



## Original Research

# Evaluation of different staging systems and prognostic analysis of nasal-type extranodal NK/T-cell lymphoma based on consistent LVDP chemotherapy regimen

Wanchun Wu<sup>a</sup>, Kexin Ren<sup>b</sup>, Na Li<sup>c</sup>, Qian Luo<sup>d</sup>, Caigang Xu<sup>e,\*</sup>, Liqun Zou<sup>f,\*\*</sup>

<sup>a</sup> Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China

<sup>b</sup> Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China

<sup>c</sup> Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China

<sup>d</sup> Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China

<sup>e</sup> Department of Hematology, Hematology Research Laboratory and Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

<sup>f</sup> Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, Chengdu, China



## ARTICLE INFO

## Keywords:

Extranodal NK-T-cell lymphoma  
Chemotherapy  
Prognoses  
Survival  
Staging system

## ABSTRACT

Nasal-type extranodal NK-T-cell lymphoma (ENKTL) is a rare non-Hodgkin lymphoma. The optimal staging system for it remains undefined. In this study, we evaluated different staging systems in 205 patients with nasal-type ENKTL based on a consistent LVDP (L-asparaginase, etoposide, dexamethasone, cisplatin) regimen. All patients were staged by Ann Arbor staging system (AASS) and CA staging system (CASS). Their characteristics, treatment responses, survival outcomes, prognostic factors, and prognostic values of AASS and CASS were analyzed. The median follow-up time was 78 months. All patients received a median 4 cycles of the LVDP chemotherapy. Based on CASS, patients with stages I through IV were more evenly distributed than with AASS, and numbered at 56 (27.3%), 70 (33.2%), 45 (21.9%), and 34 (17.6%), respectively. At the end of therapy, the objective response rate (ORR) was 81.2% for all patients. For all patients, the 5-year progression-free survival (PFS) and overall survival (OS) were 61.6% and 67.8%. According to AASS, the 5-year OS of patients with stages I through IV were 77.9%, 61.2%, 60.0%, and 38.7%, respectively ( $\chi^2=20.578$ ,  $p<0.001$ ). Based on CASS, the 5-year OS of patients with stages I to IV were 89.1%, 65.5%, 58.6%, and 45.4%, respectively ( $\chi^2=22.973$ ,  $p<0.001$ ). In ROC analysis of OS, the area under the curve (AUC) for CASS was 0.70 and 0.64 for AASS. CASS was better in discriminating survival than AASS ( $p = 0.018$ ). In conclusion, the LVDP regimen is effective for nasal-type ENKTL and the CASS has a better prognostic value in survival analysis than the AASS.

## Introduction

Nasal-type extranodal NK-T-cell lymphoma (ENKTL) is an Epstein-Barr virus (EBV) associated, aggressive non-Hodgkin lymphoma [1]. This disease has a remarkable geographical distribution, with a particularly high incidence in East Asia compared with Europe and North America [2,3]. In China, it accounts for 11% of all malignant lymphomas [4].

Unlike other kinds of lymphomas, NK/T cell lymphoma is almost exclusively extranodal, and about 80% of cases occur in the nasal or paranasal area [1,5]. Survival of patients with ENKTL has been

markedly improved by using L-asparaginase-based chemotherapy regimens and the development of radiotherapy technology. However, patients are currently staged and treated primarily depending on the Ann Arbor staging system (AASS), which was originally established for Hodgkin Lymphoma [6]. Patients are classified into one of four stages (I-IV), each with a distinct survival outcome. According to the AASS, most patients (70–90%) have early-stage disease (stage I/II) at diagnosis, and advanced stage (III/IV) is uncommon. Due to unbalanced distribution of patients, the predictive accuracy of this staging system has been shown to be limited for ENKTL [5]. The Prognostic Index for Natural Killer lymphoma with EBV (PINK-E) is a routine prognostic

\* Caigang Xu, Department of Hematology, Hematology Research Laboratory and Pathology, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, China.

\*\* Liqun Zou, Department of Medical Oncology of Cancer Center, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, China.

E-mail addresses: [sucaigang@wchscu.cn](mailto:sucaigang@wchscu.cn) (C. Xu), [zouliqun1971@wchscu.cn](mailto:zouliqun1971@wchscu.cn) (L. Zou).

<https://doi.org/10.1016/j.tranon.2022.101437>

Received 20 February 2022; Received in revised form 23 March 2022; Accepted 20 April 2022

1936-5233/© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Table 1**  
Clinical characteristics of 205 patients with nasal-type ENKTL.

Characteristic	Patients	
	No	%
<b>Age, years</b>		
≤60	174	84.9
>60	31	15.1
<b>Sex</b>		
Male	131	63.9
Female	74	36.1
<b>ECOG PS</b>		
0–1	195	95.1
2–4	10	4.9
<b>B symptoms</b>		
Absent	97	47.3
Present	108	52.7
<b>Serum LDH level</b>		
Normal	153	74.6
Elevated	52	25.4
<b>Plasma EBV-DNA</b>		
Negative	67	32.7
Positive	138	67.3
<b>PINK-E</b>		
0–1	162	79.0
≥2	43	21.0
<b>LTI</b>		
Absent	82	40.0
Present	123	60.0
<b>RLN</b>		
Absent	142	62.3
Present	63	30.7
<b>BM involvement</b>		
Absent	199	97.1
Present	6	2.9
<b>AASS</b>		
I	118	57.6
II	53	25.9
III	6	2.9
IV	28	13.7
<b>CASS</b>		
I	56	27.3
II	68	33.2
III	45	21.9
IV	36	17.6
<b>WBC( × 10<sup>9</sup>L<sup>-1</sup>)</b>		
>4	173	84.4
<4	32	15.6
<b>Platelet( × 10<sup>9</sup>L<sup>-1</sup>)</b>		
>100	195	95.1
<100	10	4.9
<b>Hb (g/L)</b>		
>110	174	84.9
<110	31	15.1
<b>Treatment regimens</b>		
CT alone	21	10.2
CTFRT	54	26.3
CTSRT	129	62.9
RTFCT	1	0.5

Abbreviation: AASS, Ann Arbor staging system; BM, bone marrow; CASS, CA staging system; CT, Chemotherapy; CTFRT, Chemotherapy followed by radiotherapy; CTSRT, Chemotherapy sandwiched radiotherapy; EBV, Epstein–Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; LTI, local tumor invasion; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus; RLN, regional lymph node; RTFCT, radiotherapy followed by chemotherapy; WBC, white blood cell.

system for patients with ENKTL, which consists of five clinical factors (age older than 60 years, stage III/IV of AASS, distant lymph node involvement, non-nasal-type disease, and EBV-DNA). Based on the PINK-E model, most early-stage patients are classified into the low-risk group, but a significant difference is not found for OS and PFS among the low-risk and the intermediate-risk group ( $p = 0.068$  and  $p = 0.079$ , respectively). PINK-E could not predict prognosis for patients with ENKTL [6]. Therefore, a new staging system and optimal prognostic

**Table 2**  
The short-term efficacy of the LVDP chemotherapy in different staging systems.

Treatment outcomes	No. of patients(%)			
	AASS Stage I-II (n = 171)	Stage III-IV (n = 34)	CASS Stage I-II (n = 124)	Stage III-IV (n = 81)
<b>CR</b>	113(66.1)	7(20.6)	89(71.8)	31(38.3)
<b>PR</b>	38(22.2)	9(26.5)	21(16.9)	26(32.1)
<b>SD</b>	4(2.3)	2(5.8)	4(3.2)	2(2.5)
<b>PD</b>	16(9.4)	16(47.1)	10(8.1)	22(27.1)
<b>ORR</b>	151(88.3)	16(47.1)	110(88.7)	57(70.4)

Abbreviation: AASS, Ann Arbor staging system; CASS, CA staging system; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

model are needed for extranodal nasal-type NK/T-cell lymphoma.

