

CLINICAL REPORT

Dermatoscopic Prediction of Melanoma Thickness Using Latent Trait Analysis and Likelihood Ratios

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Breslow thickness and Clark level can be used to determine surgical procedures for cutaneous malignant melanoma and patient eligibility for experimental adjuvant therapy. Efforts to predict the thickness of melanomas using dermatoscopy have focused on differences between single dermatoscopic findings. The aim of this study was to develop a method for preoperative identification of melanomas of ≥ 1 mm Breslow thickness using the entire range of dermatoscopic findings. Sixty-five melanomas were assessed for the presence of 22 dermatoscopic features. Ten dermatoscopic features showed differences in thick and thin melanomas and were selected for further analysis. A latent trait analysis construct implied that a progression in dermatoscopic features was associated with advancement of melanomas. Early melanomas are characterized by a light brown colour, a pigment network and irregularity or heterogeneity. Gray–blue areas, white scar-like areas and an atypical vascular pattern gradually displace these features. Likelihood ratios were determined for these 6 dermatoscopic findings and an algorithm for calculating the probability of thick malignant melanoma was established. Key words: melanoma; dermatoscopy; latent trait analysis; likelihood ratio.

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Expert dermatoscopy facilitates the clinical diagnosis of malignant melanoma (MM) (1, 2). Breslow (3) and Clark et al. (4) described a close association between thickness, as well as level of invasion of MM, and prognosis. Surgical treatment and eligibility for investigative protocols are dependent on the thickness of the tumour. In Denmark a cut-off of 1 mm Breslow thickness is used. Surgical margins of 10 mm and 20–40 mm, both to the fascia, are used for Breslow thicknesses < 1 mm and > 1 mm, respectively. If the primary excision is 10 mm and the tumour > 1 mm Breslow thickness a secondary, potentially disfiguring, wider excision of 20–40 mm from the scar and to a subfascial level is performed. Argenziano et al. (5) found significant associations between MM < 0.76 mm and the presence of a pigment network, and between gray–blue areas, atypical vascular pattern (AVP) and MM > 0.76 mm. In our experience a pigment network can be found in the majority of MM and the association between gray–blue areas and thick MM is not strong. The aim of the present study was to develop a model where in entire patterns, rather than individual findings, predict melanoma thickness.

MATERIAL AND METHODS

Sixty-five MM were consecutively assessed and excised at our skin cancer clinic. Clinical photos and oil-immersion dermatophotos (Dermaphot: Heine optotechnik, Germany) were taken of all lesions. Lesions were excised and sent for histopathological assessment. Sections were stained with hematoxylin and eosin and with the immunostains HMB-45 (6) and S-100 (7). Breslow thickness and Clark level were established but not communicated to the dermatologists assessing the dermatoscopic photo slides. These were projected onto an 80×120 cm² screen in a darkened room. Two dermatoscopic experts assessed and discussed the cases and agreed on the presence or absence of a dermatoscopic finding in each case, according to the risk stratification method (8–10) and the dermatoscopic ABCD rule (Table I). Dermatoscopic findings were classified as “yes” or “no” and the histological thickness was coded as thin MM (< 1 mm) or thick MM (≥ 1 mm) for latent trait analysis (LTA). Frequencies of dermatoscopic findings in the thin and thick MM groups were compared using Fisher’s exact test. Findings where $p \leq 0.10$ were included in the subsequent LTA (Table I). Bleeding or ulceration, which would always lead us to regard the MM as thick, were excluded.

LTA (see Appendix) was performed on the data in order to establish an underlying scale of primary MM progression that could explain the relationship with the observable data (dermatoscopic findings). Maximum likelihood methodology was used to establish models fitting the data. Histological thickness was compulsory for LTA and as a compromise between model flexibility and the sparseness of data compared to possible response patterns we included 6 dermatoscopic features, giving $2^7 = 128$ possible response patterns. Six dermatoscopic findings can be combined from 8 possible factors in 28 possible ways. The combination of dermatoscopic signs that best fitted the data was selected by use of the Akaike information criterion. The latent trait model was also compared with an ordinal latent class model and with unrestricted latent class models with varying numbers of latent classes. The Akaike information criterion was used to compare the fit of the different models with the data.

