doi:10.4149/neo_2022_211004N1407

Does the primary tumor site in stage I extranodal natural killer/T-cell lymphoma matter?

Juan-Juan Cui1,2, Jing Cai1, Qi-Wei Zhu1, Yuan-Qi Bei1, Bai-Xia Yang1, Xue-Jun Ma2,*

[1]Department of Radiation Oncology, Affiliated Tumor Hospital of Nantong University, Nantong, Jiangsu, China; [2]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China

**Correspondence: chateauma@hotmail.com*

Received October 4, 2021 / Accepted January 17, 2022

The purpose of this study was to investigate whether the primary tumor site in stage I extranodal natural killer/T-cell lymphoma (ENKTCL) had a prognostic value. Between January 2009 and December 2015, 152 stage I ENKTCL patients with primary disease in the nasal cavity and Waldeyer's ring were enrolled for this retrospective study. All patients received extended field intensity-modulated radiotherapy alone without prophylactic cervical node irradiation at a total dose of 50 Gy. In this study, there were 122 patients whose primary tumors were localized in the nasal cavity (NC group), and no adjacent structures were involved. A total of 18 patients had a primary disease involving the nasal cavity and Waldeyer's ring (NC-WR group), and the remaining 12 patients had primary tumors confined to Waldeyer's ring (WR group). We found that there was no significant difference in cervical lymph node failure rates among the NC, NC-WR, and WR groups. In terms of the 5-year overall survival (OS) rates, there was a significant difference among the NC, NC-WR, and WR groups (p=0.004), with the WR group having the worst OS. Multivariate analyses showed that the primary site (p=0.011) and ECOG (Eastern Cooperative Oncology Group) score (p=0.013) were independent prognostic factors for OS. In summary, patients with stage I ENKTCL had a good local control rate with radiotherapy alone and without prophylactic cervical node irradiation (PCNI), regardless of the site of the primary tumor. So, we think PCNI for stage I ENKTCL patients is not necessary. Patients with a primary tumor site located in Waldeyer's ring had the worst prognosis. And combined treatment with radiotherapy and chemotherapy should be considered in patients with primary tumors located outside the nasal cavity.

Key words: stage I extranodal natural killer/T-cell lymphoma; primary tumor site; radiotherapy

Extranodal natural killer (NK)/T-cell lymphoma nasal-type (ENKTCL) is a subtype of non-Hodgkin lymphoma (NHL) characterized by central vascular lesions and is a highly aggressive malignancy. The incidence of ENKTCL is low in Western countries [1, 2] but is relatively common in Asian and Latin American countries. The percentage of ENKTCL in T-cell lymphomas ranged from 6% in Europe to 31% in the Middle/Far East [3, 4]. In China, ENKTCL occurred in 40 to 50 % of T-cell lymphomas [5, 6]. Most ENKTCLs occur in the upper aerodigestive tract (UADT), especially in the nasal cavity and Waldeyer's ring. A smaller proportion of patients with ENKTCL had tumors that originated in the non-upper aerodigestive tract (NUADT), such as the skin, liver, spleen, and testis [7, 8]. It is worth noting that more than 80% of ENKTCLs were in the early stage at diagnosis.

Due to the rarity of ENKTCL worldwide and the absence of large prospective randomized clinical trials, there is no consensus on the optimal treatment strategy. While the optimal combination and sequence of radiotherapy (RT) and chemotherapy (CT) is unidentified [9–11], the National Comprehensive Cancer Network (NCCN) guidelines recommend that patients in stage I–II can consider RT alone if they cannot tolerate chemotherapy [12]. However, based on the multi-institution large sample study of Yang et al. [13] and the study of Li et al. [14] in China, if there are no risk factors for patients in stage I, RT alone can be considered. For early-stage ENKTCL patients, there is no large sample of phase III clinical trials to guide clinical work, so the NCCN guidelines also recommend clinical trials. There is no doubt that radiotherapy is an indispensable part of the treatment for early-stage ENKTCL patients [12–17]. Previous studies found that ENKTCL with different extents of primary tumor invasion tended to have different treatment responses and prognoses [2, 18–21]. However, it remains unclear whether different primary tumor sites have prognostic value, especially in stage I extranodal natural killer/T-cell lymphoma patients treated with RT alone.

