# Outcome of combined modality treatment in first-line for stage I(E) peripheral T-cell lymphoma; a nationwide population-based cohort study from the Netherlands

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## Abstract

Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of mature T-cell neoplasms with an unfavorable prognosis; presentation with stage I(E) disease is uncommon. In clinical practice, an abbreviated chemotherapy treatment regimen combined with radiotherapy (combined modality treatment [CMT]) is commonly used, although evidence from clinical trials is lacking. The aim of this nationwide population-based cohort study is to describe first-line treatment and outcome of patients with stage I(E) PTCL. All newly diagnosed patients ≥18 years with stage I(E) anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma NOS (PTCL not otherise specified [NOS]) in 1989-2020 were identified in the Netherlands Cancer Registry. Patients were categorized according to treatment regimen, i.e., chemotherapy (CT), radiotherapy (RT), CMT, other therapy and no treatment. The primary endpoint was overall survival (OS). Patients with stage I(E) ALCL, AITL and PTCL NOS (n=576) were most commonly treated with CMT (28%) or CT (29%), 2% underwent SCT. RT only was given in 18%, and 8% received other therapy and 16% no treatment. Overall, the 5-year OS was 59%. According to subtype, 5-year OS was superior for ALCL as compared to PTCL NOS and AITL (68% *vs*. 55% and 52%, respectively; *P*=0.03). For patients treated with CMT, 5-year OS was significantly higher (72%) as compared to patients treated with either CT or RT alone (55% and 55%, respectively; *P*<0.01). In multivariable analysis, age per year increment (hazard ratio [HR] =1.06, 95% confidence interval [CI]: 1.05-1.07), male sex (HR=1.53, 95% CI: 1.23-1.90), and CT, or no treatment (HR=1.64, 95% CI: 1.21-2.21, and HR=1.55, 95% CI: 1.10-2.17, respectively) were associated with a higher risk of mortality. For stage I(E) ALCL, AITL and PTCL NOS, 5-year OS is 59%, comparing favorably to historical outcome in advanced-stage disease. Superior outcome estimates were observed in patients treated with CMT.

# Introduction

Peripheral T-cell lymphomas (PTCL) are mature lymphoproliferative diseases that form a heterogenous group of >20 distinct subtypes. PTCL account for approximately 10% of newly diagnosed lymphomas worldwide. The most prevalent subtypes in Europe and North America are anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma not otherwise specified (PTCL NOS), which together account for approximately 80-86% of all PTCL diagnoses.[1,2] The prognosis of patients with PTCL is generally poor, with a median 5-year overall survival (OS) of 28-43%, where ALCL anaplastic lymphoma kinase (ALK)$^+$ is a positive exception with a 5-year OS of 72-78%.[3-8]

The majority of PTCL patients present with advanced-stage disease. These patients are generally treated with six cycles of cyclophosphamide, doxorubicin, vincristine and prednisone - either with or without etoposide (CHO(E)P). More recently brentuximab vedotin + CHP was shown to be superior to CHOP in ALCL, but a direct comparison with CHOEP is lacking.[9] In young and fit patients, current data largely support the use of consolidative autologous stem cell transplant (SCT).[3,7,8,10-14]

A minority of patients present with limited-stage disease whereby the incidence strongly depends on subtype.[3-5] A recent population-based study conducted in Denmark and Sweden indicated that the outcome in patients with limited-stage disease is superior to to those with extensive disease.[15] Clinical trials on the optimal treatment of patients with limited stage are lacking. Derived from its use in aggressive B-cell lymphoma, an abbreviated treatment regimen with three cycles of CHO(E)P combined with radiotherapy (combined modality treatment [CMT]) has been adapted in daily practice of stage I(E) PTCL, but only sporadically in stage II.[8,16-18]

Clinical trials addressing the efficacy of different first-line treatment modalities in stage I(E) PTCL have, to the best of our knowledge, not been performed. Our nationwide population-based cohort study aims to describe the various first-line treatment regimens and the outcome of patients with stage I(E) PTCL in the Netherlands.

# Methods

## Registry and study population

The nationwide population-based Netherlands Cancer Registry (NCR) is maintained and hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and has nationwide coverage of at least 95% of all malignancies since 1989.[19] The NCR relies on comprehensive case notification through the Nationwide Histopathology and Cytopathology Data Network and the Nationwide Registry of Hospital Discharges (i.e., inpatient and outpatient discharges). Information on dates of birth and diagnosis, sex, topography and morphology, hospital type of diagnosis, and first-line therapy is routinely recorded by trained registrars of the NCR through retrospective medical records review. Information on last known vital status for all patients (i.e., alive, dead, or emigration) is obtained through annual linkage with the Nationwide Population Registries Network that holds vital statistics on all residents of the Netherlands.

