

Predictive models of melanoma metastasis based on dermatoscopy in an international retrospective human reader study

Supplementary File

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Supplementary Tables

Supplementary Table 1: Number of lesions evaluated per reader and frequencies of lesions evaluated in non-metastatic and metastatic patients

Reader	Lesions evaluated (n)	Non-metastatic (n, %)	Metastatic (n,%)
1	130	64 (49.2)	66 (50.8)
2	21	12 (57.1)	9 (42.9)
3	105	54 (51.4)	51 (48.6)
4	103	63 (61.2)	40 (38.8)
5	208	113 (54.3)	95 (45.7)
6	99	59 (59.6)	40 (40.4)
7	176	99 (56.3)	77 (43.8)
8	102	53 (52)	49 (48)
9	110	61 (55.5)	49 (44.5)
10	102	63 (61.8)	39 (38.2)
11	105	56 (53.3)	49 (46.7)
12	102	55 (53.9)	47 (46.1)
13	101	55 (54.5)	46 (45.5)
14	105	59 (56.2)	46 (43.8)
15	123	67 (54.5)	56 (45.5)
16	120	61 (50.8)	59 (49.2)
17	104	57 (54.8)	47 (45.2)
18	104	58 (55.8)	46 (44.2)
19	110	64 (58.2)	46 (41.8)
20	134	75 (56)	59 (44)
21	112	55 (49.1)	57 (50.9)
22	104	59 (58.7)	45 (43.3)
23	102	49 (48)	53 (52)
24	100	54 (54)	46 (46)
25	40	24 (60)	16 (40)
26	104	61 (58.7)	43 (41.3)
27	102	55 (53.9)	47 (46.1)
28	113	56 (49.6)	57 (50.7)
29	190	95 (50)	95 (50)
30	101	56 (55.4)	45 (44.6)

n: number of lesions evaluated

Supplementary Table 2: Interrater agreement on the dermatoscopic criteria of melanoma based on dermatoscopic images (Number of readers=30)

Structure	Krippendorf alpha (95%CI)	Interpretation*
Pigmentation	0.577 (0.491 – 0.604)	Moderate
Brown color	0.325 (0.244 – 0.405)	Fair
Blue/gray color	0.355 (0.274 – 0.435)	Fair
Red color	0.363 (0.283 – 0.442)	Fair
White color	0.204 (0.120 – 0.287)	Fair
Black color	0.416 (0.338 – 0.493)	Moderate
Ulceration	0.579 (0.509 – 0.648)	Moderate
Regression structures	0.245 (0.161 – 0.328)	Fair
White shiny streaks	0.392 (0.313 – 0.470)	Fair
Blue-white veil	0.389 (0.310 – 0.467)	Fair
Eccentric blotch	0.203 (0.119 – 0.286)	Fair
Angulated lines	0.262 (0.08 – 0.342)	Fair
Parallel ridge	0.455 (0.378 – 0.531)	Moderate
Vessels	0.559 (0.488 – 0.629)	Moderate

CI: confidence interval

*Interpretation of Krippendorf alpha was based on Landis and Koch classification

Supplementary Table 3: Frequencies of dermoscopic features in the total cohort and in patients with and without metastasis at diagnosis or during follow up

	Total (N=524)	Non-metastatic (N=302)	Metastatic (N=222)	X ² -test (p-value)
Pigmentation (n, %)				<0.001
Absent	42 (8)	15 (5)	27 (12.2)	
25	95 (18.1)	29 (9.6)	66 (29.7)	
50	91 (17.4)	36 (11.9)	55 (24.8)	
75	121 (23.1)	86 (28.5)	35 (15.8)	
100	175 (33.4)	136 (45)	39 (17.6)	
Colors (n, %)				
Brown	433 (82.6)	269 (89.1)	164 (73.9)	<0.001
Blue/gray	329 (62.8)	175 (57.9)	154 (69.4)	0.008
Red	311 (59.4)	146 (48.3)	165 (74.3)	<0.001
White	302 (57.6)	149 (49.3)	153 (68.9)	<0.001
Black	247 (47.1)	155 (51.3)	92 (41.1)	0.025
Dermatoscopic ulceration (n, %)				<0.001
Absent	352 (67.2)	238 (78.8)	114 (51.4)	
1-49	106 (20.2)	51 (16.9)	55 (24.8)	
>50	66 (12.6)	13 (4.3)	53 (23.9)	
Regression structures (n, %)				0.036
Absent	353 (67.4)	192 (63.6)	161 (72.5)	
1-49	120 (22.9)	73 (24.2)	47 (21.2)	
>50	51 (9.7)	37 (12.3)	14 (6.3)	
White shiny streaks (n, %)	285 (54.4)	151 (50)	134 (60.4)	0.019
Blue-white veil (n, %)	269 (51.3)	127 (42.1)	142 (64)	<0.001
Eccentric blotch (n, %)	201 (38.4)	108 (35.8)	93 (41.9)	0.154
Angulated lines (n, %)	23 (4.4)	12 (4)	11 (5)	0.588
Parallel ridge (n, %)	20 (3.8)	8 (2.6)	12 (5.4)	0.104
Vessels (n, %)				<0.001
Absent	223 (42.6)	157 (52)	66 (29.7)	
1-49	154 (29.4)	83 (27.5)	71 (32)	
>50	147 (28.1)	62 (20.5)	85 (38.3)	
Type of vessels (n, %)				<0.001
Dotted/Coiled	78 (14.9)	54 (17.9)	24 (10.8)	
Linear/Irregular	120 (22.9)	61 (20.2)	59 (26.6)	
Two types of vessels	103 (19.6)	30 (9.9)	73 (32.9)	

N: number of patients. Pigmentation, dermatoscopic ulceration, regression structures, vessels are expressed as percentages of feature extent in the lesion. Two-sided p-values for categorical variables were obtained from the Pearson's chi-squared test. Exact p-values are provided for pigmentation ($p=6.06 \times 10^{-18}$), brown ($p=5.67 \times 10^{-6}$), red ($p=2.19 \times 10^{-9}$) and white color ($p=7.38 \times 10^{-6}$), dermatoscopic ulceration ($p=3.81 \times 10^{-13}$), blue-white veil ($p=7.10 \times 10^{-7}$), vessels ($p=2.83 \times 10^{-7}$) and type of vessels ($p=4.66 \times 10^{-7}$).

