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ORIGINAL REPORT

Treatments and Outcomes of Patients With Extranodal Natural Killer/T-Cell Lymphoma Diagnosed Between 2000 and 2013: A Cooperative Study in Japan

Motoko Yamaguchi, Ritsuro Suzuki, Masahiko Oguchi, Naoko Asano, Jun Amaki, Takeshi Akiba, Takeshi Maeda, Satoshi Itasaka, Nobuko Kubota, Yoshihiro Saito, Yukio Kobayashi, Jun Itami, Kyoko Ueda, Kana Miyazaki, Noriko Ii, Naoto Tomita, Nodoka Sekiguchi, Jun Takizawa, Bungo Saito, Tohru Murayama, Toshihiko Ando, Hideho Wada, Rie Hyo, Yasuo Ejima, Masatoshi Hasegawa, and Naoyuki Katayama

Author affiliations appear at the end of this article.

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Corresponding author: Motoko Yamaguchi, MD, PhD, Department of Hematology and Oncology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan; e-mail: myamaguchi@clin.medic.mie-u.ac.jp.

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A B S T R A C T

Purpose

To elucidate the management and outcomes of patients with extranodal natural killer/T-cell lymphoma, nasal type (ENKL), who were diagnosed between 2000 and 2013 in Japan.

Patients and Methods

Data from 358 patients with ENKL diagnosed between 2000 and 2013 from 31 institutes were retrospectively analyzed.

Results

Patients' median age was 58 years, and 257 (72%) had localized disease. The most common first-line treatment was radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC) (66%) for localized ENKL and L-asparaginase–containing chemotherapy (30%) for advanced ENKL. With a median follow-up of 5.8 years, overall survival (OS) rates at 5 years for localized and advanced ENKL were 68% and 24%, respectively. The prognostic index of natural killer lymphoma was validated in our study, although only 4% of patients with localized ENKL were classified as high risk. With a median follow-up of 5.6 years, OS and progression-free survival at 5 years in the 150 patients who received RT-DeVIC in clinical practice were 72% (95% CI, 63% to 78%) and 61% (95% CI, 52% to 69%), respectively. Toxicities of RT-DeVIC were comparable to those in a previous trial. Multivariate analysis in patients with localized ENKL who received RT-DeVIC identified elevated soluble interleukin-2 receptor as an independent predictive factor for worse OS and progression-free survival (adjusted hazard ratios, 2.28 and 2.46; 95% CI, 1.24 to 4.23 and 1.42 to 4.28; $P = .008$ and .0014, respectively).

Conclusion

Favorable OS in response to new treatments was demonstrated in a large number of patients. Improved treatment approaches are needed for localized ENKL exhibiting elevated pretreatment soluble interleukin-2 receptor.

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL), is a rare lymphoma entity characterized predominantly by extranodal involvement and association with Epstein-Barr virus (EBV).[1] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy has failed to show sufficient efficacy.[2-4] Since the early 2000s, clinical trials of concurrent chemoradiotherapy for localized ENKL, such as radiotherapy with dexamethasone, etoposide, ifosfamide, and dexamethasone (RT-DeVIC)[5,6] and concurrent chemoradiotherapy with cisplatin once per week followed by etoposide, ifosfamide, cisplatin, and dexamethasone (CCRT-VIPD)[7,8] or L-asparaginase–containing chemotherapies for disseminated ENKL, including corticosteroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE)[9,10] and L-asparaginase, methotrexate, and dexamethasone (AspaMetDex),[11,12] have been conducted. These trials have dramatically changed the clinical management of ENKL.[13,14] For example, National Comprehensive Cancer Network

ASSOCIATED CONTENT

Appendix
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guidelines have recommended these new treatments for ENKL and removed CHOP chemotherapy since 2010.

Because of the rarity of this disease, current recommendations for first-line treatment of ENKL were established on the basis of the results of phase II studies including fewer than 40 participants. Few studies have evaluated the efficacy and toxicity of new treatments in clinical practice,[15,16] and there is no consensus on the best first-line therapy for localized ENKL. Outcome studies investigating the relevance of new treatments in practice are important initial steps in establishing a standard therapy for rare diseases.

The development of new treatments for ENKL was initiated in Japan in the early 2000s,[3] and therapeutic experience for new treatment has been accumulating. To elucidate the current status of the next-generation therapies for ENKL, validate the results from clinical trials of RT-DeVIC and SMILE, and identify prognostic factors, we conducted a large retrospective cooperative study of patients with ENKL diagnosed between 2000 and 2013 in Japan.

PATIENTS AND METHODS

Study Design

This study was designed as a retrospective study of ENKL to clarify the current status of treatments for ENKL in Japan (Next-Generation Therapy for NK/T-Cell Lymphoma in East Asia [NKEA] project), with collaboration among Japanese hemato-oncologists and a study group of radiation oncologists (the Japanese Radiation Oncology Study Group [JROSG]). Data were retrospectively collected on consecutive patients diagnosed with ENKL between 2000 and 2013 in each participating institute. We consecutively selected patients diagnosed with ENKL regardless of enrollment in clinical trials. Twenty-five patients received first-line therapy in clinical trials (Japan Clinical Oncology Group [JCOG] 0211,[5] N = 19; SMILE phase I study,[9] N = 1; SMILE phase II [SMILE-P2] study,[10] N = 6). In cases in which information on diagnostic markers (CD3, cytotoxic molecules, EBV-encoded RNA, and CD56) was unavailable, central pathology review was conducted using unstained tissue slides. The diagnostic criteria for nasal and extranasal ENKL were on the basis of a previous report.[17] Information on radiotherapy planning and image studies before first-line therapy was also collected. The study was approved by the institutional review board at each study site and conducted in accordance with the Declaration of Helsinki.

Treatment Choice

Treatment choice was generally left to the discretion of the treating physicians; however, the first results of JCOG0211 were published in 2005,[18] and experts in Japan have recommended radiotherapy with a two-thirds dose of DeVIC (RT-2/3DeVIC)[5] for newly diagnosed, localized ENKL since the publication of the final results in 2009.[5] For advanced ENKL, experts in Japan have recommended SMILE chemotherapy since the publication of the final results in 2011.[10] Moreover, there was a community consensus to avoid the use of SMILE in clinical practice for elderly or frail patients who did not fulfill the inclusion criteria of SMILE-P2. Considering these backgrounds, three treatment eras were defined in our study: the first era, 2000 to 2004; the second era, 2005 to 2009; and the third era, 2010 to 2013.