All patients ≥18 years with stage I(E) PTCL diagnosed between 1989-2020 were identified in the NCR, using the International Coding system of Disease - Oncology (ICD-O) of the World Health Organization (WHO), morphology codes 9702-9705, 9714 and 9715. Stage I(E) was defined according to the Ann Arbor staging system, determined by physician assessment, in which IE is defined as extranodal localization of the lymphoma.

The PTCL subgroups analyzed included ALCL, AITL and PTCL NOS. Enteropathy associated T-cell lymphoma (EATL), extranodal natural killer-T-cell lymphoma nasal type (ENK-TCL), and anaplastic large cell lymphoma, seroma associated - also known as breast-implant associated anaplastic large cell lymphoma (BIA-ALCL) - and several other, rare PTCL subtypes were excluded from analyses as treatment regimens of these disease entities are different from ALCL, AITL and PTCL NOS. Moreover, patients with a defined primary cutaneous T-cell lymphoma, including the primary cutaneous T-cell lymphomas subcutaneous panniculitis-like T-cell lymphoma (ICD-O 9708), mycosis fungoides (ICD-O 9700), primary cutaneous ALCL (ICD-O 9718), primary cutaneous γ/δ T-cell lymphoma (ICD-O 9726), CD4$^+$ small/medium T-cell lymphoproliferative disorder (ICD-O 9709) and CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphomas (ICD-O 2513) were disregarded for this study. Furthermore, PTCL patients with primary involvement of the central nervous system have been excluded. ALK$^+$ and ALK$^-$ ALCL were registered as distinct entities in the NCR as of 2008, according to WHO classification of 2008 (4$^{th}$ edition). Patients were categorized according to treatment modality, i.e., chemotherapy (CT; +/- SCT), radiotherapy (RT), CMT, other therapy and no treatment. Anatomical localization of first clinical presentation according to treatment modality is presented in *Online Supplementary Figure S1*. Information on the exact therapeutic regimen and number of cycles was registered in the NCR for patients diagnosed as of January 1, 2014. Furthermore, patients were categorized in two calendar periods, i.e., 1989-1999, and 2000-2020. The 'cutoff' year was based on the implementation of CMT for patients with PTCL in the Netherlands adapted from the pivotal study of Miller *et al*. in large B-cell lymphoma published in 1998.[18]

According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

### Statistical analysis

Descriptive statistics were used to present patient characteristics across the six treatment modalities. In addition, for 58 patients treated with CT and diagnosed in 2014-2020, type of chemotherapy, number of cycles and best response, determined by physician assessment using the Lugano classification, were evaluated. The primary endpoint was OS, defined as the time between PTCL diagnosis and all-cause-death with survival follow-up through February 1, 2022 (patients alive were censored on this date). With a median follow-up time of 70 months post-diagnosis, all survival analyses were restricted to 5 years of follow-up. The Kaplan-Meier method served to estimate OS, and the log-rank test to examine differences in survival distributions. OS was calculated for the two calendar periods, three subtypes of PTCL (AITL, PTCL NOS and ALCL) and for the five treatment strategies (CT, CMT, RT, other therapy and no treatment). For $ALK^+$ and $ALK^-$ ALCL have been classified as distinct entities as of 2008, OS was calculated for 77 patients with $ALK^+$ ALCL and $ALK^-$ ALCL diagnosed as of 2008. Moreover, 2-year progression-free survival (PFS) of patients treated with CT and diagnosed in 2014-2020 was calculated. PFS was defined as the time between diagnosis and tumor progression or all-cause-death, whichever occurred first.

Finally, the impact of age, sex, subtype, period of diagnosis, Ann Arbor stage (meaning stage I *vs*. stage IE or extranodal *vs*. nodal disease) and treatment on risk of mortality was evaluated using uni- and multivariable Cox proportional hazard regression analysis. For the latter, co-variates were introduced in the regression models with a backward selection method, and the final model was accomplished when the *P* value for the covariates was below 0.05. The results from the Cox regression analyses produce hazard ratios (HR) with associated 95% confidence intervals (CI). The proportional hazard assumption was tested based on the Schoenfeld residuals. Overall, a *P* value below 0.05 was considered statistically significant. All analyses were performed using STATA/SE 17.1 (StataCorp LP, College Station, Texas, USA).

