Int J Clin Exp Med 2018;11(4):3235-3244
www.ijcem.com /ISSN:1940-5901/IJCEM0064061

Original Article

A retrospective clinical study: combined treatment of chemotherapy and radiotherapy results in optimal outcome for limited-stage extranodal NK/T-cell lymphoma

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Received May 30, 2017; Accepted January 25, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Extranodal NK/T-cell lymphoma (ENKL) is an aggressive lymphoma with higher prevalence in Asia. Optimal therapeutic strategies for early-stage ENKL remain controversial. Here, we report a retrospective clinical study with 137 patients to assess the prognostic factors and optimal treatment for localized ENKL. The 5-year overall survival (OS) and progression-free survival (PFS) were 54.7% and 48.2%, respectively. Patients were grouped by the therapies received: chemotherapy alone (CT, n = 16), radiotherapy alone (RT, n = 24), and combined modality therapy (CMT, n = 97). Compared with the patients who received CT or RT alone, the patients who received CMT had more favourable OS outcomes (5-year OS, CMT: 66.9% vs. RT: 40.4% vs. CT: 0%, P<0.001). A multivariate analysis identified disease stage, lactate dehydrogenase levels and treatment strategy as prognostic factors that influenced PFS and OS. In the CMT subgroups, patients who received CT followed by RT (CRT) exhibited longer survival than patients who received RT followed by CT (RCT). In conclusion, for early-stage ENKL, CMT is the treatment modality that will most likely lead to long-term remission.

Keywords: Extranodal NK/T-cell lymphoma, treatment, prognostic factor, retrospective analysis

Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL), is tightly related to Epstein-Barr virus (EBV) infection and is recognized as a distinctive subtype in the World Health Organization (WHO) classification from 2001. ENKL is an aggressive lymphoma with a geographical predilection for South American and Asian populations [1, 2]. ENKL is the most common peripheral T-cell lymphoma (PTCL) in China and accounts for 6% of all lymphomas in China [3]. The incidence of ENKL is approximately 4 cases per 1,000,000 in China. Most patients are diagnosed with ENKL in their 40 s, and the disease is more prevalent in males. ENKL is frequently localized to the upper aerodigestive tract, including the nasal cavity, paranasal sinuses, tonsils, nasopharynx, hypopharynx, and larynx [4, 5]. Localized ENKL is present in 70% to 90% of patients; however, the treatment strategy for limited-stage ENKL remains controversial [6-10]. Currently, the options include radiotherapy (RT) alone, concurrent chemoradiotherapy, chemotherapy followed by radiotherapy (CRT) or radiotherapy followed by chemotherapy (RCT). During the past decades, the beneficial affect of additional chemotherapy (CT) has been under debate, and RT has been accepted as the primary treatment. However, accumulating numbers of recent studies have suggested CT as a vital treatment option. The 5-year overall survival (OS) rate for early-stage ENKL varies from 38% to 85% [2, 6-8, 10-15], which reflects the malignancy heterogeneity, differences in clinical management, and lack of optimal prognostic factors. Most of the current clinical data were generated by small prospective series and retrospective analyses. Due to the rarity and limited regional distribution of ENKL, prospective, multicentre, randomized clinical trials that compare the different treatment modalities have not been reported. Here, we conducted a retrospective analysis to test the hypothesis

Table 1. Univariate analysis of the association between the clinical characteristics and the survival outcomes for all patients with limited-stage ENKL

