

INVESTIGATIVE REPORT

Survival Data for 299 Patients with Primary Cutaneous Lymphomas: A Monocentre Study

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The aim of this study was retrospectively to assess the validity of the 2005 WHO-EORTC classification for primary cutaneous lymphomas (PCL) in a large cohort of patients of a single German skin cancer unit. All patients with PCLs consecutively visiting our hospital between January 1980 and December 2005 were included in a retrospective monocentre study, analysing their histological and clinical data. A total of 312 patients fulfilled the inclusion criteria for PCL. In 299 patients clinical information and paraffin material were sufficient for detailed classification. Of the 299 patients, 63% expressed a T-cell and 37% a B-cell phenotype. Mycosis fungoides was the entity with the highest frequency (30.9%), followed by primary cutaneous follicle centre lymphomas (16.9%) and lymphomatoid papulosis (15.9%). The mean follow-up period was 38.4 months. Five-year disease-specific survival was 80.5% for mycosis fungoides, 92.5% in primary cutaneous anaplastic large cell lymphoma, 100% in lymphomatoid papulosis, 98.1% in primary cutaneous follicle center lymphoma, 100% in primary cutaneous marginal zone lymphoma and 63.2% in diffuse large B-cell lymphoma, leg type. Our data are in line with the data collected by the WHO-EORTC. This is further evidence for the reliability of the WHO-EORTC classification and staging system. **Key words:** cutaneous lymphoma; B-cell; T-cell; survival; prognosis.

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Lymphoproliferative diseases may affect the skin primarily or secondarily (1). They represent a heterogenic group in respect of clinical appearance, prognosis, histopathology, immunohistochemistry, cytogenetic and gene-expression analyses (1, 2). Primary cutaneous lymphoma (PCL) has been defined as lymphoma restricted to the skin at the time of diagnosis. To establish this diagnosis appropriate staging procedures are necessary (2).

In the last two decades there has been investigative discussion about the correct classification.

In 2004 a consensus conference introduced the so-called World Health Organization - European Organization for Research and Treatment of Cancer (WHO-EORTC) classification system (2). This is the first classification for primary cutaneous lymphomas, based on the integration of clinical symptoms and courses, histopathology, immunohistology and recently described cytogenetic and molecular-genetic findings (3–6), and is accepted by the WHO as well as the EORTC (2).

PCL is the second most common type of extra-nodal non-Hodgkin's lymphoma besides the gastrointestinal tract. Nevertheless, it has a very low incidence of 1/100,000 (7). For that reason, single-centre studies with an acceptable number of patients are rare.

The aim of this study was to correlate entities as defined by the WHO-EORTC classification with clinical parameters and follow-up data.

METHODS

Patients

During the period 1980 to 2005, 312 patients with PCL in a single-centre retrospective cohort analysis had been retrospectively classified by an expert panel using the clinical, histopathological, immunophenotyping and molecular criteria of the WHO-EORTC classification (2). Histology and immunohistochemistry of every patient had been re-evaluated and re-classified by two experts for dermatopathology (H-JS, CH). In all patients, the presence of extracutaneous disease at the time of diagnosis had been excluded by standard staging procedures.

Exclusion criteria

Patients with iatrogenic immunosuppression (e.g. transplantation patients) were excluded from the study (8, 9). Secondary cutaneous lymphomas were also excluded. Even so, patients with the diagnosis "clonal dermatitis" (10), "dyscrasia with undetermined significance" (11, 12), or "cutaneous lymphoid hyperplasia" (13) "were excluded from this study. Because of its poor definition no patient with the diagnosis small digitate or large plaque parapsoriasis was included in this study (14, 15).

Clinical and follow-up data

The analysed clinical data included the age of the patients at time of diagnosis, sex, date of first diagnosis, duration of follow-up, and status of disease at the last follow-up examination.

All patients were treated with one or more treatment modalities, including surgical excision of the lesions, local radio-

therapy, ultraviolet (UV)-radiation therapy, psoralen plus UVA (PUVA) therapy, retinoid-PUVA therapy, interferon-PUVA therapy, cobalt-60 radiation, extracorporeal photopheresis, interferon alpha 2a, anti-CD20 antibody therapy, antibiotics, topical and systemic mono- or poly-chemotherapy or “watch and wait” therapy.

Histological review

For each patient identified as evaluable in this study, paraffin-embedded lesional skin, taken as a biopsy before treatment started, was collected from the archive of this single-centre study. In all 312 cases 4 µm sections were processed for haematoxylin-eosin and Giemsa’s staining.

