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Short-Course Versus Long-Course Chemoradiotherapy for Stage IE–IIE Extranodal Natural Killer/T cell Lymphoma, Nasal Type: A Multicenter Retrospective Study

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Background: This study compared clinical outcomes and adverse events between L-asparaginase/pegaspargase-based short-course and long-course chemoradiotherapy in newly diagnosed stage IE–IIE extranodal natural killer/T cell lymphoma, nasal type (ENKTL).

Material/Methods: Patients were categorized into a short-course (2–4 chemotherapy cycles, median: 4, n=153) and long-course group (5–6 cycles, median: 6, n=83). The chemotherapy regimens included GELOX, SMILE, and VLP. The radiotherapy dose was 40–63 Gy (median: 55 Gy). Adverse events, treatment responses, and survival outcomes between the 2 groups were compared.

Results: Ann Arbor stage IIE and short-course chemotherapy adversely affected overall survival (OS). Ann Arbor stage IE favorably affected progression-free survival (PFS). Grade 3–4 hematological toxicities were higher in the long-course group (25.3% *vs.* 14.4%, p=0.038). Ann Arbor stage was the single different clinical feature between the 2 groups, and independently affected survival outcomes. In subgroup analysis of stage IE, there was no difference in response rates and survival outcomes between the 2 groups. In subgroup analysis of stage IIE, the recurrence and death rates were significantly lower in the long-course group (6.1% *vs.* 23.2%, p=0.015; 12.2% *vs.* 39.3%, p=0.002; respectively), and the 3-year OS and PFS rates were much longer in the long-course group (87.8% *vs.* 62.5%, p<0.001; 83.7% *vs.* 57.1%, p=0.001; respectively).

Conclusions: When radiotherapy was combined with L-asparaginase/pegaspargase-based chemotherapy to treat early-stage ENKTL patients, 2–4 cycles of chemotherapy might be sufficient for stage IE patients, while stage IIE patients might require 5+ cycles.

MeSH Keywords: Drug Therapy • Lymphoma, Extranodal NK-T-Cell • Radiotherapy

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Background

Extranodal natural killer/T cell lymphoma, nasal type (ENKTL) is classified into mature T cell and NK cell non-Hodgkin's lymphoma according to the WHO classification [1]. ENKTL is much more prevalent in Asia and Latin America than in the Western countries [2]. ENKTL often occurs in middle-aged male patients with localized stage predominance and elevated LDH level and B symptoms. ENKTL mostly involves the nasal cavity, paranasal sinuses, and other facial structures [3–5]. Although ENKTL often presents at an early stage, its aggressive clinical course leads to a poor prognosis [6,7].

Early-stage ENKTL is sensitive to radiotherapy with high complete response (CR) rates [8,9]. However, radiotherapy alone is not enough effective to treat early-stage ENKTL because of its high recurrence rate [10]. Therefore, chemotherapy combined with radiotherapy is necessary [11]. A traditional CHOP (cyclophosphamide, Adriamycin, vincristine, prednisolone) regimen for the treatment of B-cell lymphoma is not effective in ENKTL due to the P-glycoprotein, which is encoded by the multidrug resistance gene and exports drugs (e.g., cyclophosphamide and Adriamycin) outside of lymphoma cells. The introduction of L-asparaginase/pegaspargase completely changed the treatment of ENKTL. L-asparaginase/pegaspargase specifically catalyzes the decomposition of asparagine to aspartate and ammonia, which in turn depletes the asparagine in plasma and cleaves the exogenous asparagine from tumor cells. Tumor cells with low asparagine synthetase activity are unable to synthesize endogenous asparagine, resulting in severe inhibition of intracellular protein synthesis. Normal cells can avoid death by synthesizing sufficient endogenous asparagine through asparagine synthetase [12]. Currently, regimens of GELOX (gemcitabine, oxaliplatin, L-asparaginase/pegaspargase) [13], SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase/pegaspargase, etoposide) [14], VLP (vincristine, L-asparaginase/pegaspargase, prednisone) [15], VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase/pegaspargase) [16], and MIDLE (methotrexate, ifosfamide, dexamethasone, L-asparaginase/pegaspargase, etoposide) [17] are proven to be effective to treat ENKTL. The treatment modalities of early-stage ENKTL include concurrent, sequential, and "sandwich" chemoradiotherapy. NCCN guidelines recommend 6 cycles of chemotherapy with or without radiotherapy for the treatment of peripheral T cell lymphoma, whether it is early or advanced stage. Currently, NCCN guidelines recommend 2–6 cycles of chemotherapy combined with radiotherapy for limited-stage ENKTL [1].

