Epidemiological and clinical aspects of T-cell lymphoma

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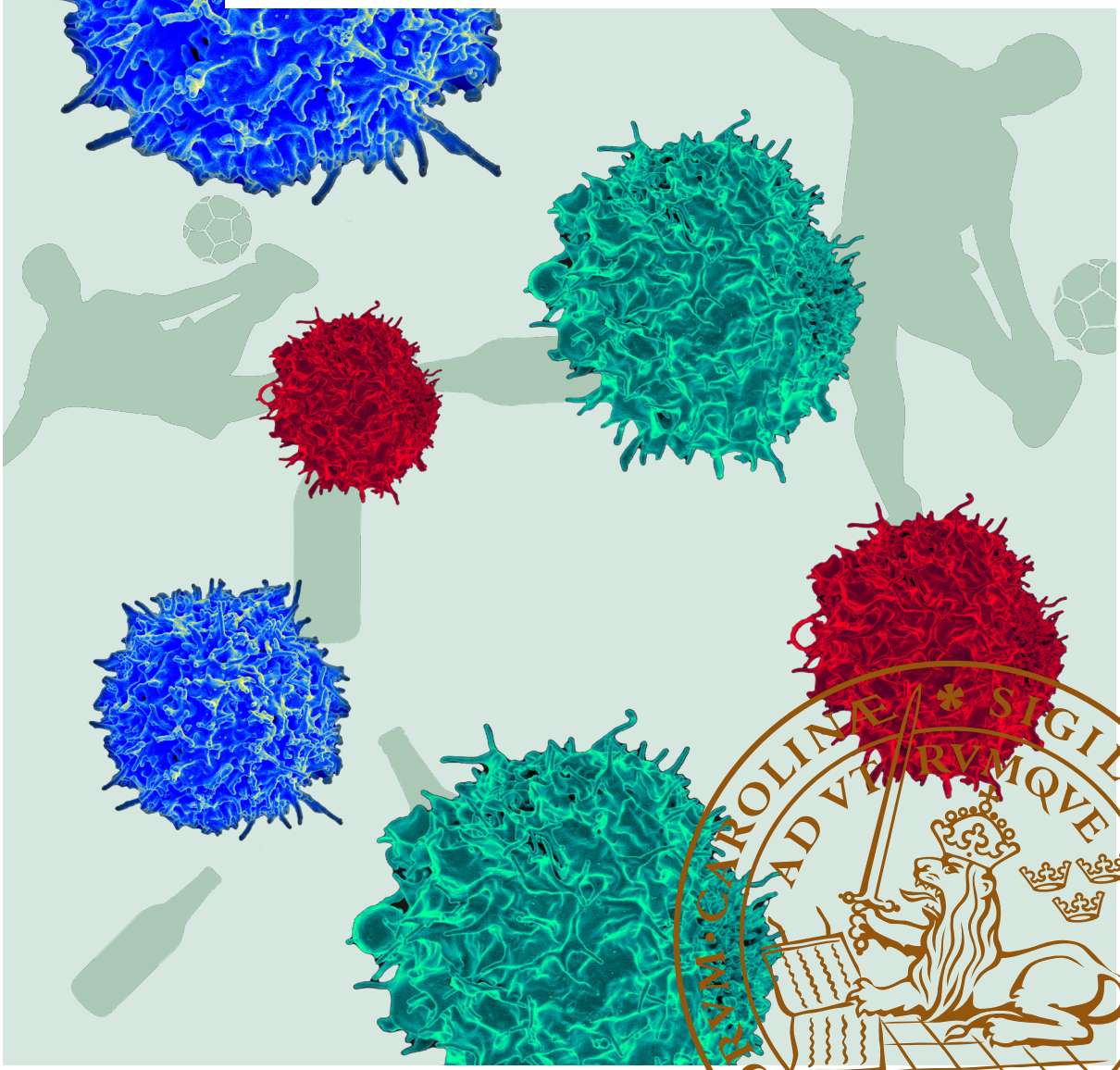

I am a Medical Oncologist at Skåne University Hospital focused on lymphoma and sarcoma. When not working, I like football, Britpop, my (most often) wonderful kids, espresso, NEIPA, and bearnaise sauce. Not necessarily in that order.

In this thesis, population-based information has been used to better understand prognostic factors and outcome after treatment in T-cell lymphoma.

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Epidemiological and clinical aspects of T-cell lymphoma

Henrik Cederleuf

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Abstract

T-cell lymphoma (TCL) is a rare group of malignancies and one of the important aims in this thesis has been to broaden the general knowledge of TCL with descriptive patient data. Main focus has been to examine prognostic factors for overall survival (OS) and progression-free survival (PFS), and to evaluate different treatment approaches and follow-up (FU) after treatment.

The purpose of the first study was to analyse outcome and risk factors in newly diagnosed anaplastic lymphoma kinase positive (ALK+) anaplastic large cell lymphoma (ALCL) patients from Denmark and Sweden and to compare outcome after CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) vs CHOEP (CHOP + etoposide) treatment. Male gender was associated with worse OS and all 10 patients with bone marrow involvement had a relapse, progression or died. CHOEP treatment was associated with better OS than standard treatment with CHOP in patients aged 41-65 years, and the addition of etoposide to CHOP could therefore be a reasonable choice in ALK+ ALCL patients < 65 years.

In the second study, the outcome and FU of Swedish and Danish peripheral (P)TCL patients in first complete remission (CR) was investigated. FU guidelines in Sweden and Denmark were similar except that routine imaging was not recommended in Sweden. There was no significant difference in outcome between the countries, neither when analysing all patients, nor in subtype specific analyses. For patients without relapse 2 years after CR, the mortality was significantly higher than for a matched background population, possibly to some extent related to late relapses and poor response to salvage treatment.

The third study aimed to describe clinical characteristics and outcomes of > 800 older (≥ 70 years) PTCL patients from Sweden and California. Comorbidity information was organized according to the Charlson Comorbidity Index (CCI). Increased CCI score was related to worse survival although prognosis for patients without comorbidity was poor as well, with a median OS of less than a year. Lymphoma was the most common cause of death regardless of CCI score. For Swedish patients responding to treatment, survival was over 3.5 years and no survival difference was seen between untreated patients and patients not receiving CR/CR unconfirmed (u) after chemotherapy. Some older PTCL patients benefit from multiagent chemotherapy, and it is important not to exclude the elderly from potentially curative treatment.

In the fourth study (manuscript), outcome and prognostic factors in limited-stage nodal PTCL patients from Denmark and Sweden were analysed. Adult patients receiving CHOP(-like) treatment ± radiotherapy (RT) were included. Achieving CR/CRu compared to partial response (PR) was associated with significantly increased survival. Age ≥ 60 years and B-symptoms were the risk factors associated with worse prognosis. No significant differences in response rates or survival after treatment were seen between patients treated with 3-4 cycles of CHOP ± RT vs 6-8 cycles ± RT after adjusting for risk factors. For patients in continous CR/CRu, survival was normalized to a matched background population within 24 months from remission. To end FU at this timepoint could therefore be reasonable in limited-stage PTCL.

In summary, survival and response to treatment in T-cell lymphoma is poor. In this thesis four comparatively large population-based studies with valuable data on prognostic factors, clinical characteristics, and treatment are presented. Information about the rarely studied subgroups of older and limited-stage patients is provided, and hopefully the knowledge of T-cell lymphoma is increased to some extent with this thesis.

Key words population-based, peripheral T-cell lymphoma, anaplastic large cell lymphoma, AITL, elderly, ASCT, comorbidity, prognostic factors, follow-up, limited stage, etoposide, CHOP, CHOEP, overall survival, radiotherapy

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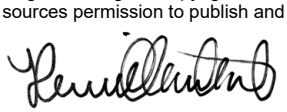
Signature 

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Cover print: Created by the author. Scanning electron micrograph of human T lymphocytes. Credit: National Institute of Allergy and Infectious Diseases, United States.

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When the seagulls follow the trawler, it's because they think sardines will be thrown into the sea.

Eric Cantona

Till August och Elsa

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It's tough to make predictions, especially about the future.

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Cederleuf H, Bjerregård Pedersen M, Jerkeman M, Relander T, d'Amore F, Ellin F.

II. Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study. Leuk Lymphoma. 2017 Dec;58(12):2815-2823. doi: 10.1080/10428194.2017.1300888. Epub 2017 Mar 20. PMID: 28317459.

Cederleuf H, Hjort Jakobsen L, Ellin F, de Nully Brown P, Stauffer Larsen T, Bøgsted M, Relander T, Jerkeman M, El-Galaly TC

III. Impact of comorbidity in older patients with peripheral T-cell lymphoma: an international retrospective analysis of 891 patients. Blood Adv. 2022 Apr 12;6(7):2120-2128. doi: 10.1182/bloodadvances.2021004269. PMID: 34570186; PMCID: PMC9006283.

Mead M[*], **Cederleuf H**[*], Björklund M, Wang X, Relander T, Jerkeman M, Gaut D, Larson S, Ellin F. * Contributed equally to this work.

IV. Outcome of Limited-Stage Peripheral T-Cell Lymphoma After CHOP(-like) Therapy: A Population Based Study of 240 Patients from the Nordic Lymphoma Epidemiology Group.

A. L. Al-Mashhadi[*], **H. Cederleuf**[*], R. K. Jensen, T. H. Nielsen, M. B. Pedersen, T. B. Mortensen, T. Relander, M. Jerkeman, A. O. Gang, A. L. Kristensen, M. R. Clausen, P. de Nully Brown, M. T. Severinsen, L. H. Jakobsen, F. Ellin[‡], T. C. El-Galaly[‡] *‡ Contributed equally to this work. *Manuscript*

My contributions to the papers

Paper I

I was responsible for analysis of the data and for writing the paper.

Paper II

I participated in the collection of data and was together with a statistician responsible for analysis of data. I was responsible for writing the paper.

Paper III

I was involved in the design of the study and collection of data. Together with the co-author, I was responsible for analysis of the data and for writing the manuscript.

Paper IV

I participated in collection and analysis of the data and was responsible for writing the manuscript together with the additional first author.

Monomorphic Epitheliotropic Intestinal T-cell Lymphoma

Selected abbreviations

ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
AITL	Angioimmunoblastic T-cell Lymphoma
Allo SCT	Allogeneic Stem Cell Transplantation
ASCT	Autologous Stem Cell Transplantation
CCI	Charlson Comorbidity Index
CD	Cluster of Differentiation
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CHOEP	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, and Prednisone
CR	Complete Remission
DLBCL	Diffuse Large B-cell Lymphoma
EATL	Enteropathy-associated T-cell Lymphoma
EBV	Epstein-Barr Virus
EFS	Event-free Survival
ENKTCL	Extranodal Natural Killer/T-cell Lymphoma, Nasal Type
HR	Hazard Ratio
HSTCL	Hepatosplenic T-cell Lymphoma
IPI	International Prognostic Index
LYFO	Danish National Lymphoma Registry
MBP	Matched Background Population
MEITL	Monomorphic Epitheliotropic Intestinal T-cell Lymphoma
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
ORR	Overall Response Rate

OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Remission
PTCL	Peripheral T-cell Lymphoma
PTCL, NOS	Peripheral T-cell Lymphoma, Not Otherwise Specified
RLOL	Restricted Loss of Lifetime
SD	Stable Disease
SLR	Swedish Lymphoma Registry
SMR	Standardized Mortality Ratio
SPTCL	Subcutaneous Panniculitis-like T-cell Lymphoma
TFH	T Follicular Helper

Populärvetenskaplig sammanfattning

Lymfom, även kallade maligna (elakartade) lymfom är en typ av cancersjukdom som utgår från delar av kroppens immunförsvar/lymfsystemet. Det finns ca 50 olika lymfomtyper med mycket varierande symptom och biologi där några har ett aggressivt förlopp, s.k. aggressiva lymfom, och andra en långsammare tillväxt, s.k. indolenta lymfom.

I Sverige insjuknar varje år ca 2500 personer i lymfom, varav 55–60% är män och ca 2/3 av patienterna är över 65 år. Vanliga symptom vid insjuknandet är förstorade lymfkörtlar och så kallade B-symptom (feber, viktnedgång och nattliga svettningar).

Lymfom kan utgå från B- eller T-lymfocyter där en stor majoritet är B-cellslymfom och ca 10 % är T-cellslymfom. Det finns ca 15 undergrupper av T-cellslymfom och nästan alla dessa räknas som aggressiva. Bakomliggande orsaker till T-cellslymfom är huvudsakligen okända och inga tydliga kopplingar till levnadsvanor eller ärftlighet är kända. Chans till överlevnad är sämre vid T-cellslymfom än vid B-cellslymfom, och vid de vanligaste typerna av T-cellslymfom lever färre än hälften av patienterna 5 år efter diagnos.

Pga. att sjukdomarna är så sällsynta är det svårt att göra jämförande kontrollerade läkemedelsstudier med enbart T-cellslymfompatienter. Därför är T-cellslymfom ofta med i studier där även B-cellslymfom undersöks. Historiskt har det varit så att behandlingseffekt ibland kunnat visas för nya läkemedel på lymfom generellt och på B-cellslymfom som undergrupp men inte specifikt på T-cellslymfom, ofta pga. för få patienter för att få tillräcklig statistisk styrka. Nuvarande standardbehandling för de flesta undertyper av T-cellslymfom, cellgiftskombinationen CHOP (cyklofosfamid, doxorubicin, vinkristin och prednison), används till exempel utan att det egentligen har säkerställts rent statistiskt att behandlingen är en förbättring från tidigare. Det finns också ett flertal studier som visar att patienter med T-cellslymfom har sämre effekt av CHOP än vad B-cellslymfompatienter har.

För att öka kunskapen om T-cellslymfom, vilka faktorer som påverkar överlevnad och hur bra effekt olika behandlingar ger krävs studier. Då kliniska läkemedelsstudier är svåra att genomföra med så få patienter är i stället insamling av data och sammanställning i efterhand ett alternativ. I Sverige och Danmark finns två av världens mest heltäckande databaser med information om lymfompatienter, där Svenska Lymfomregistret (SLR) har funnits sedan år 2000 och Dansk Lymfom Database (LYFO) sedan 1982.

Denna avhandling är baserad på data från SLR i kombination med LYFO (artikel I, II, IV) och ett register i Kalifornien, California Cancer Registry (artikel III).

I första studien analyserades 122 patienter i en undergrupp av T-cellslymfom som heter ALK-positivt anaplastiskt storcelligt lymfom (ALCL). Vid denna undergrupp är vanligen patienterna yngre än vid andra T-cellslymfom; så även i den här studien där medianåldern var 40 år. 78% av alla patienter levde 5 år efter att de fått sin diagnos och män hade ungefär dubbelt så stor risk att dö som kvinnor.

Vid en jämförelse mellan standardbehandlingen CHOP mot CHOEP (CHOP med tillägg av cellgiftet etoposid) såg vi att de patienter i åldern 41-65 år som fått CHOEP levde längre, även om man tog hänsyn till andra riskfaktorer.

I den andra studien undersöktes överlevnaden och uppföljningen hos över 200 T-cellslymfompatienter i Danmark och Sverige efter behandling med CHOP eller CHOEP. Alla patienter följdes upp med läkarundersökning och blodprover ca 3–4 gånger om året i minst 2 år. I Danmark genomgick patienterna dessutom en skiktröntgen inför läkarbedömningarna medan detta i Sverige bara gjordes för patienter där det fanns en nytillkommen misstanke om återfall (pga. till exempel B-symptom, avvikande blodprover eller tillväxande lymfkörtlar). Resultaten visade ingen skillnad i överlevnad mellan danska och svenska patienter och det verkade inte som att de danska patienterna hade någon tydlig nytta av att genomgå röntgenundersökningar rutinmässigt.

Den tredje studien var ett samarbete med forskare vid UCLA (University of California, Los Angeles) i USA med fokus på bland annat samsjuklighet hos ca 900 T-cellslymfompatienter över 70 år. Patienter utan någon samsjuklighet hade längst genomsnittlig överlevnad (12 månader) jämfört med patienter med en samsjukdom (8,4 månader) eller fler än en samsjukdom (4,4 månader). Överlevnaden var generellt väldigt låg i den här studien, i genomsnitt 9 månader från diagnos. I en delundersökning av svenska patienter såg vi att de som svarade bra på cellgiftsbehandlingen levde klart längre (3,7 år i genomsnittlig överlevnad). Därefter jämfördes patienter som inte fått någon behandling alls mot de som fått behandling som inte lyckats ta bort all sjukdom och där sågs ingen skillnad i överlevnad mellan grupperna. En del äldre patienter med T-cellslymfom kan således ha stor nytta av cellgiftsbehandling och det är viktigt att inte pga. ålder utesluta någon från potentiellt botande behandling.

Den fjärde studien beskriver 240 T-cellslymfompatienter i låga stadier (stadie I-II) från Danmark och Sverige. Ålder över 60 år och/eller B-symptom vid diagnos var relaterat till sämre överlevnad. För patienter som levt utan återfall i två år efter avslutad behandling fanns inte längre någon överdödlighet, dvs ingen ökad risk att dö i förtid jämfört med befolkningen i övrigt. Att avsluta den planerade uppföljningen vid denna tidpunkt torde vara rimligt och utan stora risker för T-cellslymfompatienter i låga stadier.

Sammanfattningsvis är överlevnaden och svar på standardbehandling dålig för patienter med T-cellslymfom. Här presenteras fyra internationellt sett stora, populationsbaserade studier med täckande information om riskfaktorer och behandling. Förhoppningsvis kan denna avhandling på så vis bidra till ökad kunskap inom T-cellslymfom.