Patients and methods

Patients. Between January 2009 and December 2015, a total of 309 consecutive patients with stage I nasal-type ENKTCL treated at Fudan University Cancer Center were retrospectively reviewed. Patients who met the following criteria were included in this study: 1) All cases were independently diagnosed and classified by two pathologists in accordance with the WHO classification [20]. 2) All patients were staged as I according to the Lugano staging system by whole-body 18FDG-PET/CT scan with primary site magnetic resonance (MR) or computed tomography (CT). 3) All patients received extended field radiotherapy alone without prophylactic cervical node irradiation (PCNI). The exclusion criteria were as follows: 1) patients who developed disease progression during radiotherapy; 2) patients who failed to complete the whole course of radiotherapy; and 3) patients with other primary malignant tumors previously or concurrently. Finally, a total of 152 patients were included in this study. The study was approved by the Human Research Ethics Committee of Fudan University Shanghai Cancer Center. All patients provided written informed consent. Based on the imaging data of the patients, they were divided into the following three groups: 1) NC group, the primary tumor was limited in the nasal cavity and no adjacent organs or structures were invaded; 2) NC-WR group, the primary tumor originated from the nasal cavity and invaded Waldeyer's ring; 3) WR group, the primary tumor originated from Waldeyer's ring, which included the nasopharynx, tonsil, tongue base, and oropharynx. When the tumor invaded both the nasal cavity and the nasopharyngeal cavity, we defined the primary site of the tumor according to the central part of the lesion with the imaging data.

Radiotherapy. All patients were treated with intensity-modulated radiotherapy (IMRT) alone. If the tumor was limited to one side of the nasal cavity, the CTV encompassed the bilateral nasal cavity, ipsilateral maxillary sinus, bilateral anterior ethmoid sinuses, and hard palate. If the bilateral nasal cavity was involved, the CTV covered the bilateral nasal cavity, bilateral maxillary sinus, bilateral anterior ethmoid sinuses, and hard palate. If the tumor extended beyond the nasal cavity, the CTV extended to the adjacent organs or structures involved. If the tumor was in the posterior nostril or invaded the nasopharynx, the CTV included the nasopharyngeal cavity. For patients with stage I Waldeyer's ring primary ENKTCL, the CTV covered the entire Waldeyer's ring and adjacent structures. All cases were treated with extended-field radiotherapy alone, but no PCNI was performed. The total dose of radiotherapy was 50 Gy in 25 fractions at 2 Gy per fraction in five weeks.

Statistical methods. The difference in clinical characteristics between the subgroups was evaluated by Pearson's chi-square test or Fisher's exact test. Overall survival (OS) was measured from the beginning of radiation to the date of death by any cause or the last follow-up. Progression-free survival (PFS) was measured from the beginning of treatment to the first progression, relapse, last follow-up, or any cause of death. Distant recurrence-free survival (DRFS) was measured from the beginning of treatment to the first distant recurrence or the last follow-up. OS, PFS, and DRFS were calculated using the Kaplan-Meier method, and the groups were compared using the log-rank test. Kaplan-Meier method is commonly used for survival estimation, with the horizontal axis being the survival time and the vertical axis being the corresponding survival rate. Univariable and multivariable Cox proportional hazards models were used to confirm independent prognostic factors. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software, version 20.0.

Results

Patient characteristics. Of the 152 patients, there were 140 patients with primary tumors originating in the nasal cavity, including 122 patients whose primary tumor was localized to the nasal cavity (NC group) and 18 patients with primary tumors invading Waldeyer's ring (NC-WR group). The remaining 12 patients belonged to the WR group (Figure 1). The clinical characteristics of all 152 patients are summarized in Table 1. The median age of the 152 patients was 51 years old (range, 15–81). Only 39 patients (25.7%) were over sixty years old. Twenty-four patients (15.8%) presented B symptoms. A small number (4.6%) of patients had an elevated lactate dehydrogenase (LDH) level. The majority (97.4%) of patients had a good performance, with ECOG (Eastern Cooperative Oncology Group) scores of 0–1. In addition, according to the PINK (Korean Prognostic

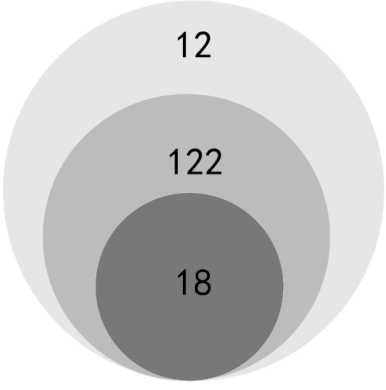

Figure 1. Venn diagram of population distribution with stage I ENKTCL. A total of 140 patients with primary tumors originating from the nasal cavity. The dark grey area (n=18) represents the patients of the NC-WR group who originated from the nasal cavity and invaded Waldeyer's ring. The grey area (n=122) represents the patients of the NC group who localized to the nasal cavity. The light grey area (n=12) represents the patients of the WR group who originated from the Waldeyer's ring.

Table 1. Clinicopathological characteristics of patients with stage I extra nodal natural killer (NK)/T-cell lymphoma.