Characteristic	No. (%)	5-year PFS	P	5-year OS	P
		% (95% CI)		% (95% CI)	
Sex			0.572		0.674
Male	98 (71.53)	49.1 (38.71-59.49)		55.0 (44.61-65.39)	
Female	39 (28.47)	45.9 (29.04-62.76)		53.9 (37.24-70.56)	
Age (years)			0.007		0.001
≤60	113 (82.48)	54.1 (44.50-63.70)		60.8 (51.39-70.21)	
>60	24 (17.52)	20.0 (1.77-38.23)		25.7 (6.69-46.71)	
ECOG PS			<0.001		<0.001
0-1	126 (91.97)	52.4 (43.19-61.61)		59.5 (50.48-68.52)	
≥2	11 (8.03)	0		0	
B symptoms			0.140		0.040
Absent	86 (62.77)	53.9 (42.92-64.88)		61.8 (51.01-72.58)	
Present	51 (37.23)	38.1 (23.60-52.60)		42.4 (27.70-57.10)	
Primary location			0.001		0.010
UADT	130 (94.89)	50 (40.98-59.02)		56.2 (47.18-65.22)	
Extra-UADT	7 (5.11)	14.3 (0-40.17)		28.6 (0-62.12)	
LDH Level			0.001		0.004
Normal	75 (54.74)	62.7 (51.37-74.07)		64.9 (51.14-76.66)	
Elevated	62 (45.26)	31.9 (19.75-44.05)		42.0 (29.26-54.74)	
Local Invasion			0.002		0.026
Absent	122(89.05)	52.4 (43.39-61.81)		58.8 (49.59-68.01)	
Present	15(10.95)	13.3 (0-30.55)		26.7 (4.36-49.04)	
Ann Arbor stage			<0.001		<0.001
I	94 (68.61)	59.3 (48.72-69.88)		67.0 (57.20-76.8)	
II	43 (31.39)	24.4 (11.27-37.53)		25.0 (9.71-40.29)	
KIPI			<0.001		<0.001
0	50 (36.50)	81.0 (68.65-93.35)		87.1 (77.30-96.90)	
>0	87 (63.50)	29.8 (19.80-39.80)		36.2 (25.42-46.98)	
IPI			<0.001		<0.001
0	53 (38.69)	74.4 (62.05-86.75)		78.0 (65.26-90.74)	
>0	84 (61.31)	32.6 (22.21-42.99)		40.0 (29.22-50.78)	
Treatment			<0.001		<0.001
RT Alone	24 (17.52)	38.20 (16.64-59.76)		40.4 (17.86-62.94)	
CT Alone	16 (11.68)	0		0	
CMT	97 (70.80)	58.6 (48.21-68.99)		66.9 (57.10-76.70)	

UATD, the upper aerodigestive tract; IPI, international prognostic index; KIPI, the Korean international prognostic index.

that the combination of CT and RT, especially CRT, may result in improved survival for limited-stage ENKL patients.

Materials and methods

Subjects

A total of 137 early-stage ENKL patients admitted to the Cancer Hospital affiliated with Fujian Medical University between January 2004 and December 2014 were included in this study. A definitive diagnosis was established by pathological examination, and all patients had measurable cancer lesions and complete clinical records. Diagnostic biopsy samples were categorized based on the 2008 World Health Organization classification. According to a comprehensive staging assessment (computerized tomography and/or positron emission computed tomography scan, bone marrow biopsy and aspirate), this research enrolled patients with localized disease (stage I/II). The following de-

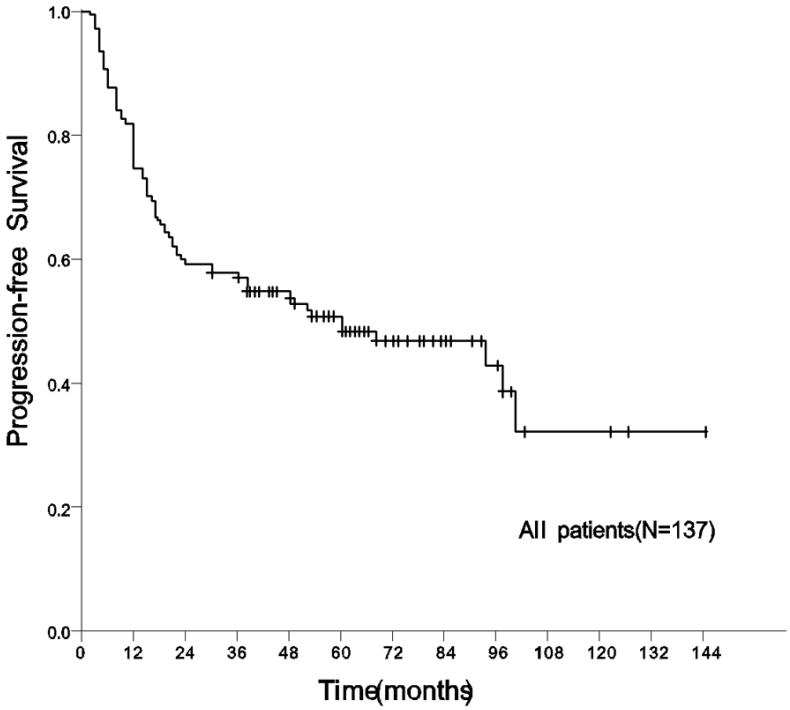

Figure 1. Kaplan-Meier curve of PFS for all study subjects (n = 137).

