Clinical staging and prognostic factors in folliculotropic mycosis fungoides

Santen, S. van

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CLINICAL STAGING AND PROGNOSTIC FACTORS IN FOLLICULOTROPIC MYCOSIS FUNGOIDES

S. van Santen[1], R.E.J. Roach[1], R. van Doorn[1], B. Horváth[2], M.S. Bruijn[2], C.J.G. Sanders[3], J.C. de Pooter[3], M.M. van Rossum[4], E.R.M. de Haas[5], J.C.J.M. Veraart[6], M.W. Bekkenk[7], M.H. Vermeer[1], R. Willemze[1]

Departments of Dermatology, Leiden University Medical Center[1], University Medical Center of Groningen[2], University Medical Center Utrecht[3], Radboud University Medical Center Nijmegen[4], Erasmus Medical Center Rotterdam[5], Maastricht University Medical Center[6], Academic Medical Center and Vrije University Medical Center Amsterdam[7]; the Netherlands.

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ABSTRACT

Importance: Large case series suggest that patients with folliculotropic mycosis fungoides (FMF) have a worse prognosis than patients with classic mycosis fungoides (MF). However, recent studies described a subgroup of FMF patients with a more favorable prognosis. Distinction between indolent and aggressive FMF may have important therapeutic consequences, but is hampered by the inability of the current tumor-node-metastasis-blood (TNMB) system to classify patients with FMF in a clinically meaningful way.

Objective: To differentiate between indolent and aggressive FMF, using clinico-pathological criteria and to define prognostic factors in patients with FMF.

Design: In this prospective cohort study, we followed 203 patients with FMF, included in the Dutch Cutaneous Lymphoma Registry between October 1985 and May 2014 at a tertiary referral center hosting the Dutch Cutaneous Lymphoma Registry. Overall, 220 patients with FMF had been registered, but 17 patients with incomplete follow-up data or a history of classic MF were excluded.

Main outcomes and measures: Main outcomes included clinical and histological characteristics, disease progression and survival. Prognostic factors were investigated using Cox proportional hazards regression analysis. Distinction between early plaque-stage FMF and advanced plaque-stage FMF was made by a blinded review of skin biopsies from patients presenting with plaques.

Results: In a cohort of 147 men and 56 women (median [range] age 59 [19-93] years) patients with histologically early plaque-stage FMF had a very similar overall survival (OS) rate to patients with only patches and/or follicular papules (10-year OS, 71% vs. 80%), while the survival rate of patients with histologically advanced plaque-stage FMF was almost identical to that of patients presenting with tumors (10-year OS, 25% vs. 27%). Subsequently, three clinical subgroups with significantly different survival data were distinguished: early skin-limited FMF (group A; n=84; 5- and 10-year OS: 92% / 72%); advanced skin-limited FMF (group B; n=102; 5- and 10-year OS: 55% / 28%); and FMF presenting with extracutaneous disease (group C; n=17; 5- and 10-year OS:

23% / 2%). Age at diagnosis, large cell transformation and secondary bacterial infection were independent risk factors for disease progression and/or poor survival.

Conclusion and relevance: The results of this study provide useful criteria to differentiate between indolent and aggressive FMF and confirm the existence of a subgroup of FMF with a favorable prognosis.

INTRODUCTION

In the last decade folliculotropic mycosis fungoides (FMF) has been widely recognized as a distinct variant of mycosis fungoides (MF).[1-9] Clinical and histologic features characteristic of FMF, but not or uncommonly found in classic type of MF include: 1) the histological presence of folliculotropic instead of epidermotropic neoplastic infiltrates, with or without follicular mucinosis[1,3-13]; 2) preferential localization of skin lesions in the head and neck region, with eyebrow involvement and concurrent alopecia as most characteristic feature [1,3-7,9-11,14,15]; 3) the presence of (grouped) follicular papules, alopecia, acneiform and cystic lesions [1-7,9,11,13] ; 4) the frequent occurrence of pruritus and secondary bacterial infections. [2,4-7,9] In addition, patients with FMF were shown less responsive to several first line skin-directed therapies used in classic MF, such as PUVA, and had a worse prognosis as compared to classic MF.[1,3,5-9] In our initial study 51 patients with FMF were compared with 158 patients with classic type MF, including 122 patients with plaque-stage disease (T2N0M0; stage IB) and 36 patients with tumor stage MF (T3N0M0). Survival data of patients with FMF were significantly worse than patients with plaque-stage classic MF and similar to patients with tumor stage MF, although only 14 of 51 patients had tumors or nodules at the time of diagnosis.[9] These observations were confirmed in subsequent studies and clearly indicate that the clinical staging system (TNMB system) used for MF cannot be used to classify FMF, in particular patients with plaques, in a clinically meaningful way.[3,4,16] The worse prognosis of FMF is also supported by large retrospective cohort studies of patients with MF, showing that FMF is an independent risk factor for disease progression and lower survival.[17-19] Because of its characteristic clinicopathologic features and worse prognosis, FMF was included as a distinct entity in recent cutaneous lymphoma classifications.[20,21]

