Guideline

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S2k-Guidelines – Cutaneous lymphomas (ICD10 C82 - C86): Update 2021

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ADO Project Leader Guidelines: Prof. Dr. Stephan Grabbe, Mainz

Coordinator and corresponding author: Prof. Dr. Edgar Dippel

Edgar Dippel[1], Chalid Assaf[2], Jürgen C. Becker[3], Michael von Bergwelt-Baildon[4], Sophie Bernreiter[1], Antonio Cozzio[5], Hans T. Eich[6], Khaled Elsayad[6], Markus Follmann[7], Stephan Grabbe[8], Uwe Hillen[9], Wolfram Klapper[10], Claus-Detlev Klemke[11], Carmen Loquai[8], Frank Meiss[12], Christina Mitteldorf[13], Ulrike Wehkamp[14], Dorothee Nashan[15], Jan P. Nicolay[16], Ilske Oschlies[10], Max Schlaak[17], René Stranzenbach[18], Rose Moritz[19], Christoph Stoll[20], Tibor Vag[21], Michael Weichenthal[14], Marion Wobser[22], Rudolf Stadler[23]

(1) Department of Dermatology, Hospital Ludwigshafen, Germany
(2) Department of Dermatology and Venereology, Helios Hospital Krefeld, Germany
(3) West German Tumor Center, University Hospital Essen, Germany
(4) Department I of Internal Medicine, University Hospital Cologne, Germany
(5) Department of Dermatology, Venereology and Allergology, Canton Hospital St. Gallen, Switzerland
(6) Department of Radiation Therapy and Radio-Oncology, University Hospital Münster, Germany
(7) German Cancer Society, Berlin, Germany
(8) Department of Dermatology, University Hospital Mainz, Germany
(9) Department of Dermatology, University Hospital Essen, Germany
(10) Institute of Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Germany
(11) Department of Dermatology, Municipal Hospital of Karlsruhe, Academic Teaching Hospital for the University of Freiburg, Karlsruhe, Germany
(12) Department of Dermatology and Venereology, University Hospital Freiburg, medical Faculty, Albert-Ludwigs University Freiburg, Germany
(13) Department of Dermatology, Venereology and Allergology, University Hospital Göttingen, Germany
(14) Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein, Campus Kiel, Germany
(15) Department of Dermatology, Dortmund Hospital GmbH, Dortmund, Germany
(16) Department of Dermatology, Venereology and Allergology, University Hospital Mannheim, Germany
(17) Charité – Universitätsmedizin Berlin, Department of Dermatology, Venereology and Allergology, Berlin, Germany
(18) Department of Dermatology, Venereology and Allergology, University Hospital at Ruhr University Bochum, Germany
(19) Department for Dermatology, University Hospital Halle, Germany
(20) Rehabilitation Hospital, Herzoghöhe Bayreuth, Germany
(21) Department of Nuclear Medicine, Technical University of Munich, Germany
(22) Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Germany
(23) Department of Dermatology, Venereology, Allergology, and Phlebology, Johannes Wesling University Hospital Minden, University Hospital at Ruhr University Bochum, Germany

1. General Remarks

1.1. Epidemiology, clinical presentation

Statements

Cutaneous lymphomas are a heterogeneous group of lymphoproliferative skin diseases with very variable clinical presentations and prognoses. Their incidence in Germany is estimated at about one per 100,000 inhabitants per year.

Cutaneous lymphomas (CL) are categorized as extranodal non-Hodgkin lymphomas, constituting the second most common form in this group (MALT lymphomas of the stomach are the most common extranodal form). Their incidence is estimated at one new diagnosis per 100,000 inhabitants per year in Germany [1–3]. Primary CL, by definition, present in the skin first, and at the time of diagnosis after staging is completed do not show any involvement of other organs. Secondary CL, on the other hand, are cutaneous manifestations of disseminated [4], primarily nodal lymphomas or leukemias. Primary CL comprise a large, clinically and histologically heterogeneous spectrum, with 73 % of CL categorized as cutaneous T-cell lymphomas (CTCL) and 22 % as cutaneous B-cell lymphomas (CBCL). There are other, rare forms of CL as well. Primary CL and nodal or extracutaneous lymphomas with the same cytomorphology actually differ greatly as to clinical presentation, but also prognosis and indicated treatments [5]. CL patients should therefore be treated in close collaboration between a specialized center and the primary physician. Cutaneous lymphomas are usually characterized by clonality of lymphocytes in the skin (with the exception of $CD4^+/CD56^+$ blastic plamacytoid dendritic cell neoplasia). Their cytomorphological presentation is comparable to lymphomas in other locations. Based on the specific cutaneous microenvironment, clinical and histological presentation will vary. It is essential to differentiate primary CL from skin manifestations of extracutaneous lymphomas or leukemias.

2. Classification

Statements

Cutaneous lymphomas are classified according to the current WHO/EORTC classification [6–8], based on clinico-pathological (respectively, immunohistological and molecular biological) correlation. Cutaneous lymphomas are differentiated from extracutaneous (disseminated) lymphomas based on their primary manifestation in the skin. Thus, primary cutaneous lymphomas are defined as lymphomas that at the time of diagnosis after staging according to current guidelines are limited to the skin.

Despite sometimes similar names (such as in marginal zone lymphoma and diffuse large B-cell lymphoma), cutaneous and extracutaneous/disseminated lymphomas differ as to their clinical as well as histopathological and molecular properties. One special feature in the classification of cutaneous lymphomas is the importance of clinical presentation for the final classification and prognosis. For example: A γ/δ-T-cell phenotype in itself is not sufficient for a classification as a cutaneous γ/δ-T-cell lymphoma. The classification also includes entities with unclear malignant potential (such as lymphomatoid papulosis, primary cutaneous CD4-positive small-medium T-cell lymphoproliferative disease). In analogy to systemic lymphomas, we differentiate between T-cell and B-cell neoplasias (Table 1); blastic plasmacytoid dendritic cell neoplasia is itemized as a hematological myeloic precursor neoplasia with typical primary manifestation in the skin.

