# Pigmented nodular melanoma: the predictive value of dermoscopic features using multivariate analysis

M.A. Pizzichetta,[1] H. Kittler,[2] I. Stanganelli,[3] R. Bono,[4] S. Cavicchini,[5] V. De Giorgi,[6] G. Ghigliotti,[7] P. Quaglino,[8] P. Rubegni,[9] G. Argenziano[10] and R. Talamini[11] for the Italian Melanoma Intergroup[†]

[1]Division of Medical Oncology – Preventive Oncology, and [11]Unit of Epidemiology and Biostatistics, Centro di Riferimento Oncologico, National Cancer Institute, Via Franco Gallini 2, 33081 Aviano, Italy
[2]Department of Dermatology, University of Vienna, Vienna, Austria
[3]Skin Cancer Unit, Istituto Tumori Romagna (IRST), Meldola, Italy
[4]Istituto Dermopatico Immacolata, IRCCS, Rome, Italy
[5]Department of Dermatology, Fondazione Ospedale Maggiore Policlinico IRCCS, Milan, Italy
[6]Department of Dermatology, University of Florence, Florence, Italy
[7]Clinic of Dermatology, IRCCS San Martino – Ist, Genoa, Italy
[8]Dermatologic Clinic, Department of Medical Sciences, University of Turin, Turin, Italy
[9]Department of Dermatology, University of Siena, Siena, Italy
[10]Skin Cancer Unit, Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy

## Summary

*Background* Nodular melanoma (NM), representing 10–30% of all melanomas, plays a major role in global mortality related to melanoma. Nonetheless, the literature on dermoscopy of NM is scanty.
*Objectives* To assess odds ratios (ORs) to quantify dermoscopic features of pigmented NM vs. pigmented superficial spreading melanoma (SSM), and pigmented nodular nonmelanocytic and benign melanocytic lesions.
*Methods* To assess the presence or absence of global patterns and dermoscopic criteria, digitized images of 457 pigmented skin lesions from patients with a histopathological diagnosis of NM (n = 75), SSM (n = 93), and nodular nonmelanocytic and benign melanocytic lesions (n = 289; namely, 39 basal cell carcinomas, 85 seborrhoeic keratoses, 81 blue naevi, and 84 compound/dermal naevi) were retrospectively collected and blindly evaluated by three observers.
*Results* Multivariate analysis showed that ulceration (OR 4·07), homogeneous disorganized pattern (OR 10·76), and homogeneous blue pigmented structureless areas (OR 2·37) were significantly independent prognostic factors for NM vs. SSM. Multivariate analysis of dermoscopic features of NM vs. nonmelanocytic and benign melanocytic lesions showed that the positive correlating features leading to a significantly increased risk of NM were asymmetric pigmentation (OR 6·70), blue–black pigmented areas (OR 7·15), homogeneous disorganized pattern (OR 9·62), a combination of polymorphous vessels and milky-red globules/areas (OR 23·65), and polymorphous vessels combined with homogeneous red areas (OR 33·88).
*Conclusions* Dermoscopy may be helpful in improving the recognition of pigmented NM by revealing asymmetric pigmentation, blue–black pigmented areas, homogeneous disorganized pattern and abnormal vascular structures, including polymorphous vessels, milky-red globules/areas and homogeneous red areas.

### What's already known about this topic?

- Nodular melanoma (NM) often exhibits features associated with deep tumour extension and less commonly displays the classic dermoscopic features of superficial spreading melanoma (SSM).

**Correspondence**
Maria Antonietta Pizzichetta.
E-mail: pizzichetta@cro.it

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## What does this study add?

- The study identifies dermoscopic features that are significantly associated with pigmented NM compared with pigmented SSM and nonmelanoma nodular lesions.
- This study validates, with a multivariate analysis, the dermoscopic features leading to a significantly increased likelihood of a diagnosis of pigmented NM.

Nodular melanoma (NM) represents 10–30% of all melanomas and nearly 50% of all melanomas thicker than 2 mm, and it plays a major role in the global mortality related to this cancer.[1] Unlike other melanoma subtypes, NM appears to lack the initial radial growth phase, beginning with vertical growth.[2]

The 'ABCD' warning signs for melanoma are better at detecting superficial spreading melanoma (SSM) than NM, as the latter is often small in diameter, symmetric, with regular borders and less colour variegation, and is frequently amelanotic.[1,3] For this reason, the 'EFG' rule (Elevation, Firmness on palpation, continuous Growth over 1 month), summarizing the most frequent features of NM, has been introduced for the identification of this subtype of melanoma.[4] Dermoscopically, in a study of 10 NM lesions, an asymmetric colour and pattern distribution was observed in all lesions; in addition, all lesions exhibited at least three colours, although the number of colours and structures was significantly lower in the NM group than in the SSM group.[5] In a study of 11 thin NMs, most lesions had a homogeneous disorganized asymmetric pattern or a featureless pattern; although many dermoscopic features seen in SSM were frequently absent, some features such as a blue–white veil, structureless areas, atypical vessels and a pink veil were often identified.[4] In a large series of NM, Menzies *et al.*[6] found that pigmented NM, compared with non-nodular invasive melanoma, more frequently displayed a symmetrical pigmentation pattern, large-diameter vessels, areas of homogeneous blue pigmentation, a symmetrical shape, predominant peripheral vessels, a blue–white veil, a pink colour, a black colour and milky-red/pink areas.

In this study, 457 pigmented skin lesions, including 75 NM, were evaluated dermoscopically to examine the predictive value of dermoscopic features of NM using a multivariate analysis.

