

Prognostic significance of locally invaded sites and tissue types in patients with nasal extranodal natural-killer/T-cell lymphoma: a single-center retrospective analysis

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Abstract

Background: Extranodal natural killer/T-cell lymphoma (ENKTL), nasal type, is an aggressive entity within the World Health Organization classification of lymphoid tumors. The International Prognostic Index is reported to be prognostically meaningful for ENKTL, but lacks discriminatory power for stage I/II ENKTL with extensive local invasion. This study aimed to evaluate the prognostic effects of local invasion by site and tissue type in patients with ENKTL.

Methods: We retrospectively analyzed data of 86 patients who were diagnosed with ENKTL by the Department of Pathology of Beijing Tongren Hospital from June 2002 to April 2016, and ascertained tumor infiltration of adjacent structures (AS), bone, and soft tissue for each patient, using physical findings and imaging scans. We used univariate and multivariate analysis to assess the association of each involved tissue or site with patients' overall survival (OS).

Results: Of the 86 patients, 71(82.6%) experienced invasion of AS, 22(25.6%) of soft tissue, and 26(30.2%) had bone involvement. Overall, patients with AS involvement did not show significantly shorter survival than those without AS involvement (Log rank $\chi^2 = 1.177$, $P = 0.278$); however, patients who had involved eyeballs or brains showed significantly lower 2-year OS rates than those without eyeball involvement (Log rank $\chi^2 = 4.105$, $P = 0.043$) or brain involvement (Log rank $\chi^2 = 7.126$, $P = 0.008$). Patients with involved local soft tissue or bones, respectively, showed lower 2-year OS rates than those without involved local soft tissue (Log rank $\chi^2 = 10.390$, $P = 0.001$) or bones (Log rank $\chi^2 = 8.993$, $P = 0.003$). Multivariate analysis showed that involvement of the cheek or facial muscles (hazard ratio, HR = 5.471, 95% confidence interval [CI]: 1.466–20.416, $P = 0.011$) and the maxilla bone (HR = 6.120, 95% CI: 1.517–24.694, $P = 0.011$) were significantly independent predictors of lower 2-year OS rates.

Conclusions: Imaging can accurately detect ENKTL invasion of AS, soft tissue, and bone. Involvement of local soft tissue or bone was significantly associated with lower 2-year OS rates. Involvements of the cheek or facial muscle, as well as maxilla bone, are independent predictors of lower 2-year OS rates in ENKTL patients.

Keywords: Lymphoma; Natural killer cells; T-cell; Neoplasm; Invasiveness; Prognosis

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL), nasal type, is an aggressive entity within the World Health Organization (WHO) classification of lymphoid tumors.^[1] T-cell and NK-cell neoplasms comprise less than 10% of all non-Hodgkin lymphomas.^[2] The 2016 WHO classification includes both nasal and extranasal ENKTLs in this type of non-Hodgkin lymphoma. Nasal NK/T-cell lymphoma

comprises approximately 80% of ENKTL cases; it occurs in the nose, nasopharynx, oropharynx, Waldeyer ring, and parts of the upper aerodigestive tract.^[3] Current treatment methods include radiotherapy, chemotherapy, and hematopoietic stem cell transplantation.^[4-6] Although most patients are diagnosed in early stages of the disease, the reported 5-year overall survival (OS) rates are limited to 42% to 60%;^[2,5-8] moreover, no gold-standard treatment has been established for patients with advanced, refractory, and/or relapsed ENKTL.^[4-6]

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The International Prognostic Index (IPI) is reportedly prognostically meaningful for ENKTL,^[9] but lacks discriminatory power for stage I/II ENKTL with extensive local invasion. The Korean Prognostic Index considers B symptoms and regional lymph node involvement to stratify ENKTL patients on the basis of risk levels.^[7] Both IPI and KPI models use the Ann Arbor staging system. However, Kim *et al*^[10] showed that the Ann Arbor system did not predict survival differences between stage I_E and stage II_E in a Korean multicenter study because ENKTL is clinically heterogeneous, such that it includes variations in paranasal extension, bone destruction, and skin involvement.

Kim *et al*^[10] defined local tumor invasiveness (LTI) as bony invasion, or as perforation or invasion of the skin. They demonstrated that LTI was independently associated with a low probability of complete response, as well as shorter OS and disease-free survival (DFS; $P < 0.001$). In contrast, Lee *et al*^[7] found that LTI was significantly associated with shorter OS in univariate analysis ($P = 0.0097$), but not in multivariate analysis. Cheung *et al*^[11] reported no prognostic significance for paranasal extension in stage I ENKTL. Wu *et al*^[12] showed that primary tumor invasion (PTI; defined as primary disease extending into neighboring structures or organs, regardless of stage or primary site^[13]) had a significant impact on 5-year OS for patients with early-stage ENKTL ($P = 0.012$). However, they did not find that bone or skin invasion was associated with significantly shorter 5-year OS ($P = 0.087$).^[12] Yan *et al*^[14] considered LTI to be sufficiently important that they designed a new tumor node metastasis (TNM) staging system for ENKTL.

To help address this controversy, we performed the current study, in which we assessed the effects of tissue and structure invasion on 2-year OS in a cohort of 86 patients with ENKTL, including adjacent structures (ASs), soft tissue, and bone. We evaluated the prognostic significance of involvement of these structures and tissue types in ENKTL patients, with the aim of providing better predictive data for clinicians who treat these patients.

