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Computer-aided Diagnosis of Melanocytic Lesions

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Abstract. *Background: The clinical diagnosis of melanoma could be difficult for a general practitioner and, in some cases, for dermatologists. To enhance and support the clinical evaluation of pigmented skin lesions a computer-aided diagnosis has been introduced. Materials and Methods: Images of melanocytic lesions (477 total, 42 melanomas and 435 melanocytic nevi) evaluated in epiluminescence microscopy and recorded with x16 magnification were selected. A training set of 22 melanomas and 218 nevi was randomized from the dataset. The test set was formed by the complement (the remaining 20 melanomas and 217 nevi). Furthermore, a set of images consisting of 31 melanomas and 103 nevi was selected to compare the discrimination capacity of three general practitioners and three dermatologists with experience in dermoscopy (2 years), and with the automatic data analysis for the melanoma early detection system (ADAM). Sensitivity and specificity were estimated for observer assessments and computer diagnosis. Results: The entire dataset used to test the implementation of the diagnostic algorithms ADAM showed a good sensitivity and specificity performance. Compared with the physicians, the ADAM system showed a slightly higher diagnostic performance in terms of sensitivity and a lower one in terms of specificity. Dermatologists showed higher levels of specificity, but lower levels in terms of sensitivity, when compared with the general practitioners. Conclusion: Image analysis has the potential to distinguish nevi and melanomas and to support the clinical diagnosis of melanocytic lesions by the general practitioner.*

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The incidence of malignant melanoma in fair-skinned patients has increased dramatically in most parts of the world over the past few decades. Because the prognosis of melanoma depends almost entirely on tumor thickness, early detection of thin melanoma is important for the survival of patients (1, 2).

Melanoma recognition is generally easy where the clinical ABCDE rule is applied (2). However, the diagnosis may be more complex in the early phase of melanoma progression or in the absence of classic clinical features (2). The diagnostic accuracy for melanoma is estimated to be about 50%-75% in specialized dermatological centers and lower for general practitioner offices (2-7). In the last decade, epiluminescence microscopy (ELM, dermoscopy) has completely changed the dermatologist's approach to suspicious pigmented skin lesions, but only a skilled clinician can improve in a statistically significant way the diagnosis of melanoma with the help of ELM, compared with naked eye evaluation (8-10).

However, the technological standard of ELM and its practical impact on the handling of pigmented skin lesions, the use of diagnostic algorithms and their intra- and interobserver reproducibility, the histological correlation and the training necessary to become an expert are still under discussion (8-18).

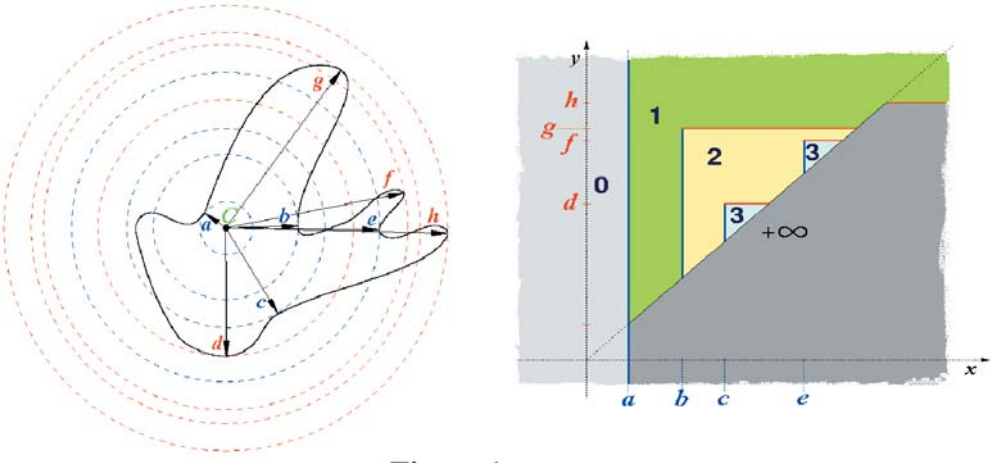


Figure 1. *A curve and its Size Function.*

To enhance the reproducibility of clinical judgment and to help inexperienced operators, computer-aided diagnosis ELM instruments have been introduced (19-33).

The aims of our study were: i) to evaluate the usefulness of a digital epiluminescence microscopy device equipped with a specific program for the computer-aided diagnosis of melanocytic lesions and ii) to compare the discriminatory capacity of dermatologists and general practitioners, with the image analysis system.

