Blood First Edition Paper, prepublished online June 24, 2015; DOI 10.1182/blood-2015-04-639336

Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: a comprehensive analysis from a multicenter study

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Running head: Risk-Adapted Therapy for Extranodal NK/T-Cell Lymphoma.

Key Points

- Patients with early-stage nasal-type extranodal NK/T-cell lymphoma were classified as low-risk or high-risk using five independent prognostic factors.
- Risk-adapted therapy of radiotherapy alone for the low-risk group and radiotherapy consolidated by chemotherapy for the high-risk group proved the most effective treatment.

ABSTRACT

The optimal combination and sequence of radiotherapy (RT) and chemotherapy (CT) for extranodal nasal-type NK/T-cell lymphoma (NKTCL) are not well defined. The aim of this study was to create a risk-adapted therapeutic strategy for early-stage NKTCL. A total of 1273 early-stage patients from ten institutions were reviewed. Patients received CT alone (n = 170), RT alone (n = 253), RT followed by CT (n = 209), or CT followed by RT (n = 641). A comprehensive comparative study was performed using multivariable and propensity score-matched analyses. Early-stage NKTCL was classified as low-risk or high-risk based on five independent prognostic factors (stage, age, performance status, lactate dehydrogenase, primary tumor invasion). RT alone and RT with or without CT were more effective than CT alone (5-year overall survival [OS], 69.6% and 67.7% versus 33.9%, P<0.001). For low-risk patients, RT alone achieved a favorable OS (88.8%); incorporation of induction or consolidation CT did not provide additional benefit (86.9% and 86.3%). For high-risk patients, RT followed by CT resulted in superior OS (72.2%) compared to induction CT and RT (58.3%, P=0.004) or RT alone (59.6%, P=0.017). After adjustment, similar significant differences in OS were still observed between treatment groups. New CT regimens provided limited benefit in early-stage NKTCL. Risk-adapted therapy involving RT alone for low-risk patients and RT consolidated by CT for high-risk patients is a viable, effective strategy for early-stage NKTCL.

Keywords: NK/T-cell lymphoma; radiotherapy; chemotherapy; risk-adapted therapy; prognosis.

Introduction

In recent two decades, extranodal nasal-type NK/T-cell lymphoma (NKTCL) has been recognized as a distinct clinicopathologic entity with an aggressive clinical course.[1-3] NKTCL can arise within any extranodal organ or tissue, but usually involves the upper aerodigestive tract (UADT) such as the nasal cavity and Waldeyer's ring.[3-8]

Early-stage NKTCL represents 70-90% of cases; however, the clinical management of early-stage NKTCL is inconsistent.[1-5,7-13] Current guidelines from the National Comprehensive Cancer Network (NCCN) are equivocal regarding the optimal therapy for early-stage NKTCL, and include radiotherapy (RT) alone, sequential chemotherapy (CT) and RT, or concurrent chemoradiotherapy.[14] The reported 5-year OS rates for localized NKTCL vary from 30% to 90%,[1-13,15-25] reflecting different treatment strategy, disease heterogeneity and the lack of prognostic factors to enable further tailoring of therapy such as the optimal combination and sequence of RT and CT.

We previously demonstrated that RT is a critical component of curative therapy for early-stage NKTCL,[4,5,15-17] and leads to excellent locoregional control rates of > 90% and 5-year overall survival (OS) of 70-90%.[4,5,9,10,15-17,25] Other studies reported similar improvement after upfront RT over CT alone.[1,18-20] However, this advantage needs to be validated in a multi-institution setting. On the other hand, although previous studies showed that adding CT to RT provided no survival benefit for early-stage disease,[1,4,10,12,18,21-25] most patients in these studies received combined

modality therapy (CMT) with different sequences and combinations of CT. However, the benefit of adding CT is difficult to assess in a small sample of patients; we hypothesize that adding CT to RT may provide a greater survival improvement for high-risk patients. Other recent studies demonstrated promising results for dose intensity adjustments and new CT regimens in refractory or advanced NKTCL.[26,27] With the development of more effective systemic therapies, the additive effect of CT regimens combined with RT for early-stage NKTCL remains of interest.

Using a large cohort of patients with NKTCL from several institutions, we conducted a comprehensive analysis to stratify patients with early-stage disease into different risk categories, compare the efficacy of RT and CT, and finally optimize a risk-adapted therapeutic strategy.

Patients and Methods

Patient eligibility

A total of 1273 patients with previously untreated NKTCL at ten Chinese institutions were reviewed between 2000 and 2011. Eligibility requirements included the typical histological and immunophenotypic features of NKTCL (WHO classification); stage I and II disease (Ann Arbor staging system); and complete clinicopathologic and follow-up information. Patients underwent standard staging procedures with routine physical and endoscopic examination, biochemistry, computed tomography scans and/or magnetic resonance imaging of the head and neck, chest, abdomen and pelvis, and a bone marrow examination. Positron emission

tomography was recommended but not mandatory. Primary tumor invasion (PTI) was defined as the presence of primary disease that extended into neighboring structures or organs (eg. primary tumor in the nasal cavity with extension of the paranasal sinuses and/or nasopharynx), or the involvement of multiple, contiguous primary sites (eg. primary tumor involving the nasopharynx and oropharynx; primary tumor involving the nasal cavity, nasopharynx and oropharynx), regardless of the stage or primary site. This project was approved by our institutional review board and conducted in accordance with the Declaration of Helsinki.

Treatment

Due to poor consensus, treatment options varied between and within institutions, mainly depending on the physician choice. Patients received CT alone (*n* = 170), RT alone (*n* = 253), RT followed by CT (RT + CT, *n* = 209), or CT followed by RT (CT + RT, *n* = 641). Radiotherapy included extended-field or extended involved-field encompassing the primary tumor and adjacent regions at a radical dose of 50 Gy, with a 6-10 Gy boost to residual disease.[15,16] Median dose was 50 Gy (range, 36-74 Gy; dose per fraction, 1.8-2 Gy). Of patients receiving CT, 827 (81.1%) received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like regimens (old regimens); whereas 193 (18.9%) received L-asparaginase-based (*n* = 125) or gemcitabine-based (*n* = 68) regimens (new regimens), such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide), GDP (gemcitabine, cisplatin, dexamethasone) or DIMG (dexamethasone, ifosfamide,

methotrexate, gemcitabine). The median number of CT cycles was 4 (range, 1-14) for all patients: 4 (range, 1-9) for patients with CT alone, 3 (range, 1-14) for patients with CT + RT , and 4 (range, 1-9) for patients with RT + CT.

Statistical analyses

Cox proportional hazards regression model was performed to identify independent risk factors for OS in stage I and II patients. Age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary site, B symptoms, lactate dehydrogenase (LDH), stage, PTI and treatment were included as covariates in multivariate analysis. Propensity score-matched (PSM) analysis was conducted to mirror randomized study design and generate comparable study arms; 1:1 patient matching without replacement was used to pair each patient receiving RT alone with another receiving CT only or CMT whose propensity score was within the designated caliper size. After PSM, baseline covariates and survival rates were compared between treatment groups.

OS and progression-free survival (PFS) were defined as described previously,[4-6] assessed with the Kaplan-Meier product limit method and compared using the log-rank test. When detecting non-proportional hazards, a better estimate of treatment effect was provided by the restricted mean survival time (RMST) for comparison of new and old CT regimens.[28] Cox proportional hazards regression was performed using rms package and RMST determined using surv2sampleComp package in R

version 3.0.2 (http://www.r-project.org/). PSM was performed with Stata12; other analyses with IBM SPSS Statistics Version 20.0.

Results

Patient Characteristics

Clinical characteristics and survival rates are presented in Table 1. Median age was 43 (range, 9-87 years); male:female ratio was 2.26:1. Most patients had good PS and primary disease in the UADT. Elevated LDH was present in 31.7% of patients, 40.0% had B symptoms, PTI was observed in 54.1%, and the majority (74.4%) had stage I disease.

Risk Stratification and Survival

The prognostic significance of clinical features for OS and PFS was evaluated for all early-stage patients (Table 1). In accordance with our previous study,[29] age, ECOG PS, stage, LDH and PTI significantly influenced OS in multivariate analysis (Table 2). Treatment strategy was also an independent prognostic factor for OS. CT alone provided the poorest outcome (hazard ratio [HR] 3.707; $P < 0.001$). Within the median follow-up of 53 months for surviving patients, 5-year OS and PFS for all patients were 63.7% and 54.9% (Fig 1A).

