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Early disease progression in patients with localized natural killer/T-cell lymphoma treated with concurrent chemoradiotherapy

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Abbreviations: CCRT, concurrent chemoradiotherapy; CCRT-MIDLE, CCRT with cisplatin and L-asparaginase followed by methotrexate, ifosfamide, dexamethasone, L-asparaginase, and etoposide; CCRT-VIDL, CCRT with cisplatin followed by etoposide, ifosfamide, dexamethasone, and L-asparaginase; CCRT-VIPD, CCRT with cisplatin followed by etoposide, ifosfamide, cisplatin, and dexamethasone; CI, confidence interval; CRP, C-reactive protein; EBV, Epstein-Barr virus; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; FL, follicular lymphoma; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; NKEA, next-generation therapy for NK/T-cell lymphoma in East Asia; NPV, negative predictive value; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years after diagnosis; POD, progression of disease; PPV, positive predictive value; RT-DeVIC, radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin; RT, radiotherapy; sIL-2R, soluble interleukin-2 receptor; SMC, Samsung Medical Center.

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Prognosis of patients with localized nasal extranodal natural killer/T-cell lymphoma, nasal type (ENKL) has been improved by non-anthracycline-containing treatments such as concurrent chemoradiotherapy (CCRT). However, some patients experience early disease progression. To clarify the clinical features and outcomes of these patients, data from 165 patients with localized nasal ENKL who were diagnosed between 2000 and 2013 at 31 institutes in Japan and who received radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC) were retrospectively analyzed. Progression of disease within 2 years after diagnosis (POD24) was used as the definition of early progression. An independent dataset of 60 patients with localized nasal ENKL who received CCRT at Samsung Medical Center was used in the validation analysis. POD24 was documented in 23% of patients who received RT-DeVIC and in 25% of patients in the validation cohort. Overall survival (OS) from risk-defining events of the POD24 group was inferior to that of the reference group in both cohorts ($P < .00001$). In the RT-DeVIC cohort, pretreatment elevated levels of serum soluble interleukin-2 receptor (sIL-2R), lactate dehydrogenase, C-reactive protein, and detectable Epstein-Barr virus DNA in peripheral blood were associated with POD24. In the validation cohort, no pretreatment clinical factor associated with POD24 was identified. Our study indicates that POD24 is a strong indicator of survival in localized ENKL, despite the different CCRT regimens adopted. In the treatment of localized nasal ENKL, POD24 is useful for identifying patients who have unmet medical needs.

KEYWORDS
concurrent chemoradiotherapy, early progression, Epstein-Barr virus, NK/T-cell lymphoma, soluble interleukin-2 receptor

1 | INTRODUCTION

Extranodal NK/T-cell lymphoma, nasal type is a rare lymphoma entity characterized predominantly by extranodal involvement and association with EBV.[1] During the last decade, first-line treatment for localized nasal ENKL has changed from conventional anthracycline-containing chemotherapies to RT with or without non-anthracycline chemotherapy.[2,3] RT-DeVIC was developed in Japan.[4,5] CCRT-VIPD,[6,7] CCRT-VIDL,[7] and CCRT-MIDLE[8] were developed in Korea. These CCRT regimens can achieve 2-year PFS among approximately 70% of patients. These treatments are considered as the standard options for first-line therapy for localized ENKL, which has led to the development of various CCRT regimens outside Japan and Korea.[9-13] However, there are a considerable number of patients with localized ENKL who experience early disease progression despite these new treatments, and the clinical characteristics of these patients remain unknown.

Recently, the National LymphoCare Study in the USA reported that 19% of patients with FL experienced POD24.[14] Of note, POD24 was strongly associated with a worse prognosis for FL patients.[14] Because the prognosis of patients with localized nasal ENKL has improved substantially during the last decade, POD24 as an indicator of early progression may be useful for future trials of novel treatments for ENKL.

To determine the clinical features and outcomes of patients who experienced early disease progression after CCRT, investigators who conducted a large retrospective study in Japan (NKEA Part A)[15] and at SMC in Korea collaborated on an analysis of POD24 in newly diagnosed localized nasal ENKL. First, we analyzed POD24 among patients who received RT-DeVIC using a dataset from the NKEA study. Subsequently, we validated the results using a dataset of patients who received CCRT at SMC.