Routine immunostaining was performed on formalin-fixed, paraffin-embedded tissue sections, which were de-waxed and then subjected to antigen retrieval by microwaving and then using a three-step immunoperoxidase technique with the following antibodies: CD1a (Immunotech, Cary, NC, USA), CD3 (DAKO, Glostrup, Denmark), CD4 (Novocastra, Newcastle upon Tyne, Great Britain), CD8 (DAKO), CD10 (Novocastra), CD20 (DAKO), CD30 (DAKO), CD45 RO (DAKO), CD 45 RA (DAKO), CD 56 (Zymed, San Francisco, USA), CD79a (DAKO), BCL2 (DAKO), BCL6 (DAKO), Ki 67 (DAKO), lambda (DAKO), kappa (DAKO), CK 20 (DAKO), NSE (DAKO), S100 (DAKO), PCNA (DAKO), LCA (DAKO), CD5 (DAKO), CD138 (DAKO), FOXP1 (Alison Banham), MUM1 (DAKO) (Table SI, available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1112>).

BCL6, Mum1 and FOXP1 staining to distinguish between primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg-type (PCLBCL-LT) was considered positive if more than 50% of the neoplastic B cells showed unequivocal positive staining (5).

Definition of investigating variables

To determine the stage of primary cutaneous T-cell and NK-cell lymphoma (PCTCL) the tumour-node-metastasis (TNM) system was used (16, 17). The clinical staging was performed as proposed by Bunn & Lamberg (17). The quantity of cutaneous affection was assessed by rule of Wallace at initial presentation (18). The primary cutaneous B-cell lymphoma (PCBCL) were staged according to recently published Smith Index (19) (Table SII, available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1112>).

Statistical analysis

All statistical calculations were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Overall survival (OS) was calculated from the date of diagnosis until the patient’s death or last follow-up. Disease-specific (or disease-related) survival (DSS) was calculated from the date of diagnosis until the patient’s death due to the PCL.

Comparison between two categorical data or (sub) groups was performed using Pearson’s χ^2 test, Yates’ correction for continuity or the Fisher’s exact test to examine the relationship between variables. Comparison between two continuous variables, after confirmation of normal (Gaussian) distribution by Kolmogorov-Smirnov or Shapiro-Wilk test was performed using the Student’s *t*-test or the Mann-Whitney test.

Comparison between more than two variables with non-parametric distribution was done using the Kruskal-Wallis analysis of variance or, if parametric distribution was detected, by a one-way analysis of variance (ANOVA) (F-test). The Levene’s test was used to determine the equal or unequal variance (the homoscedasticity) and thus following the correct multi *post-hoc*

comparisons tests: Dunnett’s test, Tukey’s Tukey’s honestly significant test or Games-Howell tests.

Spearman’s correlation coefficients (ρ) procedure was used to detect a statistical significance in the non-parametric relationship between two variables.

Survival curves were estimated by the method of Kaplan and Meier, and statistical comparison between curves was performed by log-rank testing in cases of non-crossing functions and with the Wilcoxon test (Breslow test) and/or Tarone-Ware test for crossing curves.

Prognostic factors within the different entities were evaluated by univariate and multivariate analyses with OS and DSS as end-points, and *p*-values <0.05 were considered significant.

Parameters included for univariate analysis were “age at PCL diagnosis”, “sex”, “T-category of the TNM system at diagnosis”, “Bunn-Lamberg stage at diagnosis”, “Smith prognostic Index at diagnosis”, and T- or B-phenotype.

Log-rank testing was used to calculate univariate differences in outcomes. We performed the univariate analysis by using the first block of the multivariate proportional hazard regression method model, which resulted in a χ^2 -score (“chi-square goodness-of-fit test” or “overall or global chi-square”) (20).

The multivariate Cox analysis was performed to identify/quantify which of the significant variables in univariate analysis were associated independently with survival by using the method: stepwise forward (Wald). The log likelihood value leads to the estimation of the variable-specific odds ratio and thus consecutive hazard ratio (HR) and/or relative risk (RR) estimation. To exclude multicollinearity a correlation matrix of the coefficients of regression was performed.

All statistical tests were two-tailed, and *p* < 0.05, when necessary dividing by the number of factors examined (Bonferroni adjustment), was considered to be statistically significant.