In view of the fundamental role of radiotherapy in stage IE–IIE ENKTL, it remains unclear whether chemotherapy courses can be appropriately reduced. There are no prospective clinical data on this issue. Therefore, we conducted this retrospective study to investigate the appropriate courses of chemotherapy combined with radiotherapy in stage IE–IIE ENKTL. We classified 2–4 cycles of chemotherapy into a short-course group, and 5–6 cycles into a long-course group. Furthermore, the treatment toxicities, objective response rates, and survival outcomes between short-course and long-course treatment for stage IE–IIE ENKTL were compared.

Material and Methods

Patients

This retrospective study enrolled 236 patients with stage IE–IIE ENKTL from Hunan Cancer Hospital, Xiangya Hospital of Central South University, Second Xiangya Hospital of Central South University, and Changsha Central Hospital, between 2010 and 2017. All of the cases were newly diagnosed ENKTL. Three pathologists independently reviewed and confirmed all cases according to the current World Health Organization criteria [18,19]. All of the patients underwent routine blood examination, blood biochemistry, bone marrow smear and biopsy, CT or MRI scans of the involved fields, CT scans of the neck, chest, abdomen, and pelvis, or whole-body PET/CT scan before treatment. Plasma EBV DNA level was tested in 104 patients. The clinical characteristics, including gender, age, ECOG score, Ann Arbor stage, LDH, B symptoms, PINK score, and PINK-E score were recorded.

Informed consent forms were endorsed by all patients. This study process conforms to the Declaration of Helsinki and the guiding principles of local ethics committees of the above-mentioned 4 hospitals.

Treatment and response criteria

All patients were administered radiotherapy and 2–6 cycles of L-asparaginase/pegaspargase-based chemotherapy regimens. Radiotherapy was performed with intensity-modulated radiation therapy. L-asparaginase/pegaspargase-based regimens consisted of GELOX (gemcitabine, 800 mg/m^2, d1 and d8; oxaliplatin, 85 mg/m^2, d1; L-asparaginase, 5000 IU/m^2, d1–7/pegaspargase, 2500 IU/m^2, d1), SMILE (dexamethasone, 15 mg, d1–7; methotrexate, 60 mg/m^2, d1; ifosfamide, 1.5 g/m^2, d2–4; L-asparaginase, 5000 IU/m^2, d1–7/pegaspargase, 2500 IU/m^2, d1; etoposide, 100 mg/m^2, d2–4), and VLP (vincristine, 2 mg, d1; L-asparaginase, 5000 IU/m^2, d1–7/pegaspargase, 2500 IU/m^2, d1; prednisone, 100 mg/d, d1–5). Treatment information, including radiotherapy doses, chemotherapy regimens, and number of chemotherapy cycles were recorded. All patients were classified into 2 groups according to the number of chemotherapy cycles. Patients who underwent 2–4 cycles of chemotherapy were classified into the short-course group, and

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5–6 cycles into the long-course group. Efficacy evaluation was conducted every 2 cycles of chemotherapy, and before and after radiotherapy. Response criteria were according to the Lugano response criteria for non-Hodgkin's lymphoma [20]. Treatment toxicities were evaluated on the basis of the National Cancer Institute Common Toxicity Criteria, Version 3 [21].

Statistical analysis

Overall survival (OS) was defined as the date of diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was defined as the date of diagnosis to the date of disease progression, first relapse, or death for any reasons. Differences in patient characteristics and toxicities between the short-course and long-course groups were evaluated by the chi-squared test or Kruskal-Wallis test. The Kaplan-Meier method and log-rank test were used to analyze the clinical features and number of chemotherapy cycles for OS and PFS. The independent prognostic factors for OS and PFS was analyzed by Cox regression analysis. Statistical analyses were performed using SPSS 24.0 software (IBM Corp., New York, NY, USA)). $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 236 newly diagnosed stage IE–IIE ENKTL patients from 2010 to 2017 were enrolled in this retrospective study. One hundred fifty-three patients were categorized into the short-course group and 83 into the long-course group. All patients' clinical features are listed in Table 1. The short-course and long-course groups were both male-predominant (male: female, 105: 48 *vs.* 58: 25, $p=0.842$). Patients in both groups were mainly aged ≤60 years (90.8% *vs.* 95.2%, $p=0.231$). There were no statistic differences in ECOG performance status ($p=0.947$), LDH elevation ($p=0.073$), B symptoms ($p=0.146$), PINK score ($p=0.171$), and PINK-E score ($p=0.906$) between the short-course and long-course groups. The short-course group contained more patients with Ann Arbor stage IE (63.4% *vs.* 41.0%, $p=0.001$).

The original tumor sites included nasal cavity (n=174; 114 in the short-course group and 60 in the long-course group), upper aerodigestive tract (n=58; 38 in the short-course group and 20 in the long-course group), and non-upper aerodigestive tract (n=4; 1 in the short-course group and 3 in the long-course group). Plasma EBV DNA levels were tested in 104 patients, and 51 patients were detectable (28 in the short-course group and 23 in the long-course group).

