Peripheral NK/T-cell neoplasms are an uncommon group of diseases that show distinct racial and geographic variation. The prognostic significance of the T-cell phenotype has been clearly defined in recent studies by using modern lymphoma classification systems. However, within this heterogeneous group of neoplasms, some have a more favorable prognosis, such as ALK-positive anaplastic large-cell leukemia (ALCL) and primary cutaneous ALCL, and some have ultimately fatal courses with standard chemotherapy programs (e.g., hepatosplenic γδ T-cell lymphomas).

Further, unlike the benefits observed with CHOP chemotherapy in the treatment of diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphomas (PTCL), other than ALK-positive ALCL, are relatively chemo-resistant to this regimen. Given disease rarity and biological heterogeneity, advances in diagnosis, prognosis and treatment have lagged behind DLBCL. Recently, however, studies are emerging that focus specifically on PTCLs with the ultimate goal of better understanding disease biology and developing more effective therapies.

Introduction
The importance of the T- or NK-cell phenotype in the diagnosis of non-Hodgkin lymphoma (NHL) and its impact on prognosis is a relatively recent advance. Earlier lymphoma classification systems were largely morphologically based and some, including the Working Formulation (WF), did not incorporate immunophenotypic information. Thus, early trials of aggressive lymphomas based on these classification systems included some cases of unrecognized T-cell lymphomas. Although the updated Kiel classification separated B- and T-cell lymphomas, some subtypes were not included and poor reproducibility was a concern. With a growing lack of consensus on which lymphoma classification and terminology to apply, cross-study comparisons were difficult. The International lymphoma Study Group (ILSG) was established to develop criteria integrating all available information to reach a consensus diagnosis for each lymphoma subtype, and in 1994 the REAL (Revised European American Lymphoma) classification was established. In this classification, “precursor” T-cell lymphomas were distinguished from “peripheral” T- and NK-cell neoplasms (PTCLs), and this became the platform for the WHO (World Health Organization) classification.

Studies that first attempted to evaluate the prognostic significance of the T-cell phenotype were discrepant, likely for the following reasons: use of older immunophenotyping techniques; lack of available molecular techniques to establish T-cell clonality; evaluation of diverse PTCL cohorts that may have included indolent subtypes or subtypes now recognized as having a more favorable prognosis; and, conversely, other studies may have included cases that have a uniformly fatal course with standard therapy. More recent large comprehensive analyses on patients diagnosed by either the updated Kiel REAL or WHO classification confirm that patients with PTCL have a worse outcome in comparison with their B-cell lymphoma counterparts. However, under the category of “PTCLs” a large heterogenous group of diseases exists, demonstrating a range of prognoses (Figure 1).

