CHAPTER 18 PRIMARY CUTANEOUS LYMPHOMAS

18.1 Epidemiology

Primary cutaneous lymphomas comprise both T-cell (75%+) and B-cell lymphomas. They are rare conditions representing 2% of all lymphomas, with an annual incidence of 0.3–1 per 100,000.[1,2] The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF), which is typically found in adults of 40–60 years of age, in all races, with men afflicted by the disorder twice as commonly as women. Primary cutaneous B-cell lymphomas (PCBCL) comprise the second largest group of extranodal B-cell lymphomas, after gastrointestinal.

18.2 Classification

The aetiology and clinical features of the cutaneous lymphomas has been thoroughly reviewed recently.[1,3–5]

1 Primary cutaneous T-cell lymphomas

- Mycosis fungoides
- Sézary syndrome
- CD30+ve T-cell lymphoproliferative disorders
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Unspecified

2 Primary cutaneous B-cell lymphomas

- Cutaneous follicle centre lymphoma
- Diffuse large B-cell lymphoma
- Marginal zone lymphoma

The majority of cases can be diagnosed on haematoxylin and eosin (H&E) sections with appropriate immunophenotyping, most commonly by immunohistochemistry, and in some cases by flow cytometry.[6] Furthermore, review by a pathologist colleague experienced in these disorders is strongly recommended. The need for clinicopathological correlation cannot be overemphasised. Molecular analysis examining for the presence of a clonal T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR) on fresh and formalin-fixed tissue is useful, particularly in difficult cases[7,8] (see Section 7.2).

The classification of these disorders is controversial.[9] The two most widely used classifications have been the World Health Organization (WHO)[10] and the European Organisation for Research and Treatment of Cancer (EORTC)[11] (see Table 18.1). It is recommended that pathologists classify these conditions according the WHO classification, which aligns the cutaneous lymphomas with systemic lymphomas.[9] (See Section 18.11).

18.3 Staging system

Cutaneous T-cell lymphomas can be classified into four stages (see Table 18.1).

Table 18.1 Classification of cutaneous T-cell lymphomas

Stage I	Disease confined to the skin with limited patches/plaques (stage Ia), disseminated patches/plaques (stage Ib), or skin tumours (stage Ic)
Stage II	Lymph nodes enlarged but uninvolved histologically
Stage III	Lymph node involvement documented by histology
Stage IV	Visceral dissemination

Source: Van Doorn et al. [12]

This simple clinical staging system can be converted into the TNM classification[13] (Table 18.2), which can be applied to all the cutaneous lymphomas. However, most of the data correlating stage with prognosis relate to the most common form, MF, which is typically a chronic, slowly progressive disease of 10–20 years duration (see Section 18.4.1).

Table 18.2 TNM classification for mycosis fungoides/Sézary syndrome

T_1	Limited patch/plaque (< 10% of skin surface)
T_2	Generalised patch/plaque (> 10% of skin surface)
T_3	Tumours
T_4	Generalised erythroderma
M_0	No visceral metastases
M_1	Visceral metastases
B_0	Atypical circulating cells not present (< 5%)
B_1	Atypical circulating cells present (> 5%)
N_0	No clinically abnormal peripheral lymph nodes
N_1	Clinically abnormal peripheral lymph nodes
NP_0	Biopsy performed, not CTCL
NP_1	Biopsy performed, CTCL
LN0	Uninvolved
LN1	Reactive node
LN2	Dermatopathic node, small clusters of convoluted cells (< 6 cells per cluster)
LN3*	Dermatopathic node, large clusters of convoluted cells (> 6 cells per cluster)
LN4*	Lymph node effacement

Table based on Bunn and Lamberg[13]
T = tumour; N = node; B = blood; L = lymph; M = metastasis
*Pathologically involved lymph nodes.

There is no specific staging system for PCBCL. Indeed, if the disease has systemic (nodal, marrow or visceral) involvement, it is frequently reclassified as a systemic lymphoma with secondary skin involvement.[13] Nonetheless, if the disease is felt to arise primarily from the skin, it should still be staged, like other lymphomas, according to the standard Ann Arbor criteria, with isolated lesions considered as stage I and multi-focal lesions as stage IV.

