Published in final edited form as:

J Am Acad Dermatol. 2019 January ; 80(1): 178–188.e3. doi:10.1016/j.jaad.2018.08.028.

The Clinical Spectrum of Cutaneous Melanoma Morphology

Nikolai Klebanov, BS^{1,*}, Nicole Gunasekera, MD^{1,*}, William M. Lin, MD², Elena B. Hawryluk, MD, PhD², David M. Miller, MD, PhD^{1,2,3}, Bobby Y. Reddy, MD^{1,2}, Mitalee P. Christman, MD¹, Derek Beaulieu, MD¹, Suvithan Rajadurai, BS¹, Lyn M. Duncan, MD⁴, Arthur J. Sober, MD², and Hensin Tsao, MD, PhD^{1,2}

¹Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

²Department of Dermatology, Massachusetts General Hospital, Boston, MA

³Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, MA

⁴Pathology Service, Massachusetts General Hospital, Boston, MA

Abstract

Background: Melanoma can mimic other cutaneous lesions, but the full spectrum and prevalence of these morphological variants remain largely unknown.

Objective: To classify non-acral cutaneous melanomas into distinct morphological “clusters” and characterize clusters’ clinicopathological features.

Methods: All pathological melanoma diagnoses (2011–2016) were reviewed for routine pre-biopsy digital photographs (n=400). Six dermatologists independently assigned lesions into one of 14 diagnostic classes based on morphology. Image consensus clusters were generated by K-means; clinicopathological features were compared with ANOVA and chi-square.

Results: Five morphological clusters were identified: “typical melanoma” (n=136), “nevus-like” (n=81), “amelanotic/non-melanoma skin cancer (NMSC)-like” (n=70), “seborrheic keratosis (SK)-like” (n=68), and “lentigo/lentigo maligna (LM)-like” (n=45). Nevus-like melanomas were found in younger patients. Nevus- and lentigo/LM-like melanomas tended to be thinner and more likely identified on routine dermatological exam. NMSC-like melanomas were tender, thicker, more mitotically active, and associated with prior NMSC. Typical and SK-like melanomas had similar clinicopathological features.

Limitations: Cluster subdivision yielded diminished sample sizes. Visual assignment was performed without clinical context.

Corresponding author: Hensin Tsao, MD, PhD, Wellman Center for Photomedicine, 50 Blossom Street, EDR 221, Boston MA 02114-2605, Telephone: 617-726-9569, Fax: 617-726-1206, HTSAO@mg.harvard.edu.

*These authors contributed equally to this work.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Disclosure: None declared for all authors.

Conclusion: When primary cutaneous melanomas were assigned into diagnostic groups and subjected to novel consensus clustering, recurrent morphological patterns emerged. The spectrum of these morphologies was unexpectedly diverse, which may have implications for visual training and possibly clinical diagnosis.

CAPSULE SUMMARY

- Melanoma can mimic many cutaneous lesions, impairing correct diagnosis. By clustering of diagnostic assignments, five common melanoma morphological groupings were identified: typical, nevus-like, amelanotic/NMSC-like, SK-like, and lentigo/lentigo maligna-like.
- Awareness of the diversity of melanoma appearances and their associated clinical factors may help dermatologists improve their diagnostic accuracy.

Keywords

melanoma; morphology; pigmented lesions; nevi; melanoma mimics; melanoma appearance; unusual-appearing melanoma; early diagnosis; diagnostic accuracy; education

INTRODUCTION

Melanoma is a prevalent and potentially fatal malignancy, with over 90,000 estimated new cases and 9,000 new deaths in 2018 in the United States¹. While surgical excision is often curative for localized disease, advanced metastatic melanoma carries a poor prognosis. Increased time to diagnosis is associated with increased stage, thickness, and likelihood of distant metastasis². Some studies ascribe delayed diagnosis to patient-related causes^{3–6}, such as inability to identify early melanoma features⁷ or lack of concern or knowledge^{8, 9}, while some ascribe it to physician delay^{10–12}. Patients identify most melanomas^{13, 14}, but melanomas identified by dermatologists are associated with thinner and more curable tumors^{4, 6, 15–19}. Thus, early patient and clinician melanoma detection is crucial for improving outcomes²⁰. The ABCDE system^{21, 22} and ugly duckling (UD) sign²³ are currently taught as easily-accessible rules to guide examination of potential cutaneous malignancies²⁴.

“Textbook images” of melanoma are self-reinforcing since classic-appearing lesions are likely to be photographed more often as exemplars. However, unusual-appearing melanomas are often not photographically documented since the unexpected diagnosis occurs much later. Melanomas with unusual morphologies are of particular interest, as they represent a rarely-studied visual spectrum and are often difficult to diagnose *a priori*. Melanoma can mimic other skin lesions (e.g. NMSC²⁵ and SK^{26–30}), delaying proper diagnosis. Melanoma more frequently mimics benign skin lesions in pediatric populations; these mimics are often thicker and of higher stage³¹. The characteristics of patients who develop unusual-appearing melanomas have not been systematically described. This study aims to portray melanoma morphological sub-groupings based on “consensus clustering” with emphasis on unusual-appearing lesions, and to identify associated factors which may assist in their diagnosis.

METHODS

Study subjects

Electronic medical record review was approved by the Partners HealthCare Institutional Review Board. All patients were from Massachusetts General Hospital (MGH). For purposes of site identification during routine care, prospectively-ascertained pre-biopsy images were often (2011–2013), or always (2013–), documented by a quick-grab image in the clinic. All consecutive histologically-proven melanoma cases (2011–2016) were initially identified through pathology record search. Clinical information extraction and image-pathological record pairing were performed by EMR review. Of 443 preliminary cases, 400 remained after excluding 34 for reasons related to their digital images and 9 given lack of clinical information (Supplemental Figure 1).

