A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis

Seok Jin Kim, Dok Hyun Yoon, Arnaud Jaccard, Wee Joo Chng, Soon Thye Lim, Huangming Hong, Yong Park, Kian Meng Chang, Yoshinobu Maeda, Fumihiro Ishida, Dong-Yeop Shin, Jin Seok Kim, Seong Hyun Jeong, Deok-Hwan Yang, Jae-Cheol Jo, Gyeong-Won Lee, Chul Won Choi, Won-Sik Lee, Tsai-Yun Chen, Kiyeun Kim, Sin-Ho Jung, Tohru Murayama, Yasuhiro Oki, Ranjana Advani, Francesco d'Amore, Norbert Schmitz, Cheolwon Suh, Ritsuro Suzuki, Yok Lam Kwong, Tong-Yu Lin, Won Seog Kim

Summary

Background The clinical outcome of extranodal natural killer T-cell lymphoma (ENKTL) has improved substantially as a result of new treatment strategies with non-anthracycline-based chemotherapies and upfront use of concurrent chemoradiotherapy or radiotherapy. A new prognostic model based on the outcomes obtained with these contemporary treatments was warranted.

Methods We did a retrospective study of patients with newly diagnosed ENKTL without any previous treatment history for the disease who were given non-anthracycline-based chemotherapies with or without upfront concurrent chemoradiotherapy or radiotherapy with curative intent. A prognostic model to predict overall survival and progression-free survival on the basis of pretreatment clinical and laboratory characteristics was developed by filling a multivariable model on the basis of the dataset with complete data for the selected risk factors for an unbiased prediction model. The final model was applied to the patients who had complete data for the selected risk factors. We did a validation analysis of the prognostic model in an independent cohort.

Findings We did multivariate analyses of 527 patients who were included from 38 hospitals in 11 countries in the training cohort. Analyses showed that age greater than 60 years, stage III or IV disease, distant lymph-node involvement, and non-nasal type disease were significantly associated with overall survival and progression-free survival. We used these data as the basis for the prognostic index of natural killer lymphoma (PINK), in which patients are stratified into low-risk (no risk factors), intermediate-risk (one risk factor), or high-risk (two or more risk factors) groups, which were associated with 3-year overall survival of 81% (95% CI 75–86), 62% (55–70), and 25% (20–34), respectively. In the 328 patients with data for Epstein-Barr virus DNA, a detectable viral DNA titre was an independent prognostic factor for overall survival. When these data were added to PINK as the basis for another prognostic index (PINK-E)—which had similar low-risk (zero or one risk factor), intermediate-risk (two risk factors), and high-risk (three or more risk factors) categories—significant associations with overall survival were noted (81% [95% CI 75–87%], 55% (44–66), and 28% (18–40%), respectively). These results were validated and confirmed in an independent cohort, although the PINK-E model was only significantly associated with the high-risk group compared with the low-risk group.

Interpretation PINK and PINK-E are new prognostic models that can be used to develop risk-adapted treatment approaches for patients with ENKTL being treated in the contemporary era of non-anthracycline-based therapy.

Funding Samsung Biomedical Research Institute.

Introduction

Extranodal natural killer T-cell lymphoma (ENKTL) is an uncommon subtype of non-Hodgkin lymphoma that can be discriminated from other subtypes on the basis of its unique characteristics, such as predominant involvement of the nasal cavity and nasopharynx, high prevalence particularly in east Asia and South America, and invariable infection of lymphoma cells with the Epstein-Barr virus.[1] Because natural killer cells express high concentrations of the multidrug-resistant P-glycoprotein, which results in resistance to anthracycline, patients with ENKTL have poor responses to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like regimens.[2–4] However, the development of chemotherapy regimens that incorporate etoposide, methotrexate, ifosfamide, platinum, and L-asparaginase has improved outcomes.[5–7] Upfront use of radiotherapy for localised disease has also improved outcomes because of improved local control. Thus, concurrent chemoradiotherapy followed by non-anthracycline-based chemotherapy is reportedly associated with better outcomes than is conventional chemotherapy (eg, CHOP followed by radiotherapy) in patients with localised nasal involvement.[8–10] Nevertheless, treatment is still unsuccessful in a substantial proportion of patients with ENKTL because of relapse and treatment-related mortality.

Lancet Oncol 2016

Published Online
February 9, 2016
http://dx.doi.org/10.1016/S1470-2045(15)00533-1

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(16)00007-3

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (Prof S Jin Kim MD, Prof W Seog Kim MD); **University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea** (D Hyun Yoon MD, Prof C Suh MD); **Centre Hospitalier Universitaire Limoges, Limoges, France** (A Jaccard MD); **National University Cancer Institute, Singapore, Singapore** (W Joo Chng MD); **National Cancer Centre, Singapore, Singapore** (S Thye Lim MD); **Sun Yat-sen University Cancer Center, Guangzhou, China** (H Hong MD, Prof T-Y Lin MD); **Korea University Anam Hospital, Seoul, South Korea** (Y Park MD); **Ampang Hospital, Ampang, Malaysia** (K Meng Chang MD); **Okayama University Hospital, Okayama, Japan** (Y Maeda MD); **Shinshu University, Matsumoto, Japan** (Prof F Ishida MD); **Korea Cancer Center Hospital, Seoul, South Korea** (D-Y Shin MD); **Yonsei University College of Medicine, Seoul, South Korea** (J Seok Kim MD); **Ajou University School of Medicine, Suwon, South Korea** (S Hyun Jeong MD); **Chonnam National University Hwasun Hospital, Gwangju, South Korea** (D-H Yang MD); **University of Ulsan College of Medicine, Ulsan, South Korea** (J-C Jo MD); **Gyeongsang National University Hospital, Gyeongsang National University School of Medicine,**

Jinju, South Korea (G-W Lee MD)**; Korea University Guro Hospital, Seoul, South Korea** (Prof C Won Choi MD)**; Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea** (W-S Lee MD)**; National Cheng Kung University Hospital, Tainan, Taiwan** (T-Y Chen MD)**; Biostatistics and Clinical Epidemiology Center, Samsung Medical Center, Seoul, South Korea** (K Kim, S-H Jung PhD)**; Hyogo Cancer Center, Akashi, Hyogo, Japan** (T Murayama MD)**; University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Y Oki MD)**; Stanford University, Stanford, CA, USA** (R Advani MD)**; Aarhus University Hospital, Aarhus, Denmark** (Prof F d'Amore MD)**; Asklepios Hospital St Georg, Hamburg, Germany** (Prof N Schmitz MD)**; Shimane University, Shimane, Japan** (R Suzuki MD)**; and Queen Mary Hospital, Pokfulam Road, Hong Kong, China** (Prof Y Lam Kwong MD)

Correspondence to: Prof Won Seog Kim, Division of Hematology–Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, South Korea
wskimsmc@skku.edu

Research in context

Evidence before this study

We searched PubMed with the search terms "extranodal NK/T-cell lymphoma" and "prognostic model" for reports published in English between Jan 1, 2000, and Dec 31, 2014. Our search returned more than 60 results. However, most studies included patients who were given anthracycline-containing chemotherapy. Conventional prognostic indicators, including the International Prognostic Index and the Korean Prognostic Index, which are useful for extranodal natural killer T-cell lymphoma (ENKTL), were devised on the basis of use of anthracycline-containing regimens. Thus, they might not be relevant to the contemporary era of non-anthracycline-based chemotherapy. So far, no prognostic models based on pretreatment characteristics of patients given non-anthracycline-based therapy have been developed. There is thus an urgent need to define valid prognostic indicators. Additionally, because of the rarity of ENKTL, previous studies were variable in size but generally small (between around 50 and 200 patients), and, although several prognostic models were proposed previously, none was validated in an independent cohort.