## Patients and methods

Between January 2007 and December 2011, all consecutive cases of histopathologically confirmed pigmented NM, pigmented SSM, pigmented nodular benign melanocytic lesions (e.g. compound/dermal naevus, blue naevus) and pigmented nodular nonmelanocytic lesions [e.g. seborrhoeic keratosis, basal cell carcinoma (BCC)] seen at the 15 participating Italian centres were collected for this study with the aim of identifying dermoscopic features significantly associated with pigmented NM compared with pigmented SSM and non-NM lesions. In this study, only pigmented lesions were considered, which were defined as those having black, dark brown, grey or blue structures that occupied > 25% of the total surface area of the lesion.[7]

NM was defined as an invasive melanoma that lacks significant intraepidermal tumour cells beyond the margins of the dermal invasive component.[6]

There were no SSMs with a nodular component in this series of NMs, nor were there any *in situ* melanomas in the non-NM set.

Two separate files were provided for each case, one containing the dermoscopic images and a second containing all patient-related information, such as sex, age at diagnosis, skin lesion site, type of dermoscopy (polarized or nonpolarized), date of excision, clinical diagnosis, dermoscopic diagnosis and histopathological diagnosis.

By the end of December 2011, all the dermoscopic images ($n = 560$) from the 15 centres were merged into a database at the Epidemiology and Biostatistics Unit of the Centro di Riferimento Oncologico, Aviano (Italy), with a new identification link to the patient information on clinical features and diagnosis. Of the 560 submitted images, 457 were found to be of sufficiently good quality for the evaluation of the dermoscopic criteria. Of these, 310 (67·8%) were taken with a camera using nonpolarized dermoscopy and 147 (32·2%) with a camera using polarized dermoscopy. All the dermoscopic images were examined to assess the presence or the absence of global patterns and specific dermoscopic criteria in NM, non-NM, nonmelanocytic and benign melanocytic lesions. We assessed the lesions using the features reportedly associated with melanoma, BCC, seborrhoeic keratosis, common naevi and blue naevi;[8–10] all features assessed were also considered in the analysis. All cases were evaluated by a panel of three blinded observers; the dermoscopic features were scored based on the agreement of two observers (M.A.P. and R.B.) and in the case of disagreement between them, a third observer (I.S.) was consulted. The evaluation of the dermoscopic criteria, as well as the final dermoscopic diagnosis, was made when at least two of the three observers agreed.

### Statistical analysis

Statistical analysis was performed with SAS 9·1 (SAS Institute Inc., Cary, NC, U.S.A.).[11] Unconditional logistic regression models were used to assess odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) to quantify

**Table 1** Frequency of histopathological diagnosis of 457 pigmented skin lesions

| Diagnosis | n (%) |
|---|---|
| Invasive melanoma | |
| Nodular melanoma | 75 (16·4) |
| Superficial spreading melanoma | 93 (20·4) |
| Nonmelanocytic lesions | |
| Basal cell carcinoma | 39 (8·5) |
| Seborrhoeic keratosis | 85 (18·6) |
| Benign melanocytic lesions | |
| Blue naevus | 81 (17·7) |
| Compound/dermal naevus | 84 (18·4) |

dermoscopic features of pigmented NM vs. pigmented SSM and pigmented nodular nonmelanocytic and benign melanocytic lesions. Variables that were statistically significant in the univariate analysis were included in the multivariate model. In addition, the $\chi^2$ test or Fisher's exact test were used, when appropriate, to evaluate differences in clinical characteristics and melanoma thickness. Results were considered to be statistically significant when P-values were $\leq 0{\cdot}05$ (two-sided).

## Results

### Patient demographics and classification of lesions

The diagnostic categories of the study lesions are shown in Table 1. Of 457 lesions, 75 were NM, 93 were SSM and 289 were nonmelanocytic (39 BCCs and 85 seborrhoeic keratoses) and benign melanocytic lesions (81 blue naevi and 84 compound/dermal naevi). The study included 457 patients (236 men, 221 women) with a median age of 51 years (range 11–95) (Table 2). The sites of the skin lesions included head and neck (n = 107); anterior trunk (n = 90); back (n = 129); lower limbs (n = 80); and upper limbs (n = 51). The median age was 61 years (range 21–92) for patients with NM, 57 years (range 16–92) for patients with SSM and 46 years (range 11–95) for patients with nonmelanocytic and benign melanocytic lesions (Table 2).

No differences emerged between NM and SSM in distribution by sex, age and sites of the melanomas. By contrast, the median Breslow thickness of NMs (3·40 mm, range 0·05–11·00) was significantly greater than that of SSMs (0·80 mm, range 0·01–5·00; $P < 0{\cdot}01$) (Table 2).

### Dermoscopic features of pigmented nodular melanoma vs. pigmented superficial spreading melanoma

Table 3 shows the uni- and multivariate analyses of the dermoscopic features of pigmented NM vs. pigmented SSM. The univariate analysis was used to identify the relevant factors (i.e. listed according to P-value) in determining NM. The multivariate analysis was used to estimate the independent effect of each factor that gave a significant result in the univariate analysis. The multivariate analysis showed that ulceration, a homogeneous disorganized pattern and homogeneous blue-pigmented, structureless areas were significant independent