Table 18.3 Stage classification for mycosis fungoides/Sézary syndrome

	Staging classification
IA	T_1, N_0NP_0, M_0
IB	T_2, N_0NP_0, M_0
IIA	$T_{1,2}$, N_1NP_0, M_0
IIB	T_3, N_0NP_0, M_0
III	T_4, N_0NP_0, M_0
IVA	$T_{1–4}$, $N_{0,1}NP_1$, M_0
IVB	$T_{1–4}$, $N_{0,1}NP_{0,1}$, M_1

18.4 Primary cutaneous T-cell lymphomas

18.4.1 Mycosis fungoides

Summary of clinicopathological features of mycosis fungoides and Sézary syndrome

Clinical	Adults, M>F. Protracted history of cutaneous patches, plaques and ultimately nodules, mainly trunk but may become extensive, with later extracutaneous nodal +/- hepatosplenic, other organ and blood involvement. Cutaneous variants include Pagetoid reticulosis, follicular mucinosis and granulomatous slack skin. Patients with Sézary syndrome manifest erythroderma, lymphadenopathy and circulating lymphoma cells (>1000/mm^3 of blood). Course of MF is stage-dependent; excellent if limited cutaneous disease. Sézary syndrome has aggressive behaviour.
Morphology	Epidermotropic infiltrate of small- to medium-sized lymphocytes with cerebriform nuclei, Pautrier microabscesses, accompanying inflammatory infiltrate in early stages.
Immunophenotype	TCRαβ+, CD3+, CD45RO+, CD2+, CD5+, CD4+, CD8-, CD7-, cutaneous lymphocyte antigen+. Rarely CD8+ or TCRγδ+.
Genetics	Clonally rearranged TCR genes. Complex but no-recurring chromosomal abnormalities in advanced disease.

The management of MF needs to be individualised, giving particular consideration to the stage of the disease, symptoms, age and performance status of the patient. Due to the complexity in the diagnosis and management of the disease, it is strongly recommended that patients be managed in highly-specialised centres with a multidisciplinary approach that involves a dermatologist, haematologist/medical oncologist and radiation oncologist, and a close liaison with a pathologist experienced in examining skin lymphomas. Consensus United Kingdom guidelines for CTCL have also been produced recently.[14]

The interval between onset of symptoms and the establishment of a histological diagnosis frequently takes many years and often requires repeated biopsies.[2] Indeed, for patients in whom MF is suspected, and there are a limited number of patch-stage lesions, this approach is very reasonable. It avoids embarking on numerous investigations in a disease that is indolent and where outcome is not altered by aggressive early intervention.

18.4.2 Prognosis

The most important factor in planning management and determining prognosis is the stage of the disease. Indeed, the vast majority of patients with early-stage disease (stage IA, IB, IIA) do not progress to more advanced-stage disease.[2,15] Patients presenting with isolated patch or plaque disease

(stages I and IIA) have a median survival of more than twelve years. Moreover, patients with stage IA disease do not appear to have a decreased survival when compared with an age-, sex-, and race-matched population.[15] Patients with advanced-stage disease (stages IIB, III and IVA) with tumours, erythroderma, and lymph node or blood involvement, but no visceral involvement, have a median survival of five years from time of presentation. Patients with visceral involvement (stage IVB) have a median survival of only 2.5 years or less.[5,11,15,16]

Although most patients with early-stage disease (patches or plaques confined to the skin) having an indolent course, progression to cutaneous tumours, nodal or visceral disease can occur. Cutaneous tumours can develop either as increasing depth of the small atypical lymphocytes of MF, or as a result of large-cell transformation. Large-cell transformation is defined as large cells (≥4 times the size of a small lymphocyte) in more than 25% of the infiltrate, or if these cells formed microscopic nodules.[17,18] There is a variable incidence of 8–39% reported and it is associated with a very poor prognosis.[17–19] The risk of transformation relates to the presence of stage IIB-IV (31% versus 14%), tumour-stage disease, elevated β2 microglobulin and elevated lactate dehydrogenase (LDH).

18.4.3 Staging investigations

For patients with patches and/or plaques with no palpable lymphadenopathy (i.e. clinically early-stage I–IIA disease), extensive staging investigations are not required and usually restricted to physical examination and full blood examination (Sézary cells are very rarely detected). Occasional patients will present with loco-regional lymphadenopathy, which may reflect dermatopathic changes in the node rather than true nodal involvement with MF. A recommended approach in these cases is to stage the patient with computed tomography and bone marrow examination (including flow cytometry and molecular analysis for T-cell receptor gene-rearrangement). If small loco-regional nodes do not resolve following local skin therapy, lymph node biopsy is performed. Conversely, if large nodes (>3–4 cm) are detected, a representative node biopsy should be performed before initiating therapy, given the major prognostic impact of such a finding and the required alteration in the therapy applied to include systemic sites. The hesitancy in performing node biopsies relates to the high incidence of skin colonisation with pathogenic organisms in patients with CTCL, which increases the risk of infection following surgery.