Table 2. Multivariable analysis of the associations between clinical variables and treatment and PFS for all patients with limited-stage ENKL

Variable	PFS		
	HR	95% CI	P
Ann Arbor stage (II vs. I#)	2.401	1.446-3.984	0.001
LDH Level (Elevated vs. Normal#)	2.021	1.212-3.369	0.007
ECOG PS (≥2 vs. 0-1#)	2.317	1.011-5.310	0.047
Treatment modality			
RT Alone#			
CT Alone	4.025	1.681-9.638	0.002
CMT	0.485	0.255-0.922	0.027
Age (>60 vs. ≤60#)	1.036	0.542-1.978	0.916
Primary location (Extra-UADT vs. UADT#)	1.472	0.603-3.595	0.396
Local Invasion (Present vs. Absent#)	1.523	0.726-3.196	0.266

HR, hazard ratio; #indicates the reference groups.

mographic and clinical features were retrospectively collected: sex, age, the primary tumour location, the presence or absence of B symptoms, the international prognostic index (IPI), the Ann Arbor stage (stage I/II), local invasion status, elevated lactate dehydrogenase (LDH) levels, performance status, the Korean international prognostic index (KIPI) and treatment modality (including radiation dose and response to CT).

Evaluating response to treatment

The response to CT was evaluated after 2 cycles of treatment using the Lymphoma Curative Standard (version 2007), and the responses were categorized as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD).

Estimation of survival

OS was defined from the time of original diagnosis to the time of death, whereas PFS was calculated from the time of original diagnosis to the time of relapse, progression, or death due to any cause. Patients who did not experience any of these outcomes were censored at the final follow-up.

Follow-up

All 137 patients were followed up by either visits to the hospital for re-examination or telephone interviews until death or the date of final follow-up in December 2016. The follow-up period ranged from 4 to 144 months (median, 44 months). The follow-up rate was 92.70%. During the follow-up period, 60 subjects died.

Statistics

OS and PFS were defined as previously described and estimated using the Kaplan-Meier estimator. Univariate analyses were conducted with a log-rank test, and multivariate analyses were conducted using a Cox proportional regression model. The statistical software SPSS version 22.0 was used to perform all the statistical analyses (SPSS, Inc.; Chicago, IL, USA). A P value <0.05 was considered significant, and a chi-square test was utilized to determine the

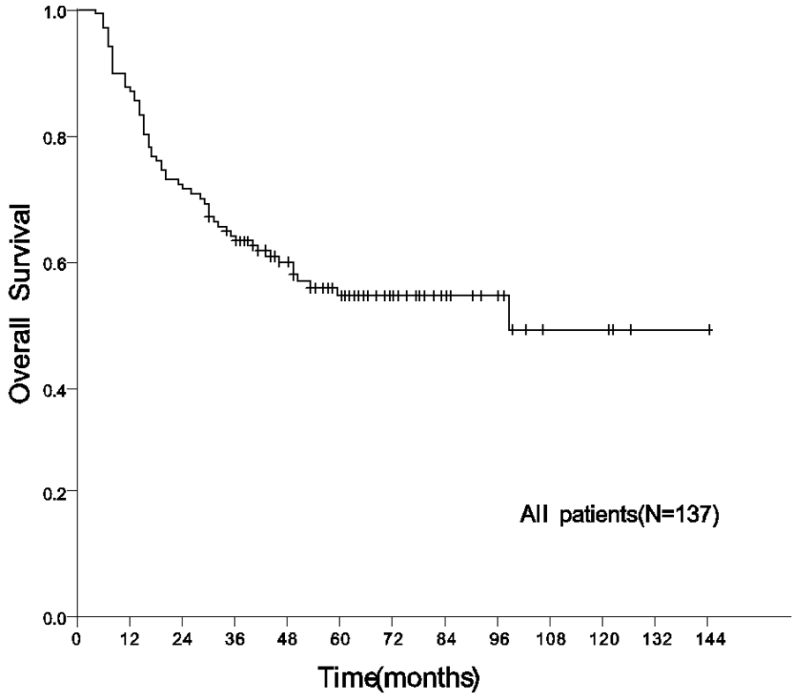

Figure 2. Kaplan-Meier curve of OS for all study subjects (n = 137).

