The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients

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PROCLIPI Study investigating Prognostic Factors in Early Stage MF

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What's already known about this topic?

- MF is a rare skin cancer which may closely mimic common inflammatory dermatoses in early stage disease
- There is no singular diagnostic test for mycosis fungoides
- Diagnosis or early stage mycosis fungoides requires close clinical, pathologic and genotypic correlation

What does this study add?

- This study reports on the clinical characteristics of a large international cohort of early-stage MF patients whose diagnosis has been confirmed centrally following clinicopathologic review
- The median age of presentation is 57yrs which is significantly younger than those presenting with advanced-stage MF at 66yrs
- This study confirmed a worldwide male predominance in early-stage MF (1.7males:1female)
- A diagnostic delay of early-stage MF is frequent with a median delay of 3 years

Abstract

Survival in mycosis fungoides (MF) is varied and may be poor. PROCLIPI (PROspective Cutaneous Lymphoma International Prognostic Index) Study is a web-based data collection system for early-stage MF with legal data sharing agreements

permitting international collaboration in a rare cancer with complex pathology. Clinicopathological data must be 100% complete and in-built intelligence in the database system ensures accurate staging.

Pre-defined datasets for clinical, haematological, radiological, immunohistochemical, genotypic, treatment and quality-of-life are collected at first diagnosis of MF and annually to test against survival with the aim of developing a prognostic index. Biobanked tissue samples are recorded within a Federated Biobank for translational studies.

430 patients were enrolled from 29 Centres in 15 countries spanning 5 continents. 348 were confirmed as early-stage MF at Central Review. The majority had classical MF (81.6%) with a CD4 phenotype (88.2%). Folliculotropic MF was diagnosed in 17.8%. Most presented with stage I (IA:49.4%,IB:42.8%) but 7.8% presented with enlarged lymph nodes (stage IIA). A diagnostic delay between first symptom development and initial diagnosis was frequent (85.6%), with a median delay of 36 months (interquartile range=12-90 months). This highlights the difficulties in accurate diagnosis, which is contributed by lack of a singular diagnostic test for MF.

This confirmed early-stage MF cohort is being followed-up to identify prognostic factors, which may allow better management and improve survival by identifying patients at risk of disease progression. This study design is a useful model for collaboration in other rare diseases, especially where pathological diagnosis can be complex.

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Introduction

Mycosis fungoides (MF) is a rare cancer with an incidence of <1 per 100,000 but much higher prevalence given the long survival in early-stage disease (stages IA-IIA)[1]. Meaningful studies in rare disease require large-scale international collaboration to power them. Such collaboration requires expert co-ordination, accessible data collection systems and legal data share agreements to be implemented which is challenging. Here we present the PROCLIPI (PROspective International Cutaneous Lymphoma Prognostic Index) Study for early-stage MF as a prototype study for international collaborations in rare disease and present our initial findings and central review process.

Diagnosis of early-stage MF (IA-IIA) is complex due to a number of factors including varied clinical appearance and similarity to inflammatory skin diseases such as eczema/psoriasis, subtle variations in pathological/immunohistochemical features and lack of a singular specific diagnostic test. Indeed, inter-observer variation for diagnosis of T-cell lymphomas, including MF is well recognized and a definite diagnosis often requires careful clinicopathologic correlation with discordance in diagnosis ~20%[2]. Hence misdiagnosis and diagnostic delay are frequent. To confirm diagnosis in PROCLIPI, all recruited patients were subject to expert central clinicopathological review. This is of paramount importance to ensure patients meet criteria for a diagnosis of early-stage MF and those with benign inflammatory dermatoses are rejected.

Patients with early-stage MF typically have a slowly progressive evolution over years or even decades to widespread patches or more infiltrated plaques. Morbidity can be considerable with pain, pruritus and disfigurement and patients have been demonstrated to have a poor quality of life[3,4]. However, disease specific mortality may occur in some patients[5] and up to one-third of patients presenting with early-stage disease progress within 10 years to advanced stage [IIB-IVB][6] characterized by cutaneous tumours or erythroderma and/or nodal/leukaemic/visceral involvement. If patients with a poor prognosis could be pre-selected and referred for more intensive management there may be improved disease control and potentially survival. Given the rarity of MF, only a large international multicentre prospective study will improve our understanding and allow better diagnostic tests for more efficient diagnosis.

