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# EORTC Cutaneous Lymphoma Task Force

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**Abstract**

The Cutaneous Lymphoma Task Force has represented the European Organisation for Research and Treatment of Cancer (EORTC) over the last two decades and has received worldwide acceptance and the highest respect. The group has been able to bring together the world's experts in this field to try to solve the basic problems associated with primary lymphomas of the skin and to create a productive scientific research basis. The definition and the classification of the disease *per se* has been a major controversial problem and the development of an EORTC classification for primary cutaneous lymphoma has been one of the main goals of the group. The purpose of this paper is to highlight and to provide a historical perspective regarding the contribution of the EORTC Cutaneous Lymphoma Group to the development of consensus guidelines for securing uniform diagnosis, classification and management of the heterogeneous group of primary cutaneous lymphomas. Some future perspectives and strategies of the group are also presented. 

*Keywords:* Cutaneous lymphoma; EORTC; Classification; Lymphoma registry

## 1. Introduction and history

Dermatologists interested in cutaneous lymphoma gathered together in 1973 and a close cooperation, primarily between the Departments of Dermatology of Munich (Burg) and of Graz (Kerl), was started. It was expanded to include pathologists, radiologists, surgeons, oncologists and haematologists in 1980. Project group status in the European Organisation for Research and Treatment of Cancer (EORTC) was applied for in 1982 (Burg and Kerl) and was approved. The first evaluation of the group by the 'Breur' Committee of the EORTC took place 14 March 1984 in Amsterdam.

## 2. Aims

Historically, the main goals of the Society, as defined in the report of the EORTC 'Breur' Committee in 1984, were:

1. To set up a registry.
2. To explore staging procedures.
3. To study the prognosis and therapy of cutaneous lymphomas.
4. Histological evaluation and other diagnostic procedures were also included (at a later stage).

The definition of this uncommon disease *per se* has been a major and controversial problem during the years and the development of a unified classification has been one of the main goals of the group so that proper clinical trials, testing new therapies in this disease, can be initiated. The development of consensus guidelines in order to further secure uniform diagnosis, management and treatment of the heterogenous group of primary cutaneous lymphomas which were included in the published EORTC classification continues to be one of the major goals of the group in recent years. With respect to this aim, a questionnaire, assessing the management and treatment of the different types of primary cutaneous lymphoma, was sent to all members of the group and also to other groups in Europe and the United States of America (USA). The results of the questionnaire revealed large differences in approach and further discussions and consensus are needed.

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The EORTC group continues to encourage the further development of regional and national collaborative cutaneous lymphoma groups. Such collaborative groups of dermatologists, pathologists and haemato-oncologists exist already for more than a decade in The Netherlands, France and Switzerland. New groups have been formed in Austria, Italy and the UK. A collaboration is also planned with the International Society for Cutaneous Lymphoma analysing staging and prognostic parameters in cutaneous T-cell lymphoma (CTCL).

Presently, the EORTC Cutaneous Lymphoma Task Force is concentrating its efforts on developing clinical trials investigating different therapeutic modalities in each subtype of cutaneous lymphoma. It is also the aim of the Task Force to develop translational research programmes investigating prognostic markers in this disease.

## 3. Achievements

### 3.1. Cutaneous Lymphoma Registry

The Cutaneous Lymphoma Registry was started in 1982. Several forms of various sizes (1–20 pages) have been used and filled in retrospectively (from 1956) and prospectively (until 1992). A total number of 827 cases, from 27 European centres, were collected. The statistical evaluations were performed by Thomas Zwingers, Munich. Financial support was provided by Bundesministerium für Raumfahrt und Technologie (BMFT) from 1986 to 1989 and through resources from the Department of Dermatology in Munich and Würzburg.

The implementation of the registry has now been expanded to include worldwide cases of unusual interest. Initially, it was meant to be a tool for collecting in a centralised form all patients having this disease or its variants in Europe. Due to the complexities, and particularly expense involved in collecting this information from every centre, the registry has now been modified with the aim of mainly collecting unusual cases or cases that need to be reviewed by a panel of EORTC experts to make further recommendations regarding classification and therapy. With the advances in communications technology, it is the intention of the group to further initiate a project following the lines of an advisory and supporting group for inquiring physicians treating these patients.

