The clinical and dermoscopic features of invasive cutaneous squamous cell carcinoma depend on the histopathological grade of differentiation

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Summary

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Conflicts of interest
None.

Background Little is known about the variability of the dermoscopic criteria of squamous cell carcinoma (SCC) according to the histopathological differentiation grade.

Objectives To evaluate whether specific dermoscopic criteria can predict the diagnosis of poorly differentiated SCC compared with well- and moderately differentiated SCC.

Methods Clinical and dermoscopic images of SCCs were retrospectively evaluated for the presence of predefined criteria. Univariate and adjusted odds ratios were calculated. Discriminant functions were used to plot receiver–operator characteristic curves.

Results Of 143 SCCs included, 48 (33·5%) were well differentiated, 45 (31·5%) were moderately differentiated and 50 (35·0%) were poorly differentiated. Flat tumours had a fourfold increased probability of being poorly differentiated. Dermoscopically, the presence of a predominantly red colour posed a 13-fold possibility of poor differentiation, whereas a predominantly white and white–yellow colour decreased the odds of poorly differentiated SCC by 97% each. The presence of vessels in more than 50% of the tumour's surface, a diffuse distribution of vessels and bleeding were significantly associated with poor differentiation, while scale/keratin was a potent predictor of well- or moderately differentiated tumours.

Conclusions Dermoscopy may be regarded as a reliable preoperative tool to distinguish poorly from well- and moderately differentiated SCC. Given that poor differentiation of SCC represents an independent risk factor for recurrence, metastasis and disease-specific death, identifying poorly differentiated tumours *in vivo* may enhance their appropriate management.

What's already known about this topic?

- While the dermoscopic criteria of squamous cell carcinoma (SCC) have been well described, little is currently known about the variability of these criteria with respect to the histopathological grade of differentiation in SCC.

What does this study add?

- Poorly differentiated SCC is dermoscopically typified by a predominantly red colour, attributed to the presence of bleeding and/or dense vascularity.
- Identifying poorly differentiated tumours *in vivo* may enhance their appropriate management.

Cutaneous squamous cell carcinoma (SCC) is the second most common skin cancer, with a rising incidence over recent decades.[1] Only about 2% of SCCs are lethal, while the majority of SCCs have a generally favourable prognosis.[2] However, SCC can cause significant morbidity. This is because the majority of tumours arise on the head/neck area, where surgery for advanced tumours may be disfiguring and clear margins difficult to obtain. The recurrence rate of SCC after surgery has been reported to range from 3·5% to 28·0%.[3]

The risk of recurrence depends on the patient's immune efficiency. It also depends on factors related to the tumour, including body site, tumour size, invasion into the subcutaneous tissue, perineural involvement and the grade of histopathological differentiation.[4] Poor differentiation represents an independent risk factor for recurrence, metastasis and disease-specific death.[5,6] In contrast, well-differentiated SCC is associated with a 5-year recurrence-free survival rate of 83%.[7]

Despite the medical problems related to the cure of recurrent SCC, it also places a significant economic burden on the healthcare system. The treatment of skin cancer has been shown to rank fifth among the most expensive cancers to treat.[8]

Therefore, diagnosis of SCC at a highly curable stage, and risk assessment for recurrence, appear critical to reducing morbidity, mortality and its related costs. Recent guidelines suggest that the management of high-risk SCC, including poorly differentiated tumours, should be as early and aggressive as possible, with Mohs surgery considered the optimal choice.[9,10]

There is mounting evidence that dermoscopy improves early diagnosis of skin cancer compared with the unaided eye. Dermoscopic criteria have been described for SCC, including keratin, scale, blood spots, white circles, white structure-less zones and perivascular white halos.[11,12] Keratin and white circles reached a diagnostic sensitivity and specificity for SCC of 79% and 87%, respectively.[11]

However, while the dermoscopic criteria of SCC have been well described, little is currently known about the variability of these criteria with respect to the histopathological grade of differentiation. The purpose of this study was to evaluate whether specific dermoscopic criteria can predict the diagnosis of poorly differentiated SCC.

Materials and methods

This was a retrospective study conducted at three dermatology clinics: one in Australia, one in Chile and one in Italy. Ethical approval for the study was obtained from the University of Queensland, Australia. Patients recorded in our databases were screened for their eligibility to be included in the study.