Statistical Analysis

The response assessment complied with the International Working Group Criteria[19] or the Revised Response Criteria for Malignant Lymphoma[20] at each participating institute, because positron emission tomography for response assessment has been reimbursed in Japan since 2012. Toxicity was graded retrospectively according to the Common Terminology Criteria for Adverse Events (version 4.0). Late toxicities resulting from radiotherapy were evaluated as previously reported.[6] The distribution of variables between the two 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. Progression-free (PFS) and overall survival (OS) were calculated according to the Kaplan-Meier method. Multivariate analysis was performed using Cox regression. All *P* values were two sided, with an overall significance level of .05. Statistical analyses were performed using IBM SPSS Statistics 23 (IBM Japan, Tokyo, Japan).

The planned analysis included baseline clinical features, first-line treatment, response, survival, toxicity, prognostic factors, and validation of known prognostic models: the Natural Killer/T-Cell Lymphoma Prognostic Index (NK-PI)[21] and the Prognostic Index of Natural Killer Lymphoma (PINK).[22] For the validation of PINK, patients treated with non–anthracycline-containing regimens with or without radiotherapy were included.

To identify prognostic factors, the risk factors of the International Prognostic Index,[23] NK-PI (B symptoms, stage III or IV disease, lactate dehydrogenase level > upper limit of normal [ULN], and regional lymph node involvement),[21] and PINK (age > 60 years, stage III or IV disease, distant lymph node involvement, and non–nasal-type disease)[22] were selected. Furthermore, the following known prognostic factors of ENKL were selected: lymphocyte count less than 1,000/μL, hemoglobin less than 11 g/dL, platelet count less than 150×10^3 /μL, C-reactive protein greater than ULN, soluble interleukin-2 receptor (sIL-2R; sCD25) greater than ULN, and detectable pretreatment EBV-DNA load in peripheral blood.[24-27] In Japan, the measurement of sIL-2R has been approved for monitoring tumor burden of lymphoma by health insurance since 1994.[28,29] Chemiluminescent enzyme immunoassay or enzyme-linked immunosorbent assay was usually used for the analysis.[29] On the basis of previous results of lymphoma studies in Japan,[28,30-32] 519 U/mL was used as a cutoff for the ULN. Multivariate analyses were performed with variables showing $P < .10$ in univariable analyses.

RESULTS

Patient Characteristics

A total of 383 patients diagnosed with ENKL between 2000 and 2013 were retrospectively registered in this study from 31 participating centers. In 64 patients, the diagnosis of ENKL was confirmed through central pathology review in previous studies.[5,10,17] The diagnosis in the remaining 319 patients was reviewed in the central pathology review of this study. Unstained tissue slides were used for confirming the diagnosis of ENKL in 13 patient cases with incomplete diagnostic information. Application of our exclusion criteria resulted in 358 patients being finally included in our analysis. The detailed reasons for the exclusion of 25 ineligible patients included inadequate diagnosis (n = 7), diagnosis before 2000 or after 2013 (n = 5), and incomplete clinical information (n = 13).

The median age of all patients at diagnosis was 58 years. Advanced ENKL exhibited aggressive clinical features at diagnosis (Table 1).

First-Line Treatment in Patients With Localized ENKL

Of 257 patients with localized ENKL, 244 (95%) received radiotherapy during first-line therapy (Table 2). Among these patients, 182 (75%) received radiotherapy at 50 Gy. Concurrent chemoradiotherapy was the most common modality as first-line

Table 1. Clinical Characteristics and Outcomes (N = 358)

Characteristic	No. of Patients (%)					
		Disease Stage			Treated in Clinical Practice	
	Total (N = 358)	Localized (n = 257)	Advanced (n = 101)	*P*	RT-DeVIC for Localized ENKL (n = 150)	SMILE for Advanced ENKL (n = 13)
Age, years						
Median	58	58	59		56	60
Range	16 to 88	16 to 88	18 to 86		16 to 83	18 to 75
Age > 60 years	155 (43)	108 (42)	47 (47)	.48	55 (37)	6 (46)
Male sex	240 (67)	177 (69)	63 (62)	.26	111 (74)	7 (54)
Stage III to IV	101 (28)	0 (0)	101 (100)	< .001	0 (0)	13 (100)
Elevated LDH	157 (44)	79 (31)	78 (77)	< .001	42 (28)	11 (85)
ECOG PS > 1	79 (22)	29 (11)	50 (50)	< .001	8 (5)	3 (23)
Extranodal sites > 1	105 (29)	23 (9)	82 (81)	< .001	13 (9)	12 (92)
Nasal subgroup	311 (87)	251 (98)	60 (59)	< .001	149 (99)	11 (85)
B symptoms	156 (44)	87 (34)	69 (69)	< .001	51 (35)	9 (69)
Unknown	5	4	1		4	0
HgB < 11 g/dL	77 (22)	41 (16)	36 (36)	< .001	16 (11)	4 (31)
Elevated CRP	204 (59)	134 (54)	70 (71)	.005	84 (58)	7 (54)
Unknown	11	9	2		5	0
Elevated sIL-2R	171 (57)	100 (46)	71 (88)	< .001	55 (42)	11 (92)
Unknown	60	40	20		18	1
NK-PI group				< .001		
1	111 (31)	111 (44)	0 (0)		69 (47)	0 (0)
2	95 (27)	83 (33)	12 (12)		44 (30)	1 (8)
3	71 (20)	50 (20)	21 (21)		28 (19)	4 (31)
4	78 (22)	10 (4)	68 (67)		6 (4)	8 (62)
Not calculable	3	3	0		3	0
PINK				< .001		
Low	146 (41)	146 (57)	0 (0)		94 (63)	0 (0)
Intermediate	127 (35)	102 (40)	25 (25)		53 (35)	5 (38)
High	85 (24)	9 (4)	76 (75)		3 (2)	8 (62)
OS, years (%)						
1	71	84	40		87	59
2	66	78	33		82	59
5	56	68	24		72	40
PFS, years (%)						
1	61	74	29		78	39
2	56	68	26		74	39
5	45	56	16		61	21

Abbreviations: CRP, C-reactive protein; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ECOG, Eastern Clinical Oncology Group; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; HgB, hemoglobin; LDH, lactate dehydrogenase; NK-PI, Natural Killer/T-Cell Lymphoma Prognostic Index; OS, overall survival; PFS, progression-free survival; PINK, Prognostic Index of Natural Killer Lymphoma; PS; performance status; RT, radiotherapy; sIL-2R, soluble interleukin-2 receptor; SMILE, corticosteroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.

therapy (n = 183; 71%). The most common treatment was RT-DeVIC (n = 169; 66%). The proportion of RT-DeVIC in clinical practice increased throughout the three treatment eras (first, 32%; second, 65%; third, 82%; Appendix Table A1, online only).