18.4.4 Prognostic markers

There are currently no definitive prognostic factors beyond clinical stage for MF. Although the absence of CD7, high LDH, large-cell size, periodic acid-Schiff (PAS) inclusions and the number of circulating Sézary cells (SC) have been implicated as adverse prognostic markers, these features are usually associated with advanced-stage disease, leaving the problem of determining which patients with early-stage disease are destined to do poorly.

18.4.5 Treating early-stage (IA–IIA) mycosis fungoides

Overview

As the vast majority of patients present with early-stage disease, the treatment guidelines focus on this group of patients. Very few randomised trials have been performed in this disease and the guidelines are therefore based largely on level III evidence. Indeed, there has been only one randomised trial comparing aggressive systemic chemotherapy combined with total skin electron beam (TSEB) to skin-directed therapy involving emollients, topical chemotherapy, phototherapy and superficial radiation. This landmark study, which demonstrated no advantage in early aggressive therapy, has underpinned the approach to the management of CTCL[16] (level II evidence). As the use of early application of systemic therapy does not affect survival, non-aggressive approach to therapy is warranted, with treatment aimed at improving symptoms and cosmesis while limiting toxicity. Given that multiple skin sites are often involved, the initial treatment choices are usually topical or intralesional corticosteroids, or phototherapy with psoralen plus ultraviolet-A radiation (PUVA), or ultraviolet-B (UVB). Ultraviolet B is only effective in patients with patch disease. PUVA is usually

required for patch/plaque disease, but it too becomes less effective as the lesions thicken. For even thicker plaques, particularly if localised, radiotherapy is effective. There is the very occasional patient who presents with truly localised MF (single lesion); whether this is curable is unknown and our approach is to treat such patients with local radiotherapy with 'curative' intent.

'Second-line' therapy for early-stage disease is often topical chemotherapy using mechlorethamine (nitrogen mustard — NM) or carmustine (BCNU). Retinoids can be effective for disease refractory to topical therapies and are usually considered before the use of chemotherapy. Very large tumours may require orthovoltage/megavoltage radiotherapy. Total skin electron beam therapy is usually reserved for patients with extensive skin involvement that has failed previous therapy. Local experience is that TSEB is most successful in patients with relatively indolent disease, as early relapses (months) are common in patients with rapidly progressive disease.

Topical corticosteroids

Early-stage CTCL, especially patch-stage MF, can be treated with topical corticosteroids. Class I (potent) topical corticosteroids such as betamethasone dipropionate 0.05% or mometasone furoate 0.1% are the most effective at obtaining objective disease regression.[20] Patients with stage T1 disease (limited patch/plaque with <10% of skin surface involved) have an approximately 60–65% complete response (CR) rate (biopsy proven), and a 30% partial response (PR) rate. Patients with T2 disease (generalised patch/plaque with >10% of skin surface involved) have a 25% CR rate and a 57% PR rate.

Phototherapies

CTCL can be treated effectively with the various forms of phototherapies, including PUVA, UVB and electron beam radiation therapy (see below). PUVA therapy can be useful in treating patch- and plaque-stage CTCL, but tumour-stage disease is less responsive. Response rates to PUVA therapy in patients with patch disease are high, with CR rates of approximately 58–83% and overall response rates of up to 95%.[21–23] Furthermore, remission is often prolonged, with a reported mean duration of 43 months.[22]

Topical chemotherapy

In early-stage disease, chemotherapy for CTCL is frequently administered topically. Active agents include NM and carmustine. However, the use of these agents can be impractical if lesions are extensive and with long-term use, they carry a risk of secondary epidermal cancer.[24,25]

Alpha interferon

Alpha interferon (IFN), a biological response modifier, can be effective using doses of 3–15 million units (MU) daily (most commonly 5 MU daily).[26,27] Although it does appear to have a synergistic effect with phototherapy[28], there is no advantage in using it in combination with retinoids.[29]

Retinoids

Retinoids belong to the family of steroid hormones that bind to the nuclear receptors (retinoic acid receptor — RAR; retinoid X receptor — RXR) and subsequently interact with various transcription factors. RAR and RXR have various isoforms (α, β and γ) that are differentially expressed in tissues. The skin contains both RAR and RXR. Non-RXR-selective retinoids such as etretinate, arotinoid, acitretin and isotretinoin (13-*cis*-retinoic acid) have been used alone or in combination with PUVA, interferon alpha, or even chemotherapy. They are reported to have response rates in the range of 5–65%.[30–40] Bexarotene is a new synthetic retinoid that selectively binds to the RXR subfamily and is formulated as either as capsule or a topically applied gel.[41–44] However, it is not commercially available in Australia.