The sensitivity and specificity of single dermatoscopic findings for diagnosing MM > 1 mm were used for the calculation of positive and negative likelihood ratios: LR+ (= sensitivity/[1–specificity]) and LR- (= [1–specificity]/sensitivity). A post-test (after dermatoscopy) probability of MM > 1 mm was calculated as the pretest (before dermatoscopy) probabilities LR+ and LR- for the presence and absence, respectively, of the dermatoscopic findings. As pre-test probability we used the proportion of MM > 1 mm found in our material.

RESULTS

Sixteen (24.6%) MM had a Breslow thickness of > 1 mm and 49 (75.4%) were < 1 mm. Light-brown coloration, a pigment network, irregularity or heterogeneity of the network ($p \leq 0.05$) and whitish veil and pseudopods ($p \leq 0.10$) were more frequent in thin MM, whereas white scar-like areas,

Table I. Fisher's exact test of dermatoscopic elements modified from the dermatoscopic ABCD rule (13, 23, 24) and the risk stratification method (8–10).

The second column lists the proportion of thick malignant melanoma (MM) presenting the dermatoscopic features listed in the first column. The third column lists the corresponding proportions for thin MM. The fifth (and sixth) columns list the positive (negative) likelihood ratios, i.e. the degree by which the odds of thick MM is strengthened (weakened) given the presence (absence) of the dermatoscopic finding

Dermatoscopic feature	MM		P	LR+	LR-
	≥1 mm	<1 mm		>1 mm	>1 mm
WSA	0.722	0.233	0.0003	3.4	0.4
Light brown	0.500	0.915	0.0006	0.5	5.9
PN	0.278	0.574	0.0008	0.5	1.7
Bleeding	0.333	0.021	0.001	15.7	0.7
Ulceration	0.389	0.085	0.007	4.6	0.7
GBA	0.611	0.234	0.007	2.6	0.5
Irregular heterogeneous	0.556	0.830	0.05	0.7	2.6
Whitish veil	0.278	0.553	0.06	0.5	1.6
AVP	0.444	0.213	0.07	2.1	0.7
Pseudopods	0.278	0.532	0.10	0.5	1.5
Eccentricity	0.500	0.723	0.14	0.7	1.8
Teleangiectasias	0.278	0.149	0.29	1.9	0.8
Red	0.389	0.255	0.36	1.5	0.8
Blue	0.444	0.340	0.38	1.3	0.8
Black	0.611	0.723	0.39	0.8	1.4
Asymmetry	0.778	0.872	0.44	0.9	1.7
Dark-brown	0.778	0.872	0.44	0.9	1.7
Globules	0.167	0.277	0.52	0.6	1.2
Peppering	0.167	0.213	0.74	0.8	1.1
Homogenous areas	0.667	0.617	0.78	1.1	0.9
White	0.556	0.511	0.79	1.1	0.9
Dots	0.167	0.213	1	0.8	1.1

WSA= white scar-like areas; PN= pigment network; GBA= gray-blue areas; AVP= atypical vascular pattern. LR: likelihood ratio.

gray-blue areas, bleeding, ulceration and AVP were more frequent in thick MM.

Using the Akaike information criterion a LTA including pigment network, light-brown colour, irregularity or heterogeneity of the network, white scar-like areas, gray-blue areas and AVP was selected. Fig. 1 depicts the latent trait model.

Fig. 1. Latent trait analysis. WSA= white scar-like areas; L-brown= light brown colour; PN= pigment network; GBA= gray-blue areas; Irreg= irregularity or heterogeneity of network; AVP= atypical vascular pattern; Br= Breslow thickness. For explanations see text.

