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Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project

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Summary

Background Extranodal natural killer (NK) T-cell lymphoma (ENKTL) is a unique clinicopathological entity, typically associated with poor survival outcomes. Most published data have come from east Asian study groups, with little information available from international cohorts. The effects of treatment advances on routine clinical practice across continental territories has not been clear. We aimed to improve understanding of the clinical characteristics and outcomes of patients with ENKTL.

Methods We did a substudy of patients with ENKTL from the T-cell Project, a global prospective cohort study. The T-cell Project registered consecutively diagnosed adults (>18 years) with newly diagnosed, untreated mature T-cell or NK lymphomas (WHO 2001 or 2008 classifications) from 74 centres in 13 countries (in Asia, Europe, North America, and South America). In total, 1695 patients with mature T-cell or NK lymphomas were enrolled between Oct 12, 2006 and Feb 28, 2018 in the T-cell Project. The first patient with ENKTL was enrolled on Feb 15, 2007, and the last on May 26, 2017. Data on baseline characteristics, first-line treatment, treatment response, and survival outcomes were recorded in a central database (locked March 30, 2019). The primary outcome was 5-year overall survival. The T-cell Project is registered on ClinicalTrials.gov, NCT01142674.

Findings 166 patients were diagnosed with ENKTL, comprising 11% of 1553 eligible registered cases and distributed across 40 participating centres in four continents. At a median follow-up of 44 months (IQR 20–61), overall survival at 5 years was 54% (95% CI 44–63) in patients with nasal disease (n=98) and 34% (27–46) in patients with extranasal disease (n=68).

Interpretation To our knowledge, this study presents the largest international cohort of patients with ENKTL. We describe a clinically significant improvement in the survival of patients with ENKTL treated in routine clinical practice over the past decade, likely to be attributable to the increasing use of treatment protocols specific for ENKTL.

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Introduction

Extranodal natural killer (NK) T-cell lymphoma (ENKTL) is a unique clinicopathological entity, formally incorporated into the WHO classification of hematopoietic and lymphoid tumours in 1999, with the classification updated in 2017.[1,2] This rare and aggressive lymphoma has a peculiar geographical distribution, with infrequent cases in Europe and North America and higher incidence in east Asia and Central and South America.[3,4]

The causes of ENKTL are not well understood, but its association with Epstein-Barr virus is invariable, irrespective of geographical origin.[5] ENKTL is clinically aggressive and typically resistant to anthracycline-based chemotherapy.[6] Radiation therapy is active in patients with ENKTL[7] and has become a central component of therapy for localised disease.[8] Extranasal and advanced-stage disease confer poor outcomes for most patients.[5,9,10] Retrospective data from the previous International Peripheral T-Cell Lymphoma Project,[5] notwithstanding a majority of nasal cases (n=91, 75% of the study cohort), reported a median failure-free survival of 6 months and an overall survival of 8 months for the whole ENKTL cohort (n=136), representing the worse survival outcomes of all T-cell lymphoma subtypes.[11]

In recent years, the treatment landscape for ENKTL has evolved, with accumulating evidence supporting concurrent or sequential non-anthracycline-based chemoradiotherapy for localised disease,[6,12] and non-anthracycline-based chemotherapy incorporating L-asparaginase for advanced-stage and relapsed or refractory ENKTL.[13–16] The

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Research in context

Evidence before this study

We searched PubMed with the search terms "extranodal NK/T-cell lymphoma", "survival" AND/OR "international", for reports published between Jan 1, 2000, and Dec 31, 2018, for studies published in all languages. The only previous publication (in 2009) from an international collaborative project on extranodal natural killer (NK) and T-cell lymphoma (ENKTL) assessed 136 patients registered with the previous retrospective International Peripheral T-Cell Lymphoma Project. In that study, most patients were treated at institutions located in east Asia. The survival outcomes of those patients represented the worse of all T-cell lymphoma subtypes studied in the project. Subsequently, a number of prospective studies, mostly single-arm phase 2 cohorts or retrospective studies, have shown the clinical value of treatment protocols specific for ENKTL. Accordingly, international clinical guidelines have shifted towards chemotherapy regimens that include L-asparaginase, and non-anthracycline-based regimens. A large retrospective study from Japan described clinical outcomes in patients with ENKTL treated between 2000 and 2013. The majority had localised disease, but nevertheless, outcomes appeared improved compared with those in the Peripheral T-Cell Lymphoma Project cohort. The Japanese study also validated the prognostic index of NK lymphoma (PINK), which was initially developed and validated in a large international ENKTL cohort treated with non-anthracycline regimens by a South Korean research group.

Added value of this study

No published prospective international cohort studies are available in this rare disease. The present study analyses data on a cohort of consecutively diagnosed ENKTL cases that were contemporaneously registered in the database of the T-cell Project, a global prospective cohort study initiated in 2006. To the best of our knowledge, this cohort of ENKTL patients from 40 centres in 14 countries, across four continents, is the largest reported from an international study and exemplifies the value of a global collaborative approach. We describe significant improvements in the survival outcomes of patients with ENKTL in the past decade, representing the largest step change among all T-cell lymphoma subtypes studied. Such improvements in survival are likely to be attributable to a paradigm shift in clinical management, including a move away from anthracycline-based therapy to asparaginase-based and platinum-based protocols, and increasing recognition of the importance of radiation therapy.

Implications of all the available evidence

ENKTL is a rare and unique clinicopathological entity with a peculiar geographical distribution. Most of the published data on this rare and aggressive lymphoma have arisen from study groups in east Asia, but understanding of clinical characteristics and outcomes in other geographical regions is limited. In our planned substudy of an international ENKTL cohort from the T-cell Project, we report improved survival outcomes and confirm therapeutic progress across geographical locations. Notwithstanding, the indicated improvements in prognosis and survival outcomes continue to be worse compared with the more common B-cell lymphoma subtypes. The complementary role of prospective cohort studies alongside interventional clinical studies is vital to improve understanding of rare malignancies such as T-cell and NK lymphomas.

T-cell Project is an international prospective cohort study, designed to more accurately define prognosis and treatment outcomes in patients with mature T-cell and NK cell lymphomas. A key objective of the T-cell Project was to better define the clinical characteristics and survival outcomes of uncommon peripheral T-cell lymphoma subtypes, such as ENKTL. This manuscript presents data from a substudy of the T-cell Project, focusing on the participants with ENKTL. To the best of our knowledge, this substudy represents the largest international cohort of patients with ENKTL to date, with a focus on the evolving treatment landscape and factors influencing clinical outcomes.