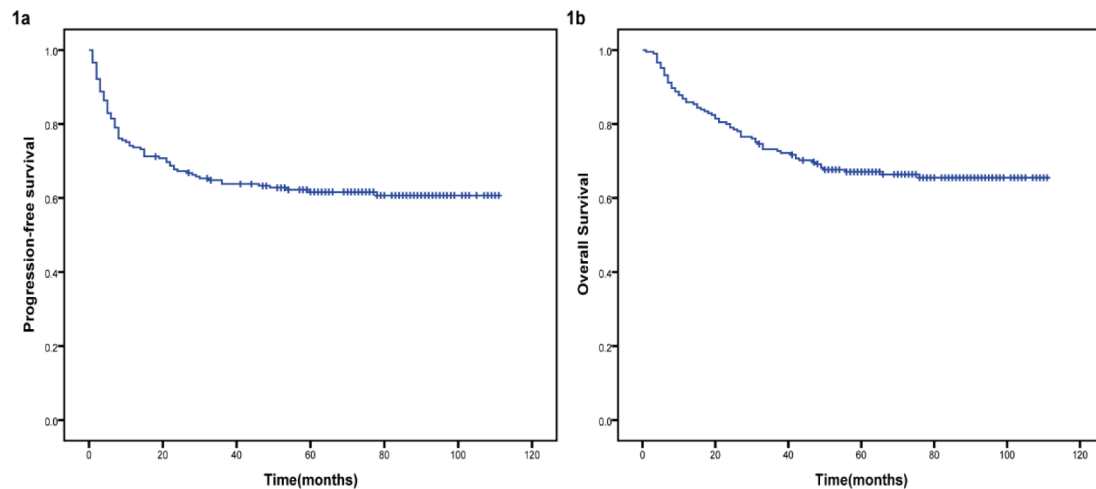
The Chinese Southwest Oncology Group and Asia Lymphoma Study Group (CA) staging system (CASS) is a new staging system, which was established in 2020 based on anatomic factors [7]. Stage I is defined as primary tumor localized to the nasal cavity or nasopharynx without local structures and regional lymph node involvement; stage II is defined as primary tumor localized to the nasal cavity or nasopharynx with local structures involvement without regional lymph node involvement; stage III is defined as primary tumor with regional lymph node involvement; and stage IV is defined as involvement of distant lymph node regions or lymph node regions on both sides of the diaphragm or disseminated involvement of one or more extralymphatic organs or tissues [7]. According to the CASS, the proportions of patients classified as stages I through IV are 27.4%, 35.2%, 18.7%, and 18.7%, respectively [7]. The CASS distribution for these patients is more symmetrical than AASS. Most early-stage patients defined by AASS are categorized as stage III by CASS. As a result, the CASS is better in stratifying survival than the AASS. However, heterogeneous chemotherapy regimens may have an impact on this result. Therefore, we conducted a retrospective study for comparing the value of different staging systems in nasal-type ENKTL based on the first-line, consistent LVDP chemotherapy regimen.

## Method

### Patients

We conducted a retrospective study for patients with newly diagnosed nasal-type ENKTL from January 2012 to January 2017. The inclusion criteria were: (1) pathologically and immunohistochemically confirmed as nasal-type ENKTL based on the 2008 World Health Organization (WHO) classification of lymphomas [8]; (2) received at least two cycles of LVDP chemotherapy with or without radiotherapy; (3) sufficient clinical and laboratory data for staging and survival analyses; and (4) absence of other malignancies. Patients with non-nasal-type ENKTL were excluded. This retrospective analysis was approved by the biomedical research ethics committee of our hospital (ID of ethics approval: SCHX-2020-1039).

Clinical and laboratory data before treatment were collected for analysis and included the following: age, sex, Eastern Cooperative Oncology Group performance status (ECOG) score, presence of B symptoms, complete blood cell count (CBC), lactate dehydrogenase (LDH), plasma EBV DNA, and bone marrow examination including biopsies. Computed tomography (CT) of the head, neck, chest, abdomen, and pelvis; and positron emission tomography/computed tomography (PET/CT) scans were applied for staging. PET/CT was also used for response assessment. PINK-E scores were calculated in this study. Local tumor invasion (LTI) was defined as paranasal involvement or bone destruction or skin involvement according to the previous study [9]. Regional lymph node (RLN) involvement was defined according to definition of N1, N2, or N3 in tumor-node-metastasis (TNM) system.



**Fig. 1.** The long-term survival outcomes of the LVDP chemotherapy for nasal-type ENKTL. a, PFS in all patients; b, OS in all patients. Abbreviations: ENKTL, extranodal NK-T-cell lymphoma; OS, overall survival; PFS, progression free survival.

### Treatment

Except for 21 patients who received LVDP chemotherapy alone, a total of 184 patients received LVDP combined with radiotherapy. Of them, 129 patients received chemotherapy sandwiched radiotherapy (CTSRT) (patients received radiation after 2–3 cycles of LVDP chemotherapy, then continued to receive 2–3 cycles of chemotherapy after radiotherapy), 56 patients received chemotherapy followed by radiotherapy (CTFRT), and only one patient received radiotherapy followed by chemotherapy (RTFCT), due to nasal bleeding. The LVDP regimen was repeatedly given every 21 days as follows: L-asparaginase (5500IU/m<sup>2</sup> intravenously on days 1–5), etoposide (80 mg/m<sup>2</sup> intravenously on days 1–3), dexamethasone (40 mg/day intravenously on days 1–4), and cisplatin (25 mg/m<sup>2</sup> intravenously on days 1–3). Before each cycle, an L-asparaginase skin test was administered; if the result was positive, L-asparaginase was replaced by pegaspargase (3750 IU intramuscularly on day 4). The median number of LVDP cycles was four (range, 2–8). As for radiotherapy, involved fields radiation was performed according to the guidelines of the International Lymphoma Radiation Oncology Group [10]. The median dose of radiotherapy was 50.4 Gy (range, 44–60 Gy).

At initial diagnosis with early-stage ENKTL according to AASS, patients received the LVDP regimen combined with involved-field radiation therapy (IFRT). At initial diagnosis with advanced stage ENKTL according to AASS, patients received consolidation radiation therapy of the primary tumor site or local residual lesion after completing planned chemotherapy. In addition, patients could receive hematopoietic stem cell transplantation (HSCT) after achieving CR or PR. Due to a lack of consensus, treatment methods varied and depended largely on physician choice.

### Efficacy evaluation

All patients underwent efficacy assessment. The treatment efficacy was assessed based on the response criteria of malignant lymphoma and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [11]. The objective response rate (ORR) was defined as the proportion of patients with CR or PR. OS was defined as the time from the date of diagnosis to death or the last follow-up. OS after first relapse or progression was defined as the time from the date of disease recurrence or progression to death or the last follow-up. PFS was designated as the time from the date of diagnosis to the date of disease recurrence, progression, or any-cause death.

### Toxicity evaluation

Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All toxicity data came from physical examinations and blood tests (including CBC, liver and kidney function).

### Statistical analysis

Statistical analysis was performed by SPSS version 22.0 (SPSS Inc, Chicago, IL). All categorical variables were presented through frequency with percentage, and the chi-square test was applied to identify associations between categorical variables. Survival results were performed via the Kaplan-Meier method, and the Log-Rank test was used to compare survival curves. Univariate and multivariate Cox regression analysis were used to identify independent prognostic factors for nasal-type ENKTL. We used receiver operating characteristic (ROC) curves to compare the sensitivity and specificity of different staging systems. If the two-sided P-value was less than 0.05, it was considered statistically significant.