Methods

Ethical approval

Written informed consent was obtained from all patients, and this project was approved by the Ethics Committee of Beijing Tongren Hospital Clinical Research (No. TRECKY2013-KS-03).

Study design

We retrospectively analyzed data of 86 patients who were diagnosed with ENKTL by the Department of Pathology of Beijing Tongren Hospital from June 2002 to April 2016. The follow-up period ended in November 2017. The inclusion criteria were (1) a diagnosis confirmed by two pathologists, based on the 2008 WHO classification of malignant tumors of the lymphatic hematopoietic system^[15]; (2) detailed follow-up and available clinical information; and (3) available positron emission tomography/computed tomography (PET/CT) scans, or CT and

magnetic resonance imaging (MRI) scans of the head and neck. We excluded patients who (1) had inadequate follow-up data; or (2) had no PET/CT, MRI, or CT imaging information. The pathological data were retrospectively reviewed by GHD and XL; imaging data were retrospectively reviewed by YL and JYD.

We characterized infiltration of the patients' AS, bone, and local soft tissue by physical findings, CT, MRI, or PET/CT scans. Cervical, inguinal, or axillary lymphadenopathies, as well as hepatomegaly and splenomegaly, were also evaluated by PET/CT scan or B-ultrasound examination. Among the 86 patients, 59 (68.6%) had PET/CT data, and 27 (31.4%) had both CT and MRI data.

Technical information

Imaging methods

All PET/CT scans were performed by using the following protocols. In brief, approximately 60 min after intravenous injection of ¹⁸F-fluorodeoxyglucose (FDG) (370–555 MBq), CT and subsequent whole-body PET were performed. Maximum standardized uptake values (SUV_{max}) were obtained and corrected for body weight using the standard formula:

$$\text{SUV}_{\text{max}} = \text{mean regions of interest activity (MBq/mL) / (injected dose [MBq] / \text{body weight [kg]})^{[16]}$$

Interpretation was based on the method described by Cashen *et al*^[17] and criteria established by the International Harmonization Project for end-of-treatment PET.^[18]

All CT scans were performed using Philips Brilliance 32-row/64-row CT machine (Philips Medical Systems, Best, the Netherlands; scanning parameter matrix: 512 × 512 pixels, vision: 18 cm × 18 cm, and layer thickness: 0.67 mm). Coronal and sagittal images were reconstructed after completion of the scan. The enhanced scan used the three fat-inhibition images from the cross-section, coronal, and sagittal planes.

MRI scans used a GE Signa HDxt1.5T/3.0T MRI scanner (GE Healthcare Technologies, Ohio, Cincinnati, USA; Scanning parameter matrix: 512 × 512 pixels, field: 24 cm × 24 cm, and layer thickness: 2.5 mm). Scanning was performed along the axial, sagittal, and coronal planes in the head and neck region.

Pathological methods

Specimens were fixed with 4% formaldehyde solution and embedded with paraffin. Immunohistochemistry was performed using formalin-fixed paraffin-embedded 4- μm -thick tissue sections. Antibodies included those specific for cytoplasmic CD3 ϵ , CD8, CD20, CD56, granzyme B, T-cell intracellular antigen, and perforin. We performed *in situ* hybridization (ISH) using Epstein-Barr virus-encoded RNA (*EBER*) for all cases. Antibodies and *EBER* ISH kits were purchased from Beijing Zhong Shan Jinqiao Biological Company (Beijing, China). Known positive and negative specimens were used as positive and negative controls.

Statistical analysis

Statistical analysis was performed with SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA). OS was defined as the length of time from initial diagnosis to death from any cause, or to last follow-up. Estimated OS was calculated using the Kaplan-Meier method, then compared among groups with log-rank tests. Univariate analysis was used to assess the associations of respective clinical factors and local invasion types with OS. Cox regression modeling was used to estimate hazard ratios (HRs) and confidence intervals (CIs) for variables that were significant in multivariate analysis. A $P < 0.05$ was considered to be significant.

Results

Clinical characteristics of patients with ENKTL

Complete data were available for 86 patients. All patients' clinical features are summarized in Table 1. The median age at diagnosis was 42.5 years (range: 13–76 years). Seventy-seven (89.5%) patients were younger than 60 years of age. The male-to-female ratio was 2.9:1. All of the patients' lesions were present in the upper aerodigestive tract, including 71 (82.6%) with nasal cavity lesions (28 unilateral lesions and 43 bilateral lesions) and 15 (17.4%) with extranasal lesions (two sinus lesions, five laryngopharynx lesions, and eight nasopharynx lesions). Additionally, 57 (66.3%) patients had B symptoms (weight loss of >10% within 6 months, night sweats, and fever of unknown origin). Among the 86 patients, 19 (22.1%) had stage I_E disease and 36 (41.9%) had stage II_E disease; 76 (88.4%) had Eastern Cooperative Oncology Group (ECOG) performance status 0–1. Lactate dehydrogenase was elevated in 29.1% (23/79). According to the IPI, 46 (53.5%) patients were at low risk (IPI 0–1). In this study, all patients received anthracycline or asparaginase-based chemotherapy regimens as primary treatments; 55 (63.5%) patients also received radiotherapy.

