressive clinical course and short survival [2-4]. In contrast to B-cell NHL, and despite the development of new chemotherapeutic agents, there is no single effective treatment for PTCL. In addition, patients with relapsed or refractory PTCL are unlikely to survive for more than a few months [5,6]. Therefore, early identification of those at risk of relapse or progression is critical for the timely initiation of appropriate treatment.

Overall survival (OS) is the most important endpoint in clinical trials; however, in order for OS to be estimated with high precision, long-term patient follow-up is necessary. Under the perspective that disease-related events decrease after 12 and 24 months, event-free survival (EFS) and progression-free survival have been suggested as surrogate endpoints in diffuse large B-cell lymphoma (DLBCL) [7,8]; these outcomes also require a shorter follow-up time compared to OS. Patients with DLBCL who achieved EFS at 24 months (EFS24) were unlikely to die from lymphoma-related causes. As a result, their subsequent OS was comparable to that of the general population [7]. Similar findings have been reported in patients with Hodgkin's lymphoma and follicular lymphoma [9,10]. Moreover, a clinical risk calculator for EFS24 composed of age, stage, lactate dehydrogenase (LDH), absolute lymphocyte count (ALC), performance status, bulky disease, and sex has been developed, which predicts the probability for failing EFS24 in DLBCL [11].

Recent data showed that EFS24 achievement could predict favorable subsequent outcomes in PTCL patients [12,13]. There is no study for predictors of achieving EFS24 in PTCL. Herein, we evaluated the role of EFS24 in PTCL compared to DLBCL and assessed the predictive factors for EFS24 in patients with PTCL.

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Materials and Methods

1. Patients with PTCL

TWe evaluated 223 patients with any of the following subtypes of newly diagnosed PTCL between 2006 and 2017: anaplastic lymphoma kinase (ALK)–negative anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), enteropathy related T-cell lymphoma, adult T-cell lymphoma/leukemia and PTCL not otherwise specified (PTCL-NOS). The pathology was determined and reviewed by a hematopathology specialist, based on the 2016 World Health Organization classification of tumors of hematopoietic and lymphoid tissues [4]. This was a single-center retrospective medical chart review study of patients diagnosed with PTCL between 2006 and 2017 at the Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. The year 2017 was chosen as the cutoff date for patients' diagnoses for all patients to have a minimum 24-month follow-up time at the time of chart abstraction in order to meet the study objectives. In order to minimize patient-selection bias, patients were consecutively enrolled. Of the 223 patients, 178 had been treated with anthracycline-based chemotherapy, mainly with the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and were included in the analysis. Those who had been treated with a different type of therapy or had received upfront autologous stem cell transplantation (ASCT) were excluded. The International Prognostic Index (IPI) and the prognostic index for PTCL-unspecified (PIT) scores were assessed as described in previous studies [14,15], based on data available in the patients' medical charts. The Freelite assay (The Binding Site Ltd., Birmingham, UK) was used to measure serum κ and λ free light chain (FLC) concentrations, elevated κ or λ FLC was defined as κ > 18.4 mg/L and/or λ > 26.3 mg/L [16].

2. Patients with DLBCL

To generate a validation set, we evaluated 194 patients with newly diagnosed DLBCL between 2010 and 2012. All patients were treated with CHOP and rituximab as front-line therapy. This group of patients has been previously described [16]; the survival data were updated before inclusion in the present study. We excluded patients with primary mediastinal (thymic) large B-cell lymphoma, primary DLBCL of the central nervous system, post-transplantation lymphoproliferative disorders, and primary cutaneous DLBCL. The IPI score was determined for all patients [14].

3. Statistical analysis

EFS was defined as the time from the date of diagnosis to progression, re-treatment, or death from any cause. EFS12 and EFS24 were defined as being alive and without any event registered within 12 and 24 months after the date of diagnosis, respectively. OS was the time interval from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Subsequent OS was the time elapsed from 24 months after diagnosis to the date of death from any cause or the date of last of follow-up in those who achieved EFS24. In patients with progression within 24 months, subsequent OS was defined as the time interval between the date when progression was first confirmed to the time of death from any cause [7,12]. To identify a cohort that would adequately adjust for the imbalance of demographic characteristics between patients with PTCL and DLBCL, propensity score matching was performed with a 1:1 matching protocol without replacement. The survival rates of the Korean general population were obtained from kosis.kr (https://kosis.kr/index/index.do). To evaluate the subsequent OS in patients with PTCL and compare it with that of the general Korean population, the log-rank test was used. Logistic regression was used for selecting the best-fitted multivariate model. For all analyses, a p-value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS for Windows ver. 23.0 (IBM Corp., Armonk, NY) and R package ver. 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Patient characteristics