2 | PATIENTS AND METHODS

2.1 | Patients

The NKEA project is a collaborative study conducted by hemato-oncologists in Japan, a study group of radiation oncologists in Japan (the Japanese Radiation Oncology Study Group [JROSG]), and collaborators in East Asia. The study was approved by the institutional review board at each study site and conducted according to the Declaration of Helsinki. Details of the NKEA project (clinical trial registration number: UMIN000015491) were reported previously.[15]

Briefly, data were retrospectively collected from consecutive patients diagnosed with ENKL between 2000 and 2013 at 31 participating institutes in Japan and then analyzed.

Analysis for the current study included patients with newly diagnosed localized (stage IE or contiguous stage IIE with cervical lymph node involvement) nasal ENKL who received CCRT. Patients with extranasal ENKL[16] or who had distant lymph node involvement, such as axillar or mediastinal lymph node involvement, were excluded from the analysis. POD24[14] was used as the definition of early progression. According to that definition, patients who were lost to follow up or died without POD within 2 years of diagnosis were excluded. Patients analyzed in NKEA Part A who received RT-DeVIC (the RT-DeVIC cohort) were included in 2 categories for the present study: patients with POD24 (the POD group) and patients without POD24 (the reference group).

An independent dataset of patients with ENKL at SMC was used for the validation analysis. Patients from the SMC dataset were diagnosed between August 2008 and June 2013, and they received one of the following concurrent chemoradiotherapies as first-line therapy: CCRT-VIPD,[6] CCRT-VIDL,[7] CCRT-MIDLE,[8] and CCRT with weekly cisplatin alone. Data of the validation cohort were analyzed with the same methodology used for the RT-DeVIC cohort.

2.2 | Statistical analysis

Distribution of variables between the 2 groups was assessed using Fisher's exact test. Progression was defined as a documented progression or relapse of lymphoma or death resulting from any cause. OS was calculated according to the Kaplan-Meier method. OS from a risk-defining event was defined as survival from the time of POD for the POD24 group or from 2 years after diagnosis for the reference group.[14] Multivariate analysis was done using Cox regression. All *P*-values were 2-sided with an overall significance level of .05. Statistical analyses were carried out using IBM SPSS Statistics 23 (IBM Japan, Tokyo, Japan).

The same clinical factors analyzed in a previous study[15] were tested in the present analysis. Moreover, serum total bilirubin, serum creatinine, and serum albumin were added to them in multivariate analysis in the POD group of the RT-DeVIC cohort. Cut-off vales for CRP and sIL-2R (sCD25) were 0.30 mg/dL and 519 U/mL, respectively, which were the same values as used in the previous study. Because of problems concerning health insurance coverage, most patients in the RT-DeVIC cohort were missing data for EBV-DNA load, whereas information on sIL-2R was unavailable for patients in the SMC cohort. Multivariate analyses were carried out with variables showing $P < .05$ in univariate analyses.

3 | RESULTS

3.1 | Patient characteristics of the RT-DeVIC cohort

A consort diagram of the present study is shown in Figure 1. The dataset of NKEA Part A comprised 257 patients with newly diagnosed localized ENKL. Among them, 1 patient with extranasal ENKL (testicular ENKL) and 3 patients with distant lymph node involvement were excluded for the purpose of the present analysis. RT-(2/3)DeVIC was selected in 165 patients with nasal ENKL of stage I or contiguous stage II with cervical lymph node involvement. Median dose of RT was 50 Gy. Of those patients, 38 patients (23%) experienced POD24. After excluding 4 patients who were lost to follow up within 2 years of diagnosis and 3 patients who died without