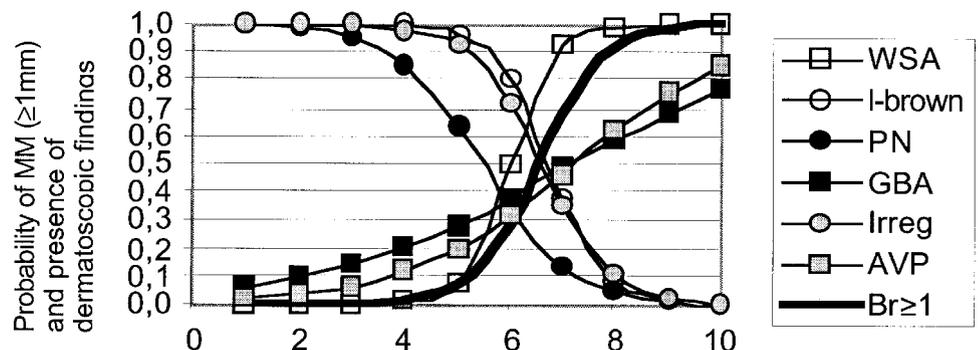


Table II. Dermatoscopic patterns and corresponding probability (in %) that the malignant melanoma (MM) is thicker than 1 mm (P>1 mm).

Post-test probability of thick MM= pretest probability × LR+ (if present) or LR- (if absent) for PN × LR (light brown-colour) × LR (irregularity/heterogeneity) × LR (GBA) × LR (AVP) × LR (WSA). Prevalence of MM>1 mm in our series was used as pretest probability

PN	Light brown	Irregular	GBA	AVP	WSA	P>1 mm (%)
+	+	+	-	-	-	0.7
+	+	+	+	-	-	3.6
+	+	+	+	+	-	10.0
+	+	+	+	+	+	51.7
+	-	-	-	-	+	74.7
-	-	-	+	-	-	84.6
-	-	-	-	-	+	91.1
-	-	-	-	+	+	96.8
-	-	+	+	+	+	97.6
-	-	-	+	+	+	99.4

PN= pigment network; GBA= gray-blue areas; AVP= atypical vascular pattern; WSA= white scar-like areas.

The ordinate is the probability of a dermatoscopic feature being present and the probability of a Breslow thickness>1 mm. The abscissa is an arbitrary latent continuum. A probable interpretation of the increased probability of MM>1 mm is that it reflects progression of the tumor. At the arbitrary latent level 1 all MM are <1 mm, the probability of light-brown colour, heterogeneity and pigment network is 100% whereas the probability of white scar-like areas, AVP and gray-blue areas is 0%. At the other end of the scale, where all MM are thick, the probability of light-brown colour, pigment network and heterogeneity approaches 0% and the probability of white scar-like areas, AVP and gray-blue areas approaches 100%.

Using the Akaike information criterion a latent trait model was favoured compared to latent class analysis and ordinal latent class models with similar numbers of latent levels.

LR+ and LR- for the dermatoscopic findings identifying MM>1 mm are given in Table I. There are 2⁶= 64 possible combinations of responses to the 6 dermatoscopic features. Post-test probabilities are listed for 10 of these patterns in Table II.

DISCUSSION

Choice of treatment of MM is guided by tumour thickness. Dermatoscopy is an inexpensive method and, besides increasing diagnostic accuracy, the method can also provide preoperative clues to thin (<1 mm) and thick MM.

A pigment network has been found more frequently in MM <0.76 mm and an AVP and gray-blue areas have been found more frequently in MM ≥0.76 mm (5, 11). Our data confirm these findings. In addition we found bleeding—including the “poppy-field sign”—and ulceration to be significantly more prevalent in MM >1 mm and heterogeneity or irregularity of the pigment network, as described by Kenet et al. (10), to be more frequent in MM <1 mm.

Latent structure models have been used to suggest typologies in psychiatric research. We employed LTA to propose an underlying model that could explain the relationship between the observed dermatoscopic findings and the histopathological thickness. With the number of possible response patterns exceeding the number of observed responses, absolute measures of fit, such as L-squared, are unreliable and we relied instead on the information criterion. The LTA suggested an underlying progression scale. Early findings are a pigment network, light-brown colour and irregularity. These findings gradually disappear and are replaced by an AVP, gray-blue areas and white scar-like areas.

At the 1989 consensus meeting (12) and in the atlas of Stolz et al. (13) a pigment network, as seen on dermatoscopy, has been described as a reflection of a histological accumulation of melanin in the basal keratinocytes at the epidermal crests. Melanoma cells accumulated at the epidermal crests and “shoulders” cause a coarseness of the pigment network. A preserved pigment network throughout the lesion therefore indicates thin lesions (in situ or Clark level II) where the tumour has not destroyed the epidermal-dermal border, as was also found by Argenziano et al. (5, 11). Kenet and co-workers (9, 10) described heterogeneity of the pigment network, thick, dark extensions at the periphery, streaming, pseudopods and eccentricity as indicators of probable MM. The dermatoscopic disturbances at the periphery of the lesion are due to horizontal growth, characteristic of in situ and superficial spreading MM. Gray-blue areas were observed in a small proportion of thin lesions and their occurrence increased steadily along the scale. They are caused by accumulation of pigment in melanocytes and melanophages located in the papillary dermis and at deeper levels. The slate-blue colour is due to the Tyndall effect, i.e. scattering and reflection of visible light of short wavelength. In the study of Argenziano et al. (11) there was a significantly higher prevalence of gray-blue areas in thick MMs, but they were also found in some of the MM <0.76 mm. With 1 mm cut-off used in this study, gray-blue areas could probably be expected in more thin MM.

White scar-like areas may be a dermatoscopic pendant to histological regression, where the invasive tumour component is replaced by mononuclear cell infiltration and fibrosis. Peppering is another probable dermatoscopic reflection of histological regression. The association between regression and the above-mentioned dermatoscopic findings still needs investigating. Trau et al. (14) found that histological regression was more likely to be found in MM with areas

of whiteness clinically. Regression with scar formation possibly adversely affects prognosis for thin MM (15, 16) although this has not been definitively clarified (17). The dermatoscopic elements chosen for our analysis are primarily derived from the risk stratification method. We have previously described higher diagnostic performance of risk stratification compared to the dermatoscopic ABCD rule (8). Eccentricity is a special case of asymmetry. With progression of the tumour, the cancerous tissue will be found not only at the periphery but will also cause bulk asymmetry, displacing the tissue with a less abnormal appearance. Gray-blue and white scar-like areas are also found in the dermatoscopic ABCD classification as homogenous areas (blue and white, respectively). We have previously advocated a probabilistic view for the diagnosis of MM (1) and extend this to identification of thick MM. From the presence or absence of specific dermatoscopic findings the pre-test expectation can be multiplied by the likelihood ratios to give the post-test expectation. The pre-test expectation may be altered by the clinical assessment or by the population examined. Prediction of MM thickness has been investigated using high-frequency ultrasound (18) and a combination of high-frequency ultrasound and dermatoscopy (19). The lymphocyte infiltrate below the MM contributes to the ultrasound measurement and, for this reason, the thinner the MM, the lower the precision of ultrasound. Furthermore, high-frequency ultrasound is not a standard technique in most dermatology clinics.

A prospective study, in which our progression model will be validated, is currently being performed at our skin cancer clinic.

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REFERENCES

- Lorentzen H, Weismann K, Sand Petersen C, Grønhoj Larsen F, Skødt V. Clinical and dermatoscopic diagnosis of malignant melanoma—assessed by an expert and non-expert group. *Acta Derm Venereol* 1999; 79: 301–304.
- Binder M, Schwarz M, Winkler A, Steiner A, Kaider A, Wolff K, et al. Epiluminescence microscopy. A useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. *Arch Dermatol* 1995; 131: 286–291.
- Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970; 172: 902–908.
- Clark W, From L, Bernardino EA, Mihm MC. The histogenesis and biological behavior of primary human malignant melanoma of the skin. *Cancer Res* 1969; 29: 705–727.
- Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Delfino M. Epiluminescence microscopy: criteria of cutaneous melanoma progression. *J Am Acad Dermatol* 1997; 37: 68–74.
- Wick MR, Swanson PE, Rocamora A. Recognition of malignant melanoma by monoclonal antibody HMB-45. An immunohistochemical study of 200 paraffin-embedded cutaneous tumours. *J Cutan Pathol* 1988; 15: 201–207.
- Kahn HJ, Baumal R, Marks A. The value of immunohistochemical studies using antibody to S100 protein in dermatopathology. *Int J Dermatol* 1984; 23: 38–44.
- Lorentzen H, Weismann K, Kenet RO, Secher L, Grønhoj Larsen F. Comparison of the dermatoscopic ABCD rule and the

