

Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project

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Background: Peripheral T-cell lymphoma (PTCL) is rare in most parts of the world. Therefore, we have evaluated the 96 cases of PTCL diagnosed within the Non-Hodgkin's Lymphoma Classification Project (NHLCP) (1378 cases) for their geographical distribution, pathologic features and diagnostic reliability, as well as clinical presentation and outcome.

Materials and methods: Diagnoses of all cases were rendered independently by five experienced hematopathologists based on morphology only, and after introduction of the immunophenotype and clinical data. Divergent diagnoses were jointly discussed and a final consensus diagnosis was established in each case. Reliability of the diagnoses was evaluated statistically, and the clinical features and outcome were analyzed according to the consensus diagnoses.

Results: Seven per cent of all non-Hodgkin's lymphoma (NHL) cases reviewed were classified as PTCL and the frequency varied from 1.5% to 18.3% in different countries. The interobserver agreement with the consensus diagnosis of PTCL was 86% in the Revised European–American Lymphoma (REAL) classification, but the designation of subtypes was less reliable. Diagnostic reliability improved from 41% to 86% after immunophenotyping, but did not improve further with the addition of detailed clinical data. Clinically, angiocentric nasal lymphoma presented in young females (median age 49 years) at extranodal sites, but with few adverse risk factors, whereas angioimmunoblastic lymphoma presented most often in older males (median age 65 years) at nodal and extranodal sites with numerous risk factors. The 5-year overall and failure-free survivals for patients with PTCL treated with doxorubicin (Adriamycin)-containing regimens were only 26% and 20%, respectively. Both failure-free and overall survival were strongly correlated with the performance status and International Prognostic Index scores at presentation, but differences in survival were not observed between the major histological types. However, within the PTCL 'not otherwise specified' category, but not angioimmunoblastic lymphoma, the number of transformed blasts was prognostically relevant.

Conclusions: PTCLs can be diagnosed reliably by experienced hematopathologists, but immunophenotyping is absolutely necessary. Currently, all types of PTCL should be considered high-grade lymphomas. An increased ability to distinguish T-lymphocyte subsets is needed in order to better subclassify the PTCLs for therapeutic and prognostic purposes.

Key words: clinicopathologic correlations, diagnostic reliability, peripheral T-cell lymphoma

Introduction

The Non-Hodgkin's Lymphoma Classification Project (NHLCP) [1] was carried out as a retrospective clinical evalu-

ation of the practical utility and clinical relevance of the REAL classification [2] in comparison with the updated Kiel classification [3] and the Working Formulation [4]. The ability of hematopathologists to apply these classification systems was evaluated, and both inter- and intraobserver reproducibility were considered. Special attention was given to the role of immunohistochemistry and clinical data for the diagnosis. The study design also elucidated the relative

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frequencies of the various types of non-Hodgkin's lymphoma (NHL) in different locations around the world [5]. Additionally, data on the clinical presentation and follow-up of well-classified cases were collected and evaluated [6]. Within this project, a total of 1378 cases of NHL were reviewed, including 129 cases of peripheral T-cell lymphoma (PTCL) (9.4%). In this report, we describe in detail our experience with the 96 cases of PTCL other than anaplastic large-cell lymphoma (ALCL). The cases diagnosed as ALCL according to the criteria of the REAL classification have been reported separately [7].

PTCL consists of a variety of uncommon and rare entities, some of which show typical clinical presentations [i.e. nasal T/natural killer (NK)-cell lymphoma] and/or are linked to specific pathogenic agents (i.e. EBV, HTLV-1). However, the correct diagnosis is often difficult to make due to a lack of diagnostic experience with the various entities, the lack of reliable immunohistochemical markers of clonality and, moreover, still unsettled disagreement as to the classification of PTCL [8].

Since immunophenotyping was not considered a necessary prerequisite for the diagnosis of malignant lymphoma in the Working Formulation [4], PTCL did not receive special attention within the different categories. In contrast, the Kiel classification [3, 9–11] recognized nodal T-cell lymphomas and distinguished them according to their histology and cytomorphology. Additionally, in the Kiel classification, clinical groups (low-grade versus high-grade lymphoma) were defined according to the cellular composition of the lymphomas. However, the entities defined were poorly reproducible, at least in one study [12]. In addition, the Kiel classification did not delineate primary extranodal lymphomas and therefore failed to recognize some new and well-recognized entities with extranodal presentations, such as the nasal or intestinal T/NK-cell lymphomas.