Nineteen of 22 patients treated with radiotherapy alone were older than 68 years of age. Of the remaining three patients, two presented with no obvious mass before therapy and one was lost to follow-up after radiotherapy. Two patients received no therapy as a result of impaired organ function.

First-Line Treatment in Patients With Advanced ENKL

L-asparaginase–containing chemotherapy was the most common regimen (n = 30; 30%; Table 2). The proportion of L-asparaginase–containing chemotherapy in clinical practice increased throughout the three treatment eras (first, 17%; second, 18%; third, 32%; Appendix Table A1). Twenty-three patients with advanced ENKL received radiotherapy for local disease control during first-line therapy; 15 had nasal involvement. Twenty-nine patients underwent hematopoietic stem-cell transplantation (HSCT); nine patients underwent autologous HSCT, and 20 underwent allogeneic HSCT. Twenty-six patients with a median age of 44 years (range, 18 to 64 years) received HSCT after first-line therapy: 14 patients had achieved complete response (CR), 10 had achieved partial response, and two had stable or progressive disease at the time of HSCT. Nine patients received no antilymphoma therapy because of poor general condition.

Survival of All Patients With ENKL and Validation of Known Prognostic Models

The median follow-up time for survivors was 5.8 years (range, 0.1 to 16.0 years). OS and PFS at 5 years were 56% and 45%, respectively, in all 358 patients (Table 1; Appendix Fig A1, online only). Patients with localized ENKL exhibited better OS and PFS than those with advanced ENKL (Fig 1). OS rates at 5 years for

Table 2. Treatment of Newly Diagnosed ENKL (N = 358)

Treatment	No. (%)
Localized ENKL (n = 257)	
Concurrent chemoradiotherapy	183 (71)
RT-DeVIC	169 (66)
RT-2/3DeVIC in clinical practice	124 (48)
RT-2/3DeVIC in JCOG0211	15 (6)
RT-100%DeVIC in clinical practice	26 (10)
RT-100%DeVIC in JCOG0211	4 (2)
RT–CHOP-like chemotherapy	14 (5)
Sequential chemoradiotherapy	39 (15)
RT followed by DeVIC-like chemotherapy	17 (7)
RT followed by CHOP-like chemotherapy	9 (4)
DeVIC-like chemotherapy followed by RT	2 (1)
L-asparaginase–containing chemotherapy followed by RT	3 (1)
CHOP-like chemotherapy followed by RT	8 (3)
RT alone	22 (9)
Chemotherapy alone	11 (4)
DeVIC	2 (1)
SMILE	2 (1)
CHOP-like chemotherapy	7 (3)
None	2 (1)
Advanced ENKL (n = 101)	
Chemotherapy alone	69 (68)
L-asparaginase–containing chemotherapy	27 (27)
SMILE in clinical practice	13 (13)
SMILE in SMILE phase I or II	7 (7)
Other L-asparaginase–containing chemotherapy	7 (7)
DeVIC-like chemotherapy	23 (23)
CHOP-like chemotherapy	19 (19)
Concurrent chemoradiotherapy	11 (11)
RT-2/3DeVIC	6 (6)
RT-100%DeVIC	2 (2)
RT–CHOP-like chemotherapy	2 (2)
RT-SMILE	1 (1)
Sequential chemoradiotherapy	9 (9)
DeVIC-like chemotherapy followed by RT	2 (2)
L-asparaginase–containing chemotherapy followed by RT	2 (2)
CHOP-like chemotherapy followed by RT	5 (5)
RT alone	3 (3)
None	9 (9)

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; JCOG, Japan Clinical Oncology Group; RT, radiotherapy; SMILE, corticosteroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.

localized and advanced ENKL were 68% and 24%, respectively (Table 1; Fig 1). OS of patients with localized ENKL in the third treatment era was significantly better than that in the second (P = .036) and first eras (P = .047; Appendix Fig A2A, online only). PFS in the third era showed a trend toward being better compared with that in the first era (P = .088; Appendix Fig A2B).

NK-PI was effective in separating each risk group according to OS in all patients with ENKL; however, it could not separate each risk group for OS in patients with localized ENKL (Appendix Fig A1). In an analysis of patients treated with non–anthracycline-based chemotherapies with or without radiotherapy (n = 258), PINK correctively separated the three risk groups for OS in patients at all stages (P < .001; 3-year OS: low, 82%; intermediate, 69%; high, 29%; Fig 1C). It was also prognostic for patients with localized disease (P < .001), although only five patients were classified into the high-risk group of PINK in this analysis (Fig 1D). There was no significant difference in OS between the low- and intermediate-risk groups of PINK (Fig 1D). Analyses of PFS showed results similar to those of OS (data not shown).

Response and Survival in Patients With Localized ENKL Treated With RT-DeVIC in Clinical Practice

The baseline clinical characteristics of 150 patients with localized ENKL who received RT-DeVIC in clinical practice are listed in Table 1. RT-2/3DeVIC was selected in 124 patients (Table 2). The remaining 26 patients received full-dose DeVIC for concurrent chemoradiotherapy (RT-100%DeVIC). There was no difference in baseline clinical characteristics between the RT-2/3DeVIC and RT-100%DeVIC groups in clinical practice (data not shown). The median dose of radiotherapy in 150 patients treated with RT-DeVIC in clinical practice was 50 Gy (range, 36 to 60 Gy). In 83% (n = 124) of the patients, the radiotherapy dose was 50 Gy.

The CR and overall response rates (ORRs) of RT-DeVIC in clinical practice were 82% and 89%, respectively. Only two patients received autologous HSCT in the first CR. With a median follow-up of 5.6 years, 5-year OS and PFS of RT-DeVIC in clinical practice were 72% (95% CI, 63% to 78%) and 61% (95% CI, 52% to 69%), respectively (Table 1; Fig 2A). Three-year OS and PFS in 30 patients older than age 65 years were 72% and 68%, respectively, with a median follow-up of 3.2 years (data not shown). In all 169 patients who received RT-DeVIC, regardless of their enrollment in clinical trials, 5-year OS and PFS were 72% and 63%, respectively (Fig 2B).