Materials and Methods

Equipment. The equipment consisted of a LEICA Wild 650 M with a 150 W light source at 3200 °K, that provides 5 magnifications from x6 to x40, allowing a field of view horizontally ranging from 6 mm to 4 cm, connected to a Sony 3CCD-930 color video camera. The camera was calibrated weekly using special Kodak paper for white balance. The components of the video signal were connected to a frame-grabber, mounted in a computer, equipped with a 1.2 gigabyte hard disk and a magneto-optical drive for image storage. The digital images were archived with the software DBDERMO Mips (11, 16). The digital images were processed at 768 x 576 pixels and 16 bit per pixel (11, 16).

Image processing system ADAM. The Automatic Data Analysis for Melanoma early detection (ADAM) software is based on a quite recent mathematical technique of shape representation: the Size Functions. These are very general invariants designed to capture, in a formal and quantitative way, the essential behaviour of some specified aspects (the so called *measuring functions*) of a signal (27, 28). In the present case, the examined signal is the image of a melanocytic lesion, and the aspects concerned are: boundary shape, texture and color distribution. Size Functions are standardized objects, easy to compute, to store and to compare. So the study is performed on the Size Function instead of the original image. This yields a great simplification and, above all, a greatly focussed analysis. The Size Function obtained from a curve with the distance from point C as measuring function is shown in Figure 1.

a) Classification. Size Functions have a standard structure, represented by the superimposed triangles in Figure 1. This has an important outcome, since the relevant information can be condensed in the vertices of those triangles. Comparison of two images (as far as the criterion intrinsic to the measuring function is concerned) can then be carried out by comparing the sets of these points. Several distances can be defined on the set of Size Functions; one is the *matching distance* illustrated in Figure 2. The distance from templates generally provides some significance with respect to classification. Unfortunately, archetypal nevi or melanomas do not exist, so the task is harder than for classic classification problems. We use distances for measuring asymmetries, as described below. These distances produce other characteristic numbers. Thus, the recent and powerful method, termed Statistical Learning, can be applied. The basic tool of this method, the so-called Support Vector Machines (SVM), is constructed to take into account other parameters not related to Size Functions. SVM process all the numbers, yielding a single parameter. This is compared with a threshold value, which is supposed to discriminate nevi from melanomas. By setting the threshold at two different values, we get two distinct SVM one "optimistic", the other "pessimistic". If their diagnoses coincide, the system emits a definite answer of low, or high risk, respectively. If they disagree, the output is of intermediate risk.

b) Segmentation. The first processing step is segmentation, *i.e.* the isolation of the skin lesion from its background. (see Figure 3; the separating curve is drawn in green). This is carried out with well-tested methods depending on several parameters, most of which have been fixed by experiment. The tuning of one of the remaining permits the removal of most hairs. This is a notoriously serious problem in the processing of dermatological images and has been solved by the operations of erosion and dilation coming from mathematical morphology.

c) Boundary. Once segmented, the first important feature a lesion offers to evaluation is its boundary. This curve, with the measuring function distance from center of mass, yields remarkably different Size Functions of nevi and melanomas, in most cases (see Figure 4 and Figure 5).

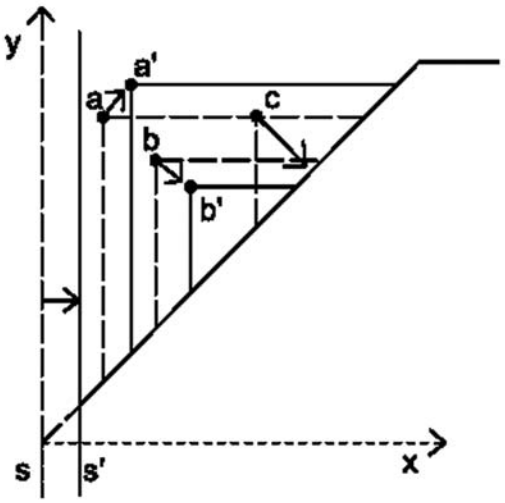
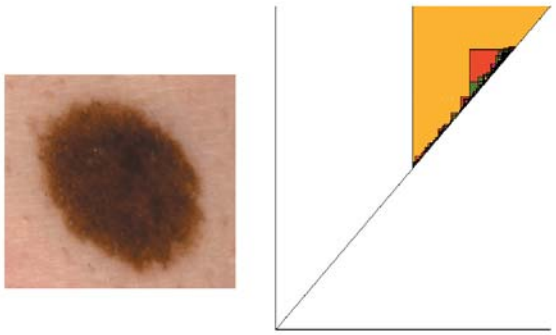


Figure 2.