To establish risk-adapted therapy, early-stage patients were stratified as low- and high-risk groups based on five independent risk factors (age > 60 years, ECOG ≥ 2, stage II disease, elevated LDH, PTI) unrelated to treatment (Table 2). Low-risk

early-stage patients (defined as no risk factors, 23.4%) had significantly better outcome than high-risk early-stage patients (defined as ≥ 1 risk factor, 76.6%), with 5-year OS and PFS rates of 86.6% and 73.3% for the low-risk group and 56.9% (P < 0.001, Fig 1B) and 49.3% (P < 0.001, Fig 1C) for the high-risk group. The 5-year relapse rate was 22.1% for low-risk group and 35.3% for high-risk group (P < 0.001).

Primary RT Improves Survival

First, we evaluated the efficacy of RT versus CT only. In the unadjusted population, patients treated with CT alone tended to have more risk factors than those treated with RT (Table 3). RT achieved a much better outcome than CT alone; CT alone had a very poor outcome. The 5-year OS and PFS rates were only 33.9% and 19.4% for CT alone, compared with 69.6% (P < 0.001) and 65.1% (P < 0.001) for RT alone and 67.7% (P < 0.001) and 59.8% (P < 0.001) for RT with or without CT (Fig 2A and 2B). The 5-year relapse rate was 68.6% for CT alone and 28.2% for RT with or without CT (P < 0.001). Similar differences between RT and CT alone were also observed when patients were stratified as the low- and high-risk groups (data not shown).

After adjustment by PSM, prognostic factors were comparable between treatment groups (Table 3), and RT still resulted in significantly better survival than CT alone. The 5-year OS and PFS rates were 60.6% and 56.3% for RT alone, and 39.9% (P = 0.004, Fig 2C) and 21.7% (P < 0.001, Fig 2D) for CT alone. The corresponding OS

and PFS rates for RT with or without CT were 53.9% and 45.9%, respectively, and 35.2% ($P < 0.001$, Fig 2E) and 19.5% ($P < 0.001$, Fig 2F) for CT alone.

Excellent Outcome for RT but No Additional Benefit from CT in Low-Risk Patients

We subsequently evaluated whether adding CT to RT modified the outcome in different risk groups. For low-risk patients, RT achieved very favorable long-term survival. Neither induction nor consolidation CT provided additional survival benefit; 5-year OS rate was 88.8% for RT alone compared to 86.9% ($P = 0.896$) for RT + CT and 86.3% ($P = 0.794$) for CT + RT, respectively (Fig 3A). The corresponding PFS rate was 79.2% for RT alone, 81.6% for RT + CT ($P = 0.731$) and 71.5% for CT + RT ($P = 0.177$, Fig 3B). The 5-year relapse rate was 18.8% for RT alone, 10.3% for RT + CT and 23.8% for CT + RT ($P = 0.255$), respectively. PSM analysis was not performed as no low-risk patient had any adverse factor.

RT Followed by CT Improves Survival in High-Risk Patients

To further define the additional benefit of CT and optimize the RT/CT sequence for high-risk patients, we compared the outcomes between RT alone, CT + RT and RT + CT. In the unadjusted population, older patients tended to receive RT alone, whereas patients with stage II disease and B symptoms were more likely to receive CMT (Table 4). RT followed by CT significantly improved survival compared to RT alone or induction CT and RT; 5-year OS rate was 72.2% for RT + CT compared to

59.6% for RT alone (P = 0.017, Fig 4A) and 58.3% for CT + RT (P = 0.004, Fig 4C), with comparable OS for the latter two groups (P = 0.913, Fig 4E). The corresponding relapse rate was 23.1% for RT + CT, 30.3% for RT alone and 34.0% for CT + RT, respectively.

PSM adequately balanced clinical variables affecting treatment selection (Table 4). After adjustment, the risk of lymphoma-related death remained significantly lower in high-risk patients receiving RT followed by CT; 5-year OS rate was 72.8% for RT + CT compared to 57.9% for RT alone (P = 0.042, Fig 4B) and 57.3% for CT + RT (P = 0.002, Fig 4D). The OS rate was comparable for RT alone and CT + RT (P = 0.757, Fig 4F), indicating induction CT provided no additional benefit in high-risk patients.

Limited Benefit of New CT Regimens

We compared the outcomes for new and old regimens in patients receiving CT alone or CMT. Most clinical characteristics were comparable between groups (Table 5). The overall response rate (ORR, complete and partial response) was 77.9% for new regimens and 61.3% for old regimens (P < 0.001). However, these ORR were significantly lower than that after initial RT (93.3%, P < 0.001). The complete response (CR) rate was 31.6% for new regimens, 25.1% for old regimens (P = 0.121) and 82.2% for RT (P < 0.001). Furthermore, the CR rate was 37.6% for L-asparaginase–based regimens, with 45.5% after more than 2 cycles of CT and 21.9% after 1-2 cycles of CT, respectively (P = 0.024).

For patients treated with CT alone, the OS curves for the new and old regimens were not significantly different (P = 0.255, log-rank test; Fig 5A). RMST (OS) up to 36 months was 27.5 months for new regimens and 21.7 months for old regimens (difference, 5.8 months; ratio, 1.27; P = 0.030). For RT followed by CT, the OS rates for the new and old regimens were not significantly different in either the log-rank test or RMST analysis (Fig 5B). For CT followed by RT, the OS rates for the two regimens were not significantly different (P = 0.479, log-rank test); estimated RMST up to 36 months was 31.9 months for new regimens and 29.9 months for old regimens (difference, 2 months; ratio, 1.07; P = 0.020, Fig 5C). After adjustment by PSM, similarly different RMST was observed between both regimens (P = 0.035, Fig 5D).

Discussion

The optimal combination and sequence of RT and CT for early-stage NKTCL has not been defined. This multi-institution study assessed the treatment outcomes of risk-adapted therapy in the largest cohort of patients reported to date. Patients with early-stage NKTCL were classified as low-risk or high-risk group using five independent prognostic factors. We have demonstrated that RT is an effective treatment for early-stage NKTCL and is significantly better than CT alone. For low-risk patients, RT alone achieved a favorable outcome; induction or consolidation CT did not provide additional benefit. For high-risk patients, RT followed by CT resulted in superior OS compared with RT alone or induction CT and RT. Furthermore, following reports of improved OS and PFS after RT for early-stage NKTCL,[4-6,9-13]

this is the first study to confirm the additional benefit of consolidation CT in high-risk patients. Additionally, new CT regimens provide only limited benefit in early-stage NKTCL.

Patients with early-stage NKTCL represent a heterogeneous population with 5-year OS rates ranging from 36.6% to 86.6% (Table 1). As indicated in Table 2, the risk of death is highly variable due to the interactions between clinical characteristics and treatment. However, no previous study has examined the value of risk-adapted therapy based on clinical characteristics in early-stage NKTCL. A nomogram model based on five independent prognostic factors has been developed and validated in our previous study.[29] Moreover, in this large cohort of patients with early-stage NKTCL, we developed a new dedicated risk category system according to these risk factors including age > 60 years, elevated LDH, ECOG PS ≥ 2, stage II, and PTI; these were most significant prognostic factors and criteria for treatment decisions, and provided discrimination between low-risk and high-risk patients.

The rarity and heterogeneity of NKTCL and lack of prospective trial data have resulted in a variety of treatment options, CT regimens and RT volumes and doses at different institutions.[1,3,15-21] Based on experience with diffuse large B-cell lymphoma (DLBCL), early-stage aggressive T-cell lymphoma is traditionally treated with doxorubicin-based CT with or without RT. However, the most common subtypes of peripheral T-cell lymphoma (PTCL), such as NKTCL and PTCL, not otherwise specified, are resistant to CT. The outcomes for CT alone in early-stage NKTCL have been poor (CR, 20-50%; ORR, 50-70%; 5-year OS, 10-35%, and even poorer

PFS).[1-3,18,19,30-33] Similarly, we confirmed the unfavorable prognosis of early-stage patients treated with CT alone - regardless of regimens - and obtained a significant survival improvement after RT (in both multivariable and PSM analysis). In the unadjusted population, 5-year OS was only 33.9% for CT alone compared to 69.6% for RT alone and 67.7% for RT with or without CT. Similar significant differences in OS and PFS between RT and CT alone were also observed in the adjusted population. These results are consistent with other studies that compared survival across different treatments in early-stage NKTCL,[1,3,7,18-21,30,33] with reported 5-year OS rates ranging from 50% to 90% after RT versus < 30% for CT alone. The striking difference in 5-year OS (> 20%) between RT and CT alone suggests RT is an essential treatment for early-stage NKTCL and CT alone should not be routinely administrated. The high cure rate obtained in this large cohort of patients across a substantial number of institutions demonstrates the efficacy and feasibility of primary RT in early-stage NKTCL.