Inclusion criteria were a clinical and dermoscopic image of SCC with a definite histological diagnosis, including grade of differentiation. We first searched for tumours with poor differentiation fulfilling the inclusion criteria. Subsequently, in order to obtain comparable numbers for each category, we included sequential cases of moderate and well-differentiated subtypes collected during the same period. We excluded all cases for which a clinical or dermoscopic image or information about the differentiation grade in the histopathological report was lacking.

Dermoscopic images had been captured with a Dermlite® Foto (3Gen, Dana Point, CA, U.S.A.) at a magnification of 10 ×. In all the centres involved it is the standard of care to take dermoscopic images of skin tumours by applying minimal pressure and using ultrasound gel in order to preserve the vessels' morphology to ensure they are visible.

Patient demographics and tumour characteristics were recorded, and two independent investigators (C.L. and F.S.), blinded to the dermoscopic and histopathological diagnosis, evaluated all clinical images and classified each tumour as flat, elevated or nodular. Disagreements between them were resolved through the involvement of a third investigator (E.M.).

Two independent investigators (A.L. and I.Z.) evaluated the dermoscopic images for the presence of predefined criteria. Both were blinded to the clinical and histopathological diagnosis. If the two dermoscopists failed to reach a consensus, a third investigator was involved (G.A.). Dermoscopic variables were selected on the basis of previously published data on dermoscopy of SCC and our preliminary observations on the dermoscopic findings of poorly differentiated SCC. A list of the included criteria and their definitions is shown in Table 1.

Statistical analysis

The outcome variable was set to a definite SCC histological differentiation grade ('well', 'moderately', 'poorly'). All separate dermoscopic variables were included in the analysis. Colinearity was assessed via a correlation matrix using Spearman's rho correlation coefficient. Pearson's χ^2 was used for group variables comparisons. Relative risks were calculated for all dichotomous variables. Crude odds ratios (ORs), adjusted ORs and corresponding 95% confidence intervals (CIs) were

Table 1 Definitions of the criteria used in the evaluation of dermoscopic images

Dermoscopic criterion	Definition
Predominant colour (white, white–yellow, red or combination)	The colour observed in >50% of the lesion's surface. Combination refers to the presence of white or white–yellow and red colour in almost equal parts of the lesion's surface
Dotted vessels	Tiny red dots, usually densely distributed next to each other
Hairpin vessels	Vascular loops sometimes twisted and bending
Linear irregular vessels	Linear or slightly curved, irregularly shaped vascular structures
Vessel morphology (monomorphous or polymorphous)	The presence of one or more than one of the morphological type of vessels described above
Vessel calibre (small, large or small and large)	The presence of vascular structures of small diameter, large diameter or both
Vessel quantity (0, 1–10, 11–50 or > 50)	Vascular structures not detected at all (0%), detected at up to 10% of the lesion's surface (1–10), from 11% to 50% of the lesion's surface (11–50) or present in more than half of the lesion's surface (> 50), respectively
Vessel distribution (diffuse, central, peripheral or clustered)	Arrangement of vascular structures – all over the lesion, in the centre, at the periphery or in clusters
Bleeding	Blood clearly visible in areas covering > 10% of the lesion's surface
Ulceration	Yellowish structure-less amorphous areas
Pigment	Any type of pigmented structures of brown, black or blue colour
Scales/keratin	White or yellow areas lying on the surface, without any recognizable structure
Scale distribution (diffuse, central or patchy)	Arrangement of scales or keratin in the centre, at the periphery or asymmetrically throughout the lesion
White circles	Roundish structures composed of yellow-to-light brown structure-less centre and white outer structure-less rim
White halos	White rim surrounding vascular structures
White structure-less areas	Whitish areas, not corresponding to scales/keratin, in the absence of any recognizable structure
Pinkish areas	Pinkish areas in the absence of any recognizable structure

calculated through univariate and conditional multivariate logistic regression, respectively. Conditional backward elimination proved more parsimonious. The alpha level was set at 0·05, while an alpha level of 0·10 was used as the cut-off for variable removal in the automated model selection for multivariate logistic regression.

Discriminant analysis was performed and functions were saved. We then used receiver–operator characteristic curves to choose between competing classification schemes. Specificity and sensitivity were extracted from classification tables.

Linear regression may not be appropriate for situations in which there is no natural ordering to the values of the dependent variable. In these cases, multinomial (polytomous) logistic regression may be the best alternative. As our SCC group was segmented into three differentiation grade subgroups, we explored whether dermoscopic data could be used to predict group membership. The model included forward stepwise entry of variables. We elected to use 'well differentiated' as the reference category.