Pathological characteristics

Of the 86 patients, 76 (88.4%) exhibited an angiodesructive growth pattern and 65 (75.6%) exhibited various degrees of coagulative necrosis. Immunohistochemical analysis showed that tumor cells in 86 (100%) patients were positive for cytoplasmic CD3, but negative for CD20, and 84 (97.7%) were positive for CD56. Expression of the cytotoxic markers granzyme B and T-cell intracellular antigen was observed in 83 (96.5%) and 85 (98.8%) patients, respectively. Eighty-six (100%) patients were Epstein-Barr virus-positive, according to the ISH analysis.

Involvement of local AS, soft tissue, and bone

Involvement of local AS, soft tissue, and bone is described in Table 2. Of the 86 patients, 71 (82.6%) showed extension to the AS, including nasopharynx (46.5%), oropharynx (18.6%), laryngopharynx (9.3%), sinus (26.7%), tonsil (7.0%), soft palate (18.6%), hard

Table 1: Clinical characteristics and univariate analysis of their effects on 2-year OS in 86 patients with extranodal natural killer/T-cell lymphoma.

Characteristics	n (%)	2-year OS (%)	χ^2	P
Gender			0.496	0.481
Male	64 (74.4)	71.2		
Female	22 (25.6)	65.9		
Age			2.994	0.084
<60 years	77 (89.5)	66.6		
≥60 years	9 (10.5)	100.0		
Ann Arbor staging			18.240	<0.001
I	19 (22.1)	100.0		
II	36 (41.9)	74.6		
III	8 (9.3)	57.1		
IV	23 (26.7)	44.4		
ECOG score			4.233	0.040
0–1	76 (88.4)	73.9		
2–4	10 (11.6)	30.0		
IPI score			16.225	0.001
0–1	46 (53.5)	84.9		
2	22 (25.6)	66.0		
3	17 (19.8)	35.3		
4–5	1 (1.2)	100.0		
B Symptoms			1.313	0.252
Yes	57 (66.3)	66.7		
No	29 (33.7)	75.3		
Elevated LDH*			0.960	0.327
Yes	23 (29.1)	59.7		
No	56 (70.9)	74.5		
Elevated β 2-MG [†]			0.471	0.492
Yes	38 (55.1)	74.6		
No	31 (44.9)	69.4		
Lymphadenopathy			1.249	0.264
Yes	65 (75.6)	66.7		
No	21 (24.4)	79.0		
Hepatomegaly			0.329	0.566
Yes	2 (2.3)	50.0		
No	84 (97.7)	70.0		
Splenomegaly			0.133	0.715
Yes	14 (16.3)	84.4		
No	72 (83.7)	67.8		
BM involvement			0.060	0.807
Yes	4 (4.7)	75.0		
No	82 (95.3)	69.3		

β 2-MG: β 2-microglobulin; BM: Bone marrow; ECOG: Eastern Cooperative Oncology Group; ENKTL: Extranodal natural killer/T-cell lymphoma: nasal type; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OS: Overall survival. *7 patients missed LDH data. [†]17 patients missed β 2-MG data.

palate (12.8%), eyeball (4.7%), and brain (3.5%). Involved local soft tissue was present in 22 (25.6%) patients, including eyelid (10.5%), upper lip (14.0%), and cheek or facial muscle (16.3%). Local bone destruction or erosion was present in 26 (30.2%) patients, including orbit (17.4%), hard palate (12.8%), maxilla (7.0%), and base of skull (5.8%). Lymphadenopathy was observed in 65 (75.6%) patients and splenomegaly in 14 (16.3%) patients. Two (2.3%) patients showed hepatomegaly [Table 1].

Table 2: Involvement of adjacent structures, soft tissue, or bones in 86 patients with ENKTL.

Characteristic	n	%
Involvement of adjacent structure	71	82.6
Nasopharynx	40	46.5
Oropharynx	16	18.6
Laryngopharynx	8	9.3
Sinus	23	26.7
Tonsil	6	7.0
Soft palate	16	18.6
Hard palate	11	12.8
Eyeball	4	4.7
Brain	3	3.5
Involvement of soft tissue	22	25.6
Eyelid	9	10.5
Upper lip	12	14.0
Cheek or facial muscle	14	16.3
Involvement of bone	26	30.2
Hard palate	11	12.8
Orbit	15	17.4
Maxilla	6	7.0
Base of skull	5	5.8

ENKTL: Extranodal natural killer/T-cell lymphoma: nasal-type.

OS analysis

The median follow-up time was 28.6 months (range: 1–118 months). The 2 and 5-year OS rates for all patients were 69.7% and 61.2%, respectively [Figure 1A]. Correlations between clinicopathological factors and OS are listed in Table 1. Stage, IPI, and ECOG performance status were prognostic for OS in univariate analysis [Figure 1B–1D]. Two-year OS rates for patients with stages I, II, III, and IV disease were 100%, 74.6%, 57.1%, and 44.4%, respectively (Log rank $\chi^2 = 18.240$, $P < 0.001$). Patients with ECOG scores 0–1 had a statistical significantly higher 2-year OS rate (73.9%) than patients with ECOG score ≥ 2 (30.0%; Log rank $\chi^2 = 4.233$, $P = 0.040$). Similarly, 2-year OS rates for patients with IPI scores 0–1, 2, 3, and 4–5 were 84.9%, 66.0%, 35.3%, and 100%, respectively (Log rank $\chi^2 = 16.225$, $P = 0.001$).

