Published in final edited form as:

J Eur Acad Dermatol Venereol. 2020 November ; 34(11): 2541–2547. doi:10.1111/jdv.16815.

Dermoscopic features of thin ($\leq$ 2mm Breslow thickness) versus thick ($>$ 2mm Breslow thickness) nodular melanoma and predictors of nodular melanoma versus nodular non-melanoma tumors: a multicentric collaborative study by the International Dermoscopy Society

D. Sgouros¹, A. Lallas², H. Kittler³, A. Zarras¹, A. Kyrgidis⁴, C. Papageorgiou², S. Puig⁵, A. Scope⁶, G. Argenziano⁷, I. Zalaudek⁸, M.A. Pizzichetta^{8,9}, A. Marghoob¹⁰, K. Liopyris^{1,10}, J. Malvehy⁵, C. Oikonomou¹, A. Flórez¹¹, R. Braun¹², H. Cabo¹³, G. Nazzaro¹⁴, S. Lanssens¹⁵, S. Menzies¹⁶, J. Paoli^{17,18}, G. Kaminska – Winciorek¹⁹, C. Longo^{20,21}, A. Katoulis²², Z. Apalla²³, D. Ioannides², L. Thomas²⁴, I. Tromme²⁵, D. Ogata²⁶, C. Desinioti¹, A. Geller²⁷, A. Stratigos¹

¹1st Department of Dermatology-Venereology, Andreas Sygros Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece

²1st Department of Dermatology, Aristotle University, Thessaloniki, Greece

³Department of Dermatology, Medical University of Vienna, Vienna, Austria

⁴Department of Clinical Pharmacology, Aristotle University, Thessaloniki, Greece

⁵Melanoma Unit, Dermatology Department, Hospital Clinic Barcelona, Universitat de Barcelona IDIBAPS, Barcelona, Spain & CIBER de Enfermedades Raras, Instituto de Salut de Carlos III, Barcelona, Spain.

⁶Medical Screening Institute, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Israel

⁷Dermatology Unit, University of Campania “Luigi Vanvitelli”, Naples, Italy

⁸Department of Dermatology, University of Trieste, Italy

⁹Division of Medical Oncology - Preventive Oncology, National Cancer Institute, Aviano, Italy

¹⁰Memorial Sloan Kettering Cancer Center, Hauppauge, New York

¹¹Department of Dermatology, Pontevedra University Hospital, Spain.

¹²Department of Dermatology, University Hospital Zürich, Zürich, Switzerland

¹³Dermatology Institute of Medical Research, University of Buenos Aires, Argentina

Corresponding author: Alexander J. Stratigos, MD, 1st Department of Dermatology – Venereology, Andreas Sygros Hospital, 5 I. Dragoumi Str, 16 121, Athens, Greece, tel/fax: +302107265212 alstrat2@hol.gr.

*The two authors contributed equally to this manuscript.

Conflicts of interest: The authors have no conflict of interest to declare

IRB approval status: Waiver decision obtained by Ethics Committee, Andreas Sygros Hospital, Athens, Greece, ref. number 2511/1.3.2017

- ¹⁴Dermatology Unit, Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
- ¹⁵Private practice Dermatology Maldegem, Maldegem, Belgium
- ¹⁶Discipline of Dermatology, Sydney Medical School, The University of Sydney and Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Camperdown, NSW Australia
- ¹⁷Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
- ¹⁸Region Västra Götaland, Sahlgrenska University Hospital, Department of Dermatology and Venereology, Gothenburg, Sweden
- ¹⁹Department of Bone Marrow Transplantation and Onco-Hematology, Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRIO), Gliwice Branch, Gliwice, Poland.
- ²⁰Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
- ²¹Centro Oncologico ad Alta Tecnologia Diagnostica, Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Italy
- ²²2nd Department of Dermatology-Venereology, "Attikon" General University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece
- ²³State Clinic of Dermatology, Hospital for Skin and Venereal Diseases, Thessaloniki, Greece
- ²⁴Department of Dermatology, Lyon University, France
- ²⁵Department of Dermatology, King Albert II Institute, Cliniques Universitaires Saint Luc, Brussels, Belgium
- ²⁶Department of Dermatology, Saitama Medical University, Japan
- ²⁷Department of Social and Behavioral Sciences, Harvard TH School of Public Health, Boston, MA, United States.

Abstract

Background: Thin nodular melanoma (NM) often lacks conspicuous melanoma-specific dermatoscopic criteria, and escapes clinical detection until it progresses to a thicker and more advanced tumor.

Objective: To investigate the dermatoscopic morphology of thin (<2mm Breslow thickness) versus thick (>2mm) NM and to identify dermatoscopic predictors of its differential diagnosis from other nodular tumors.