Radiotherapy

Treatment is usually aimed at improving symptoms and cosmesis, although in truly localised disease, the intent of therapy may be curative. There is a clear gradient of both diminishing likelihood of CR and length of remission with increasing stage of disease; patients with T1 disease have a >80% CR rate with radiotherapy (either local field or total skin electron beam therapy), compared to 20–30% CR rates for T4 disease. Five-year relapse-free survival rates with radiation alone are 40–60% for T1 disease, but <10% for T4 disease.[45–51] Irrespective of stage and curability, however, radiotherapy can provide excellent palliation of troublesome symptoms of CTCL such as pruritus, scaling and ulceration.

18.4.6 Target volume

For most patients, the target volume is the epidermis and/or dermis. Most lesions may therefore be treated with very soft (low penetrance) beams — superficial x-ray therapy (50–145 kvp) for small areas, or 4–9 MeV electron beams for larger areas. Higher energy beams (orthovoltage/megavoltage) are occasionally necessary for thicker lesions.

The technique of total skin electron beam therapy (TSEB) has been developed to treat patients with extensive disease. The technique is now generally limited to patients with T3/4 disease, and to those who are no longer responding to topical therapies.

18.4.7 Dose

Although very small doses of radiation can provide effective palliation of CTCL lesions, there does appear to be a dose–response relationship for complete remission. Doses of 35–40 Gy are associated with higher CR rates than doses of <25 Gy, particularly with more advanced stages of disease.[45,52–55]

18.4.8 Fractionation

Fraction size depends on several factors. Small fields in cosmetically insignificant areas may be hypofractionated, for example, 30 Gy in ten fractions, three or five times per week. However, in cosmetically-sensitive areas where large fields are being irradiated and there is pre-existing damage to the skin, or in cases of re-treatment, doses of only 1.0–1.5 Gy per fraction may need to be used. This may result in a course of treatment taking up to ten weeks.[16,56]

Guideline — Indications for specific treatment modalities in early-stage (IA–IIA) mycosis fungoides		Level of evidence	Refs
Topical steroids	Limited patch-stage	III	16, 20, 48
PUVA/UVB	Extensive patch-stage	III	16, 21–23, 57–59
Topical chemotherapy	Limited patch/plaque stage	III	16, 24, 25
Retinoids	Extensive patch-stage (2nd-line)	III	33–39
Bexarotene	3rd line*	III	41, 42, 44
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26–28, 60
Radiotherapy	Plaque- or tumour-stage	III	16, 45–47, 49–56, 61
Oral methotrexate	2nd or 3rd line	III	62–64
Systemic chemotherapy	3rd line	III	63–70
Denileukin diftitox	3rd line	III	71

*not commercially available in Australia

18.4.9 Treating advanced-stage (IIB–IV) mycosis fungoides

Overview

Treatment of advanced-stage disease (or indeed refractory early-stage disease) is more problematic. It always requires a multidisciplinary approach involving dermatologist, oncologist/haematologist and radiation oncologist. Although systemic multi-agent chemotherapy is often considered early in patients with advanced-stage disease, the randomised National Cancer Institute study demonstrated that combination chemoradiotherapy offered no survival benefit over 'conservative' topical therapy.[16] Consequently, topical therapy should be utilised first where practicable, and systemic therapy considered in refractory or rapidly progressive disease. The type of systemic therapy depends largely on age, performance status of patients and extent and tempo of the disease. For indolent but progressive disease, IFN can be effective. The single- or multi-agent chemotherapy regimens described below are selected depending on disease characteristics and side-effect profile. The value of photopheresis is limited to patients with circulating malignant cells or clonal population detected by molecular analysis[72] (see Sézary syndrome below). The biological regulators denileukin diftitox (DAB_{389}IL-2) and interleukin (IL)-12 tend to be used for advanced multi-relapsed disease, but are not commercially available in Australia. There is limited information about the efficacy of autologous or allogeneic transplantation for MF.[5]