### 3.2. Recent achievements

Many studies showed that primary cutaneous lymphomas have a different clinical behaviour and prognosis, and therefore require a different therapeutic approach, compared with systemic nodal lymphomas. Because the previous classification systems did not recognise the special characteristics of these lymphomas, it was not unusual that the primary cutaneous lymphomas were diagnosed incorrectly and/or treated inappropriately with unnecessarily aggressive therapies. For this reason, the Cutaneous Lymphoma Group of the EORTC proposed a separate classification for the group of primary cutaneous lymphomas that is based on a combination of clinical, histological, immunophenotypical and molecular criteria, and includes well-defined and recognisable disease entities. The EORTC classification of the primary cutaneous lymphomas [1] now provides the opportunity for well designed clinical trials and pathogenetic studies. Encouragingly, the recent World Health Organization (WHO) classification has recognised many of these entities delineated by the the EORTC classification. The results of a large study of the French Cutaneous Lymphoma Group [2] have also recently confirmed the prognostic value of the EORTC classification of primary cutaneous lymphomas.

The group has recently prepared and submitted to the *Journal of American Academy of Dermatology* (JAAD) a consensus guidelines manuscript on Total Skin Electron Beam Radiation (TSEB) in CTCL. The manuscript has been accepted for publication.

Individual national groups have completed several clinical trials on the early stages of mycosis fungoides [3].

In order to develop a cohesive strategy, especially with regard to clinical trials, a scientific committee consisting of national representatives and officers has been established.

#### 3.2.1. EORTC classification for primary cutaneous lymphomas

*3.2.1.1. A classification proposal for primary cutaneous lymphomas from the Cutaneous Lymphoma Study Group of the EORTC [1].* Primary cutaneous lymphomas represent a heterogeneous group of T- and B-cell lymphomas that show considerable variation in histology, phenotype and prognosis. Recently, the EORTC Cutaneous Lymphoma Project Group has reached consensus on a new classification for this group of diseases. The EORTC classification for primary cutaneous lymphomas is based on a combination of clinical, histological and immunophenotypic criteria, and thus contains well-defined disease entities rather than histological subgroups. In addition, this new classification contains a number of provisional entities, which may display characteristic histological features, but are not yet well defined clinically. These provisional entities account for less than 5% of all primary cutaneous lymphomas. In this report, the basic principles of this new classification, as well as the characteristic features of the different disease entities, are described. In addition, survival data of 626 patients with primary cutaneous lymphomas derived from the registry of the Dutch Cutaneous

Lymphoma Working Group, illustrating the clinical validity of this new classification, are presented.

*3.2.1.2. EORTC classification for primary cutaneous lymphomas: the best guide to good clinical management [4].* In 1997, the Cutaneous Lymphoma Study Group of the EORTC published a proposal for a classification for the group of primary cutaneous lymphomas. The EORTC classification is the first and only classification that is designed exclusively for the group of primary cutaneous lymphomas. It is also the only classification that has been clinically validated for this group of diseases. This classification has resulted not only in the discussion of the definition and terminology of some types of CTCL and cutaneous B-cell lymphoma (CBCL), but also in a discussion of whether organ-based classification schemes (separate from existing haematopathological classification schemes for non-Hodgkin's lymphomas) should be used. Controversies between the EORTC classification versus the REAL classification and the proposed WHO classification, which still impede the usage of one common classification system, still exist.

### *3.2.2. Studies on histological/cytological evaluation of the primary cutaneous lymphoma*

*3.2.2.1. Variability in the evaluation of cutaneous lymphoproliferative T-cell infiltrates [5].* Histological and cytological evaluation of CTCL is one of the most difficult challenges in dermatopathology. It was the purpose of this study to evaluate the reliability and reproducibility of histological criteria in CTCL and the inter-rater and intra-rater variabilities. An overall of 2375 ratings of sections from 41 patients with CTCL were given by a panel of 22 dermatopathologists and pathologists familiar with lymphoma histology, some of whom were looking repeatedly at the same series of sections. The results clearly indicate that inter-rater, as well as intra-rater variabilities are significant and can be decreased by discussion preceding the evaluation, as well as by repeated rating indicating a learning effect. Therefore, histological evaluations of criteria have to be taken with caution, and statistical evaluation of the level of agreement expressed by kappa coefficients is always mandatory in this type of study.