Toxicity in Patients With Localized ENKL Treated With RT-DeVIC in Clinical Practice

Toxicity data obtained during RT-DeVIC were available in 145 of 150 patients who received this treatment in clinical practice (Appendix Table A2, online only). Seventy-one patients (49%) experienced grade 3 or 4 nonhematologic toxicities. The most common grade 3 or 4 nonhematologic toxicity was mucositis (38%). Grade 3 or 4 infection was observed in 31 patients (22%). All toxicities were transient and resolved.

Data on late toxicity were available in 142 patients (Appendix Table A3, online only). Seventy patients (49%) experienced at least one late toxicity. The most frequent late toxicity was observed in the mucous membranes of the head and neck (n = 30; 21%).

Seven (5%) of 150 patients experienced the following potential second malignancies: pancreatic cancer (n = 1), malignant glioblastoma (n = 1), lung cancer (n = 1), gastric cancer (n = 2), localized diffuse large B-cell lymphoma of the stomach (n = 1), and leiomyosarcoma of the gingiva (n = 1). Six of the seven patients were men and were older than 60 years of age. The remaining patient (a 39-year-old woman), who was diagnosed with leiomyosarcoma of the gingiva in a radiation field of RT-DeVIC, had received consolidative high-dose chemotherapy followed by autologous HSCT. In the other patients, there was no apparent association with irradiated volume.

Clinical Features, Response, and Toxicity in Patients With Advanced ENKL Who Received SMILE Chemotherapy As First-Line Therapy in Practice

Thirteen patients with advanced ENKL received SMILE chemotherapy as first-line therapy in practice (Table 2). Four of

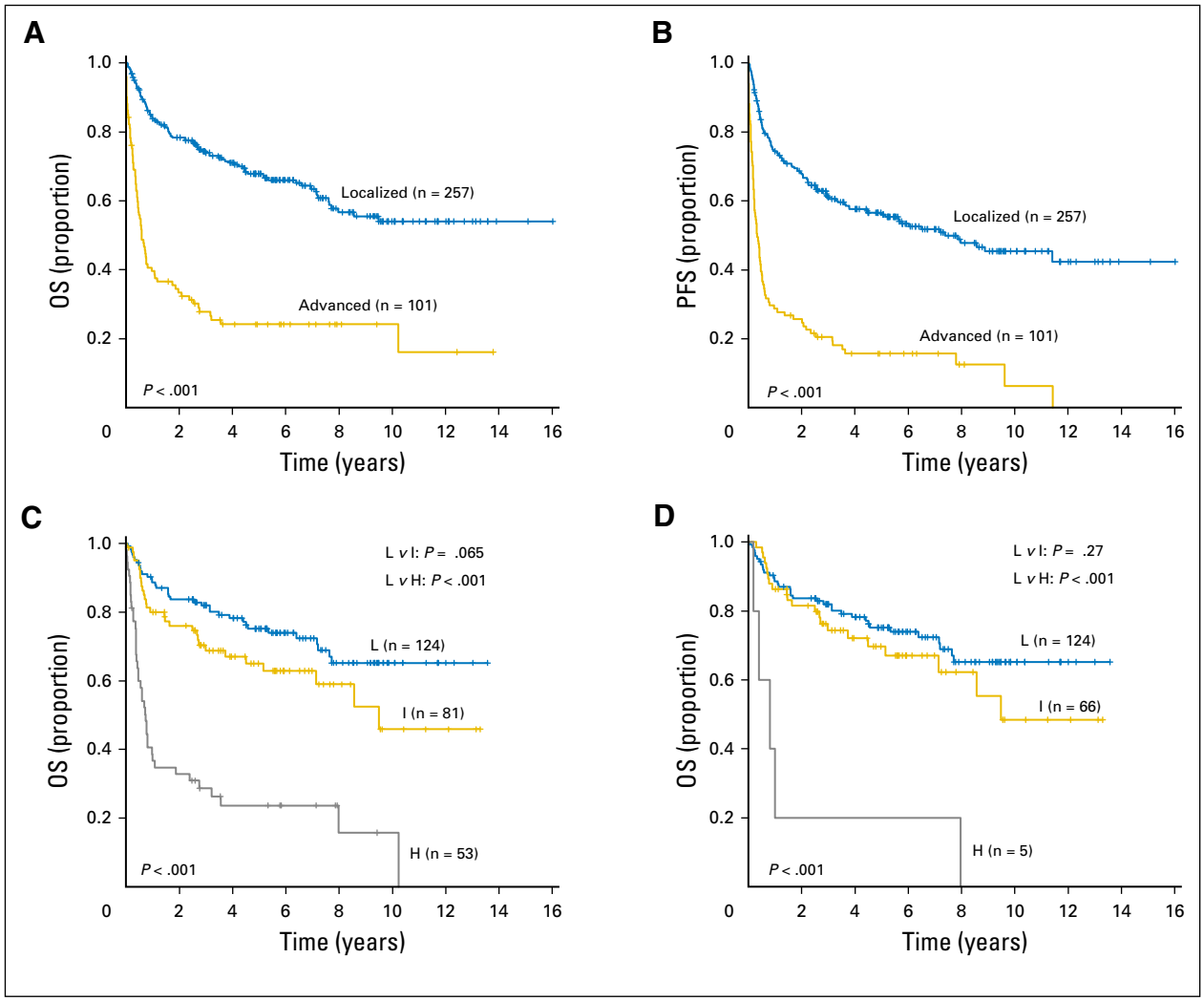

Fig 1. Survival curves of patients with extranodal natural killer (NK)/T-cell lymphoma, nasal type. (A) Overall (OS) and (B) progression-free survival (PFS) of patients with localized and advanced diseases (N = 358). (C) OS of each risk group of the prognostic index of NK lymphoma in patients who received nonanthracycline-based chemotherapy with or without radiotherapy (n = 258). (D) OS of each risk group of the prognostic index of NK lymphoma in patients with localized disease who received nonanthracycline-based chemotherapy with or without radiotherapy (n = 195). H, high; I, intermediate; L, low.

them were older than 65 years of age. The median number of cycles of SMILE was two (range, one to nine). The CR rate and ORR with SMILE chemotherapy were 23% and 62%, respectively. The most frequent nonhematologic grade 3 or greater toxicity was an abnormal liver test (n = 6; 46%). Febrile neutropenia was reported in two patients. Grade 3 allergic reactions to L-asparaginase were observed in two patients. One patient (a 71-year-old man with performance status of 3) died as a result of pancreatitis; this death was considered treatment related. No other nonhematologic grade 3 or greater toxicity was observed.