## Results

### Patient characteristics

From 1989 to 2020, among the 4,795 patients with PTCL, 851 (18%) patients were diagnosed with stage I(E) disease. Of the stage I(E) patients, 343 were diagnosed with PTCL-NOS (40%), 205 with ALCL (24%), 28 with AITL (3%), and 275 with other subtypes of PTCL (32%; Figure 1). Patients with PTCL NOS, ALCL and AITL were included, leaving 576 patients with stage I(E) disease for further analyses. Over time, the share of patients with PTCL NOS decreased from 74% to 46%, whilst more patients were diagnosed with ALCL in the latter time period (24% *vs*. 47%); the percentage of AITL patients remained relatively stable (2% *vs*. 7%). The majority of the 576 patients were diagnosed between 2000 and 2020 (n=320, 56%), although the incidence of stage I(E) disease among patients with PTCL NOS, ALCL, or AITL decreased over time when compared to patients with stage II-IV (*Online Supplementary Figure S2*). Overall, the median age was 61 years with a male preponderance (58%). Median age varied between 55 and 67 years for patients treated with CMT *versus* patients treated with RT only or without therapy. Most patients treated with CMT had ALCL, whereas most patients treated with RT only were diagnosed with PTCL NOS (Table 1). Regarding ALCL, 77 patients were diagnosed after 2007 of whom 29 were $ALK^+$, 47 were $ALK^-$ and for one patient the ALK status was unknown.