Table 3. Multivariable analysis of the associations between clinical variables and treatment and OS for all patients with limited-stage ENKL

Variable	OS		
	HR	95% CI	P
Ann Arbor stage (II vs. I#)	2.132	1.226-3.706	0.007
LDH Level (Elevated vs. Normal#)	1.982	1.138-3.453	0.016
ECOG PS (≥2 vs. 0-1#)	2.168	0.898-5.236	0.085
Treatment modality			
RT Alone#			
CT Alone	4.934	1.962-12.412	0.001
CMT	0.363	0.179-0.736	0.005
Age (>60 vs. ≤60#)	1.268	0.640-2.515	0.496
Primary location (Extra-UADT vs. UADT#)	1.078	0.400-2.904	0.881
Local Invasion (Present vs. Absent#)	1.316	0.571-3.033	0.519
B symptoms (Present vs. Absent#)	1.614	0.911-2.858	0.101

HR, hazard ratio; #indicates the reference groups.

differences in the percentages as well as the significance of these percentages.

Results

The clinical characteristics for all patients

The clinical features of these patients are summarized in **Table 1**. The median age of the patients was 45 years (range, 13-81 years), and the male-to-female ratio was 2.51:1. B symptoms were detected in 37.23% of the patients. Sixty-two patients (45.26%) had elevated LDH levels. Most patients had good PS scores, with only 11 (8.03%) presenting with a PS score greater than 1. Fifteen patients (10.95%) had local tumour invasion in the bone or skin, and 68.61% of the patients were diagnosed with stage I disease. In most of the cases, ENKL were present primarily in the upper aerodigestive tract; in only 7 cases, we found lymphoma presented primarily outside the upper aerodigestive tract, including 1 in the gastrointestinal tract, 1 in the adrenal glands, 1 in the cervix uteri, 2 on the dermis, and 2 in soft tissue. Of the 7 patients who presented with lesions primarily outside the upper aerodigestive tract, 1 patient had haemophagocytic syndrome.

PFS of all patients in the study

The median PFS of the 137 subjects was 60 months (95% CI: 24.53-95.47 months) (**Figure 1**). The PFS rates at 1, 2, and 5 years were 74.5%, 59.1%, and 48.2%, respectively. A univariate analysis revealed that PFS was significantly influenced by age, Ann Arbor stage, LDH level, primary location, local invasion, performance status (ECOG PS score), treatment modality, KIPI score, and IPI score (**Table 1**). A multivariate Cox regression analysis revealed that PFS was significantly influenced by Ann Arbor stage, LDH level, performance status (ECOG PS score), and treatments received (**Table 2**).

Table 4. Patient characteristics

Characteristic	RT		CT		CMT		P
	NO.	%	NO.	%	NO.	%	
No. of patients	24		16		97		
Sex							0.281
Male	19	79.17	9	56.25	70	72.16	
Female	5	20.83	7	43.25	27	17.84	
Age (years)							0.233
≤60	19	79.17	11	68.75	83	85.57	
>60	5	20.83	5	31.25	14	14.43	
ECOG PS							0.031
0-1	20	83.33	13	81.25	93	95.88	
≥2	4	16.67	3	18.75	4	4.12	
B symptoms							0.609
Absent	17	70.83	9	56.25	60	61.86	
Present	7	29.17	7	43.75	37	38.14	
Primary location							0.030
UADT	23	95.83	13	81.25	94	96.91	
Extra-UADT	1	4.17	3	18.75	3	3.09	
Local invasion							0.513
Absent	21	87.50	13	81.25	88	90.72	
Present	3	12.50	3	18.75	9	9.28	
LDH level							0.426
Normal	16	66.67	8	50.00	51	52.58	
Elevated	8	33.33	8	50.00	46	47.42	
Ann Arbor stage							0.074
I	17	70.83	7	43.75	70	72.16	
II	7	29.17	9	56.25	27	17.84	
KIPI							0.351
0	11	45.83	2	0.12	37	38.14	
1	5	20.83	6	0.38	29	29.90	
2	7	29.17	6	0.38	21	21.65	
3	1	4.17	2	0.12	10	10.31	
IPI							0.606
0	10	41.67	4	0.25	39	40.21	
1	10	41.67	10	0.63	49	50.51	
2	4	16.66	2	0.12	9	9.28	

UATD, the upper aerodigestive tract; IPI, international prognostic index; KIPI, the Korean international prognostic index.

