Mycosis Fungoides is a T-cell lymphoma having a broad clinical spectrum ranging from localized cutaneous to rapidly fatal systemic disease. Early clinical presentation is non specific, delaying correct diagnosis.

Compared to clinical, the insurable spectrum is narrow. Staging for skin, lymph node and other organ manifestations is presented. Factors which influence mortality within each stage are elucidated. The survival curves of stages and stage groupings are illustrated and discussed to facilitate risk classification.

Cutaneous (T) and lymph node (LN) stages are the most important prognosticators. Substages T1/T2, LN1/LN2 without associated palpable adenopathy, eosinophilia, visceral and blood positive findings are insurable. It would be most appropriate to place them in a tumor class of mild/moderate risk after the initial excessive mortality period ends.

Higher T and LN substages, adenopathy and visceral disease have highly adverse mortality. These ultimately reveal a flattening of survival curves at 8-10 years.

Although numerous treatment modalities have been used, none appear to consistently prolong life expectancy except in the earliest stage skin disease.

The key to risk selection of MF is correct clinical and histopathologic staging.

The purpose of this review is to assist the underwriter to correctly stage MF and to discuss the mortality implications of each stage.

Pathology

MF is a lymphoma produced by monoclonal proliferation of T-helper-cells. Although initially cutaneous, ultimately it can involve lymph nodes, viscera and blood.¹²

Historical

Mycosis Fungoides was originally used by Jean Louis Alibert in 1806 to describe distinctive fungating tumors resembling mushrooms appearing on a patient with diffuse cutaneous desquamation.³

Etiology

Several hypotheses have been promulgated as an etiology for the T-cell malignant transformation including a T-cell retrovirus (HTLV-5) and exposure to industrial solvents.¹² An association between MF and manufacturing occupations such as petroleum, textiles (cotton), rubber, fabricated metal and printing industries has been observed by some and refuted by others.¹⁴

Epidemiology

The annual incidence of MF doubled from 1973 to 1984 to .0042 cases per 1,000 population.¹

Males have twice the incidence of females. Blacks are more commonly afflicted than whites.¹

The disease presents most often between ages 50-70. Childhood onset is rare and carries a more ominous prognosis.²⁴

Clustering of MF is suggested by observation that four percent of patients have first-degree relatives with leukemia or lymphoma.³
Clinical Presentation

MF is commonly misdiagnosed in its early stages as eczema or a non specific dermatitis. The mean duration of symptoms before diagnosis is approximately eight years. Often, symptomatic treatment with topical steroids prolongs the time to diagnosis both clinically and histopathologically. Multiple biopsies may be required before a definitive diagnosis is achieved. Early lesions range from macular patches to indurated, infiltrated plaques. Initial involvement of buttocks, thighs and breasts in females is common. Cutaneous progression is usual, but highly variable, with ultimate involvement of peripheral lymph nodes, viscera and blood. Transformation to a diffuse, large cell or diffuse, large cell immunoblastic lymphoma has been reported. An association between MF and second malignancies other than skin cancers and Hodgkin's disease exists with a relative risk of 3.3.

Sezary syndrome is an erythrodermic variant associated with a leukemic form of the disease. The skin shows generalized redness and desquamation with intense puritis. More than ten percent of circulating cells are Sezary cells. The syndrome carries an especially poor prognosis.

An unusual variant of MF, pagetoid reticulosis has a highly favorable prognosis. It presents with localized hypertrophic or verrucous lesions on an extremity. Local destruction can occur. Radiation is the treatment of choice.

Staging

Two staging systems for MF have been proposed. The Mycosis Fungoides Cooperative Group (MFCG) and the National Cancer Institute (NCI) are both based on tumor, node and metastasis. The NCI additionally includes histopathologic evaluation of peripheral blood, lymph nodes and visceral sites.

I believe the NCI classification can produce a more comprehensive risk assessment, thus is emphasized. Comparison results from the MFCG study will be discussed. Table 1 details the NCI staging system for MF.

