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Extranodal nasal type NK/T-cell Lymphoma: Elucidating clinical prognostic factors for risk-based stratification of therapy

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Abstract

The purpose of this study was to define distinctive clinical features of ''nasal'' and ''nasal-type'' NK/T cell lymphomas by assessing prognostic factors. The anatomic definition of extranasal NK/T cell lymphoma has been vague resulting in variable definitions of extranasal sites by different groups. We analysed the clinical behavior of 90 NK/T cell lymphoma patients and attempted to elucidate the prognostic factors for risk-based stratification of therapy. We observed no significant difference between ''nasal'' and ''nasal-type'' NK/T cell lymphomas in regards to clinical features and survival using the conventional anatomic classification. We suggest the categorisation of the two subtypes of NK/T cell lymphoma as follows: UNKTL (upper aerodigestive tract NK/T cell lymphoma) including all lymphomas confined to nasal cavity, nasopharynx, and the upper aerodigestive tract and EUNKTL (extra-upper aerodigestive tract NK/T cell lymphoma) group to include all sites other than the UNKTL group. The EUNKTL group in this study had advanced stage at diagnosis, higher LDH, higher IPI score, poorer performance and inferior response to the anthracycline-based chemotherapy with statistical significance. There was a significant difference in survival rate between EUNKTL and UNKTL group (20.0%, 54.0%, respectively, $P = 0.0068$). More aggressive treatment should be sought for this particular group of patients for EUNKTL patients.
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Keywords: NK/T-cell lymphoma; Classification; Nasal-type

1. Introduction

Mature natural killer (NK)–cell neoplasm has recently been accepted as a distinct clinicopathologic entity and can be subdivided into extranodal NK/T cell lymphoma and aggressive NK-cell leukaemia [1,2].

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Extranodal NK/T cell lymphoma shows a strong association with Epstein-Barr virus (EBV) and presents typically within the nasal cavity. The World Health Organization (WHO) classification of extranodal NK/T cell lymphoma, nasal-type, states that the ''nasal-type'' NK/T-cell lymphomas are those occurring outside the nasal cavity and have variable presentations depending upon the major site of involvement [1]. However, the Hong Kong workshop, held in 1994, recognised NK/T cell tumours with an identical phenotype, genotype, and morphology occurring in extranasal sites [3]. The workshop recommended the term ''nasal-type'' NK/T cell lymphoma for extranasal lesions and the term ''nasal'' for classical midline facial lesions since these two subtypes were thought to behave differently.

''Nasal-type'' NK/T cell lymphoma has recently been reported to pursue highly aggressive clinical course. The largest study on ''nasal-type'' CD56+ lymphoma reported a retrospective review of 34 cases and concluded that it showed a rapidly progressive course, often refractory to combined chemotherapy [4]. Since ''nasal-type'' NK/T cell lymphoma represents one of the most aggressive lymphomas, it is increasingly important to refine its definition and biological features for accurate diagnosis and appropriate therapeutic plan. As the term ''nasal-type'' implies the fact that the nasal cavity is the commonest site of involvement, the current categorisation of the two subtypes depends on the anatomic site of the presentation. The Hong Kong workshop [3] or the WHO classification, however does not specify the anatomic boundary for nasal and ''nasal-type'' NK/T cell lymphoma, resulting in inconsistent definition of ''extranasal'' sites. Previous studies have employed variable classifications of nasal and ''nasal-type'' NK/T cell lymphomas, most of them categorising extranasal NK/T cell lymphoma as lymphomas primarily occurring outside nasal cavity and nasopharynx including upper aerodigestive tract, soft tissue, and visceral organs [3–17]. The categorisation of upper aerodigestive tract has been varied in particular; most studies included upper aerodigestive tract diseases as ''nasal-type'' while others have classified them as ''nasal'' [3–7,9–17].

To better define the clinical features of ''nasal'' and ''nasal-type'' NK/T cell lymphomas, we conducted a retrospective analysis and attempted to delineate proper definitions for NK/T cell lymphomas by elucidating the clinical prognostic factors and survival.