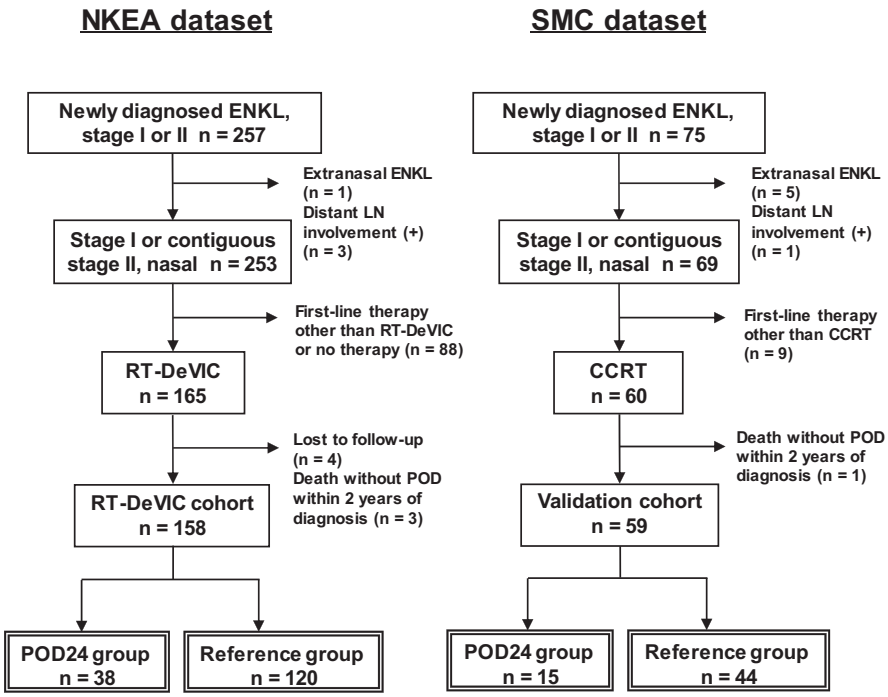

FIGURE 1 Consort diagrams of the present study. CCRT, concurrent chemoradiotherapy; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; LN, lymph node; NKEA, next-generation therapy for NK/T-cell lymphoma in East Asia; POD, progression of disease; POD24, progression of disease within 2 y after diagnosis; RT-DeVIC, radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin

POD within 2 years of diagnosis, 38 patients were analyzed as the POD24 group and 120 as the reference group. POD events occurred within 6 months after diagnosis in 23 patients (61%), 7-12 months after diagnosis in 11 patients (29%), and 13-24 months after diagnosis in 4 patients (11%). Because the results for POD12 were almost the same as for POD24 (data not shown), we selected POD24 for further analysis.

Second-line therapy for the POD24 group included steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for 10 patients, L-asparaginase only for 2 patients, RT alone for 2 patients, cytarabine-containing chemotherapy for 6 patients, other chemotherapeutic regimens for 4 patients, and HSCT for 4 patients. Among the other 10 patients, 5 received no therapy because of poor performance status, and information on second-line therapy was missing for 5 patients. Ten patients in the POD24 group underwent HSCT, of which 3 received autologous HSCT alone, 5 received allogeneic HSCT, and 2 patients received both autologous HSCT and allogeneic HSCT.

Clinical characteristics of the patients at diagnosis are shown in Table 1. Median age at diagnosis was 55 years in 158 patients, 56 years in the POD group, and 54 in the reference group. The POD24 group showed more frequently elevated serum sIL-2R (24/33, 73%; $P < .01$), a detectable EBV-DNA load (15/17, 88%; $P = .032$), an elevated LDH level (40%, $P = .035$), and an elevated CRP level (27/37, 73%; $P = .036$) compared to those of the reference group. Treatment periods and doses of RT and DeVIC were not associated with the incidence of POD24 (data not shown).

Positive predictive value and NPV of elevated sIL-2R for POD24 were 42% (95% CI, 29%-55%) and 89% (95% CI, 82%-96%), respectively. PPV and NPV of elevated LDH for POD24 were 37% (95% CI, 22%-51%) and 80% (95% CI, 73%-88%), respectively. PPV and NPV of elevated CRP for POD24 were 31% (95% CI, 21%-40%) and 85% (95% CI, 76%-93%), respectively. Additionally, PPV and NPV of detectable EBV-DNA for POD24 were 39% (95% CI, 24%-55%) and 90% (77%-103%), respectively. Of the 8 patients who were negative for all 4 factors, none of them experienced POD24.

3.2 | POD24 and subsequent survival of the RT-DeVIC cohort

Median follow-up time from diagnosis for the RT-DeVIC cohort was 5.8 years (range, 0.9-13.3 years). OS rates from a risk-defining event at 2 and 5 years were 28% and 18%, respectively, in the POD24 group. In contrast, the 2 and 5-year OS rates from a risk-defining event were 93% and 86%, respectively, in the reference group (Figure 2A). POD24 was associated with markedly reduced OS and a HR of 11.31 (95% CI, 6.16-20.75) compared with those of the reference group.