Patient characteristics are shown in Table 1. The median age of the patients was 64 years (range, 18 to 82 years) with male predominance (63.4%). The following subtypes of PTCL were identified: PTCL-NOS (n=102, 66.7%), ALK-negative ALCL (n=24, 15.7%), AITL (n=23, 15.0%), and other subtypes (n=4, 2.6%). Twenty-six patients (17.0%) had poor performance status and 51 (33.3%) presented with B symptoms. Most patients had stage III-IV disease (n=120, 78.4%) and 95 (62.1%) had elevated LDH levels. According to the patients' IPI scores, 34 (22.2%), 42 (27.5%), 49 (32.0%), and 28 (18.3%) patients were classified as low, low-intermediate, high-intermediate, and high risk, respectively. In terms of PIT scores, 19 (12.4%), 39 (25.5%), 52 (34.0%), and 37 (24.2%) of patients with available data were classified into groups 1, 2, 3, and 4, respectively.

2. Subsequent OS in patients with PTCL who achieved EFS12 and EFS24

The expected survival rates of patients with PTCL and the age- and sex-matched general population are listed in Table 2. The median follow-up duration for patients with

Table 1. Characteristics at diagnosis of PTCL patients

Characteristic	No. (%) (n=153)
Age, median (range, yr)	64 (18-82)
Male sex	97 (63.4)
ECOG performance status 2-4	26 (17.0)
B symptoms	51 (33.3)
Stage III or IV	120 (78.4)
Extranodal involvement > 1 site	49 (32.0)
Elevated LDH	95 (62.1)
Bone marrow involvement	64/147 (41.8)
EBV positive	51/120 (33.3)
Absolute lymphocyte count < 1,000	56 (36.6)
Elevated free light chain	77/97 (50.3)
IPI	
Low/Low-intermediate	34/42 (22.2/27.5)
High-intermediate/High	49/28 (32.0/18.3)
PIT	
Group 1/2	19/39 (12.4/25.5)
Group 3/4	52/37 (34.0/24.2)
Subtype	
PTCL-NOS	102 (66.7)
ALK-negative ALCL	24 (15.7)
AITL	23 (15.0)
Other	4 (2.6)

AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PIT, prognostic index for PTCL-unspecified; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

PTCL was 17.0 months (range, 0 to 131 months). In total, 105 patients (68.6%) experienced events during the follow-up period, with 85 patients (55.6%) experiencing events within 12 months. The subsequent 2-year OS was 77.6% in patients who achieved EFS12 and 14.2% in those who did not. These values were lower than the 97.0%, 97.8% expected 2-year survival rate of the general population. Furthermore, the subsequent OS in patients with PTCL was inferior to the expected survival rate of the general population regardless of the event-free status at 12 months ($p < 0.001$ for both) (Fig. 1A and B). One-hundred and two patients (66.7%) experienced events within 24 months. In patients who achieved EFS24, the subsequent 2-year OS was 88.0%; it was inferior to 97.7% of the general population (p=0.002) (Fig. 1C). In contrast, those who failed to achieve EFS24 had a subsequent 2-year OS of 14.7%, which was inferior to the expected value of 97.7% of the general population ($p < 0.001$) (Fig. 1D). Patients who achieved EFS24 showed superior OS compared to patients who did not (hazard ratio, 21.347; 95% confidence interval [CI], 8.971 to 50.797; $p < 0.001$).

3. Subsequent OS in patients with PTCL compared to those with DLBCL who achieved EFS12 and EFS24

To verify the role of achieving EFS24 on the subsequent OS in PTCL, we compared the findings in the PTCL group to those in the DLBCL group. Propensity score matching was performed to match age, sex, and IPI between patients with PTCL and DLBCL. As a result, we selected 113 patients from each group. Among patients with PTCL, 59 (52.2%) and 72 (63.7%) experienced events within 12 and 24 months, respectively. The subsequent 2-year OS for those who achieved and those who failed EFS12 was 75.0% and 11.7%, respectively

Table 2. Subsequent survival rates of patients with PTCL who achieved and failed to achieve event-free survival at 12 and 24 months compared to expected age- and sex-matched survival of the general population