2. Patients and methods

Ninety consecutive patients, who were diagnosed as extranodal NK/T cell lymphoma from July 1994 to September 2003 were included in the analysis. All patients were Korean. The criteria for case inclusion were as following: (1) histologically confirmed diagnosis of NK/T cell lymphoma, according to WHO classification [1]; (2) proven NK/T cell type by immunohistochemistry, flow cytometry, or EBV *in situ* hybridisation; (3) availability of all clinical data for appropriate staging. Blastic NK-cell leukaemia, aggressive NK cell lymphoma/leukaemia, and peripheral T cell lymphoma, unspecified were excluded from the analysis. The pathologic diagnosis of nasal-type NK/T cell lymphoma was based on the following criteria: expression of cytoplasmic CD3 and CD56 and positive status for EBV *in situ* hybridisation. If EBV *in situ* hybridisation was negative, the immunophenotype studies should demonstrate cytoplasmic CD3 expression and positive cytotoxic molecules such as TIA-1.

The following clinical data were collected from the record: patient demographics, complete blood count, lactic dehydrogenase (LDH) level, Ann Arbor stage, IPI, bone marrow findings, the presence of B symptoms, performance status, date of diagnosis, type of treatment, treatment response, date of last follow-up, vital status and cause of death.

2.1. Histology

In all cases, haematoxylin-eosin-stained slides were reviewed by two pathologists. Immunophenotyping was performed using a panel of monoclonal antibodies including antibodies against cytoplasmic 1:400 CD3 (Dakopatts, Copenhagen, Denmark), 1:400 CD20 (Dakopatts), and 1:50 CD56 (Monosan, Uden, the Netherlands). EBV RNA was detected by an *in situ* hybridisation technique. Briefly, paraffin sections were pretreated with xylene, followed by treatment with proteinases K and hybridised with FITC-conjugated EBV oligonuecleotides (Dakopatts) complementary to the nuclear RNA portion of the EBER 1 and 2 genes.

2.2. Definition of ''nasal'' and ''nasal-type'' NK/T cell lymphomas

The most commonly used definition of ''nasal'' NK/T cell lymphoma is classified as lesions confined within nasal cavity and nasopharynx, and ''nasal-type'' NK/T cell lymphoma as lesions involving sites outside nasal cavity/nasopharynx such as oral cavity, palate, larynx, tonsil, skin, soft tissues, visceral organs [3–7,9–17]. Involvement of nasal cavity and secondary spread to other sites is categorised as ''nasal'' NK/T cell lymphoma as recommended at the Hongkong workshop [3].

2.3. Treatment

Patients were categorised according to the initial treatment modality: (1) anthracycline-based chemotherapy with or without involved-field radiotherapy (IFRT),

(2) non-anthracycline-based chemotherapy with or without IFRT, (3) IFRT only, and (4) supportive care only.

The anthracycline-based chemotherapy regimen used were as following: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), dose-escalated CHOP-(deCHOP), COPBLAM (cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine), and EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone). The non-anthracycline-based chemotherapy regimens were DICE (dexamethasone, ifosfamide, cisplatin, etoposide) and CVP (cyclophosphamide, vincristine, prednisone). The treatment response was assessed according to standard response criteria [18]. IFRT began three weeks after the completion of planned chemotherapy. The total radiotherapy dose was 45 Gy administered over five weeks by conventional fractionation schedule (1.8 Gy/fraction, 5 fractions/week) to the prechemotherapy gross disease extent.

All patients provided written informed consent before treatment.

2.4. Statistical analysis

Categorical variables in two groups were compared by the χ^2 test, while continuous variables were analysed by Student t test. P values less than 0.05 were considered statistically significant and all P values correspond to two-sided significance tests. Overall survival (OS) was estimated using the Kaplan–Meier product-limit method [19]. OS was measured from the date of diagnosis to the date of death or the last follow-up visit. Survival rates were compared for statistical differences by using log-rank analysis. Significant variables in the univariate analysis, except for variables included in IPI, were considered as variables for the multivariate analysis for survival. The latter was performed by Cox's proportional hazard regression model.