**Table 2** Clinical characteristics and melanoma thickness of 457 pigmented skin lesions by histopathological diagnosis

| | Nodular melanoma (n = 75) | Superficial spreading melanoma (n = 93) | Nonmelanocytic and benign melanocytic lesions (n = 289) |
|---|---|---|---|
| Sex | | | |
| Male | 39 (52) | 54 (58) | 143 (49·5) |
| Female | 36 (48) | 39 (42) | 146 (50·5) |
| P-value | | 0·43[a] | 0·70[a] |
| Median age, years (range) | 61 (21–92) | 57 (16–92) | 46 (11–95) |
| P-value | | 0·55[b] | < 0·01[b] |
| Sites | | | |
| Back | 26 (35) | 32 (34) | 71 (24·6) |
| Lower limbs | 20 (27) | 28 (30) | 32 (11·1) |
| Anterior trunk | 13 (17) | 15 (16) | 62 (21·4) |
| Head and neck | 9 (12) | 7 (7) | 91 (31·5) |
| Upper limbs | 7 (9) | 11 (12) | 33 (11·4) |
| P-value | | 0·86[a] | < 0·01[a] |
| Melanoma thickness (mm) | | | |
| ≤ 1·00 | 9 (12) | 59 (63) | – |
| 1·01–2·00 | 16 (21) | 13 (14) | – |
| 2·01–4·00 | 34 (45) | 19 (20) | – |
| > 4·00 | 16 (21) | 2 (2) | – |
| Median (range) | 3·40 (0·05–11·00) | 0·80 (0·01–5·00) | – |
| P-value | | < 0·01[b] | |

Values are given as n (%) unless otherwise indicated. [a]Compared with nodular melanoma P-value of the $\chi^2$ test. [b]Compared with nodular melanoma P-value of the Wilcoxon rank test.

**Table 3** Uni- and multivariate analyses of positive and negative dermoscopic features of pigmented nodular melanoma vs. pigmented superficial spreading melanoma

| | Nodular melanoma (n = 75) | Superficial spreading melanoma (n = 93) | Univariate | | Multivariate[a] | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Positive features | | | | | | |
| Ulceration | 28 (37) | 10 (11) | 4·95 (2·21–11·07) | < 0·01 | 4·07 (1·71–9·69) | < 0·01 |
| Homogeneous disorganized pattern | 15 (20) | 3 (3) | 7·50 (2·08–27·02) | < 0·01 | 10·76 (2·69–42·99) | < 0·01 |
| Homogeneous blue-pigmented structureless areas | 28 (37) | 16 (17) | 2·87 (1·41–5·85) | < 0·01 | 2·37 (1·08–5·22) | 0·03 |
| Multiple (≥ 3) colours | 69 (92) | 73 (78) | 3·15 (1·20–8·31) | 0·02 | | NS |
| Polymorphous vessels + milky-red globules/areas | 10 (13) | 4 (4) | 3·42 (1·03–11·39) | 0·05 | | NS |
| Symmetric shape | 32 (43) | 26 (28) | 1·92 (1·01–3·65) | 0·05 | | NS |
| Polymorphous vessels + homogeneous red areas | 7 (9) | 2 (2) | 4·68 (0·94–23·26) | 0·10 | | |
| Blue–white veil | 58 (77) | 61 (66) | 1·79 (0·90–3·57) | 0·10 | | |
| Linear irregular vessels | 2 (3) | 0 (0) | 6·36 (0·30–134·53) | 0·11 | | |
| Diffuse homogeneous blue pigmentation | 7 (9) | 3 (3) | 3·09 (0·77–12·38) | 0·11 | | |
| Milky-red globules/areas | 7 (9) | 3 (3) | 3·09 (0·77–12·38) | 0·11 | | |
| Blue–black pigmented areas | 32 (43) | 30 (32) | 1·56 (0·83–2·94) | 0·17 | | |
| Linear irregular vessels + milky-red globules/areas | 7 (9) | 4 (4) | 2·29 (0·64–8·14) | 0·20 | | |
| Featureless pattern | 3 (4) | 1 (1) | 3·83 (0·39–37·63) | 0·25 | | |
| Arborizing vessels | 1 (1) | 0 (0) | 3·77 (0·15–93·77) | 0·27 | | |
| Homogeneous red areas | 4 (5) | 2 (2) | 2·56 (0·46–14·39) | 0·29 | | |
| Irregular black dots/globules | 48 (64) | 54 (58) | 1·28 (0·69–2·40) | 0·43 | | |
| Polymorphous vessels | 3 (4) | 2 (2) | 1·90 (0·31–11·66) | 0·49 | | |
| More than one shade of pink | 13 (17) | 13 (14) | 1·29 (0·56–2·98) | 0·55 | | |
| Globular homogeneous pattern | 3 (4) | 3 (3) | 1·25 (0·25–6·38) | 0·79 | | |
| Homogeneous pattern | 2 (3) | 2 (2) | 1·25 (0·17–9·07) | 0·83 | | |
| Black colour | 51 (68) | 62 (67) | 1·06 (0·56–20·3) | 0·85 | | |
| Hairpin vessels | 1 (1) | 1 (1) | 1·24 (0·08–20·21) | 0·88 | | |
| Linear irregular vessels + homogeneous red areas | 1 (1) | 1 (1) | 1·24 (0·08–20·21) | 0·88 | | |
| Negative features | | | | | | |
| Atypical network | 17 (23) | 50 (54) | 0·25 (0·13–0·50) | < 0·01 | | NS |
| Multicomponent pattern | 34 (45) | 70 (75) | 0·27 (0·14–0·52) | < 0·01 | | NS |
| Peripheral light-brown structureless areas | 9 (12) | 36 (39) | 0·22 (0·10–0·49) | < 0·01 | 0·26 (0·11–0·65) | < 0·01 |
| Asymmetric shape | 39 (52) | 69 (74) | 0·38 (0·20–0·72) | < 0·01 | | NS |
| Irregular streaks | 22 (29) | 47 (51) | 0·41 (0·21–0·77) | < 0·01 | | NS |
| Linear irregular + dotted vessels + milky-red globules/areas | 2 (3) | 11 (12) | 0·20 (0·04–0·95) | 0·04 | | NS |
| Shiny white structures | 13 (17) | 28 (30) | 0·49 (0·23–1·03) | 0·06 | | |
| Irregular dots/globules | 58 (77) | 82 (88) | 0·46 (0·20–1·05) | 0·06 | | |
| Milia-like cysts | 0 (0) | 5 (5) | 0·11 (0·06–1·96) | 0·07 | | |
| Linear irregular + dotted vessels | 1 (1) | 7 (7) | 0·17 (0·02–1·38) | 0·10 | | |
| Depigmentation/structureless areas | 40 (53) | 59 (63) | 0·66 (0·35–1·22) | 0·19 | | |
| Comedo-like openings | 0 (0) | 1 (1) | 0·41 (0·02–10·17) | 0·37 | | |
| Symmetric pigmentation pattern | 3 (4) | 6 (6) | 0·60 (0·15–2·50) | 0·49 | | |
| Peripheral black dots/globules | 34 (45) | 45 (48) | 0·89 (0·48–1·63) | 0·69 | | |
| Asymmetric pigmentation pattern | 69 (92) | 87 (93) | 0·79 (0·25–2·57) | 0·70 | | |
| Regression structures | 54 (72) | 68 (73) | 0·95 (0·48–1·87) | 0·87 | | |
| Irregular blotches | 49 (65) | 61 (65) | 0·99 (0·52–1·87) | 0·97 | | |
| Predominant blue clods | 7 (9) | 9 (10) | 0·98 (0·35–2·78) | 0·97 | | |