Added value of this study

We developed a prognostic model to predict overall and progression-free survival in patients with newly diagnosed ENKTL on the basis of data from the largest study population published so far. We also validated the model in an independent cohort. Our study provides mature data for the largest registered cohort, and is the only study in which a prognostic model for patients with ENKTL treated with non-anthracycline-based treatment has been developed. A substantial proportion of patients relapse, so identification of patients who will not respond well to treatment is important to improve this treatment outcome. Our model might help to identify patients who could need additional treatment.

Implications of all the available evidence

We propose a new prognostic index for ENKTL, the prognostic index for natural killer cell lymphoma (PINK), which includes four independent risk factors: age greater than 60 years, stage III/IV disease, distant lymph-node involvement, and non-nasal type disease. In PINK, patients are stratified into low-risk (no risk factors), intermediate-risk (one risk factor), and high-risk (≥2 risk factor) groups. Among patients with data for peripheral blood Epstein-Barr virus DNA status, detectable viral titres in the blood were also independently prognostic for overall and progression-free survival. Thus, when we added Epstein-Barr virus DNA data to the PINK model (PINK-E) with similar risk classification—low risk (no or one risk factor), intermediate risk (two risk factors), and high risk (≥3 risk factors)—we noted significant associations with overall and progression-free survival. The prognostic value of the models was confirmed in the validation cohort. We think that PINK and PINK-E could be used to develop risk-adapted treatment approaches for patients with ENKTL being treated in the contemporary era of non-anthracycline-based therapy.

Thus, patients should be stratified such that treatment intensity can be modified according to the each patient's individual risk. Although previous prognostic factors and prognostic models for ENKTL have been proposed—such as the International Prognostic Index from the International Peripheral T-Cell Lymphoma Project,[11] the Korean Prognostic Index from a Korean multicentre study,[12] and the prognostic nomogram from a Chinese multicentre study[13]—they were all developed on the basis of cohorts of patients who were primarily treated with CHOP or CHOP-like regimens. Thus, a new prognostic model based on non-anthracycline-based chemotherapy is needed to predict outcomes in ENKTL. In this study, we established a prognostic index for ENKTL by analysing the pretreatment characteristics and survival outcomes of patients with this disease, and validated our prognostic index in an independent cohort.

Methods

Study design and participants

We did a retrospective study of patients who were diagnosed with ENKTL between 1997 and 2013 in 38 hospitals in 11 countries (China [Hong Kong], Denmark, France, Germany, Japan, Malaysia, Singapore, South Korea, Sweden, Taiwan, and the USA) that participated in the International NK/T-Cell Lymphoma Project, to establish the training cohort. All investigators had expertise in the treatment of lymphomas, and each participating hospital had pathologists experienced in lymphoma pathology. Our inclusion criteria were presence of newly diagnosed ENKTL without any previous treatment history for ENKTL, and treatment with non-anthracycline-based chemotherapy with or without radiotherapy, with curative intent. Because the study was retrospective and ENKTL could occur in very old patients with comorbidities, we did not limit eligibility by age or the presence of comorbidities. Thus, patients who received any type of non-anthracycline-based chemotherapy regimen as their first treatment were included. We also included patients who received upfront radiotherapy or concurrent chemoradiotherapy with weekly cisplatin administration, even if they did not receive chemotherapy after radiotherapy because their treatment was not based on CHOP treatment strategy.

Nasal and non-nasal types were defined on the basis of involvement of the nasal area.[14] If there was nasal or paranasal involvement—as assessed by physical examination and imaging, including CT, MRI, and PET—the case was designated as nasal type, irrespective of whether other extranodal areas were involved. The involvement of lymph nodes and extranodal sites was determined according to the results of imaging studies or biopsy, or both.

The validation cohort was retrospectively recruited from nine hospitals—Sun Yat-sen University Hospital in China and eight hospitals in South Korea.

After the development of a prognostic model for ENKTL, we validated the results obtained in the training cohort in an independent cohort of patients from the Sun Yat-sen University Hospital, China, and at eight hospitals in South Korea who were not included in the training cohort. We also validated a second prognostic model that included Epstein-Barr virus DNA as a parameter in this validation cohort.

The Institutional Review Board of the Samsung Medical Center (Seoul, South Korea) reviewed and approved all aspects of this study and waived the requirement for signed informed consent for the study, because of its retrospective nature (2013-03-071). The project was also approved by the institutional review board of each participating institution. Because the validation cohort was based on retrospective data, the need for informed consent was waived.

Procedures

Data were gathered at each site by a trained local coordinator or doctor after the review of medical records. The case report forms included clinical and laboratory data collected at diagnosis, such as age, sex, performance status, Ann Arbor stage, number of extranodal sites involved, serum lactate dehydrogenase concentrations, and involvement of the nasal cavity or nasopharynx, regional or distant lymph nodes, or extranasal sites. Events for overall survival and progression-free survival were based on the data provided by each institute without additional central review for death and disease progression or relapse. After we obtained case report forms from participating institutes, we checked whether cases satisfied the inclusion criteria. We excluded patients who were initially given anthracycline-based chemotherapy, such as CHOP, and those with subtypes of non-Hodgkin lymphoma other than ENKTL. Designated pathologists reviewed pathology data according to the 2008 WHO classification criteria.[15] Cases for which follow-up data were incomplete—ie, last follow-up date was not provided or pretreatment characteristics for the international or Korean prognostic indices were missing—were also excluded.

Because no staging system specific for ENKTL exists, we used the Ann Arbor staging system, which was also used in previous studies of ENKTL.[16–18] The definition of stage IV ENKTL included diffuse involvement of one or more extranodal organs, including the liver and bone marrow. The presence of more than two separate lesions in the same extranodal organ and bilateral extranodal involvement (eg, lungs, adrenal glands) were also sufficient to class disease as stage IV. Lymph-node involvement was classified as regional (ie, invasion of a lymph-node region corresponding to primary extranodal sites) or distant (ie, the presence of enlarged lymph nodes beyond regional lymph nodes). Patients could be subdivided within the same stage on the basis of distant lymph-node involvement.

Because we used heterogeneous methods of quantitative PCR to detect circulating Epstein-Barr virus DNA in the plasma or whole blood, a cutoff for a high titre was difficult to establish. Thus, any detectable concentration of Epstein-Barr virus DNA was defined as positive.

We collected data for overall survival, to compare overall survival outcomes with all pretreatment characteristics in our model. We defined overall survival as the time from the initial diagnosis to the last follow-up date or the date of death from any cause. The last follow-up date was based on the case report forms provided by each participating investigator on the basis of medical records at each institution. If patients were alive at the last contact and were lost during follow-up, they were censored at the date of the last confirmed contact. We also collected data for progression-free survival, and compared progression-free survival outcomes with all clinical characteristics in our model. We defined progression-free survival as the time from the initial diagnosis to the date of relapse, progression, last follow-up, or any kind of death. The occurrence of relapse or disease progression was defined as the development of a new lesion or progression of the lesion, as assessed by physical or radiographical examination at each participating institute. Central review of disease progression or relapse was not done because of the retrospective nature of this study. However, because all participating investigators were experts in treatment of lymphomas, we accepted the diagnoses made at each participating institute. In patients with several recurrences, we used the first relapse or progression as the event to calculate progression-free survival. The response to primary treatment was based on reports from each participating institution and was determined according to the response criteria that were relevant at the time of assessment.