Methods

Study design and patients

We did a substudy of patients with ENKTL who had been enrolled in the T-cell Project, a global prospective cohort study initiated in 2006 that builds on the retrospective study previously undertaken by the International Peripheral T-Cell Lymphoma Project Group.[11] Throughout the T-cell Project, 74 hospitals in 13 countries (Argentina, Brazil, Chile, France, Israel, Italy, South Korea, Slovakia, Spain, Switzerland, the UK, the USA, and Uruguay) served as enrolment sites. Consecutively diagnosed patients at the participating institutions, with newly diagnosed, previously untreated, mature T-cell or NK lymphomas according to WHO 2001 or WHO 2008 classifications (peripheral T-cell lymphoma, not otherwise specified; angioimmunoblastic T-cell lymphoma; ENKTL; enteropathy-type T-cell lymphoma; hepatosplenic γδ T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma; anaplastic large-cell lymphoma [all subcategories]; and unclassifiable peripheral T-cell or NK lymphoma) were registered into the T-cell Project at initial diagnosis before initiation of treatment. Eligible patients were aged 18 years and older, had adequate tissue biopsies for diagnosis and classification by central review, and had clinical data including baseline information on disease staging and laboratory parameters at diagnosis, types of treatment received, and follow-up for at least 5 years. Some patients were included on the basis of local diagnosis and central review of histology reports if centralisation of samples was not possible. No upper age limit nor other

exclusions related to performance status or other clinical parameters were applied. Full inclusion and exclusion criteria are listed in the appendix (pp 12–13).

The study was done in compliance with the Declaration of Helsinki and approved by research ethics committees and institutional review boards at each participating institution. All patients provided written informed consent before study entry.

Procedures

The first patient was enrolled on the T-cell Project on Oct 12, 2006, and the last patient on Feb 28, 2018, constituting a total of 1695 patients. The first patient with ENKTL was enrolled on Feb 15, 2007, and the last patient on May 26, 2017. The T-cell Project used a central dedicated database (http://www.tcellproject.org; now inactive) to store all patient data, hosted at the University of Modena and Reggio Emilia, Modena, Italy, which was locked for analysis on March 30, 2019.

Patient registration onto the study was based on local histological diagnosis. A central panel of expert haematopathologists based at the University of Modena and Reggio Emilia subsequently undertook histopathological reviews when possible for registered patients. Patients were removed from the study if deemed ineligible on histology review or if consent was withdrawn. Staging (Ann Arbor system) and evaluation of treatment response[17] were undertaken by local investigators following institutional imaging protocols at times according to local standard practice and following completion of first-line therapy.

Data were collected on baseline clinical and disease characteristics, first-line treatment, and response evaluation, and updated with survival follow-up until database lock. Full details of the dataset are provided in the appendix (pp 15–16). Data on radiotherapy dose and field and Epstein-Barr viral load were not routinely collected.

Additionally, we analysed the ENKTL cohort according to the prognostic index of NK lymphoma (PINK), a prognostic index for ENKTL first published in 2016.[18] This index comprises four risk factors: age >60 years, stage III or IV disease, distant lymph-node involvement, and non-nasal type disease.[18] According to the established PINK categories, we stratified patients as low risk (0 factors), intermediate risk (1 factor), and high risk (≥2 factors).

Outcomes

The primary outcome was 5-year overall survival. The secondary outcome was 5-year event free survival, not reported here. Additional prespecified endpoints were 5-year progression free survival and the proportion of patients in remission after initial therapy. 3-year overall survival and progression-free survival were also analysed post-hoc.

Overall survival was defined as the time between diagnosis until death from any cause, or the date of last known contact for living patients. Progression-free survival was defined as the time between diagnosis until disease progression or death due to T-cell Lymphoma.

See **Online** for appendix

Statistical analysis

The sample size for the prospective T-cell Project cohort was calculated on the basis of characteristics of the two more frequent subtypes of peripheral T-cell lymphomas (peripheral T-cell lymphoma unspecified and angioimmunoblastic lymphoma). As the definition of a sample size for more uncommon T-cell lymphoma subtypes was not possible due to their rarity, the study was designed to prospectively collect all cases of rarer histologies in the same time frame (appendix p 17).

For the purposes of this study, data on patients with ENKTL were analysed using Fisher's exact test to identify associations between categorical variables. Two-tailed p values of less than 0·05 were considered statistically significant. The Mann-Whitney test was used to compare median age between groups. Overall survival and progression-free survival distributions were calculated with the Kaplan-Meier method, and time-to-event

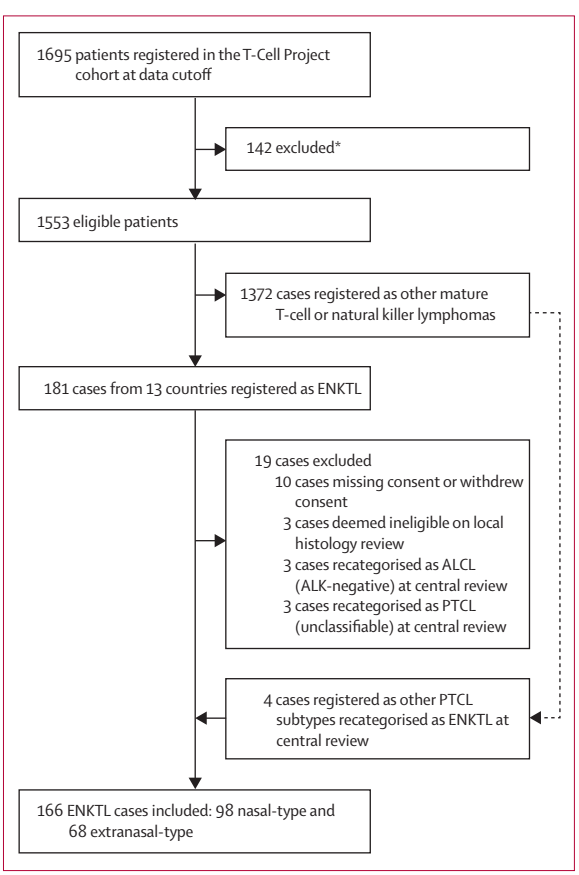

Figure 1: **Study profile**
ENKTL=extranodal natural killer T-cell lymphoma. ALCL=anaplastic large-cell lymphoma. ALK= anaplastic lymphoma kinase. PTCL=peripheral T-cell lymphoma. *Due to missing consent, withdrawal of consent, ineligibility on local review, or other reasons (unspecified).

