ARTICLE - Non-Hodgkin Lymphoma

Evidence of cure for extranodal nasal-type natural killer/T-cell lymphoma with current treatment: an analysis of the CLCG database

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Supplementary data

Methods

Definitions of primary site and primary tumor invasion

Primary site is defined according to primary symptoms and radiologic findings. As described in detail in our previous study,[1] primary disease can be classified by the anatomic site of origin, including the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, trachea, oral cavity (gingiva, buccal mucosa, mouth floor) and, more rarely, skin and soft tissues, stomach, small intestine, colon, lung, testis, central nervous system, orbit, or other sites. Accordingly, ENKTCL can be further divided into three distinct clinical subgroups: (i) nasal, (ii) non-nasal-UADT ((i) and (ii) combined are represented as the upper aerodigestive tract [UADT]), and (iii) extra-UADT. Nasal ENKTCL refers to lesions in the nasal cavity and paranasal sinuses. Non-nasal-UADT ENKTCL refers to lesions in the nasopharynx, oropharynx (tonsil, base of tongue, oropharyngeal wall), hypopharynx, oral cavity, larynx, and trachea. Extra-UADT ENKTCL (often termed as “non-nasal” or “extranasal” in the literature) is rare, most commonly reported in cutaneous and soft tissues, gastrointestinal tract, testis, lung, central nervous system, and orbit. In patients with localized disease, it is usually easy to define primary site. In patients with disseminated disease, primary site is usually defined as the extranodal site (e.g., UADT, cutaneous and soft tissues, gastrointestinal tract, testis, lung, central nervous system, orbit, or other sites) according to the first or major clinical symptoms/presentations.[1] If the UADT was involved, patients were designated as nasal or non-nasal UADT ENKTCL (UADT ENKTCL), irrespective of whether other extranodal organs were involved.[2]

Primary tumor invasion (PTI) is defined as the growth of the primary tumor beyond the boundary

of the original extranodal site into a neighboring structure or tissue or as contiguous multisite involvement, regardless of stage.[1] Accordingly, PTI for nasal origin was defined as nasal disease extending to any of the following structures: maxillary sinus, ethmoid sinus, sphenoid sinus, facial skin, orbit, nasopharynx, hard palate or oral cavity. PTI for extra-nasal UADT origin was defined as involvement of multiple sites (nasopharynx, oropharynx, tonsil, tongue base, oral cavity, or larynx) or adjacent structures or tissues (such as the nasal cavity). PTI of extra-UADT origin was defined as primary disease directly extended to adjacent structures or tissues (such as gastric or intestinal lesions to adjacent organs; skin and soft tissue lesions to neurovascular structure or bone; testicular lesions to skin).

Treatment

A total of 1593 patients received chemotherapy. The chemotherapy regimens were summarized in Supplementary Table 1. Of them, 1296 (81.4%) patients received asparaginase-based regimens. The most commonly used asparaginase-based regimens were CHOP/CHOP-like plus ASP (cyclophosphamide, doxorubicin, vincristine, prednisolone, and L-asparaginase or pegaspargase), followed by PGEMOX (pegaspargase plus gemcitabine and oxaliplatin), GELOX (L-asparaginase plus gemcitabine and oxaliplatin) and LVP (L-asparaginase, vincristine, and prednisolone) regimens. The remaining 297 (18.6%) patients received other non-anthracycline-based regimens, mainly with GDP (gemcitabine, dexamethasone, cisplatin) and DICE (etoposide, cyclophosphamide, cisplatin, dexamethasone) regimens.

Radiotherapy was given according to the principles of involved-site radiation therapy (ISRT) with the primary tumor and adjacent sites encompassed.[1] The median RT dose was 50 Gy.