*3.2.2.2. Reliability of histological criteria in early cutaneous T-cell lymphoma [6].* Researchers in many fields have become increasingly aware of the observer variability as an important source of measurement error. Consequently, reliability studies must be conducted in experimental or survey situations to assess the level of observer variability in the measurement procedures to be used in data acquisition. The present investigation demonstrated that inter-observer and intra-observer variability is generally high, even between investigators internationally recognised for their experience in lymphomatous disorders and even when dealing with non-initial CTCL lesions. Similarly, sensitivity and specificity are generally low, the former astonishingly so, without significant differences between early and non-initial CTCL lesions.

*3.2.2.3. Efficacy of histological criteria for diagnosing early mycosis fungoides: an EORTC cutaneous lymphoma study group investigation [7].* The correct classification of lymphoproliferative disorders provides valuable information regarding subsequent clinical evolution of the disease. The ability of pathologists to distinguish such lesions is generally low, especially when dealing with minimal lymphoid infiltrates. To improve the efficacy of histopathology in the diagnosis of early lesions of mycosis fungoides, we reviewed 24 skin biopsies from 18 patients with patch stage lesions of mycosis fungoides early in the course of their disease and 13 slides of lichenoid, spongiotic, or psoriasiform simulators of mycosis fungoides as a control series. A series of cytoarchitectural features was assessed, and differences in the distribution of histopathological parameters between the two groups (early mycosis fungoides lesions and mycosis fungoides simulators) were evaluated by the Chi-square test and Fisher's exact test. For these parameters, sensitivity and specificity were also calculated. A multivariate log-linear analysis was performed to estimate which of the morphological parameters yielded independent diagnostic information. We found that the most important feature for the diagnosis of lymphoma was the presence of lymphocytes with extremely convoluted, medium–large (7–9 microm in diameter) nuclei (medium–large cerebriform cells), singly or clustered in the epidermis and in small sheets in the dermis. Additional significant histological features were epidermotropism as single cells lined up along the basal keratinocytes of the dermal–epidermal junction, absence of significant papillary dermis fibrosis, and absence of significant numbers of dermal blastlike cells. We conclude that the efficacy of single histopathological features in the diagnosis of early mycosis fungoides is generally poor. Only the presence of medium–large cerebriform cells in the epidermis or in clusters in the dermis proved to be a highly reliable feature. However, the histopathological diagnosis of early mycosis fungoides lesions and their discrimination from inflammatory simulators can be achieved using the constellation of cytoarchitectural parameters proposed.

### *3.2.3. Studies on prognostic factors in cutaneous lymphomas*

*3.2.3.1. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicentre study [8].* Most primary cutaneous B-cell lymphomas have an excellent prognosis. However, primary cutaneous large

B-cell lymphomas (PCLBCLs) of the leg have been recognised as a distinct entity with a poorer prognosis in the EORTC classification. This distinction on the basis of site has been debated. Our aim was to identify independent prognostic factors in a large European multicentre series of PCLBCL. The clinical and histological data of 145 patients with PCLBCL were evaluated. According to the EORTC classification, 48 patients had a PCLBCL of the leg and 97 had a primary cutaneous follicle centre-cell lymphoma (PCFCCL). Data from both groups were compared. Univariate and multivariate analyses of specific survival were performed using a Cox proportional hazards model. Compared with PCFCCL, PCLBCL-leg were characterised by an older age of onset, a more recent history of skin lesions, a more frequent predominance of tumour cells with round nuclei and positive bcl-2 staining, and a poorer 5-year disease-specific survival rate. Univariate survival analysis in the entire study group showed that older age, a more recent onset of skin lesions, the location on the leg, multiple skin lesions, and the round-cell morphology were significantly related to death. In multivariate analysis, the round-cell morphology, the location on the leg, and multiple skin lesions remained independent prognostic factors. The round-cell morphology was an adverse prognostic factor both in PCLBCL-leg and in PCFCCL, whereas multiple skin lesions were associated with a poor prognosis only in patients with PCLBCL-leg. In conclusion, with site, morphology, and number of tumours taken into account, guidelines for the management of PCLBCL are proposed.