RT is the backbone of curative intent for early-stage NKTCL; however, the additive effect of CT and optimal RT/CT sequence remains unclear. Generally, CMT is frequently used, with CT mainly preceding RT.[1-8] However, most previous studies did not confirm the survival benefit of adding CT to RT in early-stage NKTCL.[4,10-12,21,34,35] In light of the low efficacy of CT, the benefit of adding CT to RT may be limited in low-risk patients but greater in high-risk patients. Here, we demonstrated that RT achieved a very favorable outcome, with 5-year OS of approximately 90% for low-risk patients, who comprise one quarter of cases of

early-stage disease. However, induction or consolidation CT failed to provide additional survival benefit, suggesting that RT alone is a viable option for low-risk patients. For high-risk patients, RT and consolidation CT proved most effective. The additive benefit of CT was only observed in patients treated with RT followed by CT - in that order exclusively - suggesting that delaying RT may negatively impact the effectiveness of treatment. Moreover, CT followed by RT and RT alone had similarly poor outcomes, indicating that induction CT may be ineffective. RT followed by CT provided a 15% increase in 5-year OS (after correcting for treatment selection bias with PSM). Moreover, the limited improvements in initial response and survival provided by the new regimens compared to the old regimens in the CT group or CMT group in this study suggests that the new CT regimens may not be as effective as expected in early-stage NKTCL.[26,36-38] Consistently, a recent study reported a better outcome with early RT than late RT in patients treated with L-asparaginase-containing CT and RT.[36] On the other hand, high levels of acute toxicity induced by dose intensity CT,[26,27,36] which may delay effective RT, is a critical concern when defining CT/RT sequences. To avoid a delay in RT, several prospective trials applied concurrent chemoradiotherapy, with reported 5-year OS rates of 60-73%.[37-40] In this large cohort of early-stage patients, the 5-year OS rates after RT alone for the low-risk group (88.8%) or after sequential RT and CT for the high-risk group (72.2%) were superior or comparable to other recent small series of concurrent, sequential or "sandwich" CT and RT, regardless of the CT regimen.[36-44]

Therefore, RT followed by optional CT offers the advantage of effective RT and has a more tolerable safety profile,[4-6,15,16] and may reduce the risk of chemoresistance.

Based on our findings, risk-adapted therapy involving RT alone for low-risk patients and RT consolidated with CT for high-risk patients should be considered the optimal strategy for early-stage NKTCL. This approach is inspired by and mirrors the standard of care for early-stage DLBCL (CT followed by optional RT).[45-47] In contrast to DLBCL, NKTCL is resistant to CT but highly sensitive to RT. RT alone achieved similar 5-year OS in early-stage NKTCL as CT alone in early-stage DLBCL (50-90%);[4-6,16-22,45-47] however, CT alone achieved a similarly low OS in early-stage NKTCL (10-35%) as RT alone in early-stage DLBCL (30-50%).[1-3,7,8,48-50] Henceforth, it is logical to reverse the order of CT and RT in initial risk-adapted therapy for early-stage NKTCL.

This retrospective study has some limitations. Although the data confirm important findings regarding improved survival after risk-adapted therapy, the treatments were not randomly assigned. High-risk patients were more likely to receive CMT; therefore, the results may be affected by selection biases. We attempted to circumvent this limitation using PSM to account for prognostic factors. After PSM adjustment, the numbers of patients (n > 100 in each group) were sufficient to compare survival differences between treatment groups. The CR rate with L-asparaginase-based chemotherapy in this study was similar to some previous studies,[41,51-57] but lower than other studies.[26,27,42,58-62] The different CR rates in these studies were probably due to small sample size, different clinical stage included,

heterogeneous L-asparaginase containing regimens and cycles, use of radiotherapy, and other unknown factors (Supplemental Table 1). As a minority of our patients (12%) received new CT regimens and had a shorter follow-up time, incorporation of more effective CT regimens into risk-adapted therapy warrants further investigation. The conclusions on initial risk-adapted radiotherapy for early stage NKTCL may be affected by the use of modern effective chemotherapy.

Based on current data, we suggest risk-adapted therapy for early-stage NKTCL: RT alone for low-risk patients and RT followed by CT for high-risk patients. Future prospective studies are required to refine treatment by incorporating more effective CT regimens and novel molecular markers.

Authorship

Contribution: Y.X.L. designed the research; Y.X.L., Y.Y. collected and analyzed data; Y.Z., Y.Y., and Y.X.L. wrote the paper; all authors provided study materials or patients and approved the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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REFERENCES

1. Au WY, Weisenburger DD, Intragumtornchai T, et al. International Peripheral TCLP: 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(17):3931-3937.
2. Suzuki R, Suzumiya J, Yamaguchi M, et al. Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. Ann Oncol. 2010;21(5):1032-1040.
3. Kim TM, Lee SY, Jeon YK, 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(8):1477-1484.
4. Li YX, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol. 2006;24(1):181-189.
5. Li YX, Fang H, Liu QF, et al. Clinical features and treatment outcome of nasal-type NK/T-cell lymphoma of Waldeyer ring. Blood. 2008;112(8):3057-3064.
6. Liu QF, Wang WH, Wang SL, 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(4):806-813.
7. Vazquez A, Khan MN, Blake DM, et al. Extranodal natural killer/T-Cell lymphoma: A population-based comparison of sinonasal and extranasal disease. Laryngoscope. 2014;124(4):888-895.

8. Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol. 2006;24(4):612-618.
9. Li YX, Wang H, Jin J, 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(5):1809-1815.
10. Li YX, Liu QF, Wang WH, L et al. Failure patterns and clinical implications in early stage nasal natural killer/T-cell lymphoma treated with primary radiotherapy. Cancer. 2011;117(22):5203-5211.
11. Kim TM, Park YH, Lee SY, et al. Local tumor invasiveness is more predictive of survival than International Prognostic Index in stage I(E)/II(E) extranodal NK/T-cell lymphoma, nasal type. Blood. 2005;106(12):3785-3790.
12. Cheung MMC, Chan JKC, Lau WH, et al. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol Phys. 2002;54(1):182-190.
13. Li YX, Liu QF, Fang H, et al. Variable clinical presentations of nasal and Waldeyer Ring natural killer/T-cell lymphoma. Clin Cancer Res. 2009;15(8):2905-2912.
14. NCCN guidelines, non-Hodgkin's lymphomas (2015 Version I) http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nhl
15. Bi XW, Li YX, Fang H, et al. High-dose and extended-field intensity modulated radiation therapy for early-stage NK/T-cell lymphoma of Waldeyer's Ring:

dosimetric analysis and clinical outcome. Int J Radiat Oncol Biol Phys. 2013;87(5):1086-1093.

16. Wang H, Li YX, Wang WH, et al. Mild toxicity and favorable prognosis of high-dose and extended involved-field intensity modulated radiotherapy for patients with early-stage nasal NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys. 2012;82(3):1115-1121.
17. Wang ZY, Liu QF, Wang H, et al. Clinical implications of plasma Epstein-Barr virus DNA in early-stage extranodal nasal-type NK/T-cell lymphoma patients receiving primary radiotherapy. Blood. 2012;120(10):2003-2010.
18. Li CC, Tien HF, Tang JL, et al. Treatment outcome and pattern of failure in 77 patients with sinonasal natural killer/T-cell or T-cell lymphoma. Cancer. 2004;100(2):366-375.
19. Huang MJ, Jiang Y, Liu WP, 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(1):166-174.
20. Aviles A, Neri N, Fernandez R, et al. Combined therapy in untreated patients improves outcome in Nasal NK/T lymphoma: results of a clinical trial. Med Oncol. 2013;30(3):637.
21. Kim GE, Lee SW, Chang SK, et al. Combined chemotherapy and radiation versus radiation alone in the management of localized angiocentric lymphoma of the head and neck. Radiother Oncol. 2001;61(3):261-269.

22. Deng T, Zhang C, Zhang X, et al. Treatment outcome of radiotherapy alone versus radiochemotherapy in IE/IIE extranodal nasal-type natural killer/T cell lymphoma: a meta-analysis. PLoS One. 2014;9(9):e106577.

23. Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood. 2004;103(1):216-221.