However, recent studies focused attention on a subgroup of FMF patients with a favorable prognosis.[5,10,11] Distinction between FMF patients with an indolent and an aggressive clinical disease course may have important therapeutic consequences, but criteria for this indolent subgroup are still ill-defined. In the present study we reviewed the clinical and follow-up data of 203 patients with FMF, who had been followed prospectively after inclusion in the Dutch Cutaneous Lymphoma Registry. The main goal of this study was to develop criteria which could be used to differentiate between indolent and aggressive FMF. In addition, the large size of our cohort offered

the opportunity to define additional risk factors for poor outcome. Detailed treatment results and treatment recommendations will be reported separately.

PATIENTS AND METHODS

Between October 1985 and May 2014, 220 patients with FMF were included in the registry of the Dutch Cutaneous Lymphoma Group. Seventeen of 220 were excluded: eight patients because of incomplete (follow-up) data, six patients because of a history of classic epidermotropic MF for two to nine years before they developed skin tumors on the face or scalp with the histologic features of FMF, and three patients presenting with a solitary skin lesion, in whom another type of cutaneous T-cell lymphoma, in particular a primary cutaneous anaplastic large cell lymphoma could not be excluded. The final study group consisted of 203 patients. Forty-one of these 203 patients had also been included in our initial study.[9] The study was performed in accordance with the Declaration of Helsinki and the Dutch Code for Proper Secondary Use of Human Tissue, approved by the Ethics Committee of the Leiden University Medical Center.

In all cases, the diagnosis was made by an expert panel of dermatologists and pathologists at one of the regular meetings of the Dutch Cutaneous Lymphoma Group, and all cases met the diagnostic criteria of FMF as described previously.[9,20,21] The date of the first diagnostic biopsy was considered the time of diagnosis. Clinical records, clinical illustrations (available in more than 85% of patients) and follow-up data, which had been collected yearly, were evaluated. The following variables were recorded: age; sex; duration of skin lesions before diagnosis; type, preferential localization and extent of skin lesions; stage of disease according to the revised TNMB system[16]; presence of pruritus and secondary bacterial infection; presence of follicular mucinosis and presence of large cell transformation either at diagnosis or during follow-up according to established criteria[18]; type and result of initial therapy; date and type of disease progression; date of last contact or death if applicable.

Disease progression was defined by the development of clinically overt tumors in patients previously having only patch- or plaque stage disease, the development of histologically documented nodal involvement in patients with previously only skin-limited disease, the development of visceral involvement in patients with previous

skin and/or nodal disease, and death due to lymphoma. Histological lymph node involvement was assessed using the ISCL-EORTC classification system.[16]

Assessment of clinical stage

While patients with only patches, follicular papules, acneiform lesions or keratosis pilaris-like lesions clearly have early-stage disease (stage IA-IIA) and patients presenting with nodules, tumors, erythroderma and/or extracutaneous disease have advanced-stage FMF (stage IIB-IV), it is uncertain if patients presenting with plaques should be classified as early-stage FMF (stage IA-IB) or as advanced-stage FMF (stage IIB).[9] For the purpose of our study, skin biopsies from all patients presenting with plaques were reviewed in a blinded fashion. Lesions histologically showing sparse perifollicular and/or intrafollicular infiltrates containing relatively few and mainly small neoplastic T-cells were considered early plaque-stage FMF, while plaques showing more extensive confluent or diffuse infiltrates containing many often medium-sized to large tumor cells were considered to have advanced plaque-stage FMF.

Prognostic parameters

The following parameters were analyzed for their prognostic significance in FMF: sex, age at diagnosis (≤ 60 vs. >60 years), duration of skin lesions prior to diagnosis (<12months vs. 12-60months vs. >60months), extent of skin lesions (solitary vs. regional vs. generalized); large cell transformation (LCT) in the first diagnostic biopsy; presence of follicular mucinosis, pruritus, secondary bacterial infection (no vs. focal vs. extensive) and clinical stage. The term extensive secondary bacterial infection was used for patients with widespread honey-colored crusted lesions at first presentation (**Figure 1D**).