OS of all patients in the study

The OS rates at 1, 2, and 5 years were 86.9%, 71.5%, and 54.7%, respectively, with a mean OS of 86.62 months (95% CI: 75.43-97.81 months) (**Figure 2**). The univariate analysis showed that OS was considerably influenced by age, Ann Arbor stage, LDH level, primary location, local invasion, performance status (ECOG PS score), the presence or absence of B symptoms, the treatment modality, the KIPI score, and the IPI score (**Table 1**). A multivariate Cox proportional regression analysis revealed that OS was significantly influenced by Ann Arbor stage, LDH levels, and treatments received (**Table 3**). Of the 137 patients, 56 died due to PD, and 4 deaths occurred for other reasons.

Different treatments for all patients

Patients were treated with combined modality therapy (CMT, n = 97), RT alone (n = 24), or CT alone (n = 16). The RT field contained an extended region that encompassed the primary tumour and adjacent areas. The median dose was 50 Gy (range, 36-60 Gy). Of the patients who underwent CT, 37 patients received either cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) or CHOP-like regimens, and 76 patients received either an L-asparaginase-based regimen (n = 30) or a VIPD regimen (n = 46) (etoposide, ifosfamide, cisplatin, and dexamethasone). The number of CT cycles ranged from 2 to 6 (median, 4). Of the 16 patients who received CT alone, 8 patients stopped further treatment due to tumour progression, and the remaining 8 patients did not undergo RT for personal reasons.

Different treatments result in different survival

The three treatment arms were well matched for age, sex, Ann Arbor stage, LDH level, the presence or absence of B symptoms, local invasion, the KIPI score, and the IPI score (**Table 4**). To further define the benefits of the treatments, we compared the outcomes among CT alone, RT alone, and CMT. The 5-year PFS rate for patients undergoing CMT was 58.6% vs. 38.2% for RT alone and 0% for CT alone. The 5-year OS rate for patients undergoing CMT was 66.9% vs. 40.4% for RT alone and 0% for CT alone (**Figure 3**). Compared with either CT alone or RT alone, survival was greatly improved by CMT.

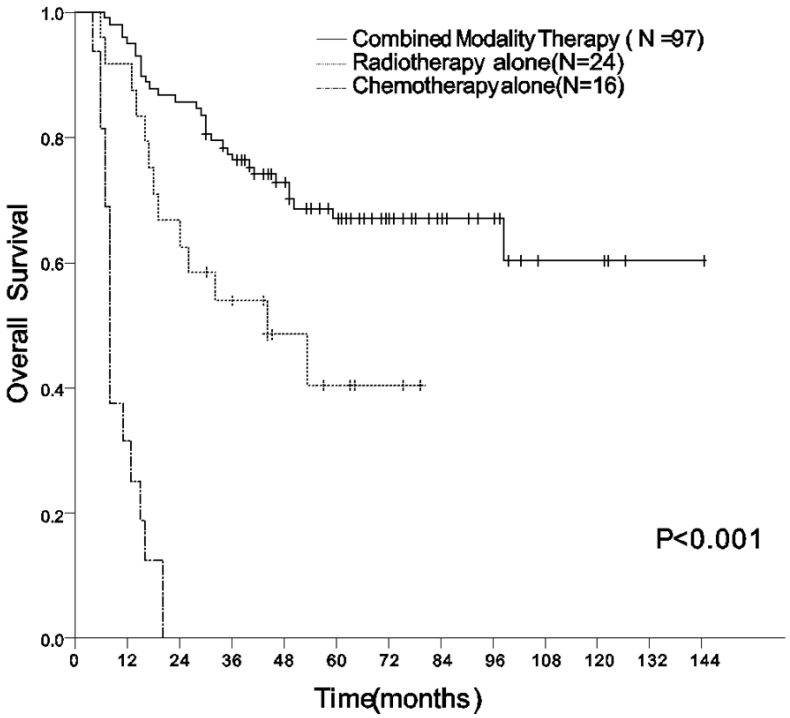

Figure 3. Kaplan-Meier curves of OS stratified by treatment modality.