24. Yang Y, Zhang YJ, Lin XB, et al. Role of radiotherapy in the combined treatment of patients with early stage extranodal nasal type NK/T-cell lymphoma and analysis of prognostic factors. Chin J Radiat Oncol. 2009;18:285-289.

25. Wang ZY, Li YX, Wang WH, et al. Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents. Blood. 2009;114(23):4771-4776.

26. Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood. 2012;120(15):2973-2980.

27. Kim M, Kim TM, Kim KH, et al. Ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) plus L-asparaginase as a first-line therapy improves outcomes in stage III/IV NK/T cell-lymphoma, nasal type (NTCL). Ann Hematol. 2015;94(3):437-444.

28. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol. 2014;32(22):2380-2385.

29. Yang Y, Zhang YJ, Zhu Y, et al. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. Leukemia Feb 20. doi: 10.1038/leu.2015.44. [Epub ahead of print]

30. You JY, Chi KH, Yang MH, et al. Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. Ann Oncol. 2004;15(4):618-625.

31. Pongpruttipan T, Sukpanichnant S, Assanasen T, et al. Extranodal NK/T-cell lymphoma, nasal type, includes cases of natural killer cell and alphabeta, gammadelta, and alphabeta/gammadelta T-cell origin: a comprehensive clinicopathologic and phenotypic study. Am J Surg Pathol. 2012;36(4):481-499.

32. Fang H, Jin J, Wang WH, et al. Prognostic factors and treatment outcomes for patients with stage II extranodal nasal-type NK/T-cell lymphoma of the upper aerodigestive tract. Leuk Lymphoma. 2014;55(8):1832-1837.

33. Ahn HK, Suh C, Chuang SS, et al. Extranodal natural killer/T-cell lymphoma from skin or soft tissue: suggestion of treatment from multinational retrospective analysis. Ann Oncol. 2012;23(10):2703-2707.

34. Ma HH, Qian LT, Pan HF, et al. Treatment outcome of radiotherapy alone versus radiochemotherapy in early stage nasal natural killer/T-cell lymphoma. Med Oncol. 2010;27(3):798-806.

35. Aikemu W, Wang RZ, Li PD. A clinical study of 57 patients with extranodal natural killer/T-cell lymphoma,nasal-type. J Xinjiang Med Univ. 2008;31:1507-1509.

36. Zang J, Li C, Luo SQ, et al. Early radiotherapy has an essential role for improving survival in patients with stage I-II nasal-type of NK/T cell lymphoma treated with L-asparaginase-containing chemotherapy - a single institution experience. Ann Hematol. 2015;94(4):583-591.

37. Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: consortium for improving survival of lymphoma study. J Clin Oncol. 2009;27(35):6027-6032.

38. Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin Oncol. 2009;27(33):5594-5600.

39. Kim SJ, Yang DH, Kim JS, et al. Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. Ann Hematol. 2014;93(11):1895-1901.

40. Tsai HJ, Lin SF, Chen CC, et al. Long-term results of a phase II trial with frontline concurrent chemoradiotherapy followed by consolidation chemotherapy for localized nasal natural killer/T-cell lymphoma. Eur J Haematol.

2015;94(2):130-137.

41. Jiang M, Zhang H, Jiang Y, et al. Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer. 2012;118(13):3294-3301.
42. Wang L, Wang ZH, Chen XQ, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119(2):348-355.
43. Lee J, Kim CY, Park YJ, et al. Sequential chemotherapy followed by radiotherapy versus concurrent chemoradiotherapy in patients with stage I/II extranodal natural killer/T-cell lymphoma, nasal type. Blood Res. 2013;48(4):274-281.
44. Ke QH, Zhou SQ, Du W, et al. Concurrent IMRT and weekly cisplatin followed by GDP chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma. Blood Cancer J. 2014;4:e267.
45. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med. 1998;339(1):21-26.
46. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol. 2004;22(15):3032-3038.

47. Phan J, Mazloom A, Medeiros LJ, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol. 2010;28(27):4170-4176.

48. Spicer J, Smith P, Maclennan K, et al. Long-term follow-up of patients treated with radiotherapy alone for early-stage histologically aggressive non-Hodgkin's lymphoma. Br J Cancer. 2004;90(6):1151-1155.

49. Qi SN, Li YX, Wang H, et al. Diffuse large B-cell lymphoma: clinical characterization and prognosis of Waldeyer ring versus lymph node presentation. Cancer. 2009;115(21):4980-4989.

50. Persky DO, Miller TP, Unger JM, et al. Ibritumomab consolidation after 3 cycles of CHOP plus radiotherapy in high-risk limited-stage aggressive B-cell lymphoma: SWOG S0313. Blood. 2015;125(2):236-241.

51. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotehrapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-cell Tumor Study Group study. J Clin Oncol. 2011;29(33):4410-4416.

52. Jaccard A, Petit B, Girault S, et al. L-Asparaginased-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. Ann Oncol. 2009;20(1):110-116.

53. Zhou Z, Li X, Chen C, et al. Effectiveness of gemcitabine, pegaspargase, cisplatin, and dexamethasone (DDGP) combination chemotherapy in the

treatment of relapsed/refractory extranodal NK/T cell lymphoma: a retrospective study of 17 patients. Ann Hematol. 2014;93(11):1889-1894.

54. Wang YQ, Yang Y, Zhuo HY, et al. Trial of LVDP regimen (L-asparaginase, etoposide, dexamethasone, and cisplatin, followed by radiotherapy as first-line treatment for newly diagnosed, stage III/IV extranodal natural killer/T cell lymphoma. Med Oncol. 2015;32(2):435.
55. Ding H, Chang J, Liu LG, et al. High-dose methotrexate, etoposide, dexamethasone and pegaspargase (MEDA) combination chemotherapy is effective for advanced and relapsed/refractory extronodal natural killer/T cell lymphoma: a retrospective study. Int J Hematol 2015 May 22. [Epub ahead of print], DOI 10.1007/s12185-015-1809-x
56. Kim SJ, Park S, Kang ES, et al. Induction treatment with SMILE and consolidation with autologous stem cell transplantation for newly diagnosed stage IV extranodal natural killer/T cell lymphoma patients. Ann Hematol. 2015;94(1):71-78.
57. Bi XW, Jiang WQ, Zhang WW, et al. Treatment outcome of patients with advanced stage natural killer/T-cell lymphoma: elucidating the effects of asparaginase and postchemotherapeutic radiotherapy. Ann Hematol. 2015;94(7):1175-1184.
58. Jaccard A, Nathalie Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood. 2011;117(6):1834-1839.

59. Lin NJ, Song YQ, Tu MF, et al. A prospective phase II study of L-asparaginase-CHOP plus radiation in newly diagnosed extranodal NK/T-cell lymphoma, nasal type. J Hematol Oncol. 2013;6:44.

60. Guo HQ, Liu L, Wang XF, et al. Efficacy of gemcitabine combined with oxliplatin, L-asparaginase and dexamethasone in patients with newly-diagnosed extranodal NK/T-cell lymphoma. Mol Clin Oncol. 2014;2(6):1172-1176.

61. Yong W, Zheng W, Zhu J, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol. 2009;88(7):647-652.

62. Ji J, Xiang B, Liu WP, et al. A study of gemcitabine, L-asparaginase, ifosfamide, dexamethasone and etoposide chemotherapy for newly diagnosed stage IV, relapsed or refractory extranodal NK/T-cell lymphoma, nasal type. Leuk Lymphoma. 2014;55(12):2955-2957.