Education is an admirable thing, but it is well to remember from time to time that nothing that is worth knowing can be taught.

Oscar Wilde

Introduction

The first known description of the lymph nodes is from the 17th century by the physician and embryologist Marcello Malpighi (1628 - 1694). With the use of a compound microscope, he described the white pulp of the spleen and the splenic lymph nodes, although not using the word lymph. He also found diseases with enlargement of the spleen and lymph nodes, which could be one of the first descriptions of lymphoma[1, 2]. In 1652 the Danish physician Thomas Bartholin (born in Malmö, a part of Denmark at the time) published the first full description of the human lymphatic system. He observed a separate vascular system with what he called "lymph" (Latin *lympha*, meaning "clear spring water"). More than 100 years later, the English surgeon and physiologist William Hewson developed the description of the lymphatic system and was first to describe the main cells in the thymus and spleen, called lymphocytes. He was also first to describe blood coagulation and has been called the father of haematology[3].

In 1832, the British pathologist Thomas Hodgkin described diseases in 7 patients with lymphadenopathy and splenomegaly[4]. It was the first time where this kind of findings were said to originate from the lymphatic organs. 25 years later the physician Samuel Wilks investigated Hodgkin's patient cases and started to call the disorders "Hodgkin's disease" [5].

The first study presenting diseases where the malignant cells had T-cell characteristics, Sézary syndrome, was published in 1973[6]. The knowledge evolved during the following years with more distinctive definitions of lymphomas with T-cell origin [7, 8], but it was not until 1988 that T-cell lymphoma was recognized as an own entity in a widely used classification system, the Kiel classification[9].

Today, *The 2016 revision of the World Health Organization classification of lymphoid neoplasms[*10*]* is used when classifying T-cell and other lymphomas. About 50 different types of lymphomas are included and in line with the continuously expanding diagnostic possibilities, this number will probably increase even more in the future.

Classification of T-cell lymphomas

T lymphocytes arise from progenitor cells in the bone marrow that mature to thymocytes and acquire different functions in the thymus and then mature further in different stages to become T lymphocytes. In the thymic cortex, antigen-specific T-cells mature. These cortical thymocytes have an immature T-cell phenotype and express CD3, CD5, and CD7, but are negative for both CD4 and CD8. CD4 *and* CD8 are co-expressed in maturing thymocytes whereas more mature T-cells express either CD4 *or* CD8. Medullary thymocytes are more similar to mature T-cells and are divided into two classes depending on the structure of the T-cell receptor (TCR); alpha beta (αβ) T-cells and gamma delta (γδ) T-cells[10]. Mature T-cells need signals from the TCR to be activated, and rearrangement of genes coding the TCR is common in TCL[10, 11].

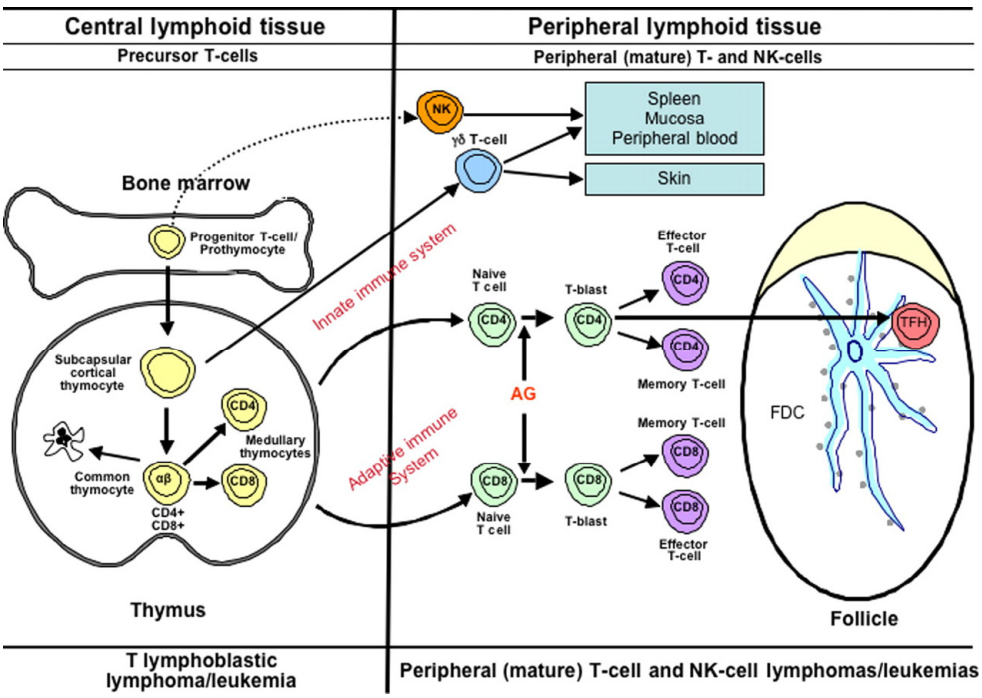

Figure 1. T-cell differentiation. Precursor T-cells in the thymus develop into naïve T-cells. The innate immune system include NK cells and γδ T-cells, giving a primitive type of immune response without memory or specificity. αβ T-cells are a part of the adaptive immune system, and they leave the thymus and transform to CD4+ and CD8+ effector and memory T-cells.

TCL originated from the innate immune system are often extranodal and more common in children and young adults whereas TCL evolving from the adaptive immune system primarily affects adults and are mostly nodal. The complexity of the immune system and maturation of T and NK cells contributes to the very heterogenous spectrum of malignancies with T or NK cell origin[10, 12].

Diagnosis of T-cell lymphoma

The diagnosis of TCL is a combination of clinical features, lab tests and radiology, together with analysis of tumour tissue. Fine-needle aspiration is seldom enough, and a surgical biopsy is recommended, preferably of an entire lymph node with suspect malignancy. Bone marrow biopsy and aspiration is recommended, and lumbar punction if suspicion of CNS involvement[13-16].

Although certain antigens are expressed differently in different TCL subtypes, no antigen is specific for a subtype. A combination of morphologic, immunophenotypic and (sometimes) genetic information is needed for subtype specific diagnosis.

Epidemiology

TCL is relatively uncommon and in most areas of the world about 10 % of non-Hodgkin lymphomas (NHL)s are TCL, except for East Asia where 15-20 % of NHL are of TCL type[17-20]. The distribution of different TCL subgroups varies geographically, demonstrated by the International TCL project, analysing > 1300 cases of TCL or NKTCL from South Africa, North America, Europe, and Asia. PTCL NOS was the most common subtype worldwide. Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is more common in Asia with about 8% compared to <1% of NHL cases in Europe and North America. Enteropathy-associated T-cell lymphoma (EATL) on the other hand, is overrepresented in Northern Europe due to the connection to celiac disease which is common there[17].

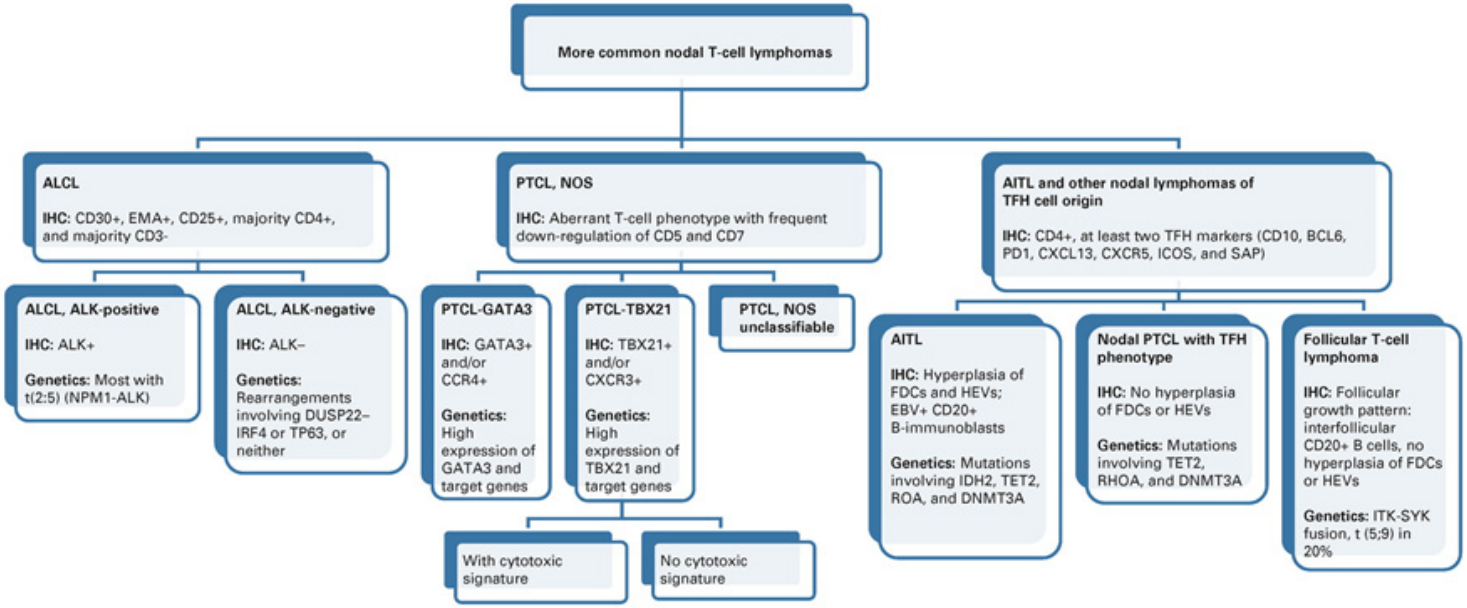

Figure 2. Improved precision in T-cell lymphoma classification. The more common nodal T-cell lymphomas include ALCL, PTCL, NOS and AITL, and other nodal lymphomas of TFH cell origin. IHC and genetics unique to each T-cell lymphoma subtype are shown. ALCL is subclassified as ALCL, ALK-positive and ALCL, ALK-negative, which are distinguished by the presence or absence of ALK expression and t (2;5) translocation. ALCL, ALK-negative may be further subdivided into three groups on the basis of the presence of genetic rearrangements involving DUSP22-IRF4, TP63, or neither. PTCL, NOS may be subdivided into PTCL-GATA3 and PTCL-TBX21 on the basis of upregulation of GATA3 or TBX21 and their associated genes. Although PTCL-TBX21 is generally associated with more favorable outcomes, a subgroup within PTCL-TBX21 characterized by upregulation of a cytotoxic T-cell gene signature is associated with a less favorable outcome. AITL and other nodal lymphomas of TFH cell origin are identified by the presence of neoplastic CD4+ T cells with at least two TFH markers and include AITL, nodal PTCL with TFH phenotype, and FTCL. These entities have overlapping IHC and mutational profiles, as well as similarities in clinical behavior. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; FDC, follicular dendritic cells; FTCL, follicular T-cell lymphoma; HEV, high endothelial venules; IHC, immunohistochemistry; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; TFH, T-follicular helper

T-cell lymphoma subtypes

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) is a rare CD30+ peripheral T-cell lymphoma (PTCL) further classified into whether it expresses the *NPM-ALK* gene (ALK+) or not (ALK-)[10, 21]. ALCL hallmark cells are typically large and pleomorphic with kidney- or horseshoe-shaped nuclei. No obvious morphological differences between ALK+ and ALK- ALCL are known, and the detection of the *NPM-ALK* t(2;5) translocation, occurring in about 80 % of ALK+ patients has been vital to distinguish between the two. The remaining ALK+ patients have rearrangements involving chromosome 2 and other different partner genes. Immunohistochemistry staining of ALK is used in routine care[22].

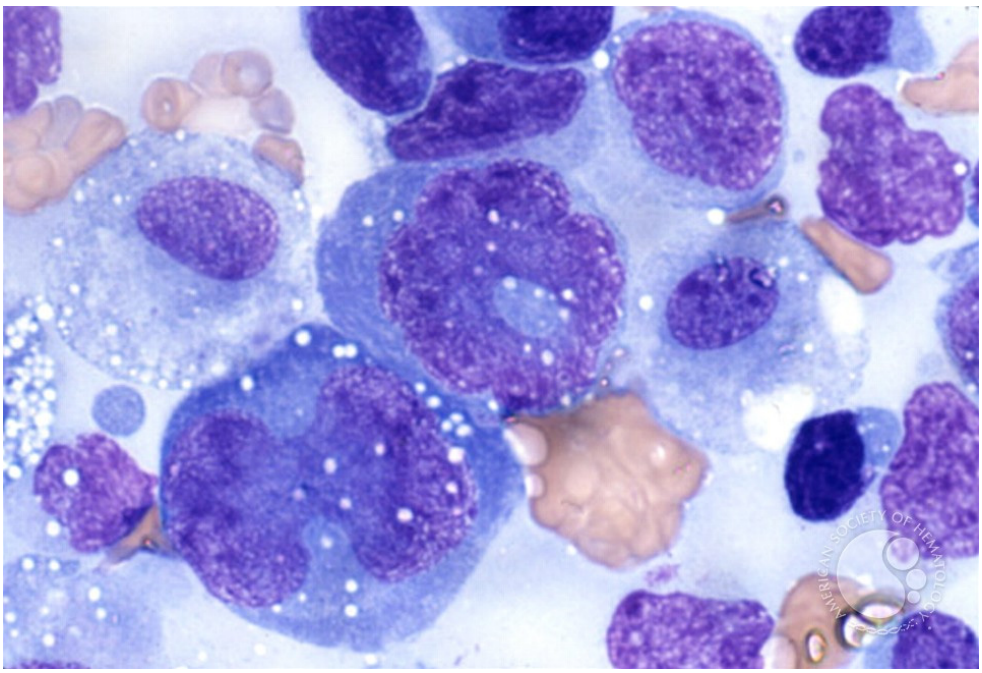

Figure 3. Anaplastic large cell lymphoma. Cytology of tumor cells showing binucleate and ring-shaped nuclei. This image was originally published in ASH Image Bank. Marshall Kadin. 2002; 1766. © the American Society of Hematology.

ALK+ ALCL has been an own lymphoma entity since the 2008 WHO classification of lymphoid neoplasms[21], whereas the diagnosis of ALK- ALCL is harder to distinguish from other PTCLs[23, 24]. The genetic background of ALK+ and ALK- ALCL is similar, but some differences are seen. A 3-gene model (*TNFRSF8*,

BATF3, and *TMOD1*) validated in 2012 distinguished between ALK- ALCL and CD30+ PTCL NOS[23]. Iqbal and colleagues applied the described 3-gene model and developed an ALCL signature able to distinguish ALK- ALCL from both ALK+ ALCL and from other PTCLs[25], and in 2016 ALK- ALCL was recognized as an entity of its own[10].

Mutations that lead to activation of the known oncogenic *JAK/STAT3* pathway are seen in many ALCL patients. Rearrangements with possible prognostic importance in ALK- ALCL are *DUSP22* reported to be associated with good survival and *TP63* with poor survival[10, 26, 27]. Further studies are needed to validate the importance of these rearrangements.

ALK+ ALCL is a disease mostly diagnosed in children and young adults with a median age of 30 years whereas ALK- ALCL arises in older adults, and median age is about 55 years[17, 22].

A new provisional entity in the 2016 WHO classification is breast implant-associated ALCL (BIA ALCL), a rare form of ALK- ALCL arising around breast implants[28]. Over 80 % of patients with BIA ALCL present with localized disease and are normally cured with surgery, whereas patients with advanced stage disease are treated similarly to other ALCL patients with chemotherapy and/or radiotherapy[28, 29].

Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper cell origin

The entity of angioimmunoblastic T-cell lymphoma (AITL) was recognized in the Kiel classification of 1988[30]. AITL is characterized by a polymorphous infiltrate of neoplastic T-cells with clear cytoplasm, mixed with follicular dendritic cells (FDC), eosinophils, and plasma cells. Prominent arborizing blood vessels are usually present as are large EBV-positive B-cell blasts. Some B-cell blasts can look like Hodgkin-Reed-Sternberg (HRS) cells, risking diagnostic problems[10].

Usually, the background is more abundant than the neoplastic T-cells and the small number of malignant cells can make diagnosis difficult[31].

Genetically, Ten-Eleven-translocation (TET) proteins are involved in the epigenetic transcription control via DNA methylation[32] and *TET2* mutations are shown to increase the risk of myeloid[33] and lymphoid neoplasms[34]. *TET2* mutations are present in about 40 % of AITL cases and associated with advanced stage disease, B-symptoms and thrombocytopenia[35]. Other important genetic alterations linked to AITL are mutations of *IDH2*[36, 37] and *DNMT3A*[33], both related to DNA methylation, and *RHOA* mutations where impaired RHOA function seems to contribute to the pathogenesis of AITL[38].

Gene expression in AITL is similar to normal T-follicular helper (TFH) cells, suggesting that TFH cells are precursor cells to AITL[31, 35, 39]. In 20-30 % of PTCL, NOS, the same expressed markers as in AITL can be observed[37, 40, 41]. This has been recognized in the 2016 WHO classification where nodal PTCL with TFH phenotype is a provisional entity of its own, requiring at least two (preferably three) of the markers CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5. AITL, nodal PTCL with TFH phenotype, and follicular T-cell lymphoma (FTCL) are all included under the new category nodal T-cell lymphomas with T-follicular helper phenotype[10]). FTCL seems to biologically differ from AITL in that FTCL does not have the same polymorphous background or FDC network[42], whereas rosette-forming of T-cells around HRS-like cells seems more common in FTCL than in AITL[42, 43].