RESULTS

The mean age at time of diagnosis was approximately 63 years for all entities together and for PCBCL and PCTCL separately. With regard to T-cell lymphomas, patients with mycosis fungoides (MF) were older by a statistically significant amount than patients with CD30-positive lymphoproliferative disease. In the B-cell group the entities PCFCL/primary cutaneous marginal zone B-cell lymphoma (PCMZL) vs. PCLBCL-leg-type significantly differ in the age of presentation (mean PCFCL 58.4; PCMZL 54.4; PCLBCL-leg-type 70.2 years). The mean follow-up time was 3.2 years.

We could categorize 299 out of the 312 PCL patients according to the WHO-EORTC classification system using clinical, histomorphological, immunophenotyping and molecular information. The remaining cases have been excluded because of insufficient clinical data or missing paraffin material for additional stainings. The frequency of each entity, the median age at time of diagnosis, observation time and DSS are illustrated in Tables I, II and Table SIII (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1112>). At the time of presentation, the 5-year DSS for all 299 PCL patients irrespective of diagnosis, was 87%, with a survival time of 14.24 ± 0.88 years (95% CI 12.50–15.97), the 5-year OS rate was 79%, with a median survival time of 10.94 ± 1.09 years (95%

Table I. T-cell and natural killer (NK) cell lymphomas (n = 189)

Diagnosis	Total n (%)	Sex, M/F		Age (years)	Follow-up (months)	5-year DSS ^a %
		n				
Mycosis fungoides	97 (30.9)	64/33		63.1 (median)	28.0 (median)	80.5
Folliculotropic mycosis fungoides	3 (0.9)	2/1		76.3 (median)	60.0 (median)	
Pagetoid reticulosis	2 (0.6)	0/2		753.0 (median)	6.0 (median)	
Granulomatous slack skin	1 (0.3)	1/0		36 (mean)	3 (mean)	
Sézary syndrome	3 (0.9)	2/1		57.0 (median)	26.0 (median)	
Primary cutaneous CD4 ⁺ small/medium pleomorphic T-cell lymphoma	5 (1.5)	4/1		68.5 (median)	9.0 (median)	
Primary cutaneous NK/ T-cell lymphoma, nasal-type	1 (0.3)	1/0		48 (mean)	0 (mean)	
Subcutaneous panniculitis-like T-cell lymphoma	1 (0.3)	1/0		67 (mean)	7 (mean)	
Primary cutaneous γ/δ T-cell lymphoma	1 (0.3)	1/0		52 (mean)	3 (mean)	
Primary cutaneous anaplastic large cell lymphoma	26 (8.3)	14/12		61.4 (median)	23.0 (median)	92.5
Lymphomatoid papulosis	50 (15.9)	21/29		58.4 (median)	8.0 (median)	100.0

^aNo values given when too few case numbers.

DSS: disease-specific survival.

CI 8.79–13.09). With respect to PCTCL, the 5-year DSS rate was 87.2%, with a median survival time of 15.04 ± 5.28 years (95% CI 4.68–25.40), and the 5-year OS rate was 81.4%, with a median survival time of 9.61 ± 1.74 years (95% CI 6.44–13.28). Focussing on MF we saw a 5-year DSS in T1 of 100%, in T2 of 89.44% (mean 7.22; 95% CI 6.21–8.22), in T3 of 68.1% (mean 8.02; 95% CI 5.05–10.98) and in T4 of 71.43% (mean 6.05; 95% CI 3.31–8.79).

In the case of PCBCL, the 5-year DSS rate was 88.1%, with a 17.02 ± 0.60 median years survival time (95% CI 15.71–18.43), and 5-year OS rate of 74.3%, and a median survival time of 11.3 ± 0.60 years (95% CI 10.04–12.06). The difference in DSS between T- and B-cell lymphomas was not statistically significant (for DSS $\chi^2=0.04$; $p=0.8$; for OS $\chi^2=0.4$; $p=0.41$). Focussing on the prognostic factors in PCL, the parameters “age > 60 at the time of diagnosis” and “sex” had no effect on the DSS rate according the log-rank/Breslow analysis of the Kaplan–Meier functions ($p=0.90$ for both).

The following parameters were significantly associated with survival in PCTCL: the T-category (T2 against T3 for MF) of the TNM system, the Bunn-Lamberg clinical stage for MF, and the disease entity according to WHO-EORTC (Table SIV, available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/0015555-1112>; Fig. 1).

