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Sequential digital dermatoscopic imaging of patients with multiple atypical nevi

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ABSTRACT Patients with multiple atypical nevi are at higher risk of developing melanoma. Among different techniques, sequential digital dermatoscopic imaging (SDDI) is a state-of-the art method to enhance diagnostic accuracy in evaluating pigmented skin lesions. It relies on analyzing digital dermatoscopic images of a lesion over time to find specific dynamic criteria inferring biologic behavior. SDDI can reduce the number of necessary excisions and finds melanomas in an early—and potentially curable—stage, but precautions in selecting patients and lesions have to be met to reach those goals.

Introduction

Dermatoscopy has progressed to a state-of-the art technique not only to distinguish melanoma from nevi [1,2], but also to diagnose all kinds of pigmented and nonpigmented skin tumors [3]. This is due to its proven increase in diagnostic accuracy compared to the unaided eye [4], an improvement that recently has also been shown to be present in nonpigmented lesions that are inherently more difficult to diagnose [5].

But there is a specific aspect of pigmented and nonpigmented skin lesion diagnosis with dermatoscopy that stands apart, namely, screening high-risk patients. Why is this different? Not only are these patients much more likely to be diagnosed with melanoma [6,7], they are also more difficult to diagnose [8]. This is partially because early melanoma can be featureless, but also because nevi on those patients can have a worrisome morphology. Some approaches have been proposed to tackle these problems.

The morphologic differentiability can be overcome partly by comparing nevi clusters of the same pattern in a patient [9,10], which has become well known as the comparative approach set forth by Argenziano [11]. This comparative approach has its limitations though; for example, in an experimental setting, dermatologists were not able to distinguish melanomas and nevi well in lesions of high-risk patients [8,12].

Total-body imaging is widely used for screening high-risk patients, but because pigmented skin lesions can change or occur, especially in young patients [13-15], it is most commonly not applied solely but in combination with other diagnostic methods [16,17].

A German group presented a rather innovative method in which they removed the skin of the entire back of a patient to reduce his melanoma risk [18]. Though seemingly promising, this approach may not be a solution for usual high-risk patients: The removed nevi are most likely not the precursors of a potential melanoma [19], and possible melanoma risks due to germline mutations [20] would still be present. Finally, such an overwhelming surgical procedure defeats the purpose of a screening method, namely reducing invasive procedures. Rather, a noninvasive and more specific method has to be chosen for that purpose. One technique that fulfills those requirements, and overcomes some drawbacks mentioned previously, is digital dermatoscopic follow-up, or sequential digital dermatoscopic imaging (SDDI) [21,22].

By comparing 2 images of a lesion taken at different time points, additional information about the dynamics, and thus biologic behavior, can be obtained. This additional information has gained interest when being added as an additional "E" criterion to the classic "ABCDs" [23]. In a study of patients with a high risk of melanoma [24], about 20% to 50% of melanomas could only be detected with the help of digital follow-up, but not with a single dermatoscopic examination. In addition to monitoring multiple nevi, digital dermatoscopy is also used to enhance specificity on individual suspicious lesions. Here, a shorter interval (2-3 months [25]; short-term follow-up) is usually chosen [26] for single lesions and even small dermatoscopic changes are regarded as suspicious, whereas in the screening of patients with many nevi an interval of 6-12 months (long-term follow-up) is more common. In the following sections, general rules for practical application of SDDI are discussed.

Selection

Risk Factors

The first consideration in applying digital dermatoscopic monitoring is the patient collective, as it has to meet certain criteria [27]. A previous report [24] has shown that digital dermatoscopy is particularly useful for patients with a familial atypical mole and multiple melanoma (FAMMM) syndrome and an atypical mole syndrome (AMS; >50 nevi and >3 atypical nevi) in a strict sense. Conversely, conventional dermatoscopy was sufficient for the detection of melanomas in patients with solely a large number of (inconspicuous) nevi: in this patient group, more than 80% of melanomas were diagnosed over a period of 10 years by means of a single dermatoscopic examination or other clinical information. In 2 additional studies with a shorter period of time, no melanoma was found in patients with low risk among the dermatoscopically monitored lesions [28,29]. Thus, there is no compelling evidence for applying digital dermatoscopic monitoring to low-risk patient groups. They most likely will not benefit from it at all; instead, it may even do harm, as recent literature shows a positive association of false positive findings with a number of monitored lesions in a patient [30].