Characteristics	All patients (n = 152)	NC group (n = 122)	NC-WR group (n = 18)	WR group (n = 12)	p-value
Gender					0.259
Male	102 (67.1%)	80 (65.6%)	15 (83.3%)	7 (58.3%)	
Female	50 (32.9%)	42 (34.4%)	3 (16.7%)	5 (41.7%)	
Age					0.651
≤60	113 (74.3%)	92 (75.4%)	12 (66.7%)	9 (75.0%)	
>60	39 (25.7%)	30 (24.6%)	6 (33.3%)	3 (25.0%)	
ECOG					0.166
0	100 (65.8%)	84 (68.9%)	9 (50.0%)	7 (58.3%)	
1	48 (31.6%)	36 (29.5%)	8 (44.4%)	4 (33.3%)	
2	4 (2.6%)	2 (1.6%)	1 (5.6%)	1 (8.3%)	
LDH					0.025
Normal	145 (95.4%)	119 (97.5%)	15 (83.3%)	11 (91.7%)	
> ULN	7 (4.6%)	3 (2.5%)	3 (16.7%)	1 (8.3%)	
B symptoms					0.003
Negative	128 (84.2%)	108 (88.5%)	10 (55.6%)	10 (83.3%)	
Positive	24 (15.8%)	14 (11.5%)	8 (44.4%)	2 (16.7%)	
PINK score					0.651
0	113 (74.3%)	92 (75.4%)	12 (66.7%)	9 (75.0%)	
1	39 (25.7%)	30 (24.6%)	6 (33.3%)	3 (25.0%)	

Notes: NC group-the primary tumor was limited in the nasal cavity; NC-WR group-the primary tumor originated from the nasal cavity and invaded the Waldeyer's ring; WR group-the primary tumor originated from the Waldeyer's ring. Abbreviations: LDH-lactate dehydrogenase; PINK-Korean Prognostic Index

Index) score, there were 113 patients with a score of 0. After the comparisons among the NC, NC-WR, and WR groups, there was no significant difference in the distribution of gender, age, ECOG score, and PINK score.

Local and distant recurrence rates in the three primary site groups. The median follow-up time was 57 months. Until the end of April 2019, 17 patients had died. Eleven patients had locoregional relapse without cervical lymph node involvement and 10 patients had cervical lymph node recurrence. There were 23 patients who developed distant metastasis. The failure rates of cervical lymph nodes in the three primary site groups were 5.74%, 11.11%, and 8.33%. The local recurrence rates in the three groups were 6.56%, 11.11%, and 8.33%, and the distant metastasis rates were 11.48%, 22.22%, and 41.67%, respectively. Fisher test analyses showed that there was no significant difference in cervical lymph node failure and local recurrence among the three groups. However, there was a significant difference in distant failure (p=0.014), and the risk of systemic relapse in the WR group was much higher than that in the other two groups.

Associations between the primary site and OS. In this study, the 5-year OS for all patients was 90.1% (Figure 2A). Further analysis showed that the 5-year OS rates for the patients in the NC, NC-WR, and WR groups were 91.8%, 94.4%, and 65.6%, respectively. Survival analyses using the Kaplan-Meier method revealed (Figure 2B) different outcomes of survival among the three groups (p=0.004), and the NC group and NC-WR group patients had better OS than the WR group patients (p=0.001, p=0.029). However, there was no difference in OS between the NC group and the NC-WR group (p=0.678). In addition, univariate Cox survival analyses (Table 2) revealed that the primary site and ECOG score were significantly associated with OS. After adjusting for multiple clinicopathological factors, multivariate analyses (Table 3) showed that the primary site (p=0.011) and ECOG score (p=0.013) were independent prognostic factors for OS. The patients in the NC-WR group had a similar OS to patients in the NC group (HR, 0.23, 95% CI 0.02–2.29), and the WR group patients had worse OS than the NC group patients (HR, 4.05, 95% CI 1.35–12.13), which was consistent with the results of the univariate analysis.

Associations between the primary site and PFS. In this study, the 5-year PFS for all patients was 81.9% (Figure 2A). Further analysis showed that the 5-year PFS rates for the patients in the NC, NC-WR, and WR groups were 83.6%, 71.4%, and 58.3%, respectively. Survival analyses showed (Figure 2C) significantly different PFS among the three groups (p=0.011). Patients in the NC group had better PFS than patients in the WR group (p=0.003). However, there was no difference in PFS between the NC group and the NC-WR group (p=0.325) and no difference in PFS between the NC-WR group and the WR group (p=0.179). In addition, univariate Cox survival analyses (Table 2) revealed that the primary sites, ECOG scores, and B symptoms were significantly associated with PFS. After adjusting for multiple clinicopathological factors, multivariate analyses (Table 3)