The REAL classification proposed by the International Lymphoma Study Group (ILSG) [2], building mainly on the criteria of the Kiel classification, adopted several new entities with primary extranodal presentations and characteristic pathological features. Among the PTCLs with primary nodal presentation, angioimmunoblastic T-cell lymphoma (AILT) is regarded as a well-defined entity, as are ALCL and adult T-cell leukemia/lymphoma. The various remaining PTCLs were grouped together as 'peripheral T-cell lymphoma, not otherwise specified' (PTCL-NOS), a category that was regarded as heterogeneous in which the subtypes could not be distinguished reproducibly by pathologists. This approach has been challenged, because in some series, different histological types have been correlated with cytogenetic data, which appears to justify subcategorization [13–15]. However, because no clinical differences were seen and the distinguishing histological features were not clear-cut, the ILSG proposal was accepted and histological variants within this group were considered optional for research purposes. Within this PTCL-NOS category, a stratification was proposed

according to cell size. In addition, lymphoepithelioid (Lennert's) lymphoma was considered to represent a cytologic variant. However, data on the diagnostic reproducibility and clinical relevance of this classification are still lacking. Therefore, we have analyzed the data on our cases of PTCL in an attempt to shed some light on these issues.

Patients and methods

The design of our study has been described in detail previously [1]. Briefly, up to 200 consecutive cases were prepared by each site pathologist in collaboration with the participating oncologist. Some cases diagnosed on bone marrow trephine only, and some cutaneous lymphomas diagnosed and treated by dermatologists may have been excluded. Tissue biopsies adequate for diagnosis and classification were available in all cases, and slides and data on immunophenotyping were required to determine cellular lineage in all cases. Auxiliary data, such as molecular or cytogenetic studies, were also included if available.

Independent diagnoses were rendered by five expert hematopathologists (J.D., K.A.M., H.K.M.H., B.N.N., D.D.W.) in three classification systems: the Working Formulation [4], the updated Kiel classification [3, 10] and the REAL classification [2]. Within each classification system, cases were diagnosed according to the published criteria for each category, and independently from the diagnoses in other classification systems. As no criteria for the subclassification of PTCL-NOS were given in the REAL classification, the definitions were adopted from the respective categories of the Kiel classification.

Diagnoses were initially based on morphology and basic clinical information (age, sex, biopsy site and major site of involvement). Then, diagnoses were made after introduction of the immunophenotype. For this, both the interpretation of the site pathologist and immunostained slides were available for review. Given the retrospective nature of the study at various locations, the available phenotypic data were heterogeneous, but included various markers for T cells (CD3, CD45R0 or CD43, etc.) and B cells (CD20) in all cases. All cases included in this report stained positive for one or more T-cell markers and negative for B-cell markers. Immunostains for follicular dendritic cells (CD21, CD23) were used to delineate AILT from PTCL-NOS. Cases of ALCL were excluded based on the criteria of the REAL classification [2], and all such cases were positive for CD30 antigen [7]. Finally, the diagnoses were made after review of the detailed clinical data (i.e. detailed sites of involvement, performance status, laboratory studies) at the time of diagnosis [1]. All individual diagnoses were recorded and a consensus diagnosis was reached if at least four of the five pathologists agreed on the final diagnosis of PTCL in the REAL classification, regardless of subtype. Otherwise, the cases were jointly discussed at a multiheaded microscope and a consensus diagnosis was reached. The subtype within PTCL was considered a consensus if at least three of the experts agreed. If no agreement was achieved, additional studies were required to resolve the case. For such cases, a final consensus diagnosis could only be rendered after the results of these studies (i.e. immunophenotyping, molecular studies) became available. For research purposes, transformed blasts were counted in 10 random high-power fields on the hematoxylin–eosin stain for all PTCL by each expert (high-power field = 0.0159 mm²). Transformed blasts were defined as medium-sized or large lymphoid cells with open chromatin and one or more prominent nucleoli. The counts of the five expert pathologists were then averaged for each case. As a measure of variability of this investigation, the coefficient of variation (standard deviation/mean) was computed.

After consensus diagnosis, 23 cases of PTCL were subjected to re-review by the pathologists in order to estimate the intraobserver reproducibility. Altogether, 115 PTCL re-review diagnoses were made by the five pathologists. Agreement was noted when the pathologists' re-review diagnosis agreed with either their original diagnosis (simple agreement) or the consensus diagnosis (expanded agreement).