Methods: Retrospective, morphological case-control study, conducted on behalf of the International Dermoscopy Society. Dermatoscopic images of NM and other nodular tumors from 19 skin cancer centers worldwide were collected and analyzed.

Results: Overall, 254 tumors were collected (69 NM of Breslow thickness <2 mm, 96 NM >2mm and 89 non-melanoma nodular lesions). Light brown coloration (50.7%) and irregular brown dots/globules (42.0%) were most frequently observed in <2mm NMs. Multivariate analysis revealed that dotted vessels (3.4-fold), white shiny streaks (2.9-fold) and irregular

blue structureless area (2.4-fold) were predictors for thinner NM compared to non-melanoma nodular tumors. Overall, irregular blue structureless area (3.4-fold), dotted vessels (4.6-fold) and serpentine vessels (1.9-fold) were predictors of all NM compared to non-melanoma nodular lesions.

Limitations: Absence of a centralized, consensus pathology review and cases selected from tertiary centers may not reflect the broader community.

Conclusions: Our study sheds light into the dermatoscopic morphology of thin NM in comparison to thicker NM and could provide useful clues for its differential diagnosis from other non-melanoma nodular tumors.

Keywords

nodular melanoma; thickness; pigmented tumors; non-pigmented tumors; non-melanoma tumors; dermatoscopy

Introduction

Melanoma is a malignant skin tumor with an increasing incidence over the last decades. Melanoma is responsible for the majority of deaths from cutaneous malignancies, with more than 95,000 new cases and almost 7,200 deaths estimated in 2019 in the US representing a major public health issue.^{1,2}

Nodular melanoma (NM) comprises 12–30% of all melanomas, but however, it accounts for at least 50% of all melanomas thicker than 2mm; hence it has the worst prognosis and associated survival.^{3,4,5} A recent observational study including approximately 120,000 patients showed that the nodular histopathologic subtype was an independent risk factor of mortality, after adjustment for other prognostic factors such as Breslow thickness, ulceration and stage.⁶ The early detection of NMs while they are still thin could potentially improve the prognosis, however it remains particularly challenging.

Several studies have explored the dermatoscopic characteristics of NM, suggesting that they substantially differ from the features known to typify superficial spreading melanoma.^{7–11} However, the diagnostic accuracy of dermatoscopy for NM is considered to be lower when compared with other melanoma subtypes.¹¹

The primary aim of this international multicenter study was to investigate the dermatoscopic morphology of NM with Breslow thickness up to 1mm and identify dermatoscopic predictors for its differential diagnosis from other nodular tumors. However, NM tend to be diagnosed at a more advanced stage, hence only 12 NM thinner than 1mm were collected and the threshold for analysis was re-defined to 2mm accordingly. The secondary aim of this study was (1) to compare the dermatoscopic features seen in thin NM (as defined above) with those found in thicker NM, and (2) to assess the dermatoscopic morphology of pigmented and non-pigmented NMs in comparison to non-melanoma tumors with nodular appearance.

Materials and methods

This was a retrospective, morphological case-control study, conducted on behalf of the International Dermoscopy Society (IDS), and was publicized on the IDS website calling for participation. The Ethics Committee approval was waived, since the study was retrospective, did not affect in any way patient's management and was conducted on anonymized datasets (waiver decision obtained by Ethics Committee, Andreas Sygros Hospital, Athens, Greece, ref. number 2511/1.3.2017).

Inclusion Criteria:

Patients with available close-up clinical and dermatoscopic images of: i) tumors surgically excised and histopathologically diagnosed as NMs, routinely defined by the presence of a dermal component with no or with a minimal junctional component with a maximum of 3 histopathologically involved rete ridges; or ii) surgically excised tumors with a nodular clinical morphology (with no or minimal flat component), for which melanoma was included in the clinical differential diagnosis, but the histopathologic diagnosis was other than melanoma.

Tumor characteristics and patient epidemiologic data (age and sex) were recorded in a de-identified database.

Exclusion Criteria:

Non-biopsied lesions and lesions lacking a definite histopathologic diagnosis were not eligible.

Feature Selection:

The selection of the dermatoscopic variables was based on the latest consensus and an expert consensus meeting held by the IDS particularly for the present study.¹²

The variables included in the analysis were divided into 4 categories : overall architecture and colors, pigmented structures, non-pigmented structures excluding vessels, vascular structures. (analytic list of criteria in e-figure 1 of the supplement)

Image Evaluation:

The clinical and dermatoscopic images were evaluated by 5 independent investigators (DS, CP, HK, AS, SP) who were blinded for the histopathologic diagnosis. The evaluation of pre-defined variables was performed using an on-line platform (Survey Monkey) and the images were randomly presented to the evaluators. The statistical analysis was performed on the basis of agreement by at least three of the five evaluators.