The new provisional WHO category of EBV-positive mucocutaneous ulcer should be mentioned as an Epstein-Barr virus (EBV)-associated skin disease, and must be differentiated from the rare EBV-positive diffuse large B-cell lymphoma. EBV-associated hydroa-vacciniforme-like lymphoproliferative disease is almost never seen in Germany. *Consensus:* 100 %, modified 2021

The WHO classification does not classify the cutaneous lymphomas in groups with indolent, intermediary, or aggressive growth.

3. Diagnostics

Recommendations

The primary examination must include an inspection of the whole skin, palpation of all lymph node stations, and a general physical examination.

Diagnosis of a cutaneous lymphoma shall be performed via biopsy with histological examination of a representative lesion.

Precise classification requires additional immunohistological investigations which should therefore be part of the diagnostic process.

If involvement of the blood is suspected, FACS analysis/flow cytometry is recommended, see Table 2.

Molecular biological clonality analysis should be performed. *Consensus:* 100 %, modified 2021

Imaging procedures, lymph node/bone marrow biopsy, and laboratory invest igations to exclude extracutaneous involvement or secondary cutaneous lymphoma should be performed depending on the histological subtype of the lymphoma and the tumor stage according to Tables 2 and 3.

Consensus: 100 %, modified 2021

Table 1 WHO-EORTC classification of cutaneous lymphomas.

Cutaneous T-cell and NK-cell lymphomas	Cutaneous B-cell lymphomas
Mycosis fungoides (MF) Mycosis fungoides variants: – Folliculotropic MF – Pagetoid reticulosis – Granulomatous slack skin Sézary syndrome (SS)* Adult T-cell leukemia/lymphoma (HTLV+)* Primary cutaneous CD30+ lymphoproliferative diseases – Primary cutaneous anaplastic large cell lymphoma (PCALCL) – Lymphomatoid papulosis (LyP) Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) Extranodal NK/T-cell lymphoma, nasal type* Primary cutaneous peripheral T-cell lymphoma, rare subtypes: – *Primary cutaneous γ/δ-T-cell lymphoma* – *Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma* – *Primary cutaneous CD4⁺ small-medium T-cell lymphoproliferative disease* – *Primary cutaneous acral CD8+ T-cell lymphoma* Primary cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS)	Primary cutaneous follicle center lymphoma (PCFCL)** Primary cutaneous marginal zone B-cell lymphoma (PCMZL) Primary cutaneous diffuse large B-cell lymphoma, leg type (PCBLT) *EBV-positive mucocutaneous ulcer* (EBV-positive diffuse large B-cell lymphoma, not otherwise specified)*** Primary cutaneous intravascular large B-cell lymphoma* **Hematological precursor neoplasms** Blastic plasmacytoid dendritic cell neoplasm (BPDCN)*

*Entities that manifest as primary cutaneous lymphomas but are often already disseminated/systemic at the time of diagnosis.
**Primary cutaneous follicle center lymphoma: Synonymous with German term "primär kutanes Keimzentrumslymphom (PCFCL)"
***The EBV-positive diffuse large B-cell lymphoma is not explicitly classified as a „cutaneous lymphoma", but can present as isolated skin involvement and remains an important differential diagnosis to PCBLT and EBV-positive mucocutaneous ulceration.
Provisional entities are presented in *italics*

In the majority of skin lymphomas, clinical examination will already offer a provisional diagnosis, yet histological immunohistological, and molecular biological investigations are essential for confirmation. Apart from inspection of the whole skin, clinical examination of all lymph node stations is part of the primary examination.

4. Staging

Recommendations

Staging of CL should be performed according to the TNM classification proposed by the ISCL-EORTC/EORTC CL update B (blood) classification.
Consensus: 100 %, modified 2021

Staging of CTCL is performed using the TNM classification which also offers a certain prognostic factor. Especially in mycosis fungoides (MF), early stages (IA–IIA) usually have a very good prognosis with mean survival times of about 10 to 20 years. This T classification is not suitable for other types of lymphoma. The N category is also not the optimal solution in a clinical sense (for example N1/N2: clinically normal lymph nodes are usually not biopsied). For these reasons, the TNM classification for MF and Sézary syndrome (SS) has been revised and is now available as an updated TNMB classification, including changes regarding B staging (Tables 4, 5) [18, 19]. Future investigations and studies should utilize the revised classification.

The International Society of Cutaneous Lymphomas (ISCL) and the EORTC have proposed a dedicated classification of stages for CTCL, excluding MF and Sézary syndrome [20], which should find application in the future (Table 6).

It should be noted that, as opposed to the staging of MF/SS [18], the current "Non-MF/SS staging" does not offer any prognostic significance but at this point in time only reflects anatomical spreading. The position of clonality analysis in removed lymph nodes has been introduced for the first time [21, 22].

Table 2 Diagnostics for cutaneous lymphomas.