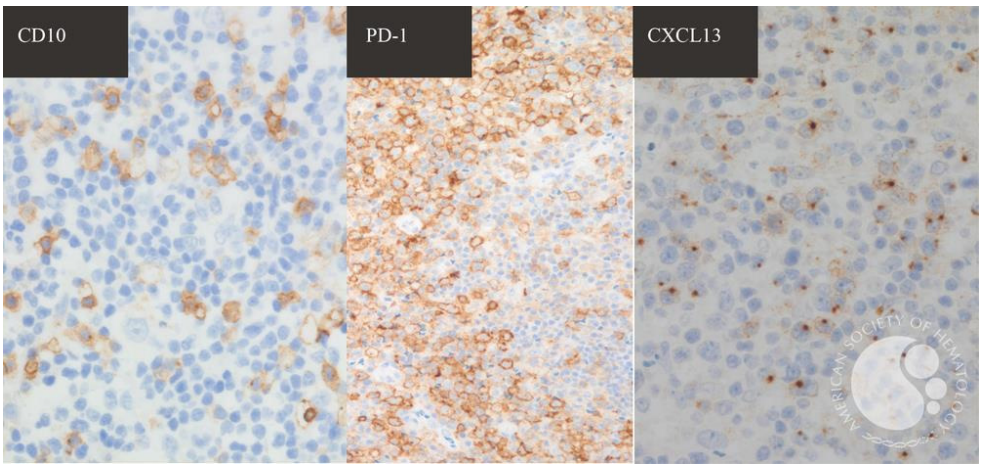

Figure 4. Follicular helper T-cell markers in AITL. CD10, PD-1 and CXCL13. This image was originally published in ASH Image Bank. Girish Venkataraman. 2017; 61034. © the American Society of Hematology.

More than 85 % of AITL patients present with advanced stage disease. Rashes with pruritus are frequent. Hypergammaglobulinemia, hepatosplenomegaly, and bone marrow involvement is common[21].

Peripheral T-cell lymphoma, not otherwise specified

Peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS) is a heterogenous type of TCL, partly an exclusion diagnosis for PTCL not fitting to any other subtype. The cytological spectrum is wide, with most cases having many medium-sized or large cells with pleomorphic, irregular nuclei. Reed-Sternberg-like cells can also be seen. Inflammatory cells are common and the distinction from AITL can be difficult. 30 % of cases are CD30+ and until some years back, the

discrepancy to ALK- ALCL sometimes have been tricky, but now the morphology usually can separate PTCL NOS from ALCL and Hodgkin lymphoma[44].

Two major subgroups can be found within the PTCL NOS group with expression of either GATA3 or TBX21[25]. These two subgroups seem to have different genetic backgrounds and vary in survival, with GATA3 associated with TP53 and PTEN codeletions and PI3-kinase pathway activation, and with poor OS[37].

With the evolving understanding of the genetic background in PTCL, the proportion of PTCL, NOS is likely to decrease and cases that previously would have been called PTCL, NOS, will get more distinct diagnoses in the future.

Enteropathy-associated T-cell lymphoma

Enteropathy-associated TCL (EATL), formerly called EATL type I, is a tumour of intraepithelial T lymphocytes in the intestine, commonly jejunum or ileum. The tumour cells are usually large but vary in size and appearance and the common infiltration of inflammatory cells around can make it difficult to recognize the tumour. The tumour cells are often CD3+, CD4-, CD5- and a varying degree of CD8-/+ and TCRβ+/-[10]. EATL is related to celiac disease (CD) and most common in Northern Europe and almost all patients are Caucasian[45]. Patients often have intestinal symptoms and can sometimes present with untreatable CD or are diagnosed with EATL and CD at the same time[10]. Complications to CD such as ulcerative jejunitis and loss of effect to gluten-free diet have similar monoclonality of T-cells as in EATL, consisting of non-invasive intraepithelial T lymphocytes, suggesting that these cases have a T-cell neoplasm[46].

Monomorphic epitheliotropic intestinal T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly known as EATL type 2, is recognized as an own entity in the latest WHO classification. The lymphoma cells are monomorphic and often small to medium-sized[47]. MEITL seem to have somewhat same genetic background as EATL with many mutations present in both types[48] but differs from EATL with its lack of association to celiac disease and that it is usually positive for CD8 and CD56, and commonly expresses TCRγδ[10, 47].

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

Indolent T-cell lymphoproliferative disorder (LDP) of the gastrointestinal (GI) tract, a provisional entity in the WHO 2016 classification, can affect any part of the intestine. Cases often have CD8+ and CD56- tumour cells and a rearrangement of

the TCRγ chain. They can look like inflammatory diseases or other intestinal TCL, and therefore be misdiagnosed. Since it has an indolent clinical course where aggressive treatment rarely is necessary, it is important to differentiate indolent T-LPD of the GI tract from more aggressive lymphomas[49].

Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is an aggressive lymphoma most common in Asia and South America, associated with EBV-infection. ENKTCL most often is located in or around the nasal cavity, but other locations such as the GI tract can also be involved. Cases commonly have an angiocentric growth with ulceration and necrosis with tumour cells expressing CD56 and negative for CD4, CD5, and CD8. Most cases derive from NK cells and a small part from cytotoxic T cells[10, 50].

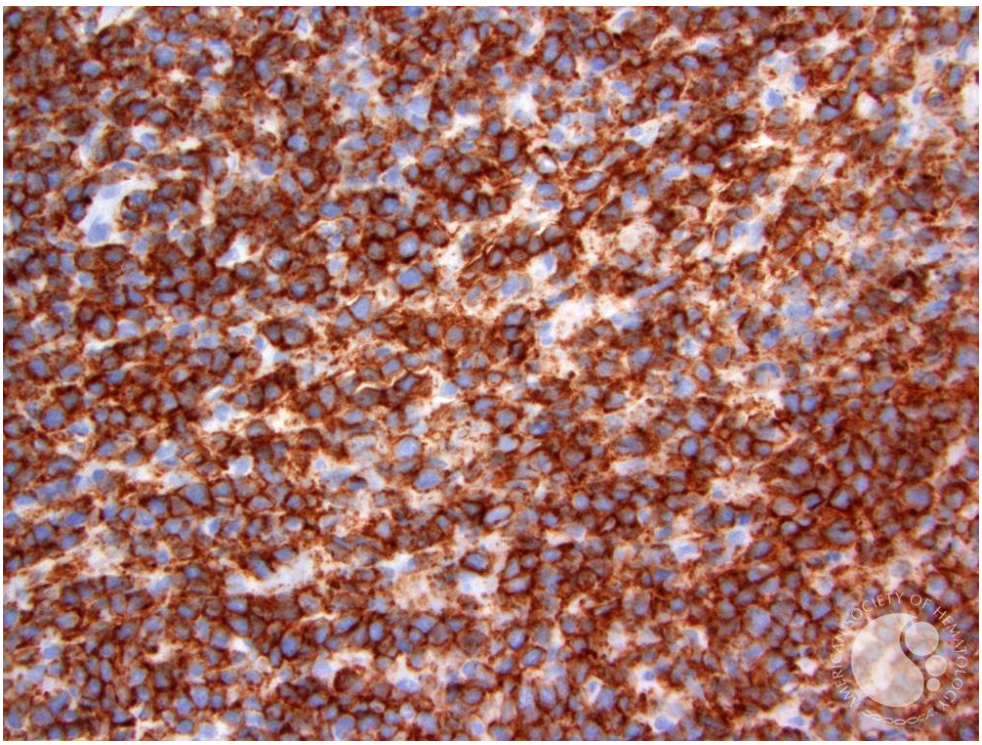

Figure 5. Extranodal NK/T-cell lymphoma. CD56 positive neoplastic cells. This image was originally published in ASH Image Bank. Joo Y. Song, MD. 2016; 60493. © the American Society of Hematology.

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare extranodal T-cell neoplasm derived from cytotoxic T-cells. Tumour cells are medium-sized and usually TCRγδ+ and CD56+, CD4-, CD5- and CD8-. The disease is most common in young men and often clinically aggressive with many patients presenting with bone marrow infiltration, B-symptoms, and hepatosplenomegaly[10].

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a subcutaneous neoplasm with tumour cells of various sizes, expression α/β+, CD8+, CD4-, CD30, CD56-. The tumour often consists of nodules in the trunk, arms, and legs and has a good prognosis[51, 52].

In the latest WHO revision, cases earlier known as SPTCLγδ are now included under primary cutaneous γδ (PCGD) TCL[10].

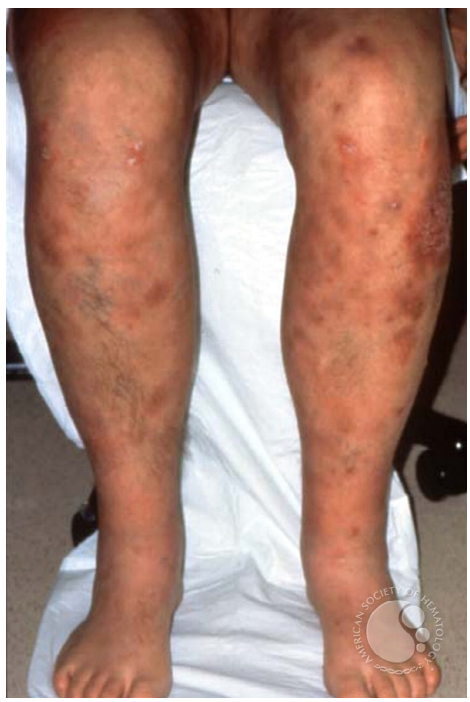

Figure 6. Subcutaneous panniculitis-like T-cell lymphoma. Subcutaneous plaques. This image was originally published in ASH Image Bank. Marshall Kadin. 2003; 2192. © the American Society of Hematology

Background to studies

Patient characteristics and prognosis in T-cell lymphoma

The clinical background of TCL patients has been explored internationally within the earlier mentioned International T-cell Lymphoma Project analysing over 1300 patients from across the world. Median age is around 60-65 years at diagnosis but younger for some subtypes, with ALK+ ALCL, HSTCL, and SPTCL patients having median ages of about 35-45 years. Most patients present with advanced stage disease (Ann Arbor III/IV) and male sex is more frequent in all subtypes[17, 19](see table 1).

Table 1. Patient characteristics by histologic type.

Diagnosis	Distribution	Median Age (yr)	Male	Stage III/IV	BM inv.	IPI 0/1	IPI 2/3	IPI 4/5
PTCL-NOS	26%	60	66%	69%	22%	28%	57%	15%
AITL	19%	65	56%	89%	29%	14%	59%	28%
ENKTCL	7.0%	52	64%	27%	10%	51%	47%	2%
ATLL	9.6%	62	55%	90%	28%	19%	65%	16%
ALCL, ALK+	6.6%	34	63%	65%	12%	49%	37%	14%
ALCL, ALK−	5.5%	58	61%	58%	7%	41%	44%	15%
EATL	4.7%	61	53%	69%	3%	25%	63%	13%
Primary cALCL	1.7%	55	64%	14%	0%	86%	14%	0%
HSTCL	1.4%	34	68%	95%	74%	5%	47%	47%
SPTCL	0.9%	33	75%	83%	8%	42%	42%	17%
Other/Unclassed	18%							

Yr, years; BM inv, bone marrow involved; IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; AITL, Angioimmunoblastic T-cell lymphoma; TCL, T-cell lymphoma; ENKTCL, extranodal natural killer TCL; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EATL, Enteropathy-associated T-cell lymphoma; cALCL, cutaneous ALCL; HSTCL, hepatosplenic TCL; SPTCL, Subcutaneous panniculitis-like TCL.

Survival in PTCL in general is poor with reported 5-year OS from 20-40 % in most subtypes with the exception of ALK+ ALCL (5-year OS = 70-80%), although the good prognosis seems partly related to younger age and less risk factors, and survival for ALK+ ALCL patients with many risk factors (IPI score 4-5) is poor as well[17, 19] (see table 2).

Table 2. 5-year overall survival by histologic type and IPI score.

Diagnosis	5-year Overall Survival (%)		
	All patients	IPI 0/1	IPI 4/5
PTCL-NOS	32%	50%	11%
Angioimmunoblastic TCL	32%	56%	25%
ENKTCL	42%	57%	0%
ATLL	14%	28%	7%
ALCL, ALK+	70%	90%	33%
ALCL, ALK-	49%	74%	13%
Enteropathy-associated TCL	20%	29%	14%
Primary cutaneous ALCL	90%	100%	NA
Hepatosplenic TCL	7%	0%	0%
Subcutaneous panniculitis-like TCL	64%	60%	0%

IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ENKTCL, extranodal natural killer TCL; TCL, T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NA, not applicable.

Reprinted from Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008 Sep 1;26(25):4124-30. Table 3. doi: 10.1200/JCO.2008.16.4558. Copyright © 2008, with permission from the American Society of Clinical Oncology.

First-line treatment in T-cell lymphoma

During the inclusion years for the papers in this thesis, CHOP has been considered the standard treatment for nodal PTCL and has been so for the last four decades. Nevertheless, the effect of CHOP has been demonstrated mostly in cohorts with a majority of B-cell lymphoma, and PTCL in general have worse outcomes than BCL[53, 54], with the exception of ALK+ ALCL[53, 55]. Few randomized trials have compared CHOP to other regimens first-line in PTCL, and these studies have not showed any survival benefit with other approaches[56, 57]. The addition of etoposide to CHOP has been investigated to some extent, with Schmitz et al retrospectively analysing German patients enrolled in prospective trials randomized to CHOP or CHOEP, showing improved 3-year event-free survival but not OS in CHOEP treated ALK+ ALCL patients < 60 years with normal LDH[58]. In a large Swedish population-based cohort, Ellin et al found similar results in multivariate

analysis with superior PFS in PTCL patients < 60 years treated with CHOEP compared to CHOP, but no significant difference in OS[19].

Involved site radiotherapy (ISRT) consolidation after chemotherapy have shown effect in limited-stage PTCL[59, 60] and is recommended in stage I disease in most guidelines, often 30-40 Gray (Gy) after 3-4 cycles of CHO(E)P, although no randomized trials have showed better survival with this approach[16]. In ENKTCL, radiotherapy is more vital and doses >50 Gy are sometimes given as single treatment in stage I disease although a combination with 6 cycles of chemotherapy is often recommended with RT after the third cycle[61].

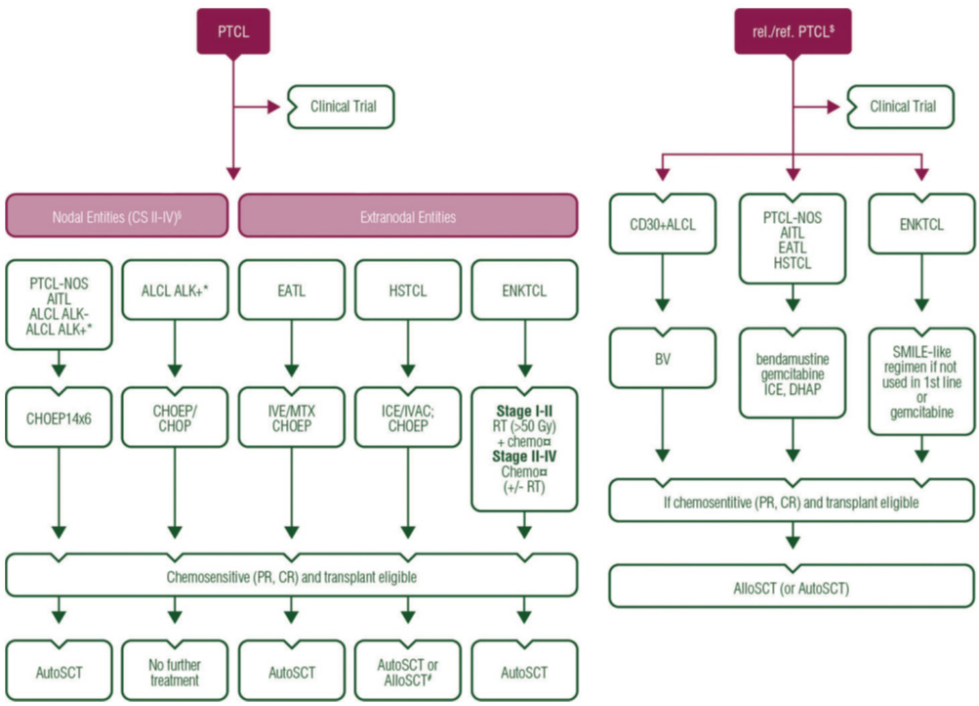

Figure 7. Integrated management algorithm from 2015 (according to, e.g. risk factors, stage and histological subtype) in the (A) front-line and (B) relapsed/refractory setting. (A) § Stage I: shortened chemotherapy schedule (e.g. 3 courses) followed by curatively intended RT. *ALCL ALK+ with a high-risk profile (e.g. IPI >2) should be considered for autoSCT consolidation. # if donor available. ¤ SMILE or AspaMetDex. (B) $: Pralatrexate and romidepsin: FDA but not EMA approved.; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; CHOEP, CHOP + etoposide; IVE/MTX, ifosfamide, vincristine, etoposide/methotrexate; ICE, ifosfamide, etoposide, and carboplatin; IVAC, ifosfamide, cytarabine, etoposide; PR, partial response; CR, complete response; alloSCT, allogeneic stem-cell transplantation; autoSCT, autologous SCT; rel/ref, relapsed/refractory; BV, brentuximab vedotin; DHAP, dexamethasone, high-dose cytarabine, cisplatin; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide; CS, clinical stage; RT, radiotherapy. *First published in Annals of Oncology 26 (Supplement 5): v108–v115, 2015 doi:10.1093/annonc/mdv201, with permission.*

Consolidation or not with high-dose chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) in PTCL is a debatable question. D'Amore et al showed somewhat encouraging results in the NLG-T-01 phase II study investigating response to HDT/ASCT in untreated PTCL patients (ALK+ ALCL excluded). PTCL patients aged 18-67 years (median, 57 years) were treated with CHOEP x 6 (no etoposide if > 60 years) and consolidated with HDT/ASCT if responding to induction. 5-year PFS was 44 % in this cohort with adverse risk factors[62].