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

		5-year OS		5-year PFS	
Characteristic	No. (%)	% (95% CI)	*P*	% (95% CI)	*P*
Sex			0.373		0.811
Male	882 (69.3)	62.4 (58.5 to 66.1)		54.1 (50.4 to 57.8)	
Female	391 (30.7)	66.6 (60.9 to 71.6)		55.8 (50.1 to 61.1)	
Age (years)			<0.001		0.022
≤60	1099 (86.3)	65.4 (62.0 to 68.6)		55.5 (52.2 to 58.8)	
>60	174 (13.7)	52.7 (43.4 to 61.2)		48.7 (39.8 to 56.9)	
B symptoms			0.160		0.019
Yes	509 (40.0)	60.9 (55.0 to 65.4)		50.6 (53.2 to 61.0)	
No	764 (60.0)	65.5 (61.4 to 69.2)		57.2 (44.7 to 57.5)	
Elevated LDH			<0.001		<0.001
Yes	403 (31.7)	55.9 (50.2 to 61.2)		48.7 (43.4 to 53.9)	
No	870 (68.3)	67.7 (63.9 to 71.2)		57.4 (53.5 to 61.1)	
ECOG PS			<0.001		<0.001
0-1	1202 (94.4)	65.4 (62.2 to 68.5)		56.3 (53.1 to 59.4)	
≥2	71 (5.6)	36.6 (24.3 to 48.9)		28.0 (17.3 to 39.6)	
Primary location			0.907		<0.001
UADT	1260 (99.0)	63.7 (60.5 to 66.7)		55.1 (52.0 to 58.2)	
Extra-UADT	13 (1.0)	68.2 (29.7 to 88.6)		0	
Ann Arbor stage			<0.001		<0.001
I	947 (74.4)	67.6 (64.0 to 71.0)		58.3 (54.6 to 61.7)	
II	326 (25.6)	51.3 (44.7 to 57.5)		44.0 (37.8 to 50.1)	
PTI			<0.001		<0.001
Yes	689 (54.1)	53.0 (48.4 to 57.4)		45.2 (40.9 to 49.4)	
No	584 (45.9)	75.9 (71.7 to 79.6)		65.6 (61.1 to 69.7)	
Risk group			<0.001		<0.001
Low-risk	298 (23.4)	86.6 (81.5 to 90.3)		73.3 (66.9 to 78.6)	
High-risk	975 (76.6)	56.9 (53.3 to 60.6)		49.3 (46.6 to 53.8)	

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; OS, overall survival; PFS, progression-free survival; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; UADT, upper aerodigestive tract; PTI, primary tumor invasion.

Table 2. Multivariable analysis of the association between clinical variables and treatment with overall survival for all patients with early-stage NKTCL

	Overall Survival		
Variable	HR	95% CI	*P*
Ann Arbor stage (II vs. I)	1.551	1.258 to 1.912	< 0.001
Primary tumor invasion (yes vs. no)	1.951	1.578 to 2.411	< 0.001
Age (>60 vs. ≤60 years)	1.645	1.273 to 2.126	0.002
Elevated LDH level (yes vs. no)	1.240	1.013 to 1.518	0.037
ECOG PS (≥2 vs. 0-1)	1.935	1.401 to 2.671	0.009
Treatment modality			
RT + CT			
CT + RT	1.481	1.081 to 2.027	0.014
RT alone	1.561	1.072 to 2.273	0.020
CT alone	3.707	2.599 to 5.288	< 0.001

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PS, performance status; RT, radiotherapy; CT, chemotherapy; RT + CT, radiotherapy followed by chemotherapy; CT + RT, chemotherapy followed by radiotherapy.

Table 3. Clinical characteristics of patients with early-stage NKTCL before and after propensity score-match stratification by treatment

	RT alone	CT alone		RT w/o CT	CT alone	
	No. (%)	No. (%)	P	No. (%)	No. (%)	P
Before match						
Total number	253	170		1103	170	
Gender, male	169 (66.8)	121 (71.2)	0.342	761 (69.0)	121 (71.2)	0.566
Age, >60 years	51 (20.2)	28 (16.5)	0.340	146 (13.2)	28 (16.5)	0.253
B symptoms	62 (24.5)	80 (47.1)	<0.001	429 (38.9)	80 (47.1)	0.043
Elevated LDH	58 (22.9)	66 (38.8)	<0.001	337 (30.6)	66 (38.8)	0.031
ECOG ≥2	8 (3.2)	21 (12.4)	<0.001	50 (4.5)	21 (12.4)	<0.001
UADT	252 (99.6)	163 (95.9)	0.008	1097 (99.5)	163 (95.9)	0.001
Stage II	42 (16.6)	61 (35.9)	<0.001	265 (24.0)	61 (35.9)	0.001
PTI	100 (39.5)	104 (61.2)	<0.001	585 (53.0)	104 (61.2)	0.047
After match						
Total number	107	107		158	158	
Gender, male	77 (72.0)	75 (70.1)	0.763	119 (75.3)	111 (70.3)	0.312
Age, >60 years	16 (15.0)	17 (15.9)	0.850	28 (17.7)	25 (15.8)	0.651
B symptoms	38 (35.5)	37 (34.6)	0.886	85 (53.8)	75 (47.5)	0.261
Elevated LDH	33 (30.8)	32 (29.9)	0.882	60 (38.0)	64 (40.5)	0.645
ECOG ≥2	3 (2.8)	1 (0.9)	0.621	12 (7.6)	12 (7.6)	1.000
UADT	106 (99.1)	105 (98.1)	1.000	154 (97.5)	154 (97.5)	1.000
Stage II	34 (31.8)	35 (32.7)	0.884	53 (33.5)	56 (35.4)	0.723
PTI	64 (59.8)	64 (59.8)	1.000	98 (63.0)	101 (63.9)	0.727

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; RT, radiotherapy; CT, chemotherapy; RT w/o CT, radiotherapy with or without chemotherapy; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PS, performance status; UADT, upper aerodigestive tract; PTI, primary tumor invasion.

Table 4. Clinical characteristics of high-risk patients with early-stage NKTCL before and after propensity score-match stratification by treatment

	RT + CT	RT alone		RT + CT	CT + RT		RT alone	CT + RT	
	No. (%)	No. (%)	P	No. (%)	No. (%)	P	No. (%)	No. (%)	P
Before match									
Total	155	163		155	509		163	509	
Gender, male	111 (71.6)	113 (69.3)	0.655	111 (71.6)	363 (71.3)	0.943	113 (69.3)	363 (71.3)	0.626
Age, >60 years	20 (12.9)	51 (31.3)	<0.001	20 (12.9)	75 (14.7)	0.569	51 (31.3)	75 (14.7)	<0.001
B symptoms	69 (44.5)	43 (26.4)	0.001	69 (44.5)	240 (47.2)	0.565	43 (26.4)	240 (47.2)	<0.001
Elevated LDH	59 (38.1)	58 (35.6)	0.646	59 (38.1)	220 (43.2)	0.255	58 (35.6)	220 (43.2)	0.085
ECOG ≥2	12 (7.7)	8 (4.9)	0.298	12 (7.7)	30 (5.9)	0.408	8 (4.9)	30 (5.9)	0.635
UADT	155 (100)	163 (100)	1.000	155 (100)	506 (99.4)	1.000	163 (100)	506 (99.4)	1.000
Stage II	40 (25.8)	42 (25.8)	0.994	40 (25.8)	183 (36.0)	0.019	42 (25.8)	183 (36.0)	0.016
PTI	114 (73.5)	100 (61.3)	0.020	114 (73.5)	371 (72.9)	0.871	100 (61.3)	371 (72.9)	0.005
After match									
Total	119	119		151	151		140	140	
Gender, male	86 (72.3)	80 (67.2)	0.397	109 (72.2)	114 (75.5)	0.943	98 (70.0)	98 (70.0)	1.000

Age, >60 years	18 (15.1)	18 (15.1)	1.000	18 (11.9)	18 (11.9)	0.569	30 (21.4)	27 (19.3)	0.656
B symptoms	48 (40.3)	31 (26.1)	0.019	66 (43.7)	66 (43.7)	0.565	40 (28.6)	37 (26.4)	0.688
Elevated LDH	43 (36.1)	43 (36.1)	1.000	55 (36.4)	57 (36.4)	0.255	52 (37.1)	52 (37.1)	1.000
ECOG ≥2	5 (4.2)	5 (4.2)	1.000	8 (5.3)	8 (5.3)	0.408	4 (2.9)	4 (2.9)	1.000
UADT	119 (100)	119 (100)	1.000	151 (100)	151 (100)	1.000	140 (100)	140 (100)	1.000
Stage II	28 (23.5)	28 (23.5)	1.000	39 (25.5)	39 (25.5)	0.019	40 (28.6)	40 (28.6)	1.000
PTI	84 (70.6)	84 (70.6)	1.000	111 (73.5)	111 (73.5)	0.871	99 (70.7)	99 (70.7)	1.000

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; RT, radiotherapy; CT, chemotherapy; RT + CT, radiotherapy followed by chemotherapy; CT + RT, chemotherapy followed by radiotherapy; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; UADT, upper aerodigestive tract; PTI, primary tumor invasion.

Table 5. Clinical characteristics of patients with early-stage NKTCL stratified by treatment and chemotherapy regimen.