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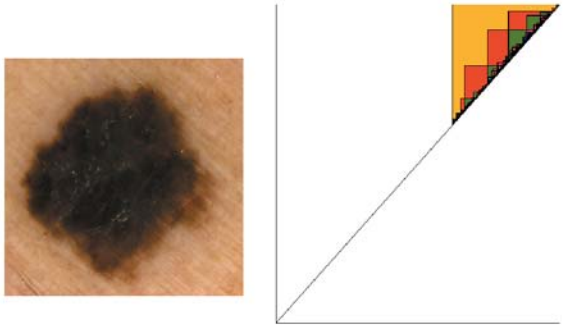

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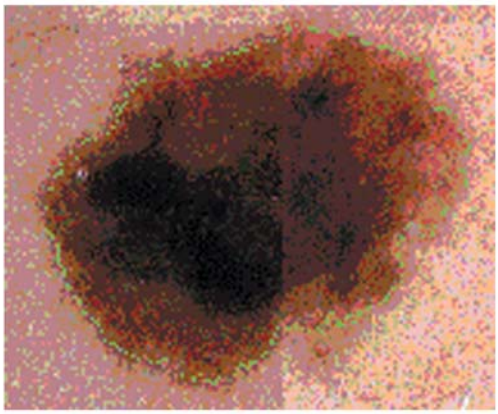

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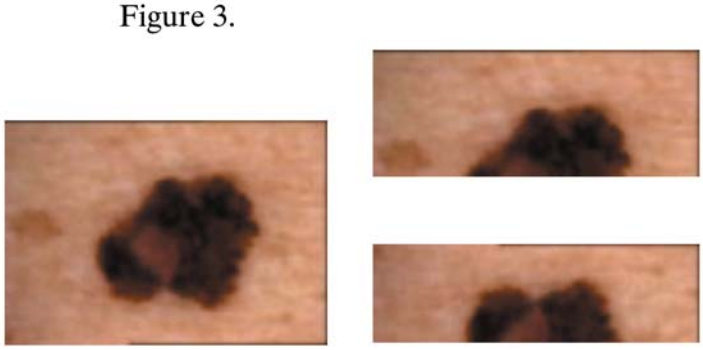

Figure 6.

Figure 2. *The matching distance.*
Figure 3. *A segmentation example.*
Figure 4. *A nevus and the Size Function of its boundary (not depicted).*
Figure 5. *A melanoma and the Size Function of its boundary (not depicted).*
Figure 6. *One of the splittings of a lesion and the whole curve of distances.*

d) Asymmetries. The asymmetry of various aspects of the tumor has been evaluated by splitting each lesion in two halves by a straight line passing through the center of the mass. Comparison of the two halves is then performed by computing the distance between their Size Functions. This represents a definite progress with respect to classic methods for detecting asymmetry: these detected only *geometrical* asymmetry, while distance of Size Functions also determine *qualitative* asymmetry. We repeat the splitting for a number of equally spaced radial lines, thus obtaining distance as a function of angle (see Figure 6). From this curve the software extracts a set of characteristic numbers with which it finally feeds the Support Vector Machines.

Dataset. The dataset used to test the implementation of the diagnostic algorithms developed by ADAM has already been the subject of a formal study of clinical diagnostic validation using the local population-based cancer registry (*i.e.* Registro Tumori Romagna, Italy) to identify false-negative cases. For the ADAM image processing, we selected 477 images of melanocytic lesions from a database of 3274 lesions from 1556 consecutive patients referred to Skin Cancer Unit in Ravenna undergoing clinical and ELM examination. Digital images included melanocytic lesions evaluated in ELM with a fixed x16 magnification. The reference diagnosis was established using the histology report of known surgical excisions, including those obtained from original referral hospitals for cases identified using a cancer-registry-based follow-up of benign diagnoses.

The dataset contained 42 melanomas (26 of them with thickness less than 0.75 mm) and 435 melanocytic nevi. A training set of 22 melanomas and 218 melanocytic nevi was randomized from the dataset. The test set was formed by the complement (the remaining 20 melanomas and 217 nevi) and was, thus, completely independent.

Comparison between ADAM and human operators. Three general practitioners (GPs) and three dermatologists with experience in ELM (2 years) were used for the comparison of the discrimination capacity with the ADAM system. A set of images of the previous dataset, consisting of 31 melanomas and 103 nevi, was shown to each of the 6 physicians independently. Only images corresponding to lesions in which a histological examination was possible were considered.