Prognosis of PTCL Subtypes
Systemic ALK-positive anaplastic large cell lymphoma
Anaplastic large cell lymphoma (ALCL) was initially recognized in large as a group of tumors with a characteristic anaplastic morphology and uniform, strong expression of the Ki-1 (CD30). Since the original description, several morphologic subtypes have been recognized; only those cases that are of T- or null-cell phenotype are included in the WHO category of peripheral T/NK-cell neoplasms. Further, in the WHO classification, systemic ALCL is distinguished from primary cutaneous ALCL due to differences in pathology and clinical behavior. The Non-Hodgkin Lymphoma Classification project reported that, compared with other types of PTCL, patients with ALCL had a more favorable prognosis. However, a balanced translocation, t(2;5)(p23;q35), was identified to be non-randomly associated with a proportion of cases of ALCL, resulting in juxtaposition of the ALK (anaplastic lymphoma kinase) gene (2p23) with the NPM (nucleophosmin) promoter (5q35) and may be important in disease pathogenesis. Other less common fusion partners of the ALK gene have been identified, all resulting in the expression of the ALK protein (ALK-positive) (also see Table 2A in the accompanying article by de Leval, beginning on page 272). The frequency of ALCL cases that are ALK-pos ranges from 50% to 85%.
for cytotoxic markers). Studies evaluating either the clinical or molecular characteristics of ALK-neg ALCL have been inconsistent in the reporting of EMA and cytotoxic markers. It has been suggested that since ALK-neg ALCL lacks distinctive immunophenotypic features and its outcome appears to be similar to that of PTCL, not otherwise specified (PTCL-NOS) or unspecified, it should be considered a subtype PTCL-NOS. However, a large-scale international collaboration, the International Peripheral T-cell Lymphoma Project (ITLP), supports that these entities should be considered separately. Immunophenotypically, ALK-neg ALCL is always CD30+, frequently EMA+ and cytotoxic marker+ and demonstrates less consistent expression of various T-cell markers (CD2, CD3, CD4) than PTCL-NOS. Clinically, cases of PTCL-NOS appear to have more frequent bone marrow infiltration and thrombocytopenia. Further, patients with ALK-neg ALCL appear to have a more favorable prognosis than those with PTCL-NOS (5-year overall survival [OS] 49% vs 32%, \( P = .032 \), Figure 2; 5-year failure-free survival [FFS] 36% vs 20%, \( P = .012 \)). In this analysis, the survival estimates for ALK-neg ALCL are comparable to other studies; thus, the lack of statistical difference in a prior study may be related to small patient numbers (Table 1). Interestingly, if the comparison is limited to patients with PTCL-NOS who have high CD30 expression, a group that can be challenging to differentiate from ALK-neg ALCL, the difference is magnified (PTCL-NOS CD30 ≥ 80% cells FFS 9%; 5-year OS 19%). CGH studies support genetic differences with loss of 9p, 5q or 12q seen in approximately 30% of cases of PTCL-NOS, whereas these changes are infrequently observed in ALK-neg ALCL (0%-5%). In contrast, gains in chromosome 1q are observed in up to 50% of cases of ALK-neg ALCL but depending on the population studied, as it is more commonly observed in the pediatric age groups. Several studies have now demonstrated that patients with ALK-pos ALCL have a much more favorable prognosis than those that have ALK-negative (ALK-neg) ALCL and other PTCLs (Figure 1 and Table 1). Clinically, patients with ALK-pos ALCL are more likely to have bone involvement; however, other observations regarding sites of extranodal involvement and frequency of extranodal involvement have been discrepant. In addition to clinical differences, recent gene expression and comparative genomic hybridization (CGH) studies demonstrate that ALK-pos and ALK-neg tumors have unique gene expression signatures and genomic imbalances, providing further evidence that they are distinct entities at a molecular and genetic level.

**Table 1. Overall survival of ALK-neg anaplastic large-cell lymphoma (ALCL) across studies.**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. cases ALK-neg ALCL</th>
<th>Definition of ALK-neg ALCL</th>
<th>5-year Survival ALK-neg ALCL, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gascoyne19</td>
<td>26</td>
<td>Stein67</td>
<td>OS 37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFS 37</td>
</tr>
<tr>
<td>Suzuki22</td>
<td>60</td>
<td>Stein</td>
<td>OS 40</td>
</tr>
<tr>
<td>Falini25</td>
<td>46</td>
<td>REAL4</td>
<td>OS 30</td>
</tr>
<tr>
<td>ten Berge28</td>
<td>21</td>
<td>WHO5</td>
<td>OS 40</td>
</tr>
<tr>
<td>Salavaerria33</td>
<td></td>
<td>WHO5</td>
<td>OS 51</td>
</tr>
<tr>
<td>Savage for the ITLP24</td>
<td>72</td>
<td>WHO5</td>
<td>OS 49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFS 36</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; FFS, failure-free survival; ITLP, International Peripheral T-cell Lymphoma Project; REAL, Revised European American Lymphoma Classification; WHO, World Health Organization; PTCLU, peripheral T-cell lymphoma unspecified.
are much less common in PTCL-NOS. In the 4th edition of the WHO classification, ALK-neg ALCL is considered a provisional entity, distinct from both ALK-pos ALCL and PTCL-NOS.31