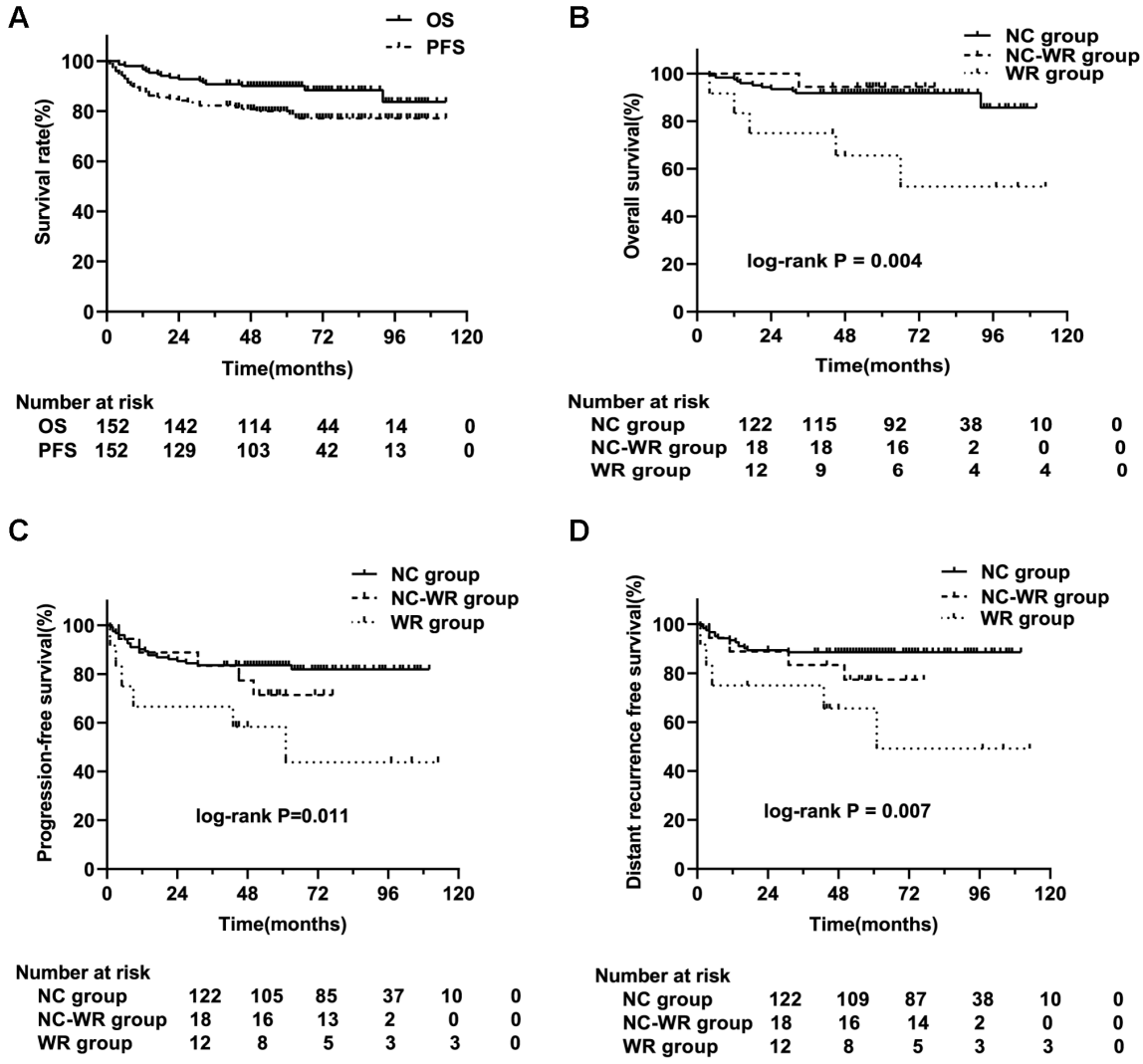

Figure 2. A) Overall survival (OS), progression-free survival (PSF) of patients with stage I ENKTCL treated with radiotherapy alone. B) Kaplan-Meier plots of OS among the three groups. C) Kaplan-Meier plots of PFS among the three groups. D) Kaplan-Meier plots of distant recurrence-free survival among the three groups.

showed that the primary site (p=0.015) and B symptoms (p=0.014) were independent prognostic factors for PFS. The patients in the NC-WR group had a similar PFS to patients in the NC group (HR, 0.92, 95% CI 0.30–2.80), and the NC group patients had a favored PFS compared to the WR group patients (HR, 3.88, 95% CI 1.52–9.91), which was consistent with the results of the univariate analysis.