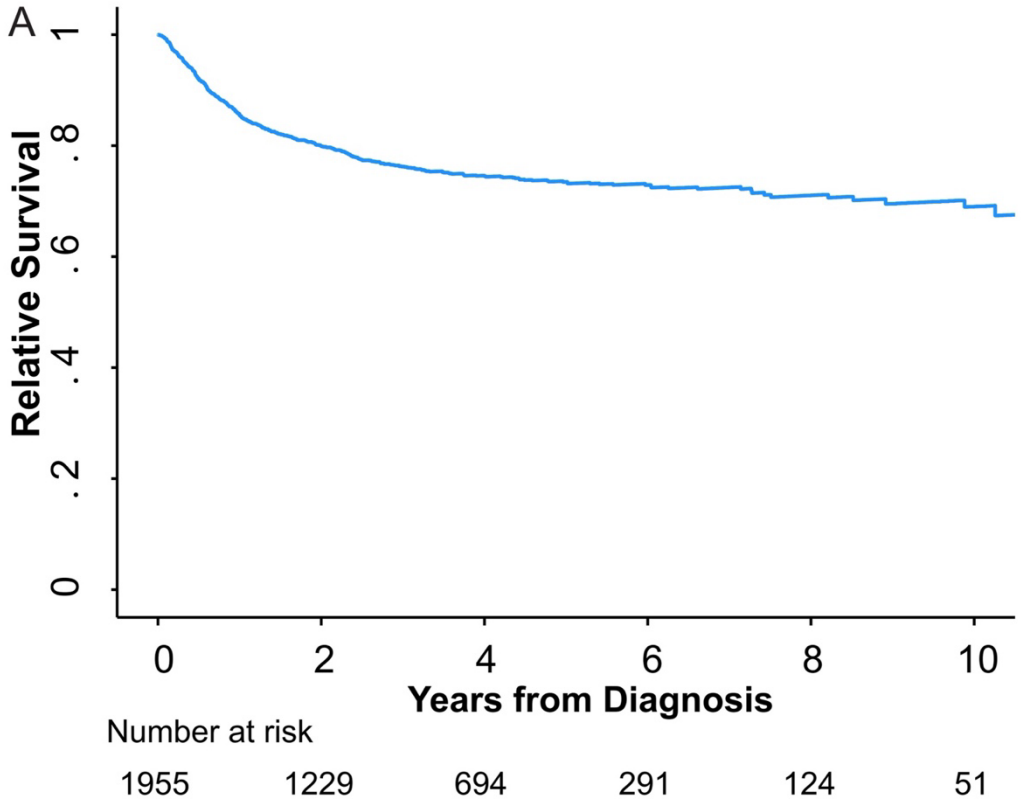
Statistical Methods

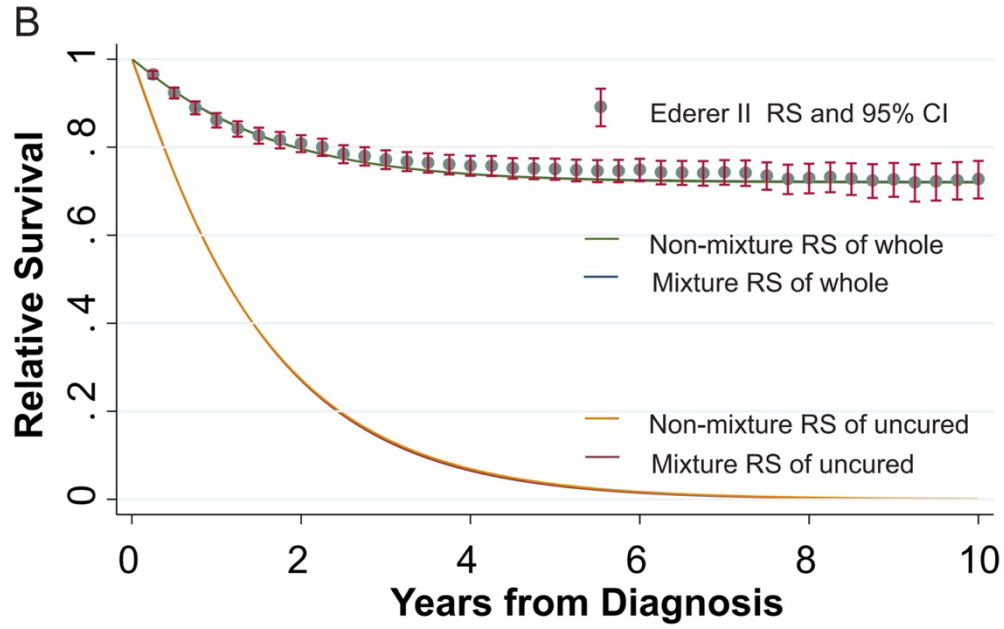
Outcome measure

The population mortality files by age and calendar year for male (Supplementary Table 2) and female (Supplementary Table 3) in China were used to calculate the expected survival in an age-, sex-, and calendar year–matched general Chinese population.

