Supporting the diagnosis of Dysplastic Nevi Syndrome via Multiple Instance Learning approaches

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Abstract. Malignant melanoma is the form responsible for the greatest number of deaths among skin cancers. The possibility of ensuring survival passes through an early diagnosis and subsequent skin excision. One of the problems that most hinders early diagnosis, conducted both with the naked eye and through dedicated frameworks, is the extreme similarity of melanoma with other skin lesions such as dysplastic nevi. The possibility of intercepting recurring patterns through increasingly advanced diagnostic tools pushes the research community to propose software solutions that favor the detection of melanoma. Currently the existing solutions are typically concentrated in the binary discrimination of melanoma from common nevi. The high presence of common and atypical nevi on the body surface constitutes a potential risk factor for the onset of melanoma and characterizes the current debate on *Dysplastic Nevi Syndrome (DNS)*. The presence of dysplastic nevi complicates the classification of melanoma from benign nevi, and raises a new classification problem relating to the distinction between dysplastic and common nevi, mostly unexplored. Over time, several machine learning algorithms have been proposed to support the image classification phase. In this article, we highlight multiple-instance learning approaches to discriminate melanoma from dysplastic nevi and to address the new challenge of classifying dysplastic from common nevi.

- Image Classification, Melanoma Detection, Multiple Instance Learning

1 Introduction

The World Health Organization reports that in 2020 more than 57.000 persons died due to melanoma and the new cases are over 320.000 as reported in Fig.1 [1].

Melanoma is affecting both male and female populations of the whole world, and in particular that of Europe, North America, and Asia. In particular, in Europe 144.409 new cases are recorded with a percentage of 50,1% of the total cases while in North America there are 79.644 cases with a percentage of 27,7% on the total cases (see Fig. 2 [1]).

The number of cases and the incidence rates of melanoma are even more worrying. As reported in Figure 3, melanoma ranks 5-th for estimated age-standardized incidence and mortality rates (World) in 2020, both for males and females, considering all ages.

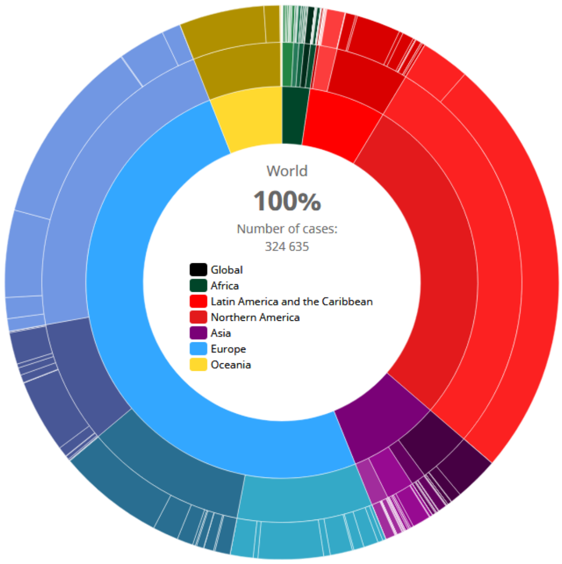

Figure 1. Estimated number of new cases in 2020, melanoma of skin, all age [1]

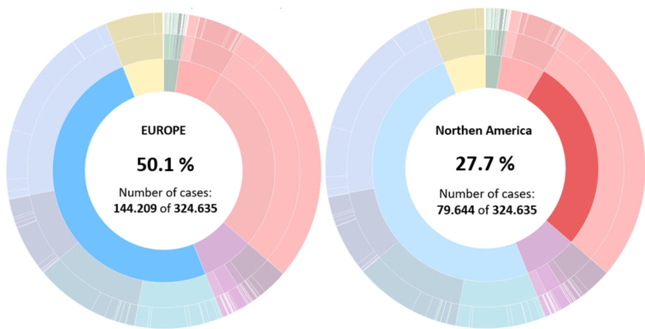

Figure 2. New Cases of Melanoma in 2020 in Europe and Northen America [1]