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>TI: Limited plaque, less than 10% body surface area</td>
<td></td>
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<tr>
<td>T2: Generalized plaque, 10% or greater of body surface area</td>
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<tr>
<td>T3: Cutaneous tumor (one or more)</td>
<td></td>
</tr>
<tr>
<td>T4: Erythroderma (generalized)</td>
<td></td>
</tr>
<tr>
<td>Ad+: Palpable adenopathy</td>
<td></td>
</tr>
<tr>
<td>Ad-: No palpable adenopathy</td>
<td></td>
</tr>
<tr>
<td>LN1: Reactive node</td>
<td></td>
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<tr>
<td>LN2: Dermatopathic node, small clusters of convoluted cells</td>
<td></td>
</tr>
<tr>
<td>LN3: Dermatopathic node, large clusters of convoluted cells</td>
<td></td>
</tr>
<tr>
<td>LN4: Lymph node effacement</td>
<td></td>
</tr>
<tr>
<td>V+: Positive visceral biopsy</td>
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<tr>
<td>V-: Negative visceral biopsy</td>
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</tbody>
</table>

Stages

IA: T1; Ad-; LN1, LN2; V-
IB: T2; Ad-; LN1, LN2; V-
IIA: T1, T2; Ad+; LN1, LN2; V-
IIB: T3; Ad+; LN1, LN2; V-
IIIA: T4; Ad+; LN1, LN2; V-
IV: T4-T5; Ad+; LN3, LN4; V-
IVB: T1-T4; Ad+; LN1-LN4; V+

Blood

B+: Positive blood smear
B-: Negative blood smear
The cutaneous lesions comprising the T stages are patch, plaque, tumor and erythroderma; each has a characteristic histopathologic appearance.¹

When adenopathy is detected, biopsy is done. In the absence of palpable nodes, blind biopsy of axillary, inguinal or supraclavicular nodes is advocated. Biopsied nodes are graded histopathologically LN1-4. In this system, LN1 and LN2 are not diagnostic of tumor infiltration; LN1 nodes deviate from normal with nonspecific changes, such as sinusoidal histiocytosis or follicular hyperplasia. Nodes classified as LN2 reveals, at most, small clusters of atypical, convoluted lymphocytes in the paracortical zones, usually with concomitant dermatopathic lymphadenitis, including melanin deposition with prominent paracortical histocytes. Nodes classified as LN3 show evidence of dermatopathic change but with large clusters of cytologically atypical cells, and nodes classified as LN4 show effacement of nodal architecture by tumor cell infiltration.²

Visceral biopsies are undertaken only in selected patients.

A blood smear is considered positive if more than 20% lymphocytes with atypical convolutions are present. Abel considers five or more abnormal blood cells to be positive.¹ The stage of MF at presentation is shown in Table 2.

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>III</th>
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<tbody>
<tr>
<td></td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>IB</td>
<td>16%</td>
<td>IVA</td>
</tr>
<tr>
<td>IIA</td>
<td>8%</td>
<td>IVB</td>
</tr>
<tr>
<td>IIB</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
</tr>
</tbody>
</table>

Nearly 60% of patients are older than age 50 at presentation. Fifty percent of the study group presented with advanced stage IV disease.²

Risk Classification

As with any malignancy, correct staging is mandatory to achieve successful risk classification. All cases of MF must be staged according to Table 1. Follow up attending physician’s statements may be required to ascertain whether clinical or histopathologic staging procedures were completed and, if so, the results. Often, the medical director will be called upon to assimilate the data to estimate the stage. Differentiation between substages T1 or T3 and LN1 or LN3 can have a profound effect on risk classification and mortality outcome.

The NCI survival curves in Figures 1A-F (reproduced with permission of reference 2) include deaths from all causes. In the NCI group, 81% of patients died from MF, its complications (mainly infection) or treatment. Therefore, deviation of the configuration of these survival curves from expected can overwhelmingly be attributed to the excess mortality of MF itself.

