

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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epidemiology

Primary cutaneous lymphomas (PCLs) are defined as non-Hodgkin's lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. After the gastrointestinal lymphomas, PCLs are the second most common group of extranodal non-Hodgkin's lymphomas with an estimated annual incidence of 1/100 000 in Western countries. PCLs must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily, which often have another clinical behaviour, have a different prognosis and require a different therapeutic approach. In recent lymphoma classifications, PCLs are therefore included as separate entities. Within the group of PCLs, distinct types of cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL) can be distinguished [1, 2]. In the western world, CTCL constitutes ~75%–80% of all PCLs, with mycosis fungoides (MF) as the most common type of CTCL, and CBCL ~20%–25% [1]. However, different distributions have been observed in other parts of the world. In southeast Asian countries, CTCLs other than MF, in particular Epstein-Barr virus-associated natural killer/T-cell lymphomas, are much more common than in Western countries, while CBCLs are much more uncommon [3, 4].

diagnosis

The diagnosis and classification of PCLs should always be based on a combination of clinical, histological and immunophenotypical data. Demonstration of clonal T-cell receptor or immunoglobulin gene rearrangements in lesional

skin or peripheral blood may be a valuable adjunct in selected cases. However, clinical and histopathological features are, in most cases, the most important deciding factors for therapeutic planning. PCLs should be classified according to the criteria of the World Health Organisation–European Organisation for Research and Treatment of Cancer (WHO–EORTC) classification (Table 1) [1].

staging

In all cases, adequate staging should be carried out to exclude the presence of extracutaneous disease. Staging includes complete physical examination, complete and differential blood cell count and serum biochemistry and appropriate imaging studies (computed tomography scans ± [¹⁸F]2-fluoro-2-deoxy-D-glucose–positron emission tomography scans in all but stage IA), although they are not required in patients with lymphomatoid papulosis (LyP) [5, 6]. Flow cytometry of the peripheral blood should only be carried out in selected cases, but is mandatory in patients with (suspected) Sézary syndrome (SS). Bone marrow biopsy and aspiration should be carried out in cutaneous lymphomas with an intermediate or aggressive clinical behaviour, but is not required in cutaneous lymphomas with an indolent clinical behaviour (MF, cutaneous anaplastic large-cell lymphoma and cutaneous marginal zone lymphoma), unless indicated by other staging assessments [5, 6]. The significance of bone marrow examination in primary cutaneous follicle centre lymphoma (PCFCL) is controversial [6, 7]. Prognosis is extremely variable depending on the type of PCL and the stage of disease. For clinical staging of MF and SS, the revised International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) TNMB (tumour–node–metastasis–blood) staging system should be used (Tables 2 and 3) [5]. For PCL other than MF/SS, a separate ISCL/EORTC TNM classification system has been published [6]. This staging system is primarily intended to document the extent of disease and cannot be used as a prognostic guide.

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Table 1. World Health Organisation–European Organisation for Research and Treatment of Cancer (WHO–EORTC) classification

Cutaneous T-cell lymphoma (CTCL)
Mycosis fungoides (MF)
Variants of MF
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome (SS)
Primary cutaneous CD30-positive lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal natural killer (NK)/T-cell lymphoma, nasal-type
Primary cutaneous peripheral T-cell lymphoma-not otherwise specified
Aggressive epidermotropic CD8+ CTCL ^a
Cutaneous γ/δ T-cell lymphoma ^a
CD4+ small/medium-sized pleomorphic CTCL ^a
Cutaneous B-cell lymphoma (CBCL)
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle centre lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type

^aProvisional entities.

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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 PCLs are almost non-existent, with a 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, the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC) and the International Lymphoma Radiation Oncology Group. Consensus recommendations for clinical end points and response criteria in MF/SS and in PCLs other than MF/SS have recently been published (Olsen EA, Willemze R, Wood GS et al. Clinical end points and response criteria in primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a Consensus Statement of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC) and the Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC). Blood. In preparation.) [8].

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

Table 2. Revised TNMB classification of mycosis fungoides (MF) and Sézary syndrome (SS)

T (skin)	
T ₁	Limited patch/plaque (involving <10% of total skin surface)
T ₂	Generalised patch/plaque (involving ≥10% of total skin surface)
T ₃	Tumour(s)
T ₄	Erythroderma
N (lymph node)	
N ₀	No clinically abnormal peripheral lymph nodes
N ₁	Clinically abnormal peripheral lymph nodes; histologically uninvolved
N ₂	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture uneffaced)
N ₃	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture (partially) effaced)
N _x	Clinically abnormal peripheral lymph nodes; no histological confirmation
M (viscera)	
M ₀	No visceral involvement
M ₁	Visceral involvement
B (blood)	
B ₀	No circulating atypical (Sézary) cells (or <5% of lymphocytes)
B ₁	Low blood tumour burden (≥5% of lymphocytes are Sézary cells, but not B2)
B ₂	High blood tumour burden (≥1000/μl Sézary cells and positive clone)