Analysis of Prognostic Factors Affecting OS and PFS in Patients With ENKL

Because a majority of the patients with localized ENKL received RT-DeVIC and only 13 patients with advanced ENKL received SMILE during the study period, we analyzed prognostic factors only in patients with localized ENKL who received RT-DeVIC. Multivariate analysis in 145 patients with localized ENKL who received RT-DeVIC revealed elevated sIL-2R as an independent prognostic factor for worse OS and PFS (adjusted hazard ratios, 2.28 and 2.46; 95% CI, 1.24 to 4.23 and 1.42 to 4.28; $P = .008$ and .0014, respectively; Table 3). The 5-year OS and PFS rates for patients with localized ENKL with elevated pretreatment sIL-2R levels who received RT-DeVIC were 54% and 44%, respectively (Fig 3).

DISCUSSION

The NKEA study of patients diagnosed with ENKL between 2000 and 2013 in Japan has provided critical evidence contributing to the current and future management of ENKL, revealing favorable OS via RT-DeVIC for localized ENKL in practice, the limited value of PINK for patients with localized ENKL, and the importance of sIL-2R for predicting survival after RT-DeVIC treatment. Our study has validated the results of the JCOG0211 trial[5,6] in terms of

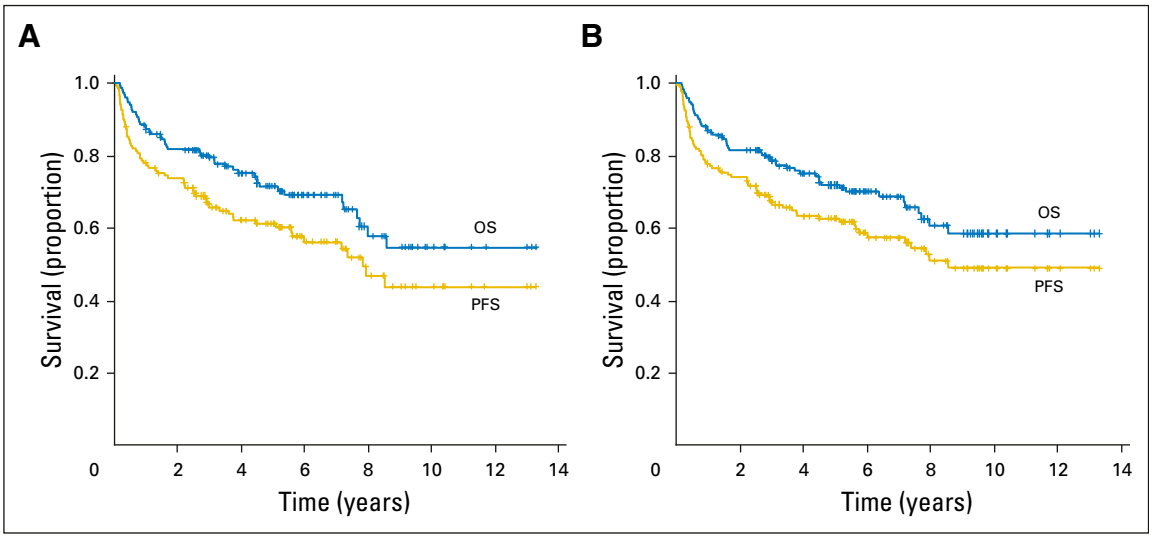

Fig 2. Survival curves of patients with newly diagnosed localized extranodal natural killer/T-cell lymphoma, nasal type, who received radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC). (A) Overall (OS) and progression-free survival (PFS) of patients treated with RT-DeVIC in clinical practice (n = 150). (B) OS and PFS of all patients treated with RT-DeVIC (n = 169).

5-year OS (JCOG0211 *v* patients in practice in our study: 73% *v* 72%, respectively), 5-year PFS (67% *v* 61%), CR rate (75% *v* 82%), and ORR (78% *v* 89%). Only two patients received consolidative autologous HSCT, indicating that consolidative autologous HSCT in the first CR with RT-DeVIC is not necessary. The median age at diagnosis (58 years) was higher than that in previous large studies of ENKL.[21,22,25,33,34] However, age older than 60 years was not associated with inferior survival among patients who received RT-DeVIC.

The acute and late toxicities of RT-DeVIC were consistent with those in JCOG0211.[5,6] Potential second malignancies were observed in 5% of patients at a median follow-up of 5.6 years, and this incidence was not higher than that observed in the normal population in Japan.[35] Only one patient who had received consolidative autologous HSCT experienced an in-field second malignancy. Longer follow-up is needed to properly assess for second malignancies.

A new prognostic model for ENKL, PINK,[22] was successfully validated in the whole ENKL population, but not in those with localized ENKL, in our study. In localized nasal ENKL, age older than 60 years and distant lymph node involvement are effective risk factors in PINK. The lack of prognostic value for age older than 60 years with RT-DeVIC might reflect the absence of a difference in OS between low- and intermediate-risk groups in PINK. A specific predictive factor or model for each treatment might be required for localized ENKL.

The prognostic value of pretreatment sIL-2R in ENKL was proposed in a previous study involving 36 patients.[26] Our study supports this assertion in a cohort of patients with localized ENKL treated uniformly with RT-DeVIC. The 5-year OS and PFS rates were not sufficient in patients with elevated pretreatment sIL-2R (54% and 44%, respectively); therefore, more effective treatments are needed for those patients. Prognostication on the basis of pretreatment sIL-2R levels might be more useful in terms of objective assessment than image-based risk factors, such as local tumor invasiveness[36] or primary tumor invasion,[34] which depend on the quality of the imaging and require careful evaluation by radiologists. Poor performance status, elevated C-reactive protein, and elevated sIL-2R were observed more frequently in advanced ENKL in our study, suggesting that occult involvement may be associated with short survival in localized ENKL.

