

Radiation dose reduction for patients with extranodal NK/T-cell lymphoma with complete response after initial induction chemotherapy

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Abstract: Previous studies have found that radiotherapy (RT) dose less than 50 Gy resulted in inferior outcomes for early stage extranodal NK/T-cell lymphoma (ENKTL). Nowadays, induction chemotherapy (CT) followed by RT consolidation is often used. For patients who get complete response (CR) after CT, whether RT dose can be safely reduced or not remains unknown. This retrospective study compared the survival outcomes between patients who received higher dose (>50 Gy) and lower dose (≤50 Gy) RT after CR was attained by CT. One hundred and forty four patients of early stage ENKTL got CR after induction CT and received RT consolidation. Thirty-one patients received lower dose RT (median 46 Gy, range, 36–50 Gy), and 113 patients received higher dose RT (median 56 Gy, range, 52–66 Gy). In univariate survival analysis, age >60, local tumor invasion, and non-asparaginase-based CT were associated with inferior progression-free survival (PFS) and overall survival (OS). However, there were no differences in PFS and OS between patients treated with higher and lower dose RT, which was confirmed in the multivariate survival analysis. Furthermore, reduced dose RT did not affect local control rate. Most common RT-related side effects were grade 1/2 mucositis and dermatitis, and the incidence rate of grade 3 mucositis or dermatitis was lower in patients treated with reduced dose RT (9.7% vs 15.0% for mucositis, and 6.5% vs 17.7% for dermatitis). In conclusion, this study found that RT dose could be safely reduced without compromising survival outcomes and further improved RT-related side effects. Prospective randomized controlled trials are warranted to validate our findings.

Keywords: extranodal NK/T-cell lymphoma, radiotherapy, prognosis, asparaginase, radiation-related toxicity

Introduction

Extranodal NK/T-cell lymphoma (ENKTL), closely associated with Epstein–Barr virus (EBV) infection, is relatively common in East Asia, Southeast Asia, and Central and South America.¹ Most patients of ENKTL have early stage disease at diagnosis, and thus radiotherapy (RT) has been adopted as the primary treatment during the past decades.² RT alone or combination of RT and consolidative chemotherapy (CT) can achieve a complete response (CR) rate of 87% and 5-year overall survival (OS) rate of 71%.³ However, local relapse or systemic failure is very common in patients who are treated with RT alone.⁴ Therefore, increasing evidence has proven the benefit of CT in reducing the risk of disease relapses. Previous studies have demonstrated poor efficacy with anthracycline-based CT (such as CHOP or EPOCH regimens) due to overexpression of multidrug resistance genes in ENKTL cells.⁵ In recent years, asparaginase-based regimens have been demonstrated to be highly active in

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the treatment of ENKTL, and can attain a CR rate of 70% in early stage ENKTL.⁶⁻¹⁰ Increasingly cancer centers are using a combination of asparaginase-based CT and RT for the treatment of early stage ENKTL, although the optimal combination strategy has not been defined yet.

Previous studies using RT as primary treatment for early stage ENKTL concluded that higher dose (>50 Gy) and extended involved-field RT (IFRT) can get superior outcomes than lower dose (<50 Gy) and small IFRT.¹¹ However, with increasing application of asparaginase-based CT as primary treatment for early stage ENKTL patients, many patients can get CR before RT.^{9,10} Thus, in order to reduce the toxicity of higher dose RT and improve the quality of life, whether the RT dose can be safely reduced or not without compromising survival outcomes needs to be investigated in patients with CR after induction CT.

Materials and methods

Patients

From January 2003 to December 2015, a total of 221 patients of early stage ENKTL with complete follow-up information in Sun Yat-sen University Cancer Center received CT as primary treatment, among whom 144 patients got CR before RT. Only patients with disease in upper aerodigestive tract were included in this study. Sun Yat-sen University Cancer Center Research Ethics Board has approved us to use the data in this retrospective study, and all patients included in this study gave their written informed consent for publishing the medical information at their first visit to our center.

Treatments

All 144 patients received CT as primary treatment (anthracycline-based regimens, n=93; asparaginase-based regimens, n=51) and got CR before initiation of RT. As previously reported,⁹ IFRT was delivered using 6-MeV linear accelerator using conventional planning RT, 3-dimensional conformal treatment planning, or intensity modulated RT. The RT prescription was 200 cGy per fraction, once a day, and 5 fractions every week (Figure 1).