Despite the ever increasing diffusion and its aggressiveness, if melanoma is identified by an early diagnosis it is a type of curable cancer. Some clinical protocols such as the ABCDE rule [2] and the 7-PCL [3] have been established to facilitate the task of specialists in

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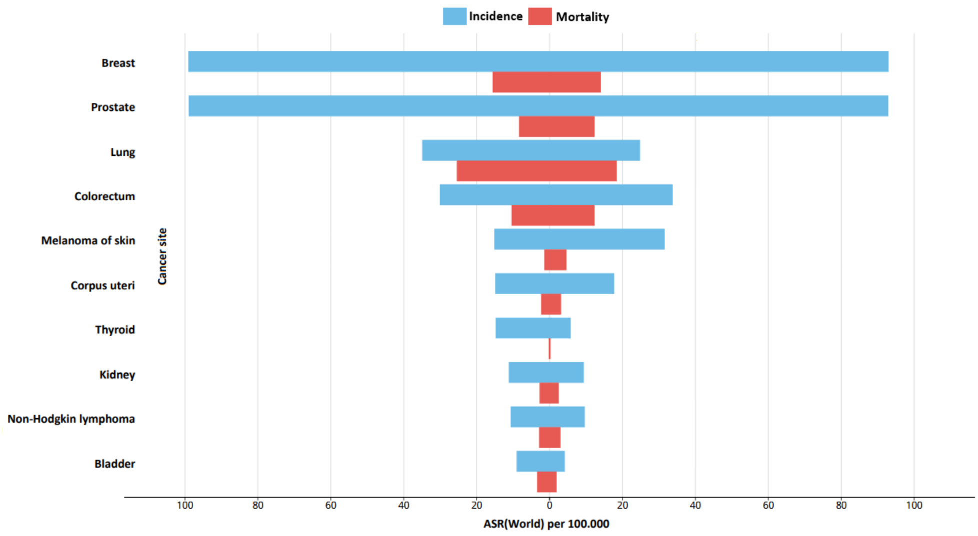

Figure 3. Estimated age-standardized incidence and mortality rates (World) in 2020, both sexes, all ages [1]

identifying the lesion from its initial phase.

These protocols outline a series of criteria to support specialists in identifying a melanoma. The evolution of the lesion over time, the presence of symmetry, the irregularity of the edges, the extension of the lesion characterized by diameters greater than 6mm, and above all the specificity of colors are the most significant features.

The impossibility of repeating the detection, together with the importance of the early diagnosis of melanoma, have led the research communities to propose automatic solutions for the analysis of skin lesions.

These systems referred to as Computer Aided Diagnosis (CAD) aim to support effective injury analysis. CADs are typically structured in various steps that include image acquisition, preprocessing, segmentation, feature extraction and selection, and finally lesion classification.

Each step is challenging and has to be correctly performed for the entire process to be effective. Regarding the image acquisition, it is increasingly adopted the use of advanced techniques such as imaging with dermatoscopy, also known as *epiluminescence microscopy* (ELM), which allows much more detailed images.

The aim of these tools is to help specialists to recognize melanoma at its initial stadium by performing an automatic analysis of the lesion using some specific features but this task is far from being easy. In fact, the similarities of melanoma with other skin lesions such as dysplastic nevi, constitute a pitfall for early diagnosis. Different approaches and algorithms have been proposed by the research community in the last decades, but they all have had as main focus the dichotomous distinction of melanoma from benign lesions.

Currently, there is a debate about dysplastic nevi syndrome, also referred as atypical mole syndrome concerning the number of moles present on the human body as potential melanoma risk factor. In this work we focus on the specific task of discriminating melanoma from dysplastic nevi and dysplastic nevi from common ones.