The general practitioners evaluated only clinical images, while the dermatologists examined both clinical and epiluminescence images to obtain conditions similar to those seen in clinical practice by the single operators. The ADAM system evaluated the same set of images, with the same tuning described above, considered as optimal.

Percentage sensitivity and specificity rates were calculated according to standard methods.

Results

Over the entire dataset, the ADAM system showed an 80% sensitivity and 79.77% specificity (test *vs.* training set). In a further experiment the whole dataset was used both as training set and as test set. In this case the best results obtained were 90% sensitivity and 77.12% specificity.

The results of the assessment performed by the observers and the computer are provided in Table I. Different results were observed both between the two operator subgroups and between the operators and ADAM. The results obtained by the dermatologists, compared with those of the GPs, were lower for clinical diagnosis in terms of sensitivity and higher in terms of specificity. The ELM evaluation by the dermatologists was improved in terms of sensitivity, but slightly reduced in terms of specificity, both of limited clinical value. The results of the GPs are excellent compared with those published in the literature regarding diagnostic ability of melanomas. The ADAM system scores showed slightly higher diagnostic performance in terms of sensitivity than the two subgroups of operators. Specificity, however, was lower.

Table I. *Comparison between ADAM and human operators.*

	Dermatologists°(%)		GP°°(%)	ADAM(%)
	ELM	Clin		
Sensitivity	75	74	81	84
Specificity	80	83	73	72

°Dermatologists: ELM = epiluminescence diagnosis; Clin=clinical diagnosis
°°GP= general pratictioner (clinical diagnosis)

Discussion

Computerized systems were introduced in cutaneous oncology at the end of the eighties (19, 20), but only recently has the development of digital epiluminescence systems reached a sufficient level of reliability for practical uses in routine dermatology practice (9, 10, 12) as well as in research (11, 12, 22-24, 33). The computerized evaluation of images allows for the identification of objective parameters for evaluation (22, 23). In principle, these are expected to be free of the inter- and intraobserver variability commonly associated with clinical and epimicroscopic subjective examination (11, 12).

In a recent review of the literature data (31), the sensitivity of computer-based devices varied between 80% and 100% and specificity between 47% and 92%. These figures suggested that the accuracy of computer-based diagnosis using different techniques for image acquisition does not differ significantly from that of the clinical diagnosis and is unrelated to the optical method of acquisition in operation.

Although these results are of importance, the published studies have been criticized because they generally lacked randomization of the processed images and did not take into account either lesion size or the Breslow thickness of

melanomas (31, 32). Other limitations derived from the varying number of lesions included in the analyses (melanomas from 5 to 67; non-melanomas from 31 to 770), the uneven melanoma: nevi ratio (from 1:2 to 1:20), and the absence of information concerning calibration systems and standardization of the images, a prerequisite for the correct segmentation and processing of the lesion (31, 32).

In this study, our primary aim was to assess whether computer processing of pigmented skin lesion images could support clinical diagnosis. We used a program that was essentially based on the measuring functions represented by a triplet of functions which distill the structure of boundary, texture and color. Automatic systems for melanoma diagnosis are currently available, but their background techniques were developed for rigid, mechanical shapes, whereas *size functions* are mathematical shape descriptors, expressly created for recognition of natural shapes (27, 28). We demonstrated that image analysis has the potential to distinguish nevi and melanomas.

The sensibility and specificity performances of ADAM are comparable with those of other research groups (31, 32). Based on preliminary results, the impact of our system as a support to the clinical diagnosis of melanocytic lesions for the GP seems to be important for lesions that should be referred to a specialist. In the same way, it gives further support to the dermatologist to be integrated in the specific diagnostic pathway of pigmented skin lesions.

The good level of sensitivity observed provides the essential prerequisite for the introduction of the ADAM system as a first-line diagnostic instrument aimed at the parametric objective selection of pigmented skin lesions for further assessment, that is for a global anamnestic and clinical-dermatoscopic evaluation by the specialist.

As shown in Table I, the ADAM score allows for the identification of "high risk" lesions, despite clinical characteristics of low significance. These lesions have to be assessed by the specialist. Clinical evaluation – as combined with the ADAM score for apparently benign lesions – has the potential to improve overall sensitivity at the GP level. In this perspective, the responsibility of reducing the frequency of unnecessary excisions rests with the specialist.