The following parameters were significantly associated with survival in PCBCL: disease stage according to Smith, and disease entity according to WHO-EORTC.

The latter was an independent prognostic parameter (Table SIV, Fig. 2). The 5-year-DSS rate for PCFCL was 98.1%, with a mean survival time of 18.7 years (95% CI 18.04–19.44). Of the 27 PCLBCL-leg-type, the 5-year DSS was 63.5% and the mean survival time 9.6 years (95% CI: 7.02–12.30). None of the 30 patients with PCMZL died due to lymphoma during the follow-up period (Fig. 3).

DISCUSSION

In 2005 the WHO-EORTC classification for primary cutaneous lymphomas was introduced, which is an agreement between representatives of both organizations and which is now widely accepted worldwide. Considerable progress has been made in a better definition of some controversial groups of cutaneous lymphoma, in particular the group of PCFCL/PCLBCL and the group of cutaneous T-cell lymphomas (CTCL) other than MF, Sezary syndrome, and the group of primary cutaneous CD30⁺ lymphoproliferative disorders. Other neoplasms that may also first present in the skin in a minority of cases, such as CD4⁺/CD56⁺ haematodermic neoplasm (formerly also known as blastic natural killer (NK) cell lymphoma) and adult T-cell leukaemia/lymphoma, as well as precursor B-lymphoblastic leukaemia/lymphoma, acute myeloid leukaemia, and secondary cutaneous manifestations of systemic lymphomas, are not evaluated because, due to the heterogeneity and rarity of these tumours, their classification is still confusing. Together, they constitute

Table II. B-cell lymphomas (n = 110)

Diagnosis	Total n (%)	Sex, M/F n	Age (years) Median	Follow-up (months) Median	5-year DSS %
Primary cutaneous marginal zone B-cell lymphoma	30 (27)	20/10	53.3	19.5	100.0
Primary cutaneous diffuse large B-cell lymphoma, leg-type	27 (25)	13/14	71.1	34.2	63.25
Cutaneous B-cell lymphoma (total)	110 (100)	56/54	63.0	31.2	88.1

DSS: disease-specific survival.

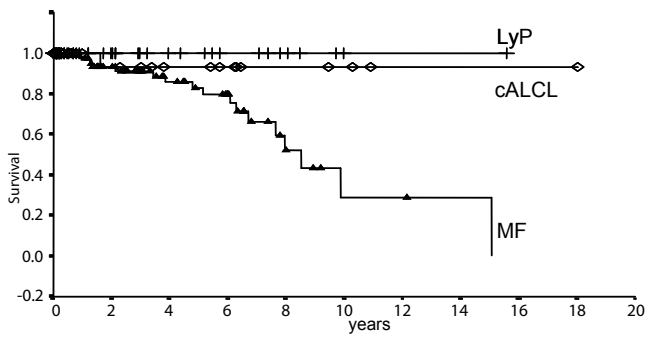


Fig. 1. Kaplan–Meier estimates of disease-specific survival (DSS): actual DSS of 173 patients with primary cutaneous T-cell and NK-cell lymphoma stratified according to World Health Organization - European Organization for Research and Treatment of Cancer (WHO-EORTC) classification. LyP: lymphomatoid papulosis; cALCL: cutaneous anaplastic large cell lymphoma; MF: mycosis fungoides.

less than 10% of all PCLs. With few exceptions, these lymphomas are clinically aggressive and, in most cases, systemic chemotherapy is required.

Our retrospective long-term study clearly demonstrates the applicability and practical relevance of the WHO-EORTC classification in the routine setting of a large skin tumour clinic. The term “primary cutaneous lymphoma” refers to CTCL and cutaneous B-cell lymphomas (CBCL) that present in the skin with no evidence of extracutaneous manifestation at the time of diagnosis.

The evaluation of our data confirms, that patients with PCL show a completely different clinical course, with either indolent, intermediate, or aggressive clinical behaviour. Our follow-up data of 299 patients with PCL show that relative frequency and survival, age of onset of PCL presentation, male/female ratio and clinical manifestation and distribution of the various entities (Table SIII) are almost identical to the data derived from Dutch and Austrian cutaneous lymphoma registries. As a result, our monocentre study illustrates the clinical significance and confirms the clinical validity of the WHO-EORTC classification. The disease-specific 5-year survival of 299 primary cutaneous lymphomas shows a favourable proportion ratio of 87.0%, which is in accordance with