Supplementary Table 4: Results from univariate and multivariate logistic regression for the prediction of melanoma metastasis based on dermatoscopy in the total cohort

	Univariate			Multivariate		
	OR	p-value	95%CI	OR	p-value	95%CI
Pigmentation						
Absent	Ref.			Ref.		
25	1.26	0.54	0.58 – 2.72	1.07	0.79	0.45 – 2.54
50	0.84	0.67	0.39 – 1.81	0.50	0.05	0.20 – 1.22
75	0.22	<0.001	0.10 – 0.47	0.14	<0.001	0.05 – 0.33
100	0.16	<0.001	0.07 – 0.32	0.07	<0.001	0.03 – 0.18
Colors						
Brown	0.34	<0.001	0.21 – 0.55			
Blue/gray	1.64	0.008	1.14 – 2.37			
Red	3.09	<0.001	2.12 – 4.50			
White	2.27	<0.001	1.58 – 3.27			
Black	0.67	0.025	0.47 – 0.95			
Dermatoscopic ulceration						
Absent	Ref.			Ref.		
1-49	2.25	<0.001	1.44 – 3.50	1.46	0.14	0.87 – 2.42
>50	8.51	<0.001	4.59 – 16.24	3.45	0.001	1.63 – 7.69
Regression structures						
Absent	Ref.			Ref.		
1-49	0.77	0.22	0.50 – 1.17	0.75	0.30	0.44 – 1.27
>50	0.45	0.016	0.23 – 0.86	0.42	0.026	0.19 – 0.89
White shiny streaks	1.52	0.019	1.07 – 2.16			
Blue-white veil	2.44	<0.001	1.71 – 3.49	6.43	<0.001	3.87 – 11.06
Eccentric blotch	1.29	0.154	0.90 – 1.84			
Angulated lines	1.26	0.589	0.54 – 2.91			
Parallel ridge	2.10	0.111	0.84 – 5.22			
Vessels						
Absent	Ref.					
1-49	2.03	<0.001	1.32 – 3.12			
>50	3.26	<0.001	2.10 – 5.04			
Type of vessels						
One type	1.56	0.03	1.04 – 2.34			
Two types of vessels	6.44	<0.001	3.83 – 10.82			

OR: Odds ratio, CI: confidence interval, Ref.: Reference level. 524 patients analyzed. Pigmentation, dermatoscopic ulceration, regression structures, vessels are expressed as percentages of feature extent in the lesion. Variables included in multivariate model: brown, blue/gray, red, white, black color, pigmentation, derm. ulceration, regression structures, white shiny streaks, blue-white veil, vessels. Variables included in last step of multivariable analysis after applying backward elimination are presented. Multivariable model was adjusted for age, sex, anatomic location. Two-sided p-values were obtained from Wald tests. Exact p-values – univariate: pigmentation 75% (p=0.0001), pigmentation 100% (p=2.28 x 10⁻⁶), brown (p=1.12 x 10⁻⁵), red (p=4.21 x 10⁻⁹) and white color (p=9.96 x 10⁻⁶), derm. ulceration 1-49 (p=3.0 x 10⁻⁴) and >50

($p=3.08 \times 10^{-11}$), blue-white veil ($p=9.52 \times 10^{-7}$), vessels 1-49 ($p=0.0013$), vessels >50 ($p=1.22 \times 10^{-7}$), two types of vessels ($p=2.06 \times 10^{-12}$). Exact p-values – multivariable: pigmentation 75% ($p=1.35 \times 10^{-5}$), pigmentation 100% ($p=1.77 \times 10^{-8}$) and blue-white veil ($p=3.21 \times 10^{-12}$), Adjustment for multiple comparisons for the univariate analysis is available in Supp. Table 14.

Supplementary Table 5: Univariate and multivariate logistic regression analysis for the prediction of melanoma metastasis based on clinical and histopathological factors in the total cohort

	Univariate			Multivariate		
	OR	p-value	95%CI	OR	p-value	95%CI
Age (continuous)	1.01	0.01	1.01 – 1.024			
Sex						
Male	Ref.					
Female	0.90	0.58	0.64 – 1.28			
Anatomic location						
Head and neck	1.20	0.49	0.71 – 2.02			
Trunk	Ref.					
UE	0.93	0.82	0.53 – 1.65			
LE	0.77	0.32	0.47 – 1.28			
Acral	1.19	0.79	0.31 – 4.59			
Subungual	Inf.					
Breslow thickness (continuous)	1.53	<0.001	1.37 – 1.70	1.32	<0.001	1.17 – 1.43
Histopathologic ulceration (present)	4.95	<0.001	3.34 – 7.33	2.30	<0.001	1.41 – 3.74
Mitosis (n=444)						
Absent	Ref.					
1-5/mm ²	4.21	<0.001	1.98 – 8.90	2.64	0.014	1.21 – 5.74
>5/mm ²	15.48	<0.001	7.10 – 33.74	4.64	<0.001	1.97 – 10.91

OR: Odds ratio, CI: confidence interval, Ref.: Reference level, Inf.: infinitive, UE: upper extremities, LE: lower extremities. 524 patients analyzed. Two-sided p-values were obtained from Wald tests. Exact p-value – univariate: Breslow thickness ($p=1.12 \times 10^{-14}$), histopathologic ulceration ($p=1.55 \times 10^{-15}$), mitosis 1-5/mm² ($p=1.77 \times 10^{-4}$) and mitosis >5/mm² ($p=5.57 \times 10^{-12}$). Exact p-value – multivariable: Breslow thickness ($p=5.58 \times 10^{-8}$), histopathologic ulceration ($p=8.17 \times 10^{-4}$) and mitosis >5/mm² ($p=4.40 \times 10^{-4}$). Adjustment for multiple comparisons was not applied.

