

Long-term Outcome of 525 Patients With Mycosis Fungoides and Sézary Syndrome

Clinical Prognostic Factors and Risk for Disease Progression

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Objectives: To study and update the clinical characteristics and long-term outcome of our patients with mycosis fungoides (MF) and Sézary syndrome (SS), and to identify important clinical factors predictive of survival and disease progression.

Design: A single-center, retrospective cohort analysis.

Setting: Academic referral center for cutaneous lymphoma.

Patients: Five hundred twenty-five patients with MF and SS evaluated and managed at Stanford University Cutaneous Lymphoma Clinic, Stanford, Calif, from 1958 through 1999.

Main Outcome Measures: We calculated long-term actuarial overall and disease-specific survivals and disease progression by the Kaplan-Meier method, and relative risk (RR) for survival calculated from expected survivals in control populations.

Results: The majority of our patients presented with T1 (30%) or T2 (37%) disease; 18% presented with T3 and 15% with T4 skin involvement. Forty-three percent of deaths were attributable to MF, primarily in patients with T3 or T4 disease. The patients with a more advanced T classification and clinical stage had a worse survival outcome. Except for patients with T1 or stage IA disease, the RR for

death is greater in patients with MF than in a control population (RR, 2.2 in stage IB/IIA disease, 3.9 in stage IIB/III disease, and 12.8 in stage IV disease). Despite similar overall survival in patients with stage IB or IIA disease, their disease-specific survivals were significantly different ($P = .006$). The most significant clinical prognostic factors in the univariate analysis were patient age, TNM and B classifications, overall clinical stage groupings, and the presence or absence of extracutaneous disease. In the multivariate analysis, patient age, T classification, and the presence of extracutaneous disease were the most important independent factors. The risk for disease progression to a more advanced TNM or B classification, worse clinical stage, or death due to MF correlated with the severity of the initial T classification. The risk for development of extracutaneous disease also correlated with T classification; none of these patients had T1 disease when their extracutaneous disease was detected.

Conclusions: Patients with MF and SS have varying risks for disease progression or death. The most important clinical predictive factors for survival include patient age, T classification, and the presence of extracutaneous disease. The significant disease-specific survival differences between different clinical stages validate the usefulness of the present MF clinical staging system of the National Cancer Institute.

Arch Dermatol. 2003;139:857-866

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MYCOSIS fungoides (MF) and the Sézary syndrome (SS) are a group of extranodal non-Hodgkin lymphomas of T-cell origin with primary cutaneous involvement.¹ The group distinguishes itself from other cutaneous T-cell lymphomas by its unique clinical and histological features. Mycosis fungoides is an uncommon lymphoma; however, it is the most common primary lymphoma of the skin.

Previous studies have shown that other than in limited patch and/or plaque (T1) disease, the overall survival of patients with MF is worse than that of age-, sex-, and race-

matched control populations.²⁻⁴ Multiple studies have attempted to identify clinical factors predictive of survival in patients with

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MF and SS.¹⁻¹³ These factors include basic demographic factors, the extent and type of skin involvement, the presence of extracutaneous disease, lymphadenopathy, and peripheral blood involvement.¹⁴⁻¹⁷ Other potential prognostic factors that have been studied include large-cell transformation,^{18,19} levels of serum lactate dehydrogenase level and β_2 -microglobulin, eosino-

Table 1. TNM and B Classification and Clinical Staging System for Mycosis Fungoides*

N and M Classification	T Classification			
	T1 Limited Patch/Plaque†	T2 Generalized Patch/Plaque‡	T3 Tumor	T4 Erythroderma
N0 M0§	IA	IB	IIB	IIIA
N1 M0	IIA	IIA	IIB	IIIB
N2-N3 M0¶	IVA	IVA	IVA	IVA
N0-N3 M1#	IVB	IVB	IVB	IVB

*Categories and overall staging system are described by the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas.²⁵ B classification is not incorporated into the clinical stage (B0 indicates absence of significant peripheral blood Sézary cells; B1, presence of significant peripheral blood Sézary cells).

†Indicates <10% of body surface area.

‡Indicates ≥10% of body surface area.

§Indicates nodes are clinically uninvolved.

||Indicates nodes are enlarged but histologically uninvolved.

¶Indicates nodes are clinically normal (N2) or enlarged (N3) and histologically involved.

#Indicates visceral involvement.

philia, levels of serum interleukin 2 receptor²⁰ and tumor-infiltrating T cells,²¹ expressions of cytokines and adhesion molecules, histological variables,²² tumor burden index,²³ thickness of cutaneous infiltrate, erythrocyte sedimentation rate, B symptoms, and clinical response to therapy. Despite these reports, long-term follow-up studies of large groups of patients with MF and SS are limited. However, such reports are essential to improve our understanding of prognostic factors in this rare lymphoma.

In this study, we have updated and summarized the clinical characteristics and long-term outcome in a cohort of patients with MF and SS at our institution. We limited our study subjects to 525 patients who underwent diagnosis and management at our clinic. Our previous outcome studies focused on patients with specific T classifications and were not comprehensive in our analysis.^{2,3,12} In this study, we identified and studied several clinical features predictive of survival using univariate and multivariate analyses. We also analyzed the risk for disease progression from initial presentation.

METHODS

PATIENT SELECTION AND STAGING

From 1958 through 1999, 688 patients with MF and SS underwent evaluation at the Stanford University Cutaneous Lymphoma Clinic, Stanford, Calif. The clinical and pathological definition of MF and SS in our study is consistent with that of the updated World Health Organization classification for lymphoma, in which SS is considered a clinical variant of MF.²⁴ Since the mid-1980s, the clinic has used immunohistochemical and molecular diagnostic studies (Southern blot since the mid-1980s and polymerase chain reaction technique since late 1990s) as ancillary methods for diagnosis. We identified 525 patients who received a diagnosis no longer than 6 months before their initial evaluation at the clinic. Patients whose diagnosis of MF and SS was made more than 6 months before were excluded from this study to limit the analyses to those patients who were managed at the clinic. For TNM and B classifications and clinical staging, patients underwent a complete physical examination, complete blood cell count with examination for Sézary cells, a general chemistry panel, chest radiography, and skin biopsy. Patients with palpable lymph nodes clinically suspected of involvement with MF underwent needle aspiration or lymph node biopsy. When

indicated because of advanced skin involvement or palpable lymphadenopathy, patients underwent additional staging evaluation, including bone-marrow biopsy and/or additional imaging studies. Suspected involvement of any visceral sites was confirmed with biopsy whenever possible. All patients underwent staging according to the TNM and B categories and overall staging system described at the National Cancer Institute workshop by the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas (**Table 1**).²⁵

EVALUATION AND DEFINITION OF DISEASE PROGRESSION

In this study, we defined disease progression as progression of disease to more advanced TNM and B classifications, a more advanced clinical stage, or death due to MF or SS. The reason for selecting these specific events for progression rather than the criterion of greater than 25% worsening of disease from baseline is that these specific events are associated with worse survival outcome. The date of disease progression was determined as the date of the first identification of any defined events of progression. Patients with T1 or T2 disease that progressed to T2 through T4 or to T3 or T4 disease, respectively, and patients with stage IA or IB disease that progressed to stage IIA disease or a more advanced clinical stage were considered to have progressive disease. Also, patients whose B classification progressed from B0 (absence of significant peripheral blood Sézary cells) to B1 (presence of significant peripheral blood Sézary cells) or patients whose N classification progressed from N0 to N1 or N3 or from N1 to N3 were considered to have disease progression. The patients who died due to MF or SS rather than unrelated causes were also considered to have progressive disease, regardless of the status of other disease characteristics.