### Treatment

In total, 331 patients (57%) were treated with CT (Table 1),

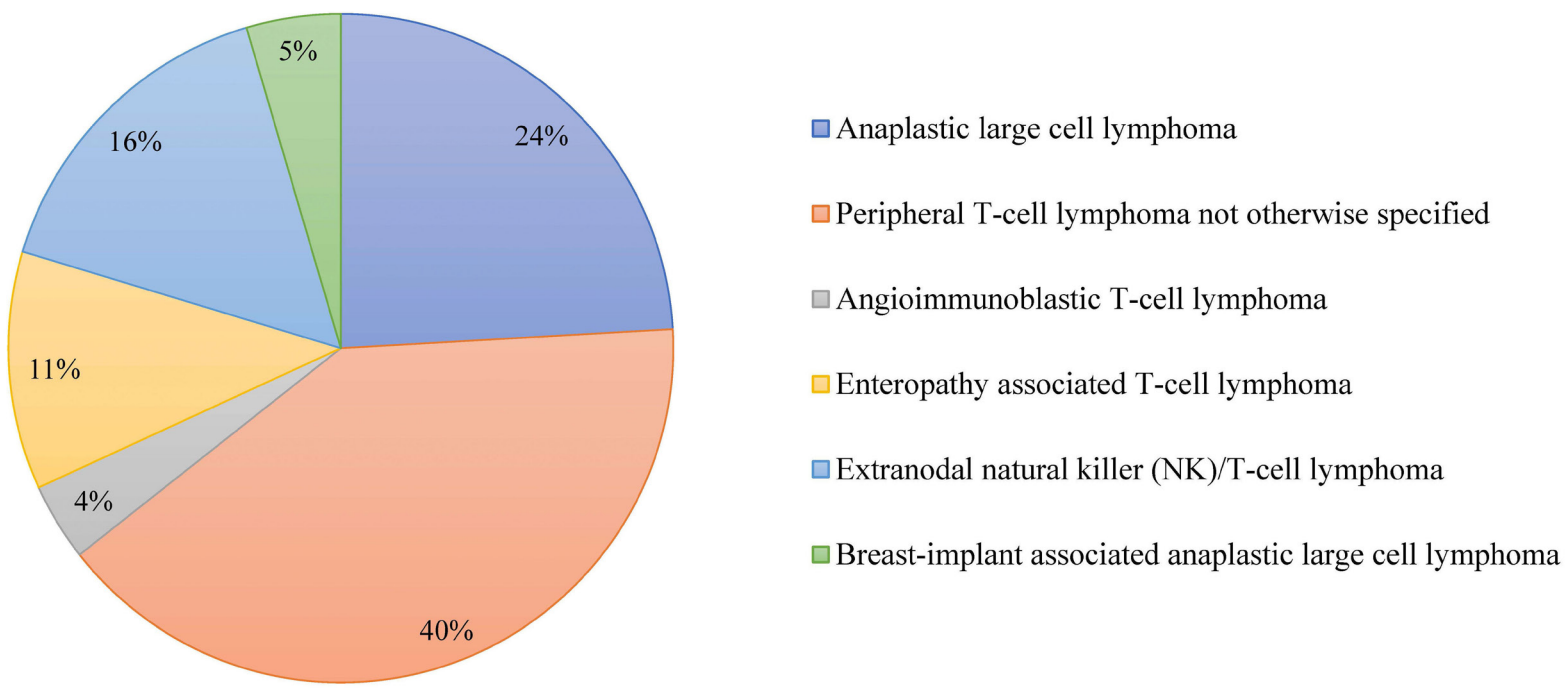


**Figure 1. Incidence of stage I(E) peripheral T-cell lymphoma in 1989-2020 in the Netherlands, according to all subtypes.**

of whom 157 (47%) received CT only, 163 (49%) received CMT and 11 patients (3%) received consolidative SCT. RT was used in 102 patients (18%), 48 patients (8%) were treated otherwise, i.e., by means of surgical resection or with steroids and 95 patients did not receive any treatment at all (16%). From 2000 onwards, more patients were treated with CMT (39% *vs*. 131%) and less with RT (36% *vs*. 6%), as compared to patients diagnosed before 2000 ($P$<0.01; Figure 2).

Of the 58 patients with stage I(E) disease diagnosed in 2014-2020 that were treated with CT, 39 received CHOP, 17 received CHOEP, one patient received CEOP and one patient brentuximab vedotin. Of the 56 patients with CHO(E)P, 31 patients received CT in combination with RT. The majority