Image classification

Since all lesions were histologically melanomas, the exercise was not an issue of diagnostic accuracy. We aimed to identify recurrent morphological groupings as independently adjudicated by six board-certified dermatologists practicing in the MGH Melanoma and Pigmented Lesion Clinic. Digital images were randomized and presented to the panel. Without any clinical information, each dermatologist was asked to select the best diagnostic assignment from these choices: Actinic keratosis (AK), Basal cell carcinoma (BCC), Compound nevus (CN), Dermal nevus, Dysplastic nevus (DN), Eczema, Lentigo maligna (LM), Melanoma (amelanotic), Melanoma (pigmented), Seborrheic keratosis (SK), Squamous cell carcinoma (SCC), Solar lentigo, Wart. Free text input (“Other”) was recoded: SCC included SCCis; SK - inflamed-SK; vascular lesions - hemorrhage, trauma, hemangioma, and ecchymoses; pigmented nevus -Reed’s/Spitz/combined nevi; angiomas - angiosarcoma, angiokeratoma, thrombosed angioma, and cherry angioma. Categories with fewer than the median assignments were aggregated to Other. Data was normalized to assignment percent.

Statistical Methods

R (version 3.4.4)³², ‘irr’³³, ‘ggpubr’³⁴, ‘superheat’³⁵, and ‘factoextra’³⁶ packages were used for analysis. “Consensus clustering” was performed using Hartigan-Wong unsupervised K-means algorithm³⁷ on image assignment data (n=400) with 100 random starts. Unsupervised hierarchical clustering using Ward algorithm³⁸ on Manhattan distances was used to visualize relationships between individual morphological assignments and to independently validate cluster choice by the K-means algorithm (Figure 1). Fleiss’ kappa³⁹ was used to assess concordance between the six dermatologists. Clinical and pathological factors were then compared between clusters. Continuous means were compared by Kruskal-Wallis one-way ANOVA (linear ANOVA residuals were not normally distributed by Shapiro-Wilk test). Post-hoc analyses were performed by paired-Wilcoxon tests with Bonferroni correction. Categorical variables were analyzed by chi-square.

RESULTS

Five consensus clusters represent common melanoma appearance groupings

Total cluster number was determined empirically. Statistical simulations with 1–10 centroids and individual review of 4–6-centroid algorithms revealed a 5-centroid algorithm provided optimal resolution (Supplemental Figures 2–3).

Cluster 1 (CL1) (n=136) represented images most frequently assigned pigmented melanoma (70%), followed by DN (8%) or SK (7%). Cluster 2 (CL2) (n=81) images were predominately assigned DN (54%), followed by pigmented melanoma (16%) and CN (14%). Cluster 3 (CL3) (n=70) images were assigned BCC (26%), SCC (19%), AK (12%), amelanotic melanoma (12%), or Other (7%). Cluster 4 (CL4) (n=68) were assigned SK (47%), then pigmented melanoma (30%). Lastly, Cluster 5 (CL5) (n=45) contained lesions most often assigned LM (30%) and solar lentigo (30%), followed by SK (16%) (Supplemental Figure 3A). Representative cluster member images are shown (Figure 2). In aggregate, $k=0.308$ for concordance among the six raters.

Hierarchical morphological grouping clustering (Figure 1) revealed close relationships between solar lentigo/lentigo maligna, dermal nevus/amelanotic melanoma/AK-SCC-BCC-compound nevus-other, and SK-DN; pigmented melanoma represented a unique branch. Taken together, the results of K-means and hierarchical clustering support five morphological clusters: a typical pigmented melanoma (CL1), a nevus-like (CL2), an amelanotic/NMSC-like (CL3), a SK-like (CL4), and a lentigo/LM-like cluster (CL5).

Clinical features of individual clusters

No significant gender differences among clusters were observed (Table I). Approximately 40–50% patients were female. Mean and median age at diagnosis, with exception of CL2, was between 60–70 years. Subjects with nevus-like melanomas were significantly younger (52.8 years mean, 53.6 median) than other clusters ($p<0.001$) (Figure 3A). Typical and amelanotic/NMSC-like melanomas were most likely initially noted by the patient or a family member. In contrast, nevus- and lentigo/LM-like melanomas were most likely to be first identified by a dermatologist on routine exam (Figure 3B). Amelanotic/NMSC-like melanomas were the most likely to arise in subjects with a personal history of NMSC (74%, $p<0.001$), followed by lentigo/LM-like melanomas (64%). Amelanotic/NMSC- and Lentigo/LM-like subjects were the most likely to have a history of melanoma (36% and 31% respectively, $p<0.001$). Differences in family history of melanoma, history of sunburns, or history of tanning bed use were not significant. Fitzpatrick skin types were similar among clusters, with most patients (54–65%) having skin types II or II/III. More than 50% patients in each cluster had low nevi density. Amelanotic/NMSC-like and lentigo/LM-like melanomas were most often found in the setting of severe dermatoheliosis.

Comparisons of morphological features and symptoms reported in the medical record

There were no significant differences in lesion laterality between clusters (Table II). Typical, nevus-like, and SK-like melanomas favored the trunk, amelanotic/NMSC-like melanomas - the upper limbs, and lentigo/LM-like melanomas - the head/neck (Figure 3C). Amelanotic/

NMSC-like melanomas were the most likely to cause pain or irritation (17%, $p=0.001$). Typical melanomas were growing in 35% cases, followed by lentigo/LM-like (31%) and SK-like (28%).