The risk factors for the development of melanoma are divided into genetic and environmental. The lethality of these skin cancers has triggered research since 1820, when the first studies relating to the predisposition of a family to melanoma were presented [4]. The introduction of the tumor progression model of melanocytic nevi melanoma is due to Clark [5] through which it was witnessed an increased incidence of cutaneous melanoma in families characterized by multiple melanocytic lesions [6].

It was Clark again who introduced the term BK mole syndrome, a term coined using the initials of the patients' surnames. Currently this type of condition is referred by the acronym AMS, dysplastic nevus syndrome or by the acronym FAMMM familial syndrome of atypical multiple mole melanoma. The danger of dysplastic nevi was highlighted also by Elder [7], who extended the theory of "nevus-melanoma" to sporadic dysplastic nevi as a possible sporadic melanoma.

Recent studies confirmed that the presence of dysplastic nevi is associated with an increased risk of developing melanoma. Therefore, dysplastic moles, in addition to being potential precursors of the disease, can be interpreted as an important risk markers [8]. The quantification of the increased risk does not find convergence in the literature, but appears to be connected to a series of factors including the type of skin according to the Fitzpatrick scale [9] and the ethnicity of the population considered [10].

It is worth recalling some studies that have shown that some ethnic groups are characterized by a greater number of common and dysplastic nevi on their skin. In [11], the authors in fact reported that 8 % of the Caucasian population has dysplastic nevi or unusual lesions that may resemble melanoma. The concomitant presence of dysplastic nevi syndrome and family history of melanoma poses a greater risk of developing melanoma: individuals with 10 or more atypical moles have an up to 12 times greater risk of developing melanoma [12].

There is currently an open debate in the scientific community regarding the clinical definition, dermoscopic characteristics and histopathological, genetic and molecular patterns of dysplastic nevi.

In the light of what has been introduced, it becomes important for a correct diagnosis of melanoma to face the classification tasks of melanoma vs dysplastic nevi and dysplastic vs common nevi.

Both of these specific classification contexts are complex. The difficulty of discriminating melanoma from dysplastic nevi is linked to the great similarity of the two types of lesions [13], which sometimes makes them indistinguishable. The challenge related to the classification of dysplastic nevi from common ones is completely new: besides our recent interest [14, 15], to the best of our knowledge, it has not been addressed in the literature. Difficulties in classification due to the extreme similarity of the skin lesions persist both in the case of traditional diagnosis, made by specialists, and in the case of support frameworks that adopt classification algorithms.

In this paper we refer to the main works in the literature that investigate the task of classification of dysplastic nevi, highlighting the emerging role of multiple-instance learning approaches.

2 Dysplastic nevi

The term "dysplastic nevus" (DN) derives from the Greek "dis-" (bad or malfunction) and "-plasia" (development of growth or change) [16]; this term, referring to a nevus with histological and genetic characteristics different from the common nevus, indicates a lesion that can be dangerous.

Several authors study the implications in terms of the potential onset of melanoma due to the presence of dysplastic nevi [11, 17, 18].

However, the picture that emerges is not well defined, even if characterized by common factors.

Even recently, some studies focus on the presence of dysplastic nevi and on the onset of melanoma [19, 20]. In particolar, in [19], the study of a 35-year-old woman is reported; this woman had the main symptom of multiple itchy brown lumps in her left cheek that first appeared 20 years earlier. At the first visit, a complete excision was performed and the subsequent biopsy confirmed that they were dysplastic nevi. In the following 3 years new dysplastic nevi reappeared 3 times in the same site: also in this case the histological examination confirmed the nature of dysplastic nevi. Five years after the final excision, a brownish lump developed in the left cheek, along with other lesions on the body. All of these lesions have been histologically diagnosed as malignant melanoma: the possibility of malignant melanoma should also be considered in follow-up of cases involving repeatedly recurrent dysplastic nevi.