STATISTICAL ANALYSIS

Actuarial survival was calculated from the date of initial visit to the Stanford Cutaneous Lymphoma Clinic, at which time the diagnosis was confirmed and plotted according to the Kaplan-Meier technique.²⁶ Disease-specific survival (DSS) is defined as a survival calculation in which death events must be specifically related to MF, such as progressive disease, fatal infections, and MF-related complications. Freedom-from-progression curves were plotted from the date of diagnosis using the Kaplan-Meier method. Analysis of differences in actuarial curves was performed by means of the Gehan test.²⁷ All *P* values correspond to 2-sided significance tests, and 95% confidence intervals (CIs) were determined using standard meth-

ods.²⁸ The expected survival used as the expected outcome of the race-, age-, and sex-matched control population for our analyses was obtained from US decennial life tables.²⁹

We performed the multivariate analysis with the identified significant univariate prognostic factors using the proportional-hazards regression method to establish their significance as independent prognostic indicators.³⁰ Patient age was considered a continuous variable in the multivariate analysis.

RESULTS

PATIENT DEMOGRAPHICS AND CURRENT STATUS

Clinical characteristics of the 525 patients in this study are summarized in **Table 2**. Patient age at presentation ranged from 12 to 88 years, with a median of 57 years. The median age distribution by T classification demonstrated that patients with T1 disease were younger than those with T2 or T3 disease ($P < .001$), and those with T4 disease were older than those with T2 or T3 disease ($P < .005$). The female-male ratio was 1:1.7. Eighty-six percent of our patients were white. The majority of our patients had T1 (30%) or T2 (37%) skin involvement at presentation; a third of our patients had T3 (18%) or T4 skin involvement (15%). Their clinical stage at presentation is summarized in Table 2. Thirty-four patients (6%) presented with extracutaneous disease.

The median time from onset of symptoms related to MF until the time of diagnosis (symptom duration) of our 525 patients was 4.2 years (range, 0.1-70.1 years). The median symptom duration by T classification was 5.0 years for patients with T1, 4.2 years for those with T2, 4.0 years for those with T3, and 2.6 years for those with T4 disease. These differences were not statistically significant.

Current patient status, categorized by initial T classification, is summarized in **Table 3**. Two hundred seventy-eight (53%) of the 525 patients have died. Of these deaths, 120 (43%) were attributable to MF, including 3 (2%) of 159 patients with T1 disease, 29 (15%) of 192 with T2 disease, 51 (53%) of 96 with T3 disease, and 37 (47%) of 78 patients with T4 disease. Other causes of death included other malignancies and/or cardiopulmonary diseases. At the time of our analysis, 134 patients (26%) were alive in remission, including 84 (53%) of 159 with T1 disease, 37 (19%) of 192 with T2 disease, 10 (10%) of 96 with T3 disease, and 3 (4%) of 78 with T4 disease. Among the 34 patients who presented with extracutaneous disease (stage IV), 29 have died, and 26 deaths (90%) were due to MF.

LONG-TERM OVERALL AND DISEASE-SPECIFIC SURVIVALS AND RELATIVE RISK FOR DEATH

The overall survival and disease-specific survivals of our 525 patients with MF are shown in **Figure 1**. The median survival was 11.4 years, and the actuarial overall survival rates at 5, 10, and 30 years were 68%, 53%, and 17%, respectively. The median follow-up time was 5.5 years (range, 0.1-38.5 years). The median DSS for our 525 patients has not been reached. The DSS rates at 5, 10, and 30 years were 81%, 74%, and 64%, respectively.

The overall actuarial survival of our 525 patients with MF is worse than the predicted survival of the age-, sex-, and race-matched control population without MF ($P < .001$).

Table 2. Clinical Characteristics of 525 Patients With MF and SS

Characteristics	Values
Age by T classification, median (range), y	
All patients (n = 525)	57 (12-88)
T1 (n = 159)	49 (22-82)
T2 (n = 192)	58 (12-88)
T3 (n = 96)	58 (19-86)
T4 (n = 78)	65 (36-87)
Sex, No. (%)	
Female	195 (37)
Male	330 (63)
Race, No. (%)	
Asian	10 (2)
Black	20 (4)
Hispanic	43 (8)
White	452 (86)
TNM classifications by clinical stage and B classification, No. (%)	
T1 N0	
IA	155 (30)
T2 N0	
IB	133 (25)
T1-T2 N1	
IIA*	60 (11)
T3 N0-N1	
IIIB†	84 (16)
T4 N0-N1	
IIIA	15 (3)
IIIB	44 (8)
T2-T4 N2-N3	
IVA‡	30 (6)
IVB§	4 (1)
T1-T4 N0-N3 M0-M1	
B0	490 (93)
B1	35 (7)

Abbreviations: B0, absence of significant peripheral blood Sézary cells; MF, mycosis fungoides; SS, Sézary syndrome.

*Includes 4 patients with T1 disease and 56 with T2 disease.

†Includes 42 patients with N0 disease and 42 with N1 disease.

‡Includes 3 patients with T2 disease, 10 with T3 disease, and 17 with T4 disease.

§Includes 2 patients with T3 disease and 2 with T4 disease.

||Includes 1 patients with T1 disease, 1 with T2 disease, 5 with T3 disease, and 28 with T4 disease.

The relative risk (RR) for death for all patients with MF compared with the general population was 2.4 (95% CI, 2.1-2.6).

LONG-TERM OUTCOME BY PATIENT AGE, SEX, AND RACE

We studied the influence of patient age, sex, or race on survival in our 525 patients. The median age at presentation was 57 years. We found significant differences in actuarial survival results in patients who presented at younger than 57 years ($n = 261$) compared with those who were 57 years or older ($n = 264$) ($P < .001$). The DSS analysis ($P < .001$) confirmed that these differences were attributable to deaths caused by MF and not age-associated health risks.