Statistical analysis:

Absolute and relative frequencies were obtained for the dermatoscopic characteristics. For the logistic regression analysis, outcome variables were set to thin NM or other diagnosis. Using the threshold of 1mm of Breslow thickness, the test group (thin NM) consisted of only 12 NM. Because of the large number of variables to be assessed, this sample size was

deemed as inadequate for analysis. Therefore, the threshold was changed to 2mm. Relative risks were calculated for the dichotomous variables. Adjusted ORs and corresponding 95% CI were calculated by conditional multivariate logistic regression (backward elimination according to likelihood criteria). The alpha level was set at 0.05 while an alpha level of 0.10 was used as the cut-off point for removal of the variable in the automated model selection for multivariate logistic regression. Statistical analyses were performed using IBM SPSS ver. 23 (Armonk, NY, USA).

A subgroup analysis for dermatoscopically pigmented versus non-pigmented tumors was performed for each study group. The tumors were classified as pigmented or not based on the presence of at least one dermatoscopic color corresponding to melanin (black, light brown, dark brown, gray, blue), according to the dermatoscopic evaluation.

Results

Study sample and patients' demographics:

Our study included 254 tumors in 254 unique patients. Sixty-nine lesions (27.2%) were NMs 2mm Breslow thickness, 96 lesions (37.8%) were NMs >2mm Breslow, and 89 lesions (35.0%) were non-melanoma nodular lesions. The latter group included 31 SK, 28 BCC, 10 dermal nevi, 10 SCC, 5 benign adnexal tumors, and 5 angiomas. The basic clinical and histopathological features of the 254 tumors and the demographic characteristics of the patients are shown in Table 1. Sex distribution differed among study groups, with NMs 2mm Breslow thickness being more common among females (female/male=1.4), whereas thicker NM had a predilection for males (male/female=1.63). Regarding anatomic location, NMs 2mm Breslow thickness tended to develop on the extremities (60.3%) compared to the group of thicker NM (>2 mm Breslow thickness) which mostly arose on the trunk (44.7%).

Dermatoscopic features

The analytic results of the dermatoscopic analysis are shown in supplementary e-tables 1–4. Out of the 69 NMs 2mm Breslow thickness, 50 (72.5%) displayed a dermatoscopic asymmetry of colors and 44 (63.8%) had an asymmetric distribution of structures. Thicker NMs exhibited color and structure asymmetry in 77.1% and 74.0%, respectively and non-melanomas in 39.3% and 53.9%, respectively. Light brown was the most commonly observed color in NMs up to 2mm Breslow (50.7%), followed by white (46.4%), blue (44.9%), and pink (43.5%). In thicker NMs, the most frequent colors were blue (64.6%), white (53.1%), and pink (52.1%) (e-table 1).

The most common dermatoscopic structures in NMs up to 2mm of Breslow thickness were irregular brown dots/globules (42.0%), irregular blue structureless area (33.3%), ulceration (29%), shiny white blotches/strands (27.5%), shiny white streaks (26.0%) and irregular (eccentric) black blotch (24.6%). In thicker NMs, the most frequent dermatoscopic structures were ulceration (68.7%), irregular blue structureless area (53.1%), shiny white blotches/strands (41.6%) and shiny white streaks (23.9%) (e-tables 2–3). In terms of vascular structures, the most commonly observed morphologic types of vessels in NMs

up to 2mm of Breslow thickness were dotted (21.7%) and serpentine (18.8%), whereas in thicker NM, serpentine (43.7%), dotted (24.0%) and corkscrew vessels (17.8%) were the most common. (e-table 4).

Multivariate analysis revealed three important predictors of NMs $\leq$ 2mm Breslow thickness as compared to non-melanomas: dotted vessels, shiny white streaks and irregular blue structureless area, which were associated with a 3.4-fold, 2.9-fold and 2.4-fold higher probability for melanoma, respectively (Table 2). In total, irregular blue structureless areas, dotted vessels and serpentine vessels represented predictors of NMs, irrespectively of Breslow thickness, as compared to non-melanomas with a 3.4-fold, 4.6-fold and 1.9-fold probability, respectively (Table 3). In the comparative analysis between thinner and thicker NM, irregular brown dots/globules were found to be a predictor of NM up to 2mm of Breslow thickness (1.8-fold) and serpentine vessels a predictor of thicker NM (3.3-fold).