All data elements—age, sex, performance status, serum lactate dehydrogenase, stage, number of sites, extranodal involvement, non-nasal type disease, B symptoms, bone-marrow involvement, serum creatinine, serum albumin, haemoglobin, lymphocyte count, platelet count, and involvement of liver, gastrointestinal tract, skin, spleen, lung, and bone—were used as parameters for the development of a prognostic model on the basis of samples from patients in 11 countries. The presence of a detectable concentration of Epstein-Barr virus DNA in the blood at diagnosis was also included as a parameter, if these data were available, and used to develop prognostic models including Epstein-Barr virus DNA. Although we also gathered results of immunohistochemistry analyses, we did not include the degree of tissue expression of Ki-67 because the available data were not sufficient.

Statistical analysis

See Online for appendix

We used Fisher's exact test to identify associations between categorical variables, the Kaplan-Meier method to estimate overall and progression-free survival, and the log-rank test to compare results. Median duration of follow-up was based on the potential duration, which was estimated by the reverse Kaplan-Meier method, with death events censored as previously reported.[19] We used internal data to develop Cox prediction models for overall and progression-free survival. 0·76–3·4% of data were missing for different risk factors. The missing data were imputed: we used means for continuous variables and modes for categorical variables. We then used the imputed data to select risk factors by applying the forward stepwise method with a selection criterion of a two-sided p value of less than 0·05.

In retrospective studies, univariate p values can be very misleading because of the correlation among different factors, so we did not use results of univariate analysis for model selection. Univariate analysis for survival outcome was done by the log-rank test as mentioned above. We fitted a multivariable model on the basis of the dataset with complete data for the selected risk factors for an unbiased prediction model. The final model was applied to the patients in the training cohort dataset who had complete data for the selected risk factors. Model fitting including significant factors is a standard practice to construct a prediction model. Validation with an independent dataset can replace calibration and discrimination.[20,21] Although we did not intend to derive a predictive index to predict the response to a specific chemotherapy, we did an exploratory analysis of whether our indices predict the response of chemotherapy that patients had received during the course of treatment (appendix). We used SAS (version 9.4) for all statistical analyses.

Covariates that potentially affected overall survival and progression-free survival were included in the establishment of the prognostic model. Age was separated into two groups (>60 years *vs* ≤60 years), because 60 years is a well known cutoff in prognostic models for patients with lymphoma, such as the International Prognostic Index.[22] We wanted to develop a prognostic model that clinicians could easily remember and use in their practice, so we also separated other continuous variables—such as albumin and haemoglobin concentrations and lymphocyte and platelet counts—into low and high groups on the basis of the usual cutoff value for the normal range, as described in previous studies in which the prognostic value of these parameters in patients with ENKTL was reported.[16,23,24] This study is registered at ClinicalTrials.gov, number NCT02386813.

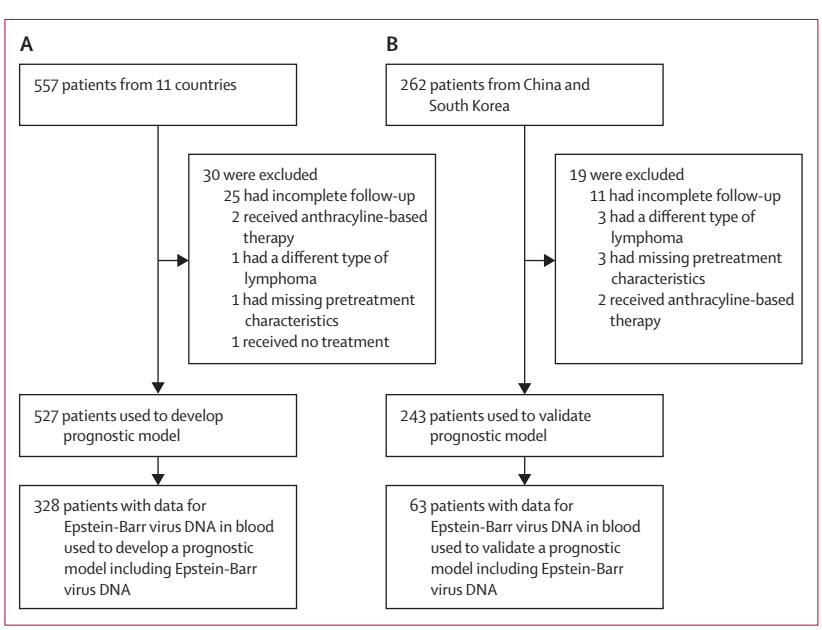

Figure 1: **Flow chart for establishment of the training (A) and validation (B) cohorts**

Role of the funding source

This study was supported by a grant from the Samsung Biomedical Research Institute (GFO1150161). The funding source did not have access to the raw data and had no role in study design; data collection, analysis, or interpretation; or writing of the report. The corresponding author had full access to all the data and final responsibility for the decision to submit the Article for publication.

Results

Complete data were available for 557 patients, 30 of whom were ineligible for inclusion in the training cohort. Thus, the final analyses included 527 patients in the training cohort (figure 1). 328 (59%) of 527 patients had available data for Epstein-Barr viral DNA in blood at diagnosis and were used to develop a model that included Epstein-Barr virus as a risk factor. 506 (96%) of the included patients received their diagnosis between 2004 and 2013; for the other 21 patients, ENKTL was diagnosed and mainly treated with radiotherapy or non-anthracycline-based chemotherapy regimens, or both, between 1997 and 2003. The training cohort was derived mainly from Asian countries (475 patients from South Korea [n=317], Japan [n=50], China [Hong Kong, n=37], Singapore [n=50], Taiwan [n=15], and Malaysia [n=6]); the other patients were from western countries (52 patients, France [n=31], Germany [n=10], Denmark [n=6], the USA [n=4], and Sweden [n=1]). Patients from China (n=160) and South Korea (n=102) were included in the validation cohort. Patients were mainly of Asian ethnic origin (470 [89%] of 527); 43 (8%) were white, and the remaining 14 (3%) consisted of other ethnic groups. Median age at diagnosis was 52 years (range 14–86). 361 (69%) of 527 patients were younger than 60 years (table 1), and six (1%) were younger than 20 years.

	n (%)
Age	
≤60 years	361 (69%)
>60 years	166 (31%)
Sex	
Male	341 (65%)
Female	186 (35%)
B symptoms	
Absence	332 (63%)
Presence	195 (37%)
ECOG performance status	
0/1	461 (87%)
≥2	66 (13%)
Stage	
I	228 (43%)
II	116 (22%)
III	16 (3%)
IV	167 (32%)
Lymph-node involvement	
None	243 (46%)
Regional	198 (38%)
Distant	86 (16%)
Non-nasal type	
No	421 (80%)
Yes	106 (20%)
Extranodal involvement (n)	
0 or 1	340 (65%)
≥2	187 (35%)
Bone-marrow involvement	
No	444 (84%)
Yes	83 (16%)
Site of tumour	
Liver	39 (7%)
Gastrointestinal tract	33 (6%)
Skin	62 (12%)
Spleen	35 (7%)
Lung	29 (6%)
Bone	31 (6%)
Others*	90 (17%)
Epstein-Barr virus DNA in blood	
Detectable	189 (36%)
Non-detectable	139 (26%)
Unknown	199 (38%)
Serum lactate dehydrogenase	
Normal†	306 (58%)
Increased	221 (42%)