	Total	Nasal-type	Extranasal-type
Median age, years*	53 (18–90)	53 (21–89)	51·5 (18–82)
Age >60 years	52/166 (31%)	30/98 (31%)	22/68 (32%)
Gender			
Male	108/166 (65%)	65/98 (66%)	43/68 (63%)
Female	58/166 (35%)	33/98 (34%)	25/68 (37%)
ECOG performance status			
0	65/149 (44%)	31/87 (36%)	34/62 (55%)
1	60/149 (40%)	46/87 (53%)	14/62 (23%)
2	18/149 (12%)	8/87 (9%)	10/62 (16%)
>2	6/149 (4%)	2/87 (2%)	4/62 (6%)
B symptoms†	60/152 (39%)	30/89 (34%)	30/63 (48%)
>1 extranodal site	80/166 (48%)	68/98 (69%)	56/68 (82%)
Bone marrow involvement	9/134 (7%)	4/77 (5%)	5/57 (9%)
Ann Arbor stage			
I	74/153 (48%)	43/91 (47%)	31/62 (50%)
II	30/153 (20%)	21/91 (23%)	9/62 (15%)
III	7/153 (5%)	4/91 (4%)	3/62 (5%)
IV	42/153 (27%)	23/91 (25%)	19/62 (31%)
Lactate dehydrogenase > upper limit of normal	55/141 (39%)	23/81 (28%)	32/60 (53%)
Bulky disease >10 cm	7/166 (4%)	3/98 (3%)	4/68 (6%)
Distant lymph node involvement	76/140 (54%)	56/85 (66%)	20/55 (36%)
First-line treatment			
Chemotherapy alone	43/130 (33%)	14/75 (19%)	24/55 (44%)
Radiotherapy alone	5/130 (4%)	4/75 (5%)	1/55 (2%)
Chemotherapy and radiotherapy	73/130 (56%)	52/75 (69%)	21/55 (38%)
Chemotherapy and consolidation high-dose treatment	14/130 (11%)	5 (7%)	9 (16%)
Chemotherapy regimen			
L-asparaginase+, anthracycline–, platinum– (SMILE, VIDL, MIDLE, PEGS, other)	54/130 (42%)	30/75 (40%)	24/55 (44%)
L-asparaginase–, anthracycline–, platinum+ (VIPD, DEVIC, ICE, ESHAP, other)	21/130 (16%)	16/75 (21%)	5/55 (9%)
L-asparaginase–, anthracyline+, platinum–	50/130 (38%)	27/75 (36%)	23/55 (42%)
L-asparaginase+, anthracycline–, platinum+	5/130 (4%)	2/75 (3%)	3/55 (5%)

Data are n/total cases (%) or median (IQR) of available data. Percentages do not always add up to 100% due to rounding. ENKTL=extranodal natural killer T-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. SMILE=dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide. VIDL=etoposide, ifosfamide, dexamethasone, and L-asparaginase. MIDLE=methotrexate, ifosfamide, etoposide, dexamethasone, and L-asparaginase. PEGS=cisplatin, etoposide, gemcitabine, and methylprednisolone. VIPD=etoposide, ifosfamide, cisplatin, and dexamethasone. DEVIC=dexamethasone, etoposide, ifosfamide, and carboplatin. ICE=ifosfamide, carboplatin, and etoposide. ESHAP=etoposide, methylprednisolone, cisplatin, and cytarabine. *Total cases, n=166; nasal-type, n=98; extranasal-type, n=68. †Fever, weight loss, and night sweats.

Table: **Clinical characteristics and treatment details of patients with ENKTL (n=166)**

distributions were compared with the log-rank test (univariate regression). Median duration of follow-up was based on the potential duration, which was estimated by the Kaplan-Meier method. Cox models were used to investigate the association between survival outcomes and covariates (nasal and extranasal subtypes, Ann Arbor stage, PINK, chemotherapy regimens, and response to therapy) with hazard ratios (HRs) used as a summary measure. In addition to prespecified factors, the individual PINK parameters were included post-hoc in the multivariable analysis as a validation measure of the score. The cumulative incidence of relapse was estimated by Gooley's method,[19] with death from any cause considered as a competing event.

Statistical analyses were done with Stata (version 14.2) and SPSS (version 20.0).

The T-cell Project was registered on ClinicalTrials.gov, NCT01142674.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

At the data cutoff (March 30, 2019), 1695 patients were registered for the T-cell Project, of whom 1553 were eligible for analysis. Of the 74 participating centres, 40 centres from the 13 participating countries across four continents registered patients with ENKTL for the study. Of the 181 cases locally registered as ENKTL, 98 (54%) underwent central pathological review. The diagnostic concordance of local pathological diagnosis with the international histopathology panel was 94% (n=92 concordant cases), with the six discordant cases deemed to be ineligible. For 81 (45%) registered ENKTL cases, diagnostic samples were not centralised and were evaluated based on the local diagnosis, with central review of the histology report. Two (1%) cases could not be adequately classified by central reviewers and were retained in the study based on local diagnosis and central review. Four cases were registered as other peripheral T-cell lymphoma subtypes by local pathology review and subsequently recategorised as ENKTL by the central review panel. In total, 166 cases (11%) of the 1553 eligible cases were categorised as ENKTL, of which 98 (59%) were designated as nasal, and 68 (41%) as extranasal. Figure 1 shows the study profile.

The frequency of ENKTL among the 1553 evaluable cases was significantly higher in Asian countries than in Europe and the USA (54 [31%] of 175 patients *vs* 82 (8%) of 1053, p=0·0008), with Asian cases across the T-cell Project predominantly registered in South Korea (n=118). Interestingly, the frequency of nasal ENKTL versus extranasal ENKTL differed across continents (appendix p 45).

The key baseline clinical characteristics of patients are shown in the table. As expected, patients with extranasal disease presented with more adverse clinical characteristics than those with nasal disease, particularly with regard to stage III–IV disease, involvement of more than one extranodal site, and high serum lactate dehydrogenase.

