RESEARCH ARTICLE

"Sandwich" Chemotherapy (CT) with Radiotherapy (RT) Improves Outcomes in Patients with Stage I_E/II_E Extranodal Natural Killer (NK)/T-cell Lymphomas

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Abstract

The extranodal natural killer/T-cell lymphoma (ENKTL) shows high local or systemic failure rates when radiotherapy (RT) is taken as the primary treatment, suggesting a role for chemotherapy (CT) added to RT for this disease. However, the appropriate mode of combined modality therapy (CMT) has not been fully defined. A total of one hundred and twenty-one patients with ENKTL receiving sandwich CT with RT were reviewed between January 2003 and August 2012. The primary endpoints were the response rate, progression-free survival (PFS), overall survival (OS), and the relapse rate. After the initial CT, there were 84 (69.4%) patients in CR, 22 (18.2%) patients in PR, 9 (7.4%) patients in SD, and 6 (5%) patients in PD, respectively. At the end of RT, the CR, PR, SD, and PD rates for all patients were 90.9% (n=110), 1.7% (n=2), 4.1% (n=5), and 3.3% (n=4), respectively. After a median follow-up of 42.3 months (3.5~112.3 months), the 5-year PFS was 74.7% (95% CI 70.4%~79.0%), and 5-year OS was 77.3% (95% CI 67.9%~86.7%). Disease progression was documented in 25 (20.7%) patients. The rates of systemic failure, local failure, and regional failure were 18.2%, 5.8%, 1.7%, respectively. Twenty death events (16.5%) were observed for the entire group of patients (18 deaths related to PD). Furthermore, CR to the initial CT and low Korean Prognostic Index (KPI) can independently predict long PFS and OS. The sandwich CMT achieved an excellent outcome for localized ENKTL with acceptable toxicity. We recommend it can be applied as the optimal choice for localized ENKTL.

Keywords: Chemotherapy - radiotherapy - extranodal natural killer/T-cell lymphoma - treatment outcome

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Introduction

Extranodal NK/T-cell lymphoma (ENKTL) has been a distinct entity in the World Health Organization (WHO) classification since 2008. It is more common in Central and South America and particularly Asia (Jaffe et al., 1996). The data on distribution of 4,638 lymphoid neoplasm cases from five large hospitals in China show ENKTL is the second common subtype (11%), only inferior to diffuse large B-cell lymphoma (36.2%) (Sun et al., 2012), which is consistent with the results of a previous study (Liu et al., 2011). At diagnosis, approximately 80% of cases are localized to the nasal and upper aero-digestive tract (Oshimi et al., 2005; Lee et al., 2006; Jo et al., 2012). The overall survival (OS) at 5 years is 49.5~72% (Lee et al., 2006; Ma et al., 2010; Li et al., 2011; Yamaguchi et al., 2012). Until now, there remains a lack of consensus on treatment of ENKTL and no therapy is considered standard (Kohrt et al., 2009).

RT has been taken as the primary treatment for early stage nasal ENKTL (Li et al., 2006; Wang et al., 2009; Li et al., 2012), but the systemic failure is seen in 21.9~27% of early-stage diseases treated with RT alone (Smalley et al. 1988; Kim et al., 2000; Koom et al., 2004; Li et al., 2011), suggesting a role for CT added to RT for this highly aggressive lymphoma. Like hematological malignant diseases, ENKTL tends to disseminate many other tissues or organs (Chan et al., 1997). Thus, many series emphasize on the efficacy of the combined modality therapy (CMT) of RT plus CT. Recently, two phase II trials from Japan and Korea have showed excellent survival outcomes of concurrent chemoradiotherapy (CCRT) for localized ENKTL (Kim et al., 2009; Yamaguchi et al., 2012). Another phase II trial indicates the "sandwich" protocol of combined CT with RT is a safe and effective treatment in this setting (Jiang et al., 2012). However, CMT was not accompanied by an improvement on survival in a lot of studies (Shikama et al., 1997; Kim et al., 2001b; Li et al., 2006; Ma et al., 2010). Specifically, the significance of initial CT needs to be further clarified. In the present study, we evaluated the role of initial CT in patients with stage I_E/II_E ENKTL.

