Surveillance of patients at high risk for melanoma using digital dermoscopy.

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Short title: Digital dermoscopy reduced excisions of melanocytic nevi.

Abbreviations: AMS – atypical mole syndrome; CM – cutaneous melanoma; MN – melanocytic nevus

Summary

Background: Dermoscopy has improved sensitivity and specificity of clinical melanoma diagnosis from 60% to over 90%. However, in order not to miss melanoma a certain percentage of suspicious but benign lesions has to be excised.

Objectives: To evaluate the dermoscopic changes and the rates of excised benign melanocytic nevi and cutaneous melanoma in long-term follow-up of high-risk patients using digital dermoscopy.

Methods: Digital dermoscopic images of 2,015 atypical melanocytic nevi of 196 high-risk patients were retrospectively analyzed. Among others, the following data were collected for each nevus: changes of surface area, overall architecture, dermoscopic patterns, and distribution of pigmentation. All tumours suspicious for melanoma or showing asymmetric changes were excised.

Results: During a median follow-up time of 25 months 128 (6.4%) of all nevi showed changes in size or architecture. 86% of all changes in patients who attended more than one visit were observed at first follow-up visit. 33 changing lesions were excised and two melanomas in situ and 31 melanocytic nevi were diagnosed.

Conclusions: Follow-up examinations using digital dermoscopy revealed unchanged morphology in the large majority of melanocytic nevi. Excisions have only been performed in cases of asymmetric growth, asymmetric changes of pigmentation, or development of dermoscopic features indicative of melanoma. The ratio of 33 lesions excised in order to identify two melanomas in situ seems reasonable and may be further reduced in future.

Key Words: atypical melanocytic nevi, atypical mole syndrome, cutaneous melanoma, dermoscopy, follow-up

Introduction

Common as well as atypical melanocytic nevi (MN) are established risk factors for cutaneous melanoma (CM) [1] and they are considered to be precursor lesions of a substantial proportion (20% to 60%) of CM [2;3]. Pigmentary features like number of common and atypical MN and patients and family history of CM have been used to define persons at high risk [1]. Early detection of CM is mandatory to avoid progression to metastatic disease [4]. It has been shown that surveillance of high risk patients can help to detect early thin CM [5;6] and that screening is cost effective [7].

Dermoscopy (synonym: epiluminescence microscopy) has been developed for early detection of CM and it has improved sensitivity and specificity of clinical diagnosis of CM from 60% to over 90% [8-11]. However, sensitivity and specificity of the method do not reach 100% and in order not to miss CM a certain percentage of suspicious but benign lesions has to be excised. In Germany currently the excision rate is about 120 melanocytic nevi in relationship to the diagnosis of one single melanoma (Personal communication Dr Heino Hügel, Referral Laboratory of Dermatopathology, Friedrichshafen, Germany). To reduce unnecessary excisions of benign MN additional information on the biological behaviour of individual melanocytic tumours is needed. Digital dermoscopy allows to easily archive digital images and follow-up skin lesions in patients with numerous atypical MN [12]. The present study analyzes the results of four years surveillance of patients at high risk for CM in our Pigmented Skin Lesions Clinic using digital dermoscopy.

Patients and Methods

Patients and study design: The present study retrospectively analysed digital dermoscopic images of 2,015 atypical melanocytic nevi in 196 patients (58.2% males) aged seven to 78 years (mean 40.5; SD ± 16.3) attending the Pigmented Skin lesions Clinic of the Department of Dermatology in Tübingen, Germany. Patients were included into the follow-up due to atypical mole syndrome (AMS) (n = 168) or a history of CM (n = 68). Fourty patients suffered from AMS and had a history of CM. Atypical mole syndrome was defined as five or more atypical MN plus 50 or more common MN [13]. An atypical MN had to fulfil at least three of the following five criteria: diameter five or more millimetres, ill-defined border, irregular border, varying colours within the lesion, and simultaneous presence of papular and macular components [13]. Follow-up was scheduled between every six months (positive melanoma history and/or pronounced AMS) to every 12 months (patients with AMS). Patients with severely atypical MN without suspicion for CM were revisited after three to six months. All tumours suspicious for CM at first visit were initially excised and not part of this follow-up study. Patients were clinically investigated, all clinically atypical MN were further studied using digital dermoscopy. For each patient the following data were collected: sex, age, estimated total body number of MN, total number of MN followed-up, presence of atypical mole syndrome, and history of CM. All lesions included into the study were overall judged not suspicious for CM. All tumours showing asymmetric growth, asymmetric changes of pigmentation, or development of dermoscopic features of melanoma during follow-up were excised and evaluated by histopathology.