Systemic chemotherapy

In slowly progressive disease that has systemic manifestations or has proven refractory to topical therapy and/or retinoids, single-agent therapies such as low-dose oral methotrexate (15–25 mg/m^2/week)[62], chlorambucil, cyclophosphamide or etoposide may be employed with very low risk of side effects. For more aggressive disease, multi-agent chemotherapy is usually considered. There is no recognised superior multi-agent chemotherapy regimen for MF and no proven advantage of utilising anthracyclines as initial therapy. Regimens often include one or more of

cyclophosphamide, vincristine, vinblastine, prednisolone, methotrexate or mechlorethamine.[5,63,64,73] Other effective agents include liposomal doxorubicin[67,74] and nucleoside analogues/pathway inhibitors such as 2-chlorodeoxyadenosine, deoxycoformycin, fludarabine or gemcitabine.[65,66,68] Response rates are in the range of 30%, with reported median response durations varying from months to years depending on patient selection criteria. Nonetheless, patients invariably relapsed, with no evidence in literature of regimens with curative potential. Of note, combination chemotherapy increases the risk of infection in a group of patients frequently colonised with potentially pathogenic bacteria.[5] High-dose chemotherapy with autologous transplantation achieves high response rates, but durable remissions are very rare. There is emerging evidence that a graft versus lymphoma effect exists in CTCL, and the use of allogeneic transplantation requires further investigation.

Biological response modifiers

Newer therapies have been explored using biological regulators including the recombinant targeted fusion protein that combines the receptor binding sequence of IL-2 with the cytotoxic A-chain and translocation B chain of diphtheria toxin (denileukin diftitox; ONTAK®; DAB_{389}IL-2).[71] Interleukin-12[75] and alemtuzumab (Campath-1H), the humanised monoclonal antibody targeted against CD52w (a pan-lymphocyte antigen)[76,77], have demonstrated efficacy in CTCL. However, the side-effect profile with all these biological agents is substantial, at times. Cyclosporine in not recommended.[78]

Guideline — Indications for specific treatment modalities in advanced-stage (IIB–IV) mycosis fungoides		Level of evidence	Refs
Topical steroids	Symptomatic control	III	16, 20, 48
Radiotherapy	Symptomatic control	III	45–47, 49–56, 61
Oral methotrexate	2nd or 3rd line	III	62–64
Systemic chemotherapy	2nd or 3rd line	III	63–70
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26, 27, 60
Alemtuzumab	2nd or 3rd line	III	76, 77
Bexarotene	3rd line*	III	43
Extracorporeal photopheresis**	1st, 2nd or 3rd line	III	72, 79–88
Denileukin diftitox	3rd line*	III	71

* not commercially available in Australia; **patients with circulating clonal cells only (i.e. Sézary syndrome)

18.5 Sézary syndrome

The most common definition of Sézary syndrome (SS) is one of pruritic exfoliative or infiltrated erythroderma (with histological features of CTCL) accompanied by circulating Sézary cells (SC). Although there is no consensus about the number of SC required to define the syndrome, most commonly, a SC count $>1x10^9$/L or >5% of peripheral blood leukocytes is accepted.[89–91] As SS is considered the leukaemic variant of MF, an elevated SC count should be considered an essential component of the diagnosis.

In general terms, the treatment is similar to that of advanced-stage MF.

One treatment that is more effective in SS compared to other CTCL is extracorporeal photopheresis (ECP). The first trial reported that 83% of patients with erythroderma responded to photopheresis.[92] Further and large phase II studies have reported the therapeutic benefit of ECP in CTCL, though the response data have been variable, ranging from 30% to 80% depending on study entry criteria, patient selection, and intervals between diagnosis and treatment.[72,79–88,93,94] As ECP has been used in CTCL patients refractory to all other therapies, no phase III (randomised) trials have been performed.

