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ORIGINAL ARTICLE

Identifying unmet needs and challenges in the definition of a plaque in mycosis fungoides: An EORTC-CLTG/ISCL survey

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Dedicated to the memory of Prof Eric Vonderheid for his tireless search for treatments to help his patients.

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Abstract

Background: Consensus about the definition and classification of 'plaque' in mycosis fungoides is lacking.

Objectives: To delineate a comprehensive view on how the 'plaque' entity is defined and managed in clinical practice; to evaluate whether the current positioning of plaques in the TNMB classification is adequate.

Methods: A 12-item survey was circulated within a selected panel of 22 experts (pathologists, dermatologists, haematologists and oncologists), members of the EORTC and International Society for Cutaneous Lymphoma. The questionnaire discussed clinical and histopathological definitions of plaques and its relationship with staging and treatment.

Results: Total consensus and very high agreement rates were reached in 33.3% of questions, as all panellists regularly check for the presence of plaques, agree to evaluate the presence of plaques as a potential separate T class, and concur on the important distinction between plaque and patch for the management of early-stage MF. High agreement was reached in 41.7% of questions, since more than 50% of the responders use Olsen's definition of plaque, recommend the distinction between thin/thick plaques, and agree on performing a biopsy on the most infiltrated/indurated lesion. High divergence rates (25%) were reported regarding the possibility of a clinically based distinction between thin and thick plaques and the role of histopathology to plaque definition.

Conclusions: The definition of 'plaque' is commonly perceived as a clinical entity and its integration with histopathological features is generally reserved to specific cases. To date, no consensus is achieved as for the exact definition of thin and thick plaques and current positioning of plaques within the TNMB system is considered clinically inadequate. Prospective studies evaluating the role of histopathological parameters and other biomarkers, as well as promising diagnostic tools, such as US/RM imaging and high-throughput blood sequencing, are much needed to fully integrate current clinical definitions with more objective parameters.

INTRODUCTION: BACKGROUND AND LITERATURE REVIEW

The classic definition of mycosis fungoides (MF) is typically based on an evolution throughout the years, from scaly patches usually localized to body areas infrequently exposed to sunlight ('bathing trunk'), to plaques. In some patients, further cutaneous progression to tumours or rarely to erythroderma can occur (advanced-stage skin disease).[1,2] There are profound differences between patients with early-stage and advanced-stage MF. Early-stage MF encompasses most MF patients, presents with patches and/or plaques, shows a good prognosis (median survival >15 years), carries a low risk of extracutaneous involvement, and is generally treated with skin-directed approaches.[3–5] However, disease progression and disease mortality can occur, and the 5-year survival is >80%.[6] By contrast, most patients with advanced-stage show poorer prognosis (median survival of 4–5 years and 5-year survival around 50%), more frequently extracutaneous involvement and are more likely to receive skin directed plus systemic therapies, including new targeted therapies, such as brentuximab vedotin and mogamulizumab, traditional chemotherapy and allogeneic haematopoietic stem cell transplant.[3–10]

According to the currently used TNMB (Tumour Node Metastasis Blood) classification for MF, T1 is defined as a cutaneous involvement with patches and/or plaques (differentiated only by the subscript 'a' if exclusively patches or 'b' if plaques +/− patches) affecting less than 10% of BSA (body surface area), while T2 is characterized by these clinical features affecting 10% or more of BSA; presence of tumours or erythroderma define T3 and T4, respectively.[11] Thus, this classification does not modify the stage according to the presence of plaques, recognizing a higher prognostic significance to the extent of cutaneous involvement. Moreover, the distinction between thin and thick plaques is not mentioned.