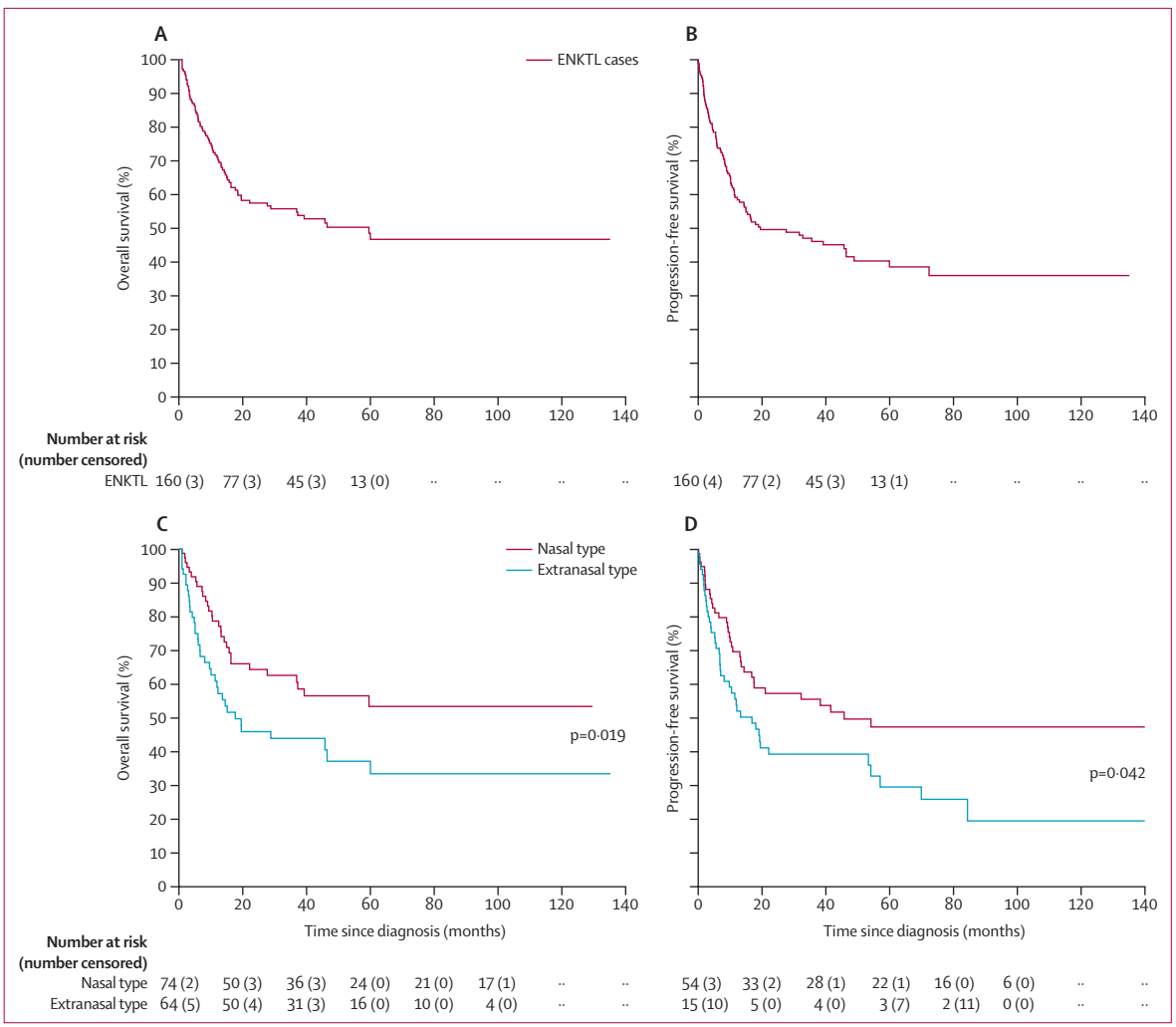

Figure 2: **Survival analyses in all patients and by ENKTL subtype**
Overall survival (A) and progression-free survival (B) in the total ENKTL cohort. Overall survival (C) and progression-free survival (D) by ENKTL presentation (nasal or extranasal). Log-rank p values are shown. ENKTL=extranodal natural killer T-cell lymphoma.

With a median follow-up of 44 months (IQR 20–61), we estimated a median overall survival of 59 months (95% CI 41–86) and a median progression-free survival of 20 months (1–39) for the whole ENKTL cohort (figure 2A and 2B).

The median overall survival of patients with nasal involvement (not reached [95% CI not reached–not reached]) was significantly higher than that in patients with extranasal disease (18 months [9–32]; HR 9·6 [95% CI 9·2–32·4]; p=0·019; figure 2C). In patients with nasal disease, overall survival at 3 years was 63% (45–77) and at 5 years was 54% (44–63). In patients with extranasal disease, overall survival at 3 years was 44% (27–87) and at 5 years was 34% (27–46; figure 2C). 71 deaths were registered, comprising 43% of the evaluable cohort. 46 (65%) deaths were due to lymphoma. Of the remaining deaths, 9 (13%) were attributed to infection, 3 (4%) to treatment toxicity, and 1 (1%) to a second primary malignancy. For 12 (17%) patients, the cause of death was not available. Median progression-free survival in patients with nasal disease was significantly improved compared with that of patients with extranasal disease (39 months [21–59]) *vs* 14 months [5–29]; HR 5·7 [5·1–28·9]; p=0·042; figure 2D). Progression-free survival at 3 years was 51% (29–69) and at 5 years was 47% (36–57) for patients with nasal disease, compared with 39% (19–58) and 26% (17–38) for those with extranasal disease (figure 2D). For the whole ENKTL cohort, the cumulative incidence of disease progression or relapse was 41% (33–50) at 3 years and 44% (35–52) at 5 years. The cumulative risk of non-relapse mortality was 9% (5–14) at 3 years and 13% (7–20%) at 5 years (data not shown).

