Time course, clinical pathways, and long-term hazards risk trends of disease progression in patients with classic mycosis fungoides: A

Original Article

Time Course, Clinical Pathways, and Long-Term Hazards Risk Trends of Disease Progression in Patients With Classic Mycosis Fungoides

A Multicenter, Retrospective Follow-Up Study From the Italian Group of Cutaneous Lymphomas

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BACKGROUND: Mycosis fungoides (MF) is an indolent primary cutaneous T-cell lymphoma. To the authors' knowledge, no data currently are available regarding the evolution over time of the risk of developing specific pathways of disease progression. **METHODS:** This retrospective study analyzed 1422 patients with MF who were diagnosed and followed from 1975 through 2010 in 27 Italian Study Group for Cutaneous Lymphoma centers. The primary objectives were to ascertain the time course, pathways, and hazards risk trends of cutaneous/extracutaneous disease progression; to evaluate whether different tumor-lymph node-metastasis-blood (TNMB) stages have different pathways of disease progression; and to analyze differences between tumor-stage and erythrodermic MF with regard to clinical onset, disease evolution, and prognosis. The secondary objective was to provide a further validation for the revised International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (ISCL/EORTC) classification. **RESULTS:** The median follow-up was 14.5 years; stage progression occurred in 29.7% of patients and blood involvement was the most frequent extracutaneous site of disease progression. Patients with stage IA to stage IB disease demonstrated a steady low annual incidence of disease progression to tumor-stage (1%-2%); patients with stage IIA disease had a higher risk within the first years (up to 9.4%). Erythroderma evolved with a significantly higher frequency from patches/plaques (13.9%/28.2%) than tumors ($P = .028$ and $P = .013$, respectively). Hazards rates of extracutaneous involvement were low ($< 1\%$). The T-score was found to be associated with extracutaneous involvement site, tumor-stage disease with lymph node/visceral lesions, and erythroderma with blood involvement. TNMB classification and stage progression resulted as independent

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prognostic variables being detected on multivariate analysis; the type of extracutaneous involvement was found to affect survival . **CONCLUSIONS:** The data from the current study support the need for a stage-tailored follow-up, suggest that the classification of tumor-stage disease at a stage below erythroderma could be modified, and offer a further validation for the revised TNMB classification. ***Cancer*** **2012;000:000–000.** © *2012 American Cancer Society.*

KEYWORDS: mycosis fungoides, cutaneous T-cell lymphoma, prognosis, tumor-lymph node-metastasis-blood (TNMB), classification, erythroderma, tumor-stage, multivariate analysis.

INTRODUCTION

Mycosis fungoides (MF) is an indolent, primary, cutaneous T-cell lymphoma characterized by a proliferation of small to medium-sized T lymphocytes with cerebriform nuclei.[1-3] It constitutes the most common cutaneous T-cell lymphoma (53.7%[4] to 72% of cases[5]), with an incidence of 4.1 cases per 1 million.[4] Clinical features are represented by long-standing, scaly, patch lesions preferentially involving the buttocks and body areas infrequently exposed to sunlight ("bathing trunk") and by a slow evolution over years from patches to plaques and eventually tumors or erythroderma.[1-3,6-8] Lymph node and visceral involvement, as well as large cell transformation,[9-11] usually occur in the late stages of the disease; moreover, patients with MF can develop typical manifestations of Sezary syndrome (SS),[1-3,12] so-called "secondary" SS.[13] The prognostic relevance of the extent of skin involvement and extracutaneous localizations has been known since the 1970s, when the Mycosis Fungoides Cooperative Group classification was developed.[7,14] The revision by the International Society for Cutaneous Lymphoma (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC)[6] brought significant changes with respect to the previous classification,[7] among them the prognostic relevance of the B (blood) score. Indeed, a series of studies have demonstrated that a B2 rating,[15] as well as a hematologic stage of ≥ 3 according to the suggested British classification,[16,17] are associated with a poor prognosis.

However, the rarity of the disease has impaired the collection of numerically representative patient series.[18-25] To date, Kim et al[19] and Zackheim et al[20] have collected data regarding 525 and 489 patients, respectively, with MF. What to our knowledge is the largest study to date was recently conducted on an impressive single-center cohort of 1502 patients with MF/SS by Agar et al in the United Kingdom.[18] Multivariate analyses demonstrated that advanced T-score, peripheral blood clonality, elevated lactate dehydrogenase, and folliculotropic MF were independent prognostic predictors of poor survival and an increased risk of disease progression; large-cell transformation and tumor distribution (solitary, regional, and disseminated) were associated with an increased risk of disease progressions; and TNMB stage, age, male gender, and a diagnosis of poikilodermatous MF were found to be significant for overall survival.