3. Results

3.1. Clinical characteristics of "nasal" NK/T cell lymphoma and "nasal-type" NK/T cell lymphoma

The clinical characteristics of patients in two groups, "nasal" and "nasal-type" NK/T cell lymphoma are outlined in Table 1. "Nasal-type" NK/T cell lymphomas ($n = 30$) included primary lesions at the following sites: oropharynx ($n = 4$), tongue ($n = 1$), tonsil ($n = 4$), palate ($n = 1$), gastrointestinal tract ($n = 7$), skin ($n = 7$), soft tissue ($n = 3$), muscle ($n = 2$), and liver ($n = 1$). Approximately two-thirds of patients in the nasal and the extranasal group presented with localised disease (stages I, II). However, the performance status was poorer in patients with NK/T cell lymphoma presenting at extranasal sites. There was a male bias for both groups. IPI scoring was available in all patients and accordingly 39 (65%) patients were classified as low risk, 5 (8%) patients as intermediate–low, 10 (17%) as intermediate–high, and 6 (10%) as high risk in the "nasal" NK/T cell lymphoma group. In "nasal-type" NK/T cell lymphoma, 13 patients (43%) were classified as low risk, 7 patients (23%) as low-intermediate, 5 patients (17%) as high-intermediate, and 5 patients (17%) as high risk. Taken

Table 1
Patient characteristics

	Nasal ($n = 60$)	Nasal-type overall ($n = 30$)	Nasal-type UA ($n = 10$)	Nasal-type non-UA ($n = 20$)	Nasal *vs.* nasal-type overall, P value	Nasal *vs.* nasal-type UA, P value	Nasal-type UA *vs.* nasal-type non-UA, P value
Median age (years, range)	44 (21–68)	50 (22–81)	54 (28–65)	50 (22–81)	0.880	0.332	0.717
Sex (Male%)	62%	63%	70%	65%	0.878	0.588	0.660
Performance status (ECOG) 0–2	58 (97%)	21 (70%)	10 (100%)	11 (56%)	0.015	0.555	0.039
B symptom(+)	17 (29%)	11 (37%)	0 (0%)	11 (55%)	0.259	0.635	–
Stage I/II	44 (73%)	22 (73%)	9 (90%)	11 (55%)	0.713	0.090	0.014
IPI							
Low	39 (65%)	13 (43%)	8 (80%)	5 (25%)	0.131	0.272	0.032
Low–intermediate	5 (8%)	7 (23%)	2 (20%)	5 (25%)			
High–intermediate	10 (17%)	5 (17%)	0 (0%)	5 (25%)			
High	6 (10%)	5 (17%)	0 (0%)	5 (25%)			
LDH (high)	27 (45%)	14 (47%)	3 (30%)	14 (70%)	0.331	0.405	0.050
EBV ISH (+)	41/44 (93%)	18/22 (82%)	7/8 (88%)	11/14 (79%)	0.091	0.525	0.132
CR rate achieved after anthracycline-based chemotherapy[a]	36/59 (61%)	10/20 (50%)	8/10 (80%)	2/10 (20%)	0.286	0.301	0.010

Abbreviations: nasal-type UA = upper aerodigestive nasal-type NK/T cell lymphoma; nasal-type non-UA = non-upper aerodigestive nasal-type NK/T cell lymphoma.

[a] Only in patients who were primarily treated with anthracycline-based chemotherapy.

Table 2
Adverse clinical parameters influencing survival

Variables	OS (*P* value)	
	Univariate	Multivariate
Age (>60)	0.442	0.391
Sex (Male)	0.305	0.769
PS (ECOG 2–4)	<0.0001	<0.0001
B symptom (+)	<0.0001	0.922
LDH (high)	<0.0001	0.001
BM (+)	<0.0001	0.107
EBV (+)	0.203	0.147
Extra-upper aerodigestive tract lesion	0.019	0.080

PS, performance status; BM, bone marrow; EBV, Epstein-Barr virus.