	CT alone			CT + RT			RT + CT		
	New regimens	Old regimens		New regimens	Old regimens		New regimens	Old regimens	
	No. (%)	No. (%)	*P*	No. (%)	No. (%)	*P*	No. (%)	No. (%)	*P*
Total	39	131		118	523		37	172	
Gender, male	32 (82.1)	89 (67.9)	0.088	82 (69.5)	366 (70.0)	0.917	22 (59.5)	122 (70.9)	0.172
Age, >60 years	9 (23.1)	19 (14.5)	0.205	15 (12.7)	60 (11.5)	0.705	3 (8.1)	17 (9.9)	1.000
B symptoms	21 (53.8)	59 (45.0)	0.333	53 (44.9)	231 (44.2)	0.883	21 (56.8)	62 (36.0)	0.020
Elevated LDH	16 (41.0)	50 (38.2)	0.748	35 (29.7)	185 (35.4)	0.238	13 (35.1)	46 (26.7)	0.304
ECOG ≥2	5 (12.8)	16 (12.2)	1.000	4 (3.4)	26 (5.0)	0.463	1 (2.7)	11 (6.4)	0.697
UADT	1 (2.6)	6 (4.6)	1.000	1 (0.8)	4 (0.8)	1.000	37 (100)	172 (100)	1.000
Stage II	15 (38.5)	46 (35.7)	0.702	35 (29.7)	148 (28.3)	0.767	13 (35.1)	27 (15.7)	0.006
PTI	17 (43.6)	87 (66.4)	0.010	61 (51.7)	310 (59.3)	0.132	27 (73.0)	87 (50.6)	0.013

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; CT, chemotherapy; RT, radiotherapy; CT + RT, chemotherapy followed by radiotherapy; RT + CT, radiotherapy followed by chemotherapy; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; UADT, upper aerodigestive tract; PTI, primary tumor invasion.

Figure Legends

Figure 1. Overall survival (OS) and progression-free survival (PFS) for all patients with early-stage NKTCL (A), and OS (B) and PFS (C) for patients with early-stage NKTCL stratified into the low-risk and high-risk groups.

Figure 2. Overall survival (OS, A) and progression-free survival (PFS, B) for patients with early-stage NKTCL after chemotherapy (CT) alone, radiotherapy (RT) alone, and RT with or without CT (RT w/o RT) before match stratification; OS (C) and PFS (D) after RT alone and CT alone after match stratification; and OS (E) and PFS (F) after RT with or without CT and CT alone after match stratification.

Figure 3. Overall survival (OS, A) and progression-free survival (PFS, B) for low-risk patients with early-stage NKTCL stratified by radiotherapy (RT) alone, RT followed by chemotherapy (RT + CT), and CT followed by RT (CT + RT).

Figure 4. Overall survival (OS) for high-risk patients with early-stage NKTCL after radiotherapy (RT) followed by chemotherapy (RT + CT) or RT alone before (A) and after match (B) stratification; OS after RT + CT and CT followed by RT (CT + RT) before (C) and after (D) match stratification; and OS after RT alone and CT + RT before (E) and after (F) match stratification.

Figure 5. Overall survival (OS) for patients with early-stage NKTCL receiving chemotherapy (CT) alone (A) or radiotherapy (RT) followed by CT (RT + CT, B) stratified by the new or old regimens before match stratification. OS for patients with early-stage NKTCL who received CT followed by RT (CT + RT) stratified by the new or old regimens before (C) and after match (D) stratification. RMST, restricted mean survival time.

Figure 1

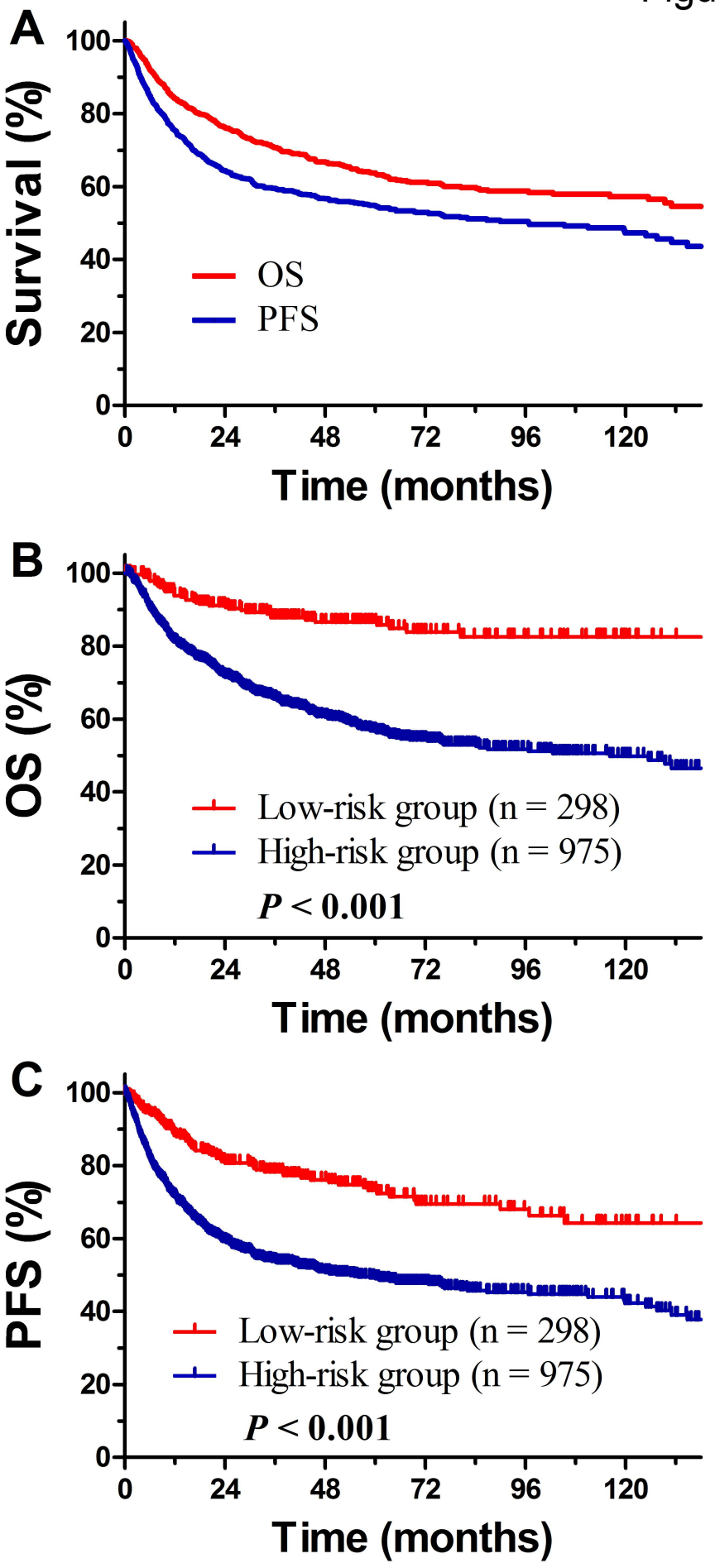

A
Survival (%)
100
80
60
40
20
0
OS
PFS
0
24
48
72
96
120
Time (months)
B
OS (%)
Low-risk group (n = 298)
High-risk group (n = 975)
P < 0.001
Time (months)
C
PFS (%)
Low-risk group (n = 298)
High-risk group (n = 975)
P < 0.001
Time (months)