	Investigations	Remarks
Medical history	Duration, type, and extent as well as temporal development of skin manifestations, B symptomatology.	
Clinical examination	Precise skin findings (Recommended: investigation record and photographic documentation) lymph node status, palpation of liver and spleen.	
Laboratory investigations	CRP, differential blood count, liver enzymes, creatinine, LDH, electrolytes. Immune electrophoresis if indicated* Borrelia serology in B-cell lymphoma if indicated* Special hematological investigations if indicated* Further laboratory investigations depending on planned treatments	*For B-cell lymphomas:* – Bone marrow biopsy (cytology and histology) – mandatory for PCBLT, optional for PCMZL and PCFCL [9] – Immune electrophoresis of serum and urine – Borrelia serology *For T-cell lymphomas:* – Blood smear for Sézary cells** – FACS, CD4/CD8 ratio, investigation of $CD4^+CD7^-$ cells and/or $CD4^+CD26^-$ cells (Tab.4) (optional: CD158k/KIR3DL2 expression) [10, 11] – Clonality analysis in the blood (PCR, BIOMED-2 protocol) – Bone marrow biopsy is not indicated for diagnosis
Biopsy	Histology, immune histochemistry, and molecular biological diagnostics (including clonality analysis according to the BIOMED-2 protocol if indicated) from lesional skin as well as from suspiciously enlarged lymph nodes and (if applicable) if organ infiltration is suspected	Molecular biological investigations *For B-cell lymphomas:* – PCR for immunoglobulin according to BIOMED-2 protocol *For T-cell lymphomas:* – PCR for T-cell receptor gene rearangement according to BIOMED-2 protocol [12]

*The recommendations apply for first-time staging. Staging examinations adapted to the individual patient situation should be performed after therapy, in case of disease progression, and for aggressive types of lymphoma.
**Blood smears for Sézary cells: optional, as FACS analysis is the primary diagnostic tool.

5. Treatment

Statement

Treatment strategies are based on a precise diagnosis, previous treatments, and disease stage.

Recommendations

Treatment of MF shall be performed according to the recommendations in Table 7.
Consensus: 100 %, modified 2021

Treatment of SS shall be performed according to the recommendations in Table 8.
Consensus: 100 %, modified 2021

Treatment of $CD30^+$-lymphoproliferative skin diseases shall be performed according to the recommendations in Table 9.
Consensus: 100 %, modified 2021

Treatment of cutaneous B-cell lymphomas shall be performed according to the recommendations in Table 10a, 10b.
Consensus: 100 %, modified 2021

Since the CL represent a heterogeneous group of diseases, treatment strategies must be based on a precise diagnosis (entity-appropriate), prognosis, previous treatments, and tumor staging (stage-appropriate). There are only a handful of controlled studies that contain this essential information.

Treatment of CTCL must always be differentiated from treatment of CBCL. For the more common CTCL types, a stage-appropriate and basically restrictive treatment approach is recommended. In the early stages, topical treatments such as topical steroids, phototherapy, topical chemotherapy with cBCNU/chlormethine, topical bexarotene gel, or topical immunotherapy with imiquimod are preferred. In stages IA, IB, and IIA, phototherapy with narrow-band UVB (UVB

Table 3 Staging studies in cutaneous lymphoma.*

Cutaneous B-cell lymphomas	Instrumental diagnostics
Primary cutaneous follicle center lymphoma (PCFCL)	Full-body CT scan°, lymph node sonography [13], PET CT scan if indicated°°
Primary cutaneous marginal zone lymphoma (PCMZL)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCBLT)	Full-body CT scan°, lymph node sonography, MRI of the affected limb if indicated + PET CT scan if indicated°°
Primary cutaneous diffuse large B-cell lymphoma, other types	Full-bod y CT scan°, lymph node sonography, PET CT scan if indicated°°
Primary cutaneous intravascular large B-cell lymphoma	Full-body CT scan°, lymph node sonography, skull MRI, PET CT scan if indicated°°
Cutaneous T-cell and NK-cell lymphomas	**Instrumental diagnostics**
Mycosis fungoides (MF)	Chest X-ray, abdominal and lymph node sonography
Mycosis fungoides variants – folliculotropic MF – pagetoid reticulosis – granulomatous slack skin	Chest X-ray, abdominal and lymph node sonography
Mycosis fungoides from stage IIB onwards	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°° [14–17]
Sézary syndrome (SS)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
Adult T-cell leukemia/lymphoma (HTLV+)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
Primary cutaneous CD30+ lymphoproliferative diseases – primary cutaneous anaplastic large cell lymphoma (PCALCL) – lymphomatoid papulosis (LyP)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°° Chest X-ray, lymph node sonography
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
Extranodal NK/T-cell lymphoma, nasal type	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
Primary cutaneous peripheral T-cell lymphoma, rare subtypes – primary cutaneous γ/δ-T-cell lymphoma – primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)	Full-body CT scan°, lymph node sonography, PET CT scan if indicated°°
– Primary cutaneous CD4+ small-medium T-cell lymphoproliferative disease (provisional) – Primary cutaneous acral CD8+ T-cell lymphoma (provisional) – Primary cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS)	Chest X-ray, abdominal and lymph node sonography (in cases of clinical uncertainty, staging may be performed via sectional imaging)
Blastic plasmacytoid dendritic cell neoplasia (BPDCN)	Full-body CT scan°, cMRI, (lymph node sonography), PET CT if indicated°°, bone marrow biopsy, CSF analysis if indicated

*The recommendations apply for first-time staging. Staging examinations adapted to the individual patient situation should be performed after therapy, in case of disease progression, and for aggressive types of lymphoma.
°Full-body CT scans: neck, thorax, abdomen, pelvis using intravenous contrast agents
°°Retrospective examinations with small number of cases predominantly showed a significant superiority of 18F-FDG PET/CT scans compared to conventional imaging methods, especially in the detection of lymph node and organ manifestations [14–17]. Nevertheless, larger prospective studies with sufficient evidence are currently lacking. In general, the costs for PET-CT-examinations for this indication are not covered by the statutory health insurances.

Table 4 ISCL/EORTC revision of classification and staging of mycosis fungoides and Sézary syndrome/EORTC CL update B classification.

