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First-line non–anthracycline-based chemotherapy for extranodal nasal-type NK/T-cell lymphoma: a retrospective analysis from the CLCG

Shu-Nan Qi,[1,*] Yong Yang,[1,*] Yu-Qin Song,[2,*] Ying Wang,[3] Xia He,[4] Chen Hu,[5] Li-Ling Zhang,[6] Gang Wu,[6] Bao-Lin Qu,[7] Li-Ting Qian,[8] Xiao-Rong Hou,[9] Fu-Quan Zhang,[9] Xue-Ying Qiao,[10] Hua Wang,[11] Gao-Feng Li,[12] Hui-Qiang Huang,[13] Yu-Jing Zhang,[13] Yuan Zhu,[14] Jian-Zhong Cao,[15] Jun-Xin Wu,[16] Tao Wu,[17] Su-Yu Zhu,[18] Mei Shi,[19] Li-Ming Xu,[20] Zhi-Yong Yuan,[20] Hang Su,[21] Jun Zhu,[2] and Ye-Xiong Li[1]

[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [2]Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital & Institute, Beijing, People's Republic of China; [3]Chongqing University Cancer Hospital–Chongqing Cancer Hospital, Chongqing, People's Republic of China; [4]Jiangsu Cancer Hospital–Jiangsu Institute of Cancer Research, Nanjing, People's Republic of China; [5]Division of Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; [6]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; [7]The General Hospital of Chinese People's Liberation Army, Beijing, People's Republic of China; [8]The Affiliated Provincial Hospital of Anhui Medical University, Hefei, People's Republic of China; [9]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences–Peking Union Medical College, Beijing, People's Republic of China; [10]The Fourth Hospital of Hebei Medical University, Shijiazhuang, People's Republic of China; [11]Second Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China; [12]Beijing Hospital, National Geriatric Medical Center, Beijing, People's Republic of China; [13]Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China; [14]Zhejiang Cancer Hospital, Hangzhou, People's Republic of China; [15]Shanxi Cancer Hospital and the Affiliated Cancer Hospital of Shanxi Medical University, Taiyuan, People's Republic of China; [16]Fujian Provincial Cancer Hospital, Fuzhou, People's Republic of China; [17]Affiliated Hospital of Guizhou Medical University, Guizhou Cancer Hospital, Guiyang, People's Republic of China; [18]Hunan Cancer Hospital–Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, People's Republic of China; [19]Xijing Hospital of Fourth Military Medical University, Xi'an, People's Republic of China; [20]Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention–Therapy, National Clinical Research Center for Cancer, Tianjin, People's Republic of China; and [21]The Fifth Medical Center of PLA General Hospital, Beijing, People's Republic of China

Key Points

- Non–ANT-based regimen chemotherapy was associated with a survival improvement in the entire cohort and risk subgroups.

The present study investigated the survival benefit of non–anthracycline (ANT)-based vs ANT-based regimens in a large-scale, real-world cohort of patients with extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTCL). Within the China Lymphoma Collaborative Group (CLCG) database (2000-2015), we identified 2560 newly diagnosed patients who received chemotherapy with or without radiotherapy. Propensity score matching (PSM) and multivariable analyses were used to compare overall survival (OS) and progression-free survival (PFS) between the 2 chemotherapy regimens. We explored the survival benefit of non–ANT-based regimens in patients with different treatments in early-stage disease and in risk-stratified subgroups. Non–ANT-based regimens significantly improved survivals compared with ANT-based regimens. The 5-year OS and PFS were 68.9% and 59.5% for non–ANT-based regimens compared with 57.5% and 44.5% for ANT-based regimens in the entire cohort. The clinical advantage of non–ANT-based regimens was substantial across the subgroups examined, regardless of stage and risk-stratified subgroup, and remained significant in early-stage patients who received radiotherapy. The survival benefits of non–ANT-based regimens were consistent after adjustment using multivariable and PSM analyses. These findings provide additional evidence supporting non–ANT-based regimens as a first-line treatment of patients with ENKTCL.

Introduction

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTCL) is rare in Western populations but more frequent in East Asia.[1-3] The disease is unique among aggressive lymphomas in terms of its clinical

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*S.-N.Q., Y.Y., and Y.-Q.S. contributed equally as first authors.

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For data sharing, contact Ye-Xiong Li (e-mail: yexiong@yahoo.com or yexiong12@163.com).

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features and treatment principle. ENKTCL is resistant to anthracycline (ANT)-based regimens but sensitive to radiation.[2,4-6] Radiotherapy plays an important role in both locoregional disease control and maintaining long-term survival in early-stage patients.[2-6] In a recent registry study from the National Cancer Database,[2] the omission or inadequate dose (<50 Gy) of radiotherapy is negatively associated with overall survival (OS). Furthermore, in a previous study from the China Lymphoma Collaborative Group (CLCG),[6] improved locoregional control using appropriate radiotherapy is associated with prolonged OS and progression-free survival (PFS). Primary radiotherapy achieves a favorable prognosis in patients with early-stage ENKTCL,[4-6] whereas adding ANT-based chemotherapy into radiotherapy significantly improves survival in high-risk early-stage patients.[5] However, the prognosis of patients with localized or disseminated diseases is poor using ANT-based chemotherapy alone.[2,5]

Prospective phase 1/2 trials and retrospective studies demonstrated that non–ANT-based regimens provided survival benefits compared with ANT-based regimens in newly diagnosed or relapsed/refractory ENKTCL.[7-18] A variety of non–ANT-based regimens, mainly asparaginase (ASP)-based regimens, have been recommended as first-line treatments for ENKTCL. However, evidence supporting the clinical use of non–ANT-based regimens is limited to single-arm phase 1/2 trials or retrospective studies with small cohorts of patients. The restrictive recruitment criteria in prospective uncontrolled trials might select out suitable young patients with preserved organ function, leading to favorable treatment outcomes. Therefore, the beneficial effect of non–ANT-based regimens needs to be validated in a large comparative study.

Given the rarity of ENKTCL and the difficulty in conducting randomized controlled trials, we designed a large-scale retrospective study to compare the survival benefit of non–ANT-based over ANT-based regimens.

Methods

Patient inclusion

The renewed ENKTCL database from the CLCG included 3046 patients between 2000 and 2015 from 20 institutions. The eligibility criteria for this study included: (1) a newly diagnosed ENKTCL with the typical histological and immunophenotypic evaluations that included CD20/CD79α, CD3ε, CD3s, CD56, cytotoxic molecules (TIA-1, Gram-B, perforin), and Epstein-Barr virus–encoded RNA in situ hybridization, according to the World Health Organization classification of lymphomas; (2) patients received chemotherapy with or without radiotherapy; and (3) complete clinicopathologic and follow-up information. Patients receiving radiotherapy alone (n = 389) or unknown regimens (n = 97) were excluded. Finally, 2560 patients formed the study population. The institutional review boards approved the project and waived the need for informed consent because of the deidentification of patient data.

Evaluation, definition, and treatment

Clinical staging evaluation and the definition of primary tumor invasion (PTI) have been described previously.[18] Briefly, clinical evaluation included history and physical examination; endoscopy of the upper-aerodigestive tract (UADT); blood biochemistry; computed tomography (CT) scans of the head and neck, chest, abdomen, and pelvis; magnetic resonance imaging of the head and neck; and bone marrow examination. Positron emission tomography (PET) CT has been recommended for all patients since 2010, particularly for those with locally advanced-stage or disseminated diseases. Patients were staged using the Ann Arbor staging system and stratified using 3 ENKTCL-specific models: the nomogram-revised risk index,[3,19] the Korea prognostic index,[20] and the prognostic index of natural killer lymphoma.[21] Quantitative measurement of circulating Epstein-Barr virus DNA was not performed in this study.

Chemotherapy was dichotomized into non–ANT-based (n = 1351, 52.8%) and ANT-based regimens (n = 1209, 47.2%). ANT-based regimens included CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone; n = 919) or CHOP-like (CHOP plus etoposide; n = 290), whereas the most commonly used non–ANT-based regimens were ASP (L-ASP or pegaspargase)–containing regimens (n = 1054), followed by platinum-containing (n = 166) and gemcitabine (GEM)–containing (n = 131) regimens. Based on previous systematic review and meta-analysis studies on efficacy and toxicity,[22,23] we further subclassified non–ANT-based regimens into 5 categories (supplemental Table 1): ASP/ANT based (30.3%), ASP/GEM based (25.5%), ASP/methotrexate based (8.8%), ASP/not otherwise specified based (13.4%), and platinum/other regimens (18.9%, usually with GEM). The median number of chemotherapy cycles was 4. Extended involved-site radiotherapy was delivered, with a median dose of 50 Gy.