A number of clinical questions still remain. Even if it is generally accepted that MF evolves from patches to plaques, nodules, and erythroderma, to the best of our knowledge there are no data reported in the largest series in the literature regarding the evolution of cutaneous lesions and the pathways leading to advanced stage disease and extracutaneous involvement. Second, the percentage of stage progression from early phase disease ranges widely from 9% to 34%.[18-25] To the best of our knowledge, only 3 studies to date have reported disease progression risks according to the clinical stage[18,19,22]; no data currently are available concerning the evolution of the risk of developing specific pathways of disease progression (such as tumor-stage, erythroderma, or blood/lymph node/visceral involvement). Finally, the prognostic differences between patients with tumor-stage and those with erythroderma are still controversial: some articles have reported a similar prognosis,[18,20] whereas others have found a survival advantage for erythrodermic[23] or tumor-stage patients.[21]

Therefore, we decided to analyze the course of MF, taking into consideration not only the clinical staging at diagnosis but also the modifications of the cutaneous/extracutaneous pattern of involvement as sequentially observable during follow-up to identify the modalities of disease progression rather than only the overall percentage of patients in whom the disease progressed. A multicenter, retrospective study was therefore designed to collect MF cases diagnosed and followed between 1975 and 2010 in dermatologic and hematologic institutions belonging to the Italian Group of Cutaneous Lymphomas (Gruppo Italiano Linfomi Cutanei [GILC]). The aims were to ascertain the time course and pathways of cutaneous and extracutaneous disease progression and the trends of associated hazards rates over time; to evaluate whether different TNMB stages of disease have not only different risks of disease progression but also different pathways of disease progression; and to analyze the differences between tumor-stage and erythrodermic MF in terms of clinical onset, pathways of disease evolution, and prognosis. A

Table 1. Therapeutic Approaches On The Basis of Clinical Stage of Disease

Approach	Stage I	Stage II	Stage III	Stage IV
"Wait and see"	13.8%	—	—	—
Topical steroids	16.7%	3.3%	9.3%	—
Phototherapy alone	43.2%	24.2%	9.2%	2.6%
Phototherapy and interferon	9.7%	3.3%	2.1%	—
Phototherapy and retinoids	0.9%	3.3%	2.8%	3.1%
Acitretin	2.5%	2.6%	—	—
Bexarotene	0.2%	4.4%	9.2%	4.2%
Interferon	8.9%	12.1%	23.4%	10%
Local radiotherapy	2.3%	16.5%	2.1%	6.7%
Total-skin electron beam therapy	0.1%	1.8%	—	3.3%
Monochemotherapy[a]	1.7%	15.7%	22.0%	30.0%
Extracorporeal photochemotherapy	—	7.7%	13.3%	16.7%
Polichemotherapy[b]	—	5.1%	6.4%	23.3%

[a] Includes methotrexate, fludarabine, gemcitabine, and liposomal pegylated doxorubicin.
[b] CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens were administered to the majority of patients.

secondary objective was to provide further clinical validation for the recently revised ISCL/EORTC classification.

MATERIALS AND METHODS

Patient Selection

A retrospective review of clinical data from patients with MF collected from 1975 to 2010 in 27 GILC referral centers was performed. Inclusion criteria were: 1) a pathologic diagnosis of MF; 2) complete clinical information and imaging obtained at the time of the initial diagnosis (chest x-rays, abdominal ultrasound, computed tomography, or positron emission tomography); and 3) clinical and radiological follow-up of at least 1 year.

A diagnosis of MF was confirmed according to ISCL/EORTC criteria[2,3] and, if necessary, based on the proposed algorithm for early phase disease.[26] All patients were reclassified according to the new ISCL/EORTC classification.[6,27] Patients with evidence of cutaneous tumor lesions at the time of first diagnosis were included only if they also presented with patches and/or plaques. MF variants (folliculotropic, pagetoid reticulosis, and granulomatous slack skin) were excluded because of their different prognosis[3] as well as patients with SS at the time of first diagnosis. The development of SS (secondary SS[13]) during follow-up was defined in the presence of erythroderma, palpable adenopathies, and peripheral blood involvement according to ISCL recommendations.[3,6,15] Transformation into high-grade lymphoma was defined based on the presence of $>$ 25% of large cells in skin lesions.[6,9-11] The pathologic diagnosis was made on the basis of the (dermato)pathologist report; no review of biopsy specimens was performed.