Subgroup analysis

In the subgroup analysis for pigmented and non-pigmented tumors, the respective numbers of tumors in each group were: 57/69 (82.6%) pigmented and 12/69 (17.4%) non-pigmented NMs $\leq$ 2mm, 75/96 (78.1%) pigmented and 21/96 (21.9%) non-pigmented NMs thicker than 2mm, and 46/89 (51.7%) pigmented and 43/89 (48.3%) non-pigmented non-melanomas. Of the remaining dermatoscopic criteria, those with the most important differences in frequency between pigmented and non-pigmented NMs are shown in e-tables 5–6 of the supplement.

We found that non-pigmented NMs were more symmetric, especially in terms of colors. Vascular structures were more frequently detected in non-pigmented NMs as compared to pigmented ones in both groups (thinner and thicker NMs). In the group of NMs $\leq$ 2mm Breslow thickness, dotted vessels was the predominant type of vessels in non-pigmented tumors whereas serpentine vessels occurred more frequently in pigmented NMs. In the group of thicker NMs, serpentine vessels prevailed in both pigmented and non-pigmented subgroups. A noteworthy finding of the subgroup analysis was the greater frequency of dermatoscopically observed ulceration in non-pigmented NMs $\leq$ 2mm Breslow thickness (41.7%) as compared to pigmented ones (26.3%). This difference was reversed in the group of thicker NMs, with respective frequencies of 51.3% for non-pigmented tumors and 73.4% for pigmented NMs.

The multivariate analysis was repeated within the subgroups of pigmented and non-pigmented tumors in order to identify predictors of NM $\leq$ 2mm Breslow thickness as compared to non-melanomas (Table 2). No predictor was found for non-pigmented tumors, whereas irregular blue structureless area represented a melanoma predictor among pigmented tumors (2-fold increased probability).

Discussion

Herein we investigated the dermatoscopic morphology of NM at a relatively early phase of its progression based on histopathologic thickness. We attempted to identify dermatoscopic predictors for its differential diagnosis from other tumors and provide insights into the morphologic evolution of NM as tumor thickness increases.

Interestingly, patients presenting with NM ≤ 2 mm had a mean age of 52 years, 8 years younger when compared to those with thicker tumors (60 years). In addition, patients with thinner NMs were more likely to be female compared with the male-dominated thicker NMs (Table 1). While this difference might be partially attributed to sex-related biologic characteristics, it is more likely to be explained by the increased awareness for the presence of melanoma among females as compared to males.^{13–17} Additionally, 35% of NMs ≤ 2 mm Breslow thickness and 23% of thicker NMs were clinically non-pigmented. This finding is in line with prior literature suggesting that NM is much more frequently hypo- or amelanotic, as compared to other melanoma subtypes.^{18–20} A noteworthy finding in our dataset was NMs of the head/neck area accounted for only 2% of NMs ≤ 2 mm and for 11% of NMs > 2 mm. Similarly, none of the NMs ≤ 2 mm was located on acral sites, whereas 2.1% of thicker melanomas were acral. These findings highlight that early diagnosis of NM is more problematic on the head/neck area and on acral skin as compared to the trunk and extremities. (Table 1).

Dermatoscopic analysis revealed that NM ≤ 2 mm Breslow thickness typically presents with 2 or more colors; usually light brown, blue, white and pink color (Fig. 1). However, in line with previous publications, we found that an important proportion of NMs (up to 30%) remain symmetric in terms of dermatoscopic colors and structures.^{2, 8–10, 21, 22}

Irregular brown dots/globules, irregular blue structureless area, ulceration, white shiny blotches/strands and white shiny streaks were the most frequently encountered dermatoscopic structures in the group of thin NMs (Fig. 1). In contrast, atypical network, regression structures and irregular streaks were rarely found in our overall sample of NM. The latter finding is consistent with pre-existing literature^{8, 10, 22} and is explained by the fact that these features correspond to histopathologic alterations at the level of the dermo-epidermal junction, which are absent or minimal in NM.^{11, 24, 25}

The multivariate analysis revealed 3 important predictors of NM ≤ 2 mm Breslow thickness as compared to non-melanomas: dotted vessels, white shiny streaks/lines and irregular blue structureless area (Fig. 1). A comparison of these results with previously reported findings is problematic because of the scarcity of published evidence. The largest previous case-control study that included 83 cases of NM reported numerous univariate predictors of NM, but a multivariate logistic regression analysis was not performed.⁸

Dotted vessels can be found in several benign and malignant skin tumors and inflammatory skin diseases (i.e. common nevi, Spitz nevi, dermatofibromas, LPLK, BD, superficial BCCs on the legs, psoriasis, eczema)^{26–31} as well as in flat pigmented and amelanotic melanoma.^{10, 32} However, almost all of the aforementioned conditions manifest as clinically flat lesions, whereas dotted vessels in nodular tumors have not been frequently described. Considering that dotted vessels represented also the strongest predictor in the entire set of NM, irrespectively of Breslow thickness, (tables 2–3), our data combined with pre-existing evidence strongly suggest that a nodule displaying dotted vessels should be considered as highly suspicious for NM (Fig. 1).^{8, 18, 33}