Supplementary Table 6: Models derived from Cox regression analysis for the prediction of RFS and DMFS in patients with stage I-II melanoma

Recurrence-Free Survival (RFS)			
	Model 1 (HR, 95%CI)	Model 2 (HR, 95%CI)	Model 3 (HR, 95%CI)
Pigmentation			
Absent	Ref.	-	Ref.
25	0.82 (0.34 – 1.98)	-	0.89 (0.36 – 2.15)
50	0.51 (0.20 – 1.32)	-	0.58 (0.23 – 1.53)
75	0.40 (0.15 – 1.04)	-	0.54 (0.21 – 1.42)
100	0.15 (0.05 – 0.40)	-	0.18 (0.06 – 0.50)
Dermatoscopic ulceration			
Absent	Ref.	-	Ref.
1-49	1.42 (0.83 – 2.45)	-	1.23 (0.70 – 2.17)
>50	2.99 (1.47 – 6.04)	-	2.23 (1.05 – 4.72)
Regression structures			
Absent	Ref.	-	Ref.
1-49	0.64 (0.36 – 1.15)	-	0.69 (0.38 – 1.24)
>50	0.38 (0.14 – 0.97)	-	0.35 (0.13 – 0.93)
Blue-white veil	4.37 (2.43 – 7.87)	-	4.19 (2.30 – 7.61)
Breslow thickness (Cont.)	-	1.10 (1.05 – 1.15)	1.09 (1.04 – 1.14)
Histopathologic ulceration (Present)	-	2.32 (1.43 – 3.78)	1.55 (0.90 – 2.68)
Distant metastasis-free Survival (DMFS)			
	Model 1 (HR, 95%CI)	Model 2 (HR, 95%CI)	Model 3 (HR, 95%CI)
Pigmentation			
Absent	Ref.	-	Ref.
25	0.75 (0.26 – 2.09)	-	0.82 (0.29 – 2.31)
50	0.58 (0.21 – 1.68)	-	0.67 (0.23 – 1.98)
75	0.39 (0.13 – 1.15)	-	0.57 (0.19 – 1.69)
100	0.16 (0.05 – 0.48)	-	0.21 (0.05 – 0.63)
Dermatoscopic ulceration			
Absent	Ref.	-	Ref.
1-49	1.51 (0.84 – 2.71)	-	1.33 (0.72 – 2.47)
>50	2.69 (1.09 – 6.62)	-	1.98 (0.76 – 5.11)
Regression structures			
Absent	Ref.	-	Ref.
1-49	0.65 (0.34 – 1.25)	-	0.63 (0.32 – 1.24)
>50	0.25 (0.07 – 0.81)	-	0.22 (0.06 – 0.77)
Blue-white veil	4.27 (2.23 – 8.17)	-	3.97 (2.05 – 7.67)
Breslow thickness (Cont.)	-	1.10 (1.05 – 1.15)	1.09 (1.04 – 1.15)
Histopathologic ulceration (Present)	-	2.48 (1.43 – 4.29)	1.68 (0.90 – 3.12)

HR: Hazard ratio, CI: confidence interval, Ref.: Reference level, RFS: recurrence-free survival, DMFS: distant metastasis free survival, n.s: not significant, Cont.: continuous. 381 patients with early-stage melanoma analyzed. Breslow thickness was included as a continuous variable, histopathologic ulceration and blue-white veil as binary variables (present vs absent). Pigmentation, dermatoscopic ulceration, regression structures, vessels are expressed as percentages of feature extent in the lesion. Variables included in model 1: brown, red, white color, pigmentation, dermatoscopic ulceration, regression structures, angulated lines, blue-white veil, vessels. Significant variables included in last step of backward elimination are presented. Variables included in model 2: Breslow thickness, histopathologic ulceration. Variables included in model 3: Breslow thickness, histopathologic ulceration, pigmentation, dermatoscopic ulceration, regression structures, blue-white veil. All models were adjusted for age, sex and anatomic location.

Supplementary Table 7: Frequencies of clinical and histopathological characteristics of patients with early-stage melanoma according to training and test set

	Total sample (N=381)	Train set (N=306)	Test set (N=75)	p-value
Follow-up time (median, range) (months)	60 (37 – 83)	60 (37 – 79.5)	58 (39.5 - 86)	0.716
Events (n, %)				
Metastasis	79 (20.7)	66 (21.6)	13 (17.3)	0.417
Distant metastasis	63 (17.3)	51 (17.5)	12 (16.2)	0.799
Stage at diagnosis (n, %)				0.410
IB	227 (59.6)	181(59.1)	46 (61.3)	
IIA	66 (17.3)	55 (18)	11 (14.7)	
IIB	53 (13.9)	45 (14.7)	8 (10.7)	
IIC	35 (9.2)	25 (8.2)	10 (13.3)	
Age (mean, SD)	61.9 (16.9)	62.2 (17)	60.6 (16.7)	0.348
Sex (n, %)				0.613
Male	203 (53.3)	165 (53.9)	38 (50.7)	
Female	178 (46.7)	141 (46.1)	37 (49.3)	
Anatomic location (n, %)				0.725
Head and neck	69 (18.1)	53 (17.3)	16 (21.3)	
Trunk	127 (33.4)	99 (32.4)	28 (37.8)	
UE	59 (15.5)	49 (16)	10 (13.5)	
LE	85 (22.4)	72 (23.5)	13 (17.6)	
Acral	38 (10)	30 (9.8)	8 (10.8)	
Subungual	3 (0.8)	3 (1.0)	-	
Breslow thickness (mean, SD)	2.55 (3.4)	2.5 (2.8)	2.7 (3.62)	0.308
Histopathologic ulceration (n, %)	96 (25.5)	78 (25.7)	18 (24.3)	0.802
Mitosis (n, %)				0.794
Absent	67 (21.5)	51 (20.7)	16 (24.6)	
1-5/mm ²	160 (51.4)	128 (52)	32 (49.2)	
>5/mm ²	84 (27)	67 (27.2)	17 (26.2)	

N: number of patients, IQR: interquartile range, SD: standard deviation, UE: upper extremities, LE: lower extremities, n: number of patients included in the variable, SLNB: sentinel lymph node biopsy, CLND: complete lymph node dissection. Two-sided p values for continuous variables were obtained from the Mann-Whitney U test, as appropriate. Two-sided p-values for categorical variables were obtained from the Pearson's chi-squared test.