Values are given as n (%). OR, odds ratio; CI, confidence interval; NS, not significant. [a]Unconditional multiple logistic regression including all significant features in the univariate analysis.

prognostic factors for NM. The presence of ulceration was 37·3% in the NM group and 10·8% in the SSM group, and led to a significantly increased risk of diagnosing NM (OR 4·07, 95% CI 1·71–9·69). Moreover, significant risks of diagnosing NM were also found when the lesion was characterized by the presence of a homogeneous disorganized pattern (OR 10·76, 95% CI 2·69–42·99) and homogeneous blue-pigmented, structureless areas (OR 2·37, 95% CI 1·08–5·22) (Table 3). Conversely, when evaluating the negative features, the presence of peripheral light-brown, structureless areas was 12·0% in the NM group and 38·7% in the SSM group, leading to a significantly reduced risk of NM (OR 0·26, 95% CI 0·11–0·65) (Table 3).

### Dermoscopic features of pigmented nodular melanoma vs. pigmented nodular nonmelanocytic and benign melanocytic lesions

Table 4 shows the uni- and multivariate analyses of the dermoscopic features (i.e. listed according to P-value) of pigmented NM vs. pigmented nodular nonmelanocytic and benign melanocytic lesions. Multivariate analysis showed that the significant positive correlating features leading to a significant increased risk of NM were asymmetric pigmentation (OR 6·70, 95% CI 1·49–30·11), blue–black pigmented areas (OR 7·15, 95% CI 1·54–33·30), a homogeneous disorganized pattern (OR 9·62, 95% CI 1·62–57·13), the combination of polymorphous vessels and milky-red globules/areas (OR 23·65, 95% CI 1·65–339·93), and the combination of polymorphous vessels and red homogeneous areas (OR 38·88, 95% CI 1·72–877·07) (Table 4). By contrast, the homogeneous pattern was a negative correlating feature, leading to a significant reduced risk of NM (OR 0·05, 95% CI 0·01–0·22) (Table 4).

## Discussion

Based on our results, a large number of features such as ulceration, homogeneous disorganized pattern, homogeneous blue-pigmented structureless areas, multiple (≥ 3) colours, the combination of polymorphous vessels and milky-red globules/areas and symmetric shape were only significantly more frequent in pigmented NM compared with pigmented SSM in the univariate analysis. When we compared our results with those of Menzies *et al.*,[6] they appeared to be in agreement in relation to the areas of homogeneous blue pigmentation and symmetrical shape, which were positively correlated with NM in both studies, while Menzies *et al.*[6] also found a symmetrical pigmentation pattern, pink colour, a blue–white veil and black colour to be positively correlated with NM. Regarding negative features, we found a large number of features – such as an atypical network, a multicomponent pattern, peripheral light-brown structureless areas, asymmetric shape, irregular streaks, and the combination of linear irregular, dotted and milky-red globules/area – to be negatively correlated with NM compared with SSM only in the univariate analysis. When we compared our results with those of Menzies *et al.*,[6] the atypical network was the only feature found to be in agreement. By contrast, in the study by Menzies *et al.*,[6] other negative correlating features of pigmented NM were found, such as pigment network/pseudonetwork, multiple blue–grey dots (granularity), scar-like depigmentation, irregular brown dots/globules, tan colour, irregular shape depigmentation and irregular dots/globules of any colour. The inconsistencies between the two studies could depend on the different sample sizes of both NMs and SSMs and on the different terminology used to describe some features of the vascular pattern; the regression structures, including both multiple blue–gray dots (granularity) and scar-like depigmentation instead of multiple blue–gray dots (granularity) or scar-like depigmentation; and irregular dots/globules instead of irregular dots/globules of any colour or irregular brown dots/globules.

The most striking results obtained from our study were that the only significant features distinguishing pigmented NM from pigmented SSM in the multivariate analysis were ulceration, homogeneous disorganized pattern and homogeneous blue-pigmented structureless areas. The overall homogeneous pattern is typically exhibited by common and blue naevi, consisting of a diffuse homogeneous tan, brown, or blue structureless pigmentation.[12,13] By contrast, in NM, in agreement with that reported by other authors,[4,14] the colours are distributed in a disorganized and asymmetric fashion, characterizing the overall disorganized homogeneous pattern (Fig. 1).