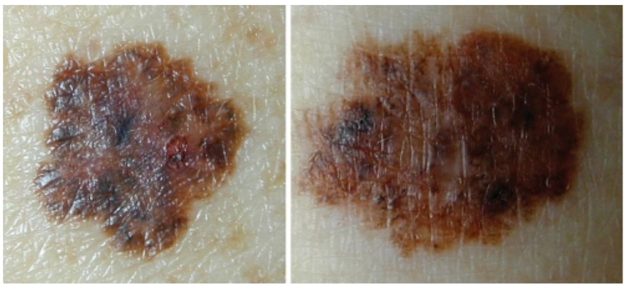

Figure 4. Macroscopic image of two melanocytic lesions whose characteristics are superimposed by the ABCD rule (asymmetry, irregular borders, varied coloration, diameter greater than 6 mm): Left - dysplastic nevus; Right – cutaneous melanoma.

In general, *Dysplastic nevus syndrome (DNS)* refers to individuals who have a high number of both benign and dysplastic nevi on the surface of their body. This syndrome has become of particular interest as individuals with dysplastic nevi, if familial conditions of melanoma also exist, are more likely to be associated with malignant lesion degeneration.

From a more global perspective, the risk for an individual is also emphasized by a genetic predisposition to the formation of melanoma. In [21], the authors report a model for the evaluation of the cumulative risk during the life of individuals who have dysplastic nevi and have a genetic predisposition to melanoma: in these circumstances about 30% of melanomas occur within in the atypical. Having ascertained the extreme similarity that dysplastic nevi can have both with common nevi and with melanoma, from a clinical point of view, the diagnosis of a severe DNS should not be neglected, since it could reflect the dermo-pathological uncertainty related to misdiagnosis, ie it could indicate a misdiagnosed melanoma in situ [22].

Various studies on the exact cause-effect correlations have been provided over time, as well as solutions for the automatic identification of skin lesions.

3 Classification performances of Machine Learning methods on dermoscopic images

The proposals for new algorithms as well as the adoption of increasingly advanced techniques for the diagnosis of dermoscopic images underlie the need to compare the methods used to classify skin lesions. An interesting recent road map on the classification approaches currently considered and on the algorithms adopted is [23].

In [24], the authors propose a framework that considers the combination and the comparison of different texture features as well as well-used color and shape features based on the clinical "ABCD" rule in the literature. Focusing on dermoscopic images, the authors evaluate the performance of the framework using two features extraction approaches, global and local (bag of word) and three classifiers such as support vector machine, gradient boosting, and random forest. The potential of texture features and random forest as a near-independent classifier is highlighted. The authors analyze the performance of various proposals, taking into account the particular value that sensitivity, specificity and size of the data set have in the medical context.

Beyond the formal definition, in fact, sensitivity (SE) typically refers to the occurrences of cancer correctly identified with respect to the total number of cancer cases in the dataset and at the same time, specificity (SP) refers to the proportion of non-negative cases compared to the total number of non-cancer cases in the dataset. Comparing frameworks with different values of SE and SP is always delicate: in the medical context, the assumption is that a false positive is in any case preferable to a false negative. In general, measures such as accuracy or F-score are taken to have a unique index of the quality of the classification.

In [24] various proposals are compared highlighting the classification task addressed: melanoma from benign ($M\ vs\ B$), melanoma from benign and dysplastic ($M\ vs\ (B + D)$) and melanoma versus dysplastic nevi ($M\ vs\ D$).

Comparing different approaches is very complex as the proposals analyzed different data sets adopting different features sets both global and local. Global features are extracted by taking the lesion as a whole, while local features are extracted from parts of the image. As regards a comparison between global and local characteristics, it should be noted that the local approach allows to increase the dimension of the features vector, but also the complexity of the features space.

In fact, in the study reported in [24] the only common point is that the investigation is aimed at a binary classification on images obtained through a dermatoscope.

A particularly delicate aspect is associated with the imbalance of the data set. Proposals are often tested on data sets where the class of melanoma is numerically smaller than that of benign and / or dysplastic moles.

Several approaches have been proposed in the literature to manage these drawbacks: the bag of features (BoF) approach in [25], together with the use of MIL approaches aimed, among other things, at simplifying the annotation of the training set [26, 27, 28].