Cutaneous disease progression was based on hospital reports and clinical photographs were reviewed whenever available. Imaging procedures were comprised of chest x-rays and abdominal ultrasound for patients with T1 to T2 disease, and computed tomography scans were performed for patients with T3 to T4 disease. All the patients included in the current study underwent imaging procedures at the time of diagnosis and at least once yearly during follow-up. Positron emission tomography was performed since 2002 in selected patients with T3 or T4 disease .

Lymph node/visceral involvement was defined by pathological confirmation. Peripheral blood involvement was defined by at least 1 of the following criteria[15]: 1) absolute circulating Sezary cell counts of $\geq 1000/mm^3$; 2) a CD4/CD8 ratio of $\geq$ 10; 3) increased lymphocyte counts with evidence of a T-cell clone in the peripheral blood by polymerase chain reaction; 4) a circulating CD4+CD7- value of $\geq$ 40%; 5) aberrant expression of T-cell markers; and 6) a chromosomally abnormal T-cell clone. Disease progression was defined as a change in TNMB stage with respect to initial diagnosis.

Table 1 summarizes the therapeutic approaches according to clinical stage of disease. Phototherapy was the mostly used treatment in patients with stage I and stage II disease. Interferon, local radiotherapy, and monochemotherapy were also administered in patients with stage II disease. In those with stage III disease, interferon was used in 23.4% and monochemotherapy in 22% of patients. Extracorporeal photochemotherapy was performed in 13.3% of patients with stage III disease and 16.7% of patients with stage IV disease. Monochemotherapy or polychemotherapy were the most frequent treatments for patients with stage IV disease.

Statistical Analysis

Data retrieved for each patient were: gender, age at diagnosis, time elapsed between the onset of cutaneous lesions

Table 2. Disease Stage Progression According to the Initial Stage of Disease at Diagnosis[a]

Maximum stage / Stage at diagnosis	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB	Disease Stage Progression
IA (n=552)	412 (74.6%)	40 (7.2%)	20 (3.6%)	37 (6.7%)	16 (2.9%)	1 (0.2%)	12 (2.2%)	5 (0.9%)	9 (1.6%)	140 (25.4%)
IB (n=556)		396 (71.2%)	24 (4.3%)	63 (11.3%)	29 (5.2%)	7 (1.3%)	14 (2.5%)	12 (2.2%)	11 (2.0%)	160 (28.8%)
IIA (n=122)			73 (59.8%)	12 (9.8%)	12 (9.8%)	2 (1.6%)	9 (7.4%)	11 (9.0%)	3 (2.5%)	49 (40.2%)
IIB (n=78)				44 (56.4%)	6 (7.7%)	0	10 (12.8%)	10 (12.8%)	8 (10.2%)	34 (43.6%)
IIIA (n=82)					50 (61.0%)	7 (8.5%)	15 (18.3%)	7 (8.5%)	3 (3.7%)	32 (39.0%)
IIIB (n=11)						5 (45.5%)	4 (36.4%)	2 (18.2%)	0	6 (54.5%)
IVA1 (n=1)							1	0	0	–
IVA2 (n=9)								8 (88.9%)	1 (11.1%)	1
IVB (n=1)									1	–

[a] The number reported is the number of patients (percentages set in parentheses were calculated based on the total number of patients for each stage of disease). Gray-shaded cells represent patients who maintained the stage of disease noted at the time of the initial diagnosis to the end of the follow-up period.

and diagnosis, T-score and TNMB staging at the time of the initial diagnosis according to the ISCL/EORTC, disease evolution over time (cutaneous and/or extracutaneous disease progression, large cell lymphoma transformation, development of SS), and maximum TNMB stage reached during follow-up.

Nonparametric tests were applied to analyze the differences in sample distribution. The Mann-Whitney *U* test was used to evaluate the differences between 2 different groups of patients at a set interval, and the Fisher exact probability test was used for cross-table comparisons.