Correlations between LTI and OS are listed in Table 3. Notably, 2-year OS rate did not significantly differ between patients with and without AS involvement (Log rank $\chi^2 = 1.177$, $P = 0.278$) [Figure 2A]. However, patients with involved eyeballs or brain had significantly lower respective

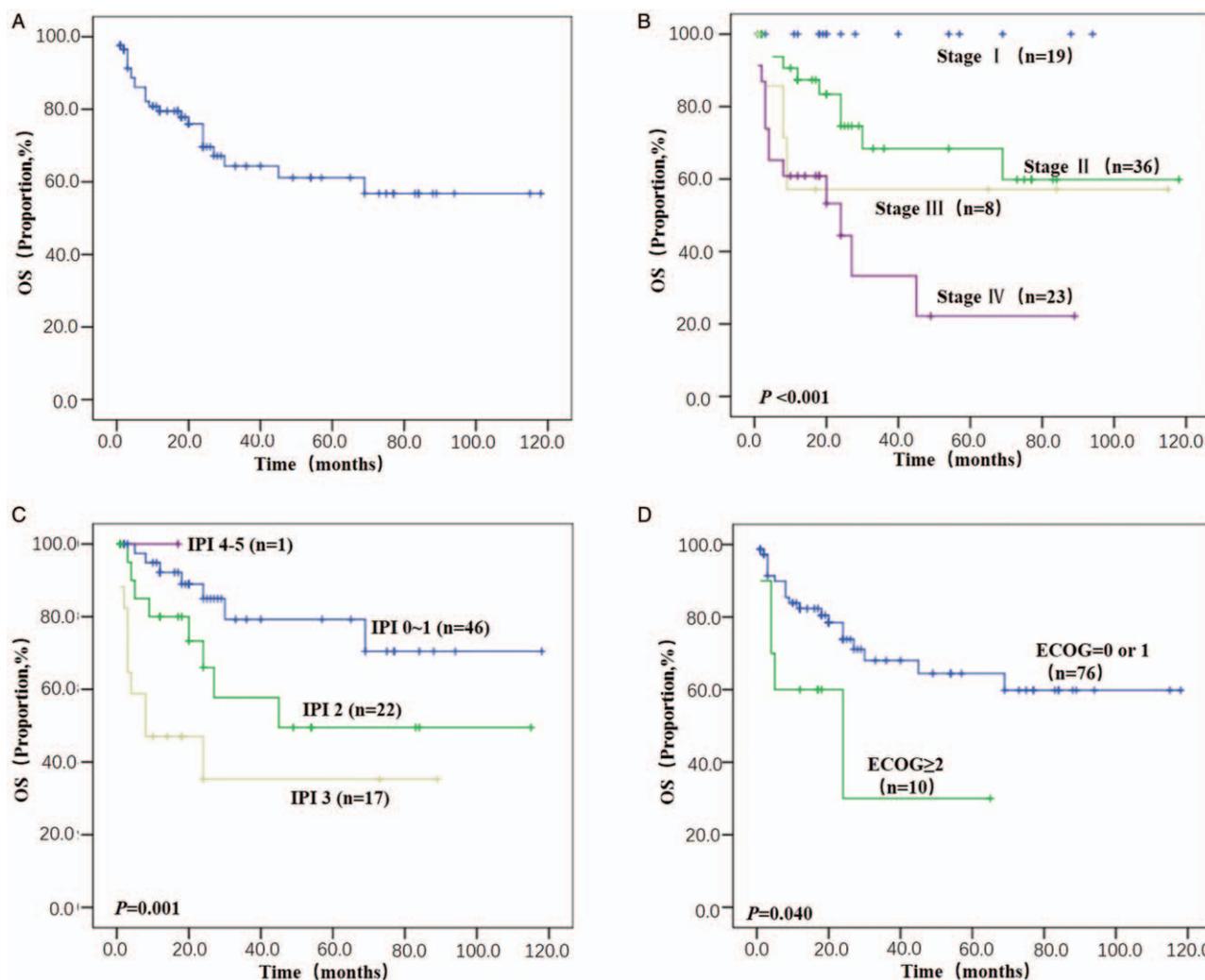


Figure 1: Kaplan-Meier curves (log-rank test) for overall survival (A; OS); Ann Arbor stage (B); International Prognostic Index (C; IPI); and Eastern Cooperative Oncology Group (ECOG) score (D) among 86 patients with natural killer/T-cell lymphoma.

Table 3: Correlations between local tumor invasiveness and OS by univariate analysis.

