BLOOD RESEARCH
VOLUME 58 · NUMBER S1
April 2023
REVIEW ARTICLE

Mycosis fungoides and Sézary syndrome

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p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2023.2023023
Blood Res 2023;58:S66-S82.

Received on January 26, 2023
Revised on April 16, 2023
Accepted on April 17, 2023

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Abstract

Mycosis fungoides (MF) and Sézary syndrome (SS) are a distinct disease entity of cutaneous T-cell lymphoma with heterogenous clinical features and prognosis. MF mainly involves skin and usually shows an indolent and favorable clinical course. In patients with advanced-stage disease, extracutaneous involvement including lymph nodes, viscera, and blood, or large cell transformation may be observed. SS is a leukemic form of advanced-stage MF, characterized by generalized erythroderma. Early-stage MF can be treated with skin-directed therapy. However, patients with refractory or advanced-stage disease are associated with severe symptoms or poor prognosis, requiring systemic therapy. Recent progress in understanding the pathogenesis of MF/SS has contributed to advances in the management of these rare diseases. This review aims to describe the clinical manifestations, diagnosis, risk stratification, and treatment strategy of MF/SS, focusing on the recent updates in the management of these diseases.

Key Words Mycosis fungoides, Sézary syndrome, Cutaneous T-cell lymphoma, Diagnosis, Prognosis, Treatment

INTRODUCTION

Primary cutaneous lymphoma (PCL) refers to a group of non-Hodgkin lymphoma (NHL) subtypes with unique characteristics, which specifically involve the skin at diagnosis [1]. Primary cutaneous T-cell lymphoma (CTCL), the disease entity of T-cell derived PCLs, accounts for 70–85% of PCLs, whereas B-cells predominate in other NHLs [2, 3]. A consensus classification of cutaneous lymphomas was established by the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) in 2005 [4] and then updated in 2018 [5]. Recently, the classification was further refined by the WHO and the International Consensus Classification (ICC) [6, 7].

CTCL is a rare disease, making up 4% of all NHLs [8]. In the United States, the incidence is 6.4–7.7 per million persons, according to the Surveillance, Epidemiology and End Results (SEER) database [9, 10]. Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes, together comprising two thirds of CTCLs [4]. Both MF and SS have a male predominance, with a 2:1 ratio versus females. The median age at diagnosis is 55 years, with the incidence increasing with age. However, MF/SS can occur in younger individuals and even in children [11]. While the prognostic impact of age is not clear, ethnic differences have been reported, with a higher incidence in Blacks and non-Hispanics (11.5), followed by Hispanics (7.9) and Asian/Pacific Islanders (7.1) [12, 13]. A recent study showed that MF in Black patients is associated with a female predominance, younger age, and a worse prognosis [12, 13]. The incidence of CTCL in Korea is low, with an age-adjusted rate of 1.3 per million persons in 2012, based on the Korean National Cancer Incidence Database (KNCIDB) [14]. The estimated 5-year survival rate in all registered patients, between 2008 and 2012 was 87.7%, with a trend of a worse outcome according to age.

MF first presents in the skin, but in its advanced stage it can also involve the lymph nodes, other organs, or blood. Typical skin lesions are patches and plaques with various morphologic and pathologic findings. SS is a distinctive disease category defined by erythroderma and neoplastic T-cells typically involving the blood [4, 5]. It is regarded as a leukemic form of MF, with refractory symptoms and a poor prognosis.

Although some studies have suggested an association of MF or SS with environmental exposure to radiation and

chemicals and with infections, especially Human T-lymphotropic virus type I (HTLV-I) [15-17], the causes of these two diseases are unclear. MF and SS are sporadic, but a few cases of familial MF/SS have been described, thus implicating genetic alterations in the development of MF/SS [18-20]. Accumulated knowledge on the cell of origin, genetic landscape, and immunologic changes has led to a better understanding of the pathogenesis of MF/SS and provided new insights into potential therapeutic targets [21-24]. Here we review the clinical manifestations, diagnosis, risk stratification, and treatment strategy of MF and SS, focusing on the recent advances in the management of MF/SS.

CLINICAL MANIFESTATION

The majority of patients with MF suffer from persistent, slowly progressive skin lesions. The most common and exhausting symptom is pruritus, occurring in over two-thirds of MF patients and significantly affecting their quality of life [25, 26], due to its association with insomnia, anxiety, and depression. Accordingly, skin-directed treatment is main approach to the management of early-stage MF.

The skin lesions in MF are heterogenous, varying in size and shape. They initially present as localized or generalized patches, plaques, and/or papules, with possible progression to tumor formation and generalized erythroderma (Fig. 1A–C, G). Patches/plaques/papules extending over a body surface area of $<10\%$ (T1) are seen in 30%, and more generalized manifestations (T2) in 35% of MF patients. A dome-shaped solid tumor ≥ 1 cm in diameter develops in 20% and erythroderma in 15% of patients, especially those with advanced disease [27]. Hypo/hyperpigmentation, alopecia, erosions, bullous lesions, and dry scaling are common accompanying findings. More than 30% of MF patients suffer from alopecia, which varies in its extent from patchy to generalized and in some patients is irreversible [28].

The term Sézary syndrome originated with the 1938 publication of a landmark case series that identified lymphocytosis with typical grooved, cerebriform nuclei in patients with MF [29]. SS is a distinctive leukemic involvement of CTCL, characterized by generalized erythroderma but also sharing clinical and pathologic features with MF, as well as the same diagnostic approach and staging system [30]. However, SS is associated with more severe symptoms, a more unfavorable response to treatment, and worse survival than is MF. The skin lesions in SS are generally diffuse, rather than the progression from patches to plaques to tumors that occurs in MF. Lymphadenopathy and pruritus are frequent features of the disease.

The lymph nodes are the most common extracutaneous site and are involved in 30% of MF/SS patients [31]. Bone marrow involvement is rare, but peripheral blood involvement exclusively correlates with the extent of the skin lesions. Other extracutaneous lesions are rare but may develop in the lungs, spleen, liver, gut, and central nervous system, especially in patients with generalized erythroderma including those with SS [1, 32, 33].

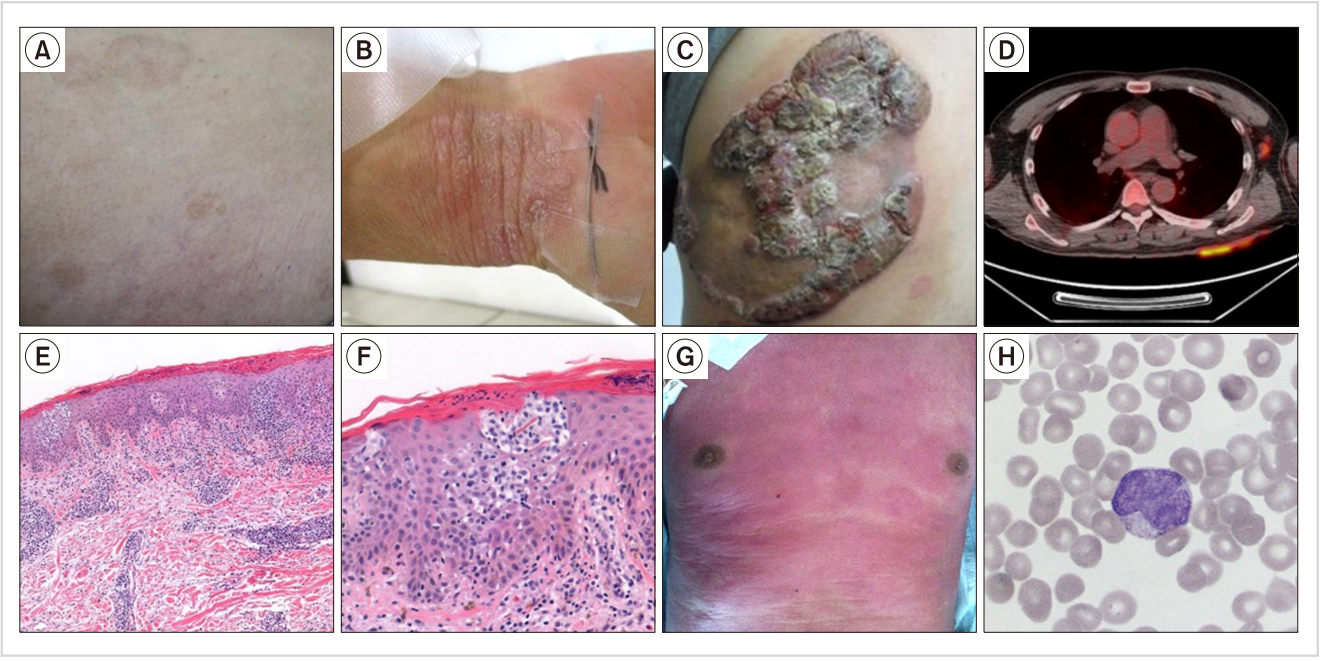

Fig. 1. Clinical manifestation and pathologic findings. Patchy **(A)**, plaque **(B)**, and tumor-type **(C)** skin lesions in a patient with advanced stage mycosis fungoides. PET scan showed FDG-uptake on large extent plaque and tumor stage lesions and axillary lymph nodes **(D)**. Histology of plaque-type MF lesion with epidermotropic infiltration of lymphocytes, in which clonality of TCR gene rearrangement was confirmed **(E)**. Higher resolution of **E**, representing grouped aggregation of large lymphocytes in the epidermis, forming early form of Pautrier's micro-abscess **(F)**. Generalized erythroderma in a patient with Sézary syndrome **(G)**. Atypical lymphocyte with cerebriform nuclei, so called 'Sézary cell', was observed on peripheral blood smear **(H)**.

MF/SS is also associated with impaired cellular/humoral immunity and an increased risk of opportunistic infections [34]. A higher risk of secondary malignancies, such as other types of lymphoma, has also been reported [35, 36].

DIAGNOSTIC APPROACH

The initial diagnostic work-up for MF should consist of a comprehensive physical exam, laboratory tests, including a complete blood cell count, routine chemistry including lactic dehydrogenase (LDH), and histologic confirmation. During the physical exam, the size, location, and degree of involved skin surface area should be recorded. To detect changes in skin lesions, standardized photographs are encouraged at baseline and at each subsequent assessment. Obtaining a representative skin biopsy is the most important step in the diagnostic work-up. Imaging studies such as computed tomography (CT) and fluorodeoxyglucose-positron emission tomography (FDG-PET) scans are required to evaluate extracutaneous disease (Fig. 1D). A bone marrow examination is not mandatory but is highly recommended.

The diagnosis of early-stage MF is challenging because the skin manifestations and biopsy findings may be misinterpreted as nonspecific and reactive changes. Many patients will have had other dermatologic presentations, such as nonspecific dermatitis, poikiloderma, or erythroderma and symptoms for years to decades before receiving a definitive diagnosis of MF [11, 27, 37]. For those patients, the clinical course should raise suspicion of MF even if the skin biopsy is non-diagnostic. Multiple skin biopsies, each consisting of at least 4-mm punch biopsy over the most indurated area are recommended. Topical treatment should be stopped for >2 weeks before the skin biopsy. The ISCL suggested diagnostic algorithm for early MF as shown in Table 1 [38].

The characteristic histopathologic finding in a patch/plaque MF is an epidermotropic infiltration of neoplastic T cells (Fig. 1E, F). In early-stage, small cerebriform lymphocytes are observed in epidermis along the basal layer. When the disease progresses, denser band-like infiltration occurs, sometimes forming Pautrier's micro-abscess, which are aggregates of tumor cells in the epidermis. It is not common, but they are specific for MF/SS. In tumor-stage, dense monomorphic infiltration of neoplastic lymphocytes involves the full thickness of dermis in nodular or diffuse pattern. In advanced stage MF and SS with blood involvement, lymphocytosis with typical grooved, cerebriform nuclei, so called Sézary cells, can be observed on peripheral blood smear (Fig. 1H).

There are some clinicopathologic variants of MF. Folliculotropic MF has a tropism for the epithelium of hair follicles, which often involves face and neck. Its manifestation includes a grouped papule, cysts, comedones, localized alopecia, and pseudo-tumors. Superficial form of this variant shows favorable survival similar to classic MF, however, a deep variant is associated with aggressive disease course and poor prognosis [39, 40]. Pagetoid reticulosis is a localized form with strong epidermotropism, generally involving distal areas of extremities [5]. It is usually indolent and can be treated with local radiation. Granulomatous slack skin is

Table 1. Diagnostic algorithm for early Mycosis Fungoides [38].

Criteria	Scoring system
Clinical	2 points for basic criteria and two additional criteria 1 point for basic criteria and one additional criterion
Basic	
Persistent and/or progressive patches/thin plaques	
Additional	
1. Non-sun-exposed location	
2. Size/shape variation	
3. Poikiloderma	
Histopathologic	2 points for basic criteria and two additional criteria 1 point for basic criteria and one additional criterion
Basic	
Superficial lymphoid infiltrate	
Additional	
1. Epidermotropism without spongiosis	
2. Lymphoid atypia[a)]	
Molecular biologic	1 point for clonality
1. Clonal T cell receptor gene rearrangement	
Immunopathologic	1 point for one or more criteria
1. <50% CD2+, CD3+, and/or CD5+ T cells	
2. <10% CD7 T cells	
3. Epidermal/dermal discordance of CD2, CD3, CD5, or CD7[b)]	

[a)]Lymphoid atypia is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours. [b)]T cell antigen deficiency confined to the epidermis.
A total of 4 points is required for the diagnosis of mycosis fungoides based on any combination of points from the clinical, histopathologic, molecular biologic, and immunopathologic criteria.

another rare variant of MF, which develops redundant skin slowly but progressively, typically in axillary and inguinal area. Histopathology of this variant shows dense infiltration of lymphocytes with granulomatous features and infiltration of atypical lymphocytes into the superficial layers with a variable distribution into the epidermis [5].

In MF/SS, malignant T-cells are predominantly CD4+, with a high CD4/CD8 ratio, and the aberrant loss of other pan-T-cell antigens, including CD2, CD3, CD5, and CD7. Immunohistochemical staining of biopsy specimens and flow cytometry of the peripheral blood can be facilitate the detection of clonal T-cells allowing a presumptive diagnosis of MF/SS. For SS, in addition to the morphological evaluation, multicolor flow cytometry is useful to detect Sézary cells, which are generally CD3+, CD4+ and CD8- [41]. The aberrant loss of other T-cell antigens, including CD2, CD3, CD4, CD5, CD7 and CD26, is a common finding, similar to the neoplastic cells found in MF [42-44]. The loss of CD7 or CD26 is sensitive and highly specific for SS [45].

Clonal gene rearrangement of the T-cell receptor (TCR) can be detected by PCR-based methods in formalin-fixed, paraffin-embedded tissues [46]. Its sensitivity is high, but it should be cautiously interpreted because it may not be specific for malignancy, as it is also detected in older adults and in patients with benign diseases. The presence of identical T-cell clones in multiple sites is considered as specific for

Table 2. Mycosis Fungoides Cooperative Group TNMB classification of cutaneous T cell lymphoma [55].

Skin (T)	
T0	Absence of clinically suspicious lesions
T1	Patches, plaques, papules <10% BSA
T1a	Patch only lesions
T1b	Plaque/papule$^{+/-}$ patch lesions
T2	Patches, plaques, papules ≥10% BSA
T2a	Patch only lesions
T2b	Plaque/papule$^{+/-}$ patch lesions
T3	One or more tumors ≥1 cm diameter
T4	Confluence of erythema covering ≥80% BSA
Node (N)	
N0	No clinically abnormal lymph nodes; biopsy not required
N1	Clinically abnormal lymph nodes; pathology Dutch grade 1 or NCI LN 0-2
N1a	Clone negative or equivocal
N1b	Clone positive and identical to skin
N2	Clinically abnormal lymph nodes; pathology Dutch grade 2 or NCI LN 3
N2a	Clone negative or equivocal
N2b	Clone positive and identical to skin
N3	Clinically abnormal lymph nodes; pathology Dutch grade 3-4 or NCI LN 4
N3a	Clone negative or equivocal
N3b	Clone positive and identical to skin
Nx	Clinically abnormal peripheral or central lymph node but no pathologic determination of representative lymph nodes. Other surrogate means of determining involvement may be determined by Tri-Society consensus
Visceral (M)	
M0	No visceral involvement
M1	Visceral involvement
M1a	BM only involvement; clone positive and identical to skin, clone negative or indeterminate
M1b	Non-BM visceral involvement; clone positive and identical to skin, clone negative or indeterminate
Mx	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment
Blood (B)	
B0	No significant blood involvement: ≤5% of Sézary cells. For clinical trials, B_0 may also be defined as <250/μL Sézary cells; CD4+CD26- or CD4+CD7- cells or CD4+CD26- and CD4+CD7- cells <15 % by flow cytometry
B0a	Clone negative or equivocal
B0b	Clone positive and identical to skin
B1	Low blood tumor burden: does not meet the criteria of B_0 or B_2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumor burden: positive clone plus one of the following: ≥1,000/μL Sézary cells; CD4/CD8 ≥10; CD4+CD7- cells ≥40%; or CD4+CD26- cells ≥30%. For clinical trials, B_2 may also be defined as >1,000/μL CD4+CD26- or CD4+CD7- cells.

MF/SS [47], but cases of MF without a detectable T-cell clone have also been reported [48]. Next-generation sequencing (NGS) is a highly sensitive and specific approach to assessing the clonality of T cells in MF/SS [49, 50]. It will be helpful to make a diagnosis of MF, however, NGS also cannot discriminate T-cell clonality in early-stage MF from reactive lymphocytes completely [51]. The clonality of neoplastic T-cells can also be confirmed by flow cytometric analysis for TCR-β chain variable region family members (TCR-Vβ), in addition to PCR-based analysis. An altered ratio of two segments (C1 and C3) in TCR-β chain constant region is a useful biomarker of α/β T-cell clonality [52, 53].

In endemic areas, assays aimed at the detection of HTLV-I virus should be performed to aid in the differential diagnosis. In patients with extracutaneous lesions, such as in the lymph nodes, tissue should be obtained from those sites as well. Lymph node involvement is assessed according to the Lugano classification [54].

STAGING AND RISK ASSESSMENT

The revised tumor, node, metastasis, and blood (TNMB) staging system was established for the staging of MF/SS and includes several revisions to the original TNM staging system [30, 54, 55]. It is based on findings in the skin (T1–T4), lymph nodes (N0–N3), viscera (M0–M1), and blood (B0–B2) as shown in Table 2. A recent update by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the EORTC includes the role of clonality testing in the determination of blood involvement and staging. Bone marrow involvement was also defined and added to the visceral staging. For clonality assessment, PCR-based detection of a TCR-γ/β gene rearrangement and NGS are recommended.

As discussed above, SS is a unique form of advanced MF, defined by the presence of generalized erythroderma (T4) and of >1,000/μL Sézary cells in the peripheral blood (B2). Staging is based on the findings in the lymph nodes and/or visceral involvement and ranges from stage IVA1 to stage IVB. MF is diagnosed in patients with lymph node and/or visceral lesion but no B_2 blood involvement.

Survival outcomes according to the staging system are shown in Table 3 [56]. Stage I–IIA is considered representative of early- or limited-stage disease. In these patients, overall survival (OS) is prolonged, measured in decades. In fact, the survival of patients with stage IA disease is comparable to that of the age-matched healthy population [27, 37]. Late- or advanced-stage diseases, defined as stage IIB or higher, are associated with a worse outcome; the median survival is <5 years. In patients with stage IVB disease, the median OS is 1.4 years, and 5-year survival is only 18% [56]. A recent meta-analysis reported a similar OS [57], as improvements resulting from new treatment approaches have yet to be included in survival analyses.

For a specific variant, considering its unique clinical course with relatively better prognosis, an alternative staging system for folliculotropic MF has been proposed [39, 58].

Clinical prognostic indices for early- and advanced-stage diseases have been investigated. For early-stage disease, the cutaneous lymphoma international prognostic index (CLIPi) has been widely used. Adverse prognostic factors include age (>60), sex (male), type of skin lesion (plaques or folliculotropic), and nodal stage (N1/Nx) [59]. The 10-year OS is 90.3% for low-risk disease (0–1 factors) and 48.9% for high-risk disease (3–5 factors).

For advanced-stage disease, the Cutaneous Lymphoma International Consortium (CLIC) suggested prognostic index, which included age >60 years, stage IV, elevated LDH level, and large cell transformation (LCT) as independent prognostic factors associated with worse survival outcomes [60]. The presence of large cells, which is frequently CD30+, may be seen in patient with MF/SS. LCT, increased large cell count >25% of the infiltrated lymphocytes, may occur in advanced-stage MF/SS and is associated with an adverse prognosis [61-64]. The 5-year OS is 68% in low-risk patients (0–1 factors) and 28% in high-risk patients (3–4 factors).

In addition, molecular biomarkers have been widely studied for the heterogenous MF/SS. Gene expression analysis showed 17 genes including *IL2RA, CCR4, STAT5A,* and *TOX* were associated with risk of disease progression in MF/SS and could distinguish MF from SS [65]. Later validation study showed that *T-plastin* and *Twist* are useful for the differential diagnosis of SS/MF from reactive changes and *KIR3DL2* was

Table 3. Clinical staging and prognosis of mycosis fungoides and Sézary syndrome [56].

Clinical stage	TNMB classification				Median OS (yr)
IA	T1	N0	M0	B0 or B1	35.5
IB	T2	N0	M0	B0 or B1	21.5
IIA	T1 or T2	N1 or N2	M0	B0 or B1	15.8
IIB	T3	N0 to N2	M0	B0 or B1	4.7
IIIA	T4	N0 to N2	M0	B0	4.7
IIIB	T4	N0 to N2	M0	B1	3.4
IVA1	T1 to T4	N0 to N2	M0	B2	3.8
IVA2	T1 to T4	N3	M0	B0 to B2	2.1
IVB	T1 to T4	N0 to N3	M1	B0 to B2	1.4

associated with short response duration [66]. Several microRNAs, such as miR-223, miR-214, miR-486, and miR155, have been reported that their expression was prognostic, but it should be validated further [67-70]. Recent advances in technical analysis, high-throughput and more detailed analysis have been enabled; constitutive activation of oncogenic signaling pathway such as *JAK-STAT* signaling, altered cell cycle regulation, and epigenetic remodeling [71]. Mutations in genes involving T-cell activation, apoptosis, *NF-kB* signaling, and DNA repair, and frequent copy number variations in driver mutations have been demonstrated [22]. These findings enabled to understand the pathogenesis of MF/SS better and gave new insights into new therapeutic strategy as well as precise diagnosis and risk assessment. Detailed list of suggested biomarkers for MF/SS are shown in Supplementary Table 1.

TREATMENT OF MF/SS

Treatment of early-stage MF

Early-stage (IA-IIA) MF is an indolent disease that primarily involves the skin. Treatment is focused on skin-directed therapies rather than systemic chemotherapy or immunotherapy, given the excellent survival outcomes of these patients. The main therapeutic goal for early-stage MF is the relief of symptoms (pruritus, pain, abnormal sensation, and cosmetic restoration). Less toxic but nonetheless effective treatments should be chosen to reduce the risk of disease progression. Thus, treatment should be determined according to disease extent, age, comorbidity, treatment availability, and safety profiles.

Skin-directed therapies include topical corticosteroids, retinoids, mechlorethamine, and imiquimod, localized radiation, total skin electron beam therapy (TSEBT), and phototherapy with the latter consisting of narrow band ultraviolet B (NBUVB) and psoralen with ultraviolet A (PUVA) (Fig. 2). Systemic therapies including oral bexarotene, interferon, immunomodulating agents, monoclonal antibodies, and targeted agents, can be used in patients with refractory disease and extensive symptoms. In this setting, drugs with a better safety profile are generally preferred, such as oral bexarotene and low-dose methotrexate.

The most common first-line therapy is topical corticosteroids, such as clobetasol propionate. Its efficacy was established based on retrospective reports of an overall response rate (ORR) of 95% for stage IA/IB disease and minimal toxicity [72, 73]. Topical mechlorethamine (0.02% gel) was evaluated in a phase II trial for stage IA-IIA MF, in which an ORR of 58.5% and a complete response rate (CRR) of 13.8% with some contact dermatitis and irritation were reported [74].

For refractory or persistent skin lesions, bexarotene (retinoic acid, 1% gel) can be used; its ORR in prospective trials ranged from 44 to 63% [75]. Topical bexarotene and other retinoids may cause excessive skin irritation when applied over large areas and are thus appropriate only for stage IA disease.

Topical toll-like receptor (TLR) agonists induce the production of cytokines, such as interferons, leading to anti-tumor immunity [76]. Studies of imiquimod, a TLR7 agonist, reported an ORR of 80% and a CRR of 45% [76, 77]. Fatigue and flu-like symptoms were reported as side effects but were rare. Clinical improvement and a reduction of neoplastic cells were also demonstrated for the TLR7/8 agonist resiquimod [78].

Generally, a topical corticosteroid, mechlorethamine, or phototherapy is recommended as the initial treatment.

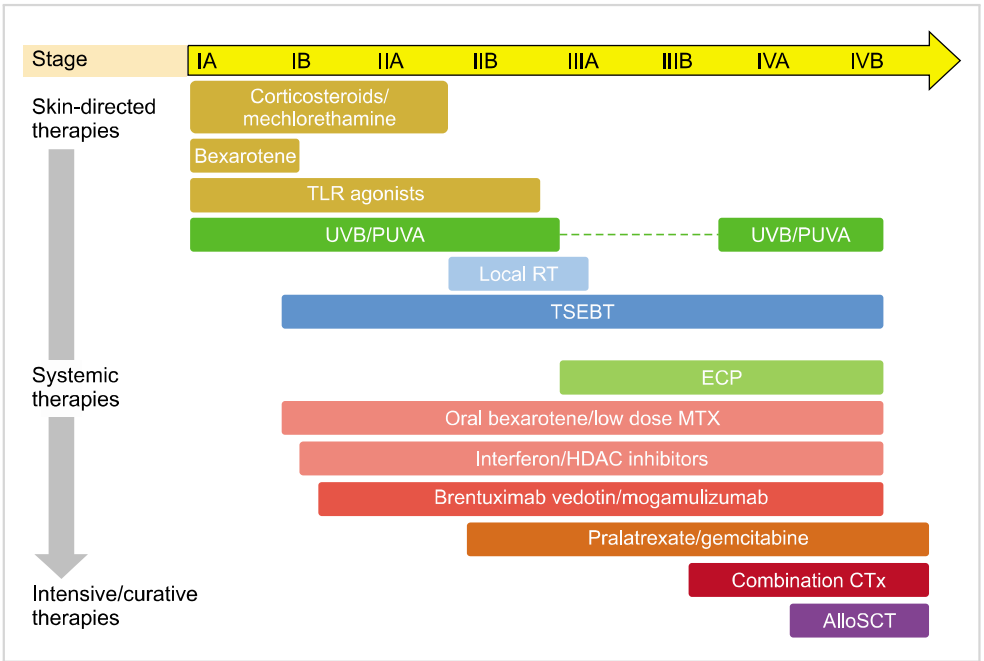

Fig. 2. Therapeutic options for mycosis fungoides and Sézary syndrome based on the stage of disease.

However, for patients with very severe symptoms and generalized, thick plaques, TSEBT will likely be more effective. In patients with disease relapse or failure to respond to one skin-directed therapy, another topical therapy or a combined strategy should be considered before systemic therapy is provided.

Phototherapy (UVB or PUVA), alone or in combination with other agents, is another effective skin-directed therapy. Either UVB or PUVA is indicated in patients with stage IA-IIA MF [79], but thick plaques or folliculotropic MF may be more responsive to PUVA because of its superior skin penetration. PUVA is also the first choice in patients of color, including Asians. A consensus guideline for phototherapy was published by the USCLC [80].

For localized MF refractory to topical agents, local radiation may be considered, especially in patients with a single skin lesion. In patients with widely distributed lesions, TSEBT using low-dose radiation may be effective [81].

Treatment of advanced-stage disease

The goal of therapy in patients with advanced-stage disease is not only symptom relief and long-term disease control but also the prolongation of survival. The treatment modality should be chosen based on the goals of therapy at different time points during the disease course (Fig. 2). For long-term disease control, agents without cumulative toxicities or immunosuppression are a good choice whereas the treatment of life-threatening disease requires curative but more toxic therapies.

For patients with localized skin involvement, skin-directed therapies can be applied with or without systemic therapy. In those with extensive skin involvement or visceral involvement, systemic therapy is required. TSEBT in combination with systemic therapy is preferred for generalized diseases, however, its use in patients with erythroderma may be contraindicated because of the risk of severe desquamation [81].

Systemic therapy ranges from immunomodulatory drugs (bexarotene, interferon, and low-dose methotrexate) to targeted agents, such as histone deacetylase inhibitors (vorinostat and romidepsin), monoclonal antibodies (alemtuzumab), antibody-drug conjugates (brentuximab vedotin and mogamulizumab), immune checkpoint inhibitors (pembrolizumab), and other investigational drugs. Data on commonly used systemic therapies are provided in Table 4. Most traditional agents have been used based on the results of phase II or retrospective studies; consequently, their true efficacies are often unclear. Novel agents targeting the unique biology of MF/SS have been recently introduced. Their superior efficacy over historical systemic therapies has been demonstrated in randomized phase III trials. With increasing therapeutic options, the decision regarding the optical treatment approach has become more complicated.

For MF and SS, the response to treatment should be assessed based on overall skin, nodal, visceral, and blood responses. In early clinical trials and retrospective reports, response criteria and outcome endpoints were not uniformly defined. In 2011 and 2022, the ISCL/USCLC/EORTC published consensus recommendations for clinical end points for MF/SS (Supplementary Table 2) [54, 55].

The systemic use of bexarotene, an oral retinoid-X re-

Table 4. Systemic therapies for refractory or advanced-stage mycosis fungoides and Sézary syndrome.

Reference	Agents	Phase	Prior Tx[a)]	N	Outcomes	Comments
Duvic *et al.* 2001 [82]	Bexarotene	II/III	2	56	ORR 45% (CRR 2%)	Pancreatitis, hypertriglyceridemia, thyroid dysfunction
Zinzani *et al.* 2000 [103]	Gemcitabine	II	3	44	ORR 70.5% (CRR 11.5%)	Myelosuppression, elevated hepatic enzyme
Dummer *et al.* 2012 [102]	Peg-L-doxorubicin	II	2	49	ORR 40.8% (CR 6.1%)	Myelosuppression, gastrointestinal toxicity
Duvic *et al.* 2007 [93]	Vorinostat	II	5	33	ORR 24.2% (CRR 0%)	Fatigue, diarrhea, nausea, thrombocytopenia, abnormal echocardiogram
Whittaker *et al.* 2010 [96]	Romidepsin	II	4	96	ORR 38% (CR 5%)	IB-IVA GI disturbances, asthenic conditions, ECG changes
Prince *et al.* 2017 [99] (ALCANZA)	Brentuximab vedotin vs. MTX or bexarotene	III, RCT	3	131	ORR4 50% vs. 10% PFS 16.1 vs. 3.5 M	CD30+ (≥10%) MF (SS excluded) Peripheral neuropathy in 66% (9% Gr3), discontinuation in 14%
Kim *et al.* 2018 [94] (MAVORIC)	Mogamulizumab vs. vorinostat	III, RCT		186	ORR 28% vs. 5% (68% in blood)	Stage IB-IVB MF/SS (LCT excluded) Infusion related reaction, thrombocytopenia, drug eruption, discontinuation in 7%
Khodadoust *et al.* 2020 [101]	Pembrolizumab	II	4	24	ORR 38% (CRR 8%)	IIB-IV Cutaneous flare reaction (without discontinuation)

[a)]Prior Tx means median number of lines of previous therapy.
Abbreviations: CRR, complete response rate; MTX, methotrexate; ORR, overall response rate.

ceptor-selective retinoic acid, was first approved by the FDA in 1999, prior to the development of the topical agent. In a multicenter phase II/III trial, patients who received 300 mg bexarotene/m^2/day had an ORR 0f 45% [82]. Common toxicities included hypertriglyceridemia, pancreatitis, and hypothyroidism and were dose dependent. Treatment for >6 months without adjuvant therapy, until disease progression if the drug is well-tolerated, is recommended [83].

Interferon α-2b or γ-1b is another immunomodulatory agent used in the treatment of MF/SS. An ORR of 50–70% and a CRR of 20–30% have been reported [84, 85]. In patients with early-stage disease, interferon can be a second-line option, and in those with advanced-stage disease, including tumor-stage lesions, a first-line option. Interferon can also be successfully combined with other skin-directed therapies, such as PUVA, bexarotene, and extracorporeal photopheresis (ECP) [86], a type of phototherapy in which psoralen exposure precedes extracorporeal circulation. Psoralen binds to DNA after UVA radiation and leads to apoptosis of lymphocytes as well as an enhanced host immune response induced by monocyte activation and dendritic cell differentiation [87, 88]. Following a landmark report of a response in 73% of patients, ECP has become a first line treatment for advanced-stage MF and SS [89]. A favorable response around rate of 60% and a durable response of >8 years in patients with a complete response have been reported [90, 91]. The median time to response is 6 months, but the long-term use of ECP may be associated iron deficiency. ECP can also be combined with other therapies.

Histone deacetylase (HDAC) inhibitors have an established safety profile, and their potential efficacy has been demonstrated in phase I studies for T-cell lymphomas, including some CTCLs [92]. A phase II trial for vorinostat showed an acceptable and durable response (ORR of 30% for a median 185 days in patients with advanced-stage disease) [93]. However, in the MAVORIC trial, vorinostat was inferior to mogamulizumab [94]. Romidepsin, evaluated in phase II trials, resulted in an ORR of 38% that was durable for >1 year in advanced-stage disease [95, 96]. With maintenance at a lower dosing schedule, responders achieved a durable response of 7–34 (median 15) months [97]. For both HDAC inhibitors, QT prolongation and cardiac toxicity are potential complications and should be monitored regularly [98].

Based on the phase III ALCANZA and MAVORIC trials, both BV and mogamulizumab were approved by the FDA, for patients with relapsed or refractory disease [94, 99]. Brentuximab vedotin (BV) and mogamulizumab are novel agents that have been evaluated in randomized phase III trials. In the ALCANZA trial, the efficacy and safety of BV compared with physician's choice of therapy (methotrexate or bexarotene) were investigated [99]. The ORR4 (lasting at least 4 mo) and progression-free survival (PFS) were 50% and 16.1 months in the BV group vs. 10% and 3.5 months in the control group. After 1 year, 34.5% of patients in the BV group but 86.6% of those in the control group required next-line treatment. The efficacy of BV was observed at any level of CD30 expression and was independent of the presence of LCT. Mogamulizumab is a humanized monoclonal antibody for the chemokine receptor 4 (CCR4) that enhances antibody-dependent cell-mediated cytotoxicity and inhibits Treg-mediated immune suppression, leading to anti-tumor activity against MF/SS. In the above-mentioned MAVORIC trial, a randomized phase III study, mogamulizumab was tested for its efficacy in patients with relapsed/refractory CTCL and resulted in a better ORR and PFS than achieved in patients treated with vorinostat (28% vs. 5% and 7.7 vs. 3.1 mo) [94]. A favorable response in the blood compartment, frequently involved in SS, was evidenced by an ORR of 68%. The side effects of mogamulizumab included drug eruptions, which were mostly tolerable and not a cause of drug discontinuation.

Clinical features may guide the choice of a systemic therapy in patients with specific disease phenotypes. Romidepsin or mogamulizumab may be beneficial for patients with a high blood burden. The reported response rate in the blood compartment was 54% and 68%, respectively [94-96]. The median response duration in the subgroup of mogamulizumab treated patients with a blood response was 26 months. There is as yet no evidence of the efficacy of BV in the blood compartment, such that SS patients were excluded from the ALCANZA trial. Because patients with generalized erythroderma frequently have blood involvement, a similar strategy may be followed. For lymph node involvement, romidepsin, pralatrexate and BV are effective, as shown in clinical trials that included patients with CTCL and peripheral T-cell lymphoma. In the ALCANZA study, the extracutaneous response rate at 4 months was 46% in the BV-treated group vs. 9% in the control group [99]. However, in the MAVORIC trial, the nodal response rate to mogamulizumab was 17% [94]. LCT is a significant adverse factor in MF/SS patients and should be considered in the selection of systemic therapy. Although CCR4 is commonly expressed in transformed cells, mogamulizumab failed to show activity in patients with LCT in early-phase trials [100]. Thus, in the phase III MAVORIC trial, patients with LCT were excluded [94].

The feasible activity of immunomodulatory agents against MF/SS and the observation of high PD-L1 expression in some CTCLs have raised interest in immune checkpoint inhibitors. In a phase II trial of pembrolizumab [101], the ORR was 38%. However, the role of checkpoint inhibitors in the management of MF/SS has yet to be fully investigated.

For refractory and aggressive disease, cytotoxic chemotherapy, such as gemcitabine and liposomal doxorubicin, can be considered for disease control [102, 103]. Patients with very aggressive disease and thus with a reduced survival, such as those with LCT or B2 disease, will require curative agents that provide a rapid and strong response. The treatment strategy developed for aggressive T-cell lymphomas may be effective.

Despite the introduction of novel agents, allogeneic stem cell transplantation (SCT) remains the only curative modality in patients with advanced-stage MF/SS, although the data

are thus far limited. Based on registry data, the 5-year PFS and OS were 17% and 32% with a 1-year non-relapse mortality (NRM) of 19% [104]. Similar results were reported in a systematic review and meta-analysis, in which the relapse rate was 47% and the NRM 19% [105]. Earlier transplantation in patients with CR1/CR2 or in those with relapse after a maximum of three systemic therapies were associated with a better outcome [106]; however, the optimal timing of allogeneic SCT is unclear yet. High-risk patients with an expected survival of <5 years may be a candidate for allogeneic SCT. As a bridging therapy, BV can be used without increasing pre- and post-transplant toxicities [107]. However, mogamulizumab should be considered cautiously because of its association with severe acute graft-versus-host disease as well as a report of treatment-related/non-relapse mortality in a study of other types of lymphoma [108].

CONCLUSION

MF/SS is a rare but distinct disease entity that is highly heterogenous with respect to its clinical features and prognosis. Recent progress in understanding the pathogenesis of MF/SS has contributed to advances in the diagnosis, staging, and risk assessment of MF/SS as well as to the development of novel therapies. However, with accumulating data obtained from studies of novel drugs, decisions regarding the optimal form of therapy and its timing are becoming increasingly complex. The efficacy and safety of combination therapies should be investigated further. Well-designed clinical trials are warranted and the participation of patients in those trials is encouraged.

ACKNOWLEDGEMENT

I appreciate Dr. Weon Seo Park, Dr. Hyo Eun Shim, Dr. Jong Heon Jung, and Dr. Hyeon-Seok Eom at National Cancer Center, Korea, for providing clinicopathological photographs and their insightful comments on this article.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Supplementary Table 1. List of suggested biomarkers for MF and SS.

Category	Biomarkers
Serum biomarkers	LDH [1] Beta2 microglobulin [2] Soluble IL-2 receptor [3] IL-13 [4], IL-31 [5], IL-12 [3] CCR4 [6] TNFR1/2 [3] HSP60/75/A5 [7]
Cell population changes	Elevated WBC, ALC, eosihophil count [8-10] CD4/CD8 ratio [11] Large cell transformation [12]
Cell surface markers	CD26 [13], $CD3^{dim}$ [14], CD27 [15], CD52 [16], CTLA-4 [17], CD45R0 [18] KIR3DL2 [19, 20] NKp46 [21] PD-1 [22]
Gene and epigenetic markers	Gene expression; TOX [23], T-plastin [24-26], JUNB [25], GATA3 [25], SATB1 [27], STAT4 [25, 28], Twist [26, 29], Fas [30] Non-coding RNAs; miRNAs; miR-21, miR-155, miR-214, miR-486, miR-42-5p, miT-146a [31-34] Long non-coding RNAs [35] Chromosomal changes; Altered 17p11.2–q25.3, 8q24.1–8q24.3, and 10p12.1–q26.3 [36-38] Gains of *TCRB, TCRG, TNFR2*, and *cMYC* [38-40] Loss of *BCL2*, cMYC antagonists [38, 41] Genetic mutations; NFKB2 truncations, TNFAIP3, PLCG1, PRKCQ and TNFAIP3 [42, 43] ZEB1 [44] PDGFR, ERK, JAK/STAT, and MAPK [43, 45] DNMT3A, ASLX3, TET1-3 [46] RAD51C, BRCA2, POLD1 [43] TP53 [44, 46]

Supplementary Table 1 References

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Supplementary Table 2. Response criteria for MF and SS (modified from Olsen EA *et al.* Blood. 2022;140:419-37).

Response in specific tissues				
Sites	Response	Definition		
Skin	CR*	100% clearance of skin lesions[b]		
	PR	50 to <100% clearance of skin disease[b] from baseline without advancement in stage. May designate subset of Very Good PR based on 90 to <100% clearing of total body involvement. Without new tumors (T3) in MF/SS patients with T1, T2, or T4 only skin disease		
	SD	<25% increase or <50% clearance in skin disease from baseline[b] Without new tumors (T3) in MF/SS patients with T1, T2, or T4 only skin disease		
	PD[a]	1. ≥25% increase in skin disease from baseline[b] OR 2. Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score. New tumors (T3) in MF/SS patients with T1, T2, or T4 only skin disease Additional suggestions for confirming PD in T1 MF and T1 non-MF/non-SS PCLs may be considered depending on the aims of the study[c]		
Lymph nodes**	CR	Complete metabolic response. Score 1, 2, or 3[d] with or without a residual mass on 5PS.	Target LNs[e]/nodal masses must regress to ≤1.5 cm LDi	All target LNs or nodal masses that previously were >1.5 cm are now ≤1.5 cm LDi by method used to assess size of LNs at baseline/screening or biopsy negative for lymphoma
	PR	Partial metabolic response. Score of 4 or 5[d] with reduced uptake compared with baseline.	≥50% decrease in SPD of up to 6 target measurable LNs. No clear increase in nonmeasured LNs or new LN1.5 cm LDi.	Cumulative reduction >50% of the SPD of up to 6 target LNs and no new LN >1.5 cm LDi unless proven pathologically negative for lymphoma
	SD	No metabolic response. Score of 4 or 5[d] with no significant change in FDG uptake from baseline.	<50% decrease from screening/ baseline in SPD of up to 6 target measurable LNs. Criteria for PD not met.	Fails to meet criteria for CR, PR or PD
	PD	Progressive metabolic disease. Score of 4 or 5[d] with an increase in intensity of uptake.	1. Any LN of LDi 1.5 cm which has increased by ≥50% from PPD nadir 2. New LN 1.5 cm any axis 3. New or clear progression of preexisting nonmeasured LNs	1. Any LN >1.5 cm LDi which has increased by ≥50% from PPD nadir 2. Any prior LN <1.5 cm LDi, which has increased by >50% from PPD nadir to >1.5 cm LDi
Viscera**	CR	Complete metabolic response. Score of 1, 2, or 3[d] with or without a residual mass on 5PS. No evidence of FDG-avid disease.	No extralymphatic sites of disease. Any abnormal size of organ at screening/baseline has returned to normal size. BM normal by morphology.	
	PR	Partial metabolic response. Score of 4 or 5[d]with reduced uptake compared with baseline and residual mass(es) of any size. Residual uptake in BM higher than normal but less than baseline.	1. ≥50% decrease in SPD from baseline of any measurable extranodal site 2. Spleen 50% regression in length beyond normal (≤13 cm) 3. No new lesions 4. No increase in nonmeasured lesions	
	SD	No metabolic response. Score of 4 or 5[d] with no significant change in FDG uptake from baseline. BM no change from BL.	Fails to attain criteria CR, PR, or PD. No clear progression or improvement.	
	PD	1. Progressive metabolic disease 2. New FDG-avid foci consistent with lymphoma	1. New extranodal site >1 cm any axis or if <1 cm, must be attributable to lymphoma 2. An increase in LDi or SDi from nadir of 0.5 cm for lesions ≤2 cm or 1 cm for lesions >2 cm 3. Regrowth of previously resolved lesions 4. In the setting of splenomegaly at BL, an increase in splenic length by >50% from BL or if no splenomegaly at BL, new increase length >2 cm from BL 5. New or clear progression of preexisting nonmeasured lesions	
Blood	CR	B0[f], ***		
	PR	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with B2 classification[f,g], ***		
	SD	Fails to attain criteria for CR, PR, or PD		
	PD[h]	B0 to B2[f], *** OR >50% increase from baseline and ≥5,000 neoplastic cells/μL[i] OR Loss of response in those with PR who were originally B2 at baseline, >50% increase from nadir and ≥5,000 neoplastic cells/μL[i]		

Supplementary Table 2. Continued.

Global response score[¶]					
Global score[§]	Definition	Skin	Lymph nodes	Viscera	Blood
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI.		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD.		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR.		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any.		
		SD	R/NI, PR, SD in any category and no category has a PD.		
PD	Progressive disease	PD in any category.			
Relapse	Recurrence of disease in prior CR	Relapse in any category.			

[a)]Whichever criterion occurs first. [b)]One form of assessment of skin disease should be used throughout a given clinical trial. For a global response score and a designation of Very Good PR, a comparison of total body skin assessment based on mSWAT assessment or sum of the product of perpendicular tumor measurements (SLAT score is one example) at baseline is necessary. Regional or lesional skin scoring may also have CR, PR, SD and PD response but may not be representative of the response of skin disease on the entire body skin surface and cannot be used to assess global response. [c)]For patients with limited T1 stage disease, there is a potential for a ≥25% increase inpatch/plaque skin score to lead to a PD despite an insignificant change in total skin lymphoma. This is of particular concern in studies where global response is the primary endpoint and skin the primary determinant of that response. In these cases, study design may elect to add additional requirements for PD in patients with T1 disease at BL, including a T1 to T2 change in skin classification in addition to the ≥25% increase in skin score. [d)]5PS: 1=no FDG uptake >background; 2=FDG uptake ≤mediastinum; 3=FDG uptake >mediastinum but ≤liver; 4=FDG uptake moderately > liver; 5=FDG uptake markedly >liver and/or new lesions. [e)]Target LNs are those >1.5 cm with representative abnormal node positive pathologically for lymphoma. In MF/SS, this is currently the LN classification of N3. [f)]The absolute number of CD4+CD26- and/or CD4+CD7- lymphocytes may be used to assess blood involvement in clinical trials. In the case where more than one aberrant population of lymphocytes is recorded, the population with the highest absolute number at baseline should determine the B classification and the highest absolute number at each assessment should be used to determine the number of aberrant lymphocytes for response purposes. [g)]There is no PR in those with B1 disease at baseline as the difference within the range of neoplastic cells that define B1 is not considered significant and should not affect determination of global objective response. [h)]Whichever occurs first. [i)]The determination of what constitutes a significantly high count of neoplastic cells above 1,000 neoplastic cells/μL and what should be used here to help define PD in MF/SS blood involvement is at present arbitrary and based on expert opinion. We cede modification of this number to published data showing prognostic value for a different number of neoplastic cells per microliter than what is published here.

*A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exist. If histologic changes are suspicious or suggestive of PCL, the response should be considered a PR only.

**Based on Cheson *et al.* J Clin Oncol. 2014;32:3059-68.

***As determined by absolute numbers of neoplastic cells/mL by flow cytometry.

[¶]Modified from Olsen *et al.* J Clin Oncol. 2011;29:2598-607 and Kempf *et al.* Blood. 2011;118:4024-35. This table assumes that (1) all patients at baseline have measurable skin disease and (2) in patients with PCL and no extracutaneous disease at baseline, any new nodal or visceral involvement constitutes PD in those compartments.

[§]This assumes that the response (CR, PR, SD, PD, or relapse) has been maintained for at least 4 weeks in any involved category.

Abbreviations: 5PS, 5-point scale; FDG, fluorodeoxyglucose; LDi, longest diameter; LN, lymph node; NI, noninvolved; PD, progressive disease; SD, stable disease; SDi, short axis (longest perpendicular diameter to the LDi); SPD, sum of the products of the perpendicular diameters for multiple lesions.