*3.2.3.2. Prognostic factors in primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome. The French Study Group on Cutaneous Lymphomas [2].* Prognostic studies of primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome (SS; non-mycosis fungoides/SS primary cutaneous lymphomas) have been mainly performed on subgroups or on small numbers of patients by using univariate analyses. Our aim was to identify independent prognostic factors in a large series of patients with non-mycosis fungoides/SS primary cutaneous lymphomas. We evaluated 158 patients who were registered in the French Study Group on Cutaneous Lymphomas database from 1 January 1986 to 1 March 1997. Variables analysed for prognostic value were: age; sex; type of clinical lesions; maximum diameter, location and number of skin lesions; cutaneous distribution (i.e. local, regional or generalised); prognostic group according to the EORTC classification for primary cutaneous lymphoma; B- or T-cell phenotype; serum lactate dehydrogenase (LDH) level; and B symptoms. Univariate and multivariate analyses were performed using a model of relative survival. 49 patients (31%) died. The median relative survival time was 81 months. In univariate analysis, EORTC prognostic group, serum LDH level, B symptoms, and variables related to tumour extension (i.e. distribution, maximum diameter and number of skin lesions) were significantly associated with survival. When these variables were considered together in a multivariate analysis, EORTC prognostic group and distribution of skin lesions remained statistically significant, independent prognostic factors. This study confirms the good predictive value of the EORTC classification for primary cutaneous lymphomas and shows that the distribution of skin lesions at initial evaluation is an important prognostic indicator.

*3.2.4. Clinical trials of individual national groups*

*3.2.4.1. Prospective randomised multicentre clinical trial on the use of interferon alpha-2a plus acitretin versus interferon alpha-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II [3].* The response rate of early stage mycosis fungoides to phototherapy is high, but the duration of response is often short and there is currently no clear evidence that this affects overall disease-free survival. The combination of interferon-alpha-2a and PUVA is attractive, but there have been no controlled trials. This study of 98 patients has attempted to answer some of these questions and the results suggest that PUVA and interferon-alpha-2 produce much higher complete response rates (70%) compared with interferon and acitretin (38%) with a shorter time to response. A comparison between PUVA alone and PUVA plus interferon-alpha-2a is now required.

## References


1. Willemze R, Kerl H, *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organisation for Research and Treatment of Cancer. *Blood* 1997, **90**, 354–371.
2. Grange F, Hedelin G, Joly P, *et al*. Prognostic factors in primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome. The French Study Group on Cutaneous Lymphomas. *Blood* 1999, **93**, 3637–3642.
3. Stadler R, Otte H, Luger T, *et al*. Prospective randomised multicentre clinical trial on the use of interferon alpha-2a plus acitretin versus interferon alpha-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998, **10**, 3578–3581.
4. Willemze R, Meijer CJ. EORTC classification for primary cutaneous lymphomas: the best guide to good clinical management. European Organisation for Research and Treatment of Cancer. *Am J Dermatopathol* 1999, **21**, 265–273.
5. Burg G, Zwingers T, *et al*. Interrater and intrarater variabilities in the evaluation of cutaneous lymphoproliferative T-cell infiltrates. EORTC-Cutaneous Lymphoma Project Group. *Dermatol Clin* 1994, **12**, 311–314.
6. Santucci M, Burg G, *et al*. Interrater and intrarater reliability of histologic criteria in early cutaneous T-cell lymphoma. An EORTC Cutaneous Lymphoma Project Group study. *Dermatol Clin* 1994, **12**, 323–327.

7. Santucci M, Biggeri A, *et al*. Efficacy of histologic criteria for diagnosing early mycosis fungoides: an EORTC cutaneous lymphoma study group investigation. European Organisation for Research and Treatment of Cancer. *Am J Surg Pathol* 2000, **24**, 40–50.

8. Grange F, Bekkenk MW, Wechsler J, *et al*. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. *J Clin Oncol (United States)* 2001, **19**, 3602–3610.