Category	Definition
T: Skin	
T1	Macules, papules, and plaques ≤ 10 % of skin surface a) Macules b) Plaques ± macules
T2	Macules, papules, and plaques ≥ 10 % of skin surface a) Macules b) Plaques ± macules
T3	One or more tumors (≥ 1 cm)
T4	Erythroderma (≥ 80 % of skin surface)
N: Lymph nodes	
No	No palpable lymph nodes
N1	Palpable lymph nodes; no histological evidence for CTCL ($NCILN_{0-2}$) a) clone negative b) clone positive
N2	Palpable lymph nodes; histological evidence for scant T-cell lymphoma infiltrations ($NCILN_{3}$) a) clone negative b) clone positive
N3	Palpable lymph nodes; histological evidence for extensive T-cell lymphoma infiltrations ($NCILN_{4}$), clone positive or negative
Nx	Clinically abnormal lymph nodes, no histological confirmation
B: Peripheral blood*	
Bo	< 250 $CD4^+CD7^-$ or $CD4^+CD26^-$ T lymphocytes/µl [19]
B1	250 bis <1000 $CD4^+CD7^-$ or $CD4^+CD26^-$ T lymphocytes/µl [19]
B2	≥ 1000 $CD4^+CD7^-$ or $CD4^+CD26^-$ T lymphocytes/µl with identical clonal T-cell receptor gene rearangement of the skin clone [19]
M: Visceral organs	
Mo	No involvement of visceral organs
M1	Histologically confirmed visceral involvement with organ specification

Table 5 Clinical staging for mycosis fungoides and Sézary syndrome.

ISCL / EORTC 2007				
	T	N	M	B
IA	1	0	0	0.1
IB	2	0	0	0.1
IIA	1–2	1–2	0	0.1
IIB	3	0–2	0	0.1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

311 nm) or PUVA (psoralen plus UVA, e.g. oral PUVA, bath-, creme- or shower PUVA) may be performed. PUVA should be utilized primarily for patients with thick plaques or folliculotropic MF. Both PUVA and UVB 311 nm are appropriate for treating erythrodermic MF [23].

For localized CTCL, radiotherapy with a total dose of typically ≥ 30 Gy in single doses of 2 Gy will lead to sustained local disease control in 90–100 % of cases [24].

Low-dose palliative radiotherapy (4–8 Gy) for cutaneous B-cell and T-cell lymphoma is an alternative approach [25]. New studies show that radiotherapy with 4 Gy can adequately control the lesions of indolent cutaneous BCL [26]. For CTCL, use of 8 Gy in one or two fractions led to complete remission in ≥ 92 % of patients [27]. In stage IIB, this approach can be combined interferon-PUVA or bexarotene-PUVA or bexarotene alone, to achieve sustained disease control in the early stages. Other multimodal therapeutic combinations are feasible as well. In cases of low tumor burden, a combination of topical or systemic treatment with low dose radiation has proven successful, especially due to the reassuring side-effect profile. In general, total skin electron beam treatment at conventional doses (30–36 Gy) is a feasible option in patients with cutaneous T-cell lymphoma; however, this is associated with higher-grade skin toxicity [28, 29]. Newer studies show that low-dose total skin electron beam treatment at 10–12 Gy over a period of 2–3 weeks can be considered a reliable and safe treatment option to achieve short-term success with a lower toxicity profile [28, 30, 31]. Subsequently, adjuvant topical or systemic treatment should be considered to maintain remission (maintenance therapy) [32, 33].

Systemic treatments, such as a combination of PUVA with retinoids or recombinant interferon-alpha, are the obvious choice for advanced stages (Table 7) [34–36]. Bexarotene, another systemic medication, can also be recommended [37–40].

Table 6 ISCL/EORTC proposal for TNM classification of cutaneous lymphomas other than mycosis fungoides and Sézary syndrome.

Category	Definition
T: Skin	
T1	Solitary skin lesions a) solitary lesion, diameter < 5 cm b) solitary lesion, diameter > 5 cm
T2	Regional skin involvement with multiple skin lesions, limited to one body region or two adjacent regions a) Involvement limited to a diameter of < 15 cm b) Involvement diameter between 15 and 30 cm c) Involvement diameter > 30 cm
T3	Generalized skin involvement a) multiple skin lesions distributed over two non-adjacent body regions b) multiple skin lesions > 3 body regions
N: Lymph nodes	
No	No clinical or pathological involvement of lymph nodes
N1	Involvement of one peripheral LN region representing the draining area of current or previous skin involvements
N2	Involvement of 2 or more peripheral LN regions, or involvement of other LN regions not located in the draining area of skin involvement
N3	Involvement of central lymph nodes
M: Visceral organs	
Mo	No evidence of extracutaneous involvement
M1	Extracutaneous organ involvement, excluding lymph nodes

Use of interferon-alpha is, however, limited by the fact that the approved preparation Roferon has been withdrawn and is no longer available for treating patients with cutaneous lymphomas. There are no generic alternatives. There are some case reports in the literature of patients successfully treated with pegylated interferons (PEG-IFN) off label. Two larger studies on PEG-IFN have been published. PEG-IFNα-2a was used in CTCL patients (n = 13) at doses of 180 µg/week and 270 or 360 µg/week, respectively. The medication was effective and well tolerated, with no significant differences in the efficacy of lower or higher doses [41]. In a total of 17 patients, PEG-IFNα-2b (1.5 µg/kg body weight [BW]/weeks) plus PUVA (n = 9) was compared with the former standard treatment of IFNα-2a (9 MIU 3 x/week) plus PUVA (n = 8). This study showed excellent efficacy for PEG-IFNα-2b, although side effects such as liver toxicity and myelosuppression were observed more frequently in comparison, highlighting the need for special attention in such cases and the need of starting with a moderate dose e.g. 180 ug of PEG-IFNa-2b [42].

The antibody conjugate brentuximab vedotin is another treatment option for advanced CD-30-positive MF (tumor stage). In 2019, the monoclonal anti-CCR4 antibody mogamulizumab was approved as a systemic second-line treatment for treatment-refractive and advanced MF and SS. It is especially effective for blood involvement [43]. Alternatively, there are two histone deacetylase inhibitors: vorinostat [44] (approved in the USA in 2006) and romidepsin [45] (approved 2011, USA), as well as the antimetabolite pralatrexate [46] (approved 2011, USA). The fusion toxin denileukin diftitox is currently no longer available [47]. Monochemotherapies, for example with gemcitabine which may be used in low-dose [48, 49] or doxorubicin [50], are preferred over polychemotherapies due to a more favorable side effect profile. The latter can induce massive immunosuppression without any improvement in survival [51]. The stage-adapted treatment recommendations are still based on the TNM classification published by the *MF Cooperative Group* in 1979. In the future, treatment recommendations will be based on the revised TNM classification [18].