Year	No event at 12 months		Event at 12 months		No event at 24 months		Event at 24 months	
	Expected survival rate	Subsequent OS rate	Expected survival rate	Subsequent OS rate	Expected survival rate	Subsequent OS rate	Expected survival rate	Subsequent OS rate
0	100	100	100	100	100	100	100	100
1	98.7	83.0	98.8	28.2	98.6	97.4	98.7	29.2
2	97.0	77.6	97.8	14.2	97.7	88.0	97.7	14.7
3	96.1	68.6	96.5	7.6	96.3	84.2	96.5	10.1
4	94.6	65.7	96.5	7.6	94.9	84.2	96.2	10.1
5	93.2	65.7	-	-	93.1	75.8	95.9	10.1
6	91.4	59.8	-	-	91.7	75.8	95.9	10.1
7	90.0	59.8	-	-	91.7	75.8	95.9	10.1
8	90.0	59.8	-	-	89.4	75.8	-	-
9	88.0	59.8	-	-	-	-	-	-

OS, overall survival; PTCL, peripheral T-cell lymphoma.

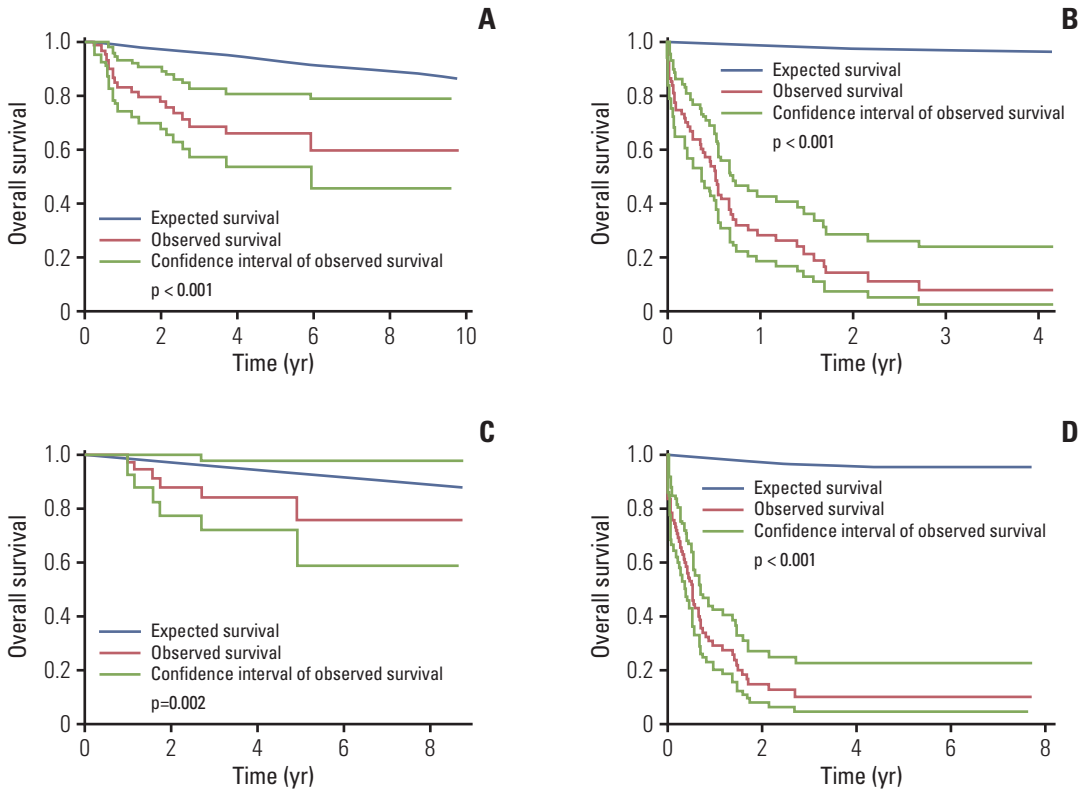

Fig. 1. Subsequent overall survival of the peripheral T-cell lymphoma patients. (A) Subsequent overall survival of patients who achieved event-free survival (EFS) at 12 months (EFS12). (B) Subsequent overall survival of patients who did not achieve EFS12. (C) Subsequent overall survival of patients who achieved event-free survival at 24 months (EFS24). (D) Subsequent overall survival of patients who did not achieve EFS24.