Involvement site	n (%)	2-year OS	χ^2	P
Adjacent structure	71 (82.6)	68.4	1.177	0.278
Nasopharynx				
Yes	40 (46.5)	62.7	1.610	0.204
No	46 (53.5)	76.6		
Oropharynx				
Yes	16 (18.6)	84.4	0.413	0.520
No	70 (81.4)	66.3		
Laryngopharynx				
Yes	8 (9.3)	85.7	0.931	0.334
No	78 (90.7)	78.9		
Sinus				
Yes	23 (26.7)	64.4	2.629	0.105
No	63 (73.3)	71.7		
Tonsil				
Yes	6 (7.0)	83.3	0.001	0.970
No	80 (93.0)	68.5		
Soft palate				
Yes	16 (18.6)	51.4	0.507	0.477
No	70 (81.4)	73.1		
Hard palate				
Yes	11 (12.8)	63.6	1.965	0.161
No	75 (87.2)	71.5		
Eyeball				
Yes	4 (4.7)	50.0	4.105	0.043
No	82 (95.3)	71.0		
Brain				
Yes	3 (3.5)	33.3	7.126	0.008
No	83 (96.5)	71.3		
Soft tissue	22 (25.6)	42.9	10.390	0.001
Eyelid				
Yes	9 (10.5)	33.9	11.780	0.001
No	77 (89.5)	73.8		
Upper lip				
Yes	12 (14.0)	33.3	2.048	0.152
No	74 (86.0)	73.1		
Cheek or facial muscle				
Yes	14 (16.3)	35.7	16.122	<0.001
No	72 (83.7)	76.4		
Bone	26 (30.2)	51.5	8.993	0.003
Hard palate				
Yes	11 (12.8)	63.6	1.965	0.161
No	75 (87.2)	71.5		
Orbit				
Yes	15 (17.4)	47.9	3.024	0.082
No	71 (82.6)	72.3		
Maxilla				
Yes	6 (7.0)	33.3	17.329	<0.001
No	80 (93.0)	72.8		
Base of skull				
Yes	5 (5.8)	40.0	5.246	0.022
No	81 (94.2)	71.6		

ENKTL: Extranodal natural-killer/T-cell lymphoma: nasal-type; OS: Overall survival.

2-year OS rates than did patients without involved eyeballs (Log rank $\chi^2 = 4.105$, $P = 0.043$) or brain (Log rank $\chi^2 = 7.126$, $P = 0.008$) [Figure 2B and 2C].

Patients with involved local soft tissue had lower respective 2-year OS rates than those without involved soft tissue

(Log rank $\chi^2 = 10.390$, $P = 0.001$). In particular, patients with involved cheek or facial muscles, as well as patients with involved eyelids, had lower respective 2-year OS rates than patients without these involvements (Log rank $\chi^2 = 16.122$, $P < 0.001$ and Log rank $\chi^2 = 11.780$, $P = 0.001$, respectively). However, upper lip involvement

