International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) revisions to the staging and classification of mycosis fungoides and Sézary syndrome.

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Abstract

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She is certified in Internal Medicine and Dermatology. She has been a principal and co-principal investigator on numerous clinical trials studying the immunology of T-cell mediated disorders and skin cancers, as well as clinical drug development and translational research in T-cell lymphomas, melanoma, and various skin cancers. A prolific author, she has written manuscripts, book chapters, abstracts, and over 300 peer-reviewed journal articles. She is co-author on a recent book on Retinoids and Carotenoids in Dermatology.

Dr. Olsen is Professor of Dermatology and Oncology at Duke University Medical Center and the founder and Director of the Duke Cutaneous Lymphoma Research and Treatment Center. She is a Past President, Secretary-Treasurer and member of the Board of Directors of the International Society for Cutaneous Lymphomas (ISCL) and has chaired the ISCL initiatives on the revisions to 1) the staging and classification of Mycosis Fungoides (MF) and Sezary Syndrome (SS) (published in Blood 2007) and 2) standardized response criteria and endpoints for MF and SS (in progress). She is a founder and current President of the United States Consortium for Cutaneous Lymphomas (USCCL), a multidisciplinary group whose mission is to enhance patient care through a national registry of patients with cutaneous lymphoma and collaborative clinical trials. She has authored over 90 original articles and is the editor of two textbooks. Dr. Olsen is currently on the Board of Directors of the American Academy of Dermatology (AAD) and Deputy Chair of the AAD Patient Advocacy Task Force.

As background to the following educational activity, this brief review will discuss the International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) revisions to the staging and classification of mycosis fungoides and Sézary syndrome.

PURPOSE OF REVISION

The Mycosis Fungoides Cooperative Group (MFCG) developed a staging system for CTCL [1] designed for the particular clinical findings in the mycosis fungoides (MF)/ Sézary syndrome (SS) subtypes and based on the TNM (tumor-node-metastasis) classification advocated by the International Union Against Cancer (UICC) [2] and American Joint Committee on Cancer. [3] This classification and staging system was modified in conjunction with the National Cancer Institute (NCI) and the Veteran's Administration (VA) Hospital and published in 1979. [4]

The updated International Society of Cutaneous Lymphoma (ISCL)/ European Organization of Research and Treatment of Cancer (EORTC) staging and classification applies to MF and SS and has maintained the major components of the MFCG system to allow for continued comparison of patient outcomes within both systems. [5] WHO/EORTC considers SS to be a separate entity from cases that otherwise meet the criteria for SS but has been preceded by clinically typical MF. [6]

PURPOSED CHANGES TO T CLASSIFICATION

In both the original MFCG [4] and the revised staging system [5], the T_1 skin rating is defined as papules, patches, and/or plaques covering less than 10% body surface area (BSA) and T_2 skin rating is defined as patches and/or plaques covering 10% or more BSA (Table 1).

Figure 1

TNMB stages

Skin	
T_1	Limited patches,* papules, and/or plaques† covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors‡ (≥ 1-cm diameter)
T_4	Confluence of erythema covering ≥80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B_{0a}	Clone negative#
B_{0b}	Clone positive#
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative#
B_{1b}	Clone positive#
B2	High blood tumor burden: ≥1000/μL Sézary cells‖ with positive clone#

TNMB STAGES

* For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

† For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (> 25% large cells), $CD30^+$ or $CD30^-$, and clinical features such as ulceration are important to document.

‡ For skin, tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

§ For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Minimal nodal groups examined on physical examination should include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N_3 histopathologically.

¶ For viscera, spleen and liver may be diagnosed by imaging criteria.

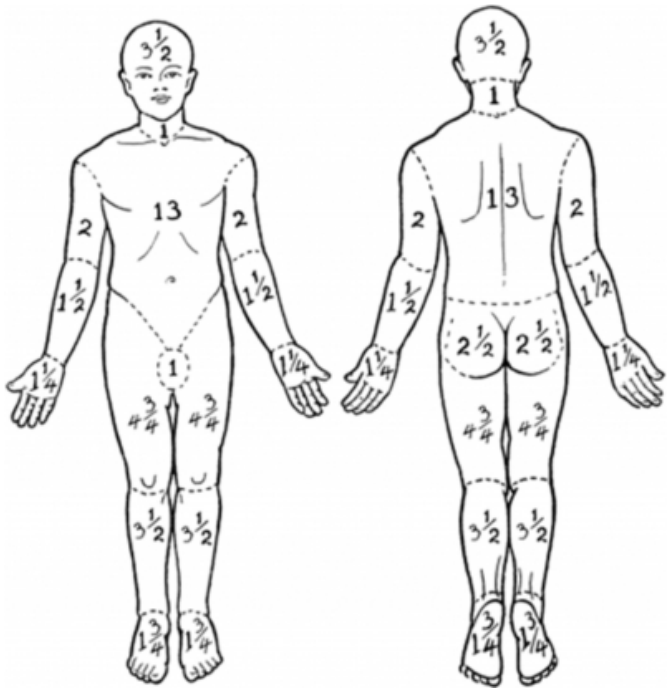
‖ For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B_2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of 10 or more, (2) expanded $CD4^+$ cells with abnormal immunophenotype including loss of CD7 or CD26.