The hazard functions were used to evaluate the trends in the risk of disease progression from early (stage IA/IB/IIA) to advanced (stage IIB/III/IV) phase disease over time. The hazard of progression of advanced phase disease was defined as the probability per time unit that a patient with early phase disease at the beginning of the respective interval will progress to advanced phase disease during that interval. It was computed as the number of advanced phase disease progressions within the respective time interval divided by the number of patients with early phase disease entering the same time interval. The HRs were calculated yearly, up to 5 years from the time of initial diagnosis and then at the 10th and 15th years. The hazards differences were analyzed using the Cochran test for linear trend.[28]

The primary endpoint for multivariate analysis was overall survival (OS). OS was established from the time of diagnosis until death, counting all deaths as events. Life-table estimates of survival were derived by the Kaplan-Meier method and compared statistically using the Mantel stratified log-rank test.[29] Multivariate OS analysis, stratified for patient age at the time of first diagnosis, was performed using the Cox proportional hazards regression model with a stepwise selection of the significant variables.[30] Variables included were gender, time interval between the onset of cutaneous lesions and diagnosis, TNMB stage at the time of initial diagnosis, stage progression during follow-up, transformation to high-grade lymphoma, and the development of SS during follow-up. The variable "time interval between the onset of cutaneous lesions and diagnosis" was continuous whereas the others were categorical. The variables "stage progression," "transformation to high-grade lymphoma," and "development of SS" were included as time-dependent covariates. No differences in OS were noted according to whether the date of diagnosis was before or after 1995 and based on center accrual number (> 50 patients or < 50 patients).

RESULTS

Clinical Data at the Time of Diagnosis

A total of 1422 patients were consistent with the inclusion criteria. Demographic features demonstrated a male prevalence (male/female ratio of 1.72) and a median age at first diagnosis of 59 years (range, 8 years-97 years). The median age of the patients diagnosed with T4 disease (67 years; 25th-75th percentile: 54 years-73 years) was significantly higher than that of others (59 years; 25th-75th percentile: 45 years-68 years) ($P < .0001$, Mann-Whitney *U* test). Male prevalence within those patients diagnosed with T4 disease (73.7%) was significantly higher than that of other stages (58.2%) ($P = .027$, Fisher exact test).

The median time from the onset of cutaneous lesions and diagnosis was 2 years. At the time of diagnosis, the majority of patients (77.9%) had stage I disease (stage IA in 38.8% and stage IB in 39.1% of patients). Stage IIB disease was diagnosed in 5.5% of patients, and stage III in 6.6%. Extracutaneous involvement was documented at the time of first diagnosis in only 0.8% of patients. With regard to the T-score at the time of diagnosis, nearly one-half of the patients (47.7%) had patches and/or plaques on $> 10\%$ of their body surface; patches/plaques on $< 10\%$ of the body surface were found in 38.9% of patients, whereas a minority of patients were found to have tumor lesions or erythroderma.

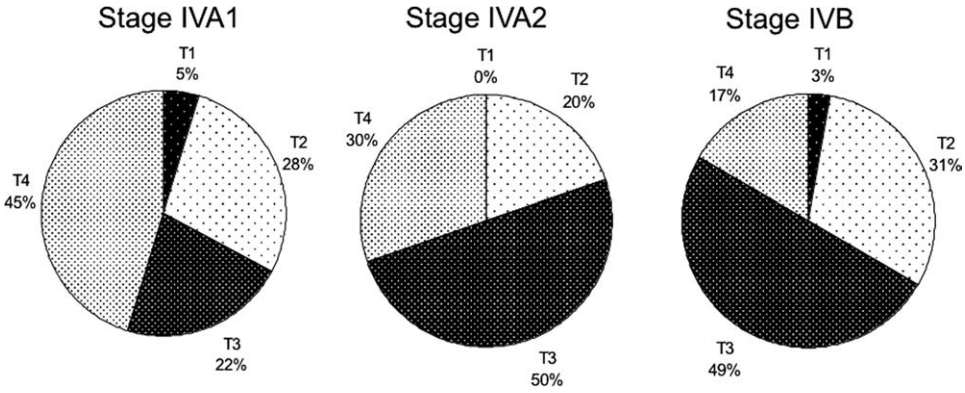

Figure 1. Distribution of cutaneous T scores at the time of extracutaneous involvement is shown.

Incidences of Stage Progression and Maximum Follow-Up Stage

The median follow-up was 14.5 years (range, 1 year-35 years).

A stage progression occurred in 422 patients (29.7%), with a significantly higher incidence for stage II compared with stage I disease ($P = .001$, Fisher exact test). Table 2 summarizes the disease evolution according to the initial stage in terms of maximum stage reached during follow-up. Tumor-stage disease represented the maximum stage in 6.7% to 11.3% of patients with stage IA/IB/IIA disease at the time of initial diagnosis, whereas erythroderma was less frequent. A small percentage of patients (3.7%) developed erythroderma and blood involvement, fulfilling the criteria for secondary SS.[15] High-grade lymphoma transformation was noted in 3% of patients. The cumulative percentage of progression to advanced stage disease (stage IIB/III/IV) in patients diagnosed with early phase MF (stage IA/IB/IIA) was 21.5%, ranging from 14.5% for stage IA to 40.1% for stage IIA disease. The cumulative incidence of stage IV as the maximum disease stage reached during follow-up in patients with stage IA/IB and IIA disease at the time of the initial diagnosis ranged from 2.2% to 7.4% for stage IVA1 disease, from 0.9% to 9% for stage IVA2 disease, and only up to 2.5% for stage IVB disease.