End point and statistics

Primary end points were OS and PFS. OS was calculated from the date of first treatment until the time of death or last follow-up and PFS from the date of first treatment until the date of disease progression, relapse, death, or time of last follow-up. Survival was estimated using the Kaplan-Meier method and compared using a log-rank test. Propensity score matching (PSM) analysis was applied to adjust confounding variables and generate comparable study arms; 1:1 patient matching without replacement was used to pair each patient receiving non–ANT-based regimens with another patient receiving ANT-based regimens whose propensity score was within the designated caliper size. After PSM, baseline covariates and survival rates were compared between chemotherapy groups. Standardized mean difference is used to examine the balance of covariate distribution between treatment groups. Covariates were considered well balanced when the standardized mean difference was <0.10. The measured covariate balances were assessed both graphically and analytically. Cox proportional hazards regression was performed for multivariable analysis in entire group and prespecified subgroups based on ENKTCL-specific models. The interactions between covariates and treatment in Cox model were checked.

Results

Patient characteristics

The patient characteristics are summarized (Table 1). The median age was 43 years (range, 6-84 years), and the male-to-female ratio was 2.42:1. Most patients had good performance status and primary UADT site (93.8%). Elevated LDH was present in 31.5% of patients, PTI was present in 57.3%, and the majority had early-stage disease (87.0%).

Table 1. Patient characteristics stratified by chemotherapy regimens before and after PSM for patients with all stages, early-stage, and advanced-stage disease

Characteristic	Total	Before PSM			After PSM		
		Non–ANT based	ANT based	*P*	Non–ANT based	ANT based	*P*
All stages (n = 2560)	2560	1351	1209		1114	1114	
Male sex	1811 (70.7)	956 (70.8)	855 (70.7)	.981	731 (65.6)	766 (68.8)	.114
Age >60 y	309 (12.1)	165(12.2)	144 (11.9)	.815	129 (11.6)	128 (11.5)	.947
B symptoms	1106 (43.2)	575 (42.6)	531 (43.9)	.488	560 (50.3)	525 (47.1)	.138
ECOG score ≥2	198 (7.7)	89 (6.6)	109 (9.0)	.022	72 (6.5)	72 (6.5)	1.000
Stage I-II	2226 (87.0)	1156 (85.6)	1070 (88.5)	.028	979 (87.9)	979 (87.9)	1.000
PTI	1466 (57.3)	777 (57.5)	689 (57.0)	.789	635 (57.0)	638 (57.3)	.898
Elevated LDH	807 (31.5)	392 (29.0)	415 (34.3)	.004	346 (31.1)	346 (31.1)	1.000
UADT site	2400 (93.8)	1248 (92.4)	1152 (95.3)	.002	1060 (95.2)	1060 (95.2)	1.000
Regional LN involvement	984 (38.4)	564 (41.7)	420 (34.7)	<.001	410 (36.8)	410 (36.8)	1.000
Distant LN involvement	160 (6.2)	88 (6.5)	72 (6.0)	.560	61 (5.5)	70 (6.3)	.418
Stage I-II (n = 2226)	2226	1156	1070		968	968	
Male sex	1576 (70.8)	812 (70.2)	764 (71.4)	.548	625 (64.6)	664 (68.6)	.060
Age >60 y	271 (12.2)	145 (12.5)	126 (11.8)	.580	116 (12.0)	112 (11.6)	.778
B symptoms	929 (41.7)	469 (40.6)	460 (43.0)	.247	405 (41.8)	405 (41.8)	1.000
ECOG score ≥2	126 (5.7)	46 (4.0)	80 (7.5)	<.001	37 (3.8)	37 (3.8)	1.000
Stage II	788 (35.4)	447 (38.7)	341 (31.9)	.001	330 (34.1)	330 (34.1)	1.000
Elevated LDH	634 (28.5)	293 (25.3)	341 (31.9)	.001	272 (28.1)	272 (28.1)	1.000
PTI	1269 (57.0)	647 (56.0)	622 (58.1)	.303	552 (57.0)	552 (57.0)	1.000
UADT site	2152 (96.7)	1119 (96.8)	1033 (96.5)	.216	933 (96.4)	943 (97.4)	.190
Stage III-IV (n = 334)	334	195	139		101	101	
Male sex	235 (70.4)	144 (73.8)	91 (65.5)	.098	65 (64.4)	60 (59.4)	.469
Age >60 y	38 (11.4)	20 (10.3)	18 (12.9)	.445	10 (9.9)	10 (9.9)	1.000
B symptoms	177 (53.0)	106 (54.4)	71 (51.1)	.554	52 (51.5)	52 (51.5)	1.000
ECOG score ≥2	72 (21.6)	43 (22.1)	29 (20.9)	.795	34 (33.7)	26 (25.7)	.218
Elevated LDH	173 (51.8)	99 (50.8)	74 (53.2)	.565	49 (48.5)	49 (48.5)	1.000
PTI	197 (59.0)	130 (66.7)	67 (48.2)	.001	64 (63.4)	64 (63.4)	1.000
UADT site	236 (70.7)	129 (66.2)	107 (77.0)	.032	77 (76.2)	77 (76.2)	1.000
Distant LN involvement	160 (47.9)	130 (66.7)	67 (48.2)	.001	45 (44.6)	45 (44.6)	1.000

Data are presented as n (%) of patients.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LN, lymph node.

Benefit of non–ANT-based regimens in the entire cohort

We investigated the survival benefit of non–ANT-based regimens in the entire cohort. With a median follow-up time of 48 months for surviving patients, the 5-year OS and PFS rates were 68.9% (95% confidence interval [CI], 65.9-72.1) and 59.5% (95% CI, 56.3-62.9) for non–ANT-based regimens compared with 57.5% (95% CI, 54.5-60.6; hazard ratio [HR], 0.69; 95% CI, 0.60–0.78; $P < .001$; Figure 1A) and 44.5% (95% CI, 41.6-47.6; HR, 0.65; 95% CI, 0.57-0.73; $P < .001$; Figure 1B) for ANT-based regimens.

After adjustment using PSM, the clinical variables were comparable between the 2 groups (Table 1; supplemental Table 2). Non–ANT-based regimens resulted in significantly better OS (HR, 0.64; 95% CI, 0.55-0.75; $P < .001$; Figure 1C) and PFS (HR, 0.62; 95% CI, 0.54-0.71; $P < .001$; Figure 1D) than ANT-based regimens. After adjusting for confounding variables, treatments, and time periods via multivariable analysis, in addition to other clinical factors (age, performance status, stage, LDH, regional and distant lymph node involvement, and PTI), both non–ANT-based regimens and radiotherapy were independent prognostic factors for survival (Table 2). The HRs for OS and PFS of radiotherapy vs no radiotherapy were 0.42 (95% CI, 0.35-0.49; $P < .001$) and 0.38 (95% CI, 0.33-0.44; $P < .001$). The HRs for OS and PFS of non–ANT-based regimens vs ANT-based regimens were 0.72 (95% CI, 0.60-0.85; $P < .001$) and 0.63 (95% CI, 0.54-0.73; $P < .001$). Thus, non–ANT-based regimens are associated with ~30% improvement in OS and PFS in the entire cohort. Since 26.5% of the patients in the non–ANT-based regimens were treated with CHOP plus ASP (CHOP-ASP), a crude comparison with CHOP and CHOP-ASP was made to address the role of ASP in ENKTCL. The addition of ASP to CHOP was associated with significantly