Statistical analysis

All statistical analyses were performed using the SPSS statistical software (IBM Corp). Disease-specific survival (DSS) was calculated from the date of first diagnostic biopsy until death as result of lymphoma or date of last follow-up. Overall survival (OS) was calculated from the date of diagnosis until patient's death from any cause or date of last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to the time of disease progression or date of last follow-up. Survival curves were estimated by the method of Kaplan and Meier and comparison between curves was done by log-rank testing. Univariate analysis of parameters with possible

prognostic significance for DSS, OS or PFS was performed using Cox proportional hazards regression analysis. Factors significant at the 0.05 level in univariate analysis and age at diagnosis, regardless of statistical significance, were included in a multivariate analysis model. In this model P values below 0.05 were considered significant. To compare clinical outcome parameters among different subgroups of FMF patients a chi-square test for goodness of fit was performed for categorical variables and a Kruskal-Wallis test was performed to compare medians between subgroups. P values below 0.05 were considered significant for both tests.

RESULTS

Clinical characteristics at diagnosis

The main clinical characteristics are summarized in **Table 1**. The study included 147 males and 56 females (male to female ratio: 2.6). The median age at diagnosis was 59 years (range: 15 - 93 years). Only three of 203 patients (1.5%) were aged 18 years or younger. Most patients (86%) presented with generalized skin lesions involving multiple body regions, while nine (4%) and 20 (10%) patients had presented with solitary or localized skin lesions, respectively. Thirteen patients showed erythroderma at first presentation. This group included six patients with stage III (skin-limited disease) and seven patients with stage IV, four of whom met the criteria for peripheral blood involvement of Sézary syndrome (SS).

In 129 of 203 patients (64%) skin lesions were preferentially located and most pronounced in the head and neck area **(Figure 1)**. Infiltrated plaques in the eyebrows with concurrent alopecia were observed in more than 50% of patients, either at the time of diagnosis or during follow-up. Three patients presented with a leonine face. Only 20 of 203 (10%) patients had no skin lesions in the head and neck area at first presentation. Associated alopecia on affected skin sites was seen in about 80% of patients. Secondary bacterial infection was observed in 43 patients (21%) and was extensive in 21 of them. Almost 80% of patients complained of moderate to severe pruritus.

Four patients had a history of Hodgkin lymphoma, nine to 22 years before the diagnosis FMF was made. Three patients had a coexistent hematological disorder, including one patient with a B-cell chronic lymphocytic leukemia, one patient with a myelodysplastic syndrome and one patient with essential thrombocytosis.

Table 1. Clinical characteristics of 203 patients with follicular mycosis fungoides

Age at diagnosis, median (range) in years	59 (15-93)
Male-female ratio	2.6 (147:56)
Duration of skin lesions before diagnosis, median (range) in months	24 (1-400)
Most severe type of skin lesions at diagnosis	
Patches a/o follicular papules	67 (33%)
Plaques	58 (29%)
Tumors and nodules	55 (27%)
Erythroderma	6 (3%)
Nodal/visceral involvement	17 (8%)
Mainly head/neck involvement	129 (64%)
Alopecia	
Yes	150 (81%)
No	36 (19%)
Unknown	17
Eyebrow involvement	
At diagnosis	85 (44%)
During follow up	25 (13%)
No involvement	83 (43%)
Unknown	10
Extent of skin lesions	
Generalized	174 (86%)
Localised	20 (10%)
Solitary	9 (4%)
Pruritus	
Yes	133 (77%)
No	40 (23%)
Unknown	30
Secondary bacterial infection	
Focal	21 (10%)
Prominent	21 (10%)
Follicular mucinosis	
Present	156 (78%)
Absent	43 (22%)
Unknown	4
Large cell transformation	
Skin	33 (16%)
Extracutaneous	1 (0.5%)
Initial treatment	
Topical steroids	21 (10%)
UVB	12 (6%)
PUVA	61 (30%)
PUVA with retinoids or with IFN-a	19 (9%)
PUVA + local radiotherapy	28 (14%)
Local radiotherapy	21 (10%)
Total skin radiotherapy	20 (10%)
Systemic chemotherapy	14 (7%)
Other	7 (3%)
Complete remission on initial therapy	51 (25%)