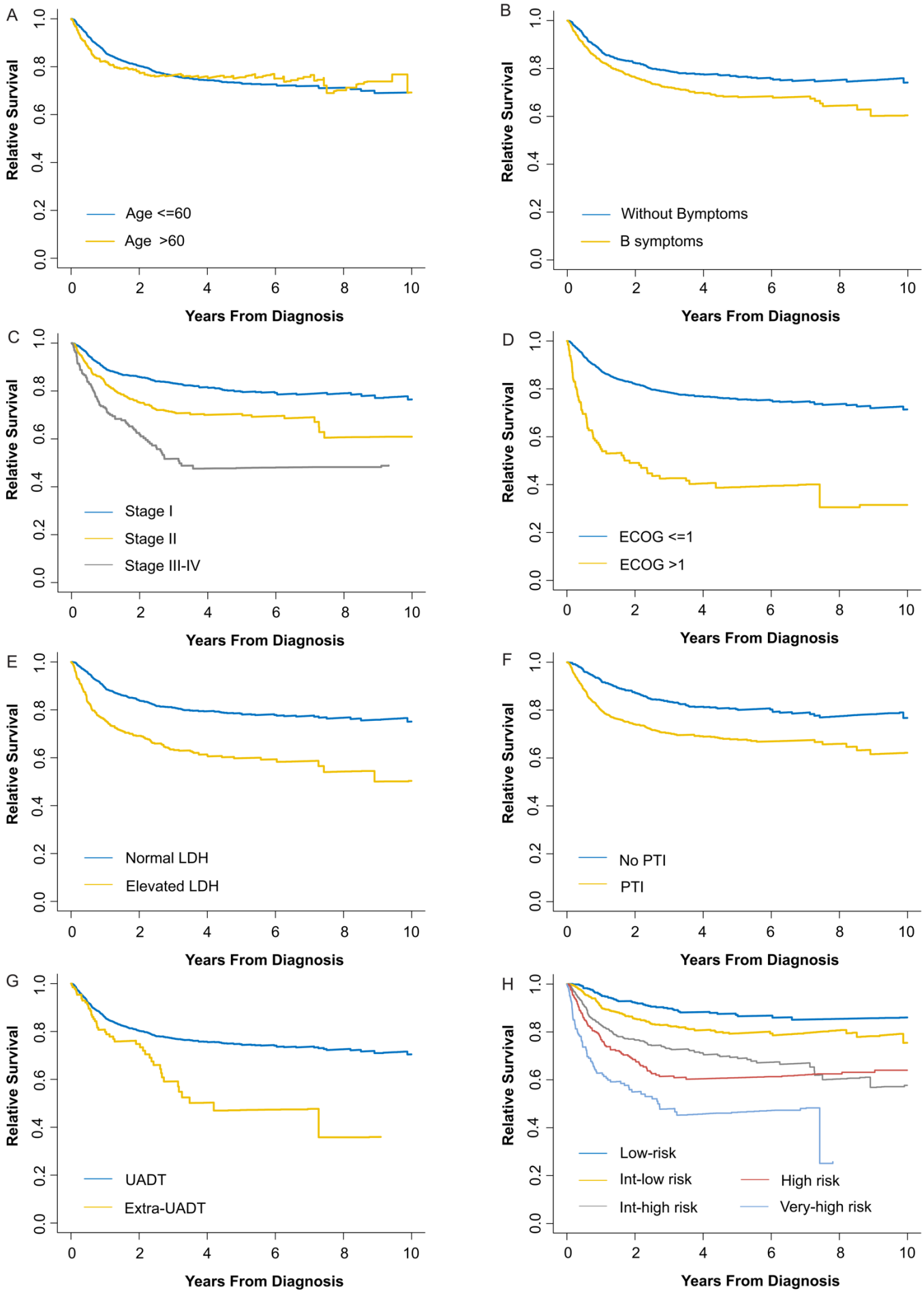
Cure model

For sensitivity analysis, we fitted mixture and non-mixture cure models. Both models showed good fit on visual examination and gave reasonable estimates of cure fractions, as shown by the closeness of estimated cure fractions to the plateau level of the Ederer II RS curve (Supplementary Fig. 1); however, the non-mixture cure model had a slightly lower Akaike information criterion (Supplementary Table 4).[3] Time to cure was defined as the time between diagnosis and the moment at which excess mortality reaches zero, i.e. the population is considered statistically cured.[4] As Chauvenet et al. proposed, time-to-cure can be estimated as the time at which “almost” all uncured patients would have died.[5] In this study, we estimated cure time as the time at which 95% of the “uncured" patients would have died. This threshold of 95% was considered clinically relevant. Thus, among all the patients who were expected to die from cancer, cure occurred at the moment when 95 patients of 100 had died. From that time, excess mortality attributed to ENKTCL becomes statistically negligible. We restricted follow-up to 10 years, because the number of at-risk patients beyond 10 years was limited, and their inclusion might have led to unreliable estimates.

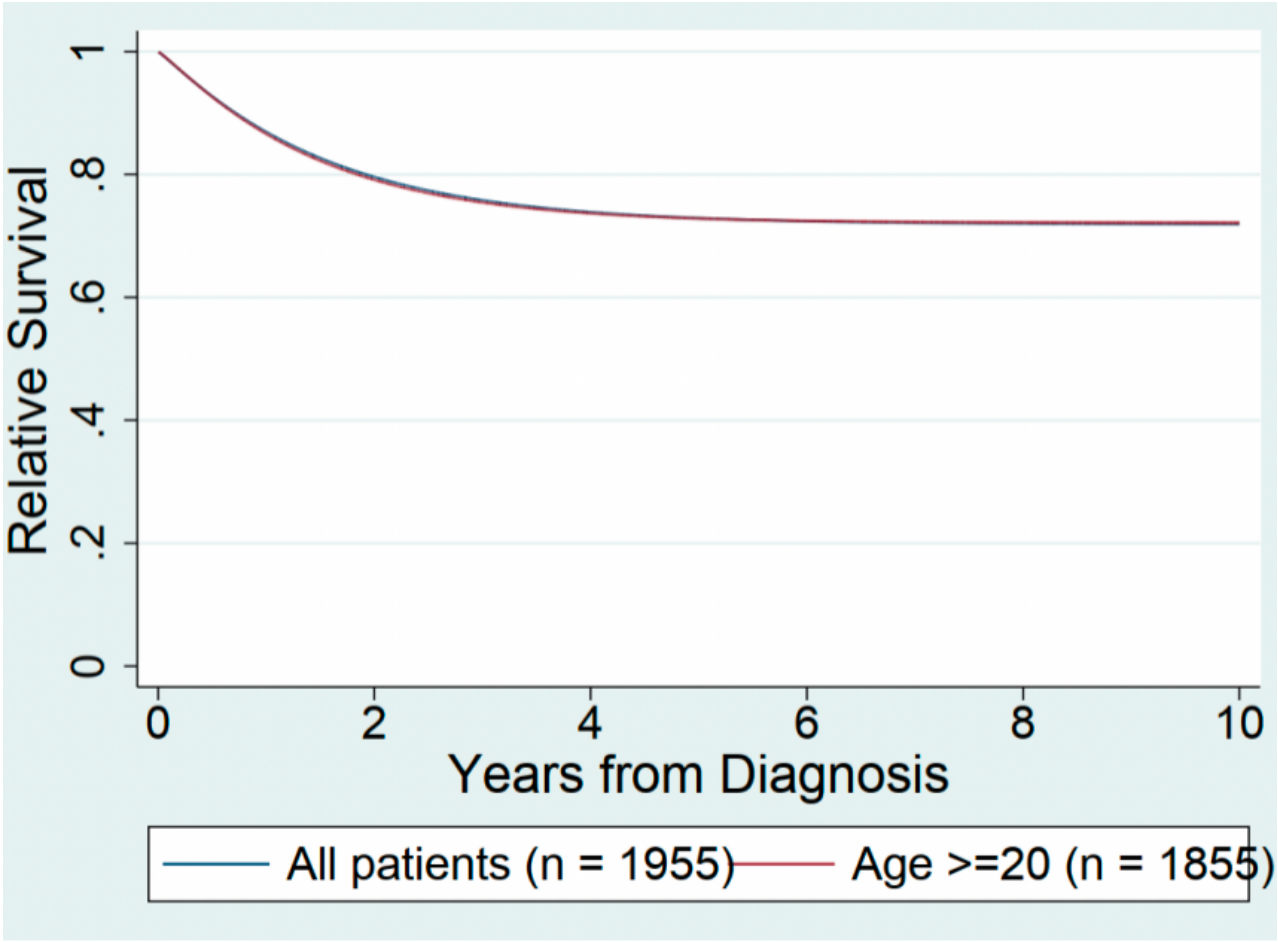




Supplementary Figure 1



Supplementary Figure 2



Supplementary Fig. 3

Figure legends

Supplementary Fig. 1. **RS and model fit of non-mixture and mixture cure model**. (A) RS estimated using the Ederer II method. (B) Model fit of non-mixture and mixture cure model. Figure 1B shows the Ederer II estimates of RS with 95% confidence intervals, predicted RS curves of the whole cohort from the non-mixture cure model (green line) and mixture cure model (blue line), and predicted RS curves of the uncured patients from the non-mixture cure model (orange line) and mixture cure model (red line). Compared with the Ederer II RS estimates, the predicted RS curves from non-mixture and mixture models fit well and almost overlap. RS, relative survival.

Supplementary Fig. 2. **RS curves by prognostic factors**. RS curves stratified by age (A), B symptoms (B), stage (C), ECOG score (D), LDH (E), PTI (F), primary UADT disease site (G), and NRI-defined risk group (H). RS, relative survival; ECOG, Eastern Cooperative Oncology Group; PTI, primary tumor invasion; LDH, lactate dehydrogenase; UADT, upper aerodigestive tract; NRI, nomogram-revised risk index. Int-low, intermediate-low; Int-high, intermediate-high.

Supplementary Fig. 3. **Sensitivity analysis to assess the potential influence of different eligibility criteria.** Predicted relative survival curves of the whole cohort of patients with ENKTCL (n = 1955, bule line) and the cohort that excluded patients younger than 20 years old (n = 1855, red line). As is shown, the relative survival curves for the two cohorts almost overlap.

Supplementary Table 1. Summary of non-anthracycline-based regimen chemotherapy in 1593 patients who received chemotherapy

Regimens	No. (%)	Definition and agents
Asparaginase-based regimens	**1296 (81.4)**	
CHOP/CHOP-like plus ASP	425 (26.7)	Cyclophosphamide, doxorubicin, vincristine, prednisolone, L-asparaginase or pegaspargase
PGEMOX	170 (10.7)	Pegaspargase, gemcitabine, oxaliplatin
GELOX	157 (9.9)	Gemcitabine, oxaliplatin, L-asparaginase
LVP (LOD)	153 (9.6)	L-asparaginase, vincristine, prednisone
GDPL	60 (3.8)	Gemcitabine, dexamethasone, cisplatin, L-asparaginase
Gem + ASP	53 (3.3)	Gemcitabine, pegaspargase
GAD-M	49 (3.1)	Gemcitabine, pegaspargase, dexamethasone, methotrexate
SMILE	29 (1.8)	L-asparaginase, ifosfamide, methotrexate, etoposide, dexamethasone
AspaMetDex	29 (1.8)	L-asparaginase, methotrexate, dexamethasone
SVILE	28 (1.8)	Ifosfamide, dexamethasone, pegaspargase, vindesine, and etoposide
DDGP	24 (1.5)	Dexamethasone, cisplatin, gemcitabine, and pegaspargase
MESA	22 (1.4)	Methotrexate, etoposide, dexamethasone, pegaspargase
IPGDP	21 (1.3)	Ifosfamide, pegaspargase, gemcitabine, dexamethasone, cisplatin
VIDL	15 (0.9)	Etoposide, ifosfamide, dexamethasone, L-asparaginase
Asp alone	9 (0.6)	L-asparaginase or pegaspargase
VDLP	7 (0.4)	Vincristine, daunorubicin, L-asparaginase, prednisolone
GDLE	4 (0.3)	Gemcitabine, dexamethasone, L-asparaginase, etoposide
DICE-L	3 (0.2)	Etoposide, cyclophosphamide, cisplatin, dexamethasone, L-asparaginase
IMEP-L	1 (0.1)	Ifosfamide, methotrexate, etoposide, prednisolone, L-asparaginase
ASP-other	37 (2.3)	Asparaginase with other combination of cytotoxic drugs
PLA/Gem/Other regimens	**297 (18.6)**	
GDP	98 (6.2)	Gemcitabine, dexamethasone, cisplatin
DICE	57 (3.6)	Etoposide, cyclophosphamide, cisplatin, dexamethasone
ATT	49 (3.1)	Three regimens combination with ASHAP (doxorubicin, cisplatin, ara-C, solu-medrol), m-BACOS (methotrexate, leucovorin, doxorubicin, oncovin, bleomycin, cytoxan, solu-medrol), and MINE (mesna, ifosfamide, novantrone, etoposide)
VIDP	17 (1.1)	Etoposide, ifosfamide, cisplatin, and dexamethasone
GEMOX	15 (0.9)	Gemcitabine, oxaliplatin
GP	7 (0.4)	Gemcitabine, cisplatin
DIMG	7 (0.4)	Dexamethasone, ifosfamide, methotrexate, gemcitabine
DEVIC	4 (0.3)	Dexamethasone, etoposide, ifosfamide, carboplatin
IMEP	2 (0.1)	Ifosfamide, methotrexate, etoposide, prednisolone
Other	41 (2.6)	Other combination of cytotoxic drugs without asparaginase

Abbreviations: ASP, asparaginase (L-asparaginase or pegaspargase); GEM, gemcitabine; MTX, methotrexate; PLA, platinum.

Supplementary Table 2. Mortality by age and calendar year for male in China (uploaded as a separated file).

Supplementary Table 3. Mortality by age and calendar year for female in China (uploaded as a separated file).

Supplementary Table 4. The exploratory model fit analyses of mixture and non-mixture cure model with Weibull distribution for ENKTCL

	Mixture Weibull	Non-mixture Weibull
Cure fraction (%, 95% CI)	72.1 (69.5-74.6)	71.9 (69.3-74.5)
Median survival time of uncured	1.10 (0.96-1.26)	1.10 (0.96-1.26)
Survival time of 95% probability of cure	2.99 (2.43-3.69)	3.04 (2.46-3.78)
Survival time of 90% probability of cure	1.92 (1.56-2.37)	1.94 (1.56-2.42)
Time to cure (95%)	4.38 (3.61-5.31)	4.48 (3.66-5.49)
Time to cure (90%)	3.42 (2.86-4.09)	3.48 (2.89-4.19)
AIC	3216.88	3214.31
BIC	3233.62	3231.05
Probability of cure given survival of 5 year	98.8 (97.3-99.5)	98.7 (97.1-99.4)

ENKTCL, extranodal nasal-type NK/T-cell lymphoma; CI, confidence interval; AIC, Akaike information criterion; BIC, Bayesian information criterion. Time to cure (95%) was estimated as the time at which 95% of the “uncured" patients would have died. Time to cure (90%) was estimated as the time at which 90% of the “uncured" patients would have died.