Regarding the homogeneous blue-pigmented structureless areas, some authors use a unifying definition of blue–white structures over raised areas associated with dense melanin within melanocytes in the dermis;[14] the uniform distribution of blue hue may be focal in the case of homogeneous blue-pigmented structureless areas or diffuse in the case of a blue–white veil (Fig. 2).[15]

Concerning negative features, the only significant negatively correlated feature of pigmented NM in the multivariate analysis was peripheral light-brown structureless areas, which have already been reported to be associated with thin melanoma.[16]

When comparing the univariate analyses of the positive features of pigmented NM with pigmented nodular nonmelanocytic and benign melanocytic lesions in our study and that of Menzies *et al.*,[6] most of the features were in agreement, namely peripheral black dots/globules, irregular black dots/globules, blue–white veil, pseudopods, homogeneous blue pigmentation, multiple colours, black colour, irregular blotches, irregular dots/globules, blue–black structures and asymmetric shape. The differences between the two studies concerned some positive correlating features found only in our study, such as linear irregular vessels plus milky-red globules/areas, more than one shade of pink, homogeneous red areas, asymmetric pigmentation pattern, multicomponent pattern, regression structures, ulceration, homogeneous disorganized pattern, atypical network, shiny white structures, predominant blue clods, featureless pattern, peripheral light-brown structureless areas and irregular depigmentation. Conversely, some positive correlating features found by Menzies

**Table 4** Uni- and multivariate analyses of positive dermoscopic features of pigmented nodular melanoma vs. pigmented nonmelanocytic and benign melanocytic lesions

| | Nodular melanoma (n = 75) | Nonmelanocytic and benign melanocytic lesions (n = 289) | Univariate | | Multivariate[a] | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Positive features | | | | | | |
| Linear irregular vessels + milky-red globules/areas | 7 (9) | 0 (0) | 63·39 (3·58–1123·46) | < 0·01 | | NS |
| More than one shade of pink | 13 (17) | 1 (0·3) | 60·39 (7·76–470·18) | < 0·01 | | NS |
| Homogeneous red areas | 4 (5) | 0 (0) | 36·44 (1·94–648·62) | < 0·01 | | NS |
| Asymmetric pigmentation | 69 (92) | 94 (32·5) | 23·86 (10·00–56·93) | < 0·01 | 6·70 (1·49–30·11) | 0·01 |
| Irregular blotches | 49 (65) | 26 (9·0) | 19·06 (10·22–35·56) | < 0·01 | | NS |
| Irregular black dots/globules | 48 (64) | 26 (9·0) | 17·98 (9·67–33·44) | < 0·01 | | NS |
| Multicomponent pattern | 34 (45) | 13 (4·5) | 17·61 (8·58–36·11) | < 0·01 | | NS |
| Regression structures | 54 (72) | 37 (12·8) | 17·51 (9·51–32·26) | < 0·01 | | NS |
| Blue–black pigmented areas | 32 (43) | 12 (4·1) | 17·18 (8·22–35·90) | < 0·01 | 7·15 (1·54–33·30) | 0·01 |
| Peripheral black dots/globules | 34 (45) | 15 (5·2) | 15·15 (7·59–30·22) | < 0·01 | | NS |
| Ulceration | 28 (37) | 11 (3·8) | 15·06 (7·02–32·29) | < 0·01 | | NS |
| Blue–white veil | 58 (77) | 57 (19·7) | 13·89 (7·52–25·64) | < 0·01 | | NS |
| Multiple (≥ 3) colours | 69 (92) | 132 (45·7) | 13·67 (5·75–32·49) | < 0·01 | | NS |
| Black colour | 51 (68) | 42 (14·5) | 12·50 (6·96–22·44) | < 0·01 | | NS |
| Irregular streaks | 22 (29) | 12 (4·1) | 9·58 (4·47–20·54) | < 0·01 | | NS |
| Irregular dots/globules | 58 (77) | 110 (38·1) | 5·55 (3·08–10·02) | < 0·01 | | NS |
| Homogeneous disorganized pattern | 15 (20) | 13 (4·5) | 5·31 (2·40–11·74) | < 0·01 | 9·62 (1·62–57·13) | 0·01 |
| Asymmetric shape | 39 (52) | 52 (18·0) | 4·94 (2·87–8·50) | < 0·01 | | NS |
| Atypical network | 17 (23) | 18 (6·2) | 4·41 (2·15–9·08) | < 0·01 | | NS |
| Homogeneous blue-pigmented structureless areas | 28 (37) | 35 (12·1) | 4·32 (2·41–7·77) | < 0·01 | | NS |
| Polymorphous vessels + milky-red globules/areas | 10 (13) | 1 (0·3) | 44·30 (5·57–352·16) | < 0·01 | 23·65 (1·65–339·93) | 0·02 |
| Shiny white structures | 13 (17) | 15 (5·2) | 3·83 (1·73–8·46) | < 0·01 | | NS |
| Polymorphous vessels + homogeneous red areas | 7 (9) | 1 (0·3) | 29·63 (3·59–244·79) | < 0·01 | 38·88 (1·72–877·07) | 0·02 |
| Milky-red globules/areas | 7 (9) | 1 (0·3) | 29·63 (3·59–244·79) | < 0·01 | | NS |
| Predominant blue clods | 7 (9) | 8 (2·8) | 3·57 (1·25–10·19) | 0·02 | | NS |
| Featureless pattern | 3 (4) | 1 (0·3) | 12·00 (1·23–117·05) | 0·03 | | NS |
| Peripheral light-brown structureless areas | 9 (12) | 14 (4·8) | 2·68 (1·11–6·45) | 0·03 | | NS |
| Depigmentation/structureless areas | 40 (53) | 114 (39·4) | 1·75 (1·05–2·93) | 0·03 | | NS |
| Linear irregular + dotted vessels + milky-red globules/areas | 2 (3) | 1 (0·3) | 7·89 (0·71–88·22) | 0·10 | | |
| Linear irregular + dotted vessels | 1 (1) | 0 (0) | 11·66 (0·47–289·08) | 0·10 | | |
| Polymorphous vessels | 3 (4) | 3 (1·0) | 3·97 (0·79–20·09) | 0·10 | | |
| Linear irregular vessels + homogeneous red areas | 1 (1) | 2 (0·7) | 1·94 (0·17–21·68) | 0·59 | | |
| Negative features | | | | | | |
| Milia-like cysts | 0 (0) | 77 (26·6) | 0·02 (0·01–0·30) | < 0·01 | | NS |
| Comedo-like openings | 0 (0) | 80 (27·7) | 0·02 (0·01–0·28) | < 0·01 | | NS |
| Symmetric pigmentation | 3 (4) | 152 (52·6) | 0·04 (0·01–0·12) | < 0·01 | 0·05 (0·02–0·19) | < 0·01 |
| Symmetric shape | 32 (43) | 193 (66·8) | 0·37 (0·22–0·62) | < 0·01 | | NS |
| Homogeneous pattern | 2 (3) | 71 (24·6) | 0·08 (0·02–0·35) | < 0·01 | 0·16 (0·04–0·73) | 0·02 |
| Diffuse homogeneous blue pigmentation | 7 (9) | 65 (22·5) | 0·36 (0·16–0·81) | 0·12 | | |
| Comma vessels | 0 (0) | 20 (6·9) | 0·09 (0·01–1·46) | 0·10 | | |
| Leaf-like areas | 0 (0) | 19 (6·6) | 0·09 (0·01–1·54) | 0·10 | | |
| Large blue-grey ovoid nests | 2 (3) | 27 (9·3) | 0·27 (0·06–1·14) | 0·10 | | |
| Multiple blue globules | 1 (1) | 23 (8·0) | 0·16 (0·02–1·18) | 0·12 | | |
| Globular-homogeneous pattern | 3 (4) | 27 (9·3) | 0·40 (0·12–1·37) | 0·15 | | |