Specific clinical characteristics have been associated with a worse prognosis in MF. However, most are associated with advanced-stage disease and their relevance in early-stage disease is unknown. These include male sex, higher age, raised serum lactate dehydrogenase (LDH) and histological features such as folliculotropism[7-12] and large cell transformation (LCT)[11-17]. Some favourable prognostic factors have been identified for early-stage disease and include poikiloderma[18], hypopigmented patches, a CD8+ve phenotype[19] and co-existing lymphomatoid papulosis[16,20,21]. However, these studies are typically single-centre cohorts and there is frequent discordance between reports. Benton et al 2013 developed a CLIPI but future publications could not validate this[5,22] and large international collaborations are required to develop useful PI's. An international PI may select patients with early MF at higher risk of disease progression for improved management choices.

METHODS:

Study Design & Patients

Datasets [Appendix I] were prospectively defined by the Cutaneous Lymphoma International Consortium (CLIC) over a series of meetings and teleconferences (2012-2014). A secure web-based data system was designed by University Hospital Birmingham (UHB) with in-built intelligence to stage patients which does not allow data to be saved unless clinicopathological datasets are complete[1]. Selected fields are duplicated to cross-check for data consistency. No patient identifiable data are shared and patients are anonymised centrally.

Specialist international centres treating MF were selected via Membership to expert international groups (European Organization for Research and Treatment of Cancer (EORTC), International Society for Cutaneous Lymphoma (ISCL)). A data sharing agreement was signed between each participating Centre and UHB[2].

Since July 2015, all patients referred to the participating centres with a new diagnosis of early-stage MF within the prior 6 months were eligible. The study was reviewed and approved by local ethical committees/institutional review boards prior to recruitment. Patients were given verbal and written patient information about PROCLIPI in their native language. Written consent for participation in this study,

[1] This database is housed on a secure UHB server which is a secure SQL Server housed behind Threat Management Gateway (TMG's) and firewalls. The security of both the web application and technical infrastructure has been penetration tested by an independent ethical hack/security company.[1]

[2] On most occasions the generic agreement was signed but due to the complexity of data sharing and different stipulations between countries, if required, minor amendments were made.

analysis of data and use of blood, skin and lymph tissue for future translational research (Federated Biobank) was obtained at trial entry.

For each recruited patient data on clinical, haematological, pathological, lymph nodes, viscera, bone marrow, genotypical, treatment and quality-of-life information[3] (Skindex–29, Appendix I) is collected at time of diagnosis and updated annually or earlier in the event of disease stage progression or death [Appendix II]. The time in months from onset of MF lesions (as reported by the patient) and first diagnosis of MF at their Centre was recorded to investigate any delay in diagnosis. Delay in diagnosis includes both failure of patients to present to physicians and physicians delay and was pre-defined as the time from occurrence of the patient's first skin lesions and a clinicopathological diagnosis made by their clinician. Note, this time didn't include the time to central pathology review.

Data Monitoring

The PROCLIPI database has an in-built intelligence system which creates email alerts for missing or overdue data, disallows saving of numerically impossible/highly unlikely data, prevents saving of incomplete data and autocalculates mSWAT (modified severity weighted assessment tool) which reflects skin tumour burden and provides a numerical value between 0-400[23-24], blood classification and overall stage (using TNMB)[25]. Additionally, a Data Monitoring Committee, DMC, [Appendix III]

[3] Quality of life data to be recorded using USA Skindex 29 questionnaire (permission granted by MAPI Research Trust, Lyon, France) with translations into English, Spanish, German, Dutch & Italian

manually reviews data for inaccuracies. Queries are raised to the respective institutions if data inaccuracies are suspected and for missed updates.

Central Review

All patients were subject to a clinicopathological review prior to the patient's data being included in the analysis. This was performed to confirm early-stage MF and prevent inclusion of patients with either reactive skin changes or advanced MF. Three internationally recognised leading dermatologists and dermatopathology specialists formed the Central Review panel (RW,LC,WK). The diagnosis of early-stage MF was based on a combination of clinical, histopathologic and immunophenotypic criteria, as published previously[2]. An initial Virtual-Review of representative clinical photographs of cutaneous lesions together with photomicrographs of Haematoxylin & Eosin, CD3, CD4 and CD8 stains was performed. In unclear cases slides were requested for a Real-Time Central Review. Details of the review processes are described in Appendix IV.

Statistical Analysis

The Kruskal-Wallis test was used to analyse difference in medians for the non-parametric continuous variables. The Chi-squared test was used to determine differences in categorical variables. Variables are presented as medians and interquartile ranges for the non-parametric continuous variables. Analyses were performed using STATA SE v15 (StataCorp LP, College Station, Tex, USA).