T Stage - Figure 1A

Both surface area and histopathologic findings determine the correct T stage. The authors combined stages T1/T2 and T3/T4 since there was no statistical difference in survival between the two stages within the pair. The difference between each pair, T1/T2 and T3/T4, is significant. In Figure 1A, survival curves for T stages 1 and 2 reveal approximate 85% and 80% survival at the end of five years. Ultimate 13 year survivals are approximately 70% and 55%, respectively. Median survival for stages T1 and T2 is about eight years.² For T3 and T4, median survival is three and one half years.² Nearly all patients with T4 had positive blood smears. Visceral disease is strongly associated with higher T stages.²

Adenopathy (Clinical) - Figure 1B

There is a correlation between T and adenopathy (Ad) stages. Most T1 individuals do not have adenopathy, whereas 50% of T2 have adenopathy.² Nearly all T3 and T4 have adenopathy.² The presence of clinical adenopathy has a deleterious, statistically significant, effect on survival. Figure 1B shows the five year survival without adenopathy to be about 92%; with, about 38%. Ten year survivals without and with are about 80% and 20%, respectively. Those without palpable nodes median survival is 12 years; with nodes, median survival is three and one half years.²
Figure 1A
Survival Related to the Type of Skin Disease Present at Diagnosis.

T1 - less than 10% of skin surface involved by plaque (18 patients); T2 - more than 10% of surface involved by plaque (61 patients); T3 = cutaneous tumors (31 patients); T4 = erythroderma (42 patients). P < 0.001 for significant difference in survival of T1 or T2 groups compared with T3 or T4 groups. P > 0.5 for any difference between the T1 and T2 groups or between the T3 and T4 groups. Reproduced with permission of Ref. 2.

Figure 1B
Survival of Patients Related to Adenopathy at Diagnosis.

Adenopathy was absent in 56 patients and present in 92 (P < 0.001). Reproduced with permission of Ref. 2.
Figure 1C
Survival Related to Histologic Classification of Lymph Node Biopsy.

LN1 and LN2 = atypical nodes or dermatopathic change without large clusters of convoluted cells (50 patients); LN3 = dermatopathic change with large clusters of atypical lymphocytes (51 patients); LN4 = effacement of lymph node architecture by malignant lymphoma (21 patients). P = 0.0017 for LN1 and LN2 groups compared with the LN3 group, and P = 0.0056 for the LN3 compared with the LN4 group. Reproduced with permission of Ref. 2.

Lymph Node Class (Histopathologic) - Figure 1C
As previously noted, palpable nodes should be biopsied. Blind biopsy is advocated when no clinical adenopathy is present. The deteriorating survival curves for progressive LN classes (1 and 2 combined) is evident in figure 1C. Approximate five year survivals are LN1-2 75%, LN3 45% and LN4 15%. The difference between each group is statistically significant. Approximate ten year survivals are 50%, 25%, 0%, respectively. Median survival for LN1-LN2 is nearly eight years, LN3 four and one half years and LN4 two and one half years.

Peripheral Blood Involvement, Visceral Involvement and Eosinophilia - Figures 1D, E, and F
These three groups illustrate similar, rapidly deteriorating survival with positive findings. Five year survival in those with positive results is 10 to 25 percent with few survivors at 10 years. Median survival for those with positive smears is three and one half years. Negative smear yields a 10 year median survival. Those with eosinophilia (greater than 700 cells/10^6 L) have a median survival of two years.

Figure 1D
Survival Related to Involvement of the Peripheral Blood by Malignant Cells.
Blood was positive in 52 patients and negative in 93 (P < 0.001). Reproduced with permission of Ref. 2.
**Figure 1E**

*Survival Related to Involvement of Visceral Sites by Mycosis Fungoides or the Sezary Syndrome.*

At least one site was positive in 22 patients, and negative in 126 ($P < 0.001$). Reproduced with permission of Ref. 2.

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**Figure 1F**

*Survival Related to the Presence of Eosinophilia.*

Seventy-two patients were without eosinophilia and 21 had eosinophilia ($P = 0.0033$). Reproduced with permission of Ref. 2.
Comparison of the survival curves in Figures 1A-F reveals a consistent pattern. Substages T1/T2, LN1/LN2, adenopathy/ eosinophilia absent and blood/viscera negative all have similar survival curves. Highly unfavorable survival curves are evident for the more advanced stages and those with positive findings.

Figure 2 (reproduced below with permission of Reference 2) illustrates survival by three stage groupings. Two prognostic groups were created by combining stages IA, IB, IIA and stages IIB, III, IVA since analysis did not show significant differences in survival among the three stages in each group. However, the difference in survival between each group was statistically significant. The overall survival for combined stages IA, IB, IIA is about 90% at 5, 80% at 10 and remains 80% at 15 years. The median survival is 12 years. Combined stages IIB, III, IVA have a survival at five years of about 50%, 10 years about 25%, with no survivors beyond 11 years. Median survival is 5 years. The third prognostic group, stage IVB has only 5% survival at 5 years. Median survival is two and one half years. Of patients presenting in these three groups, 25% are stage IA, IB, IIA, 50% are IIB, III, IVA. The remaining 25% are IVB.