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Materials and Methods

Eligibility Criteria

Adult patients with nasal ENKTL who received primary CT in Sun Yat-Sen University Cancer Center between January 2003 and August 2012 were systemically reviewed in an intention-to-treat analysis. Eligibility criteria for inclusion in this study were as follows: 1) pathologically confirmed diagnosis of ENKTL according to the WHO classification; 2) positive for Epstein-Barr virus in situ hybridization and at least one NK or T-cell marker, and negative for B-cell markers; 3) primary sites localized in nasal cavity; 4) stage I or II diseases; 5) no previous anti-tumor therapy, such as surgery, CT and RT; 6) CT as the initial treatment; 7) complete follow-up results. Patients with prior or concomitant malignant tumors and blastic NK cell lymphoma were excluded. All patients signed a written informed consent, and this study was approved by the institutional review board of Sun Yat-Sen University Cancer Center.

A total of one hundred and twenty-one cases formed the population of the study. All enrolled patients underwent standard Ann Arbor staging with history, physical examination, the whole body positron emission tomography/computed tomography scans, or either magnetic resonance imaging (MRI) or computed tomography scans of the head and neck, computed tomography scans of the chest, abdomen, and pelvis, and bone marrow examination. Complete blood count and serum biochemistry were routinely examined. Serum β2-microglobin was examined only in some patients.

Treatment

Patients received one of the following initial CT regimens: 1) CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). 2) EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone). 3) Alternating triple therapy (ATT): CHOP-B (cyclophosphamide, doxorubicin, vincristine, bleomycin, prednisone), IMVP-16 (ifosfamide, methotrexate, etoposide, prednisone), DHAP (dexamethasone, cisplatin, cytarabine); 4) GELOX or modified GELOX (gemcitabine, oxaliplatin, L-asparaginas) (Wang et al., 2013). 5) Others: DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin); VIPD (etoposide, ifosfamide, cisplatin, dexamethasone); high-dose MTX, etoposide plus ifosfamide; Ara-c plus methylprednisolone; L-asparaginas, vincristine plus dexamethasone. Patients started to receive the involved field RT (IFRT) at the following situations: 1) patients experienced the stable disease (SD) after two cycles first-line CT; 2) those experiencing partial remission (PR) after two cycles treatment received another 2 cycles treatment, but complete remission (CR) was still not obtained; 3) those experiencing CR after two or four cycles treatment were referred to RT at the oncologists' discretion; 4) diseases progressed at any cycle of the initial CT; 5) patients did not tolerate the treatment well.

A dose of 50 to 60 grays (Gy) was given to the primary tumor at the RT experts' discretion, for example, 50~54 Gy was given when the initial CT made CR, but a higher dose was administered if local tumor invasiveness existed at baseline examination or local residues did after the initial CT. Patients were treated with 1.8~2.0 Gy a day and five fractions each week. The clinical target volume included the whole nasal cavity, ipsilateral maxillary sinus, bilateral ethmoid sinus and anatomically adjacent regions. The full neck was generally not irradiated for limited stage I patients, but all stage II patients received bilateral neck irradiation (40~52.6 Gy). After the completion of irradiation, patients who achieved ≥ good PR before irradiation completed a total of six cycles CT based on the initial effective regimen, for example, patients received four cycles of first-line CT before irradiation and achieved the CR, so they finished the remaining two cycles after irradiation. When treatment was over, patients who still remained CR were going into the follow-up stage, or they received the subsequent salvage CT.