Analysis according to Ann Arbor stage revealed a median progression-free survival of 46 months (11–81) and a median overall survival of 59 months (not estimable–not estimable) for patients with stage I or II

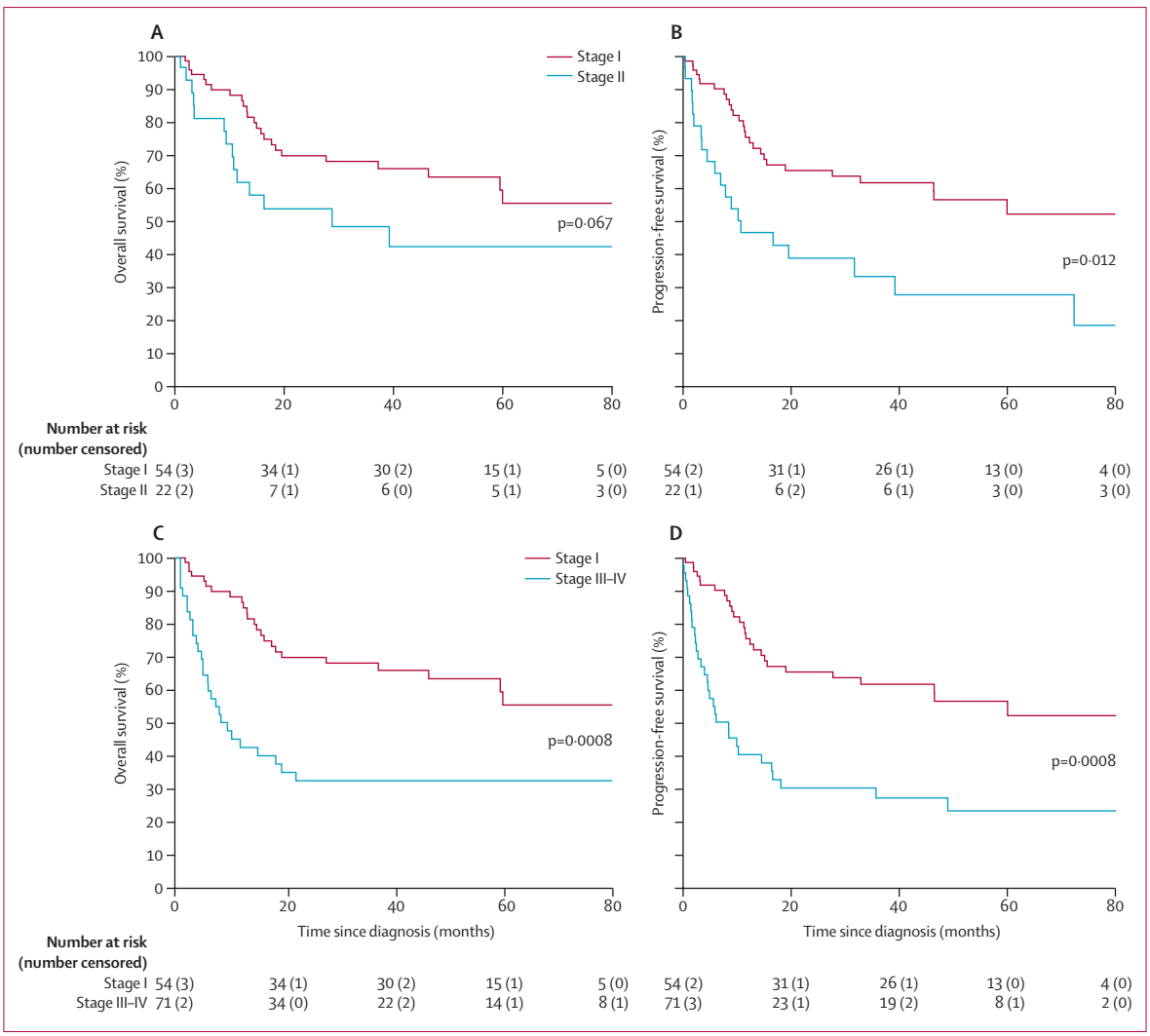

Figure 3: **Survival analyses by disease stage**
Overall survival (A) and progression-free survival (B) of patients with stage I versus stage II disease; and overall survival (C) and progression-free survival (D) of patients with stage I versus stage III and IV disease. Log-rank p values are shown.

ENKTL, compared with 15 months (9–20; HR 7·2 [5·4–19·9]; p=0·021) and 19 months (4–34; p=0·042) for those with stage III or IV disease. Notably, we observed significant differences in progression-free survival and overall survival between stage I and stage II disease (median progression-free survival, not reached [not-reached–not-reached] *vs* 13 months [1–16]; HR 3·2 [0–21]; p=0·012); and median overall survival, not reached [not-reached–not-reached] *vs* 29 months [2–34]; HR 3·1 [1–62]; p=0·067). Overall survival at 3 years was 69% (40–81) and at 5 years was 55% (21–79) in patients with stage I disease, compared with 48% (17–58) and 42% (17–58) in those with stage II disease (figure 3A and 3B). In patients with stage III–IV disease, median progression-free survival was 8 months (3–13; *vs* stage I disease, HR 2·7 [2·1–14·2]) and median overall survival was 10 months (4–15; *vs* stage I disease, HR 2·9 [2·4–16·1]); overall survival at 3 years was 33% (9-38) and at 5 years was 24% (8–29; figure 3C and 3D).

From the available data, calculation of PINK score was possible in 144 cases. Of these, 34 (24%) were classified as low-risk, 41 (28%) as intermediate-risk, and 69 (48%) as high-risk cases in terms of prognosis. 5-year overall survival was 54% (31–70) in patients of low risk, 51% (21–64) in patients of intermediate risk, and 35% (10–41) in patients of high risk (p=0·0021; figure 4A). Progression-free survival at 5 years was 56% (29–60) in low-risk cases, 34% (17–49) in intermediate-risk cases, and 28% (9–34) in high-risk cases (p=0·0082; figure 4B). The appendix (p 45) reports the predictive value of the individual PINK variables with respect to 5-year overall survival and progression-free survival.