Associations between the primary site and DRFS. In this study, the 5-year DRFS rate for all patients was 85.3%. Further analysis showed that the 5-year DRFS rates for those patients in the NC, NC-WR, and WR groups were 88.5%, 77.4%, and 65.6%, respectively. Survival analyses using the Kaplan-Meier method (Figure 2D) showed differences in the DRFS rate among the three groups (p=0.007). The patients in the NC group had better DRFS than the patients in the WR group (p=0.002). However, there was no difference in DRFS between the NC group and the NC-WR group (p=0.235) and no difference in DRFS between the NC-WR group and the WR group (p=0.222). In addition, univariate Cox survival analyses (Table 2) revealed that the primary site, ECOG score, and B symptoms were significantly associated with DRFS. After adjusting for multiple clinicopathological factors, multivariate analyses (Table 3) showed that the primary site (p=0.011) and B symptoms (p=0.006) were still independent prognostic factors of DRFS. The patients in the NC-WR group had a similar DRFS as the patients in the NC group (HR, 1.25, 95% CI 0.37–4.19), and the NC group patients still had a better DRFS than the WR group patients (HR, 5.03, 95% CI 1.75–14.41), which was consistent with the results of the univariate analysis.

Table 2. Univariate survival analysis of prognostic factors with stage I extranodal natural killer (NK)/T-cell lymphoma.

Factors	OS		PFS		DRFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender		0.069		0.132		0.091
Male	1.00		1.00		1.00	
Female	2.42 (0.93–6.28)		1.71 (0.85–3.44)		2.02 (0.89–4.59)	
Age		0.767		0.793		0.663
≤60	1.00		1.00		1.00	
>60	1.17 (0.41–3.33)		0.90 (0.40–2.00)		1.22 (0.51–2.97)	
ECOG		0.002		0.014		0.042
0	1.00		1.00		1.00	
1	4.44 (1.44–13.12)	0.009	2.48 (1.20–5.12)	0.015	2.87 (1.23–6.72)	0.015
2	14.8 (2.87–77.05)	0.001	5.06 (1.56–22.19)	0.031	3.46 (0.44–27.11)	0.237
LDH		0.088		0.116		0.939
Normal	1.00		1.00		1.00	
> ULN	3.64 (0.83–16.07)		2.60 (0.79–8.54)		1.08 (0.15–8.03)	
Primary tumor site		0.010		0.011		0.015
NC group	1.00		1.00		1.00	
NC-WR group	0.64 (0.08–4.96)	0.667	1.79 (0.67–4.74)	0.245	1.98 (0.65–6.02)	0.229
WR group	4.85 (1.67–14.13)	0.004	3.95 (1.59–9.79)	0.003	4.42 (1.59–12.28)	0.004
PINK score		0.767		0.793		0.663
0	1.00		1.00		1.00	
1	1.17 (0.41–3.33)		0.90 (0.40–2.00)		1.22 (0.50–2.97)	
B symptoms		0.097		0.005		0.004
Negative	1.00		1.00		1.00	
Positive	2.42 (0.85–6.88)		2.92 (1.38–6.17)		3.48 (1.47–8.21)	

Notes: NC group-the primary tumor was limited in the nasal cavity; NC-WR group-the primary tumor originated from the nasal cavity and invaded the Waldeyer's ring; WR group-the primary tumor originated from the Waldeyer's ring. Abbreviations: ECOG-Eastern Cooperative Oncology Group; LDH-lactate dehydrogenase; PINK-Korean Prognostic Index

Table 3. Multivariate survival analysis of prognostic factors with stage I extranodal natural killer (NK)/T-cell lymphoma.

Factors	OS		PFS		DRFS	
	HR (95% CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
ECOG		0.013		0.116		0.084
0	1.00		1.00		1.00	
1	4.13 (1.36–12.60)	0.013	2.04 (0.96–4.35)	0.066	2.45 (1.03–5.83)	0.042
2	15.96 (1.64–155.33)	0.017	4.10 (0.61–27.78)	0.148	6.14 (0.42–90.26)	0.186
LDH		0.881		0.647		0.189
Normal	1.00		1.00		1.00	
> ULN	0.85 (0.09–7.65)		0.68 (0.13–3.51)		0.16 (0.01–2.46)	
Primary sites		0.011		0.015		0.011
NC group	1.00		1.00		1.00	
NC-WR group	0.23 (0.02–2.29)	0.209	0.92 (0.30–2.80)	0.882	1.25 (0.37–4.19)	0.720
WR group	4.05 (1.35–12.13)	0.012	3.88 (1.52–9.91)	0.005	5.03 (1.75–14.41)	0.003
B symptoms		0.113		0.014		0.006
Negative	1.00		1.00		1.00	
Positive	2.51 (0.80–7.81)		2.98 (1.25–7.09)		3.92 (1.49–10.35)	
PINK score		0.623		0.732		0.678
0	1.00		1.00		1.00	
1	1.31 (0.45–3.81)		0.87 (0.38–1.96)		1.21 (0.49–2.98)	