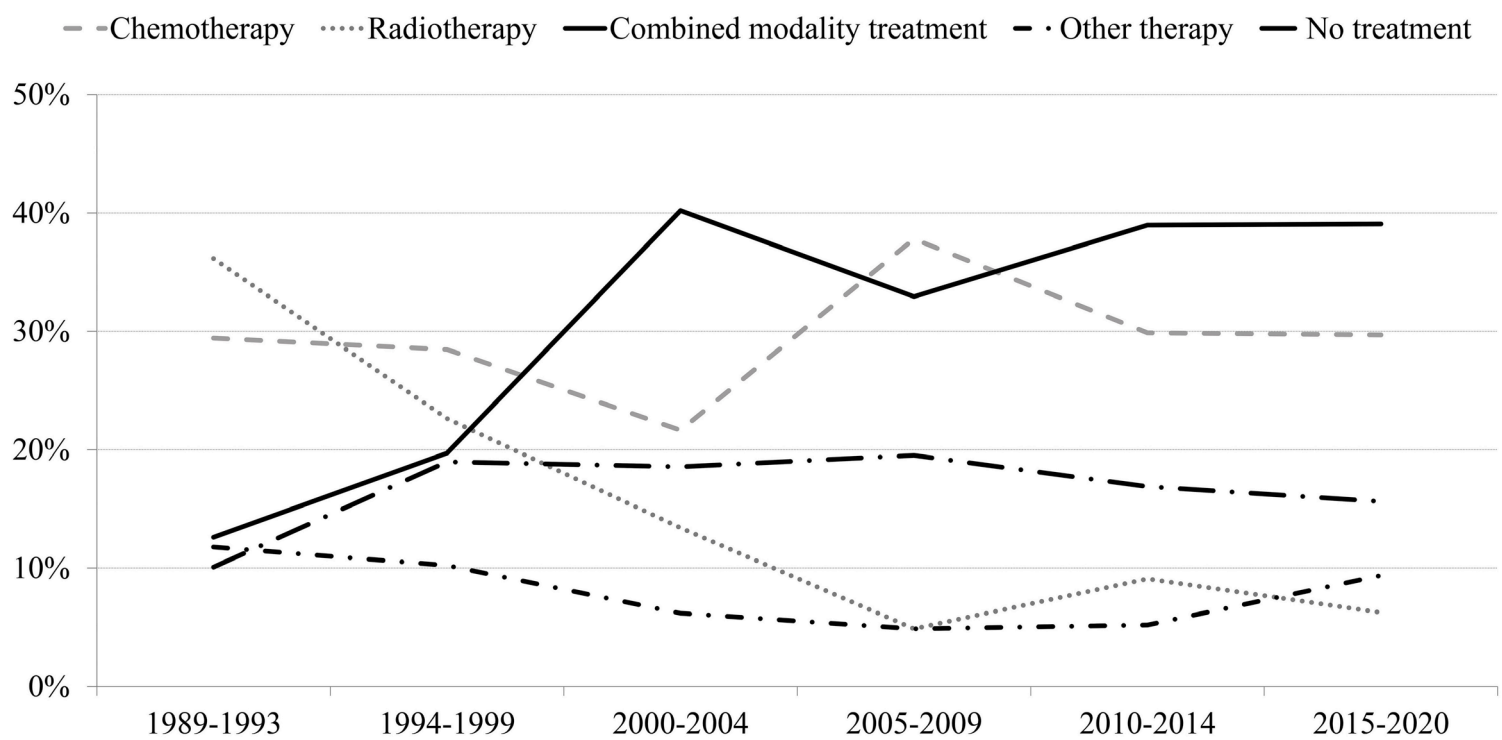


**Figure 2. Treatment modalities according to period of diagnosis for patients with a stage I(E) peripheral T-cell lymphoma (ALCL, AITL, PTCL NOS).** ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified.

**Table 1.** Baseline characteristics of patients with stage I(E) ALCL, PTCL NOS and AITL diagnosed in 1989-2020 in the Netherlands, according to first-line treatment modality.

| Characteristics | CT N=168 | | CMT N=163 | | RT N=102 | | Other treatment N=48 | | No treatment N=95 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
| Male sex | 101 | 60 | 92 | 56 | 58 | 57 | 26 | 54 | 55 | 58 |
| Period of diagnosis | | | | | | | | | | |
| 1989-1999 | 74 | 44 | 42 | 26 | 74 | 73 | 28 | 58 | 38 | 40 |
| 2000-2020 | 94 | 56 | 121 | 74 | 28 | 27 | 20 | 42 | 57 | 60 |
| Age in years at diagnosis | | | | | | | | | | |
| Median age (range) | 58 (18-86) | | 55 (19-87) | | 67 (19-91) | | 64 (18-93) | | 67 (31-99) | |
| ≤60 | 90 | 54 | 97 | 60 | 32 | 31 | 20 | 42 | 41 | 43 |
| >60 | 78 | 46 | 66 | 40 | 70 | 69 | 28 | 58 | 54 | 57 |
| ALCL subtype | 77 | 45 | 84 | 52 | 19 | 19 | 6 | 13 | 19 | 20 |
| ALK$^+$ | 12 | 16 | 18 | 21 | 0 | 0 | 0 | 0 | 1 | 5 |
| ALK$^-$ | 17 | 22 | 18 | 21 | 2 | 11 | 2 | 33 | 9 | 47 |
| ALK NOS | 48 | 62 | 48 | 57 | 17 | 89 | 4 | 67 | 9 | 47 |
| PTCL NOS | 81 | 48 | 73 | 45 | 79 | 77 | 40 | 83 | 70 | 74 |
| AITL | 10 | 6 | 6 | 4 | 4 | 4 | 2 | 4 | 6 | 6 |
| Localization | | | | | | | | | | |
| Nodal | 132 | 79 | 121 | 74 | 57 | 56 | 29 | 60 | 61 | 64 |
| Extranodal | 35 | 21 | 42 | 26 | 45 | 44 | 19 | 40 | 34 | 36 |

CT: chemotherapy; CMT: combined-modality therapy; RT: radiotherapy; ALK: anaplastic lymphoma kinase; NOS: not otherwise specified; N: number; ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; PTCL: peripheral T-cell lymphoma.

(29/31, 94%) of patients treated with CMT received 2-4 cycles of CHO(E)P. Of the 25 patients with CHO(E)P (of whom 5 with SCT), 76% (n=19) received ≥6 cycles.

### Outcome

Overall, the 5-year OS of stage I(E) PTCL was 59%. The 5-year OS estimates for ALCL, PTCL NOS and AITL were 68% (median OS 88 months), 55% (median OS 67 months) and 52% (median OS 44 months), respectively (*P*=0.03; Figure 3A). For patients with ALCL ALK$^+$, 5-year OS was 80% as compared to 68% for patients with ALCL ALK- (*Online Supplementary Figure S3*; *P*=0.28). For patients with ALCL, PTCL NOS and AITL, 5-year OS was significantly higher when treated with CMT (72%) as compared to either chemotherapy or radiotherapy alone (55% 5-year OS for both; *P*<0.01; Figure 3B). There was no significant difference in the 5-year OS for stage I(E) PTCL over time, e.g., 56% in 1989-1999 and 62% in 2000-2020 (*P*=0.15).