A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

In the classification published by the MFCG, 1% BSA was defined as equal to the “palmar surface of the hand.” [1] but it has since been determined that the palm and fingers of the patient’s hand is a better approximation of 1% BSA. [5] Another method of determining BSA is to estimate the percentage of skin involvement in each of 12 regions of the body (each with a relative assigned percent BSA [7] multiplying this number by the percentage of the BSA for that particular region and adding up the regional percentages to obtain the total BSA involved with MF/SS.

Figure 2

Figure 1. Regional percent body surface area (BSA) in the adult



The MFCG originally required that a diagnosis of tumor-stage disease include at least 3 tumors, [8] but this was changed to one or more tumors in the final MFCG staging system. [4] The proposed ISCL/EORTC classification revision retains the requirement of at least one tumor (1.5 cm in diameter) for the definition of T_3. [5] Whether there should be a minimum histologic depth of infiltrate to distinguish plaque from tumor in order to corroborate this important assignment of T stage based on a single lesion has not been yet been determined. There is currently no distinction in the updated staging system for subclassifying T_4 based on varying degrees of induration, erythema, or scale.

The ISCL/EORTC recommends tracking folliculotropic MF and large-cell transformation to determine if either warrants an advance in stage. Folliculotropic MF has been shown to be associated with a worse prognosis than expected for clinical stage and is considered equivalent to T3 tumors [9][10][11] .

REVISIONS TO THE N (NODE) CLASSIFICATION

The ISCL/EORTC revision defines clinically abnormal peripheral nodes as 1.5 cm or larger in the longest transverse diameter or any palpable peripheral node, regardless of size, that on physical examination is firm, irregular, clustered, or fixed. These clinically enlarged or abnormal nodes should be corroborated by an imaging study (computed tomography [CT] ± [18] F-fluorodeoxyglucose positron emission tomography [FDG-PET] or by magnetic resonance imaging (MRI) (in cases where patients may be allergic to contrast dye) or ultrasound prior to biopsy.

Because a biopsy of a clinically abnormal node is not always done at initial staging, the revised ISCL/EORTC classification has added a new category, the Nx node rating, to facilitate capture of at least this clinical information.

PATHOLOGY OF LYMPH NODES

The two main histopathologic grading systems for lymph nodes in MF/SS are the NCI/VA classification system, [12] first proposed by Matthews and Gazdar, [13] and the Dutch System [14] (Table 2). The major difference between these classification systems resides in the criteria used to define "abnormal" lymphocytes. [14] Specifically, the NCI/VA system, [12] although it defines abnormal (neoplastic) cells as small (6-10 µm) or large (> 11.5 µm) cells with cerebriform, irregularly folded, hyperconvoluted nuclei (ie, Sézary cells), does not use the size of cells but instead uses the relative numbers of such cells in the paracortex of the lymph node for the LN_{0-2} definition. The Dutch system uses the diameter of the cerebriform cells (> 7.5 µm) to define abnormal (neoplastic) cells, and if present, this constitutes early involvement (grade 2). [14]

N_1 and N_2 ratings can be further classified into 2 subgroups: N_{1a} and N_{2a} (clone negative) and N_{1b} and N_{2b} (clone positive). [5] It is hoped that by capturing this information longitudinally, it can be determined if there is a similar prognosis of patients with and without clonal involvement and between N_{2b} and N_3.. Prognosis in MF/SS is clearly related to partially or completely effaced nodal architecture as defined by either the NCI-VA (LN_4) or Dutch (grade 3/4) grading system, [15] and continues to define the N_3 node rating in the updated ISCL/EORTC staging system.