Notes: NC group-the primary tumor was limited in the nasal cavity; NC-WR group-the primary tumor originated from the nasal cavity and invaded the Waldeyer's ring; WR group-the primary tumor originated from the Waldeyer's ring. Abbreviations: ECOG-Eastern Cooperative Oncology Group; LDH-lactate dehydrogenase; PINK-Korean Prognostic Index

Discussion

In this study, we reported the outcome of radiotherapy alone in 152 patients with stage I ENKTCL, and the 5-year OS rate was 90.1%. In the study of Li et al. [14], the 5-year OS rate was 80% among 87 patients with stage I ENKTCL who were also treated with radiotherapy alone. In our cohort, there were more patients with good performance (ECOG score 0–1) and fewer patients with adverse prognostic factors (elevated LDH level and B symptoms) than in Li's study. Further analysis of Li's report showed that patients who had a very good prognosis exhibited an approximately 90% 5-year OS rate. In a retrospective study of 1,273 early ENKTCL patients at 10 institutions, Yang and his co-authors also found that the 5-year OS was 88.8% in low-risk patients with radiotherapy alone, which was consistent with our result [13].

A growing body of evidence has suggested that the survival outcomes of ENKTCL patients with different primary sites differ [19, 21–23], but this does not apply to all tumor stages. At present, the difference in the prognosis of the primary site of I stage patients is still controversial. In Liu's report [22], the 5-year overall survival rate for extra-nasal UADT-ENKTCL was similar to that of nasal UADT-ENKTCL for stage I disease (75.9% vs. 79.2%, p=0.786). A previous study by Li et al. [19] indicated that stage I Waldeyer's ring primary ENKTCL patients had better 5-year OS and 5-year PFS than nasal cavity primary ENKTCL patients, but there was no statistical significance (p=0.381 for OS and p=0.417 for PFS). However, in the subgroup analysis for stage II patients, the 5-year OS and PFS rates for WR-ENKTCL were higher than those for NC-ENKTCL (p<0.001 for OS and PFS). Moreover, Liu's study [24] also showed that there were no significant differences in 5-year OS and PFS between patients with primary sites of the nasopharynx (NP ENKTCL) and of the nasal cavity with nasopharynx extension (NC-NP ENKTCL) (p=0.168 for OS and p=0.241 for PFS). Yamaguchi et al. [25] analyzed ENKTCL data from 31 Japanese institutes between 2000 and 2013 and found that patients with stage I and II extra-nasal ENKTCL tended to have worse outcomes than those with nasal ENKTCL. Moreover, Niu et al. [26] found that the 5-year OS of patients with Ann Arbor stage I nasal ENKTCL was higher than that of patients with stage I extra-nasal ENKTCL (71.5% vs. 40.2%, p=0.019), and there was a higher PFS for nasal ENKTCL, but there was no statistical significance (56.4% vs. 30.0%, p=0.071). The difference in these study results might be attributed to differences in clinical characteristics and treatment options among the enrolled patients.

Our study also confirmed that patients with stage I ENKTCL with different primary sites had different prognoses. Compared with the WR group patients, the NC group and NC-WR group patients had better outcomes. The OS of the NC group and NC-WR group was better than that of the WR group, but there was no difference between the NC and NC-WR groups. Moreover, the patients in the NC group had the best PFS and DRFS rates among the three groups, the patients in the WR group experienced the worst, and the NC-WR group patients had better PFS and DRFS rates than the WR group patients, but a worse outcome than the NC group patients, which was not significantly different. This was probably because patients in the NC-WR group had the primary lesion originating in the nasal cavity and extending to Waldeyer's ring. The different primary sites of ENKTCL affect its prognosis, but the reason is not clear. In the future, more studies are needed to explore the mechanism, such as the microenvironment of the tumor, the blood supply of different lesions, the infiltration of tumor lymphocytes, and the distribution of tumor matrix fibers.

In addition, the real benefit of PCNI for stage I nasal ENKTCL with or without Waldeyer's ring involvement and Waldeyer's ring primary ENKTCL have not been identified. In Li's report [14], PCNI was not given to patients with stage I nasal ENKTCL, but it was routinely provided to patients with stage I Waldeyer's ring primary ENKTCL. Additionally, in Li's other report [27], only one of 159 (0.6%) patients who did not receive PCNI developed cervical lymph node relapse in patients with nasal cavity confined disease, whereas 1 of 23 (4.3%) stage I patients with the localized nasal disease who received PCNI had regional lymph node failure. Liang's study found that PCNI provided no benefit in PFS and OS, regardless of the primary tumor site or local tumor invasion [28]. In our cohort, regardless of the primary site of the tumor, PCNI was not applied in all cases. Our results showed that only 10 patients had cervical lymph node recurrence. Using Fisher's test analyses, we found that there was no significant difference in the cervical lymph node failure rates of the different groups. However, the risk of distant failure in the WR group was higher than that in the other two groups.