Treatment toxicities

The majority of patients could tolerate treatment-related adverse effects. No treatment-related deaths were observed. Neutropenia and transaminase elevation were the most common hematological and non-hematological adverse effects, respectively. As expected, hematological adverse effects were more common in the long-course group than in the short-course group, including grade 1/2 (42.2% *vs.* 28.8%, $p=0.037$) and grade 3/4 neutropenia (24.1% *vs.* 13.7%, $p=0.045$), and grade 1/2 anemia (50.6% *vs.* 34.0%, $p=0.013$). For non-hematological adverse effects, transaminase elevation was still more common in the long-course group than in the short-course group (42.2% *vs.* 28.1%, $p=0.028$) (Table 2).

Prognostic factors

In univariate survival analysis, Ann Arbor stage IIE (74.3% *vs.* 87.0%, $p=0.009$) adversely influenced OS (Figure 1A). A long chemotherapy course (90.4% *vs.* 76.5%, $p=0.007$) was a favorable factor of OS (Figure 2A). Ann Arbor stage IIE (69.5% *vs.* 84.0%, $p=0.009$) was an unfavorable factor of PFS (Figure 1B). In multivariate analysis, Ann Arbor stage IIE (HR 2.061, 95% CI 1.059–4.012, $p=0.033$) and a short chemotherapy course (HR 3.288, 95% CI 1.646–6.568, $p=0.001$) were independent prognostic factor of OS. Ann Arbor stage IIE (HR 1.983, 95% CI 1.178–3.336, $p=0.009$) adversely affected PFS (Table 3).

Treatment and response

The median chemotherapy cycle of the short-course group was 4. In the short-course group, 37 patients underwent 2 cycles, 28 underwent 3 cycles, and 88 underwent 4 cycles. One hundred sixteen (75.8%) patients were treated with the GELOX regimen, 15 (9.8%) with SMILE, and 22 (14.4%) with VLP. The median chemotherapy cycle of the long-course group was 6. In the long-course group, 18 patients underwent 5 cycles of chemotherapy and 65 underwent 6 cycles. Sixty-eight (81.9%) patients were treated with the GELOX regimen, 10 (12.0%) with SMILE, and 5 (6.0%) with VLP. The percentage of patients using each chemotherapy regimen was not different between the 2 groups ($p=0.204$). The median radiotherapy dose was 55 Gy (range: 40–63 Gy) for all patients. The median doses were 55 Gy for both the short-course group (range: 40–60 Gy) and long-course group (range: 40–63 Gy). A smaller proportion of patients treated with doses >55 Gy in both groups (43.8% *vs.* 44.6%, $p=0.907$).

For the entire study population, complete response (CR), partial response (PR), and progressive disease (PD) was observed in 199 (84.4%), 23 (9.7%), and 14 (5.9%) patients. For the short-course group, CR, PR, and PD was observed in 125 (81.7%), 17 (11.1%), and 11 (7.2%) patients. For the long-course group,

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Table 1. Patient characteristics.

Characteristic	Short-course group (%)	Long-course group (%)	p	N (%)
Gender			0.842	
Male	105 (68.6)	58 (69.9)		163 (69.1)
Female	48 (31.4)	25 (30.1)		73 (30.9)
Age			0.231	
>60	14 (9.2)	4 (4.8)		18 (7.6)
≤60	139 (90.8)	79 (95.2)		218 (92.4)
ECOG			0.947	
0–1	2 (1.3)	1 (1.2)		3 (1.3)
2–4	151 (98.7)	82 (98.8)		233 (98.7)
Ann Arbor stage			0.001	
IE	97 (63.4)	34 (41.0)		131 (55.5)
IIE	56 (36.6)	49 (59.0)		105 (44.5)
LDH			0.073	
Elevated	40 (26.1)	31 (37.3)		71 (30.1)
Normal	113 (73.9)	52 (62.7)		165 (69.9)
B symptoms			0.146	
Present	57 (37.3)	39 (47.0)		96 (40.7)
Absent	96 (62.7)	44 (53.0)		140 (59.3)
PINK			0.171	
Low-risk	133 (86.9)	77 (92.8)		210 (89.0)
Intermediate-risk	20 (13.1)	6 (7.2)		26 (11.0)
PINK-E			0.906	
Low-risk	63 (94.0)	35 (94.6)		98 (94.2)
Intermediate-risk	4 (6.0)	2 (5.4)		6 (5.8)
Chemotherapy regimen			0.204	
GELOX	116 (75.8)	68 (81.9)		184 (78.0)
SMILE	15 (9.8)	10 (12.0)		25 (10.6)
VLP	22 (14.4)	5 (6.0)		27 (11.4)
Radiotherapy dose			0.907	
>55 Gy	67 (43.8)	37 (44.6)		104 (44.1)
≤55 Gy	86 (56.2)	46 (55.4)		132 (55.9)

CR, PR, and PD was observed in 74 (89.2%), 6 (7.2%), and 3 (3.6%) patients. The CR rates between the 2 groups were similar (p=0.132).