Information on the sites of progression in the POD24 group was available for 35 patients. Of those patients, locoregional progression was recorded in 7 patients (20%), and either distant or systemic progression was documented in 28 patients (80%).

In the reference group of the RT-DeVIC cohort, the causes of death at more than 5 years after diagnosis included ENKL (n = 3), esophageal cancer as a synchronous malignancy (n = 1), rhabdomyosarcoma as a second malignancy (n = 1), aortic rapture (n = 1), cerebrovascular disease (n = 1), and heart failure (n = 1). Only 1 patient experienced a relapse of ENKL at more than 5 years after diagnosis.

3.3 | Factors affecting OS in the POD24 group of the RT-DeVIC cohort

Multivariate analysis in 33 patients in the POD24 group of the RT-DeVIC cohort showed elevated sIL-2R (HR 4.00; 95% CI, 1.18-13.54) and hypoalbuminemia (HR 3.34; 95% CI, 1.34-8.30) as independent prognostic factors for short OS after a risk-defining event (Table 2).

3.4 | Validation analysis

Clinical characteristics of the validation cohort are shown in Table 1. Median age at diagnosis was 51 years. Compared to the RT-DeVIC cohort, the validation cohort showed significantly lower proportions of patients with detectable EBV-DNA ($P < .001$) and B symptoms ($P = .0499$). No clinical factors analyzed in this study were significantly associated with POD24.

First-line treatment was CCRT-VIDL in 36 patients, CCRT-VIPD in 11 patients, CCRT-MIDLE in 7 patients, and CCRT with cisplatin in 5 patients. Median dose of RT was 40 Gy. The most common second-line therapy in patients who experienced POD24 was L-asparaginase-containing chemotherapy. Six patients underwent high-dose chemotherapy followed by autologous HSCT after salvage therapy, and no-one received allogeneic HSCT. With a median follow up of 3.4 years, OS from a risk-defining event at 2 years was 32% in the POD24 group and 100% in the reference group (Figure 2B).

Information on the sites of progression in the POD group of the validation cohort was available for 12 patients. Among these, locoregional progression was recorded in 6 patients (50%), and either distant or systemic progression was documented in 6 patients (50%).

4 | DISCUSSION

This cooperative study showed that one-quarter of patients with newly diagnosed localized nasal ENKL treated with CCRT, including RT-DeVIC, CCRT-VIPD, CCRT-VIDL, CCRT-MIDLE, and CCRT with cisplatin only, experienced POD24. More than half of the patients in the RT-DeVIC and validation cohorts received standard approaches to relapsed ENKL (ie, L-asparaginase-containing chemotherapy followed by HSCT); however, OS after risk-defining events was approximately only 20%. This outcome clearly indicates that patients in the POD24 group have unmet treatment needs.

Accumulating data have indicated that treatment failure or disease progression within 24 months after diagnosis is associated with

survival in several lymphoma subtypes.[14,17-20] In a study of diffuse large B-cell lymphoma, the OS of patients who achieved event-free survival at 24 months (EFS24) was comparable to the expected survival in the general population.[17] In a study of classical Hodgkin lymphoma, patients who achieved EFS24 had an excellent outcome regardless of baseline prognostic factors.[19] In a study of FL, EFS24 was associated with a short OS in patients who received rituximab and CHOP as first-line therapy.[18] In peripheral T-cell lymphoma, the

TABLE 1 Clinical characteristics in 2 cohorts of patients who received concurrent chemoradiotherapy