In our study population of 525 patients, 37% were female. The increased prevalence of MF in males was observed similarly in all T classifications, with a female-male ratio of 1:1.6 to 1:1.8. We found no significant differences in the long-term overall or disease-specific survival outcomes between male and female patients ($P = .14$ and

Table 3. Current Status of 525 Patients With MF and SS by T Classification*

Status	T Stage				Total
	T1 (n = 159)	T2 (n = 192)	T3 (n = 96)	T4 (n = 78)	
Alive, NED, never relapsed	66	23	4	1	94
Alive, NED, previous relapse	18	14	6	2	40
Alive with MF	48	48	11	6	113
Dead, NED, never relapsed	9	22	7	11	49
Dead, NED, previous relapse	6	14	3	3	26
Dead with MF, due to other causes	9	42	14	18	83
Dead due to MF	3	29	51	37	120

Abbreviations: MF, mycosis fungoides; NED, no evidence of disease; SS, Sézary syndrome.

*Data are given as number of patients.

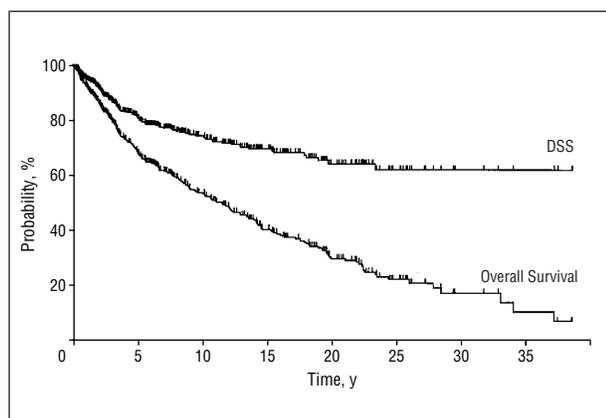


Figure 1. Actuarial overall survival and disease-specific survival (DSS) of 525 patients with mycosis fungoides and Sézary syndrome undergoing management at Stanford University Cutaneous Lymphoma Clinic, Stanford, Calif, from 1958 through 1999.

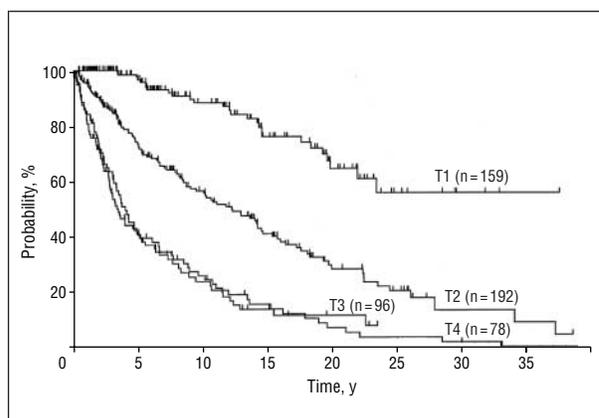


Figure 2. Actuarial overall survival of 525 patients with mycosis fungoides and Sézary syndrome according to their T classification at diagnosis (T1-T4). For T1 vs T2, T3, or T4 disease, $P < .001$; T2 vs T3 or T4 disease, $P < .001$; and T3 vs T4 disease, $P < .001$. *P* values were calculated using the Gehan test.

$P = .68$, respectively). Overall, 86% of our patients were white, with similar percentages in all T classifications. Again, we found no significant differences in the overall or disease-specific survival outcomes between white and nonwhite patients ($P = .64$ and $P = .14$, respectively).

SURVIVAL OUTCOMES AND RR BY T CLASSIFICATION

The overall survival results by T classification are shown in **Figure 2**. The overall survival of patients with MF was worse in those with a more advanced T classification. Patients with T1 disease had the most favorable overall and disease-specific survival, followed by patients with T2 disease ($P < .001$, T1 vs T2, T3, or T4; and $P < .001$, T2 vs T3 or T4). The patients with T3 and T4 (erythrodermic) disease had similar less favorable outcomes. The differences in actuarial overall and disease-specific survivals of patients with T3 and T4 diseases were not statistically significant ($P = .90$ and $P = .67$, respectively). The median survival of patients with T1 disease has not been reached, whereas the median survivals of patients with T2, T3, and T4 disease were 12.1, 3.3, and 4.0 years, respectively. The overall survival rates at 5, 10, and 20 years were 97%, 88%, and 64%, respectively, in patients with T1 disease; 72%, 55%, and 28%, respectively, in patients with T2 disease; 40%, 26%, and 11%, respectively, in patients with T3 dis-

ease; and 41%, 24%, and 7%, respectively, in patients with T4 disease. The RR for death compared with the age-, sex-, and race-matched control populations was assessed according to the patients' T classifications. They were 0.7 (95% CI, 0.4-1.0; $P = .02$) in T1, 2.3 (95% CI, 1.9-2.7; $P < .001$) in T2, 4.7 (95% CI, 3.6-5.8; $P < .001$) in T3, and 4.2 (95% CI, 3.2-5.1; $P < .001$) in T4 disease.

SURVIVAL OUTCOMES AND RR BY CLINICAL STAGE

Overall, we found significant survival differences among patients with different clinical stages, with worse survival in more advanced clinical stages (**Figure 3**). We grouped patients with stage IA, IB/IIA, IIB/III, and IV disease according to differences in overall survival outcome (stage IA vs IB/IIA, IIB/III, and IV, $P < .001$; stage IB/IIA vs IIB/III and IV, $P < .001$; stage IIB/III vs IV, $P < .001$). We found no significant overall survival differences between patients with stage IB vs IIA ($P = .71$) or stage IIB vs III ($P = .35$) disease. The median survivals of patients by clinical stage varied widely, with 12.9 years in the stage IB/IIA group, 4.0 years in the stage IIB/III group, and 1.5 years in the stage IV group. Median survival was not reached in the stage IA group. The 5- and 15-year overall survival rates were 96% and 73%, respectively, in the stage IA group; 75% and 46%, respectively,

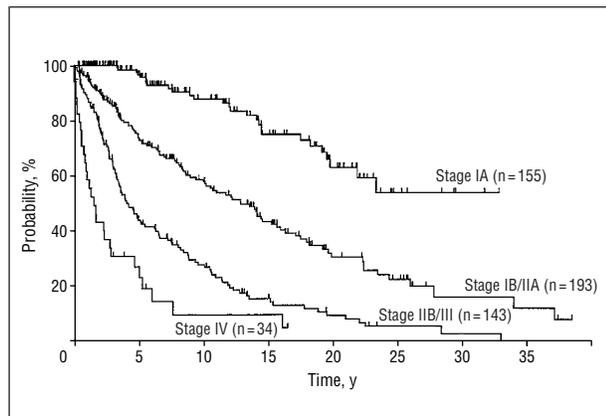


Figure 3. Actuarial overall survival of 525 patients with mycosis fungoides and Sézary syndrome according to their clinical stage at diagnosis (stages IA-IV). For stage IA vs IB/IIA disease, $P < .001$; for stage IB/IIA vs IIB/III disease, $P < .001$; and for stage IIB/III vs IV disease, $P < .001$. P values were calculated using the Gehan test.