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Table 3. Revised clinical staging system for mycosis fungoides (MF) and Sézary syndrome (SS)

Clinical stage	T	N	M	B
IA	T ₁	N ₀	M ₀	B ₀₋₁
IB	T ₂	N ₀	M ₀	B ₀₋₁
IIA	T ₁₋₂	N ₁₋₂	M ₀	B ₀₋₁
IIB	T ₃	N ₀₋₂	M ₀	B ₀₋₁
III	T ₄	N ₀₋₂	M ₀	B ₀₋₁
IVA ₁	T ₁₋₄	N ₀₋₂	M ₀	B ₂
IVA ₂	T ₁₋₄	N ₃	M ₀	B ₀₋₂
IVB	T ₁₋₄	N ₀₋₃	M ₁	B ₀₋₂

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MF and its variants [9–12]. Patients with only patches and/or plaques covering <10% (stage IA) or ≥10% of the skin surface (stage IB) should be treated with skin-directed therapies, including topical steroids, psoralens + ultraviolet A (PUVA), narrow-band ultraviolet B (UVB) and topical cytostatic agents, such as mechlorethamine or carmustine (BCNU). Narrow-band UVB should only be used in patients with patches or very thin plaques. Topical steroids can be recommended as monotherapy for patches/flat plaques stage IA disease. In stage IB, topical steroids can be used as adjuvant therapy for selected skin lesions. In patients developing one or few infiltrated plaques or tumours (stage IIB), additional local radiotherapy may suffice. Local radiotherapy can be curative in patients with early localised disease, particularly in patients with unilesional MF and pagetoid reticulosis. Local radiotherapy is most commonly administered with electrons (energy dependent on the thickness of the lesion), with bolus to achieve full skin dose, a margin of ≥2 cm and a total dose of 24–36 Gy. For patients with more extensive infiltrated plaques and tumours or patients refractory to skin-directed therapies, a combination of PUVA and interferon alpha or PUVA and retinoids (including bexarotene), a combination of interferon alpha and retinoids or total skin electron beam irradiation can be considered. However, these treatments are not curative, although remission may last for several years. Total skin electron beam irradiation was often given to total doses of 30–36 Gy, but recently lower doses (10–12 Gy) have been employed with the advantages of shorter duration of the treatment period, fewer side-effects and opportunity for re-treatment [13]. In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered [14, 15]. Other agents like the fusion toxin denileukin diftitox and histone deacetylase (HDAC) inhibitors, such as vorinostat and romidepsin, have been approved in the United States by the Food and Drug Administration (FDA) for patients with relapsed and refractory CTCL, but have not yet been registered for CTCL in Europe [16–18]. Multiagent chemotherapy is only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF which cannot be controlled with skin-targeted and immunomodulating therapies. Local palliation of cutaneous as well as extracutaneous lesions may be achieved with local radiotherapy to doses ≥8 Gy [19]. In relatively young patients with refractory, progressive MF or with SS, allogeneic stem cell transplantation may be considered. Durable responses have been reported, but experience is still limited, and the optimal conditioning regimen and the optimal timing for an allogeneic transplant are currently unknown [20]. Results with autologous stem cell transplantation in MF and SS have been disappointing.

Sézary syndrome

Being a systemic disease (i.e. leukaemia) 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 such as interferon alpha, retinoids, total skin electron beam and PUVA, has been

suggested as the treatment of choice in SS and erythrodermic MF [10–12]. Overall response rates range from 30% to 80% with complete response rates ranging from 14% to 25%, depending on the ECP regimen and the type of combination used. However, the suggested superiority of ECP over the traditional low-dose chemotherapy regimens has not yet been substantiated by randomised, controlled trials [21]. Prolonged treatment with a combination of low-dose chlorambucil and prednisone is often effective in controlling the disease, but is unlikely to yield complete responses. Low-dose methotrexate, bexarotene, denileukin diftitox, alemtuzumab (low-dose) and multiagent chemotherapy have been recommended as second-line treatment of SS [10–12, 22]. It should be emphasised that comparison of treatment results in the different studies is almost impossible due to differences in diagnostic criteria used for SS.

primary cutaneous CD30-positive lymphoproliferative disorders (LPDs)

