A novel and simple prognostic index for nasal NK/T-cell lymphoma

Hiroyuki Hanakawa[1], M.D., Yorihisa Orita[1], M.D., PhD., Yasuharu Sato[2], M.D., PhD., Soshi Takao[3], M.D., PhD., Hidenori Marunaka[4], M.D., Tokiwa Morishita[5], M.D., Yasuhiko Yamashita[6], M.D., Yasutaka Hori[7], M.D., Shuhei Domae[8], M.D., Ikuo Inokuchi[9], M.D., PhD., Seiko Akagi[10], M.D., Eisei Kondo[11], M.D., PhD., Noriko Iwaki[2, 12], M.D., Kana Motomiya[13], M.D., Hirokazu Okumura[13], M.D., PhD., Tadashi Yoshino[2], M.D., PhD., and Kazunori Nishizaki[1], M.D., PhD.

From the Departments of [1]Otolaryngology Head and Neck Surgery, [2]Pathology, [3]Epidemiology, and [11]Hematology and Oncology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [4]Department of Otolaryngology, Okayama Medical Center, Okayama, Japan, [5]Kagawa *Rosai* Hospital, Kagawa, Japan, [6]Fukuyama City Hospital, Hiroshima, Japan, [7]Kagawa Prefectural Central Hospital, Kagawa, Japan, [8]Okayama *Saiseikai* General Hospital, Okayama, Japan, [9]Hiroshima City Hospital, Hiroshima, Japan, [10]Okayama Red Cross Hospital, Okayama, Japan, [12]Department of Hematology and Oncology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan, and [13]Department of Internal Medicine, Toyama

Prefectural Central Hospital, Toyama, Japan.

Presented at the 113th annual meeting of the Japan Otolaryngological Society, Niigata, Japan, May 9-12, 2012.

Correspondence: Yorihisa Orita, MD, PhD, Department of Otolaryngology, Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-Cho, Kita-Ku, Okayama 700-8558, Japan.

Tel: (+81)-86-235-7307, Fax: (+81)-86-235-7308, E-mail: y.orita@live.jp

Running title: Nasal NK/T-cell lymphoma

Key Words: nasal NK/T-cell lymphoma; prognostic index; local invasion; blood examination; prognosis.

ABSTRACT

Background. Few studies have investigated the prognostic factors for nasal natural killer (NK)/T-cell lymphoma.

Methods. A retrospective study.

Results. High serum levels of C-reactive protein (≥1.0 mg/dl), lactate dehydrogenase (≥350 IU/l), and soluble interleukin-2 receptor (≥600 U/ml) were associated with worse prognosis. A prognostic score was devised by totaling the number of these three predictors: 0 or 1 = score 0; and 2 or 3 = score 1. As for tumor invasion, local invasion beyond the nasal cavity was associated with poor prognosis, and a prognostic score was devised as: tumor restricted to nasal cavity, yes = score 0; no = score 1. A novel prognostic index was established based on these scores, from 0 to 2. Disease-specific survival rates at five years were: 90.0% for NPI=0; 29.3% for NPI=1; and 0.0% for NPI=2.

Conclusion. Our NPI is valid for anticipating prognosis of nasal NK/T-cell lymphoma.

INTRODUCTION

The subsets of extranodal natural killer (NK)/T-cell lymphoma, nasal type, are classified as nasal or extranasal NK/T-cell lymphoma. Nasal NK/T-cell lymphoma covers the subclassification of upper aerodigestive tract NK/T-cell lymphomas including nasal cavity, nasopharynx, oral cavity, oropharynx, and hypopharynx, while non-upper aerodigestive tract NK/T-cell lymphomas include skin, gastrointestinal tract, bone marrow, lung, extremities, orbit, adrenal gland, testis and central nervous system [1]. Although the definition of the primary region of nasal NK/T-cell lymphoma indicates a very limited area (nasal cavity, nasopharynx), about 80% of extranodal NK/T-cell lymphoma, nasal type, represent nasal NK/T-cell lymphoma [2].