Table 3. Univariable and Multivariable Analyses of Predictors of OS and PFS in Patients With Localized ENKL Treated With RT-DeVIC (n = 145)

	OS						PFS					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Elevated LDH	1.47	0.80 to 2.72	.22	—	—	—	1.65	0.97 to 2.80	.063	1.21	0.70 to 2.11	.49
ECOG PS > 1	3.86	1.80 to 8.29	< .001	2.24	0.99 to 5.07	.052	3.03	1.43 to 6.40	.0037	1.86	0.83 to 4.16	.13
Regional LN involvement	2.02	1.10 to 3.69	.023	1.81	0.99 to 3.33	.055	1.54	0.88 to 2.70	.13	—	—	—
HgB < 11 g/dL	2.83	1.40 to 5.70	.0037	2.05	0.98 to 4.29	.057	2.14	1.11 to 4.11	.023	1.49	0.74 to 2.99	.26
Elevated CRP	2.09	1.13 to 3.87	.019	1.39	0.71 to 2.72	.34	1.71	1.01 to 2.89	.044	1.12	0.63 to 2.00	.69
Elevated sIL-2R	2.99	1.65 to 5.44	< .001	2.28	1.24 to 4.23	.008	2.95	1.76 to 4.94	< .001	2.46	1.42 to 4.28	.0014

Abbreviations: CRP, C-reactive protein; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ECOG, Eastern Clinical Oncology Group; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; HgB, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; LN, lymph node; OS, overall survival; PFS, progression-free survival; PS; performance status; RT, radiotherapy; sIL-2R, soluble interleukin-2 receptor.

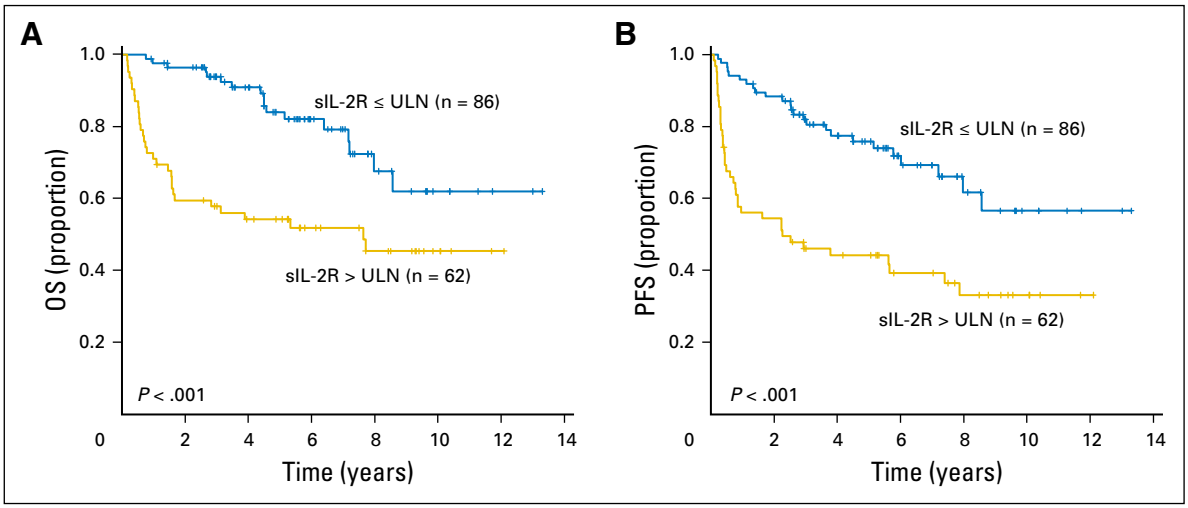

Fig 3. Survival curves of patients with newly diagnosed localized extranodal natural killer/T-cell lymphoma, nasal type, who received radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (n = 148). (A) Overall (OS) and (B) progression-free survival (PFS) according to pretreatment soluble interleukin-2 receptor (sIL-2R) levels. ULN, upper limit of normal.

Only 13% of patients with advanced ENKL in practice received SMILE chemotherapy as first-line treatment. This may have been the result of a community consensus in Japan, as described in Patients and Methods. The therapeutic outcome of SMILE in previous clinical trials was confirmed in our study, as reported in a larger study,[15] although we found a higher incidence of grade 3 or greater abnormal liver test (46%) compared with previous studies of L-asparaginase–containing chemotherapies.[10,12,15] Liver damage should also be considered during SMILE chemotherapy and bone marrow suppression and infection.

Our study has some limitations because of its retrospective nature and the lack of sufficient data for the pretreatment EBV-DNA load. Additional studies and prospective evaluations, particularly regarding the prognostic significance of sIL-2R, are needed to confirm our results. However, the cooperation of hemato-oncologists and radiation oncologists reduced potential biases in patient selection and provided adequate clinical information.

In conclusion, the results of our study have elucidated the current condition of the treatment of ENKL in Japan and validated the clinical usefulness of RT-DeVIC with a large number of patients. More effective treatment approaches are required for localized ENKL exhibiting elevated pretreatment sIL-2R.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Conception and design: Motoko Yamaguchi, Ritsuro Suzuki, Masahiko Oguchi
Financial support: Motoko Yamaguchi, Ritsuro Suzuki
Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: Motoko Yamaguchi, Ritsuro Suzuki, Masahiko Oguchi, Naoko Asano
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Motoko Yamaguchi, **Kana Miyazaki**, **Noriko Ii**, and **Naoyuki Katayama**, Mie University Graduate School of Medicine, Tsu; **Ritsuro Suzuki**, Shimane University Hospital, Izumo; **Masahiko Oguchi** and **Kyoko Ueda**, Cancer Institute Hospital of the Japanese Foundation for Cancer Research; **Yukio Kobayashi** and **Jun Itami**, National Cancer Center Hospital; **Bungo Saito**, Showa University School of Medicine, Tokyo; **Naoko Asano**, Nagano Prefectural Suzaka Hospital, Suzaka; **Jun Amaki** and **Takeshi Akiba**, Tokai University School of Medicine, Isehara; **Takeshi Maeda** and **Satoshi Itasaka**, Kurashiki Central Hospital, Kurashiki; **Nobuko Kubota** and **Yoshihiro Saito**, Saitama Cancer Center, Ina; **Naoto Tomita**, Yokohama City University Graduate School of Medicine, Yokohama; **Nodoka Sekiguchi**, Shinshu University School of Medicine, Matsumoto; **Jun Takizawa**, Niigata University Faculty of Medicine, Niigata; **Tohru Murayama**, Hyogo Cancer Center, Akashi; **Toshihiko Ando**, Saga University, Saga; **Hideho Wada**, Kawasaki Medical School, Kurashiki; **Rie Hyo**, Nagoya University Graduate School of Medicine, Nagoya; **Yasuo Ejima**, Kobe University, Kobe; and **Masatoshi Hasegawa**, Nara Medical University, Kashihara, Japan.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatments and Outcomes of Patients With Extranodal Natural Killer/T-Cell Lymphoma Diagnosed Between 2000 and 2013: A Cooperative Study in Japan