For the whole cohort, uni- and multivariable analyses were performed (*Online Supplementary Table S1*). In multivariable analyses, age had a negative impact on outcome (per year increment, HR=1.06, 95% CI: 1.05-1.07) as well as male sex (HR=1.54, 95% CI: 1.24-1.91). Treatment with CT or no treatment were associated with a higher risk of mortality compared to CMT (HR=1.64, 95% CI: 1.211-2.21, and HR=1.55, 95% CI: 1.10-2.17, respectively; Figure 4; *Online Supplementary Table S1*).

Response and 2-year PFS were calculated for the 55 patients treated in 2014-2019. In this subpopulation, 50 patients received CT and five patients RT only. Of the patients with CT, 17 (34%) received CT only, 29 (58%) with RT (CMT), and four (8%) with SCT. Regarding best response, three patients with CT only had refractory disease, one patient early progression. Refractory disease or early progression was not observed in patients treated with CMT or RT. Two-year PFS was 67% for patients with CT, and 79% for patients with CMT (*Online Supplementary Figure S4; P=0.33*).

## Discussion

In this nationwide population-based study, we show that 18% of patients with PTCL present with stage I(E) disease. Although the outcome of stage I(E) patients with ALCL, AITL and PTCL-NOS compares favorably to historical outcomes in patients with stage II-IV, the 5-year OS of 59% remains unsatisfactory.

The reported incidence of patients with PTCL presenting with limited-stage PTCL (stage I and II) varies between 23% and 48%.[3,6,20,21] The incidence of stage I(E) disease is reported to be 9.5-11%.[15,22] The incidence of stage I(E) PTCL in this cohort as compared to advanced-stage disease varies per subtype, i.e., patients with AITL rarely have limited-stage disease, which is in line with previous studies.[23,24] There has been a remarkable shift in diagnoses between the two time periods from predominantly PTCL NOS to a more or less equal divide between PTCL NOS and ALCL. This might be due to better understanding of the disease and therefore more accurate diagnostic classifications like immunohistochemical stainings for better discrimination between the different PTCL subtypes or reflect the actual higher percentage of patients with ALCL presenting with limited-stage disease. Furthermore, the increased use of positron-emission tomography for the staging of aggressive lymphoma helps to more accurately distinguish those patients that truly have stage I(E) disease from those that have low volume advanced-stage disease that might be missed when using the less accurate method of computed

