Melanoma Management

EDITORIAL

Can we improve melanoma detection methods?

"The incidence and mortality of melanoma have been steadily increasing over the last decade, leading this tumor to be considered a public health issue."

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The incidence and mortality of melanoma have been steadily increasing over the last decade, leading this tumor to be considered a public health issue.

In 2016, the estimated number of new melanoma cases in the USA was 76,380, with an incidence rate of 23.6 per 100,000 inhabitants [1].

In the European Union, melanoma incidence accounts for 9 per 100,000 people per year, with higher rates in fair-skin populations; however, the real incidence is thought to be higher because of underestimation of the most superficial and indolent cases [1].

Melanoma generally affects younger patients more than other tumors; in fact, it represents the third most frequent tumor before 49 years of age [1].

Concerning mortality, melanoma accounts for up to 65% of the deaths for skin cancers, while representing only 3–5% of all skin tumors, with a rate of 2.3 per 100,000 inhabitants per year [2].

The rising rates in melanoma detection seem to be only partially due to the development and wider use of noninvasive diagnostic tools. In fact, while this could justify the higher incidences of indolent and noninvasive melanomas, it does not explain the increasing mortality rates.

Several factors may contribute in defining the prognostic profile of melanoma patients. Among these, Breslow's thickness plays a major role. In fact, in thin melanomas (≤1.0 mm), a 90% 5-year survival has been reported; survival rates dramatically decrease in visceral metastatic cases, with a 1-year survival as low as 33% [3].

Even though new oncogenic and immunological target therapies for metastatic cases have been increasing survival rates, early diagnosis and excision with proper margins remain the best therapeutic option. Optimal diagnostic methods that might increase the diagnostic accuracy for melanoma are crucial.

Histopathological examination still represents a necessary stage to confirm melanoma diagnosis. Nevertheless, noninvasive diagnostic methods have, in

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the past decades, significantly decreased the number of unnecessary biopsies and excisions, and increased the sensibility and specificity in diagnosing melanocytic lesions. Undoubtedly, dermoscopy and reflectance confocal microscopy (RCM) played a leading role in the field of diagnostic imaging techniques.

The role of dermoscopy in improving melanoma detection was clearly demonstrated by a recent meta-analysis, in which 90% sensibility was reported, compared with 74% from the naked-eye examination [4]. The ease of use and the development of new handheld and portable instruments have favored the worldwide diffusion of this technique.

Furthermore, the performance of dermoscopy varies consistently according to the expertise of users. In fact, it has been estimated that, in nonspecialized clinical settings, a number of 29.4 nevi are biopsied for every melanoma detected; however in experienced hands, the number needed to excise decreases to 8.7 [5].

In 2003, an online consensus meeting answered the need for better standardization of dermoscopic terminology, defining the letters of the dermoscopic alphabet [6]. A two-step procedure was proposed, the first differentiating melanocytic from nonmelanocytic lesions, the second differentiating melanoma from benign melanocytic lesions through four different algorithms: modified pattern analysis [7]; ABCD rule of dermoscopy [8]; Menzies method [9]; and seven-point checklist [10].

Sensitivity levels >90% in diagnosing melanoma were calculated for the first step while, for the second, the pattern analysis showed the best performance, with sensitivity and specificity levels >80% [6].

Some limitations of this procedure are represented by fully regressive and amelanotic lesions, lesions located on the face and patients with multiple atypical nevi.

In fully regressive and amelanotic lesions, the evaluation of the first step may be very challenging because of the featureless nature of amelanotic lesions and the similarity in the dermoscopic appearance of regression between melanocytic and nonmelanocytic lesions. Even though some dermoscopic differences and algorithms have been described, in these cases a biopsy remains mandatory [11,12].

The location on the face may also affect the evaluation of the initial step. In 2000, specific dermoscopic criteria for the diagnosis of lentigo maligna were described along with a progression model toward multiple steps from *in situ* to invasive lentigo maligna [13]. Nevertheless, because of the anatomic structure of skin of the face, solar lentigo and pigmented actinic keratosis may be dermoscopically indistinguishable from lentigo maligna. In such cases, a biopsy and/or the use of confocal microscopy is strongly recommended [14].

Finally, in patients with multiple atypical nevi, the second step of the two-step analysis may overestimate the number of unnecessary surgical excisions. In such cases, the digital monitoring of selected skin lesions and the comparative approach has shown to significantly decrease the number of unnecessary excisions, while increasing the probability to diagnose a melanoma. In particular, a short (3-month) follow-up should be performed in these patients, after the first visit, in order to re-evaluate the patient and to catch even little modifications in the monitored lesions [15].

Recently, new applications of dermoscopy have been also explored; in particular, a correlation between certain dermoscopic criteria and the mutational status of the *BRAF* gene were demonstrated. Bombonato *et al.* [16] showed that the presence of ulceration and irregular peripheral streaks was positively associated with a *BRAF* mutated state, while dotted vessels were predictors of wild-type melanomas.

RCM is an add-on tool for noninvasive diagnosis of skin tumors, which provides a horizontal visualization of the skin at a nearly histological resolution. The use of RCM in the clinical practice has allowed to narrow the grey zone of doubtful clinical and dermoscopic lesions, and to save a larger number of benign lesions from excision.

We recently reviewed our 3-year experience using RCM as a tertiary referral center, and calculated that the number needed to treat for melanoma is 1:2.4 [17].

Since the use of RCM is more time consuming than dermoscopy and is not feasible in some body sites, such as acral skin, there is a need to select the lesions to examine with this technique. Interestingly, the best indications for RCM use in clinical practice are represented by lesions located on the head and neck, damaged by chronic sun exposure and typified through dermoscopy by regression [17].

Focusing on melanocytic lesions, confocal microscopy showed high levels of accuracy in differentiating melanoma from nevi. In 2005,

Pellacani *et al.* developed a diagnostic algorithm for melanoma diagnosis with 97.3% sensitivity and 72.3% specificity [18].

In 2009, Segura *et al.* defined a two-step approach for the confocal diagnosis of skin tumors, borrowed from the dermoscopic two-step analysis. For the first step, the following criteria were found to be associated with melanocytic lesions: cobblestone pattern of epidermal layers, pagetoid spread, mesh appearance of the dermoepidermal junction and the presence of dermal nests. In the second step, the presence of roundish suprabasal cells and atypical nucleated cells in the dermis was associated with melanoma, and the presence of edged papillae and typical basal cells was associated with nevi [19].

Even combining clinical, dermoscopic and RCM evaluations, the diagnosis of certain types of melanoma is still challenging. In particular, the definition of confocal criteria for *in situ* melanoma is still lacking, except for lentigo maligna.

Finally, convolutional neural networks (CNNs) have been recently explored to classify skin lesions using a single CNN [20]. In this study, the authors tested its performance against 21 board-certified dermatologists on biopsy-proven clinical images with two critical binary classifications: keratinocyte carcinomas versus benign seborrheic keratosis; and melanomas versus nevi. Notably, the CNN achieved an excellent performance across both tasks, demonstrating that an artificial intelligence is capable to classify skin cancer with a level of competence similar to dermatologists. Although these data look promising and open new frontiers on automated diagnosis, as clinicians we should always take into account that diagnosis of melanoma is a complex process that involves patient's data, lesion history, familial history and clinical overview that are not included in a static dermoscopic image but are rather part of the face-to-face visit.

In conclusion, several new techniques have been developing, which allow for an increase in the level of accuracy in diagnosing melanoma. In the near future, we envision the development of handy and low-cost imaging tools combined with software that might help the clinicians in the detection of difficult-to-diagnose melanomas.

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