(data not shown); both values were lower than the expected values of 96.9% and 98.5% for the age- and sex-matched general population, respectively. The subsequent 2-year OS in patients who achieved EFS24 was 91.5% compared to 97.7% in the general population, while it was 12.1% in EFS24 failures compared to 98.3% in the general population.

Of the patients with DLBCL, 38 (33.6%) and 44 (38.9%) experienced events within 12 and 24 months, respectively. Patients who achieved EFS12 had a subsequent 2-year OS of 95.6% compared to an expected survival rate of 97.6%, while those who failed EFS12 had a subsequent OS of 20.0% compared to an expected survival rate of 99.4%. Patients who achieved EFS24 had a subsequent 2-year OS of 100%, compared to an expected OS of 99.0%. In contrast, those who failed to achieve EFS24 had a subsequent OS of 26.1%. The subsequent OS in patients with DLBCL who did not achieve EFS12 or EFS24 was inferior to that of the general population ($p < 0.001$ for both). Although the event-free status at 12 months was related to a lower survival (p=0.018), those who were event-free at 24 months had a subsequent OS comparable to that of the general population (p=0.124).

The subsequent OS in patients with PTCL who achieved EFS12 was inferior to that of patients with DLBCL who achieved EFS12 (p=0.001) (Fig. 2A), while it was poor in both the PTCL and the DLBCL groups of patients who failed to achieve EFS12 (p=0.666) (Fig. 2B). There was also no difference between groups in terms of OS in those who achieved EFS24 (p=0.094) (Fig. 2C). The causes of death among those who achieved EFS24 were disease relapse (n=3), transformation to myelodysplastic syndrome (n=2), and disease-unrelated causes (n=3). Although the subsequent OS in patients with PTCL who did not achieve EFS24 was not statistically different to that of those with DLBCL who did not achieve EFS24 (p=0.294) (Fig. 2D), both groups had an inferior subsequent OS than the expected value in the general population ($p < 0.001$ for both; data not shown).

4. Predictive factors of achieving EFS24

In patients with PTCL, univariate analysis showed that advanced age (p=0.004), advanced stage ($p < 0.001$), elevated LDH (p=0.016), extranodal involvement more than one site (p=0.014), positive Epstein-Barr virus (EBV) (p=0.043),