Our study had some limitations. First, this was a retrospective study, and the sample sizes in the three groups were not well balanced, although there were no significant differences in patient characteristics. Second, not all the primary sites of stage I ENKTCL treated in our department were included in this study because there were too few patients. Thus, there may be some bias in this study, and a prospective clinical trial is needed to validate our results.

In summary, patients with stage I ENKTCL had a good local control rate with radiotherapy alone without prophylactic irradiation of the cervical lymph node. So, we do not recommend PCNI for stage I ENKTCL patients. Compared to patients with nasal-originated diseases, patients with primary tumors located in Waldeyer's ring had a worse prognosis. Patients with primary tumors outside the nasal cavity may need combined treatment. Chemotherapy in combination with radiotherapy will be a good choice. In the future, it's necessary to investigate the optimal chemotherapy regimens with improved efficacy and less toxic side effects and find the best sequence of radiotherapy and chemotherapy, in order to get a better prognosis for the stage I ENKTCL patients with Waldeyer's ring.

Acknowledgments: We would like to thank the Fudan University Shanghai Cancer Center for their assistance. This work was supported by grants from the Project of Clinical Medicine of Nantong University (Grant numbers [no.2019JY014]).

References

[1] CHIM CS, MA SY, AU WY, CHOY C, LIE AK et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood 2004; 103: 216–221. https://doi.org/10.1182/blood-2003-05-1401

[2] AU WY, WEISENBURGER DD, INTRAGUMTORNCHAI T, NAKAMURA S, KIM WS 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 2009; 113: 3931–3937. https://doi.org/10.1182/blood-2008-10-185256

[3] AOZASA K, TAKAKUWA T, HONGYO T, YANG WI. Nasal NK/T-cell lymphoma: epidemiology and pathogenesis. Int J Hematol 2008; 7: 110–117. https://doi.org/10.1007/s12185-008-0021-7

[4] BELLEI M, CHIATTONE CS, LUMINARI S, PESCE EA, CABRERA ME et al. T-cell lymphomas in South america and europe. Rev Bras Hematol Hemoter 2012; 34: 42–47. https://doi.org/10.5581/1516-8484.20120013

[5] YANG QP, ZHANG WY, YU JB, ZHAO S, XU H et al. Subtype distribution of lymphomas in Southwest China: analysis of 6,382 cases using WHO classification in a single institution. Diagn Pathol 2011; 6: 77. https://doi.org/10.1186/1746-1596-6-77

[6] SUN J, YANG Q, LU Z, HE M, GAO L et al. Distribution of lymphoid neoplasms in China: analysis of 4,638 cases according to the World Health Organization classification. Am J Clin Pathol 2012; 138: 429–434. https://doi.org/10.1309/AJCP7YLTQPUSDQ5C

[7] KIM TM, LEE SY, JEON YK, RYOO BY, CHO GJ et al. Clinical heterogeneity of extranodal NK/T-cell lymphoma, nasal type: a national survey of the Korean Cancer Study Group. Ann Oncol 2008; 19: 1477–1484. https://doi.org/10.1093/annonc/mdn147

[8] DONG GH, LI Y, DONG JY, LI X, WAN HF et al. Prognostic significance of locally invaded sites and tissue types in patients with nasal extranodal natural-killer/T-cell lymphoma: a single-center retrospective analysis. Chin Med J (Engl) 2019; 132: 1305–1313. https://doi.org/10.1097/CM9.0000000000000263

[9] WANG HY, NIU SQ, YANG YY, LI YY, CHEN HB et al. Promising clinical outcomes of sequential and "Sandwich" chemotherapy and extended involved-field intensity-modulated radiotherapy in patients with stage IE /IIE extranodal natural killer/T-cell lymphoma. Cancer Med 2018; 7: 5863–5869. https://doi.org/10.1002/cam4.1755

[10] TSE E, KWONG YL. Nasal NK/T-cell lymphoma: RT, CT, or both. Blood 2015; 126: 1400–1401. https://doi.org/10.1182/blood-2015-07-655191

[11] QI F, CHEN B, WANG J, LIN X, QI S et al. Upfront radiation is essential for high-risk early-stage extranodal NK/T-cell lymphoma, nasal type: comparison of two sequential treatment modalities combining radiotherapy and GDP (gemcitabine, dexamethasone, and cisplatin) in the modern era. Leuk Lymphoma 2019; 60: 2679–2688. https://doi.org/10.1080/10428194.2019.1599111

[12] NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES VERSION 1.2021 Extranodal NK/T-Cell Lymphoma, nasal type. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf [As accessed on September 2021]