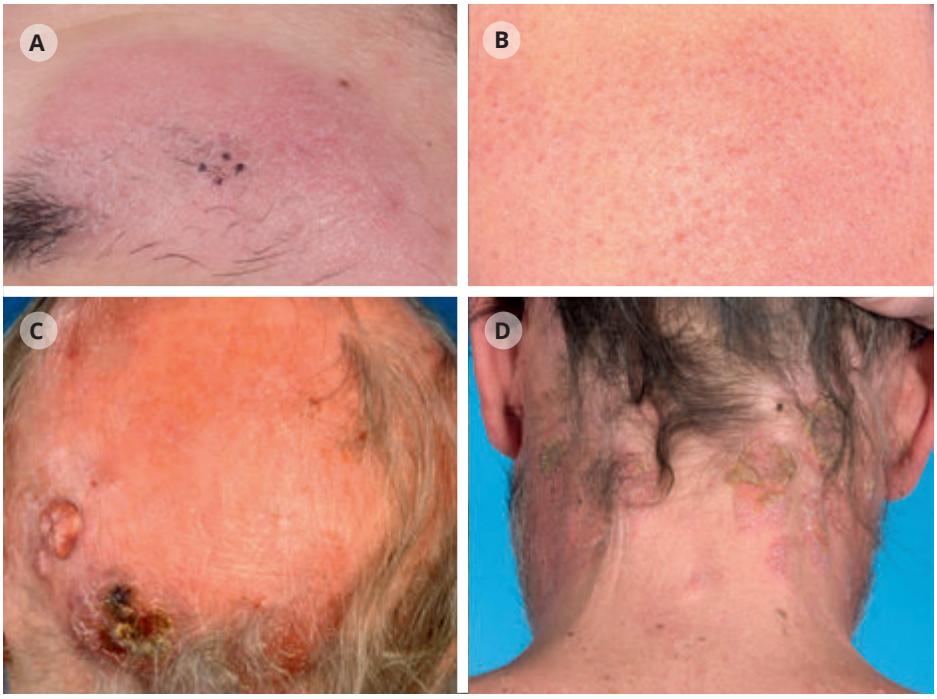

Figure 1. Clinical appearances of FMF. Solitary patch with associated alopecia in left eyebrow (A). Grouped follicular papules on the trunk (B). Alopecia and ulcerating tumors on the scalp (C); and plaques in the neck showing follicular accentuation and secondary bacterial infection (D).

Clinical stage at diagnosis

At time of diagnosis 186 patients (92%) had skin-limited disease, while seventeen patients (8%) had nodal or visceral disease at first presentation (stage IV). Among those patients with skin-limited disease 67 patients presented with only patches, follicular papules, acneiform or keratosis pilaris-like lesions (stage IA-IIA), 55 patients with nodules or tumors (stage IIB), six patients with erythroderma (stage III) and 58 patients with plaques. As noted before, it is uncertain on the basis of clinical evaluation alone, if patients presenting with plaques should be classified as stage IA-IIA or stage IIB. Based on histologic criteria (see section Patients and Methods) distinction was therefore made between patients presenting with early plaque-stage disease (n=17) and patients with advanced plaque-stage disease (n=41) **(Figure 2)**. The OS and DSS of the whole group of patients presenting with plaques (n=58) were intermediate between those of patients presenting with only follicular papules and/or patches and those of patients presenting with nodules, tumors or erythroderma. However, patients histologically

classified as early plaque-stage FMF had almost identical survival and progression data as patients presenting with only patches and follicular papules, while patients histologically classified as advanced plaque-stage FMF had a very similar course to patients presenting with tumors or nodules **(Supplementary Table 1)**. The differences in 10-year OS (80% vs. 25%; p=0.004) and 10-year DSS (100% vs. 35%; p=0.006) between those two subgroups of patients with early plaque-stage and advanced plaque-stage FMF were highly significant, which confirms the usefulness of the clinicopathologic approach used (**Figure 3A-3B**). Taken together, three clinically relevant stages were distinguished: patients with early skin-limited disease (n=84; Group A), patients with advanced skin-limited disease (n=102; Group B) and patients presenting with extracutaneous disease (n=17; Group C) (**Figure 3C-3D**).