Treatment failure and survival

For all patients, the median follow-up duration was 30.9 months (range: 2.6–88.6 months) by October 2017. The median follow-up durations were 23.5 months (range: 2.6–88.6 months) and 40.1 months (range: 6.1–87.6 months) for the short-course and long-course groups, respectively. Up to the follow-up time, recurrence and death were observed in 34 (14.4%; 19 with regional recurrence, 15 with distant recurrence) and 48 (20.3%) patients, respectively. The recurrence rates were 15.7% (n=24; 13 with regional recurrence, 11 with distant recurrence) and 12.0% (n=10; 6 with regional recurrence, 4

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Table 2. Treatment toxicities.

Adverse events	Grade 1–2			Grade 3–4		
	Short-course group (%)	Long-course group (%)	p	Short-course group (%)	Long-course group (%)	p
Hematologic	77 (50.3)	51 (61.4)	0.102	22 (14.4)	21 (25.3)	0.038
Neutropenia	44 (28.8)	35 (42.2)	0.037	21 (13.7)	20 (24.1)	0.045
Anemia	52 (34.0)	42 (50.6)	0.013	2 (1.3)	2 (2.4)	0.531
Thrombocytopenia	17 (11.1)	7 (8.4)	0.516	7 (4.6)	3 (3.6)	0.726
Non-hematologic	61 (39.9)	44 (53.0)	0.052	28 (18.3)	8 (9.6)	0.077
Nausea/vomiting	41 (26.8)	29 (34.9)	0.191	11 (7.2)	3 (3.6)	0.267
Transaminase elevation	43 (28.1)	35 (42.2)	0.028	4 (2.6)	2 (2.4)	0.924

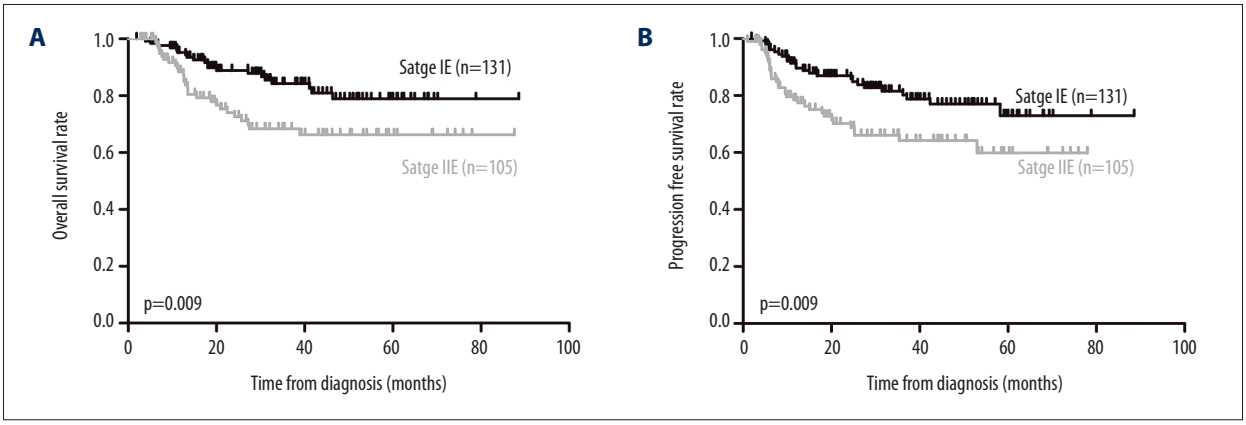

Figure 1. (**A**) Ann Arbor stage and OS. The 3-year OS rates between Ann Arbor stage IE and Ann Arbor stage IIE were 74.3% and 87.0% (p=0.009). (**B**) Ann Arbor stage and PFS. The 3-year PFS rates between Ann Arbor stage IE and Ann Arbor stage IIE were 84.0% and 69.5% (p=0.009).