Significant differences were found with regard to the distribution of the maximum stage of disease according to the initial stage at diagnosis. Patients with stages IB and IIA disease as their maximum stage demonstrated a similar incidence of tumor lesions, whereas patients with stage IIA disease had a significantly higher percentage of lymph node involvement ($P = .001$). Patients with stages IIA and IIB disease shared a similar incidence of stage progression; however, those with stage IIB disease demonstrated a higher risk of extracutaneous involvement and a lower incidence of erythroderma progression ($P = .001$). Patients with stage III disease had a higher incidence of hematological involvement and a lower risk of visceral involvement than patients with

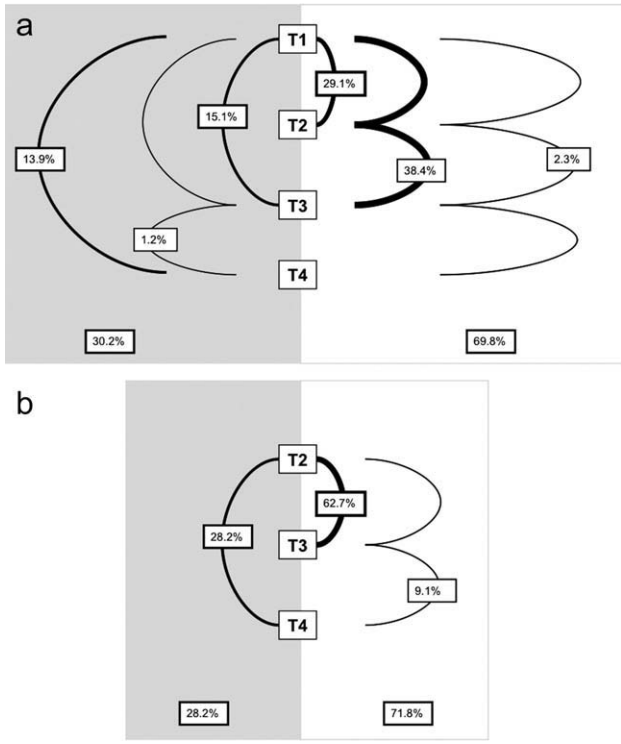

Figure 2. T score evolution of patients with (a) T1 lesions and (b) T2 lesions at the time of initial diagnosis is shown. The number represents the percentage of patients who developed disease progression calculated based on the total number of patients whose disease progressed from either T1 or T2. Gray-shaded areas at the left of each figure include those patients whose cutaneous disease evolution spared ≥ 1 consecutive stages. The thickness of each line is proportional to the number of patients who developed disease progression after this specific evolution.

Table 3. Annual Hazard of Progression to Different Manifestations of Advanced Phase Disease According to the Initial Early Phase Diagnosis

	First Year	Third Year	Fifth Year	10th Year	15th Year	
IA	2.0%	1.4%	1.1%	1.9%	1.9%	To stage IIB
IB	1.8%	2.7%	1.8%	1.8%	1.2%	
IIA	9.4%	6.1%	1.1%	1.3%	0.9%	
All	2.6%	2.7%	1.5%	1.0%	1.0%	
IA	1.2%	0.6%	0.5%	0.5%	0.4%	To stage III
IB	0.6%	1.2%	0.3%	0.6%	0.5%	
IIA	6.3%	3.6%	1.4%	1.1%	0.4%	
All	1.4%	1.1%	0.4%	0.4%	0.5%	
IA	0	0.5%	0.4%	0	0	To stage IVA1
IB	0.9%	0.7%	0.3%	0.5%	0	
IIA	0.8%	1.3%	0.6%	0	0	
All	0.5%	0.5%	0.1%	0.3%	0	
IA	0.2%	0.2%	0.2%	0.4%	0	To stage IVA2
IB	0.3%	0.4%	1.0%	0.9%	1.0%	
IIA	0.8%	0.4%	1.0%	0.9%	1.1%	
All	0.5%	0.4%	0.6%	0.5%	0.7%	
IA	0	0	0.3%	0.6%	0	To stage IVB
IB	0.2%	0	0.8%	0.6%	0	
IIA	0.8%	1.0%	0.7%	0	0	
All	0.2%	0.3%	0.5%	0.3%	0	

stage IIB disease ($P = .05$). These figures were confirmed by the distribution of T-score at the time of extracutaneous involvement (Fig. 1). Stage IVA1 disease was found to be significantly associated with erythroderma (45%; $P = .03$), whereas lymph node and visceral involvement were found to be significantly associated with the presence of tumor lesions (50% and 49%, respectively) ($P = .002$).

Pathways of Cutaneous Disease Progression

The evolution of cutaneous disease is shown in Figures 2a (T1 patients at the time of initial diagnosis) and 2b (T2 patients). The most frequent pattern for patients with T1 disease was the evolution to T2 and T3 disease (38.4% of patients with T1 disease progressed); similarly, the most common pathway of cutaneous evolution for patients with T2 disease was T3 progression (62.7%). For both T1 and T2 patients, approximately 30% of patients (30.2% for those with T1 and 28.2% for those with T2 disease) had a cutaneous disease evolution sparing ≥ 1 consecutive stages. In particular, T4 disease evolved with a significantly higher frequency from either T1 or T2 disease (13.9% and 28.2%, respectively) than from T3 disease ($P = .028$ and $P = .013$, respectively).

Time Course of Cutaneous and Extracutaneous Disease Progression

The hazards rate of progression to advanced disease are shown in Table 3.

The hazards rate of disease progression to stage IIB during the first year after diagnosis was significantly higher in patients with stage IIA disease (9.4%) compared with those with stage IA (2%) and IB (1.8%) disease ($P = .0001$). Thereafter, patients with stage IA/IB disease demonstrated a steady annual incidence of progression to stage IIB disease (approximately 1% and 2%, respectively), which was maintained until the 15th year; conversely, the incidence of progression to stage IIB for patients with stage IIA disease decreased significantly during the first 5 years ($P = .031$, Cochran test for linear trend), thereafter reaching steady values similar to those for stage IA and stage IB disease. A similar behavior was demonstrated for stage III progression, even if the hazards values were lower than for stage IIB disease. Patients with stage IIA disease demonstrated significantly higher values since the first year after diagnosis (6.3%; $P = .002$ vs stage IA/IB disease), and thereafter showed a progressive reduction; conversely, patients with stage IA and stage IB disease presented with steady values during follow-up. The hazards rates for extracutaneous involvement were low ($< 1\%$) and both stage IA/IB and stage IIA patients maintained steady values during follow-up. Patients with stage IIA disease demonstrated significantly higher hazards rates during the first year after diagnosis ($P < .001$) for blood/lymph node and visceral involvement.

OS and Validation of the Revised EORTC/ISCL Staging System

OS according to the stage of disease at the time of the initial diagnosis is shown in Figure 3a. The 5-year and 10-

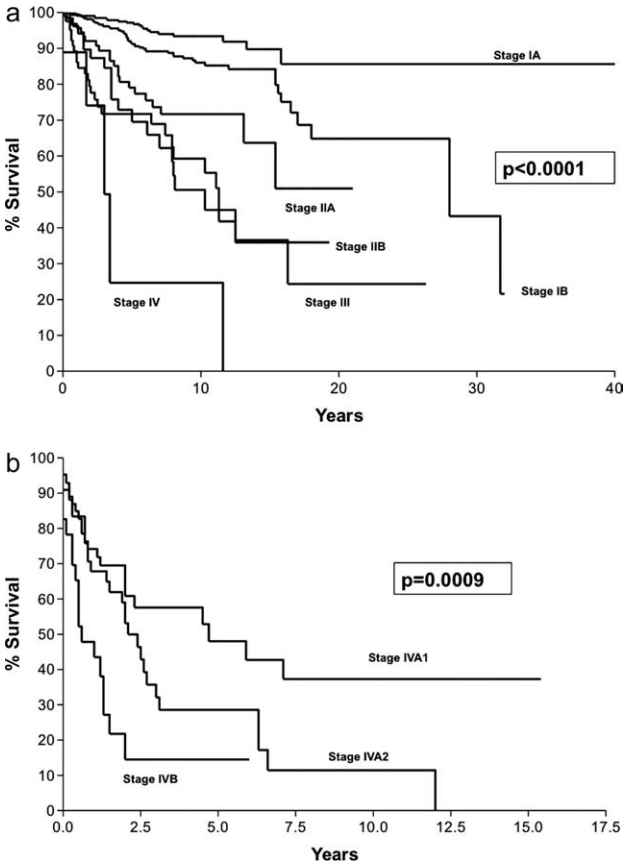

Figure 3. (a) Time-to-disease progression (TTP) is shown from early stage disease (stage IA/IB/IIA) to advanced phase disease. Each curve represents the TTP toward the reported advanced stage disease (from stage IIB to stage IVB). (b) Survival of patients with stage IV disease is shown.

year survival rates were 97% and 93%, respectively, for stage IA disease and decreased significantly to 91% and 86%, respectively, for stage IB disease ($P = .003$); 79% and 72%, respectively, for stage IIA disease (stage IB vs stage IIA: $P = .0002$); and 69% and 51%, respectively, for stage IIB disease (stage IIA vs stage IIB: $P = .014$). No differences were found between stage IIB and stage III disease, whereas patients with stage IV disease demonstrated an extremely poor prognosis (5-year survival rate of 24%).

Survival rates were also calculated from the date of diagnosis of each stage of disease during follow-up. No differences were demonstrated between stage IIIA and IIIB, whereas the distinction between stage IVA1, stage IVA2, and stage IVB carried a relevant prognostic value (Fig. 3b): patients with blood involvement were found to have a better survival than those with lymph node/visceral disease.

Multivariate OS analysis stratified for age identified stage at the time of initial diagnosis (HR, 1.45) and stage progression during follow-up (HR, 2.92) as variables with independent prognostic relevance (Table 4).

DISCUSSION

The current study presents a retrospective analysis of clinical and long-term follow-up data from 1422 Italian patients with classic MF who were reclassified according to the new ISCL/EORTC system.[6,27] To the best of our knowledge, the current series is the largest cohort of MF patients together with that recently reported by the UK group,[18] which analyzed survival outcomes and prognostic factors related to OS, disease-specific survival, and risk of disease progression as calculated from an impressive single-center cohort of 1502 patients with MF/SS . With respect to that study, we did not include either patients with MF variants or SS not preceded by MF[13] to obtain a more homogeneous patient cohort. Moreover, the follow-up of the current study (median, 14.5 years) is to the best of our knowledge longer than that of previously published series (median, 3 years-6 years).[18-25] The current study differs from that of Agar et al[18] in that our analysis was focused on the patterns and time course of disease evolution over time to identify the pathways of cutaneous and extracutaneous disease progression and to ascertain the trends in the hazard risk of specific pathways of disease evolution (development of tumors, erythroderma, or blood/lymph node/visceral involvement). To the best of our knowledge, no data have been reported in the literature regarding this topic in large patient cohorts, despite its central relevance in the setting of clinically based, adequate follow-up and therapeutic strategies.

The current study provides a quantification of the risk and patterns of disease progression. A stage progression occurred in 29.7% of patients, which is similar to data from the literature (25%-34%).[18-25] Overall, approximately 1 of 5 patients (20%) with early phase MF developed disease progression to advanced phase during follow-up, with a significantly higher percentage noted for patients with stage IIA disease (40.1%; $P = .02$). Extracutaneous disease progression occurred in $< 5\%$ of patients, 3.7% developed SS, and 3% experienced transformation into high-grade lymphoma. MF demonstrates an indolent clinical course[18-25,31-32]; however, to the best of our knowledge, only a few studies to date have analyzed disease progression risk over time or according to the clinical stage of disease.[18,19,22] Previous studies by Agar et al,[18] Kim et al,[19] and van Doorn et al[22] found an increase in the overall risk of disease progression over time. We calculated the hazards rates of progression to advanced disease in patients with an initial diagnosis of early phase

Table 4. Multivariate Analysis of Survival

Variable	SE	HR	95% CI	*P*
TNMB stage at diagnosis	0.0787088	1.448915	1.302577-1.611693	<.001
Stage progression during follow-up	0.4336843	2.922946	2.185376-3.909449	<.001

Abbreviations: 95% CI, 95% confidence interval; HR, hazards ratio; SE, standard error; TNMB, tumor-lymph node-metastasis-blood stage.

MF. Patients with stage IA/IB disease demonstrated a low, steady annual incidence of progression to stage IIB (approximately 1%-2%) or stage III (0.5%-1%) disease, which was maintained until the 15th year. Conversely, patients with stage IIA disease demonstrated significantly higher risk of disease progression to stage IIB or stage III during the first year (9.4% and 6.3%, respectively,) followed by a progressive decrease thereafter and reaching steady values similar to stage IA/IB disease. The hazards rates of extracutaneous involvement were low (< 0.5% to 1%) and both stage IA/IB and stage IIA patients maintained steady values during follow-up. The long-term steady values of the hazard risk of disease recurrence justify the need for a prolonged follow-up.