Currently, the definition and differentiation between patches and plaques is made according to international consensus exclusively on a clinical basis. As stated by Olsen et al.[11] patch indicates any size skin lesion without significant elevation or induration, while plaque indicates any size skin lesion that is elevated or indurated. Moreover, histology can play a role in this differentiation, as clinically well-defined patches usually show a superficial perivascular lymphocytic infiltrate with epidermotropism mainly along the basal layer, whilst clinical plaques usually display a denser patchy or band-like (lichenoid) lymphoid infiltrate with more pronounced epidermotropism. While Olsen et al.'s[11] T classification mainly relates to classic MF, an interesting point emerges from the recent proposal for a new classification of folliculotropic MF (FMF), the most common variant of

MF. The studies from Hodak et al.[12] and the Dutch group[13] showed that FMF can present with two distinct patterns, referred as the early and advanced stages. The former is characterized by follicle-based patch/flat plaques, keratosis pilaris-like lesions, acneiform lesions (patch/thin plaque type of FMF) and has good prognosis, similar to early-stage classic MF; the latter is distinguished by follicle-based infiltrated/thick plaques and/or tumours (thick plaque/tumour type of FMF), with worse prognosis. The head/neck was involved in all tumour-stage cases, whereas early-stage lesions involved mainly the trunk/limbs.[12] These studies indicated that at least in FMF, in addition to clinical features, histological criteria, such as extent and depth of the peri-follicular infiltrate, are needed for a correct distinction between patch/thin plaques vs thick plaques and accordingly between early and advanced stage disease. However, standardized parameters allowing an unequivocally defined differentiation of the two forms still need to be defined.

As for this issue, some major concerns rise and need to be addressed. First, according to current criteria,[11] the distinction between patch and plaque, in particular the thin plaque, is overall not well-defined; therefore, it is quite subjective and lacks reproducibility, thus leading to potential bias in the collection of clinical patient series with homogeneous characteristics.[14] Second, the distinction between patches and plaques, as reported in the international consensus by Olsen et al., does not carry just a semantic importance, yet affects, more importantly, treatment choice and disease outcome. Accordingly, in the severity-weighted assessment tool (SWAT), which is a commonly used score in clinical trials, multiplication of patch is 1, whilst for plaque is 2, thus recognizing an adverse significance on disease course and treatment response associated in the latter scenario.[15] Plaque elevation is mentioned in the Composite Assessment of Index Lesion Severity (CAILS) score as well.[16] A relevant number of clinical data support the adverse prognostic role of plaques, as well as the need of a different treatment approach in these patients. For instance, both European and US guidelines[17–21] recommend NB-UVB as the primary option for patch MF, whilst for plaque disease (T1b or T2b) PUVA is recommended, as UVA penetrate deeper into the dermis. As for the distinction between thin and thick plaques, NCCN[19] and ESMO guidelines[18] do recommend NB-UVB for patch-thin plaques while PUVA for thicker plaques. However, interobserver and intra-observer variability can be relevant also in the clinical distinction between thin and thick plaques.[22]

There is accumulating body of literature suggesting the differential prognosis of early-stage MF with patches only vs with plaques (Table 1). Series of single-centre studies clearly reported an improved survival for patients with patches compared to plaques.[23–27] In the study by Zackheim et al., in which the survival of 489 patients with CTCL registered between 1957 and 1999 was compared with Californian control population, the overall survival (OS) of T1 patients was similar to the one recorded in the control group; on the contrary, T2 plaque-stage patients had an inferior OS (p = 0.001), whereas T2 patch-stage patients showed an OS similar to the control.[27]

In an updated series of 450 patients from the same centre,[23] a significant OS difference was found between patients with extensive patch versus plaque stage disease; therefore, the authors suggested to split T2 into patch-stage versus plaque-stage disease.[23] The adverse prognostic relevance of plaques reflects the presence of a deeper and more pronounced infiltrate; these data agree with the results of a small cohort of MF patients,[24] which showed that the OS of T1 and T2 patients with a thicker infiltrate on histology (>1 mm) was lower than OS recorded in patients with a thinner infiltrate.