Of the 166 patients with ENKTL, treatment details were not available for 32 (19%) patients and a further

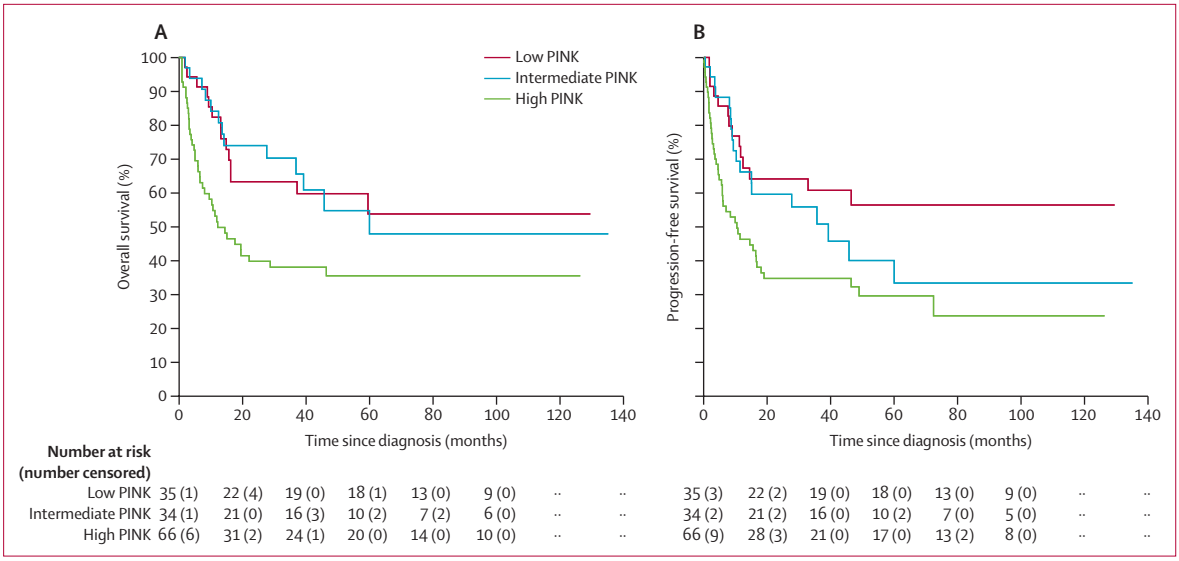

Figure 4: **Survival analyses by PINK score**

Overall survival (A) and progression-free survival (B) according to PINK score[18] (low PINK, 0 prognostic factors; intermediate PINK, 1 factor; and high PINK, ≥2 factors). Log-rank p values are shown. PINK= prognostic index of natural killer lymphoma.

four patients (2%) received best supportive care only; thus, 36 patients were excluded from treatment analyses. Of the 130 patients analysed, 75 had nasal disease and 55 extranasal. 73 (56%) patients underwent chemotherapy plus radiotherapy as a first-line treatment (table). Among the 59 regimens incorporating L-asparaginase, the SMILE protocol (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), administered in 23 (39%) patients, was the most commonly used. 14 (11%) of the 130 patients analysed underwent high-dose chemotherapy with autologous stem cell support as first-line consolidation.

In patients with early-stage (I and II) disease receiving chemotherapy alone (n=11), overall survival at 3 years was 12% (not estimable–not estimable) and at 5 years was 12% (not estimable–not estimable), compared with 70% (41–91) and 59% (31–78) in those receiving chemotherapy and radiotherapy (n=48; p=0·0091; figure 5A). In patients with advanced-stage (III and IV) disease receiving chemotherapy alone (n=27), overall survival at 3 years was 24% (8–32) and at 5 years was 24% (7–33), compared with 66% (33–87) and 58% (39–76) in patients receiving chemotherapy and radiotherapy (n=27; p=0·0006 (data not shown). Progression-free survival at 3 years was 0% (not estimable–not estimable) and at 5 years was 0% (not estimable–not estimable) in early-stage patients receiving chemotherapy alone, compared with 66% (40–87) and 53% (33–69) in those receiving chemotherapy and radiotherapy; the progression-free survival difference was significant (log-rank p=0·0003; figure 5B). In patients with advanced-stage (III or IV) disease receiving chemotherapy alone, progression-free survival at 3 years was 14% (7–25) and at 5 years was 0% (not estimable–not estimable), compared with 59% (31–72) and 40% (27–69) in patients receiving chemotherapy and radiotherapy (p=0·0009; data not shown).

We subsequently explored the effects of different chemotherapeutic regimens on survival outcomes in ENKTL. On analysis by treatment type, 5-year progression-free survival was 42% (11–64) and 5-year overall survival was 50% (32–74) in patients receiving an L-asparaginase-based regimen, compared with 26% (9–40) and 31% (11–58) in those receiving an anthracycline-based regimen, and 59% (30–77) and 66% (31–94) in those not receiving either drug (largely platinum-based regimens). The associations of different chemotherapeutic regimens with overall survival and progression-free survival, in isolation and by disease stage, are reported in the appendix (pp 48–49).

Overall, a response to first-line therapy was observed in 93 (72%) of 130 patients, with 84 (65%) patients (54 with nasal disease and 30 with extranasal disease) achieving a complete response and nine (7%; two with nasal disease and seven with extranasal disease) a partial response (appendix p 50). In patients who achieved complete response, 5-year overall survival was 63% (48–77; figure 5C; 68% [41–79] for nasal-type and 54% [38–60] for extranasal type [not shown]) and 5-year progression-free survival was 61% (40–74; figure 5D; 66% [40–74] for nasal-type and 46% [37–56] for extranasal-type [not shown]). By contrast, patients who achieved only partial response had notably poor outcomes: 5-year overall survival was 32% (12–39) and 5-year progression-free survival was not estimable (not estimable–not estimable; figure 5C and 5D).

In patients with stage I or II disease, response to therapy by treatment group (chemotherapy alone, radiotherapy alone, and chemotherapy plus radiotherapy) was

