Diagnostic and prognostic markers in tumor stage mycosis fungoides and Sézary syndrome

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Quantitation of tumor development correlates with prognosis in tumor stage (stage IIB) mycosis fungoides

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ABSTRACT

Background Patients with mycosis fungoides (MF) tumor stage IIB disease show considerable variation in the number of tumors and time interval between each tumor occasion.

Objectives To quantify the extent of tumor formation in patients with stage IIB MF and correlation with survival.

Methods The variability in tumor development of 46 patients with stage IIB MF was quantified by calculating a frailty score with the use of a statistical frailty model, based on both the number of tumors developed during follow-up and the time interval between each tumor occasion. The prognostic value of the frailty scores and the number of tumors at 6 and 12 months after first tumor development were studied.

Results Frailty scores varied between 0.05 en 6.94. Patients with high frailties (> 1.0, n = 14) had the worst disease-specific survival (DSS) and overall survival (OS), compared with patients in the low frailty group (0-0.35, n = 17) and medium frailty group (0.35-1.0, n = 15). Differences in DSS and OS between the three frailty groups were highly significant (both $P < 0.001$). The number of tumors that developed within 6 months after the diagnosis of MF stage IIB was prognostic for subsequent DSS and OS ($P < 0.001$ and $P = 0.021$, respectively).

Conclusions The number of tumors and time interval between tumor formation differs greatly among patients with stage IIB MF and these differences correlate with survival. Patients with an adverse prognosis can be identified by quantifying the number of tumors that develop within 6 months after diagnosis of MF stage IIB.

INTRODUCTION

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, accounting for almost 50% of all cutaneous lymphomas. The disease course is characterized clinically by progression through defined clinical stages − from patches to plaques to tumors − and in a minority of patients to extracutaneous localisations.[1]

The staging of MF is based on the tumor-node-metastasis-blood (TNMB) staging system, which classifies both type and extent of skin lesions, the presence and degree of lymph nodes and visceral and blood involvement. In the latest revisions to the staging and classification of MF by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC), tumor stage disease is defined by the presence of at least one tumor ≥ 1 cm in diameter.[2]

The prognosis of patients with MF is closely correlated with disease stage. While the survival in MF stage IA is comparable with an age-, race- and sex-matched control population, the prognosis deteriorates with progression of disease.[3-6] Patients with tumor stage MF without extracutaneous disease, stage IIB, have a reduced 5-year disease-specific survival (DSS) of 56−80% and are at risk for progression to extracutaneous sites.[7;8] Apart from clinical stage, folliculotropic MF and large cell transformation have been associated with adverse prognosis in MF.[6-11]

Although patients with stage IIB MF are categorized as a homogeneous group, clinical observations show considerable variation in patients with MF stage IIB disease. Some patients present with a solitary tumor whereas others present with extensive tumor formation. Also, the time interval between the development of new tumors differs greatly among patients with stage IIB disease. Previous studies addressing the relationship between tumor formation and prognosis focused on tumor distribution at diagnosis. Two studies reported that patients who have generalized skin tumors at presentation have a reduced survival compared with those who present with only a solitary tumor.[9;12] In contrast, Agar et al did not find an association between the extent of skin tumors at diagnosis and survival.[8] However, in these studies the exact number of tumors was not quantified and the number of tumors developing during follow-up was not investigated.

The aim of the current retrospective follow-up study was to investigate the relationship between tumor formation and survival in more detail. We quantified the extent of tumor development in patients with MF stage IIB disease using a statistical frailty model fitted on the basis of both the number of tumors that developed during follow-up and the time interval between each tumor occasion, and correlated results with survival. In addition, we evaluated whether the number of tumors that developed within 6 and 12 months after the appearance of the first tumor is prognostic for subsequent survival.

METHODS

PATIENT SELECTION

Forty-six patients, who were managed at the Department of Dermatology of the Leiden University Medical Center (LUMC) between 1984 and 2012, were selected from the cutaneous lymphoma database of the Dutch Cutaneous Lymphoma Group (DCLG).

Inclusion criteria were (i) clinical and histological features of MF, as assessed by a panel of dermatologists and pathologists during one of the quarterly meetings of the DCLG; (ii) stage IIB disease at first diagnosis of MF or development of stage IIB disease during follow-up; and (iii) under regular surveillance in the LUMC. Stage IIB was defined according to the classification, proposed by the ISCL and EORTC, requiring at least one tumor ≥ 1 cm in diameter.[2]

CLINICAL EVALUATION

Medical records and photographs taken at the time of first tumor presentation and during follow-up were reviewed for all patients. Each occasion of tumor growth was registered with dates, and clinical information was obtained about the number of tumors (categorized as 1, 2, 3, 4, 5 or more tumors), therapy and response to therapeutic regime.