Response and toxicity criteria

The treatment efficacy was evaluated after each two cycles of CT, before and after RT using MRI or PET-CT scan. Follow-up visits were done every 3 months within the first 2 years, every 6 months within the next 3 years, and annually thereafter for the whole life. The National Cancer Institute Common Terminology Criteria of Adverse Events v3.0 was used to grade all treatment toxicities.

Statistical analysis

OS was defined as the interval from the date of diagnosis of ENKTL to the date of death or the date of last follow-up visit for patients who were still alive. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression or death, or to the date of last follow-up visit, whichever came first. Survival analysis was done using the Kaplan–Meier method with log-rank test. Two-sided $P<0.05$ was considered statistically significant. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis.

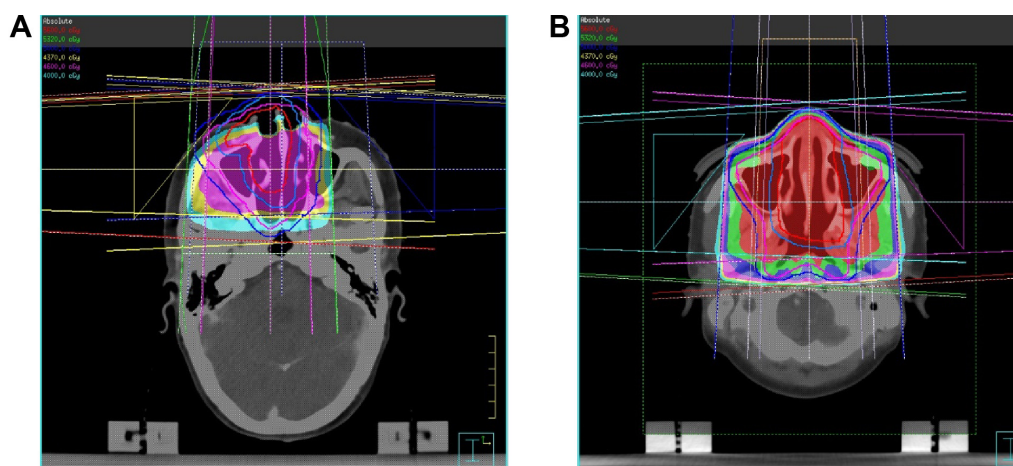


Figure 1 Three-dimensional conformal radiotherapy target volume delineation and radiation fields arrangement for two typical patients with nasal cavity originated ENKTL and complete remission after induction chemotherapy.

Notes: (A) Tumor invaded right nasal cavity and the septum, prescription dose DT 4,600 cGy in 23 fractionations; (B) Tumor invaded the whole nasal cavity, prescription dose DT 5,600 cGy in 28 fractionations.

Abbreviation: ENKTL, extranodal NK/T-cell lymphoma.

Results

Patients' characteristics and treatments

All patients' characteristics are shown in Table 1. The median age was 41 years old (range 11–75), and 18 patients (12.5%) were older than 60; 63.9% of patients had stage I disease, and serum lactate dehydrogenase (LDH) level was elevated in only 19.4% patients; 55.6% of patients had local tumor invasion. In this study, all patients received CT followed by RT consolidation, and 64.6% of patients had anthracycline-based CT regimens, and the remaining 35.6% of patients had asparaginase-based CT regimens. All patients got CR after at least two cycles of CT. Thirty-one patients (21.5%) received reduced dose RT (median 46 Gy, range, 36–50 Gy), and 113 patients (78.5%) received higher dose RT (median 56 Gy, range, 52–66 Gy). There were no significant differences between patients treated with higher dose RT or lower dose RT in regard to clinical characteristics ($P>0.05$).