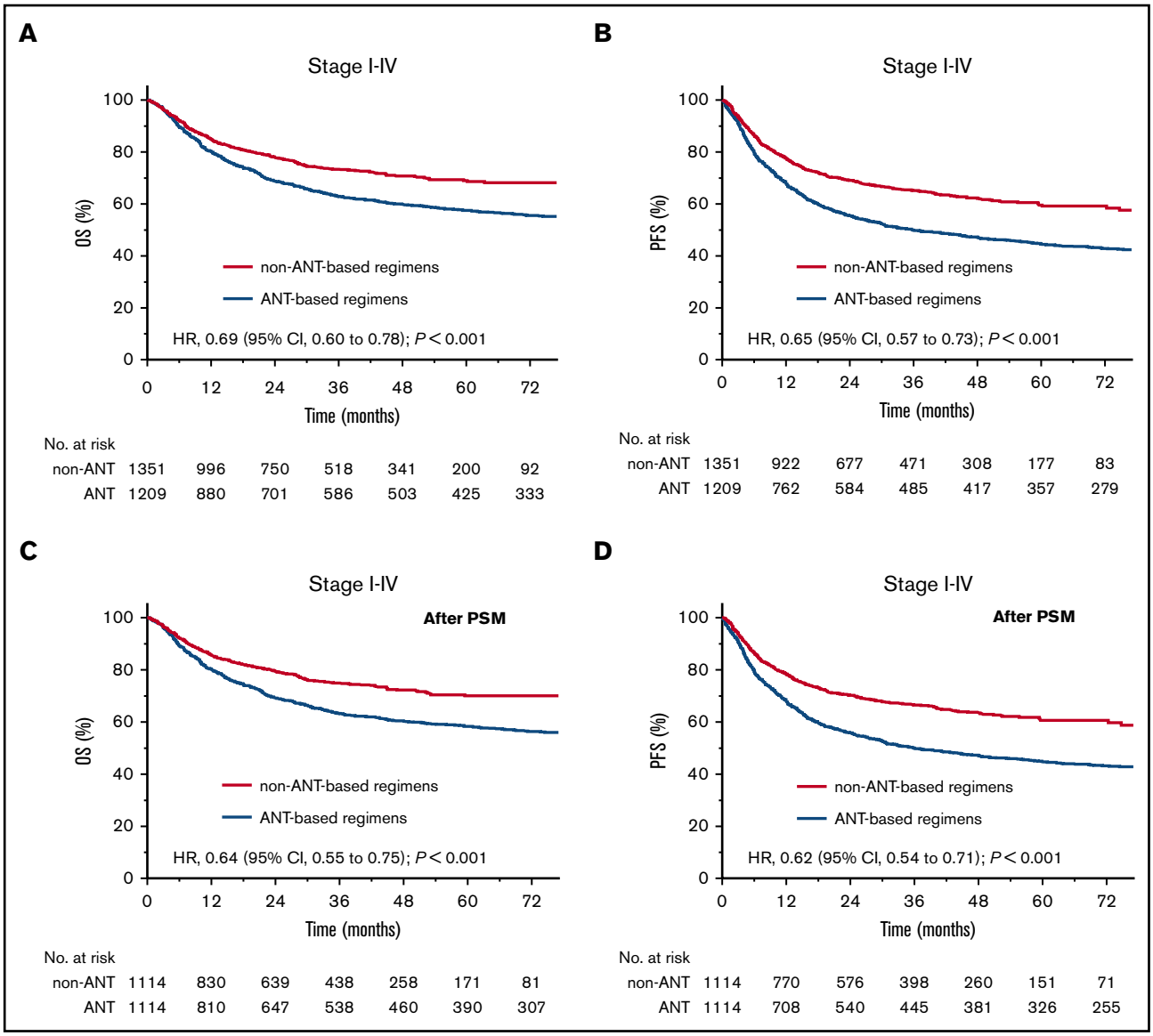

Figure 1. OS and PFS stratified by chemotherapy regimens in the entire cohort. OS (A) and PFS (B) of non–ANT-based regimens vs ANT-based regimens before PSM. OS (C) and PFS (D) of non–ANT-based regimens vs ANT-based regimens after PSM.

better OS and PFS in the entire cohort (supplemental Figure 1). Explorative analysis of survival outcomes with other non–ANT-based regimens was not performed.

Benefit of non–ANT-based regimens in different stages

We evaluated the survival benefit of non–ANT-based regimens in different stages, because treatment strategies and prognosis varied between early-stage and advanced-stage diseases. In early-stage disease, the 5-year OS and PFS rates were 73.3% (95% CI, 70.2-76.6) and 64.0% (95% CI, 60.6-67.5) for non–ANT-based regimens compared with 61.0% (95% CI, 57.8-64.2; HR 0.65, 95% CI, 0.55–0.75; $P < .001$; Figure 2A) and 47.8% (95% CI, 44.7-51.1; HR 0.62, 95% CI, 0.54-0.70; $P < .001$; Figure 2B) for ANT-based regimens. In advanced-stage disease, the 5-year OS and PFS rates were 39.8% (95% CI, 31.7-49.9) and 30.1% (95% CI, 22.8-39.9) for non–ANT-based regimens compared with 29.9% (95% CI, 22.5-39.8; HR 0.70, 95% CI, 0.51-0.92; $P = .013$; Figure 2C) and 18.8% (95% CI, 12.8-27.7; HR 0.67; 95% CI, 0.50-0.86; $P = .003$; Figure 2D) for ANT-based regimens.

PSM adequately balanced the clinical variables between the chemotherapy groups (Table 1; supplemental Table 2). The adjusted HRs for OS and PFS of non–ANT-based regimens vs ANT-based regimens were 0.65 (95% CI, 0.55-0.77; $P < .001$) and 0.61 (95% CI, 0.53-0.70; $P < .001$) for early-stage patients and 0.63 (95% CI, 0.44-0.89; $P = .009$) and 0.58 (95% CI, 0.42-0.80; $P = .001$) for advanced-stage patients. In multivariable analysis (Table 2), the HRs for OS and PFS were 0.79 (95% CI, 0.64-0.97; $P = .021$) and 0.67 (95% CI, 0.56-0.79; $P < .001$) for early-stage patients and 0.55 (95% CI, 0.38-0.78; $P = .001$) and 0.54 (95% CI, 0.39-0.75;

Table 2. Multivariable analysis of OS and PFS for patients with all stages, early-stage, and advanced-stage disease

Variables	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
All stages (n = 2560)				
Year of treatment				
2000-2004	Reference		Reference	
2005-2009	0.99 (0.81-1.21)	.889	1.09 (0.91-1.30)	.343
2010-2015	0.87 (0.70-1.09)	.220	0.97 (0.80-1.18)	.763
Sex (female vs male)	0.91 (0.78-1.06)	.216	0.93 (0.80-1.06)	.287
Age (>60 y vs ≤60 y)	1.61 (1.33-1.95)	<.001	1.34 (1.13-1.59)	.001
B symptoms (yes vs no)	1.01 (0.88-1.17)	.873	1.06 (0.94-1.20)	.365
ECOG score (≥2 vs 0-1)	2.15 (1.76-2.62)	<.001	1.80 (1.50-2.17)	<.001
Ann Arbor stage (III-IV vs I-II)	2.26 (1.77-2.89)	<.001	1.96 (1.57-2.45)	<.001
Elevated LDH (yes vs no)	1.39 (1.20-1.60)	<.001	1.17 (1.03-1.32)	.017
PTI (yes vs no)	1.58 (1.37-1.83)	<.001	1.50 (1.33-1.70)	<.001
UADT site (yes vs no)	1.00 (0.76-1.31)	.987	0.90 (0.71-1.14)	.386
Regional LN involvement (yes vs no)	1.40 (1.21-1.62)	<.001	1.25 (1.10-1.42)	<.001
Distant LN involvement (yes vs no)	1.77 (1.30-2.39)	<.001	1.78 (1.35-2.35)	<.001
Radiotherapy (yes vs no)	0.42 (0.35-0.49)	<.001	0.38 (0.33-0.44)	<.001
Regimen (non-ANT vs ANT based)	0.72 (0.60-0.85)	<.001	0.63 (0.54-0.73)	<.001
Stage I-II (n = 2226)				
Year of treatment				
2000-2004	Reference		Reference	
2005-2009	0.93 (0.75-1.16)	.517	1.06 (0.88-1.29)	.519
2010-2015	0.76 (0.59-0.97)	.027	0.91 (0.74-1.13)	.401
Sex (female vs male)	0.85 (0.71-1.02)	.073	0.92 (0.79-1.06)	.252
Age (>60 y vs ≤60 y)	1.54 (1.25-1.91)	<.001	1.32 (1.10-1.59)	.004
B symptoms (yes vs no)	0.99 (0.85-1.16)	.918	1.09 (0.95-1.25)	.213
ECOG score (≥2 vs 0-1)	2.27 (1.77-2.91)	<.001	1.97 (1.57-2.47)	<.001
Ann Arbor stage (II vs I)	1.44 (1.23-1.70)	<.001	1.29 (1.13-1.49)	<.001
Elevated LDH (yes vs no)	1.25 (1.06-1.48)	.008	1.08 (0.93-1.24)	.315
PTI (yes vs no)	1.63 (1.37-1.93)	<.001	1.55 (1.35-1.79)	<.001
UADT site (yes vs no)	0.95 (0.59-1.55)	.843	1.24 (0.87-1.78)	.237
Radiotherapy (yes vs no)	0.43 (0.35-0.51)	<.001	0.37 (0.32-0.43)	<.001
Regimen (non-ANT vs ANT based)	0.79 (0.64-0.97)	.021	0.67 (0.56-0.79)	<.001
Stage III-IV (n = 334)				
Year of treatment				
2000-2004	Reference		Reference	
2005-2009	1.44 (0.83-2.48)	.192	1.30 (0.78-2.14)	.312
2010-2015	1.67 (0.96-2.89)	.070	1.26 (0.76-2.09)	.371
Sex (female vs male)	1.02 (0.73-1.41)	.934	0.93 (0.69-1.25)	.619
Age (>60 y vs ≤60 y)	2.24 (1.44-3.48)	<.001	1.47 (0.96-2.27)	.079
B symptoms (yes vs no)	1.16 (0.86-1.58)	.334	0.98 (0.74-1.30)	.888
ECOG score (≥2 vs 0-1)	1.76 (1.26-2.47)	.001	1.53 (1.12-2.08)	.008
Elevated LDH (yes vs no)	1.97 (1.44-2.69)	<.001	1.59 (1.20-2.10)	.001
PTI (yes vs no)	1.42 (1.04-1.93)	.028	1.36 (1.02-1.80)	.036
Distant LN involvement (yes vs no)	0.69 (0.53-0.94)	.020	0.61 (0.46-0.82)	.001
Radiotherapy (yes vs no)	0.38 (0.26-0.54)	<.001	0.44 (0.32-0.60)	<.001
Regimen (non-ANT vs ANT based)	0.55 (0.38-0.78)	.001	0.54 (0.-0.75)	<.001