In the UK retrospective analysis of 1502 MF patients, a significant difference in survival and progression was found in early stage with patches alone (T1a/T2a), compared with patches and plaques (T1b/T2b).[3] The presence of plaques at diagnosis was confirmed to carry a significant adverse prognostic factor, with independent values on both OS and progression-free survival (PFS) also in the validation group of 1221 US patients.[28]

Similar results were also reported in the prospective cohort of 1263 MF patients at MD Anderson Cancer Center, which confirmed that OS and PFS were significantly better for early-stage patients with patches (T1a/T2a) than with patches/plaques (T1b/T2b).[5]

According to the data from early-stage patients in the PROCLIPI study, based on the analysis of 395 early-stage MF patients (IA-IIA), the presence of plaques was found to be associated with a more frequent systemic treatment as first-line (17% versus 5% in those with only patches, in multivariate analysis). Moreover, skin plaques (T1b/T2b) predicted a higher risk to tumour-stage progression, with a 4.2 Odds Ratio (OR) of progression.[29] Accordingly, the updated version of the NCCN guidelines clearly separates stage IA from IB and IIA, as skin-directed therapies (SDTs) represent first-line approach in the former group, whilst SDTs and systemic therapies, especially in the presence of high tumour burden and/or plaque disease, are mentioned as first-line approaches in the latter.[20]

Altogether, these data testify the need for a consensus on well-defined and reproducible criteria for an adequate distinction between patches and plaques in daily practice, based not only on clinical but also histological parameters, with possible further subdivision into thin vs thick or possibly redefining plaque as thicker and including previous defined thin plaque with patch, and the need for an internationally revised status of plaques into the current TNMB classification.

AIMS AND METHODOLOGY

This is a collaborative survey-based study between the European Organisation for Research and Treatment of Cancer-Cutaneous Lymphoma Tumours Group (EORTC-CLTG) and the International Society for Cutaneous Lymphoma (ISCL), aiming to delineate a comprehensive view on how the issue

TABLE 1 Main publications addressing the definition of "plaque" and its prognostic role in mycosis fungoides.

Authors	Journal	Year	Key aspects	Summary of results
Martì et al.[24]	Archives of dermatology	1991	Influence of clinicopathologic data on survival in patients with CTCL	At multivariate analysis major prognostic factors in a clinical model, T category and LDH level; in a clinicopathologic model, T category and the thickness of cutaneous infiltrate of the clinically thickest lesion.
Zackhaim et al.[27]	Journal of the American Academy of Dermatology	1999	Relative survival analysis according to skin stages	• 10-year OS: T2 67.4%, T3 39.2%, T4 41.0%. • T2 plaque patients had inferior relative survival ($p = 0.001$) vs T2 with only patches
Kashani-Sabet et al.[23]	Journal of the American Academy of Dermatology	2001	Difference in survival between patients with extensive patch versus extensive plaque stage disease	Significant difference in survival between patients with extensive patch versus extensive plaque stage disease. Modification of the current classification by splitting T2 into patch versus plaque stage disease and incorporating tumours and erythroderma into stage III proved superior.
Agar et al.[3]	Journal of clinical oncology	2010	Significant difference in survival and progression between T1a-T2a versus T1b-T2b patients	• Advanced skin and overall clinical stage, increased age, male sex, increased LDH, large-cell transformation associated with reduced survival and increased risk of disease progression (RDP). • Hypopigmented MF, MF with lymphomatoid papulosis, poikilodermatous MF associated with improved survival and reduced RDP. • Folliculotropic MF associated with an increased RDP.
Talpur et al.[5]	Clinical Cancer research	2012	Better survival rates in early-stage patients with patches compared to patches/plaques.	• OS and PFS significantly better for early-stage patients with patches (T1a/T2a) than with patches/plaques (T1b/T2b). • Risk factors associated with progression or deaths: advanced age, plaque stage, LDH level, and tumour area.
Benton et al.[28]	European Journal of cancer	2013	Cutaneous lymphoma international prognostic index (CLIPi) development	• Significant adverse prognostic factors at diagnosis for early stage (male gender, age > 60, plaques, folliculotropic disease, stage N1/Nx) and late stage (male gender, age > 60, stages B1/B2, N2/3, visceral involvement). • 3 risk groups: 0–1 factors (low), 2 (intermediate), and 3–5 (high). • 10-year OS in the early-stage model 90.3% (low), 76.2% (intermediate) and 48.9% (high) and for the late-stage model 53.2% (low), 19.8% (intermediate) and 15.0% (high).
Fernández-de-Misa et al.[14]	Dermatology	2015	Agreement assessment of morphological evaluation of MF lesions	• Agreement of 67% with respect to the patch or plaque status ($p < 0.001$). • Current systemic treatment (56%; $p = 0.01$) associated with lower agreement. • Younger age at diagnosis, younger age at enrolment and time on systemic treatment independent risk factors for disagreement ($p < 0.001$)
Hodak et al.[12]	Journal of the American Academy of Dermatology	2016	Clinicopathologic features of early-stage and late-stage FMF	OS and disease-specific survival significantly better in the early- (patches and thin plaques) than the advanced-stage group (thick plaques/tumours) ($p = 0.03$ and $p = 0.04$, respectively); 5-year survival of 94% for early- and 69% for tumour-stage FMF.
van Santen S et al.[13]	British Journal of Dermatology	2017	Evaluation of initial treatment results in early- and advanced-stage FMF	• Early-stage FMF patients: SDTs resulting in 28% CR and 83% OR for topical steroids, 0% and 83% for UVB, and 30% and 88% for PUVA. • Advanced-stage FMF: SDTs less effective, with CR and OR rates of 10% and 52%, respectively. Local radiotherapy (CR 63%; OR 100%), total skin electron beam irradiation (CR 59%; OR 100%) and PUVA combined with local radiotherapy (CR 5%, OR 75%) most effective.
Quaglino et al.[31]	British Journal of Dermatology	2021	Plaques and FMF as two major characteristics influencing physicians' treatment choices	In univariate analysis, the use of systemic therapy was significantly associated with higher clinical stage, presence of plaques, higher mSWAT and FMF ($p < 0.001$). Multivariate analysis demonstrated significant associations with the presence of plaques and FMF.