Extracorporeal photopheresis is effective for SS, with few side effects. This can also be combined with interferon-alpha, PUVA, topical corticosteroids, or bexarotene (Table 8) [63].

In late stages, palliative chemotherapy is also an option (Table 8). It should be noted, however, that this has no proven effect on survival and may result in further immunosuppression with more frequent infectious complications.

Second-choice treatments include bexarotene (preferably in combination with PUVA and ECP), low-dose methotrexate (MTX; preferably in combination with PUVA and ECP), or total skin electron beam treatment. Doxorubicin or gemcitabine can be considered for debulking in advanced staged of Sézary syndrome. Alemtuzumab should be preferably used at low doses since high doses are associated with a high rate of infection. Allogenic stem cell transplants may be indicated for selected patients. If the tumor cells show CD30 expression, brentuximab vedotin may be used as an alternative [56]. Since 2019, the monoclonal anti-CCR4 antibody mogamulizumab has been available as a systemic second-line treatment for SS (after at least one previous systemic treatment), and is generally well tolerated [43]. Several HDAC inhibitors (vorinostat, romidepsin) are approved for treating SS outside Europe.

Table 7 Therapy recommendations for MF and MF special forms.

Stages	Recommended treatment First line*	Recommended treatment Second line*	Comment
I A	– topical steroids class III–IV – PUVA – UVB-311 nm – Chlormethine hydrochloride 0.02 % Gel°°	– topical BCNU/carmustine++ – Bexarotene gel** – Topical immune therapy (such as imiquimod++ [52], resiquimod** [53])	
Unilesional MF, pagetoid reticulosis	– Topical radiotherapy (RT) (30–36 Gy or 2 × 4 Gy)	– topical steroids class III–IV – PUVA cream	These entities can be considered special presentations of stage IA MF.
I B–II A	– PUVA – UVB-311 nm	– see stage I A – PUVA + IFNα – PUVA + bexarotene – Bexarotene – Acitretin*** – Low-dose methotrexate (MTX) – Topical radiotherapy – Low-dosed total skin electron beam treatment (8-12 Gy) (12 Gy) – Mogamulizumab+++ [42] – Brentuximab vedotin++ [54, 55]	IFNα is currently only available as a pegylated formulation.
II B	– PUVA, if indicated combined with IFNα, oral bexarotene [54] and RT for tumors	– Low-dose MTX – Topical radiotherapy for tumors – Gemcitabine – Doxorubicin+ – Low-dosed total skin electron beam treatment (8–12 Gy) – Brentuximab vedotin [55, 56] – Pralatrexate** – Mogamulizumab+++ [43] – If indicated: allogenic stem cell transplant ++++ [57, 58]	Many of these compounds are not approved for this indication in Germany/Europe. Possibly: maintenance therapy with PUVA+IFNα/bexarotene/MTX once remission has been achieved.
III****	– PUVA/UVB-311 nm, if indicated combined with IFNα, bexarotene – Photopheresis, if indicated combined with IFNα [59], MTX, bexarotene, or PUVA	– As for stage II B – Alemtuzumab [60] – Chlorambucil/steroid (Winkelmann program or Knospe program) [61]	Alemtuzumab: Low-dose therapy only for patients with cutaneous T-cell lymphoma and exclusive involvement of the blood.
IV A	– PUVA, if indicated combined with IFNα [36], bexarotene, RT for tumors	– See stage II B	
IV B	– PUVA, if indicated combined with IFNα, bexarotene – RT for tumors	– See stage II B – CHOP/CHOP-like-polychemotherapy – Alemtuzumab – Cladribine, Fludarabine, Cyclophosphamide	Possibly: maintenance therapy with PUVA+IFNα/bexarotene/MTX once remission has been achieved.

°Individual multimodal therapy options are prioritized.
°°Topical chlormethinhydrochlorid gel can be used as a combination therapy in all stages.
*The order within a column does not imply a valuation.
**Not authorized in Germany.
***Acitretin: possible as an alternative in cases where bexarotene is contraindicated.
****Erythrodermic MF: RT: Superficial x-rays or electrons; photons, where appropriate.
+Pegylated liposomal doxorubicin is generally not prescribable at the expense of the statutory health insurance funds. For details on prescribability, please refer to the GBA [62].
++Off-label use.
+++Mogamulizumab preferably in cases of MF with blood involvement and Sézary syndrome.
++++Allogeneic stem cell transplantation: reduced conditioning, preferably through clinical trials; "clinical option" only in case of matching donor.

Table 8 Therapy recommendations for Sézary syndrome.°

Treatment options: First choice	Treatment options: Second choice
Extracorporeal photopheresis (ECP), if indicated combined with PUVA, IFNα, and/or bexarotene PUVA combined with IFNα and/or bexarotene	– Mogamulizumab [43] – Chlorambucil/steroid (Winkelmann program) – Bexarotene – Low-dose methotrexate – Total skin electron beam treatment – Alemtuzumab i.v. or low-dose s.c. (anti-CD52 antibody) [64] – Doxorubicin*, fludarabine, cladribine, gemcitabine – Allogenic stem cell transplant*** – Brentuximab vedotin**

°The order within a column does not imply a valuation.
*Pegylated liposomal doxorubicin is generally not prescribable at the expense of the statutory health insurance funds. For details on prescribability, please refer to the GBA [62].
**Off-label use.
***For selected patients, allogeneic stem cell transplantation may be indicated.