Survival analysis and relapse patterns

Till January 2016, 27 patients died of ENKTL, and the median follow-up time was 42 months (range, 2–135 months)

Table 1 Clinical characteristics of patients with extranodal NK/T-cell lymphoma, nasal type

Variable	RT dose >50 Gy (n=113) (%)	RT dose ≤50 Gy (n=31) (%)	P-value
Gender			0.754
Male	75 (66.4)	19 (61.3)	
Female	38 (33.6)	12 (38.7)	
Age			0.592
>60	15 (13.3)	3 (9.7)	
≤60	98 (86.7)	28 (90.3)	
ECOG score			0.809
0	92 (81.4)	24 (77.4)	
≥1	21 (18.6)	7 (22.6)	
LDH level			0.434
Elevated	24 (21.2)	4 (12.9)	
Normal	89 (78.8)	27 (87.1)	
B symptoms			0.958
Yes	43 (38.1)	11 (35.5)	
No	70 (61.9)	20 (64.5)	
Ann-Arbor stage			0.474
I	70 (61.9)	22 (71.0)	
II	43 (38.1)	9 (29.0)	
Local tumor invasiveness			0.768
Yes	64 (56.6)	16 (51.6)	
No	49 (43.4)	15 (48.1)	
Induction CT regimen			0.058
Anthracycline-based	68 (60.2)	25 (80.6)	
Asparaginase-based	45 (39.8)	6 (19.4)	

Note: B symptoms include: fever greater than 38 °C; drenching sweats, especially at night; unintentional weight loss of >10% of normal body weight over a period of 6 months or less.

Abbreviations: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NK, natural killer; RT, radiotherapy.

for surviving patients. Five-year OS rate was 76%. Relapsed disease occurred in 46 patients (including 35 patients treated with higher dose RT and eleven patients with lower dose RT). Among those 46 patients, most of them (29/46, 63.0%) had systemic relapses, including gastrointestinal tract invasion, skin invasion, liver invasion, lung invasion, bone marrow invasion, or hemophagocytic syndrome. Seventeen patients (37.0%) had locoregional relapse within the radiation field (ten patients with higher dose RT and seven patients with lower dose RT). Overall, 5-year PFS rate was 64%, and 5-year local control rate (LCR) was 85%. As is shown in Figure 2, whether patients received higher dose RT or lower dose RT did not affect OS and PFS ($P=0.375$ and 0.809 , respectively). Patients with older age, local tumor invasion, and treated with anthracycline-based CT regimens had significantly inferior OS and PFS ($P<0.05$). A subgroup survival analysis was also done in patients treated with higher RT dose (56–66 Gy) and lower RT dose (36–46 Gy), and similar results can be reached, which showed that OS and PFS were not affected by RT dose (Figure 3). As is shown in Figure 4, no significant difference was found in 5-year LCR between patients treated with higher dose RT and lower dose RT. In a multivariate Cox regression survival analysis including age, Eastern Cooperative Oncology Group Performance Status score, LDH level, local tumor invasion, induction CT regimens, Ann-Arbor stage, and RT dose (Table 2), only age (>60 years old) and induction CT regimens (anthracycline-based regimens) were found to be independent poor prognostic factors for PFS and OS, and lower RT dose (≤50 Gy) did not affect the survival outcomes.

Treatment toxicities

The most common toxicities related to RT were mucositis, dermatitis, and dysphagia, but most of these adverse events were mild in severity. Grade 3 mucositis and dermatitis occurred in 15% and 17.7% of patients treated with high dose RT, both higher than that in patients treated with low dose RT (9.7% and 6.5%, respectively). The incidence rate of grade 3 dysphagia was 6.5% and 8.8% in patients treated with low dose and high dose RT, respectively. No RT-related deaths occurred in this study.

Discussion

ENKTL, a distinct subtype of non-Hodgkin lymphoma, is very sensitive to RT, and it is reported that RT with or without CT can result in very high CR rate.^{2,3,11,12} However, systemic relapse is very common in patients treated with RT alone, and it is now recommended that CT should be added in combination