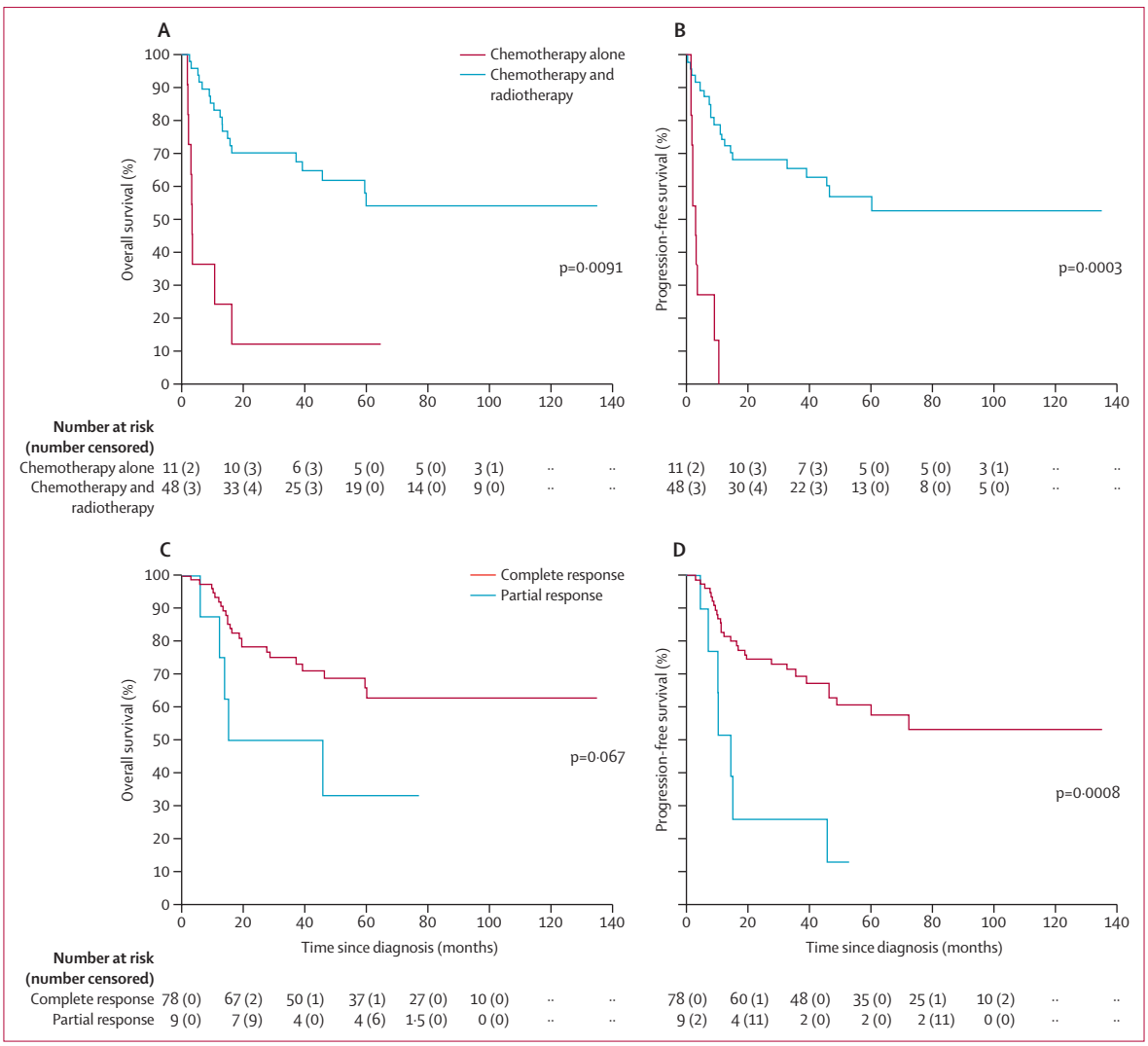

Figure 5: **Survival analyses in early-stage patients according to first-line treatment**
Overall survival (A) and progression-free survival (B) of patients with early-stage (I and II) disease according to first-line treatment with chemotherapy alone (n=11) or chemotherapy plus radiotherapy (n=48). Overall survival (C) and progression-free survival (D) of evaluable patients (n=130) with a complete response or partial response. Log-rank p values are shown.

evaluable in 60 patients. Of these, complete remission was achieved in 1 (13%) of 8 patients receiving only chemotherapy, 1 (25%) of 4 patients receiving only radiotherapy, and 38 (79%) of 48 patients receiving chemotherapy plus radiotherapy. In patients with stage III or IV disease, we analysed response to therapy in three treatment groups: L-asparaginase-based therapy, anthracycline-based therapy, and non-anthracyline, non-asparaginase protocols. In 60 evaluable patients, complete remission rates were 67% (n=40), 30% (n=18), and 1% (n=2). We also did an exploratory analysis of response to therapy and overall survival by geographical region. Although no significant differences were observed, response and survival outcomes appeared to be superior in ENKTL patients enrolled at Asian centres (data not shown).

Discussion

To our knowledge, this Article presents the largest prospective international study of patients with ENKTL done to date.[18,20] Initiated in 2006, the T-cell Project registered a total of 1695 patients with mature T-cell and NK cell lymphomas, with 166 cases classified as ENKTL, comprising 11% of eligible cases in the T-cell Project cohort. Compared with the previous International Peripheral T-Cell Lymphoma Project,[5] we identified notable improvements in the survival of patients with ENKTL, representing the largest change in clinical outcomes in the past decade among all of the T-cell lymphoma subtypes studied.[5] This improvement is possibly attributable to an evolution in clinical management, including a move away from anthracycline-based therapy and towards asparaginase-based and

platinum-based protocols, and increasing use of radiation therapy. In this study, improved survival was markedly associated with stage I disease, a low-risk PINK score, achievement of complete remission, and the use of radiation therapy.

We recognise the potential limitation in the 46% of cases that were not classified centrally, which were included on the basis of local pathology diagnosis alone, in line with the WHO pathological classification for ENKTL.[1] However, of cases centrally reviewed within the T-cell Project, concordance was high between local and centrally assigned diagnosis. This high diagnostic concordance is likely to reflect the high sensitivity and specificity of Epstein-Barr encoding region in-situ hybridisation, as the standard clinical method for diagnosis of ENKTL in this clinicopathological context. The registered ENKTL cases were distributed widely across Asia, Europe, and North and South America. Notably, cases from Europe and North America constituted almost half (82 [49%] of 166 cases) of the entire ENKTL cohort, compared with 32 (24%) of 136 cases in the previous T-cell project report.[5] As expected, ENKTL cases represented a higher proportion of all T-cell and NK lymphoma cases in Asia, compared with in the USA and countries in Europe. Interestingly, for the whole ENKTL cohort, we observed a higher proportion of extranasal cases (68 [41%]) than previously reported in population-based studies (35 [26%] of 136 cases[5] and 47 [13%] of 362[20]); this was particularly notable in cases from Europe (24 [47%] of 51 European cases). Given that the T-cell Project protocol required participating institutions to register consecutively diagnosed patients with T-cell or NK lymphoma, we consider the risk of selection bias to be low. Interestingly, we noted differences in overall survival by geographical region, although the numbers are too small to be conclusive (data not shown). Although speculative, the more frequent use of both radiotherapy and L-asparaginase in Asia (data not shown) might be relevant factors.