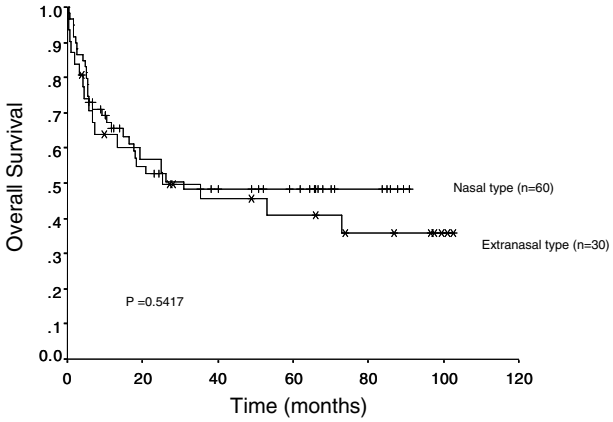

Fig. 1. Overall survival according to subtypes.

together, there was no notable difference between the two groups in regards to clinical features when "nasal" and "nasal-type" lymphomas were classified according to the conventional definition. There were no statistically significant differences in age, sex, the presence of B symptoms, stage, IPI score, LDH, or EBV positive status between the two groups. The notable finding was that there was no significant difference between "nasal" *vs.* "nasal-type" lymphomas or between "nasal" *vs.* "nasal-type" upper aerodigestive lymphomas in clinical features (Table 2).

3.2. Treatment and response

Of 90 patients, 79 patients (88%) received anthracycline-based chemotherapy as the initial treatment. The overall CR rate was 58.2% (46 of 79) in these anthracycline-treated patients; PRs were observed in 8.8% (7 of 79). Seven patients (8%) received non-anthracycline-based chemotherapy. Three patients received supportive care and one patient received involved-field radiotherapy alone. "Nasal" NK/T cell lymphoma patients showed higher CR rate to the anthracycline-based primary chemotherapy (61%) than the "nasal-type" NK/T cell lymphoma patients (50%) with no statistical significance ($P = 0.286$) (Table 1).

3.3. Survival analysis

The cumulative probability of survival at 5 years for all patients was 45.3%. The 5-year OS of patients with "nasal" NK/T cell lymphoma was 48.2% and that of patients with "nasal-type" NK/T cell lymphoma was 45.5% that is if the two groups were classified according to the conventional definition, which included all patients with lesions outside nasal cavity ($P = 0.5417$, Fig. 1). The important clinical factors predicting reduced survival were poor performance status (ECOG 2–4), presence of B symptoms, elevated LDH, and bone marrow involvement in the univariate analysis (Table 2). Patients with primary sites other than upper aerodigestive tract particularly showed poorer survival than those with upper aerodigestive tract lymphoma ($P = 0.0225$). In stepwise Cox multivariate regression analysis, poor performance and high LDH levels had an independent effect on survival (Table 2).

3.4. New classification model

When NK/T cell lymphoma were subcategorised into "nasal" and "nasal-type" according to the conventional anatomic definition, there were 30 extranasal NK/T cell lymphoma cases in this series, of which 10 primarily involved upper aerodigestive tract. These patients (upper aerodigestive tract NK/T cell lymphoma, UA group) had lymphomas presenting primarily at oropharynx, oral cavity, tonsil, and palate, and behaved in a distinctive pattern when compared to other extranasal NK/T cell lymphoma patients (Table 1). The UA group presented with better performance (100% *vs.* 56%, $P = 0.039$), lower initial stage (90% *vs.* 55%, $P = 0.014$), and lower IPI score (100% *vs.* 50%, $P = 0.032$) when compared to those of nasal-type non-UA group. The CR rate achieved after anthracycline-based chemotherapy was also higher in the UA group (80% *vs.* 20%, $P = 0.010$) than the non-UA group. Thus, the UA group had more favorable clinical features than the non-UA group among "nasal-type" NK/T cell lymphomas and behaved more similar to "nasal" NK/T cell lymphoma rather than "nasal-type" lymphoma (Table 1).