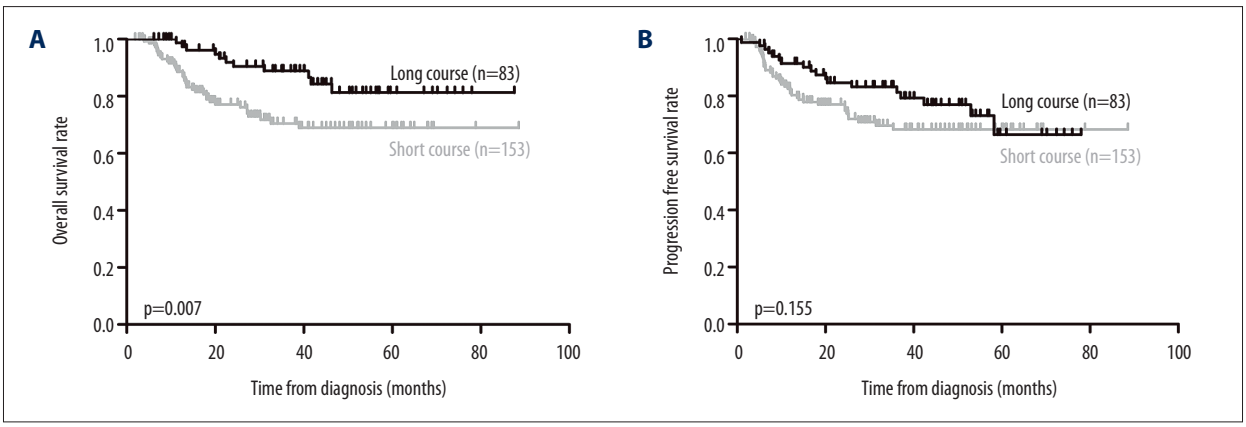

Figure 2. (**A**) Chemotherapy courses and OS. The 3-year OS rates between the short-course and long-course groups were 76.5% and 90.4% (p=0.007). (**B**) Chemotherapy courses and PFS. The 3-year PFS rates between the short-course and long-course groups were 73.9% and 84.3% (p=0.155).

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Table 3. Univariate and multivariate analyses for factors affecting survival outcomes.

Clinical factor	Overall survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)
Female	0.440	0.773 (0.402–1.486)			0.282	0.719 (0.394–1.312)		
Age ≤60	0.165	0.545 (0.232–1.283)			0.156	0.564 (0.256–1.244)		
ECOG 0-1	0.454	0.469 (0.065–3.405)			0.546	0.544 (0.075–3.933)		
Ann Arbor stage IIE	0.009	2.115 (1.191–3.758)	0.033	2.061 (1.059–4.012)	0.009	1.983 (1.178–3.336)	0.009	1.983 (1.178–3.336)
Normal LDH	0.549	1.215 (0.642–2.297)			0.755	1.094 (0.621–1.927)		
Absent B symptoms	0.496	1.225 (0.683–2.198)			0.573	1.165 (0.685–1.980)		
PINK Intermediate-risk	0.169	1.703 (0.797–3.641)			0.428	1.353 (0.641–2.854)		
PINK-E Intermediate-risk	0.112	3.470 (0.748–6.106)			0.194	2.713 (0.601–2.246)		
Short course	0.007	2.445 (1.245–4.801)	0.001	3.288 (1.646–6.568)	0.155	1.494 (0.855–2.610)		
>55 Gy	0.615	0.865 (0.491–1.524)			0.561	0.858 (0.513–1.437)		

with distant recurrence) in the short-course and long-course groups, respectively (p=0.447). The death rate was higher in the short-course group than in the long-course group (24.2% *vs.* 13.3%, p=0.046).

For all patients, the 3-year OS and 3-year PFS rates were 81.4% and 77.5%, respectively. The 3-year OS rate for the long-course group was longer than that for short-course group (90.4% *vs.* 76.5%, p=0.007) (Figure 2A). The 3-year PFS rate of the long-course group tended to be longer than that of the short-course group (84.3% *vs.* 73.9%, p=0.155) (Figure 2B).

A subgroup analysis was conducted because Ann Arbor stage was the single different clinical feature between the 2 groups, and it independently affected survival outcomes. Regardless of stage IE or IIE, the characteristics of patients were balanced between the 2 groups (data not shown). In stage IE, there were no significant differences in the CR rate (87.6% *vs.* 94.1%, p=0.292), recurrence rate (11.3% *vs.* 20.6%, p=0.178), death rate (15.5% *vs.* 14.7%, p=0.916), 3-year OS rate (84.5% *vs.* 94.1%, p=0.537) (Figure 3A), and 3-year PFS rate (83.5%, *vs.* 85.3%, p=0.421) (Figure 3B) between the short-course and long-course groups. In stage IIE, the CR rate in the long-course group showed an increasing trend compared to that in the short-course group (85.7% *vs.* 71.4%, p=0.077). The recurrence rate (6.1% *vs.* 23.2%, p=0.015) and death rate (12.2% *vs.* 39.3%, p=0.002) in the long-course group were significantly lower than those in the short-course group. The 3-year OS rate (87.8% *vs.* 62.5%, p<0.001) (Figure 3C) and 3-year PFS rate (83.7% *vs.* 57.1%, p=0.001) (Figure 3D) in the long-course group were much higher than those in the short-course group.