- dermatoscopic risk stratification for diagnosing malignant melanoma. *Acta Derm Venereol* 2000; 80: 122–126.
9. Kenet RO, Fitzpatrick TB. Reducing mortality and morbidity of cutaneous melanoma: a six year plan identifying high and low risk pigmented lesions using epiluminescence microscopy. *J Dermatol* 1994; 21: 881–884.
 10. Kenet RO, Kang S, Kenet BJ, Fitzpatrick TB, Sober AJ, Barnhill RL. Clinical diagnosis of pigmented lesions using digital epiluminescence microscopy. *Arch Dermatol* 1993; 129: 157–174.
 11. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Delfino M. Clinical and dermatoscopic criteria for the preoperative evaluation of cutaneous melanoma thickness. *J Am Acad Dermatol* 1999; 40: 61–68.
 12. Bahmer FA, Fritsch P, Kreutsch J, Pehamberger H, Rohrer C, Schindera I, et al. Meeting report: terminology in surface microscopy. *J Am Acad Dermatol* 1990; 23: 1159–1162.
 13. Stolz W, Braun-Falco O, Bilek P, et al. Color atlas of dermatoscopy. Oxford: Blackwell Science Ltd., 1994.
 14. Trau H, Kopf AW, Rigel DS, Levine J, Rogers G, Levenstein M, et al. Regression in malignant melanoma. *J Am Acad Dermatol* 1983; 8: 363–368.
 15. Gromet MA, Epstein WL, Blois MS. The regressing thin melanoma. A distinctive lesion with metastatic potential. *Cancer* 1978; 42: 2282–2292.
 16. Sondergaard K, Hou Jensen K. Partial regression in thin primary cutaneous malignant melanomas clinical stage I. A study of 486 cases. *Virchows Arch A Pathol Anat Histopathol* 1985; 408: 241–247.
 17. Kelly JW, Sagebiel RW, Blois MS. Regression in malignant melanoma. A histological feature without independent prognostic significance. *Cancer* 1985; 56: 2287–2291.
 18. Reali UM, Santucci M, Paoli G, Chiarugi C. The use of high resolution ultrasound in preoperative evaluation of cutaneous malignant melanoma thickness. *Tumori* 1989; 75: 452–455.
 19. Dummer W, Blaheta H-J, Bastian BC, Schenk T, Bröcker E-B, Remy W. Preoperative characterization of pigmented skin lesions by epiluminescence microscopy and high-frequency ultrasound. *Arch Dermatol* 1995; 131: 279–285.
 20. Heinen T. Latent class and discrete latent trait models: similarities and differences. Thousand Oales, London. Sage Publications, 1996.
 21. McCutcheon AL. Latent class analysis. London: Sage Publications, 1987.
 22. Vermunt JK. IEM. Tilburg University: Tilburg, Netherlands, 1997.
 23. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. *J Am Acad Dermatol* 1994; 30: 551–559.
 24. Stolz W, Rieman A, Cognetta AB, Pillet L, Abmayr W, Hölzel D, et al. ABCD rule of dermatoscopy: a new practical method for early recognition of malignant melanoma. *Eur J Dermatol* 1994; 4: 521–527.

APPENDIX

Latent trait analysis (LTA) belongs to the group of statistics called latent structure models (20, 21), in which heterogeneity of the investigated population is assumed. Typologies or internally homogenous subgroups can be determined in latent class analysis. For example, different subgroups of depression can be identified using questionnaires. Members of a latent group have the same probability of giving certain answers to a set of items. In latent trait models a latent continuous scale is established from a collection of responses to nominal or categorical items, for example the establishment of an intelligence quotient from responses to a multiple-choice test. Possible combinations of responses to items can be listed by cross-tabulating data. If a χ^2 or L-squared test is performed on the cross-tabulation a significant result indicates dependence between responses. If response profiles can be arranged into subsets, which leads to non-significance (preferably $p > 0.10$), the latent classes or latent scale explain the dependence between the observed data. Within each latent class or latent level, response patterns are homogenous, i.e. locally independent. For example, individuals with comparable intelligence quotients will have similar capabilities to solve posed problems. Each specific latent level in LTA is characterized by the probability of certain responses to the items.

Latent classes and latent levels are not known in advance. Therefore an iterative algorithm has to be employed. The computer program IEM (22) was used for estimating parameters. This program employs the Expectation Maximization algorithm to identify parameter values that optimize a maximum likelihood criterion.