From theses results, we categorised NK/T cell lymphoma patients according to a newly proposed classification: UNKTL (upper aerodigestive tract NK/T cell lymphoma) included all lymphomas confined to nasal cavity, nasopharynx, and upper aerodigestive tract such as, larynx, pharynx, and oral cavity. Lymphomas involving all other sites were categorised into EUNKTL (extra upper aerodigestive tract NK/T cell lymphoma) group. The EUNKTL had advanced stage at diagnosis, higher LDH, higher IPI score, poorer performance and inferior response to the anthracycline-based chemotherapy with statistical significance as shown in Table 3. Most importantly, there was a significant difference in

Table 3
Clinical features according to modified classification

	EUNKTL ($n = 20$)	UNKTL ($n = 70$)	P value
Age	50 (22–81)	46 (21–68)	0.422
Sex (% Male)	65%	61%	0.973
Stage I/II	11 (55%)	55 (79%)	0.050
IPI			
Low	5 (25%)	47 (67%)	0.010
Low–intermediate	5 (25%)	8 (11%)	
High–intermediate	5 (25%)	10 (14%)	
High	5 (25%)	5 (7%)	
LDH (high)	14 (70%)	29 (41%)	0.041
B symptom (+)	11 (55%)	18 (26%)	0.050
Performance (ECOG > 2)	11 (56%)	2 (3%)	<0.0001
EBV *in situ*	11/14 (79%)	48/52 (92%)	0.921
CR rate achieved after anthracycline-based chemotherapy[a]	2/10 (20%)	44/69 (64%)	0.008

[a] Only in patients who were primarily treated with anthracycline-based chemotherapy.

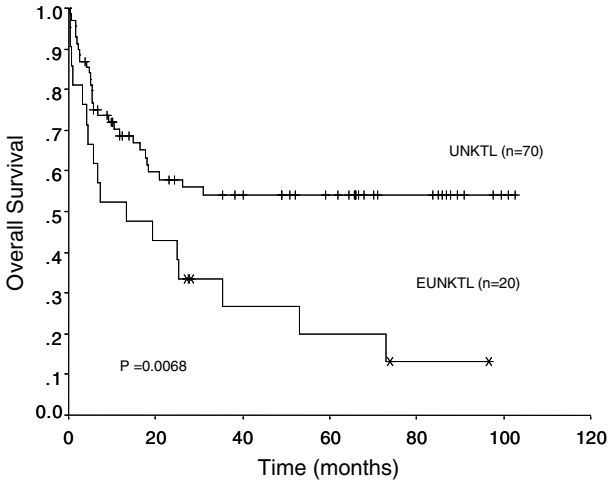

Fig. 2. Overall survival curve according to new classification model.

survival rates between the EUNKTL and UNKTL group (20.0%, 54.0%, respectively, $P = 0.0068$, Fig. 2).

4. Discussion

Nasal NK/T cell lymphoma has recently been recognised as a distinctive clinicopathologic entity, and classified as angiocentric lymphoma in the Revised European American Lymphoma (REAL) classification [2,3,20]. Since the term "angiocentric" is not entirely specific, the term "nasal" NK/T cell lymphoma has been adopted in the WHO new classification of haemato-lymphoid neoplasm [1]. A clinical advisory committee of international hematologists held a consensus meeting in 1997 and emphasised the importance of clinical features and location (nodal *vs*. extranodal and specific extranodal sites) in determining the biologic behavior and definition of T and NK-cell neoplasms [21]. This is the first report to analyse clinical features of "nasal" and "nasal-type" NK/T cell lymphoma and review the current classification system.