Ann Arbor stage IIE was an adverse factor affecting OS and PFS. Moreover, in the above subgroup analyses, long-course chemotherapy was superior to short-course chemotherapy in response rates and survival outcomes for stage IIE patients. Therefore, we speculated whether long-course of chemotherapy could overcome the poor prognosis of stage IIE. We further compared the survival outcomes between patients with stage IIE with long-course chemotherapy and patients with stage IE. The CR rate (85.7% *vs.* 89.3%, p=0.503), 3-year OS rate (87.8% *vs.* 84.7%, p=0.561), and 3-year PFS rate (81.6% *vs.* 80.9%, p=0.860) were similar between the 2 groups, suggesting that extending the course of chemotherapy might improve the prognosis of stage IIE patients.

Statistical analysis for GELOX patients

The majority of the patients were treated with GELOX regimen. Therefore, we separately analyzed treatment efficacies

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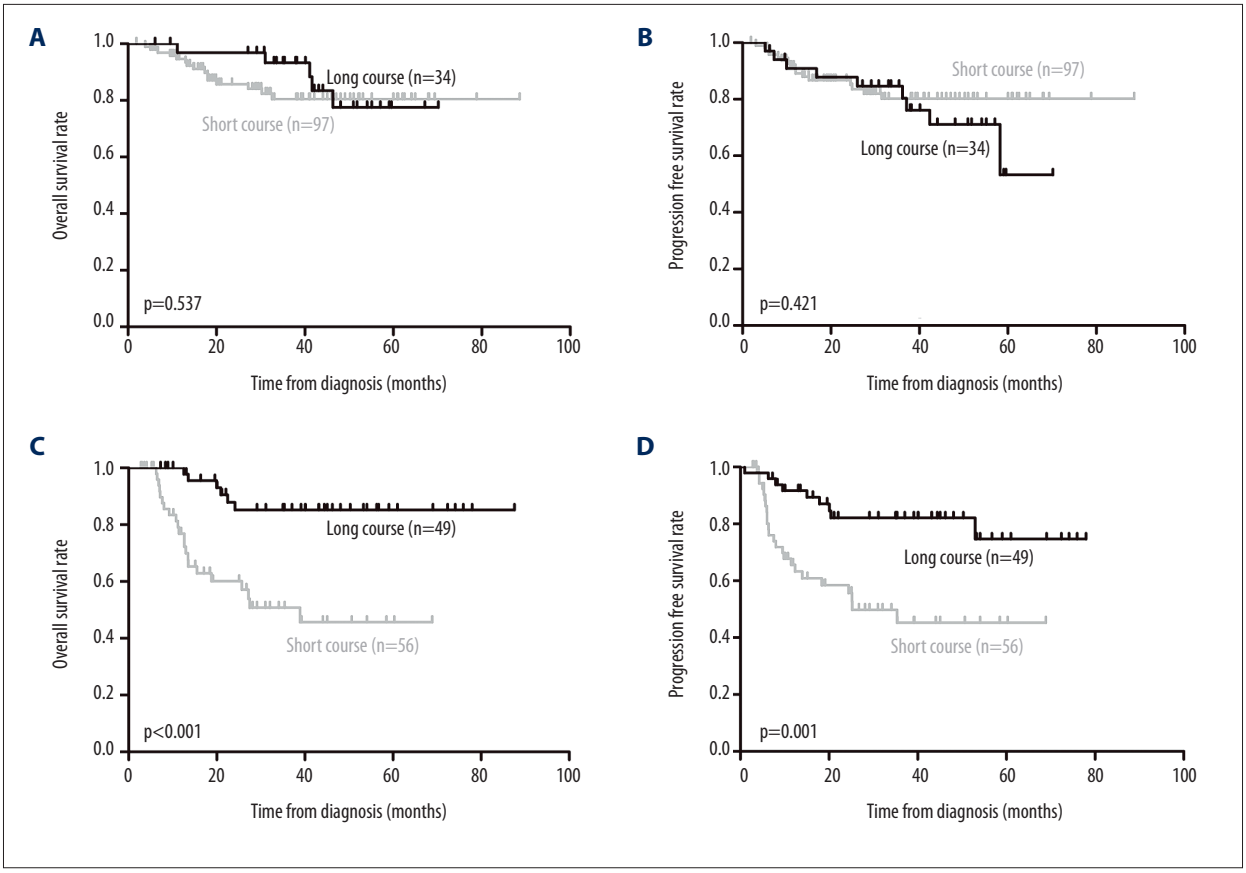