In contrast, nevus-like melanomas were growing in significantly fewer cases (10%, $p=0.01$). Amelanotic/NMSC-like melanomas were the most likely to be reported as a new lesion (11%), however differences were not statistically significant. Bleeding or itching were rarely reported, regardless of lesion type. Lesion colors documented at initial examination varied significantly. Amelanotic/NMSC-like melanomas were less likely described as brown (29%), compared to other clusters (80%, $p<0.001$), but rather as pink/erythematous (88%, $p<0.001$). Typical melanomas were more often described as black (29%) than other clusters (11% and fewer, $p<0.001$). Color and border irregularity were noted in 285 (71%) and 79 (20%) of cases respectively. Irregular color was less frequent among amelanotic/NMSC-like lesions (73% versus 84%, $p=0.03$). Border irregularity revealed no significant variation. Amelanotic/NMSC-like melanomas most commonly presented as raised lesions (81%, $p<0.001$). Lentigo/LM-like melanomas were more commonly flat.

Pathological profiles of melanoma morphological clusters

While all diagnoses were primary cutaneous melanomas, final pathologic features displayed significant variation (Table III, Figure 4A). CL1-4 melanomas were most commonly superficial spreading melanoma, while lentigo/LM-like melanoma was often confirmed lentigo maligna melanoma. Amelanotic/NMSC-like melanomas were least likely diagnosed as malignant melanoma in situ (MMIS), but the most likely diagnosed as nodular or another subtype (including 2 desmoplastic, 3 nevoid, 1 spindle cell). Most nevus-like and lentigo/LM-like melanomas were anatomic level II or II/III, and most amelanotic/NMSC-like melanomas were anatomic level IV+ (Figure 4B). Typical and amelanotic/NMSC-like had significantly greater thickness than nevus-like and lentigo-like melanomas ($p<0.001$) (Figure 4C).

Amelanotic/NMSC-like melanomas displayed the highest mitotic activity ($p<0.001$) (Figure 4D), were least likely (75%) to display a radial growth phase, and most likely to display vertical growth phase (86%).

DISCUSSION

To increase diagnostic accuracy and decrease diagnostic delay, it is important to understand the clinical spectrum of melanoma and the factors associated with melanoma morphological types. A classification of melanomas based on their morphological features was determined with an unsupervised algorithm. The results suggest five distinct clusters with discriminating clinical factors that may aid in melanoma recognition.

There is perhaps unappreciated diversity in the appearance of cutaneous melanomas. Since images were captured pre-biopsy for routine clinical care, it is untethered to diagnostic impression; this offers a morphologic spectrum that is likely to be less biased than a teaching set of melanoma images. For instance, a keratotic surface response (CL4) in melanomas was surprisingly common in our set, yet rarely shown in textbook images. There are case reports

of verrucous-keratotic melanomas^{40–42}. Similarly, there appears to be a group (CL3) of early ill-defined, erythematous, scaly melanomas resembling AKs or possibly eczematous patches (Figure 2). We developed consensus clustering to empirically collapse a larger number of diagnostic classes into clinically-plausible morphologic groups. For instance, pink/erythematous plaques and nodules with variable degrees of scaling characterize amelanotic melanomas and BCC; thus, these two diagnostic classes logically co-cluster (CL3).

The data also indicate that nevus-like melanomas occur more frequently in younger adult patients. New nevi occur more frequently in younger patients, peaking at age 30 and continuing into the fifth decade^{2, 43}. The propensity of nevogenesis with younger age mostly likely underpins the mimicry between benign/dysplastic nevi and melanoma. Many of the thin melanomas among the younger subjects appear to be morphologically identical to banal or clinically-atypical moles (Figure 2). The true clinical “false negative” rate may thus be underestimated since these lesions are unlikely to draw any attention during a routine skin exam.

In patients with a prior history of NMSC presenting with a pink/erythematous, raised, painful or irritated lesion, clinicians may consider including melanoma on the differential along with BCC or SCC (CL3 melanomas comprised 18% of our cohort). We found higher frequency of nodular melanoma within this cluster (Figure 4A) – this subtype frequently presents as amelanotic and raised^{44, 45}. We found the clinicopathological features of SK-like lesions similar to those of typical melanomas. SKs are known to be difficult to distinguish from melanoma^{46, 47}, which is reflected in the assignment overlap between pigmented melanoma (30%) and SK (47%) in CL1/4 (Supplementary Figure 3A). Carrera and colleagues reported 24/132 cases (18%) of melanomas had clinical and dermoscopic features consistent with SK lesions. Features associated with these 24 SK-like melanomas included hyperkeratosis (34%), yellowish keratin (31%), comedo-like openings (31%), and milia-like cysts (22.4%). Retrospective analysis indicated that presence of blue-white veil, pseudopods or streaks, and pigment network were helpful in achieving the correct dermoscopic analysis⁴⁸. Thus, nearly 1 in 5 melanoma lesions are vulnerable to misdiagnosis of an SK.

While melanomas with a “typical” appearance had a high likelihood of being identified by the patient first, nevus-like and lentigo-like lesions were more commonly identified by a dermatologist during routine exam. This is consistent with prior findings showing that melanomas identified by dermatologists were associated with thinner tumors^{4, 6, 15–19}. It is interesting to note that patients with NMSC-like and lentigo/LM-like melanomas had the highest burden of severe dermatoheliosis (33% and 34%, respectively). Furthermore, over 90% of patients with NMSC-like, SK-like, and lentigo/LM-like melanomas reported a personal history of sunburns, compared to only 70–80% among typical and nevus-like clusters. As UV exposure correlates with histologic⁴⁹ and genomic⁵⁰ melanoma subtyping, it is not surprising that sun damage patterns, even among non-acral cutaneous lesions, may contribute to morphological diversity.