Although the nasal cavity is the most common site of involvement, NK/T cell lymphoma is also known to occur outside nasal cavity. This "nasal-type" NK/T cell lymphoma is important to recognise because it is known to be one of the most aggressive forms of lymphoma with mortality reported up to 82% [4]. This disease entity has not been extensively studied due to its rarity and there has been no previous report comparing clinical features of "nasal-type" NK/T cell lymphoma with "nasal" NK/T cell lymphoma. The anatomic definition of extranasal NK/T cell lymphoma has been vague resulting in variable definitions of extranasal sites by different groups [3–17]. Chan and colleagues reported a summary of 32 cases of non-nasal NK/T cell lymphomas and defined extranasal sites as lymphomas with preference for skin, upper aerodigestive tract, testis, gastrointestinal tract, soft tissues, and spleen [4]. Two patients with upper aerodigestive tract involvement in their study were alive with disease in 2 and 5 years, respectively. Other studies have also subcategorised lymphomas of upper aerodigestive tract as extranasal NK/T cell lymphoma [3–7,9–17]. Ko and colleagues recently reviewed their experience with NK/T cell lymphomas at extranasal sites and showed that CD56+ lymphomas of upper aerodigestive tract excluding nasal cavity and nasopharynx achieved better overall survival [7]. Another study also found no difference in OS between "nasal" and "nasal-type" NK/T cell lymphoma as they defined "nasal-type" as lesions occurring outside nasal cavity [10]. Because these subtypes pursue different clinical course, and possibly, a different therapeutic approach, a clear definition should be established, as they may need more aggressive therapeutic approach.

For these reasons, we conducted a retrospective analysis in order to characterise distinctive clinical features of the two subcategories of extranodal NK/T cell lymphoma, nasal-type. Considering the fact that upper aerodigestive tract diseases pursue less aggressive clinical behavior, with more favorable prognostic factors such as low LDH, good performance and localised disease than the rest of extranasal NK/T cell lymphomas while sharing similar clinical features with nasal NK/T cell lymphoma, we suggest to categorise lymphomas primarily involving the nasal cavity and the upper aerodigestive tract to "nasal" NK/T cell lymphoma. We postulate that the clinical course of upper aerodigestive tract lymphomas is similar to that of "nasal" NK/T cell lymphoma due to similar tumorigenesis by EBV infection. Although the exact pathogenesis of NK/T cell lymphomas in relation to EBV infection remains undefined,

there are indirect evidences that EBV infection plays a crucial role in tumorigenesis. Recently, the EBV-carrying NK cell line has been established *in vitro* by EBV infection of human NK cells for the first time indicating its direct infectivity for human NK cells [22]. Increased circulating EBV DNA titer in serum is associated with poor prognosis in NK/T cell lymphoma, which is further supported by better survival observed in EBV-negative extranasal NK/T cell lymphomas [7,23]. The mucosa of nasal cavity, nasopharynx and upper aerodigestive tract may be directly exposed and infected with EBV and could result in more localised and thus, less aggressive clinical course in ''nasal'' NK/T cell lymphoma. It can be further postulated that a systemic EBV infection with circulating EBV in plasma may induce ''nasal-type'' NK/T cell lymphoma, which often present with disseminated disease. In our study, the EUNKTL group initially showed high IPI score, higher LDH, more B symptoms, and poorer performance when compared to those of the UNKTL group. Thus, systemic treatment should be administered early in the treatment course for the EUNKTL group.

The role of radiation therapy has been increasingly recognised, especially in localised nasal NK/T cell lymphomas [15–17]. Due to the various anatomic presentations of ''nasal-type'' NK/T cell lymphoma including gastrointestinal lymphomas, the radiation therapy is not always feasible in these patients. Four of the 11 patients in non-UA group have received the sequential radiation therapy and the remaining patients had gastrointestinal presentation. Therefore, the role of radiation therapy in localised ''nasal-type'' NK/T cell lymphoma is yet to be established.

According to our analysis, we suggest to exclude upper aerodigestive tract disease from the ''nasal-type'' NK/T cell lymphoma to better reflect the prognosis. ''Nasal'' NK/T cell lymphoma should include upper aerodigestive tract lesions as well as those confined to nasal cavity. Different therapeutic approaches should be sought for each group of patients, perhaps employing more aggressive treatment for EUNKTL patients.

Conflict of interest statement

None declared.