Stage IIA primarily differs from IA and B by the presence of adenopathy (Table 1). Figure 1B reveals the statistically significant adverse survival effect of adenopathy. From an underwriting standpoint, stages IA and B (they differ only by T1 and T2 which have no statistically significant survival difference) should have a considerably better survival than IIA which has positive adenopathy. Whether one is a lumper or splitter (and more risk tolerant) is personal preference and/or company underwriting philosophy; however, separating stages IA and B from IIA for risk selection appears warranted. Stages IIB, III and IVA, according to the authors, have no difference in survival. These three stages contain one or more of the highly adverse T3, T4, LN3 or LN4. For underwriting, any differences are not important due to the highly excessive mortality. The same applies to stage IVB.

Further information on survival of MF is available from the MFCG study whose primary limitation is the short follow up of only five years. In this group, as in NCI, deaths from all causes were used in analysis. The authors felt this was necessary because the exact cause of death was often difficult to establish and the effects of treatment may have been inseparable from MF itself. These two limitations should not detract from the usefulness of the data. Relative differences in survival categories and stages in each group can be useful to the underwriter. The T stages are the same as NCI except T3

![Figure 2](reproduced with permission of Ref. 2)

Patients were placed into stage groups using definitions adapted from Bunn and Lamberg (Table 1). For stages IA, IB and IIA compared with IIB, III, IVA, 49 and 80 patients, respectively, \( P < 0.001 \); for stages IA, IB, and IIA compared with IVB, 49 and 23 patients, respectively, \( P < 0.001 \); and for stages IIB, III, and IVA compared with IVB, 80 and 23 patients, respectively, \( P < 0.001 \). Reproduced with permission of Ref. 2.
Micosis Fungoides

is defined as at least three tumors whereas NCI used one or more. T3 by MFCG, therefore, may have more advanced disease. Comparison of five year survivals for MFCG and NCI are shown in Table 3.

**Table 3**

Comparison of Approximate Five Year Percent Survivals in MF by T Stage from the MFCG and NCI Study Groups.

<table>
<thead>
<tr>
<th>T Stage*</th>
<th>MFCG</th>
<th>NCI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>55%</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>35%</td>
<td>35%</td>
</tr>
</tbody>
</table>

*T0 and T1 were combined in the MFCG group.

The survival difference among the four MFCG groups using life-table analysis is highly significant. MFCG survival curves for T1 and T2 reveal a steady, gradual decline. T3 and T4 survival curves have a strong downslope, each with a plateau at three and one half years. Except for T2, the five year survivals between the NCI and MFCG study groups are similar.

MFCG also examined the prognosis of clinical lymphadenopathy. Whereas NCI distinguished between palpable and nonpalpable node survival, MFCG categorized the number of clinically enlarged nodal sites: N0, no nodes; N1, one nodal site; N2-4, two to four nodal sites and N5-8, five to eight nodal sites. Nodal sites included right and left cervical, right and left axillary, right and left inguinal, epitrochlear and submandibular. The survival of each nodal site is shown in Table 4.

For each of the four N categories, the survival curves (each statistically significant) reveal progressive deterioration to the end of the five year follow up.

**Table 4**

Approximate Five Year Percent Survival in MF by Nodal Sites from MFCG Study

<table>
<thead>
<tr>
<th>Number of Sites (N)</th>
<th>Survival (5 yr) Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>70%</td>
</tr>
<tr>
<td>N1</td>
<td>55%</td>
</tr>
<tr>
<td>N2-4</td>
<td>55%</td>
</tr>
<tr>
<td>N5-8</td>
<td>35%</td>
</tr>
</tbody>
</table>

The MFCG concludes skin involvement (T) and the number of clinically enlarged lymph nodes (N) are the most important prognostic variables. These two variables are combined into four clinical stages. Table 5 defines each stage with its accompanying five year survival. This table is modified from reference five with the addition of five year survivals.

MFCG defines T0 as no skin involvement and T3 as at least three or more tumors. T1, T2 and T4 are the same as NCI staging.