RESULTS

Central Review

29 international Centres enrolled 430 patients [Fig.1]. Centres unable to comply with the Central Review process were not eligible for this study. Virtual Central Review confirmed 329 patients as early-stage MF. 64 were referred for a Real-Time Central Review and 37 failed (13 advanced-stage and 24 non-diagnostic of MF). Real-time review has been possible for 41/64 patients with 19/41 (46.3%) passing. At the time of manuscript writing, 23 are awaiting real-time review thus, 407/430 patients have completed central review; 348/407 patients were confirmed as early-stage MF (85.5%),16/407 considered advanced-stage disease (3.9%) and 43/407 not diagnostic of MF (10.6%) [Flow diagram of central review results shown in Figure 2].

This report focuses on the 348 patients passing the central review process. However, all patients entered into the PROCLIPI database are followed-up as it is appreciated some of these patients may develop MF or have true MF which could not be confirmed by the Central Review process. In-reality all these patients may be receiving MF treatment from their local Centre.

Patient Demographics

Of the 348 patients there was a male predominance with 219 males and 129 females (ratio1.7:1). Table 1 shows the clinical characteristics.

The clinical stage was IA in 172 (49.4%), IB in 149 (42.8%) and IIA in only 27 patients (7.8%). The median age at diagnosis was 57 years (interquartile range (IQR)=44-67yrs), without significant differences between stage IA (median age=54yrs, IQR=44-66yrs), stage IB (median age=57, IQR=45-67yrs) and stage IIA (median age=61yrs, IQR=44-73yrs) P=0.285. 298 patients (85.6%) reported a diagnostic delay with a median delay of 36 months (IQR=12,90). This was similar in all stages (p=0.1410); 36 months (IQR=12-72months) for stage IA, 48months (IQR=24-100months) for IB and 33 months (IQR=15-87) for IIA. ECOG scores were 0 in 338 patients, 1 in 8 patients, 2 in 1 patient and 4 in 1 patient.

The median mSWAT score at diagnosis of stage IA was 5 (IQR=2-8), IB was 26 (IQR=17-45) and IIA was 32.2 (IQR=11-70). The clinical phenotype was patch-only lesions in 160 patients (46.0%) significantly more often in stage IA/B (53.5% and 42.3%, respectively) than IIA (18.5%), P=0.002; 52 patients (14.9%) had plaque-only lesions, 31/172(18.0%) with stage IA, 18/149 (12.1%) patients with IB and 3/27(11.1%) with IIA. The remaining 136 patients (39.1%) had co-existing patches and plaques. Other clinical features recorded included follicular lesions (24.4%), poikiloderma (15.2%) and hypopigmented lesions (8.0%).

Follicular lesions (clinical lesions of MF showing predilection for hair follicles and include follicular papules, plaques, alopecia, milia and cysts) were present in 85 patients, 67 met a diagnosis of folliculotropic MF, but follicular lesions also occur in classical MF. Follicular lesions were less common in patients with IA (14.4%) than IB (32.2%) or IIA (26.0%) (P=0.009); Whilst poikiloderma and hypopigmentation were

found at a similar frequency in all stages (p= 0.452 and p=0.313 respectively but had a positive association with patches. 12(3.4%) patients had co-existing lymphomatoid papulosis lesions which is similar to previously reported[15,16.]

Skin Histology and Clonality

From central pathology review 284 had classical MF (81.6%), 62 patients (17.8%) had folliculotropic MF (FMF) and 2 syringotropic MF (0.6%). The T-cell phenotype was CD4+ in 307 patients (88.2%). In the 41 with negatively staining CD4 tumour cells 34 were positive for CD8 and 7 double-negative (CD4-CD8-). In addition to CD4 positivity, 7 also had tumour cells staining for CD8 (CD4+CD8+ or double-positive). Six patients (1.7%) had LCT in the skin and 2 of these had FMF.

Not all sites perform T-cell receptor gene analysis in the skin. This was recorded in 205 patients and was clonal in 132 patients (64.4%) at a similar percentage in all stages (P=0.848); 70/109 (64.2%) with stage IA, 46/73 (63.0%) with IB and 16/23 (69.6%) with IIA.

Haematological Parameters and Serum LDH

B-classification data was available in 121/348 patients and was B0 in 96/121 patients (79.3%) and B1 in 25/121 patients (20.7%) (Table 2). By staging definition, no patients had B2 which is criteria for advanced-stage disease (IVA1 or higher). Of the 25 patients with B1 10/55 (18.2%) had IA, 12/46 (26.1%) IB and 3/21 (14.3%) IIA.

Only 33.6% had TCR in blood tested and this was clonal in 8.5% (10 patients). Full blood count (FBC) and differential was tested in 68.7%. Lymphopenia was a frequent abnormality found in 10.3%, 1.7% had lymphocytosis.