The group of primary cutaneous CD30-positive LPDs includes primary cutaneous anaplastic large lymphoma (C-ALCL) and LyP, which form a spectrum of disease. Both C-ALCL and LyP have an excellent prognosis, with a 10-year survival of 90% and almost 100%, respectively [23, 24]. Patients with C-ALCL generally present with solitary or localised (ulcerating) tumours or nodules and should be treated with radiotherapy or surgical excision. Patients with C-ALCL presenting with multifocal skin lesions can be best treated with low-dose methotrexate, as in LyP, or radiotherapy in case of only a few lesions. Radiotherapy is commonly administered with electrons, with bolus, a margin of ≥2 cm and a total dose of 40 Gy [25]. This dose is effective and well-tolerated. Lower doses may achieve the same result, but data have not been published. In patients with multiple lesions, lower doses of radiation may be used for palliation. In cases not responsive to these treatments, systemic retinoids including bexarotene or interferon alpha can be used [24]. Recent preliminary studies report high response rates of brentuximab vedotin (anti-CD30 monoclonal antibody coupled to the anti-tubulin agent monomethyl auristatin E) in patients with C-ALCL as well as patients with MF expressing CD30, but controlled clinical trials have just started [26, 27]. Multiagent chemotherapy is only indicated in patients presenting with or developing extracutaneous disease and in rare patients with rapidly progressive skin disease.

subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

The term SPTCL is only used for cases with an α/β T-cell phenotype, which have a favourable prognosis, particularly if not associated with a haemophagocytic syndrome (HPS), which is frequently an extremely aggressive clinical syndrome requiring immediate intervention. One study reported 5-year overall survival rates of 91% and 46% in SPTCL patients without and with an HPS, respectively [28]. In SPTCL without associated HPS, systemic steroids or other immunosuppressive agents should be considered first, whereas in cases of solitary or localised skin lesions, radiotherapy with electrons is advised.

Table 4. Recommendations for the initial management of CBCL

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

^aIn case of evidence for *Borrelia burgdorferi* infection,

^bor other single or combination regimens appropriate for low-grade B-cell lymphomas,

^cin exceptional cases or for patients developing extracutaneous disease i.l. intralesional; i.v.: intravenous; IFRT: involved field radiotherapy.

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Little information on radiation dose is available, but a dose of 40 Gy has been used. Bexarotene may be also effective in SPTCL [29]. Multiagent chemotherapy is required only in cases with progressive disease not responding to immunosuppressive therapy or in cases with HPS.

extranodal natural killer (NK)/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type is a rare, nearly always Epstein-Barr virus-positive lymphoma, which is more common in Asia and Central and South America. The skin is the second most common site of involvement after the nasal cavity/nasopharynx. Patients generally present with multiple (ulcerating) plaques and tumours, or in the case of nasal NK/T-cell lymphoma with a midfacial destructive tumour. Skin involvement may be a primary or secondary manifestation of the disease. One study reported a median survival of 27 months for patients presenting with only skin lesions, compared with 5 months for patients presenting with cutaneous and extracutaneous diseases [30]. Since both groups have an aggressive clinical behaviour, distinction between primary and secondary cutaneous involvement seems not to be useful for this category. In patients with stage I disease, radiotherapy is the first choice of treatment. Recommended radiation doses are higher than for other lymphomas, with 50 Gy to the initial lesion and a boost of 5–10 Gy to residual disease. In the case of

more advanced disease, these lymphomas show an aggressive clinical behaviour and are often resistant to chemotherapy. Recently, an intensive chemotherapy regimen including L-asparaginase (the SMILE regimen) was shown to be effective [31].

primary cutaneous peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS)

Within the group of primary cutaneous PTCL-NOS, three somewhat better defined subgroups have been included as provisional entities (see Table 1). However, most of the cases have in common a generally aggressive clinical course and poor survival, and should therefore be treated as systemic PTCL-NOS with multiagent 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 present with a solitary tumour, most commonly 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

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

(PCMZL), 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 rate of 90%, while PCLBCL-LT has a more unfavourable prognosis (disease-related 5-year survival, ~50%). EORTC/ISCL consensus recommendations for the management of these three types of CBCL have been formulated and are summarised in Table 4 [32]. Recommended radiation doses for localised PCMZL and PCFCL are 24–36 Gy, whereas for palliative treatment of multifocal disease, low-dose radiation (4 Gy) is often sufficient [19]. For the more aggressive PCLBCL-LT, a radiation dose of 40 Gy is recommended.

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

follow-up

The frequency of follow-up visits depends on the type of PCL and the stage of disease. It may vary from every 6 or 12 months in patients with indolent types of PCL and stable disease or patients in complete remission 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 carried out if required.

note

According to the levels of evidence and grades of recommendation shown in Table 5, the levels of evidence in these guidelines are mostly level IV and the recommendations are grade B. This is due to the heterogeneity and rarity of the diseases.

conflict of interest

Dr Ladetto has reported speaker's bureau from Celgene, Janssen-Cilag, Roche, Bayer, Amgen, Mundipharma; research contracts from Celgene, Pfizer, Mundipharma, Roche; funds received from Amgen, Roche, Italfarmaco. The other authors have declared no potential conflicts of interest.

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