The results of our study may have potential implications for computer-aided diagnosis (e.g. deep learning with convolutional neural networks (CNNs)) and the reliability of digital images. CNNs are critically reliant on classic images for their training. While such models

show promising diagnostic performance in dermatology^{51, 52}, a much larger collection of morphologically-diverse melanomas are required to fine-tune accuracy. While some assignment errors have minimal clinical impact since a biopsy is likely to be performed regardless of diagnosis (e.g. BCC/SCC vs. melanoma), other misclassifications (e.g. SK or benign nevi vs. melanoma) may have more substantial implications. As alluded to above, computer-aided diagnoses could be made more reliable by assembling training sets that include images representative of a variety of melanoma appearance classes and by improving performance in niche binary classifications such as SK vs. SK-like melanoma, or benign lentigo versus lentigo-like melanoma.

There are several limitations to the study. First, images were intended for site identification only and were quick-captured in clinic by consumer cameras and cell phones thereby compromising image resolution and color balance. While more faithful to clinical practice than research, it can reduce the interpretability of the images. Second, the reviewers were provided images without the opportunity to perform a standard-of-care physical exam. Palpation, re-directed lighting and dermoscopy are all likely to enhance diagnostic accuracy. Studies have shown that, in the hand of expert users, dermoscopy can improve diagnosis of thin melanomas⁵³, amelanotic/hypomelanotic melanomas⁵⁴, LMM⁵⁵, and melanoma-in-situ⁵⁶. Third, study clinicians may have been variably affected by Gambler's fallacy; in cases of successive melanoma images, they may have subjected a bias toward remaining images being benign by presuming that, in subsequent images, benign lesions were disproportionately evident to offset the number of malignant ones. Fourth, clusters had unequal membership with CL1 containing the most members. Given the resulting small sample sizes, statistical power may have been insufficient to detect certain differences in factors. Fifth, given the random distribution of unknown data, covariance between related factors could not be reliably assessed. Sixth, this study did not include acral or mucosal lesions, which are important melanoma variants with an array of unique and challenging morphological presentations. Lastly, this study does not address an important challenge, which is the identification of a biologic, rather than histologic (as in this study), false negative. Melanomas so banal as to elude even initial sampling were not captured in this analysis.

CONCLUSION

Consensus clustering analysis of 400 melanoma images revealed five morphological classes: typical, nevus-like, amelanotic/NMSC-like, SK-like, and lentigo/LM-like. Nevus-like melanomas were found among younger patients, and similar to lentigo-like lesions, were thinner and invaded more superficial anatomic levels. Nevus-like and lentigo-like lesions were more likely identified on routine dermatological examination than by the patient or patient's family. Amelanotic/NMSC-like melanomas were thick, mitotically active, tender, and associated with prior NMSC. SK-like and typical melanomas were clinicopathologically similar. The melanoma morphology spectrum has been widely reported but poorly codified. Pre-biopsy impressions may have inadvertently limited the availability of images of benign simulants within the canon of "textbook" melanoma photographs. In the absence of an easily-accessible and computationally-robust neural network for morphological

stratification, we have introduced “consensus clustering” to empirically define morphological groupings with hopes of improving diagnostic accuracy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding sources:

NIH K24CA149202 (to HT), and the generous donors at MGH on behalf of melanoma research.

ABBREVIATIONS

AK	Actinic keratosis
BCC	Basal cell carcinoma
CL	Cluster (e.g. CL1: Cluster 1)
CN	Compound nevus
CNN	Convolutional neural network
DN	Dysplastic nevus
LM	Lentigo maligna
NMSC	Non-melanoma skin cancer
SK	Seborrheic keratosis
SCC	Squamous cell carcinoma

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30. [PubMed: 29313949]
2. Goodson AG, Grossman D. Strategies for early melanoma detection: Approaches to the patient with nevi. *J Am Acad Dermatol* 2009;60:719–35; quiz 36–8. [PubMed: 19389517]
3. Schmid-Wendtner MH, Baumert J, Stange J, Volkenandt M. Delay in the diagnosis of cutaneous melanoma: an analysis of 233 patients. *Melanoma Res* 2002;12:38–94.
4. Krige JE, Isaacs S, Hudson DA, King HS, Strover RM, Johnson CA. Delay in the diagnosis of cutaneous malignant melanoma. A prospective study in 250 patients. *Cancer* 1991;68:2064–8. [PubMed: 1913555]
5. Doherty VR, MacKie RM. Reasons for poor prognosis in British patients with cutaneous malignant melanoma. *Br Med J (Clin Res Ed)* 1986;292:987–9.
6. Richard MA, Grob JJ, Avril MF, Delaunay M, Thirion X, Wolkenstein P et al. Melanoma and tumor thickness: challenges of early diagnosis. *Arch Dermatol* 1999;135:269–74. [PubMed: 10086447]
7. Gajda M, Kaminska-Winciorek G. Do not let to be late: overview of reasons for melanoma delayed diagnosis. *Asian Pac J Cancer Prev* 2014;15:3873–7. [PubMed: 24935566]
8. Xavier MH, Drummond-Lage AP, Baeta C, Rocha L, Almeida AM, Wainstein AJ. Delay in cutaneous melanoma diagnosis: Sequence analyses from suspicion to diagnosis in 211 patients. *Medicine (Baltimore)* 2016;95:e4396. [PubMed: 27495055]