In the COMPLETE cohort study, Park et al analysed the role of ASCT in patients with newly diagnosed PTCL in the United States. ASCT after CR was associated with better OS in patients with high IPI score or advanced-stage disease[63]. In another large US study, Abramson et al reported significantly poorer outcomes in PTCL compared to DLBCL and found no clear benefit for PTCL patients receiving ASCT[54].

Although results are contradictory regarding the benefit, HDT with ASCT is recommended as standard consolidation after chemotherapy in eligible, chemo responding PTCL patients (except stage I patients and low-intermediate risk ALK+ ALCL patients) in both the ESMO and the NCCN guidelines[15, 16].

Treatment in specific T-cell lymphoma subtypes

Anaplastic large cell lymphoma

In ALCL patients, standard treatment today is brentuximab vedotin (BV)-CHP (CHOP without vincristine), based on the ECHELON-2 trial[64] (see Discussion > Improving treatment in TCL).

Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of TFH origin

CHOP is the standard treatment for this group although the recognition that TFH cells are the cells of origin of AITL and that there are specific genetic markers related to malignant TFH cells, have increased the interest in new potential treatment targets[41] (see Discussion > Improving treatment in TCL).

Enteropathy-associated T-cell lymphoma

CHOP is standard treatment in most guidelines. An approach with CHOP followed by IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate (MTX) as initial therapy was tested in a British study reporting improved PFS and OS in patients with EATL and could be used as frontline treatment [15, 65].

Extranodal NK/T-cell lymphoma, nasal type

Anthracycline-based chemotherapy is not effective in ENKTCL, and L-asparaginase-containing regimens is often recommended instead. Most patients present with localized disease and are recommended consolidation with radiotherapy after chemotherapy, whereas advanced stage disease patients are recommended full L-asparaginase-containing chemotherapy consolidated with HDT and ASCT if responding[16, 66].

Hepatosplenic T-cell lymphoma

This rare TCL is often difficult to treat and has a poor prognosis. Intense treatment with dose-dense CHOEP/EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) or the combination ICE (ifosfamide, carboplatin, etoposide) can be used followed by ASCT or AlloSCT[67].

Prognostic indices

The International prognostic index (IPI)[68] developed for BCL is commonly used and recommended in PTCL as well[15, 16] and some studies have investigated if other similar prognostic models better could identify risk groups with different prognosis in PTCL. Although good at predicting outcomes, no obvious benefit has been seen when using the Prognostic Index for T-cell lymphoma (PIT) score instead of IPI[19, 59]. The NCCN-IPI, a weighted version of IPI giving age, elevated LDH and localization of extranodal site more importance, has shown better risk group discrimination than IPI in DLBCL[69], but this was not seen in PTCL[70].

Table 3. The International Prognostic Index (IPI). *Adapted from International Non-Hodgkin's Lymphoma Prognostic Factors Project, NEJM 1993[68].*

Risk Factor	0 Point	1 Point
Age	≤ 60 years	> 60 years
Ann Arbor stage	I or II	III or IV
Serum LDH level	Normal	Elevated
Extranodal sites involved	0-1	>1
ECOG performance status	0-1	>1

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

The impact of age and comorbidity in T-cell lymphoma

PTCL usually affects older adults, ALK+ ALCL excepted, and a median age of 60-67 years has been seen in most large PTCL cohorts[17, 19, 71]. CHOP-like treatment is considered standard of care also in older PTCL patients, but randomized data in this group is sparse. In a phase II trial with 150 DLBCL patients aged > 79 years, 6 cycles of low-dose CHOP (miniCHOP) and rituximab was given. Toxicity was mild and results were good with 62% receiving complete response and 2-year OS for all patients was 59 %[72]. However, no comparable drug to rituximab (except BV in CD30+ ALCL) exists as standard addition to CHOP in PTCL, and response rates to chemotherapy is generally worse in PTCL than in DLBCL[54], making it difficult to extrapolate the effect of R-miniCHOP to elderly PTCL patients.

In a Swedish population-based study, no difference was seen in OS between curative and low-intensive treatment in a subgroup analysis of PTCL patients ≥ 75 years, and the authors suggested that the poor effect of standard treatment with CHOP partly could explain this, questioning CHOP as standard treatment in elderly PTCL and suggesting prospective studies in this group[73].

Multiagent chemotherapy can be hard to tolerate for older patients[74], but studies indicate that comorbidity and not age itself is related to survival in B-cell lymphoma[75]. To analyse the impact of comorbidity, the widely practiced and validated Charlson Comorbidity Index (CCI) has been used[76]. To what extent comorbidity affects survival in older PTCL patients has not been widely studied, with data from a few retrospective cohorts being small and showing diverse results[73, 77].

In patients not suitable for anthracyclines, CEOP (etoposide instead of doxorubicin) can be considered. For patients not fit for curative treatment, single agents bendamustine or gemcitabine could be considered, but randomized studies on how to best treat frail PTCL patients are lacking.

Table 4. Charlson Comorbidity Index. *Adapted from Charlson et al., table 3[76]*

Condition	Assigned weight
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Liver disease, mild	1
Diabetes	1
Hemiplegia	2
Renal disease, moderate or severe	2
Diabetes with end organ damage	2
Any tumour	2
Leukemia	2
Lymphoma	2
Liver disease, moderate or severe	3
Metastatic solid malignancy	6
Acquired immunodeficiency syndrome (AIDS)	6

Relapse treatment in T-cell lymphoma

In relapsing CD30+ ALCL today, brentuximab vedotin (BV) is strongly recommended in patients that did not receive BV in first-line or progressed during BV. This is based on studies with high response rates in heavily treated ALCL patients[78]. BV can also be used in relapsing patients with prior response to BV, but there is an increased risk of neuropathy[79]. 5-yr follow-up of BV in R/R ALCL showed long response duration after BV also in patients that was not consolidated with SCT[14, 80].

For other TCL subtypes, no evidence to recommend a certain treatment instead of another exists. ICE (ifosfamide, carboplatin, etoposide), GDP (gemcitabine, dexamethasone, cisplatin) and DHAP (dexamethasone, high dose cytarabine, cisplatin) have all shown effect and can be recommended[15, 16, 81].

If responding to relapse treatment, HDT and ASCT should be considered. For young, fit patients that received ASCT in first-line, allogeneic SCT after induction is an option.

In patients not fit for curative treatment, single agent treatment with bendamustine or gemcitabine are two of the most studied. In the prospective phase 2 one-arm

BENTLY trial evaluating bendamustine, TCL patients who had progression after one or more prior lines of chemotherapy were included. All patients received bendamustine day 1 and 2 every 3 weeks for six cycles. > 90 % of the patients had AITL or PTCL, NOS and 87% had stage III-IV disease. ORR was 50% (28% CR, 22% PR). The authors concluded that this was an encouraging high response rate and a treatment associated with acceptable toxicity[82].

In 2009, Zinzani et al evaluated the effect of gemcitabine in pre-treated mycosis fungoides (MF) and PTCL, NOS patients. 20 patients with PTCL, NOS, all of them in stage III-IV, were treated with gemcitabine days 1, 8, and 15 in 28-day cycles for 3-6 cycles. ORR for PTCL, NOS patients was 55% (30% CR, 25% PR). Of the 6 PTCL, NOS patients achieving CR, 5 were in continuous CR when follow-up ended, with a median follow-up of 35 months[83].

Aims of this thesis

In this rare group of malignancies, one of the important aims has been to broaden the general knowledge in T-cell lymphoma with description of clinical characteristics in different subtypes. Our main focus has been to examine prognostic factors for PFS and OS, and to evaluate different treatment approaches and follow-up after treatment.

- The aim of paper I was to present clinical characteristics and to examine outcome and prognostic factors including comparison of treatment with CHOP vs CHOEP in systemic ALK+ ALCL patients from Denmark and Sweden in a population-based patient cohort.
- In paper II, the aim of the study was to describe clinical background, outcome, and prognostic factors for PTCL patients in first remission and to evaluate differences between follow-up strategies in Denmark and Sweden, particularly the use of routine imaging.
- In the third study (paper III), the aim was to describe clinical characteristics, prognostic factors, and outcome in PTCL patients ≥ 70 years from California and Sweden, and to evaluate treatment strategies and the impact of comorbidity on survival using the Charlson Comorbidity Index (CCI).
- The aim of the fourth study (manuscript) is to report prognostic factors in CHOP(-like) treated limited-stage PTCL patients from Denmark and Sweden, including comparison of combined modality treatment (chemotherapy + radiotherapy) vs chemotherapy alone.

People say nothing is impossible, but I do nothing every day.

Winnie the Pooh

Methods

Patients

In Sweden, a compulsory cancer registry where both pathologists and clinicians report newly diagnosed cancers to the Regional Oncology Centre exists since 1958. The Swedish Lymphoma Group (SLG) developed in 1979 to improve treatment and support research in lymphoma. In 2000, the Swedish Lymphoma Registry (SLR) was introduced by the SLG to get more specific lymphoma information than in the Cancer Registry. When a lymphoma patient is reported to the Regional Oncology Centre, the responsible clinician receives a form to register more lymphoma related information. In this way, clinical characteristics, involved organs and prognostic factors are collected, and SLG together with the Regional Oncology Centre are responsible to store the data in a national database. This SLR data is regularly merged with the national cancer registry to warrant good coverage. Researchers can then apply to the SLR for certain data to a planned study[84].

The Danish National Lymphoma Registry (LYFO), founded in 1982, is a nationwide registry for Danish lymphoma patients. In a merge and comparison with the Danish Cancer Registry and the Danish National Patient Registry, a coverage of 90-100% for the LYFO was seen[85].

The LYFO and the SLR are somewhat unique in its nationwide coverages and completeness of clinical data, which makes them very useful in lymphoma research.

Most patient data for this thesis was collected directly from the SLR and LYFO (paper I, II, IV) or the California Cancer Registry (CCR) (paper III). Some data, e.g., on comorbidity and date of response evaluation (before/after ASCT/RT) were gathered from patient files.

Paper I

All patients ≥ 18 years diagnosed with systemic ALK+ ALCL in the SLR or the LYFO between years 2000 and 2010 were included in the study.

Paper II

Inclusion criteria were patients ≥ 18 years with nodal PTCL including ALK+ and ALK- ALCL, AITL, and PTCL NOS registered in the LYFO or the SLR between 2007 and 2012, and that had received CR after CHOP or CHOEP treatment.

Paper III

PTCL patients aged ≥ 70 years diagnosed from 2010 to 2015 reported in the CCR or SLR were included.

Paper IV

Limited-stage patients ≥ 18 years diagnosed with ALCL, AITL, or PTCL NOS between 2000 and 2014 were included if they had received at least one cycle of CHOP or CHOP-like therapy.

Statistics

General for all papers

Overall survival (OS) was defined as time from diagnosis to death of any cause or latest follow-up. Progression-free survival (PFS) was defined as the time from diagnosis until death, relapse, progressive disease, or latest follow-up. All p-values were 2-sided and differences with $p < 0.05$ were considered statistically significant.

Paper I

Descriptive statistics were used for patient characteristics, and group differences were compared with the χ^2 test, Fisher's exact test and the Mann-Whitney *U* test. Survival probabilities were estimated with the Kaplan-Meier method, and groups were compared with the log-rank test. Cox proportional hazard regression models were used to analyse prognostic factors, where factors with $p \leq 0.10$ in univariate analysis were included in multivariate analyses.

Statistical analysis was performed with SPSS, version 22.0 (IBM Corp., Armonk, NY, USA).

Paper II

Descriptive statistics were used for patient characteristics, and group differences were compared with Fisher's exact test or Wilcoxon's rank sum test. Survival probabilities were estimated with the Kaplan-Meier method, and groups were compared with the log-rank test. Cox proportional hazard regression models were used to analyse prognostic factors, where factors with $p \leq 0.05$ in univariate analysis were included in multivariate analyses. The cumulative relapse incidence was analysed with a nonparametric test and groups were compared with Gray's

competing risk test statistic. The relative survival for PTCL patients in CR compared to the general population was examined using national lifetables matched on age, sex, and calendar year. Survival differences were analysed with standardized mortality ratios (SMR)[86].

The programming language R was used for all statistics (http://www.r-project.org).

Paper III

Descriptive statistics were used for patient characteristics, and group differences were compared with the χ^2 test or Fisher's exact test. Survival probabilities were estimated with the Kaplan-Meier method, and groups were compared with the log-rank test. Cox proportional hazard regression models were used to analyse prognostic factors.

Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc. 2013) and SPSS, version 25 (IBM Corp., Armonk, NY, USA).

Paper IV

Descriptive statistics were used for patient characteristics, and group differences were compared with the χ^2 test, Fisher's exact test and the Mann-Whitney *U* test. Survival probabilities were estimated with the Kaplan-Meier method, and groups were compared with the log-rank test. To minimize confounding, treatment groups were compared using inverse probability of treatment weighting (IPTW)[87]. The definition of refractory disease was stable or progressive disease as best response, or relapse/progression within six months from diagnosis. Cox proportional hazard regression models were used to analyse prognostic factors. The relative survival for PTCL patients in CR compared to the general population was examined using national lifetables matched on age, sex, and calendar year. The restricted loss of lifetime (RLOL) was calculated with the Ederer I method[88].

Statistical analysis was performed with "R" (version 4.0.3, Vienna Austria http://www.r-project.org).

Methodological considerations and limitations

This part considers different methodological approaches and limitations from the papers in this thesis. One important limitation from all papers is how diagnoses were controlled.

Dedicated pathology review was not performed in any of the studies. Original review was most often made by experienced haemato-pathologists, but to diagnose and subclassify PTCL is complex. In paper I, including only ALK+ ALCL patients, this is probably not a big problem, since the staining of ALK-protein in immunohistochemistry is a robust method. In paper II-IV however, it is likely that some patients would get changed diagnoses if a dedicated pathology review was done, especially if the review was made today because of the increased diagnostic possibilities mostly in terms of genetic profiling[11].

For some of the patients consolidated with radiotherapy (RT) and/or ASCT after chemotherapy, information on whether response assessment was made before or after consolidation was missing. It would not affect OS or PFS, measured from time of diagnosis in all papers, but it makes it difficult to evaluate the effect of RT and ASCT.

Also, intention-to-treat data is not included in the analyses, which increases the risk of immortal time bias and makes it difficult to know whether a patient was selected for full chemo (instead of 3-4 cycles) and RT as a choice up-front or because of poor response at interim assessment.

Progression-free survival (PFS) and response data can be more uncertain outcome measures than OS in register-based studies. This is partly because there is no standardized imaging, neither regarding at what time the imaging is made (especially during follow-up), nor which type of imaging (CT or PET/CT). Also, lesions are not consistently reviewed according to standardized Lugano criteria[89], making response analysis somewhat subjective to the radiologist accountable and to the responsible clinician.

Another potential problem in population-based studies is the risk of bias between groups. In paper II for example, Swedish and Danish patients are compared head-to-head. Although demographics were comparable and Denmark and Sweden have similar publicly funded health care with equal access, there could be differences not measured biasing the results. To compensate for this, comparisons were made using Gray's competing risk test statistic[90]. In paper IV, inverse probability of treatment weighting (IPTW) was used for this[87]. However, in paper I and III, except the adjustment for other prognostic factors in Cox proportional hazard regression models, no specific statistic method was used to minimize bias between compared groups.

Results

This is a summary of the main findings from each of the included papers. For more detailed data, see the original papers.

Paper I

The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study

The purpose of the first study was to analyse outcome and risk factors in ALK+ ALCL patients and to compare CHOP vs CHOEP treatment. 122 adult patients from the Swedish and Danish lymphoma registries diagnosed with ALK+ ALCL between 2000 and 2010 were included.

Median age was 40 years and 58 % were men. About half of the patients had an IPI score > 1.

The 5-year OS and PFS was 78 % and 64 %. Age was the most important negative prognostic factor, and with age group 18-40 as reference (HR = 1.00), OS for patients aged 41-60 years (HR = 6.23) and > 60 years (HR = 16.1) was significantly worse. Male gender was associated with worse OS (HR = 2.34, p = 0.030).

All 10 patients with bone marrow involvement had relapse, progression or died (PFS: HR = 8.57, p < 0.001), with 6 of 10 patients dead within 7 months of diagnosis.

CHOEP instead of CHOP treatment was associated with better OS in patients aged 41-65 years, also after adjustment for risk factors (HR = 0.38, p = 0.047).