LDH was recorded in 244/348patients (70.1%) and was raised in 27 patients (11.1%) particularly in stage IIA (10/23, 43.5%) with respect to IA (8/120, 6.7%) and IB (9/101, 8.9%) ($P<0.001$).

Lymph node involvement

Radiological imaging was not mandatory for this study. It was performed in 143 patients (41.1%) and 23/143 patients (16.1%) had lymph node (LN) enlargement by CT criteria for MF defined as ≥15mm in the greatest diameter (long-axis) by staging definition these patients are IIA. No patients had visceral disease which would be advanced stage (IVB).

Of the 23 patients with enlarged LN on imaging, 9 patients had enlarged nodes at 1 region, whilst the remaining had 2 or more (5 at 2, 4 at 3, 4 at 4 and 1 at 5+ regions). Mostly lymphadenopathy was found at peripheral sites; 69.5% inguinofemoral, 56.5% axillary and 21.7% cervical. Only 1 patient had centrally enlarged LN (1 abdominal). 6 patients had a LN biopsy;4 classed as N1 (dermatopathic lymphadenopathy) and 2 as N2 (early nodal involvement)[25]. The remaining 21 stage IIA patients were recorded as Nx (4 with LN identified by clinical exam alone, no imaging/biopsy and 17 with LN identified on imaging without biopsy).

Discussion

PROCLIPI is a prototype data collection study for rare cancers. The PROCLIPI database is an easily accessible secure web-based system with predefined datasets to allow prospective collection of international data. This unique database checks accuracy of information using in-built intelligence which auto-calculates stage, prevents entry of obscure data and disallows saving of incomplete data. In addition, a Data Monitoring Committee [Appendix I] annually trawls data for inaccuracies which are then raised as queries to Centres. Legal data sharing agreements allow anonymised international data share. An associated Federated Biobank registers tissue stored for future translational studies providing an invaluable resource of detailed clinicopathological/genotypic data linked to pre-treatment biobanked samples.

PROCLIPI recruited a cohort of 430 patients suspected with-early-stage MF in 3 years from 29 Centres in 15 countries spanning 5 continents. This unprecedented collaboration will test parameters recorded against survival to develop a prognostic index powered to identify early-stage MF patients at higher risk of disease progression.

Diagnosis of early-stage MF is complex[2]. Hence, all enrolled patients are subject to a rigorous clinicopathological review. Overall, the central review process was concordant with the diagnosis of early-stage MF in 85.5% of patients with most 'passing' on the initial 'Virtual Central Review' process. 41 patients had Real-Time

review and the 'pass-rate' was 46.3%. Failure of central review was due to advanced-stage disease 3.9% and non-diagnostic in 10.6%. Interestingly, despite the strict criteria for passing central review, of those tested for T-cell clonality in skin (performed at individual sites not centrally) only 64.4% had identification of a T-cell skin clone with similar frequency in each stage P=0.848. Methodology most frequently included the Biomed 2 panel[26] with only one centre using high-throughput-sequencing (HTS) platforms[27]. The sensitivity of standard PCR (and subjective reading by gel electrophoresis) is less than clinically used HTS platforms[28]. Results cannot be standardised given the heterogeneity of methods used regionally/locally. Thus, clonality alone is not a reliable sensitive diagnostic test.

There was a diagnostic delay in 85.6% of patients from onset of lesions to diagnosis of early MF in participating Centres with a median delay of 36 months (not including time for central review) highlighting the need for improved diagnostic tests in early-stage MF. Most patients presented with stage I (49.4%=IA, 42.8%=IB) but 7.8% presented with nodal enlargement (IIA). No difference in delay was noted between stages suggesting that stage IB-IIA are not late diagnosis of 'IA' patients. This could be interpreted that a delay does not result in progression of skin involvement (to a higher stage at least). Nonetheless, delay can be stressful for patients and has the potential to lead to inappropriate treatments. Indeed, at worst, misdiagnosis particularly when followed by inappropriate use of immunosuppressive therapy which may result in a more rapid disease progression[29].

Most (81.6%) presented with classical MF and 17.8% with FMF ratified at central review. FMF has previously been associated with more aggressive disease and a prognosis more similar to tumour-stage disease[7]. However recent publications have shown a subgroup of FMF patients with early-stage disease with a good prognosis[30-32] and these patients will be tracked to determine the prognostic relevance of FMF in early-stage MF.

Distinguishing patches from plaques of MF is subjective but may determine treatment approaches in early-stage disease[33-34]. Benton et al 2013[10] found the presence of plaques to be an independent factor for poor survival in early-stage disease but an adverse outcome due to plaque lesions at diagnosis has not been shown in a prospective study. The revised 2007 staging guidelines doesn't include plaques as a determinant of stage but recommended recording the presence of patch only or patches/plaques ('a' for patches and 'b' for patches/plaques). 46.0% of our cohort presented with patch-only disease and 39.1% with patches/plaques. Plaques were seen in 46.5% with IA but were more frequent in IB disease (57.7%) P=0.045.

