RESEARCH ARTICLE

Clinical, dermoscopic and histological assessment of melanocytic lesions: a comparative study of the accuracy of the diagnostic methods

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Abstract

Background: Worldwide, the incidence of melanoma is increasing, while late diagnosis is related to poor prognosis. A significant risk marker for melanoma is the presence of atypical nevi; therefore, it is of outstanding importance to make accurate clinical classification of common benign nevi, atypical nevi, and melanomas. The non-invasive method of dermoscopy allowed for the visualization of structures invisible to the naked eye and undoubtedly advanced the assessment of melanocytic lesions to a new dimension. This study aimed to evaluate the sensitivity and specificity of naked-eye examination and dermoscopy in diagnosing melanocytic lesions compared to the histopathological results, constituting the gold standard of diagnosis.

Material and Methods: One hundred eighteen melanocytic lesions were clinically evaluated via the naked eye and dermoscopic examination, using Pattern Analysis Methodology, and afterward, they were excised. The histopathological results were correlated with the findings.

Results: According to the final histopathological analysis, 63 common benign nevi, 41 dysplastic nevi, and 14 cutaneous melanomas were excised in total. Clinical examination via the naked eye showed 78.2 % sensitivity and 71.4 % specificity in identifying the clinical atypia, while dermoscopy demonstrated 89.1 % sensitivity and 93.7 % specificity.

Conclusions: The results of the present study indicate a higher sensitivity and specificity of dermoscopy in evaluating and diagnosing melanocytic lesions compared to the naked-eye examination. HIPPOKRATIA 2021, 25 (4):156-161.

Keywords: Melanocytic lesions, dermoscopy, atypia, dysplasia

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Introduction

Malignant melanoma, a potentially lethal cancer with its incidence in rapid increase worldwide, is evolving into one of the most frequent malignancies affecting the white populations[1]. Delays in diagnosis and hence advanced disease on presentation are related to high mortality rates, despite the continuous efforts for novel therapies[2]. Therefore, the medical community is presently focused on developing strategies for early melanoma detection, aiming to improve patient survival and decrease the cost of treatment.

Melanocytic nevi are located in the epidermis, dermis, or both areas and comprised of benign nevomelanocyte accumulations either in cohesive nests or as singly disposed cells. Atypical melanocytic nevi are commonly larger than five mm, with an asymmetric outline, indistinct borders, and variable pigmentation, and usually display simultaneously papular and macular components[3]. Early recognition of an atypical nevus is of great importance as the presence of even a single one is related to an increased risk for melanoma[3].

Dermoscopy is a practical, easy, and non-invasive examination that increases diagnostic precision when evaluating pigmented lesions since it allows pattern visualization not perceptible with the naked eye, thus contributing to early melanoma detection and reducing unnecessary biopsies[4]. However, it remains an intermediate tool between the clinical diagnosis and histopathological examination of the melanocytic lesions since the latter remains the gold standard for diagnosis[3].

This study aimed to evaluate the sensitivity and specificity of the clinical examination and dermoscopic assessment in diagnosing melanocytic lesions, compared to the histopathological results, and to evaluate the accuracy of the methods mentioned above in early melanoma diagnosis.

Material and Methods

The study was designed to follow the principles of current legislation and regulations and was approved by the local Research Ethics Committee of the University Hospital of Patras (decision No: 2931/20194). The size of the sample required was estimated with the use of G* Power, and for effect size (0.3), the required sample size was calculated at 88 lesions (alpha-level at 0.05, G* Power at 0.80).

Eighty consecutive patients (34 men and 46 women), with a total of 118 melanocytic lesions, attended from June 2020 to December 2021 the Dermatology department of the University of Patras for skin cancer screening and were prospectively recruited in the study. All melanocytic lesions with clinical or dermoscopic atypia and lesions of patients who desired their excision for aesthetic or functional reasons constituted the study's sample. Patients gave informed verbal consent before enrollment and examination and subsequently written consent before the excision of the skin lesions. We excluded from the study patients with lesions located on mucosal areas.

Two dermatologists with (at least) five-year experience independently examined clinically and dermoscopically all participants. Demographic and clinical data recorded for each patient included age, sex, lesion's topography, diameter, borders, symmetry, colors, phototype, and personal or family history of malignant melanoma.