Compliance

An often-underestimated drawback is lack of patient compliance [29,31]; that is, patients do not show up for the follow-up appointments. The reason this is an issue is changed sensitivity at the baseline visit [32]. One basic mechanism of the increased diagnostic accuracy of digital dermatoscopic monitoring is that one increases specificity by leaving a lesion untouched in good faith, the lesion—on the patient—will come back after a specified interval. This increased specificity comes at the price of lower sensitivity, which can only be overcome by finding missed melanomas at a second examination. Thus, the physician has to ensure the patient returns to the office. While the lack of compliance is not without dispute [33], an Italian group [28] found compliance was higher for shorter intervals and that long-term monitoring may be started with shorter periods.

Lesions

Previous studies have shown that in high-risk patients one cannot estimate at baseline which of the lesions on the patient is more prone to become a melanoma [8,12]. While other authors argue that only lesions with some sign of atypia should be followed over time [34], those results suggest a possible benefit in integrating inconspicuous lesions. One should not follow, though, that all lesions on a patient have to be monitored at every visit. Taking photographs of all lesions at every visit is not only impossible to do in a reasonable amount of time, but it may also decrease diagnostic accuracy as more monitored lesions per patient are positively correlated with false positive findings [30]. A survey showed that the majority of experts in the field in fact do not perform dermatoscopic monitoring of every single lesion on a patient [35], and indirect evidence indicates this is truly not necessary. In a retrospective analysis of our own high-risk center, where only a random subset of lesions is monitored at every visit with monitoring being stopped after no change has been seen for 2 (or 3) years, almost half of melanomas were in situ and mean invasion depth was well below 1 mm for 10 years [30]. Therefore, because we cannot estimate which pigmented skin lesion turns out to be a melanoma, selection of lesion monitoring has to be random and can be incremental to save resources (incremental SDDI, Figure 1).

One cannot choose which lesions specifically should be monitored, but there are rules as to which lesions should not be. Important exclusion criteria are: (1) nodular (black, brown, gray, red or blue) lesions, as thick melanomas would progress to higher invasion depths more quickly [36,37];

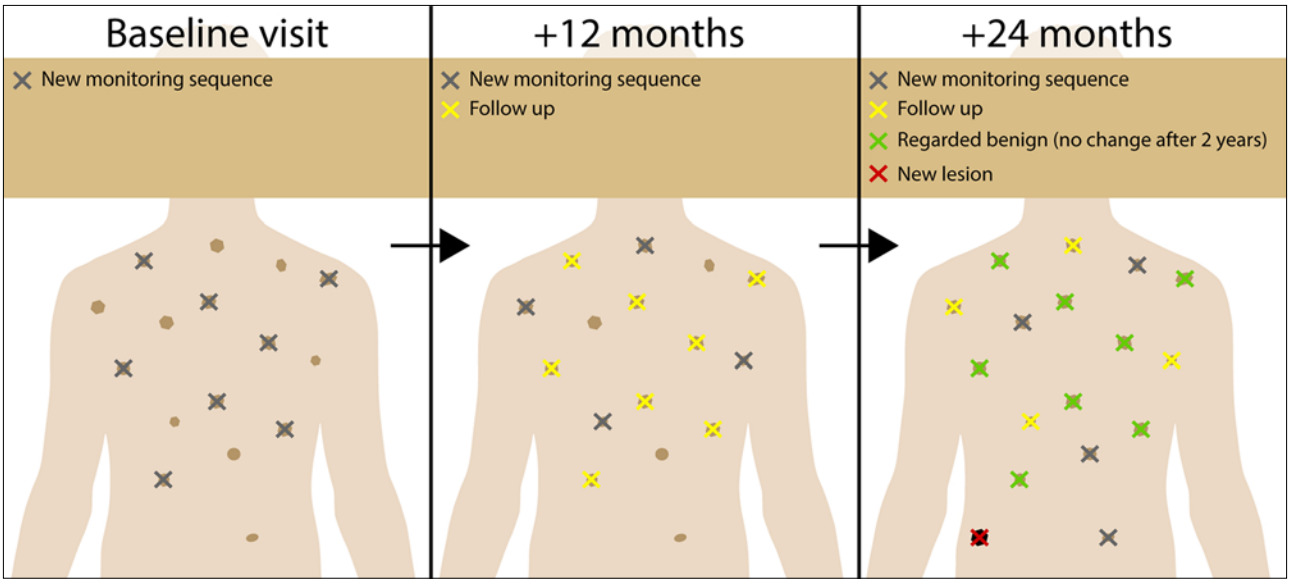

Figure 1. Incremental SDDI. Because with current methods it is not feasible to image every lesion at every visit, we selected a random sample of new lesions at every visit (gray), which were imaged in subsequent visits (yellow), but were discarded from follow-up after showing no change for 2 years (green). With this method, we were able to map all lesions eventually, to suggest if one lesion has occurred in the last interval even without TBP (red). [Copyright: ©2018 Tschandl.]