White shiny streaks/lines have been previously suggested to represent a melanoma-specific structure and our findings support this also for NM ≥ 2 mm Breslow thickness,¹⁸ while white shiny blotches/strands – a feature of BCC as well – lost their diagnostic significance in the multivariate analysis. (Fig. 1).³⁴

Irregular blue structureless area was an independent multivariate predictor of NM in the entire set, of NM ≥ 2 mm (tables 2–3), and in the subgroup analysis for pigmented tumors only (Fig. 1). The presence of blue pigmentation in NM had been reported in previous studies.^{7–8, 35–36} Our results corroborate Argenziano et al. findings that the combination of blue and black color within a nodular lesion is strongly suggestive of NM (“blue-black rule”).¹¹ However, only 13% of NMs ≥ 2 mm Breslow thickness displayed blue-black coloration.

Our comparative analysis between the two groups of NMs may provide insights into the dermatoscopic evolution of NM. A reasonable finding of the latter analysis was that the proportion of NMs with a dermatoscopic symmetry decreases as the thickness of NM increases. In terms of colors, the most important difference was the predominance of light brown color in thinner NMs and blue color in thick NMs. The most striking difference in terms of dermatoscopic structures was the predominance of irregular brown dots/globules in NMs ≥ 2 mm Breslow thickness (Fig. 1), as compared to their much lower frequency in thicker NMs. Concerning vascular morphology, dotted vessels prevailed in NMs ≥ 2 mm Breslow thickness (Fig. 1) whereas serpentine vessels in the group of thicker tumors (Fig. 2). Corkscrew vessels were also much more frequent in thicker NMs, possibly corresponding to the increased tumor neo-angiogenesis (Fig. 2). These findings are consistent with pre-existing literature on the vascular pattern of melanoma.^{8, 26, 33, 37–40} In summary, the main dermatoscopic changes in NM as thickness increases are that brown color becomes less evident and blue more prominent, dermatoscopically observed ulceration increases and dotted vessels are replaced by serpentine and highly tortuous linear vessels (Fig. 2).

The subgroup analysis of non-pigmented and pigmented tumors revealed that non-pigmented NMs were much more frequently symmetric in terms of colors as compared to pigmented ones, a feature that reflects a common problem in everyday practice leading to delayed diagnosis or inappropriate treatment.⁴¹ In contrast, most of the pigmented NMs displayed a dermatoscopic asymmetry of colors and structures which is consistent with 2 previous case-control studies on pigmented NM that reported a high frequency of asymmetric pigmentation.^{9, 24}

Limitations:

The main limitation of our study is that it included a highly selected case series, from tertiary centers, which may not be representative of the broader community. However, our study represents the largest to date collection of images from NM of different tumor thicknesses, including thinner tumors of Breslow ≤ 2 mm. Another limitation is the absence of a centralized, consensus pathology review, which carries the potential of diagnostic misclassification, a problem often seen with the diagnosis of nodular melanoma.

Conclusion:

In conclusion, our study confirms the insidious nature of a NM at its early stages and suggests that irregular brown dots/globules, irregular blue structureless area, white shiny streaks/lines and dotted vessels can be useful dermatoscopic clues for its clinical diagnosis. Considering the scant available evidence on the topic, our findings need to be further elucidated, but may assist in the early recognition of this aggressive type of melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The project was supported by the Institute of Dermatological Education and Research (Athens, Greece) / **The patients in this manuscript have given written informed consent to publication of their case details**

Funding sources: None

Abbreviations

NM	Nodular Melanoma
IDS	International Dermoscopy Society
OR	Odds Ratio
CI	Confidence Intervals
SK	Seborrheic Keratosis
BCC	Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
LPLK	Lichen planus-like keratosis
BD	Bowen's Disease

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*2019;69:7–34. doi: 10.3322/caac.21551. Epub 2019 Jan 8. [PubMed: 30620402]
2. Klebanov N, Gunasekera N, Lin Wet al.Clinical spectrum of cutaneous melanoma morphology. *J Am Acad Dermatol*2019; 80:178–188.e3. doi: 10.1016/j.jaad.2018.08.028.
3. Weir HK,Thompson TD, Soman A, Møller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020. *Cancer*2015;121:1827–1837. doi: 10.1002/cncr.29258. Epub 2015 Feb 3. [PubMed: 25649671]
4. Chamberlain A, Giles G, Dowling J, Kelly J. Nodular Type and Older Age as the Most Significant Associations of Thick Melanoma in Victoria, Australia. *Arch Dermatol*2002;138:609–614 [PubMed: 12020221]
5. Demierre MF, Chung C, Miller D, Geller A. Early Detection of Thick Melanomas in the United States. *Arch Dermatol*2005;141:745–750 [PubMed: 15967921]