The lesions were considered atypical if, during clinical examination, the presence of at least three of the following characteristics were noted: i) asymmetric shape, ii) poorly defined and irregular borders, iii) presence of erythema/variable shades of brown, iv) a diameter equal to or greater than five mm, and v) simultaneous presentation of papular and macular components.

We analyzed the lesions dermoscopically afterward through Pattern Analysis Methodology. As a first step, the global dermoscopic pattern of each lesion (reticular, globular, homogeneous, parallel, starburst, multi-component, atypical, and nonspecific) was analyzed, and each lesion was classified as melanocytic or not. As a second step, the melanocytic lesions were assessed as benign or malignant based on the following features: a) the general appearance of the lesion, regarding the uniformity or heterogeneity and surface texture of the lesion, b) the pigmentation pattern, based on the presence of pigment network, dots, and globules, c) pigment network, assessing the presence of irregularity in the network, d) brown globules, assessing the variety in size and the irregularity in distribution, e) black dots, based on their spreading out in the periphery, f) irregular and peripheral depigmentation, g) irregular borders in the periphery[5].

The lesions with regular borders and outline, pigment network thinning out at the periphery, without radial streaming or pseudopods, were classified as benign melanocytic nevi. The lesions with irregular borders, pigment network stopping abruptly at the periphery, and peripheral aggregation of brown globules, without, however, radial streaming or pseudopods, were classified as atypical nevi. In contrast, the presence of pseudopods and/or radial streaming, except for the features mentioned above, was suggestive of melanoma (in situ/invasive)[5].

The "inverse approach" was added to the Pattern Analysis Methodology for correctly categorizing the lesions located in head and neck areas. Specifically, the absence of specific dermoscopic characteristics for pigmented actinic keratosis or flat seborrheic keratosis was adequate to classify the lesion as lentigo maligna, even without the presence of other specific features[6].

We took the pigmented lesions' clinical images with 28 optical zoom in 20 megapixels analysis, using the Nikon L340 digital camera (Nikon Corp., Tokyo, Japan), and we obtained and stored the dermoscopic images in the Dino-Lite Digital Microscopy (AnMo Electronics Corp., Taipei, Taiwan). In cases of disagreement between the two dermatologists who examined the participants, images were also assessed by a third (expert) dermatologist to ensure the inter-rater reliability of the study. We classified the melanocytic lesions into three categories: common benign nevi, atypical nevi, and melanomas, based on the findings of the clinical and dermoscopic examination, and the skin lesions were then excised.

The histopathological evaluation was performed in the Pathology department of the University of Patras. In four cases of ambiguous correlation between (both) the clinical and dermoscopic diagnoses and the histopathological results, a second opinion was requested from an expert in melanocytic lesions Dermatopathologist. No diagnostic disagreement was documented between the histopathologists.

Statistical analysis

The naked-eye examination and dermoscopy results were correlated with the histopathological diagnoses. We divided the diagnoses into four categories: true positive (TP), false positive (FP), true negative (TN), and false negative (FN). TP defines lesions assessed as melanomas (one group) or atypical nevi (second group) by naked-eye clinical examination or dermoscopy and confirmed as melanomas or dysplastic nevi, respectively, on the histopathological examination. FP characterization refers to lesions assessed as atypical (melanomas or atypical nevi) by naked-eye examination with or without dermoscopy, but the diagnosis was not confirmed on histopathology. TN defines lesions assessed as common benign nevi by naked-eye clinical or dermoscopic examination, and the diagnoses were confirmed on the histological examination. FN characterization refers to lesions considered common benign nevi but proved to be melanomas or dysplastic nevi on histopathological examination. Based on the correlation between the clinical, dermoscopic, and histological diagnoses, we calculated the sensitivity [TP/(TP + FN)] and the specificity [TN/(TN+ FP)] of the clinical and dermoscopic examination in the diagnosis of the atypia of the melanocytic lesions[7].

We calculated the positive predictive value [PPV: TP/(TP+FP)] and the negative predictive value [NPV:

TN/(FN+TN)] of the diagnostic modalities utilizing 2 x 2 tables. The calculation of the positive likelihood ratio (LR+: sensitivity/1-specificity) and the negative likelihood ratio (LR-: 1-sensitivity/specificity) was utilized as a measure of the overall diagnostic accuracy, independent of the prevalence of atypical lesions[7,8].