Cutaneous Anaplastic Large Cell Lymphoma
In contrast to systemic ALCL, cutaneous ALCL has an indolent course, lacks the t(2;5)(p23;35) and are ALK– and EMA– but usually express CLA (cutaneous lymphocyte antigen). It typically occurs in older men as solitary, asymptomatic cutaneous or subcutaneous reddish-violet nodules/tumors. Extracutaneous disease can occur in 10% of patients, mainly in regional lymph nodes, and most often in patients with multiple lesions. A recent large review of 146 cases of primary cutaneous ALCL from the Dutch and Austrian cutaneous lymphoma registries demonstrated a 10-year disease-specific survival (DSS) of 95%.32 This is also consistent with other reports where the DSS (95%-100%) and OS (83%-100%) are reflective of the indolent course with a propensity to relapse (progression-free survival 55%).24, 33

PTCL-not otherwise specified
PTCL-NOS represents the largest PTCL subgroup in Western populations and outcomes are poor, with a 5-year FFS and OS rates of approximately 20% to 30%.9,15 Attempts have been made to identify biologically and prognostically distinct subgroups within the heterogeneous PTCL-NOS subtype, often referred to as the “wastebasket” of PTCLs. Although morphologic variants have been recognized, it is unknown whether clear differences in prognosis exist.

Most nodal cases of PTCL-NOS are of T-helper phenotype (CD4+CD8+), prompting speculation that some of the biological heterogeneity may be explained by variable expression of TH1 and/or TH2 surface chemokine receptors.34 In one study, two distinct subgroups with PTCL-NOS were identified: group 1 positive for any of ST2(L)(TH2 marker, IL-1R family member), CCR5 (TH1), CXCR3 (TH1); group 2 negative for all these markers.35 Group 1 cases, considered “functional” based on the receptor expression, had a more favorable prognosis compared to group 2 cases35 (Table 2). In a separate study, CXCR3 expression was associated with intermediate prognosis, CCR3 (TH2) expression was a favorable marker and CCR4 (TH2) expression was found to be associated with a poor outcome35 (Table 2). Neither of these studies adjusted for known clinical prognostic factors such as the IPI (International Prognostic Index). The functional significance of these chemokine receptor profiles remains unknown and confirmation of prognostic value in independent analyses awaits further study. Optimistically, CCR4 may provide a rational new target for novel therapies in this poor-risk population.34,35

Epstein-Barr virus (EBV) is found in approximately 30% of all cases of PTCL-NOS and may be associated with a more aggressive course. In one study a more unfavorable prognosis was seen in EBV-positive patients (evaluated by in-situ...
in elderly patients (> 60 years); however, this is in contrast to a study by the ITLP where the presence of EBV was only prognostic in young patients (Table 2). Cytotoxic granule expression is seen more frequently in EBV-positive PTCL-NOS and in one analysis was associated with a more aggressive course, adjusting for the IPI (Table 2).

A high proliferative index (Ki-67 ≥ 80%) is found in approximately 11% of cases of PTCL-NOS and emerged as a stronger predictor of survival compared to clinical factor variables (Table 2), although this marker suffers from poor reproducibility. In another study, p53 overexpression was found to correlate with high Ki-67 expression and poor outcome. In the ITLP, a high frequency of transformed cells (> 70%) correlated with an aggressive disease course (Table 2).

Several investigators have attempted to elucidate the biological heterogeneity and better define prognostic markers within PTCL-NOS through the evaluation of molecular signatures. However, in comparison to B-cell lymphomas, large-scale studies are lacking. A recent study evaluating 35 cases of nodal PTCL-NOS found that high expression of proliferation-associated genes was associated with a worse prognosis (Table 2). However, although Ki-67 expression did correlate with the proliferation signature, it did not correlate with survival. This may reflect low patient numbers as only 6 patients had > 80% positive Ki-67 cells and/or technical limitations and lack of reproducibility with this marker as described above. Another study by the same Spanish group found that expression of NFκB pathway genes was associated with a more favorable prognosis in PTCL-NOS.

**Extranodal NK/T-cell Lymphoma, Nasal-Type**

Extranodal NK/T-cell lymphomas, nasal type (NK/TCL) are so called since although most cases appear to be NK-cell derived (CD2+,CD56+,CD3ε[cytoplasmic]+, EBV+), rare cases with identical clinical and cytologic features exhibit an EBV+CD56+ cytotoxic T-cell phenotype. The qualifier “nasal-type” is assigned due to the common presentation in the nasal region and associated structures; however, other identical tumors can also occur at “extranasal sites” such as the skin, soft tissue, gastrointestinal tract and testis. The prognosis of patients with extranasal NK/TCL, nasal type is inferior to those individuals with nasal disease (5-year OS 9% vs 42%). One group has proposed dividing cases into upper aerodigestive tract (nasal, cavity, nasopharynx and upper aerodigestive tract) versus all others and found that the latter cases had an inferior prognosis that was not observed in a nasal versus nasal-type comparison. Given that occult nasal disease is occasionally discovered in cases of apparent extranasal disease, it may be that in some cases the poor prognosis is reflective of more advanced stage as opposed to differences in disease biology. High Ki-67 expression may have prognostic importance in localized disease.

The majority of cases of NK/TCL are encountered in the Far East. There also may be prognostic racial differences, with at least one study in Caucasian Italian patients with NK/TCL reporting rare long-term survivors (5-year OS 17%) despite predominantly localized nasal disease.

**Angioimmunoblastic T-cell Lymphoma**

Angioimmunoblastic T-cell lymphoma (AILT) was initially described as an atypical reactive process in patients presenting with generalized lymphadenopathy, rash, hepatosplenomegaly, fever and hypergammaglobulinemia, but molecular studies confirm the presence of a T-cell clone in the majority of cases. The outcome of AILT is poor, with most series reporting a 5-year OS of approximately 30%, comparable to that observed with PTCL-NOS (Figure 1). Many patients will die of infectious complications that may be the result of underlying immunodeficiency.

**Prognosis of Uncommon PTCL Subtypes**

Cases of hepatosplenic T-cell lymphoma, enteropathy T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma (SCPTCL) are rarely encountered in clinical practice. SCPTCL represents only 0.9% of cases evaluated in the International PTCL project. Recently, it has been determined that tumors that are γδ T-cell phenotype have a far inferior prognosis to those that are αβ phenotype. The largest published series of 83 cases of SCPTCL confirms that cases with an αβ T-cell phenotype should be separated from cases with a γδ T-cell phenotype due to wide differences in prognosis (5-year OS αβ 82% vs γδ 11%). The more common αβ SCPTCL typically has a CD4+CD8+, CD56-, BF1+ phenotype and is rarely associated with hemophagocytic syndrome (HPS) (17%), which is associated with a worse prognosis (5-year OS 91% vs 46%, P < .001). In contrast γδ SCPTCLs often show epidermal involvement and/or ulceration and CD4-, CD8-, CD56+, BF1- phenotype and more frequently exhibit HPS, although even patients without HPS have a poor outcome. In the jointly published WHO-EORTC classification of cutaneous lymphomas and in the revised WHO classification, the diagnosis of SCPTCL is limited to cytotoxic tumors with an αβ phenotype, whereas cases with a γδ phenotype will be grouped with primary cutaneous γδ T-cell lymphoma, which has a similar aggressive course.

Enteropathy-type T-cell lymphoma (ETTL) can occur in individuals with an established history of gluten-sensitive enteropathy but most often occurs following a short history of celiac disease and/or dermatitis herpetiformis. Clinically, it affects older males presenting with refractory celiac disease or abdominal pain. It typically
involves the jejunum, often in association with intestinal perforation or obstruction. Treatment delivery is often complicated by poor nutrition and significant risk of bowel perforation. Consequently, survival is extremely poor with rare long-term survivors. For the 62 patients (4.7%) identified in the ITLP with ETTL, the 5-year FFS was 4% and 5-year OS was 20%.\textsuperscript{15}

Hepatosplenic γδ TCR is frequently associated with a history of immunosuppression (e.g., renal transplant and treatment with immunosuppressives or treatment with tumor necrosis factor-α inhibitors).\textsuperscript{51} The clinical course is aggressive, and standard chemotherapy does not appear to be curative; however, long-term survivors have been reported following allogeneic transplant.

**Clinical Prognostic Factors in PTCLs**

The IPI was developed and validated in aggressive lymphomas prior to routine immunophenotyping with diagnoses based on the WF (diffuse large cell, immunoblastic). There has not been a study of similar magnitude evaluating the IPI specifically in PTCLs; however, several retrospective studies have demonstrated that the IPI is a useful prognostic tool in some PTCL subtypes. The IPI is effective in identifying different prognostic risk groups in PTCL-NOS diagnosed according to the WHO\textsuperscript{9,52,53} (Figure 3a). The ITLP evaluated the IPI in PTCLs including 340 cases of PTCL-NOS and found that it remained the most useful predictor of survival.\textsuperscript{24,37} A new prognostic model for PTCL-NOS has also been proposed that incorporates many of the current IPI factors (age, PS, LDH) but also recognizes the importance of bone marrow involvement.\textsuperscript{52} In this model, the so-called PIT (prognostic index for T-cell lymphoma) was also able to identify patients with different 5-year OS ranging from 18% (4 factors) to 62% (1 factor).

The IPI has also been applied to other subtypes. In systemic ALCCL it effectively separates patients into different risk groups,\textsuperscript{24} although patients with an IPI of 3 have a very similar prognosis to those with an IPI of 4 or 5 (Figure 4a and 4b). Importantly, patients with ALK-pos ALCCL and a high or high intermediate IPI risk score have a poor prognosis (5-year OS 23%-33%) (Figure 4a). The IPI is not useful in those PTCL subtypes that primarily fall into the high-risk categories. It appears to have limited usefulness in AILT, where other clinical factors not present in the IPI (i.e., male sex and anemia) may have a greater impact on prognosis.\textsuperscript{49}

For NK/TCL the IPI has been useful in defining risk categories.\textsuperscript{54,55} Recently, a Korean prognostic index has been proposed based on a retrospective analysis of 262 patients with NK/TCL based on 4 factors (B symptoms, stage III/IV, abnormal LDH and regional lymph node involvement) that had better discrimination than the IPI (5-year OS by group: group 1, 0 factors 81%; group 2, 1 factor 64%; group 3, 2 factors 34%; group 4, 3 or 4 factors 7%).\textsuperscript{55}

**Primary Therapy of PTCLs: Limitations of CHOP**

CHOP or CHOP-type chemotherapy is considered to be the standard treatment of PTCLs. The large Intergroup trial that established that CHOP was as equally efficacious and less toxic than intensive second and third generation in diffuse large-cell lymphoma (DLBCL) was performed in an era when routine immunophenotyping was not performed with diagnoses based on the WF.\textsuperscript{56} Thus, CHOP has been widely utilized in PTCL largely as a result of the treatment paradigm adopted for DLBCL. Unfortunately, with the notable exception of ALK-pos ALCCL, outcomes with CHOP in PTCL have been poor. Despite these suboptimal results, few studies have compared CHOP to other regimens in the initial treatment of PTCL. Further, there is some evidence...
that anthracyclines may not improve outcome in PTCLs, in particular in PTCL-NOS. In the ITLP, the outcome of PTCL-NOS patients who received anthracycline-based combination chemotherapy was compared to those who received non-anthracycline containing regimens and there was no difference in OS \(^{15}\) (Figure 3b), suggesting that CHOP-like chemotherapy may not be the optimal combination in PTCL and new combinations or dose-intensified approaches should be explored.