6. Lattanzi M, Lee Y, Simpson D, et al. Primary Melanoma Histologic Subtype: Impact on Survival and Response to Therapy. *J Natl Cancer Inst* 2019;111:180. doi: 10.1093/jnci/djy086 [PubMed: 29912415]
7. Rosendahl C, Hishon M, Cameron A, Barksdale S, Weedon D, Kittler H. Nodular melanoma: five consecutive cases in a general practice with polarized and non-polarized dermatoscopy and dermatopathology. *Dermatol Pract Concept* 2014;4:69–75. doi: 10.5826/dpc.0402a15. eCollection 2014 Apr
8. Menzies SW, Moloney FJ, Bythe Ket al. Dermoscopic evaluation of nodular melanoma. *JAMA Dermatol* 2013; 149:699–709. doi: 10.1001/jamadermatol.2013.2466. [PubMed: 23553375]
9. Kalkhoran S, Milne O, Zalaudek I et al. Historical, clinical, and dermoscopic characteristics of thin nodular melanoma. *Arch Dermatol* 2010; 146:311–318. doi: 10.1001/archdermatol.2009.369. [PubMed: 20231503]
10. Pizzichetta MA, Kittler H, Stanganelli I et al. Pigmented nodular melanoma: The predictive value of dermoscopic features using a multivariate analysis. *Br J Dermatol* 2015;173:106–114. doi: 10.1111/bjd.13861. Epub 2015 Jun 2 [PubMed: 25916655]
11. Argenziano G, Longo C, Cameron A et al. Blue-black rule: a simple dermoscopic clue to recognize pigmented nodular melanoma. *Br J Dermatol* 2011;165:1251–1255. doi: 10.1111/j.1365-2133.2011.10621.x. [PubMed: 21916885]
12. Kittler H, Marghoob AA, Argenziano G, et al. Standardization of terminology in dermoscopy/dermatoscopy: Results of the third consensus conference of the International Society of Dermoscopy. *J Am Acad Dermatol* 2016;74:1093–1106. doi: 10.1016/j.jaad.2015.12.038 [PubMed: 26896294]
13. 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;95:1562–1568. Doi: 10.1002/cncr.10880 [PubMed: 12237926]
14. Swetter S, Layton C, Johnson T, Brooks K, Miller D, Geller A. Gender differences in melanoma awareness and detection practices between middle-aged and older men and their female spouses. *Arch Dermatol* 2009;145:488–490. Doi: 10.1001/archdermatol.2009.42 [PubMed: 19380679]
15. Lee KC, Higgins HW 2nd, Lindon O, Cruz AP. Gender differences in tumor and patient characteristics in those undergoing Mohs surgery. *Dermatol Surg* 2014;40:686–690. Doi: 10.1111/dsu.0000000000000020 [PubMed: 24852474]
16. Al-Dujaili Z, Henry M, Dorizas AS, Sadick NS. Skin cancer concerns particular to women. *Int J Womens Dermatol* 2017;3(1 Suppl): S49–S51. Doi: 10.1016/j.ijwd.2017.02.009 [PubMed: 28492039]
17. Buchanan Lunsford N, Berkthold J, Holman D, Stein K, Prempeh A, Yerkes A. Skin cancer knowledge, awareness, beliefs and preventive behaviors among black and hispanic men and women. *Prev Med Rep* 2018;12:203–209 doi: 10.1016/j.pmedr.2018.09.017 [PubMed: 30364862]
18. Corneli P, Zalaudek I, Magaton-Rizzi G, Di Meo N. Improving the early diagnosis of early nodular melanoma: can we do better? *Expert Rev Anticancer Ther* 2018;18:1007–1012. doi: 10.1080/14737140.2018.1507822. Epub 2018 Aug 13. [PubMed: 30079779]
19. Wee E, Wolfe R, Mclean C, Kelly JW, Pan Y. Clinically amelanotic or hypomelanotic melanoma: anatomic distribution, risk factors, and survival. *J Am Acad Dermatol* 2018;79:645–651.e4 doi: 10.1016/j.jaad.2018.04.045
20. Gong HZ, Zheng HY, Li J. Amelanotic melanoma. *Melanoma Res* 2019;29:221–230. Doi: 10.1097/CMR.0000000000000571 [PubMed: 30672881]
21. Warycha MA, Christos PJ, Mazumdar M, et al. Changes in the presentation of nodular and superficial spreading melanomas over 35 years. *Cancer* 2008;113:3341–3348 doi: 10.1002/cncr.23955 [PubMed: 18988292]
22. Dessinioti C, Dimou N, Geller A, et al. Distinct clinicopathological and prognostic features of thin nodular primary melanomas: an international study from 17 centers. *J Natl Cancer Inst* 2019 pii: djz034. doi: 10.1093/jnci/djz034. [Epub ahead of print]
23. Fargnoli MC, Sera F, Suppa M, et al. Dermoscopic features of cutaneous melanoma are associated with clinical characteristics of patients and tumours and with MC1R genotype. *J Eur Acad Dermatol Venereol* 2014;28:1768–1775 doi: 10.1111/jdv.12411 [PubMed: 24588892]