Computed dermoscopy and evaluation of changes in melanocytic tumours: For routine clinical investigation as well as for scientific purposes we used a FotoFinder dermoscope (TeachScreen Software, Bad Birnbach, Germany). The software allows for an easy allocation and follow-up of individual atypical MN. Images of all atypical MN of patients were taken at 20-fold magnification and stored as jpg-files. Only in patients with an exceedingly high numbers of atypical MN a selection of the 20 most atypical MN was made for follow-up. All images were evaluated at least by two persons experienced in dermoscopy (C.G., J.B., or A.B.). The following data were collected for all melanocytic nevi: localization (head and neck, arms, legs, trunk), date of first and of follow-up

examinations, and whether a nevus was changed or remained unchanged. The latter was judged by the investigators directly comparing the follow-up images of each nevus. In nevi showing changes, surface area was determined using the software „Mole Analyser“ [12] at the first and final follow-up examination. For changes in size a threshold level of ±10% was assumed. Architectural changes were also assessed: (1) Changes in the overall architecture (changes in shape, symmetry, dermoscopic features, or pigmentation). Subtle changes were categorized as “minor changes” and more evident changes as “major changes”. (2) Changes in the dermoscopic patterns of atypical MN (reticular, globular, or homogeneous patterns, or combinations of these), and (3) distribution of pigmentation (uniform, central hypopigmented or hyperpigmented, eccentric peripheral hypopigmented or hyperpigmented, or patchy pigmentation) as recently published [14].

Statistical analysis: Statistical analysis was performed using SPSS for Windows, release 11.5 (SPSS Inc., Chicago, IL, USA). For bivariate analysis a two-sided Pearson-chi-square test was used. Throughout the statistical analysis a significance level of 0.05 was assumed.

Results

General characteristics: Using digital dermoscopy a total of 2,015 melanocytic tumours was followed-up in 196 high risk patients for a median of 25 months (minimum two months, maximum 44 months, mean 23.6 months, SD ± 12.0 months). 77% of all patients had an estimated total body MN number between 51 and 100. The number of followed-up MN in each patient ranged from one to 34 with an median of 9 (mean 10.3; SD ± 6.6). The MN included into the study were localised mainly on the trunk in males as well as in women. However, bivariately in women significantly more MN were documented on the legs than in men ($p < 0.001$). Overall 33 lesions were excised because they showed asymmetric growth, newly developed eccentric hyperpigmentation, or any dermoscopic structures associated with melanoma. Histopathologically 23 dysplastic MN, seven common MN, one combined MN (blue nevus plus compound MN), and two CM in situ were diagnosed (Fig. 1). One of the CM in situ developed in association with a common compound MN.

Growth and regression in benign MN: From the 2,013 MN (excluding CM) 128 (6.4%) showed changes: 21 only architectural changes without change of size and 107 changed in size (90 grew, 17 regressed). The 90 growing MN (4.5% of all MN) (Fig. 2a & b) increased in surface area between 10.2% and 308.3% (mean = 54.1%; SD ± 52.2%). Growth was observed after a period of three to 35 months (mean 11.3; SD ± 6.3). The 17 regressing MN (0,8% of all MN) lost between 12.9% and 44.2% of their initial surface area (mean = -22.7%; SD ± 9.2%). Regression was observed between three and 36 months (mean 16.8; SD ± 9.8). Most changes were observed within the first 16 months of follow-up (Fig. 3), with a mean interval to the first changes of 12.5 months (SD ± 7.2 months). In patients who attended more than one follow-up visit 88 MN changed, and 76 (86.4%) of these changes were already detected at first follow-up visit. Bivariate analysis of possible risk factors for MN growth and regression (Table 1) showed a significantly higher risk for MN growth in younger patients ($p < 0.001$), for MN localised on the trunk ($p < 0.001$), and for patients with positive CM history ($p = 0.040$). Sex and presence of AMS or high numbers of MN were neither associated with an increased risk for MN growth nor with regression.