	RT-DeVIC cohort				Validation cohort			
	All patients (n = 158) No. (%)	POD24 group (n = 38) No. (%)	Reference group (n = 120) No. (%)	*P*	All patients (n = 59) No. (%)	POD24 group (n = 15) No. (%)	Reference group (n = 44) No. (%)	*P*
Median age, years	55	56	54		51	51	50	
Range	16-83	17-78	16-83		24-75	24-67	30-75	
Age > 60	48 (30)	9 (24)	39 (33)	.42	13 (22)	3 (20)	10 (23)	1.00
Male gender	114 (72)	32 (84)	82 (68)	.064	41 (70)	10 (67)	31 (71)	.76
Elevated LDH	41 (26)	15 (40)	26 (22)	.035	14 (24)	3 (20)	11 (25)	1.00
ECOG PS > 1	11 (7)	4 (11)	7 (6)	.30	1 (2)	1 (7)	0 (0)	.25
Regional lymph node involvement	28 (18)	8 (21)	20 (17)	.63	13 (22)	3 (20)	10 (23)	1.00
B symptom (+)	57 (37)	15 (42)	42 (36)	.56	13 (22)	3 (20)	10 (23)	1.00
Unknown	4	2	2		0	0	0	
Hb <11 g/dL	18 (11)	5 (13)	13 (11)	.77	3 (5)	0 (0)	3 (7)	.56
PLT <150 × $10^3/\mu L$	14 (9)	4 (11)	10 (8)	.74	5 (9)	2 (13)	3 (7)	.59
Albumin < LLN	35 (23)	9 (24)	26 (22)	.82	NA	NA	NA	
Unknown	3	1	2					
Elevated CRP	88 (58)	27 (73)	61 (53)	.036	27 (48)	6 (40)	21 (51)	.55
Unknown	5	1	4		3	0	3	
Elevated sIL-2R	57 (41)	24 (73)	33 (31)	<.01	NA	NA	NA	
Unknown	20	5	15					
Detectable EBV-DNA	38 (66)	15 (88)	23 (56)	.032	12 (20)	3 (20)	9 (21)	1.00
Unknown	100	21	79		0	0	0	

CRP, C-reactive protein; EBV, Epstein-Barr virus; Hb, hemoglobin; LDH, lactate dehydrogenase; LLN, lower limit of normal; NA, not available; PLT, platelets; POD24, progression of disease within 2 y after diagnosis; PS, performance status; RT-DeVIC, radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin; sIL-2R, serum soluble interleukin-2 receptor.

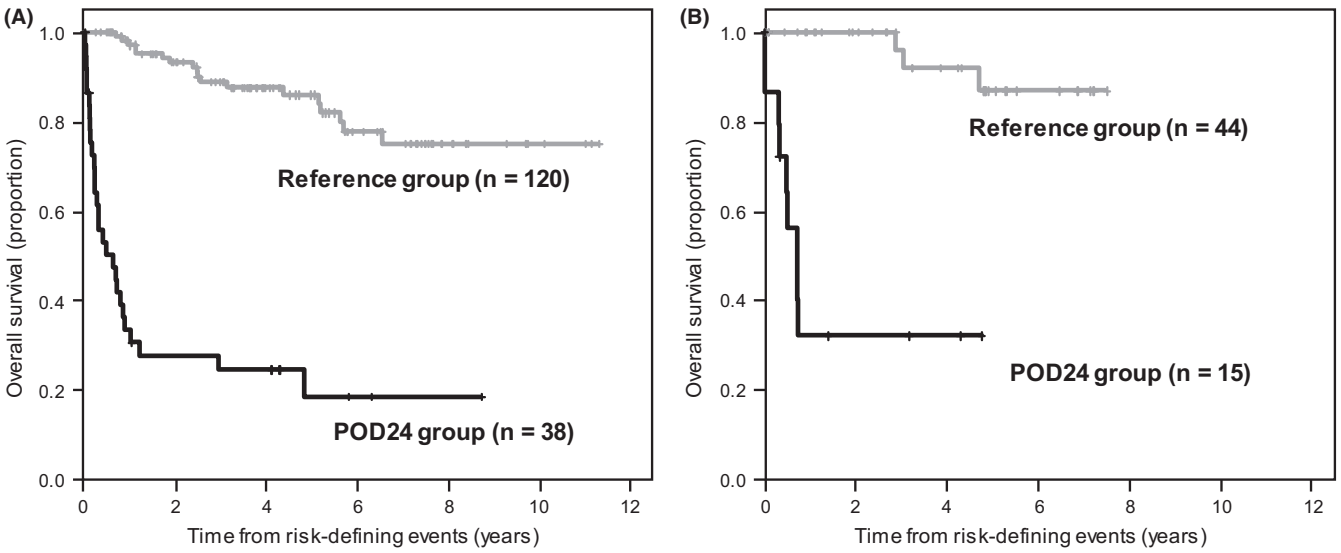

FIGURE 2 Overall survival after a risk-defining event in the 2 cohorts. A, Radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC) cohort (n = 158) and (B) the validation cohort (n = 59). POD24, progression of disease within 2 y after diagnosis

TABLE 2 Univariate and multivariate analysis of predictors of OS after a risk-defining event in the POD24 group of the RT-DeVIC cohort (n = 33)

	Univariate			Multivariate (final model)		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Albumin < LLN	3.47	1.39-8.66	.008	3.34	1.34-8.30	.010
Elevated CRP	3.05	1.12-8.35	.030	-	-	-
Elevated sIL-2R	4.11	1.22-13.91	.023	4.00	1.18-13.54	.026

-, indicated that Elevated CRP was not included in the final model of the multivariate analysis; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; LLN, lower limit of normal; OS, overall survival; POD24, progression of disease within 2 y after diagnosis; RT-DeVIC, radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin; sIL-2R, serum soluble interleukin-2 receptor.