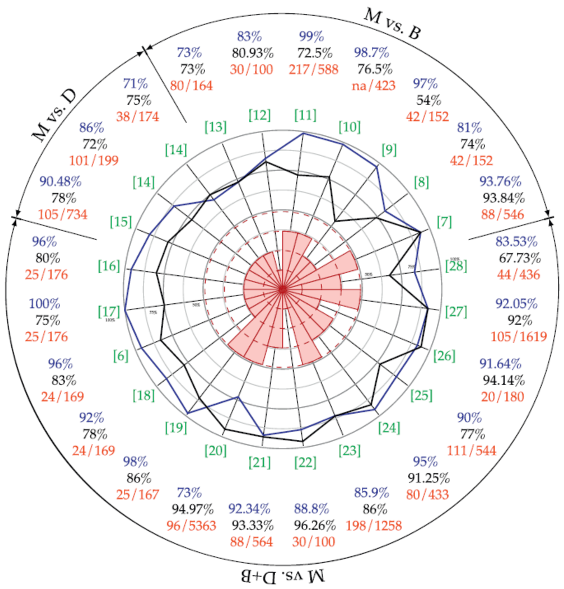

Figure 5. Summary of the classification performances of the methods reviewed from the dermoscopic imaging literature [24].

In fig.5 the authors summarize the results of the most significant methodologies, reporting the values of sensitivity (in blue), specificity (in black) and data set size expressed as the number of melanoma images out of the total number of images (in red).

Through a radar graph with four levels placed in the center, a visual feedback regarding the size of the data set is presented. It is possible to appreciate the less attention on the task of discrimination between dysplastic nevi and melanoma and how the task of discriminating dysplastic nevi from common ones is unexplored.

The proposed frameworks are aimed at the diagnosis of dermoscopic images. The possible responses include, in addition to a dichotomous distinction between two different classes, also the determination of a probability value indicative of the type of class to which the image belongs.

Support Vector Machines are among the most commonly used models for binary classification while logistic regression, artificial neural networks, K-nearest neighbor and decision trees are all members of the second approach.

It emerge that AdaBoost (AdB), Artificial Neural Network (ANN) and Support Vector Machines (SVM) are among the most effective methods.

4 Multiple Instance Leaning approaches

The role of dysplastic nevi has been considered only marginally in the literature, while the task of classifying dysplastic and common nevi is still unexplored. In [29], the authors highlighted the emerging approaches of machine learning methods, semi-supervised learning, multiple instance learning and transfer learning.

To face very delicate challenges that involving classes of skin lesions characterized by extreme similarity, we have resorted to Multiple Instance Learning ([30]), an emerging paradigm for the classification of medical images and videos characterized from a local analysis.

In the formulation of a MIL problem it is necessary to classify sets of objects called *bags* while single portions of images inside them are called *instances*. Solving this problem requires knowledge of the labels of the bags, and not of those of the instances: a bag will be positive if it contains at least one positive instance and will be negative if it does not contain any positive instances [31, 32]. This approach fits in with the problems of images classification in medical context, where an image is indicative of a pathology detectable only in some sub-regions (instances) of the image (bag): global information is obtained starting from a local survey.

To date, proposals for the classification of skin lesions that adopt MIL approaches are very rare. In [33], a MIL approach to skin biopsy imaging is used, a different task than the classification of dermatoscopic images of the lesions.

In [30], it is presented an original application for the melanoma detection using the MIL approach applied on an SVM-type model. By applying the MIL-RL [34] algorithm on some clinical data consisting of color dermatoscopic images, the authors discriminate between melanomas (positive images) and common nevi (negative images).