The type I error probability associated with all tests in this study was set to 0·05. All statistical calculations were made with SPSS 17.0 (IBM, Armonk, NY, U.S.A.).

Results

Of 159 cases of histopathologically diagnosed SCC screened for eligibility, nine were excluded because there was no dermoscopic image, and seven were excluded because the histopathological report did not include information about the differentiation grade. A total of 143 SCC from 143 patients (mean age 77·0 ± 11·9 years), including 106 men (mean age 76·0 ± 11·6 years) and 36 women (mean age 80·0 ± 12·5 years; Student's t-test $P = 0·08$) were included in the study. The head and neck area was the most frequent site of tumour development (108/143; 75·5%), followed by extremities (24/143; 16·8%) and trunk (11/143; 7·7%). Histopathologically, 48 (33·6%) tumours were scored as well differentiated, including 16 (11·2%) keratoacanthomas (KA), 45 (31·5%) as moderately differentiated and 50 (35·0%) as poorly differentiated (Table 2). There was no difference in respect to the patient demographics and grade of tumour differentiation.

Based on the clinical image analysis, 50 of 143 tumours (35·0%) were evaluated as flat, 54 (37·8%) were elevated and 39 (27·2%) were nodular. Table 2 details the results of clinical evaluation of the surface morphology according to the differentiation grade of the tumours. Multinomial regression revealed that flat tumours had a fourfold increased probability of being poorly differentiated (OR 4·25, 95% CI 1·45–12·41; $P = 0·01$).

Table 3 shows the descriptive results of the dermoscopic analysis. A correlation matrix was plotted using Spearman's rho coefficient. Dermoscopic variables that significantly correlated with the histopathological differentiation grade were univariately examined.

Table 2 Squamous cell carcinoma: comparison of the surface morphology with the grade of differentiation

	Surface morphology			
Grade of differentiation	Flat	Elevated	Nodular	n (%)
Well differentiated	10 (20·8)	21 (43·8)	17 (35·4)	48 (33·5)
Moderately differentiated	15 (33·3)	18 (40·0)	12 (26·7)	45 (31·5)
Poorly differentiated	25 (50·0)	15 (30·0)	10 (20·0)	50 (35·0)
n (%)	50 (35·0)	54 (37·8)	39 (27·3)	143 (100·0)

Values are given as n (%).

Table 3 Squamous cell carcinoma: frequency of the dermoscopic criteria by the grade of differentiation

Grade of differentiation	Well differentiated (n = 48)	Moderately differentiated (n = 45)	Poorly differentiated (n = 50)	Total (n = 143)	P-value[a]
Predominant colour					
White	21 (43·7)	9 (20·0)	2 (4·0)	32 (22·4)	< 0·01
White–yellow	24 (50·0)	28 (62·2)	2 (4·0)	54 (37·8)	
Red	1 (2·1)	4 (8·9)	40 (80·0)	45 (31·5)	
Combination	2 (4·2)	4 (8·9)	6 (12·0)	12 (8·4)	
Dotted vessels	20 (41·7)	22 (48·9)	22 (44·0)	64 (44·8)	0·78
Hairpin vessels	16 (33·3)	8 (17·8)	7 (14·0)	31 (21·7)	0·05
Linear irregular vessels	17 (35·4)	24 (53·3)	37 (74·0)	88 (61·5)	< 0·01
Vessel morphology					
Monomorphous	22 (45·8)	21 (46·7)	25 (50·0)	68 (47·6)	0·22
Polymorphous	14 (29·2)	16 (35·6)	23 (46·0)	53 (37·1)	
Vessel calibre					
Small	13 (27·1)	16 (35·6)	37 (74·0)	66 (46·2)	< 0·01
Large	13 (27·1)	6 (13·3)	2 (4·0)	21 (14·7)	
Small and large	10 (20·8)	15 (33·3)	9 (18·0)	34 (23·8)	
Vessel quantity					
0	12 (25·0)	8 (17·8)	2 (4·0)	22 (15·4)	< 0·01
1–10	23 (47·9)	11 (24·4)	3 (6·0)	37 (25·9)	
10–50	11 (22·9)	23 (51·1)	7 (14·0)	41 (28·7)	
> 50	2 (4·2)	3 (6·7)	38 (76·0)	43 (30·0)	
Vessel distribution					
Diffuse	9 (18·8)	19 (42·2)	44 (88·0)	72 (50·3)	< 0·01
Central	0	1 (2·2)	0	1 (0·7)	
Peripheral	26 (54·2)	17 (37·8)	4 (8·0)	47 (32·9)	
Clustered	1 (2·1)	0	0	1 (0·7)	
Bleeding	8 (16·7)	12 (26·7)	35 (70·0)	55 (38·5)	< 0·01
Ulceration	8 (16·7)	12 (26·7)	5 (10·0)	25 (17·5)	0·10
Pigment	3 (6·3)	4 (8·9)	1 (2·0)	8 (5·6)	0·33
Scales/keratin	38 (79·2)	33 (73·3)	9 (18·0)	80 (55·9)	< 0·01
Scale distribution					
Diffuse	8 (16·7)	9 (20·0)	4 (8·0)	21 (14·7)	< 0·01
Central	27 (56·3)	18 (40·0)	1 (2·0)	46 (32·2)	
Patchy	3 (6·3)	6 (13·3)	4 (8·0)	13 (9·1)	
White circles	18 (37·5)	14 (31·1)	3 (6·0)	35 (24·5)	< 0·01
White halos	19 (39·6)	12 (26·7)	7 (14·0)	38 (26·6)	0·02
White structure-less areas	25 (52·1)	13 (28·9)	5 (10·0)	43 (30·1)	< 0·01