Abbreviation: CR, complete response; FMF, Folliculotropic Mycosis Fungoides; OR, Overall response; OS, Overall survival; PFS, progression-free survival; SDT, skin-directed therapies.

«plaque» is clinically managed in the daily practice in referral centres in Europe, Asia, and America and to evaluate whether the current positioning of plaques in the TNMB classification is adequate. A survey consisting of a 12-item questionnaire was developed by four principal investigators of the present study belonging to the two societies (PQ, JS, MB and EH) and then circulated within a selected panel of EORTC/ISCL experts (pathologists, dermatologists, haematologists and oncologists). The questionnaire deals with the definition of plaques (clinical and/or histological parameters) in the daily clinical management of patients and the relationship with staging and treatment (Table 2). A total of 22 panellists completed the questionnaire and their responses were collected and analysed. Along with multiple guided choice answers, each panellist could add comments from his/her own experience as a free text. Definition of consensus based on per cent agreement was set a priori.[30] Inter-rater agreement was defined as 'total consensus' when 100% of the participants gave the same answer; as 'very high agreement' and 'high agreement' when ≥90% and ≥50% of the responders agreed, respectively; as 'disagreement' when divergence rates ≥50% were recorded. This publication was prepared according to the results discussed in a dedicated workshop during the EORTC-CLTG meeting in Marseille (October 14th–16th 2021).

RESULTS

All 22 panellists responded to all 12 questions (completion rate of 100%). Of 264 answers, 215 were given in the 'closed-ended' form (i.e. multiple-choice) (81.4%) and 49 in the "open-ended" form (i.e. open text format) (18.6%). Agreement rates higher than 50% were recorded in 75% of the questions, while high divergence was found in the remaining 25% of the questions (Table 2), as it follows:

- **Total consensus reached in 16.6% of questions** (Questions 2 and 12): all panellists (100%) state to regularly check for the presence of plaques in daily clinical practice (Q2) and agree to evaluate in a future study whether the presence of plaques, as identified in a shared and reproducible definition, would constitute a separate T class with respect to patches (Q12).
- **Very high agreement reached in 16.6% questions** (Questions 1 and 3): 90.9% of panellists consider relevant the distinction between patches and plaques for the management of early-stage MF patients (Q1). Interestingly, the large majority concurs with the fact that COVID pandemic, despite the impact that personal protective equipment has had on clinical examinations, has not affected the ability to differentiate patches and plaques in daily practice (Q3).
- **High agreement reached in 41.7% of questions** (Questions 4, 5, 6, 10 and 11): most of the panellists (i.e. more than 50% of the responders) use Olsen's definition of plaque (Q4). As for the defining features, 22.7% of responders describe 'induration' as 'any lesion which is harder than normal skin', while 63.6% integrate this concept with a more specific physical feeling of 'higher distance between fingertips during the action of pinching' (Q5). Moreover, most of the panellists would use/recommend the distinction between thin/thick plaques (Q6). Regarding histopathological confirmation, most of the responders agree on obtaining a biopsy from the more infiltrated/indurated lesion, while 13.6% disagree with this approach (Q10). Overall, current positioning of plaques within the TNMB system is generally considered inadequate (Q11).
- **Disagreement reported in 25% of questions** (Questions 7, 8 and 9): high divergence rates (i.e. disagreement ≥50% of the responders) were reported regarding the possibility of a clinically based distinction between thin and thick plaques: 27.3% of the responders believe that this can be achieved through clinical examination, 27.3% dissent from this view, and the remaining 45.4% call on specific clinical and/or histopathological settings in which this differentiation could be possibly achieved. (Q7). Likewise, no agreement was reached regarding the role of pathologic analysis in the definition of plaque and the distinction between thin and thick plaques. Indeed, 50% of panellists do not use pathologic analysis to define plaques and a minority (13.6%) consider pathology only in selected cases (particularly in presence of FMF) (Q8). Similarly, only a minority would use or recommend histology for both the definition of plaques and distinction between patches/plaques or nodules (13.6%), the majority suggesting a potential use only in selected cases (FMF, suspicion of large cell transformation, clinical trials) (Q9).

DISCUSSION

This collaborative survey-based study between the EORTC-CLTG and ISCL has conveyed critical evidence, as far as the status of 'plaque' in MF is concerned, highlighting interesting points regarding the definition of plaques and its relationship with staging and treatment. The main emerging issues are summarized in Table 3.

First, it confirms that detection of plaques in daily clinical practice is unanimously recognized as essential by all the different specialist figures that completed the questionnaire. Coherently, this seems to be firmly related to its perceived impact on clinical management (i.e. Q1), regardless of the impact that the current SARS-CoV-2 pandemic has had on daily practice (i.e. Q3). When it comes to a specific definition of this entity, however, differences emerge in several aspects.

The definition of 'plaque' is commonly perceived as a clinical entity, rather than a histopathological one. The integration of its clinical appearance with histopathological features, to achieve a more precise definition, is generally reserved to specific cases, such as clinically challenging situations. From a clinical point of view, all responders describe 'plaques' according to Olsen's clinical characterization, with some variability with respect to its defining terms (e.g. the expression 'induration' does not seem to

TABLE 2 Questionnaire regarding plaque-analysis of the results.