The majority of cases with nasal NK/T-cell lymphoma might be first diagnosed in an otolaryngology and head and neck surgery department. Due to the rarity of this disease, nasal polyps or nasal carcinoma will usually be suspected at the first presentation, and the diagnosis mainly depends on pathological studies including immunohistochemical staining. Correct diagnosis may thus be delayed, and after establishment of the diagnosis, almost all patients are referred to hematologists or oncologists for treatment. The patient will then be re-classified to determine a therapeutic strategy. This represents a time-consuming process from first presentation to the start of

treatment. Otolaryngologists and head and neck surgeons seldom take part in the treatment of this disease, but are the most familiar with the anatomy and imaging studies of this region. A good, original prognostic index for nasal NK/T-cell lymphoma for use mainly by otolaryngologists and head and neck surgeons would be valid for promptly anticipating prognosis and facilitating timely decision-making on treatments for this disease.

Prognostic factors in extranodal NK/T-cell lymphoma, nasal type, have yet to be fully defined. Ann Arbor staging for lymphomas and the international prognostic index (IPI) [3] have generally been applied to predict prognosis for this type of lymphoma. However, these methods are not necessarily suitable, particularly for nasal NK/T-cell lymphoma. Ann Arbor staging was originally developed for Hodgkin lymphoma [4], and according to this classification system, most cases of nasal NK/T-cell lymphoma are categorized as stage I or II [5] regardless of their poor prognosis. Tumors in the nasal ± paranasal/nasopharynx regions are simply counted as occupying one site, irrespective of whether the tumor is bulky or not. Some authors have reported that Ann Arbor staging system did not predict the prognosis of extranodal NK/T-cell lymphoma [6]. IPI, which was developed for aggressive non-Hodgkin lymphoma, includes age, serum lactate dehydrogenase (LDH) level, extranodal sites, and performance status (PS) [3]. This index

does not consider local tumor invasiveness as a prognostic factor. Similar to the situation with the Ann Arbor staging system, the majority of nasal NK/T-cell lymphomas show low IPI scores [5, 6]. However, despite the classification as early stage according to these systems, overall outcomes for this disease are poor [7]. Due to the unbalanced distribution of patients within these systems and their inability to identify patients with more aggressive disease among the low-risk category, more suitable classifications are needed to more accurately predict the prognosis of nasal NK/T-cell lymphoma. Kim et al. [6] reported local tumor invasiveness as the most important prognostic factor predicting poor prognosis of early stage nasal NK/T-cell lymphoma. Robbins et al. [8], as head and neck surgeons, staged nasal lymphoma using the American Joint Committee TNM system for nasal carcinoma. Although NK/T-cell lymphoma had been excluded from their study, this method made it easy to understand the progress of nasal lymphomas.

The present study analyzed several prognostic factors, including blood examinations and local invasion of the tumor. The aim of the study was to develop a novel prognostic index (NPI) specifically for nasal NK/T-cell lymphoma, in cooperation with pathologists, hematologists, oncologists, and epidemiologists, to be utilized for outpatients presenting to otolaryngology and head and neck surgery departments.

SUBJECTS AND METHODS

Patients

The clinical records of 36 patients with nasal NK/T-cell lymphoma who had been first treated between 1996 and 2011 were collected from 12 hospitals. The study protocols were approved by the institutional review board at Okayama University.

For the diagnosis of NK/T-cell lymphoma, histopathological examination was conducted on paraffin sections of formalin-fixed tissue after staining with hematoxylin and eosin. Immunohistochemical staining for cCD3+, CD5-, TIA-1+, granzyme B+ and CD56+, and positive in situ hybridization for Epstein-Barr virus (EBV)-encoded RNA were required to confirm the diagnosis [9]. All cases were diagnosed in the Department of Pathology at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. The anatomical boundaries of extranodal NK/T-cell lymphoma remain still ambiguous. In the present study, according to a recent review article [1], nasal NK/T-cell lymphoma was defined as a primary tumor involving the nasal cavity (± nasopharynx), regardless of dissemination to other sites.