CBCL without further manifestations offer a much better prognosis than nodal B-cell lymphomas. Thus, in many cases topical treatment is sufficient. Surgical removal or radiotherapy are feasible options. In individual cases, interferon treatment may result in complete remission. Polychemotherapy is only indicated for extracutaneous manifestations.

For most rare CL, there are no large studies and thus no evidence-based treatment recommendations or approved therapeutic options.

For the treatment of indolent CTCL, acral $CD8^+$ T-cell lymphoproliferation, and $CD4^+$ small-/medium size T-cell lymphoproliferative disease, excision or topical treatment are sufficient.

For blastic plasmacytoid dendritic cell neoplasia (BPDCN) in a CR1 situation (complete remission directly after the first chemotherapy course), the primary recommendation is an allogenic or autologous bone cell transplant [69, 70]. Hematooncologists must therefore be consulted early for optimal treatment planning. Tagraxofusp was approved in November 2020 as a first-line monotherapy for adult patients with BPDCN. This compound consists of a shortened diphtheria toxin (DT) fusion protein linked with recombinant human interleukin-3 (IL-3) to target CD123-expressing cells. Tagraxofusp irreversibly inhibits protein synthesis of target cells by inactivating elongation factor 2 (EF2). This induces apoptosis (cell death) [71].

Table 9 Therapy recommendations for $CD\ 30^+$ lymphoproliferative disorders of the skin.

Extent	First choice	Second choice
Solitary or localized lesions	– Excision and/or radiotherapy (PCALCL) [65, 66] – Observation (LyP) – Topical steroids layout? (LyP)	
Multifocal lesions relapsing, possibly with spontaneous remission	– Observation (LyP) – Low-dose methotrexate – PUVA/UVB1 (LyP)	– (pegylated) IFNα – Bexarotene – Gemcitabine – Brentuximab vedotin

For subcutaneous panniculitis-like T-cell lymphomas without evidence of hemophagocytic syndrome (HPS),

Table 10a Therapy recommendations for low-malignant primary cutaneous B-cell lymphomas (follicular center lymphoma, marginal zone lymphoma.

Extent	First choice	Second choice
Solitary lesions	– "Watch & wait"+++ – Antibiotics (if associated with borrelia) – Excision and/or radiotherapy – intralesional rituximab* – intralesional steroid	
Multiple lesions	– Antibiotics (if associated with borrelia) – Radiotherapy – Intralesional rituximab* – i.v. rituximab	– Bendamustine, combined with i.v. rituximab** if indicated – Doxorubicin or gemcitabine, combined with rituximab if indicated [67]

*Off-label use.
**Analogous to the experience in systemic indolent B-cell lymphomas, bendamustine may be considered as an alternative.
+++Watch & wait: not in case of follicular lymphoma of the lower leg.

Table 10b Therapy recommendations for diffuse large B-cell lymphoma, leg type.

Extent	First choice	Second choice
Solitary or grouped lesions	– Radiotherapy and/layout? or R-CHOP [68] – Excision	
Multiple lesions	– R-CHOP	– Bendamustine – Doxorubicin or gemcitabine, combined with rituximab if indicated

prednisolone monotherapy is recommended [72], if indicated also in combination with ciclosporin or MTX [73–75].

6. Innovative future treatments

Statement

As with traditional treatments, innovative therapies must consider the precise diagnosis, comorbidities, previous treatments, and tumor stage. Their use has been documented in individual case reports or case series, and occasionally also controlled clinical multicenter trials [56, 76].

Recommendation

Due to the limited number of newly approved therapies, treatment of primary cutaneous lymphomas with innovative forms of therapy should preferably be performed in the context of clinical trials (www.clinicaltrials.gov). In the course of improved decoding of the molecular bases and differentiated immune phenotyping, individualized treatment with targeted drugs may also become possible off-label, outside of clinical trials. For a better understanding of individual responses, data should also be collected in registries (such as ADOReg, PROCLIPI).
Consensus: 100 %, modified 2021

Alternative experimental topical treatments

In cutaneous T-cell lymphomas, activating phospholipase Cγ mutations with constitutive activation of the T-cell receptor-dependent NFAT pathway represent the rationale for using topical calcineurin inhibitors for MF [77]. Analogously, inhibition of deregulated toll-like receptor signaling is observed in MF [78]. Immunomodulators such as imiquimod and resiquimod could induce local remission and may thus offer a potential corticoid-free alternative in the future [52, 53]. To date, however, use of these topical treatments has only been studied in individual case reports/case series, and in the case of resiquimod in one small monocentric clinical trial (NCT01676831). Another innovative therapeutic option is intralesional application of a CD47 antibody which regulates innate immunity for tumor control.

Alternative experimental systemic therapies

Numerous new, promising systemic therapies for CL have become available in clinical studies or off-label for systemic hematological B-cell and T-cell neoplasias.

An innovative antibody targeting the surface molecule KIR3DL2 has shown promising preliminary clinical data. Drugs that interfere with epigenetic mechanisms, such as histone deacetylase inhibitors (vorinostat, romidepsin, belinostat, and panobinostat, all currently approved in the USA), or immunomodulatory compounds such as lenalidomide, constitute alternative or additive therapeutic options for MF, SS, and peripheral T-cell lymphomas [79–81]. HDAC inhibitors are not currently available in Germany outside of clinical studies (resminostat, NCT02953301).

Proteasome inhibitors such as bortezomib, which interfere with the aberrantly activated NFκB pathway, may show clinical effects in MF or peripheral T-cell lymphomas in combination with conventional therapeutic options in the absence of other alternatives [82, 83]. In view of activating mutations, inhibition of the JAK/STAT pathway may also constitute an innovative therapeutic option in the future for MF and peripheral T-cell lymphomas, in analogy to its use in systemic peripheral T-cell lymphomas [84, 85].