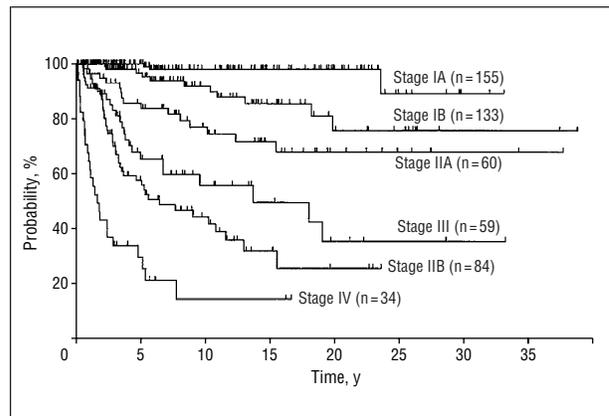


Figure 4. Actuarial disease-specific survival of 525 patients with mycosis fungoides and Sézary syndrome according to their clinical stage at diagnosis (stages IA-IV). For stage IA vs IB disease, $P = .007$; for stage IB vs IIA disease, $P = .006$; for stage IIA vs IIB disease, $P < .001$; for stage IIA vs III disease, $P = .03$; for stage IIB vs III disease, $P = .09$; and for stage IA-III vs IV disease, $P < .001$. P values were calculated using the Gehan test.

in the stage IB/IIA group; 44% and 15%, respectively, in the with stage IIB/III group; and 27% and 10%, respectively, in the stage IV group. The RR for death compared with control populations was assessed in the patients according to their clinical stage groupings. They were 0.7 (95% CI, 0.4-1.0; $P = .59$) in the stage IA group, 2.2 (95% CI, 1.8-2.6; $P < .001$) in the stage IB/IIA group, 3.9 (95% CI, 3.2-4.6; $P < .001$) in the stage IIB/III group, and 12.8 (95% CI, 8.1-17.3; $P < .001$) in the stage IV group.

The actuarial DSS curves of our 525 patients according to their clinical stages are shown in **Figure 4**. We found significant DSS outcome differences among the clinical stages, with worse survival in more advanced stages. Although the overall survivals were similar between patients with clinical stage IB vs IIA and IIB vs III disease, their DSS outcomes were significantly different (stage IB vs IIA disease, $P = .006$) or trended toward statistical significance (stage IIB vs III disease, $P = .09$). The 5- and 15-year DSS rates were 100% and 98%, respectively, in patients with stage IA disease; 95% and 85%, respectively, in those with stage IB disease; 84% and 71%, respectively, in those with stage IIA disease; 56% and 32%, respectively, in those with stage IIB disease; 65% and 49%, respectively, in those with stage III disease; and 30% and 14%, respectively, in those with stage IV disease.

SURVIVAL OUTCOMES BY N AND B CLASSIFICATIONS

The N classification of our 525 patients included 345 (66%) with N0 (clinically normal), 147 (28%) with N1 (clinically enlarged, not lymphoma), and 33 (6%) with N3 (clinically enlarged, confirmed lymphoma) disease. The distribution of T classification in patients with N1 disease was T1 in 4 patients, T2 in 56, T3 in 42, and T4 in 45. We found significant overall survival differences among these N classification groups ($P < .001$) with median survivals of 17.5 years in patients with N0, 6.5 years in those with N1, and 1.7 years in those with N3 disease. When we compared the N0 and N1 groups by T classification, we found no significant differences in overall survival (T2 N0 [n=133] vs T2 N1 [n=56], $P = .71$; T3 N0 [n=42] vs T3 N1 [n=42], $P = .11$; and T4 N0

[n=15] vs T4 N1 [n=44], $P = .37$). However, their DSS differences between N1 vs N1 groups in patients with T2, T3, and T4 disease were more significant (T2 N0 [n=133] vs T2 N1 [n=56], $P = .003$; T3 N0 [n=42] vs T3 N1 [n=42], $P = .01$; and T4 N0 [n=15] vs T4 N1 [n=44], $P = .18$).

Thirty-five patients (7%) had blood involvement (B1) at presentation as determined by morphologic evaluation of peripheral blood smears. The majority of these patients with B1 disease (n=31) had absolute Sézary cell counts of greater than 1000/mm³; 4 patients had Sézary cell counts of greater than 20% lymphocytes and less than 1000/mm³. The distribution of T classification in patients with B1 disease was T1 in 1 patient, T2 in 1, T3 in 5, and T4 in 28. The majority of patients with T4 B1 disease had N1 (n=15) or N3 (n=11) node involvement. Overall, we found a significant difference in actuarial survival between patients with B0 and B1 involvement, with median survivals of 12.3 and 3.0 years, respectively ($P < .001$). When the analysis was limited to patients with T3 and T4 disease, the survival outcome was still significantly worse in the patients with B1 vs B0 involvement, although the differences were less dramatic (median survivals of 2.9 and 4.5 years, respectively; $P = .04$).

MULTIVARIATE ANALYSIS OF CLINICAL FACTORS INFLUENCING SURVIVAL

The results of the univariate prognostic factors that were studied are summarized in **Table 4**. The prognostic factors that had a significant impact on survival were patient age, T classification, clinical stage groupings, the presence or absence of extracutaneous disease, and N and B classifications. To determine which of the univariate factors were important, independent predictors of survival, we used the Cox proportional hazards regression method.³⁰

Initial analysis entering age and T, N, and B classifications as variables demonstrated that all 4 were independently significant ($P < .001$, $P < .001$, $P < .005$, and $P < .025$, respectively) in the Cox regression model. A second analysis entering age, N and B classifications, and clinical stage groupings showed that age ($P < .001$), B classification ($P < .05$), and the clinical stage groupings ($P < .001$) were

Table 4. Univariate Factors Predictive of Survival in 525 Patients With MF and SS

Prognostic Factors	No. of Patients	Median Survival, y	5-Year Survival, %	P Value	
				OS	DSS
Age, y					
<57	261	19.7	80	<.001	<.001
≥57	264	6.5	56		
Sex					
Female	195	13.5	74	.14	.68
Male	330	10.0	65		
Race					
White	452	11.5	69	.64	.14
Nonwhite	73	10.6	65		
T classification					
T1	159	Not reached	97	<.001	<.001
T2	192	12.1	72		
T3	96	3.3	40	<.001	<.001
T4	78	4.0	41	.90	.67
Clinical stage					
IA	155	Not reached	96	<.001	<.001
IB/IIA	193	12.9	73		
IIB/III	143	4.0	44	<.001	<.001
IV	34	1.5	27	<.001	<.001
N classification					
N0	345	17.4	80	<.001	<.001
N1	147	6.5	53		
N3	33	1.7	28	<.001	<.001
B classification					
B0	490	12.3	72	<.001	<.001
B1	35	3.0	20		