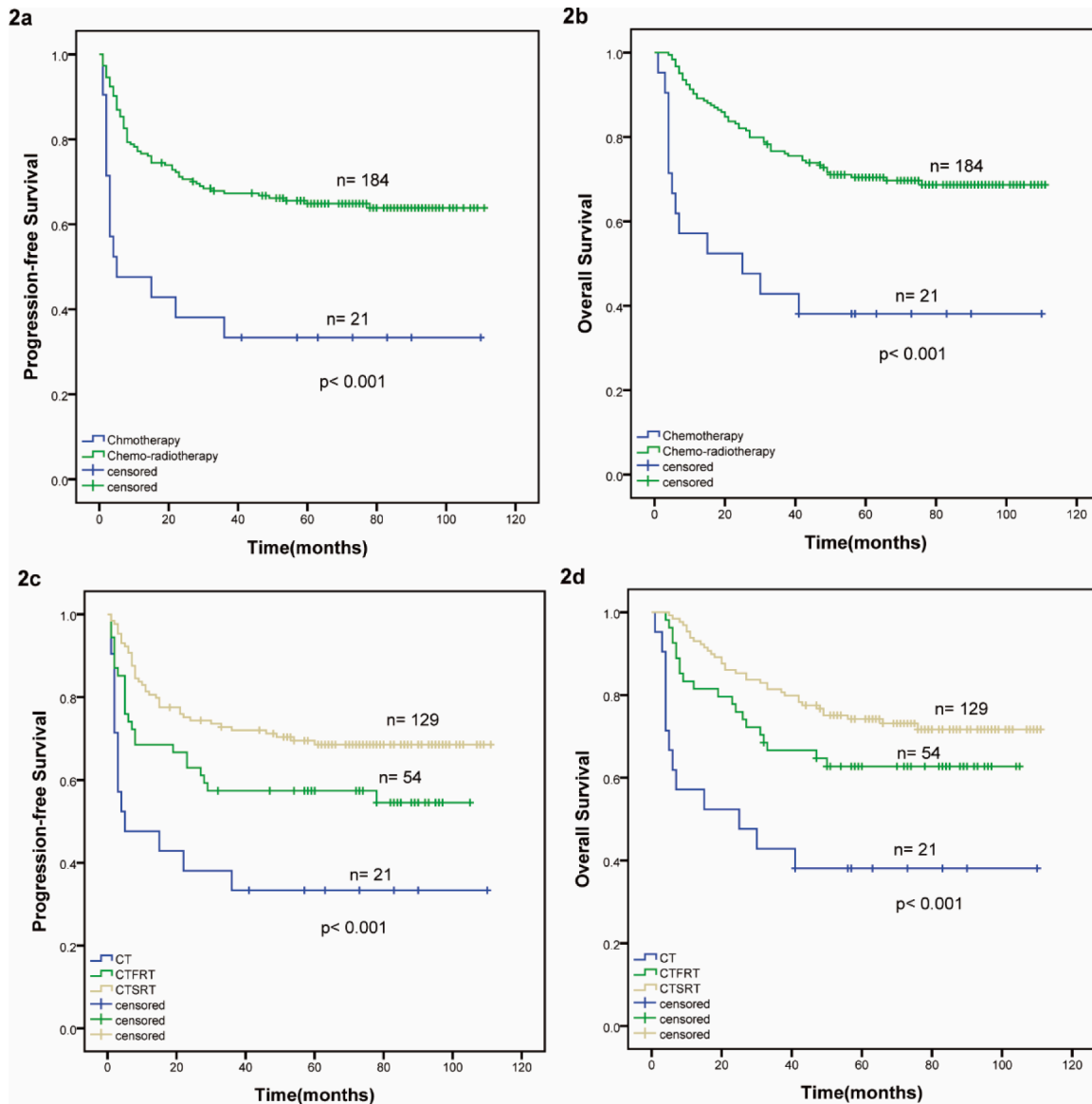
## Results

### Patient characteristics

In total, 205 patients with nasal-type ENKTL were enrolled in this study. The median age was 44 years (range, 13–76 years), and 31 (15.1%) patients were older than 60. Male patients accounted for 131 (63.9%), and the male-to-female ratio was 1.8:1. About 108 (52.7%) patients had B symptoms. One hundred and twenty-three (60.0%) patients presented with LTI, and 63 (30.7%) patients presented with RLN. Only six patients had bone marrow involvement. Based on CASS, patients with stages I through IV were more evenly distributed than with AASS, and numbered at 56 (27.3%), 70 (33.2%), 45 (21.9%), and 34 (17.6%), respectively. Based on PINK-E scoring, most patients were low-risk (0 or 1). The baseline characteristics were displayed in Table 1.

### The short-term efficacy of the lvdp chemotherapy

The median number of LVDP cycles was four (range, 2–8). All 205 patients were assessed, including 120 (58.5%) CRs, 47 (22.9%) PRs, 6 (2.9%) SDs, and 32 (15.6%) PDs, with an ORR of 82%. Only three patients who were staged IV received upfront auto-HSCT after achieving CR. According to AASS, the CR rates for stage I/II and stage III/IV patients



**Fig. 2.** The long-term survival of different treatment methods for nasal-type ENKTL. a, PFS in chemotherapy and chemo-radiotherapy groups; b, OS in chemotherapy and chemo-radiotherapy groups; c, PFS in CT, CTFRT, and CTSRT groups; d, OS in CT, CTFRT, and CTSRT groups; Abbreviations: ENKTL, extranodal NK-T-cell lymphoma; CT, chemotherapy; CTFRT, chemotherapy followed by radiotherapy; CTSRT, chemotherapy sandwiched radiotherapy; OS, overall survival; PFS, progression free survival.

were 116 (67.1%) and 5 (15.6%), respectively, and the corresponding ORRs were 88.5% and 46.9%, respectively. According to CASS, there were 97 (72.9%) CRs, 22 (16.5%) PRs, 4 (3%) SDs, and 10 (7.5%) PDs for stage I/II patients, and 24 (33.3%) CRs, 25 (34.7%) PRs, 2 (2.8%) SDs, and 21 (29.2%) PDs for stage III/IV patients. The ORR for stage I/II and stage III/IV patients were 89.3% and 68%, respectively (Table 2).

*The long-term efficacy of the lvdp chemotherapy*

All patients were followed up for a median 78 months (95% CI, 72.7–83.3) and the median PFS and OS were not reached. Among the 205 patients, 69 died. Of those, 4 patients died from unknown causes and 65 patients died from disease progression. For all patients, the 3- and 5-year PFS were 63.8% and 61.6%, respectively (Fig. 1a). The 3- and 5-year OS were 73.4% and 67.8%, respectively (Fig. 1b). About 90% patients received chemo-radiotherapy, and their long-term survival outcomes were superior to patients who received chemotherapy alone (PFS,  $\chi^2=14.169$ ,  $p<0.001$ ; OS,  $\chi^2=16.887$ ,  $p<0.001$ ; Fig. 2a-b). In the

chemotherapy-alone group, the median PFS and OS were 5 months (95% confidence interval [CI], 0–22.9 months) and 25 months (95% CI, 0–59.4 months), respectively; the 3- and 5-year PFS were 38.1% and 33.3%, respectively; and the 3- and 5-year OS were 42.9% and 38.1%, respectively (Fig. 2c-d). In the CTFRT group, the median PFS and OS had not yet been reached at the time of the last follow-up. Both the 3- and 5-year PFS were 57.4%, and the 3- and 5-year OS were 66.6% and 62.8%, respectively (Fig. 2c-d). In the CTSRT group, the median PFS and OS similarly had not yet been reached. The 3- and 5-year PFS were 72.0% and 68.5%, respectively, and the 3- and 5-year OS were 81.4% and 74.2%, respectively (Fig. 2c-d). There were statistically significant differences in PFS ( $\chi^2=17.792$ ,  $p<0.001$ ) and OS ( $\chi^2=19.410$ ,  $p<0.001$ ) between each treatment method, and the patients who received chemotherapy alone had the worst prognosis (Fig. 2c-d).