**Table 4** (continued)

| | Nodular melanoma (n = 75) | Nonmelanocytic and benign melanocytic lesions (n = 289) | Univariate | | Multivariate[a] | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Hairpin vessels | 1 (1) | 19 (6·6) | 0·19 (0·03–1·46) | 0·11 | | |
| Arborizing vessels | 1 (1) | 11 (3·8) | 0·34 (0·04–2·69) | 0·31 | | |
| Linear irregular vessels | 2 (3) | 10 (3·5) | 0·76 (0·16–3·57) | 0·73 | | |

Values are given as n (%). OR, odds ratio; CI, confidence interval; NS, not significant. [a]Unconditional multiple logistic regression including all significant features in the univariate analysis.

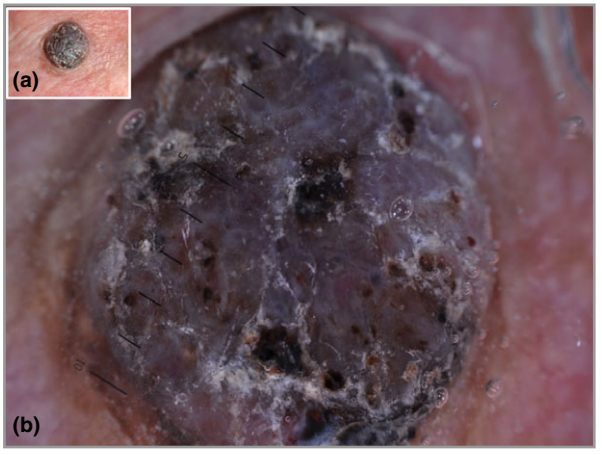


**Fig 1.** Clinical and dermoscopic image of a 24-mm-thick nodular melanoma (NM) on the cheek of an 80-year-old woman. (a) In the clinical image (inset), a blue–greyish scaly symmetrical nodule can be seen. (b) An overall homogeneous disorganized pattern consisting of a diffuse homogeneous blue pigmentation plus foci of irregular black dots/globules and blotches can be seen. The presence of additional features and colours distributed in disarray and in an asymmetric fashion help to distinguish NM from blue naevus (original magnification 10×).

*et al.*[6] did not correspond to those evaluated in our study, such as pink colour, abrupt edge, blurred 'out-of-focus' colours, red–blue colour, multiple brown dots and central black dots/globules. Regarding negative features, agreement emerged only for milia-like cysts and comedo-like openings, while arborizing vessels, multiple blue globules, leaf-like areas and large blue–grey ovoid nests, were negatively associated with NMs only in the study by Menzies *et al.*[6] The different terminology used for some features, as well as the different diagnostic categories of lesions included in the two studies, may explain the differences in the results between these two different series; our series did not include, in relation to benign melanocytic lesions, Spitz naevi and deep penetrating naevi, and in relation to nonmelanocytic lesions, haemangioma, dermatofibroma and other nodular lesions.