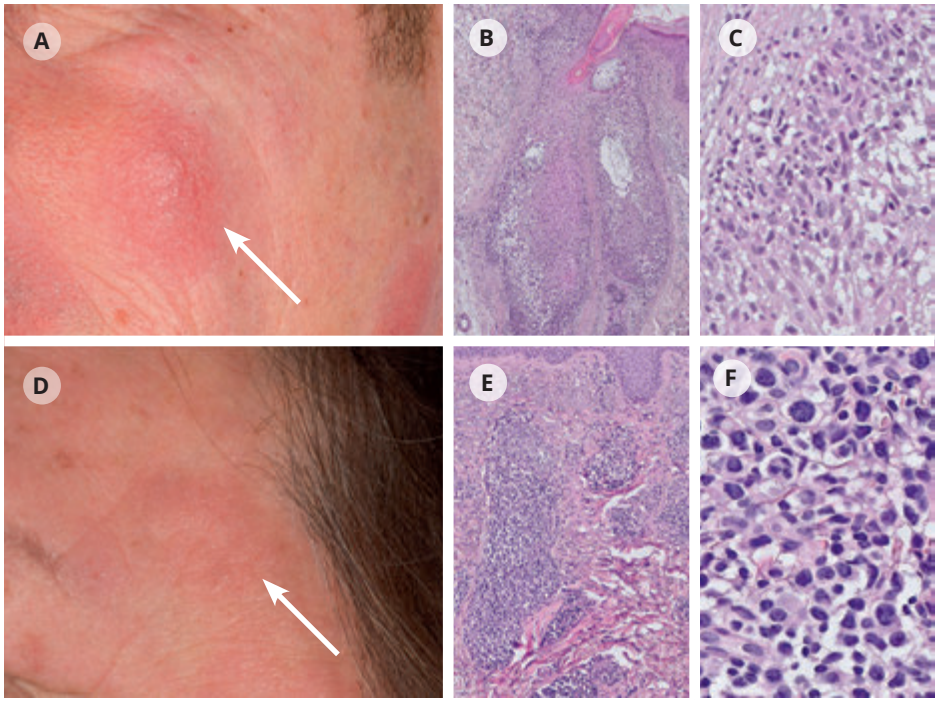

Figure 2. Clinicopathologic classification in 2 patients with FMF presenting with similar plaques on the face. Histological examination of a plaque on the left cheek of the first patient (A) shows mucin depositions (follicular mucinosis) and a sparse perifollicular and intrafollicular infiltrate (B); Detail of the infiltrate shows small neoplastic T-cells with pleomorphic nuclei (C). Histological examination of a plaque on the left temple of the second patient (D) shows dense intrafollicular infiltrates with a predominance of medium-sized to large neoplastic T-cells (E and F).

Prognostic factors

Both in univariate and multivariate analysis, age at diagnosis >60 years, clinical stage (as defined above) and the presence of extensive secondary bacterial infection were independent factors associated with reduced OS, DSS and PFS, while gender, the extent of skin lesions, the duration of skin disease prior to diagnosis, follicular mucinosis and the presence of pruritus had no effect on survival or disease progression **(Supplementary Table 2).** The presence of large cell transformation at first presentation was independently associated with reduced PFS, but not with reduced OS. The relation between LCT and DSS was borderline significant (p=0.05). Large cell transformation at first presentation was observed in 33 patients, including 21 cases in group B, 10 in group C and only two in group A. The median survival of these 33 cases was 32 months, the 5- and 10-year OS 40% and 20%, respectively, and the 5- and 10-year DSS 41% and 20%, respectively.

Extensive secondary bacterial infection was particularly found in patients with advanced FMF (19 of 21 patients) and in most cases affected skin lesions in the head and neck region (17 of 19 patients) **(Figure 1D).** The median survival of these 21 patients was only 22 months, the 5-year OS and DSS 20% and 26% respectively.

Clinical course and survival

After initial therapy, 25 of 203 (12%) patients never had a relapse and the median duration of this sustained complete remission was 68 months (range: 12-169 months); 101 patients (50%) showed continued disease without progression to a higher stage, while 77 patients (38%) showed disease progression **(Table 2)**. Altogether, 25 patients presented with (n=1) or developed visceral involvement. Visceral sites most commonly affected were the central nervous system (n=11), lungs (n=9), bone marrow (n=6) and oral or nasal mucosa (n=5), while three patients developed peripheral blood involvement. After a median follow-up of 51 months (range 3-260 months) 32 of 203 patients were in complete remission, 78 patients were alive with disease, 59 patients died of lymphoma and 34 died of unrelated disease. For those 203 patients the 5- and 10-year OS were 67% and 45%, respectively and the 5- and 10-year DSS were 75% and 60%, respectively, with significant differences between the three clinical subgroups **(Table 2; Figure 3C-3D)**. Among 84 patients with early skin-limited disease (group A) 17 patients (20%) developed skin tumors and 2 (2%) extracutaneous disease. Five (6%) patients died of

lymphoma after a median follow-up of 76 months (range: 32-198 months). The clinical presentation and histology of these five cases did not differ from other patients in group A. Interestingly, all five patients had presented with widespread follicular papules and patches, and none of them with plaques.