As anticipated, patients with extranasal disease had significantly worse survival outcomes than those with nasal disease. Consistent with this result, advanced-stage (III and IV) disease conferred significantly worse outcomes over stage I and II ENKTL. However, this difference appeared to be explained by the favourable prognosis of stage I disease. This observation was unexpected, although patients with stage II disease comprised a relatively small subgroup (n=30; table), and only 10 patients (43%) with stage II disease received radiotherapy as part of first-line treatment (data not shown). The reasons for this low use of radiotherapy are not clear, but might reflect heterogeneity within the stage II group. Furthermore, the unpexpectedly poorer outcomes with stage II versus stage I disease highlights inherent limitations of both the Ann Arbor staging system for ENKTL, and the use of staging by CT imaging. The T-cell Project was initiated in 2006, before the incorporation of PET-CT imaging into lymphoma staging and response assessment criteria, and thus PET-CT might have altered the staging of some patients in the study. Similarly, we recognise the limitations of CT as a response assessment method for ENKTL, being less sensitive than PET for identifying extranodal disease, and acknowledge that our dataset did not capture the imaging modality (ie, PET-CT versus CT or MRI) used for each patient.

In their study from the previous retrospective International Peripheral T-Cell Lymphoma Project, Au and colleagues[5] reported outcomes on a large international series of ENKTL cases, largely including patients from east Asian countries. More than a decade after, we report significant improvements in progression-free survival and overall survival for both nasal and extranasal disease. We acknowledge that, consistent with this previous study, progression-free survival and overall survival were calculated from date of diagnosis rather than date of treatment initiation. The median overall survival reported in the retrospective Peripheral T-Cell Lymphoma Project series of patients with extranasal disease was 4 months, and in those with nasal disease was 19 months, compared with 18 months [95% CI 9–32] and not reached (not reached–not reached) in the present study. This magnitude of improvement exceeds that of any other T-cell lymphoma subtypes studied, and represents a paradigm shift in the clinical management of patients with ENKTL. Notable differences in patterns of treatment in the past decade include a large reduction in the proportion of patients receiving anthracycline-based therapy and, accordingly, an increase in those receiving either platinum-based or asparaginase-based protocols. Several prospective clinical studies have shown the prognostic value of asparaginase in treatment regimens for ENKTL.[13,15,16] However, we were unable to show a definitive advantage of asparaginase within treatment protocols, even in advanced-stage disease (appendix p 49). This lack of apparent benefit in the present study could be confounded by a number of factors, including treatment selection bias and and geographical variation in treatment approaches.

The important role of radiotherapy in the management of ENKTL was highlighted by our study. In patients with early-stage disease, combined modality therapy with chemotherapy plus radiotherapy was associated with improved survival; chemotherapy alone was associated with poor outcomes (12% survival at 5 years). Unfortunately, further details on the radiotherapy dose, schedule, and anatomical field were not available in the T-cell Project database. Furthermore, the potential influence of different chemotherapy regimens on the effect and dose requirement of radiotherapy remains to be clarified. Anthracyline-based chemotherapy was used in a substantial proportion of patients in this study; however, reduced radiotherapy doses or fields might be

feasible with non-anthracycline regimens, given the potential superior efficacy of such regimens. Interestingly, the addition of radiotherapy in patients with stage III or IV disease was associated with a highly significant improvement in overall survival. We believe such a strong abscopal effect to be unlikely in this disease, although the potential effect of radiation therapy on antigen presentation[21] might be relevant in a lymphoma that expresses antigens encoded by Epstein-Barr virus. We also recognise the potential for treatment bias, given that patients responsive to chemotherapy might be more likely to undergo radiation therapy than those with early disease progression or early mortality after diagnosis. However, given the apparent size of effect associated with radiotherapy, this observation warrants further study.

For more on the **T-cell Project 2.0** see https://www.tcellproject2.org/

Differentiating early-stage from advanced-stage disease is essential for both treatment planning and predicting treatment outcome,[22] although outcome prediction has not been straightforward in ENKTL. In 2016, the ENKTL-specific prognostic index, PINK, was described, which showed improved prognostic delineation in the context of non-anthracycline based therapy.[18] This score was further refined in advanced-stage disease by including Epstein-Barr virus DNA when detectable in peripheral blood as an additional parameter (PINK-E).[18] We validated the PINK score in our international ENKTL cohort of patients treated with anthracycline-based and non-anthracycline-based protocols, confirming that a high-risk PINK score identifies patients with a particularly poor prognosis. For these patients, investigational therapies are warranted. Unfortunately, longitudinal data on Epstein-Barr virus DNA values, recognised to be a useful monitoring tool in ENKTL,[23] were not routinely collected in this study.

Prospective global studies for rare malignancies such as T-cell and NK lymphomas are crucial to improve understanding of epidemiological and clinical factors affecting the disease course and to provide information on treatment patterns and survival outcomes. Such studies are particularly required for very rare subtypes such as ENKTL, for which treatment algorithms have been largely derived from small non-randomised studies in restricted geographical areas. Our ENKTL dataset, as a planned substudy of the T-cell Project, has both strengths and limitations. The prospective design, with the registering of data centrally on consecutively diagnosed patients with ENKTL from 40 centres in 13 countries across 4 continents, permits substantial insight into the clinical characteristics of ENKTL, and offers a truly international picture of its modern-day clinical management. Furthermore, the long follow-up of the study allowed for confident interpretation of survival outcomes. However, an international study of this size and scope is inherently limited by the granularity of data that are routinely collected on patients. Similarly, correlative biological studies were not feasible within the main study.

Further therapeutic progress will require an improved understanding of the pathobiology of ENKTL, as a rare clinicopathological entity, to allow the development of rationally designed, biologically driven treatment approaches for those patients who do not respond to modern chemoradiation protocols. Examples of such a strategy have been reported in recent years,[24,25] and several academic and commercial prospective studies are underway, including the T-cell Project 2.0, initiated in 2019 (NCT03964480). The complementary role of such prospective cohort studies, alongside interventional clinical studies, remains vital to understanding rare lymphomas and improving outcomes.

Contributors

CPF, WSK, and MF designed the study and wrote the manuscript. MC did the statistical analyses. All authors provided study material, interpreted data, and contributed to the drafting of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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