$P < .001$) for advanced-stage patients. Thus, non–ANT-based regimens provided significantly better survival than ANT-based regimens, independent of stages.

Benefit of non–ANT-based regimens with or without radiotherapy for early-stage disease

We determined whether the benefit of non–ANT-based regimens existed in early-stage patients receiving radiotherapy. For patients receiving combined modality therapy (CMT), the 5-year OS and PFS rates were 77.0% (95% CI, 73.6-80.2) and 67.7% (95% CI, 64.0-71.5) for the non–ANT-based regimens compared with 65.3% (95% CI, 61.9-68.7; HR; 0.64, 95% CI, 0.54-0.77; $P < .001$; Figure 3A) and 54.4% (95% CI, 51.0-58.0; HR, 0.65; 95% CI, 0.56-0.76; $P < .001$; Figure 3B) for ANT-based regimens. For patients receiving chemotherapy only, the 5-year OS and PFS rates were 50.1% (95% CI, 42.0-62.1) and 39.7% (95% CI, 33.5-51.3) for non–ANT-based regimens compared with 36.7% (95% CI, 30.2-47.2; HR, 0.75; 95% CI, 0.55-1.03; $P = .078$; Figure 3C) and 14.1% (95% CI, 9.7-21.8; HR, 0.55; 95% CI, 0.42-0.71; $P < .001$; Figure 3D) for ANT-based regimens.

After adjustment with PSM, matched cohorts were well balanced in early-stage disease (supplemental Tables 2 and 3). The adjusted HRs for OS and PFS (non–ANT-based vs ANT-based regimens) were 0.60 (95% CI, 0.49-0.74; $P < .001$) and 0.59 (95% CI, 0.50-0.71; $P < .001$) for CMT, and 0.78 (95% CI, 0.55-1.10; $P = 0.161$) and 0.57 (95% CI, 0.43-0.76; $P < .001$) for chemotherapy only. In multivariable analysis (supplemental Table 4), the HRs for OS and PFS were 0.64 (95% CI, 0.50-0.83; $P = .001$) and 0.60 (95% CI, 0.48-0.74; $P < .001$) for CMT, and 1.11 (95% CI, 0.73-1.69; $P = 0.633$) and 0.69 (95% CI, 0.48-0.98; $P = .037$) for chemotherapy only. Thus, non–ANT-based regimens significantly improved the PFS for early-stage ENKTCL, independent of radiotherapy.

In early-stage patients who received either non–ANT-based regimens or ANT-based regimens, chemotherapy alone was associated with significantly inferior survivals compared with CMT (Figure 4). The HRs of CMT vs chemotherapy alone were 0.36 (95% CI, 0.24-0.54; $P < .001$; Figure 4A) for OS and 0.38 (95% CI, 0.27-0.54; $P < .001$; Figure 4B) for PFS in the non–ANT-based regimens group; and 0.43 (95% CI, 0.32-0.59; $P < .001$; Figure 4C) for OS and 0.33 (95% CI, 0.25-0.43; $P < .001$; Figure 4D) for PFS in the ANT-based regimens group.

The sequences of treatment with radiotherapy and chemotherapy were evaluated in early-stage patients who received either non–ANT-based or ANT-based regimens. The baseline characteristics in each group are listed in supplemental Table 5. In either group, radiotherapy followed by chemotherapy was associated with a better survival than chemotherapy followed by radiotherapy (supplemental Figure 2).

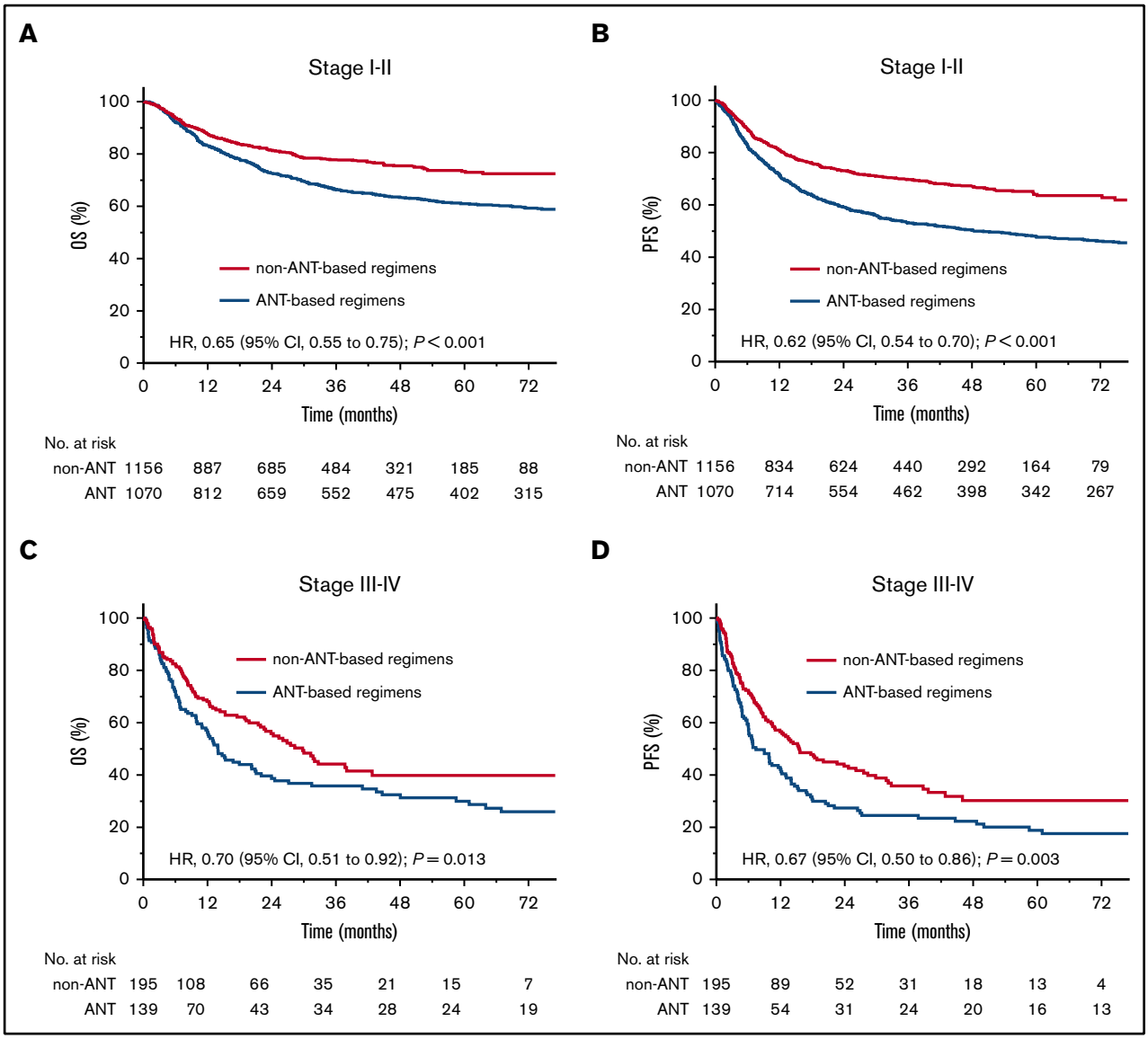

Figure 2. OS and PFS stratified by chemotherapy regimens in early-stage and advanced-stage diseases. OS (A) and PFS (B) of non–ANT-based regimens vs ANT-based regimens in early-stage patients before PSM. OS (C) and PFS (D) of non–ANT-based regimens vs ANT-based regimens in advanced-stage patients before PSM.