Other variables recorded for each patient were sex, duration of skin lesions before diagnosis MF, age at diagnosis of MF, stage at diagnosis of MF, age at progression to stage IIB, response to initial therapy, progression towards stage IV, the presence of folliculotropic MF, duration of follow-up and survival status.

Additionally, from available skin biopsies from tumors at first development of stage IIB disease, large cell transformation (presence of large T cells exceeding 25% of the total lymphoid infiltrate or forming microscopic nodules) was recorded.[13]

FRAILTY SCORE

The frailty model is a statistical approach to test for and quantify differences in the occurrence of a specific event between individuals of a defined group.[14] We used this method to investigate the propensity to develop tumors in patients with MF stage IIB disease. This frailty model takes into account both the number of tumors developed during follow-up (including tumors at the time of the diagnosis of stage IIB) and the time interval between each tumor occasion. The frailty model specifies that the tumor recurrence rate of an individual equals a baseline rate multiplied by a random effects term, called the frailty. These unmeasured effects are assumed to follow a given statistical distribution (γ) with mean equal to 1 and unknown variance σ^2. The frailty variance σ^2 quantifies the heterogeneity in recurrence rates between the patients. After having estimated the unknown parameters in the model, the clinical heterogeneity was translated into a numerical score for each individual, called the frailty score, using this formula:

$$\text{Frailty score}_i = \frac{n_i(t) + \frac{1}{\sigma^2}}{H_i(t) + \frac{1}{\sigma^2}}$$

Here t denotes the total follow-up time from first diagnosis of MF stage IIB disease of the individual, $H_i(t)$ the cumulative recurrence rate and $n_i(t)$ the total number of tumors developed in individual i. To correlate the frailty scores with survival we divided the patients into three categories of approximately the same size, namely the low, medium and high frailty scores.

STATISTICAL ANALYSIS

All statistical calculations were performed using SPSS Statistics 20.0 (IBM, Armonk, NY, USA), with the exception of the frailty and landmark analyses (below), which were performed in R, version 2.15.0 (http://www.r-project.org). For comparison between groups the ANOVA test or, in case of discrete data, the χ^2 test, was used. Survival was calculated from the date of development of stage IIB disease until the patient's death or date of last follow-up. The Kaplan-Meier method was used to estimate survival curves, and comparison between curves, was performed using the log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method.

In order to study whether the number of tumors during follow-up was predictive of survival, a landmark analysis was performed, where the number of tumors that developed in the first 6 and 12 months of follow-up was used as a predictor of subsequent survival in all individuals who were still at risk after 1 year. In the analysis the number of tumors present at first development of stage IIB was included. Analysis with DSS was performed accounting for death of other causes as a competing risk.[15]

Univariate analysis of parameters with possible prognostic significance for DSS and overall survival (OS) was performed using Cox proportional hazards regression analysis. Parameters that were analyzed for their prognostic significance were sex (male vs female), age at development of stage IIB (continuous variable), time interval between first diagnosis of MF and development of stage IIB disease (continuous variable), folliculotropic MF (absent vs present) and large cell transformation at development of stage IIB (yes vs no). These parameters were combined with (i) the frailty score (continuous; after log-transformation), or (ii) the number of tumors at the first development of stage IIB, and (iii) the first 6 months or (iv) the first 12 months after development of stage IIB (continuous variable). The parameters that were significant at the 0.25 level were included in a multivariate analysis model. *P*-values below 0.05 were regarded as statistically significant.

RESULTS

CLINICAL CHARACTERISTICS AND FOLLOW-UP

The main clinical characteristics and follow-up data of the 46 patients with stage IIB disease are summarized in **Table 1**. There was a male predominance (male/female ratio of 2.5) and the median age at development of stage IIB was 69 years (range = 39-90 years). Twenty-three patients had stage IIB at the time of first diagnosis of MF, the other 23 patients developed stage IIB during follow-up, varying from 1 to 181 months after first diagnosis of MF. Of the 46 patients, 20 patients (43%) were diagnosed with folliculotropic MF. Forty-two patients had skin biopsies available from tumors at development of stage IIB disease, of whom 23 patients showed large cell transformation.