Response Assessment and Follow-up

The tumor response was generally assessed after every two cycles of CT and after RT according to the standardized response criteria for non-Hodgkin lymphoma (Cheson et al., 1999). Side effects were graded according to the version 3.0 of National Cancer Institute Common Terminology Criteria of Adverse Events. If nasal obstruction, fever, and other related symptoms became more serious or recurred quickly after any cycle, an immediate tumor response assessment was reasonable. After the completion of treatment, patients were evaluated by their oncologists in the outpatient department. The follow-up interval was based on the regular standard. Follow-up visit involved the symptoms and physical examinations, routine blood tests, and computed tomography scans or MRI scans of the involved area for each patient. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression, relapse, and death from any cause or the last follow-up. OS was measured as the time from diagnosis to death from any cause, with surviving patient follow-up censored at the last contact date.

Statistical Analysis

Simple descriptive statistics were used to report general clinical information. PFS and OS were estimated using the Kaplan-Meier method, and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model to compare the factors proven significant in the univariate analysis. A two-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics 18.0 software (Apache Software Foundation, Forest Hill, Md).

Results

Patient Characteristics

The clinical characteristics of the one hundred and twenty-one patients were presented in Table 1. The median age was forty years old with a male-female ratio 2.03:1. Nearly all patients had good performance status. 62 (51.2%) patients initially presented as stage I and 59

Table 1. Clinical Characteristic for All Patients at Baseline

Characteristic		No. of patients	(%)
Gender	Male	81	66.9
	Female	40	33.1
Age (years)	Median (range)	40 (19~68)	
	≤60	106	87.6
	>60	15	12.4
ECOG	0~1	117	96.7
performance status	2	4	3.3
Ann Arbor stage	I	62	51.2
	II	59	48.8
Serum LDH	Normal	80	66.1
	Elevated	41	33.9
B symptom	Absent	67	55.4
	Present	54	44.6
LN involvement	Absent	65	53.7
	Present	56	46.3
IPI	0~1	115	95
	2	6	5
KPI	0	29	24
	1	48	39.7
	2	30	24.8
	3~4	14	11.5
Serum β2	Normal	26	43.3
microglobulin (n=60)	Elevated	34	56.7
Initial CT regimen	CHOP	9	7.4
	EPOCH	42	34.7
	ATT	23	19
	GELOX	42	34.7
	Others	5	4.2

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LN, lymph node; IPI, International Prognostic Index; KPI, Korean Prognostic Index

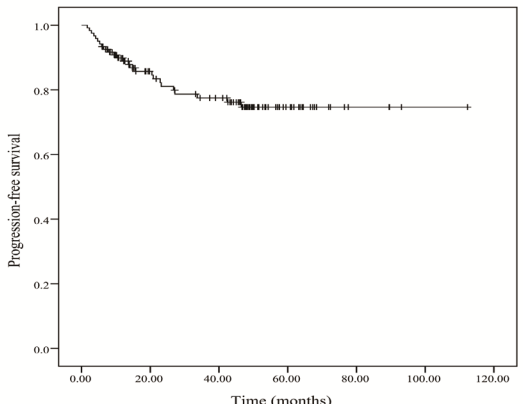

Figure 1. The Progression-free Survival (PFS) for All Patients (n=121). The 5-year PFS was 74.7%

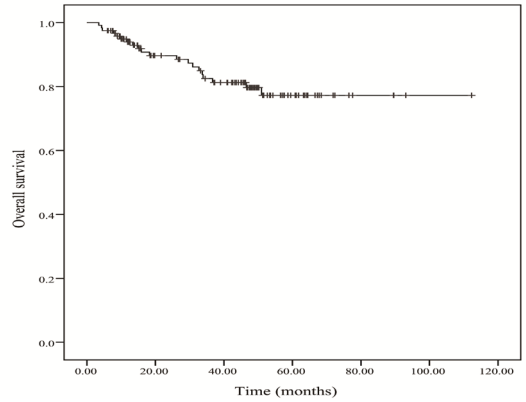

Figure 2. The Overall Survival (OS) for all Patients (n=121). The 5-year OS was 77.3%

(48.8%) patients as stage II. No patients were included in the intermediate-high and high-risk groups according to the International Prognostic Index (IPI), but 36.4% of all patients had the unfavorable prognosis according to Korean Prognostic Index (KPI).