24. Segura S, Pellacani G, Puig Set al. In vivo microscopic features of nodular melanomas: dermoscopy, confocal microscopy, and histopathologic correlates. *Arch Dermatol* 2008;144:1311–1320. doi: 10.1001/archderm.144.10.1311. Erratum in: *Arch Dermatol*. 2009 May;145(5):556. [PubMed: 18936395]
25. Russo T, Piccolo V, Ferrara G, et al. Dermoscopy, pathology correlation in melanoma. *J Dermatol* 2017;44:507–514 doi: 10.1111/1346-8138.13629 [PubMed: 28447355]
26. Zalaudek I, Kreusch J, Giacomel J Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: A review of vascular structures seen with dermoscopy: part II. Nonmelanocytic skin tumors *J Am Acad Dermatol* 2010;63:377–386; quiz 387–8. doi: 10.1016/j.jaad.2009.11.697. [PubMed: 20708470]
27. Lallas A, Apalla Z, Ioannides D, et al. Update on dermoscopy of Spitz/Reed naevi and management guidelines by the International Dermoscopy Society. *Br J Dermatol* 2017;177:645–655 doi: 10.1111/bjd.15339 [PubMed: 28118479]
28. Ferrari A, Argenziano G, Buccini P, et al. Typical and atypical dermoscopic presentations of dermatofibroma. *J Eur Acad Dermatol Venereol* 2013;27:1375–1380 doi: 10.1111/jdv.12019 [PubMed: 23176079]
29. Liopyris K, Navarette-Dechent C, Dusza S, et al. Clinical and dermoscopic features associated with lichen planus-like keratoses that undergo skin biopsy: a single center observational biopsy. *Australas J Dermatol* 2019;60:e119–e126 doi: 10.1111/ajd.2955 [PubMed: 30450536]
30. Papageorgiou C, Apalla Z, Variaah G, et al. Accuracy of dermoscopic criteria or the differentiation between superficial basal cell carcinoma and Bowen's disease. *J Eur Acad Dermatol Venereol* 2018;32:1914–1919 doi: 10.1111/jdv.14995 [PubMed: 29633377]
31. Sgouros D, Apalla Z, Ioannides D, et al. Dermoscopy of common inflammatory disorders. *Dermatol Clin* 2018;36:359–368 doi: 10.1016/j.det.2018.05.003 [PubMed: 30201145]
32. Jaimes N, Braun RP, Thomas L, Marghoob AA. Clinical and dermoscopic characteristics of amelanotic melanomas that are not of the nodular subtype. *J Eur Acad Dermatol Venereol* 2012;26:591–596 doi: 10.1111/j.1468-3083.2011.04122 [PubMed: 21585561]
33. Menzies S, Kreusch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Arch Dermatol* 2008;144:1120–1127 doi: 10.1001/archderm.144.9.1120 [PubMed: 18794455]
34. Navarette-Dechent C, Bajaj S, Marchetti MA, Rabinovitz H, Dusza SW, Marghoob AA. Association of shiny white blotches and strands with nonpigmented basal cell carcinoma: Evaluation of an additional dermoscopic diagnostic criterion. *JAMA Dermatology* 2016;152:546–552. doi: 10.1001/jamadermatol.2015.573144. [PubMed: 26792406]
35. Longo C, Farnetani F, Moscarella E et al. Can noninvasive imaging tools potentially predict the risk of ulceration in invasive melanomas showing blue and black colors? *Melanoma Res* 2013;23:125–131. doi: 10.1097/CMR.0b013e32835d90b8 [PubMed: 23358425]
36. Longo C, Scope A, Lallas A, et al. Blue lesions. *Dermatol Clin* 2013;31:637–647 doi:10.1016/j.det.2013.07.001 [PubMed: 24075551]
37. Rosendahl C, Cameron A, Tschandl P, Bulinska A, Zalaudek I, Kittler H. Prediction without pigment: a decision algorithm for non-pigmented skin malignancy. *Dermatol Pract Concept* 2014;4:59–66 doi: 10.5826/dpc.0401a09
38. De Carvalho N, Welzel J, Schuh S, et al. The vascular morphology of melanoma is related to Breslow index: an in vivo study with dynamic optical coherence tomography. *Exp Dermatol* 2018;27:1280–1286 doi: 10.1111/exd.13783 [PubMed: 30218634]
39. Zalaudek I, Kreusch J, Giacomel J Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: A review of vascular structures seen with dermoscopy: part I. Melanocytic skin tumors *J Am Acad Dermatol* 2010;63:361–374; quiz 375–376 doi: 10.1016/j.jaad.2009.05.035 [PubMed: 20708469]
40. Pizzichetta M, Kittler H, Stanganelli I, et al. Dermoscopic diagnosis of melanotic/hypomelanotic melanoma. *Br J Dermatol* 2017;177:538–540 doi:10.1111/bjd.15093 [PubMed: 27681347]
41. Moloney F, Menzies S. Key points in the dermoscopic diagnosis of hypomelanotic melanoma and nodular melanoma. *J Dermatol* 2011;38:10–15 doi: 10.1111/j.1346-8138.2010.01140.x [PubMed: 21175750]