(Table 1 continues in next column)

(Continued from previous column)

	n (%)
Serum albumin concentration	
≤35 g/L	175 (33%)
>35 g/L	336 (64%)
Unknown	16 (3%)
Serum creatinine	
Normal†	493 (94%)
Abnormal	30 (6%)
Unknown	4 (1%)
Lymphocyte count	
≤1000 per mm³	144 (27%)
>1000 per mm³	365 (69%)
Unknown	18 (3%)
Haemoglobin concentration	
≤100 g/L	66 (13%)
>100 g/L	456 (87%)
Unknown	5 (1%)
Platelet count	
≤75 000 per mm³	43 (8%)
>75 000 per mm³	479 (91%)
Unknown	5 (1%)
Primary treatment	
Chemotherapy	202 (38%)
Concurrent chemoradiotherapy followed by chemotherapy	193 (37%)
Chemotherapy followed by radiotherapy	79 (15%)
Concurrent chemoradiotherapy	24 (5%)
Radiotherapy	20 (4%)
Radiotherapy followed by chemotherapy	9 (2%)
Chemotherapy regimen	
SMILE	134 (25%)
DeVIC	39 (7%)
VIPD	60 (11%)
VIDL	77 (15%)
MIDLE	20 (4%)
IMEP	47 (9%)
ESHAP	6 (1%)
ICE	30 (6%)
Various gemcitabine-containing regimens†	10 (2%)
L-asparaginase-containing regimens†	29 (6%)
Non-anthracycline-based regimens†	31 (6%)

Because of rounding, some percentages total more than 100%. ECOG=Eastern Cooperative Oncology Group. SMILE=corticosteroid, methotrexate, ifosfamide, L-asparaginase, and etoposide. DeVIC=dexamethasone, etoposide, ifosfamide, and carboplatin. VIPD= etoposide, ifosfamide, cisplatin, and dexamethasone. VIDL=etoposide, ifosfamide, dexamethasone, and L-asparaginase. MIDLE=methotrexate, ifosfamide, dexamethasone, L-asparaginase, and etoposide. IMEP=ifosfamide, methotrexate, etoposide, and prednisolone. ESHAP=etoposide, corticosteroid, cytarabine, and cisplatin. ICE=ifosfamide, carboplatin, and etoposide. *Includes adrenal gland (16), kidneys (six), orbit (seven), parotid gland (three), pleura (11), pericardium (two), tongue (two), tonsil (15), larynx (two), testis (nine), breast (three), ovary (one), pancreas (three), gallbladder (one), soft tissue (eight), and thyroid (one). †Excludes regimens previously listed separately.†Definition of normal varied according to institutional definition.

Table 1: **Characteristics of patients in the training cohort**

Most patients had stage I or II disease, and 421 (80%) of 527 patients had nasal type ENKTL (table 1). Of the 167 patients with stage IV disease involving extranodal sites, such as the liver, skin, and bone marrow, 101 (60%) of 167 also had nasal lesions. The presence of Epstein-Barr virus DNA was measured in the plasma (n=43) or whole

	All patients (n=527)						Patients with data for Epstein-Barr virus in DNA (n=328)					
	Overall survival			Progression-free survival			Overall survival			Progression-free survival		
	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio
Age >60 years	0·774	<0·0001	2·168	0·760	<0·0001	2·138	0·820	<0·0001	2·271	0·762	<0·0001	2·142
ECOG performance status ≥2	0·527	0·003	1·694	..	..	..				0·583	0·004	1·792
Stage III–IV	0·942	<0·0001	2·565	0·722	<0·0001	2·058	0·906	<0·0001	2·475	0·839	<0·0001	2·315
Non-nasal type	0·662	<0·0001	1·939	0·692	<0·0001	1·998	0·495	0·018	1·640	0·536	0·005	1·709
Distant lymph-node involvement	0·547	0·002	1·727	0·527	0·002	1·693	0·845	<0·0001	2·329	0·507	0·024	1·660
Serum albumin ≤35 g/L	0·530	0·001	1·699	0·400	0·006	1·492	..	..	..	..	..	..
Platelet ≤75 000 mm³	0·562	0·006	1·754	0·490	0·016	1·632	..	..	..	..	..	..
Lymphocyte ≤3·5 g/dL	..	..	..	0·312	0·032	1·366	..	..	..	..	..	..
Haemoglobin ≤100 g/L	..	..	..	..	..	..	0·672	0·004	1·958	..	..	..
Detectable Epstein-Barr virus DNA	..	..	..	..	..	..	0·516	0·011	1·675	0·538	0·002	1·712

Parameter estimates are regression estimates that are used to calculate a risk score for patients. ECOG=Eastern Cooperative Oncology Group.

Table 2: **Factors independently prognostic of overall and progression-free survival in the training cohort**

blood (n=285) of 328 patients (the test was not available at all institutions), of whom 189 (58%) had a detectable viral DNA titre according to each institute's reference value. The proportion of patients with a positive viral DNA titre was not related to the type of sample tested (ie, plasma *vs* whole blood; p=0·51). Detectable viral DNA was significantly associated with unfavourable measures, including increased serum lactate dehydrogenase (p<0·0001), stage III or IV disease (p<0·0001), presence of B symptoms (p=0·001), and two or more extranodal sites (p=0·001).

In the training cohort, 202 patients (38%; mainly with advanced disease) received chemotherapy (table 1). Frail patients or patients who refused to receive chemotherapy underwent concurrent chemoradiotherapy (n=24) or radiotherapy (n=20) only. Among the various non-anthracycline-based chemotherapy regimens, SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) was the most commonly used (table 1). Other regimens were used according to individual institutional policy. 181 patients (94%) responded to concurrent chemoradiotherapy followed by chemotherapy, and 168 (87%) had complete responses, but this modality was mainly used for patients with stage I or II disease. Chemotherapy as a single modality was used mainly for advanced-stage disease. Overall response was 49% (98 of 202 patients), and a complete response was noted in 64 patients (32%). 85 (63%) of 134 patients responded to SMILE, including 60 complete responses. Upfront autologous stem-cell transplantation was done as consolidation in 31 patients with stage I or II disease and 18 with stage III or IV. Of these patients, six with stage I or II disease and 14 with stage III or IV disease died. Four patients with stage I or II disease and nine with stage III or IV underwent consolidation allogeneic stem-cell transplantation, of whom two and six patients died, respectively.