18.6 Primary cutaneous CD30 positive T-cell lymphoproliferative disorders

In the WHO classification, lymphomatoid papulosis (LyP) (types A and B), primary cutaneous anaplastic large-cell lymphoma of T-cell type (ALCL), and borderline lesions are considered subtypes of primary cutaneous CD30(+) T-cell lymphoproliferative disorders.[10] (See Table 18.4)

Table 18.4 WHO Classification: mature T-cell neoplasms, cutaneous types: variants and subtypes

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
• Primary cutaneous anaplastic large-cell lymphoma (C-ALCL)
• Lymphomatoid papulosis (LyP) (types A and B)
• Borderline lesions: LyP type C and C-ALCL, LyP-like histology

Source: Jaffe et al.[10]

Summary of clinicopathological features of C-ALCL

Clinical	Clinical and morphologic overlap with lymphomatoid papulosis. Adults/elderly, median age 60 years, M>F. Single or localised cutaneous nodules; multicentric in ~20%. Extracutaneous dissemination in 10%, especially multicentric cases, mainly to lymph nodes. Partial/complete spontaneous regression in 25%, but relapses frequent. ~90% five-year survival.
Morphology	Dermal +/- subcutaneous involvement. Cytology as for systemic ALCL, usually with greater pleomorphism and Reed-Sternberg-like cells.
Immunophenotype	CD3+ (rarely null cell), CD4+, CD30+ and cytotoxic protein positive most cases; ALK protein negative, EMA — usually.
Genetics	Clonally rearranged TCR genes in most. Lack t(2;5) translocation.

Primary cutaneous anaplastic large-cell lymphoma (C-ALCL): This terminology is used by the WHO classification. The EORTC prefers the term 'large-cell CTCL, CD30+' and separate out 'large-cell CTCL, CD30(-)' disease because of the more aggressive clinical behaviour of the latter[9] (see below). Patients who present with cutaneous large-cell CTCL should be classified according to the WHO classification: if they are CD30(+) they fall under 'primary cutaneous ALCL, CD30(+)'; if CD30(-) they fall under 'peripheral T-cell lymphoma, unspecified**'.** In both cases, the morphological characteristics of the cells should be described by the pathologist (i.e. anaplastic, immunoblastic or plemorphic), and CD30 expression (or lack of) emphasised.

Typically, primary cutaneous CD30(+) CTCL presents with solitary nodules that frequently ulcerate and may spontaneously regress (particularly after biopsy). The prognosis of CD30(+) cutaneous lesions is extremely good. This is in sharp contrast to the CD30 (-) cutaneous lesions and systemic CD30 (+) lymphoma. Indeed, systemic ALCL is a very different condition arising from the lymph nodes and requiring management similar to other systemic lymphomas.[95] Although relapses occur in approximately 40% of patients with CD30 (+) CTCL, systemic dissemination occurs in only 10%,

with 5–10 year survival rates exceeding 95%.[96] Consequently, therapy should be relatively non-aggressive.

Prior to therapy, patients should be fully staged to determine regional-node involvement and exclude systemic ALCL. It is unknown whether localised disease is curable, but one approach to localised disease (which is the most common presentation) is to use local radiotherapy. Whether this is more effective than surgery alone remains unknown. However, it is well tolerated and has negligible long-term risks. Chemotherapy is virtually never required for localised disease, but is recommended if regional nodes are involved.[96] Systemic ALCL can have secondary cutaneous involvement (15% in one series) and should be managed as for the systemic disease. Patients with CD30 (+) ALCL developing from pre-existing MF often have a poor prognosis.[97]

Guideline—Indications for specific treatment modalities in C-ALCL		Level of evidence	Refs
Surgery and radiotherapy	If limited disease	III	95–97
Oral methotrexate	More extensive disease	IV	
Systemic chemotherapy	Very rarely needed	IV	

Lymphomatoid papulosis: Lymphomatoid papulosis is characterised by recurrent self-healing papules or nodules. Three histologic subtypes of LyP have been described.[11] Despite its histologically malignant appearance, LyP has a clinically benign course with continuing self-healing lesions. Observation only is usually required (to determine if spontaneous resolution occurs). However, if lesions are problematic, PUVA, topical corticosteroids, nitrogen mustard, IFN or oral methotrexate can be considered. Oral tetracyclines have been used, but given that LyP can undergo spontaneous resolution, the benefit of such treatment is unclear.[98] Approximately 15–30% of patients will develop lymphoma, most commonly MF or Hodgkin lymphoma, so continuing clinical review is required.[99,100]

Guideline — Indications for specific treatment modalities in LyP		Level of evidence	Refs
Observation	If limited	III	95, 98–100
Topical steroids	If localised	IV	
Phototherapy	If extensive	III	
Oral methotrexate	2nd or 3rd line	III	
Alpha interferon +/- phototherapy	2nd or 3rd line	III	
Systemic chemotherapy	Rarely needed	III	