Clinical data were obtained from patient records and overall survival and failure-free survival were calculated using the Kaplan–Meier method [16]. International Prognostic Index (IPI) scores [17] were determined and used in the survival analyses. Time-to-event distributions were compared using the log-rank test [18]. The statistical analyses for differences between groups were a combination of analyses of variance for continuous variables such as age, and χ^2 -tests for discrete variables such as sex. Agreement with consensus was analyzed for every diagnosis in each of the classification systems. Kappa statistics [19] were also calculated to compare interobserver reliability with previous studies [12].

Patients were stratified according to the treatment received into the following groups: no therapy, radiation therapy only, single agent chemotherapy, combination chemotherapy without adriamycin, and combination chemotherapy containing adriamycin. For comparison of survival curves, only patients receiving the latter treatment were included.

Results

Epidemiology and pathology

Within this project, a total of 129 cases of PTCL were diagnosed (9.4% of 1378 NHL in the study), 33 (2.4%) of which were ALCL and are the subject of a separate report [7]. The frequency of PTCL (excluding ALCL) varied geographically (Table 1), ranging from 1.5% (Vancouver) to 18.3% (Hong Kong) of all NHLs diagnosed at a specific site ($P = 0.001$).

According to the consensus diagnoses (Table 2), most of the 96 non-anaplastic PTCL cases were part of the PTCL-NOS group (55%) in the REAL classification, consisting predominantly of the mixed medium and large-cell variant. PTCL of the angiocentric nasal type was also diagnosed frequently (19 cases, 20%), but this diagnosis was much more frequent in Hong Kong (16 cases, 8% of all lymphomas) than

at all other sites combined (three cases). AILT was diagnosed in 17 cases (18%), whereas the other subtypes were rare.

The immunophenotypes that were available at the time of the diagnosis are given in Table 3. No significant differences were seen between the phenotypes of PTCL-NOS and AILT. Most angiocentric nasal lymphomas were positive for CD56.

The diagnoses of the 96 PTCL cases (excluding ALCL) in the Kiel classification (Table 4) largely corresponded to the REAL categories. Two cases diagnosed as ALCL in the Kiel classification were placed into the intestinal group in the REAL classification. Diagnoses using the Kiel classification for cases classified as PTCL-NOS in the REAL system are shown in Table 4. In the Working Formulation, the 96 non-ALCL PTCL cases were spread over a broad spectrum of categories. The largest number of cases were diagnosed as diffuse mixed small- and large-cell type ($n = 40$, 42%), diffuse large-cell not further classified ($n = 15$, 15.6%) or immunoblastic clear cell ($n = 15$, 15.6%).

Diagnostic reproducibility

Overall, the level of agreement with the consensus diagnosis of non-anaplastic PTCL (any subtype) in the REAL classification

Table 1. Geographical distribution of PTCL (excluding ALCL)

	<i>n</i>	%
Omaha	6/200	3.0
Vancouver	3/200	1.5
Capetown	16/188	8.5
London	11/119	9.2
Locarno	5/79	6.3
Lyon	10/192	5.2
Würzburg	9/203	4.4
Hong Kong	36/197	18.3

Table 2. Subtypes of non-anaplastic PTCL according to the REAL classification, along with the inter- and intraobserver diagnostic reliability

Subtype	Frequency		Interobserver agreement (%)			Intraobserver agreement		
	<i>n</i>	%	Without phenotype	With phenotype	With detailed clinical information	<i>n</i>	Simple agreement (%)	Expanded agreement (%)
PTCL-NOS	53	55	24	72	72	11	89	100
medium-sized cell	6		7	43	43	3	53	53
mixed medium and large cell	28		23	52	53	7	71	100
large cell	17		13	53	53	1	80	80
lymphoepithelioid	2		30	70	70			
Angiocentric nasal	19	20	59	85	85	7	91	97
Angioimmunoblastic	17	18	61	72	72	4	80	85
Intestinal	5	5	20	80	76	1	80	80
Hepatosplenic	1	1	20	40	40			
Adult T-cell lymphoma/leukemia	1	1	20	20	60			