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Motoko Yamaguchi
Honoraria: Chugai Pharmaceutical, Kyowa Hakko Kirin, Eisai, Zenyaku Kogyo, Takeda Pharmaceuticals

Ritsuro Suzuki
Honoraria: Kyowa Hakko Kirin, Chugai Pharmaceutical, Mochida Pharmaceutical, Novartis, Shionogi, Takeda Pharmaceuticals, Meiji Seika Kaisha, Merck Sharpe & Dohme, Otsuka, Sawai Pharmaceutical, Celgene, Bristol-Myers Squibb, Sumitomo Dainippon
Consulting or Advisory Role: Gilead Sciences, Mundipharma, Jazz Pharmaceuticals

Masahiko Oguchi
No relationship to disclose

Naoko Asano
Honoraria: Janssen Pharmaceuticals, Chugai Pharmaceutical, Kyowa Hakko Kirin

Jun Amaki
No relationship to disclose

Takeshi Akiba
No relationship to disclose

Takeshi Maeda
No relationship to disclose

Satoshi Itasaka
No relationship to disclose

Nobuko Kubota
No relationship to disclose

Yoshihiro Saito
No relationship to disclose

Yukio Kobayashi
Consulting or Advisory Role: Pfizer, Daiichi Sankyo, Celgene
Research Funding: Celgene (Inst), Novartis (Inst), Pfizer (Inst), Boehringer Ingelheim (Inst), Amgen (Inst), Astellas Pharma (Inst)
Travel, Accommodations, Expenses: Pfizer, Daiichi Sankyo

Jun Itami
Travel, Accommodations, Expenses: Kay's Japan

Kyoko Ueda
Honoraria: Novartis, Eisai, GlaxoSmithKline, Bristol-Myers Squibb

Kana Miyazaki
Honoraria: Chugai Pharmaceutical, Takeda Pharmaceuticals, Eisai

Noriko Ii
No relationship to disclose

Naoto Tomita
No relationship to disclose

Nodoka Sekiguchi
No relationship to disclose

Jun Takizawa
Honoraria: Janssen Pharmaceuticals, Kyowa Hakko Kirin, Chugai Pharmaceutical, Celgene, Takeda Pharmaceuticals, Sumitomo Dainippon
Research Funding: Kyowa Hakko Kirin (Inst), Chugai Pharmaceutical (Inst), Takeda Pharmaceuticals (Inst), Sumitomo Dainippon (Inst), Teijin Pharma (Inst)

Bungo Saito
No relationship to disclose

Tohru Murayama
Honoraria: Kyowa Hakko Kirin, Eisai

Toshihiko Ando
No relationship to disclose

Hideho Wada
No relationship to disclose

Rie Hyo
No relationship to disclose

Yasuo Ejima
No relationship to disclose

Masatoshi Hasegawa
Honoraria: Elekta, Chugai Pharmaceutical, Daiichi Sankyo, Novartis, Otsuka

Naoyuki Katayama
Honoraria: Sumitomo Dainippon, Bristol-Myers Squibb, Nippon Shinyaku, Chugai Pharmaceutical, Kyowa Hakko Kirin, Pfizer, Taisho Toyama Pharmaceutical, Celgene, Alexion Pharmaceuticals, Shire, Takeda Pharmaceuticals, Astellas Pharma, Shionogi, Daiichi Sankyo, Eisai
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Table A1. Treatments According to Treatment Eras Among Patients With Newly Diagnosed ENKL Treated in Clinical Practice (n = 332)

Treatment	First Era (2000-2004) (n = 53)		Second Era (2005-2009) (n = 108)		Third Era (2010-2013) (n = 77)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Localized ENKL (n = 238)						
RT-DeVIC	17	32	70	65	63	82
RT–CHOP-like chemotherapy	11	21	3	3	0	0
Sequential chemoradiotherapy	15	28	18	17	6	8
Chemotherapy alone	5	9	4	4	2	3
RT alone	5	9	11	10	6	8
None	0	0	2	2	0	0
Advanced ENKL (n = 94)						
L-asparaginase–containing chemotherapy	4	17	6	18	12	32
DeVIC-like chemotherapy	6	25	15	45	13	35
CHOP-like chemotherapy	10	42	9	27	7	19
RT alone	3	13	0	0	0	0
None	1	4	3	9	5	14

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; RT, radiotherapy.

Table A2. AEs During RT-DeVIC Therapy in Patients With Localized Disease Treated in Clinical Practice (n = 145)

AE	Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%
Mucositis, oral	53	37	2	1
Febrile neutropenia	24	17	0	0
Infection other than febrile neutropenia	6	4	1	1
Appetite loss	1	1	1	1
Nausea	1	1	0	0
Salivary duct inflammation	1	1	0	0
Ileus	1	1	0	0
Sinus bradycardia	1	1	0	0
Skin and subcutaneous disorders	1	1	0	0

Abbreviations: AE, adverse event; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; RT, radiotherapy.

Table A3. Late AEs in Patients With Localized Disease Treated With RT-DeVIC in Clinical Practice Who Survived ≥ 90 Days After Completion of RT (n = 142)

AE	Grade 1		Grade 2		Grade 3		Grade 4		Grade Unknown	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Mucous membrane (head and neck)	19	13	8	6	1	1	2*	1	0	0
Skin and subcutaneous	8	6	3	2	1	1	2*	1	2	1
Eye	7	5	5†	4	3‡	2	0	0	2§	1
Salivary gland	9	6	10	7	0	0	0	0	7	5

Abbreviations: AE, adverse event; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; RT, radiotherapy.
*Related to lymphomatous involvement.
†Cataract (n = 4), retinal detachment (n = 1).
‡Cataract (n = 2), panophthalmitis (n = 1).
§Cataract and retinopathy (n = 2).