Figure 1:

Nodular Melanoma (NM) with a Breslow thickness 2mm. **(a)** Irregular brown dots and globules (white arrows) at the periphery of a 1.7mm Breslow thickness melanoma along with white shiny strands and blue structureless area (white circle) in the center of the lesion. **(b)** A thin NM (1.5 mm Breslow thickness) with an eccentric black blotch (white arrow), irregular light brown coloration (white star) and white shiny structures (black arrow). **(c)** Dotted vessels (white circles) prevail in this 0.5 mm Breslow thickness NM along with an irregular blue structureless area (white arrow). **(d)** Serpentine vessels (white arrows) are prominent in this hypopigmented thin NM (1.1mm Breslow thickness) with scarce light brown coloration (white circle) at the periphery.

Figure 2:

The dermatoscopic evolution of Nodular Melanoma. As the thickness increases from a 1.05mm Breslow thickness (**a**) to a thicker 2.7mm Breslow thickness NM (**b**) blue-black pigmentation becomes more intense. In the same context, vascularization is more polymorphic in more advanced NM in terms of Breslow thickness (**c** = 0.6mm Breslow thickness and **d** = 2.1mm Breslow thickness).

Table 1.

Demographic data of included patients and clinical characteristics of the tumors

	Melanomas 2mm (n=69)	Melanomas > 2mm (n=96)	Non-melanomas (n=89)
Age			
mean (years)	52.6	60.4	59.4
range (years)	18–88	23–94	17–95
Sex			
male	27 (41.5%)	49 (62.0%)	55 (61.8%)
female	38 (58.5%)	30 (38.0%)	34 (38.2%)
Anatomic site			
head/neck	2 (2.9%)	11 (11.7%)	36 (40.4%)
trunk	25 (36.8%)	42 (44.7%)	34 (38.2%)
upper extremities	21 (30.9%)	21 (22.3%)	5 (5.6%)
lower extremities	20 (29.4%)	17 (18.1%)	12 (13.5%)
acral	0	2 (2.1%)	1 (1.1%)
mucosal	0	1 (1.0%)	1 (1.1%)
Clinically pigmented			
no	24 (34.8%)	22 (22.9%)	48 (53.9%)
yes	45 (65.2%)	74 (77.1%)	41 (46.1%)
Breslow thickness			
mean (mm)	1.4	4.4	-
range (mm)	0.5–2.0	2.1–12.0	-

Table 2.

Multivariate dermatoscopic predictors of nodular melanoma up to 2mm of Breslow thickness

Dermatoscopic predictor	p	Adjusted Odds Ratio	95% Confidence Intervals	
			Min	Max
vs non-melanoma				
Irregular blue structureless area	0.009	2.4	1.2	4.8
White shiny streaks/lines	0.034	2.9	1.1	7.8
Dotted vessels	0.015	3.4	1.3	8.9
vs melanoma thicker than 2mm				
Irregular brown dots/globules	0.037	1.8	1.0	3.2
Serpentine vessels	0.008	0.3	0.1	0.7
vs non-melanoma among non-pigmented tumors only				
None detected				
vs non-melanoma among pigmented tumors only				
Irregular blue structureless area	0.049	2.0	1.0	3.9

Table 3.

Multivariate dermatoscopic predictors of nodular melanoma (irrelevant of Breslow thickness)

Dermatoscopic predictor	p	Adjusted Odds Ratio	95% Confidence Intervals	
			Min	Max
Irregular blue structureless area	0.001	3.4	1.7	6.6
Dotted vessels	0.003	4.6	1.7	12.6
Serpentine vessels	0.040	1.9	1.0	3.6