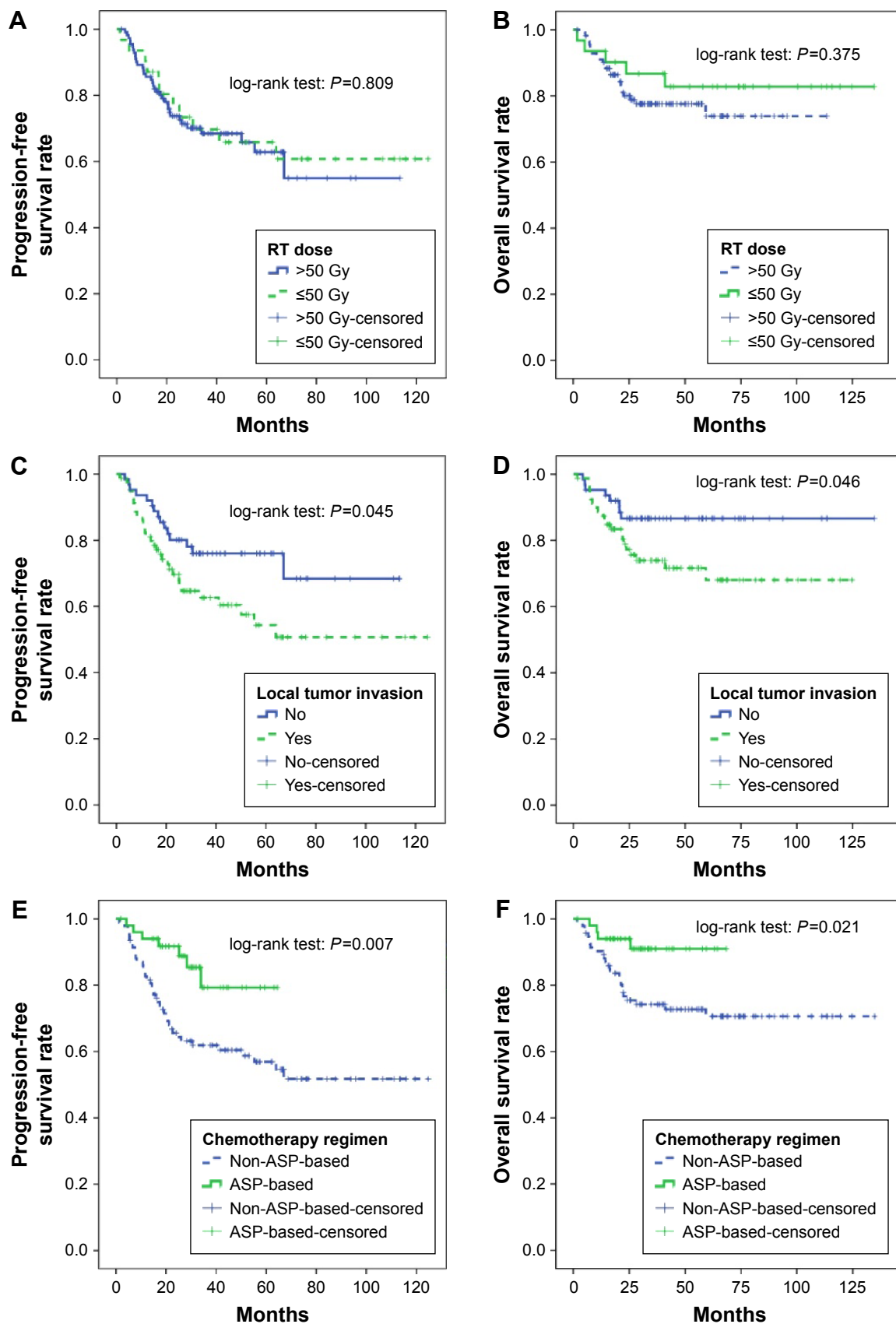


Figure 2 Survival analysis in the whole cohort of 144 patients with ENKTL.

Notes: Whether patients received higher dose RT (>50 Gy) or lower dose RT (≤ 50 Gy) did not affect OS and PFS (**A, B**). Local tumor invasion (**C, D**) and non-asparaginase-based induction chemotherapy regimens (**E, F**) were significantly associated with inferior PFS and OS.