Results

The study participants' median age was 37 (range: 14-93) years. Out of the 118 lesions, 25 (21.2 %) were located on the limbs, 86 (72.8 %) on the trunk, and 7 (6 %) on the head and neck. Based on the maximum length, the pigmented lesions' sizes ranged from 2 to 40 mm, with a median value of 7.19 mm.

From the 118 melanocytic lesions excised, 14 (12 %) were histopathologically diagnosed as cutaneous melanomas (ten invasive melanomas and four melanomas *in situ*), 41 (35 %) dysplastic nevi, and 63 (53 %) common benign nevi. Table 1 shows the distribution of the excised melanocytic lesions according to the histopathology diagnosis.

Forty-three out of the 55 histopathology-confirmed atypical melanocytic lesions (41 dysplastic nevi and 14 melanomas) were correctly diagnosed using visual inspection (TP), and twelve were incorrectly classified as common benign nevi (FN). Those were histopathology-confirmed as dysplastic nevi with mild/moderate cellular atypia. Forty-five out of 63 common benign nevi were correctly assessed by naked-eye examination as non-atypical (TN), and 18 were incorrectly diagnosed as atypical (FP), three as melanomas, and 15 as atypical melanocytic nevi (Table 2). Therefore, the sensitivity of assessing melanocytic lesions for atypia with the naked-eye examination was 78.2 % (43/55 x100), and the specificity was 71.4 % (45/63 x100), calculating an LR+ of 2.7, and an LR- of 0.3 (Table 3).

Regarding dermoscopic examination using Pattern Analysis Methodology, 49 atypical melanocytic lesions were recognized of the 55 histopathology-confirmed (TP), estimating a sensitivity of 89.1 %, and 59 common benign nevi were correctly classified of the 63 histopathology-confirmed (TN), estimating a specificity of 93.7 % (Table 2, Table 3). The LR+ was calculated at 14.1, and the LR- at 0.12 (Table 3).

Forty-three out of 61 melanocytic lesions diagnosed as atypical with the naked-eye examination were confirmed atypical, depicting a positive predictive value to diagnose the melanocytic lesion's atypia at 70.5 % (43/61). In comparison, 45 out of 57 melanocytic lesions diagnosed as non-atypical were histopathology-confirmed non-atypical, showing a negative predictive value of 78.9 % (45/57). The respective values for the dermoscopic examination were very high, with a positive predictive value of 92.5 % and a negative predictive value of 90.8 % (Table 3).

Figure 1 and Figure 2 show a paradigmatic case of a false positive diagnosis of melanoma based on the clinical examination and dermoscopy, respectively, that received the correct diagnosis of compound nevus without atypia following the histopathological examination.

Table 1: Histological diagnoses of the 118 excised melanocytic lesions clinically evaluated with the naked-eye examination and dermoscopy.

Diagnoses	Cases	%
I. Cutaneous melanomas	14	11.9
Ia. Invasive melanomas	10	8.5
Ib. In situ melanomas	4	3.4
II. Dysplastic Nevi	41	34.7
III. Benign common nevi	63	53.4
IIIa. Compound nevi	21	17.8
IIIb. Junctional nevi	17	14.4
IIIc. Lentigines	13	11.0
IIId. Halo nevi	1	0.9
IIIe. Dermal nevi	5	4.2
IIIf. Spitz Nevi	4	3.4
IIIg. Blue Nevi	2	1.7

Discussion

Malignant melanoma constitutes the fifth most common cancer in men and the sixth most common malignancy in women in the United States. Its incidence and mortality rate increase continuously worldwide[3]. Recognition of malignant melanoma at early stages is, undoubtedly, the cornerstone to ameliorating patients' survival and improving the overall prognosis.

The atypical nevus is a relatively common clinical entity representing 5 % of skin histopathology diagnoses. During adulthood, it exhibits a dynamic behavior and thus

Table 2: True positive, true negative, false positive, and false negative diagnoses through naked-eye examination and dermoscopy, in comparison to the histopathological results.