Supplementary Table 8: Frequencies of dermatoscopic criteria of patients with early-stage melanomas according to training and test set

	Total sample (N=381)	Train set (N=306)	Test set (N=75)	p-value
Pigmentation (n, %)				0.865
Absent	25 (6.6)	20 (6.5)	5 (6.7)	
25	46 (12.1)	37 (12.1)	9 (12)	
50	56 (14.7)	44 (14.4)	12 (16)	
75	102 (26.8)	79 (25.8)	23 (30.7)	
100	152 (39.9)	126 (41.2)	26 (34.7)	
Colors (n, %)				
Brown	326 (85.6)	261 (85.3)	65 (86.7)	0.762
Blue/gray	229 (60.1)	184 (60.1)	45 (60)	0.983
Red	204 (53.5)	162 (52.9)	42 (56)	0.634
White	203 (53.3)	162 (52.9)	41 (54.7)	0.788
Black	184 (48.3)	151 (49.3)	33 (44)	0.406
Dermatoscopic ulceration (n, %)				0.839
Absent	281 (73.8)	224 (73.2)	57 (76)	
1-49	70 (18.4)	58 (19)	12 (16)	
>50	30 (7.9)	24 (7.8)	6 (8)	
Regression structures (n, %)				0.728
Absent	249 (65.4)	201 (65.7)	48 (64)	
1-49	90 (23.6)	70 (22.9)	20 (26.7)	
>50	42 (11)	35 (11.4)	7 (9.3)	
White shiny streaks (n, %)	196 (51.4)	166 (54.2)	30 (40)	0.04
Blue-white veil (n, %)	179 (47)	150 (49)	29 (38.7)	0.105
Eccentric blotch (n, %)	140 (36.7)	115 (37.6)	25 (33.3)	0.494
Angulated lines (n, %)	18 (4.7)	14 (4.6)	4 (5.3)	0.782
Parallel ridge (n, %)	12 (3.1)	9 (2.9)	3 (4)	0.638
Vessels (n, %)				0.349
Absent	181 (47.5)	145 (47.4)	36 (48)	
1-49	108 (28.3)	91 (29.7)	17 (22.7)	
>50	92 (24.1)	70 (22.9)	22 (29.3)	

N: number of patients, IQR: interquartile range, SD: standard deviation, UE: upper extremities, LE: lower extremities, n: number of patients included in the variable, SLNB: sentinel lymph node biopsy, CLND: complete lymph node dissection. Pigmentation, dermatoscopic ulceration, regression structures, vessels are expressed as percentages of feature extent in the lesion. Two-sided p-values for categorical variables were obtained from the Pearson's chi-squared test.

Supplementary Table 9: AUC values for the prediction of RFS and DMFS after applying 5-fold cross validation in training set and independent validation in test set in early-stage patients with melanoma

	Model 1	Model 2	Model 3
	Recurrence-Free Survival (RFS)		
Training set			
Fold 1	0.745 (0.548 – 0.943)	0.636 (0.414 – 0.859)	0.752 (0.549 – 0.954)
Fold 2	0.717 (0.537 – 0.898)	0.726 (0.547 – 0.905)	0.779 (0.602 – 0.956)
Fold 3	0.926 (0.826 – 0.989)	0.902 (0.788 – 0.989)	0.941 (0.847 – 0.989)
Fold 4	0.756 (0.598 – 0.914)	0.709 (0.539 – 0.879)	0.776 (0.625 – 0.928)
Fold 5	0.828 (0.693 – 0.963)	0.709 (0.502 – 0.916)	0.824 (0.679 – 0.969)
Average from 5 folds	0.795 (0.721 – 0.868)	0.736 (0.650 – 0.823)	0.814 (0.764 – 0.892)
DeLong's test	<i>p</i> >0.05 (vs Model 2)	<i>p</i> >0.05 (vs Model 3)	<i>p</i> >0.05 (vs Model 1)
Test set			
	0.901 (0.811 – 0.971)	0.865 (0.734 – 0.947)	0.923 (0.823 – 0.975)
DeLong's test	<i>p</i> >0.05 (vs Model 2)	<i>p</i> >0.05 (vs Model 3)	<i>p</i> >0.05 (vs Model 1)
	Distant metastasis-free Survival (DMFS)		
Training set			
Fold 1	0.775 (0.536 – 0.989)	0.583 (0.328 – 0.838)	0.775 (0.532 – 0.988)
Fold 2	0.663 (0.439 – 0.887)	0.785 (0.611 – 0.959)	0.783 (0.584 – 0.982)
Fold 3	0.888 (0.75 – 0.988)	0.859 (0.712 – 0.988)	0.894 (0.775 – 0.987)
Fold 4	0.762 (0.593 – 0.932)	0.725 (0.534 – 0.916)	0.788 (0.623 – 0.952)
Fold 5	0.835 (0.704 – 0.967)	0.720 (0.528 – 0.912)	0.866 (0.645 – 0.987)
Average from 5 folds	0.785 (0.711 – 0.859)	0.735 (0.646 – 0.823)	0.821 (0.773 – 0.899)
DeLong's test	<i>p</i> >0.05 (vs Model 2)	<i>p</i> >0.05 (vs Model 3)	<i>p</i> >0.05 (vs Model 1)
Test set			
	0.860 (0.762 – 0.945)	0.810 (0.699 – 0.952)	0.869 (0.752 – 0.986)
DeLong's test	<i>p</i> >0.05 (vs Model 2)	<i>p</i> >0.05 (vs Model 3)	<i>p</i> >0.05 (vs Model 1)

AUC: area under curve, CI: confidence interval. Two-sided p-values derived from DeLong's test for the comparison of AUC values for training and test set.