TABLE 1. Differentiation of Nevus and Melanoma with Follow-Up Images*

Change	Nevus	Melanoma
Change in size	None or symmetrical growth	Asymmetrical growth
Change in color	No change or even lighter/darker brown or erythema	New colors, especially focally and depigmentation
Change in structure	No or subtle changes such as accentuation of existing structures	Architecture changes and the appearance of new structures including classical melanoma criteria and regression and signs of regression

*Adapted from Kittler et al [50].

(2) blue lesions [38], as monitoring cannot reliably evaluate changes in the dermis; (3) regressive lesions, as a potential melanoma may be completely regressed at follow-up; (4) lesions with a dermatoscopic clod pattern, as they show a faster growth [39]; and (5) spitzoid lesions [40], not including Reed nevi [41], as the latter can show fairly symmetric growth and stabilization. Lesions with these characteristics should be removed immediately, unless they are clearly benign at the baseline visit.

Finally, what should lesions selected for SDDI look like? Ideally, they are medium-sized, flat, and show a dermatoscopic reticular pattern. But, as with any recommendation, the preceding recommendations are due to change with new findings, specifically in the advent of automated full-body imaging, where monitoring of every single lesion of a patient seems feasible in the future. Until then, it is justifiable to discard monitoring a single lesion if no change has occurred for 2-3 years because a diagnosed single melanocytic nevus is at very low risk of transforming into a melanoma at 0.0005% to 0.003% per year [42].

Evaluation

Melanocytic nevi generally grow symmetrically and follow 1 of 3 variants: a reticular pattern (slow growth), a surrounding rim of clods (moderate to fast growth), or peripheral pseudopodia and radial lines (fast growth) [43]. The following changes (summarized in Table 1 and Figures 2-4 and adapted from Kittler et al [44]) have been associated with melanoma in previous studies [45,46] and should lead to the removal of a lesion: (1) changed architecture; (2) asymmetric increase in size; (3) new colors, depigmentation, and focal color change; and (4) the appearance of melanoma criteria such as black dots or regression.

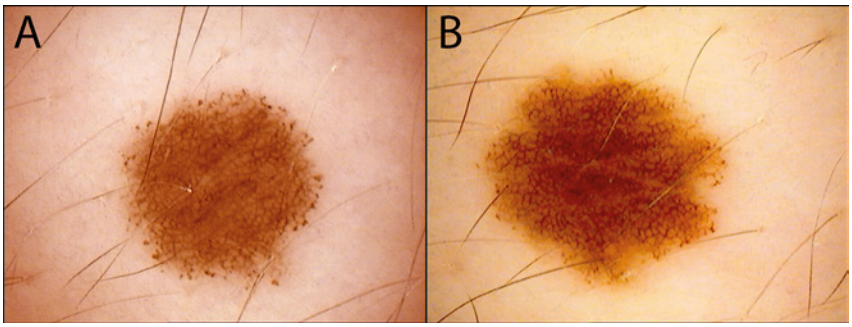

Figure 2. A compound nevus (A) with peripheral clods showing (B) symmetrical growth after 1 year. Nevi with peripheral clods very commonly show symmetric enlargement over time [70]. [Copyright: ©2018 Tschandl.]

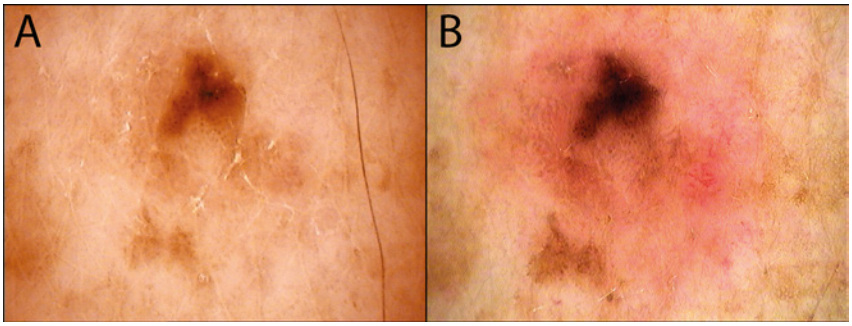

Figure 3. This histopathologically verified lentigo maligna initially presented with only structureless brown areas (A) at the baseline visit. (B) After 14 months of follow-up, the pigment has become darker, grown asymmetrically, and an additional pink structureless area can be seen. [Copyright: ©2018 Tschandl.]