Table 3. Immunophenotypes of PTCL and its entities

	All PTCL		PTCL-NOS		AILT		Angiocentric nasal	
	<i>n</i>	% positive	<i>n</i>	% positive	<i>n</i>	% positive	<i>n</i>	% positive
CD20	76	0	42	0	10	0	17	0
CD79a	6	0	5	0	0		0	
CD2	46	93	24	92	7	100	14	93
CD3	80	85	44	91	14	100	16	50
CD4	44	77	22	91	9	100	12	33
CD5	43	65	24	67	6	100	12	42
CD7	41	46	21	52	7	57	12	33
CD8	45	18	23	17	8	13	13	23
CD43	30	90	17	82	5	100	4	100
CD45R0	52	77	31	81	9	100	6	50
BetaF1	4	100	1	100	1	100	2	100
CD30	47	17	30	17	6	0	6	17
CD56	23	43	8	0	3	0	12	83

Table 4. Subtypes according to the Kiel classification for all 96 PTCL and 53 PTCL-NOS

	All 96 PTCL		53 PTCL-NOS	
	<i>n</i>	%	<i>n</i>	%
Pleomorphic small cell	7	7	3	6
Pleomorphic medium and large cell	57	60	37	70
Immunoblastic	8	8	7	13
Lymphoepithelioid	1	1	1	2
T-zone lymphoma	4	4	4	7
Angioimmunoblastic	17	18	1	2
Anaplastic large-cell lymphoma	2	2	0	0

was only 41% prior to consideration of the phenotypic information. This level improved to 86% after the phenotype was evaluated, but did not improve further with addition of the detailed clinical data.

Agreement with the consensus diagnosis of the six PTCL entities was only 37% considering morphology only, but improved to 74% after introduction of the phenotype. The levels of agreement with the consensus diagnosis for each of the entities is given in Table 2. The highest level of agreement was for the diagnosis of angiocentric nasal PTCL (85%), with lower levels for PTCL-NOS and AILT (72%). However, the variants of PTCL-NOS were diagnosed less reliably (43% to 70%). Interobserver reproducibility as calculated by the kappa statistic [19] was 0.42 for the final REAL classification diagnoses, including the phenotype and clinical information.

In the re-review process, 23 cases of PTCL were included (Table 2). The results were excellent for all major diagnoses in both simple agreement (agreement with own final diagnosis) and expanded agreement (agreement with own final or the consensus diagnosis).

Regarding the counts of transformed blasts, the coefficient of variation was 0.78 for cases with a mean transformed cell count of <300, and 0.53 for cases with a count \geq 300, both suggesting moderate variability of the counts.

Clinical presentation

Detailed clinical data were available for all 96 patients and are summarized in Table 5. These data differ from former publications based on this study [1, 6] because PTCL of the angiocentric nasal type was excluded from PTCL at that time due to the fact that the disease is rare in Western countries. The majority of the patients in this study were elderly males, often presenting with stage IV disease. Most of the patients had an ambulatory performance status. One patient presented with autoimmune hemolytic anemia. One patient with adult T-cell leukemia/lymphoma was HTLV-1 positive, and HIV infection was reported in four other patients. None of the patients was known to have had a previous organ transplant or to have received immunosuppressive drugs.

The majority (56%) of the patients (Table 5) had both nodal and extranodal sites of involvement at presentation. The most common extranodal sites in these patients were the bone marrow (44%) and liver (21%). The neoplastic lymph nodes were frequently present on both sides of the diaphragm (57%), and the spleen was involved in 37% of cases. In three patients (one PTCL-NOS and two AILT), the spleen was the only extranodal site of involvement.

The small intestine was involved in eight cases, among them five with intestinal T-cell lymphoma (ITL), two with AILT and one with PTCL-NOS and widespread disease. Three of the patients with ITL had additional involvement of the mesenteric lymph nodes and one of these presented with widespread disease. In two patients, ITL was confined to the small bowel. All five cases of ITL had a large-cell component

and lacked angiocentricity, although data on CD56 were lacking.

Thirty percent of the cases presented with extranodal disease only. A large proportion of these had involvement of the nose and nasal cavity (61%). Eight cases (27%) presented in the skin. In five of these, the skin was the only site of involvement and PTCL-NOS was the consensus diagnosis in

each case. In three other cases (PTCL-NOS, AILT and nasal type), other extranodal sites were also involved.

Only 13 patients (14%) had nodal involvement only. Nine of these presented with multiple lymph nodes on both sides of the diaphragm. Three others had supradiaphragmatic disease only, and one patient presented with mesenteric lymph node enlargement.

The clinical presentations of the most frequent PTCL entities (PTCL-NOS, AILT and angiocentric nasal lymphoma) are compared in Table 6. Statistical analysis demonstrated significant differences between these three diagnostic categories in age, sex, stage, B symptoms, IPI scores and sites of presentation. Angiocentric nasal lymphoma presented more frequently at only extranodal sites than the other two categories ($P = 0.001$), and these patients were mostly females with a median age <50 years, with fewer risk factors (IPI score) and limited stage disease. Comparing the predominantly nodal categories PTCL-NOS and AILT, patients with AILT were slightly older, more often male, and more likely to have adverse risk factors and present with both nodal and extranodal disease. However, none of these differences was statistically significant.

Therapy, survival and prognosis

The therapies of the patients in this study differed widely. Five patients were not treated at all, four received radiation therapy only, one patient received single agent chemotherapy and 19 patients received various combination chemotherapies without adriamycin. The majority of patients (70%), however, were treated with combination chemotherapy containing adriamycin. All statistics regarding survival apply to this latter cohort only. The 5-year overall survival of these patients was only 26% and the 5-year failure-free survival was 20% (Figure 1).

Survival of patients with PTCL could be predicted by patient characteristics. Performance status was the strongest univariate prognostic indicator of both overall survival and

Table 5. Clinical characteristics of 96 patients with PTCL

Median age (years)	61
Age range (years)	17–90
Male-to-female ratio	1.5
Stage	
I	2%
IE	16%
II	4%
IIE	5%
III	12%
IV	61%
B symptoms	40%
Elevated serum LDH	61%
Tumor diameter ≥ 10 cm	11%
Non-ambulatory performance status	29%
Circulating tumor cells	13%
IPI scores	
0–2	47%
3–5	53%
Presentation	
nodal only	14%
extranodal only	30%
nodal + extranodal	56%

Table 6. Clinical comparison of the major PTCL categories

	PTCL-NOS	AILT	Nasal	<i>P</i>
Age (years)	59	65	49	0.016
Sex (male) (%)	44	53	16	0.046
Stage IV (%)	60	83	37	0.001
B symptoms (%)	41	65	5	0.001
Elevated serum LDH (%)	65	60	53	0.690
Tumor diameter >10 cm (%)	9	17	11	0.767
Non-ambulatory performance status (%)	28	38	16	0.345
IPI scores 3–5 (%)	60	86	29	0.006
Presentation				
nodal only (%)	22	12	0	
extranodal only (%)	16	6	95	0.001
nodal and extranodal (%)	63	82	5	

failure-free survival (Figure 2). The IPI scores (0–2 versus 3–5) also distinguished groups with different overall survival and failure-free survival (Figure 3). However, the other components of the IPI, such as age (<60 versus >60 years), clinical stage (I/II versus III/IV), serum lactate dehydrogenase (LDH) (normal versus elevated) and the presence of extranodal involvement (more than one site), failed to predict outcome.

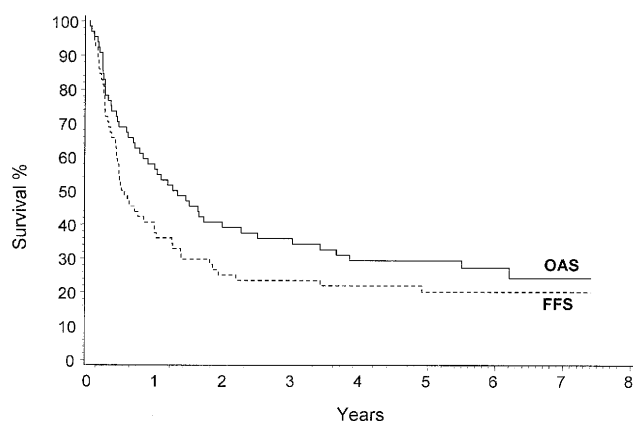


Figure 1. Overall survival (OAS) and failure-free survival (FFS) of PTCL treated with combination chemotherapy including adriamycin.

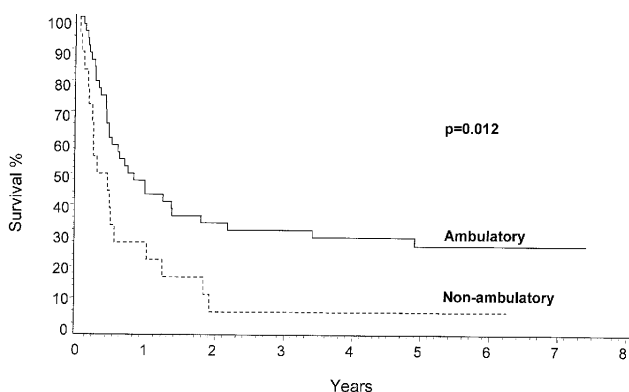


Figure 2. Failure-free survival according to the performance status.

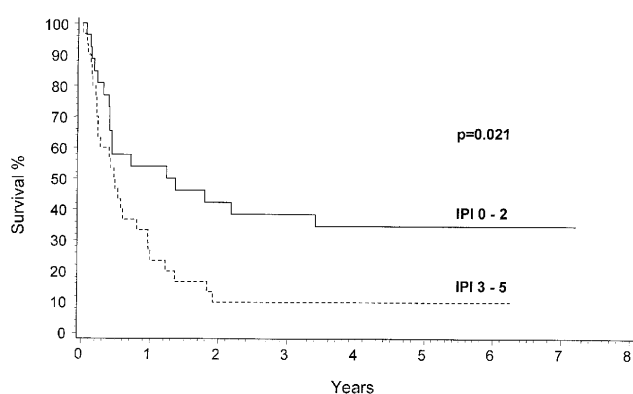


Figure 3. Failure-free survival according to the IPI scores.

No statistically significant differences were found in overall survival and failure-free survival when stratifying according to the PTCL entities defined in the REAL classification system (Figure 4), or stratifying PTCL-NOS according to cell size. In addition, there were no survival differences between the clinical groupings (low grade versus high grade) as defined in the updated Kiel classification. Also, survival analysis according to the average number of transformed blasts did not show significant differences when analyzing all cases of PTCL as a group. However, there were significant differences in both overall survival and failure-free survival for the cases diagnosed as PTCL-NOS when stratifying by the average transformed blast counts per 10 high-power fields (Figure 5). Five of six cases of medium-sized PTCL and 19 of 28 cases of medium- and large-cell PTCL had mean blast counts of <300; however, none of the 15 cases of large-cell PTCL had a mean number of large cells <300.

Discussion

In this retrospective study, 96 cases of PTCL are described from a cohort of 1378 cases of NHL diagnosed at different sites around the world [1]. As a drawback of such a study,

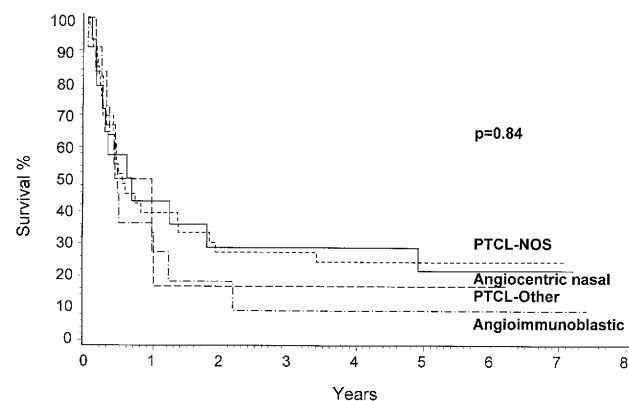


Figure 4. Failure-free survival according to the major histological types of PTCL.

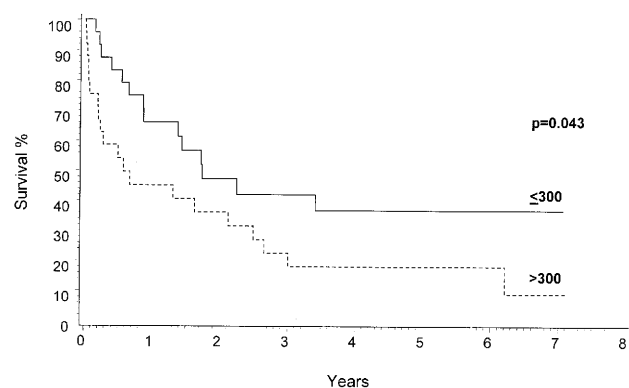


Figure 5. Failure-free survival of PTCL-NOS according to the average blast counts in 10 random high-power fields.

only limited immunohistochemical and molecular data were available in many cases. Even so, the five expert pathologists were able to diagnose the major categories of PTCL accurately and reproducibly. Additionally, the treatments were rather heterogeneous, although 70% of the patients were treated aggressively with combination chemotherapy containing adriamycin. Therefore, only this latter cohort was used in the survival analyses.