Table 2. Clinical course and outcome

	Total group (n=203)	Group A (n= 84)	Group B (n=102)	Group C (n=17)	P-value
Result initial treatment [a]					
Complete remission	51 (25%)	25 (30%)	25 (25%)	1 (6%)	0.22
Partial remission	104 (51%)	47 (56%)	52 (51%)	5 (29%)	0.34
Stable disease	29 (14%)	12 (14%)	14 (14%)	3 (18%)	0.75
Progression during therapy	16 (8%)	0	9 (9%)	7 (41%)	<0.05
Duration of follow-up (median (months); range)	51 (3-260)	70 (9-260)	46 (3-204)	20 (4-125)	<0.05
Clinical course after initial treatment					
Sustained complete remission [b]	25 (12%)	17 (20%)	7 (7%)	1 (6%)	<0.05
Continuous disease without progression	101 (50%)	48 (57%)	51 (50%)	2 (12%)	0.07
Disease progression	77 (38%)	19 (23%)	44 (43%)	14 (82%)	<0.05
PFS (median (months); range)	41 (2-247)	57 (4-247)	40 (2-189)	20 (4-125)	<0.05
Disease progression during follow-up					
Progressive skin lesions [c]	17 (8%)	17 (20%)	-	-	-
Nodal involvement	26 (13%)	2 (2%)	24 (24%)	-	<0.05
Visceral involvement	24 (12%)	1 (1%)	20 (20%)	3 (18%)	<0.05
Death of lymphoma	59 (29%)	5 (6%)	40 (39%)	14 (82%)	<0.05
Large cell transformation					
At diagnosis	33 (16%)	2 (2%)	21 (21%)	10 (59%)	<0.05
During follow-up	22 (11%)	4 (5%)	16 (16%)	2 (12%)	0.08
Status at last follow-up					
Alive without disease	32 (16%)	19 (23%)	12 (12%)	1 (6%)	0.08
Alive with disease	78 (38%)	50 (60%)	26 (26%)	2 (12%)	<0.05
Died of other cause	34 (17%)	10 (12%)	24 (24%)	0	<0.05
Died of FMF	59 (29%)	5 (6%)	40 (39%)	14 (82%)	<0.05
DSS (at 5 years / at 10 years)	75% / 60%	96% / 93%	65% / 40%	23% / 2%	<0.05
OS (at 5 years / at 10 years)	67% / 45%	92% / 72%	55% / 28%	23% / 2%	<0.05

Group A; early skin-limited FMF; Group B; advanced skin-limited FMF; Group C: FMF with extracutaneous disease at diagnosis. (a) Result of initial therapy of 2 patients in Group B and of 1 patient in group C was unknown. (b) Sustained complete remission: after initial complete remission no relapse was seen during follow-up. (c) Development of skin tumors in patients of group A. Patients presenting with advanced plaque stage FMF, who developed skin tumors during follow-up were not scored as progressive disease.

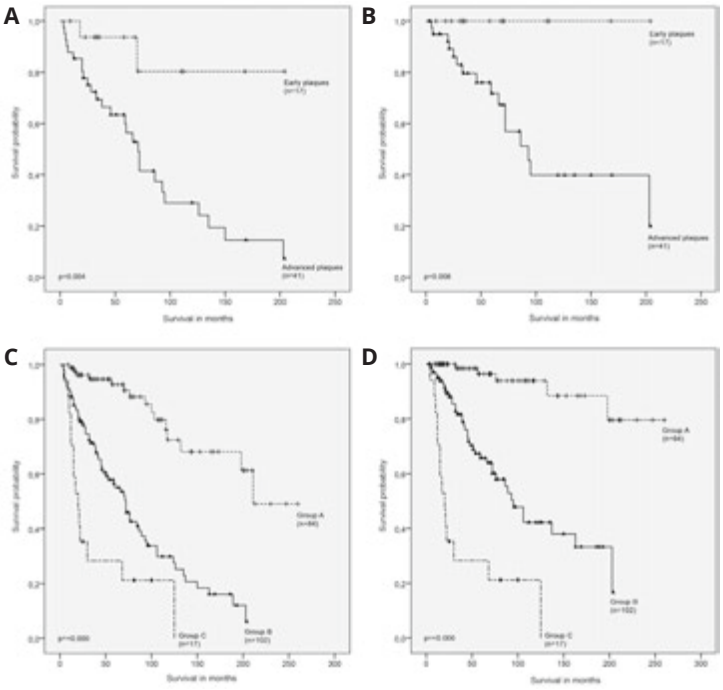

Figure 3. OS and DSS of patients with FMF. OS and DSS of patients with early and advanced plaque-stage FMF (A and B). OS and DSS of patients with early skin-limited FMF (group A), advanced skin-limited FMF (group B), and FMF presenting with extracutaneous disease (group C) (C and D). *DSS indicates disease-specific survival; FMF, folliculotropic mycosis fungoides; OS, overall survival.*

DISCUSSION

While previous studies emphasized the worse prognosis of FMF as compared to classic type MF, more recent studies focused attention on a subgroup of FMF with a favorable prognosis.[5,10,11] However, criteria to differentiate between indolent and more aggressive FMF are still ill-defined, which is mainly caused by the inability of the clinical staging system (TNMB system) to classify FMF patients presenting with plaques in a clinically meaningful way.[3,4,16] The results of the present study, in which additional histologic criteria were used to distinguish early from advanced plaque stage FMF, provide useful criteria to differentiate between indolent and aggressive FMF. Multivariate analysis showed that clinical stage, age at diagnosis, LCT and extensive secondary bacterial infection were independent risk factors for disease progression and/or poor survival.