*Survival of patients with nasal-type enkl after first relapse or progression*

After the last follow-up, total of 79 PFS events were recorded. During

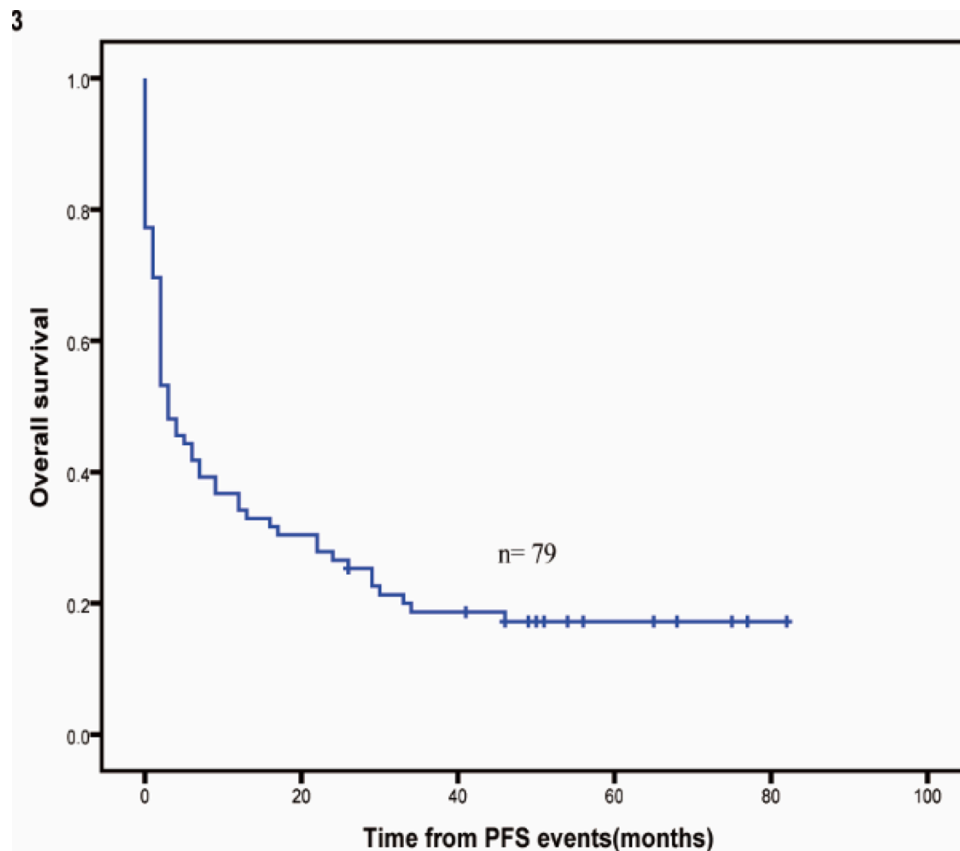


Fig. 3. OS of patients with nasal-type ENKTL after first relapse or progression. Abbreviations: ENKTL, extranodal NK-T-cell lymphoma; OS, overall survival.

Table 3

Univariate analysis of OS and PFS in nasal-type ENKTL.

	OS HR	95% CI	P	PFS HR	95% CI	P
Age >60	1.013	0.532–1.931	0.968	1.048	0.567–1.937	0.882
ECOG PS $\geq 2$	1.880	1.290–2.740	0.011*	1.996	1.410–2.826	0.003*
B symptoms	1.853	1.119–3.069	0.017*	1.786	1.130–2.823	0.013*
Elevated LDH	1.980	1.200–3.266	0.008*	2.258	1.427–3.574	0.001*
EBV-DNA positive	0.680	0.506–0.913	0.018*	0.622	0.47–0.825	0.001*
LTI	2.092	1.218–3.592	0.007*	1.721	1.065–2.782	0.027*
RLN	2.058	1.269–3.339	0.01*	1.926	1.230–3.014	0.004*
BM involvement	6.135	2.441–15.41	0.001*	7.223	3.068–17.008	0.0001*
PINK-E $\geq 2$	1.685	1.288–2.204	0.003*	1.777	1.387–2.277	0.0001*
WBC ( $\times 10^9 L^{-1}$ ) <4	1.361	0.744–2.489	0.317	1.778	1.039–3.042	0.036*
Platelet ( $\times 10^9 L^{-1}$ ) <100	1.497	0.545–4.112	0.433	1.664	0.672–4.117	0.271
Hb <110 g/L	1.838	1.037–3.258	0.037*	2.513	1.498–4.215	0.0001*

Abbreviation: BM, bone marrow; EBV, Epstein–Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; LTI, local tumor invasion; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus; RLN, regional lymph node; WBC, white blood cell. \* indicates significant difference at the 5% level.

the initial therapy, 30 patients experienced PD. After the initial therapy, 49 patients experienced disease recurrence. The median OS after first relapse or progression was 3 months, and the 5-year OS after first relapse or progression in patients with nasal-type ENKTL was 17% (Fig. 3). At the last follow-up, 14 patients after the first relapse or progression were still free of disease. Of them, six patients underwent HSCT (auto-HSCT,  $n = 4$ ; allo-HSCT,  $n = 2$ ) after receiving SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) chemotherapy, six patients received P-Gemox (pegaspargase, gemcitabine and oxaliplatin) combined with IFRT, one patient received anti-PD-1 antibody as maintenance treatment after receiving SMILE, and one patient received chidamide as maintenance treatment after receiving P-Gemox.

#### Prognostic factors

To explore the correlations between clinical variables and survival outcomes of nasal-type ENKTL patients, we conducted univariate and multivariate Cox regression analysis to identify independent prognostic factors. The clinical variables that potentially had an impact on the OS and PFS of patients were shown in Table 3. The clinical variables associated with the OS of patients included: ECOG PS (HR, 1.880; 95% CI, 1.290–2.740;  $p = 0.011$ ), B symptoms (HR, 1.853; 95% CI, 1.119–3.069;  $p = 0.017$ ), Elevated LDH (HR, 1.980; 95% CI, 1.200–3.266;  $p = 0.008$ ), EBV-DNA positive (HR, 0.68; 95% CI, 0.506–0.913;  $p = 0.018$ ), LTI (HR, 2.092; 95% CI, 1.218–3.592;  $p = 0.007$ ), RLN (HR, 2.058; 95% CI, 1.269–3.339;  $p = 0.01$ ), PINK-E  $\geq 2$  (HR, 1.685; 95% CI, 1.288–2.204;  $p$

**Table 4**  
Multivariate analysis of OS and PFS in nasal-type ENKTL.

	OS			PFS		
	HR	95% CI	P	HR	95% CI	P
ECOG PS $\geq 2$	1.387	0.877–2.194	0.162	1.13	0.465–2.748	0.787
B symptoms	1.258	0.776–2.314	0.439	1.175	0.707–1.954	0.534
Elevated LDH	1.005	0.475–1.706	0.747	1.201	0.671–2.149	0.537
EBV-DNA positive	0.412	0.596–1.236	0.089	0.708	0.526–0.952	0.022*
LTI	1.307	0.936–2.803	0.085	1.381	0.833–2.288	0.211
RLN	1410	0.817–2.436	0.217	1.367	0.808–2.312	0.244
BM involvement	3.109	1.021–9.466	0.046*	2.652	0.913–7.708	0.073
PINK-E $\geq 2$	1.255	0.866–1.819	0.230	0.593	0.339–1.037	0.067
Hb < 110 g/L	1.156	0.593–2.253	0.852	0.548	0.296–1.017	0.056
WBC ( $\times 10^9 L^{-1}$ ) < 4	NA	NA	NA	1.065	0.549–2.066	0.852

Abbreviation: BM, bone marrow; EBV, Epstein–Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; LTI, local tumor invasion; PINK-E, prognostic index of natural killer lymphoma with Epstein–Barr virus; RLN, regional lymph node; WBC, white blood cell. \* indicates significant difference at the 5% level.

**Table 5**  
Toxicity and adverse events of the LVDP regimen for nasal-type ENKTL.

Toxicity	Toxicity incidence No. (%)		
	All grades 1–4	Grades 1–2	Grades 3–4
<b>Hematologic</b>			
Leukopenia	143(69.7)	86(41.9)	57(27.8)
Neutropenia	124(60.5)	81(39.5)	43(20.9)
Anemia	124(60.5)	100(48.8)	24(11.7)
Thrombocytopenia	79(38.5)	59(28.7)	20(9.7)
<b>Nonhematologic</b>			
Hyperbilirubinemia	25(12.2)	20(9.7)	5(2.4)
Increased transaminases	85(41.5)	78(38.4)	7(3.4)
Nausea	22(10.7)	21(10.2)	1(0.5)
Diarrhea	1(0.5)	1(0.5)	0(0)
Pancreatitis	0(0)	0(0)	0(0)

= 0.003), BM involvement (HR, 6.135; 95% CI, 2.441–15.410;  $p = 0.001$ ), and Hb level < 110 g/L (HR, 1.838; 95% CI, 1.037–3.258;  $p = 0.037$ ). Similarly, the above clinical factors were also associated with the PFS of patients. Furthermore, WBC ( $\times 10^9 L^{-1}$ ) < 4 (HR, 1.778; 95% CI, 1.039–3.042;  $p = 0.036$ ) was also a prognostic factor for PFS.