The relative frequency of PTCL in various parts of the world varies considerably. We found marked geographical differences in the distribution of the various PTCL, with the angiocentric nasal type being more frequent in Hong Kong than the other sites in our study. No sites with known endemic HTLV-1 infection were visited, but one patient was diagnosed in Hong Kong with an HTLV-1-positive adult T-cell leukemia/lymphoma. These findings suggest that both genetic and environmental factors need to be investigated in future epidemiological studies. According to the selection criteria of our study [1], the distribution in our material should represent the true relative frequencies of the different entities. However, some bias cannot be excluded since some patients with primary cutaneous T-cell lymphoma might not have been seen in an oncology department in some countries.

Histological diagnoses

The PTCLs are often difficult for the pathologist to diagnose. Not only are these tumors rare in most geographical areas, but they also exhibit a wide variety of morphological and clinical features [8]. Additionally, the composition of the tumor cells may be very heterogeneous and, in some studies [20, 21], a considerable number of the T cells were found to be part of the reactive inflammatory background infiltrate, thus making the identification of tumor cells difficult. The lack of a useful marker of clonality, such as light-chain restriction in B-cell lymphoma, has also been a problem in the diagnosis of PTCL. However, this has recently been overcome to some extent by PCR-based analyses for T-cell receptor γ - or β -chain gene rearrangements.

Despite these problems, the overall agreement level with the consensus diagnosis of PTCL was 86% in our study, and ranged from 72% to 85% for the major PTCL entities. Most major types of B-cell lymphoma had similar levels of interobserver agreement with the consensus diagnosis in our study [1]. Therefore, PTCL and its major entities can be diagnosed reliably by expert hematopathologists, but the designation of variants within PTCL-NOS is less reliable. The variants of PTCL were considered to be provisional in the REAL classification [2] and their use was optional. Therefore, no specific criteria were given for their recognition. Poor reproducibility was one of the arguments for grouping these categories within PTCL-NOS in the REAL and WHO classification systems.

Kappa statistics [19] were used to estimate the interobserver reliability of the diagnostic categories. The overall kappa value for the diagnosis of PTCL was 0.42 in our study,

thus reflecting moderately good consensus [22]. This value is higher than those found in previous studies of T-cell lymphoma using the Kiel classification [12, 23], wherein kappa values of 0.35 and 0.29 were found and suggested only fair consensus. The higher kappa value in our study is most likely due to the inclusion of immunophenotypic data in our evaluation of the cases, which was not included in the former studies [12, 23]. Additionally, several distinct subtypes of PTCL listed in the Kiel classification are grouped into PTCL-NOS in the REAL classification.

Previous reports have also stressed the importance of immunophenotypic studies in the diagnosis of PTCL [24–29]. Our study allowed us to quantify the impact of immunophenotyping in the diagnosis of PTCL. We found that the inclusion of immunophenotypic data resulted in a substantial increase in the agreement rate with the consensus diagnosis, from 41% to 86%. While all CD56⁺ lymphomas diagnosed in this study were angiocentric nasal type (Table 4), phenotyping of the tumor cells did not aid in the differentiation of PTCL-NOS from AILT. However, stains such as CD23 or CD21 were helpful in detecting proliferating networks of follicular dendritic cells in AILT. Also, the addition of detailed clinical data did not have an impact on the pathologists' diagnoses, probably because the major site of disease was included in the basic clinical data provided at the time of initial diagnosis.

The well-defined entities of AILT [30, 31] and angiocentric nasal T-cell lymphoma [32] can be diagnosed reliably by expert hematopathologists, the agreements with the consensus being 72% and 85%, respectively. Disagreements with the consensus consisted mainly of other types of PTCL. However, in the differential diagnosis of PTCL, lymphomas of B-cell lineage must also be considered. Interestingly, nodal marginal zone B-cell lymphoma was the most common misdiagnosis among our consensus cases of PTCL-NOS. These lymphomas are morphologically similar to PTCL and may have a marginal zone growth pattern, as described recently [33, 34]. In those cases misdiagnosed as B-cell lymphoma, the available phenotyping was not optimal and, therefore, the phenotype of the tumor cells could not be established with certainty.