Previous treatments before development of stage IIB disease included local steroids, psoralen plus ultraviolet A (PUVA) therapy, local radiotherapy, interferon alfa and total skin electron beam therapy. None of these patients received (poly)chemotherapy prior to or during development of stage IIB disease. The first therapy after development of stage IIB disease consisted of skin-directed therapies other than local radiotherapy (local steroids, PUVA therapy, excision, topical nitrogen mustard) (n = 9), local radiotherapy (n = 31) or total skin electron beam therapy (n = 6). During follow-up a total of 11 patients received (poly)chemotherapy because of rapid and massive tumor formation and/ or progression to stage IV disease.

The median follow-up time calculated from diagnosis of MF was 96 months (range = 3-323 months) compared with 88 months (range = 2-241 months) when measured from development of stage IIB disease. During follow-up 28 patients died, including 18 MF-related deaths. After progression to stage IIB, DSS after 1, 2 and 5 years was 97%, 81% and 60%, respectively, and OS was 93%, 73% and 46%, respectively.

TIMELINE TEMPLATES

For each patient a timeline template was constructed in Excel to get a clear understanding of the tumor formation during follow-up. In these timelines the development of new tumors and the number of tumors developed at that moment are plotted against follow-up time in months, as demonstrated in **Figure 1** for three selected patients. The smaller the interval between every tumor occasion, the higher the rate of tumor recurrence. These timeline templates visualize different patterns of tumor formation in individual patients, illustrating the clinical heterogeneity in patients with stage IIB disease.

FRAILTY SCORE AND CORRELATION WITH SURVIVAL

The frailty model revealed a highly significant ($P < 0.001$) variability in tumor recurrence rates between patients, with an estimated frailty variance of 1.64. The individual frailty scores, calculated for each patient, varied from 0.05 to 6.94 with a median frailty score of 0.64.

To analyse further the correlation of the tumor recurrence rates with survival, we divided the patients into three groups of equal size, namely the low, medium and high frailty categories, defined by frailty scores from 0 to 0.35, 0.35 to 1.0 and > 1.0, respectively. The main clinical characteristics of the low (n = 17), medium (n = 15) and

Table 1. Clinical characteristics and outcomes of 46 patients with mycosis fungoides (MF) stage IIB disease.

Male:female ratio	33:13
Duration of skin lesions before MF diagnosis in months, median (range)	24 (1-480)
Age in years, median (range)	
At diagnosis of MF	66 (39-90)
At stage IIB	69 (39-90)
Clinical stage at diagnosis of MF, n	
IA-IIA	23
IIB	23
Folliculotropic MF, n	
Absent	26
Present	20
Large cell transformation at development of stage IIB	
Yes	23
No	19
No biopsy available	4
Duration of follow-up in months, median (range)	
After diagnosis of MF	96 (3-323)
After stage IIB	88 (2-241)
Progression to stage IV during follow-up, n	
Yes	14
No	29
Unknown	3
Status at date of last follow-up, n	
Alive without disease	4
Alive with disease	14
Died of other cause	9
Died of unknown cause	1
Died of MF	18
Disease-specific survival after development of stage IIB, %	
At 1 year	97
At 2 years	81
At 5 years	60
Overall survival after development of stage IIB, %	
At 1 year	93
At 2 years	73
At 5 years	46