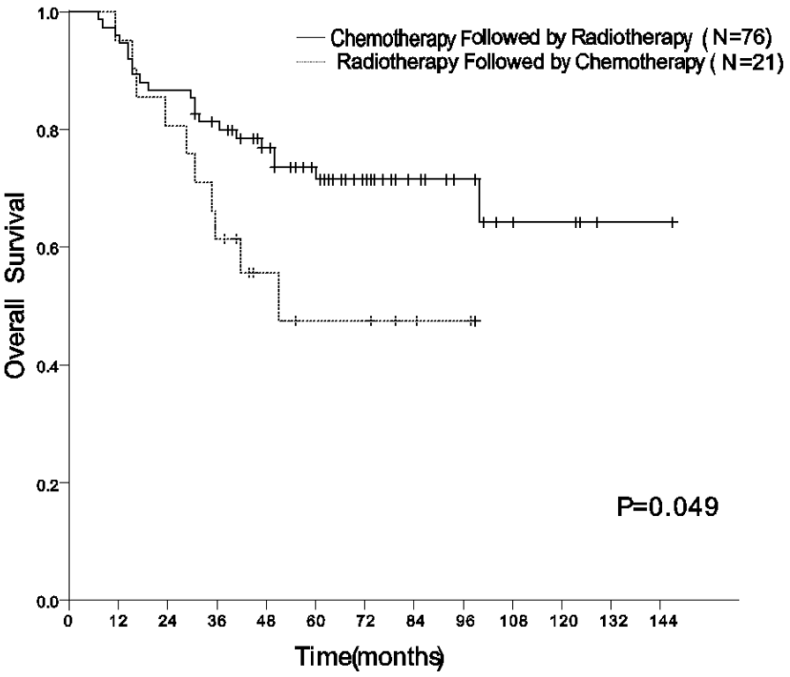

Figure 4. Kaplan-Meier curves of OS for the patients in the CMT subgroup stratified by the sequence of CT and RT.

CRT improves survival in CMT subgroup

In the CMT group, the PFS rates at 1, 2, and 5 years were 85.6%, 71.1%, and 58.6%, respectively, and the OS rates at 1, 2, and 5 years were 94.8%, 85.6%, and 66.9%, respectively. A total of 76 patients underwent CT followed by RT (CRT), while 21 patients underwent RT followed by CT (RCT). CRT significantly improved survival rate compared with RCT; the 5-year OS rate was 71.9% for CRT compared with 48.2% for RCT (P = 0.049, **Figure 4**).

New regimens improve survival in the CRT group

In the CRT subgroup, patients were treated with the following 3 different regimens: anthracycline-based regimens, n = 15; the VIPD regimen, n = 38; and L-asparaginase-based regimens, n = 23. Among the patients who received anthracycline-based regimens, the CR rate was 33.33%, which is significantly lower than the CR rate of either the VIPD group (65.79%) or L-asparaginase-based regimens group (60.87%). In the CRT subgroup, patients who received the VIPD regimen or L-asparaginase-based regimens exhibited higher CR rates (63.93% vs. 33.33%, P = 0.032) and greater survival rates than those who received anthracycline-based regimens (**Figure 5**).

CR after the induction CT results in a better outcome

In the CRT subgroup, after the induction of CT, 44 patients exhibited a CR, 14 patients had a PR, 10 patients had SD, and 8 patients had PD. The 5-year OS rate was 88.7% for patients with a CR, whereas the 5-year OS rate was 48.5% for

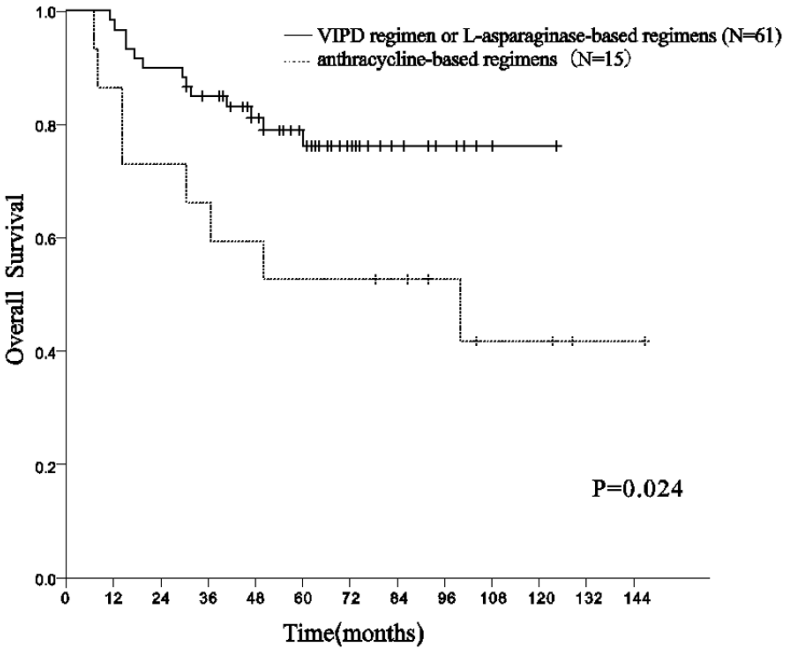

Figure 5. Kaplan-Meier curves of OS for the patients in the CRT group stratified by chemotherapy regimens.