The majority of patients (97.1%) presented in good health with an ECOG score of 0. There was a male predominance with male:female ratio1.7:1 and median age of presentation was 57 years (IQR=44-67) with no difference between stages. This is significantly younger than the median age of 64.5years (IQR=55-74) of the cohort of 1275 advanced-stage MF patients reported by our group (P<0.001)[15]. This retrospective analysis of advanced-stage MF found age>60years, LCT in skin, stage

IV and raised LDH all to be independent factors with a worse prognosis[12] but the significance of these findings in early-stage MF is unknown. In this early cohort LCT was verified at central review in 1.7% of cases. A raised serum LDH was found in 11.1% and was significantly raised in IIA (43.5%) compared to IA (6.7%)and IB (8.9%) P<0.001.

Blood involvement in early-stage MF is part of the staging for MF and is utilised in the response criteria[35,36]. The majority of patients tested had no blood involvement (B0=79.3%) but B1 level blood involvement was found in 20.7% occurring in all stages. Lymphopaenia was a frequent haematologic abnormality in this cohort with early-stage MF (10.3%) and increased to 29.6% in IIA. It should be noted these tests are at diagnosis, so MF treatment is not the cause. Lymphopaenia is associated with immunosuppression which may reduce the innate immunity ability to keep cancers, or specifically MF, in check. Cyclosporin a potent suppressor of lymphocytes is known to precipitate more aggressive MF and is contraindicated[6,29]. The significance of blood abnormalities in early-MF is unknown and tracking these patients for survival will determine the relevance.

Radiological imaging is not a recommended investigation in early-stage MF unless there is clinical lymphadenopathy or type-B symptoms but nearly half of patients had an imaging scan (143 patients, 41.1%) although only 23/143 patients (16.1%) had enlarged LN.

PROCLIPI has collected a confirmed early-stage MF cohort who will be followed-up for survival to identify prognostic factors which may allow better management and improve survival by identifying patients at risk of progression. There is frequent diagnostic delay with a median of 36 months highlighting the difficulties in accurate diagnosis which is confounded by the lack of a singular diagnostic test and currently relies on clinical, pathological and genotypic studies. Tissue samples within the PROCLIPI federated biobank may be used for future translational studies which may identify biomarkers to aid diagnosis and to identify predictive and prognostic biomarkers and novel targets for therapy. This study design is a prototype which may be useful in other rare diseases.

Legends:

Appendix I – Skindex-29 quality-of-life questionnaire

Appendix II – Datasets Collected For PROCLIPI Study

Appendix III – Members of the Data Monitoring Committee (DMC)

Appendix IV – Central Review Process - methodology

Figure 1 PROCLIPI Recruitment Plus Central Review Results per Centre

Figure 2 Flow Diagram of Central Review Process and Results

Table 1 Clinical data of 348 Early-Stage MF Patients

Table 2 Haematologic Data of 348 Early-Stage MF Patients

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Table 1: Clinical Data from 348 Early Stage PROCLIPI Patients