Supplementary Table 10: Multivariable Cox regression for the prediction of RFS and DMFS based on dermatoscopic predictors and AJCC stage in patients with stage I-II melanoma (model 4)

	RFS [HR (95%CI)]	DMFS [HR (95%CI)]
	Multivariate	Multivariate
Pigmentation		
Absent	Ref.	Ref.
25	0.87 (0.36 – 2.10)	0.79 (0.28 – 2.23)
50	0.63 (0.24 – 1.61)	0.73 (0.25 – 2.11)
75	0.52 (0.19 – 1.35)	0.55 (0.18 – 1.64)
100	0.19 (0.07 – 0.53)	0.22 (0.06 – 0.68)
Dermatoscopic ulceration		
<i>Absent</i>	Ref.	Ref.
1-49	1.05 (0.59 – 1.89)	1.03 (0.54 – 1.94)
>50	1.95 (0.92 – 4.11)	1.49 (0.59 – 3.75)
Regression structures		
<i>Absent</i>	Ref.	Ref.
1-49	0.69 (0.38 – 1.26)	0.69 (0.35 – 1.34)
>50	0.38 (0.14 – 0.99)	0.25 (0.07 – 0.83)
Blue-white veil	4.38 (2.42 – 7.92)	4.19 (2.16 – 8.12)
AJCC Stage (8th edition)		
<i>IB</i>	Ref.	Ref.
<i>IIA</i>	1.85 (0.92 – 3.71)	2.33 (1.08 – 5.02)
<i>IIB</i>	1.87 (0.94 – 3.73)	2.40 (1.09 – 5.29)
<i>IIC</i>	3.39 (1.62 – 7.06)	4.71 (2.11 – 10.53)

HR: Hazard ratio, CI: confidence interval, Ref.: Reference level, RFS: recurrence-free survival, DMFS: distant metastasis-free survival, n.s: not significant. Pigmentation, dermatoscopic ulceration and regression structures, are expressed as percentages of feature extent in the lesion. Variables included in model 4: pigmentation, dermatoscopic ulceration, regression structures, blue-white veil, AJCC stage (4 categories). Model 4 was adjusted for age, sex and anatomic location.

Supplementary Table 11: AUC values with 95%CI for the prediction of RFS and DMFS in patients with early-stage melanoma based on model 4

	RFS	DMFS
Training set		
Fold 1	0.745 (0.544 – 0.947)	0.742 (0.497 – 0.987)
Fold 2	0.674 (0.471 – 0.877)	0.663 (0.429 – 0.897)
Fold 3	0.912 (0.787 – 0.987)	0.882 (0.745 – 0.989)
Fold 4	0.738 (0.574 – 0.902)	0.754 (0.580 – 0.928)
Fold 5	0.851 (0.712 – 0.989)	0.874 (0.759 – 0.989)
Average from 5 folds	0.784 (0.70 – 0.868)	0.783 (0.701 – 0.865)
Test set	0.903 (0.841 – 0.977)	0.848 (0.724 – 0.973)

AUC: area under curve, CI: confidence interval

Supplementary Table 12: Sensitivity analysis with exclusion of patients with acral and subungual anatomic location and the prediction of metastasis based on models 1,2,3

Metastasis prediction – Logistic regression			
	Model 1 (OR, 95%CI)	Model 2 (OR, 95%CI)	Model 3 (OR, 95%CI)
Breslow thickness (<i>Cont.</i>)	-	1.35 (1.21 – 1.53)	1.20 (1.08 – 1.36)
Histopathologic ulceration (<i>Present</i>)	-	2.86 (1.76 – 4.63)	2.06 (1.17 – 3.62)
Pigmentation			
<i>Absent</i>	Ref.	-	Ref.
25	0.83 (0.29 – 2.27)	-	0.77 (0.26 – 2.18)
50	0.43 (0.15 – 1.24)	-	0.49 (0.16 – 1.45)
75	0.11 (0.04 – 0.33)	-	0.16 (0.05 – 0.48)
100	0.06 (0.02 – 0.18)	-	0.09 (0.03 – 0.25)
Dermatoscopic Ulceration			
<i>Absent</i>	Ref.	-	Ref.
1-49	1.51 (0.86 – 2.63)	-	1.12 (0.61 – 2.01)
>50	4.70 (1.95 – 12.25)	-	2.36 (0.91 – 6.50)
Regression structures			
<i>Absent</i>	Ref.	-	Ref.
1-49	0.90 (0.51 – 1.58)	-	0.99 (0.55 – 1.79)
>50	0.46 (0.20 – 1.00)	-	0.43 (0.17 – 0.98)
Blue – white veil	7.47 (4.27 – 13.68)	-	6.49 (3.58 – 11.75)

N: number of patients, OR: Odds ratio, CI: confidence interval, Ref.: Reference level, Cont.: continuous. 448 patients included in the analysis. All models were adjusted for age, sex and anatomic location.

Supplementary Table 13: Sensitivity analysis with exclusion of patients with acral and subungual anatomic location and the prediction of RFS and DMFS based on model 1,2,3