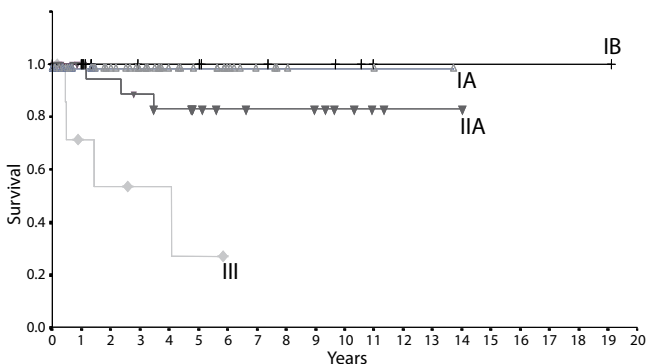


Fig. 2. Kaplan–Meier estimates of disease-specific survival (DSS): actual DSS of 110 primary cutaneous B-cell lymphoma-patients stratified according the prognostic index (Smith et al. (19)).

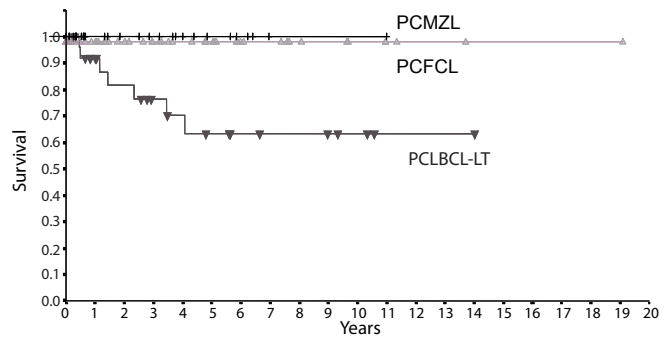


Fig. 3. Kaplan–Meier estimates of disease-specific survival (DSS): actual DSS of 110 primary cutaneous B-cell lymphoma-patients (World Health Organization - European Organization for Research and Treatment of Cancer (WHO-EORTC) classification). PCMZL: primary cutaneous marginal zone B-cell lymphoma; PCFCL: primary cutaneous follicle centre lymphoma; PCLBCL-LT: primary cutaneous diffuse large B-cell lymphoma, leg-type.

previous research by the epidemiological multicenter SEER programme (21).

The new definitions of the groups of PCFCL, PCLBCL-leg-type, and PCLBCL, as well as of other minor entities, require accurate clinicopathological correlation and a number of complementary techniques to arrive at a definite diagnosis. This allows a more reliable distinction between indolent and more aggressive types of CBCL and facilitates the decision as to whether surgery, radiotherapy or systemic immunotherapy or chemotherapy should be selected as first choice of treatment. In our study, 37% of all patients with PCL had a B-cell phenotype. This is approximately 10% higher than in former studies from comparable countries (2, 24). One possible explanation is that most other studies include large plaque parapsoriasis (25, 26). To our knowledge this is the first report that demonstrates a statistically highly significant difference in the age of onset between MF and CD30-positive lymphoma as well as PCLBCL-leg-type and the other forms of primary cutaneous B-cell lymphoma. Recently, Zinzani et al. (27) have reported a global statistical difference for the age of presentation between PCFCL/PCMZL/PCLBCL-leg-type; however, they did not present information about single entities.

Focussing on prognostic factors in our patients with PCL, neither age nor sex have any influence on the 5-year DSS. Taken together, the WHO-EORTC classification shows favourable correlation of all lymphoma entities with the prognostic situation. In this field, the Bunn-Lamberg stratification is of main prognostic impact for MF. The T-category for MF shows, for statistical reasons, significance only between T2 and T3. This is in agreement with the findings of Kim et al. (29), who also saw no significant differences between the categories T3 and T4.

Comparison of our results with former studies is limited due to the differences in classification and study design (28–30). In this context, we have also tried to classify PCBCL using the PCBCL-prognostic index (PI)

classification, as proposed by Smith et al. (19). Interestingly, this stratification was significantly associated with the 5-year DSS (Kaplan–Meier) and the overall survival rate (univariate analysis). Further studies focussing on the DSS are necessary to review the benefit of Smith's stratification in addition to the WHO-EORTC classification.

In conclusion, our results further emphasize the practicability and clinical impact of the WHO-EORTC classification for PCL and the auxiliary prognostic role of staging systems, especially routine TNM staging, Bunn-Lamberg stratification, and PCBCL-PI classification.

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