Survival curves for stages 1 and 2 reveal a continuous, gradual, downward slope. Stages 3 and 4 have a sharp downward slope reaching a plateau at four years.

Abel and her associates reported up to 30 year (all causes of death included) actuarial survival with MF limited to the skin. T1, 2, 3 are defined as in the NCI study. Survival with T1 is 65%, T2 20% and T3 5%. They note very few patients with limited plaque disease actually die of MF. Of those patients with generalized plaque disease, nearly one third succumb to MF due to progression of cutaneous tumors and/or visceral involvement. The majority of those with tumorous involvement or erythroderma die of causes related directly to MF. Virtually all patients with extracutaneous disease die from MF itself. They further report up

**Table 5**

Clinical Stages by MFCG and their Five Year Survival

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>T Category</th>
<th>Clinically Enlarged Nodal Sites</th>
<th>Five Year Approximate Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T0-T1</td>
<td>0-1</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>T0-T1</td>
<td>2-8</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>T2</td>
<td>2-8</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0-8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>T4</td>
<td>0-8</td>
<td>35%</td>
</tr>
</tbody>
</table>
to 16 year actuarial survival with extracutaneous disease in lymph nodes or viscera, 5%, and with Sezary syndrome, 0%.

Treatment

Success of treatment is dependent upon the substage at initiation. Those with plaque disease show demonstrable response in several studies. Controversy exists whether early T stage disease should be treated with topical nitrogen mustard or radiation. Poor risk patients are the subject of several experimental protocols using extracorporeal phototherapy, retinoids and interferon.

PUVA is a form of phototherapy using ultraviolet irradiation following oral ingestion of psoralen. Remission of skin disease (stages 1 and 2) is noted; unfortunately disease-free durations were short (20 months). PUVA increases the incidence of both basal and squamous cell carcinomas. No effect of PUVA therapy on ultimate survival has been demonstrated.

Radiation therapy can occasionally cure patients with limited skin disease. However, in most cases it is palliative with no improvement in long term survival. Total-body, electron-beam treatment for those with T1 and T2 disease produces a 25% disease-free survival for 3 1/2 years. No effect is noted on T3 or higher disease nor those with histopathologic node involvement. Ninety percent of those with limited plaque disease achieve a complete response. For generalized plaque disease, the complete response falls to 70% and in tumorous disease it is only 40%. Nearly one half of those with limited plaque disease and one quarter with generalized plaque disease maintain their complete response over long-term (not defined) follow up.

Topical nitrogen mustard is effective in stage IA and B disease with remissions in 68-80% of cases, some lasting up to four years. Long-term eradication of disease after a single course of nitrogen mustard therapy is most likely in those with limited plaque disease. About one third remain disease free (again duration not defined). Obviously, in these cases, remissions should not be construed as synonymous with cure. Carmustine (BCNU) is also used as a topical agent.

Chemotherapy with deoxycoformycin and alpha 2a (Roferon A) is reserved for those with advanced disease. Its effect is short lived.

Lamberg summarized the effect of treatment by noting that it is yet to be proven that any treatment presently in use affects long-term survival.

Summary

The foregoing discussion will enable the underwriter to correctly stage MF and apply the most appropriate risk classification.

The mortality of MF is discussed in general terms and trends according to groups and stages. Factors which influence mortality within each subgroup comprising a stage are elucidated.

Some generalizations are appropriate to assist the underwriter in classifying MF. Substages T1/T2, LN1/LN2 without associated palpable adenopathy, eosinophilia, visceral and blood positive findings are insurable. It would be most appropriate to place them in a tumor class of mild/moderate risk after the initial excessive mortality period ends.

Higher T and LN substages have highly adverse mortality. Whether they are insurable for individual products is dependent upon one's risk tolerance. These substages ultimately reveal a flattening of survival curves at 8-10 years, albeit with very few survivors. Prior to this, the slope of the curve appears so excessive that any tumor class rating would not cover the anticipated mortality. Insurability after 10 years may be feasible.

It is my hope that this review will become the seed for an enterprising individual to create a follow up publication wherein survival curves are analyzed by mortality methodology to determine mortality ratios and excess death rates for each substage or at least for each stage. This will permit more precise risk classification and mortality assessments.

References