The German Non-Hodgkin’s Lymphoma Group (DSHNHL) evaluated the outcome of all T-cell lymphomas based on treatment regimens received in 7 German high-grade studies (n = 331). In the NHL-B1 trial, \(^{57}\) young good-risk patients with T-cell lymphoma had an improved 3-year event-free survival (EFS) (71% vs 50%, \(P = .01\)) when etoposide was added to CHOP-14 or CHOP-21; \(^{58}\) however, many of these patients had ALCL. The GOELAMS group tested alternating VIP (etoposide, ifosfamide, cisplatin)/ ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) for a total of 6 cycles against CHOP for 8 cycles in treatment naïve patients with PTCLs and found there was no difference in EFS and OS between these regimens. \(^{59}\) A Korean group evaluated a CHOP-like regimen (CEOP-B) with epirubicin substituted for doxorubicin and the addition of bleomycin in patients with T-cell lymphomas (1 patient with lymphoblastic lymphoma) with primarily low-risk disease (38% IPI 0 or 1) and reported a 5-year OS of 49%; however, the estimated 5-year PFS was only 30%. \(^{60}\)

Generally, treatment approaches to date have been similar among the PTCL subtypes; however, given the underlying biologic heterogeneity, subtype specific therapies may be more optimal. This approach has been utilized in the treatment of NK/TCL. The majority of patients with NK/TCL present with localized disease and historically they have received combined modality therapy (CMT) with CHOP/CHOP-type chemotherapy followed by involved field radiotherapy, similar to the treatment for localized DLBCL. \(^{61}\) Frequently, disease progression occurs during anthracycline-based chemotherapy in patients with NK/TCLs, suggesting an inherent chemoresistance that may be related to expression of P-glycoprotein, resulting in multidrug resistance. \(^{62}\) Therefore, primary radiotherapy has been endorsed as the key modality in the treatment of NK/TCL; however, it has not been formally compared to CMT or chemotherapy alone in a randomized Phase III trial in this entity. A recent retrospective cohort study of 105 patients treated in China with localized NK/TCL demonstrated that patients treated with primary radiotherapy had an equivalent 5-year OS (66% vs 76%) and 5-year PFS (61% vs 66%, \(P = .01\)) compared with patients treated with CMT, suggesting that chemotherapy did not provide any additional benefit. \(^{63}\) Interestingly, the complete remission (CR) rate following radiotherapy was 83% compared with 20% after initial chemotherapy; however, the latter improved to 81% following the radiotherapy. Another study compared the survival of patients who received any radiotherapy with those who did not and found improved OS in the former group (50% vs 23%, \(P = .025\)). \(^{62}\) Improved outcome using primary radiation therapy compared to CMT has been seen in other analyses. \(^{54,64-66}\) Collectively, these results support that radiation should be used as the primary therapy in localized NK/T-cell lymphoma. Chemotherapy has been explored either during or after radiation; however, whether it impacts cure rates is unknown.

The other exception in the treatment approach in PTCLs is cutaneous ALCL. This subtype typically has an indolent natural history and propensity to relapse. The majority of patients can be treated with localized excision with or without radiotherapy, and overly aggressive systemic treatment should be avoided, particularly since it is
unknown whether chemotherapy impacts the natural disease history. Systemic therapy should be reserved for those with disseminated or extracutaneous disease.32

Summary
PTCLs represent a broad range of biologically distinct diseases exhibiting a range of prognoses. For the most part, outcome is unsatisfactory with CHOP chemotherapy, and therapies tailored specifically for PTCLs are urgently needed. With the therapeutic advances in PTCL lagging behind the success story observed in B-cell lymphomas, there are now an unprecedented number of trials evaluating new chemotherapies or combinations as well as targeted therapy. Attention is now finally turning to PTCLs.

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