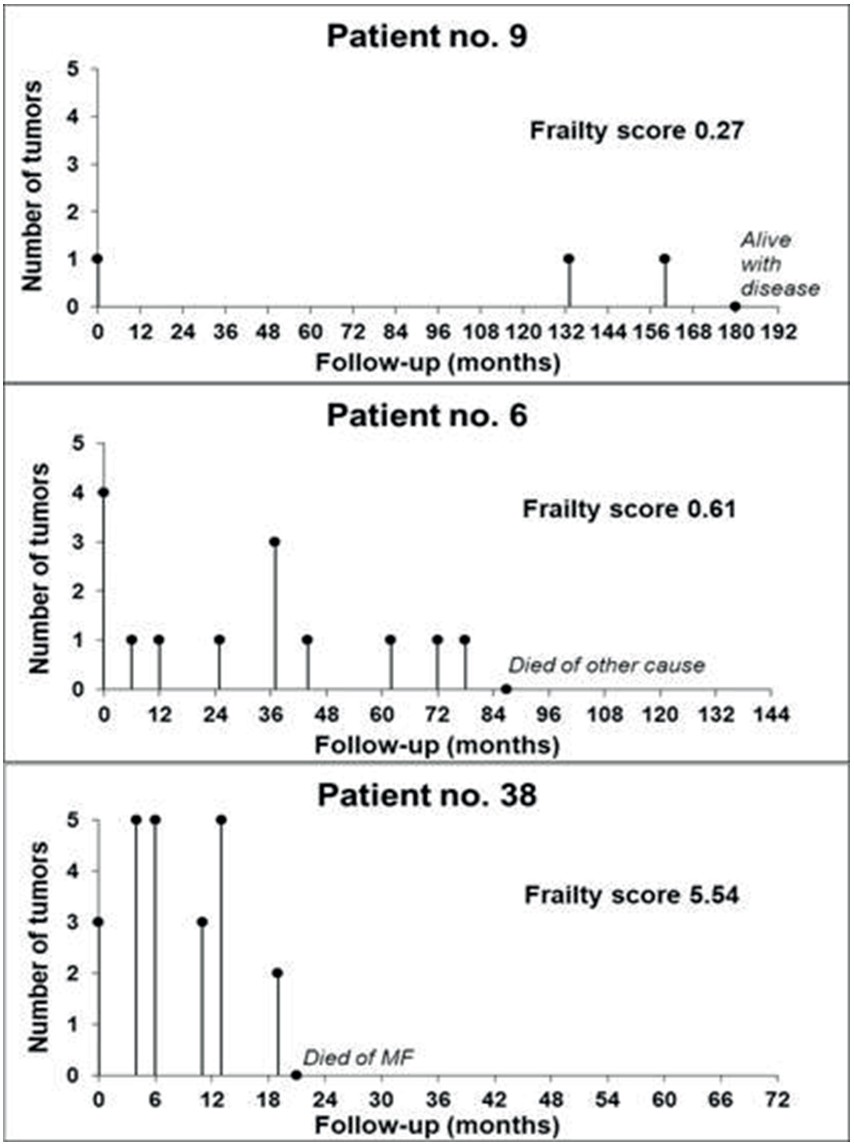


Figure 1. Three examples of the variability in number of tumors and time interval between each tumor recurrence per patient and accompanying frailty score. The dots represent a tumor occasion. Follow-up (month 0) starts at development of mycosis fungoides (MF) stage IIB.

high (n = 14) frailty groups are summarized in **Table 2.** The three groups were comparable in sex, median age at development of stage IIB disease and presence of folliculotropic MF.

The low frailty group had a DSS after 1, 2 and 5 years of 100%, 100% and 88%, respectively, and OS was 94%, 94% and 76%, respectively. The patients in the medium frailty group had a DSS after 1, 2 and 5 years of 100%, 79% and 64%, respectively, and OS

was 93%, 71% and 43%, respectively. The high frailty group had the worst survival with a DSS after 1, 2 and 5 years of 93%, 64% and 36%, respectively, and OS was 93%, 50% and 14%, respectively (**Figure 2**).

FRAILTY SCORE AND OTHER PROGNOSTIC PARAMETERS

In univariate analysis for DSS, time interval between first diagnosis of MF and development of stage IIB disease and folliculotropic MF were selected for subsequent multivariate analysis (univariate $P = 0.190$ and $P = 0.190$, respectively). Both univariate and multivariate analyses established that the differences in DSS between the three frailty groups were highly significant (multivariate $P < 0.001$; hazard ratio (HR) = 3.28; 95% confidence interval (CI) 1.69-6.38), while the time interval between first diagnosis of MF and development of stage IIB disease and presence of folliculotropic MF were not significant ($P = 0.730$ and $P = 0.670$, respectively).

In univariate analysis for OS, age at development of stage IIB was selected for subsequent multivariate analysis (univariate $P = 0.024$). Both univariate and multivariate analyses established that differences in OS between the three frailty groups were highly significant (multivariate $P < 0.001$; HR = 2.06; 95% CI 1.39-3.05). In addition, in both univariate and multivariate analyses age at development of stage IIB disease was significant for subsequent OS (multivariate $P = 0.050$; HR = 1.03; 95% CI 1.00-1.07).

Table 2. Clinical characteristics and outcomes of the low, medium and high frailty groups.

	Low frailty	Medium frailty	High frailty
Frailty score (range)	0-0.35	0.35-1.0	> 1.0
Number of patients	17	15	14
Male:female ratio	10:7	12:3	11:3
Age at stage IIB in years, median (range)	68 (39-90)	73 (46-86)	65 (54-87)
Folliculotropic MF, n	7	6	7
Large cell transformation at stage IIB, n	4	9	10
Disease-specific survival, %			
At 1 year	100	100	93
At 2 years	100	79	64
At 5 years	88	64	36
Overall survival, %			
At 1 year	94	93	93
At 2 years	94	71	50
At 5 years	76	43	14

MF, mycosis fungoides.

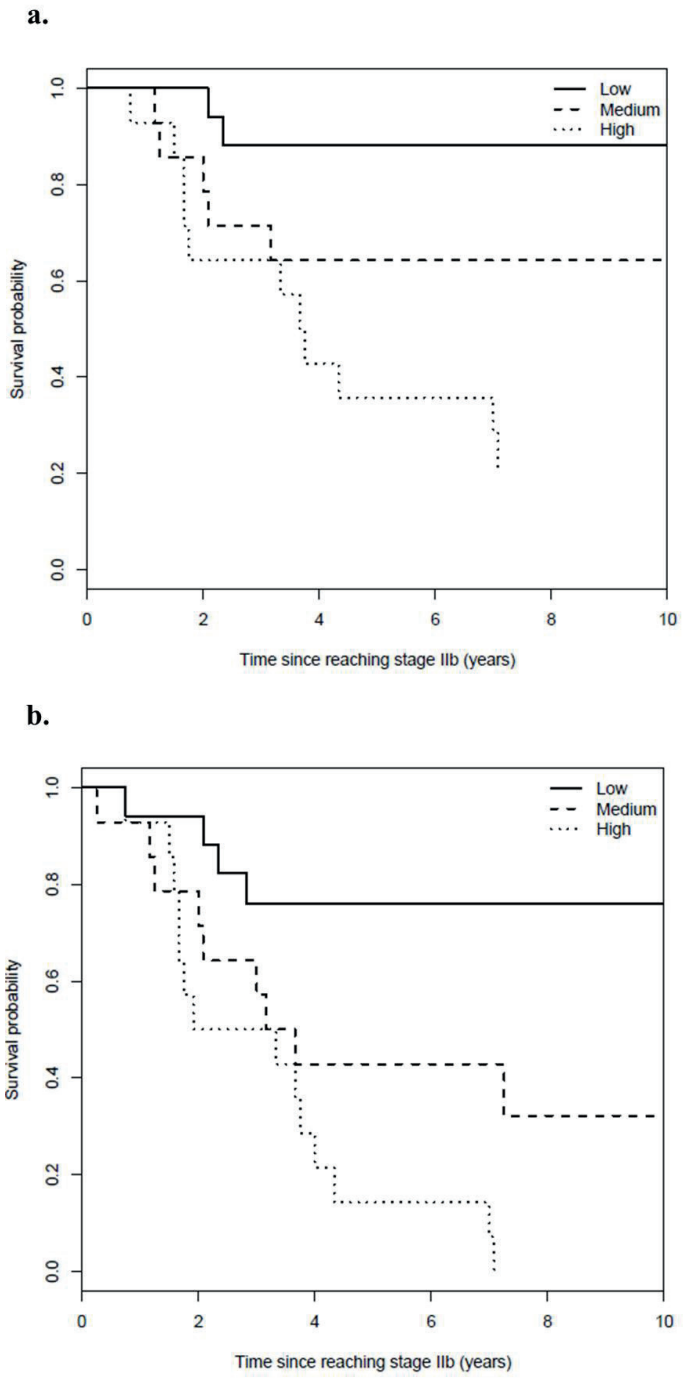


Figure 2. Disease-specific survival (a) and overall survival curve (b) according the low, medium and high frailty groups.

NUMBER OF TUMORS AT 0, 6 AND 12 MONTHS AFTER DEVELOPMENT OF STAGE IIB DISEASE AND OTHER PROGNOSTIC PARAMETERS

In univariate analysis for both DSS and OS, the number of tumors present at first presentation of MF stage IIB disease was not significant at the 0.25 level and was therefore not included in multivariate analysis ($P = 1$ and $P = 0.66$, respectively).

For the multivariate analysis with the number of tumors developed within the first 6 months after development of stage IIB disease (univariate $P = 0.002$) the same parameters were selected as described for the frailty score (see above).

Both univariate and multivariate analyses established that the number of tumors developed within the first 6 months after development of MF stage IIB disease was highly prognostic for subsequent DSS ($P < 0.001$; HR = 1.92; 95% CI 1.11-1.50). In multivariate analysis, folliculotropic MF was associated with an increased disease-specific death rate ($P = 0.044$; HR = 3.36; 95% CI 1.03-10.95), while the time interval between first diagnosis of MF and development of stage IIB disease was not prognostic ($P = 0.476$).

In multivariate analysis, the number of tumors developed within 6 months after development of MF stage IIB was prognostic for subsequent OS ($P = 0.021$; HR = 1.14; 95% CI 1.02-1.27), while age was no longer significant ($P = 0.093$).

Sensitivity analysis, performed using the total number of tumors developed during the first 12 months after diagnosis of stage IIB disease, confirmed its prognostic value for DSS and OS (data not shown).

In order to simplify the previous results, we divided the patients who had completed a 6 months follow-up after development of stage IIB disease into three categories of the same size based on the number of tumors developed within the first 6 months, namely one tumor (n = 17), 2-3 tumors (n = 12) and ≥ 4 tumors (n = 15) and correlation with survival (**Table 3**, **Figure 3** and **Supplementary Figure S1).** This implies that patients who develop four or more tumors during the first 6 months after diagnosis of stage IIB disease have a worse prognosis.

Table 3. Number of tumors developed within the first 6 months after development of stage IIB disease.

	1 tumor	2-3 tumors	≥ 4 tumors
Number of patients	17	12	15
Disease-specific survival, %			
At 1 year	100	100	93
At 2 years	88	92	67
At 5 years	71	75	47
Overall survival, %			
At 1 year	100	92	93
At 2 years	88	75	60
At 5 years	53	58	33

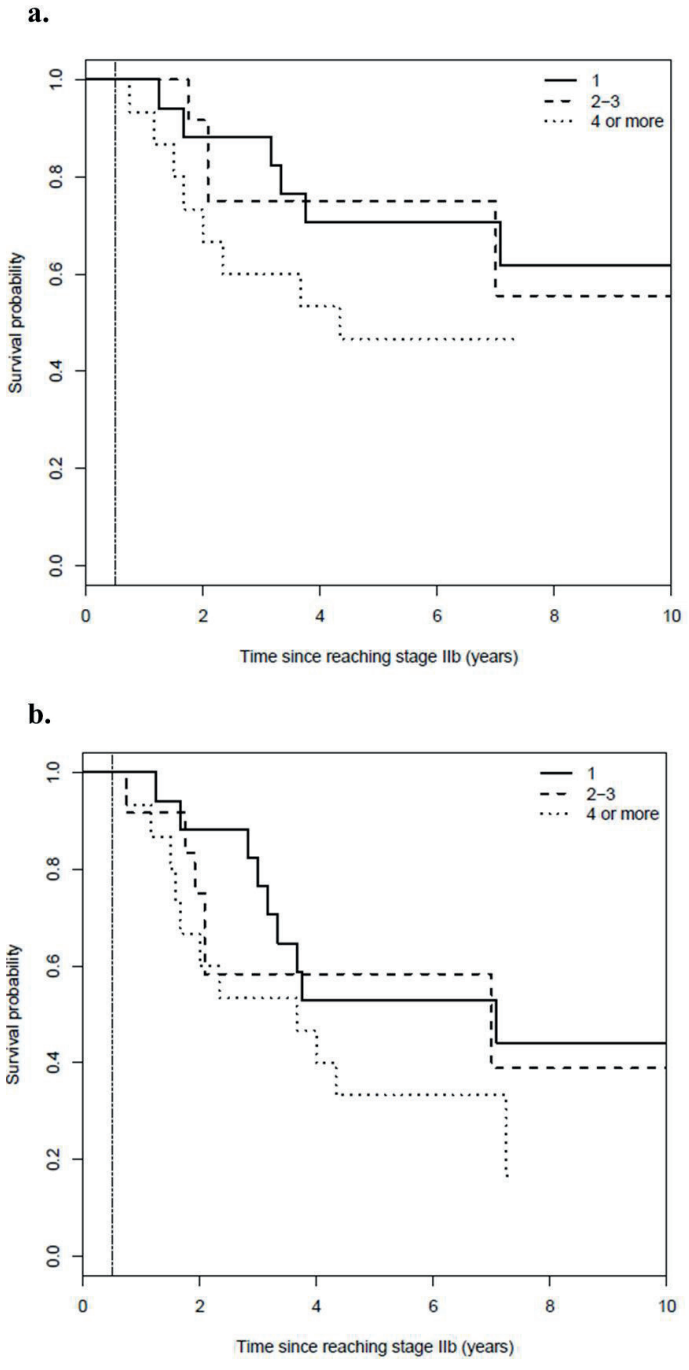


Figure 3. Disease-specific survival (a) and overall survival curve (b) according to number of tumors developed within the first 6 months after diagnosis of stage IIB.

DISCUSSION

Previous studies in MF reported a 5-year DSS varying between 56% and 80% for patients with stage IIB disease. However, patients with stage IIB disease differ greatly in the number of tumors at presentation, time interval between development of new tumors and the number of tumors that develop during follow-up. The significance of this clinical heterogeneity is controversial. In previous studies investigating the correlation between extent of tumor formation at presentation and survival no relationship was found by Agar et al, whereas two other studies reported that patients with generalized tumors had a worse prognosis than patients presenting with a solitary tumor.[8;9;12]

In the present study we quantified the extent of tumor formation in two ways. Firstly, we calculated a frailty score, which takes into account both the number of tumors that developed during follow-up and the time interval between each tumor occasion. This frailty score varied from 0.05 to 6.94 and high frailty scores (> 1.0) correlated with decreased survival. These results show that the total number of tumors that develop during follow-up and the time interval between each tumor recurrence holds prognostic information in patients with MF stage IIB disease.

Although the frailty score is statistically an attractive and sensitive method to quantify the development of tumors in patients with MF, it will be difficult to use in daily practise. Because of the positive results of the frailty score, we decided, in a second line of approach, to calculate the number of tumors that develop within the first 6 and 12 months after diagnosis of stage IIB disease. It was found that these provided prognostic information as well. The major advantage of this latter approach is that careful documentation of the number of tumors is sufficient.

The 5-year DSS and OS of the 46 patients with MF stage IIB disease was 60% and 46%, respectively. These results are similar to those reported by previous studies (5-year DSS and OS, 56−80% and 47−65%, respectively).

Our study showed no association of the number of tumors present at first diagnosis of MF stage IIB disease with survival, which is in line with the findings of Agar et al.[8] A possible explanation for this remarkable observation could be that only 17% of our patients presented with four or more tumors at first tumor development.

A more detailed method for the assessment of skin tumor burden is the modified Severity Weighted Assessment Tool (mSWAT) score, which takes into account not only tumors, but also patches and plaques. The mSWAT score is an established end point for clinical trials.[16] However, in this study, in which clinical photographs had documented all skin tumors, but not all concurrent patches and plaques, it was not possible to calculate mSWAT scores retrospectively.

Consistent with previous studies, our study showed that large cell transformation in patients with stage IIB disease was not associated with a reduced survival.[12;17]

The present study contains a high percentage of patients with folliculotropic MF (20 of 46 patients; 43%). Data from the Dutch Cutaneous Lymphoma Registry indicate that approximately 17% of all patients with MF have folliculotropic MF (R. Willemze, personal communication). Previous studies reported that patients with folliculotropic MF often have a complicated disease course and a greater risk of disease progression.[8;18] Therefore

these patients are more likely to be under continuous surveillance at our department, which may explain the high percentage of folliculotropic MF in our study. Consistent with these previous studies we also observed a reduced DSS in patients with folliculotropic MF.

In conclusion, this study shows that the number of tumors and time interval between tumor formation differs greatly among patients with MF stage IIB disease and that these differences in tumor formation correlate with survival. Patients with an adverse prognosis can be identified by quantifying the number of tumors that develop within 6 months after diagnosis of MF stage IIB. Although these observations need to be repeated in an independent study, our findings suggests that patients who develop more than four tumors within the first 6 months after diagnosis of MF stage IIB have a worse prognosis and should be monitored more carefully. We propose that patients with MF who develop stage IIB disease should be examined every 6 to 8 weeks in the first 6 months and those patients with extensive tumor formation (at least four tumors) should be under monthly surveillance.