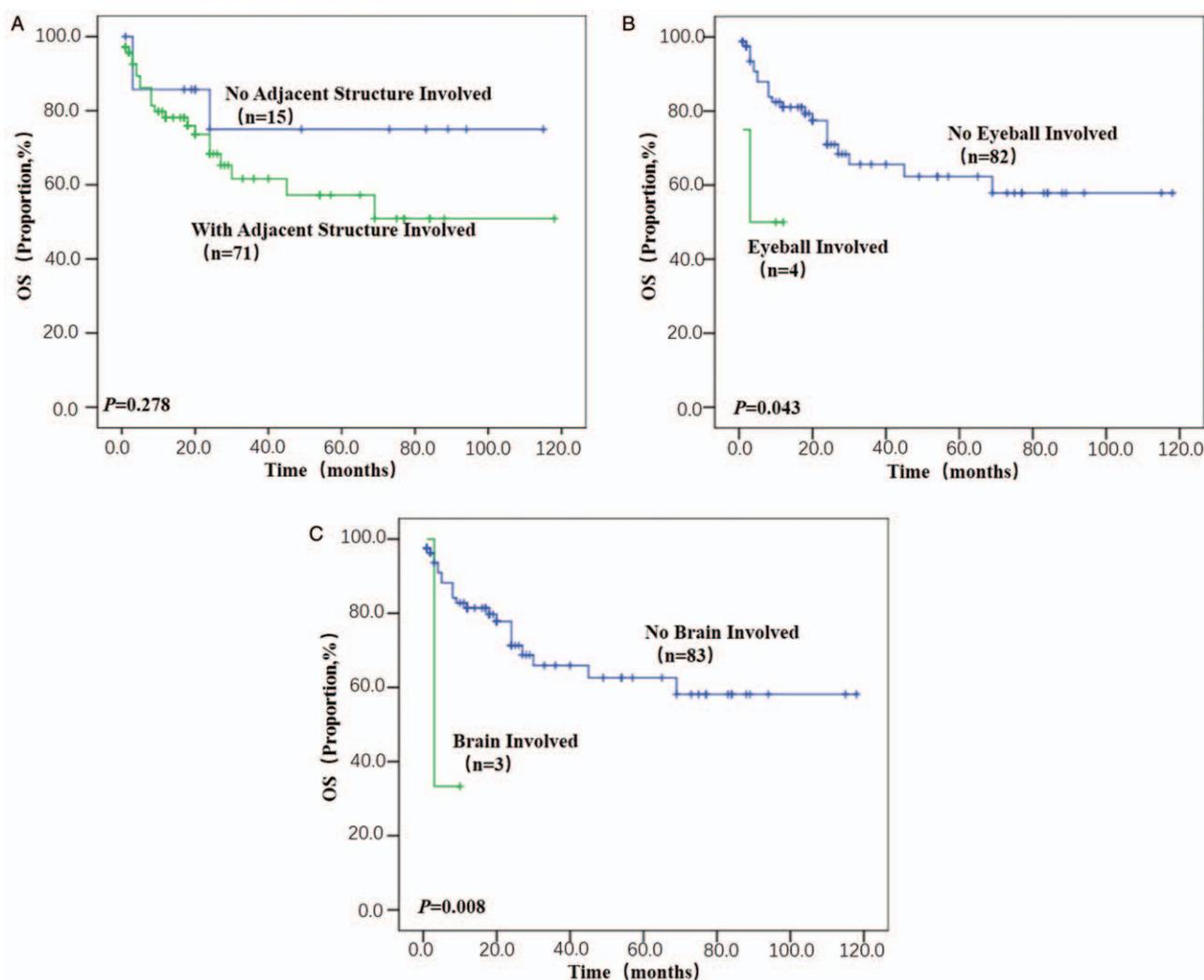


Figure 2: Kaplan-Meier curves (log-rank test) for overall survival (OS) among 86 patients with natural killer/T-cell lymphoma with and without involved adjacent structure (A); with and without involved eyeball (B); and with and without involved brain (C).

did not significantly affect OS (Log rank $\chi^2 = 2.048$, $P = 0.152$) [Figure 3A–3C].

Patients with bone involvement had shorter survival than those without bone involvement (Log rank $\chi^2 = 8.993$, $P = 0.003$). In particular, patients with involved maxilla or skull base had lower 2-year OS rates than did patients without involvement of these bones (Log rank $\chi^2 = 17.329$, $P < 0.001$ and Log rank $\chi^2 = 5.246$, $P = 0.022$, respectively) [Figure 4A–4C]. However, hard palate involvement did not significantly affect survival in this cohort (Log rank $\chi^2 = 1.965$, $P = 0.161$). Patients with orbit involvement tended to have a lower 2-year OS rate, but this effect was not statistically significant (Log rank $\chi^2 = 3.024$, $P = 0.082$).

In multivariate analysis, involvement of cheek or facial muscles and involvement of the maxilla were independent predictors of lower 2-year OS rates (HR = 5.471, 95% CI [1.466–20.416], $P = 0.011$; HR = 6.120, 95% CI [1.517–24.694], $P = 0.011$, respectively) [Table 4].

Discussion

Our study indicated that involvement of soft tissue or bone predicts significant lower 2-year OS rates than does involvement of AS. However, univariate analysis indicated that involvement of eyeball, brain, eyelid, cheek or facial muscle, maxilla, and skull base were significant prognostic predictors of lower 2-year OS rates. Furthermore, in multivariate analysis of all patients, involvement of cheek or facial soft tissue and involvement of the maxilla were independent predictors of lower 2-year OS rates.

Kim *et al*^[10] defined involved structures in LTI as the anterior and medial walls of maxillary sinuses; medial walls of the orbit; anterior and inferior walls of ethmoidal sinuses; the skull base; inferior walls of frontal sinuses, and the hard palate, nasal bone, and septal bones (perpendicular plate of ethmoid and vomer). They characterized the extent of bone involvement based on CT, PET/CT, and physical findings; they also described skin invasion as the infiltration of overlying skin around the tumor. They analyzed the prognostic significance of LTI in 114 patients