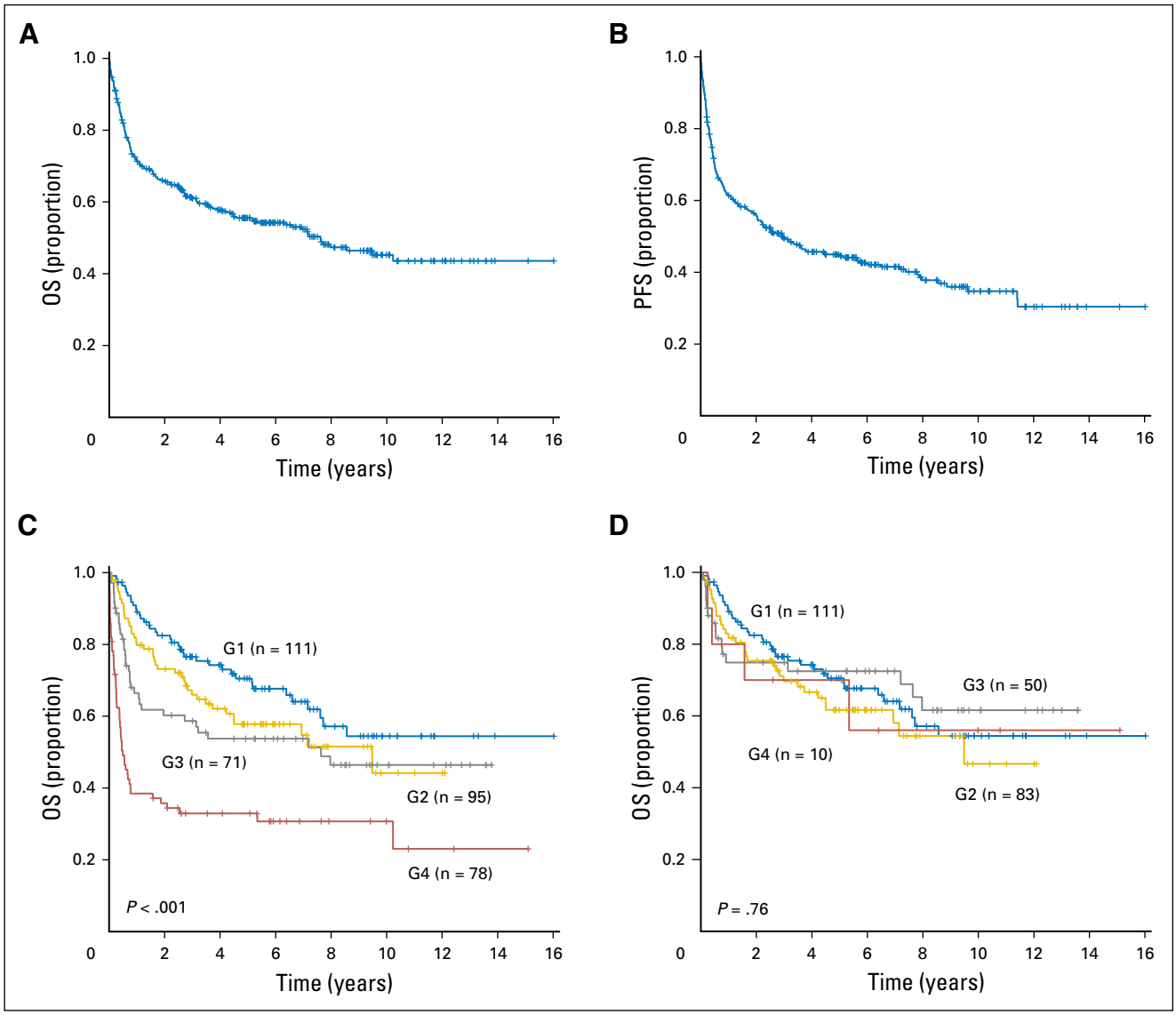

Fig A1. Survival curves of patients with extranodal natural killer (NK)/T-cell lymphoma, nasal type. (A) Overall (OS) and (B) progression-free survival (PFS) of all patients (N = 358). (C) OS of each risk group (G) of the NK/T-cell lymphoma prognostic index in all evaluable patients (n = 355). (D) OS of each risk group of the NK/T-cell lymphoma prognostic index in patients with localized disease (n = 254).

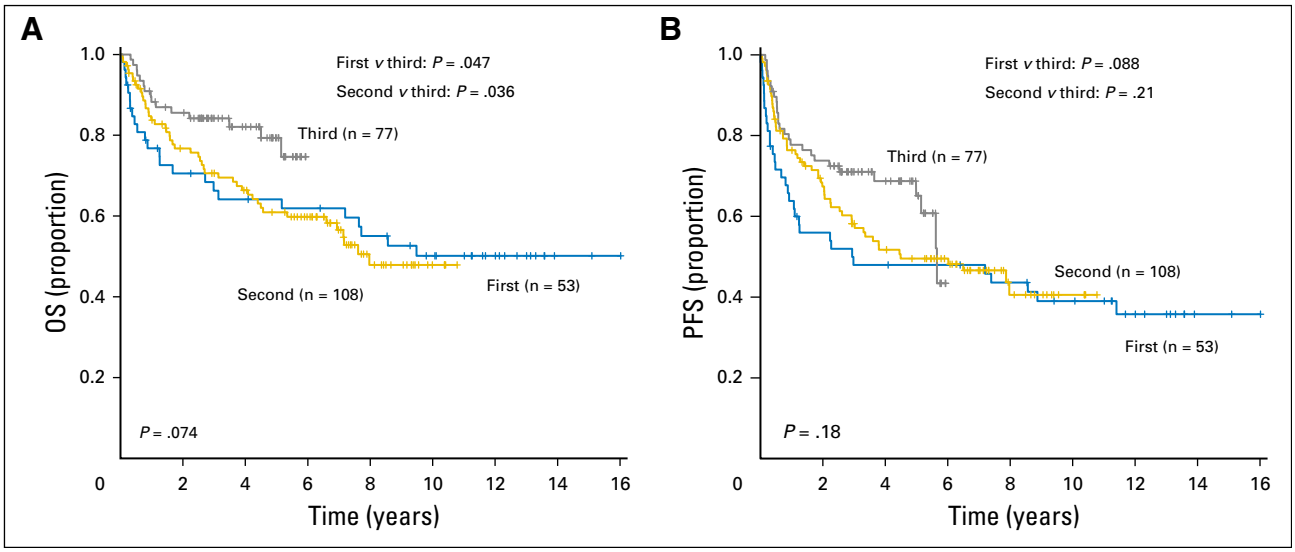

Fig A2. Survival curves of patients with localized extranodal natural killer/T-cell lymphoma, nasal type, who received first-line treatment in clinical practice (n = 238). (A) Overall (OS) and (B) progression-free survival (PFS) according to treatment eras. The median follow-up time for surviving patients in the third era was 4.3 years.