9. Betti R, Vergani R, Tolomio E, Santambrogio R, Crosti C. Factors of delay in the diagnosis of melanoma. *Eur J Dermatol* 2003;13:183–8. [PubMed: 12695136]
10. Cassileth BR, Temoshok L, Frederick BE, Walsh WP, Hurwitz S, Guerry D et al. Patient and physician delay in melanoma diagnosis. *J Am Acad Dermatol* 1988;18:591–8. [PubMed: 3351022]
11. Blum A, Brand CU, Ellwanger U, Schlagenhauff B, Stroebel W, Rassner G et al. Awareness and early detection of cutaneous melanoma: an analysis of factors related to delay in treatment. *Br J Dermatol* 1999;141:783–7. [PubMed: 10583157]
12. Brochez L, Verhaeghe E, Bleyen L, Naeyaert JM. Time delays and related factors in the diagnosis of cutaneous melanoma. *Eur J Cancer* 2001;37:843–8. [PubMed: 11313171]
13. Brady MS, Oliveria SA, Christos PJ, Berwick M, Coit DG, Katz J et al. Patterns of detection in patients with cutaneous melanoma. *Cancer* 2000;89:342–7. [PubMed: 10918164]
14. Carli P, De Giorgi V, Palli D, Maurichi A, Mulas P, Orlandi C et al. Self-detected cutaneous melanomas in Italian patients. *Clin Exp Dermatol* 2004;29:593–6. [PubMed: 15550129]
15. Epstein DS, Lange JR, Gruber SB, Mofid M, Koch SE. Is physician detection associated with thinner melanomas? *JAMA* 1999;281:640–3. [PubMed: 10029126]
16. Schwartz JL, Wang TS, Hamilton TA, Lowe L, Sondak VK, Johnson TM. Thin primary cutaneous melanomas: associated detection patterns, lesion characteristics, and patient characteristics. *Cancer* 2002;95:1562–8. [PubMed: 12237926]
17. Rampen FH, Rumke P, Hart AA. Patients' and doctors' delay in the diagnosis and treatment of cutaneous melanoma. *Eur J Surg Oncol* 1989;15:143–8. [PubMed: 2703058]
18. Richard MA, Grob JJ, Avril MF, Delaunay M, Gouvernet J, Wolkenstein P et al. Delays in diagnosis and melanoma prognosis (II): the role of doctors. *Int J Cancer* 2000;89:280–5. [PubMed: 10861505]
19. McPherson M, Elwood M, English DR, Baade PD, Youl PH, Aitken JF. Presentation and detection of invasive melanoma in a high-risk population. *J Am Acad Dermatol* 2006;54:783–92. [PubMed: 16635658]
20. Brehmer F, Ulrich M, Haenssle HA. Strategies for early recognition of cutaneous melanoma-present and future. *Dermatol Pract Concept* 2012;2:203a06.
21. Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. *CA Cancer J Clin* 1985;35:130–51. [PubMed: 3921200]
22. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA* 2004;292:2771–6. [PubMed: 15585738]
23. Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. *Arch Dermatol* 1998;134:103–4.
24. Ilyas M, Costello CM, Zhang N, Sharma A. The role of the ugly duckling sign in patient education. *J Am Acad Dermatol* 2017;77:1088–95. [PubMed: 28964538]
25. Farnetani F, Scope A, Coco V, Guida S, Cesinaro AM, Piana S et al. Paradigmatic cases of pigmented lesions: How to not miss melanoma. *J Dermatol* 2016;43:1433–7. [PubMed: 27402032]
26. Chen TY, Morrison AO, Cockerell CJ. Cutaneous malignancies simulating seborrheic keratoses: An underappreciated phenomenon? *J Cutan Pathol* 2017;44:747–8. [PubMed: 28589622]
27. Izikson L, Sober AJ, Mihm MC Jr, Zembowicz A. Prevalence of melanoma clinically resembling seborrheic keratosis: analysis of 9204 cases. *Arch Dermatol* 2002;138:1562–6. [PubMed: 12472343]
28. Carrera C, Segura S, Aguilera P, Takigami CM, Gomes A, Barreiro A et al. Dermoscopy Improves the Diagnostic Accuracy of Melanomas Clinically Resembling Seborrheic Keratosis: Cross-Sectional Study of the Ability to Detect Seborrheic Keratosis-Like Melanomas by a Group of Dermatologists with Varying Degrees of Experience. *Dermatology* 2018.
29. Salerni G, Alonso C, Gorosito M, Fernandez-Bussy R. Seborrheic keratosis-like melanoma. *J Am Acad Dermatol* 2015;72:S53–5. [PubMed: 25500043]
30. Argenziano G, Rossiello L, Scalvenzi M, Staibano S, Ruocco E, Cicale L et al. Melanoma simulating seborrheic keratosis: a major dermoscopy pitfall. *Arch Dermatol* 2003;139:389–91.