In the multivariate analysis, asymmetric pigmentation, blue–black pigmented areas, homogeneous disorganized pattern, the combination of polymorphous vessels and milky-red globules/areas, and polymorphic vessels associated with homogeneous red areas were significantly more

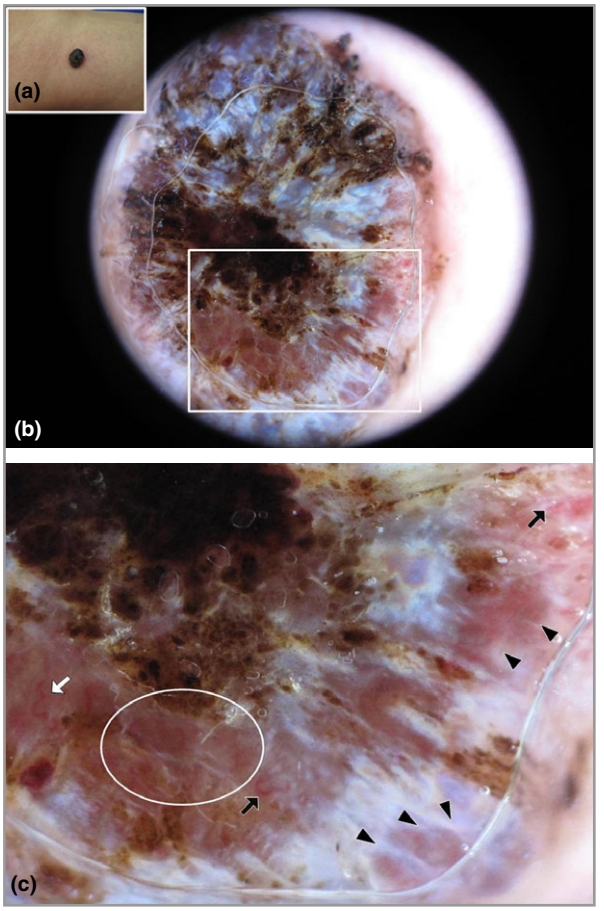


**Fig 2.** Clinical and dermoscopic images of an ulcerated 5·8-mm-thick nodular melanoma on the leg of a 69-year-old woman. (a) In the clinical image (inset), a black–greyish symmetrical nodule can be observed. (b) In the polarized dermoscopic image of the same melanoma, blue-pigmented structureless areas with different shades of blue–white pigmentation are intermixed with black dots/globules (blue–black pigmented areas) and black haemorrhagic crusts from ulceration in the centre of the lesion; framed is the area with polymorphous vascular pattern and milky-red globules. (c) Magnified detail of polymorphous vascular pattern, having linear irregular vessels (white arrow) and irregular hairpin vessels (black arrows), combined with milky-red globules (circle), appearing as unfocused polygonal structures of milky-red colour with a central linear irregular vessel and separated from each other by blurred whitish lines that may be seen within or near unfocused areas of milky-red colour (the so-called milky-red areas, also known as the pink veil) or more than one shade of pink structures (arrowheads).

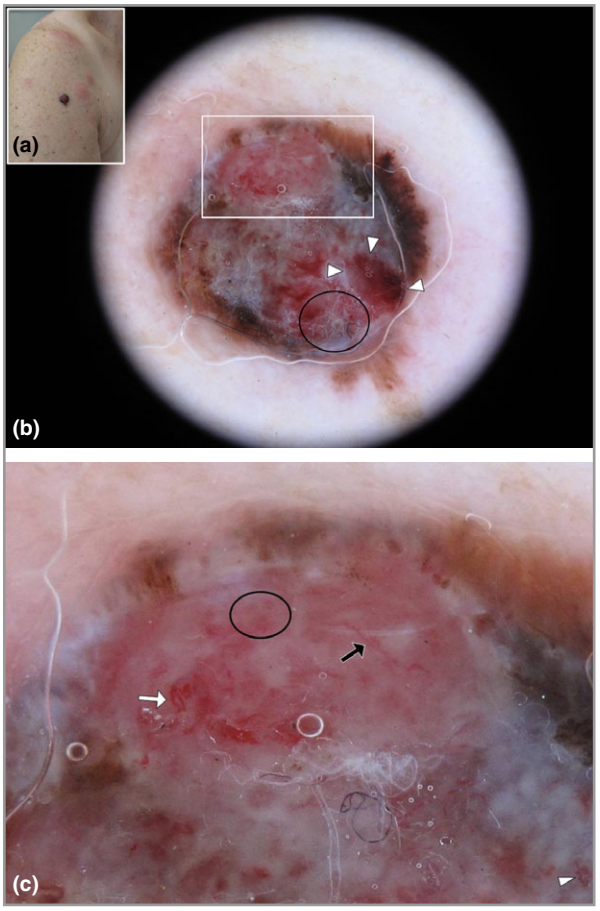


**Fig 3.** Clinical and dermoscopic images of an ulcerated 1·95-mm-thick nodular melanoma on the right upper arm of a 70-year-old woman. (a) In the clinical image (inset), a black–blue reddish symmetrical nodule can be observed; interestingly, an urticaria eruption with erythematous plaques around the lesion extending on the upper arm and shoulder can be seen. The eruption disappeared completely without any therapy once the lesion was excised. (b) In the dermoscopic image of the same melanoma, an asymmetric pigmentation, blue–black pigmented area and homogeneous red structureless areas, covering the structures lying below (white arrowheads), can be seen; framed is the area with a polymorphous vascular pattern. Interestingly, adherent fibres of clothing, as a dermatoscopic clue to ulceration (circle), can also be observed. (c) Magnified detail of polymorphous vascular pattern, having linear irregular vessels (black arrow), irregular hairpin vessels (white arrows), linear coiled (glomerular) vessels (black circle) and linear helical (corkscrew-like) vessels (white arrowheads) (original magnification 10×).