Using all of the variables established as important in univariable analysis, we performed a multivariable analysis to determine potential independent predictors for OS (Table 4). The outcomes showed that only BM involvement at diagnosis (HR, 3.109; 95% CI, 1.021–9.466;  $p = 0.046$ ) was an independent prognostic factor for OS for nasal type ENKTL. In terms of PFS, an independent prognostic factor was EBV-DNA positive (HR, 0.708; 95% CI, 0.526–0.952;  $p = 0.022$ ).

### Toxicity

Overall, the LVDP regimen was tolerable. Treatment-related toxicities were listed in Table 5. Most toxicities were grade 1/2. The most common toxicity was hematologic toxicity. Of these, the most frequent grade 3/4 hematologic toxicity was leukopenia ( $n = 57$ , 27.8%). 18 of them presented with fever, and, of these, only 2 patients had blood infections, which were successfully treated by antibacterial therapy. The most frequent grade 3/4 non-hematological toxicity was increased transaminases, which was observed in 7 (4.5%) patients. Eighteen patients experienced dose reduction or chemotherapy delay because of hematologic toxicity ( $n = 14$ ) or increased transaminases ( $n = 4$ ). No pancreatitis or treatment-related death was reported.

### Comparison of survival between AASS and CASS

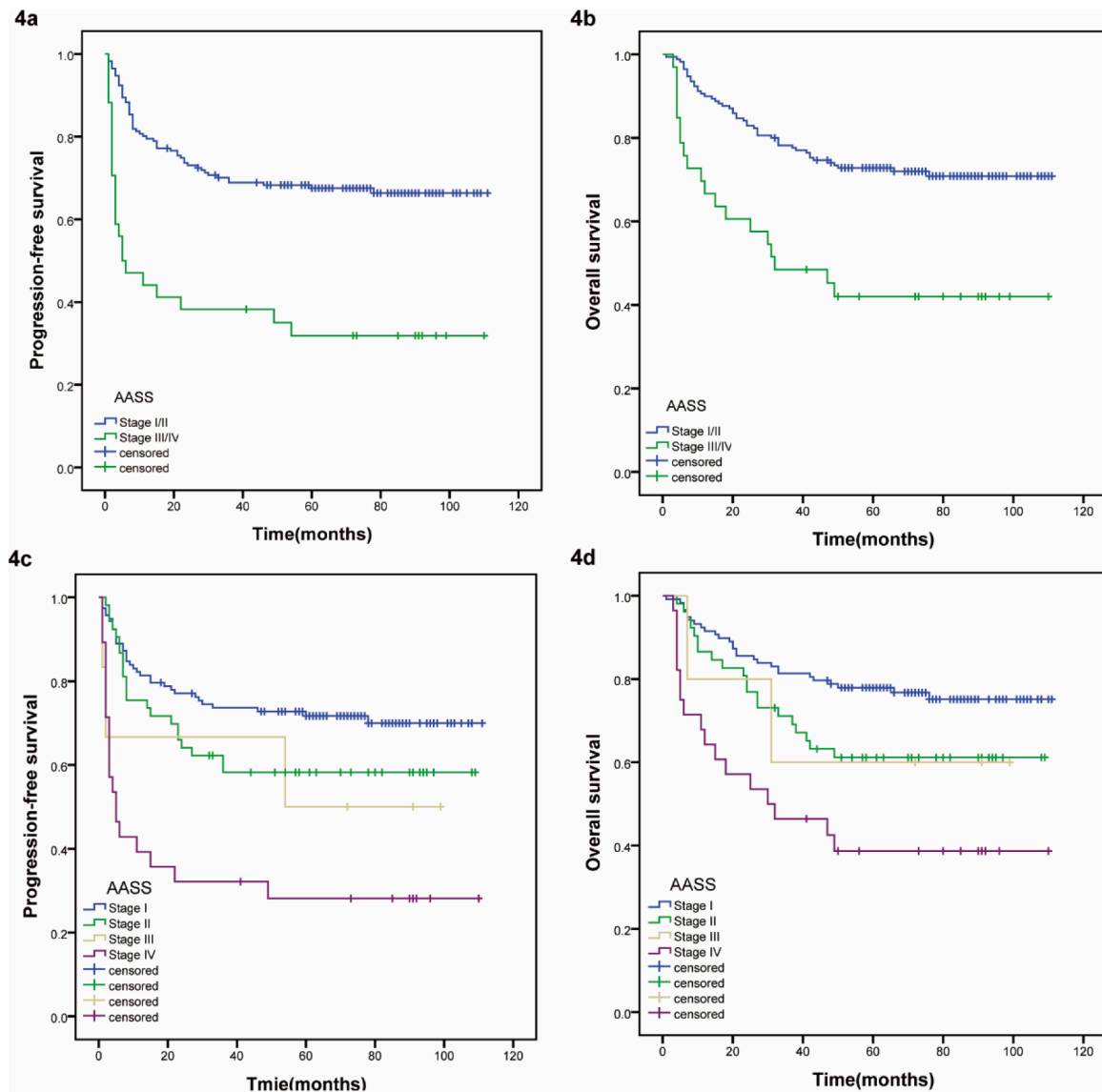
According to the AASS, patients at stages I to IV numbered at 118 (57.6%), 53 (25.9%), 6 (2.9%), and 28 (13.7%), respectively. The 3- and 5-year PFS were 70.1% and 67.5% for stage I/II patients, 38.2% and 31.9% for stage III/IV patients, respectively ( $\chi^2 = 24.895$ ,  $p < 0.001$ )

(Fig. 4a). The 3- and 5-year OS were 78.2% and 72.8%, respectively, for stage I/II patients and 48.5% and 42% for stage III/IV patients, respectively ( $\chi^2 = 15.333$ ,  $p < 0.001$ ) (Fig. 4b). The 5-year PFS of patients with stages I to IV were 71.7%, 68.2%, 50.0%, and 28.1%, respectively ( $\chi^2 = 30.082$ ,  $p < 0.001$ ) and the 5-year OS of patients with stages I to IV were 77.9%, 61.2%, 60.0%, and 38.7%, respectively ( $\chi^2 = 20.578$ ,  $p < 0.001$ ) (Fig. 4c-d). Based on the CASS, patients were classified as stages I through IV were 56 (27.3%), 68 (33.2%), 45 (21.9%), and 36 (17.6%), respectively. The 3- and 5-year PFS were 72.5% and 70.7%, respectively, for stage I/II patients and 50.6% and 47.8% for stage III/IV, respectively ( $\chi^2 = 11.760$ ,  $p < 0.001$ ) (Fig. 5a). The 3- and 5-year OS were 81.5% and 77.4%, respectively, for patients with stage I/II and 60.7% and 52.8%, respectively, for stage III/IV ( $\chi^2 = 12.594$ ,  $p < 0.001$ ) (Fig. 5b). The 5-year PFS for patients with stages I to IV were 78.5%, 64.4%, 57.6%, and 35.7%, respectively ( $\chi^2 = 23.470$ ,  $p < 0.001$ ), and the 5-year OS of patients with stages I to IV were 89.1%, 65.5%, 58.6%, and 45.4%, respectively ( $\chi^2 = 22.973$ ,  $p < 0.001$ ) (Fig. 5c-d). In the ROC analysis, the area under curve (AUC) of the AASS was 0.64 (95% CI, 0.578–0.713), and the AUC of the CASS was 0.70 (0.621–0.752). The CASS was better for discriminating survival in patients with nasal-type ENKTL than the AASS ( $p = 0.018$ ) (Fig. 6a). In comparison, the CASS was superior to PINK-E (AUC, 0.70 vs. 0.61,  $p = 0.008$ ) (Fig. 6b).

### Discussion

In this study, we retrospectively analyzed different staging systems and the efficacy of LVDP for 205 patients with nasal-type ENKTL. Our results found that the LVDP combined chemotherapy regimen was effective for nasal-type ENKTL with mild toxicity. In Cox regression analysis of prognostic factors for survival, bone marrow involvement was correlated with poor OS, and EBV DNA positive in peripheral plasma was associated with worse PFS. Further study showed that the CASS better discriminated survival for patients with nasal-type ENKTL than the AASS and PINK-E.

In recent years, due to anthracycline-resistance, L-asparaginase-based regimens have demonstrated promising efficacy for ENKTL [12–16]. Kwong et al. reported a SMILE regimen that yielded a 5-year OS of 50% and a 4-year PFS of 64% in newly diagnosed ENKTL patients [17]. In a retrospective study to evaluate the efficacy and safety of GELOX (L-asparaginase, gemcitabine and oxaliplatin) or P-Gemox for ENKTL, a 3-year OS of 65.2% and PFS rate of 57% were observed [18]. In a prospective clinical trial in China, 165 patients received P-Gemox plus thalidomide or AspaMetDex (L-asparaginase, methotrexate and dexamethasone), and the 3-year PFS and OS rates were 61.4% and 63.4%, respectively [19]. Additionally, in a large-scale, multicenter study, Qi reported the survival outcomes of 1351 ENKTL patients based on non-anthracycline chemotherapy and reported a 5-year OS and PFS of 68.9% and 59.5%, respectively [20]. In our report, we found that treatment with LVDP achieved an ORR of 81.2%, with 58.5% of patients



**Fig. 4.** The long-term survival stratified by AASS for nasal-type ENKTL. a, Comparison of the PFS between stage I/II and stage III/IV patients; b, Comparison of the OS between stage I/II and stage III/IV patients; c, PFS for patients with stages I through IV; d, OS for patients with stages I through IV. Abbreviations: AASS, Ann Arbor Staging System; ENKTL, extranodal NK-T-cell lymphoma; OS, overall survival; PFS, progression free survival.

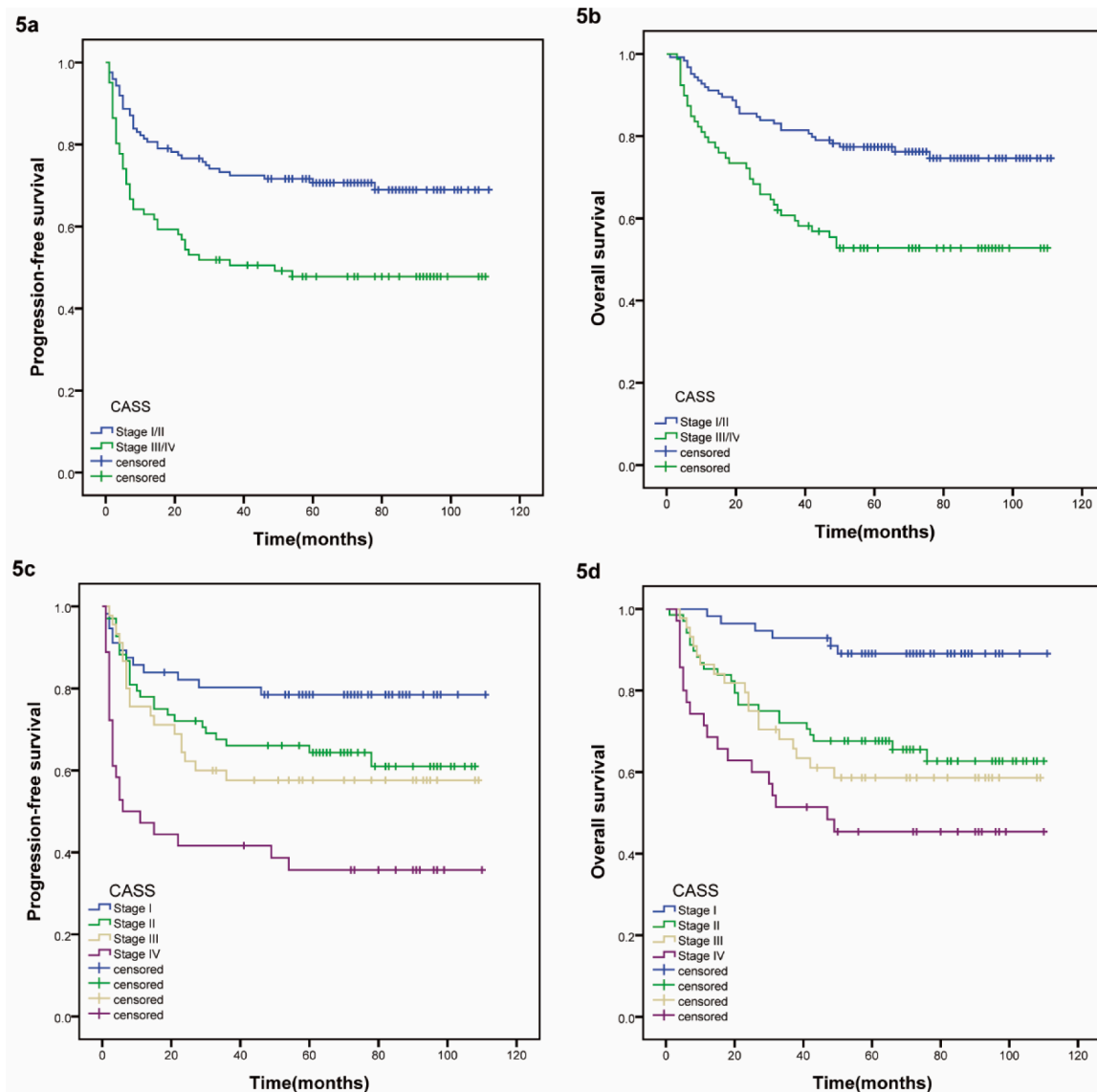
having CR. The 3-year PFS and OS were 63.8% and 73.4%, respectively, and the 5-year PFS and OS were 61.6% and 67.8%, respectively. To our knowledge, this study reported the largest cohort of nasal type ENKTL patients treated with the LVDP chemotherapy regimen. When compared with the previously mentioned studies, LVDP achieved better survival outcomes.

In addition, the toxicity of LVDP was mild. In this study, common grade 3/4 hematologic toxicities, including leukopenia (27.8%) and neutropenia (20.9%), were milder than with other L-asparaginase based chemotherapies, including DDPG (cisplatin, dexamethasone, gemcitabine and pegaspargase; leukopenia, 48.4%; neutropenia, 48.4%), P-Gemox (neutropenia, 27.7%), and SMILE (neutropenia, 92%) [12,21,17]. In summary, LVDP was a safe regimen for ENKTL.

Radiotherapy combined with chemotherapy plays a key role in nasal-type ENKTL [7]. In our study, about 90% patients received chemo-radiotherapy after initial diagnosis, and their survival outcomes were better than those of patients who received chemotherapy alone. This result was consistent with previous studies [22,23]. Vargo et al. reported that the omission of radiotherapy was associated with poor survival in patients with early-stage ENKTL [22]. In another

retrospective study from the International T-cell Lymphoma Project, radiotherapy combined with chemotherapy for early-stage ENKTL yielded better survival outcomes than chemotherapy alone ( $p = 0.045$ ) [23]. In addition, more than half of patients (129/205) with nasal-type ENKTL received “Sandwich” LVDP chemo-radiotherapy and achieved promising results, including an ORR of 88.4%, 3-year PFS of 72.8% and 3-year OS of 81.4%. The ORR and survival outcomes were comparable to previous studies for ENKTL. In a clinical trial, 66 patients with early-stage ENKTL received “Sandwich” LVD and RT. The ORR was 88.5%, the 2-year PFS and OS were 80.6% and 88.5%, respectively [24]. In another multicenter study, 173 newly diagnosed stage I/II ENKTL patients received concomitant chemoradiotherapy. The ORR was around 90% and the 5-year OS plateaued at 72%–74% [25]. In a recent report, 202 patients with early-stage ENKTL received sequential P-Gemox and radiotherapy, and the 3-year PFS and OS were 74.6% and 85.2%, respectively [26]. In summary, our results show that “Sandwich” LVDP chemo-radiotherapy is a potential option for nasal-type ENKTL.

Although the specific mechanism is still unclear, EBV is closely related to the pathogenesis of ENKTL, and plasma EBV-DNA has been considered as an important prognostic factor [6,27,28]. The level of



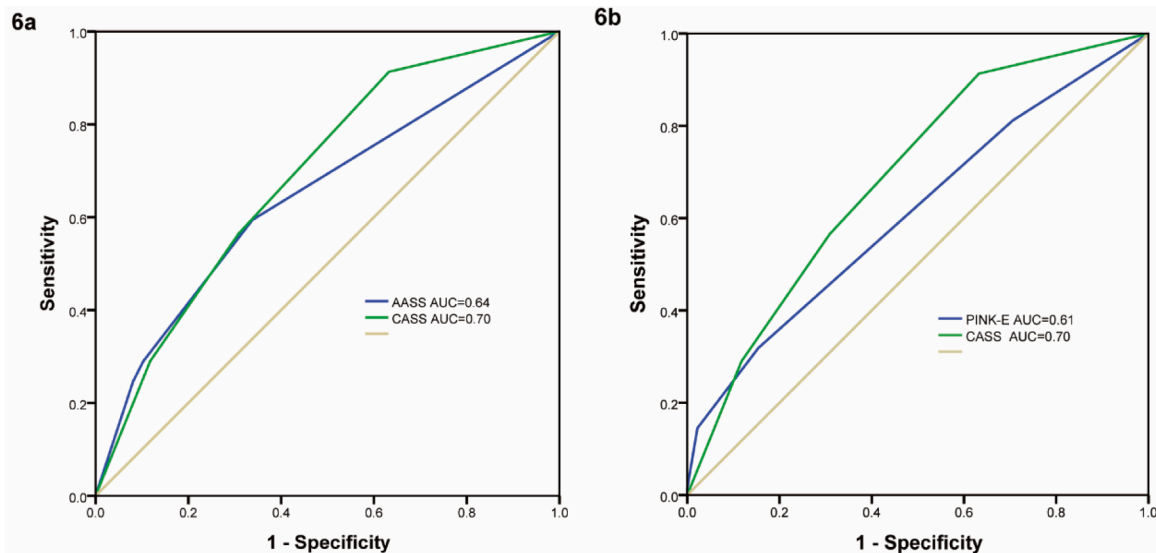
**Fig. 5.** The long-term survival stratified by CASS for nasal-type ENKTL. a, Comparison of the PFS between stage I/II and stage III/IV patients; b, Comparison of the OS between stage I/II and stage III/IV patients; c, PFS for patients with stages I through IV; d, OS for patients with stages I through IV. Abbreviations: CASS, CA Staging System; ENKTL, extranodal NK-T-cell lymphoma; OS, overall survival; PFS, progression free survival.

plasma EBV DNA decreased when the treatment effected, and the level increased when disease relapsed [29]. Consistently, EBV-DNA was an independent prognostic factor for PFS ( $p = 0.022$ ) in our report. In addition, we showed that bone marrow involvement was an independent prognostic factor for OS in our study. Bone marrow involvement at initial diagnosis is uncommon in ENKTL, but it develops within the course of disease in 2–12% of patients [30,31]. These patients likely develop a major complication, hemophagocytic syndrome (HPS). When it occurs, it is correlated with poor survival (median survival from 26 to 40 days). In our study, we showed that bone marrow involvement was an independent prognostic factor for OS. Due to the rarity of cases with bone marrow involvement, further study is needed to validate the prognostic value of it in nasal-type ENKTL.

Currently, the optimal prognostic system for ENKTL remains undefined. Several studies have established different prognostic models [5,6,32,33]. The international prognostic index (IPI) was established based on anthracycline-based chemotherapy in 1993 and is used for all non-Hodgkin's lymphoma, not exclusively for ENKTL [32]. The Korean prognostic index (KPI) and Nomogram-revised risk index (NRI) were established for ENKTL in previous studies; however, most patients

involved received anthracycline-based chemotherapy, which has demonstrated unsatisfactory effects for ENKTL [5,33]. According to the PINK-E model, most patients are classified into the low-risk group with a 3-year OS of 81%, and only 18% of patients are classified into high-risk group with 3-year OS of 28% [6]. It is evident that an unbalanced population distribution is present in this model. In addition, the above prognostic tools are established based on AASS, which couldn't evenly distribute patients into different stages. CASS is a new staging system that can evenly distribute patients into different stages, and Lin et al. reported that CASS is superior to AASS [7]. In our study, patients classified as stages I through IV according to CASS were distributed as 56 (27.9%), 68 (33.2%), 45 (21.9%), and 36 (17.6%), respectively, which was more even than the AASS. We further validated that the CASS could effectively discriminate the survival outcomes of patients who received consistent LVDP chemotherapy. The 5-year PFS and OS of patients with stages I to IV were 78.5%, 64.4%, 57.6%, and 35.7%, respectively; and 89.1%, 65.5%, 58.6%, 45.4%, respectively. The AUC of CASS was larger than that of the AASS and PINK-E in nasal-type ENKTL. Our findings further support the value of CASS as a potential staging system for nasal-type ENKTL.





**Fig. 6.** Comparison of the area under curve in nasal-type ENKTL. a, Comparison of the area under curve between AASS and CASS; b, Comparison of the area under the curve between CASS and PINK-E. Abbreviations: AASS, Ann Arbor Staging System; CASS, CA Staging System; ENKTL, extranodal NK-T-cell lymphoma; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus.

However, there were several limitations in our study. First, this study was a single-center retrospective and might cause selection bias. Second, the number of patients with ECOG-PS $\geq$ 2 and bone marrow involvement, was relatively small and might impact the results of prognostic analysis. Third, the distributions of patients in the CTRT group and the chemotherapy-alone group were unbalanced and might cause survival bias. Therefore, further multi-center randomized controlled trials are needed to validate our results.

## Conclusion

To conclude, the LVDP combined chemotherapy regimen is effective for nasal-type ENKTL with well-tolerated toxicity, and the CASS has a better prognostic value in survival analysis with balanced patient distribution than AASS and PINK-E. Therefore, we suggest that the LVDP regimen is a promising treatment option and the CASS is a potential staging system for nasal-type ENKTL.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- E. Tse, Y.L. Kwong, The diagnosis and management of NK/T-cell lymphomas, *J. Hematol. Oncol.* 10 (1) (2017) 85, <https://doi.org/10.1186/s13045-017-0452-9>. Published 2017 Apr 14.
- J. Sun, Q. Yang, Z. Lu, et al., Distribution of lymphoid neoplasms in China: analysis of 4,638 cases according to the World Health Organization classification, *Am. J. Clin. Pathol.* 138 (3) (2012) 429–434, <https://doi.org/10.1309/AJCP7YLTQPUSDQ5C>.
- T.M. Kim, S.Y. Lee, Y.K. Jeon, et al., Clinical heterogeneity of extranodal NK/T-cell lymphoma, nasal type: a national survey of the Korean Cancer Study Group, *Ann. Oncol.* 19 (8) (2008) 1477–1484, <https://doi.org/10.1093/annonc/mdn147>.
- X.M. Wang, B.A. Bassig, J.J. Wen, et al., Clinical analysis of 1629 newly diagnosed malignant lymphomas in current residents of Sichuan province, China. *Hematol Oncol.* 34 (4) (2016) 193–199, <https://doi.org/10.1002/hon.2202>.
- Y. Yang, Y.J. Zhang, Y. Zhu, et al., Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study, *Leukemia* 29 (7) (2015) 1571–1577, <https://doi.org/10.1038/leu.2015.44>.
- S.J. Kim, D.H. Yoon, A. Jaccard, et al., A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis, *Lancet Oncol.* 17 (3) (2016) 389–400, [https://doi.org/10.1016/S1470-2045\(15\)00533-1](https://doi.org/10.1016/S1470-2045(15)00533-1).
- H. Hong, Y. Li, S.T. Lim, et al., A proposal for a new staging system for extranodal natural killer T-cell lymphoma: a multicenter study from China and Asia Lymphoma Study Group, *Leukemia* 34 (8) (2020) 2243–2248, <https://doi.org/10.1038/s41375-020-0740-1>.
- E. Sabatini, F. Bacci, C. Sagramoso, S.A. Pileri, WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview, *Pathologica* 102 (3) (2010) 83–87.
- T.M. Kim, Y.H. Park, S.Y. Lee, et al., Local tumor invasiveness is more predictive of survival than International Prognostic Index in stage I(E)/II(E) extranodal NK/T-cell lymphoma, nasal type, *Blood* 106 (12) (2005) 3785–3790, <https://doi.org/10.1182/blood-2005-05-2056>.
- J. Yahalom, T. Illidge, L. Specht, et al., Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group, *Int. J. Radiat. Oncol. Biol. Phys.* 92 (1) (2015) 11–31, <https://doi.org/10.1016/j.ijrobp.2015.01.009>.
- B.D. Cheson, R.I. Fisher, S.F. Barrington, et al., Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification, *J. Clin. Oncol.* 32 (27) (2014) 3059–3068, <https://doi.org/10.1200/JCO.2013.54.8800>.
- Q. Zhao, S. Fan, Y. Chang, et al., Clinical efficacy of cisplatin, dexamethasone, gemcitabine and pegaspargase (DDGP) in the initial treatment of advanced stage (stage III-IV) extranodal NK/T-cell lymphoma, and its correlation with Epstein-Barr virus, *Cancer Manag Res* 11 (2019) 3555–3564, <https://doi.org/10.2147/CMAR.S191929>. Published 2019 Apr 24.
- L. Zhang, M. Jiang, L. Xie, et al., Five-year analysis from phase 2 trial of “sandwich” chemoradiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma, *Cancer Med.* 5 (1) (2016) 33–40, <https://doi.org/10.1002/cam4.569>.
- Y. Zhang, S. Ma, J. Cai, et al., Sequential P-GEMOX and radiotherapy for early-stage extranodal natural killer/T-cell lymphoma: a multicenter study, *Am. J. Hematol.* 96 (11) (2021) 1481–1490, <https://doi.org/10.1002/ajh.26335>.
- M. Yamaguchi, Y.L. Kwong, W.S. Kim, 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.* 29 (33) (2011) 4410–4416, <https://doi.org/10.1200/JCO.2011.35.6287>.
- A. Jaccard, N. Gachard, B. Marin, 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* 117 (6) (2011) 1834–1839, <https://doi.org/10.1182/blood-2010-09-307454>.
- M. Yamaguchi, K. Tobinai, M. Oguchi, et al., Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211, *J. Clin. Oncol.* 30 (32) (2012) 4044–4046, <https://doi.org/10.1200/JCO.2012.45.6541>.
- H. Wang, L. Wang, Z. Wuxiao, et al., Increased serum levels of interleukin-10 predict poor prognosis in extranodal natural killer/T-cell lymphoma patients receiving asparaginase-based chemotherapy, *Oncotargets Ther* 8 (2015) 2589–2599, <https://doi.org/10.2147/OTT.S91077>. Published 2015 Sep 14.
- H.-Q. Huang, G. Yan, H. Su, et al., Clinical outcome of a multicentre, randomized, phase II clinical trial for patients with extranodal NK/T cell lymphoma treated by P-Gemox or AspaMetdex, *Blood* 134 (2019), <https://doi.org/10.1182/blood-2019-123478>.

- [20] S.N. Qi, Y. Yang, Y.Q. Song, et al., First-line non-anthracycline-based chemotherapy for extranodal nasal-type NK/T-cell lymphoma: a retrospective analysis from the CLCG [published correction appears in *Blood Adv.* 2021 Jun 17;5(12):2576], *Blood Adv* 4 (13) (2020) 3141–3153, <https://doi.org/10.1182/bloodadvances.2020001852>.
- [21] G. Yan, H.-Q. Huang, X. Wang, et al., P-Gemox regimen (Pegaspargase, gemcitabine, oxaliplatin) for extranodal natural killer cell lymphoma: 10 years' real-world clinical experience from China, *Blood* 132 (2018), <https://doi.org/10.1182/blood-2018-99-116551>.
- [22] J.A. Vargo, A. Patel, S.M. Glaser, et al., The impact of the omission or inadequate dosing of radiotherapy in extranodal natural killer T-cell lymphoma, nasal type, in the United States, *Cancer* 123 (16) (2017) 3176–3185, <https://doi.org/10.1002/ncr.30697>.
- [23] Au W-y, Weisenburger DD, T. Intragumtornchai, 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* 113 (2009) 3931–3937, <https://doi.org/10.1182/blood-2008-10-185256>.
- [24] M. Jiang, H. Zhang, Y. Jiang, et al., Phase 2 trial of “sandwich” L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma, *Cancer* 118 (13) (2012) 3294–3301, <https://doi.org/10.1002/ncr.26629>.
- [25] Y.L. Kwong, S.J. Kim, E. Tse, et al., Sequential chemotherapy/radiotherapy was comparable with concurrent chemoradiotherapy for stage I/II NK/T-cell lymphoma, *Ann. Oncol.* 29 (1) (2018) 256–263, <https://doi.org/10.1093/annonc/mdx684>.
- [26] Y. Zhang, S. Ma, J. Cai, et al., Sequential P-GEMOX and radiotherapy for early-stage extranodal natural killer/T-cell lymphoma: a multicenter study, *Am. J. Hematol.* 96 (11) (2021) 1481–1490, <https://doi.org/10.1002/ajh.26335>.
- [27] C. Sánchez-Romero, R. Bologna-Molina, O. Paes de Almeida, et al., Extranodal NK/T cell lymphoma, nasal type: an updated overview, *Crit. Rev. Oncol. Hematol.* 159 (2021), 103237, <https://doi.org/10.1016/j.critrevonc.2021.103237>.
- [28] R.J. Peng, B.W. Han, Q.Q. Cai, et al., Genomic and transcriptomic landscapes of Epstein-Barr virus in extranodal natural killer T-cell lymphoma, *Leukemia* 33 (6) (2019) 1451–1462, <https://doi.org/10.1038/s41375-018-0324-5>.
- [29] M. Takahara, T. Kumai, K. Kishibe, T. Nagato, Y. Harabuchi, Extranodal NK/T-Cell Lymphoma, Nasal Type: genetic, Biologic, and Clinical Aspects with a Central Focus on Epstein-Barr Virus Relation, *Microorganisms* 9 (7) (2021) 1381, <https://doi.org/10.3390/microorganisms9071381>. Published 2021 Jun 25.
- [30] Y.J. Su, P.N. Wang, H. Chang, et al., Extranodal NK/T-cell lymphoma, nasal type: clinical features, outcome, and prognostic factors in 101 cases, *Eur. J. Haematol.* 101 (3) (2018) 379–388, <https://doi.org/10.1111/ejh.13126>.
- [31] K.F. Wong, J.K. Chan, M.M. Cheung, J.C. So, Bone marrow involvement by nasal NK cell lymphoma at diagnosis is uncommon, *Am. J. Clin. Pathol.* 115 (2) (2001) 266–270, <https://doi.org/10.1309/E5PR-6A9R-Q02N-8QVW>.
- [32] International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma, *N. Engl. J. Med.* 329 (14) (1993) 987–994, <https://doi.org/10.1056/NEJM199309303291402>.
- [33] J. Lee, C. Suh, Y.H. Park, et al., Extranodal natural killer T-cell lymphoma, nasal type: a prognostic model from a retrospective multicenter study, *J. Clin. Oncol.* 24 (4) (2006) 612–618, <https://doi.org/10.1200/JCO.2005.04.1384>.