References

1. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization classification of tumours. Pathology and genetics of tumours of the hematopoietic and lymphoid tissues*. Lyon, France, IARC Press, 2001.
2. Jaffe ES. Classification of natural killer (NK) cell and NK-like T-cell malignancies. *Blood* 1996, **87**, 1207–1210.
3. Jaffe ES, Chan JKC, Shipp M, *et al*. Report of the workshop on nasal and related extranodal angiocentric T/natural killer cell lymphomas: definitions, differential diagnosis and epidemiology. *Am J Surg Pathol* 1996, **20**, 103–111.
4. Chan JK, Sin VC, Lau WH, *et al*. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood* 1997, **89**, 4501–4513.
5. Wong KF, Chan JKC, Ng CS, *et al*. CD56 (NKH1)-positive hematolymphoid malignancies: an aggressive neoplasm featuring frequent cutaneous/mucosal involvement, cytoplasmic azurophilic granules and angiocentricity. *Hum Pathol* 1992, **23**, 798–804.
6. Kern WF, Spier CM, Hanneman EH, *et al*. Neural cell adhesion molecule-positive peripheral T-cell lymphoma: a rare variant with a propensity for unusual sites of involvement. *Blood* 1992, **79**, 2432–2437.
7. Ko YH, Cho EY, Kim JE, *et al*. NK and NK-like T-cell lymphoma in extranasal sites: a comparative cllinicopathological study according to site and EBV status. *Histopathology* 2004, **44**, 1–10.
8. Kobashi Y, Nakamura S, Sasajima YS, *et al*. Inconsistent association of Ebstein-Barr virus with CD56 (NCAM)-positive angiocentric lymphoma occurring in sites other than the upper and lower respiratory tract. *Histopathology* 1996, **28**, 111–120.
9. Nakamura S, Suchi T, Koshikawa T, *et al*. Clinicopathologic study of CD56 (NCAM) positive angiocentric lymphoma occurring in sites other than the upper and lower respiratory tract. *Am J Surg Pathol* 1995, **19**, 284–296.
10. Bekkenk MW, Jansen PM, Meijer CJLM, *et al*. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol* 2004, **15**, 1097–1108.
11. Ko YH, Ree HJ, Kim WS, *et al*. Clinicopathologic and genotypic study of extranodal nasal-type natural killer/T-cell lymphoma and natural killer precursor lymphoma among Koreans. *Cancer* 2000, **89**, 2106–2116.
12. Jaffe ES, Krenacs L, Kumar S, *et al*. Extranodal peripheral T-cell and NK-cell neoplasms. *Am J Clin Pathol* 1999, **111**(Suppl. 1), S46–S55.
13. Peiper SC. Angiocentric lymphoproliferative disorders of the respiratory system: incrimination of Epstein-Barr virus in pathogenesis. *Blood* 1993, **82**, 687–690.
14. Kim BS, Kim TY, Kim CW, *et al*. Therapeutic outcome of extranodal NK/T-cell lymphoma initially treated with chemotherapy. *Acta Oncol* 2003, **42**, 779–783.
15. 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.
16. Kim GE, Cho JH, Yang WI, *et al*. Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation treatment. *J Clin Oncol* 2000, **18**, 54–63.
17. Ribrag V, Ell Hajj M, Janot F, *et al*. Early locoregional high-dose radiotherapy is associated with long-term disease control in localized primary angiocentric lymphoma of the nose and nasopharynx. *Leukemia* 2001, **15**, 1123–1126.
18. Cheson BD, Horning SJ, Coiffier B, *et al*. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 1999, **17**, 1244–1253.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
20. Harris NL, Jaffe ES, Stein H, *et al*. A Revised European-American Classification of lymphoid neoplasm: A proposal from

the International Lymphomas Study Group. *Blood* 1994, **84**, 1361–1392.

21. Harris NL, Jaffe ES, Diebold J, *et al*. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting – Airlie House, Virginia, November 1997. *J Clin Oncol* 1999, **17**, 3835–3849.
22. Isobe Y, Sugimoto K, Yang L, *et al*. Epstein-Barr virus infection of human natural killer cell lines and peripheral blood natural killer cells. *Cancer Res* 2004, **64**, 2167–2174.
23. Au WY, Pang A, Choy C, *et al*. Quantification of circulating Epstein-Barr virus DNA in the diagnosis and monitoring of natural killer and EBV-positive lymphomas in immunocompetent patients. *Blood* 2004, **104**, 243–249.