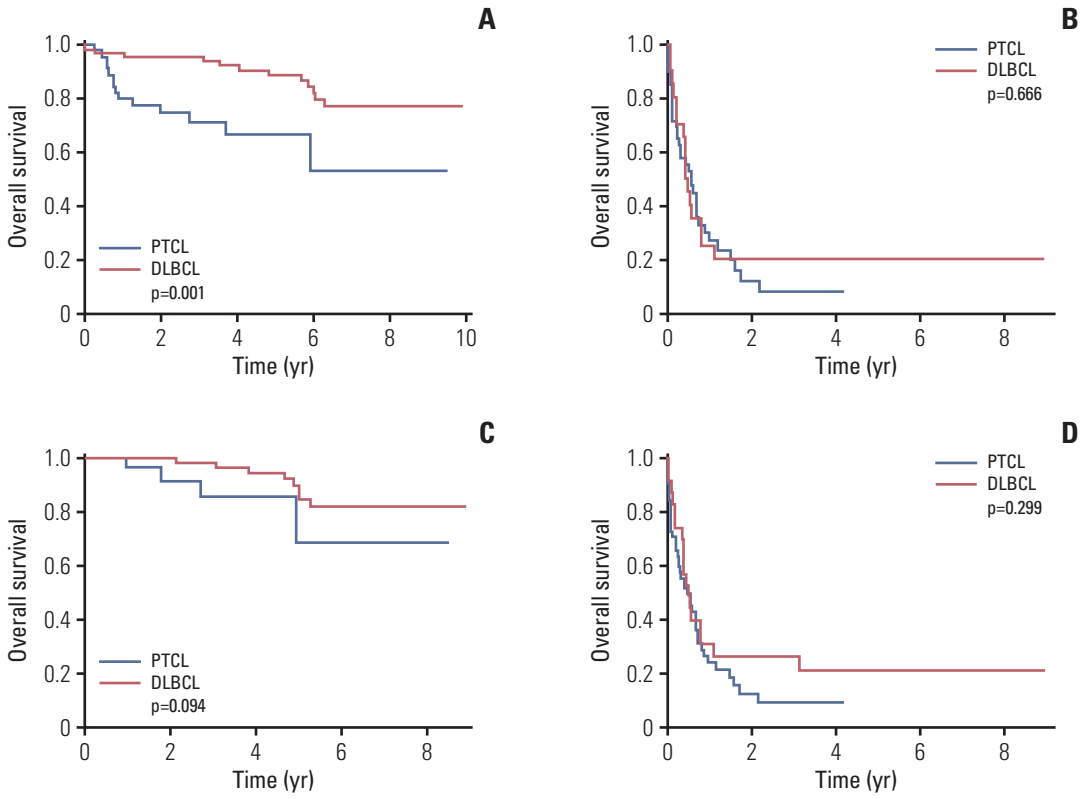

Fig. 2. Subsequent overall survival of the peripheral T-cell lymphoma (PTCL) and diffuse large B-cell lymphoma (DLBCL) patients after propensity score matching based on the International Prognostic Index. (A) Subsequent overall survival of patients who were event-free survival at 12 months (EFS12). (B) Subsequent overall survival of patients who did not achieve EFS12. (C) Subsequent overall survival of patients who were event-free survival at 24 months (EFS24). (D) Subsequent overall survival of patients who did not achieve EFS24.

elevated FLC (p=0.025) and upfront ASCT (p=0.013) were associated with EFS24 failure. Multivariate analysis showed that advanced stage (odds ratio [OR], 5.304; 95% CI, 1.901 to 14.802; p=0.001) were significantly related with EFS24 failure.

In patients with DLBCL, Eastern Cooperative Oncology Group (ECOG) performance status (p=0.005), advanced stage (p < 0.001), extranodal involvement of more than one site (p < 0.001), elevated LDH (p=0.001), bone marrow involvement (p=0.002), low ALC (p=0.002), elevated FLC (p=0.031), and low albumin level (p < 0.001), were associated with failing EFS24 by univariate analysis. On multivariate analysis, advanced stage and low albumin level were related to EFS24 failure (OR, 3.776; 95% CI, 1.877 to 7.595; p < 0.001 and OR, 2.797; 95% CI, 1.304 to 6.001; p=0.008, respectively) There was no multicollinearity between the two factors (variance inflation factors=1.235) (Table 3).

Discussion

We evaluated survival in patients with PTCL who were treated with anthracycline-based chemotherapy, based on their event-free status at 24 months. Subsequent OS in patients who could achieve EFS24 was comparable to that of DLBCL patients although it did not reach to that of the general population. Patients who experienced events before 24 months had a dismal prognosis. Advanced stage at PTCL diagnosis were shown to be predictors of EFS24 failure.

Patients with DLBCL who achieved EFS24 have a subsequent OS similar to that of the general population, suggesting that these patients have the potential to be cured [7]. Since most relapses in patients with DLBCL are observed between 12 and 18 months after diagnosis, EFS24 can be used as a surrogate marker for OS [7]. When compared with patients with DLBCL, the disease course of PTCL is more aggressive and resistant to chemotherapy [17]. Many patients with PTCL do not achieve a complete response (CR) after frontline chemotherapy, and many of those that achieve a CR, relapse [18,19]. Maurer et al. [12] reported that patients with PTCL

Table 3. Univariate and multivariate analysis of predictors of event-free survival at 24 months

Variable	PTCL		DLBCL	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Univariate analysis				
Age ≥ 60 yr	2.493 (1.328-4.679)	0.004	1.621 (0.902-2.914)	0.106
Male	0.721 (0.380-1.370)	0.318	1.588 (0.878-2.872)	0.126
ECOG performance status ≥ 2	1.072 (0.463-2.486)	0.871	3.109 (1.408-6.866)	0.005
Stage III-IV	3.808 (1.759-8.241)	0.001	5.374 (2.811-10.273)	< 0.001
Extranodal involvement > 1 site	2.446 (1.194-5.011)	0.014	3.138 (1.691-5.823)	< 0.001
Elevated LDH	2.159 (1.151-4.049)	0.016	2.724 (1.486-4.994)	0.001
BM involvement	1.709 (0.899-3.250)	0.102	4.831 (1.781-13.099)	0.002
EBV positive	2.135 (1.026-4.442)	0.043	1.138 (0.310-4.184)	0.845
ALC < 1,000	2.194 (0.684-2.447)	0.428	2.871 (1.488-5.538)	0.002
Elevated FLC	2.844 (1.139-7.098)	0.025	1.924 (1.063-3.483)	0.031
Low albumin	1.853 (0.896-3.832)	0.096	4.952 (2.462-9.962)	< 0.001
Upfront ASCT	0.333 (0.140-0.794)	0.013	1.289 (0.459-3.621)	0.631
Multivariate analysis				
Stage III-IV	5.304 (1.901-14.802)	0.001	3.776 (1.877-7.595)	< 0.001
Low albumin	-	-	2.797 (1.304-6.001)	0.008