In the future, it will be of importance to: (a) improve the parameters of sensitivity of the ADAM system; (b) compare the ADAM system with larger groups of clinicians; (3) compare the ADAM system with other computed-aided devices; and (d) evaluate the ability of the specialists to identify the false-positive lesions selected by the system. To this end, controlled studies on a large scale are necessary.

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References

1 Kopf AB, Salopek TG, Slade M, Marghoob AA and Bart RS: Techniques of cutaneous examination for the detection of skin cancer. Cancer *75*: 684-690, 1995.

2 Stanganelli I, Clemente C and Mihm MC Jr: CD Melanoma cutaneo – Atlante multimediale interattivo per la prevenzione, la diagnosi e la terapia del Melanoma e delle lesioni pigmentate cutanee. Istituto Oncologico Romagnolo Ed., MAF Torino, 2001.

3 Del Mar C, Green A, Cooney T, Cutbush K, Lawrie S and Adkins G: Melanocytic lesions excised from the skin: what percentage are malignant? Aust J Public Health *18(2)*: 221-223, 1994.

4 Cassileth BR, Clark WH Jr, Lusk EJ, Frederick BE, Thompson CJ and Walsh WP: How well do physicians recognize melanoma and other problem lesions? J Am Acad Dermatol *14*: 550-560, 1986.

5 Grin CM, Kopf AW, Welkovich B, Bart RS and Levenstein MJ: Accuracy in the clinical diagnosis of malignant melanoma. Arch Dermatol *126*: 763-766, 1990.

6 Miller M and Ackermann AB: How accurate are dermatologists in the diagnosis of melanoma? Degree of accuracy and implication. Arch Dermatol *128*: 559-560, 1992.

7 Rampen FHJ and Rumke P: Referral pattern and accuracy of clinical diagnosis of cutaneous melanoma. Acta Dermatol Venereol (Stock) *68*: 61-64, 1988.

8 Mayer J: Systematic review of the diagnostic accuracy of dermoscopy in detecting malignant melanoma. Med J Aust *167*: 206-210, 1997.

9 Bafounta ML, Beuchet A, Aegert P and Saiag P: Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to evaluation of diagnostic tests. Arch Dermatol *137*: 1343-1350, 2001.

10 Kittler H, Pehamberger H, Wolff K and Binder M: Diagnostic accuracy of dermoscopy. Lancet Oncol *3*: 159-165, 2002.

11 Stanganelli I, Burroni M, Rafanelli S and Bucchi L: Intraobserver agreement in the interpretation of digital epiluminescence microscopy. J Am Acad Dermatol *33*: 584-589, 1995.

12 Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, Binder, M, Cerroni L, De Rosa G, Ferrara G, Hofmann-Wellenhof R, Landthaler M, Menzies SW, Pehamberger H, Piccolo D, Rabinovitz HS, Schiffner R, Staibano S, Stolz W, Bartenjev I, Blum A, Braun R, Cabo H, Carli P, De Giorgi V, Fleming MG, Grichnik JM, Grin CM, Halpern AC, Johr R, Katz B, Kenet RO, Kittler H, Kreusch J, Malvehy J, Mazzocchetti G, Oliviero M, Ozdemir F, Peris K, Perotti R, Perusquia A, Pizzichetta MA, Puig S, Rao B, Rubegni P, Saida T, Scalvenzi M, Seidenari S, Stanganelli I, Tanaka M, Westerhoff K, Wolf IH, Braun-Falco O, Kerl H, Nishikawa T, Wolff K and Kopf AW: Dermoscopy of pigmented skin lesions: results of a consensus meeting *via* the internet. J Am Acad Dermatol *48*: 679-693, 2003.

13 Epstein E: Instrumentation for epiluminescence microscopy: the gap between research and practice. Arch Dermatol *132*: 91-92, 1996.