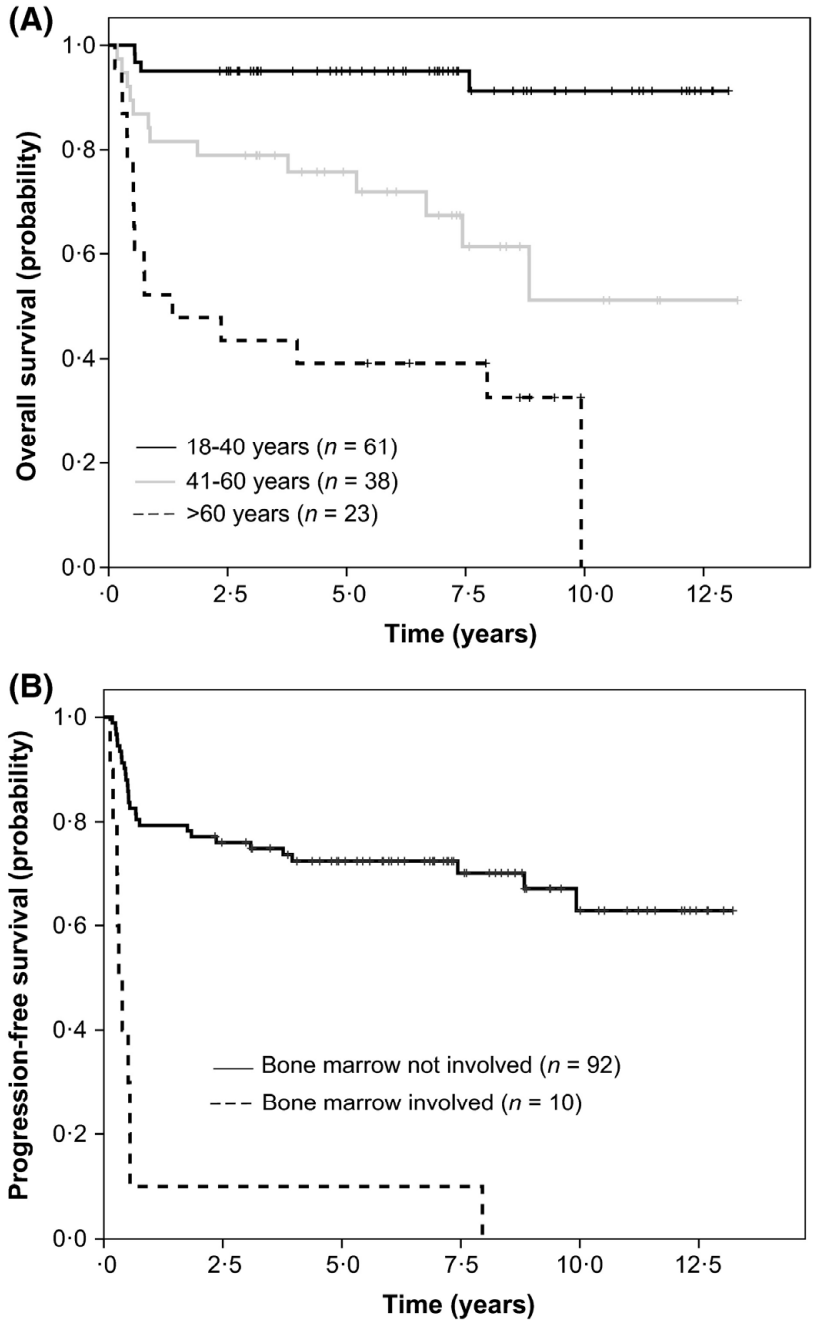

Figure 8. (A) Overall survival in ALK+ ALCL patients according to age group. (B) Progression-free survival in relation to bone marrow involvement in ALK+ ALCL patients.

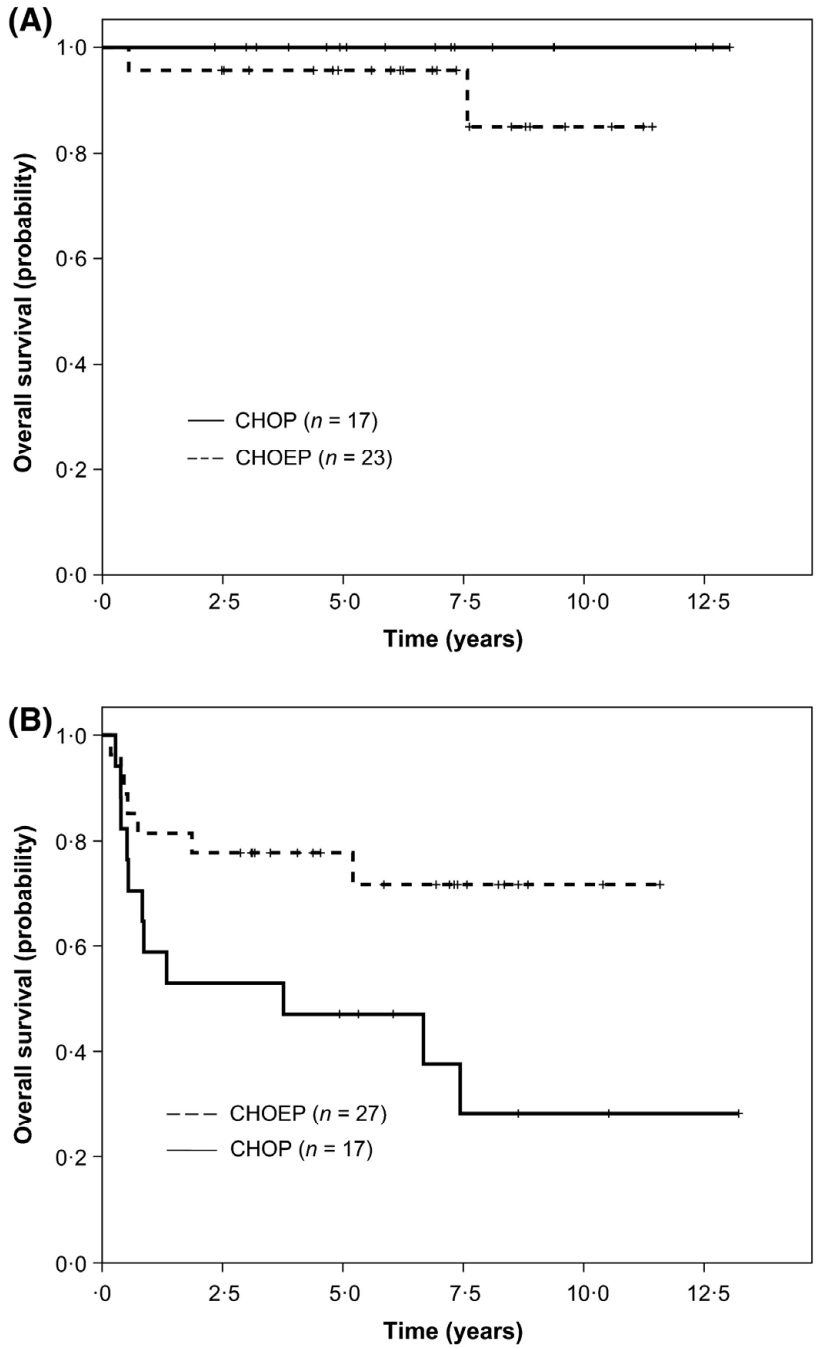

Figure 9. Comparison of overall survival in ALK+ ALCL patients aged (A) 18–40 years and (B) 41–65 years receiving CHOP and CHOEP treatment. CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHOEP, CHOP + etoposide.

Paper II

Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study.

In this study, the outcome and follow-up (FU) of 123 Swedish and 109 Danish PTCL patients in first complete remission (CR) was investigated and compared. Patients diagnosed between 2007 and 2012 ≥ 18 years and in CR after CHOP or CHOEP therapy were included.

Danish and Swedish patients were fully comparable except that consolidating radiotherapy was more used in Denmark (21 % vs 8 %, $p = 0.01$). Median FU-time was 62 months.

FU strategies in Denmark included clinical examination with symptom assessment, blood tests and routine imaging. FU guidelines in Sweden were similar except that routine imaging was not recommended. There was no significant difference in outcome between the countries, neither when analysing all patients, nor in subtype specific analyses. In multivariate analysis, country of follow-up had no impact on OS or PFS.

In multivariate regression analysis including both Danish and Swedish patients, age > 60 years and male gender were significantly associated with worse survival. HDT with ASCT was not associated with survival.

The post-remission survival in PTCL was examined in patients alive and without relapse after 1, 2, and 4 years, and compared to a matched background population (MBP). For patients without relapse at 1 and 2 years, the standardized mortality ratio (SMR) was significantly higher than the MBP (1-yr, SMR = 4.35, $p < 0.001$; 2-yr, SMR = 3.24, $p < 0.001$). A trend towards higher mortality was seen also for patients alive and without relapse after 4 years (4-yr, SMR = 2.16, $p = 0.09$).

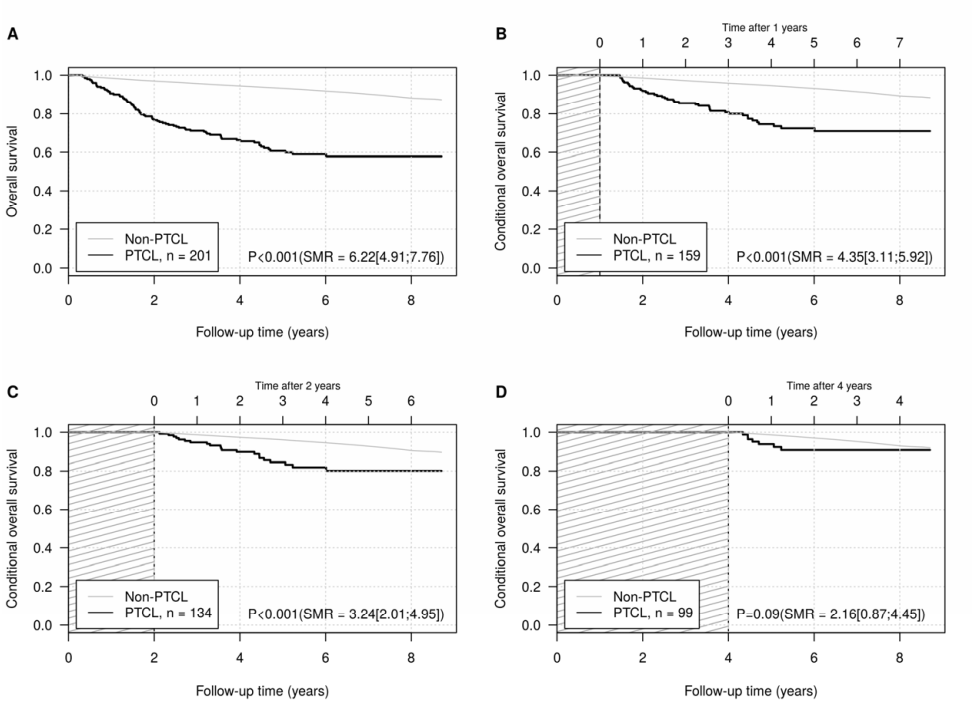

Figure 10. Standardized mortality ratio (SMR), comparing overall survival for Danish and Swedish patients with PTCL to normal population (non-PTCL), at diagnosis (A) and without events (EFS) 1, 2 and 4 (B, C and D) years after complete remission.

Paper III

Impact of comorbidity in older patients with peripheral T-cell lymphoma: an international retrospective analysis of 891 patients

This study aimed to describe clinical characteristics and outcomes of older (≥ 70 years) PTCL patients from Sweden and California, diagnosed from 2010 to 2015. 891 patients were included (SLR, n = 173; CCR, n = 718) with the diagnoses AITL, ALCL, EATL, HSTCL, ENKTCL, and PTCL, NOS. Median age was 77 (SLR) and 78 (CCR) years. AITL was more common in the CCR whereas EATL was more common in the SLR.

Comorbidity information was collected retrospectively and organized according to the Charlson Comorbidity Index (CCI). CCI scores were divided into three groups: CCI = 0 (39%), CCI = 1 (22%), and CCI > 2 (39%). No significant differences in patient characteristics were seen between the groups.

Table 5. Characteristics of 891 PTCL patients ≥ 70 years according to location.

Variable	CCR(N = 718)	SLR(N = 173)	*P*
Sex			
Male	383 (53.3)	101 (58.4)	.236
Female	335 (46.7)	72 (41.6)	
Age > 80 y			
No	439 (61.1)	126 (72.8)	.005
Yes	279 (38.9)	47 (27.2)	
Age, y			
70-74	207 (28.8)	59 (34.1)	.231
75-84	360 (50.1)	86 (49.7)	
>84	151 (21.0)	28 (16.2)	
Ann Arbor stage			
I-II	238 (36.2)	42 (27.1)	.038
III-IV	420 (63.8)	113 (72.9)	
Treatment			
No	333 (47.3)	51 (29.8)	<.0001
Yes	371 (52.7)	120 (70.2)	
Subtype			
AITL	192 (26.7)	34 (19.7)	<.0001
ALCL	95 (13.2)	27 (15.6)	
EATL	15 (2.1)	16 (9.2)	
Hepatosplenic TCL	4 (0.6)	3 (1.7)	
NK/TCL, nasal type	55 (7.7)	7 (4.0)	
PTCL, NOS	357 (49.7)	86 (49.7)	
CCI			
0	239 (38.9)	65 (40.6)	.414
1	128 (20.8)	39 (24.4)	
>1	248 (40.3)	56 (35.0)	

Patients with CCI > 1 had poorer median OS (4.4 months) compared to patients with CCI = 0 (11.9 months) and CCI = 1 (8.4 months; $p < 0.001$).

Over 80 % of patients in this study died, with lymphoma as the most common cause of death (> 70 %) regardless of CCI score.

Increasing age was the factor most related to poor survival. Age was further analysed in subgroups according to survival. Median OS for different age groups were: 70-74 yrs., 15.5 months; 75-84 yrs., 9.9 months; > 84 yrs., 3.6 months.

Data on response assessment was available in 87 patients in the SLR and no patients in the CCR. Overall response rate (ORR) was 55% in this group and patients achieving CR/CRu had significantly better survival than patients not receiving CR/CRu (median OS 3.7 vs 0.56 yrs., $p < 0.001$).

From the SLR, untreated patients (n = 40) were compared to patients not receiving CR/CRu after chemotherapy (n = 48). No differences in OS were seen in multivariate analysis, adjusting for diagnosis, stage, age, CCI, and ECOG performance status (HR = 1.03, p = 0.93).

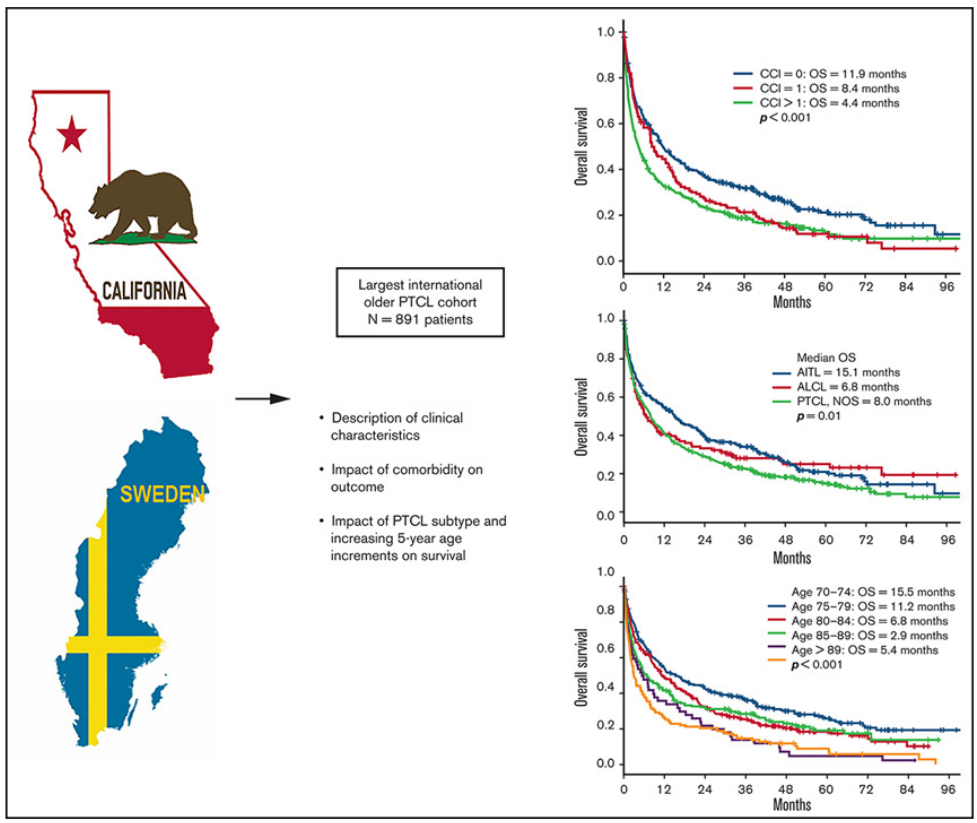

Figure 11. Visual abstract of paper III.

First published in Blood Adv. 2022 Apr 12;6(7):2120-2128. doi: 10.1182/bloodadvances.2021004269. © 2022 by The American Society of Hematology.

Paper IV

Outcome of Limited Stage Peripheral T-Cell Lymphoma After CHOP(-like) Therapy: A Population Based Study of 240 Patients from the Nordic Lymphoma Epidemiology Group (manuscript)

In this study, outcome and prognostic factors in 240 limited-stage nodal PTCL patients from Denmark and Sweden were analysed. Adult (≥ 18 years) patients diagnosed with AITL, ALCL, or PTCL, NOS between 2000-2014 and treated with at least one cycle of CHOP or CHOP-like therapy were included.

Median age was 61 years for the entire cohort. 44% presented with stage I disease. 67% of all patients received 6-8 cycles of CHOP(-like) therapy and 22% received 3-4 cycles, of which 59% were treated with radiotherapy (RT). 15% of the patients was consolidated with autologous stem cell transplantation.