Response to Treatment and Survival Analysis

Before RT, a total of 353 cycles treatment (average 2.92 cycles, range 1~4 cycles) was carried out for all the one hundred and twenty-one patients, including 27 cycles CHOP, 106 cycles EPOCH, 70 cycles ATT, 136 cycles GELOX and 14 cycles other regimens. There were 84 (69.4%) patients in CR, 22 (18.2%) patients in PR, 9 (7.4%) patients in SD, and 6 (5%) patients in progressive disease (PD), respectively. Local disease progression was observed in 5 of the 6 patients with PD, and the remaining one patient experienced systemic progression (lung infiltration). This patient received the salvage CT and died in less than four months due to frequent recurrences. 120 patients were referred to RT except the patient with systemic progression. At the end of RT, the CR, PR, SD, and PD rates for all patients were 90.9% (n=110), 1.7% (n=2), 4.1% (n=5), and 3.3% (n=4), respectively. After RT, 93 patients who achieved ≥ good PR before RT finished 278 cycles sequential CT. Thus, the numbers of average CT cycles were 5.21 for the whole patients.

After a median follow-up of 42.3 months (3.5~112.3 months), the 5-year PFS is 74.7% (95% CI 70.4%~79.0%, Figure 1), the 5-year OS is 77.3% (95% CI 67.9%~86.7%, Figure 2), and the median OS has not been reached. Disease progression was documented in 25 (20.7%) patients. 12 patients were observed systemic progression during the follow-up stage, and none of them experienced local or regional failure. The remaining 13 patients experienced relapse during the treatment. 3 of 5 patients with local PD at initial CT developed systemic PD when RT was over, except one patient die of this disease during CT, and the other 7 patients who didn't achieve CR at the end of RT experienced systemic PD (including 2 local failures and 2 regional failures) in the following salvage therapy. So the rates of systemic failure, local failure, and regional failure were 18.2%, 5.8%, 1.7%, respectively. Most patients (n=20, 80%) relapsed within 2 years, and no one relapsed beyond 5 years. Moreover, 20 death events (16.5%) were observed for the whole patients (18 deaths related to PD, 2 deaths related to no tumor factors).

Univariate and Multivariate Analysis

The clinical factors predicting survival at univariate analysis were as follows: age, performance status, Ann Arbor stage, B symptom, serum LDH level, LN involvement, IPI, KPI, and response to the initial CT (Table 2). The factors associated with reduced PFS were the present of B symptom (P=0.032), no CR to the initial CT (P<0.001, Figure 3A), and high KPI (0.046, Figure 3B) for predicting reduced PFS. Using multivariate analysis, independently significant factors were the presence of high KPI (RR=1.726, 95% CI 1.151~2.590; P=0.008), and no CR to the initial CT (RR=3.819, 95% CI 1.712~8.517; P=0.001).