Values are given as n (%). [a]Pearson's χ^2 test.

A white colour decreased the odds of poorly differentiated SCC by 97% (OR 0·03, 95% CI 0·00–0·28; P < 0·01), while a white–yellow colour also decreased the possibility of poorly differentiated tumours by 97% (OR 0·03, 95% CI 0·00–0·24; P < 0·01). In contrast, tumours with a predominantly red colour had a 13-fold possibility of being histopathologically diagnosed as poorly differentiated (OR 13·33, 95% CI 1·04–170·63; P = 0·05). Other positive and negative predictors of poorly differentiated SCC are set out in Table 4.

Table 4 Poorly differentiated squamous cell carcinoma: positive and negative predictors

	P-value	OR	95% CI
Positive predictors			
Bleeding	< 0·01	11·67	30·80–4·42
Vessels in > 50% of the lesion surface			
Compared with 0	< 0·01	114·00	898·59–14·46
Compared with 1–10	< 0·01	145·67	938·17–22·62
Compared with 11–50	< 0·01	29·86	164·87–5·41
Small vessels calibre	0·040	3·16	1·05–9·50
Negative predictors			
Scales/keratin	< 0·01	0·06	0·16–0·02
White structure-less areas	< 0·01	0·10	0·30–0·04
White halos	0·01	0·25	0·67–0·09
White circles	< 0·01	0·11	0·39–0·03
Central scales/keratin	0·01	0·03	0·00–0·34
Large vessels calibre	0·05	0·17	0·03–0·97

OR, odds ratio; CI, confidence interval.

Multinomial analysis revealed that bleeding, increased vessel quantity and small vessel calibre represented positive predictors of poorly differentiated SCC. In contrast, the presence of scales/keratin, a central distribution of scales/keratin, the presence of white structure-less areas, white halos, white circles and a large vessel calibre were predictive of a well- or moderately differentiated tumour diagnosis. The results of the multinomial analysis are given in Table 4.

Discussion

Our study suggests that poorly differentiated SCC differs morphologically from the SCC grades of moderately or well differentiated (Figs 1–3). Specifically, poorly differentiated SCC was clinically typified by a flat appearance, and dermoscopically typified by a predominant red colour, attributed to the absence of scaling and keratin, and the presence of bleeding and/or dense vascularity. In contrast, an exophytic appearance and the dermoscopic presence of white-coloured criteria, including scales, white circles, white halos and white structure-less areas, significantly reduced the likelihood of a poorly differentiated tumour.