ALC, absolute lymphocyte count; ASCT, autologous stem cell transplantation; BM, bone marrow; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; LDH, lactate dehydrogenase; OR, odds ratio; PTCL, peripheral T-cell lymphoma.

who remain event-free at 24 months have longer subsequent OS, even if it is shorter than the survival rate of the general population . Similarly, Wudhikarn et al. [13] showed that EFS24 is an independent predictor of OS for PTCL.

The survival gap between patients with PTCL and the general population decreased with time. Patients who achieved EFS24 showed a subsequent 2-year OS comparable to that of the general population (88.0% vs. 97.7%). Patients who achieved EFS12 had an inferior subsequent OS compared to the general population (77.6% vs. 97.0%). Approximately one-third of the patients were able to achieve EFS24. To evaluate the role of EFS24 in PTCL, propensity score matching based on IPI scores was used to match patients with PTCL with patients with DLBCL. The rationale for using IPI for propensity score matching of the two populations lies in the fact that advanced disease status at diagnosis is one of the main factors associated with the poor prognosis of patients with PTCL. After propensity score matching based on IPI, the subsequent OS in patients with PTCL and DLBCL who achieved EFS24 did not differ. These results suggest that PTCL patients could achieve long-term survival if they remained event-free during the first 24 months. Therefore, a landmark analysis of EFS24 could be a surrogate marker for subsequent OS in PTCL.

Finally, we evaluated patient baseline clinical factors for their ability to predict EFS24 in patients with PTCL. To evaluated the role of upfront ASCT, we included these 25 patients in this analysis. Poor performance status was not associated with a lower probability of achieving EFS24; however, this observation may be impacted by inclusion only of patients treated with anthracycline-based chemotherapy in our study, which resulted in a low percentage of patients with ECOG performance status ≥ 2. Four components of IPI (age ≥ 60, advanced stage, extranodal involvement more than one site and elevated LDH), positive EBV and elevated FLC were associated with EFS24 failure by univariable analysis. In contrast to the clinical risk calculator IPI24 developed for patients with DLBCL [11], which includes many of the parameters examined in the present study, advanced disease stage at the time of diagnosis was the only meaningful parameter identified as being predictive of EFS24 in patients with PTCL by multivariate analysis. Since patients with stage III/IV has a higher chance to experience an early relapse or disease progression, novel therapeutic strategies must be developed for these patients to achieve EFS24.

This study has some limitations. First, it was a single-center retrospective study. To minimize patient-selection bias we consecutively included all patients newly diagnosed with PTCL at our institution during the target period and we included a homogeneous population in terms of the therapeutic strategy received (anthracycline-based chemotherapy). Second, since the incidence of PTCL is low, we pooled patients with different subtypes of PTCL in our analysis. In the future, the importance of EFS24 should be studied for

each subtype of PTCL. In addition, biological markers relevant to the characterization of PTCL should be evaluated as predictive factors.

In conclusion, we have shown that EFS24 could be used to stratify the subsequent OS in patients with PTCL. About one-third of patients with PTCL who achieve EFS24 have an OS comparable to that of the general population and of patients with DLBCL who achieve EFS24. Advanced disease stage at diagnosis could be important predictive markers for EFS24 failure, underscoring the urgent need to develop novel therapeutic strategies for this population.

Ethical Statement

The study protocol was approved by the Institutional Review Board (IRB No. 3-2018-0233) from Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Obtainment of informed consent from the study participants was waived due to the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Kim YR, Kim JS.
Collected the data: Kim YR, Kim SJ, Cho H, Chung H, Jang JE, Cheong JW, Min YH, Kim JS.
Contributed data or analysis tools: Kim YR, Kim SJ, Cho H, Chung H, Jang JE, Kim JS.
Performed the analysis: Kim YR, Kim SJ, Cho H, Kim JS.
Wrote the paper: Kim YR, Kim JS.
Statistical analysis: Lee HS, Jeon S.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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