Information about each patient was collected from a questionnaire containing the following items: age and sex; dates of first presentation and last follow-up; results of blood examination at diagnosis; PS; tumor invasiveness (extracted from findings or images of computed tomography (CT) ± ^{18}F-deoxyglucose positron emission

tomography); methods of treatment; and outcome and cause of death.

Treatment and Follow-up

All patients received chemotherapy, and 29 of the 36 cases (81%) also received radiotherapy. The choice of regimen was at the discretion of the attending physician. Chemotherapeutic regimens included DeVIC (carboplatin, etoposide (ETP), ifosfamide (IFM), dexamethasone (DMS)) (n=13, 36%), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (n=13, 36%), SMILE (DMS, methotrexate, IFM, L-asparaginase, ETP) (n=5, 14%), and others (n=9, 25%). Some patients received more than one of the above-mentioned regimens. Since this was a retrospective multicenter clinical study with inconsistent treatment methods at different institutions, we did not aim to analyze relationships between survival time and detailed treatment regimens. Patients were followed until death or last medical examination.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean ± standard deviation (SD). The significance of baseline differences was determined using the χ^2 test or the unpaired t-test, as appropriate. Survival was estimated using the Kaplan-Meier method, and differences in survival between groups were assessed by log-rank test. Survival times were defined as the period of time

to death from the establishment of the diagnosis. Subjects were treated as censored when cases were lost to follow-up or the patient chose to withdraw from the study during the observation period. Cox proportional-hazards models for both uni- and multivariate analyses were used to determine the contribution of each variable. When conducting multivariate analysis, imputation was performed using median values of each variable. Since this study included only a small number of cases, analysis of many of the prognostic factors by multivariate analyses in the same model might have been problematic. To develop a NPI exclusive to nasal NK/T-cell lymphoma, we assumed two theoretically independent domains related to poor prognosis: results of blood examination; and expansion of the local tumor. For blood examinations, Pearson's correlation coefficients were calculated for potential factors that were significantly associated by survival analysis or univariate analysis before simply summing up a uni-dimensional score. We then dichotomized this score according to the distribution (dichotomous score for blood examination). Next, we considered the score for tumor invasiveness. We tried to compare the various kinds of classification for expansion of the tumor, because no standard classifications have been determined. Then, from both clinical importance and magnitude of effect with poor prognosis, we decided on one boundary for assessing tumor invasiveness (dichotomous score for tumor invasion). Lastly, we conducted multivariate

analysis using Cox's proportional hazard model to confirm that these two domains were actually associated with prognosis even after mutually adjustment and constructed NPI from these two tentative dichotomous scores.

A value of $P<0.05$ (two-sided) was considered statistically significant. All analyses were performed using SPSS version 20.0J software (SPSS, IBM Corp, Armonk, New York, USA).

RESULTS

Patient Characteristics and Outcomes

The sample for this study consisted of 36 patients with primary nasal NK/T-cell lymphoma. Baseline characteristics are shown in **Table 1**; data on some variables were missing for some patients. Of the 36 patients with nasal NK/T-cell lymphoma, 19 (53%) survived and 17 (47%) had died of the disease by the final observation. Mean age at initial presentation was 55 years (range, 21-79 years). Patients comprised 22 men (61%) and 14 women (39%). As for local tumor invasion, 15 cases (42%) were restricted to the nasal cavity. The exact distribution of Ann Arbor staging was: I, n=22; II, n=10; III, n=1; and IV, n=3. The distribution for IPI score was: 0, n=5; 1, n=18; 2, n=6; 3, n=4; and 4, n=2 (missing, n=1). Significant crude associations were identified for C-reactive protein (CRP), lactate dehydrogenase (LDH), and soluble interleukin-2 receptor (sIL-2R). CRP levels were determined in 34 patients, and the median value was 0.47 mg/dl (range, 0.0-22.0 mg/dl; reference range, <0.30 mg/dl). Serum levels of LDH were available for 35 patients, with a median value of 244 IU/l (range, 112-1418 IU/l; reference range, 120-240 IU/l). Similarly, the median sIL-2R level for 31 patients was 541 U/ml (range, 122-6976 U/ml; reference range, 145-519 U/ml).