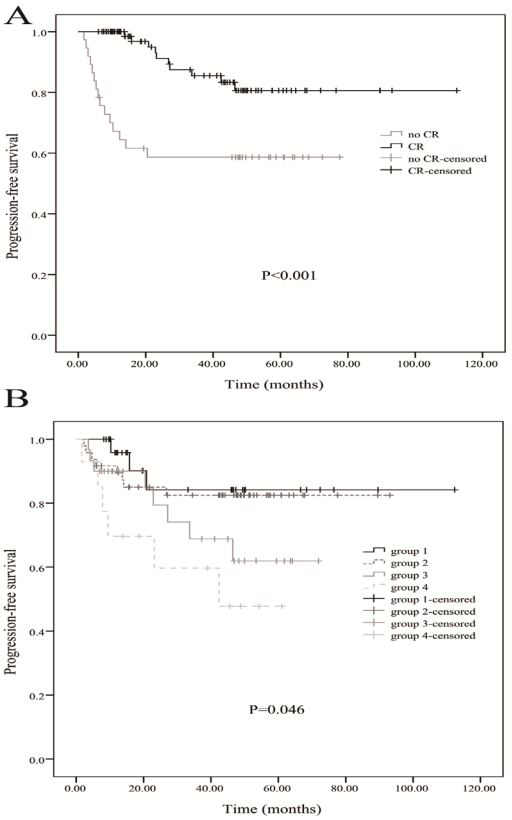

Figure 3. The Progression-free Survival (PFS) for Different Subgroups. A: patients who made complete remission (CR) (n=84) had significantly longer PFS than those who didn't made CR (n=37) after the initial chemotherapy. B: Patients with high KPI had a worse PFS than those with low KPI

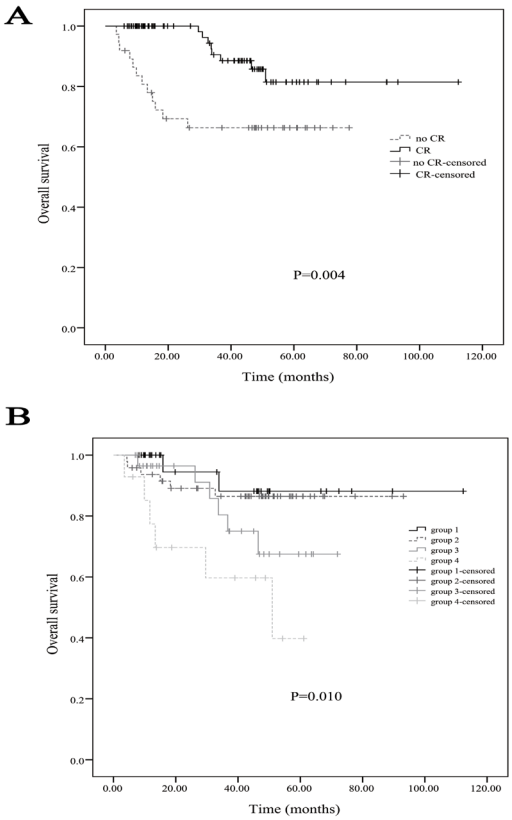

Figure 4. The Overall Survival (OS) for Different Subgroups. A: patients who made CR (n=84) had significantly longer OS than those who didn't made CR (n=37) after the initial chemotherapy. B: Patients with high KPI had a worse OS than those with low KPI

Table 2. Clinical Factors for Survival in Univariate Analysis

Parameter	PFS	OS
	P value	
Age: ≤60 vs. >60	0.148	0.672
Performance status: 0~1 vs. 2	0.439	0.502
Ann Arbor stage: I vs. II	0.952	0.826
Serum LDH: normal vs. elevated	0.18	0.259
B symptom: absent vs. present	0.032	0.032
LN involvement : absent vs. present	0.133	0.143
IPI : 0~1 vs. 2	0.516	0.333
KPI: 0/1/2/3,4	0.046	0.01
Response to the initial CT: CR vs. no CR	<0.001	0.004

In terms of OS, the factors associated with reduced survival were also the present of B symptom (*P*=0.032), no CR to the initial CT (*P*=0.004, Figure 4A), and high KPI (*P*=0.010, Figure 4B) by univariate analysis (Table 2). In the multivariate analysis, independently significant factors were still the presence of high KPI (RR=2.016, 95% CI 1.274~3.192; *P*=0.003), and no CR to the initial CT (RR=3.147, 95% CI 1.275~7.766; *P*=0.013).