Benefit of non–ANT-based regimens in risk-stratified groups

We evaluated the benefit of non–ANT-based regimens in the risk-stratified patients according to 3 ENKTCL-specific models. Figure 5 shows the 5-year OS and PFS rates and HRs of the non–ANT-based regimens vs the ANT-based regimens in each risk subgroup. Non–ANT-based regimens were associated with a significant PFS benefit across all risk subgroups within each model. The HRs for PFS ranged from 0.47 to 0.75 (all $P < .05$), whereas the HRs for OS varied from 0.47 to 0.80 across these risk subgroups. Thus, non–ANT-based regimens appear to be beneficial in risk-stratified patients.

Discussion

This is a large-scale, real-world multicenter comparison of non–ANT-based regimens with ANT-based regimens to treat ENKTCL. Non–ANT-based regimens provided OS and PFS benefits over ANT-based regimens, even after adjusting for prognostic confounders and time periods via PSM and multivariable analyses. The clinical advantage of non–ANT-based regimens was consistent across all subgroups examined, regardless of stage and risk subgroup, and was retained for early-stage patients receiving radiotherapy.

Treatment of ENKTCL has evolved, with the introduction of up-front modern radiotherapy and non–ANT-based chemotherapy that have improved survival outcomes.[2,4-18,24-28] However, there are no published data describing the benefit of non–ANT-based regimens in a randomized controlled trial or a large multicenter comparative study. The present comprehensive study from real-world data represents a critical step toward understanding the effect of non–ANT-based regimens on long-term survival. Our study provided direct comparison information with abundant sample size, which allowed statistical adjustments for potentially confounding

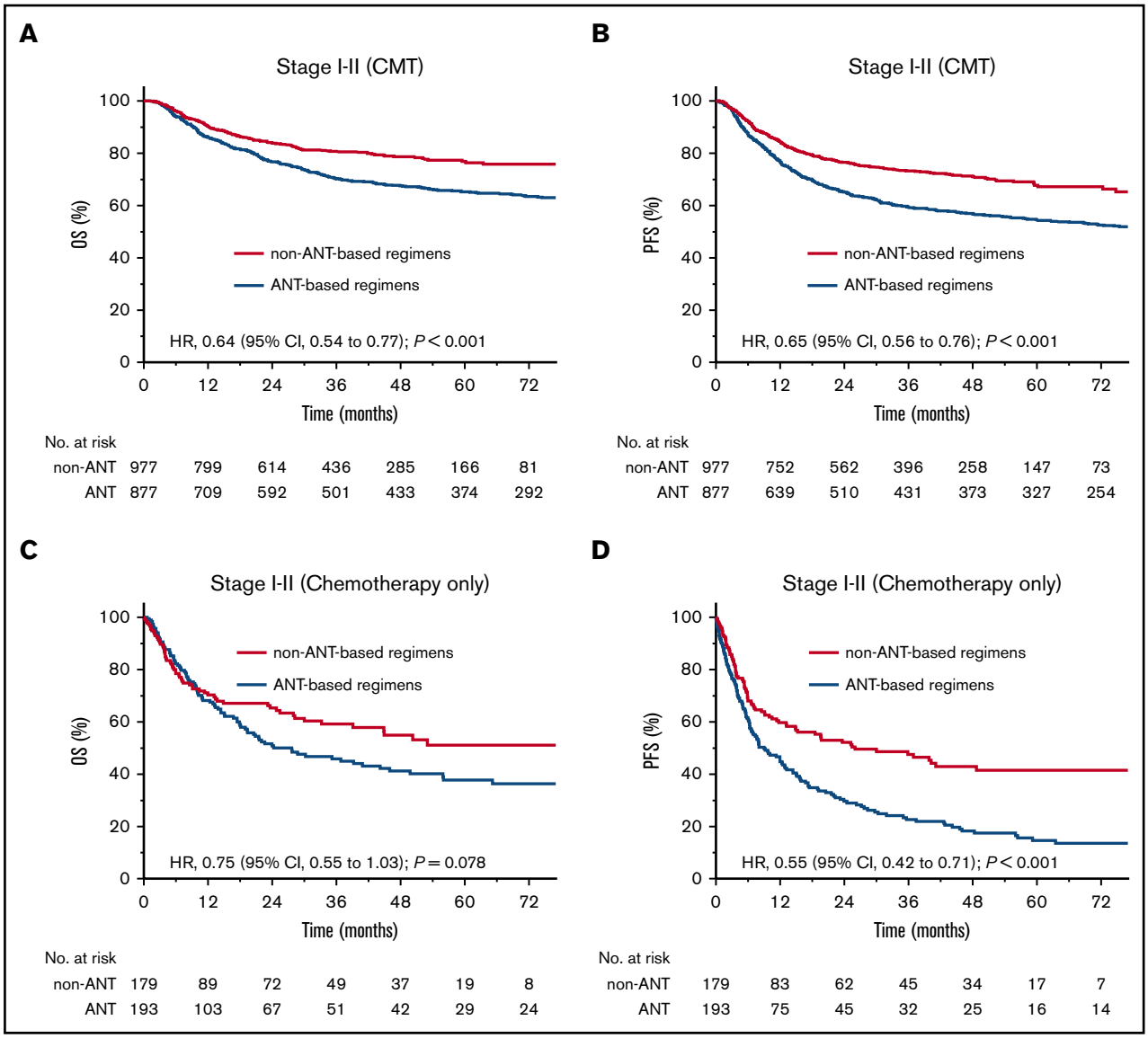

Figure 3. OS and PFS stratified by chemotherapy regimens in early-stage patients receiving CMT or chemotherapy only. OS (A) and PFS (B) of non–ANT-based regimens vs ANT-based regimens in early-stage patients receiving CMT before PSM. OS (C) and PFS (D) of non–ANT-based regimens vs ANT-based regimens in early-stage patients receiving chemotherapy only before PSM.

factors, and showed a decreased mortality risk of ~30% using non–ANT-based regimens in the entire cohort. Non–ANT-based regimens significantly improved PFS and OS for ENKTCL. The beneficial effect of non–ANT-based regimens remained consistent after adjustments using PSM and multivariable analyses and persisted within different stages and individual risk groups. The survival benefit profiles of non–ANT-based regimens after risk stratification could be used for risk-adapted therapy deintensification or intensification in ENKTCL. The survival gain in this large cohort of patients across a substantial number of institutions demonstrated the efficacy and feasibility of non–ANT-based chemotherapy for ENKTCL.