Figure 2

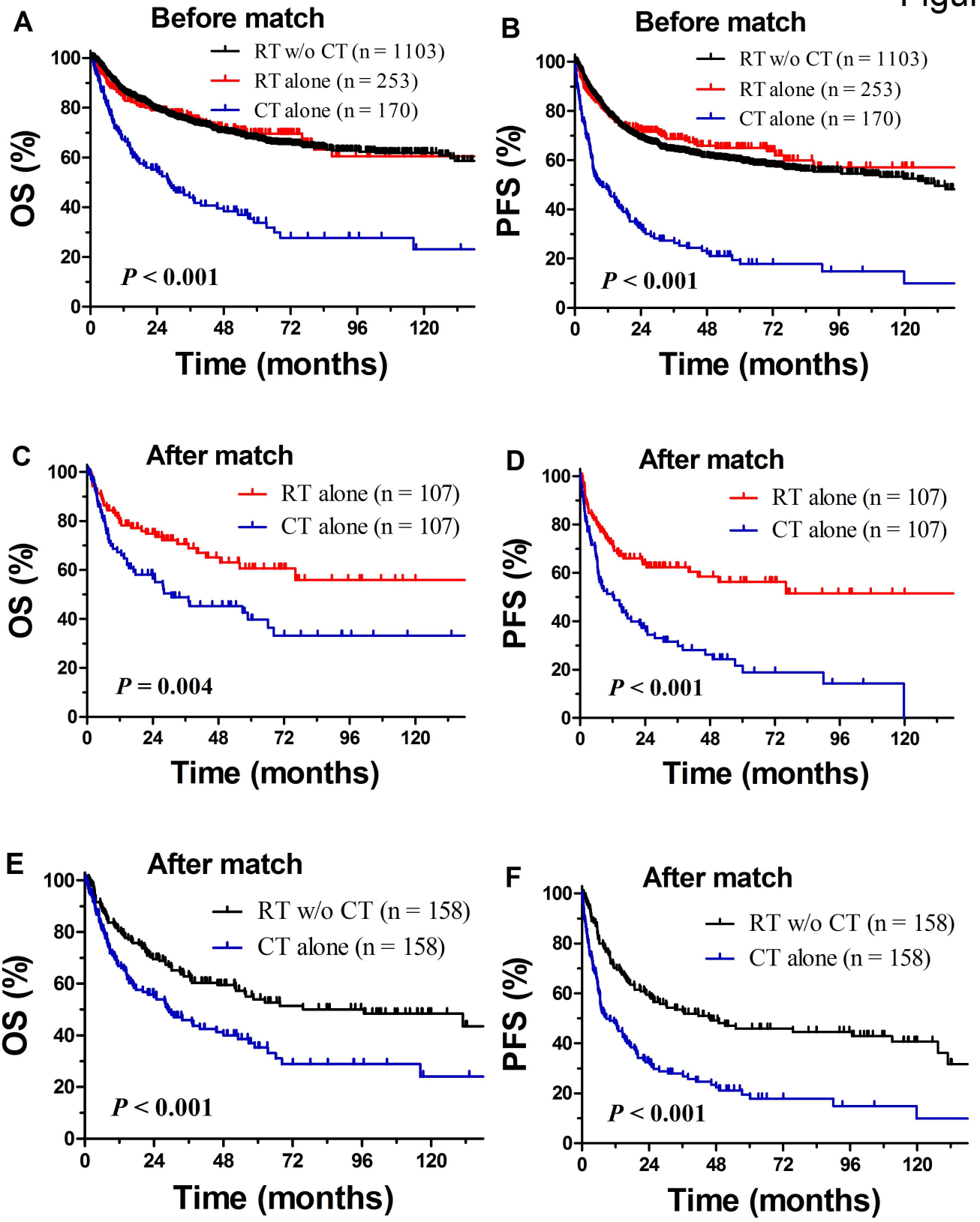

A
Before match
RT w/o CT (n = 1103)
RT alone (n = 253)
CT alone (n = 170)
OS (%)
P < 0.001
Time (months)
B
Before match
RT w/o CT (n = 1103)
RT alone (n = 253)
CT alone (n = 170)
PFS (%)
P < 0.001
Time (months)
C
After match
RT alone (n = 107)
CT alone (n = 107)
OS (%)
P = 0.004
Time (months)
D
After match
RT alone (n = 107)
CT alone (n = 107)
PFS (%)
P < 0.001
Time (months)
E
After match
RT w/o CT (n = 158)
CT alone (n = 158)
OS (%)
P < 0.001
Time (months)
F
After match
RT w/o CT (n = 158)
CT alone (n = 158)
PFS (%)
P < 0.001
Time (months)

Figure 3

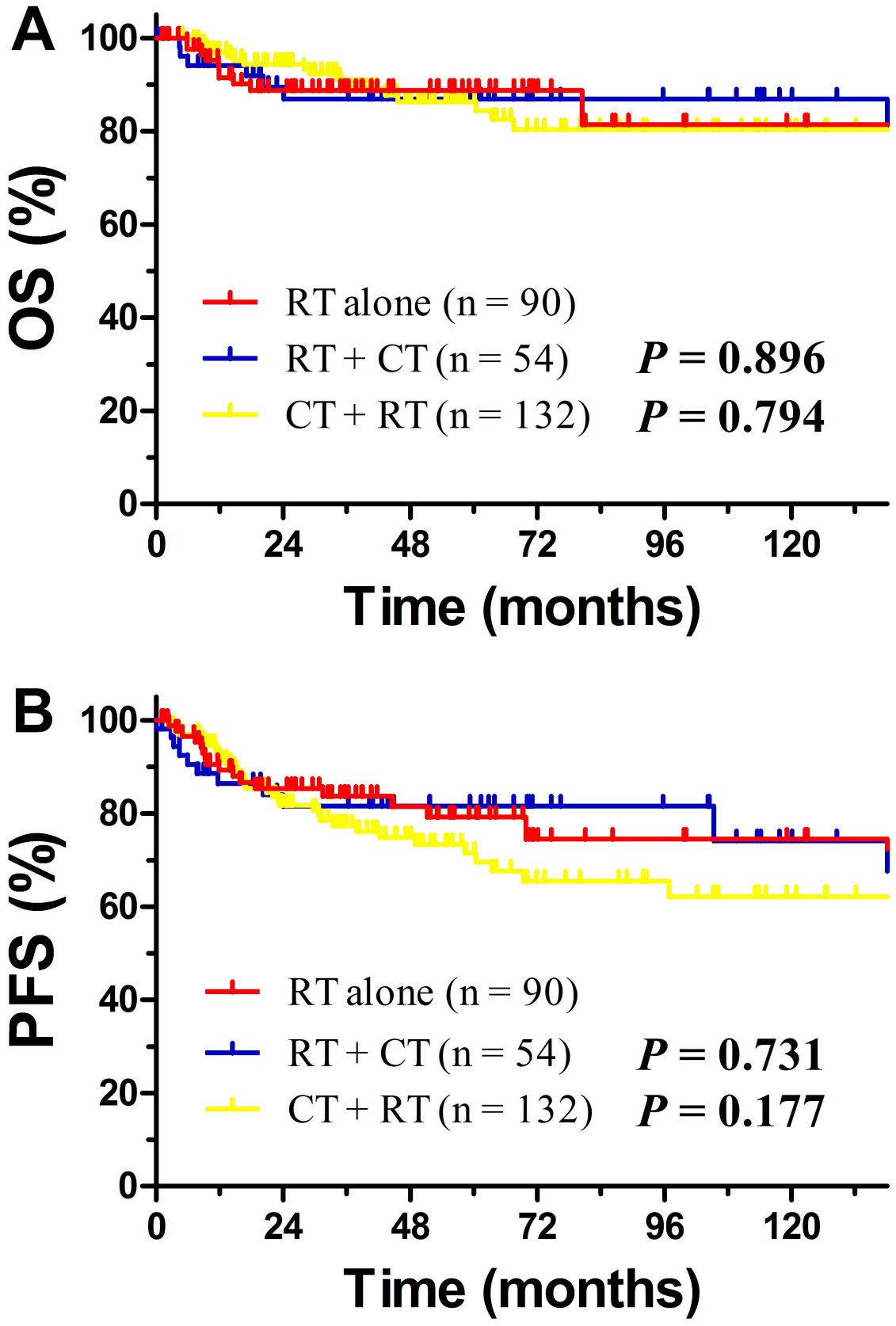

A
OS (%)
100
80
60
40
20
0
0
24
48
72
96
120
Time (months)
RT alone (n = 90)
RT + CT (n = 54)
CT + RT (n = 132)
P = 0.896
P = 0.794
B
PFS (%)
100
80
60
40
20
0
0
24
48
72
96
120
Time (months)
RT alone (n = 90)
RT + CT (n = 54)
CT + RT (n = 132)
P = 0.731
P = 0.177