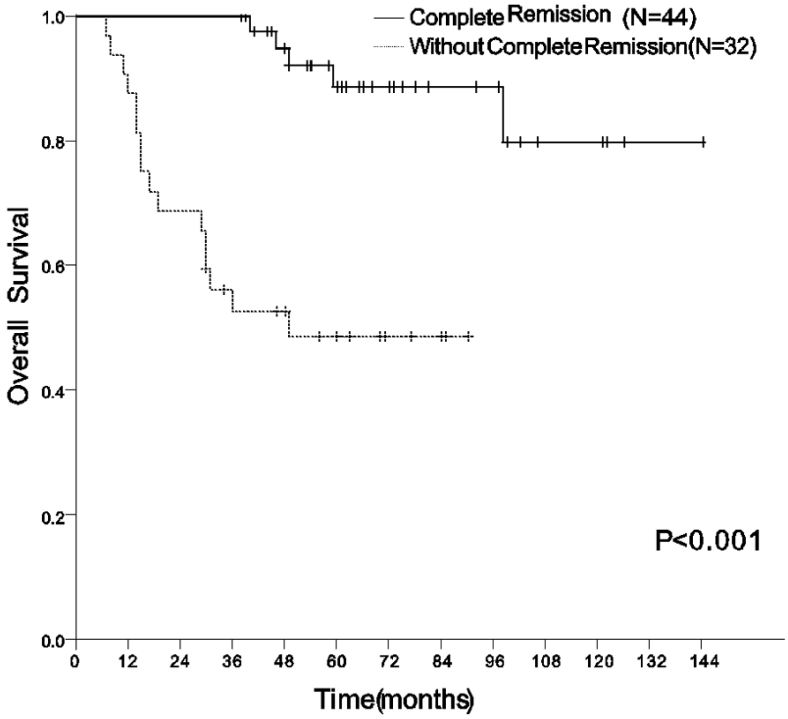

Figure 6. Kaplan-Meier curves of OS for the patients in the CRT group stratified by curative effect.

those without a CR. The patients with a CR exhibited significantly longer OS than patients without a CR (**Figure 6**).

Discussion

The optimal prognostic model for localized ENKL remains contentious. The IPI is widely used in patients with aggressive non-Hodgkin's lymphomas. Nevertheless, because the majority of ENKL patients suffer from localized disease, the use of the IPI in ENKL patients is limited. Alternative models have been proposed. One of them, KIPI, was reported by Lee et al. [16]. Based on the absence or presence of four prognostic factors-Ann Arbor stage, regional lymph node involvement, B symptoms, and LDH levels-four risk groups with different survival outcomes were identified in a retrospective analysis of 262 patients using a prognostic model. The KIPI showed better prognostic discrimination than the IPI. Yong Yang et al. proposed another prognostic model based on a retrospective multicentre study that included 1273 patients [11]. This model classified 2 risk groups with various survival results based on the absence or presence of 5 independent risk factors (stage II disease, ECOG ≥ 2, primary tumour invasion, age >60 years, and elevated LDH) regardless of treatment. High-risk localized patients had significantly worse outcomes than low-risk localized patients (defined as having no risk factors). Consistent with their model, the results of this study confirmed LDH levels as prognostic factors for OS and identified ECOG score and Ann Arbor stage as novel prognostic factors (**Tables 2**, **3**). The results of this

study indicate that normal LDH levels, an ECOG score of 0 or 1, and an Ann Arbor stage of I were good prognostic factors for PFS. Novel prognostic models have evolved beyond simple clinical factors. A comprehensive assessment of PET/CT scan and EBV DNA can predict outcome in patients with ENKL [17]. Constant efforts are devoted to incorporating these research findings with clinical parameters for better risk evaluation.

ENKLs are radiosensitive. RT is a vital component of curative treatment for patients with localized ENKL, and RT alone has been efficient in achieving favourable CR rates and longer survival time in patients with limited-stage ENKL compared with CT alone [15, 18-24]. In our study, RT alone resulted in better survival rate than CT alone (**Figure 3**). Other studies have indicated a dose-dependent survival benefit, as more favourable PFS and OS outcomes corresponded to RT doses of 50 Gy or greater [24, 25]. In our RT-alone group, the majority (18/24) of patients received RT doses that did not exceed 50 Gy, and the 5-year PFS and OS rates were only 38.2% and 40.4%, respectively. Lower doses result in increased in-field failure rates. To improve the long-term survival rate, high-dose radiation should be considered for patients undergoing RT alone.