Clinical staging in patients with FMF

In classic MF, clinical stage according to the revised TNMB criteria is the most important factor in predicting survival and risk of disease progression.[19,22] In our study FMF patients presenting with only patches and/or follicular papules (stage IA-IIA) had indeed an excellent prognosis with a 5-year OS and DSS of 92% and 95%, respectively, while patients presenting with tumors and/or nodules (stage IIB) had a 5-year OS and DSS of 50% and 59%, respectively (see **Supplementary Table 1**). The favorable prognosis of patients presenting with only patches and/or follicular papules is consistent with recent literature.[5,10,11] It is however arbitrary if FMF patients presenting with plaques should be classified as stage IA-IIA or as stage IIB.[9] Clinically identical plaques may be caused by dense neoplastic infiltrates, but also by excessive mucin depositions or an extensive inflammatory infiltrate. In the present study, distinction was therefore made between plaques histologically characterized by sparse intra- and/or perifollicular infiltrates containing relatively few and mainly small neoplastic T-cells ('early plaque-stage FMF') and plaques histologically showing more extensive confluent or diffuse infiltrates containing many often medium-sized to large tumor cells ('advanced plaque-stage FMF'). Patients histologically classified as early plaque-stage FMF had an almost equal clinical course and survival to patients presenting with only patches and/or follicular papules, while patients histologically classified as advanced plaque-stage FMF had a very similar course to patients presenting with tumors, confirming the usefulness of this clinicopathologic approach (**Supplementary Table 1**). Our results validated those of Hodak et al., presented at the 2014 meeting of the EORTC Cutaneous Lymphoma Group in Paris. Using a very similar clinicopathologic approach and very similar histologic criteria distinction could be made between early- and advanced-stage FMF (E. Hodak; personal communication). Whether patients with advanced plaque-stage disease should be classified as tumor (T3 score; stage IIB) rather than plaque-stage disease (T2 score; stage IA-IIA), as suggested by Hodak et al., is a matter of debate. The similar survival and progression rates between patients with advanced plaque-stage and tumor-stage FMF seem to justify such an upgrading. However, in the revised TNMB system, skin score is determined by clinical presentation and skin lesions histologically classified as either early or advanced plaque-stage FMF may be clinically indistinguishable (**Figure 2**).[16] Additional studies investigating the reproducibility of histology-based distinctions between early and advanced plaque-stage FMF should be awaited before further revisions of the TNMB system are made. A meeting of the EORTC Cutaneous Lymphoma

Pathology Group, in which the reproducibility of a histologic stratification is investigated by an independent panel of (dermato)pathologists is scheduled for 2017.

Prognostic factors in FMF

Previous studies have been unsuccessful to detect independent prognostic parameters, probably because of the relatively small number of patients included in these studies.[6,7] In the present study, in addition to clinical stage, age >60 years, LCT and the presence of extensive secondary bacterial infection at the time of first presentation were independent factors associated with reduced OS, DSS and/or PFS. Clinical stage of disease, age and LCT are well-known risk factors in classic MF.[19,22,23,24] The presence of secondary bacterial infection as an adverse risk factor has not been found before. It is well known that bacterial toxins acting as superantigens may stimulate the proliferation of malignant T-cells and may worsen disease in patients with a cutaneous T-cell lymphoma.[25,26] However, whether this or other mechanisms are responsible for the poor outcome in FMF patients with extensive secondary bacterial infection is unknown.

In conclusion, the results of the present study confirm the existence of a substantial subgroup of patients with FMF with a good prognosis. Apart from patients presenting with only patches and/or follicular papules, this group also contains patients with plaques histologically characterized by sparse intra- and/or perifollicular infiltrates containing relatively few and mainly small neoplastic T-cells. Distinction between patients with indolent and aggressive FMF is important, since it may have therapeutic consequences.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Overall survival, disease specific survival and progression free survival in FMF

				OS		DSS		PFS	
Skin lesions at diagnosis	Stage	Group	No (%)	5-year	10-year	5-year	10-year	5-year	10-year
Only follicular papules a/o patches	IA-IIA	A	67 (33%)	92%	71%	95%	88%	80%	67%
Plaques Total group	IA-IIA	A-B	58 (29%)	66%	37%	79%	50%	60%	45%
Plaques (PA: early-stage [a])	NA	A	17 (8%)	83%	80%	100%	100%	78%	78%
Plaques (PA: advanced-stage [b])	NA	B	41 (20%)	56%	25%	75%	35%	52%	26%
Tumors and nodules	IIB	B	55 (27%)	50%	27%	59%	40%	57%	31%
Erythroderma [c]	III	B	6 (3%)	56%	-	68%	-	58%	-
Nodal / Visceral involvement	IV	C	17 (8%)	23%	2%	23%	2%	22%	2%

Stages according to revised ISCL/EORTC criteria.[13] OS: Overall survival, DSS: Disease specific survival, PFS: Progression free survival; NA: T-score not applicable to cases of FMF presenting with plaques.