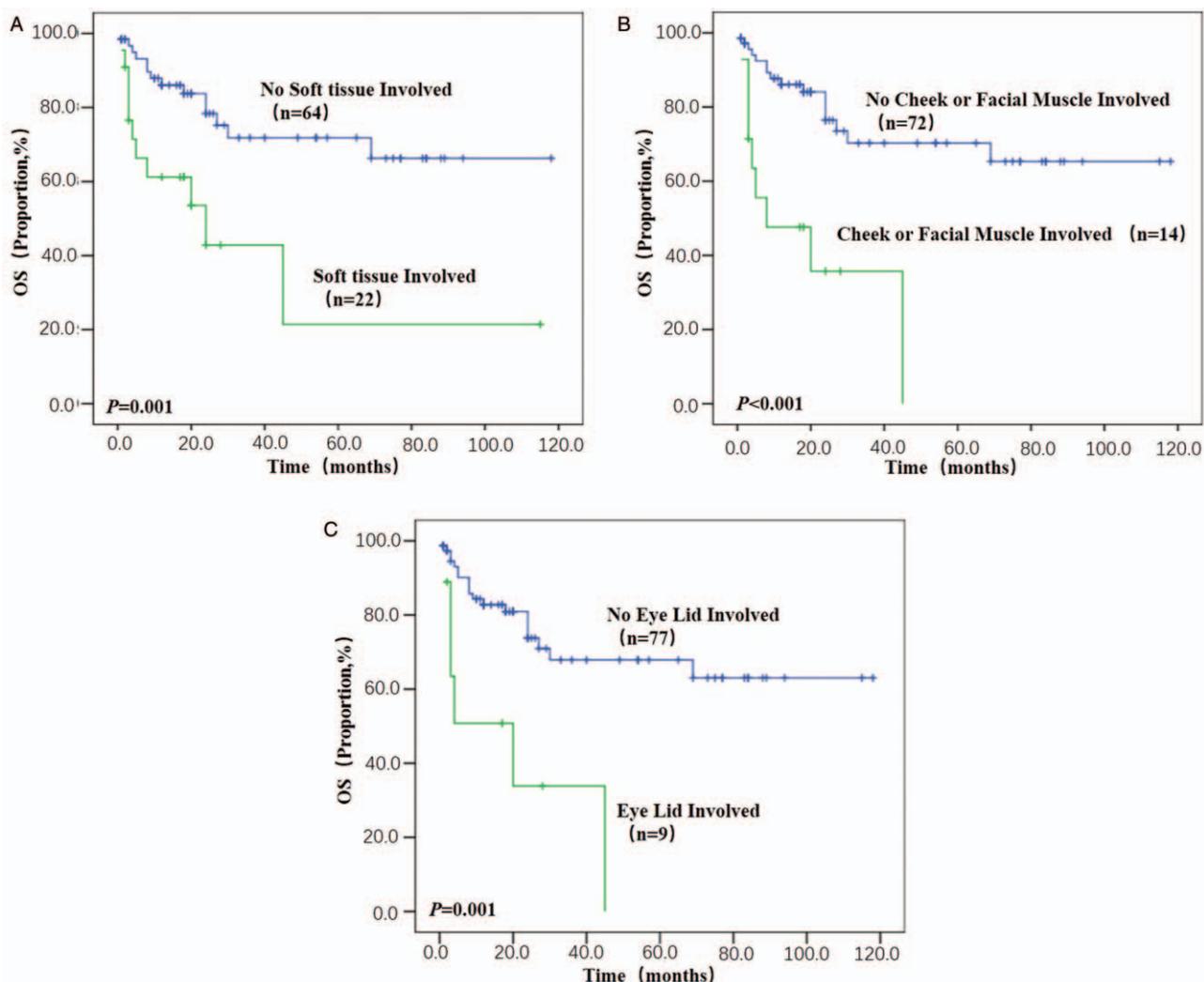


Figure 3: Kaplan-Meier curves (log-rank test) for overall survival (OS) among 86 patients with natural killer/T-cell lymphoma (A) with and without involved local soft tissues; (B) with and without involved cheek or facial muscle; and (C) with and without involved eyelid.

who were diagnosed with stage I/II nasal NK/TCL, and found that LTI was independently associated with low probability of complete response, as well as shorter OS and DFS ($P < 0.001$).

In contrast, Lee *et al*^[7] analyzed LTI in 262 patients, including 222 with upper aerodigestive tract NK/TCL and 40 with extra upper aerodigestive tract NK/TCL. Notably, they demonstrated that LTI was significantly associated with shorter OS in univariate analysis ($P = 0.0097$), but not in multivariate analysis. In subgroup analyses, they found significant survival differences on the basis of LTI in patients without lymph node invasion ($P = 0.0234$), but not in patients with lymph node invasion ($P = 0.8482$).

Cheung *et al*^[11] studied 79 patients with early-stage ENKTL and found no statistical difference in survival outcome between those with disease confined to the nasal cavity (5-year DFS: 44.5%, 5-year OS: 46.6%) and those with paranasal disease extension (5-year DFS: 53.5% [$P = 0.734$], 5-year OS: 56.0% [$P = 0.613$]).

Wu *et al*^[12] demonstrated that PTI (based on MRI scan) significantly affected the 5-year OS rate in 105 patients with early-stage ENKTL ($P = 0.012$). In their study, PTI was defined as primary disease that extended into neighboring structures or organs (eg, primary tumor in the nasal cavity extending to paranasal sinuses and/or nasopharynx, or involvement of multiple, contiguous primary sites, such as the nasopharynx and oropharynx), regardless of stage or primary site.^[13] However, they did not find that bone or skin invasion was associated with significant reduction in 5-year OS rates ($P = 0.087$).^[12]

Prognosis of patients with LTI varies, possibly because specific LTI areas are different. Thus, among patients with involved AS, we need to know exactly which area is involved as these sites and tissues have different prognostic values. For example, we found that lip involvement did not significantly affect prognosis ($P = 0.152$) but the cheek soft tissue involvement was associated with shorter survival ($P < 0.001$). Tang *et al*^[19] reported a rapidly progressing fatal case of ENKTL presenting as orbital inflammation died in 2 weeks after diagnosis.