The systemic relapse rates range from 25% to 40% [26], indicating that occult systemic metastases may occur in apparently localized ENKLs. Given the available data suggesting that RT alone is not sufficient for localized ENKL patients, CT is necessary to reduce systemic failure. Based on our data, CMT may provide a greater survival benefit. The beneficial effect of CT was also shown by Yang et al. [11]. In their study, the 5-year OS for high-risk localized patients treated with RT followed by CT was 72.8% compared with 57.9% for those who treated with RT alone. Furthermore, an open-label prospective clinical trial conducted by Aviles A's group also supported the use of combined therapy as the most efficient treatment for localized ENKL [10]. The study included 427 patients, among whom 202 received combined therapy, 109 received RT alone, and 116 received CT alone. The patient groups were also well matched according to prognostic factors and disease stage. The OS rates at 5 years were 86% for combined therapy, 64% for RT alone, and 45% for CT alone ($P<0.001$). From 2016, NCCN guidelines recommend CMT is suitable for localized ENKL patients, except for those unfit for CT.

CT is increasingly recognized as a vital treatment component. Anthracycline-based regimens are largely ineffective for ENKL because malignant cells express high levels of P-glycoprotein, which results in a multidrug resistance (MDR) phenotype [1, 27]. Consequently, non-MDR-dependent medicine has been integrated into new schedules, such as the VIPD regimen or L-asparaginase-based regimens. These new regimens, which are recommended by National Comprehensive Cancer Network (NCCN) from 2010, are effective for achieving improved CR rates and longer survival times [12-14, 28]. In the CRT group of our study, patients who received the VIPD regimen or L-asparaginase-based regimens also achieved better survival than patients who received anthracycline-based regimens (**Figure 5**).

Several prospective clinical studies showed that concomitant/sequential CT and RT yielded favourable results [12-14, 28, 29]. The most favourable sequence of CT and RT for limited-stage ENKL is not distinct. Yang et al. showed that patients who received RCT achieved better survival than patients who received CRT [11]. However, in our study, CRT significantly improved survival compared with RCT. These rather contradictory results may come from the different sample populations in the studies. The majority of the patients in Yang et al's report received anthracycline-based regimens. Many patients may have disease progression during CT because of poor response to anthracycline-based regimens. In our study, the majority of patients received newer regimens, such as the VIPD regimen or L-asparaginase-based regimens, which significantly improve survival rates, as shown in **Figure 5**. Furthermore, we hypothesize that limited-stage ENKL has a smaller distant tumour cell mass and that effective induction CT was more efficient in eradicating occult distant systemic metastases. The large decrease in the rate of distant spread in patients who undergo CRT may transform into considerable improvements in OS. Some prospective, multicentre, randomized clinical trials are underway to support our conclusion that CRT is the optimal treatment.

Obtaining a CR makes it possible to achieve the goal of oncologic curability in aggressive lymphoma patients. In this study, the patients who achieved a CR after the induction CT had significantly better outcomes. Intriguingly, it may be possible to reduce the dose of subsequent extended involved-field RT. A retrospective analysis of 144 patients who received CT as their initial treatment and achieved CR before the initiation of RT showed that the RT dose could be safely decreased without compromising survival benefits, which further reduces RT-associated adverse effects [30]. Limited-stage ENKL is curable in a significant percentage of patients; therefore, more attention should be focused on the long-term complications of the treatment. Long-term toxicities of high-dose RT are considerable and may have permanent effects on the quality of life. In tumour treatment, it is important to obtain a balance between the benefit and damage from treatment. The optimal modality must not only focus on the curative effect but also exhibit favourable long-term survival quality.

Collectively, our data analysis suggests that combined CT and RT treatment confers more survival benefits to early-stage ENKL patients compared with either CT or RT treatment alone. An effective CT scheme followed by appropriate doses of RT is recommended as the optimal modality for the treatment of localized ENKL patients.

Acknowledgements

We appreciate the cooperation of all the doctors at Fujian Provincial Cancer Hospital & Cancer Hospital Affiliated with Fujian Medical University.

Disclosure of conflict of interest

None.

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