Recurrence-Free Survival (RFS) – Cox regression			
	Model 1 (HR, 95%CI)	Model 2 (HR, 95%CI)	Model 3 (HR, 95%CI)
Pigmentation			
Absent	Ref.	-	Ref.
25	0.74 (0.27 – 2.03)	-	0.77 (0.28 – 2.09)
50	0.50 (0.17 – 1.50)	-	0.56 (0.18 – 1.71)
75	0.45 (0.14 – 1.38)	-	0.57 (0.18 – 1.82)
100	0.16 (0.05 – 0.50)	-	0.19 (0.06 – 0.59)
Dermatoscopic ulceration			
Absent	Ref.	-	Ref.
1-49	1.29 (0.71 – 2.35)	-	1.11 (0.59 – 2.08)
>50	3.84 (1.77 – 8.33)	-	2.66 (1.17 – 6.02)
Regression structures			
Absent	Ref.	-	Ref.
1-49	0.66 (0.35 – 1.24)	-	0.74 (0.39 – 1.42)
>50	0.41 (0.15 – 1.07)	-	0.40 (0.15 – 1.08)
Blue-white veil	4.53 (2.40 – 8.54)	-	4.39 (2.30 – 8.36)
Breslow thickness (Cont.)	-	1.09 (1.04 – 1.14)	1.08 (1.03 – 1.14)
Histopathologic ulceration (Present)	-	2.47 (1.47 – 4.14)	1.77 (0.99 – 3.18)
Distant metastasis-free Survival (DMFS) – Cox regression			
	Model 1 (HR, 95%CI)	Model 2 (HR, 95%CI)	Model 3 (HR, 95%CI)
Pigmentation			
Absent	Ref.	-	Ref.
25	0.66 (0.22 – 1.94)	-	0.70 (0.24 – 2.06)
50	0.44 (0.13 – 1.44)	-	0.49 (0.15 – 1.64)
75	0.34 (0.10 – 1.13)	-	0.46 (0.13 – 1.56)
100	0.14 (0.04 – 0.46)	-	0.17 (0.05 – 0.56)
Dermatoscopic ulceration			
Absent	Ref.	-	Ref.
1-49	1.51 (0.80 – 2.82)	-	1.36 (0.70 – 2.65)
>50	3.19 (1.18 – 8.60)	-	2.17 (0.70 – 6.14)
Regression structures			
Absent	Ref.	-	Ref.
1-49	0.77 (0.39 – 1.53)	-	0.80 (0.39 – 1.66)
>50	0.28 (0.08 – 0.95)	-	0.26 (0.07 – 0.94)
Blue-white veil	4.53 (2.67 – 9.08)	-	4.31 (2.12 – 8.75)
Breslow thickness (Cont.)	-	1.09 (1.04 – 1.15)	1.09 (1.03 – 1.15)
Histopathologic ulceration (Present)	-	2.53 (1.42 – 4.49)	1.78 (0.92 – 3.42)

HR: Hazard ratio, CI: confidence interval, Ref.: Reference level, RFS: recurrence-free survival, DMFS: distant metastasis free survival, Cont.: continuous. 340 patients included in the analysis. All models were adjusted for age, sex and anatomic location.

Supplementary Table 14: P-value adjustment for multiple comparisons in univariate regression analysis

	Logistic regression		RFS		DMFS	
	p-value	Holm Adjusted p-value	p-value	Holm Adjusted p-value	p-value	Holm Adjusted p-value
Pigmentation						
Absent	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25	0.54	<0.001	0.997	0.025	0.882	0.163
50	0.67	<0.001	0.924	0.025	0.754	0.163
75	<0.001	<0.001	0.10	0.025	0.20	0.163
100	<0.001	<0.001	0.002	0.025	0.01	0.163
Colors						
Brown	<0.001	0.001	0.008	0.008	0.007	0.07
Blue/gray	0.008	0.054	0.05	0.356	0.03	0.266
Red	<0.001	<0.001	0.003	0.003	0.007	0.007
White	<0.001	0.001	0.005	0.04	0.033	0.266
Black	0.025	0.129	0.06	0.39	0.196	0.421
Dermatoscopic ulceration						
Absent	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-49	<0.001	<0.001	0.006	<0.001	0.008	0.0013
>50	<0.001	<0.001	<0.001	<0.001	<0.001	0.0013
Regression structures						
Absent	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-49	0.22	0.127	0.361	0.396	0.453	0.351
>50	0.016	0.127	0.066	0.396	0.05	0.351
White shiny streaks	0.019	0.113	0.299	0.598	0.108	0.421
Blue-white veil	<0.001	<0.001	0.0001	0.001	0.0003	0.004
Eccentric blotch	0.154	0.332	0.324	0.598	0.232	0.421
Angulated lines	0.589	0.586	0.07	0.396	0.097	0.421
Parallel ridge	0.111	0.332	0.198	0.596	0.084	0.421
Vessels						
Absent	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-49	0.001	<0.001	0.025	0.024	0.029	0.077
>50	<0.001	<0.001	0.002	0.024	0.007	0.077

RFS: recurrence-free survival, DMFS: distant metastasis free survival, Ref.: Reference level. p value: unadjusted p value from univariate logistic regression for metastasis prediction and Cox regression for prediction of RFS and DMFS. Global raw p-value derive after the application of omnibus likelihood ratio test in univariate analysis for variables with multiple categories. For binary variables the predictor-level raw p-value is the Wald p-value. Holm adjusted p-value is obtained by applying Holm approach across predictors' raw p-values. Two-sided p-values are reported.

Supplementary Table 15: Frequencies of dermatoscopic features according to metastatic status at diagnosis

	Total (N=143)	Regional metastatic disease at diagnosis (n= 95)	Distant metastatic disease at diagnosis (n=48)	X ² -test (p-value)
Pigmentation (n, %)				0.405
Absent	17 (11.9)	9 (9.5)	8 (16.7)	
25	49 (34.3)	35 (36.8)	14 (29.2)	
50	35 (24.5)	26 (27.4)	9 (18.8)	
75	19 (13.3)	12 (12.6)	7 (14.6)	
100	23 (16.1)	13 (13.7)	10 (20.8)	
Colors (n, %)				
Brown	107 (74.8)	75 (78.9)	32 (66.7)	0.110
Blue/gray	100 (69.9)	68 (71.6)	32 (66.7)	0.545
Red	107 (74.8)	70 (73.7)	37 (77.1)	0.658
White	99 (69.2)	64 (67.4)	35 (72.9)	0.497
Black	63 (44.1)	39 (41.1)	24 (50)	0.309
Dermatoscopic ulceration (n, %)				0.607
Absent	71 (49.7)	47 (49.5)	24 (50)	
1-49	36 (25.2)	26 (27.4)	10 (20.8)	
>50	36 (25.2)	22 (23.2)	14 (29.2)	
Regression structures (n, %)				0.773
Absent	104 (72.7)	70 (73.7)	34 (70.8)	
1-49	30 (21)	20 (21.1)	10 (20.8)	
>50	9 (6.3)	5 (5.3)	4 (8.3)	
White shiny streaks (n, %)	89 (62.2)	60 (63.2)	29 (60.4)	0.749
Blue-white veil (n, %)	90 (62.9)	60 (63.2)	30 (62.5)	0.939
Eccentric blotch (n, %)	61 (42.7)	40 (42.1)	21 (43.8)	0.851
Angulated lines (n, %)	5 (3.5)	4 (4.2)	1 (2.1)	0.513
Parallel ridge (n, %)	20 (3.8)	8 (2.6)	12 (5.4)	0.104
Vessels (n, %)				0.02
Absent	42 (29.4)	26 (27.4)	16 (33.3)	
1-49	46 (32.2)	25 (26.3)	21 (43.8)	
>50	55 (38.5)	44 (46.3)	11 (22.9)	

n: number of patients, Two-sided p-values for categorical variables were obtained from the Pearson's chi-squared test. Pigmentation, dermatoscopic ulceration, regression structures, vessels are expressed as percentages of feature extent in the lesion.