31. Mitkov M, Chrest M, Diehl NN, Heckman MG, Tollefson M, Jambusaria-Pahlajani A. Pediatric melanomas often mimic benign skin lesions: A retrospective study. *J Am Acad Dermatol* 2016;75:706–11 e4. [PubMed: 27430613]
32. R-Core-Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
33. Matthias Gamer JL, Ian Fellows Puspendra Singh. irr: Various Coefficients of Interrater Reliability and Agreement. 2012.
34. Kassambara A ggpubr: “ggplot2” Based Publication Ready Plots. 2017.
35. Rebecca Barter BY. superheat: A Graphical Tool for Exploring Complex Datasets Using Heatmaps. 2017.
36. Alboukadel KAssambara FM. factoextra: Extract and Visualize the Results of Multivariate Data Analyses. 2017.
37. Hartigan JA, Wong MA. Algorithm AS 136: A K-Means Clustering Algorithm. *Journal of the Royal Statistical Society Series C (Applied Statistics)* 1979;28:100–8.
38. Ward JH. Hierarchical Grouping to Optimize an Objective Function. *J Am Stat Assoc* 1963;58:236–&.
39. Fleiss JL. Measuring Nominal Scale Agreement among Many Raters. *Psychol Bull* 1971;76:378–&.
40. Damianov N, Tronnier M, Koleva N, Wollina U, Gianfaldoni S, Lotti T et al. Verrucous-Keratotic Malignant Melanoma (VKMM). *Open Access Maced J Med Sci* 2017;5:547–8. [PubMed: 28785359]
41. Blessing K, Evans AT, al-Nafussi A. Verrucous naevoid and keratotic malignant melanoma: a clinico-pathological study of 20 cases. *Histopathology* 1993;23:453–8. [PubMed: 8314219]
42. Scarfi F, Galeone M, Bassi A, Arunachalam M, Massi D, Difonzo EM. Melanoma manifesting as a verrucous lesion in the interdigital toe space. *Int J Dermatol* 2014;53:1125–6. [PubMed: 25070140]
43. Kittler H, Seltenheim M, Dawid M, Pehamberger H, Wolff K, Binder M. Frequency and characteristics of enlarging common melanocytic nevi. *Arch Dermatol* 2000;136:316–20. [PubMed: 10724192]
44. Chamberlain AJ, Fritschi L, Kelly JW. Nodular melanoma: patients’ perceptions of presenting features and implications for earlier detection. *J Am Acad Dermatol* 2003;48:694–701. [PubMed: 12734497]
45. Menzies SW, Moloney FJ, Byth K, Avramidis M, Argenziano G, Zalaudek I et al. Dermoscopic evaluation of nodular melanoma. *JAMA Dermatol* 2013;149:699–709. [PubMed: 23553375]
46. MacKenzie-Wood AR, Milton GW, de Launey JW. Melanoma: accuracy of clinical diagnosis. *Australas J Dermatol* 1998;39:31–3. [PubMed: 9529686]
47. Marks R, Jolley D, McCormack C, Dorevitch AP. Who removes pigmented skin lesions? *J Am Acad Dermatol* 1997;36:721–6. [PubMed: 9146533]
48. Carrera C, Segura S, Aguilera P, Scalvenzi M, Longo C, Barreiro A et al. Dermoscopic Clues for Diagnosing Melanomas That Resemble Seborrheic Keratosis. *JAMA Dermatol* 2017;153:544–51. [PubMed: 28355453]
49. Jang HS, Kim JH, Park KH, Lee JS, Bae JM, Oh BH et al. Comparison of Melanoma Subtypes among Korean Patients by Morphologic Features and Ultraviolet Exposure. *Ann Dermatol* 2014;26:485–90. [PubMed: 25143678]
50. Hayward NK, Wilmott JS, Waddell N, Johansson PA, Field MA, Nones K et al. Whole-genome landscapes of major melanoma subtypes. *Nature* 2017;545:175–80. [PubMed: 28467829]
51. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 2017;542:115–8. [PubMed: 28117445]
52. Han SS, Park GH, Lim W, Kim MS, Na JI, Park I et al. Deep neural networks show an equivalent and often superior performance to dermatologists in onychomycosis diagnosis: Automatic construction of onychomycosis datasets by region-based convolutional deep neural network. *PLoS One* 2018;13:e0191493. [PubMed: 29352285]

53. Pizzichetta MA, Talamini R, Stanganelli I, Puddu P, Bono R, Argenziano G et al. Amelanotic/hypomelanotic melanoma: clinical and dermoscopic features. *Br J Dermatol* 2004;150:1117–24. [PubMed: 15214897]
54. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Arch Dermatol* 2008;144:1120–7. [PubMed: 18794455]
55. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. *Br J Dermatol* 2012;167:280–7. [PubMed: 22404578]
56. Lallas A, Longo C, Manfredini M, Benati E, Babino G, Chinazzo C et al. Accuracy of Dermoscopic Criteria for the Diagnosis of Melanoma In Situ. *JAMA Dermatol* 2018;154:414–9. [PubMed: 29466542]

Figure 1.

Distribution of morphological assignments of 400 digital images by six board-certified dermatologists. Five morphological clusters (typical, nevus-like, amelanotic/NMSC-like, SK-like, and lentigo/LM-like) were derived using an unsupervised K-means clustering algorithm. Depth of color corresponds to assignment percentage. A dendrogram representation of relationships between individual assignments was produced by unsupervised hierarchical clustering using Ward algorithm with Manhattan distances, and revealed close relation between solar lentigo-lentigo maligna, dermal nevus-amelanotic melanoma-AK-SCC-BCC-compound nevus-other, and SK-DN. Pigmented melanoma represented a unique dendrogram branch.

Figure 2. Malignant melanoma. Representative images are included to illustrate five distinct melanoma morphological clusters identified by “consensus clustering.”

Figure 3.

Clinical comparisons of melanoma morphological clusters. A. Nevus-like melanomas (CL2) were diagnosed at a significantly younger age than melanomas of other morphologies. B. Nevus-like and lentigo/LM-like melanomas (CL2 and 5) were more likely to be initially noted by a dermatologist, while typical and amelanotic/erythematous/keratotic melanomas were often initially noted by the patient or a family member. C. Typical and nevus-like melanomas were most often located on the trunk, amelanotic/NMSC-like melanomas favored the upper limb, and lentigo/LM-like melanomas favored the head and neck.

Figure 4.

Pathological comparisons of melanoma morphological clusters. A. Superficial spreading melanoma was the most common pathologic diagnosis for all clusters other than lentigo/LM-like (CL5), which commonly revealed lentigo maligna melanoma. Nodular and other (desmoplastic, spindle, nevoid) melanoma was most common among the amelanotic/NMSC cluster (CL3). B. Nevus-like and lentigo/LM-like melanomas were predominately anatomic level II or II/III, while amelanotic/NMSC-like melanomas (CL3) were anatomic level IV and higher (II+ includes II and II/III, III+ includes III and III/IV, IV+ includes IV, IV/V, and V). C. Nevus-like and lentigo/LM-like (CL2, 5) melanoma clusters were significantly thinner than typical and amelanotic/NMSC-like clusters (CL1 and 3). D. Typical and amelanotic/NMSC-like melanomas displayed significantly higher mitotic activity compared to nevus-like and lentigo/LM-like melanomas.

