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# Primary cutaneous lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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## epidemiology

Primary cutaneous lymphomas (PCL) are defined as non-Hodgkin lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. After the gastro-intestinal lymphomas, PCL are the second most common group of extranodal non-Hodgkin lymphomas with an estimated annual incidence of 1/100 000. PCL must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily, which often display other clinical behaviour, have a different prognosis and require a different therapeutic approach. In recent lymphoma classifications PCL are therefore included as separate entities. Within the group of PCL distinct types of cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL) can be distinguished. In Europe, CTCL constitute about 75–80% of all PCL, CBCL 20–25%, but different distributions have been observed in other parts of the world.

## diagnosis

The diagnosis and classification of PCL should always be based on a combination of clinical, histological and immunophenotypical data. Demonstration of clonal *TCR* or *Ig* gene rearrangements in lesional skin or peripheral blood may be a valuable adjunct in selected cases. However, clinical features are the most important decision makers for therapeutic planning. PCL should be classified according to the criteria of the World Health Organization–European Organization for Research and Treatment of Cancer (WHO–EORTC) classification.

## staging

In all cases, except for patients with early stage mycosis fungoides (MF) or its variants and patients with lymphomatoid

papulosis adequate staging should be performed to exclude the presence of extracutaneous disease. Adequate staging includes complete physical examination, complete and differential blood cell count and serum biochemistry, appropriate imaging techniques and optionally a bone marrow biopsy and aspirate. Prognosis is extremely variable depending on the type of PCL and the stage of disease. For clinical staging of MF and Sézary syndrome (SS) the revised TNM staging system should be used. For PCL other than MF/SS a separate TNM classification system has recently been published. This staging system is primarily meant to document extent of disease and cannot be used as a prognostic guide.

## therapy

The choice of treatment depends on the type of PCL and the stage of disease. Due to their heterogeneity and rarity, controlled clinical trials in PCL are almost non-existent, with few exceptions mainly concerning recently marketed drugs. Recommendations are therefore largely based on (retrospective) cohort studies and expert opinions discussed during consensus meetings of the EORTC Cutaneous Lymphoma Group and the International Society for Cutaneous Lymphomas (ISCL).

## mycosis fungoides and variants

Since early aggressive chemotherapy is associated with considerable side effects, but does not improve survival, a stage-adapted conservative therapeutic approach is recommended for MF and its variants. In patients with limited patches and plaques topical steroids or even a watch and wait policy can be advised. In patients with more extensive patches and plaques (stage IB) skin-directed therapies including topical steroids, PUVA (psoralens + UVA), narrow band UVB (only for patches) and topical cytostatic agents, such as mechlorethamine or carmustine (BCNU), can be used. In patients developing one or few tumors (stage II) additional local radiotherapy suffices. Local radiotherapy can be curative in patients with localized disease and in patients with pagetoid reticulosis. In patients with more extensive plaques and tumors or patients refractory to skin-directed therapies, a combination of PUVA and interferon or PUVA and retinoids, including bexarotene, or total skin electron beam irradiation can be considered.

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**Table 1.** WHO–EORTC classification

Cutaneous T-cell lymphoma	Cutaneous B-cell lymphoma
Mycosis fungoides (MF)	Primary cutaneous marginal zone B-cell lymphoma
Variants of MF	Primary cutaneous follicle centre lymphoma
Folliculotropic MF	Primary cutaneous diffuse large B-cell lymphoma, leg type
Pagetoid reticulosis	
Granulomatous slack skin	
Sézary syndrome	
Primary cutaneous CD30-positive lymphoproliferative disorders	
Primary cutaneous anaplastic large cell lymphoma	
Lymphomatoid papulosis	
Subcutaneous panniculitis-like T-cell lymphoma	
Extranodal NK/T-cell lymphoma, nasal-type	
Primary cutaneous peripheral T-cell lymphoma, NOS	
Aggressive epidermotropic CD8+ CTCL <sup>a</sup>	
Cutaneous $\gamma/\delta$ T-cell lymphoma <sup>a</sup>	
CD4+ small/medium-sized pleomorphic CTCL <sup>a</sup>	

<sup>a</sup>Provisional entities.

NOS, not otherwise specified; CTCL, cutaneous T-cell lymphoma.

In relapsed disease, alternative approaches (denileukin diftitox, varinostat) may be applied. Multiagent chemotherapy is only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumor stage MF that cannot be controlled with skin-targeted and immunomodulating therapies.

### Sezary syndrome

Being a systemic disease (leukemia) by definition, systemic treatment is required. Skin-directed therapies like PUVA or potent topical steroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities, has been suggested as the treatment of choice in SS and erythrodermic MF, with overall response rates of 30–80%, and complete response rates of 14–25%. However, the suggested superiority of ECP over the traditional low-dose chemotherapy regimens has not yet been substantiated by controlled randomized trials. Prolonged treatment with a combination of low-dose chlorambucil and prednisone is often effective in controlling the disease, but is unlikely to give complete responses. Low-dose methotrexate, bexarotene, multi-agent chemotherapy and alemtuzumab have been recommended as second-line treatment for SS. Alternative approaches include varinostat and histone deacetylase inhibitors (especially in erythrodermic stages). It should be emphasized that comparison of treatment results in the different studies is almost impossible, because of differences in diagnostic criteria used for SS.