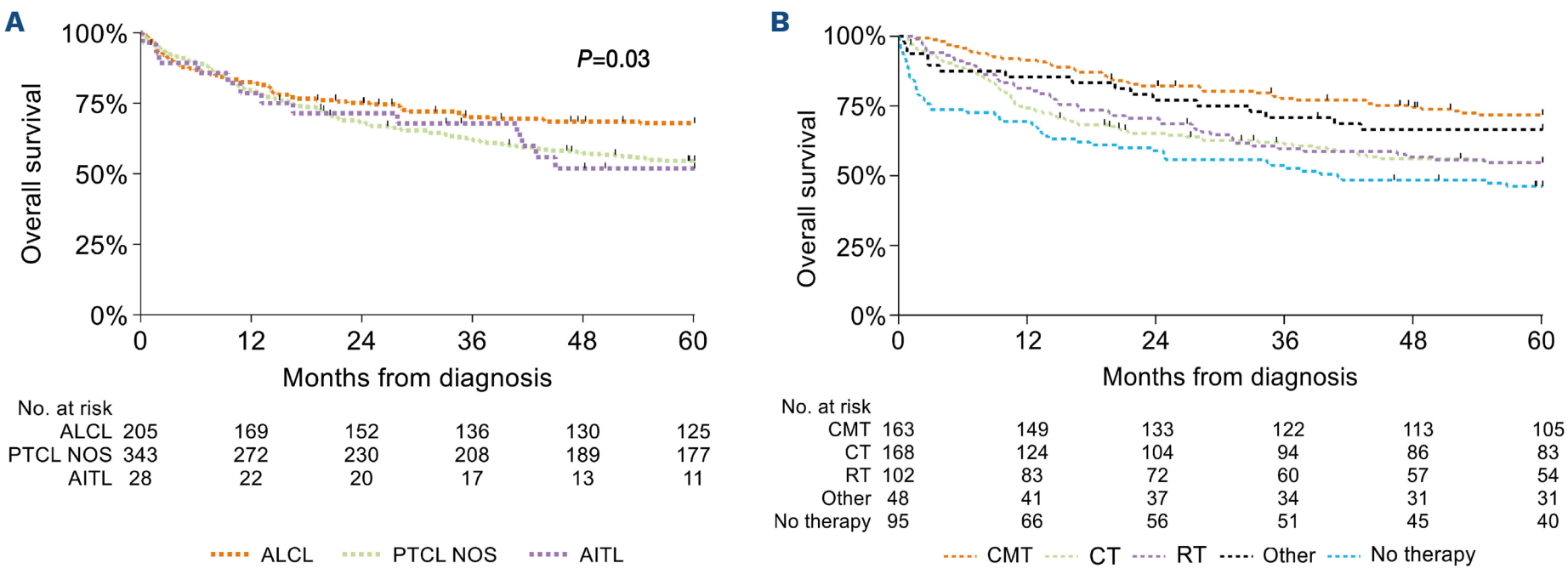


**Figure 3. Overall survival among patients with stage I(E) peripheral T-cell lymphoma.** (A) Overall survival is presented according to subtype and (B) overall survival is presented according to treatment modality. ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; CMT: combined-modality therapy; CT: chemotherapy; RT: radiotherapy.

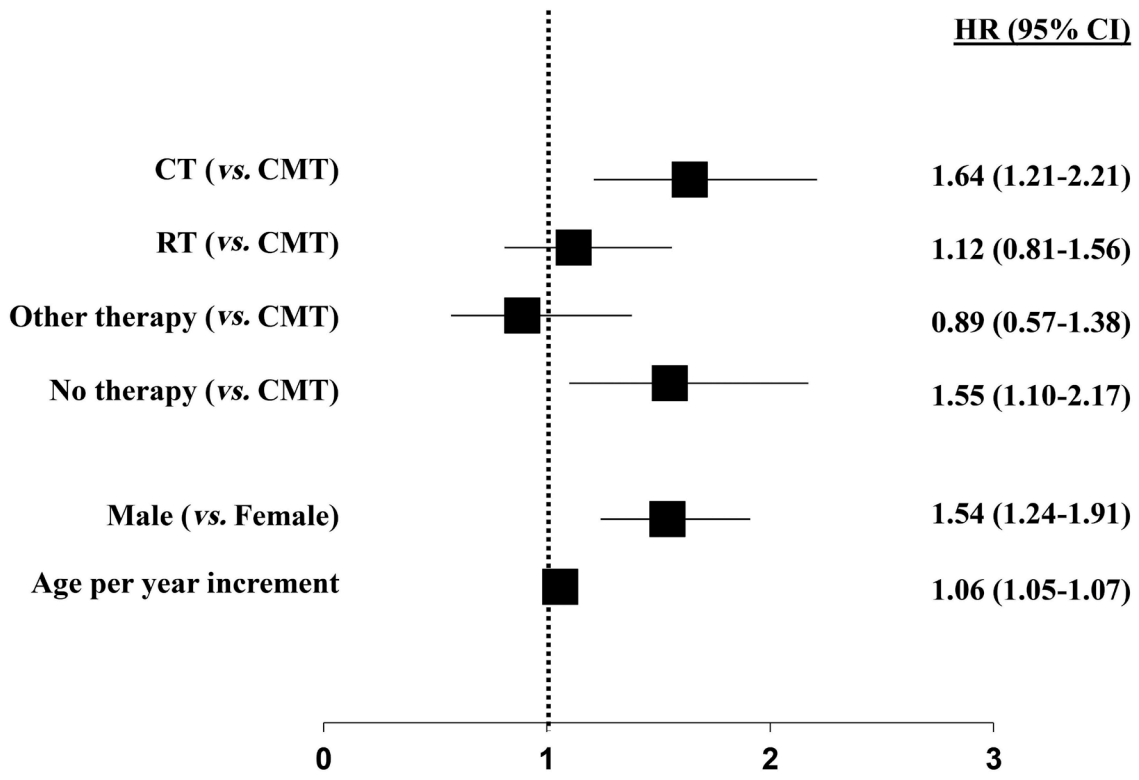


**Figure 4. Forest plot of multivariable analysis for overall survival among patients with stage I(E) peripheral T-cell lymphoma.** HR: hazard ratio; CI: confidence interval; CMT: combined modality therapy; CT: chemotherapy; RT: radiotherapy.

tomography-scanning.