At the time each participating institute supplied the case report forms, 187 patients' (36%) disease had progressed or relapsed during or after primary treatment and 220 (42%) had died, with a median follow-up of 44·9 months (IQR 22·1–64·1). 90 deaths (26%) were in the 344 patients with stage I or II disease and 130 deaths (71%) were in the 183 patients with stage III or IV disease. Thus, median overall survival was 76·1 months (95% CI 51·0–101·3), and 3-year overall survival was 59% (95% CI 55–64). Median progression-free survival was 31·1 months (95% CI 17·4–44·8), 3-year progression-free survival was 48% (44–53). All pretreatment characteristics are shown in table 1. Univariate analysis showed that all pretreatment characteristics were significantly associated with overall and progression-free survival (p<0·0001), with the exception of sex and tumours located in the gastrointestinal tract and bone (appendix p 1). In patients with available data for viral DNA titres, overall survival was significantly associated with a detectable concentration of Epstein-Barr virus DNA (table 1). Overall survival differed according to the type of treatment, but these differences were affected by a selection bias that could not be avoided, because concurrent chemoradiotherapy or radiotherapy with chemotherapy were given mainly in patients with stage I or II disease, whereas most patients with stage III or IV disease were given chemotherapy alone. Thus, chemotherapy alone was associated with shorter overall and progression-free survival than were the other treatment modalities. The observation that concurrent chemoradiotherapy followed by chemotherapy was associated with better overall survival than was concurrent chemoradiotherapy or radiotherapy alone

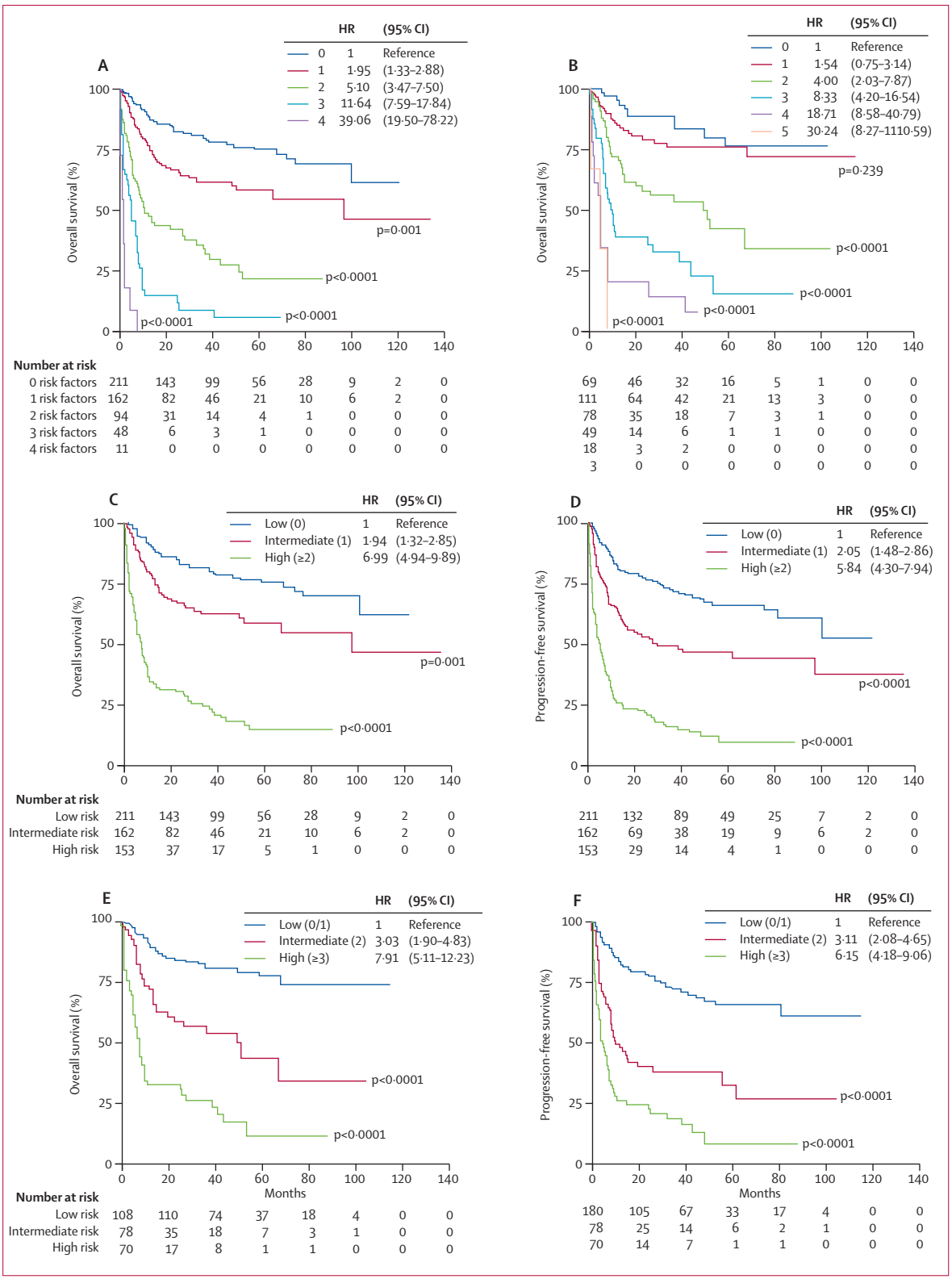

Figure 2: **Risk stratification and overall survival by number of PINK risk factors in the training cohort (A), risk stratification and overall survival by number of PINK-E risk factors in the training cohort (B), overall survival by PINK risk group (C), progression-free survival by PINK risk group (D), overall survival by PINK-E risk group (E), and progression-free survival by PINK-E risk group (F)**

Data for PINK-E come from the patients for whom Epstein-Barr virus data were available. PINK=prognostic index for natural killer lymphoma. PINK-E=prognostic index for natural killer lymphoma–Epstein-Barr virus. HR=hazard ratio.

	Validation (n=243)	Training (n=527)	p
Age			0·001
<60 years	196 (81%)	361 (69%)	
>60 years	47 (19%)	166 (31%)	
Sex			>0·99
Male	158 (65%)	341 (65%)	
Female	85 (35%)	186 (35%)	
ECOG performance status			0·181
0/1	220 (91%)	461 (87%)	
≥2	23 (9%)	66 (13%)	
Serum lactate dehydrogenase			0·179
Normal	154 (63%)	306 (58%)	
Increased	89 (37%)	221 (42%)	
B symptoms			0·233
Absence	142 (58%)	332 (63%)	
Presence	101 (42%)	195 (37%)	
Lymph-node involvement			0·027
None or regional	218 (90%)	441 (84%)	
Distant	25 (10%)	86 (16%)	
Stage			0·002
I–II	186 (77%)	344 (65%)	
III–IV	57 (23%)	183 (35%)	
Extranodal involvement (n)			<0·0001
0 or 1	195 (80%)	340 (65%)	
≥2	48 (20%)	187 (35%)	
Non-nasal type			<0·0001
No	210 (86%)	421 (80%)	
Yes	33 (14%)	106 (20%)	
Bone-marrow involvement			0·012
Absence	214 (88%)	444 (84%)	
Presence	21 (9%)	83 (16%)	
Unknown	8 (3%)	..	
Epstein-Barr virus DNA in blood			0·071
Detectable	28 (12%)	189 (36%)	
Non-detectable	35 (14%)	139 (26%)	
Unknown	180 (74%)	199 (38%)	
Primary treatment			<0·0001
Chemotherapy	130 (53%)	202 (38%)	
Concurrent chemoradiotherapy followed by chemotherapy	49 (20%)	193 (37%)	
Radiotherapy followed by chemotherapy	0	9 (2%)	
Chemotherapy followed by radiotherapy	51 (21%)	79 (15)	
Concurrent chemoradiotherapy	13 (5%)	24 (5%)	
Radiotherapy	0	20 (4%)	
(Table 3 continues in next column)			
(Continued from previous column)			
Chemotherapy regimen			<0·0001
GEMOX or GDP ± L-asparaginase	92* (38%)	10 (2%)†	
SMILE	30 (12%)	134 (25%)	
DeVIC	1 (0%)	39 (7%)	
VIPD, VIDL, or MIDLE	62 (26%)	157 (30%)	
ICE, IMEP, ESHAP	21 (9%)	83 (16%)	
L-asparaginase‡	10 (4%)	29 (6%)	
Non-anthracycline-based regimens‡	15 (65)	31 (6%)	