Supplementary Table 16: Sensitivity analysis for the prediction of metastasis based on Model 1 and after exclusion of patients with metastasis at diagnosis

	OR	p-value	95%CI
Pigmentation			
<i>Absent</i>	Ref.		
25	0.57	0.346	0.17 – 1.83
50	0.38	0.112	0.11 – 1.25
75	0.13	<0.001	0.04 – 0.44
100	0.06	<0.001	0.02 – 0.21
Dermatoscopic Ulceration			
<i>Absent</i>	Ref.		
1-49	1.20	0.61	0.58 – 2.47
>50	2.85	0.04	1.05 – 7.75
Regression structures			
<i>Absent</i>	Ref.		
1-49	0.68	0.323	0.32 – 1.44
>50	0.35	0.06	0.12 – 1.07
Blue – white veil	6.34	<0.001	3.05 – 13.76

OR: Odds ratio, CI: confidence interval, Ref.: Reference level. Pigmentation, dermatoscopic ulceration and regression structures are expressed as percentages of feature extent in the lesion. Results from multivariable analysis and Model 1 was adjusted for age, sex and anatomic location. P-values were two-sided and obtained from Wald tests. Exact p-values are provided for 75% pigmentation ($p=8.52 \times 10^{-4}$), 100% pigmentation ($p=2.73 \times 10^{-6}$) and blue-white veil ($p=1.55 \times 10^{-6}$). Multiple comparisons adjustment was not applied.

Supplementary Table 17: Sensitivity analysis for the prediction of metastasis based on Model 1 after adjustment for histopathologic subtype of the primary tumor

	OR	p-value	95%CI
Pigmentation			
<i>Absent</i>	Ref.		
25	1.01	0.984	0.34 – 3.58
50	0.43	0.100	0.17 – 2.16
75	0.14	<0.001	0.04 – 0.30
100	0.07	<0.001	0.03 – 0.19
Dermatoscopic Ulceration			
<i>Absent</i>	Ref.		
1-49	1.38	0.168	0.84 – 2.79
>50	3.22	0.016	1.34 – 8.38
Regression structures			
<i>Absent</i>	Ref.		
1-49	0.81	0.193	0.42 – 1.67
>50	0.44	0.025	0.14 – 0.81
Blue – white veil	5.90	<0.001	3.06 – 12.68

OR: Odds ratio, CI: confidence interval, Ref.: Reference level. Pigmentation, dermatoscopic ulceration and regression structures are expressed as percentages of feature extent in the lesion. Results from last step of multivariable analysis after backward elimination was provided and Model 1 was adjusted for age, sex, anatomic location and histopathologic subtype of the primary tumor. 291 patients had available data about histopathologic subtype. P-values were two-sided and obtained from Wald tests. Exact p-values are provided for pigmentation 75% ($p=1.30 \times 10^{-4}$), pigmentation 100% ($p=1.62 \times 10^{-8}$) and blue-white veil ($p=9.86 \times 10^{-7}$).

Supplementary Table 18: Subgroup analyses for the prediction of metastasis using model 1 and based on clinically relevant Breslow thickness thresholds in the total cohort

Metastasis prediction – Full dataset						
	BT<1mm (n=96)		BT<2mm (n=295)		BT>2mm (n=229)	
	OR	95%CI	OR	95%CI	OR	95%CI
Pigmentation						
<i>Absent</i>	Ref.		Ref.			
25	Inf.	Inf.	0.80	0.17 – 3.60	1.18	0.39 – 3.53
50	0.30	0.004-22.9	0.48	0.11 – 2.02	0.59	0.17 – 2.04
75	0.01	0.001 – 0.89	0.13	0.03 – 0.56	0.18	0.05 – 0.66
100	Inf.	Inf.	0.07	0.01 – 0.29	0.13	0.03 – 0.48
Dermatoscopic Ulceration						
<i>Absent</i>	Ref.		Ref.			
1-49	Inf.	Inf.	1.43	0.59 – 3.44	0.73	0.35 – 1.52
>50	Inf.	Inf.	9.76	1.30 – 73.14	1.41	0.55 – 3.61
Regression structures						
<i>Absent</i>	Ref.		Ref.		Ref.	
1-49	0.16	0.01 – 1.87	0.82	0.38 – 1.76	0.73	0.32 – 1.68
>50	0.64	0.05 – 7.43	0.56	0.18 – 1.73	0.30	0.10 – 0.91
Blue – white veil (<i>Present</i>)	8.39	1.38 – 50.86	4.10	2.03 – 8.35	8.06	3.37 – 19.25

n=number of patients, Ref.: Reference level, OR: Odds Ratio, CI: Confidence Interval, Inf.: Infinite, BT: Breslow thickness. Pigmentation, dermatoscopic ulceration and regression structures are expressed as percentages of feature extent in the lesion. Model 1 was adjusted for age, sex and anatomic location.