Innovative compounds for primary CBCL include, on the one hand, more effective and/or better tolerated CD20 antibodies such as obinutuzumab or ofatumumab, which have already been approved for treating systemic B-cell lymphomas [86, 87], or (additive) immunoregulatory compounds such as lenalidomide [88, 89]. Pixantrone, an alkylating substance with reduced cardiotoxicity compared with doxorubicin, appears especially attractive for elderly patients with primary cutaneous large B-cell lymphoma in view of commonly found (cardiac) comorbidities [90, 91].

For cutaneous B-cell lymphomas as well, future decoding of deregulated pathways will facilitate the use of targeted medications such as Bruton's kinase inhibitors (ibrutinib) or phosphoinositide 3-kinase (PI3K) inhibitors (idelalisib). Some of these have already been approved for systemic B-cell non-Hodgkin lymphoma and are thus available off-label also for cutaneous B-cell lymphomas, especially treatment-refractive large B-cell lymphoma, leg type (PCBLT) [92–94]. Another promising candidate for this indication is the fusion protein polatuzumab, which has already been approved for systemic diffuse large B-cell lymphoma in combination with rituximab and bendamustine [95].

Table 11a Follow-up recommendations for low-malignant primary cutaneous follicular center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma (PCLBCL) after complete remission.

	PCFCL	PCMZL	PCBLT, PCFCL (leg type)
Medical history and physical examination			
Year 1–2	Every 3–6 months	Every month	Every 3 months
Year 3–5	Every 6 months	Every 6 months	Every 6 months
Year 6 onwards	yearly	yearly	yearly
Lymph node sonography	–[1]	–[1]	individually
Other imaging (CT)	–[1]	–[1]	Individually[2]
Laboratory investigations	–[1]	–[1]	Differential blood count, LDH at every examination

[1]In the follow-up of PCFCL and PCMZL, routine monitoring of laboratory parameters and imaging is not recommended.
[2]PET-CT, where appropriate.

Table 11b Follow-up recommendations/controls in mycosis fungoides and Sézary syndrome after the onset of remission.

	IA–IB	IIA	IIB–IIIB	IV	Sézary syndrome
Medical history and physical examination					
Year 1–2	Every 6 months	Every 3 months	Individually	Individually	Individually
Year 3–5	Every 6 months	Every 6 months	Individually	Individually	Individually
Year 6 onwards	Yearly	Yearly	Individually	Individually	Individually
Lymph node sonography			Individually	Individually	Individually
Year 1–2	–	Every 3 months	Individually	Individually	Individually
Year 3–5	–	Every 6 months	Individually	Individually	Individually
Year 6 onwards	–	Yearly	Individually	Individually	Individually
Other imaging (CT, PET-CT if indicated)	–	–	Individually	Individually	Individually
Laboratory investigations		Differential blood count, LDH	Differential blood count, LDH	Differential blood count, LDH	Differential blood count, LDH, Sézary cells, flow cytometry

7. Maintenance therapy

Statement

Data from clinical studies on maintenance therapy in CL are insufficient.
Verified 2021

Once complete remission or an earlier stage has been achieved in advanced lymphomas, non-cytotoxic treatment recommendations in this guideline should be employed [96].

8. Supportive treatment

Pruritus, a common and distressing symptom in CL, impairs patients' quality of life at any stage of the disease [97]. It is frequently permanent and worsens toward the end of the day and with warmer temperatures, sometimes also upon contact with water. Sleep is often disturbed. Basic treatment, topical steroids, and oral antihistamines can only rarely achieve improvement [98]. Apart from specific treatment of the cutaneous lymphoma, symptomatic treatment of

Table 11c Follow-up recommendations for primary cutaneous large cell anaplastic T-cell lymphoma after the onset of complete remission.

	Cutaneous	Extracutaneous
Medical history and physical examination		
Year 1–2	Every 3–6 months	Every 3 months
Year 3–5	Every 6 months	Every 6 months
Year 6 onwards	Yearly	Yearly
Lymph node sonography		
Year 1–2	Every 6 months	Every 3 months
Year 3–5	Every 6 months	Every 6 months
Year 6 onwards	Yearly	Yearly
Other imaging (CT, PET-CT if indicated)	–	Individually

pruritus therefore deserves high priority in the therapeutic concept.

To date, the current DDG (*Deutsche Dermatologische Gesellschaft*, German Dermatological Society) guideline on treatment of chronic pruritus offers the following systemic treatment options for patients with cutaneous lymphomas [99]:

Table 11d Follow-up recommendations for lymphomatoid papulosis.

	LyP
Medical history and physical examination[1]	
Year 1–2	Yearly
Year 3–5	Yearly
Year 6 onwards	Yearly
Lymph node sonography	–
Other imaging (CT, PET-CT if indicated)	–

[1]Due to the typical course of lymphomatoid papulosis with spontaneous remission of all lesions and only short-term response to various forms of therapy, a permanent, complete remission can hardly be achieved therapeutically. Due to the increased risk of associated lymphomas in about 20 % of the patients shown in retrospective studies, an annual follow-up seems reasonable with the aim to diagnose skin changes of mycosis fungoides or other lymphoma entities at an early stage. In addition, the patient history should be evaluated with regard to B symptoms.

- Gabapentin 300 mg to 2400 mg/d in cutaneous T-cell lymphoma (CTCL)* [100],
- Mirtazapine 7.5-30 mg at night in CTCL* [101],
- Naltrexone 50–150 mg/d in cutaneous B-cell lymphoma (CBCL), MF, SS* [102],
- Aprepitant 80 mg/d in Sézary syndrome* [103],
- Off-label use.

In addition to systemic medications, basic soothing skin care is also useful. Because of similarity to atopic eczema in the impairment of the skin barrier function [104], this can be applied in analogy to atopic eczema. It can also be used in addition to specific topical treatments. Twice-daily use of hydrophilic moisturizers on affected skin and lipophilic moisturizer for non-affected, dry skin is recommended. Ingredients such as urea, glycerin and sodium chloride, or local anesthetics such as menthol, benzocaine, camphor, or similar compounds may alleviate pruritus [99, 105–107].