18.7 Large-cell cutaneous T-CD30 negative (EORTC classification)

Although in the category of 'peripheral T-cell lymphoma, unspecified' in the WHO classification, this is a separate group in the EORTC classification, and warrants discussion. These cases may present with localised or generalised nodules or tumours. They have an aggressive clinical course. The histological appearance of CD30 (-) ALCL may be identical to that of MF, undergoing transformation into large-cell lymphoma. The treatment of these tumours should be more aggressive. Once full staging is performed, it should be managed as for aggressive lymphoma (i.e. like diffuse large-cell) such that patients receive combination anthracycline-based chemotherapy followed by involved-field

radiotherapy where appropriate. In general terms, radiotherapy alone would be considered inadequate. Because of the poor outcome in these patients, novel treatment strategies should be explored.

Guideline — Indications for specific treatment modalities in CD30 negative large-cell (EORTC), peripheral T-cell lymphoma unspecified (WHO)		Level of evidence	Refs
Systemic chemotherapy	Routine	IV	101–104
Radiotherapy	Additional to chemotherapy if localised	IV	

18.8 Subcutaneous panniculitis-like T-cell lymphoma

Summary of clinicopathological features

Clinical	Wide age range and no male/female predilection. Indurated subcutaneous nodules/plaques extremities or trunk, no adenopathy. Systemic symptoms variable. Haemophagocytic syndrome may occur. Aggressive course in most (median survival ~27 months), particularly the TCRγδ+ type, but may be chemo/radio-responsive. Late dissemination to nodes and other organs.
Morphology	Diffuse subcutaneous infiltration by pleomorphic small- to medium-sized lymphocytes with rimming around individual fat cells; reactive foamy or phagocytic histiocytes common; apoptosis and karrhyorrhexis typical; angio-invasion may be present.
Phenotype	Mature activated cytotoxic phenotype (TIA-1+, granzyme B+, perforin+); most are TCRαβ+, CD3+, CD8+, CD56-; minority are TCRγδ+, CD4-, CD8-, CD56+.
Genetics	Clonal TCR gene rearrangements; EBER-; no typical cytogenetic changes.

The lesions in this condition preferentially infiltrate the subcutaneous tissue.[9,10] Patients present with multiple subcutaneous nodules and plaques, mostly on the extremities and trunk, and usually in the absence of lymphadenopathy and visceral involvement. Constitutional symptoms of fever and weight loss occur occasionally and are not infrequently related to an associated haemophagocytic syndrome.[10,105] The natural history is aggressive, although nodal and systemic dissemination is rare. The outlook is generally poor, even with aggressive chemotherapy. Relapse is frequent.[105]

Guideline — Indications for specific treatment modalities in subcutaneous panniculitis-like lymphoma		Level of evidence	Refs
Systemic chemotherapy	Routine	IV	10, 105
Radiotherapy	Additional to chemotherapy if localised	IV	

18.9 Primary cutaneous B-cell lymphomas

18.9.1 Cutaneous follicle centre lymphoma

This is the most common of the PCBCL (40%).[9,106] The WHO classification uses the term 'follicle center (FC) lymphoma' in preference to the 'follicle center cell (FCC) lymphoma' of the EORTC.[10] Lesions tend to be solitary or grouped nodules, or plaques, often localised to the scalp, forehead or back. Systemic dissemination is rare.

These are indolent lymphomas. In general terms, radiotherapy (RT) is a very important component of treatment and should encompass all lesions, if possible. Although some authors have recommended doxorubicin-based chemotherapy, the studies are small and the outcome appears similar to that expected with RT alone.[107] Surgery alone is not recommended. The overall survival is excellent (97% five-year survival), but because relapses occur frequently (30–60%), continuing follow up is required.[4,108] Recently, rituximab has been successfully used in cutaneous FC, FCC and DLBCL.[109,110]

Guideline — Indications for specific treatment modalities in cutaneous follicle centre lymphoma		Level of evidence	Refs
Surgery and radiotherapy	If limited	III	4, 108, 111–114
Systemic chemotherapy	Rarely needed	IV	
Rituximab	If extensive and relapsed or poor tolerance to chemotherapy	III	109, 110

18.9.2 Diffuse large B-cell lymphoma

The WHO classifies all lesions with a diffuse infiltrate of large B-cells into this category. In contrast, there are few patients categorised as such in the EORTC classification, with most lesions being categorised as FCC lymphoma (see Section 18.9.1). The clinical relevance of this is the very reasonable concern that with the increased use of the WHO classification, good prognosis lesions classified as FCC lymphoma by the EORTC will be now be labelled as PCLBCL and subsequently treated too aggressively.[115] Therefore it is critical to the management of this disease to stratify patients into good and poor prognosis.