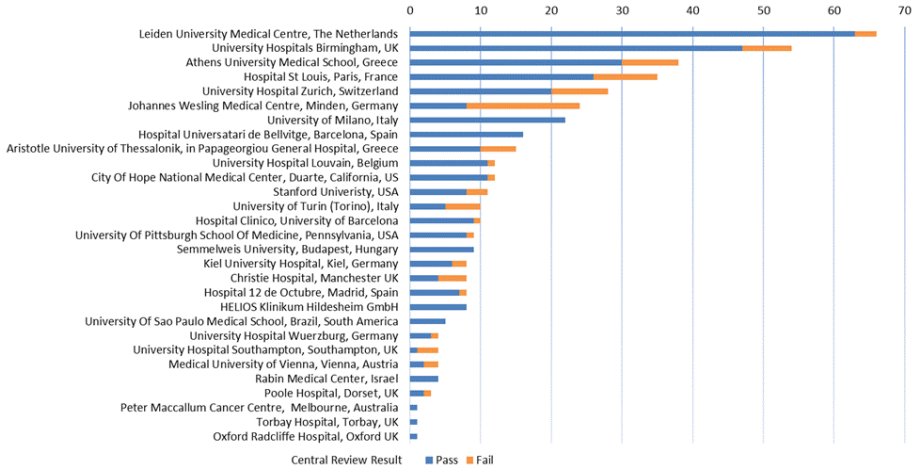
	IA	IB	IIA	All
Number of Patients	172	149	27	348
Age - median (IQR)	54 (44-66)	57 (45-67)	61 (44-73)	57 (44, 67)
Female	64 (37.2%)	58 (38.9%)	7 (25.9%)	129 (37.1%)
Male	108 (62.8%)	91 (61.1%)	20 (74.1%)	219 (62.9%)
Classical Mycosis Fungoides	140 (81.4%)	112 (75.2%)	22 (81.5%)	274 (78.7%)
Folliculotropic Mycosis Fungoides	28 (16.3%)	37 (24.8%)	5 (18.5%)	70 (20.1%)
Clinical Alopecia	13 (7.6%)	27 (18.1%)	9 (33.3%)	49 (14.1%)
Follicular Skin Lesions	30 (17.4%)	48 (32.2%)	7 (25.9%)	85 (24.4%)
Poikiloderma	22 (12.8%)	26 (17.4%)	5 (18.5%)	53 (15.2%)
Hypopigmentation	10 (5.8%)	15 (10.1%)	3 (11.1%)	28 (8.0%)
Confluent Erythema	4 (2.3%)	17 (11.4%)	6 (22.2%)	27 (7.8%)
MSWAT Patch - median (IQR)	3 (1-5)	15 (10-25)	10 (3-39.8)	6 (2, 15)
MSWAT Plaque - median (IQR)	0 (0-2)	2 (0-11)	6 (1-12)	0.9 (0, 5)
MSWAT Tumour - median (IQR)	0	0	0	0 (0,0)
MSWAT Score - median (IQR)	5 (2-8)	26 (17-45)	32.2 (11-70)	11 (5, 28)
Duration of MF like lesions months	36 (12-72)	48 (24-100)	33 (15-87)	36 (12, 90)

Table 2 Blood and Clonality Data from 348 Early Stage PROCLIPI Patients

	IA	IB	IIA	All
Number of patients	172	149	27	348
B classification				
B0*	45 (81.8%)	34 (73.9%)	17 (85.0%)	96 (79.3%)
B1*	10 (18.2%)	12 (26.1%)	3 (15.0%)	25 (20.7%)
B2*	0.00%	0.00%	0.00%	0 (0.0%)
Bx	117 (68.0%)	103 (69.1%)	7 (25.9%)	227 (65.2%)
Raised ALC	2 (1.2%)	3 (2.0%)	1 (3.7%)	6 (1.7%)
Low ALC	9 (5.2%)	19 (12.8%)	8 (29.6%)	36 (10.3%)
Missing ALC	54 (31.4%)	52 (34.9%)	3 (11.1%)	109 (31.3%)
Raised LDH	8 (4.7%)	9 (6.0%)	10 (37.0%)	27 (7.8%)
Missing LDH	52 (30.2%)	48 (32.2%)	4 (14.8%)	104 (29.9%)
Raised WCC	6 (3.5%)	13 (8.7%)	5 (18.5%)	24 (6.9%)
Low WCC	4 (2.3%)	4 (2.7%)	2 (7.4%)	10 (2.9%)
Missing WCC	44 (25.6%)	46 (30.9%)	2 (7.4%)	92 (26.4%)
% lymphocyte	30.1 (25.0, 35.1)	27.2 (21.2, 31.3)	21.2 (16.0, 29.3)	28.1 (21.7, 33.4)
Clonality skin test performed	109 (63.4%)	73 (49.0%)	25 (92.6%)	207 (59.5%)
Clonality blood test performed	51 (29.7%)	51 (34.2%)	15 (55.6%)	117 (33.6%)
Clonal Identical to Index**	5 (9.8%)	2 (3.9%)	3 (20.0%)	10 (8.5%)
Clonal Non-Identical to Index**	6 (11.8%)	7 (13.7%)	1 (6.7%)	14 (12.0%)

*Denominator excludes those classified Bx ie insufficent data to score as B class
**Denominator only includes those who have had a clonality blood test performed
ALC = absolute lymphocyte count, LDH = lactate dehydrogenase, WCC = white cell count

Figure 1 Recruitment of Early Stage MF Patients to PROCLIPI by Centre with Central Review Results