Improvements in long-term survival have been reported in the first-line treatment of early-stage patients over the last decade, mainly as a result of adding radiotherapy into the less effective ANT-based regimens.[2-5] In the modern chemotherapy era, radiotherapy remained an essential component of first-line therapy for early-stage ENKTCL,[24-27] even after a complete response to ASP-based regimens.[27] Here, we further demonstrated that non–ANT-based chemotherapy (mostly with radiotherapy) significantly improved survival outcomes for stage I–II patients. The 5-year OS rate was 73.3% in this study, comparable to the recent large multicenter studies from Japan (72%)[29] and Asian joint data (~74% to 79%),[30] but higher than the International T-cell Project registry data (median OS, 59 months),[31] probably because of more heterogeneous treatments in the latter study. Interestingly, survival outcomes in these large series were similar to that of prospective phase 1/2 trials (3-year OS, 66%-87.5%; 5-year OS, 60%-82.1%) and retrospective studies (~75%; Table 3).[7-10,12-14,26,29-40] Furthermore, the

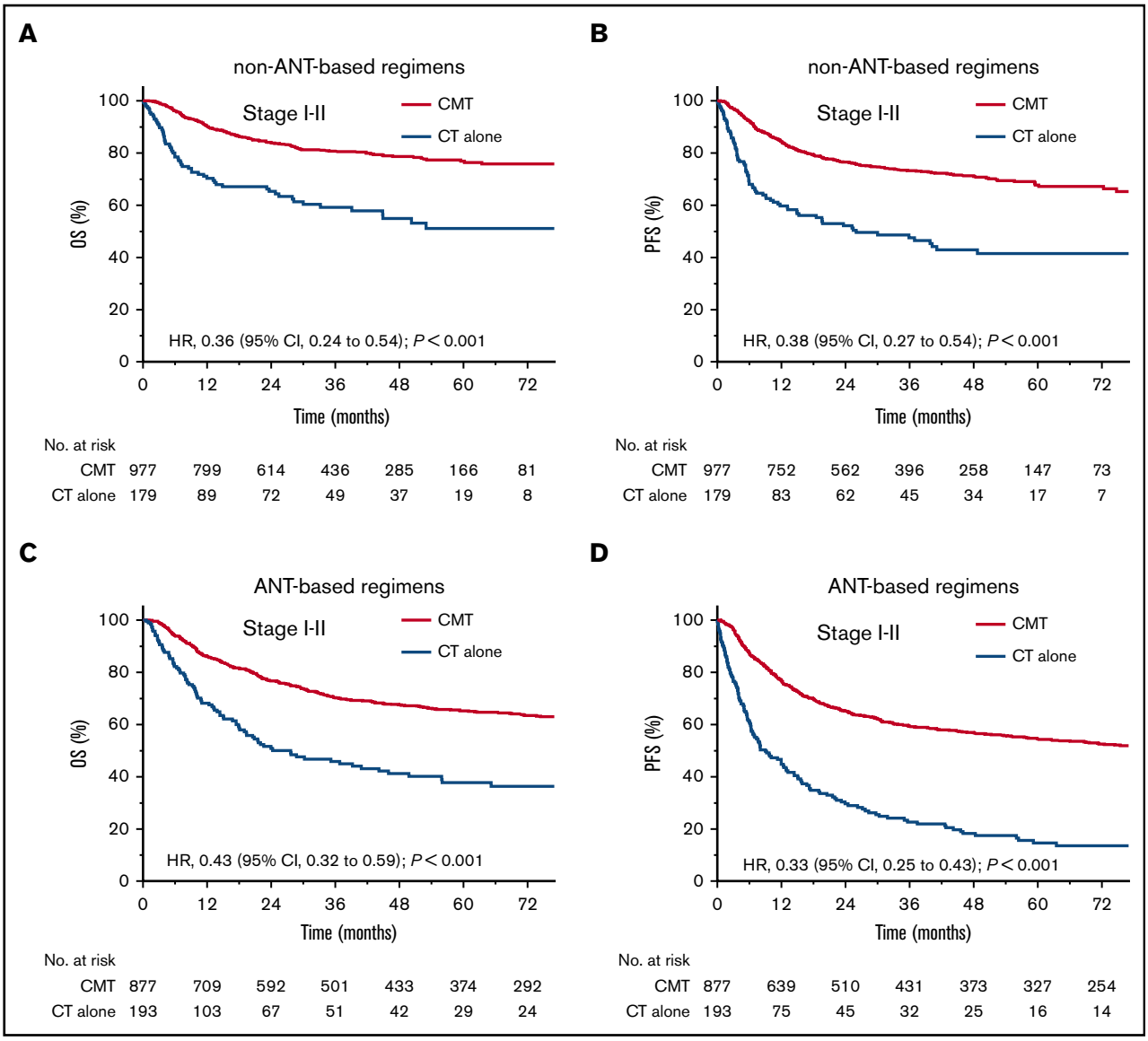

Figure 4. OS and PFS stratified by treatment options in early-stage patients receiving non–ANT-based or ANT-based regimens. OS (A) and PFS (B) of CMT vs CT alone in early-stage patients receiving non–ANT-based regimens before PSM. OS (C) and PFS (D) of CMT vs CT alone in early-stage patients receiving ANT-based regimens before PSM.

survival benefits of non–ANT-based regimens in this study were prominent in early-stage patients who underwent CMT vs chemotherapy only. In our previous study,[24] non–ANT-based regimens and radiotherapy were associated with higher conditional survival and lower annual failure hazard in early-stage patients. Consistent with the International T-cell Project registry study,[31] even with more effective non–ANT-based regimens, chemotherapy alone still resulted in inferior outcomes in early-stage patients, with both 5-year OS and PFS rates of only 50.1% and 39.7% in the present CLCG study. In our previous study, up to 46.9% of early-stage patients who achieved a complete response with ASP-based chemotherapy developed disease relapse.[27] The current study also demonstrated that radiotherapy followed by chemotherapy provided survival benefit over chemotherapy followed by radiotherapy for early-stage ENKTCL in the CMT setting with ANT-based or non–ANT-based regimens. These results emphasize the important role of radiotherapy for early-stage patients in the modern chemotherapy era. On the other hand, patients with advanced-stage disease had extremely poor prognoses after non–ANT-based regimen chemotherapy (Table 3), with a median OS of 5.4 to 36.6 months and a 5-year OS of <40% in these prospective and retrospective studies.[29,31,41-46] Furthermore, the risk of death or progression is variable due to the interactions between clinical stages and treatments in patients with relapsed/refractory ENKTCL.[7,15,16,47-49] As indicated in Table 3, the favorable outcomes of non–ANT-based regimen chemotherapy (5-year OS, 55%-66.9%) reported in these patients are partly attributable to the inclusion of those with localized-relapsed/refractory[7,15,16,47-49] or newly diagnosed early-stage ENKTCL[21,29,31,50-52] treated with effective radiotherapy. These findings support further consideration of more effective

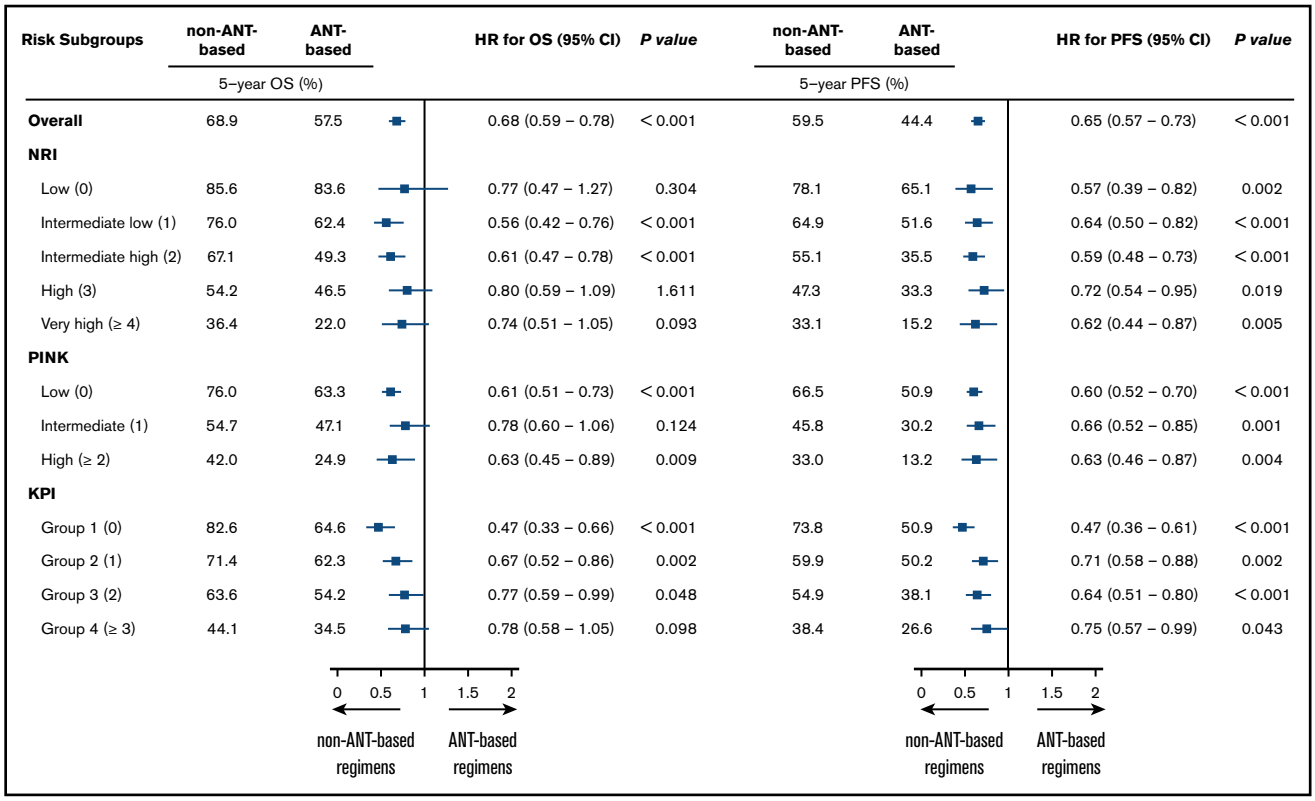

Figure 5. Forest plot depicting the HRs of non–ANT-based regimens vs ANT-based regimens in different risk subgroups according to the 3 risk models. KPI, Korea prognostic index; NRI, nomogram-revised risk index; PINK, prognostic index of natural killer lymphoma.

systematic therapy or innovative treatment strategy for patients with advanced-stage or disseminated diseases and the use of risk-adapted therapy involving radiotherapy and better-tolerated non–ANT-based chemotherapy for patients with early-stage or localized diseases.