Table 6. Risk factors associated with overall survival in limited-stage PTCL.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age ≥ 60	3.46 (2.31-5.19)	<0.001	3.03 (1.96-4.69)	<0.001
B-symptoms	1.74 (1.22-2.49)	0.002	2.00 (1.33-3.01)	<0.001
ECOG PS > 1	2.90 (1.81-4.64)	<0.001	1.49 (0.84-2.65)	0.17
Elevated LDH	1.46 (1.01-2.11)	0.042	1.34 (0.91-1.98)	0.14
Extranodal disease	1.15 (0.78-1.70)	0.48	1.16 (0.77-1.77)	0.48
Ann Arbor Stage II	1.02 (0.72-1.45)	0.92	0.86 (0.58-1.27)	0.44
Subtypes. Ref PTCL NOS:				
AITL	1.57 (0.77-3.20)	0.21	1.90 (0.90-4.02)	0.09
ALCL ALK-	0.97 (0.66-1.43)	0.88	1.06 (0.70-1.61)	0.78
ALCL ALK+	0.36 (0.20-0.66)	<0.001	0.50 (0.26-0.94)	0.03

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase.

Median follow-up was 127 months. 5-year OS was 59% and 5-year PFS was 53%. ALK+ ALCL subtype was associated with favorable outcome.

Achieving CR/CRu and partial remission were associated with 5-year OS of 74% and 35%, respectively. For patients with primary refractory disease including relapse within 6 months from diagnosis, 5-year OS was 13 %, and for patients relapsing > 12 months after remission, 5-year post-relapse OS was 20%.

In multivariable analyses, age ≥ 60 years (HR = 3.03, $p < 0.001$) and B-symptoms (HR = 2.00, $p < 0.001$) were the prognostic factors associated with worse survival.

When excluding ALK+ ALCL, patients < 60 years and without B-symptoms had a 5-year OS of 76%, patients with one of the two risk factors had a 5-year OS of 48%, and patients with both B-symptoms and age ≥ 60 years had a 5-year OS of 22%.

No significant differences in CR/CRu rates, post-remission OS (pOS) or pPFS were seen between patients treated with 3-4 cycles of CHOP ± RT vs 6-8 cycles ± RT after adjusting for risk factors.

For patients in CR/CRu, survival was normalized to a matched background population after 12 months in remission.

Discussion and future perspectives

Post-treatment follow-up in T-cell lymphoma

In paper II, no differences in outcomes were seen between Swedish and Danish patients in CR, neither when including all patients nor in subgroup analyses. Country of follow-up had no impact on OS, meaning that Danish patients did not seem to benefit from routine imaging.

Male gender was associated with worse survival, which has been documented in some earlier studies as well[19, 91]. HDT with ASCT was not associated with survival, although this data is hard to interpret since remission status prior to ASCT was not known for all patients.

Post-remission survival was poor and even for patients in continuous remission 2 years after CR, the standardized mortality ratio (SMR) was significantly higher than for a matched background population (SMR = 3.24, $p < 0.001$). This is worse than for comparable B-cell lymphoma patients[92].

Response evaluation in PTCL should be performed after 2-3 cycles and at the end of treatment. This includes clinical examination, blood tests, imaging (CT or PET/CT), and bone marrow biopsy (if involved). The length of follow-up and the use of routine imaging after remission is not prospectively assessed in PTCL. The ESMO guidelines recommend physical examination every 3 months during the first year, twice yearly for year 2 and 3, and then once a year to control long-term side-effects. CT examinations are often practiced at 6, 12 and 24 months after remission, but the lack of evidence to support this is also stated in the ESMO guidelines[16]. The National Comprehensive Cancer Network (NCCN) guidelines from 2016 (referred to in paper II) did not include recommendations for or against routine imaging[93]. In the newly published NCCN TCL guidelines from 2022, the recommendation is surveillance imaging “no more often than every 6 months for 2 years and then annually for 5 years or as clinically indicated”. PET/CT is preferred[15]. In Swedish national guidelines for TCL, both from 2014 and the newly updated version from 2021, CT or PET/CT is recommended 6-8 weeks after end of treatment. For patients in CR, follow-up imaging is only recommended if relapse is suspected[14].

The divergence from these internationally recognized guidelines in combination with the lack of evidence, enlightens the need for follow-up studies in PTCL.

Lymphoma patients with relapse detected by planned imaging seem to have a better prognosis[94], and aggressive relapses more often present with symptoms before planned imaging[94, 95]. About 15–20% of lymphoma relapses has been reported to be detected by surveillance imaging[94, 96], although Tang et al described that many of the patients with imaging detected relapses have symptoms and that only 5% of all relapsing patients were totally asymptomatic[97].

Data from earlier studies show that > 85% of relapses in PTCL occur within 2 years[62, 98] and that relapses detected by routine imaging were associated with lower disease burden and better survival[96]. Together with the poor survival after relapse, the clinical benefit of routine imaging in PTCL could be questioned.

Relapse in PTCL usually comes with symptoms before diagnosis[96]. The outcome after relapse is worse than in DLBCL and Hodgkin lymphoma, with a median OS after relapse of about 6 months, and no standardized treatment recommended before another exists in relapsed PTCL.

These factors together contribute to questioning routine imaging in follow-up – if there is (most likely) no effective treatment option, what is the meaning of (maybe) finding a relapse before symptom?

The radiation exposure accompanying CT gives a potential risk of radiation-induced secondary malignancy, and a study in NHL patients showed a significantly increased risk in patients receiving more than 8 CT scans[99]. This risk is higher in younger patients with long probable survival, especially young women[100], likely making it less important in PTCL (except ALK+ ALCL) where patients are often > 60 years. There is also reported increased anxiety close to the time of follow-up imaging in a study of aggressive lymphoma patients in remission[101], further questioning the potential benefit of routine imaging.

Figure 12. Poster summarizing paper II, presented at European Hematology Association's (EHA) 21st congress in Copenhagen 2016, Henrik Cederleuf et al.

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Routine Imaging For Peripheral T-cell Lymphoma In First Complete Remission Does Not Improve Survival: A Danish-Swedish Population-Based Study

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INTRODUCTION

Routine surveillance imaging plays a limited role in detecting lymphoma relapse and an imaging-based follow-up policy was not associated with better outcome for diffuse large B-cell lymphoma patients in a recent Danish-Swedish population-based study[1].

OBJECTIVES

Using a similar approach, we evaluated the outcome of Danish and Swedish patients with nodal peripheral T-cell lymphoma (PTCL) in first complete remission (CR) for whom traditions for routine imaging have been different.

METHODS

Patients from the Danish and Swedish lymphoma registries were selected by the following criteria: a) newly diagnosed nodal PTCL from 2007 to 2012, b) age ≥ 18 years, and c) CR after CHOP or CHOEP therapy with or without consolidating high-dose therapy. Follow-up for Swedish patients included symptom assessment, clinical examinations and blood tests at 3- to 4-month intervals for 2 years, with longer intervals later in follow-up. The national Swedish guidelines only recommended imaging when relapse was clinically suspected. Follow-up for Danish patients was similar but included routine imaging, usually computed tomography (CT) every 6 months for 2 years and at some centers annually from the 3rd till the 5th year of follow-up as well.

	DK (n=109)	SWE (n=123)	Missing (DK/SWE)	P-value
Median age (years)	61 (21-89)	64 (20-87)	0/0	0.29
Male-female ratio	1.27	1.51	0/0	0.59
IPI > 2, n (%)	31 (29.8)	36 (30.0)	5/3	1.00
ECOG >= 2, n (%)	14 (13.0)	16 (13.2)	1/2	1.00
CHOP treat., n (%)	77 (70.6)	72 (58.5)	0/0	0.07
CHOEP treat, n (%)	32 (29.4)	51 (41.5)	0/0	0.07
Radiotherapy, n (%)	23 (21.1)	10 (8.2)	0/1	0.01
ALCL, n (%)	42 (39)	46 (37)	0/0	0.33
AITL, n (%)	27 (25)	22 (18)	0/0	0.33
PTCL NOS, n (%)	40 (37)	55 (45)	0/0	0.33

Table 1. Demographic and clinicopathological information on Danish and Swedish patients with nodal PTCL.

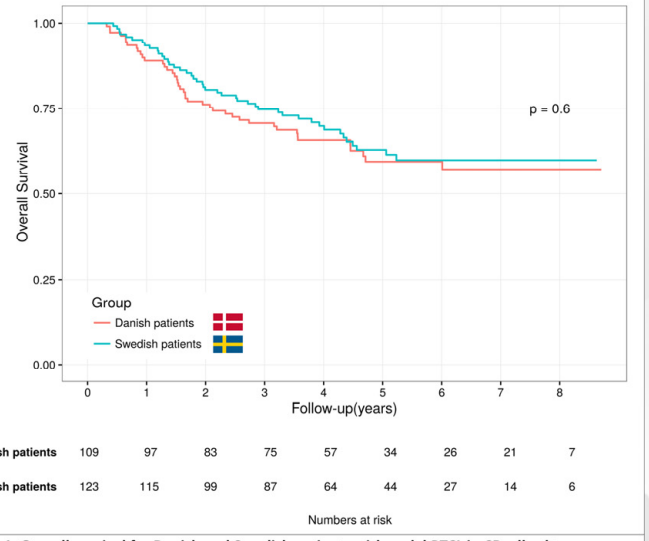

Figure 1. Overall survival for Danish and Swedish patients with nodal PTCL in CR, all subtypes.

RESULTS

In total, 109 Danish patients and 123 Swedish patients with nodal PTCL were included. The subtype frequencies and baseline demographic characteristics were fully comparable between Danish and Swedish patients (Table 1). Consolidating radiotherapy was more commonly used for Danish patients (21% vs 8%, P=0.01).

The overall survival (OS) estimates for Danish and Swedish patients in CR following frontline therapy were similar for all patients (P=0.6, Fig 1) and in PTCL subtype specific analyses. The most important adverse predictor of OS following CR was age > 60 (Hazard Ratio [HR], 3.73; 95%CI, 2.08-6.66, P<0.01). The 2-year probability of relapse was similar for Danish and Swedish patients (25%; 95%CI 16-33% vs. 29%; 95%CI 19-38%, P=0.53). The post-relapse OS was similar for Danish and Swedish patients overall (P=0.8) and in PTCL subtype specific analyses.

CONCLUSION

Relapse following frontline treatment for PTCL is typically associated with a poor prognosis and in this study, an imaging based follow-up practice did not translate into better survival.

CONTACT INFORMATION

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REFERENCES

1. El-Galaly TC et al. Routine imaging for diffuse large B-cell lymphoma in first complete remission does not improve post-treatment survival: A Danish-Swedish population-based study. *J Clin Oncol. 2015;33(34):3993-3998.*

Age and comorbidity in T-cell lymphoma

Lymphoma incidence has increased more than 50% during the last 25 years and at least half of this increase is in patients older than 65 years[74]. Large studies indicate that a higher percentage of aggressive lymphomas are reported in elderly patients[102, 103].

Paper III presents one of the largest cohorts of elderly (defined as ≥ 70 years in this study) PTCL patients published so far. Subtypes distribution was similar to younger cohorts, except fewer ALCL patients. Prognosis in general was poor and although patients without comorbidity had better survival, median OS was poor (< 1 year) in this group as well. Earlier, smaller studies have shown similar results with higher CCI score associated with worse OS[69, 77]. However, in a subgroup analysis of older (≥ 75 years) PTCL patients in a previous Swedish study, no significant association between increased CCI and OS was seen[73].

The CCI group distribution in patients receiving multiagent treatment (n = 369) was similar to the entire cohort, suggesting that other factors than comorbidity also impact treatment decisions. The lack of information on WHO PS in the CCR is a major limitation to this study and makes multivariate regression analyses harder to draw conclusions from.

AITL patients had better survival than ALCL and PTCL, NOS patients in the present study, which contrasts to most PTCL cohorts where younger patients are included. Could old AITL patients have a unique biology that impacts survival? Mourad et al reported results from a cohort of 157 AITL patients treated in the GELA LNH87-LNH93 trials from 1987 to 1999. In univariate analysis, patients > 60 years had a better prognosis than patients < 60 years, with 7-yr OS of 36% vs 23% (p = 0.071), and IPI score was not predictive for survival[91]. This is congruent with an evaluation of IPI, PIT and NCCN-IPI, where Ellin et al found some prognostic value in all three indexes for ALCL and PTCL NOS, but not for AITL. Also, age was not associated with OS in AITL, but in ALCL and PTCL, NOS patients[70]. In a recently published final report from the International T-cell Project concerning AITL, age ≥ 60 years, WHO PS > 2, elevated C-reactive protein, and elevated β2 microglobulin were associated to inferior outcomes. The authors suggested a new prognostic score for AITL patients, AITL score, based on these factors, with low-risk (0-1), intermediate-risk (2) and high-risk (3-4) subgroups with 63%, 54%, and 21% 5-year OS[104]. However, median age was 64 years which together with the suboptimal predictive value of IPI in the elderly, makes it uncertain if the AITL score is usable in AITL patients ≥ 70 years.

When analyses including age, comorbidity, and prognostic indices like IPI are not sufficient to make treatment decisions in elderly patients, other information is needed. The use of comprehensive geriatric assessment (CGA) is one way to more accurately identify an elderly patient's possibility to manage treatment. The idea

Table 7. The G-8 screening questionnaire.

Question	Score
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	
Severe decrease	0
Moderate decrease	1
No decrease	2
Weight loss during the last 3 months?	
>3 kg	0
Patient does not know	1
1–3 kg	2
No weight loss	3
Mobility	
Bed or chair bound	0
Able to get out of bed/chair but does not go out	1
Goes out	2
Neuropsychological problems?	
Severe dementia or depression	0
Mild dementia or depression	1
No psychological disorders	2
BMI (kg/m2)	
<18·5	0
18·5–<21·0	1
21·0–<23·0	2
23·0–>23·0	3
Takes more than three prescribed drugs per day?	
Yes	0
No	1
In comparison with other people of the same age, how does the patient consider his or her health status to be?	
Not as good	0
Does not know	0.5
As good	1
Better	2
Age (years)	
>85	0
80–85	1
<80	2
Total score	0-17

Patients with G-8 scores < 14 need global geriatric assessment. Reprinted from Annals of Oncology 23:8, 2012. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, Soubeyran PL. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012 Aug;23(8):2166-2172. doi: 10.1093/annonc/mdr587. Copyright © 2012 European Society for Medical Oncology, with permission from Elsevier.

with CGA is to detect patient information that is particularly relevant in elderly patients and not fully captured in normally used prognostic indices. A multidisciplinary evaluation of daily function and cognition, comorbidity, social support, and nutritional and psychologic statuses is included[105]. The method has been validated in predicting morbidity and mortality in older cancer patients[106] and has been recommended by the International Society of Geriatric Oncology since 2005 to use for cancer patients > 70 years[105].

There are different CGA methods but no consensus to recommend a certain one before another. A full CGA can though be time consuming, complex, expensive and demands trained staff[107]. A validated screening tool is the G-8 questionnaire that identifies elderly patients in need for full CGA[108] (see Table 5), although data on the benefit of using this in lymphoma patients is incoherent[109].

Some studies have investigated CGA specifically in lymphoma patients[107, 109-111]. Nabhan et al found loss of ADL function significantly associated with OS in multivariate analysis, whereas WHO PS was not[111]. This has been seen in older cancer patients in general, with Repetto reporting better prognostic possibility with CGA than WHO PS and questioning the role of WHO PS as standard in older cancer patients[112].

Garric et al reported French data on how CGA impacts treatment decision in older patients with hematologic malignancies, demonstrating that 20 % of all lymphoma patients performing CGA had a change in treatment. Changes were related to impaired mobility, impairment in daily functioning, and comorbidity[109].

In a subgroup analysis of Swedish patients in paper III, patients responding with CR/CRu to chemotherapy had significantly better survival than patients not responding with CR/CRu (3.7 vs 0.56 years). Furthermore, no survival difference was seen between untreated patients and patients not responding with CR/CRu to chemotherapy. Interestingly, this was true also in multivariate analysis (HR = 1.03, p = 0.93) including age, diagnosis, stage, CCI, but also WHO PS which could limit the risk of bias to some extent.

These results show that some elderly PTCL patients can benefit from multiagent chemotherapy. For patients not responding to chemotherapy, survival is still not worse than for untreated patients, enlightening the importance of not excluding elderly patients from potentially curative treatment.

Limited-stage peripheral T-cell lymphoma

Studies on limited-stage PTCL are rare, most data are from studies focusing on advanced stage disease, and the ones specifically investigating limited-stage patients are either small or with limited information.

In paper IV, prognostic factors, treatment-specific outcomes, and post-remission survival rates are explored in a binational population-based setting representing one of the largest cohorts of limited-stage PTCL published so far. Patients eligible for full or abbreviated CHOP therapy had acceptable outcomes with 5-year OS of 59% (95% CI: 53-65%), but patients with primary refractory disease had dismal outcomes with 5-year OS of 13% (95% CI: 6-26%).

Age ≥ 60 years and B-symptoms were the only factors significantly associated to worse OS in multivariate analysis. A speculation could be that B-symptoms is a marker for more advanced disease that was missed in staging. However, PET/CT was used in the same number of patients (29%) with B-symptoms as for the entire cohort (28%).