ECOG=Eastern Cooperative Oncology Group. GEMOX=gemcitabine, methotrexate, and oxaliplatin. GDP=gemcitabine, dexamethasone, and cisplatin. SMILE=corticosteroid, methotrexate, ifosfamide, L-asparaginase, and etoposide. DeVIC=dexamethasone, etoposide, ifosfamide, and carboplatin. VIPD=etoposide, ifosfamide, cisplatin, and dexamethasone. VIDL=etoposide, ifosfamide, dexamethasone, and L-asparaginase. MIDLE=methotrexate, ifosfamide, dexamethasone, L-asparaginase, and etoposide. IMEP=ifosfamide, methotrexate, etoposide, and prednisolone. ESHAP=etoposide, steroid, cytarabine, and cisplatin. ICE=ifosfamide, carboplatin, and etoposide.
*49 patients given GEMOX and 43 given GDP. †Various gemcitabine-containing chemotherapy regimens are included in the training cohort—eg GDP.
‡Excludes regimens previously listed separately.

Table 3: **Comparison of characteristics between the validation and training cohorts**

might be associated with the fact that old and frail patients received radiotherapy alone or concurrent chemoradiotherapy without additional chemotherapy.

A multivariate analysis of all patients showed that age greater than 60 years, stage III or IV disease, non-nasal disease, distant lymph-node involvement, decreased platelet count, and serum albumin concentrations less than 35 g/L were independent significant predictors of both overall and progression-free survival (table 2). Thus, the survival outcome of patients was significantly different within stage according to non-nasal disease and distant lymph-node involvement. 3-year overall survival was better for patients with nasal disease than for those with non-nasal disease (77% *vs* 61% for patients with stage I or II disease, p=0·030; 38% *vs* 15% for patients with stage III or IV disease, p<0·0001). In patients with stage IV disease, 3-year overall survival of patients with distant lymph-node involvement was 15% compared with 32% in those without distant lymph-node involvement (p=0·004). A multivariate analysis of patients with viral DNA in the blood showed that detectable Epstein-Barr virus DNA was also an independent significant predictor of both overall and progression-free survival (table 2). Because these data were not available for all patients, we first developed a new prognostic model, the prognostic index for natural killer cell lymphoma (PINK), consisting of four risk factors (age, stage, non-nasal type, and distant lymph-node involvement) that were significantly associated with overall and progression-free survival, irrespective of the availability of viral data. Although serum albumin and platelet count were also independent risk factors for overall and progression-free survival, they were not significantly associated in the multivariate analysis when Epstein-Barr virus DNA data were included. The range of regression estimates of the risk factors in each index was not very large (table 2); the

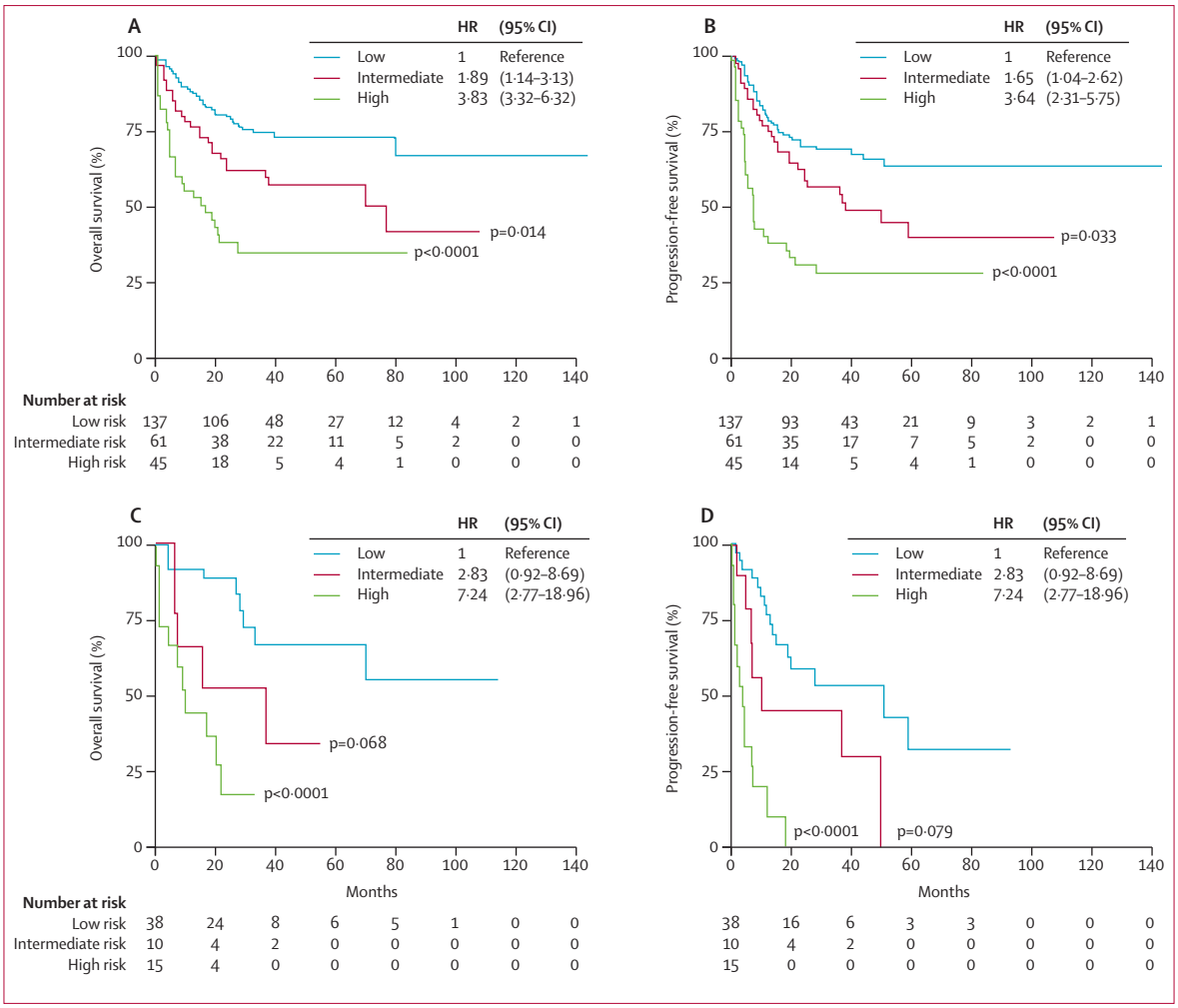

***Figure 3*: Overall (A) and progression-free (B) survival according to PINK in the validation cohort, and overall (C) and progression-free (D) survival according to PINK-E in the validation cohort**

(C) and (D) include only patients with available data for Epstein-Barr virus DNA. PINK=prognostic index for natural killer lymphoma. PINK-E=prognostic index for natural killer lymphoma–Epstein-Barr virus. HR=hazard ratio.

largest was less than twice the size of the smallest, and thus we assigned equal weights to all risk factors. Patients were stratified according to the number of risk factors present into three groups: low risk (0), intermediate risk (1), and high risk (≥2), with 3-year overall survival of 81% (95% CI 75–86), 62% (55–70), and 25% (20–34), respectively. Stratification was significantly associated with both overall and progression-free survival (figure 2A–C). We also developed another prognostic model that included Epstein-Barr data, the prognostic index for natural killer cell lymphoma–Epstein-Barr virus (PINK-E), in which we stratified patients into low-risk (0 or 1), intermediate-risk (2), and high-risk (≥3) groups, with overall survival at 3 years of 81% (95% CI 75–87), 55% (44–66), and 28% (18–40), respectively (figure 2D–F). Although we developed prognostic models for survival rather than predictive models for response to a specific chemotherapy, the response to primary treatment was also significantly related with the risk classification in our prognostic indices in an exploratory analysis ($p<0·0001$; appendix p 2).