Advanced stages of cutaneous lymphomas present a special challenge. These include disfiguring disease manifestations affecting body regions that cannot be covered, like in erythroderma, extensive infiltration of the facial skin, or large ulcerating tumors with an unpleasant smell. Quality of life near the end of patients' lives will be greatly impaired, and the burden for both patients and caregivers has been described as traumatic [108–111].

At the end of life, optimal pain relief, wound care, general measures such as mitigation of odors, as well as professional nursing, palliative, and psycho-oncological support of patients and their caregivers will be key. The reader is referred to the guideline on palliative and supportive care, which offers valuable recommendations on pain relief, palliative wound care, and interaction with patients and caregivers in the dying phase [112].

9. Follow-up

Statement

Data from clinical trials on follow-up for CL patients are insufficient.

Consensus: 100 %, verified 2021

Recommendations for follow-up for patients with CL mainly refer to patients with complete remission (CR). Patients with stable disease (SD) or partial remission (PR) are more or less continuously undergoing treatment, so the working group on guidelines (cutaneous lymphomas) has decided to focus on patients with CR, while acknowledging that the database on follow-up in this field is insufficient [113–118]).

The following goals for follow-up in CL patients were identified:

1. Detection of relapses and metastases
2. Detection of secondary lymphomas
3. Detection of treatment sequelae (such as for example PUVA-induced tumors)

In later-stage MF and in SS, complete remission is rare and follow-up is individual.

All patients with CL need to be taught how to inspect their own skin at regular intervals and palpate the lymph nodes.

For rare entities, follow-up is individual depending on clinical requirements.

10. Psychooncological aspects and health-related quality of life

Recommendation

As suggested by the comprehensive S3 guideline "Psychooncological diagnostics, counseling, and treatment of adult cancer patients (Psychoonkologische Diagnostik, Beratung and Behandlung von erwachsenen Krebspatienten [4]) psychological burden and health-related quality of life (screening) should also be investigated in patients with cutaneous lymphomas, if possible including family and social environment.

Consensus: 100 %, verified 2021

Psychooncology includes all clinical and scientific endeavors that evaluate the influence of psychological and social factors in the development and clinical course of cancerous diseases, as well as the individual, familial, and social processes of coping with the disease. It also comprises the systematic utilization of this knowledge for prevention, early detection, diagnostics, treatment, follow-up, and rehabilitation [119]. Its most important goal is to recognize strain on patients and caregivers as early as possible and initiate appropriate treatment [120, 121]. Investigation of health-related quality of life (HRQL) is now standard in patients with advanced cancer, comprising physical, emotional, cognitive, social, spiritual, and behavioral aspects of functionality and well-being. There are currently no specific instruments for evaluating HRQL in patients with cutaneous lymphomas, but these are being developed [122].

The impact of cutaneous lymphomas on the various psychosocial dimensions as well as quality of life, and consequently on the need for appropriate support, have not been systematically investigated until now [108]. Individual studies show significantly reduced quality of life in patients with cutaneous lymphomas, with fatigue, pain, and disturbed sleep emerging as the main problems [111, 123]. A survey among members of the mycosis fungoides foundation in the USA confirms that fatigue and disturbed sleep are the most common complaints in cutaneous lymphoma patients [124]. A study on the impact of pruritus on CL patients' quality of life confirmed a strong correlation between intensity of pruritus and impaired quality of life [125]. In an international observational study (PROCLIPI), female sex and alopecia were identified as independent predictors for inferior global health-related quality of life [126]. Increased values for anxiety and depression were observed especially in those patients treated with interferon and steroids, as well as specific drug-related toxicities observed in the context of treatment studies [111].

Apart from the impact on patients' psychosocial dimensions and quality of life, the disease also displays clear effects on the familial environment [109, 127].

Recent studies have shown that low-dose total skin electron beam treatment (TSEBT) as well as immunotherapies (such as brentuximab vedotin, mogamulizumab, or anti-KIR3DL2 antibodies) can improve symptoms and various dimensions of health-related quality of life in patients with MF or SS [32, 128–132].

In general, improvement of treatment options with better tumor control and reduced toxicity also result in improved quality of life.

11. Palliative Care

Palliative care encompasses holistic care for patients with advanced disease, aimed at symptom control and care for patients with progressive, incurable, and terminal disease. The WHO describes palliative care as problem-oriented management in life-threatening disease, involving both patients and caregivers. The necessity of active treatment for physical, psychological, social, and spiritual problems is determined by the patient's needs [112, 133]. Thus, palliative care can improve quality of life, symptoms, and conditions of care for both patients and their families [108]. Although evidence is limited, there is a desire among family members for better information, improved care, and the ability to cope with disease [127]. Recommendations can be found in the S3 guideline "Palliative care for patients with incurable cancer" (*Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung*) [112].

A systematic review investigated the documentation of physical and psychological requirements as well as quality of life in patients with cutaneous lymphomas and their families: 18 studies showed intense symptomatic and emotional strain on patients [108]. Pruritus is the most troublesome symptom, followed by pain with potential involvement of psychological, functional, and emotional distress [109]. There is evidence for an association between disease severity and progression. The correlation of symptom improvement with treatment success cannot be uniformly evaluated. There are

some indications of special features in the palliative evaluation of patients with cutaneous lymphoma within the overall cohort of palliative patients [134].

Further development of dedicated services/interventions requires a detailed understanding of the needs of patients with cutaneous lymphomas and their families or caregivers.

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Correspondence to

Prof. Dr. med. Edgar Dippel
Hautklinik Ludwigshafen
Bremserstraße 79

67063 Ludwigshafen am Rhein
Germany

E-mail: dippele@klilu.de

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