The clinical and epidemiological characteristics of patients with SCC in our study were comparable with existing evidence. In line with previous data, SCC was characterized by a higher male predominance rate, and developed mainly on the head and neck of elderly individuals.[7,9]

According to our analysis, linear irregular vessels, scales or keratin, bleeding and white structure-less areas were, overall, the most frequently observed dermoscopic features of SCC. Our findings are consistent with previous studies reporting on the dermoscopic criteria of SCC.[11,13,14] Recently, a progression model of actinic keratosis (AK) developing into intraepidermal carcinoma (IEK) and invasive SCC was proposed.[14] In line with our results, the authors of the aforementioned study found radial linear irregular and hairpin vessels, central keratin, white structure-less areas and ulceration to represent the most common dermoscopic criteria of invasive SCC. They also introduced the term 'targetoid hair follicles' to describe a novel dermoscopic criterion of invasive SCC, consisting of a yellowish follicular centre and a whiter perifollicular rim. The same feature was later renamed 'white circles', and was suggested to represent the most useful clue to discriminate between invasive and *in situ* SCC.[11] In the latter study, keratin, coiled vessels, blood spots, white structure-less areas and white circles were the most common dermoscopic criteria of SCC and KA. Most recently, Lin *et al.*[13] investigated dermoscopic features in a series of 50 SCCs, including KA, and compared their frequency with the findings from the former two studies.

Our analysis revealed significant differences in the dermoscopic pattern of poorly differentiated SCC compared with well- and moderately differentiated tumours. Specifically, the previously described white-coloured criteria, including scales/

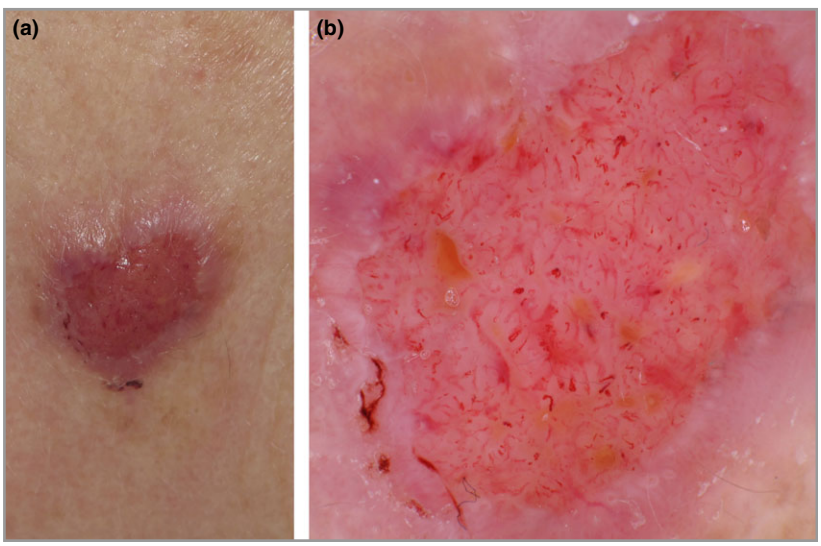

Fig 1. (a) A clinically flat and ulcerated poorly differentiated squamous cell carcinoma, dermoscopically typified by (b) a red predominant colour and numerous linear irregular vessels of small calibre.

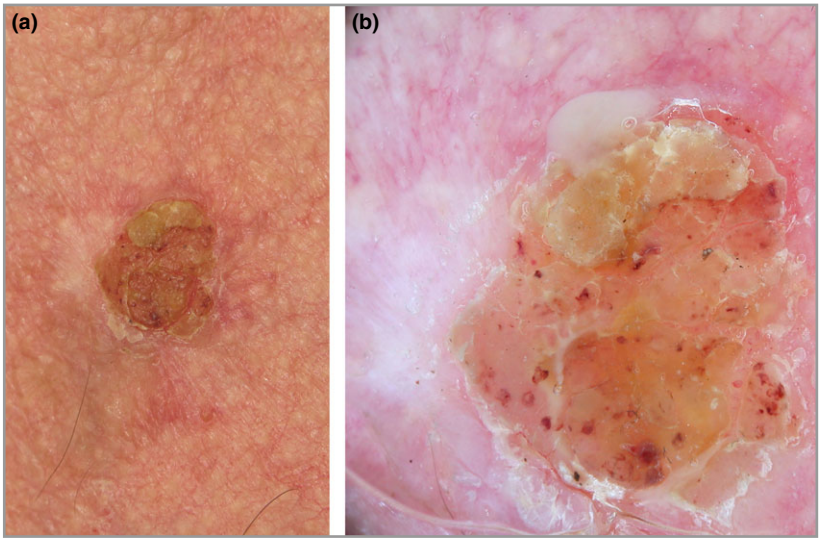

Fig 2. (a) A clinically flat ulcerated and hyperkeratotic tumour. (b) Dermoscopy reveals a yellow predominant colour, keratin with blood spots, a moderate vessel density and a white structure-less area at the periphery. Histopathologically, the tumour was diagnosed as moderately differentiated squamous cell carcinoma.

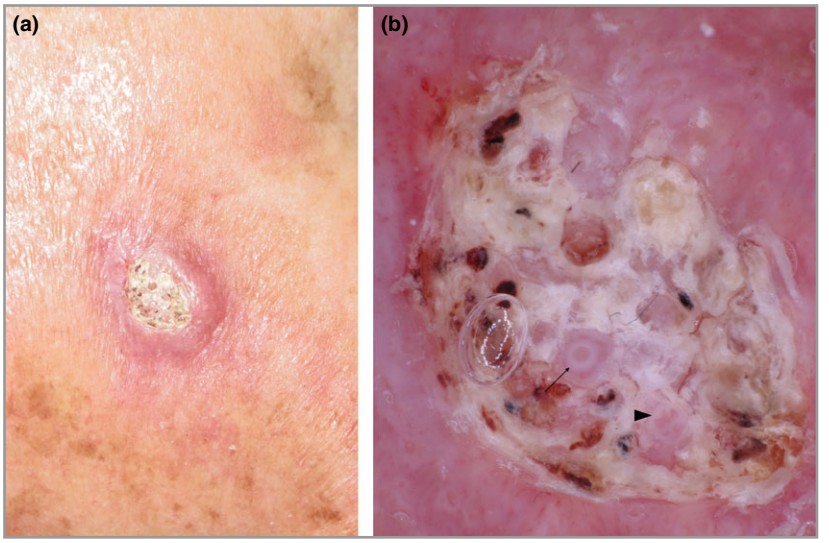

Fig 3. (a) Clinical examination of well-differentiated squamous cell carcinoma typically reveals an elevated hyperkeratotic tumour, dermoscopically displaying (b) a predominantly white colour, scales, keratin, blood spots, and the characteristic white perifollicular circles (arrow) and white perivascular halos (arrowhead).

keratin, white circles, white halos and structure-less whitish areas, were shown to be associated with well- or moderately differentiated variants. Notably, a central distribution of scales or keratin was associated with a 36-fold reduced possibility for poor differentiation.

In contrast, poorly differentiated SCC revealed a predominantly red colour, resulting from the presence of bleeding and/or dense vascularity, in the absence of scale/keratin or other white-coloured criteria (Fig. 4). The quantity of vessels significantly correlated with the differentiation grade, as tumours displaying vessels in more than 50% of the lesion surface had a 30- to 120-fold increased possibility to be of poor differentiation. The calibre of vessels was also shown to represent a significant predictor of differentiation grade, as a small calibre was associated with a threefold increased possibility for poor differentiation, while tumours with vessels of large calibre had reduced odds of 83% for poor differentiation.

The dermoscopic pattern of poorly differentiated SCC has not been reported in the literature. Former studies have separately investigated the dermoscopic pattern of KA and attempted to identify dermoscopic criteria that could discriminate this well-differentiated subtype from other invasive SCC variants. Rosendahl *et al.*[11] suggested that central keratin was the only criterion significantly more frequent in KA than SCC, while Zalaudek *et al.*[14] reported a higher frequency of linear irregular vessels in KA, and suggested that the typical dermoscopic pattern of KA consisted of peripherally distributed elongated vessels and centrally located keratin masses. In our study, KA was not considered to represent a separate group as its prognosis has not been shown to differ from other well-differentiated SCC subtypes. However, in line with the study by Zalaudek *et al.*,[14] a central distribution of scales/keratin was shown to represent a potent predictor of well-differentiated tumours.

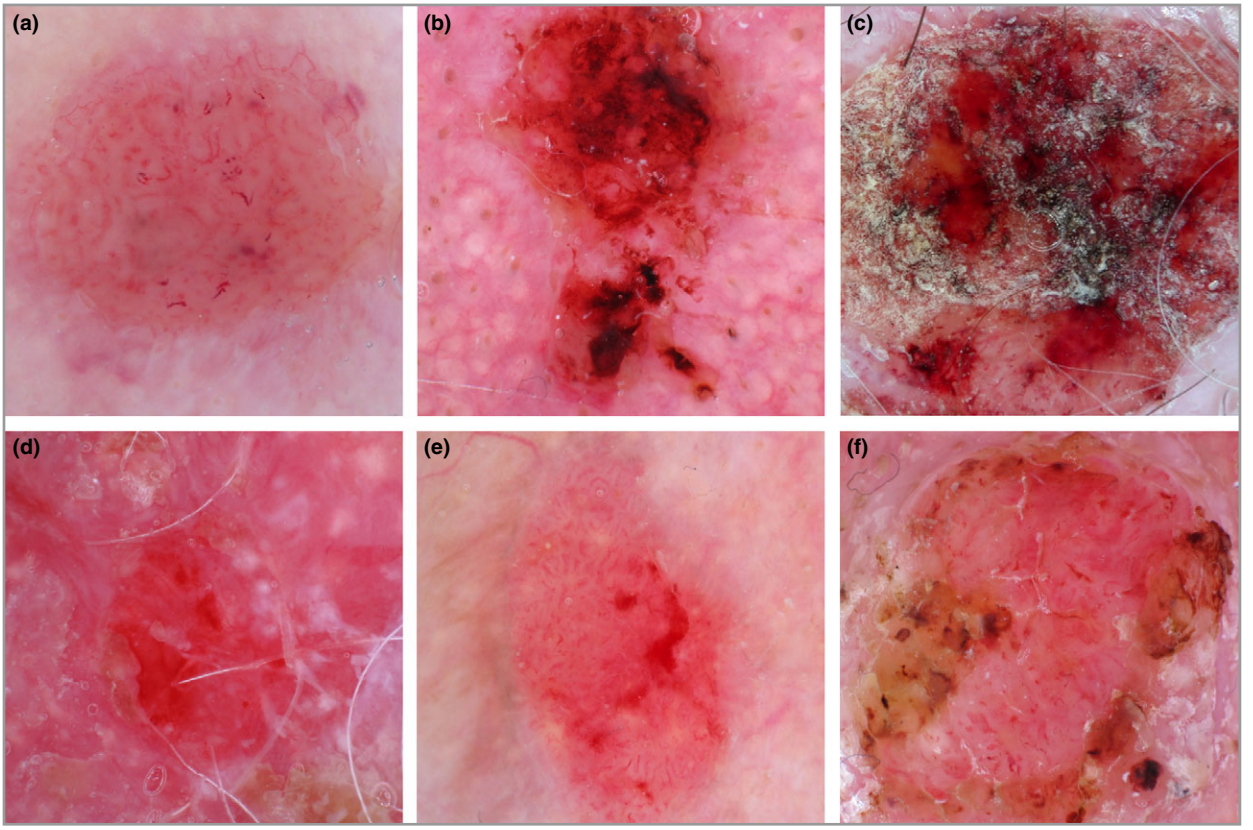

Fig 4. (a–f) Poorly differentiated squamous cell carcinoma. A repetitive dermoscopic pattern characterized by a predominantly red colour, attributed to bleeding and/or a dense vascularity, while scales and keratin are usually absent or scarce.

Our study has some limitations. Firstly, the retrospective design is subject to recall and observer biases, which have been addressed by the blinded scoring system of dermoscopic criteria. Secondly, the assessment of the tumour's palpability based on a clinical image is subject to observation bias. To minimize this problem, the evaluation was performed by two independent investigators, and a third investigator was involved in the event of disagreement. However, we still cannot rule out misclassifications, particularly between flat and elevated tumours. Thirdly, as we did not include *in situ* tumours, the value of dermoscopy in differentiating invasive SCC from AK and IEK cannot be assessed. However, previously existing data converge on the diagnostic value of white circles for distinguishing invasive SCC from *in situ* variants. In addition, it has been suggested that detection of linear irregular or hairpin vessels (instead of or in addition to dotted or glomerular vessels) might be indicative of a vertical growth phase of the tumour.[11,13–16] Finally, no conclusions can be extracted from our study on the value of the dermoscopic criteria related to poorly differentiated SCC for its discrimination from other skin tumours. Extensive bleeding, ulceration and dense vascularity can also be seen in basal cell carcinoma, amelanotic melanoma and other less common malignant skin tumours arising on the head/neck area.[17]

In conclusion, our study indicates that dermoscopy may be regarded to be a reliable preoperative tool to distinguish poorly from well- and moderately differentiated SCC, providing information that may be particularly useful for the management decisions of clinicians.

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