Supplementary Table 19: Subgroup analyses for the prediction RFS and DMFS using model 1 and based on clinically relevant Breslow thickness thresholds in patients with early-stage melanomas

Recurrence – Free Survival (RFS)						
	BT<1mm (n=82)		BT<2mm (n=254)		BT>2mm (n=127)	
	HR	95%CI	HR	95%CI	HR	95%CI
Pigmentation						
<i>Absent</i>	Ref.		Ref.		Ref.	
25	Inf.	Inf.	0.48	0.07 – 3.05	0.78	0.27 – 2.20
50	Inf.	Inf.	0.24	0.03 – 1.74	0.76	0.24 – 2.35
75	Inf.	Inf.	0.26	0.04 – 1.61	0.57	0.17 – 1.89
100	Inf.	Inf.	0.11	0.01 – 0.69	0.17	0.04 – 0.65
Dermatoscopic Ulceration						
<i>Absent</i>	Ref.		Ref.			
1-49	Inf.	Inf.	1.45	0.39 – 5.35	0.87	0.44 – 1.71
>50	Inf.	Inf.	14.97	3.49 – 64.17	1.37	0.58 – 3.21
Regression structures						
<i>Absent</i>	Ref.		Ref.		Ref.	
1-49	Inf.	Inf.	0.68	0.26 – 1.78	0.45	0.19 – 1.03
>50	Inf.	Inf.	0.53	0.11 – 2.49	0.26	0.07 – 0.89
Blue – white veil (Present)	Inf.	Inf.	2.59	1.01 – 6.72	4.76	2.08 – 10.93
Distant metastasis-free survival (DMFS)						
Pigmentation						
<i>Absent</i>	Ref.		Ref.		Ref.	
25	Inf.	Inf.	0.55	0.81 – 3.76	0.81	0.25 – 2.75
50	Inf.	Inf.	0.19	0.02 – 1.66	0.98	0.27 – 3.55
75	Inf.	Inf.	0.16	0.02 – 1.23	0.71	0.18 – 2.75
100	Inf.	Inf.	0.09	0.01 – 0.61	0.24	0.05 – 1.05
Dermatoscopic Ulceration						
<i>Absent</i>	Ref.		Ref.		Ref.	
1-49	Inf.	Inf.	1.45	0.30 – 7.03	0.86	0.41 – 1.79
>50	Inf.	Inf.	Inf.	Inf.	1.06	0.37 – 3.03
Regression structures						
<i>Absent</i>	Ref.		Ref.		Ref.	
1-49	Inf.	Inf.	0.93	0.29 – 2.96	0.50	0.21 – 1.18
>50	Inf.	Inf.	0.36	0.04 – 3.07	0.20	0.04 – 0.83
Blue – white veil (Present)	Inf.	Inf.	3.03	0.97 – 9.48	4.26	1.74 – 10.46

n=number of patients, Ref.: Reference level, HR: Hazard Ratio, CI: Confidence Interval, Inf.: Infinitive, BT: Breslow thickness. Model 1 was adjusted for age, sex and anatomic location.

Supplementary Table 20: Demographic characteristics and institutions of evaluators who participated in lesions evaluation.

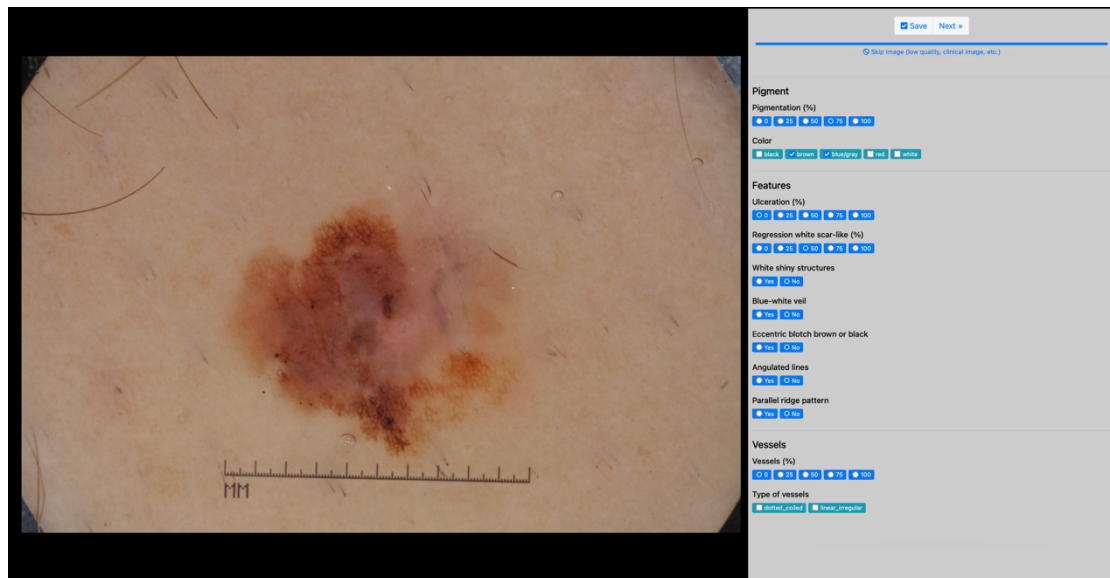
No of evaluators	Age (median, range)	Sex (n, %)	Years of experience in dermatoscopy (median, range)	Institutions of evaluators
30	52 (29 – 70)	M: 18 (60%) F: 12 (40%)	19 (2 – 35)	5 Europe, 2 South America, 1 Asia, 1 USA, 2 Australia

n: number of readers participated in image evaluation

Supplementary Table 21: Description of dermatoscopic criteria included in the analysis

Dermatoscopic criteria	Type of variable	Possible values of the variable
Grade of pigmentation	Ordinal	0, 25, 50, 75, 100
Ulceration	Ordinal	0, 25, 50, 75, 100
Regression structures	Ordinal	0, 25, 50, 75, 100
Extension of vascularity	Ordinal	0, 25, 50, 75, 100
Type of vessels	Categorical	Absent, Dotted/Coiled, Linear/Irregular
Brown color	Binary	Present / Absent
Blue/gray color	Binary	Present / Absent
Red color	Binary	Present / Absent
White color	Binary	Present / Absent
White color	Binary	Present / Absent
White shiny streaks	Binary	Present / Absent
Blue-white veil	Binary	Present / Absent
Eccentric blotch	Binary	Present / Absent
Angulated lines	Binary	Present / Absent
Parallel ridge	Binary	Present / Absent

Supplementary Figures



Supp. Figure 1: Example of the questionnaire and the web-based interface for lesion evaluation.