Optimal treatment of patients with limited-stage PTCL remains unknown. Patients with stage II disease can present with quite a variable disease burden and in the Netherlands are generally treated with full course chemotherapy.[18] In parallel with the implementation of CMT in patients with limited-stage aggressive B-cell lymphoma, there was an increase in the administration of CMT for stage I(E) PTCL patients, i.e., from 15% to 40% in the most recent time period. While SCT has been widely adopted in patients with advanced-stage PTCL, it was only offered in 2% of stage I(E) patients.

The favorable 5-year OS of patients with stage I(E) PTCL in the current study, as compared to advanced-stage disease previously reported by our group, confirms the results of the Nordic Lymphoma Epidemiology Group that reported on patients with limited-stage (I-II) AITL, ALCL and PTCL NOS (n=239) and found a similar 5-year OS (58%, including stage II patients) compared to 28% for patients with advanced-stage disease in the same time period.[8,15] It is unclear whether there was a difference in outcome between stage I and II patients. One might expect a better outcome in our cohort since it only reports on patients with stage I disease, however the Nordic Lymphoma Epidemiology Group only included patients that were treated with at least one cycle of CHOP-like therapy whereas we included all patients with stage I(E) disease. In the Netherlands, CMT is preserved for stage I PTCL patients, whereas in other countries CMT is also offered to patients with stage II disease. In our study, outcome among patients with stage I(E) disease who received CMT was similar as compared to outcomes reported in two retrospective registry studies among patients with limited-stage PTCL comparing CMT with CT.[16,17] In these studies, the effect of CMT *versus* CT on outcome was not reported separately for stage I and stage II disease. Therefore, it cannot be ruled out that only in case of stage I disease and not stage II disease, CMT is associated with an improved survival as compared to CT.

Finally, since outcomes are improved in limited-stage aggressive B-cell lymphomas when treated with CMT, we anticipated that, once the use of CMT as a treatment strategy increased, this might lead to improved OS in PTCL patients. While the use of CMT is on the rise, the majority of patients are still treated differently and, therefore the impact of the increase in the use of CMT is not sufficient to have a statistically significant impact on outcome for the whole cohort.

In recent years, many new drugs - alemtuzumab, brentuximab vedotin, romidepsin, amongst others - were studied in the first-line treatment of PTCL and most of them failed to show an improvement in outcome.[9,25,26] Brentuximab vedotin (BV) was the only positive exception. In the ECHELON-2 study, BV-CHP was superior over CHOP.[9] The study population mainly consisted of ALCL patients; only a small number of patients had AITL or PTCL NOS. In a subgroup analysis, in both limited-stage and advanced-stage disease the risk of mortality for patients treated with BV-CHP *versus* CHOP was similar. Recently, no benefit in ORR, PFS or OS was observed in a randomized clinical trial comparing CHOP to CHOP with romidepsin (Ro-CHOP) in PTCL. Separate results for stage I disease patients (3.8%) were not available in that study.[26] In a phase II study, the impact of oral azaciditine added to CHOP was studied as first-line treatment option among 21 patients with PTCL, showing an ORR of 85%. However, only two patients had limited-stage disease.[27] Despite the favorable outcome of limited-stage PTCL as compared to advanced-stage disease, these patients should not be overlooked when conducting clinical trials.

The main strength of our study includes the use of a nationwide population-based cancer registry with comprehensive

data available on first-line treatment in a homogeneous patient population. Limitations of our study include selection bias, as we do not know the motivation of the treating physician to choose a certain treatment modality, lack of information on comorbidities, potential misclassification of subtypes of PTCL, and the lack of information on the dose of radiotherapy. Furthermore, detailed information on tumor, treatment characteristics as well as response and progression-free survival were available from 2014 onward. Despite these limitations, cancer registries remain the standard for cancer surveillance activities and for population-based analysis of treatment outcomes and with little data being available on this subject, let alone prospective studies, these data are highly valuable.

### Conclusion

For stage I(E) ALCL, AITL and PTCL NOS, 5-year OS is 59%. This compares favorably to the reported outcomes in advanced-stage disease. Superior outcome estimates were observed in patients treated with CMT.

### Disclosures

*No conflicts of interest to disclose.*

### Contributions

*MN and MB designed the study. MB collected the data. MB, MN and FM analyzed the data. FM, MB and MN wrote the paper. All authors revised the manuscript and accepted its final version.*

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### Data-sharing statement

*No data sharing other than in the form of this manuscript is possible due to laws and regulations.*

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