14 Stanganelli I, Testori A, Pizzichetta MA and Cochran AJ: Dermatoscopic and histopathological diagnosis of primary and metastatic melanoma; report of a workshop at the Third Research Meeting on Melanoma, Milan, Italy, May 2003. Melanoma Res *14(3)*: 231-235, 2004.
15 Stanganelli I, Bucchi L and Dermatology and Venereology Society of the Canton of Ticino: Epiluminescence microscopy *versus* clinical evaluation of pigmented skin lesions: effects of operator's training on reproducibility and accuracy. Dermatology *196*: 199-203, 1998.
16 Stanganelli I, Serafini M and Bucchi L: A cancer registry-assisted evaluation of the accuracy of digital epiluminescence microscopy associated with clinical examination of pigmented skin lesions. Dermatology *200*: 11-16, 2000.
17 Ascierto PA, Palmieri G, Botti G, Satriano RA, Stanganelli I, Bono R, Testori A, Bosco L, Daponte A, Caraco C, Chiofalo MG, Melucci MT, Calignano R, Tatangelo F, Cochran AJ, Castello G, Melanoma Cooperative Group: Early diagnosis of malignant melanoma: proposal of a working formulation for the management of cutaneous pigmented lesions from the Melanoma Cooperative Group. Int J Oncol *22*: 1209-1215, 2003.
18 Carli P, De Giorgi V and Giannotti R: Dermoscopy and early diagnosis of melanoma: the light and the dark. Arch Dermatol *137(12)*: 1641-164, 2001.
19 Green A, Martin N, Mc Kenzie G, Pfitzner J, Quintarelli F, Thomas BW, O'Rourke M and Knight N: Computer image analysis of pigmented lesions. Melanoma Res *1*: 231-236, 1991.
20 Cascinelli N, Ferrario M, Bufalino R, Zurrida S, Galimberti V, Mascheroni L, Bartoli C and Clemente C: Results obtained by using a computerized image analysis system designed as an aid to diagnosis of cutaneous melanoma. Melanoma Res *2*: 163-170, 1992.
21 Green A, Martin N, Pfitzner J, O'Rourke M and Knight N: Computer image analysis in the diagnosis of melanoma. J Am Acad Dermatol *31*: 958-964, 1994.
22 Seidenari S, Pellacani G and Giannetti A: Digital videomicroscopy and image analysis with automatic classification for detection of thin melanomas. Melanoma Res *9*: 163-171, 1999.
23 Andreassi L, Perotti R, Rubegni P Burroni M, Cevenini G, Biagioli M, Taddeucci P, Dell' Eva G and Barbini P: Digital dermoscopy analysis for the differentiation of atypical nevi and early melanoma. Arch Dermatol *135*: 1459-1465, 1999.
24 Binder M, Kittler H, Dreiseitl S, Ganster H, Wolff K and Pehamberger H: Computer-aided epiluminescence microscopy of pigmented skin lesions: the value of clinical data for the classification process. Melanoma Res *10*: 556-561, 2000.
25 Elbaum M, Kopf AW, Rabinovitz HS, Langley RGB, Kamino H, Mihm MC, Sober AJ, Peck GL, Bogdan A, Gutkowicz-Krusin D, Greenebaum M, Keem S, Oliviero M and Wang S: Automatic differentiation of melanoma from melanocytic nevi with multispectral digital dermoscopy: a feasibility study. J Am Acad Dermatol *44*: 207-218, 2001.
26 Binder M, Kittler H, Seeber A, Steiner A, Pehamberger H and Wolff K: Epiluminescence microscopy-based classification of pigmented skin lesions using computerized image analysis and an artificial neural network. Melanoma Res *8*: 261-266, 1998.
27 Frosini P and Landi C: Size theory as a topological tool for computer vision. Pattern recogn Image Anal *9*: 596-603, 1999.
28 Donatini P, Ferri M and Frosini P: Applications of Size Theory to Computer Vision and Pattern Recognition, Joint Workshop of the AIIA - IAPR-IC IAPRVA *98*: 65-68, 1998.
29 Tomatis S, Carrara M, Bono A, Bartoli C, Lualdi M, Tragni G, Colombo A and Marchesini RD: Automated melanoma detection with a novel multispectral imaging system: results of a prospective study. Phys Med Biol *50(8)*: 1675-1687, 2005.
30 Wallace VP, Crawford DC, Mortimer PS, Ott RJ and Bamber JC: Spectrophotometric assessment of pigmented skin lesions: methods and feature selection for evaluation of diagnostic performance. Phys Med Biol *45*: 735-751, 2000.
31 Marchesini R, Bono A, Bartoli C, Lualdi M, Tomatis S and Cascinelli N: Optical imaging and automated melanoma detection: question and answer. Melanoma Res *12(3)*: 279-286, 2002.
32 Rosado B, Menzies S, Harbauer A, Pehamberger H, Wolff K, Binder M and Kittler H: Accuracy of computer diagnosis of melanoma: a quantitative meta-analysis. Arch Dermatol *140(3)*: 361-367, 2004.
33 Massone C, Di Stefani A and Soyer P: Dermoscopy for skin cancer detection. Curr Opin Oncol *17*: 147-153, 2005.

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