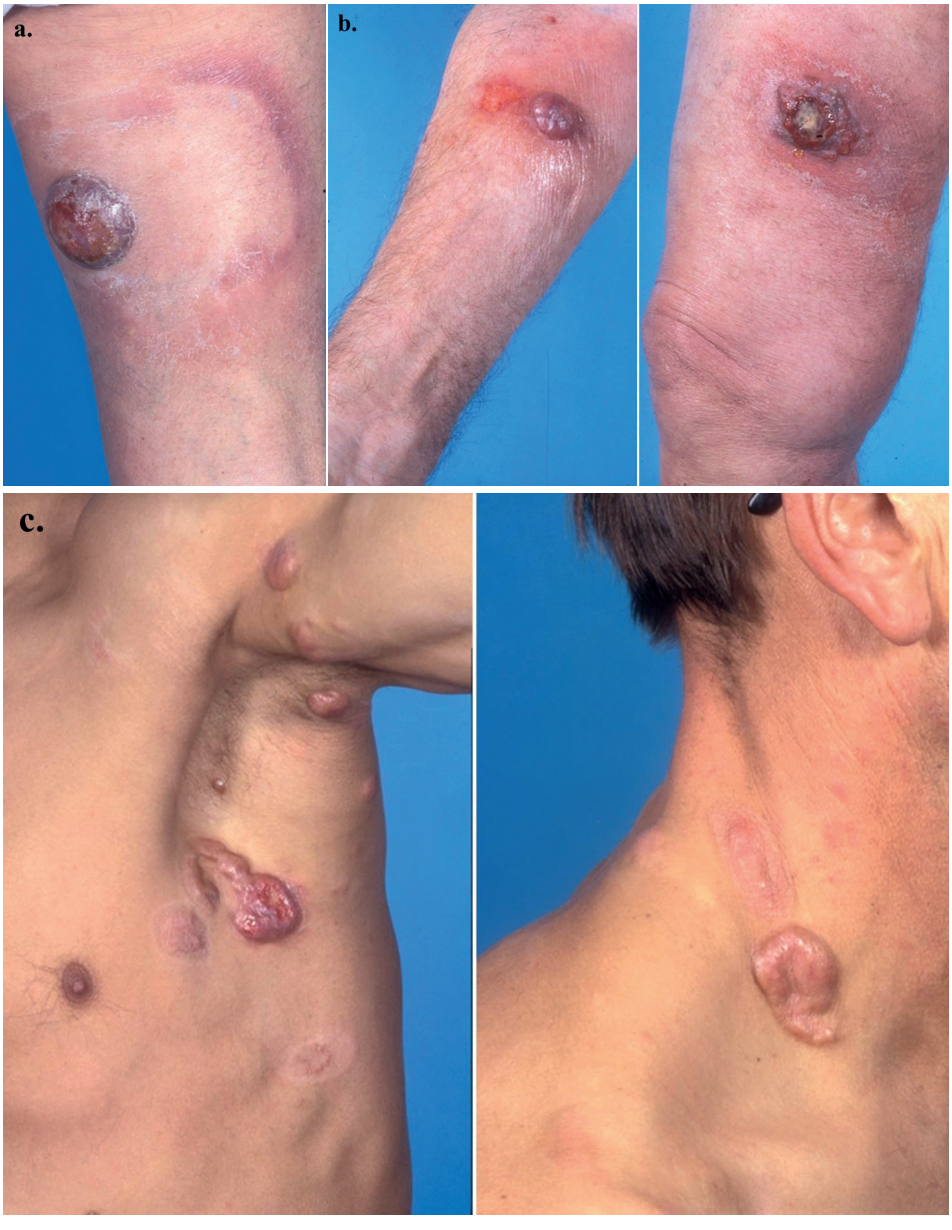
REFERENCES

1. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105: 3768-85.
2. Olsen E, Vonderheid E, Pimpinelli N et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007; 110: 1713-22.
3. Kim YH, Jensen RA, Watanabe GL et al. Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. Arch Dermatol 1996; 132: 1309-13.
4. Zackheim HS, Amin S, Kashani-Sabet M et al. Prognosis in cutaneous T-cell lymphoma by skin stage: long-term survival in 489 patients. J Am Acad Dermatol 1999; 40: 418-25.
5. Kim YH, Liu HL, Mraz-Gernhard S et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003; 139: 857-66.
6. Quaglino P, Pimpinelli N, Berti E et al. 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. Cancer 2012; 118: 5830-9.
7. van Doorn R., Van Haselen CW, van Voorst Vader PC et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 2000; 136: 504-10.
8. Agar NS, Wedgeworth E, Crichton S et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/ European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010; 28: 4730-9.
9. Talpur R, Singh L, Daulat S et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. Clin Cancer Res 2012; 18: 5051-60.
10. Diamandidou E, Colome-Grimmer M, Fayad L et al. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood 1998; 92: 1150-9.
11. Barberio E, Thomas L, Skowron F et al. Transformed mycosis fungoides: clinicopathological features and outcome. Br J Dermatol 2007; 157: 284-9.
12. Benner MF, Jansen PM, Vermeer MH et al. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 2012; 119: 1643-9.
13. Salhany KE, Cousar JB, Greer JP et al. Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. Am J Pathol 1988; 132: 265-77.
14. Hougaard P. Frailty models for survival data. Lifetime Data Anal 1995; 1: 255-73.
15. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26: 2389-430.
16. Stevens SR, Ke MS, Parry EJ et al. Quantifying skin disease burden in mycosis fungoides-type cutaneous T-cell lymphomas: the severity-weighted assessment tool (SWAT). Arch Dermatol 2002; 138: 42-8.
17. Vonderheid EC, Tam DW, Johnson

WC et al. Prognostic significance of cytomorphology in the cutaneous T-cell lymphomas. Cancer 1981; 47: 119-25.

18. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol 2002; 138: 191-8.

SUPPLEMENTARY MATERIAL



Supplementary Figure S1. Examples of patients with mycosis fungoides stage IIB disease with (a) one tumor on the dorsal side of the right upper leg, (b) two tumors lokalized on the right forearm and on the right upper leg, and (c) more than four tumors lokalized on the upper half of the body.