[13] YANG Y, ZHU Y, CAO JZ, ZHANG YJ, XU LM et al. Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: analysis from a multicenter study. Blood 2015; 126: 1424–1432; quiz 1517. https://doi.org/10.1182/blood-2015-04-639336

[14] LI YX, WANG H, JIN J, WANG WH, LIU QF et al. Radiotherapy alone with curative intent in patients with stage I extranodal nasal-type NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys 2012; 82: 1809–1815. https://doi.org/10.1016/j.ijrobp.2010.10.040

[15] HUANG MJ, JIANG Y, LIU WP, LI ZP, LI M et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008; 70: 166–174. https://doi.org/10.1016/j.ijrobp.2007.05.073

[16] VARGO JA, PATEL A, GLASER SM, BALASUBRAMANI GK, FARAH RJ 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 2017; 123: 3176–3185. https://doi.org/10.1002/cncr.30697

[17] JIANG L, LI SJ, JIANG YM, LONG JX, WANG RS et al. The significance of combining radiotherapy with chemotherapy for early stage extranodal natural killer/T-cell lymphoma, nasal type: a systematic review and meta-analysis. Leuk Lymphoma 2014; 55: 1038–1048. https://doi.org/10.3109/10428194.2013.827789

[18] LI YX, FANG H, LIU QF, LU J, QI SN et al. Clinical features and treatment outcome of nasal-type NK/T-cell lymphoma of Waldeyer ring. Blood 2008; 112: 3057–3064. https://doi.org/10.1182/blood-2008-05-160176

[19] LI YX, LIU QF, FANG H, QI SN, WANG H et al. Variable clinical presentations of nasal and Waldeyer ring natural killer/T-cell lymphoma. Clin Cancer Res 2009; 15: 2905–2912. https://doi.org/10.1158/1078-0432.CCR-08-2914

[20] JO JC, YOON DH, KIM S, LEE BJ, JANG YJ et al. Clinical features and prognostic model for extranasal NK/T-cell lymphoma. Eur J Haematol 2012; 89: 103–110. https://doi.org/10.1111/j.1600-0609.2012.01796.x

[21] LIU ZL, BI XW, ZHANG XW, LEI DX, LIU PP et al. Characteristics, Prognostic Factors, and Survival of Patients with NK/T-Cell Lymphoma of Non-upper Aerodigestive Tract: A 17-Year Single-Center Experience. Cancer Res Treat 2019; 51: 1557–1567. https://doi.org/10.4143/crt.2018.681

[22] LIU QF, WANG WH, WANG SL, LIU YP, HUANG WT et al. Immunophenotypic and clinical differences between the nasal and extranasal subtypes of upper aerodigestive tract natural killer/T-cell lymphoma. Int J Radiat Oncol Biol Phys 2014; 88: 806–813. https://doi.org/10.1016/j.ijrobp.2013.12.005

[23] FANG H, JIN J, WANG WH, WANG SL, ZHOU LQ et al. Prognostic factors and treatment outcomes for patients with stage II extranodal nasal-type natural killer/T-cell lymphoma of the upper aerodigestive tract. Leuk Lymphoma 2014; 55: 1832–1837. https://doi.org/10.3109/10428194.2013.852668

[24] LIU WX, LIU YP, JIN J, WANG SL, FANG H et al. [Clinical differences between primary nasopharyngeal NK/T-cell lymphoma and primary nasal cavity NK/T-cell lymphoma with nasopharynx extension]. Zhonghua Zhong Liu Za Zhi 2019; 41: 56–62. https://doi.org/10.3760/cma.j.issn.0253-3766.2019.01.010

[25] YAMAGUCHI M, SUZUKI R, MIYAZAKI K, AMAKI J, TAKIZAWA J et al. Improved prognosis of extranodal NK/T cell lymphoma, nasal type of nasal origin but not extranasal origin. Ann Hematol 2019; 98: 1647–1655. https://doi.org/10.1007/s00277-019-03689-9

[26] NIU SQ, YANG Y, LI YY, WEN G, WANG L et al. Primary site and regional lymph node involvement are independent prognostic factors for early-stage extranodal nasal-type natural killer/T cell lymphoma. Chin J Cancer 2016; 35: 34. https://doi.org/10.1186/s40880-016-0096-0

[27] LI YX, LIU QF, WANG WH, JIN J, SONG YW et al. Failure patterns and clinical implications in early stage nasal natural killer/T-cell lymphoma treated with primary radiotherapy. Cancer 2011; 117: 5203–5211. https://doi.org/10.1002/cncr.26167

[28] WANG L, XIA ZJ, LU Y, ZHANG YJ. Prophylactic cervical lymph node irradiation provides no benefit for patients of stage IE extranodal natural killer/T cell lymphoma, nasal type. Med Oncol 2015; 32: 320. https://doi.org/10.1007/s12032-014-0320-1