Abbreviations: ASP, asparaginase; ENKTL, extranodal NK/T-cell lymphoma; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

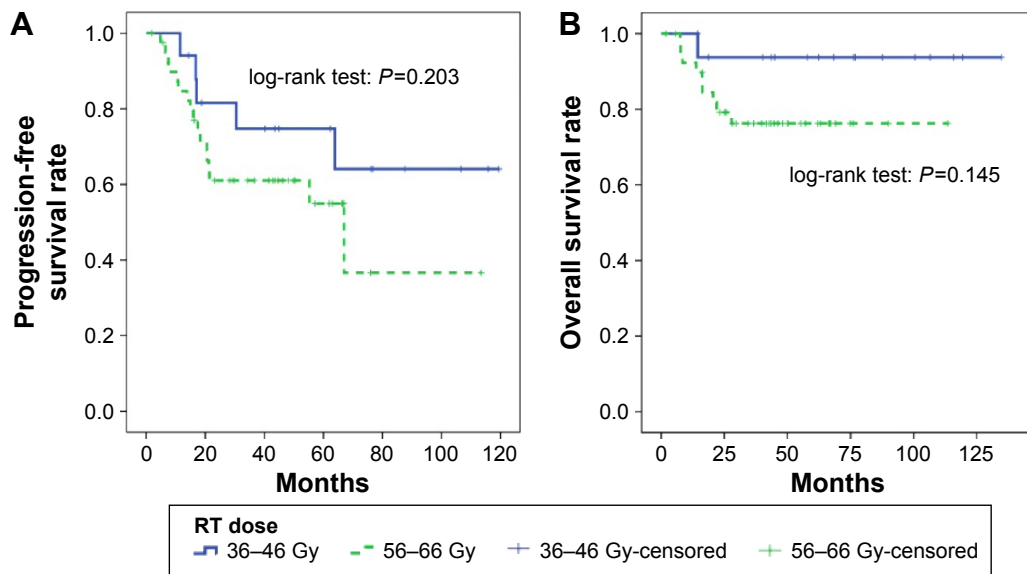


Figure 3 Subgroup survival analysis in patients with ENKTL.
Notes: No significant differences were found in PFS (A) and OS (B) between patients who received higher RT dose (56–66 Gy) and lower RT dose (36–46 Gy) ($P=0.203$ and 0.145 , respectively).
Abbreviations: ENKTL, extranodal NK/T-cell lymphoma; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

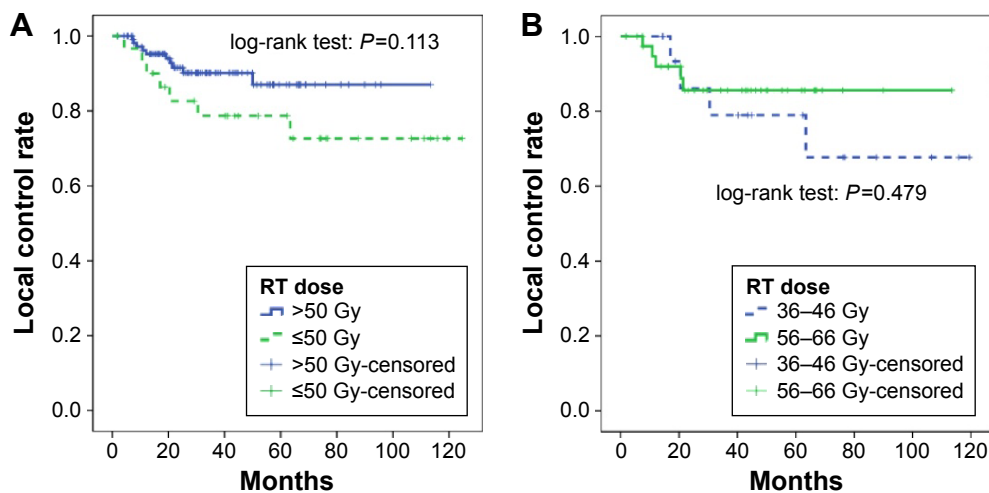


Figure 4 Local control rate analysis for ENKTL patients who got CR after induction chemotherapy.
Notes: Local control rate was not affected by RT dose (A) >50 Gy vs ≤ 50 Gy, $P=0.113$; (B) $56-66$ Gy vs $36-46$ Gy, $P=0.479$.
Abbreviations: CR, complete response; ENKTL, extranodal NK/T-cell lymphoma; RT, radiotherapy.