For PTCL-NOS, regarded as one category, there was also a good agreement with the consensus diagnosis (72%), but stratification according to cell size led to lower interobserver agreement rates (Table 2) and lacked prognostic value. Only two cases of lymphoepithelioid (Lennert's) lymphoma were observed in this study, and the agreement with the consensus was good (70%). These results support the approach of the REAL [2] and WHO [35] classification systems to form a heterogeneous group designated PTCL-NOS. However, our increasing knowledge of T-cell biology and function may serve as a basis to classify PTCL according to histogenetic derivation and functional differentiation in the future [8, 36, 37].

Clinical presentation and outcome

In our cohort of 96 PTCL patients, the median age was 61 years and males were predominant (1.5:1). Most patients presented with advanced stage disease (Table 5), but with an ambulatory performance status. B symptoms were relatively uncommon (40%) when compared with other studies of PTCL [20, 38–40], but these did not include patients with angiocentric nasal lymphoma. However, the frequency of B symptoms in our patients with PTCL-NOS and AILT is in keeping with prior studies. Both lymph nodes and extranodal sites were involved at presentation in 56% of our patients, but a significant proportion of the patients presented with only extranodal disease (36%).

Among patients with PTCL, those with well-defined entities like AILT and angiocentric nasal lymphoma have a characteristic clinical presentation (Table 6). Patients with angiocentric nasal lymphoma were more often females (84%), presenting at a younger age (median 49 years) and with limited stage disease and few adverse risk factors. In contrast, AILT occurred more often in males, with a higher median age, and these patients had numerous risk factors, as reported by others [8, 41–43]. In contrast, PTCL-NOS does not appear to have a distinctive clinical presentation, which is in keeping with the concept of the REAL proposal which regarded this group as heterogeneous [2].

Patients with PTCL who received aggressive chemotherapy including adriamycin had a 5-year overall survival of only 26% in our study. Owing to the heterogeneity of treatment in different parts of the world, this is somewhat worse than that reported in a prospective randomized clinical study [38], in which the 5-year survival was 41%. Together with mantle cell lymphoma and precursor T-lymphoblastic lymphoma, PTCL comprised the worst prognostic group of lymphomas [1]. No significant differences were found regarding overall survival or failure-free survival for any of the histological types in any of the three classification systems under consideration, but the case numbers were small in some categories. The average count of transformed blasts (<300 versus >300) in 10 high-power fields proved to be of prognostic significance in PTCL-NOS, but not PTCL as a whole, for both overall survival and failure-free survival (Figure 4). However, the approach of the Kiel classification to distinguish low-grade from high-grade lymphomas on a morphological basis, although generally successful for B-cell lymphomas, fails in PTCL. We could not detect differences in outcome when stratifying this way, and all PTCLs should be regarded as clinically aggressive [20, 39, 44, 45]. In contrast, anaplastic large-cell lymphoma showed a significantly different clinical presentation and better outcome than PTCL [1, 6, 7], as has been reported by others [20, 39, 44, 45].

As in other studies [38, 46], the outcome in PTCL could be predicted by clinical parameters. The important prognostic indicators in our study were the performance status and IPI scores [17]. Other factors reported to correlate with outcome,

such as age [40], B symptoms [20], bone marrow involvement [20] or stage [26, 40], did not predict for survival in our study. In general, the survival of patients with PTCL is worse than that for patients with B-cell lymphoma, and the diagnosis of PTCL [39, 47–49] has been proposed as an independent prognostic factor among aggressive lymphomas [38].

Summary and conclusions

In summary, although PTCL remains difficult to diagnose and subclassify, a reliable diagnosis can usually be achieved if proper immunophenotypic analysis is performed. The REAL classification system is easy to apply, and the histologically defined entities differ in their initial clinical presentation, but not prognosis. Currently, the histological subclassification of PTCL-NOS does not recognize meaningful clinical variants, but the possibility of grading these lymphomas according to the number of transformed blasts, similar to follicular lymphoma, needs to be evaluated further. Our study supports the combination of various categories of the Kiel classification into PTCL-NOS, but one should be aware of the substantial heterogeneity within this group with respect to both morphology and clinical presentation. All PTCLs are clinically aggressive, and the Kiel concept of grouping PTCL according to cell size into low-grade and high-grade lymphoma lacks clinical significance. New insight into the differentiation of T-cell lymphocytes is needed in order to better subclassify the PTCLs according to the functional status of their respective normal counterparts.

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