Toxicity

No treatment-related deaths occurred during the CT. The adverse events for the CT were summarized in Table 3. Serious neutropenia, febrile neutropenia, and thrombocytopenia were relatively common toxicities, which were mainly associated with the application of aggressive regimens, such as EPOCH and ATT. One patient who could not tolerate ATT received the definitive RT in advance. Furthermore, liver function impairment, allergy, and pancreatitis that were related to L-asparaginas needed to be given much attention. Four patients stopped the application of L-asparaginas and only received GEMOX (gemcitabine, oxaliplatin) in the following treatment due to serious toxicities resulting from L-asparaginas. Patients with the above severe events got recovery after aggressive support therapy such as anti-infection, G-CSF, antianaphylaxis, etc. The most common adverse events for RT were grade 1~2 skin toxicity, grade 1~3 mucositis, grade 1~2 pharyngitis, grade 1~2 esophagitis, and grade 1~2 salivary gland toxicity. Generally, patients tolerated well for RT.

Table 3. Adverse Events for CT

Toxicity	Grade 1/2 (%)	Grade 3/4 (%)
Hematologic		
Neutropenia	42 (34.7)	21 (17.4)
Febrile neutropenia	0 (0)	9 (7.4)
Anemia	12 (9.9)	0 (0)
Thrombocytopenia	29 (24.0)	7 (5.8)
Nonhematologic		
Nausea/emesis	52 (44.6)	8 (6.6)
Constipation	25 (20.7)	4 (3.3)
Peripheral neuropathy	34 (28.1)	5 (4.1)
Cardiotoxicity	2 (1.7)	0 (0)
Decreased fibrinogen	3 (2.8)	0 (0)
Hypoalbuminemia	2 (1.7)	0 (0)
Allergy	3 (2.8)	1 (0.8)
Acute pancreatitis	2 (1.7)	1 (0.8)
Increased transaminases	11 (9.1)	2 (1.7)
Hyperbilirubinaemia	5 (4.1)	0 (0)

Discussion

First-line RT has been considered the optimal initial treatment of choice for localized NK/T-cell lymphoma (Isobe et al., 2006; Li et al., 2006). Regrettably, RT alone is insufficient to improve survival due to a high incidence of disease progression. Thus, CT is vital even for early stage ENKTL. However, the appropriate mode of CMT for CT and RT is not clearly defined. In the present study, we evaluated the effect of "sandwich" CT with RT in a large cohort of patients with early stage ENKTL. There were three main results. First, this type of CMT achieved the high CR rate, 5-year PFS and OS, accompanied by low local or systemic failure rates; and a majority of patients tolerated treatment well, although some patients experienced serious toxicities. Second, whether the CR was achieved after the initial CT or not was critical, because patients with this CR had a significantly long survival, implying a more aggressive treatment for those who didn't achieve CR after the initial CT. Third, patients with early stage nasal ENKTL were generally characterized by good performance status and low IPI, so it was reasonable that IPI lost its prognostic significance in this disease; however, KPI could still be a significantly independent predictor for survival.

The CR rate of initial CT for localized ENKTL varies greatly from 20% to 56% (Kim et al., 2001b; Li et al., 2006; Huang et al., 2008; Jiang et al., 2012; Kwong et al., 2012; Wang et al., 2013). In these studies, the CR rates are no more than 40% for the anthracycline-containing CT, but they are beyond 42% when non-anthracycline schedules are used, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), GELOX, and LVP (L-asparaginase, vincristine, and prednisone). These data not only confirm that ENKTL are usually resistant to conventional CT, but also suggest this disease could be sensitive to combinative CT if appropriate regimens are chosen. We achieved an obviously high CR rate (69.4%) and response rate (87.6%) at the initial CT, which can be basically attributed to the more application of non-anthracycline or aggressive regimens, supporting a favorable effect of the initial CT for this disease. Compared with RT alone, whether initial CT followed by RT can improve the CR rate is controversial. It fluctuates from 74.1% to 81% for this type of CMT (Li et al., 2006; Jiang et al., 2012; Wang et al., 2013), which can be comparable to the result (77%~84.6%) for CCRT (Kim et al., 2009; Yamaguchi et al., 2009; Lee et al., 2011). However, the CR rate (66%) was lower for the initial CT followed by RT than that (69%) for RT alone (Kim et al., 2001a), and the RT alone group appeared to have the highest CR rate (97%) (Li et al., 2006). The differences on these results may be caused by the patient heterogeneity, different RT doses and CT regimens. The "sandwich" CT with RT carried out by us also achieved a high CR rate (90.9%) in this study, probably owning to the inherent RT sensitivity and choices of effective CT. We don't emphasize on the comparison of effects of different CT schedules, for the samples are relatively small and imbalanced among various CT regimens.