Figure 4

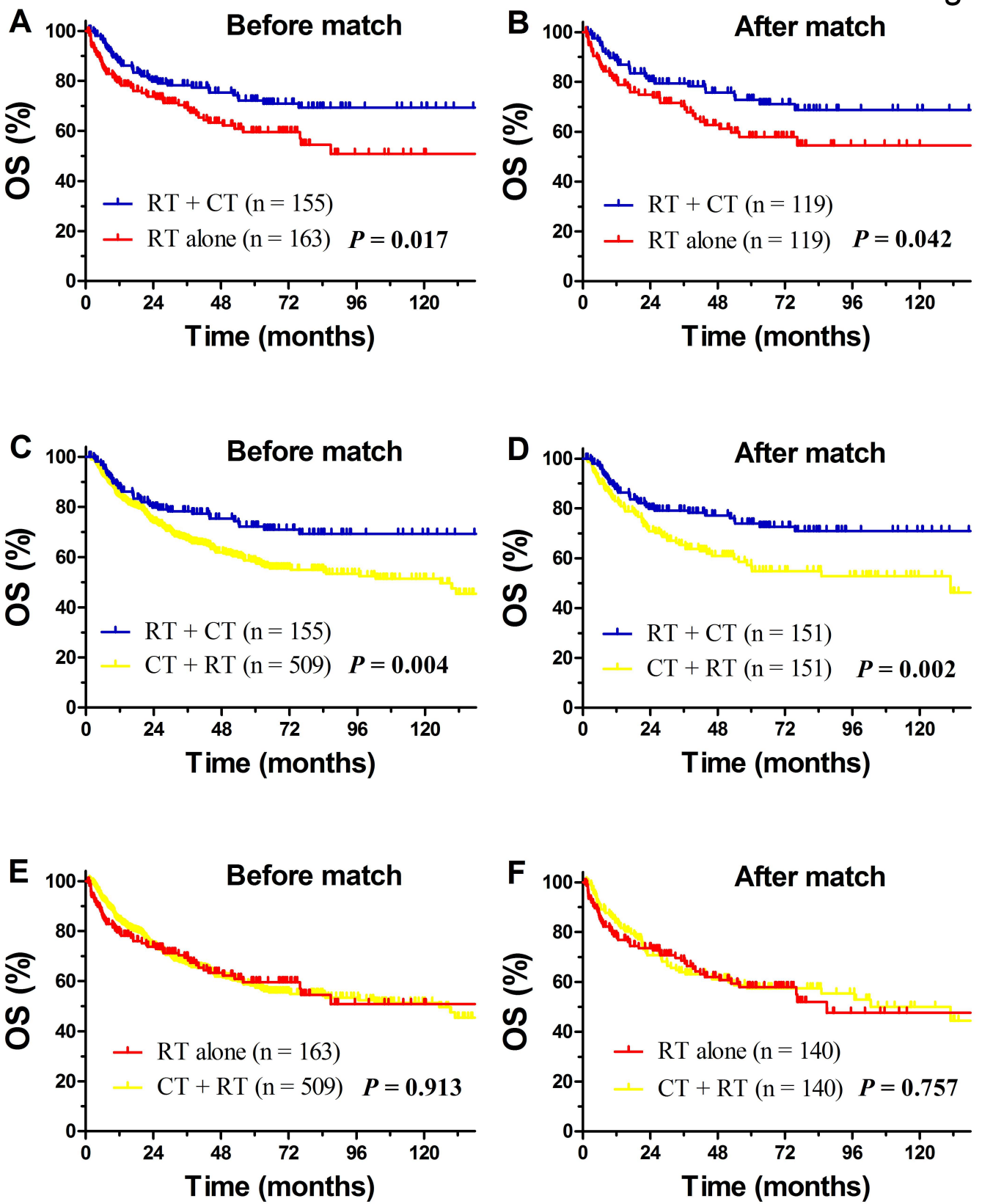
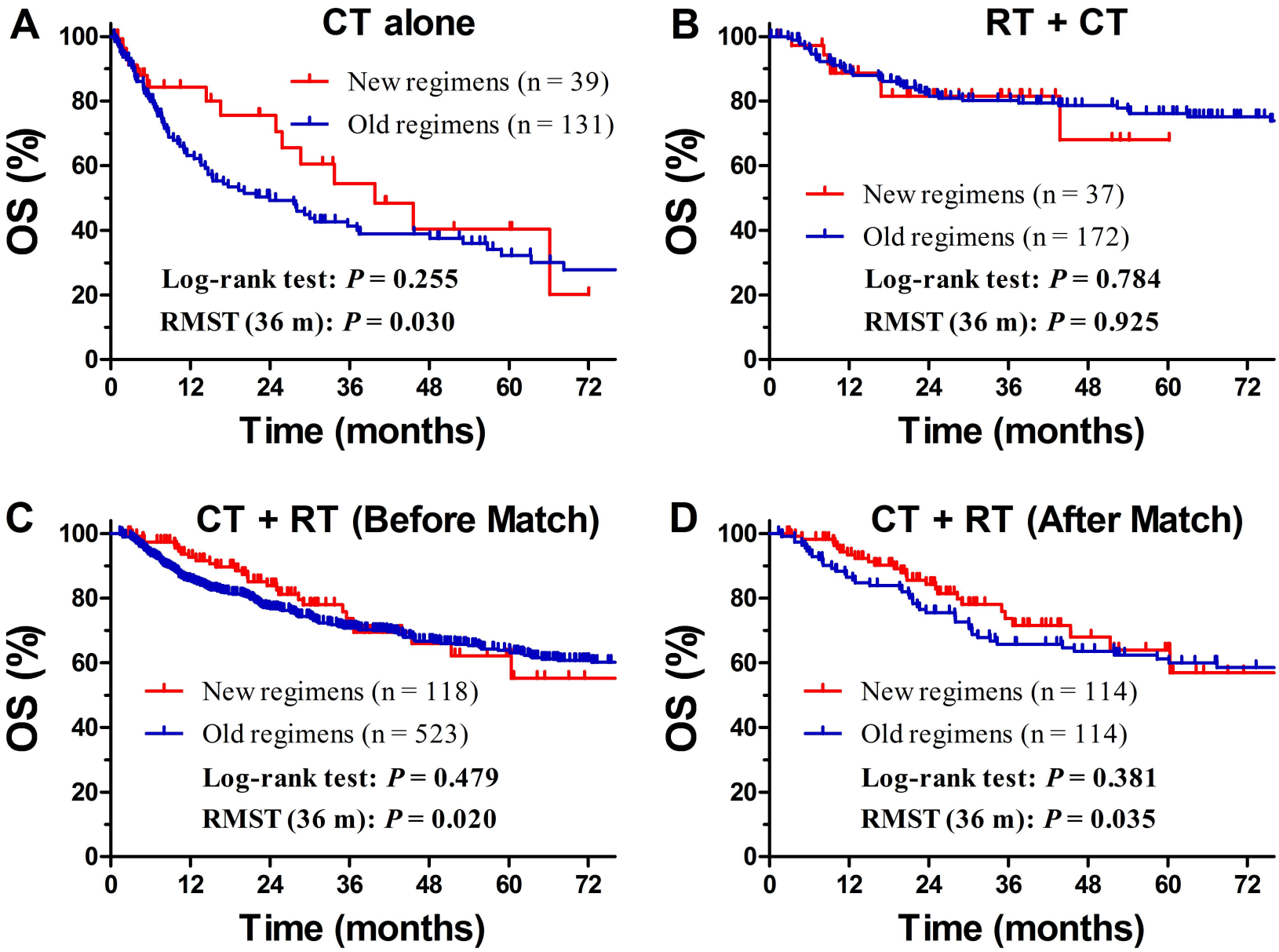

A
Before match
OS (%)
RT + CT (n = 155)
RT alone (n = 163) P = 0.017
Time (months)
B
After match
OS (%)
RT + CT (n = 119)
RT alone (n = 119) P = 0.042
Time (months)
C
Before match
OS (%)
RT + CT (n = 155)
CT + RT (n = 509) P = 0.004
Time (months)
D
After match
OS (%)
RT + CT (n = 151)
CT + RT (n = 151) P = 0.002
Time (months)
E
Before match
OS (%)
RT alone (n = 163)
CT + RT (n = 509) P = 0.913
Time (months)
F
After match
OS (%)
RT alone (n = 140)
CT + RT (n = 140) P = 0.757
Time (months)

Figure 5


A
CT alone
New regimens (n = 39)
Old regimens (n = 131)
Log-rank test: P = 0.255
RMST (36 m): P = 0.030
OS (%)
Time (months)
B
RT + CT
New regimens (n = 37)
Old regimens (n = 172)
Log-rank test: P = 0.784
RMST (36 m): P = 0.925
OS (%)
Time (months)
C
CT + RT (Before Match)
New regimens (n = 118)
Old regimens (n = 523)
Log-rank test: P = 0.479
RMST (36 m): P = 0.020
OS (%)
Time (months)
D
CT + RT (After Match)
New regimens (n = 114)
Old regimens (n = 114)
Log-rank test: P = 0.381
RMST (36 m): P = 0.035
OS (%)
Time (months)

blood

Prepublished online June 24, 2015;
doi:10.1182/blood-2015-04-639336

Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: a comprehensive analysis from a multicenter study

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.