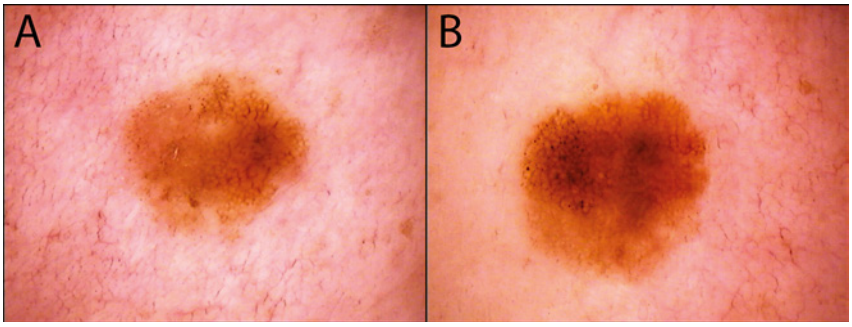

Figure 4. While this lesion (A) initially appears inconspicuous, after (B) 6 months it shows additional black dots and asymmetric growth. Histopathological evaluation revealed a superficially spreading melanoma with an invasion depth of 0.4 mm. [Copyright: ©2018 Tschandl.]

Notably, all criteria rely heavily on asymmetry (chaos), which is one of the most (interrater) reliable features in dermatoscopy [47], but evaluation of the necessary extent of change still relies on the subjective judgment of the examining physician. Additionally, many additional factors have to be taken into account and these are (1) time, (2) medication, (3) anatomic location, and (4) age. First, with shorter intervals between 2 images, less change indicates a probable melanoma [26,48], whereas nevi generally change more slowly and in a limited fashion [39,49,50]. In contrast, recurrence of a benign nevus may occur earlier than recurring melanoma [51]. Second, new checkpoint inhibitors such as dabrafenib [52] or vemurafenib [53] may lead to drastic changes in nevi. Third, congenital nevi of the nail apparatus may show growth and involution [54]. Fourth, growing lesions raise more suspicion in older patients, as nevi are expected to change in younger patients to some extent [14,15].

General Considerations

Effectiveness

Regarding diagnostic accuracy, a meta-analysis has shown that by using SDDI, 54.6% of melanomas can be excised in situ. The number of lesions needed to monitor differs significantly between studies (31-1 008), most possibly reflecting different methods of executing SDDI. Undeniably, this number is the lowest for short-term SDDI [21,48] because it is mainly used for increasing specificity (ie, avoiding excision of single suspicious lesions rather than scanning all lesions on a patient). It therefore does not have the identical purpose as long-term SDDI and is commonly combined with other screening methods such as total-body photography, conventional skin examination, and dermatoscopy [16,17]. The number of needed excisions (NNE) to find a melanoma under long-term SDDI is low (1:12; melanoma: benign nevi as diagnosed by histopathology), but here also short-term SDDI is lower (1:5) [21], as it includes only suspicious lesions, decreasing the pretest probability of false positive findings. The low NNE for any kind of SDDI is thought to be one of the main reasons the NNE has decreased in recent years in specialized centers [55].

For every screening method, not only diagnostic accuracy, but also immediate and follow-up costs have to be taken into account. Literature suggesting that even skin cancer awareness interventions can increase costs alongside even lower quality-adjusted life years [56] show the importance of being careful and constantly critical of population-wide decisions about any kind of screening method [57]. When limiting interventions to high-risk patients, there

is repeated evidence for cost-effectiveness of screening in general [58,59], and SDDI specifically [60].

Combinations

SDDI is never applied alone, but is at a minimum combined with a total-body exam from a physician with or without a handheld dermatoscope. Combinations with other examination techniques have been shown to be effective in skin cancer screening of high-risk patients.

Total-body photography (TBP): By comparing clinical images of 2 time points, TBP itself may reduce the number of excised lesions in pigmented lesion clinics [61,62] by detecting clinically new or changing lesions. Especially with the advent of high-resolution photography and automated detection of new lesions [63], TBP has the ability to become even more important in screening a large number of patients. The evidence and use of TBP for screening are promising, but an in-depth review is beyond the scope of this review. Regarding digital dermatoscopy, TBP performs very well when combined with SDDI in screening programs, as both possibly detect distinct subsets of melanoma [16,17].

Reflectance confocal microscopy (RCM): To further reduce the number of unnecessary excisions, RCM has been applied as a "second-level" exam for doubtful lesions found by digital dermatoscopy [64]. Though repeatedly found helpful in further studies [65-67], application is currently limited to highly specialized centers with access to this technique.

Limitations

At the time of publication, this review may be outdated. It gives a current review of state-of-the art knowledge about digital dermatoscopic monitoring, but screening and monitoring high-risk melanoma patients may change in the future. New methods such as automated skin lesion tracking [63,68] as well as classifications by artificial intelligence [69] will most likely fundamentally rearrange perspective in the next years.

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