Architectural changes in benign MN: Architectural changes were classified as minor in 71 and as major in 57 of the 128 changing atypical MN. In 107 lesions these architectural changes were associated with growth or regression as reported above and in 21 MN with architectural changes surface area was unchanged. Newly developed morphological features (globular, reticular, or homogeneous patterns) were found in 21 MN and in six MN a feature was lost. Most frequently in atypical MN with the reticular-homogenous pattern additional globules or dots were observed, resulting in a reticular-globular-homogenous pattern (n=5). The distribution of pigmentation changed in 24 MN and remained unchanged in 104 MN. Here the most common change was development of a central hyperpigmentation in previous uniformly pigmented MN (n=4). Two MN newly developed an eccentric hyperpigmentation (Fig. 2c & d) which were histopathogically proven to be dysplastic MN.

Melanomas in situ: (1) The first melanoma in situ was located on the chest of a 33 years old female and had a diameter below three millimetres at first visit (Fig. 1a). There were no typical dermoscopic structures indicative for CM and a heavily pigmented atypical MN was diagnosed. At first follow-up after four months a 63% growth of the surface area of the lesion and peripheral pseudopods as a feature of CM were detected (Fig. 1b). The tumour growth was relatively symmetric, pigmentation was uniformly distributed at first and second visit, and the morphologic pattern was globular-homogeneous with discrete elements of network at first visit, the latter were replaced by pseudopods at second visit. The tumour was excised and melanoma in situ was diagnosed. (2) The second melanoma in situ was associated with a compound MN and was located on the upper back of a patient with AMS. At first visit a light brown slightly atypical MN was seen (Fig. 1c). Due to limited compliance, the patient presented again tardily after 17 months. No growth of the overall surface area of the associated MN was recorded (Fig. 1d). Yet, a heavily pigmented area developed within the pre-existing nevus. Thus, the distribution of pigmentation changed from uniform to eccentrically hyperpigmented. The morphological pattern was reticular-homogeneous at first and second visit. However, the reticular area shifted into a severely atypical pigmented network. The overall architecture was completely changed. The lesion was excised and histopathology revealed a melanoma in-situ associated with a common MN.

Discussion

Patients with AMS, with multiple MN, with familial CM, or with history of CM are at high risk to develop CM [1]. It can not be predicted which specific common or atypical MN may progress to CM. Excision of all atypical lesions seems to be impracticable in many patients with AMS, and would be associated with significant disfigurement, morbidity, and cost [15]. It is generally agreed that these patients should have routinely check-up for early detection of CM [5;6;16;17]. Total body photographs have been used to follow-up patients with AMS and to detect growth and development of new pigmented tumours [18;19]. To detect early small-diameter CM is especially challenging [20-22]. Dermoscopy has significantly improved sensitivity and specificity compared to clinical diagnosis of CM [8-11]. However, sensitivity does not reach 100% and especially featureless CM might be missed [23]. Thus a certain percentage of suspicious benign lesions have to be excised in order not to miss CM. In Germany currently the ratio of excised MN to CM in private practices is about 120 to one (Personal communication Dr Heino Hügel, Referral Laboratory of Dermatopathology, Friedrichshafen, Germany). A certain proportion of these benign nevi is excised due to cosmetic reasons or trauma but the vast majority due to atypia or to exclude melanoma. An Italian study from a department of dermatology reported that the ratio of excised benign MN to CM was one CM in 4.3 MN for dermoscope users, compared to one CM in 14.4 MN for nonusers [24]. To reduce unnecessary excisions of benign MN additional information is needed. Follow-up of pigmented lesions with digital dermoscopy might allow to detect slight modifications of size and dermoscopic patterns, which would not be visible on conventional photographs [15], and which might help to diagnose featureless CM [23;25]