We applied PINK and PINK-E to an independent validation cohort, which included 243 patients. The validation cohort included a higher proportion of patients with favourable parameters, such as age 60 years or younger (47 [19%] of 243 patients), stage I or II disease (186 [77%]), nasal type disease (210 [86%]), and distant lymph-node involvement (25 [10%]), than did the training cohort (table 3). With median follow-up of 39 months (95% CI 33–45), 3-year overall survival was 65% (95% CI 58–71) and progression-free survival was 59% (52–65). Median overall and progression-free survival were not reached in the validation cohort. Overall and progression-free survival were significantly better in the validation cohort than in the training cohort (log-rank $p=0·037$ and

p=0·012, respectively). The treatment profile also differed from that of the training cohort, because more than 50% of the patients were given chemotherapy alone and the regimens that were used most commonly contained gemcitabine, such as GEMOX (gemcitabine, methotrexate, and oxaliplatin, with or without L-asparaginase (table 3). Despite these differences, the PINK model was significantly associated with overall and progression-free survival in all 243 patients (figure 3A, B). The PINK-E model was also significantly associated with overall and progression-free survival for the high-risk group, compared with the low-risk group, although overall and progression-free survival were not significant for patients in the intermediate-risk group compared with the low-risk group. Furthermore, only 63 patients underwent Epstein-Barr virus DNA detection, of whom 28 patients had a detectable viral DNA titre at diagnosis (figure 3C, D).

In an exploratory analysis, stratification of our training cohort according to the international and Korean prognostic indices both yielded significant associations with overall and progression-free survival (appendix p 3). However, the prognostic insight afforded by stratification according to the international and Korean prognostic indices was less than that afforded by using PINK: the difference in overall survival between the high and high–intermediate groups classified according to the International Prognostic Index was not significant, and the difference between groups 1 and 2 of the Korean Prognostic Index was also not significant (appendix p 3). PINK could also be used to discriminate between patients classified within the same risk group according to the international and Korean prognostic indices (appendix p 3).

Discussion

We identified four risk factors (age, stage, non-nasal type, and distant lymph-node involvement) out of various clinical parameters that were independently prognostic of overall and progression-free survival, irrespective of the availability of quantitative PCR for detection of Epstein-Barr virus DNA to develop a new prognostic model for patients with ENKTL. The treatment for this disease has changed from conventional anthracycline-based chemotherapy to non-anthracycline-based chemotherapy and upfront use of concurrent chemoradiotherapy or radiotherapy. At 3 years, 74% of patients with stage I or II disease in the training cohort were still alive, which was higher than the overall survival reported in previous studies[11,12,17] in which patients were mainly given CHOP or CHOP-like regimens with or without adjunct radiotherapy.

The patients we studied received various treatments, and chemotherapy regimens were heterogeneous. Thus, we developed prognostic models on the basis of patients' pretreatment characteristics, because a primary treatment was selected by clinicians according to risk factors at diagnosis. In this sense, treatment effect was included in our models through the risk factors. Patients who underwent upfront autologous or allogeneic stem-cell transplantation as consolidation treatment were also included in this analysis, but there were not many patients and their outcomes did not differ significantly from patients who did not undergo transplantation (appendix p 4). Although serum lactate dehydrogenase concentrations and Ki-67 expression were prognostic of survival in ENKTL in previous studies,[25,26] we did not find that lactate dehydrogenase concentrations had independent prognostic value, and could not assess Ki-67 expression because of insufficient data.

Some of the independent risk factors that we identified overlapped with those used in previous prognostic models. First, age greater 60 years was included in the International Prognostic Index, but excluded from the Korean Prognostic Index.[12] The results of a multicentre study[17] of 1383 Chinese patients with ENKTL also did not show the independent prognostic value of age greater than 60 years, although this parameter was still included in their prognostic nomogram. The inconsistent prognostic value of age might be related to different age distributions in different cohorts: in the training cohort in our study, 166 patients (31%) were older than 60 years, whereas in the study that provided the basis of the Korean Prognostic Index and the Chinese study, only 55 (21%) of 262 and 194 (14%) of 1383 patients were older than 60 years, respectively.[12,13] Additionally, because non-anthracycline-based treatments are, in general, more intense than are CHOP or CHOP-like regimens, elderly patients might be more vulnerable to treatment-related toxic effects. Thus, as the number of patients older than 60 years and the intensity of chemotherapy regimens increase, the effect of age on the outcome might increase, as we found in our study.

Second, distant lymph-node involvement was included in our prognostic model because it was an independent prognostic factor of overall and progression-free survival. In the Korean Prognostic Index, regional lymph-node involvement was an independent risk factor for worse overall survival.[12] However, in our study overall survival did not differ significantly between patients with and without regional lymph-node involvement. This difference might be related to better local control in our population because of the early use of concurrent chemoradiotherapy, because regional lymph nodes might have been included in the radiation field.

Third, the poor prognosis of non-nasal type disease (extranasal disease), implicating organs such as the skin and gastrointestinal tract, has been well described in many studies of ENKTL.[11,12] In a Japanese study[14] of 172 patients with mature natural killer cell malignancy, non-nasal type was a risk factor in the prognostic model, together with disease stage. Thus, similar to our observations for distant lymph-node involvement, the outlook of patients with non-nasal type disease could be worse than that of those with the nasal type, even in stage IV patients. This finding suggests that the biological behaviour of the non-nasal type is different from that of the nasal type.

Last, the presence of Epstein-Barr virus DNA in the blood is a well known surrogate biomarker of tumour load because ENKTL tumour cells are invariably infected with the virus and diagnosis of ENKTL is based on a positive viral titre in in-situ hybridisation. Circulating Epstein-Barr virus DNA in blood is derived from necrotic or apoptotic tumour cells,[27] and thus viral DNA in whole blood or plasma is strongly associated with survival and treatment outcomes in patients with ENKTL.[28,29] The amount of circulating viral DNA might show the burden and replication of tumours, and it might be undetectable in patients with small tumour burdens or those in whom proliferation is less active. Stratification of patients based on the PINK-E showed a significant association with overall and progression-free survival in the training and validation cohorts.