Survival Analysis of Prognostic Factors

Mean survival after initial diagnosis of nasal NK/T-cell lymphoma was 39 months (range, 4-147 months). The disease-specific five-year survival rate from initial diagnosis was 43.7% (**Fig. 1**).

Results of survival analysis are shown in **Table 2**. High serum levels of CRP, LDH, and sIL-2R represented factors significantly associated with poor prognosis. Local invasiveness of tumor beyond the nasal cavity (n=21, 58%) was also associated with poor prognosis. Ann Arbor staging was not associated with prognosis, even employing two different cut-off points. IPI ≥2 (n=12) was not associated with poor prognosis. While IPI ≥3 (n=6) was significantly associated with poor prognosis, the number of cases was small compared to the actual number of deaths (n=17).

Pearson's correlation coefficients among CRP, LDH, and sIL-2R were all significant (range, 0.483-0.542). We then summed up values to create a uni-dimensional score (range, 0-3) based on the presence/absence of these three unfavorable factors. Cox's proportional hazards analysis revealed this score as a significant factor predicting disease-specific death from nasal NK/T-cell lymphoma (**Table 3a**). We dichotomized the scores for NPI (0 or 1 = NPI 0 and 2 or 3 = NPI 1) and the dichotomous score for blood examination was also significantly associated with poor prognosis (hazard ratio (HR), 4.873; 95% confidence interval (CI), 1.813-13.096).

We tried to compare the various kinds of classification (restricted to nasal cavity and ethmoidal sinus vs. beyond; restricted to nasal cavity and maxillary sinus vs. beyond; and restricted to nasal cavity and paranasal sinuses vs. beyond) for local expansion of the tumor, and considered local invasiveness of the tumor restricted to the nasal cavity as the most predictable factor (HR, 3.575; 95%CI, 1.155-11.072), regardless of dissemination to other sites (within nasal cavity=0, beyond=1) (**Table 3b**).

Multivariate analysis using the Cox's proportional hazard model identified the dichotomous score of blood examination and the dichotomous score of local tumor invasion as independent factors for predicting death from nasal NK/T-cell lymphoma, even after mutually adjustment (**Table 4**).

Disease-specific survival rates at five years for the three groups were 90.0% for NPI=0 (low risk, n=12), 29.3% for NPI=1 (intermediate risk, n=16), and 0.0% for NPI=2 (high risk, n=8) (P<0.0001) (**Fig. 2**).

DISCUSSION

Our findings demonstrated that the prognosis of patients with nasal NK/T-cell lymphoma was well predicted by local invasion of the primary tumor and three values (CRP, LDH, and sIL-2R) from blood examination. This NPI needs only CT imaging of primary tumors and the results of blood examination in addition to accurate pathological diagnosis, and so will be valid for promptly anticipating prognosis and aiding timely decisions on treatment policy for this disease. Since the disease-specific survival rate at five years for the group classified as low-risk (NPI=0) by NPI were excellent (90.0%), those classified in the low-risk group by NPI could potentially benefit from less-aggressive therapy, such as surgery or field radiotherapy without chemotherapy.

With upper aerodigestive tract NK/T-cell lymphoma, survival outcomes of nasal and extra-nasal NK/T-cell lymphomas were comparable [1]. Including non-upper aerodigestive tract NK/T-cell lymphoma, disease type nasal came to represent a factor associated with significantly better prognosis [2, 10]. The largest retrospective study of NK cell leukemia and extranodal NK/T-cell lymphoma in Japan [2], which included 123 cases of nasal NK/T-cell lymphoma (total 172 cases), revealed tumor type (nasal or non-nasal), clinical stage, PS, and number of extranodal involvements as significant prognostic factors. The largest Korean study [11] of 262 cases of NK/T-cell lymphoma, nasal type,

identified an excellent index including B symptoms, clinical stage, serum LDH level and regional lymph node involvement. However, these classification and indices were not exclusive for nasal NK/T-cell lymphoma. Some studies have identified the IPI category as prognostic for extranodal NK/T-cell lymphoma [2, 5, 6], and in the present study, IPI $\geq$ 3 was indeed associated with worse prognostic factor on univariate analysis, although an unbalanced distribution of patients within this system was observed. Actually, IPI has been reported to perform less well in low-score groups [12].