### primary cutaneous CD30-positive lymphoproliferative disorders

The group of primary cutaneous CD30-positive lymphoproliferative disorders (LPD) includes primary cutaneous anaplastic large lymphoma (C-ALCL) and

lymphomatoid papulosis (LyP), which form a spectrum of disease. Patients with C-ALCL generally present with solitary or localized (ulcerating) tumors or nodules and should be treated with radiotherapy or surgical excision. Patients presenting with multifocal skin lesions can best be treated with radiotherapy in case of only a few lesions, or with low dose methotrexate as in LyP. Multi-agent chemotherapy is only indicated in patients presenting with or developing extracutaneous disease and rare patients with rapidly progressive skin disease.

### subcutaneous panniculitis-like T-cell lymphoma (SPTL)

The term SPTL is nowadays only used for cases with an  $\alpha/\beta$  T-cell phenotype, which have an excellent prognosis particularly if not associated with a hemophagocytic syndrome, which is frequently an extremely aggressive clinical syndrome requiring immediate intervention. A recent study reports a 5-year overall survival of 91% and 46% in SPTL patients without and with a HPS, respectively. In SPTL without associated HPS systemic steroids or other immunosuppressive agents are recommended, whereas in cases of solitary skin lesions radiotherapy is advised. Only in progressive disease not responding to immunosuppressive therapy or HPS multi-agent chemotherapy should be considered.

### extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type is a nearly always Epstein–Barr virus-positive lymphoma, which characteristically presents with a midfacial ulceronecrotic tumor and uncommonly at other skin sites. These lymphomas have an aggressive clinical course and should be treated with combined chemotherapy. In patients presenting with a solitary skin lesion and ineligible for systemic chemotherapy, radiotherapy should be considered.

**Table 2.** Recommendations for the initial management of cutaneous B-cell lymphoma

	Extent	First line therapy	Alternative therapies
PCMZL	Solitary/localized	Local radiotherapy Excision	IFN alpha i.l. Rituximab i.l. (Antibiotics) <sup>a</sup>
	Multifocal	Wait-and-see Local radiotherapy Chlorambucil <sup>b</sup> Rituximab i.v.	IFN alpha i.l. Rituximab i.l. Topical or intralesional steroids (Antibiotics) <sup>a</sup>
PCFCL	Solitary/localized	Local radiotherapy Excision	IFN alpha i.l. Rituximab i.l.
	Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP <sup>c</sup>
PCLBCL, LT	Solitary/localized	R-CHOP ± IFRT	Local radiotherapy Rituximab i.v.
	Multifocal	R-CHOP	Rituximab i.v.

<sup>a</sup>In case of evidence for *B. burgdorferi* infection.

<sup>b</sup>Or other single or combination regimens for a limited time.

<sup>c</sup>In exceptional cases or extracutaneous disease.

PCMZL, primary cutaneous marginal zone lymphoma; PCFCL, primary cutaneous follicle centre lymphoma; PCLBCL, LT, primary cutaneous diffuse large B-cell lymphoma, leg type; i.l., intralesional; i.v., intravenous; IFRT, involved field radiotherapy; R-CVP, ; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

### primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTL, NOS)

Within the group of primary cutaneous PTL, NOS three subgroups have been included as provisional entities (see Table 1). However, all cases have in common a generally aggressive clinical course and a poor survival, and should therefore be treated with multi-agent chemotherapy. Since the results are often disappointing, early allogeneic stem cell transplantation may be considered. The only exception is the group of CD4-positive small-medium pleomorphic CTCL. These patients, often presenting with a solitary tumor, preferentially on the head, should be treated with local radiotherapy or excision and have an excellent prognosis.

### cutaneous B-cell lymphoma

In the WHO–EORTC classification three main types of CBCL are distinguished: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT). PCMZL and PCFCL are indolent types of CBCL with a disease-related 10-year-survival exceeding 90%, while PCLBCL-LT has a more unfavourable prognosis (disease-related 5-year survival, ~50%). Recently, EORTC/ISCL consensus recommendations for the management of these three types of CBCL have been formulated, which are summarized in Table 2. Treatment options vary significantly in intensity and should be applied according to performance status and comorbidity.

### follow-up

The frequency of follow-up visits depends on the type of PCL and stage of disease. It may vary from every 6–12 months in patients with indolent PCL and at least stable disease to every 4–6 weeks in patients with active or progressive disease. Follow-up visits should focus on history and physical examination, and additional testing (histology, blood examination, imaging, etc) should only be performed if required.

### note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

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