Figure 3. Subgroup analyses of chemotherapy courses with OS and PFS. (**A**) Chemotherapy courses and OS in stage IE. The 3-year OS rates between the short-course and long-course groups were 84.5% and 94.1% (p=0.537). (**B**) Chemotherapy courses and PFS in stage IE. The 3-year PFS rates between the short-course and long-course groups were 83.5% and 85.3% (p=0.421). (**C**) Chemotherapy courses and OS in stage IIE. The 3-year OS rates between the short-course and long-course groups were 62.5% and 87.8% (p<0.001). (**D**) Chemotherapy courses and PFS in stage IIE. The 3-year PFS rates between the short-course and long-course groups were 57.1% and 83.7% (p=0.001).

and clinical prognoses between the short-course and the long-course groups in patients with GELOX regimen. Same as the analysis of entire patients, Ann Arbor stage was the single different clinical feature between the 2 groups (the short-course group with more stage IE patients, 70.7% *vs.* 44.1%, p<0.001), and it independently affected OS (HR 3.048, 95% CI 1.589–5.846, p=0.001) and PFS (HR 2.138, 95% CI 1.180–3.874, p=0.012) in patients with GELOX regimen. Therefore, subgroup analysis was needed. Regardless of stage IE or IIE, the characteristics of patients were balanced between the 2 groups (data not shown). In stage IE, there were no significant differences in the CR rate (87.8%% *vs.* 96.7%, p=0.163), recurrence rate (11.0% *vs.* 20.0%, p=0.214), death rate (15.9% *vs.* 13.3%, p=0.742), 3-year OS rate (84.1% *vs.* 93.3%, p=0.412) and 3-year PFS rate (84.1%, *vs.* 86.7%, p=0.649) between the short-course and long-course groups. In stage IIE, the CR rate in the long-course group showed an increasing trend compared to that in the short-course group (84.2% *vs.* 79.4%, p=0.597). The recurrence rate (5.3% *vs.* 29.4%, p=0.006) and death rate (13.2% *vs.* 50.0%, p=0.001) in the long-course group were significantly lower than those in the short-course group. The 3-year OS rate (86.8% *vs.* 50.0%, p<0.001) and 3-year PFS rate (84.2% *vs.* 50.0%, p=0.002) in the long-course group were much higher than those in the short-course group.

Discussion

In our study, Ann Arbor stage was the single different clinical feature between the short-course and long-course groups, and it independently affected survival outcomes. Therefore, the subgroup analysis of stage IE and stage IIE was necessary. In the subgroup analysis of stage IE, the response rates and survival outcomes were similar between the 2 groups. In subgroup analysis of stage IIE, the recurrence and death rates in the long-course group were significantly lower than those in the short-course group, and the 3-year OS and PFS rates were much longer in the long-course group. Moreover, the prognoses

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Table 4. Chemoradiotherapy for localized extranodal NK/T cell lymphoma, nasal type.

Study (reference)	N.	Treatment	CR	OS	PFS
Yamaguchi et al. [29] Phase I/II	33	CCRT (50–50.4 Gy) + 3 cycles DeVIC	75.0%	2-year 78.0%	2-year 67.0%
Ma et al. [30] Phase II	38	2–4 cycles CEOP+RT (50 Gy)	94.4%	2-year 77.4%	2-year 69.4%
Kim et al. [16] Phase II	30	CCRT (cisplatin, 36–44 Gy) + 2 cycles VIDL ± ASCT	86.7%	5-year 73.0%	5-year 60.0%
Ke et al. [31] Phase II	32	CCRT (cisplatin, 56 Gy) + 3 cycles GDP	84.4%	3-year 87.5%	3-year 84.4%
Oh et al. [32] Phase II+retrospective	62	CCRT (cisplatin, 40–45 Gy) + chemotherapy (3 cycles VIPD, 2 cycles VIDL, 2 cycles MIDLE)	90.3%	3-year 83.1%, 5-year 80.1%	3-year 77.1%, 5-year 69.9%
Michot et al. [33] Retrospective	13	CCRT (2 cycles ESHAP, 40 Gy) + 2–3 cycles ESHAP	92.0%	2-year 72.0%	–
Yoon et al. [17] Phase II	30	CCRT (cisplatin + L-Asp, 36–44 Gy) + 2 cycles MIDLE	82.1%	3-year 81.5%	3-year 74.1%
Dong et al. [34] Retrospective	33	4 cycles L-DICE + RT (45 Gy)	90.9%	5-year 89.2%	5-year 82.9%
Jiang et al. [35] Phase II	66	2 cycles LVDP + CCRT (cisplatin, 56 Gy) + 2 cycles LVDP	83.3%	3-year 70.1%	3-year 67.4%
Lin et al. [36] Phase II	31	6–8 cycles L-CHOP + sandwich RT (40–60 Gy)	81.6%	2-year 80.1%	2-year 81.0%
Aviles et al. [37] Retrospective	202	RT (55 Gy) + 6 cycles CMED	91.0%	5-year 86.0%	5-year 91.0%
Zang et al. [24] Retrospective	64	8–12 cycles chemotherapy (L-CHOP, SMILE) + RT (sandwich or sequential, 26–60 Gy)	64.1%	3-year 69.9%	3-year 64.7%

between stage IIE with long-course chemotherapy and stage IE patients were almost the same, suggesting that long-course chemotherapy might overcome the poor prognosis of stage IIE.