N°	Question	Option 1	Option 2	Option 3
Q1	Do you consider that the distinction between patches and plaques is relevant for the management of early-stage MF patients?	YES (n = 20, 90.9%)	NO (n = 0, 0%)	Yes, but only in case of disseminated plaques T2 (n = 2, 9.1%)
Q2	Do you always check for the presence of plaques in your daily clinical practice?	YES (n = 22, 100%)	NO (n = 0, 0%)	Yes, but only in patients not responding to SDTs (n = 0, 0%)
Q3	Do you think that COVID pandemic with the need of always wearing gloves when touching a patient has changed your ability to differentiate patches and plaques?	YES (n = 0, 0%)	NO (n = 20, 90.9%)	Yes, only in case of COVID-positive patients (n = 2, 9.1%)
Q4	Do you use the classic definition by Olsen "plaque indicates any size skin lesion that is elevated or indurated"?	YES (n = 17, 77.3%)	NO (n = 0, 0%)	Yes, but integrated with other parameters (n = 5, 22.7%)[a]
Q5	How do you define in the clinical practice the presence of "induration" (4 options): a. Any lesion which is harder (higher induration) than normal skin b. When pinching, the distance between fingertips is higher compared to a close non-involved skin c. Both d. Other parameters (please, specify)	Only a. (n = 5, 22.7%) Only b. (n = 1, 4.6%)	Both a. and b. (n = 14, 63.6%)	Other parameters (n = 2, 9.1%)[b]
Q6	Do you use and/or would you recommend the distinction between thin/thick plaques?	YES (n = 15, 68.2%)	NO (n = 4, 18.2%)	Only in selected cases (please, specify) (n = 3, 13.6%)[c]
Q7	Do you think that the distinction between thin and thick plaques can be made on a clinical basis?	YES (n = 6, 27.3%)	NO (n = 6, 27.3%)	Only in selected cases (please, specify) (n = 10, 45.4%)[d]
Q8	Do you use pathologic analysis to define plaques in your centre?	YES (n = 8, 36.4%)	NO (n = 11, 50%)	Yes, in selected cases (n = 3, 13.6%)[e]
Q9	Do you use and/or would you recommend the use of histology for the definition of plaques and the distinction between patches/plaques/nodules?	YES, always (n = 3, 13.6%)	NO (n = 7, 31.8%)	Yes, in selected cases (n = 12, 54.6%)[f]
Q10	Would you agree to perform a biopsy on the more infiltrated/indurated lesion to confirm the clinical definition of plaque?	YES (n = 13, 59.1%)	NO (n = 3, 13.6%)	Yes, in selected cases (n = 6, 27.3%)[g]
Q11	Do you consider that the actual positioning of plaques within the TNMB system is clinically adequate based on the results of PROCLIPI and other trials?	YES (n = 7, 31.8%)	NO (n = 14, 63.6%)	Yes, in most cases (n = 1, 4.6%)
Q12	Would you agree to evaluate whether the presence of plaques, as identified in a shared and reproducible definition, would constitute a separate T class with respect to patches?	YES (n = 22, 100%)	NO (n = 0, 0%)	–

Note: the number of panellists giving the reported answer is depicted in parenthesis.

[a]Pinching (1), Histology skin thickness (1), Integrated with FMF (1), More or less infiltrated (1), Massive changes in the surface texture (1).

[b]Firmness: the process is thicker than appears above the skin (1), Feeling of a mass (1).

[c]Folliculotropism (1), Not otherwise specified (2).

[d]Only for very thin versus thick plaques (2), In FMF (2), If elevation >0.3 cm (1), According to mSWAT (1), Only for trunk and limbs (1), Not otherwise specified (3).

[e]Doubtful at clinical visit (1), If FMF or tumour stage (1), not otherwise specified (1).

[f]In clinical trials (2), Doubtful at clinical visit (2), If FMF or tumour stage (2), Based to thickness of the infiltrate (2), If Large cell transformation (2), Not otherwise specified (2).

[g]In clinical trials (1), If FMF (1), If Large cell transformation is suspected (2), If involvement >10% BSA (1), If clinically indicated (1).

have a universally accepted meaning). A substantial divergence was found in the responses about histopathological definitions, as most of the panellists do not usually recur to biopsy to confirm the status of plaques and resort to it, possibly on the more infiltrated/indurated lesion, only in selected cases. This could represent an interesting point to be considered in the design of a future prospective study, as well as in the integration of clinicopathologic features in

TABLE 3 Summary of the main results of the EORTC-CLTG1 ISCL survey.