Several studies investigated the use of digital dermoscopy for the long-term surveillance of melanocytic tumours (Table 2). Almost all studies showed a rate of incident CM below one percent ranging from zero percent [26;27] to 0.6% [28]. The proportion of changing lesions showed a wider range of variation from 3.8% [28] to 69.0% [26]. This might be explained by differences of the total follow-up time of the tumours ranging from 6 months [26] to 36.2 months [29]. It could be expected, that within a longer follow-up time more lesions show changes and more CM develop. However, reviewing the published data (Table 2) this does not explain the different rates of changes given. A

more important factor might be different definition of “change”. Some studies assessed only lesions with “substantial modifications” [15] and other studies analysed an increase in the overall pigmentation without architectural changes as well as changes of size or architecture [26]. However, changes of the overall pigmentation are likely to correspond to seasonal variations [26]. Another study investigating exclusively common MN found growth to be inversely related to age and no development of CM was detected [30]. In contrast to the low rate of CM developing in the above mentioned long-term follow-up studies, short-term monitoring over a three months period showed changes in 19% of 318 atypical lesions, and seven CM (2% of all tumours) were observed [23]. This high proportion of changing lesions might be explained by the selection of cases which might have been more severely atypical or which had a history of change in the latter short-term study. Our study with a low rate of changes of six percent and only two melanomas in situ developing during a median 25 months follow-up is in the same range like the above mentioned long-term follow-up studies. Changes consisted mainly of symmetrical growth and regression, or dermoscopic structures or pigmentation have been slightly modified.

This widely constant presentation of MN over a long term as reported by the above mentioned long-term follow-up studies as well as by our study makes digital dermoscopy perfectly suited for monitoring these patients. Management of high risk patients with serial excisions would be more useful in rapidly changing tumours with a high rate of malignant transformation. In opposite, the risk of malignant transformation of MN is very low with one CM developing in thousands of common MN or hundreds of atypical MN [31;32]. Thus our approach is to perform a long term follow-up in patients with AMS and only moderately atypical MN. In our study 86% of all changes in patients who attended more than one visit were observed at first follow-up visit. If at initial visit severely atypical MN without suspicion for CM are identified an appointment for a three to six months follow-up examination is made. It has been demonstrated, that within a median of three months monitoring of 318 suspicious or changing melanocytic tumours all nine early CM showed changes [23] and no melanoma should be missed. Three months should be a relatively safe monitoring period for initial CM. However, there is nor formal evidence for this statement [23]. If there is no change after three to six months the next follow-up interval is 12 months. All tumours

suspicious for CM are excised immediately. Aim of this approach is to reduce unnecessary surgery by reaching higher sensitivity and specificity. We performed only 33 excisions among 2,015 tumours followed up, which is a clear reduction compared to the time before digital dermoscopy. However, we did not quantify this reduction. One study could show that the presentation of follow-up images could significantly increase the diagnostic accuracy and sensitivity for all examiners, and reduced the excision rates for the most experienced readers [33]. As the Fotofinder dermoscope (TeachScreen Software, Bad Birnbach, Germany) enables us to take digital images of numerous pigmented lesions within minutes, the method is not very time-consuming. A clinical total-body examination plus follow-up of about 30 lesions using digital dermoscopy takes about 10 to 15 minutes.

Our approach to follow-up patients at high risk for CM can not yet be recommended for uncritical use since the present study has several limitations: 1) It is a retrospective study and does not compare digital dermoscopy follow-up to other methods like conventional photography. However, we think that dermoscopic follow-up is superior to clinical photographs, as dermoscopy has a higher sensitivity and specificity compared to clinical diagnosis [11] and reveals changes in much more detail [15]. 2) Not all changing lesions were excised and thus there was no control whether featureless or unchanged CM were missed. All dermoscopic images were checked by at least two examiners highly experienced in dermoscopy and all ambiguous lesions have been excised. Thus we think that no CM was missed. 3) The study was performed by expert dermatologists and the results might not be transferred to inexperienced examiners. A study on risk and benefits of sequential imaging of skin lesions found that the threshold level to perform an excision increases if there is a possibility of follow-up [33]. This effect was more pronounced among experienced examiners. Thus, some CM might be overlooked at first visit but inexperienced examiners tend to be careful and perform excisions at initial visit. 4) The short-term follow-up of atypical lesions which might be excised without the opportunity to follow-up has to be based on complete agreement and consent between doctor and patient, that follow-up is mandatory and that there might be a short delay of excision in initial CM. We give an appointment for next follow-up before the patient leaves the department and patients are thoroughly educated about the advantages and risks of follow-up.

To our experience more than 90% of all patients keep their appointments exactly. In some cases there is a certain delay by several weeks. However, other studies report a bad compliance with only 46% patients attending the follow-up visit [27].

In conclusion, we think that the advances of digital dermoscopy are particularly useful for nevus screening in patients at high risk for melanoma development. Our concept for surveillance of patients at high risk for CM combines excision of pigmented tumours highly suspicious for CM, three to six monthly follow-up of severely atypical MN without signs of CM in which removal may not be justified, and yearly follow-up of moderately atypical MN. The patient has to agree and give consent, that for this concept leading to reduced excisions of MN regular follow-up visits are mandatory. In the present study MN were relatively stable, and two CM have been detected in a non-invasive phase. To our experience this concept saves patients from unnecessary excisions. We performed only 33 excisions in 196 high risk patients within a median follow-up period of two years and diagnosed two in situ CM and 31 MN. However, this approach should be further evaluated in comparative prospective studies.

Figures and Tables

	growth			regression		
	yes	no	p-value	yes	no	p-value
male	51	1,046		6	1,091	
female	39	877	0.673	11	905	0.110
AMS: yes	88	1,837		17	1,908	
no	2	86	0.308	0	88	0.376
cutaneous melano-						
ma history: yes	18	579		7	590	
no	72	1,344	0.040	10	1,406	0.296
total number of MN*						
≤ 50	24	555		7	572	
> 50	65	1,349	0.658	10	1,404	0.269
total number of MN*						
≤ 100	69	1,384		12	1,441	
> 100	20	520	0.315	5	535	0.829
localisation**						
trunk	77	1,376		13	1,440	
extremities	10	521	< 0.001	4	527	0.762
age quartile						
0 – 28	44	461		8	497	
29 - 37	22	458		1	479	
38 - 47	10	492		2	500	
≥ 48	14	512	< 0.001	6	520	0.061

Table 1: Bivariate analysis of possible risk factors for melanocytic nevus (MN) growth and regression (two-sided Pearson´s chi-square test). *For 20 patients no estimated total number of MN was available; **excluding head and neck.

Study	total number of lesions	number of lesions changing	number of incident melanomas	median total follow-up time [months]
Braun et al., 1998 [26]	113	78 (69.0%)	0	6
Kittler et al., 2000 [15]	1862	75 (4.0%)	8 (0.4%)	12.6
Menzies et al., 2001 [23]	318	61 (19.2%)	7 (2.2%)	3
Schiffner et al., 2003 [27]	272	95 (34.9%)	0	24
Robinson & Nickoloff, 2004 [29]	3482	193 (5.5%)	4 (0.1%)	36.2
Haenssle et al., 2004 [28]	2939	112 (3.8%)	17 (0.6%)	18
present study	2015	130 (6.5%)	2 (0.1%)	25

Table 2: Studies analysing follow-up of melanocytic nevi using digital dermoscopy.

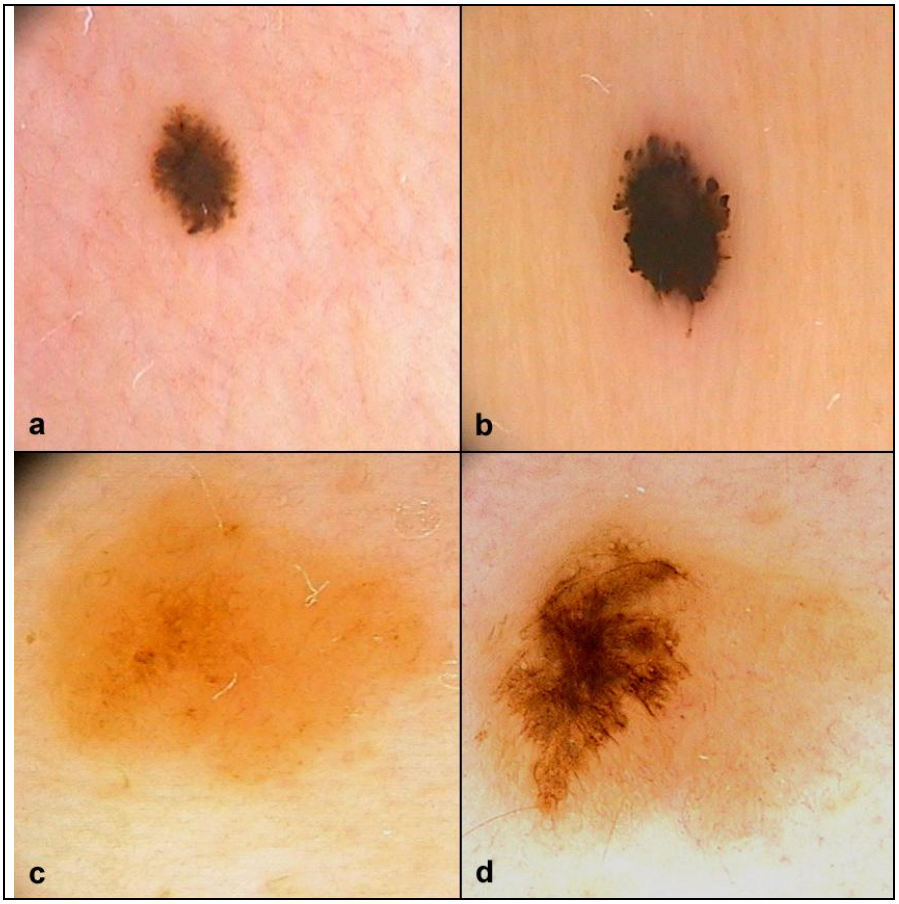

Figure 1: a) Melanoma in situ with homogeneous dark brown pigmentation and discrete elements of network. At first visit no signs of CM were detected. b) 63% growth of the surface area after four months and development of peripheral pseudopods. c) Light brown slightly atypical MN at first visit (diameter > 5mm, irregular border, simultaneous presence of central papular and peripheral macular components). d) No growth of the overall surface area 17 months later. A heavily pigmented area with severely atypical pigmented network developed within the pre-existing nevus changing pigmentation to eccentrically hyperpigmented. Histopathology: Melanoma in situ associated with a compound MN.

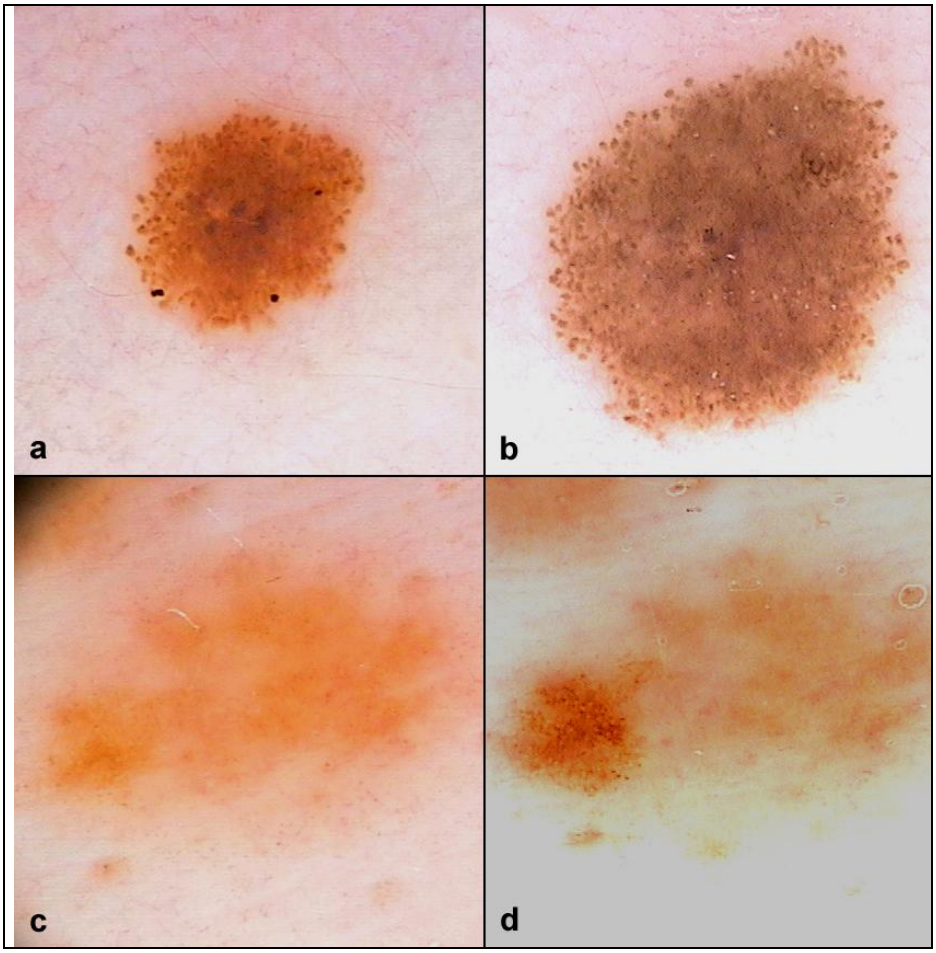

Figure 2: a+b) Symmetrical 177.5% growth of the surface area of a MN with globular pattern during 22 months of follow-up. c+d) Atypical MN with uniform pigmentation at first visit and eccentric hyperpigmentation 22 months later (Histopathology: dysplastic MN).

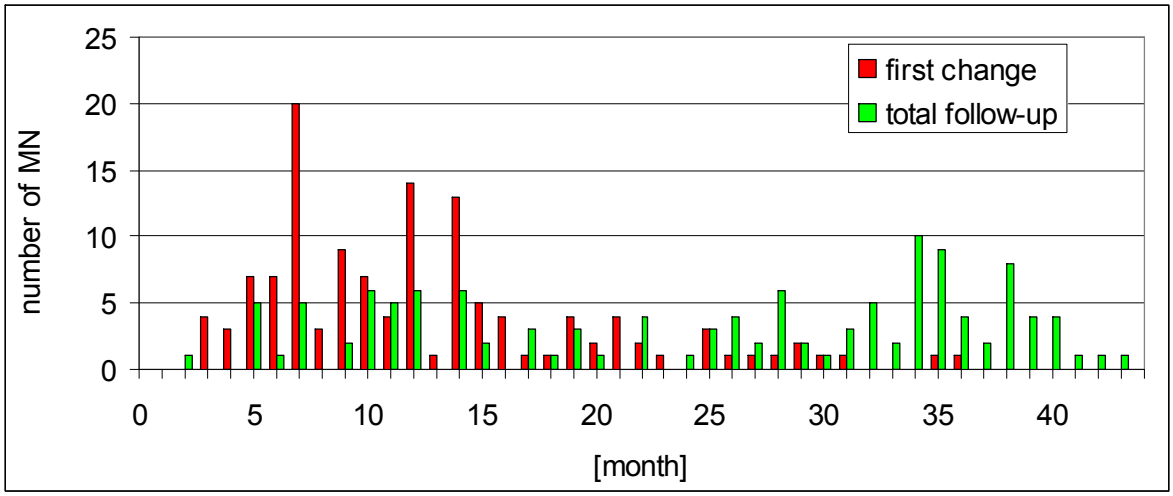

Figure 3: Time period to the first observed change (red) and total follow-up time (green) of the 128 MN showing changes in size or overall architecture.

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