	Histopathologically positive	Histopathologically negative	Total
Naked-eye examination			
Atypia - positive	43 (TP)	18 (FP)	61 (TP + FP)
Atypia - negative	12 (FN)	45 (TN)	57 (TN + FN)
Dermoscopy			
Atypia - positive	49 (TP)	4 (FP)	53 (TP + FP)
Atypia - negative	6 (FN)	59 (TN)	65 (TN + FN)
Total	55	63	118

Table 3: Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for both diagnostic methods (naked-eye examination and dermoscopy).

	Sensitivity TP/(TP +FN)	**Specificity TN/(TN+FP)**	**PPV TP/(TP+FP)**	**NPV TN/(FN+TN)**	**LR+ sensitivity/ 1-specificity**	**LR- 1-sensitivity/ specificity**
Naked-eye examination	43/55 x100 % = 78.2 %	45/63 x100 % = 71.4 %	43/61 x100 % = 70.5 %	45/57 x100 % = 78.9%	0.782/(1-0.714) = 2.7	(1-0.782)/0.714 = 0.3
Dermoscopy	49/55 x100 % = 89.1 %	59/63 x100 % = 93.7 %	49/53 x100 % = 92.5 %	59/65 x100 % = 90.8 %	0.891/(1-0.937) = 14.1	(1-0.891)/0.937 = 0.12

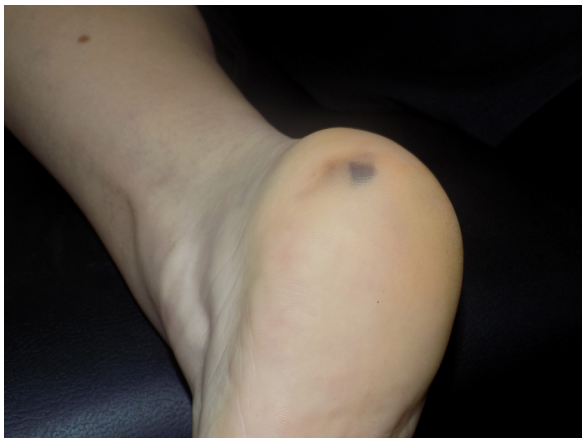

Figure 1: Clinical image demonstrating a false positive diagnosis regarding a lesion in the patient's right sole that was classified as an atypical lesion according to the ABCD rule but received the histopathological diagnosis of compound nevus.

differs from acquired common nevus[9]. The term 'atypical' nevus is noteworthy to mention that it refers to the clinical features of the pigmented lesion, in discrepancy to the term 'dysplastic' nevus, which describes its histological features. It is established knowledge that lesions without atypical clinical features may reveal, however, histopathological dysplasia[10]. The presence of dysplastic nevi is associated with an increased risk for sporadic melanoma, which illustrates the necessity for improvement of distinction between the clinical designation of atypical nevi and the definite histological diagnosis[11].

Clinical evaluation of melanocytic lesions via the naked eye examination utilizing the ABCD rule as introduced by Kopf et al[12] is founded on recognizing the following features of melanomas: Asymmetry, Border irregularity, Color variation, and Diameter (>6 mm)[12]. Although this diagnostic modality is one of the most widely employed methods to distinguish malignant from benign lesions, it has proven less accurate, particularly for detecting de novo arising melanomas that are usually smaller than six mm[12]. Additionally, it lacks specificity as the mentioned acronym may also be exhibited in benign lesions[13].

Figure 2: Dermoscopic image of the same lesion as in Figure 1 illustrating the parallel ridge pattern commonly associated with acral melanoma.

Dermoscopy is a practical, auxiliary, easy, and non-invasive modality. With its introduction to clinical practice, clinicians can visualize morphological features and patterns not visible to the naked eye, thus improving the diagnostic accuracy of evaluating melanocytic lesions[14]. Kittler et al[15] showed that dermoscopy enhances diagnostic accuracy by 49 %, with an increase of 6 and 19 % in specificity and sensitivity, respectively. In contrast, Carli et al[16] demonstrated in a randomized study that utilizing dermoscopy to evaluate pigmented lesions significantly reduces unnecessary biopsies[16].