Figure 3

Updated ISCL/EORTC classification	Dutch system[14]	NCI-VA classification[12,13]
N_1	Grade 1: dermatopathic lymphadenopathy (DL)	LN_1: occasional and isolated atypical lymphocytes (not arranged in clusters)
		LN_2: many atypical lymphocytes or in 3-6 cell clusters
N_2	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei > 7.5 µm)	LN_3: aggregates of atypical lymphocytes; nodal architecture preserved
N_3	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells (CMCs) Grade 4: complete effacement	LN_4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

REVISION TO M CLASSIFICATION

To be considered as having visceral disease (stage IVb), documentation of involvement by only one organ outside the skin, nodes, or blood is needed. The ISCL/EORTC considers splenomegaly as visceral disease, even without biopsy confirmation, when it is (a) unequivocally present on physical exam and (b) documented radiographically by either enlargement. [5] ,

Liver disease may be suspected by physical examination, abnormal liver function tests, or radiologic tests (CT, FDG-PET, liver/spleen scan) but should be confirmed by liver biopsy. [16]

The ISCL/EORTC recommends performance of a bone marrow biopsy in patients who have B_2 blood involvement or unexplained hematologic abnormalities.

If lung abnormalities or other suggestions of extracutaneous lymphomatous involvement, besides splenomegaly, are found on radiographic examination, pathological assessment is recommended before ascribing this to visceral involvement with MF/SS.

REVISIONS TO THE B (BLOOD) RATING

The ISCL/EORTC has simplified and clarified the definitions of B to B_2. B remains 5% or less Sézary cells. B_2 is now defined as a clonal rearrangement of the TCR in the blood and either 1.0 K/µL or more Sézary cells or one of the 2 criteria outlined by the ISCL, [17] that is, (1) increased $CD4^+$ or $CD3^+$ cells with CD4/CD8 of 10 or more or (2) increase in $CD4^+$ cells with an abnormal phenotype (≥ 40% $CD4^+/CD7^-$ or ≥30% $CD4^+/CD26^-$ has been suggested [18]). B_1 is defined as more than 5% Sézary cells and either less than 1.0 K/µL absolute Sézary cells, absence of a clonal rearrangement of the TCR, or both.

The assessment of blood tumor burden in MF/SS in the current staging assessment is based on morphologic features of the neoplastic cells alone (eg, Sézary cell counts). [19] Blood flow cytometry offers an alternate objective means of identifying and quantifying these neoplastic lymphocytes in the blood. The populations of CD4+CD26- or CD4+CD7- cells or V beta subtype measured by flow can be used to identify the population of SS cells.

EVALUATION AND STAGING OF THE PATIENT WITH MF/SS

The staging of MF/SS according to the TNMB system implies that an appropriate evaluation of the 4 TNMB systems has been performed. The recommended workup is detailed in Table 3 below.

Figure 4

Complete physical examination including:

- Determination of type(s) of skin lesions
  - If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions
  - If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved
- Identification of any palpable lymph node, especially those ≥1.5 cm in largest diameter or firm, irregular, clustered, or fixed
- Identification of any organomegaly
- Skin biopsy
  - Most indurated area if only one biopsy
  - Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered
  - Evaluation for clonality of TCR gene rearrangement

Blood tests

- CBC with manual differential, liver function tests, LDH, comprehensive chemistries
- TCR gene rearrangement and relatedness to any clone in skin
- Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$)

Radiologic tests

- In patients with $T_1N_0B_0$ stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with $T_2N_0B_0$ disease with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy
- In all patients with other than presumed stage IA disease or selected patients with limited T_2 disease and the absence of adenopathy or blood involvement, CT scans of chest, abdomen, and pelvis alone ± FDG-PET scan are recommended to further evaluate any potential lymphadenopathy, visceral involvement, or abnormal laboratory tests. In patients unable to safely undergo CT scans, MRI may be substituted

Lymph node biopsy

- Excisional biopsy is indicated in those patients with a node that is either ≥1.5 cm in diameter and/or is firm, irregular, clustered, or fixed
- Site of biopsy
  - Preference is given to the largest lymph node draining an involved area of the skin or if FDG-PET scan data are available, the node with highest standardized uptake value (SUV)
  - If there is no additional imaging information and multiple nodes are enlarged and otherwise equal in size or consistency, the order of preference is cervical, axillary, and inguinal areas

Analysis: pathologic assessment by light microscopy, flow cytometry, and TCR gene rearrangement

CONCLUSIONS

Although the ISCL/EORTC revisions to the staging and classification of MF and SS further narrows and defines the variables involved, it does not provide a finite staging

system that inherently incorporates all potential prognostic factors.

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