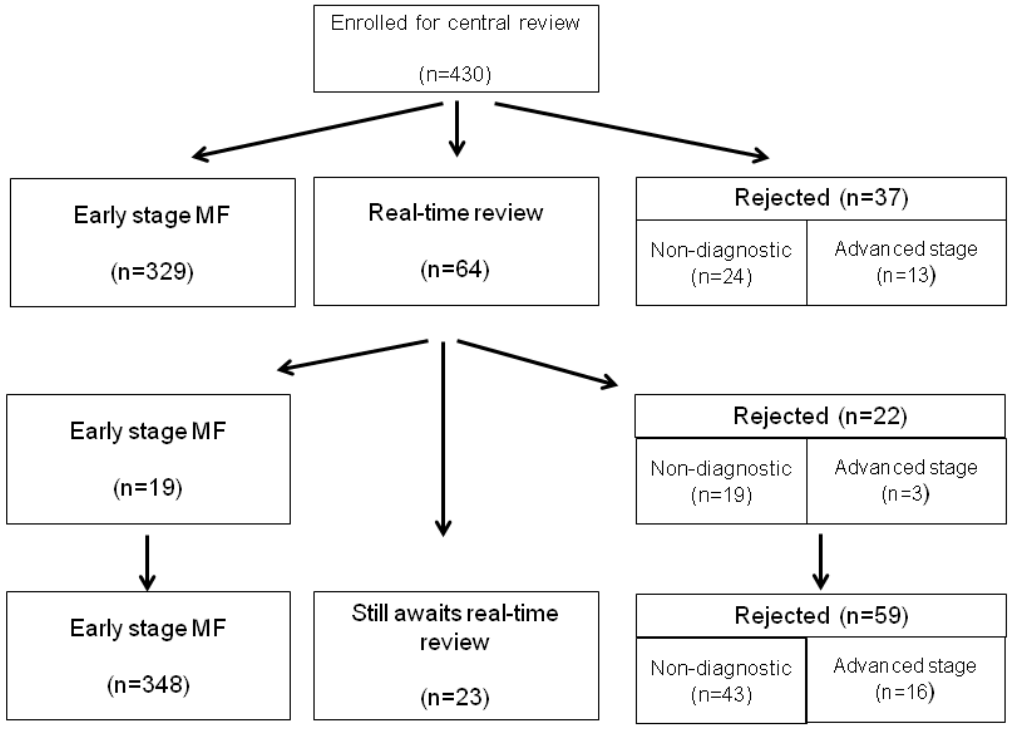


Figure 2 Flowchart showing results of virtual and real-time review processes

Skindex29

These questions concern your feelings over the past 4 weeks about **the skin condition which bothered you the most**. Tick the answer that comes closest to the way you felt.

HOW OFTEN DURING THE PAST FOUR WEEKS DID THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALWAYS
1. My skin hurt	☐1	☐2	☐3	☐4	☐5
2. My skin condition affected how well I slept	☐1	☐2	☐3	☐4	☐5
3. I worried that my skin condition might be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition made it hard to work or do things I enjoy	☐1	☐2	☐3	☐4	☐5
5. My skin condition affected my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition made me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burnt or stung	☐1	☐2	☐3	☐4	☐5
8. I tended to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worried about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itched	☐1	☐2	☐3	☐4	☐5
11. My skin condition affected how close I could be to those I love	☐1	☐2	☐3	☐4	☐5
12. I was ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worried that my skin condition might get worse	☐1	☐2	☐3	☐4	☐5
14. I tended to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I was angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothered my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition made showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worried about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin was irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affected my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

Skindex29
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These questions concern your feelings over the past 4 weeks about **the skin condition which bothered you the most**. Tick the answer that comes closest to the way you felt.

HOW OFTEN DURING THE PAST FOUR WEEKS DID THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALWAYS
21. I was embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition was a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I was frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin was sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affected my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I was humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin bled because of my skin condition	☐1	☐2	☐3	☐4	☐5
28. I was annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interfered with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition made me tired	☐1	☐2	☐3	☐4	☐5

Appendix II

Data Monitoring Committee

The data monitoring committee regularly checks data for inaccuracies. This is led by Felicity Evison, Biostatistican and includes Julia Scarisbrick (Clinical data checks), Rene Stranzenbach (Blood data), Emmilia Hodak (LN data), Rein Willemze (Pathological Data), Pietro Quaglino (Treatment Data).

Data is trawled for inaccuracies and dubious results and missing data are raised as queries to the centre.