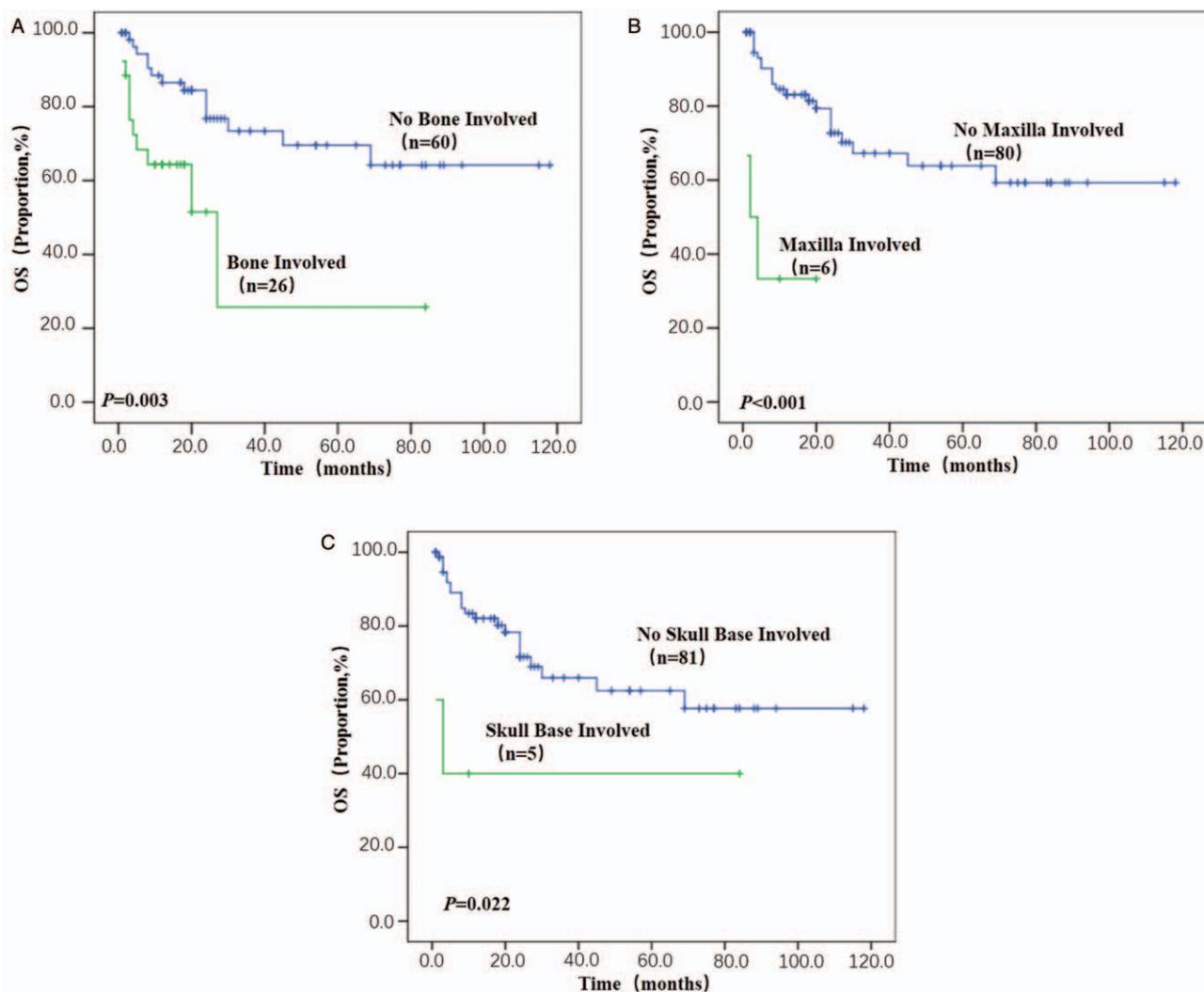


Figure 4: Kaplan-Meier curves (log-rank test) for overall survival (OS) among 86 patients with natural killer/T-cell lymphoma with and without involved local bones (A); with and without involved local maxilla (B); and with and without involved base of skull (C).

Table 4: Multivariate analysis of 86 patients with ENKTL.

Involvement	B	SE	χ^2	P	Exp (B)	95% CI for Exp (B)
Cheek or facial muscle	1.699	0.672	6.399	0.011	5.471	1.466–20.416
Eyelid	-0.096	0.727	0.017	0.895	0.908	0.219–3.777
Orbit	-0.130	0.617	0.044	0.833	0.878	0.262–2.942
Maxilla	1.811	0.712	6.477	0.011	6.120	1.517–24.694
Base of skull	0.987	1.126	0.769	0.380	2.684	0.296–24.366
Eyeball	-1.543	2.111	0.534	0.465	0.214	0.003–13.393
Brain	1.462	1.858	0.619	0.431	4.313	0.113–164.561

CI: Confidence interval; ENKTL: Extranodal natural killer/T-cell lymphoma: nasal-type.

Yan *et al*^[14] established a TNM staging system for nasal ENKTL, which showed excellent performance in prognosticating survival. In their series of 271 patients, 5-year OS rates of patients with stages I, II, III, and IV nasal ENKTL were 92%, 64%, 23%, and 0, respectively. They considered their TNM staging system to be highly effective in stratifying tumor burden and survival risk, which could improve treatment decision making for

patients with nasal ENKTL; this is consistent with our findings in the present study.

Separate analyses of the effect of each locally invaded tissue type, site, or structure on survival will enable better stratification of patients. Accurate early diagnosis is critical for optimal patient treatment. Although this is consistent with the idea of TNM staging, TNM staging has not been

widely used in clinical practice, and most studies continue to use Ann Arbor staging. Therefore, an understanding of the relationships between prognoses and invaded sites is important for the treatment of patients with ENKTL.

Conventional imaging by CT and MRI gives important information regarding the extent of local tumors; CT is more sensitive for bony lesions, whereas MRI is better for soft tissue lesions.^[20] PET/CT is currently regarded as the standard imaging modality for NK/TCL^[21,22]; moreover, PET/CT scans are important for newly diagnosed patients, for whom such scans ensure accurate staging.^[23,24]

This study had some limitations. Most importantly, it included a small cohort and used a single-center design. Our findings should be confirmed in similar studies conducted by multiple institutions with greater numbers of patients.

In summary, PET/CT, CT, and MRI scans could accurately detect involvement of AS, soft tissue, or bone in patients with ENKTL. Soft tissue involvement and bone involvement are both associated with significant reductions in 2-year OS rates. In addition, involvement of cheek or facial muscle soft tissue and involvement of the maxilla are independent predictors of lower 2-year OS rates for patients with ENKTL.

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Conflicts of interest

None.

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