The proposed approach, using only some color features and without image pre-processing steps, outperforms the results obtained, with the well-known support vector machine, both linear and with RBF-Kernel, obtaining good classification performances (accuracy = 92.50 % , sensitivity = 97.50 % and specificity = 87.50 %) in the discrimination of melanomas from in common nevi. Manual labeling of images is a time-consuming activity, and may not be necessary in clinical practice; for this reasons approaches such as semi-supervised learning, multi-instance learning and transfer learning have become popular. Multiple Instance Learning scenario is particularly useful when disposing of local annotated labels is expensive, while global labels for whole images, such as the outcome of a diagnosis, are more readily available.

In medical field it is difficult to obtain a correct classification with the classic separation approaches. In dermatoscopy, both unhealthy (positive) and healthy (negative) images are extremely similar.

This justifies the introduction of methods that adopt non-linear separation surfaces. Already in [35], Support Vector Domain Description (SVDD) is proposed with which a sphere of minimal volume is used as the separation surface. SVDD, through the use of various kernels, allows flexible and accurate data descriptions.

Also in [36] is proposed a model that uses a fixed-center sphere as separating surface. The careful choice of the center of the sphere allows good separation results: this makes this model suitable for the management of very large datasets, and also for mobile applications.

In [37], the authors present DC-SMIL a MIL algorithm useful for image classification. DC-SMIL use spherical separation surface and come out with an optimization model which is of DC (Difference of Convex) type. In particular, the adopted classification error function depend on center and radius of the sphere and the deriving optimization model aims to minimize a combination of the volume of the sphere and of the classification error. Early applications of this algorithm in the classification task between dysplastics and common nevi confirm DC-SMIL's ability to separate classes whose elements are very similar [38, 39].

5 Discussion and future developments

As reported in [24], it is not easy to compare various proposals that use different machine learning approaches and different data sets to classify types of skin lesions.

There are many variables to take into consideration starting from the composition of features vector that may differ both in nature (color, texture, shape) and in being extracted locally or globally. A local approach allows larger dimensions of the features vector, but also implies a greater complexity of the feature space. SVM and ANN are among the most used methods for the implementation of frameworks suitable to support the diagnosis of specialists.

In the following table we summarize the results obtained using the MIL-RL algorithm compared to the literature results on melanoma detection via dermatoscopic images. We also report the classification performance obtained with DC-SMIL on the new classification task of discriminating dysplastic nevi against common ones.

	10-CV			
	SE (%)	SP (%)	Dataset Size	Method
$M\ vs\ B$	92.14	89.10	40/120	MIL-RL
$M\ vs\ D$	91.08	82.12	80/160	MIL-RL
$M\ vs\ (B+D)$	90.43	92.22	80/240	MIL-RL
$D\ vs\ B$	59.63	59.88	80/160	DC-SMIL

Table 1. Classification Performance with MIL approaches

With regard to the experimental section on the classification of dysplastic nevi against common nevi, the performances of MIL-RL and of SVM tecniques appear totally unsatisfactory [39].

This is obvious because the images that were separated are very similar. The use of spherical separating surfaces, provided by DC-SMIL algorithm, allows significant improvements in the extremely difficult task of classify Dysplastic nevi from common ones [39].

The results reported in the table 1 and related to DC-SMIL must not be read by comparing them with those obtained by MIL-RL on the classification tasks involving melanoma. In fact, DC-SMIL obtains better results than the same MIL-RL on the classification task of dysplastic nevi against common ones. A remarkable result considering that it was obtained using only color features and without image pre-processing. The presence of hair on skin lesions constitutes a disturbing element for the correct classification of the images.

The removal of hair or other foreign elements such as dermoscopic gel, possibly used to allow better illumination of the lesions, would ensure better classification results [41, 42]. The adoption of a wider range of features is also worth considering for the improvement of the classification performance [44, 45, 46].

In particular, in [47] the authors show how also the adoption of a more numerous features sets, including texture features, allow better performance classification respect than those obtained with only color features, on a dataset of images publicly available.

The obtained results show that MIL approach is very promising, even using only color features and without pre-processing steps and that the use of spherical separation surfaces, seems to be an interesting proposal for the development of applications in contexts in which positive and negative elements have strong similarities.

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