(a) Survival of patients with early plaque stage FMF showed no significant differences compared to patients with follicular papules a/o patches (OS: p=0.89, DSS: p=0.36, PFS: p=0.99).

(b) Survival of patients with advanced plaque stage FMF showed no significant differences compared to patients with tumors and nodules (OS: p=0.99, DSS: p=0.75, PFS: p=0.87).

(c) Among 6 patients with skin-limited erythroderma a follow-up of 10 years was not reached.

Supplementary Table 2. Uni- and multivariate analysis of DSS, OS and PFS in 203 patients with FMF

		DSS			
	N	Univariate analysis		Multivariate analysis	
Total	**203**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Sex			0.60		
Women	56	1			
Men	147	0,9 (0,5-1,5)			
Age at diagnosis			0.12		0.02
≤60 years	111	1		1	
>60 years	92	1,5 (0,9-2,5)		2,0 (1,1-3,7)	
Extent of skin lesions			0.28		
Solitary	9	1			
Localised	20	2,3 (0,3-20,3)			
Generalised	174	3,8 (0,5-27,2)			
LCT at diagnosis			<0.001		0.05
No	170	1		1	
Yes	33	3,8 (2,2-6,7)		1,9 (1,0-3,6)	
Time to diagnosis			0.91		
≤12 months	59	1			
13-60 months	102	0,9 (0,5-1,6)			
> 60 months	42	1,0 (0,5-2,0)			
Mucinosis follicularis			0.28		
No	43	1			
Yes	156	0,7 (0,4-1,3)			
Pruritus			0.12		
No	40	1			
Yes	133	1,8 (0,9-3,9)			
Secondary infection			<0.001		<0.001
No	161	1		1	
Focal	21	2,1 (1,0-4,4)		1,8 (0,8-3,8)	
Prominent	21	4,8 (2,5-9,1)		4,6 (2,3-9,1)	
Clinical stage			<0.001		<0.001
Early skin-limited FMF	84	1		1	
Advanced skin-limited FMF	102	9,6 (3,8-24,7)		7,1 (2,7-18,6)	
Extracutaneous FMF	17	37,5 (13,2-107)		30,0 (9,7-92,3)	

Supplementary Table 2. *(continued)*

OS				PFS			
Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
	0.44				0.87		
1				1			
1,2 (0,7-2,0)				1,0 (0,6-1,7)			
	<0.001		<0.001		0.03		0.002
1		1		1		1	
2,9 (1,9-4,5)		3,2 (1,9-5,4)		1,6 (1,0-2,6)		2,2 (1,3-3,6)	
	0.22				0.20		
1				1			
4,9 (0,6-38,7)				3,5 (0,4-29,3)			
5,6 (0,8-40,4)				5,1 (0,7-36,7)			
	<0.001		0.07		<0.001		0.01
1		1		1		1	
2,5 (1,6-4,1)		1,8 (1,0-3,2)		3,0 (1,8-5,0)		2,1 (1,2-3,9)	
	0.51				0.74		
1				1			
1,0 (0,6-1,6)				1,2 (0,7-2,0)			
1,3 (0,8-2,3)				1,0 (0,5-1,9)			
	0.12				0.18		
1				1			
0,7 (0,4-1,1)				0,7 (0,4-1,2)			
	0.03		0.26		0.05		
1		1		1			
2,0 (1,1-3,8)		1,5 (0,8-2,9)		2,0 (1,0-3,9)			
	<0.001		<0.001		<0.001		<0.001
1		1		1		1	
2,0 (1,1-3,7)		1,7 (0,9-3,2)		1,4 (0,7-2,9)		1,2 (0,6-2,4)	
3,7 (2,1-6,3)		4,1 (2,1-8,0)		3,5 (2,0-6,2)		3,4 (1,8-6,2)	
	<0.001		<0.001		<0.001		<0.001
1		1		1		1	
5,4 (3,0-9,7)		3,3 (1,7-6,5)		2,8 (1,6-4,8)		1,9 (1,0-3,4)	
12,5 (5,9-26,7)		8,7 (3,6-21,0)		8,7 (4,3-17,9)		5,7 (2,5-13,0)