The rarity of the disease and lack of randomized controlled trial data have resulted in a variety of non–ANT-based regimens for ENKTCL being developed and recommended by guidelines and adopted in clinical practice among the CLCG institutions. Although treatment options and non–ANT-based regimens varied across countries and even within institutions, consistent with other studies,[29-31] ASP-based regimens have formed the mainstay of chemotherapy across China over the past decade. The wide utility of ASP-based regimens in the world indicated its feasibility in clinical practice and prompted their further validation and optimization. Interestingly, the addition of ASP to CHOP was associated with significantly improved survival compared with CHOP, indicating the important role of ASP in ENKTCL. However, only a small proportion of patients received first-line ASP/methotrexate–based regimens such as SMILE (L-ASP, ifosfamide, methotrexate, etoposide, and dexamethasone) in this study, probably because of its highly severe toxicities.[7,15,16] The heterogeneity of ASP-based regimens reflects the evolving practice pattern of chemotherapy regimens, associated with a lack of a general consensus on the standard regimens for ENKTCL. Further work is needed to determine the optimal non–ANT-based regimens.

This retrospective study had several limitations. First, the chemotherapy regimens were not randomly assigned; therefore, the results may be affected by selection bias. However, given the recognition of ENKTCL resistant to ANT-based regimens, a further prospective study designed as a direct randomized comparison of ANT-based and non–ANT-based regimens may raise ethical concerns. Second, non–ANT-based regimens were applied in more recent years, accompanied with more accurate imaging such as PET/CT or magnetic resonance imaging and advanced radiotherapy techniques.[28] As PET/CT scan was routinely used for staging of patients after 2010, the majority of patients recruited from 2000 to 2009 were therefore not staged properly according to the current standard. This would result in misleading conclusion on the effect of disease stage. We attempted to circumvent these limitations using PSM and multivariable analyses involving time period (2000-2004 vs 2005-2009 vs 2010-2015) and prognostic variables. However, even with PSM analysis, there remains a chance that the underlying confounding factors may have influenced the results. Some other factors, such as treatment toxicity and patient or physician preference, were not completely evaluated. Third, we only focused on effectiveness; however, the toxicity profiles of non–ANT-based regimens could be considered when dealing with different-stage patients or elderly patients. Finally, histologic results were not centrally reviewed in the CLCG; this may lead to misdiagnosis in few cases. However, with distinctive clinicopathological and immunophenotypic findings defined in the World Health Organization classification, ENKTCL is easily distinguished from other cytotoxic T-cell lymphomas.[53] We believe this is not likely to significantly affect our conclusions.

In summary, we demonstrated that non–ANT-based regimens significantly improved survival compared with ANT-based regimens,

Table 3. Treatment outcomes of non–ANT-based or ASP-based chemotherapy with or without radiotherapy in patients with ENKTCL

Author	Total no.	Eligibility and stage	Study type	Chemotherapy regimen	RT no. (%)	OS % (y)	PFS % (y)
Early stage (newly diagnosed, n ≥ 30)							
Yamaguchi et al[7,8]	33	Newly, I: 22, II: 11	Phase 1/2	Concurrent DeVIC/RT	33 (100)	73 (5)	67 (5)
Kim et al[9]	30	Newly, I: 15, II: 15	Phase 2	Concurrent VIDP/RT	30 (100)	86.3 (3)	85.2 (3)
Ke et al[32]	32	Newly, I: 17, II: 15	Phase 2	Concurrent GDP/RT	32 (100)	87.5 (3)	84.4 (3)
Kim et al[12]	30	Newly, I: 21, II: 9	Phase 2	Concurrent VIDL/RT	30 (100)	60 (5)	73 (5)
Kim et al[13]	44	Newly, stage I-II	Phase 2	Sequential IMEP/RT	44 (100)	66 (3)	65 (3)
Tsai et al[10]	33	Newly, I: 21, II: 12	Phase 2	Concurrent VIDP/RT	33 (100)	66 (5)	60 (5)
Xu et al[33]	40	Newly, stage I-II	Phase 2	Sequential MESA/RT	36 (90)	92 (2)	89.1 (2)
Qi et al[14]	40	Newly, I: 27, II: 13, high-risk	Phase 2	Sequential RT/GDP	40 (100)	82.1 (5)	79.4 (5)
Oh et al[34]	62	Newly, I: 46, II: 16	Retrospective	Concurrent VIDP/MIDLE/RT	13 (100)	83.1 (3)	77.1 (3)
Wang et al[35]	93	Newly, stage I-II	Retrospective	Sequential GELOX/RT	40 (100)	78.9 (5)	79 (5)
				Sequential EPOCH/RT	53 (100)	50.4 (5)	46.5 (5)
Zang et al[36]	64	Newly, I: 53, II: 11	Retrospective	Sequential CHOP-L/SMILE/RT	Early (100)	84.2 (3)	74.3 (3)
					Late (100)	57.6 (3)	55.9 (3)
Tian et al[37]	72	Newly, I: 54, II: 18	Retrospective	Sequential GDP/RT	72 (100)	72 (5)	NR
Qi et al[26]	75	Newly, I: 44, II: 31	Retrospective	Sequential RT/GDP	75 (100)	79.4 (5)	NR
Hu et al[38]	94	Newly, I: 19, II: 75	Retrospective	Sequential LVD/RT	94 (100)	74.3 (5)	NR
Wei et al[39]	71	Newly, stage I-II	Retrospective	Sequential EPOCHL/RT	68 (96)	65.3 (5)	NR
Kim et al[21]	344	Newly, I: 228, II: 11, training cohort	Large multicenter	Non-ANT-based ± RT	NR	75 (3)	63 (3)
Li et al[40]	167	Newly, stage I-II	Large multicenter	Sequential GELOXD/ P-GEMOXD±RT	142 (85)	73 (3)	72.8 (3)
Yamaguchi et al[29]	257	Newly, stage I-II	Large multicenter	Concurrent DeVIC/RT: 150	150 (100)	72 (5)	61 (5)
Kwong et al[30]	244	Newly, I: 170, II: 74	Large multicenter	Concurrent non-ANT/RT	54 (100)	79.8 (5)*	68.5 (5)*
				Sequential non-ANT/RT	190 (100)	74.4 (5)*	52.2 (5)*
Fox et al[31]	104	Newly, I: 74, II: 30	Large multicenter	Sequential non-ANT (62%) ±RT	48/59 (81)	59 m†	46 m†
Present study	1156	Newly, I: 1438, II: 788	Large multicenter	Sequential non-ANT ±RT	977 (85)	73.3 (5)	64.0 (5)
Advanced stage (newly, relapsed or refractory)							
Kim et al[41]	27	Newly, IV: 27	Phase 2	SMILE (HSCT: 11)	0	10.6 m†	5.1 m†
Wang et al[42]	18	Newly, III: 3, IV: 15	Phase 2	LVDP	18 (100)	23.0 m†	10.5 m†
Ji et al[43]	21	Newly, II: 1, III-IV: 20	Retrospective	GLIDE (HSCT: 4)	0	56 (3)	35.8 (3)
Bi et al[44]	73	Newly, III: 11, IV: 62	Retrospective	L-ASP-based: 23	17 (27)	38.3 (2)	25.4 (2)
				L-ASP absent: 46		22.7 (2)	14.9 (2)
Ding et al[45]	13	R/R, III: 8, IV: 5	Retrospective	MEDA	8 (62)	69.2 (1)	61.5 (1)
Kim et al[46]	70	Newly, III: 4, IV: 66	Multicenter	L-IMEP: 22	0	36.6 m†	10.1 m†
				IMEP: 48		5.4 m†	3.2 m†
Yamaguchi et al[29]	101	Newly, stage III-IV	Large multicenter	ASP based (70%)	69 (68)	24 (5)	NR
Fox et al[31]	49	Newly, stage III-IV	Large multicenter	Non–ANT based	NR	19 m†	15 m†
Present study	195	Newly, III: 48, IV: 147	Large multicenter	Non–ANT based	74 (38)	39.8 (5)	30.1 (5)

*Estimated from the figures.