Paranasal extension of nasal lymphomas has been identified as a significant predictor of survival in several studies [8, 13, 14], and we also investigated tumor invasion beyond the nasal cavity as an indication of advanced disease state for nasal NK/T-cell lymphoma. We tried many types of analysis for tumor invasiveness, and finally found that tumor invasion beyond the nasal cavity as the most valuable factor, significantly associated with worse disease-specific survival regardless of tumor dissemination to sites other than the primary lesion. UICC staging for nasal carcinoma seemed to be difficult to be determined by doctors other than otolaryngologists or head and neck surgeons, because the definition of subsite in the nasal cavity is too complicated. On the other hand, whether the primary tumor is restricted to the nasal cavity can be relatively easily determined by any doctor on CT imaging.

Both activated T cells and lymphoma cells produce sIL-2R, and serum levels of sIL-2R reflect the prognosis in patients with peripheral T-cell lymphoma as well as diffuse large B-cell lymphoma [15]. To the best of our knowledge, the present study might be the first report serum levels of sIL-2R as one of the prognostic factors for NK/T-cell lymphoma. Among the three values included in the score of blood examination (sIL-2R, CRP, and LDH), each of which showed significant prognostic value on univariate analysis, sIL-2R was the strongest prognostic factor. CRP is known as a prognostic marker in several malignancies, including both Hodgkin's lymphoma [16] and non-Hodgkin's lymphoma [17]. The present study revealed this as one of the prognostic factors for nasal NK/T-cell lymphoma. Although we lacked the data about B-symptoms, serum levels of CRP were said to be associated with B-symptoms [17]. Serum LDH levels are reportedly associated with survival outcomes for extranodal NK/T-cell lymphoma [18], similar to our findings. Although we did not adopt high IPI score (≥3) for our NPI due to the unbalanced distribution of patients with nasal NK/T-cell lymphoma to each category of the IPI, serum LDH level was associated with IPI score, stage, and lymph node invasiveness [18]. Our index of blood examination with the combination of these three kinds of markers thus might well indicate the status of patients with nasal NK/T-cell lymphoma.

According to a large Korean study [11] of NK/T-cell lymphoma, nasal type,

invasion of regional lymph nodes may offer a more powerful predictive factor of poor survival than local tumor invasiveness. In the present study, involvement of the cervical lymph nodes was not a worse prognostic factor for nasal NK/T-cell lymphoma. In a large retrospective study of 128 extranodal NK/T-cell lymphomas [19], absolute lymphocyte count (ALC) prior to treatment was identified as a powerful prognostic factor in extranodal NK/T-cell lymphoma. In our series, none of the patients with nasal NK/T-cell lymphoma showed low ALC. These discrepancies between other studies and the present might be a result of our limitation in focusing solely on nasal NK/T-cell lymphoma. A prospective study that included 29 cases of nasal NK/T-cell lymphoma [20] revealed EBV-DNA level in plasma and mono-nuclear cells from peripheral blood as a good indicator for response and overall survival of nasal NK/T-cell lymphoma. Although this subject was not analyzed in the present study, a key advantage of this NPI might be its simplicity.

The present study involved several limitations. First, the rarity of this disease limits large-scale randomized studies, and since this is a multicentric retrospective study some patients had incomplete dataset and the treatments were variable. However, we focused on the prognostic factors of this disease, and our findings have important implications on anticipating prognosis of this disease. Second, there was a possibility that many of the cases in the present study were in a relatively early stage of the disease, due