However, measurement of Epstein-Barr virus DNA is still associated with various obstacles, which hamper its adoption as a routine test for patients with ENKTL. Quantitative PCR for the viral DNA is not available at many hospitals. Reference values or procedures have not been standardised, and so the definition of a high titre remains unclear. In a 2015 study,[30] post-treatment plasma positivity for Epstein-Barr virus DNA was correlated with worse overall and progression-free survival in patients with ENKTL who were given L-asparaginase-containing chemotherapy.[30] Therefore, we split patients into groups on the basis of detectability of viral DNA using their centre's definition, rather than on the basis of titre. No consensus exists for the best blood sample type to be used for the measurement of Epstein-Barr virus DNA, although a strong correlation was noted between the results for whole blood and plasma in a previous study.[29] Thus, the positive value in this model should be reassessed if the issues related to the measurement of viral DNA in the blood are resolved in future studies. In view of this limitation of PINK-E, PINK might be better for stratification based on pretreatment clinical characteristics. PINK can easily be applied to patients with ENKTL, irrespective of viral DNA data, compares well with the international and Korean prognostic indices, and could discriminate patients classified within the same risk group according to these other indices (appendix p 3).

Our new prognostic models might be of use to develop risk-adapted treatment approaches for patients with ENKTL. However, the prognostic significance of these models should be verified by a future prospective study.

Contributors

SJK and WSK designed the study. SJK, DHY, WJC, STL, YO, RA, Fd'A, and WSK drafted the manuscript. SJK, DHY, AJ, WJC, STL, HH, YP, KMC, YM, FI, D-YS, JSK, D-HY, J-CJ, T-YC, TM, YO, RA, Fd'A, NS, CS, RS, YLK, SHJ, G-WL, CWC, W-SL, T-YL, and WSK collected and assembled data. KK and S-HJ did the statistical analysis. SJK, DHY, and WSK analysed and interpreted the data. All authors approved the final version.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Myung Hee Chang (National Health Insurance Service Ilsan Hospital, South Korea), Sung Yong Oh (Dong-A University Medical Center, South Korea), Jae-Yong Kwak (Chonbuk National University Medical School, South Korea), Hyeon Seok Eom (National Cancer Center, South Korea), Jong Ho Won (Soon Chun Hyang University, South Korea), Young-Woong Won (Hanyang University College of Medicine, South Korea), Young Rok Do (Keimyung University Dongsan Medical Center, South Korea), Yeung-Chul Mun (Ewha Womans University Mokdong Hospital, South Korea), Soon Il Lee (Dankook University College of Medicine, Cheonan, South Korea), Se Ryeon Lee (Korea University Ansan Hospital, South Korea), Ho-Jin Shin (Pusan National University Hospital, South Korea), Byeong Seok Sohn (Sanggye Paik Hospital, South Korea), Daryl Tan (Singapore General Hospital, Singapore), Shih-Sung Chuang (Chi-Mei Medical Center, Taiwan), Thomas Relander (Skane University Hospital, Sweden), Koji Izutsu (Toranomon Hospital, Japan), Naokuni Uike (Kyusyu Cancer Center Hospital, Japan), Sung-Yong Kim (Konkuk University Medical Center, South Korea), Hyo Jung Kim (Hallym University Sacred Heart Hospital, South Korea), and Ho Sup Lee (Kosin University College of Medicine, South Korea) for their participation in the International Extranodal NK/T-cell Lymphoma Project; the Consortium for Improving Survival of Lymphoma; the Asia Lymphoma Study Group; and the Lymphoma Study Association.

References

1 Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. *Leukemia* 2005; **19:** 2186–94.

2 Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer* 1995; **76:** 2351–56.

3 Kim WS, Song SY, Ahn YC, et al. CHOP followed by involved field radiation: is it optimal for localized nasal natural killer/T-cell lymphoma? *Ann Oncol* 2001; **12:** 349–52.

4 Lee SH, Ahn YC, Kim WS, Ko YH, Kim K, Park K. The effect of pre-irradiation dose intense CHOP on anthracyline resistance in localized nasal NK/T-cell lymphoma. *Haematologica* 2006; **91:** 427–28.

5 Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol* 2011; **29:** 4410–16.

6 Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. *Blood* 2012; **120:** 2973–80.

7 Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. *Blood* 2011; **117:** 1834–39.

8 Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. *J Clin Oncol* 2009; **27:** 6027–32.

9 Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. *J Clin Oncol* 2009; **27:** 5594–600.

10 Kim SJ, Yang DH, Kim JS, et al. Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. *Ann Hematol* 2014; **93:** 1895–901.

11 Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. *Blood* 2009; **113:** 3931–37.

12 Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. *J Clin Oncol* 2006; **24:** 612–18.

13 Yang Y, Zhang YJ, Zhu Y, et al. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. *Leukemia* 2015; **29:** 1571–77.

14 Suzuki R, Suzumiya J, Yamaguchi M, et al. Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. *Ann Oncol* 2010; **21:** 1032–40.

15 Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press, 2008.

16 Li YJ, Jiang WQ, Huang JJ, Xia ZJ, Huang HQ, Li ZM. The Glasgow prognostic score (GPS) as a novel and significant predictor of extranodal natural killer/T-cell lymphoma, nasal type. *Am J Hematol* 2013; **88:** 394–99.

17 Yang Y, Zhang YJ, Zhu Y, et al. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. *Leukemia* 2015; **29:** 1571–77.

18 Kwong YL, Pang AW, Leung AY, Chim CS, Tse E. Quantification of circulating Epstein-Barr virus DNA in NK/T-cell lymphoma treated with the SMILE protocol: diagnostic and prognostic significance. *Leukemia* 2014; **28:** 865–70.

19 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–46.

20 Simon RM, Subramanian J, Li MC, Menezes S. Using cross-validation to evaluate predictive accuracy of survival risk classifiers based on high-dimensional data. *Brief Bioinform* 2011; **12:** 203–14.

21 Pang H, Jung SH. Sample size considerations of prediction-validation methods in high-dimensional data for survival outcomes. *Genet Epidemiol* 2013; **37:** 276–82.

22 A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; **329:** 987–94.

23 Huang JJ, Jiang WQ, Lin TY, et al. Absolute lymphocyte count is a novel prognostic indicator in extranodal natural killer/T-cell lymphoma, nasal type. *Ann Oncol* 2011; **22:** 149–55.

24 Xu PP, Wang Y, Shen Y, Wang L, Shen ZX, Zhao WL. Prognostic factors of Chinese patients with T/NK-cell lymphoma: a single institution study of 170 patients. *Med Oncol* 2012; **29:** 2176–82.

25 Na II, Kang HJ, Park YH, et al. Prognostic factors for classifying extranodal NK/T cell lymphoma, nasal type, as lymphoid neoplasia. *Eur J Haematol* 2007; **79:** 1–7.

26 Kim SJ, Kim BS, Choi CW, et al. Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type. *Ann Oncol* 2007; **18:** 1382–87.

27 Suzuki R, Yamaguchi M, Izutsu K, et al. Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type. *Blood* 2011; **118:** 6018–22.

28 Kim HS, Kim KH, Kim KH, et al. Whole blood Epstein-Barr virus DNA load as a diagnostic and prognostic surrogate: extranodal natural killer/T-cell lymphoma. *Leuk Lymphoma* 2009; **50:** 757–63.

29 Ito Y, Kimura H, Maeda Y, et al. Pretreatment EBV-DNA copy number is predictive of response and toxicities to SMILE chemotherapy for extranodal NK/T-cell lymphoma, nasal type. *Clin Cancer Res* 2012; **18:** 4183–90.

30 Wang L, Wang H, Wang JH, et al. Post-treatment plasma EBV-DNA positivity predicts early relapse and poor prognosis for patients with extranodal NK/T cell lymphoma in the era of asparaginase. *Oncotarget* 2015; **6:** 30317–26.