Table 2 Univariate and multivariate survival analysis

Parameters	PFS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value	HR (95% CI)	P-value	P-value	HR (95% CI)	P-value
Age (>60)	0.006	2.818 (1.325–5.993)	0.007	0.005	3.305 (1.306–8.361)	0.012
Stage (II)	0.474	1.264 (0.619–2.578)	0.520	0.352	1.347 (0.545–3.332)	0.519
LDH (elevated)	0.452	1.250 (0.612–2.554)	0.540	0.755	1.098 (0.437–2.760)	0.842
LTI (yes)	0.045	1.554 (0.796–3.033)	0.196	0.046	1.734 (0.715–4.204)	0.223
ECOG PS score (≥ 1)	0.348	1.114 (0.558–2.224)	0.758	0.079	1.584 (0.707–3.545)	0.264
RT dose (≤ 50 Gy)	0.809	0.871 (0.430–1.766)	0.702	0.375	0.653 (0.241–1.774)	0.404
Induction CT regimens (ASP-based)	0.007	0.342 (0.152–0.772)	0.010	0.021	0.305 (0.106–0.884)	0.029

Abbreviations: ASP, asparaginase; CI, confidence interval; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; LTI, local tumor invasion; OS, overall survival; PFS, progression free survival; PS, performance status; RT, radiotherapy.

with RT to reduce relapse rate, especially for patients with high risk factors.⁵ Due to primary resistance to anthracyclines by ENKTL, previous CHOP regimen resulted in very low control rate.¹³ With the advent of asparaginase, most patients can get CR even before RT.^{8–10} Thus, it is rational to reduce the RT dose in patients who get CR before RT in order to decrease RT-related toxicities and improve the quality of life. In this retrospective study, we found that patients receiving lower dose RT (≤ 50 Gy) can achieve equal survival outcomes as patients treated with higher dose RT (> 50 Gy), and also lower dose RT did not affect the LCR, suggesting it may be safe to reduce the RT dose in patients who got CR before RT.

In this study, either anthracycline-based or asparaginase-based CT regimens were used. Though we only enrolled patients who got CR after induction CT, it is interesting to find that both PFS and OS were in favor of asparaginase-based regimens, indicating that asparaginase is a very important drug in controlling minimal residue disease (MRD). As is known, EBV infection plays a critical role in tumorigenesis of ENKTL,^{14,15} and previous studies have demonstrated that post-treatment EBV-DNA load can predict the survival outcomes.^{15–18} We also found that post-treatment EBV-DNA positivity correlates with poor PFS and OS, and can predict high relapse rate, which indicates that post-treatment EBV-DNA may be used as MRD of ENKTL.¹⁹ We also found that in all patients with CR after induction CT, the percentage of post-treatment EBV-DNA positivity was significantly higher in patients who received anthracycline-based regimens (data submitted elsewhere, not shown here), which may explain our findings that induction regimens significantly correlated with survival outcomes even though all patients got CR before RT. Kim et al demonstrated that post-treatment positron emission tomography (PET) in combination with EBV-DNA positivity can precisely predict the relapse rate and survival outcomes in patients with ENKTL.²⁰ Thus, we recommend that both PET scan and EBV-DNA test should be done before RT in order to better define the treatment response.

Several previous studies have indicated that RT with higher dose (> 50 Gy) and extended radiation field can improve the LCR in ENKTL.^{11,21} However, most of these studies were done in the era of pre-asparaginase, when CT induced very low CR rate in patients with ENKTL.^{10,13} With general application of asparaginase in the treatment of ENKTL, most patients can achieve CR (even PET negativity and EBV-DNA negativity).^{9,10,19} Major toxicities related with RT for ENKTL patients were mucositis, dermatitis, or dysphagia, all of which significantly affect the quality

of life.^{2,9,11} Our results suggest that reducing the incidence rate of these toxicities by lowering the RT dose is feasible and meaningful. However, due to the small sample size of patients who received lower dose RT, various induction CT regimens, and retrospective nature of this study, our findings need to be validated in well-designed prospective clinical trials. In fact, a Phase III clinical trial evaluating the efficacy and safety of decreasing RT dose to < 50 Gy for patients who get CR after pegaspargase-based induction CT is going on (ChiCTR-TRC-14005218).

In conclusion, this study found that RT dose could be safely reduced without compromising survival outcomes and further decreased RT side effects for patients who got CR after induction CT. Prospective randomized controlled trials are warranted to validate this finding.

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Disclosure

The authors report no conflicts of interest in this work.

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