The EORTC has recognised a specific clinical entity — primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) — as an aggressive disease confined to the legs of the elderly. It has been a topic of much debate as to whether PCLBCL-leg should be regarded as a distinct entity on the basis of site.[11,116] Consequently, two interrelated European studies have investigated the prognostic factors for PCLBCL. The most important adverse factors appear to be *bcl-2* expression followed by multiple skin lesions, age >70 years, location on the leg, and round cell morphology.[117]

Currently, all data with long-term follow up are based on studies utilising the EORTC classification, dividing patients broadly into PCLBCL-leg and FCC lymphoma with large-cell histology. The latter group have a much more indolent course and are less likely to require chemotherapy. A recent large 566-patient study has confirmed the robustness of the EORTC classification.[118]

We recommend aggressive treatment in only those patients with large-cell histology with adverse prognostic features. In the absence of comparative studies of chemoradiotherapy versus radiotherapy alone, the balance of evidence would suggest that poor prognosis patients should be managed as for *systemic* DLBCL where feasible, namely anthracycline-based chemotherapy with RT for localised lesions. However, patients with adverse prognostic features are typically elderly and consequently chemotherapy is often not feasible and RT alone is recommended. Unfortunately, the vast majority of patients relapse or have systemic progression.[113,107] The use of additional rituximab warrants further investigation.[109] Patients with a good prognosis should be treated as for FC lymphoma, predominantly with RT.

Guideline — Indications for specific treatment modalities in cutaneous diffuse large B-cell lymphoma (with poor prognostic features)*		Level of evidence	Refs
Systemic chemotherapy +/- rituximab	Routine	III	107, 109, 113, 119–121
Radiotherapy	Additional to chemotherapy if localised	III	

*Radiotherapy alone should be considered for patients who are classified as FCC by the EORTC classification, and for selected patients with few adverse prognostic features (adverse features are: *bcl-2* expression, multiple skin lesions, age >70 years, location on the leg, round cell morphology — see text for details)

18.10 Cutaneous extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type

Primary cutaneous marginal zone lymphoma (MZL) is rare, although in one series of non-nodal/non-gastrointestinal MALT lymphomas, the incidence was 12.5%.[122] There is also controversy in the literature as to the appropriate nomenclature for MZL. The WHO classification would include many cases of what the EORTC group has called immunocytoma and FCC lymphoma.[123,124]

Management includes complete staging with marrow and CT scan, particularly in patients with multiple disease sites. In other non-nodal/non-gastric MZL, localised RT is extremely effective and consequently, it is generally recommended to use localised RT in cutaneous MZL. However, for small localised lesions, the advantage of RT over surgical resection alone is unknown. The outcome of treatment is extremely good, and although relapses can occur in 50%+ of patients, the five-year survival is 98–100%.[113,118,125]

Guideline — Indications for specific treatment modalities in cutaneous marginal zone lymphoma		Level of evidence	Refs
Surgery and radiotherapy	If limited	III	113, 120, 121, 125
Systemic chemotherapy	Rarely needed	III	

18.11 Addendum

Willemze et al.[126] have recently published the WHO–EORTC classification for cutaneous lymphomas. The key modifications are:

- The PCTCL, unspecified group incorporates provisional entities of primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma, cutaneous gamma/delta T-cell lymphoma, and primary cutaneous CD4+ small/medium-sized pleotropic T-cell lymphoma.
- The entity SPLTCL is now restricted to those of alpha/beta cell origin (indolent behaviour).
- CD4+/CD56+ hematodermic neoplasm (blastic NK cell lymphoma) is recognised as a separate entity.
- Lesions previously classified by the EORTC as primary cutaneous follicle centre cell (FCC) lymphoma will now be classified as follicle centre (FC) lymphoma, using the same morphological criteria used by the EORTC for FCC lymphoma. This means that fewer cases of FC lymphoma will be classified as large B-cell lymphoma as per the 'prior' WHO classification.
- primary cutaneous large B-cell lymphoma is divided into 'leg-type' and 'other'.

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