Table I.

Clinical factors of cluster members.

Cluster:	1 (n=136)	2 (n=81)	3 (n=70)	4 (n=68)	5 (n=45)	p value*
Demographic Variables (n=400)						
n [†]	136	81	70	68	45	
Female, n (%)	56 (41)	42 (52)	30 (43)	29 (43)	18 (40)	p = 0.59
*Age, yr, mean ±SD	63.6±17.1	52.8±16.9	63.7±15.6	61.7±13.2	66.6±10.2	p < 0.001
Age, yr, median	65.7	53.6	66.4	61.7	69.1	
*First Identified By (n=400)						
n [†]	136	81	70	68	45	
Patient or Family, n (%)	70 (51)	23 (28)	35 (50)	30 (44)	19(42)	
Dermatologist, n (%)	41(30)	53 (65)	28 (40)	30 (44)	25 (55)	
Non-Derm Prof. [§] , n (%)	25 (18)	5 (6)	7 (10)	8 (12)	1 (2)	
*Personal history of NMSC(n=374)						
n [†]	126	73	66	67	42	
Yes, n (%)	42 (33)	19 (26)	49 (74)	27 (40)	27 (64)	p < 0.001
*Personal history of Melano ma (n=394)						
n [†]	132	80	69	68	45	
Yes, n (%)	12 (9)	21 (26)	25 (36)	12 (18)	14 (31)	p < 0.001
Family History of Melanoma(n=352)						
n [†]	125	69	59	63	36	
Yes, n (%)	25 (20)	26 (38)	13 (22)	17 (27)	13 (36)	p = 0.052
Personal history of sunburns (n=146)						
n [†]	50	26	25	32	13	
Yes, n (%)	42 (84)	19 (73)	23 (92)	30 (94)	13 (100)	p = 0.07
Personal history of tanning bed use(n=196)						
n [†]	86	35	25	42	8	
Yes, n (%)	17 (20)	12 (34)	10 (40)	10 (24)	3 (38)	p = 0.19
Fitzpatrick Skin Type[‡] (n=250)						
n [†]	97	37	40	50	26	
I+, n (%)	19 (20)	9 (24)	13 (32)	14 (28)	7 (28)	
II+, n (%)	55 (57)	24 (65)	23 (57)	27 (54)	17 (65)	
III+, n (%)	19 (20)	4 (11)	4 (10)	8 (16)	2 (8)	
IV, n (%)	4 (4)	0 (0)	0 (0)	1 (2)	0 (0)	
Density of Nevi^{••} (n=165)						
n [†]	67	32	27	29	10	
“Low”, n (%)	41 (61)	18 (56)	21 (78)	17 (59)	8 (80)	
“Moderate”, n (%)	15 (22)	4 (12)	4 (15)	6 (21)	2 (20)	
“High”, n (%)	11 (16)	10 (31)	2 (7)	6 (21)	0 (0)	

	Cluster: 1 (n=136)	2 (n=81)	3 (n=70)	4 (n=68)	5 (n=45)	p value *
*Dermatoheliosis [∇](n=296)						p = 0.012
n [†]	103	60	51	53	29	
“Mild”, n (%)	14 (14)	15 (25)	13 (25)	11 (21)	0 (0)	
“Moderate”, n (%)	62 (60)	37 (62)	21 (41)	32 (60)	19 (66)	
“Severe”, n (%)	27 (26)	8 (13)	17 (33)	10 (19)	10 (34)	

* Calculated by Kruskal-Wallis one-way analysis of variance for continuous variables, and by χ^2 testing for categorical variables.

[†] Number of patients for whom information on group of variables was available.

[§] Non-dermatologist professionals include primary care physicians, non-dermatologist MDs, and hair dressers.

[‡] I+ includes “I” alone or “I-II”, II+ includes “II” alone or “II-III”, III+ includes “III” alone or “III –IV.”

^ˆ Low includes “none,” “very low”; moderate includes “low-moderate”; high includes “very high.”

[∇] Mild includes “none,” “mild-moderate”; moderate includes “moderate-severe,” “present.”

Table II.

Morphological factors of cluster members.