The presence of extranodal disease was not significantly associated with poor outcome, and for the IPI factors, elevated LDH and ECOG > 1 both were associated with OS in univariate but not in multivariable analyses. Park et al demonstrated in DLBCL that the IPI factors correlate to each other, with especially elevated LDH (75%) and ECOG > 1 (94 %) associated with advanced stage disease. This could partly explain the lack of association to outcome in the present study, where less than 30 % of the patients had an IPI score > 1. That is, PTCL patients with ECOG > 1 and/or elevated LDH are rare in the present study partly because a vast majority of these patients have advanced stage disease.

No significant differences were seen between patients treated with 3-4 cycles of CHOP ± RT vs 6-8 cycles ± RT after adjusting for risk factors. A randomized phase 3 non-inferiority trial (FLYER) compared two doses of rituximab (R) + 4 R-CHOP vs 6 R-CHOP in low-risk limited-stage DLBCL. Patients between 18-60 years with normal LDH, ECOG PS 0-1 and without bulky disease were included. Results, published in Lancet 2019, showed no differences in OS or PFS and the group with 4 cycles of CHOP also had lower toxicity[113]. However, no similar randomized trial has been performed in low-risk PTCL and considering the poorer outcomes and response to first-line treatment in PTCL vs DLBCL, it is doubtful if a similar de-escalation is translatable to limited-stage PTCL.

One of the largest studies in limited-stage PTCL with comparably detailed data is from the Mayo Clinic, where outcomes in limited stage AITL, ALCL, and PTCL NOS in 75 patients evaluated between 1994-2011 was reported[114]. Median age was 52 years compared to 61 years in paper IV and a larger fraction had AITL (15% vs 6%). Only 68% of the patients from the Mayo study received anthracycline based treatment and about 25% either received palliative regimens or were not treated at all. 5-year OS was 51% in the Mayo study and 59% in paper IV, although it is hard to compare these numbers. Use of consolidating RT was not clearly associated with survival in either of the studies, although the lack of intention to treat data makes it hard to draw conclusions on the value of RT.

Survival after relapse in PTCL in general is poor with a median OS of less than 6 months. However, most relapse data in PTCL come from advanced stage disease patients, and even though limited stage PTCL has worse outcomes than limited stage DLBCL both at first line and after relapse, outcomes remain superior to advanced stage PTCL. The mortality of PTCL patients in continuous remission is still increased after 2 years according to earlier studies, related to late relapses and poor treatment options[98, 115]. In paper IV, patients in continuous remission after 12

months had the same 5-year OS as a matched background population, and for patients alive 2 years after CR, no excess mortality was seen.

To summarize, outcomes for relapsing or refractory limited-stage PTCL patients are poor, demonstrating the need for improved treatment both at relapse and up-front. But for patients responding with CR/CRu and are without relapse within 24 months, survival is normalized and a discontinuation of follow-up 2 years after remission could be reasonable.

Improving treatment in T-cell lymphoma

CHOP or CHOP-like treatment has been standard in ALK+ ALCL for decades and still was in Sweden and Denmark at the inclusion time of paper I. Some studies have examined the addition of etoposide to CHOP, but not with significant effect on OS. The result from paper I, where patients aged 41-65 had better outcome with CHOEP than CHOP adjusted for risk factors, enlightens the theory that etoposide is beneficial in ALK+ ALCL.

For patients < 40 years, survival was excellent regardless of treatment, although the CHOEP treated patients had higher IPI scores. Etoposide can probably be spared in this young group, at least for patients without many risk factors.

A newly published Dutch nationwide, population-based study investigated treatment for over 1400 patients < 65 years diagnosed with ALCL, AITL, or PTCL, NOS in the Netherlands from 1989-2018. Analyses over the impact of etoposide and ASCT treatment were made in patients diagnosed in 2014 (from when exact treatment data was registered) or later. In a subgroup of 58 ALK+ ALCL patients, the mortality risk was 6.3 times higher if treated with CHOP compared to CHOEP, adjusted for IPI score and ASCT, adding to the possible benefit of etoposide.

The data from ECHELON-2 on brentuximab vedotin (BV) up-front in CD30+ PTCL has had a major practice changing impact since paper I and II in this thesis were published. BV is a conjugate of an anti-CD30 monoclonal antibody and an antineoplastic microtubule disrupting agent, MMAE. In the ECHELON-2 randomized phase 3 trial, CHOP was compared to A-CHP (BV + CHOP without vincristine) in CD30-positive PTCL. Results, published in Lancet 2019 showed a significant improvement in both PFS and OS (HR = 0.66, p = 0.024) with A-CHP, without increased toxicity. This was (and still is) the first randomized prospective trial in untreated PTCL patients showing better OS than CHOP, and the results has been practice-changing with BV now being used in the standard treatment of CD30-positive PTCL[64]. In the 5-year update of the ECHELON-2 trial in 2021, A-CHP still showed significant improvement to CHOP with better 5-year PFS and OS[116].

This was the first prospective randomized trial to demonstrate a treatment with significantly better OS than standard in PTCL. The discussion on the importance of etoposide has somewhat diminished after the change to BV-CHP as standard treatment in ALCL.

High response rates have been shown for BV also in heavily pre-treated patients with relapsed CD30+ PTCL[78], and the possibility to use BV at relapse could have improved outcome in some patients in paper II, although the most effective use of BV likely is up-front.

The ALK inhibitors Crizotinib[117] and Alectinib[118] both have shown response rates of 80% in R/R ALK+ ALCL, and are possible options to choose from.

Table 8. Phase II results from United States for agents approved for R/R PTCL by the FDA.

	Belinostat	Pralatrexate	Brentuximab Vedotin
Evaluable patients	120/129	109/111	58/58*
Central response review	Yes	Yes	Yes
ORR	26% (CR + PR)	27% (CR/CRu + PR)	86% (CR + PR)*
Nonhematologic AEs	Nausea (42%) Fatigue (37%) Pyrexia (35%) Vomiting (29%) Constipation (23%) Diarrhea (23%) Dyspnea (22%) Rash (20%) Edema (20%)	Mucositis (70%) Nausea (40%) Fatigue (36%) Constipation (33%) Pyrexia (32%) Edema (30%) Cough (28%) Epistaxis (26%) Vomiting (25%) Diarrhea (21%)	Peripheral sensory neuropathy (53%) Fatigue (41%) Nausea (38%) Pyrexia (38%) Rash (31%) Pain (28%) Diarrhea (29%)
Hematologic AEs	Anemia (32%) TCP (16%)	TCP (41%) Anemia (34%) Neutropenia (24%) Leukopenia (11%)	Neutropenia (55%) Anemia (52%) TCP (16%)

FDA, The US Food and Drug Administration; AE, adverse event; CR(u), complete response (unconfirmed); ORR, overall response rate; PR, partial response; TCP, thrombocytopenia. *ALCL patients only. *First published in O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015 Aug 10;33(23):2492-9. doi: 10.1200/JCO.2014.59.2782. PMID: 26101246. Copyright © 2015, by the American Society of Clinical Oncology.*

For other subtypes than ALCL, no treatment has shown to be better than CHOP, although many studies have demonstrated effect of new drugs and trials are ongoing. Adding a histone deacetylase (HDAC) inhibitor to CHOP has seemed promising but not shown significantly improved survival yet. In the R/R setting, romidepsin as single agent received accelerated FDA approval in 2011 based on a phase II study with 130 PTCL patients demonstrating good ORR[119], and updated results showed durable responses in ALCL, AITL, and PTCL, NOS[120]. However, in 2021 the approval of romidepsin in R/R PTCL was withdrawn after the phase III trial comparing CHOP vs romidepsin + CHOP in untreated patients. This study did not show any significant benefit of romidepsin, and toxicity was also worse in this

cohort[121]. Subgroup analyses supported a higher effect of romidepsin in PTCL with TFH subtype, which has been reported for other HDAC inhibitors as well[122, 123] and this is further studied. Specific characteristics in TFH cells have been reported related to malignancy but also to autoimmune diseases where pre-clinical assessment and early clinical trials are proceeding[41].

The HDAC inhibitor belinostat was evaluated in the BELIEF trial including 129 pre-treated R/R PTCL patients, with a median of two prior systemic therapies[124]. ORR was 26% (CR 11%, PR 15%) and 12 patients received SCT after belinostat. Median PFS and OS was 1.6 and 7.9 months and toxicity was manageable. The results led to an FDA approval for belinostat in R/R PTCL in 2014.

In the international phase II study PROPEL with heavily pre-treated R/R PTCL, 109 patients (59 with PTCL, NOS, 13 with AITL, and 17 with ALCL) received pralatrexate[125]. ORR was 29% and CR 11%. Response was lower in AITL (8%) than ALCL (35%) and PTCL, NOS (32%). PFS and OS for all patients was 4 and 15 months, respectively. Toxicity was acceptable. FDA approved pralatrexate in R/R PTCL in 2009 following these results.

Horwitz presented interesting data with the combination of duvelisib and romidepsin in R/R TCL at ASH in December 2021[126]. 55 PTCL patients, a majority PTCL NOS (n = 20) or AITL/TFH (n = 19), were treated with duvelisib 75 mg twice daily and romidepsin 10 mg/m^2 on days 1, 8, 15 of a 28-day cycle. ORR was 58% and CR was 42 %. Of 19 AITL/TFH patients, 13 (68%) responded and 11 (58%) patients received CR. ORR in PTCL NOS was 10/19 (53%) and 6/19 (32%) received CR. More than half of the AITL/TFH patients achieved CR and the combination of duvelisib and romidepsin should be tried out more in this group.

In the ACT-2 randomized phase 3 trial including 116 elderly (61-80 years) PTCL patients, the efficacy of CHOP + the anti-CD52 monoclonal antibody alemtuzumab vs CHOP alone was investigated[127]. An increased response rate was seen with alemtuzumab, but no improvement in OS. The alemtuzumab + CHOP arm also had more severe side effects, with 40% (vs 21%) having grade ≥ 3 infections and 4 patients died in infections compared to 1 in the CHOP arm. 5-year OS in the CHOP arm was 39% and since survival data from randomized prospective trials in elderly PTCL is lacking, this could serve as benchmark for future studies.

In a retrospective study from Columbia University, New York, Ma et al compared patients that had been treated with chemotherapy to patients receiving novel therapy including approved single agents romidepsin, pralatrexate, belinostat, and BV, and some patients also a combination of non-chemotherapy drugs such as romidepsin + pralatrexate. Patients in clinical trials were included in the novel therapy group. OS was better for patients treated with novel agents both in first and second line, and novel agents were also significantly associated with response to and survival after ASCT. An important limitation to this comparison is that all but one (21/22) of the patients treated with novel agents were diagnosed after 2010, and more than half

(90/164) of the patients receiving chemotherapy were diagnosed between 1991-2009. Subgroups were also too small to compare. The authors suggest increasing enrolment in clinical trials and comment on the poor response usually seen in PTCL with chemotherapy, and that the use of novel agents is needed in earlier lines.

Stem cell transplantation

Results from studies on autologous stem cell transplantion (ASCT) and allogenic SCT (AlloSCT) are diverging, and the question whether to recommend SCT or not has been discussed and debated for decades. In a newly published retrospective PTCL study from Italy and Spain, ASCT for patients in CR was associated with better OS and PFS in multivariate analysis. The authors support the use of ASCT for PTCL patients other than ALK+ ALCL in CR. However, it is hard to draw any firm conclusions since the decision not to use ASCT in many control group patients was depending on the patient's clinical status, making it difficult to rule out that this group was biased to be more frail, even though OS and PFS were counted from the date of response assessment and not from diagnosis to minimize immortal time bias to some extent[128].

Schmitz el compared ASCT vs AlloSCT in a randomized trial including 104 nodal PTCL patients (not ALK+ ALCL) aged 18-60 years, all stages and IPI scores (except stage I and aaIPI 0). Patients were randomized to first receive 4 x CHOEP and 1 DHAP, then followed by either HDT and ASCT or myeloablative conditioning with AlloSCT. 3-year OS was 57% after AlloSCT and 70% after ASCT, no significant differences. Interestingly, none of the 21 patients proceeding to AlloSCT relapsed, whereas 13 of 36 (36%) patients receiving ASCT relapsed. However, 8 of 26 patients (31%) in the AlloSCT arm died of transplant-related toxicity, and none of 41 patients in the ASCT arm. The authors concluded that CHO(E)P + ASCT still is the preferred option for transplant-eligible patients and suggested that AlloSCT could be used for patients relapsing or not responding to ASCT[129].

On the other hand, Du et al concluded that AlloSCT is the cornerstone of salvage therapy for high-risk patients in a large systemic review and metanalysis of R/R PTCL from years 2000-2020 comparing ASCT and AlloSCT. Survival was similar between the groups although the authors saw benefits with AlloSCT[130].

Brink et al recently reported that in AITL, ALK- ALCL, and PTCL, NOS patients in CR, OS was better in patients consolidated with ASCT, with survival time counted from 9 months after diagnosis.

Even though there are many studies on ASCT and AlloSCT in PTCL, most of them are retrospective or unrandomized, and results are to some extent contradictory. Without randomized trials reporting significantly changes in survival, the debate on SCT will likely continue.

Conclusions

Paper I

The addition of etoposide to CHOP could be a reasonable choice in ALK+ ALCL patients < 65 years, except for young patients with limited disease, who seem to do excellent irrespective of treatment.

Paper II

The use of routine imaging in follow-up after treatment do not seem to improve survival in PTCL and the benefit of routine imaging is doubtful.

For PTCL patients in continuous remission after 2 years, survival is still worse than for a matched background population.

Paper III

The prognosis for PTCL patients ≥ 70 years was poor in this study with a median OS of 9 months. However, some older PTCL patients benefit much from multiagent chemotherapy, and it is important not to exclude the elderly from potentially curative treatment.

Paper IV

Survival for limited-stage PTCL patients in this study was clearly inferior to comparable limited-stage DLBCL, but better than for advanced stage PTCL.

A subgroup of patients ≤ 60 years without B-symptoms had good outcomes regardless of treatment.

For patients in CR/CRu without relapse within 2 years, survival was normalized. To end follow-up at this timepoint could therefore be reasonable in limited-stage PTCL.

Concluding remarks

The results from paper I, suggesting an association between OS and the addition of etoposide to CHOP in first-line treatment for ALK+ ALCL patients aged 41-65 were interesting when published in 2017. No randomized trial had demonstrated a treatment superior to CHOP in PTCL. Ever. With the results from the ECHELON-2 randomized trial in 2018 demonstrating superior OS and PFS for BV-CHP compared to CHOP in untreated CD30+ PTCL patients[64] and changing the standard of care in this group, the benefit of adding etoposide to BV-CHP is questioned.

For other nodal PTCL subtypes – even though results are often poor and worse than for other aggressive lymphomas – CHOP still is the standard of care, and no other treatment has been proved better in a randomized trial. This means that there are possibilities to improve treatment and with increased precision in classification mostly related to genetic profiling, new possible drug targets arise. To find the best treatment to conquer (or combine with) CHOP, new randomized clinical trials are needed up-front.

However, randomized trials in TCL are rare and retrospective population-based studies are needed to provide detailed information on treatment and prognostic factors. Denmark and Sweden have two of the most complete national lymphoma databases in the world for this purpose and although *it's tough to make predictions, especially about the future*[1], population-based studies like this thesis will probably still be of importance in T-cell lymphoma forthcoming.

[1] Quote: Yogi Berra

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References

1. Adelmann, H.B.M.M., *Marcello Malpighi and the evolution of embryology*. 1966, Ithaca, New York: Cornell University Press.
2. Lichtman, M.A., *Historical Landmarks in an Understanding of the Lymphomas*, in *Neoplastic Diseases of the Blood*, P.H. Wiernik, J.P. Dutcher, and M.A. Gertz, Editors. 2018, Springer International Publishing: Cham. p. 675-721.
3. Doyle, D., *William Hewson (1739-74): the father of haematology.* Br J Haematol, 2006. **133**(4): p. 375-81.
4. Hodgkin, *On some Morbid Appearances of the Absorbent Glands and Spleen.* Med Chir Trans, 1832. **17**: p. 68-114.
5. Wilks, S., *Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease) with remarks.* Guy's Hosp Rep, 1856. **11**: p. 56-67.
6. Brouet, J.C., G. Flandrin, and M. Seligmann, *Indications of the thymus-derived nature of the proliferating cells in six patients with Sezary's syndrome.* N Engl J Med, 1973. **289**(7): p. 341-4.
7. Lukes, R.J. and R.D. Collins, *Immunologic characterization of human malignant lymphomas.* Cancer, 1974. **34**(4 Suppl): p. suppl:1488-503.
8. Lukes, R.J. and R.D. Collins, *New approaches to the classification of the lymphomata.* Br J Cancer Suppl, 1975. **2**: p. 1-28.
9. Stansfeld, A.G., et al., *Updated Kiel classification for lymphomas.* Lancet, 1988. **1**(8580): p. 292-3.
10. Swerdlow, S.H., et al., *The 2016 revision of the World Health Organization classification of lymphoid neoplasms.* Blood, 2016. **127**(20): p. 2375-90.
11. Timmins, M.A., S.D. Wagner, and M.J. Ahearne, *The new biology of PTCL-NOS and AITL: current status and future clinical impact.* Br J Haematol, 2020. **189**(1): p. 54-66.
12. Jaffe, E.S., et al., *Classification of lymphoid neoplasms: the microscope as a tool for disease discovery.* Blood, 2008. **112**(12): p. 4384-99.
13. Fox, C.P., et al., *Guidelines for the management of mature T- and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma): a British Society for Haematology Guideline.* Br J Haematol, 2022. **196**(3): p. 507-522.
14. Samverkan, R.C.i. *T-cellslymfom, Nationellt vårdprogram (Version 2.0, 2021-02-16)*. 2021 April 26, 2022]; Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/t-cellslymfom/vardprogram/.
15. Horwitz, S.M., et al., *T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology.* J Natl Compr Canc Netw, 2022. **20**(3): p. 285-308.

16. d'Amore, F., et al., *Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2015. **26 Suppl 5**: p. v108-15.
17. Vose, J., et al., *International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes.* J Clin Oncol, 2008. **26**(25): p. 4124-30.
18. Dotlic, S., et al., *Classification of non-Hodgkin lymphoma in South-eastern Europe: review of 632 cases from the international non-Hodgkin lymphoma classification project.* Br J Haematol, 2015. **171**(3): p. 366-72.
19. Ellin, F., et al., *Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry.* Blood, 2014. **124**(10): p. 1570-7.
20. Anderson, J.R., J.O. Armitage, and D.D. Weisenburger, *Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project.* Ann Oncol, 1998. **9**(7): p. 717-20.
21. Campo, E., et al., *The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications.* Blood, 2011. **117**(19): p. 5019-32.
22. Hapgood, G. and K.J. Savage, *The biology and management of systemic anaplastic large cell lymphoma.* Blood, 2015. **126**(1): p. 17-25.
23. Agnelli, L., et al., *Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma.* Blood, 2012. **120**(6): p. 1274-1281.
24. Piccaluga, P.P., et al., *Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study.* J Clin Oncol, 2013. **31**(24): p. 3019-25.
25. Iqbal, J., et al., *Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma.* Blood, 2014. **123**(19): p. 2915-23.
26. Crescenzo, R., et al., *Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma.* Cancer Cell, 2015. **27**(4): p. 516-32.
27. Parrilla Castellar, E.R., et al., *ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes.* Blood, 2014. **124**(9): p. 1473-80.
28. Johnson, L., et al., *Breast implant associated anaplastic large cell lymphoma: The UK experience. Recommendations on its management and implications for informed consent.* Eur J Surg Oncol, 2017. **43**(8): p. 1393-1401.
29. Marra, A., et al., *Breast implant-associated anaplastic large cell lymphoma: A comprehensive review.* Cancer Treat Rev, 2020. **84**: p. 101963.
30. Stansfeld, A.G., et al., *Updated Kiel classification for lymphomas.* Lancet, 1988. **1**(8580): p. 292-3.

31. de Leval, L., et al., *The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells.* Blood, 2007. **109**(11): p. 4952-63.
32. Cimmino, L., et al., *TET family proteins and their role in stem cell differentiation and transformation.* Cell Stem Cell, 2011. **9**(3): p. 193-204.
33. Couronne, L., C. Bastard, and O.A. Bernard, *TET2 and DNMT3A mutations in human T-cell lymphoma.* N Engl J Med, 2012. **366**(1): p. 95-6.
34. Quivoron, C., et al., *TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis.* Cancer Cell, 2011. **20**(1): p. 25-38.
35. Lemonnier, F., et al., *Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters.* Blood, 2012. **120**(7): p. 1466-9.
36. Cairns, R.A., et al., *IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma.* Blood, 2012. **119**(8): p. 1901-3.
37. Heavican, T.B., et al., *Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma.* Blood, 2019. **133**(15): p. 1664-1676.
38. Sakata-Yanagimoto, M., et al., *Somatic RHOA mutation in angioimmunoblastic T cell lymphoma.* Nat Genet, 2014. **46**(2): p. 171-5.
39. Grogg, K.L., et al., *Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells?* Blood, 2005. **106**(4): p. 1501-2.
40. Rodriguez-Pinilla, S.M., et al., *Peripheral T-cell lymphoma with follicular T-cell markers.* Am J Surg Pathol, 2008. **32**(12): p. 1787-99.
41. Ahearne, M.J., et al., *Follicular helper T-cells: expanding roles in T-cell lymphoma and targets for treatment.* Br J Haematol, 2014. **166**(3): p. 326-35.
42. Kiiskila, J., et al., *Incidence and clinicopathological features of Follicular T-cell lymphoma in Finland: a population-based immunohistochemical study.* Hum Pathol, 2021. **117**: p. 79-87.
43. Nicolae, A., et al., *Peripheral T-cell lymphomas of follicular T-helper cell derivation with Hodgkin/Reed-Sternberg cells of B-cell lineage: both EBV-positive and EBV-negative variants exist.* Am J Surg Pathol, 2013. **37**(6): p. 816-26.
44. Barry, T.S., et al., *Peripheral T-cell lymphomas expressing CD30 and CD15.* Am J Surg Pathol, 2003. **27**(12): p. 1513-22.
45. Deleeuw, R.J., et al., *Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes.* Gastroenterology, 2007. **132**(5): p. 1902-11.
46. Bagdi, E., et al., *Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population.* Blood, 1999. **94**(1): p. 260-4.
47. Chan, J.K., et al., *Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent gammadelta T-cell receptor expression.* Am J Surg Pathol, 2011. **35**(10): p. 1557-69.

48. Moffitt, A.B., et al., *Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2.* J Exp Med, 2017. **214**(5): p. 1371-1386.
49. Perry, A.M., et al., *Indolent T-cell lymphoproliferative disease of the gastrointestinal tract.* Blood, 2013. **122**(22): p. 3599-606.
50. Huang, Y., et al., *Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type.* Blood, 2010. **115**(6): p. 1226-37.
51. Quintanilla-Martinez, L., et al., *Non-mycosis fungoides cutaneous T-cell lymphomas: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop.* Am J Clin Pathol, 2013. **139**(4): p. 491-514.
52. Willemze, R., et al., *Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases.* Blood, 2008. **111**(2): p. 838-45.
53. Savage, K.J., *Aggressive peripheral T-cell lymphomas (specified and unspecified types).* Hematology Am Soc Hematol Educ Program, 2005: p. 267-77.
54. Abramson, J.S., et al., *Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy.* Ann Oncol, 2014. **25**(11): p. 2211-2217.
55. Gisselbrecht, C., et al., *Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA).* Blood, 1998. **92**(1): p. 76-82.
56. Simon, A., et al., *Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95.* Br J Haematol, 2010. **151**(2): p. 159-66.
57. Fisher, R.I., et al., *Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma.* N Engl J Med, 1993. **328**(14): p. 1002-6.
58. Schmitz, N., et al., *Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group.* Blood, 2010. **116**(18): p. 3418-25.
59. Weisenburger, D.D., et al., *Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project.* Blood, 2011. **117**(12): p. 3402-8.
60. Zhang, X.M., et al., *Favorable outcome with doxorubicin-based chemotherapy and radiotherapy for adult patients with early stage primary systemic anaplastic large-cell lymphoma.* Eur J Haematol, 2013. **90**(3): p. 195-201.
61. Kwong, Y.L., et al., *Management of T-cell and natural-killer-cell neoplasms in Asia: consensus statement from the Asian Oncology Summit 2009.* Lancet Oncol, 2009. **10**(11): p. 1093-101.
62. d'Amore, F., et al., *Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01.* J Clin Oncol, 2012. **30**(25): p. 3093-9.

63. Park, S.I., et al., *The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: Report from COMPLETE, a prospective, multicenter cohort study.* Cancer, 2019. **125**(9): p. 1507-1517.
64. Horwitz, S., et al., *Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial.* Lancet, 2019. **393**(10168): p. 229-240.
65. Sieniawski, M., et al., *Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation.* Blood, 2010. **115**(18): p. 3664-70.
66. Kwong, Y.L., et al., *SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group.* Blood, 2012. **120**(15): p. 2973-80.
67. Voss, M.H., et al., *Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience.* Clin Lymphoma Myeloma Leuk, 2013. **13**(1): p. 8-14.
68. *A predictive model for aggressive non-Hodgkin's lymphoma.* N Engl J Med, 1993. **329**(14): p. 987-94.
69. Zhou, Z., et al., *An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era.* Blood, 2014. **123**(6): p. 837-42.
70. Ellin, F., et al., *Comparison of the NCCN-IPI, the IPI and PIT scores as prognostic tools in peripheral T-cell lymphomas.* Br J Haematol, 2019. **186**(3): p. e24-e27.
71. Adams, S.V., P.A. Newcomb, and A.R. Shustov, *Racial Patterns of Peripheral T-Cell Lymphoma Incidence and Survival in the United States.* J Clin Oncol, 2016. **34**(9): p. 963-71.
72. Peyrade, F., et al., *Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial.* Lancet Oncol, 2011. **12**(5): p. 460-8.
73. Ellin, F., et al., *Impact of comorbidity on survival in peripheral T-cell lymphomas: A Swedish Lymphoma Registry study.* Hematol Oncol, 2018. **36**(1): p. 159-165.
74. Thieblemont, C., S. Bernard, and T. Molina, *Management of aggressive lymphoma in very elderly patients.* Hematol Oncol, 2017. **35 Suppl 1**: p. 49-53.
75. Wieringa, A., et al., *Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study.* Br J Haematol, 2014. **165**(4): p. 489-96.
76. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
77. Jo, J.C., et al., *Peripheral T cell lymphomas in elderly patients: a retrospective analysis from the Hematology Association of South East Korea (HASEK).* Ann Hematol, 2016. **95**(4): p. 619-24.

78. Pro, B., et al., *Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study.* J Clin Oncol, 2012. **30**(18): p. 2190-6.
79. Bartlett, N.L., et al., *Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies.* J Hematol Oncol, 2014. **7**: p. 24.
80. Pro, B., et al., *Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma.* Blood, 2017. **130**(25): p. 2709-2717.
81. Park, B.B., et al., *Salvage chemotherapy of gemcitabine, dexamethasone, and cisplatin (GDP) for patients with relapsed or refractory peripheral T-cell lymphomas: a consortium for improving survival of lymphoma (CISL) trial.* Ann Hematol, 2015. **94**(11): p. 1845-51.
82. Damaj, G., et al., *Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial.* J Clin Oncol, 2013. **31**(1): p. 104-10.
83. Zinzani, P.L., et al., *Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome.* Ann Oncol, 2010. **21**(4): p. 860-863.
84. Abrahamsson, A., N. Dahle, and M. Jerkeman, *Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma Registry.* Leuk Lymphoma, 2011. **52**(10): p. 1929-35.
85. Arboe, B., et al., *The Danish National Lymphoma Registry: Coverage and Data Quality.* PLoS One, 2016. **11**(6): p. e0157999.
86. Verheul, H.A., et al., *Background mortality in clinical survival studies.* Lancet, 1993. **341**(8849): p. 872-5.
87. Austin, P.C., *The performance of different propensity score methods for estimating marginal hazard ratios.* Stat Med, 2013. **32**(16): p. 2837-49.
88. Ederer, F., L.M. Axtell, and S.J. Cutler, *The relative survival rate: a statistical methodology.* Natl Cancer Inst Monogr, 1961. **6**: p. 101-21.
89. Cheson, B.D., et al., *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.* Journal of Clinical Oncology, 2014. **32**(27): p. 3059-3067.
90. Gray, R.J., *A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk.* The Annals of Statistics, 1988. **16**(3): p. 1141-1154.
91. Mourad, N., et al., *Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials.* Blood, 2008. **111**(9): p. 4463-70.
92. Maurer, M.J., et al., *Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy.* J Clin Oncol, 2014. **32**(10): p. 1066-73.
93. Horwitz, S.M., et al., *NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016.* J Natl Compr Canc Netw, 2016. **14**(9): p. 1067-79.

94. Liedtke, M., et al., *Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population.* Ann Oncol, 2006. **17**(6): p. 909-13.
95. Cheah, C.Y., et al., *Limited clinical benefit for surveillance PET-CT scanning in patients with histologically transformed lymphoma in complete metabolic remission following primary therapy.* Ann Hematol, 2014. **93**(7): p. 1193-200.
96. El-Galaly, T.C., et al., *Role of routine imaging in detecting recurrent lymphoma: A review of 258 patients with relapsed aggressive non-Hodgkin and Hodgkin lymphoma.* Am J Hematol, 2014. **89**(6): p. 575-80.
97. Tang, T., et al., *Role of Surveillance Imaging in Patients With Peripheral T-Cell Lymphoma.* Clin Lymphoma Myeloma Leuk, 2016. **16**(3): p. 117-21.
98. Mak, V., et al., *Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors.* J Clin Oncol, 2013. **31**(16): p. 1970-6.
99. Chien, S.H., et al., *Frequency of surveillance computed tomography in non-Hodgkin lymphoma and the risk of secondary primary malignancies: A nationwide population-based study.* Int J Cancer, 2015. **137**(3): p. 658-65.
100. Smith-Bindman, R., et al., *Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer.* Arch Intern Med, 2009. **169**(22): p. 2078-86.
101. Thompson, C.A., et al., *Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors.* Ann Oncol, 2010. **21**(11): p. 2262-2266.
102. *Effect of age on the characteristics and clinical behavior of non-Hodgkin's lymphoma patients. The Non-Hodgkin's Lymphoma Classification Project.* Ann Oncol, 1997. **8**(10): p. 973-8.
103. Thieblemont, C., et al., *Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome.* Ann Oncol, 2008. **19**(4): p. 774-9.
104. Advani, R.H., et al., *Outcomes and prognostic factors in angioimmunoblastic T-cell lymphoma: final report from the international T-cell Project.* Blood, 2021. **138**(3): p. 213-220.
105. Extermann, M., et al., *Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG).* Crit Rev Oncol Hematol, 2005. **55**(3): p. 241-52.
106. Extermann, M. and A. Hurria, *Comprehensive geriatric assessment for older patients with cancer.* J Clin Oncol, 2007. **25**(14): p. 1824-31.
107. Peyrade, F., et al., *Treatment decisions for elderly patients with haematological malignancies: a dilemma.* Lancet Oncol, 2012. **13**(8): p. e344-52.
108. Bellera, C.A., et al., *Screening older cancer patients: first evaluation of the G-8 geriatric screening tool.* Ann Oncol, 2012. **23**(8): p. 2166-2172.

109. Garric, M., et al., *Impact of a comprehensive geriatric assessment on decision-making in older patients with hematological malignancies.* Eur J Haematol, 2021. **106**(5): p. 616-626.
110. Merli, F., et al., *Outcome of frail elderly patients with diffuse large B-cell lymphoma prospectively identified by Comprehensive Geriatric Assessment: results from a study of the Fondazione Italiana Linfomi.* Leuk Lymphoma, 2014. **55**(1): p. 38-43.
111. Nabhan, C., et al., *Analysis of very elderly (≥80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome.* Br J Haematol, 2012. **156**(2): p. 196-204.
112. Repetto, L., et al., *Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study.* J Clin Oncol, 2002. **20**(2): p. 494-502.
113. Poeschel, V., et al., *Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial.* Lancet, 2019. **394**(10216): p. 2271-2281.
114. Briski, R., et al., *Survival in patients with limited-stage peripheral T-cell lymphomas.* Leuk Lymphoma, 2015. **56**(6): p. 1665-70.
115. Savage, K.J., et al., *Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification.* Ann Oncol, 2004. **15**(10): p. 1467-75.
116. Horwitz, S., et al., *The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma.* Ann Oncol, 2022. **33**(3): p. 288-298.
117. Bossi, E., et al., *Phase two study of crizotinib in patients with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma relapsed/refractory to chemotherapy.* Am J Hematol, 2020. **95**(12): p. E319-e321.
118. Fukano, R., et al., *Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: An open-label phase II trial.* Cancer Sci, 2020. **111**(12): p. 4540-4547.
119. Coiffier, B., et al., *Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.* J Clin Oncol, 2012. **30**(6): p. 631-6.
120. Coiffier, B., et al., *Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses.* J Hematol Oncol, 2014. **7**: p. 11.
121. Bachy, E., et al., *Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA).* J Clin Oncol, 2022. **40**(3): p. 242-251.
122. Ghione, P., et al., *T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma.* Blood Adv, 2020. **4**(19): p. 4640-4647.

123. Falchi, L., et al., *Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study.* Blood, 2021. **137**(16): p. 2161-2170.
124. O'Connor, O.A., et al., *Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study.* J Clin Oncol, 2015. **33**(23): p. 2492-9.
125. O'Connor, O.A., et al., *Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study.* J Clin Oncol, 2011. **29**(9): p. 1182-9.
126. Horwitz, S.M., et al., *THE COMBINATION OF DUVELISIB AND ROMIDEPSIN (DR) IS HIGHLY ACTIVE AGAINST RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA WITH LOW RATES OF TRANSAMINITIS: FINAL RESULTS.* Hematological Oncology, 2021. **39**(S2).
127. Wulf, G.G., et al., *Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: the DSHNHL2006-1B/ACT-2 trial.* Leukemia, 2021. **35**(1): p. 143-155.
128. García-Sancho, A.M., et al., *Autologous stem cell transplantation as consolidation of first-line chemotherapy in patients with peripheral T-cell lymphoma: a multicenter GELTAMO/FIL study.* Haematologica, 2022.
129. Schmitz, N., et al., *A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL.* Blood, 2021. **137**(19): p. 2646-2656.
130. Du, J., et al., *Comparison of Allogeneic Stem Cell Transplant and Autologous Stem Cell Transplant in Refractory or Relapsed Peripheral T-Cell Lymphoma: A Systematic Review and Meta-analysis.* JAMA Netw Open, 2021. **4**(5): p. e219807.
131. Ellin, F., *Clinical factors and outcome in T-cell lymphoma: a population-based perspective*, in *Lund University Faculty of Medicine Doctoral Dissertation Series 2016:28*. 2016, Lund University: Lund. p. 95.