Vestergaard et al[17], in a meta-analysis that included only prospective studies, with 8,487 non-melanocytic and melanocytic lesions, documented the diagnostic odds ratio for dermoscopy 15.6 times higher than visual in-

spection[17]. Recently Dinnes et al[18], in a comprehensive meta-analysis including 104 studies, showed that in addition to naked-eye-examination, dermoscopy advances in an assessable level the sensitivity and specificity in recognition of atypical intraepidermal melanocytic variants and invasive melanomas. In contrast, dermoscopy based on in-person evaluations had higher diagnostic accuracy than teledermatology (image-based assessments)[18]. Interestingly, recent data from the literature reveal the relevant high sensitivity (74.5%) of dermoscopy, detecting the 'challenging' cases of verrucous melanomas[19].

However, as with all diagnostic tools, dermoscopy's efficiency depends on the examiner's experience[20]. Piccolo et al[21] found 92 % sensitivity and 99 % specificity in diagnosing melanoma from dermoscopic images examined by dermatologists with a five-year experience, compared to 69 % sensitivity and 94 % specificity for clinicians without experience[21]. Training in dermoscopy increases melanoma detection rate; thus, primary care physicians and inexperienced dermatologists can enhance with training their diagnostic competencies[22,23].

The most widely used dermoscopic algorithms for diagnosing melanocytic lesions constitute pattern analysis, the ABCD rule, the 7-point checklist, and the Menzies method[5]. Each algorithm is exclusive, with different specificity and sensitivity values in the differentiation between common benign nevi and atypical lesions. We selected pattern analysis in this study due to the examiners' familiarity with this methodology. All lesions were clinically evaluated with or without dermoscopy by two experienced dermatologists to improve the study's efficacy. In disagreement, the images obtained were assessed by a third expert dermatologist.

The relatively low values demonstrated for sensitivity (78.2 %) and specificity (71.4 %) in this study for the naked-eye examination are comparable with literature data, with sensitivity for differentiating melanoma from non-melanoma ranging from 4 to 86 % and specificity from 71 to 99 %[23-26]. Bono et al[25] report extremely low sensitivity (43 %) compared to the current study, probably as a consequence of their inclusion criteria as they included smaller than three mm pigmented lesions only that are more difficult to assess[25].

The high sensitivity and specificity values found in this study support dermoscopy as an efficient modality to differentiate atypical lesions and demonstrate its superiority regarding diagnostic accuracy compared to unaided visual inspection (sensitivity 89.1 vs 78.2 % and specificity 93.7 vs 71.4 %, respectively).

The values presented agree with the corresponding values of the meta-analysis by Vesteergard et al[17] that included nine studies and compared naked-eye-examination with dermoscopy directly. It showed a summary estimate of specificity and sensitivity at 90 % for dermoscopy in differentiating melanoma and non-melanoma[17]. Our results also concur with those of a recent review of 43 studies by Harrington et al[27], evaluating the 'clinical prediction rules', documenting relatively high estimates of sensitivity (77-86 %) for dermoscopic diagnostic modalities utilized at the primary health care level[27].

It is essential to comment regarding the heterogeneity in existing studies for the definition of a positive test result, ranging from any type of malignant melanoma[17, 25-27], to only melanoma *in situ*[28], or invasive cutaneous melanoma, and atypical intraepidermal melanocytic variants (i.e., lentigo maligna)[18]. In the present study, in addition to invasive or *in situ* melanomas, the atypical nevi were also included in the positive test results. A recent study from Brazil with a similar sample size (106 lesions), used the same definition and demonstrated comparable sensitivity (93 %) for dermoscopy recognizing atypical nevi but low specificity (42 %)[29]. This discrepancy in the specificity value between the two studies could be related to clinicians' expertise variations. Undoubtedly, the safest clinician aims to avoid 'missing' a melanoma, even if that means excising benign lesions in some cases. Both studies agree that dermoscopy significantly contributes to this direction.

Our study, however, is subject to a few limitations. We consider as important the relatively small ratio of melanomas to the total number of lesions included in the study (12 %). Another limitation constitutes the fact that the study population includes only Greek patients from a single institution and not from multiple referral centers. A future study with a larger sample size recruited from multiple institutions would positively affect the reliability of the results.

Conclusion

The presented data support dermoscopy as a more accurate diagnostic modality for early detection of atypical lesions, compared to naked-eye examination, specifically when performed by experienced clinicians. Thus, although dermoscopy does not substitute clinical inspection, it contributes to a low rate of unnecessary biopsies and a better prognosis for malignant melanoma patients, reducing mortality and health-related costs.

Conflict of interest

The authors declare no conflict of interest.

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