OS is inferior to the expected survival in the general population, despite the achievement of EFS24.[20] Moreover, the National LymphoCare Study used POD24 as an indicator and analyzed the clinical characteristics of patients with FL who experienced POD24.[14] We selected POD24 because it fit the purpose of our study. POD24 analysis is advantageous because it does not require information on unplanned treatment; this information is difficult to evaluate retrospectively.

The present study identified serum sIL-2R, CRP and LDH levels as well as detectable EBV-DNA in peripheral blood as risk factors for POD24 in the RT-DeVIC cohort. The high NPV of these factors would be helpful in current clinical practice, at least in Japan, where RT-DeVIC is the standard treatment approach for localized ENKL.[21] Among these factors, sIL-2R was the most powerful predictor of both OS and PFS in a previous survival analysis in NKEA.[15] In contrast, serum LDH was not associated with either OS or PFS,[15] which indicates that this factor may be specific for POD24. Elevated sIL-2R, CRP, and LDH levels were significantly associated with advanced disease.[15] Because 80% of the patients in the POD24 group experienced distant or systemic progression, occult disseminated disease might have been related to POD24 in RT-DeVIC. Thus, rigorous staging is recommended to reduce early progression after RT-DeVIC.

The present study indicated that the risk factors for POD24 in the RT-DeVIC cohort were inconsistent with those in the validation cohort, which indicates that differences in the treatment details for CCRT regimens and baseline clinical features such as EBV-DNA status and B symptoms lead to distinct risks for POD24. More than half of the patients in the validation cohort received L-asparaginase, which is a key drug for the treatment of ENKL.[2,22] This might be related to the lower incidence of distant or systemic relapse in the validation cohort (50%) than in the RT-DeVIC cohort (80%). The median dose of RT in the RT-DeVIC cohort was 50 Gy, whereas that in the validation cohort was 40 Gy, A higher dose of RT might be associated with a low incidence of locoregional progression in the RT-DeVIC cohort (20%). There were no clinical factors analyzed in this study that were associated with POD24 in the validation cohort, although data on serum sIL-2R were not available. Some molecular markers including macrophage inflammatory protein 1 alpha and survivin are known prognostic markers for patients primarily treated with CCRT regimens in the validation cohort.[23-25]

Limitations of the present study include interpretations based on retrospective analyses, no survival analysis with comparison of the general population, missing data for EBV-DNA in the RT-DeVIC cohort and sIL-2R in the validation cohort, heterogeneity of the treatments, and a lack of molecular analysis. Nevertheless, the results of this study were based on analyses using the largest number of patients who received well-known CCRT regimens for this disease. Thus, we believe the present study provides useful information for the future development of treatments for localized ENKL.

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CONFLICTS OF INTEREST

MY, RS, and KS received honoraria from Kyowa Hakko Kirin. NK received honoraria and a research grant from Kyowa Hakko Kirin. The remaining authors declare no conflicts of interest.

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APPENDIX I

Institutes participating in the present study

Tohoku University, Akita University, Gunma University, Saitama Cancer Center, International Medical Center-Saitama Medical University, National Cancer Center Hospital, Showa University, Cancer Institute Hospital, Yokohama City University Hospital, Kanagawa Cancer Center, Tokai University, Niigata University, Kanazawa Medical University, Shinshu University, Nagaoka Red Cross Hospital, Nagoya University, Nagoya City University, Toyota Kosei Hospital, Mie University, Shiga Medical Center for Adults, Kyoto Daini Red Cross Hospital, Kobe University, Hyogo Cancer Center, Nara Medical University, Tottori Prefectural Central Hospital, Shimane University, Kurashiki Central Hospital, Kawasaki Medical School, National Hospital Organization Kyushu Cancer Center, Saga University, Kumamoto City Hospital, and Samsung Medical Center.