The 5-year OS in early stage disease with RT alone differs greatly from 29.8% to 66% (Kim et al., 2001a; Isobe et al., 2006; Li et al., 2006; Kim et al., 2008). Recent studies indicate that CMT can improve the survival for patients with localized ENKTL, compared with RT alone. The estimated 3-year PFS and OS for CCRT are 85.19% and 86.28% in a Korean phase II trial, respectively (Kim et al., 2009). And CCRT also yields high 5-year PFS (67%) and OS (73%) in the JCOG0211 study (Yamaguchi et al., 2012). So CCRT is recommended as the first-line treatment for this early stage disease. But one of the main limitations for CCRT lies in the difficulty for assessing CT response. As an easily disseminating malignant disease, it is reasonable to take CT as the initial primary treatment although the lesion is only limited in nasal, because CT is helpful to eradicate the potential lesion. The rates of 2-year OS and PFS for patients receiving GELOX followed by IFRT were both 86% in a phase II study (Wang et al., 2013), which had the similar results with the study of CT and sandwiched RT that the 2-year OS was 88.5% and the 2-year PFS was 80.6% (Jiang et al., 2012). Both two prospective studies achieved excellent outcomes in a short follow-up. In the present study, the 5-year OS and PFS for a long follow-up of large samples (n=121) were 77.3% and 74.7%, respectively, which can be comparable to the historical control of CCRT (Kim et al., 2009; Yamaguchi et al., 2012). All these data suggest CT followed by RT is also an appropriate choice for stage I_E/II_E ENKTL.

The relapse rates for RT as primary treatment are fairly high. An analysis of 102 patients treated with RT alone led to the local failure in 48 cases (47%) and the systemic failure in 28 cases (27%) (Koom et al., 2004). The 5-year cumulative incidence of overall failure is as high as 32.9% in a study of 182 cases receiving RT alone or RT and CT (Li et al., 2011). However, it is obviously low (13.33%~19.2%) for CCRT or CT as the initial treatment (Kim et al., 2009; Jiang et al., 2012), which is consistent with our results that the systemic and local failure rates were 18.2%, 5.8%, respectively. We think effective CT and high RT dose are the main reasons responsible for the low relapse rate in this study. At present, the exact dose of RT is controversial in ENKTL. The 5-year OS and DFS were better in patients receiving >54 Gy of RT as compared with those of <54 Gy (OS 75.5% vs. 46.1%; DFS 60.3% vs. 33.4%) (Huang et al., 2008). However, the dose of 40~52.8 Gy has also produced satisfactory local control on CCRT (Kim et al., 2009). We employed the dose of 50~60 Gy for the nasal lesions in this sandwich CMT. Whether the dose reduced to < 50 Gy is rationale for patients who achieved CR by initial CT deserves further research.

There are several limitations to the present study, including the retrospective nature of the study design and the application of different CT schedules. Nevertheless, this report is noteworthy because it is the largest study to show the excellent outcomes of the initial CT with sandwiched RT. This type of CMT has two distinct advantages. One is the instant management for the potential distant lesions, and the other is the early recognition to CT response, which can provide the oncologists with important references for the sequential treatment choice.

In conclusion, the sandwich CMT has achieved

excellent CR rate and survival for patients with early stage ENKTL with acceptable toxicities. Achieving CR after the initial CT and low KPI can independently predict long PFS and OS. So the authors recommend that the sandwich CMT can be applied as the optimal choice for localized ENKTL. Our findings suggest the need for further large prospective studies on this kind of CMT.

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