Cluster:	1 (n=136)	2 (n=81)	3(n=70)	4 (n=68)	5 (n=45)	p value*
Left/Right Location (n=341)						
p = 0.24						
n [†]	112	69	63	58	39	
Left, n (%)	64 (57)	32 (46)	37 (59)	29 (50)	22 (56)	
Right, n (%)	47 (42)	33 (48)	25 (40)	24 (41)	16(41)	
Midline, n (%)	1 (1)	4 (6)	1 (2)	5 (9)	1 (3)	
*Body Site[§] (n=400)						
p < 0.001						
n [†]	136	81	70	68	45	
Head/Neck, n (%)	16 (12)	2 (2)	15 (21)	18 (26)	29 (64)	
Trunk, n (%)	60 (44)	47 (58)	14 (20)	25 (37)	6 (13)	
Upper limb, n (%)	28 (21)	12 (15)	27 (39)	16 (24)	8 (18)	
Lower limb, n (%)	32 (24)	20 (25)	14 (20)	9 (13)	2 (4)	
Symptoms (n=311)						
n [†]	109	67	47	53	35	
Bleeding, n (%)	9 (8)	2 (3)	5 (11)	6 (11)	0 (0)	p = 0.14
Itching, n (%)	6(6)	1 (1)	2 (4)	3 (6)	2 (6)	p = 0.74
*Pain/irritated, n (%)	6 (6)	1 (1)	8 (17)	1 (2)	0 (0)	p = 0.001
*Growing, n (%)	38 (35)	7 (10)	12 (26)	15 (28)	11 (31)	p = 0.01
Changing, n (%)	25 (23)	10 (15)	4 (9)	9 (17)	10 (29)	p = 0.11
New lesion, n (%)	7 (6)	1 (1)	5 (11)	5 (9)	0 (0)	p = 0.10
Presence of Colors (n varies)						
*Brown, n (%) (n=305)	81 (83)	58 (89)	16 (29)	44 (83)	28(85)	p < 0.001
*Black, n (%) (n=305)	28 (29)	7 (11)	2 (4)	5 (9)	2 (6)	p < 0.001
*Blue, n (%) (n=305)	6 (6)	1 (2)	0 (0)	0 (0)	0 (0)	p = 0.042
*Pink/Erythema, n (%) (n=308)	32 (32)	18 (28)	49 (88)	20 (38)	7 (21)	p < 0.001
Tan/Skin color, n (%) (n=306)	6 (6)	4 (6)	8 (14)	6 (11)	3 (9)	p = 0.41
Pigmented, n (%) (n=353)	20 (17)	10 (13)	3 (5)	10 (16)	7 (18)	p = 0.24
*Irregular Color (n=285)						
n [†]	107	61	33	51	33	
Yes, n (%)	99 (93)	51 (84)	24 (73)	47 (92)	28 (85)	p = 0.03
Irregular Borders (n=79)						
n [†]	23	22	7	12	15	
Yes, n (%)	22 (96)	18 (82)	7 (100)	11 (92)	15 (100)	p = 0.22
*Lesion Topography^f (n=345)						
p < 0.001						
n [†]	111	71	67	58	38	
Flat, n (%)	36 (32)	40 (56)	13 (19)	25 (43)	29 (76)	
Raised, n (%)	75 (68)	31 (44)	54 (81)	33 (57)	9 (24)	

* Calculated by Kruskal-Wallis one-way analysis of variance for continuous variables, and by χ^2 testing for categorical variables.

[†] Number of patients for whom information on group of variables was available.

[§] Trunk includes the upper back and scapula.

[‡] Flat includes macule, patch, and ulcer; raised includes papule, plaque, nodule, mass.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table III.

Pathological factors of cluster members.

Cluster:	1 (n=136)	2 (n=81)	3 (n=70)	4 (n=68)	5 (n=45)	p value*
*Pathologic Diagnosis[§] (n=400)						p < 0.001
n [‡]	136	81	70	68	45	
Superficial Spreading, n (%)	87 (64)	66 (81)	40 (57)	39 (57)	16 (36)	
MMIS, n (%)	16 (12)	12 (15)	3 (4)	15 (22)	8 (18)	
Nodular, n (%)	10 (7)	2 (2)	8 (11)	1 (1)	0 (0)	
Lentigo Maligna, n (%)	6 (4)	0 (0)	7 (10)	6 (9)	18 (40)	
Unclassified, n (%)	15 (11)	0 (0)	6 (9)	5 (7)	2 (4)	
Other, n (%)	2 (1)	1 (1)	6 (9)	2 (3)	1 (2)	
Thickness (n=335)						
n [‡]	121	69	65	49	31	
*Thickness (mm), mean±SD	1.1±1.2	0.48±0.24	1.3±1.5	0.80±0.82	0.49±0.53	p < 0.001
Thickness (mm), median	0.63	0.42	0.8	0.54	0.37	
*Anatomic Level[‡] (n=329)						p < 0.001
n [‡]	117	68	65	49	30	
II+, n (%)	36 (31)	38 (56)	12 (18)	20 (41)	17 (57)	
III+, n (%)	36 (31)	21 (31)	19 (29)	17 (35)	10 (33)	
IV+, n (%)	45 (38)	9 (13)	34 (52)	12 (24)	3 (10)	
*Mitoses (n=331)						
n [‡]	118	69	65	49	30	
Mits/mm ² , mean±SD	1.5±2.8	0.38±1.0	3.2±6.3	1.6±3.9	0.20±0.55	p < 0.001
*Ulceration (n=328)						
n [‡]	115	69	65	49	30	
Present, n (%)	11 (10)	0 (0)	7 (11)	2 (4)	0 (0)	p = 0.02
Regression (n=201)						
n [‡]	80	37	44	29	11	
Present, n (%)	29 (36)	12 (32)	8 (18)	6 (21)	4 (36)	p = 0.20
Lymphovascular invasion (n=278)						
n [‡]	105	56	58	39	20	
Present, n (%)	9 (9)	5 (9)	9 (16)	5 (13)	2 (10)	p = 0.69
*Radial growth phase (n=302)						
n [‡]	104	68	55	47	28	
Present, n (%)	96 (92)	66 (97)	41 (75)	45 (96)	28 (100)	p < 0.001
*Vertical growth phase (n=327)						
n [‡]	115	68	65	49	30	
Present, n (%)	84 (73)	39 (57)	56 (86)	32 (65)	12 (40)	p < 0.001

* Calculated by Kruskal-Wallis one-way analysis of variance for continuous variables, and by χ^2 testing for categorical variables.

[†] Number of patients for whom information on group of variables was available.

[§] Lentigo maligna includes lentigo maligna in situ; “other” includes acral lentiginous, amelanotic superficial spreading, desmoplastic, nevoid, and spindle cell.

[‡] II+ includes II alone and II/III, III+ includes III alone and III/IV, IV+ includes IV alone, IV/V, and V alone.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript