

The Hunt for Baby Melanomas: A Prospective Study of the Dermoscopy Features on 100 Small Melanoma Cases with *in Vivo* Surface Diameters up to a Maximum of 6 mm

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ABSTRACT **Introduction:** Early diagnosis can improve melanoma prognosis. Dermoscopy can enhance early melanoma recognition.

Objectives: Examine the dermoscopy features of early melanoma up to a maximum surface diameter of 6 mm.

Methods: Consecutive melanoma cases were collected from two medical practices in Sydney, Australia 2019-2021. Dermoscopy features were recorded for melanomas by maximum surface diameter, to the nearest 0.1 mm, to a limit of 6 mm.

Results: Total cases numbered 100; with males (N = 48) and females (N = 52), melanoma in situ (MIS, N = 96) and invasive (N = 4). The most frequent anatomic sites on both males and females were back (males N = 20, females N = 16) then knee or leg (males N = 8, females N = 12). Minimum respective MIS diameters for males/females was 1.2/2.0 mm and for invasive cases 2.0/3.4 mm. Highest frequency dermoscopy features were: light brown, dark brown, gray and asymmetric melanoma shape. Brown pigment in hair follicles were more frequent on legs compared to other anatomic sites (odds ratio [OR] 14.6; 95% CI 1.29-165.17, P 0.03). Pseudopods were substantially increased in frequency comparing diameters less than 4 mm with 4 up to 6 mm (OR 8.81; 95% CI 1.05-73.9, P 0.004). Structureless area cases recorded increased gray (OR 7.08; 95% CI 1.61-31.11, P=0.01).

Melanomas with edge angulation were noted in 20%-50% of cases across diameters 1-6 mm, less frequent were pigmented circles and polygons.

Conclusions: Watch out! MIS presented with a surface diameter of just 1.2 mm and invasive melanoma 2.5 mm. Pseudopods were a strong clue to melanomas with a surface diameter less than 5mm. We found melanomas on leg sites displayed more frequent pigmented hair follicles.

Introduction

Primary cutaneous melanoma prognosis is optimal when early diagnosis leads to prompt effective intervention. However, small diameter early melanoma cases are often feature poor and may be difficult to recognize. The use of dermoscopy has been shown to enhance diagnostic accuracy for melanoma [1-3]. Some recent publications have addressed the dermoscopy features of small early melanoma [4,5]. Additional evidence collated with the dermoscopy features of smaller melanomas may facilitate diagnosing these early cases [6].

Recent commentary has questioned the value of diagnosing melanoma with small diameters and suggested suspicious pigmented lesions not be biopsied if less than 6mm diameter [7].

Objectives

The main purpose of this study was to quantify the dermoscopy features of melanoma cases with an in vivo maximum horizontal diameter of up to and including 6 mm. A second aim was to record how these dermoscopy features varied by the surface diameters in 1mm increments for melanomas presenting with a surface diameter of 6 mm or less.

Methods

Consecutive melanoma cases were prospectively collected from routine workflow in 2 medical practices in Sydney, Australia over 28 months from 2019 until 2021. One practice was a referral practice with Vivascope 1500 confocal capability. The second practice was a primary care designated skin cancer clinic. Ethics Approval was provided by the University of Queensland, Brisbane Australia (2016001221). All patients in the study provided informed consent for their data to enter the study. There were no exclusions based on patient age or anatomic site.

Dermoscopy using either a Heine IC1 or VivaCam dermatoscope recorded each case in vivo maximum horizontal diameter, measured in 0.1 mm increments, up to and including 6.0 mm. Cases with a maximum surface diameter 6.1mm

or greater were excluded. Cases with known previous topical or ablative therapies, any previous partial biopsy or adjacent scars were also excluded. Each case was an attempted full excision with a 2mm dermoscopy identified margin. A dermoscopy image for each case was submitted along with each tissue specimen to the reporting pathologists. Further, representative Vivascope 1500 confocal images were also available to the reporting pathologists for difficult to diagnose cases.

Excised tissue was examined routinely with hematoxylin and eosin staining followed with SOX 10 and PRAME stains if required. Inclusion of each case required an independent histopathological diagnosis of melanoma from each of two experienced dermato-histopathologists. Cases where only one of two dermato-histopathologists reported melanoma were also excluded.

Atypical vessels were defined as dermoscopy identified vessels within the melanoma "footprint" displaying a different morphology or increased number of vessels per unit area compared to vessels in the adjacent background skin out to 10 mm from the edge of the melanoma, an example is displayed in Figure 5B. Asymmetric shape relates to the silhouette of the melanoma. Atypical network was defined when the width of lines forming a reticular brown network exceeded the diameter of the adjacent dermal papillae, see Figure 5C. Polygons were angular lines in polygonal shapes [8], see Figure 6B. Structureless areas displayed no distinct features within the area concerned and had to occupy at least 20% of the melanoma "footprint", see Figure 5A.

Results

All cases presented as macules with no overt surface elevation. Patients had predominately northern European ancestry with fair skin and were typically Australian born. Following histopathologic diagnostic confirmation, a total of 100 melanoma cases were collected. Cases on males numbered 48 (mean age 56) and on females 52 (mean age also 56), see Table 1. Study cases by anatomic site and sex are set out in Table 2. No cases were recorded on the following sites on either sex: scalp, eyelid, chin, cutaneous or mucosal lip, hand, fingers or toes. Females had an increased frequency of

Table 1. Patient characteristics by sex and in vivo melanoma surface diameter.

		Male (N = 48)	Female (N = 52)
Age (years)	Range (min, max)	18-78	29-90
	Mean	56	56
	IQR	45-66	42-69
Diameter of lesion (mm)	< 2.0	5	0
	2.0-3.0	13	15
	3.1-4.0	8	13
	4.1-5.0	13	16
	5.1-6.0	9	8

IQR = interquartile range.

Table 2. Number of melanoma cases by sex and anatomic site.

Anatomic Site	Male (N = 48)	Female (N = 52)
Ear	1	2
Forehead	1	0
Nose	1	0
Neck	1	1
Chest	6	6
Back	20 (1 invasive 0.5 mm)	16
Upper arm	2	8 (1 invasive 0.4 mm)
Forearm	3	3
Abdomen	2 (1 invasive 0.5 mm)	0
Thigh	2 (1 invasive 0.4 mm)	3
Knee or leg	8	12
Foot	1	1

Number of melanoma cases by sex and anatomic site. All cases were melanoma in situ except four invasive cases. These 4 invasive cases are identified by site and respective Breslow invasion depth.

melanomas on the upper arm compared to males: odds ratio [OR] 4.16, 95% CI 0.836-20.7, P 0.08. For knee combined with leg sites females also had more melanomas compared to males: OR 1.49, 95% CI 0.545- 4.05, P 0.44. Males recorded more melanomas on the back compared to females: OR 1.61, 95% CI 0.707-3.67, P 0.26. However, none of these anatomic site differences reached statistical significance.

Melanoma in situ was reported in 96 cases. The average surface diameter for the melanoma in situ cases was 3.9 mm (N = 96) and for the invasive melanoma cases 3.6 mm (N = 4). On males the smallest recorded surface diameter for a melanoma in situ case was 1.2 mm (chest) and for invasive cases 2.5 mm (back). In comparison, on females the smallest diameter melanoma in situ case was 2.0 mm (thigh) and the single invasive case 3.4 mm (upper arm). Three invasive melanoma cases were recorded on males: one with a Breslow of 0.4 mm (thigh) the other two cases both had a Breslow of 0.5 mm (abdomen and back), again see Table 2. Only one

male case recorded a mitotic count: 1 per mm² from the case on the back. The only invasive melanoma on a female was on the upper arm with a Breslow of 0.4 mm and 0 mitotic count. There was no microscopic evidence of tumor induced ulceration on all four invasive cases. No cases of acral, nodular or desmoplastic melanoma were recorded in this study.

When using dermoscopy the colors identified within the melanoma with the highest percentage presence in descending order were: light brown, dark brown and gray, see Figure 1. Figure 1 also displays these dermoscopy features with a typical frequency range from 50% up to 100% across the recorded range of diameters. In comparison, other dermoscopy identified features with moderate prevalence (frequency of feature from 15% up to 50%) are set out in Figure 2. Lower prevalence features (frequency at or below 25% of cases) are displayed in Figure 4. Although low in frequency, typically less than 10% of cases, polygons were recorded in cases over 2 mm diameter.

All colors identified (light and dark brown, gray and pink) within the melanoma rose in frequency as the diameters increased from 1 to 6 mm, again see Figure 1. The exception to this rise in frequency of color was black which had frequencies 20% to 40% over the full range of diameters, see Figure 2. Other dermoscopy features also increased in frequency as diameters increased: asymmetric melanoma shape (30 to 65%), atypical network (20 to 57%), grey circles (0 to 25%) and polygons (0 to 12%). Atypical vessels fell from 20 to zero then increased to 12%. Angles at the edge of the melanoma increased then decreased with an overall range of frequencies from 20% to 47%.

A striking finding in this study was how focal pseudopods (11% of all cases, N = 11/100) can facilitate very small diameter melanoma recognition, see Figure 3. When comparing smaller melanomas with a surface diameter less than 4.0 mm to larger diameter 4.0 to 6.0 mm inclusive cases the presence of pseudopods was substantially increased (OR 8.81, 95% CI 1.05-73.9, P 0.004). Brown pigment within hair follicle infundibula were recorded in a total of eight cases (8%, 8/100). On the leg (3 out of these 8 cases) pigment in follicles were more frequent compared to other sites (OR 14.6, 95% CI 1.29-165.17, P 0.03). Pink occurred more frequently on non-leg sites (N = 40) out of all other sites combined (N = 43), OR 4.72, 95% CI 1.22-18.2,

P 0.02. Finally, structureless areas were associated with an increased presence of gray within the whole melanoma “footprint” (OR 7.08, 95% CI 1.61-31.11, P 0.01).

Conclusions

Nearly all cases in this study were detected by pattern analysis involving attention to features dominated by melanin pigment. Predominant color pink with scant minimum brown was observed in only one case. There were no cases displaying all pink without brown. There may be a selection bias favoring brown pigment cases. Amelanotic melanoma cases: those without clinical or dermoscopy evidence of brown pigment, may be underrepresented.

We integrated and combined all the relevant clinical, dermoscopy and confocal features to facilitate diagnosis as previously described to minimize the risk of missing a melanoma [9]. In equivocal cases all relevant information was readily available to the reporting histopathologists. This may have increased our diagnostic “pick up” rate compared to other studies.

We found very similar mean surface diameters for melanoma in situ (3.9 mm) and invasive melanoma (3.6 mm). Previous studies have reported melanoma in situ and invasive melanomas with diameters up to and including 3 mm [10],

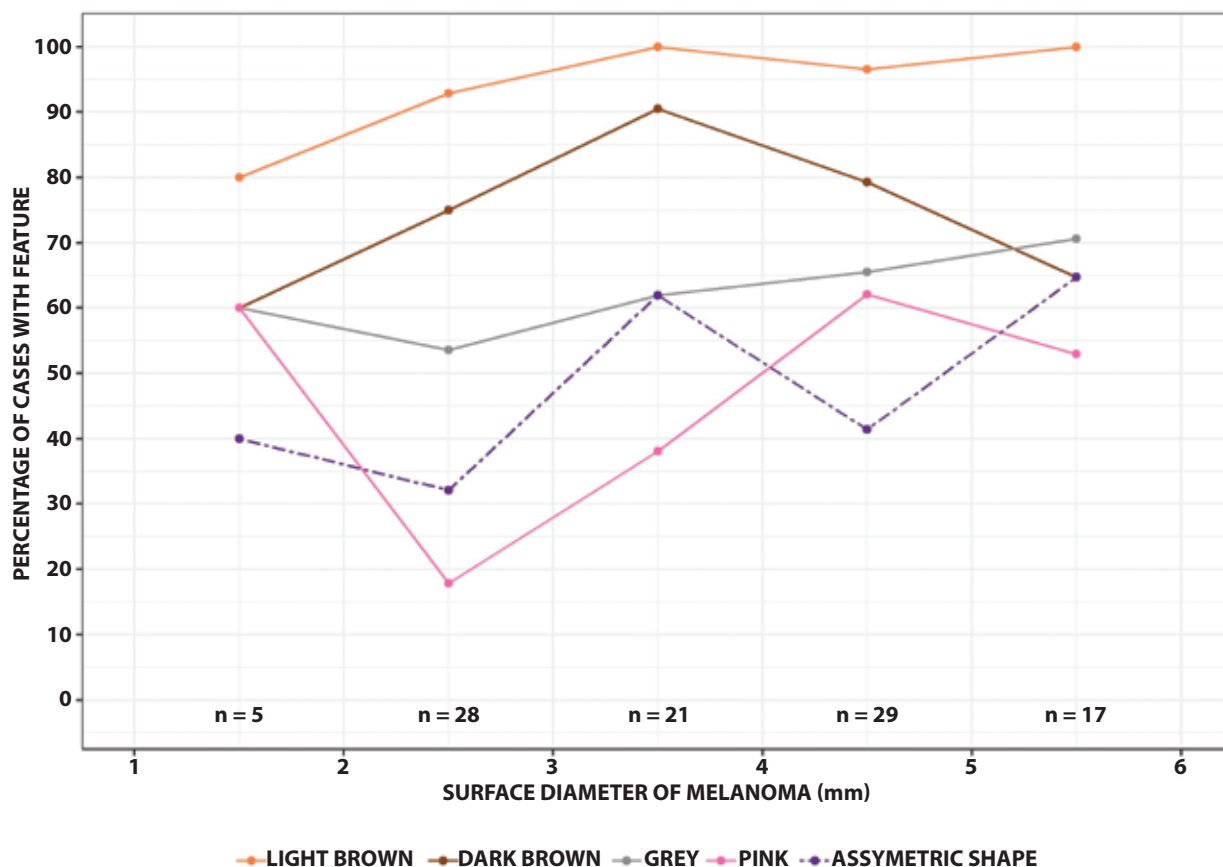


Figure 1. Dermoscopy features with high prevalence by in vivo melanoma surface diameter.

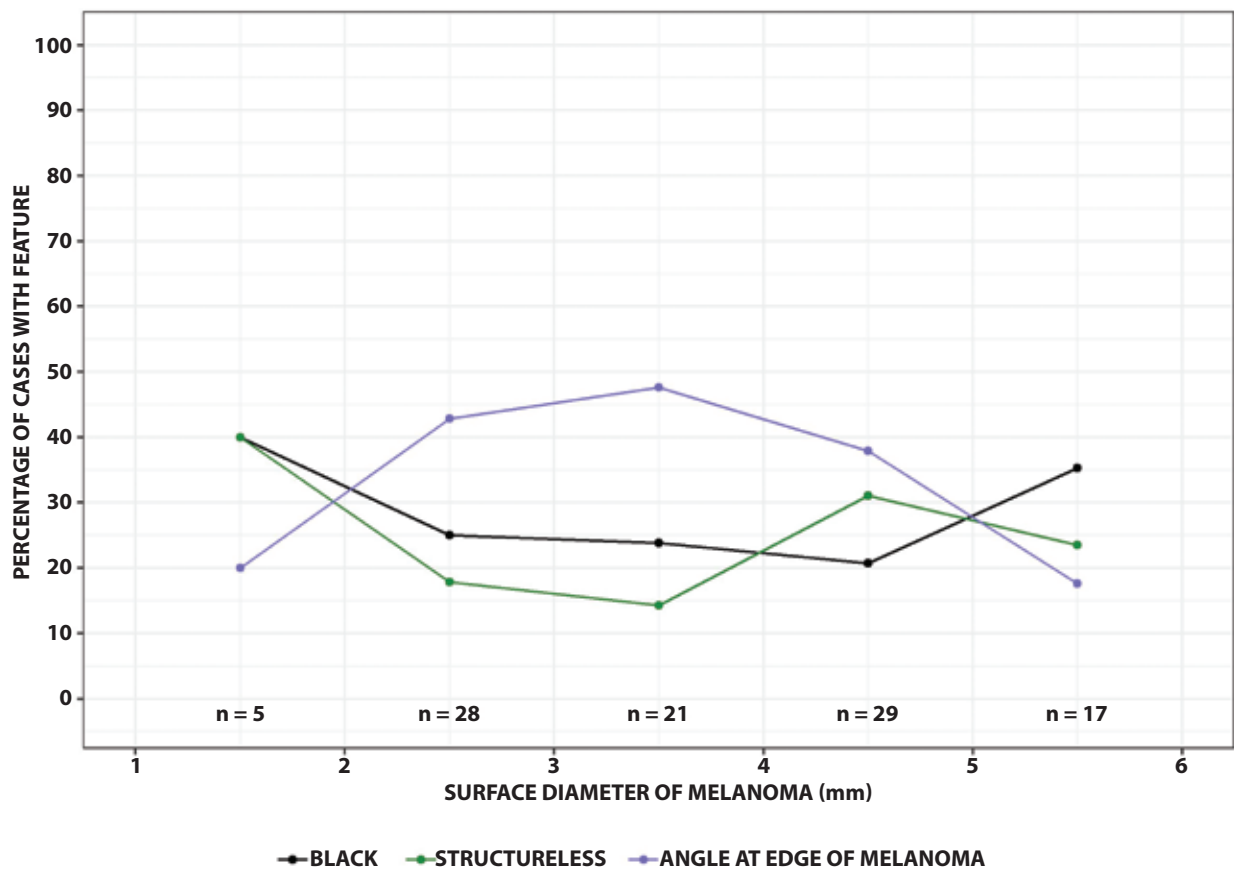


Figure 2. Dermoscopy features with moderate prevalence by in vivo melanoma surface diameter.

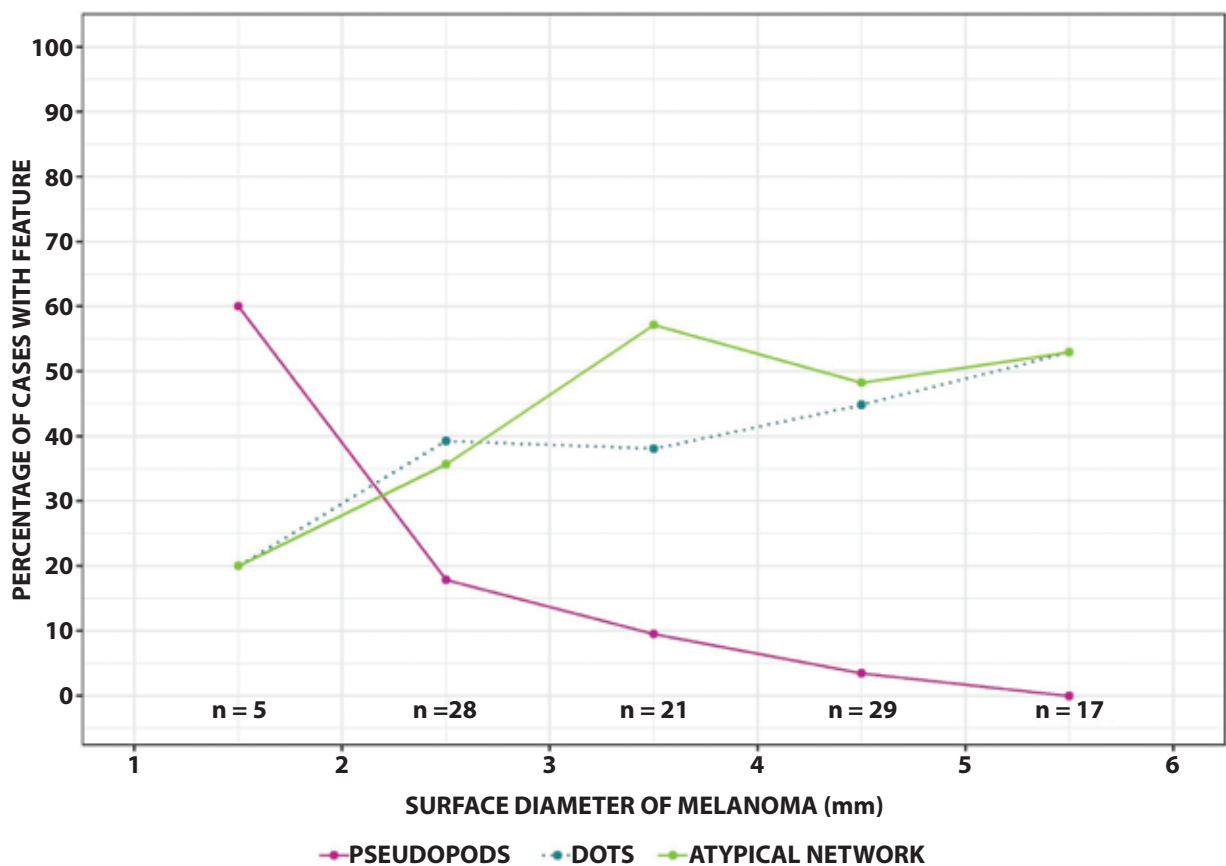


Figure 3. Dermoscopy features with progressive variation in prevalence by in vivo melanoma surface diameter.

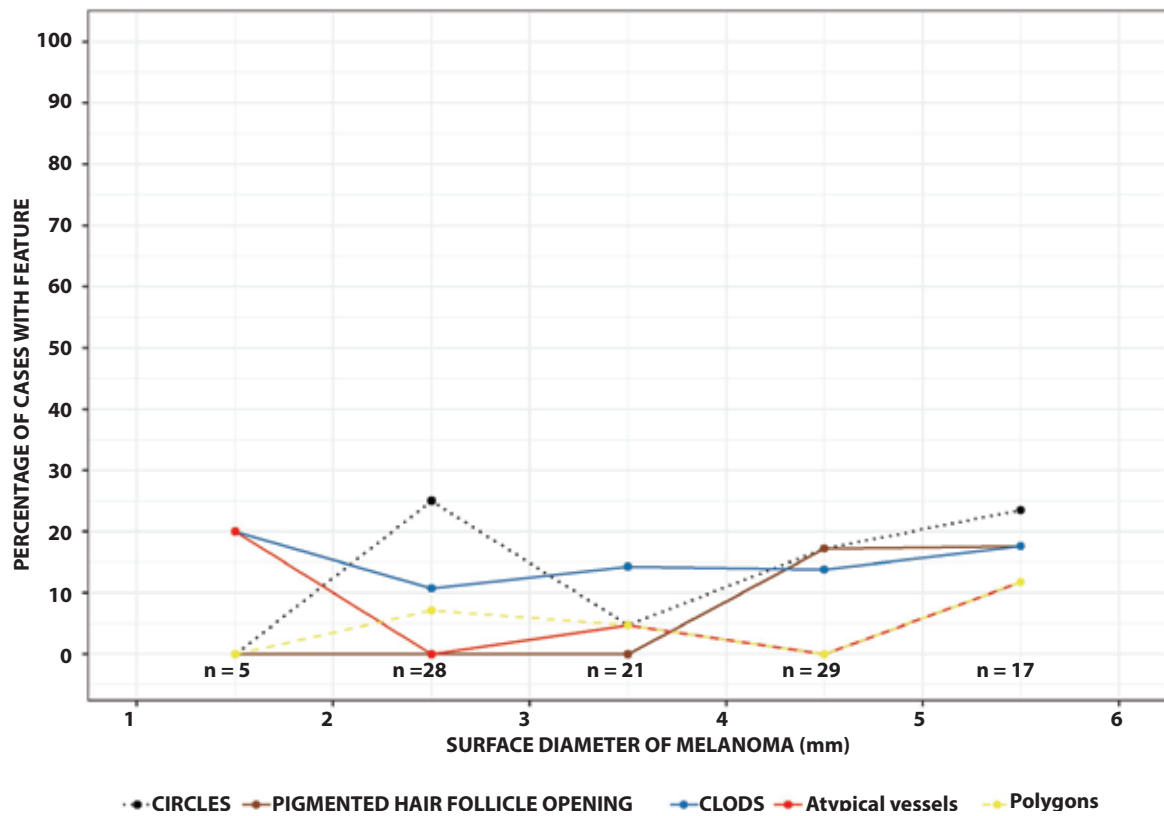


Figure 4. Dermoscopy features of melanoma with low prevalence over all surface diameters.

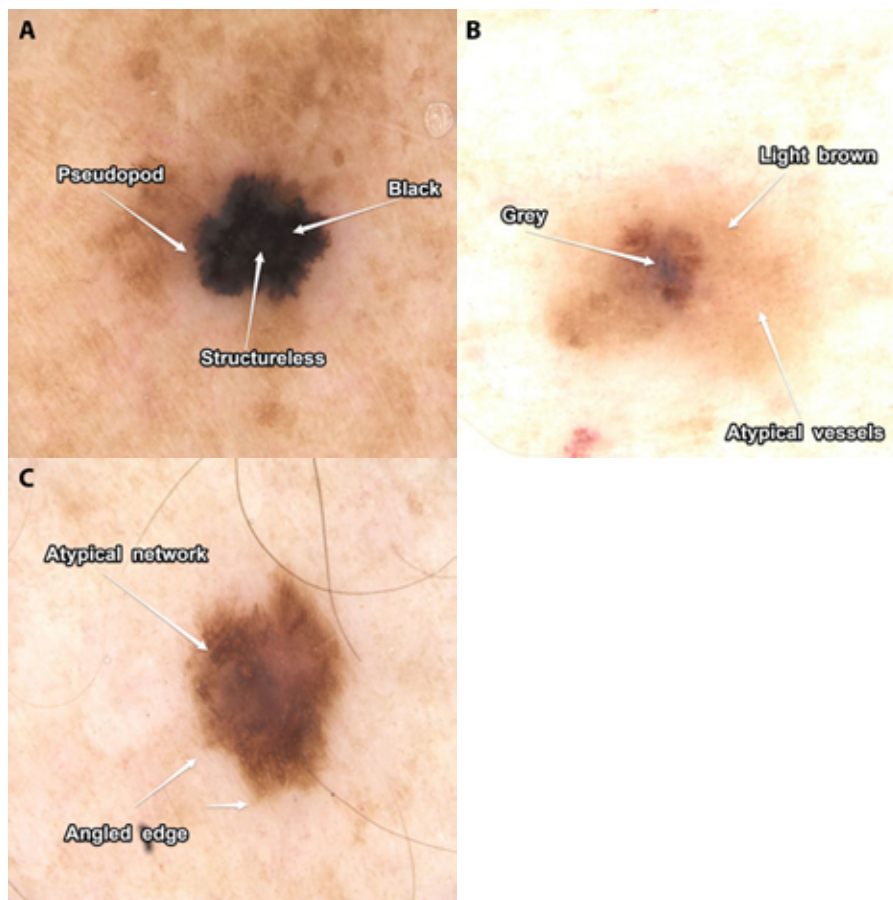


Figure 5. (ABC) Displaying pseudopods, structureless area, atypical vessels, atypical network and angular edge of melanoma.

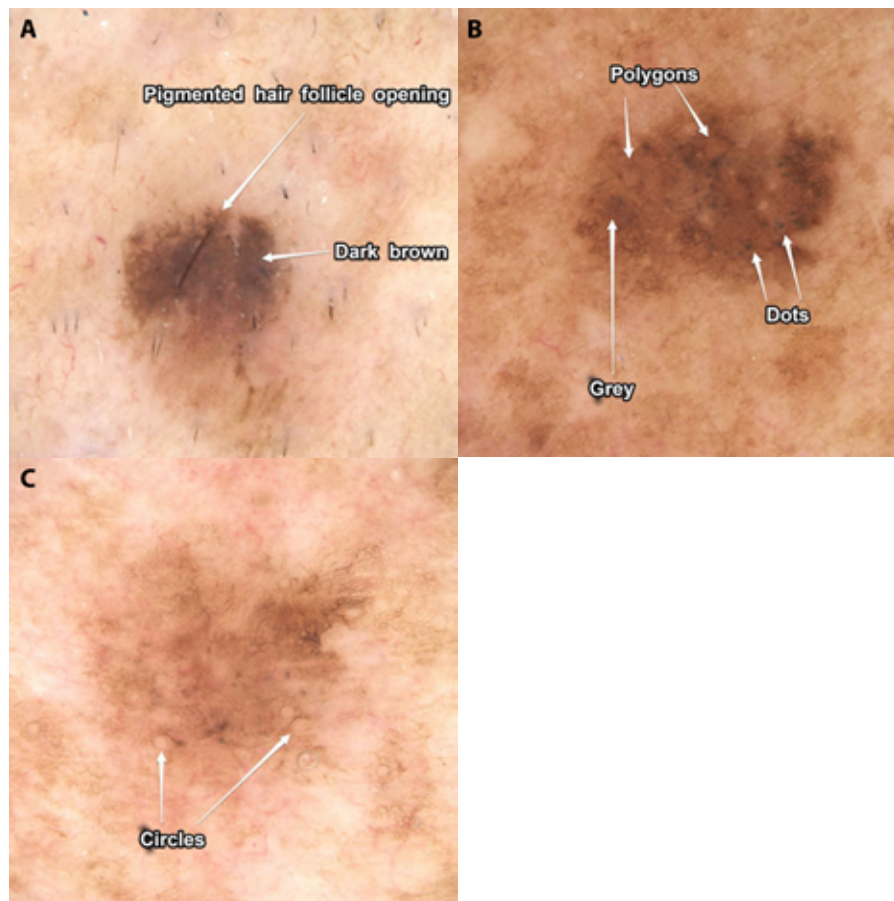


Figure 6. (ABC) Displaying pigmented hair follicular opening, polygons and circles.

(N = 23, invasive cases N = 19). These findings sound a warning to both clinicians and pathologists that macules with an in vivo diameter of 6 mm or even substantially less require vigilance for melanoma diagnosis and even early metastatic potential. Only 5 of our cases had a maximum surface diameter less than 2 mm. Except for the presence of pseudopods the lack of distinctive features in these very small cases may account for such a low detection rate.

A dermoscopy image of each case was submitted to the reporting Pathologists at the same time as the tissue submission. Confocal microscopy images were also available to enhance diagnostic certainty for some cases as this has been demonstrated [11]. Future investigation could quantify the contribution of this additional information in small size cases compared to just examining the histology slides and the routine notes supplied by the clinician on the pathology request documentation.

One explanation of brown pigment within a hair follicle infundibulum is melanocytes producing melanin at this site. We found melanomas in our study with a diameter three mm or less did not display brown pigment in hair follicle infundibula. Pigment was found in larger melanomas with diameters over 3 mm, see Figure 3. This finding suggests melanin producing melanocytes spread down into the infundibula

later in development rather than originating or appearing up out of infundibula in earlier stage development.

Our finding increased grey associated with structureless areas in the melanoma may indicate increased melanin at the level of the papillary dermis following a host immune response. This finding could be substantiated with further investigation. Atypical vessels noted in this study were typically an increase in dot vessels per unit area within the melanoma. These dot vessels may represent increased perfusion in the superficial dermal vessels as previously described [12] rather than true tumor induced neovascularization.

Clinicians and pathologists need to be vigilant with small suspicious cases displaying melanoma associated features presenting with diameters much less than 6 mm. We found the lowest recognition threshold diameter for melanoma in situ was 1.2 mm and for invasive melanomas 2.5 mm.

In descending order, we found the following colors present in melanomas with a maximum surface diameter up to 6 mm: light brown, dark brown, grey, pink then black. Other dermoscopy features which were clues to these small early melanomas include: asymmetric macule shape, angulation on the edge of the melanoma, pseudopods, pigmented follicular infundibula, structureless areas, atypical network and pigmented circles.

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