†Median survival time (months).

ASCT, allogeneic stem cell transplant; AspaMetDex, L-ASP, methotrexate, and dexamethasone; CHOP-L, cyclophosphamide, doxorubicin, vincristine, prednisolone, and L-ASP; CT, chemotherapy; DDGP, GEM, pegaspargase, cisplatin, and dexamethasone; DeVIC, carboplatin, etoposide, ifosfamide, and dexamethasone; EPOCH, etoposide, vincristine, cyclophosphamide, doxorubicin, and prednisone; ESHAP, etoposide, steroid, high-dose Ara-C, and platinum; GDP, GEM, dexamethasone, and cisplatin; GELOX, GEM, oxaliplatin, and L-ASP; GLIDE, GEM, L-ASP, ifosfamide, dexamethasone, and etoposide; GOLD, GEM oxaliplatin, L-ASP, and dexamethasone; HSCT, hematopoietic stem cell transplant; IMEP, ifosfamide, methotrexate, etoposide, and prednisolone; L-ASP, L-ASP; L-IMEP, L-ASP, ifosfamide, methotrexate, etoposide, and prednisolone; LVD, L-ASP, vincristine, and dexamethasone; LVDP, L-ASP, etoposide, dexamethasone, and cisplatin; LVP, L-ASP, vincristine, and prednisolone; MEDA/MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; MIDLE, methotrexate, etoposide, ifosfamide, mesna, and L-ASP; NR, not reported; P-Gemox, pegaspargase, GEM, and oxaliplatin; R/R, relapsed/refractory; RT, radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-ASP, and etoposide; VIDL, etoposide, ifosfamide, cisplatin, and L-ASP; VIDP, etoposide, ifosfamide, cisplatin, and dexamethasone.

Table 3. (continued)

Author	Total no.	Eligibility and stage	Study type	Chemotherapy regimen	RT no. (%)	OS % (y)	PFS % (y)
Early and advanced stage (newly, relapsed or refractory)							
Yamaguchi et al[7]	38	R/R or newly, I-II: 11, III-IV: 27	Phase 2	SMILE (HSCT: 21)	NR	55 (1)	53 (1)
Jaccard et al[15]	19	R/R, I-II: 12, III-IV: 7	Phase 2	AspaMetDex (ASCT: 5)	1 (5)	12.2 m†	12.2 m†
Kwong et al[16]	87	R/R 44, Newly, 43. I-II: 38, III-IV: 49	Phase 2	SMILE (HSCT: 24)	19 (22)	50 (5)	64 (4)
Yong et al[47]	18	Refractory, I-II2: 7, III-IV: 11	Retrospective	L-ASP based	18 (100)	55.6 (5)	NR
Yong et al[48]	45	R/R, I-II: 33, III-IV: 12	Retrospective	LVD	41 (91)	66.9 (5)	NR
Zhou et al[49]	17	R/R, I-II: 8, III-IV: 9	Retrospective	DDGP	4 (24)	82.4 (1)	64.7 (1)
Lin et al[50]	38	Newly, I-II: 31, III-IV: 7	Phase 2	CHOP-L	31 (82)	80.1 (2)	81 (2)
Guo et al[51]	55	Newly, I-II: 45, III-IV: 10	Retrospective	GOLD	45 (82)	74 (3)	57 (3)
Wang et al[52]	98	Newly, I-II: 77, III-IV: 21	Retrospective	GELOX, P-Gemox	77 (79)	65.2 (3)	57.0 (3)
Kim et al[21]	527	Newly, I-II: 344, III-IV: 183	Large multicenter	Non–ANT based (HSCT: 49)	325 (62)	59 (3)	48 (3)
Yahaguchi et al[29]	358	Newly, I-II: 257, III-IV: 101	Large multicenter	Non–ANT based	278 (78)	56 (5)	45 (5)
Fox et al[31]	166	Newly, I-II: 104, III-IV: 49	Large multicenter	Non–ANT based	87/130 (67)	59 m†	20†
Present study	1351	Newly, I-II: 1156, III-IV: 195	Large multicenter	Non–ANT based	1051 (78)	68.9 (5)	59.5 (5)

*Estimated from the figures.
†Median survival time (months).
ASCT, allogeneic stem cell transplant; AspaMetDex, L-ASP, methotrexate, and dexamethasone; CHOP-L, cyclophosphamide, doxorubicin, vincristine, prednisolone, and L-ASP; CT, chemotherapy; DDGP, GEM, pegaspargase, cisplatin, and dexamethasone; DeVIC, carboplatin, etoposide, ifosfamide, and dexamethasone; EPOCH, etoposide, vincristine, cyclophosphamide, doxorubicin, and prednisone; ESHAP, etoposide, steroid, high-dose Ara-C, and platinum; GDP, GEM, dexamethasone, and cisplatin; GELOX, GEM, oxaliplatin, and L-ASP; GLIDE, GEM, L-ASP, ifosfamide, dexamethasone, and etoposide; GOLD, GEM oxaliplatin, L-ASP, and dexamethasone; HSCT, hematopoietic stem cell transplant; IMEP, ifosfamide, methotrexate, etoposide, and prednisolone; L-ASP, L-ASP; L-IMEP, L-ASP, ifosfamide, methotrexate, etoposide, and prednisolone; LVD, L-ASP, vincristine, and dexamethasone; LVDP, L-ASP, etoposide, dexamethasone, and cisplatin; LVP, L-ASP, vincristine, and prednisolone; MEDA/MESA, methotrexate, etoposide, dexamethasone, and pegaspargase; MIDLE, methotrexate, etoposide, ifosfamide, mesna, and L-ASP; NR, not reported; P-Gemox, pegaspargase, GEM, and oxaliplatin; R/R, relapsed/refractory; RT, radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-ASP, and etoposide; VIDL, etoposide, ifosfamide, cisplatin, and L-ASP; VIDP, etoposide, ifosfamide, cisplatin, and dexamethasone.

regardless of stage, risk subgroup, or radiotherapy. These findings provide additional evidence supporting non–ANT-based regimens as first-line treatments for ENKTCL.

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Authorship

Contribution: S.-N.Q., Y.Y., Y.-Q.S., J.Z., and Y.-X.L. designed the study, analyzed the data, and wrote the manuscript; S.-N.Q., Y.Y., Y.-Q.S., C.H., J.Z., and Y.-X.L. contributed to the study concept; Y.-X.L., J.Z., Y.-Q.S., S.-N.Q., and Y.Y. contributed to the study coordination; S.-N.Q., Y.Y., C.H., and Y.-X.L. performed the statistical analysis; and all authors contributed to data collection and interpretation, and finally approved the manuscript.

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ORCID profiles: Y.Y., 0000-0002-4241-9972; C.H., 0000-0003-4672-1981; Y.-J.Z., 0000-0002-2659-6354; J.Z., 0000-0003-3479-2547; Y.-X.L., 0000-0003-0985-235X.

Correspondence: Ye-Xiong Li, State Key Laboratory of Molecular Oncology, Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, PanJiaYuan NanLi #17, ChaoYang District, Beijing 100021, People's Republic of China; e-mail: yexiong12@163.com or yexiong@yahoo.com; and Jun Zhu, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital & Institute, FuCheng Rd #52, HaiDian District, Beijing 100142, People's Republic of China, e-mail: zhu-jun2017@outlook.com.

Appendix

The members of the China Lymphoma Collaborative Group are: Y.-J.Z., Y.-X.L., J.Z., T.W., J.-Z.C., Y.Z., X.-Y.Q., M.S., H.S., Y.W., S.-Y.Z., Z.-Y.Y., X.H., G.W., H.W., B.-L.Q., J.-X.W., F.-Q.Z., L.-T.Q., and G.-F.L.

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