At present, ENKTL does not have definitive treatment strategies. The general principle of front-line therapy for localized ENKTL is radiotherapy combined with chemotherapy [11]. ENKTL is sensitive to radiotherapy with CR rates of 50% to 100% [6,8–10]. However, radiotherapy alone leads to a high recurrence rate with 25% to 40% in localized ENKTL [10]. Therefore, radiotherapy should be combined with chemotherapy to reduce the recurrence rate. Anthracycline-based regimens are ineffective due to the P- glycoprotein expressed by ENKTL cells [22]. The presence of L-asparaginase/pegaspargase has improved the treatment response and outcomes of ENKTL [23]. L-asparaginase/pegaspargase-based chemotherapy has become the mainstream for the treatment of ENKTL. Because of the importance of radiotherapy in early-stage ENKTL, the course of chemotherapy does not require as many as 6–8 cycles for peripheral T cell lymphoma. Four to 6 cycles of chemotherapy combined with radiotherapy are currently recommended for localized ENKTL [1], but the standard number of chemotherapy courses has not been determined. Therefore, we conducted this retrospective study to explore the optimal number of chemotherapy courses for stage IE–IIE ENKTL.

Table 4 lists retrospective studies or phase II trials of ≤4 cycles and ≥6 cycles of chemotherapy combined with radiotherapy in early-stage ENKTL. For short-course chemotherapy, our results were comparable with previous studies. For long-course chemotherapy, our results were consistent with previous studies, except for the study by Zang et al. [24]. In that study, the CR, 3-year OS, and PFS rates were much inferior to those of our study. This conflicting result might be because nearly half of the patients were administered anthracycline-containing regimens and a lower dose of radiotherapy than in our study. A retrospective study showed that patients treated with >8 courses of high-intensity chemotherapy had a significantly higher 5-year OS (63.5% *vs.* 45.1% *vs.* 22.9%, respectively; p=0.030) and PFS (59.1% *vs.* 36.0% *vs.* 15.1%, respectively; p=0.020) than those treated with 6–8 courses and <6 courses of standard chemotherapy [25]. Our study also showed that long-course chemotherapy induced superior outcomes in stage IIE. However, this previous study enrolled advanced-stage patients and adopted anthracycline-containing regimens. These factors might contribute to the much lower survival rates than our study.

Comparing long-course with short-course chemotherapy, the former generated a higher incidence of neutropenia, anemia, and transaminase elevation. Regardless of the course length, however, these treatment toxicities were well tolerated.

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There are several prognostic risk models for ENKTL. When ENKTL was first described, the International Prognostic Index was used to assess the prognosis of ENKTL as well as diffuse large B-cell lymphoma, with the limitation that most early-stage patients were categorized into the low or low-intermediate risk groups [26]. A Korean group proposed the NK/T cell Lymphoma Prognostic Index (NK-PI) in 2006 [27]. Because NK-PI was derived from data based on anthracycline-based chemotherapy regimens, it was controversial that NK-PI was not suitable for non-anthracycline-based populations [28]. A novel prognostic model, the prognostic index for NK/T cell lymphoma (PINK), was developed from a non-anthracycline-based international retrospective study in 2016 [4]. The PINK model was developed using 4 risk factors, including age >60-year-old, stage III–IV, distant lymph-node involvement, and non-nasal type disease. The PINK-E model includes the 4 risk factors of PINK along with the plasma EBV-DNA level. The survival rates decreased with increasing risk group levels. In this study, the trend of survival rates of PINK and PINK-E were in accordance with previous reports. The lack of significant differences in OS and PFS among these risk groups might be due to the fact that our study included only stage I/II patients and a small number of patients in intermediate-risk groups.

Our study was a multicenter investigation; however, there were certain limitations in this study. It was a retrospective analysis with a relatively small sample size. Moreover, patients were administered non-uniform chemotherapy regimens and varying radiotherapy dosages.

Conclusions

In the era of L-asparaginase/pegaspargase, when radiotherapy was combined with chemotherapy for the treatment of patients with early-stage ENKTL, 2-4 cycles of chemotherapy might be sufficient for patients with stage IE, while patients with stage IIE might require 5 or more cycles. More prospective studies with larger samples and uniform treatment are warranted to determine the optimal number of cycles of chemotherapy for stage IE and IIE patients with ENKTL.

Conflict of interest

None.

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