Appendix II

PROCLIPI Study | Dataset PROCLIPI | Dropdown Box Options

Clinical	Blood	Skin Biopsy	Lymph Node	Bone marrow	Other Viscera	Clonality	Treatment	Federated Biobank	Sub Header
Date of Clinic Visit	Sezary Cell Evaluation	Sample Method	Node Imaging	Biopsy Performed	Visceral Involvement	Test Performed	Type of Treatment	Type of Tissue Sample Stored	Date of death
Disease Progression (For FU Visit only)	Evaluation Method	Clinical Lesion Type	Imaging Date	Sample Date	Visceral Involvement Detected By Imaging	Date of Test	Date Started	Type of Skin Lesion Sampled	Cause of death (Free text)
Update date	Date of Evaluation	Diagnosis	Imaging Modality	Aspirate	Image Date	Clonality	MSWAT at start of Treatment	How was tissue stored? For skin, LN, BM or viscera	Related to lymphoma Y/N or related to MF/SS
% Body Surface Area (BSA) Patch	Result	Body Site	1 Scm LN Imaging		Visceral Site	Assay for TCR	Date Ended		
% Body Surface Area (BSA) Plaque	Blood Flow Test	Date Taken	Left supraclavicular/cervical			Identical clones between Biospecimens	MSWAT at end of Treatment	Sample depleted	
% Body Surface Area (BSA) Tumour	Date Blood Flow Test	CD3	Right supraclavicular/cervical		Image Modality		Reason for Stop		
History of MF like lesions preceeding diagnosis	ALC (absolute lymphocyte count)		Left axillary	Bone Marrow Trephine			Best Response		
Alopecia	ALC lower range for hospital	CD4	Right axillary						
Follicular MF Lesions	ALC upper range for hospital		Left inguinal femoral		Interpretation				
Hypopigmentation	CD3%	CD8	Right inguinal femoral	Bone Marrow Cellularity	Visceral Involvement Detected By Biopsy				
Poikiloderma	CD4%		Intrathoracic	Tri-lineage Haematopoiesis	Biopsy Date				
Ulceration	CD8%	CD4:CD8 Ratio	Abdominal / Pelvic	CD3	Biopsy Site				
Confluent Erythema	CD4:CD8 Ratio	CD30%	Lymph Node Biopsy	CD4	Interpretation				
Left like lesions	CD4+ CD7-	Ki-67%	Lymph Node Biopsy Date	CD8	CD3				
>1 Scm LN by Physical Exam	CD 4+ CD26-	Main phenotype (of atypical cells)	Sampling Method	CD30+	CD4				
Left supraclavicular/cervical	Other aberrant phenotype %	Presence of hair follicle	Lymph Node Site	CD7-	CD8				
Right supraclavicular/cervical	Other phenotype details	Follicutropism	Large Cell Transformation	Percentage of large cells	CD30				
Left axillary	Eosinophils Value	Presence of eccrine gland	NCI Classification		Ki-67				
Righ axillary	Eosinophils lower range for hospital	Syringotropism	Dutch Grade		Large Cells				
Left inguinal femoral	Eosinophils upper range for hospital	Large Cells	WCI/EORTC 'N' Classification						
Right inguinal femoral	LDH Value	Large Cell transformation	CD3						
Performance Status (ECOG)	LDH lower range for hospital		CD4						
WHO EORTC Classification	LDH upper range for hospital		CD8						
T Class	WCC Value		CD30						
N Class	WCC lower range for hospital		Ki-67						
M Class	WCC upper range for hospital		CD20+						
B Class			Large Cells						
Overall Stage (autocalculated)			Large Cell Transformation						

https://www.proclipi.uhb.nhs.uk

Appendix III

Central Review Process

To ensure that this cohort meets the inclusion criteria of early-stage MF, all patients were subject to a clinicopathological review prior to the patient's data being included in the analysis. This was performed to prevent inclusion of patients with either reactive skin changes or patients with advanced MF. Three internationally recognised leading dermatologists and dermatopathology specialists formed the Central Review panel (Rein Willemze, Lorenzo Cerroni, Werner Kempf).

The diagnosis of early-stage MF was based on a combination of clinical, histopathologic and immunophenotypic criteria, as published previously[2]. Representative clinical photographs of cutaneous lesions together with photomicrographs of Haemtoxylin & Eosin, CD3, CD4 and CD8 stains were sent for 'Virtual Central Review' for every patient. Both low-power field photomicrographs (2-5x) to show the cellular composition and cytology including the architectural pattern and high-power field photomicrographs (20-40x) to show cellular composition/atypia of dermal and epidermal infiltrates were reviewed. The panel viewed photomicrographs electronically independently of each other and referring Centre, and scored the clinical diagnosis, histopathologic diagnosis and final diagnosis as either i) diagnostic of early MF ii) suggestive of early MF or iii) not diagnostic of early-stage MF. If two or three reviewers scored the final diagnosis as diagnostic, the case was accepted otherwise it was rejected. In all other cases slides were requested for a Real-Time Central Review. This subsequent 'Real-Time Central Review' was performed to clarify diagnosis. Involved Centres sent original and if relevant additional histology slides and/or additional biopsies to a Real-Time meeting of the Central Review Panel, cases were re-scored.