to the fact that almost all cases in this study had first presented to the Department of Otolaryngology and head and neck surgery, probably without serious conditions. However, despite the bias of the patient selection method, characteristics of patients in this series were similar to other previous reported Asian studies [2, 5, 11]. The disease-specific survival rate from diagnoses of nasal NK/T-cell lymphoma in the present study (43.7% at five years) was also comparable with other Asian studies [5, 7]. To confirm the efficacy of the NPI, application of the NPI to some validation cohort at another institutions with no relationship to our groups will be necessary, although this might be difficult due to the paucity of patients with nasal NK/T-cell lymphoma. Third, since we could not control any other potential confounders (e.g., age, sex) due to the small sample size, residual confounding might remain. However, it is unlikely that such bias could explain all the present results. Furthermore, age is usually a strong predictive variable in most diseases, and can be taken into account when selecting treatments separately to NPI. Lastly, misclassification of exposure variables (for blood examination and for tumor invasion) was considered non-differential and might affect effect estimates to toward the null. The significant results thus did not change substantially.

CONCLUSION

In conclusion, this NPI based on simple clinical parameters may be useful to

stratify patients into different risk groups. Survival of patients with nasal NK/T-cell lymphoma could be improved by prompt anticipation of patient prognosis using this NPI.

REFERENCES

[1] Kim TM, Heo DS. Extranodal NK/T-cell lymphoma, nasal type: new staging system and treatment strategies. Cancer Sci 2009; 100: 2242-2248

[2] 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: 1032-1040

[3] A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. N Engl J Med 1993; 329: 987-994

[4] Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971; 31: 1860-1861

[5] Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the international prognostic index. Blood 2004; 103: 216-221

[6] Kim TM, Park YH, Lee SY, et al. Local tumor invasiveness is more predictive of survival than international prognostic index in stage IE/IIE extranodal NK/T-cell lymphoma, nasal type. Blood 2005; 106: 3785-3790

[7] Cheung MM, Chan JK, Lau WH, et al. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol

Phys 2002; 54: 182-190

[8] Robbins KT, Fuller LM, Vlasak M, et al. Primary lymphomas of the nasal cavity and paranasal sinuses. Cancer 1985; 56: 814-819

[9] Kwong YL, Chan AC, Liang R, et al. CD56+ NK lymphomas: clinicopathological features and prognosis. Br J Haemathol 1997; 97: 821-829

[10] Au WY, Weisenburger DD, Intraqumtornchai 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: 3931-3937

[11] 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: 612-618

[12] 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: 2176-2182

[13] Logsdon MD, Ha CS, Kavadi VS, Cabanillas F, Hess MA, Cox JD. Lymphoma of the nasal cavity and paranasal sinuses: improved outcome and altered prognostic factors with combined modality therapy. Cancer 1997; 80: 477-488

[14] You JY, Chi KH, Yang MH, et al. Radiation therapy versus chemotherapy as initial

treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. Ann Oncol 2004; 15: 618-625

[15] Kitagawa J, Hara T, Tsurumi H, et al. Serum-soluble interleukin-2 receptor (sIL-2R) is an extremely strong prognostic factor for patients with peripheral T-cell lymphoma, unspecified (PTCL-U). J Cancer Res Clin Oncol 2009; 135: 53-59

[16] Wieland A, Kerbl R, Berghold A, Schwinger W, Mann G, Urban C. C-reactive protein (CRP) as tumor marker in pediatric and adolescent patients with Hodgkin disease. Med Pediatr Oncol 2003; 41: 21-25

[17] Herishanu Y, Perry C, Braunstein R, et al. Early-mid treatment C-reactive protein level is a prognostic factor in aggressive non-Hodgkin's lymphoma. Eur J Haematol 2007; 79: 150-154

[18] 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

[19] 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 2010; 22: 149-55

[20] 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: 6018-6022

FIGURE LEGENDS

Figure 1. The disease-specific survival rate for the 36 patients with nasal NK/T cell lymphoma was 43.7% at 5 years.

Figure 2. We devised a new prognostic index (NPI) for nasal NK/T cell lymphoma based on the presence of 2 unfavorable characteristics potentially present in patients: local tumor invasion; and blood examination. Scores were assigned from 0 to 2. The disease-specific survival rate at 5 years for the 3 groups were: 90.0% for NPI=0 (n=12); 29.3% for NPI=1 (n=16); and 0.0% for NPI=2 (n=8) ($P<0.0001$)