The results of the current study also confirm that although TNM staging is associated with different progression rates,[18,19,22] there is also a relationship with different patterns of disease progression. As already reported,[32] patients with stage IIA disease had an overall higher rate of disease progression than patients with stage IB disease, with the same rate of progression to tumor-stage but a higher risk of lymph node involvement and therefore a worse prognosis. Moreover, patients with stage IIB disease demonstrated a higher percentage of extracutaneous involvement than those with stage IIA disease, despite the similar overall rate of disease progression. Tumor-stage MF demonstrates more frequent lymph node and particularly visceral involvement compared with extracutaneous disease progression, whereas erythrodermic MF mainly develops as hematological involvement and thus transformation into SS. Approximately one-half the patients with lymph node/visceral involvement demonstrated tumor-stage disease at the time of extracutaneous disease progression, whereas 45% of patients with blood involvement had erythroderma. These data emphasize the need for differentiated follow-up strategies: close radiological procedures for patients with tumor-stage MF, whereas erythrodermic patients should be tested more frequently for blood involvement. Some other literature data are in agreement with the current study findings. de Coninck et al[33] found that the majority of patients with stage IV disease had tumor-stage cutaneous disease; however, the authors did not analyze the presence of blood involvement as a separate category. Diamandidou et al[23] found peripheral blood involvement occurring almost exclusively in patients with T4 disease (78% of cases), whereas in the Dutch study,[22] patients with T3 disease were characterized by a significantly higher risk of lymph node/visceral involvement.

The differences between tumor-stage (stage IIB) and erythrodermic (stage III) MF involve not only the pathways of disease evolution but, in an earlier phase, their clinical onset, as represented by additional new evidence highlighted in the current study. We believe the current study is the first to demonstrate that the evolution from tumor-stage to erythroderma represents a very uncommon feature. In fact, T4 erythroderma developed with a significantly higher frequency from T1 or T2 disease than from T3 disease, thus suggesting that evolution to T3 and T4 disease follows two separate parallel rather than sequential clinical pathways. Patients with erythrodermic MF are also characterized in the current series by demographic differences, most significantly by being significantly older and with a more pronounced male prevalence. Similar age differences between MF stages have already been reported.[19,20]

The data from the current study provide clinical validation for the revised TNMB classification,[6] in agreement with the study by Agar et al.[18] The multivariate OS analysis stratified for age identified TNMB classification at the time of initial diagnosis and stage progression as a time-dependent covariate during follow-up as independent prognostic variables. These results are fairly similar to those reported by Agar et al,[18] even if we did not confirm the prognostic relevance of male gender. With respect to Agar et al's study,[18] we did not include MF variants or SS not preceded by MF to obtain a more homogeneous patient cohort; moreover, we could not evaluate lactate dehydrogenase values because they were available in only a minority of patients. The clinical relevance of the newly introduced split of stage IV into stage IVA1 (blood), stage IVA2 (lymph node), and stage IVB (viscera) disease was confirmed in the current study (as well as the study by Agar et al[18]) through evidence of survival differences according to the type of extracutaneous involvement. The independent tracking of these 3 prognostic indicators is

clinically relevant to identify a homogeneous series of patients and to evaluate a better therapeutic approach. We could not confirm survival differences between patients with stage IIIA and IIIB disease, most likely due to the low number of patients with stage IIIB who were available for analysis, consequent to the difficulties in the retrospective evaluation of B score. It is interesting to note that patients with tumor-stage and erythrodermic disease, who were characterized by different demographic features, patterns of onset, and disease evolution, share a similar prognosis without survival differences. Conflicting results have been reported in the literature; a series of articles did not detect any survival differences between these 2 groups,[18-20,25,34] whereas others demonstrated a worse prognosis for patients with T3 disease.[21,23,33] These data suggest that the continued classification of tumor-stage at a stage below erythroderma is not supported by clinical findings and therefore could be modified.

In conclusion, the data from the current study emphasize the need, from a biological point of view, to understand the molecular basis of the different clinical pathways of disease progression, whereas from a clinical prospective, they support the relevance of a stage-tailored, differentiated follow-up strategy. The prognostic significance of the revised TNMB classification suggests that the analysis of stage progression development represents a potential endpoint in the design of prospective clinical trials.

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The authors made no disclosures.

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