Statements	% agreement
The identification of "plaques" is essential in the daily clinical practice to define patient disease outcome and treatment.	90.9
The definition of "plaque" is commonly perceived as a clinical entity, rather than a histopathological one.	77.3
No consensus has been reached as for the exact definition of thin and thick plaques (except for FMF)	72.7
The current positioning of plaques within the TNMB system is clinically inadequate	63.6

daily practice. As a further point, the survey clearly demonstrates that most of responders do recognize a potential distinction between thin and thick plaques, yet there is no consensus as for the exact definitions. Defining features are still lacking, from both a histopathological and clinical point of view. While no univocal criteria have been reported in the literature to differentiate, with a strong level of evidence, between thin and thick plaques and their prognostic implications in classic MF, recent studies on FMF have shown that clinical features, together with histopathologic evaluation, can help distinguish between these two entities, which constitute two distinct patterns of clinicopathologic features with different prognostic implications (early-stage vs advanced/tumour stage).[12,13]

Finally, most of the panellists feel that the current positioning of plaques within the TNMB system is clinically inadequate and all responders favour a further evaluation of plaques, as identified in a shared and reproducible definition, hypothesizing a separate T class with respect to patches. As thick plaque is generally associated with denser histological infiltrate, higher risk of progression and different therapeutic management, it may be clinically relevant to separate it from patch/thin plaque in our TNMB staging.[12,13]

Some noteworthy elements also emerge from the 'open-ended' answers. First, the assessment of FMF has been repeatedly differentiated from classic MF (i.e. 8 answers Q4, Q6, Q7, Q8, Q9, and Q10): in fact, a more central role of histopathology is perceived as for the diagnosis of FMF and regarding the possible differentiation between thin and thick plaques. Second, it is a common understanding that a histopathologic integration of plaque-defined MF should be reserved to selected cases, such as diagnostic challenge, clinical severity, or trial settings (i.e. Q7, Q8, Q9, and Q10).

The results of this preliminary study pave the way towards achieving a new consensus integrating new clinical and histopathological criteria, to better characterize therapeutic options and prognostic factors of plaque-stage MF patients. The need of a prospective study aimed at achieving significant insights into the clinicopathologic correlations is recognized by all the panellists. In this scenario, the fact that most of the responders agree on performing the biopsy on the more infiltrated/indurated lesion could represent an interesting preliminary consideration. The search of new well-defined and reproducible histopathological criteria to differentiate between patches and plaques could be of great interest. In this view, an interesting proposal raised by few panellists (MB and RS) was to try to define the thickness and depth of the infiltrate by using the classic Clark's level of melanoma. Indeed, it would be preferable, as outlined in one of the items of the survey, to biopsy the thickest lesion: in fact, as shown by Marti et al.[24] in their multivariate clinicopathologic model, the T category, and the thickness of cutaneous infiltrate of the clinically thickest lesion are indeed associated with a different prognosis. However, it should be noted that a small punch biopsy performed on a plaque may not be truly representative of the entire lesion, whilst in melanoma, the wholly excised lesion is usually available for analysis. Therefore, the possibility of sampling bias in MF should be considered, as both interlesional and intralesional variability have been described.[25] As previously illustrated in other studies, histology has been shown to offer an objective means of defining MF subtype and have prognostic implications. Specifically, for plaque definition, histologic features such as folliculotropism, large-cell transformation and CD30 expression are essential to document.[31] However, as for the distinction of thin and thick plaque, standardized criteria are still needed to uniform pathology reports across the world. Moreover, as proposed by other panellists, prospective trials aimed at assessing the role of diagnostic tools, such as ultrasound or magnetic resonance imaging, in the integration of the clinical distinction between patch and plaque are much needed as well. Moreover, as recently described, modern technologies such as high-throughput sequencing will hopefully contribute to distinguish more local from more advanced disease forms.[26] At last, based on the advances of modern molecular biology, better identifying specific biological markers could be helpful in defining the specific tumour infiltrate (as suggested by RK).[32] The results of this study, as well as further evidence coming from the PROCLIPI registry study,[33] could contribute to the consensus evaluation for a revised position of plaques in the TNMB classification and achieve a standardized pathology report comprehensive of all major prognostic items outlined by the PROCLIPI study.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author [G.R.].

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