Abbreviations: B, blood involvement; B0, absence of significant peripheral blood Sézary cells; B1, presence of significant peripheral blood Sézary cells; DSS, disease-specific survival; MF, mycosis fungoides; OS, overall survival; SS, Sézary syndrome.

significant independent factors. However, N classification ($P = .58$) no longer remained as a significant factor when the clinical stage groupings were entered as a covariate instead of the T classification. In the next analysis where age; T, N, and B classifications; and clinical stage groupings were entered, age ($P < .001$) and T and B classifications ($P < .025$ and $P < .025$, respectively) remained significant; however, N classification ($P = .07$) and clinical stage groupings ($P = .44$) were not significant independent factors. When the presence or absence of extracutaneous disease rather than the clinical stage grouping was entered with age and T, N, and B classifications, age ($P < .001$), T classification ($P < .001$), and the presence or absence of extracutaneous disease ($P < .05$) remained as significant independent factors. However, the N classification ($P = .23$) was no longer significant, and the B classification was of borderline significance ($P = .06$) as independent prognostic factors in the multivariate analysis.

Finally, all significant univariate factors (ie, age, T, N, and B classifications, clinical stage groupings, and the presence or absence of extracutaneous disease) were entered in the multivariate analysis. Among all these covariates, age ($P < .001$), T classification ($P < .01$), and the presence or absence of extracutaneous disease ($P < .05$) remained as significant independent prognostic factors. However, the N classification ($P = .12$) and clinical stage groupings ($P = .23$) were no longer significant factors, and the B classification was of borderline significance ($P = .06$) when the T classification and extracutaneous disease state were entered in the analysis as covariates. Thus, these varia-

tions in the significance as independent prognostic factors in the multivariate analysis depended on the combinations of covariates studied. This demonstrated the strong interdependence among the T, N, and B classifications; clinical stage; and state of extracutaneous disease. The most consistently significant independent prognostic factors were patient age, T classification, and the presence or absence of extracutaneous disease.

RISK FOR DISEASE PROGRESSION

We studied the risk for disease progression in our 525 patients. Patients were considered to experience disease progression when one of the following events occurred: progression of MF to more advanced TNM and B classifications or clinical stage or death due to MF. The date of the first evidence of progression was entered as the disease progression date for our analysis. The median follow-up durations by T classification were 7.6 years (range, 0.4-37.3 years) in those with T1; 6.4 years (0.1-38.5 years) in those with T2; 2.9 years (range, 0.1-23.4 years) in those with T3; and 3.6 years (range, 0.1-28.3 years) in those with T4 disease. The risk for disease progression by Kaplan-Meier analysis abbreviated to 20 years according to their initial T classification is shown in **Figure 5**. The risk for disease progression at 5, 10, and 20 years was 10%, 13%, and 16%, respectively, in patients with T1; 22%, 32%, and 40%, respectively, in those with T2; 56%, 72%, and 81%, respectively, in those with T3; and 48%, 57%, and 78%, respectively, in those with T4 disease. The risk for disease

progression worsened with more advanced T classification, with a greater risk in the patients with T2 compared with T1 disease ($P < .001$) and in T3 or T4 compared with T2 disease ($P < .001$). The patients with T3 and T4 disease had a similar risk for disease progression ($P = .48$). Of those patients whose disease progressed, the median time from diagnosis to disease progression by T classification was 2.1 years (range, 1.1-13.1 years) in T1, 2.1 years (range, 0.2-25.0 years) in T2, 2.0 years (range, 0.1-15.4 years) in T3, and 1.7 years (range, 0.2-17.2 years) in T4 disease.

EXTRACUTANEOUS DISEASE

Seventy-seven patients presented with or had development of extracutaneous (stage IV) disease (stage IVA, $n = 56$; stage IVB, $n = 21$). The most common visceral sites of involvement identified were the lungs, oral cavity or pharynx, and the central nervous system. At the time when extracutaneous disease was detected, no patient had T1, 11 had T2, 39 had T3, and 27 had T4 disease. Thirty-four of these initially presented with extracutaneous disease. These patients included 19 (24%) of the 78 patients with T4 disease, 12 (13%) of the 96 with T3 disease, and 3 (2%) of the 192 with T2 disease at presentation. The median survival of the 77 patients with stage IV disease was 1.1 years, and the survival was similar, regardless of the extent of their skin involvement (T2 vs T3 vs T4, $P = .69$ to $P = .88$). The actuarial survivals of patients with stages IVA and IVB disease were similar, with median survivals of 1.2 and 0.7 years, respectively ($P = .15$).

The risk for development of extracutaneous disease was analyzed separately and plotted according to the T classification at diagnosis. The risk at 5, 10, and 20 years was 1%, 2%, and 2%, respectively, in patients with T1 disease; 8%, 9%, and 9%, respectively, in those with T2 disease; 23%, 37%, and 37%, respectively, in those with T3 disease; and 9%, 9%, and 35%, respectively, in those with T4 disease. Forty-three of our 493 patients with clinical stages I to III disease at presentation had experienced disease progression to stage IV MF at the time of our analysis. Two of these patients had T1, 13 had T2, 20 had T3, and 7 had T4 disease initially. However, at the time of development of stage IV disease, none had limited (T1) skin involvement.

COMMENT

In this study, we have presented the results of a long-term, retrospective cohort study of our patients with MF and SS who underwent management at the Stanford University Cutaneous Lymphoma Clinic. During the past 40 years, we have participated in the management of MF and SS in more than 700 patients at the clinic. We specifically limited the study subjects to the 525 patients who received a diagnosis no more than 6 months before their initial evaluation at our clinic, to exclude those whose survival and treatment outcomes may not reflect our management. It is important to emphasize the potential drawbacks of any long-term retrospective study, including the present one, that spans decades and includes changes in diagnostic methods or approaches in disease management. During these years, newer techniques in molecular methods of analysis (eg, polymerase chain reaction) and

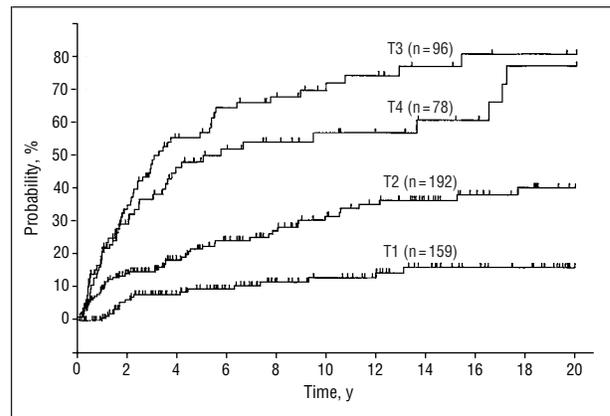


Figure 5. Risk for disease progression by Kaplan-Meier analysis for 525 patients with mycosis fungoides and Sézary syndrome according to their T classification at diagnosis. Disease progression was defined as progression to more advanced TNM and B classifications or clinical stage or death due to MF. For T1 vs T2 disease, $P < .001$; for T2 vs T3 or T4 disease, $P < .001$; and for T3 vs T4 disease, $P = .48$. *P* values were calculated using the Gehan test.

updates in antigenic characterization of malignant T cells in blood and tissue (eg, immunohistochemistry, flow cytometry) have been used for diagnosis and evaluation of disease severity.¹ Well-defined, prospective, large-scale or multicenter studies are still needed to further help identify prognostic factors and guide management decisions.

Our long-term retrospective results confirm that combined MF and SS is a very heterogeneous disease with a wide range of survival or risk for disease progression for different clinical presentations. A summary of patient clinical characteristics (Table 2) confirms many previous reports of a relative increased prevalence in white and male patients.^{4,5,7,11,13} Most of our 525 patients had limited or generalized patch and/or plaque (T1-T2) disease. None of our patients with limited skin involvement (T1) presented with extracutaneous (stage IV) disease. In support of a previous report of findings in young patients with MF,³¹ patients with T1 tended to be significantly younger than patients with T2 to T4 disease ($P < .001$), and those with T4 disease were older than those with T1 through T3 disease ($P < .005$).

More patients (57% of deaths) died of unrelated causes rather than due to MF and SS (Table 3). Deaths attributable to MF and SS occurred in 23% of our 525-patient cohort, primarily among patients who presented with more advanced skin involvement (T3-T4). Approximately half of the patients who presented with T3 or T4 disease died of their disease, in contrast to only 2% and 15% of those with T1 and T2 disease, respectively. Our patients with T1 disease accounted for the majority of the patients who were alive in remission. The patients with T4 disease had the least likelihood of enjoying sustained clinical remission, with only 3 (4%) of 78 patients alive without disease.

Age at presentation was an important demographic predictive factor in our patients in both the univariate analysis using the median age (57 years) and the multivariate analysis with age as a continuous variable. However, the predictive value of age at presentation is greatest in the earlier stages (stages I-III) and becomes less valuable in patients with extracutaneous disease (stage IV). Thus, in patients with stage IV disease, the impact of age on survival is outweighed by the overall poor survival observed in this group.

The widespread differences in survival results by type and extent of skin involvement (T classification) (Figure 2) and clinical stage (Figures 3 and 4) clearly reflect the heterogeneity of MF. As in a previous report, patients with T1 disease have an extremely favorable prognosis in which their RR for death is similar to that of their control population without MF.² In all other patients with worse T classifications, their life expectancy is less favorable than that of their matched control population. More generalized or advanced skin involvement is associated with worse prognosis. Our patients with tumor (T3) and erythrodermic (T4) skin involvement have similar less favorable outcomes. Despite their similar survival, patients with T3 and T4 disease have markedly different clinical presentations that require quite different management approaches, and thus, it is important to retain their separate designations in our T classification and overall clinical stage designation.

The patients with stage IA disease had similar life expectancy compared with their matched control population, whereas the patients who presented with extracutaneous (stage IV) disease had a 12.8-fold greater risk for death with a median survival of only 1.5 years. The DSS results of the patients by their clinical stage paralleled the overall survival outcomes. However, the DSS results of patients with stage IB (n=133) vs IIA disease (n=60) were statistically different ($P=.006$) (Figure 4). Only 4 patients with stage IIA disease had T1 skin involvement; all others had T2 skin involvement. The stage IIA group tended to include patients with a more aggressive skin involvement and generalized thicker plaques rather than generalized thin plaque and/or patch disease. The differences in DSS results of patients with stage IIB vs III disease trended toward statistical significance ($P=.09$). These different DSS outcomes of patients with stage IB vs IIA and stage IIB vs III disease further validate the usefulness of the current MF clinical staging system.²⁵

Only 35 patients (7%) presented with significant peripheral blood involvement with Sézary cells (B1) as determined by means of peripheral blood smear examination. We do not have flow cytometric or clonality results of our earlier patients, and thus our blood involvement criterion was limited to blood smear evaluation in this report. Most of our patients with B1 involvement have absolute Sézary cell counts of at least 1000/mm³, a blood involvement level currently considered a significant prognostic variable.^{15,17,32} Most patients with B1 involvement (80%) had erythrodermic disease (T4), which accounted for 36% of our patients with T4 disease at presentation. Many of our patients with B1 involvement had N3 nodal involvement, which may further account for the worse survival of patients with B1 compared with those with B0 involvement. We are currently evaluating the concordance between the Sézary cell results by means of quantitative morphologic (blood smear) assessment and flow cytometric analysis. In all cases in which the flow studies revealed significantly increased numbers of T cells with aberrant cell surface expression (CD4⁺/CD7⁻ or CD4⁺/CD26⁻), the blood smear evaluation by our veteran hematology technician also revealed increased numbers of Sézary cells (unpublished ongoing observation). However, the CD4⁺/CD7⁻ or CD4⁺/CD26⁻ population was not increased in all cases where a significant number of Sézary cells was detected by means of morphologic evaluation. We are also currently studying the levels and characteristics of Sézary

cells that may be of prognostic significance in Sézary cell count (blood smear), flow cytometric results, and molecular analysis. Scarisbrick et al¹⁷ reported that combinations of Sézary cell count (morphology) and polymerase chain reaction or Southern blotting data can separate groups of different prognostic significance. As proposed in the consensus report by the International Society for Cutaneous Lymphomas,³² the definition of significant blood involvement will need to be modified to be current with updated techniques used to assess disease in skin and other tissues. The new criteria proposed by the International Society for Cutaneous Lymphomas for significant blood involvement, including a new B2 classification that defines SS, need to be validated by a multicenter, large study. Finally, any clonal results from peripheral blood analysis should be interpreted appropriately for the possibility of detecting unrelated, benign clones.

Table 4 summarized the results of our univariate clinical factors predictive of survival. The significant prognostic factors were patient age; T (T1 vs T2 vs T3/T4 disease), N (N0 vs N1 vs N3 disease), and B classifications (B0 vs B1 involvement); clinical stage groupings (stage IA vs IB/IIA vs IIB/III vs IV); and the presence or absence of extracutaneous disease (stages I-III vs IV). **Table 5** summarizes the significant published studies of clinical prognostic factors in MF and SS involving at least 100 subjects. In these studies, patient age was generally found to be significant in the univariate analysis, but not always in the multivariate studies. The results of the SEER-based study by Weinstein and Reynes¹³ indicated that black or male patients had less favorable survival outcomes. Our results did not support an association of sex with survival, and the sample size of our black patients was too small (n=20 [4%]) to draw any significant comparative conclusions. Previous studies have also demonstrated the prognostic significance of various subsets and combinations of TNM and B classification variables, clinical stage groupings, and extracutaneous (stage IV) disease (Table 5).

Our multivariate analysis demonstrated the significant interdependence of clinical stage and the T, N, and B classification factors so that the multivariate significance depended on which covariates were entered in the analysis. When all significant univariate factors were entered in the regression model, only age at presentation, the extent and type of skin involvement (T classification), and the presence or absence of extracutaneous (stage IV) disease remained as independent predictors. Presence or absence of significant circulating Sézary cells (B classification) was of marginal independent significance. Patients' node status (N classification) and clinical stage were no longer useful as predictive factors once the information on their T classification and status of extracutaneous disease was available. Our analysis also demonstrated the strong interdependence of the T classification and the clinical stage groupings, demonstrating that they provide overlapping prognostic information.

The results of disease progression largely depend on the variables used to define progressive disease in the study cohort. We selected the events of progression to be the state at which there is an association with worse outcome, ie, more advanced TNM and B classifications or clinical stage, or death due to MF and SS. The risk for disease progression as defined in our study is greater among patients with a higher

Table 5. Summary of Published Clinical Significant Prognostic Factors in Large Cohorts of MF and SS

Prognostic Factors	No. of Patients	Significance		Source
		Univariate	Multivariate	
Patient age, y				
<40 vs 40-60 vs >60	347	+	-	Green et al ⁵
<50 vs >50	152	+	-	Sausville et al ⁷
Older age	1479	+	+	Weinstock and Reynes ¹³
<60 vs ≥60	115	+	+	Diamandidou et al ¹⁰
Older age	309	+	-	van Doorn et al ¹¹
<58 vs ≥58, T2 only	176	+	NP	Kim et al ³
<65 vs ≥65, T4 only	106	+	+	Kim et al ¹²
Race, African American vs other	1479	+	+	Weinstock and Reynes ¹³
Sex, M vs F	1479	+	+	Weinstock and Reynes ¹³
Marital status, married vs unmarried	1479	+	+	Weinstock and Reynes ¹³
TNM and B classifications				
T (T1 vs T2 vs T3 vs T4)	340	+	NP	Green et al, ⁵ Lamburg et al ⁶
T (T1 or T2 vs T3 or T4)	152	+	+	Sausville et al ⁷
T (T1 vs T2 vs T3 or T4)	556	+	NP	Kim et al ²
T (T1 vs T2 vs T3 or T4, stages I-III)	543	+	NP	Kim and Hoppe ¹
T (T1 or T2 vs T3, stages I-III)	309	+	+	van Doorn et al ¹¹
T (T1 or T2 or T4 vs T3)	115	+	+	Diamandidou et al ¹⁰
T (T1 vs T2 vs T3 or T4)	489	+	NP	Zackheim et al ⁴
T/N (No. of enlarged lymph nodes)	347	+	+	Green et al, ⁵ Lamburg et al ⁶
N (palpable vs nonpalpable)	152	+	Borderline	Sausville et al ⁷
N (LN1-2 vs LN3 vs LN4)	152	+	-	Sausville et al ⁷
N (N0 vs N1 vs N3)	309	+	+	van Doorn et al ¹¹
N (N0 vs N1 or N3)	115	+	-	Diamandidou et al ¹⁰
N (N0 vs N1-3)	489	+	NP	Zackheim et al ⁴
M (M0 vs M1)	152	+	+	Sausville et al ⁷
M (bone marrow only, M0 vs M1)	115	+	-	Diamandidou et al ¹⁰
B (B0 vs B1)	152	+	-	Sausville et al ⁷
Clinical stage				
I-IIA vs IIB-IV	115	+	-	Diamandidou et al ¹⁰
I-IIA or III vs IIB or IV	115	+	+	Diamandidou et al ¹⁰
IA-IIA vs IIB-IVA vs IVB	152	+	NP	Sausville et al ⁷
IA vs IB/IIA vs IIB vs III	600	+	NP	Kim and Hoppe ¹
III vs IV, T4 only	106	+	+	Kim et al ¹²
I-III vs IV	600	+	NP	Kim and Hoppe ¹
I-III vs IV	152	+	+	Sausville et al ⁷
I-III vs IV	309	+	+	van Doorn et al ¹¹

Abbreviations: B, blood involvement; B0, absence of significant peripheral blood Sézary cells; B1, presence of significant peripheral blood Sézary cells; MF, mycosis fungoides; NP, not performed; SS, Sézary syndrome; +, positive; -, negative.

T classification, but the risk is similar for patients with T3 or T4 disease (Figure 5). Our results of disease progression are comparable to those reported by the Dutch group of 309 patients with MF.¹¹ However, their analysis did not define disease progression in those patients with progression from T1 to T2, T1 or T2 to T4, N0 to N1, or B0 to B1 disease.

The risk for development of stage IV disease in patients who presented with stages I through III disease was again greater in patients with more advanced skin involvement (T classification). A significant proportion of patients with T3 (13%) or T4 (24%) disease initially presented with stage IV disease and was excluded in this analysis. This may account for the similar risk for progression to stage IV disease in patients with T2 and T4 disease up to approximately 15 years, despite a greater overall risk for extracutaneous disease in patients with T4 disease. The majority of patients with progression to stage IV disease, progression occurred within the first 5 years. In 2 patients with initial T1 disease, progression to development of extracutaneous disease occurred; both patients were non-

compliant with their prescribed therapy and failed to return for scheduled follow-up visits. These results of risk for progression to extracutaneous disease are consistent with a previous report from our group of Kaplan-Meier risk analysis of 434 patients with MF.¹⁴

The patients with extracutaneous (stage IV) disease as a group had a poor survival outcome regardless of whether they presented with it (n=34) or it developed at a later time (n=43). The unfavorable survival was similar, regardless of the type of skin involvement (T2-T4). None of these patients with stage IV disease had limited skin involvement (T1) at the time their extracutaneous disease was detected. This supports the previous report that the risk for development of extracutaneous disease is minimized by keeping their skin involvement to a limited state (T1 or less).¹⁴

Standard staging evaluation for patients with a diagnosis of MF includes a comprehensive physical examination with careful examination of the skin and lymph nodes, a complete blood cell count with Sézary cell studies, screening chemistries (including lactate dehydrogenase levels), and

chest x-ray. Based on our results that patients with T1 or T2 skin involvement are unlikely to present with extracutaneous disease at diagnosis, additional imaging studies (computed tomography or magnetic resonance imaging) are not recommended unless the patient has lymphadenopathy. All 3 patients with T2 skin involvement and stage IVA disease at presentation had clinically suspicious lymphadenopathy that warranted further evaluation. Since patients with T3 or T4 disease are at greater risk for extracutaneous involvement, further imaging studies should be considered. Lymph node biopsies should be obtained if lymphadenopathy is present, because the presence of lymph node involvement affects the stage, prognosis, and management. Suspected sites of visceral involvement must be confirmed by appropriate imaging studies and histological evaluation when possible. Significant bone marrow involvement is most often present in patients who meet the clinical criteria for SS.³³ Bone marrow biopsy is not routinely used as part of the initial staging procedure for patients with MF and SS. The utility of nuclear medicine scans (eg, positron emission tomography imaging) for evaluation of MF and SS has not been established.