Supplementary Table 5. Median survival time of uncured patients and time to cure by clinical characteristics and risk stratification for extranodal nasal-type NK/T-cell lymphoma

Variable	n (%)	Median survival time of uncured patients, years (95% CI)	Time to cure, years (95% CI)
Sex			
Male	1381 (70.6)	1.08 (0.91-1.27)	4.44 (3.49-5.64)
Female	574 (29.4)	1.16 (0.93-1.45)	4.22 (3.12-5.71)
Stage			
I	1123 (57.4)	1.32 (1.07-1.63)	5.08 (3.75-6.88)
II	599 (30.6)	0.97 (78.3-1.19)	3.65 (2.65-5.02)
III-IV	233 (11.9)	1.01 (0.73-1.40)	4.60 (2.77-7.63)
Elevated LDH			
No	1422 (72.7)	1.23 (1.06-1.42)	3.98 (3.24-4.87)
Yes	533 (27.3)	0.89 (0.70-1.13)	4.49 (3.22-6.27)
Age			
≤60	1667 (85.3)	1.17 (1.02-1.33)	4.34 (3.63-5.33)
>60	288 (14.7)	0.58 (0.39-0.86)	2.36 (1.29-4.34)
B symptoms			
No	1184 (60.6)	1.12 (0.94-1.33)	4.09 (3.19-5.25)
Yes	771 (39.4)	1.08 (0.86-1.35)	4.95 (3.51-6.99)
ECOG score			
0-1	1827 (93.5)	1.21 (1.05-1.39)	4.44 (3.64-5.42)
≥2	128 (6.5)	0.58 (0.41-0.81)	2.87 (1.88-4.39)
PTI			
No	868 (44.4)	1.62 (1.30-2.02)	5.19 (3.80-7.10)
Yes	1087 (55.6)	0.88 (0.76-1.02)	3.62 (2.95-4.45)
Primary site			
UADT	1829 (93.6)	1.05 (0.92-1.21)	4.12 (3.40-4.98)
Extra-UADT	126 (6.4)	2.13 (1.07-4.24)	9.11 (3.38-24.6)
NRI			
Low risk	438 (22.4)	1.63 (1.17-2.27)	4.45 (2.78-7.13)
Int-low risk	564 (28.8)	1.43 (1.13-1.82)	4.89 (3.16-6.38)
Int-high risk	517 (26.4)	1.23 (0.91-1.66)	5.57 (3.59-8.62)
High risk	277 (14.2)	0.84 (0.67-1.06)	2.95 (2.21-3.95)
Very high risk	159 (8.1)	0.61 (0.43-0.88)	3.34 (1.95-5.73)

ECOG, Eastern Cooperative Oncology Group; Int, intermediate; LDH, lactate dehydrogenase; NRI, nomogram-revised risk index; UADT, upper aerodigestive tract; PTI, primary tumor invasion. Int-low, intermediate-low; Int-high, intermediate-high. Time to cure was estimated as the time at which 95% of the “uncured" patients would have died.

References

1. Qi SN, Li YX, Specht L, et al: Modern radiation therapy for extranodal nasal-type NK/T-cell lymphoma: risk-adapted therapy, target volume, and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2021;110(4):1064-1081.
2. Kim SJ, Yoon DH, Jaccard A, et al: A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol. 2016; 17(3):389-400.
3. Lambert PC: Modeling of the cure fraction in survival studies. Stata J. 2007; 7(3):351-375.
4. Lambert PC, Thompson JR, Weston CL, et al: Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics. 2007; 8(3):576-594.
5. Chauvenet M, Lepage C, Jooste V, Cottet V, Faivre J, Bouvier AM: Prevalence of patients with colorectal cancer requiring follow-up or active treatment. Eur J Cancer. 2009; 45(8):1460-1465.