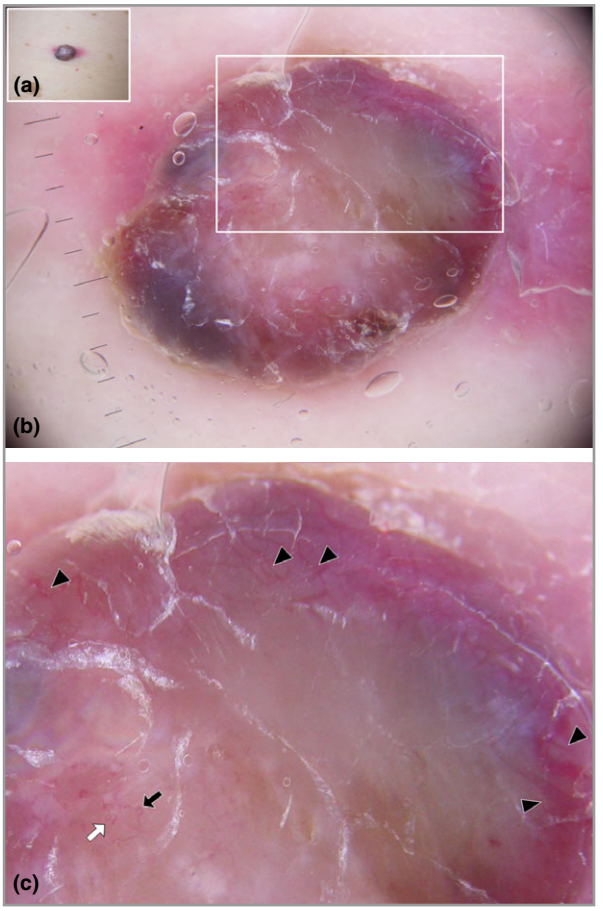


**Fig 4.** Clinical and dermoscopic images of a nodular 3·0-mm-thick melanoma on the flank of a 57-year-old man. (a) In the clinical image (inset) a brown–greyish scaly symmetrical nodule with a peripheral reddish halo can be seen. (b) In the dermoscopic image of the same melanoma, an asymmetrically pigmented lesion with a homogeneous disorganized pattern and focal blue-pigmented areas can be observed; framed is the area with a polymorphous vascular pattern. (c) Magnified detail of the polymorphous vascular pattern, having linear irregular vessels (black arrow), linear helical (corkscrew-like) vessels (white arrows) and arborizing vessels (black arrowheads) (original magnification 10×).

frequent in pigmented NM compared with pigmented nodular nonmelanocytic and benign melanocytic lesions. In agreement with our results, Argenziano *et al.*[17] found that blue–black pigmented areas, defined as a combination of structureless blue areas, black dots/globules, and blotches, involving at least 10% of the lesion surface, were significantly associated with NM (Figs 1, 2 and 3). These areas correspond to different histopathological correlates, with blue areas corresponding to pigmented melanocytes in the deep dermis and black areas, arising from superficial intraepidermal melanin or a dense dermal proliferation of pigmented melanocytes under a thinned epidermis that may predict ulceration.[18] This could also explain why we found ulceration to be significantly more frequent in NMs compared with SSMs. Abnormal vascular structures, including polymorphic vessels, milky-red globules/areas and homogeneous red areas are also significant relevant features of NM, which have been reported by other authors to be associated with NM.[19] Polymorphous vessels are defined as having more than one morphological type of vessel; the most frequent combination of vessel types seen in melanoma is linear irregular and dotted vessels. As the thickness increases, the vascular polymorphism increases with hairpin, linear coiled (glomerular), linear helical (corkscrew-like) and arborizing vessels (seemingly emerging from the dermal

plexus of the adjacent skin, possibly because vertical growth cannot be maintained by further elongation of the capillary loops), associated with milky-red globules/areas and/or homogeneous red areas (Fig. 4).[19] Milky-red globules have been defined as unfocused large ovoid or polygonal structures of pink–white colour, often showing a central linear irregular or corkscrew vessel, separated from each other by blurred whitish lines, which may be seen within or near areas with a milky-red colour (the so-called milky-red areas, also known as the pink veil) or more than one shade of pink that probably correspond to areas with increased vascular volume (Fig. 2).[19,20] The red homogeneous areas were seen in NMs and pyogenic granulomas as structureless areas of red homogeneous colour covering the structures lying below (Fig. 3).[19,21] The milky-red globules/areas, as well as the homogeneous red areas, probably represent an increased vascular volume reflecting neoangiogenesis.[19–21]

Dermoscopy may be helpful in improving the recognition of pigmented NM by revealing asymmetric pigmentation, blue–black pigmented areas, homogeneous disorganized pattern and abnormal vascular structures, including polymorphic vessels, milky-red globules/areas and homogeneous red areas. In conclusion, the abnormal vascular structures (Fig. 4), as well as the blue–black pigmented areas (Fig. 1), may be the only clue for the correct diagnosis of pigmented NM in examining asymmetrically pigmented lesions with a homogeneous disorganized pattern.

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## Appendix

### Members of the Italian Melanoma Intergroup

D. Guardoli (Skin Cancer Unit, Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy); M. Alaiback (Department of Dermatology, University of Padova, Padova, Italy); S. Astorino (Division of Dermatology, Celio Hospital, Rome, Italy); F. Ayala (National Cancer Institute, IRCCS, Naples, Italy); M.T. Corradin (Division of Dermatology, Pordenone Hospital, Pordenone, Italy); M. Gonzales and P. Zampieri (Division of Dermatology, Merano Hospital, Merano, Italy); S. Magi and L. Mazzoni (Skin Cancer Unit, Istituto Tumori Romagna – IRST, Meldola, Italy); S. Seidenari and G. Pellacani (Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy); F. Specchio (Department of Dermatology, University Tor Vergata, Rome, Italy); D. Serraino (Unit of Epidemiology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy); H.P. Soyer (Dermatology Research Centre, The University of Queensland, School of Medicine, Princess Alexandra Hospital, Brisbane, Australia).