CONCLUSIONS

The long-term survival results in our 525 patients with MF and SS are varied, with worse outcomes in patients with more advanced T classification and clinical stage. In general, our observations support the usefulness of the current TNM and B staging systems for MF and SS. Although the overall survivals may be similar between patients with stages IB vs IIA and stages IIB vs III disease, their disease-specific survival or clinical and biological differences warrant their separate clinical stage designation. The most significant univariate clinical prognostic factors are patient age at presentation; T, N, and B classifications; overall clinical stage; and the presence or absence of extracutaneous disease. However, the prognostic power of their B and N classifications and their clinical stage as an independent factor becomes less significant when their T classification and status of extracutaneous disease are known. The risk for disease progression correlates with the severity of the initial skin presentation.

Accepted for publication December 26, 2002.

This study was supported in part by the Stanford Cutaneous Lymphoma Research Fund, Stanford, Calif.

This study was presented at the 63rd Annual Meeting of the Society of Investigative Dermatology, Los Angeles, Calif, May 17, 2002.

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REFERENCES

- Kim YH, Hoppe RT. Mycosis fungoides and the Sézary syndrome. *Semin Oncol*. 1999;26:276-289.
- Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RH. Clinical stage IA (limited patch and plaque) mycosis fungoides. *Arch Dermatol*. 1996;132:1309-1313.
- Kim YH, Chow S, Varghese A, Hoppe RT. Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides. *Arch Dermatol*. 1999;135:26-32.
- Zackheim HS, Amin S, Kashani-Sabet M, McMillan A. Prognosis in cutaneous T-cell lymphoma by skin stage. *J Am Acad Dermatol*. 1999;40:418-425.
- Green SB, Byar DP, Lamberg SL. Prognostic variables in mycosis fungoides. *Cancer*. 1981;47:2671-2677.
- Lamberg SI, Green SB, Byar DP, et al. Clinical staging for cutaneous T-cell lymphoma. *Ann Intern Med*. 1984;100:187-192.
- Sausville EA, Eddy JL, Makuch RW, et al. Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome: definition of three distinctive prognostic groups. *Ann Intern Med*. 1988;109:372-382.
- Marti RM, Estrach T, Reverter JC, Mascaro JM. Prognostic clinicopathologic factors in cutaneous T-cell lymphoma. *Arch Dermatol*. 1991;127:1511-1516.
- Vonderheid EC, Diamond LW, van Vloten WA, et al. Lymph node classification systems in cutaneous T-cell lymphoma. *Cancer*. 1994;73:207-218.
- Diamandidou E, Colome M, Fayad L, Duvic M, Kurzrock R. Prognostic factor analysis in mycosis fungoides/Sézary syndrome. *J Am Acad Dermatol*. 1999;40:914-924.
- van Doorn R, van Haselen CW, van Voorst Vader PC, et al. Mycosis fungoides. *Arch Dermatol*. 2000;136:504-510.
- Kim YH, Bishop K, Varghese A, Hoppe RT. Prognostic factors in erythrodermic mycosis fungoides and the Sézary syndrome. *Arch Dermatol*. 1995;131:1003-1008.
- Weinstock MA, Reynes JF. The changing survival of patients with mycosis fungoides: a population-based assessment of trends in the United States. *Cancer*. 1999;85:208-212.
- de Coninck EC, Kim YH, Varghese A, Hoppe RT. Clinical characteristics and outcome of patients with extracutaneous mycosis fungoides. *J Clin Oncol*. 2001;19:779-784.
- Bernengo MG, Quaglino P, Novelli M, et al. Prognostic factors in Sézary syndrome: a multivariate analysis of clinical, haematological and immunological features. *Ann Oncol*. 1998;9:857-863.
- Fraser-Andrews EA, Woolford AJ, Russell-Jones R, Seed PT, Whittaker SJ. Detection of a peripheral blood T cell clone is an independent prognostic marker in mycosis fungoides. *J Invest Dermatol*. 2000;114:117-121.
- Scarbrick JJ, Whittaker S, Evans AV, et al. Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. *Blood*. 2001;97:624-630.
- Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sézary syndrome. *Blood*. 1998;92:1150-1159.
- Vergier B, de Muret A, Beylot-Barry M, et al, for the French Study Group of Cutaneous Lymphomas. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. *Blood*. 2000;95:2212-2218.
- Wasik MA, Vonderheid EC, Bigler RD, et al. Increased serum concentration of the soluble interleukin-2 receptor in cutaneous T-cell lymphoma: clinical and prognostic implications. *Arch Dermatol*. 1996;132:42-47.
- Hoppe RT, Madeiros LJ, Warnke RA, Wood GS. CD8⁺ tumor-infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides. *J Am Acad Dermatol*. 1995;32:448-453.
- Smoller BR, Detwiler SP, Kohler S, Hoppe RT, Kim YH. Role of histology in providing prognostic information in mycosis fungoides. *J Cutan Pathol*. 1998;25:311-315.
- Schmid MH, Bird P, Dummer R, Kempf W, Burg G. Tumor burden index as a prognostic tool for cutaneous T-cell lymphoma: a new concept. *Arch Dermatol*. 1999;135:1204-1208.
- Jaffe E, Harris N, Stein H, Vardiman JE. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of Hematopoietic and Lymphoid Tissues*. Lyons, France: IARC Press; 2001.
- Bunn PJ, Lamberg S. Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. *Cancer Treat Rep*. 1979;63:725-728.
- Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:475-480.
- Gehan E. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika*. 1965;52:203-233.
- Cox D, Snell E. *Analysis of Binary Data*. 2nd ed. New York, NY: Chapman & Hall; 1989.
- US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Health Statistics. *US Decennial Life Tables 1979 Through 1981*. Vol 1, No. 2. Hyattsville, Md: US Dept Health and Human Services; 1988:12-15. DHHS publication (PHS)88-1150-2.
- Cox D. Regression models and life-tables. *J R Stat Soc B*. 1972;34:187-220.
- Crowley JT, Nikko A, Varghese A, Hoppe RT, Kim YH. Mycosis fungoides in young patients. *J Am Acad Dermatol*. 1998;38:696-701.
- Vonderheid EC, Bernengo MG, Burg G, et al. Update on erythrodermic cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2002;46:95-106.
- Salhany KE, Greer JP, Cousar JB, Collins RD. Marrow involvement in cutaneous T-cell lymphoma. *Am J Clin Pathol*. 1989;92:747-754.