Dermatology Practical & Conceptual

Importance of Both Clinical and Dermoscopic Findings in Predicting High-Risk Histopathological Subtype in Facial Basal Cell Carcinomas

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ABSTRACT

Introduction: Being able to recognize high-risk facial basal cell carcinoma (BCC) may lead to fewer incomplete excisions and inappropriate treatments.

Objectives: We sought to investigate clinical and dermoscopic criteria for predicting facial BCC subtypes, analyze the interobserver agreement between readers, and develop a diagnostic algorithm to predict high-risk histopathological subtype.

Methods: In this single-center, retrospective investigation, 6 independent readers evaluated predefined clinical and dermoscopic criteria in images of histopathologically verified primary facial BCCs including: topography, border demarcation, vessels, ulceration, white porcelain areas, shiny white blotches and strands, and pigmented structures and vessels within ulceration.

Results: Overall, 297 clinical and dermoscopic image pairs were analyzed. The strongest associations with high-risk subtype were: "bumpy" topography (OR 3.8, 95% CI, 3.1-4.7), ill-defined borders (OR 3.4, 95% CI 3.1-4.7), white porcelain area (OR 3.5, 95% CI 2.8-4.5), and vessels within ulceration (OR 3.1, 95% CI 2.4-4.1). Predominantly focused vessels were a positive diagnostic criterium for either nodular (OR 1.7, 95% CI 1.3-2.2) or high-risk (OR 2.0, 95% CI 1.6-2.5) subtypes and a strong negative diagnostic criterium for superficial BCC (OR 14.0, 95% CI 9.6-20.8). Interobserver agreement ranged from fair to substantial (κ = 0.36 to 0.72). A diagnostic algorithm based on these findings demonstrated a sensitivity of 81.4% (95% CI, 78.9-83.7%) and a specificity of 53.3% (95% CI, 49.7-56.9%) for predicting high-risk BCC subtype.

Conclusions: Integration of both clinical and dermoscopic features (including novel features such as topography and vessels within ulceration) are essential to improve subtype prediction of facial BCCs and management decisions.

Introduction

The management of facial basal cell carcinoma (BCC) depends among other factors on the histopathological subtype. BCCs with a low-risk, nodular or superficial histopathologic subtype, are usually easier to treat than high-risk subtypes [1, 2]. The heterogeneous group of more aggressive, high-risk histopathological subtypes include infiltrative, micronodular and morpheaform subtypes as well as metatypical BCC (also termed basosquamous carcinoma) [1-3].

The Swedish registry for BCC employs the 'Sabbatsberg classification', which categorizes tumors into three subtypes [4]. Type I includes low-risk histopathological subtypes, whereas types II and III include high-risk subtypes as described above. The difference between types is based on four histopathological criteria: growth pattern, depth of invasion, the delineation of the tumor borders as well as the size of the tumor cords and nests. In type II BCCs, the growth pattern is infiltrative or micronodular, the depth of invasion does not extend beyond the dermis, the tumor borders are clearly demarcated, and the tumor cords and nests are mid-sized. In type III BCCs, which can have infiltrative, micronodular or morpheaform growth patterns or be of a basosquamous subtype, the depth of invasion may extend into the subcutis, muscle, bone and/or cartilage, while the tumor borders are irregular without any clear demarcation. Also, the tumor cells consist of thin cords of basaloid cells [4]. In this paper, we will refer to BCC with histopathological subtypes II or III according to the 'Sabbatsberg classification' as 'high-risk BCC' regardless of the tumor size, specific anatomical location, and other risk factors.

Currently, a high proportion of facial BCCs are excised without a prior biopsy [5-7] and incomplete surgical excisions are frequent. [5, 8-10]. Consequently, the increased risk of postoperative recurrence of histopathologically high-risk BCCs justifies a more careful surgical approach [11, 12]. Mohs micrographic surgery is therefore recommended for facial high-risk BCCs [13]. Thus, it would be useful to develop simple methods that help physicians identify such high-risk tumors preoperatively. Obtaining an accurate preoperative estimation of the BCC subtype would allow clinicians to know which tumors can easily be completely excised without a preoperative biopsy and which ones may require one in order to weed out the high-risk BCCs requiring Mohs micrographic surgery selectively and efficiently.

Since the early 2000s, dermoscopy has played an increasing role as a tool in physicians' clinical assessment of skin tumors, improving sensitivity and specificity for detecting BCCs [14]. The dermoscopic features of superficial and nodular BCCs have already been well-described in multiple studies [14-16], but fewer studies have specifically analyzed the clinical and dermoscopic features of high-risk BCCs [17-21], especially in the facial area. Furthermore, there is limited data on the interobserver agreement between physicians regarding these tumors [18, 19]. Moreover, to be useful in a clinical setting and for teaching dermoscopy, a high level of interobserver agreement on dermoscopic findings is a prerequisite [22].

The primary endpoint of the present study was to investigate which clinical and dermoscopic criteria are useful for differentiating high-risk BCCs from superficial or nodular ones in the facial area. The secondary endpoint was to analyze the level of interobserver agreement for the clinical and dermoscopic criteria observed in facial BCCs. Our ultimate aim was to develop a diagnostic algorithm that could allow physicians to predict which facial BCCs may be of a high-risk histopathological subtype and perhaps require a preoperative biopsy for improved decision-making regarding treatment.

Materials and Methods

This retrospective study was conducted at Sahlgrenska University Hospital in Gothenburg, Sweden. The study

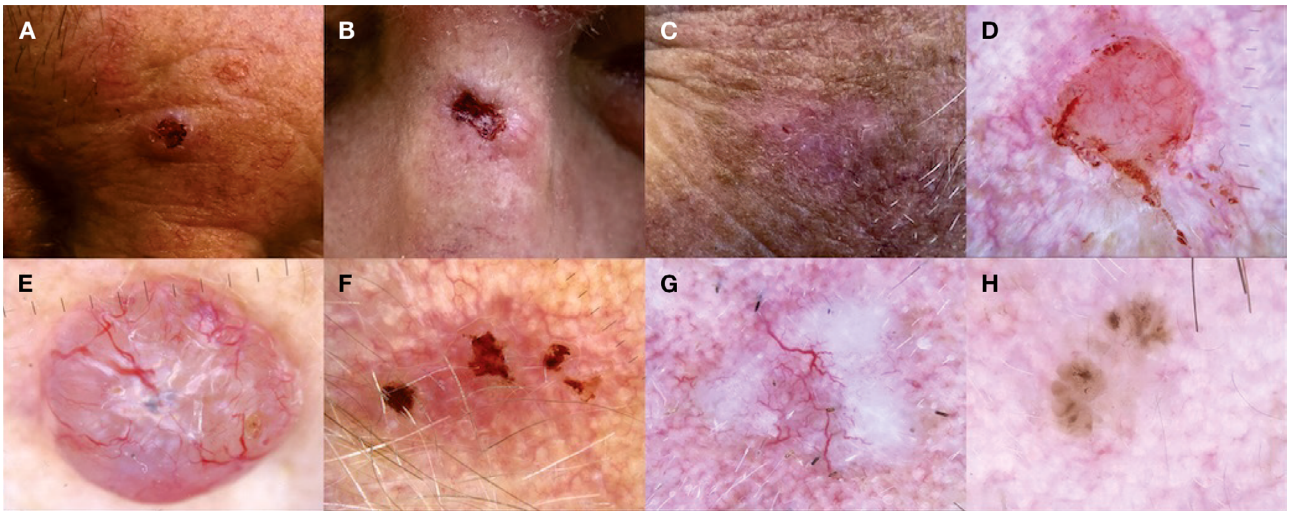

Figure 1. Examples of the clinical (A-C) and dermoscopic (D-F) features associated with different histopathological subtypes of basal cell carcinoma (BCC): A) raised topography and well-defined borders in a nodular BCC, B) "bumpy" topography and ill-defined borders in a high-risk BCC, C) flat topography and ill-defined borders in a superficial BCC, D) presence of vessels within ulceration in an infiltrative BCC, E) focused vessels, blue-gray pigmented structures as well as shiny white blotches and strands in a nodular BCC, F) unfocused vessels and ≥4 erosions in a superficial BCC, G) white porcelain areas and focused vessels in a high-risk BCC and H) gray-brown pigmented structures in a superficial BCC.

was approved by the Regional Ethical Review Board in Gothenburg and the Swedish Ethical Review Authority.

Clinical and dermoscopic images of histopathologically verified primary facial BCCs were collected from patients that had a visit at our department between January 2019 and December 2022. The distribution of included cases reflected the most commonly excised BCC subtypes in the facial area according to the Swedish registry: 40% nodular BCCs, 10% superficial BCCs, and 50% high-risk BCCs [8]. Inclusion criteria were facial BCCs with a specific histopathological subtype (i.e. not mixed subtypes] and the availability of high-quality clinical and dermoscopic images of the tumor. Basosquamous carcinomas were excluded. All histopathological slides were examined by dermatopathologists at the Department of Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden.

Data regarding the patients' sex and age at diagnosis as well as lesion diameter (in mm), anatomic location, and histopathological subtype were collected. Subsequently, the clinical and dermoscopic image pairs were evaluated by six independent readers (three from Sweden and three international readers from Chile, Israel, and the U.S.A.). All readers had more than 10 years of experience in dermoscopy. Clinical and dermoscopic images were captured with an iPhone 8 smartphone camera (Apple, Cupertino, California, USA) using a Dermlite DL4 dermoscope (DermLite LLC, Capistrano, California, USA) in polarized mode.

Before study initiation, a consensus meeting with all readers was organized. During the consensus meeting, 40 clinical and dermoscopic images (not included in the study dataset) (Supplementary Material S1) of BCC with varying histopathological subtypes were assessed and discussed until consensus was reached regarding the final list of clinical and dermoscopic findings and their definitions. Subsequently, the readers were provided with the image dataset for independent analysis. They were blinded for the histopathologic diagnosis and were asked to score the presence or absence of predefined criteria (Figure 1).

First, the readers were asked to assess the clinical image and classify the topography of each tumor as being raised, flat, depressed or any combination of these criteria. Any combination of flat, raised and/or depressed (i.e., not only flat or only raised), were grouped together during data analysis and such combinations will hereinafter be referred to as a 'bumpy' topography. Then, readers used both the clinical and the dermoscopic images to classify the tumor borders as well-defined or ill-defined. The remaining questions regarded the following dermoscopic features: (1) presence/absence of ulceration/erosion, (2) predominately focused or unfocused vessels, (3) presence/absence of a white porcelain area (4) presence/absence of shiny white blotches and/or strands, (5) presence/absence of classic pigmented structures (*i.e.*, brown-gray leaf-like, spoke-wheel or concentric areas or blue-gray dots/globules or ovoid nests) and 6) presence/absence of vessels within ulceration. Finally, the readers were asked to provide a prediction on the histopathological subtype (Supplementary Table S1.

Descriptive statistics were carried out to measure the frequency of different features using Fisher´s exact test. Odds ratios for associations between clinical and dermoscopic

criteria and the correct histopathological BCC subtype were calculated and used to construct a possible diagnostic algorithm to help predict high-risk subtype. Fleiss' kappa (κ) was used for measuring the interobserver concordance, which was interpreted as poor (≤0), slight (>0 to 0.20), fair (>0.2 to 0.4), moderate (>0.4 to 0.6), substantial (>0.6 to 0.8) or almost perfect (>0.8) [23]. *P*-values <0.05 were considered statistically significant. The analyses were conducted using R, version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 307 clinical and dermoscopic image pairs were analyzed. Ten images were excluded due to poor image quality, resulting in 297 included lesions (Supplementary material S2): 171 high-risk BCCs (57.6%), 98 nodular BCCs (33.0%), and 28 superficial BCCs (9.4%) (Figure 2). The most common locations were the cheek (n=73, 24.6%), nose (n=64, 21.5%), forehead (n=54, 18.2%), temple (n=40, 13.5%) and the periorbital area (n=29, 9.8%). The median age (range) of the included patients was 75 years (24-96 years) and 155 patients (52.2%) were females. The median tumor diameter was 8.0 mm (2–30 mm).

The most common clinical and dermoscopic features associated with the different BCC subtypes are shown in Table 1. A solely flat topography was strongly associated with superficial BCC while a solely raised topography was associated with a nodular subtype. High-risk BCCs were associated with a 'bumpy' topography. Both superficial and high-risk BCCs were associated with ill-defined borders, while nodular BCCs more commonly presented with well-defined borders. Regarding dermoscopic criteria, the presence of predominantly focused vessels was strongly suggestive that the BCC was not of the superficial subtype. White porcelain areas and vessels within ulceration were associated with high-risk BCCs, any blue pigmented structures with nodular BCCs, and the presence of >4 erosions with superficial BCCs.

Regarding the frequency of the observed dermoscopic features, vessels were observed in 94.6% of all superficial BCC assessments, in 98.3% of all nodular BCC assessments and 99.5% of all high-risk BCC assessments. Predominantly focused vessels were more frequently assessed as present in nodular (83.2%) and high-risk (82.7%) BCCs than in superficial ones (25.6%). White porcelain areas were more frequently observed in high-risk BCCs (38.6%) than in superficial (12.5%) and nodular (15.8%) BCCs. Furthermore, vessels within ulceration were found in 27.5% of high-risk BCCs as compared to 10.8% of low-risk BCCs. According to the reader assessments, shiny white blotches and/or strands were present in 42.3% of superficial BCCs, 64.3% of nodular BCCs and 71.5% of high-risk BCCs. The majority of BCCs presented without any classic pigmented structures (89.9% of superficial BCCs, 84.6% of high-risk BCCs and 71.4% of nodular BCCs). Pigmented superficial BCCs showed brown-gray pigment in 88.2% of the assessments, while pigmented nodular and high-risk BCCs showed blue pigment in 58.3% and 54.4% of the assessments, respectively.

The readers predicted the correct histopathological subtype in 52.4% (range 10.7-75.0%) of the superficial BCCs, in 66.5% (range 51.0-84.7%) of the nodular BCCs and 68.9% (range 43.3-85.4%) of the high-risk BCCs. When the predictions were incorrect, superficial and nodular BCCs

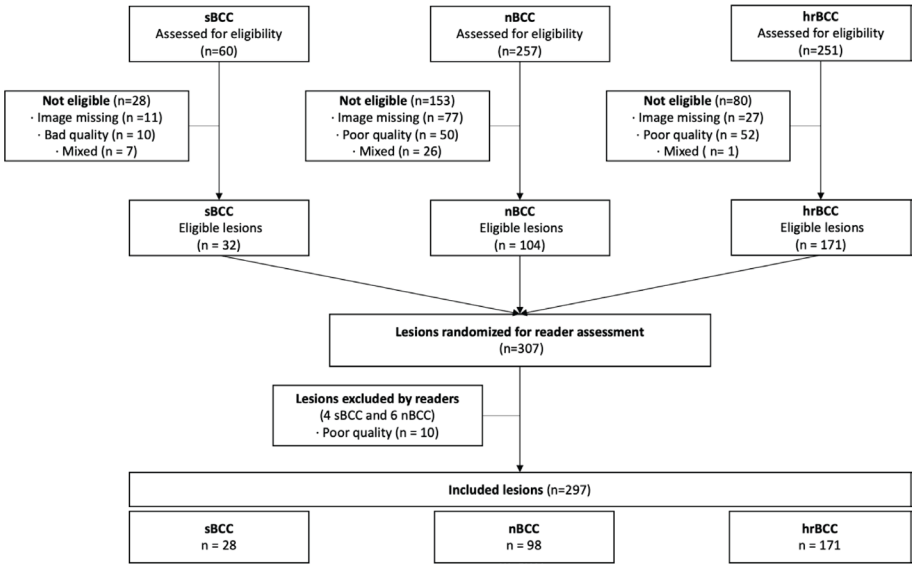

Figure 2. Flow chart of case identification, inclusion and exclusion.

*sBCC, superficial basal cell carcinoma; nBCC, nodular basal cell carcinoma; hrBCC, high-risk basal cell carcinoma.

Table 1. Clinical and dermoscopic features associated with specific basal cell carcinoma subtypes.

Superficial basal cell carcinomas					
Feature	**OR**	**95% CI**	**P-value**	**Frequency (%)**	**95% CI**
Only flat	10.0	7.0-14.3	<0.001	61	53-68
Ill-defined borders	2.4	1.6-3.5	<0.001	74	67-80
Unfocused vessels	14.0	9.6-20.8	<0.001	74	67-81
≥4 erosions	2.7	1.3-5.3	0.009	7	4-12
Nodular basal cell carcinomas					
Feature	**OR**	**95% CI**	**P-value**	**Frequency (%)**	**95% CI**
Only raised	6.1	4.9-7.7	<0.001	66	62-70
Well-defined borders	5.4	4.4-6.8	<0.001	71	67-74
Focused vessels	1.7	1.3-2.2	<0.001	83	80-86
Any blue pigment	2.5	1.8-3.4	<0.001	17	14-20
High-risk basal cell carcinomas					
Feature	**OR**	**95% CI**	**P-value**	**Frequency (%)**	**95% CI**
'Bumpy' topography	3.8	3.1-4.7	<0.001	57	54-60
Ill-defined borders	3.4	2.8-4.1	<0.001	69	66-71
Focused vessels	2.0	1.6-2.5	<0.001	83	80-85
White porcelain area	3.5	2.8-4.5	<0.001	39	36-42
Vessels within ulceration	3.1	2.4-4.1	<0.001	28	25-30

* OR, odds ratio; CI, confidence interval.

were more often mistaken for high-risk ones, whereas high-risk BCCs were more commonly mistaken for nodular BCCs.

A total of 36 of the 171 high-risk BCCs (21.1%) were assessed by the majority of readers as not having any of the 4 criteria with the strongest associations with high-risk subtype: 1) "bumpy" topography, 2) ill-defined borders, 3) presence of a white porcelain area or 4) presence of vessels within ulceration. By combining these positive criteria for high-risk subtype with negative criteria for superficial and nodular subtypes, a diagnostic algorithm was developed to predict which facial BCCs could potentially require a biopsy to rule out a high-risk histopathological subtype (Figure 3). The algorithm's output demonstrated a sensitivity of 81.4% (95% confidence interval [CI], 78.9-83.7%) and a specificity 53.3% (95% CI, 49.7-56.9%) for predicting high-risk subtype. This algorithm significantly outperformed a simpler algorithm in which only topography was used, which had a sensitivity of 57.3% (95% CI, 54.2-60.3%) and a specificity of 74.1% (95% CI, 70.8-77.2%) (p<0.001).

The highest interobserver agreements were observed for the number of areas with ulceration/erosion (κ=0.72, 95% CI 0.70-0.75), presence of classic pigmented features (κ=0.59, 95% CI 0.57-0.61), presence of white porcelain areas (κ=0.54, 95% CI 0.51-0.57), the predicted histopathological subtype (0.53, 95% CI 0.50-0.55), the presence of vessels within ulceration (κ=0.51, 95% CI 0.49-0.54) and well-defined or ill-defined borders (κ=0.51, 95% CI 0.49-0.54), thus demonstrating substantial to moderate interobserver agreement. The clinical topography (κ=0.36, 95% CI 0.34-0.37) and if the vessels were predominately focused or unfocused (κ=0.38, 95% CI 0.36-0.41) demonstrated fair interobserver agreement.

Discussion

In this retrospective study focusing on facial BCCs, we assessed the frequency of specific clinical and dermoscopic criteria that may help predict the specific histopathological subtype, resulting in fair to substantial interobserver agreement observed between the readers. Previous studies have mainly focused on the dermoscopic features of BCCs for predicting both the diagnosis and the histopathological subtype, but we show that the clinical features are equally important and relevant and should not be dismissed. Noteworthily, two of the criteria with the strongest associations with high-risk BCCs were clinical, i.e., a 'bumpy' topography and ill-defined borders.

It is well-known that nodular and superficial BCCs present clinically with a raised and flat topography, respectively. The clinical topography of high-risk BCCs has been described as a plaque with areas that can be depressed, raised and/or scar-like [1, 18, 20, 24]. Here, we propose a simpler

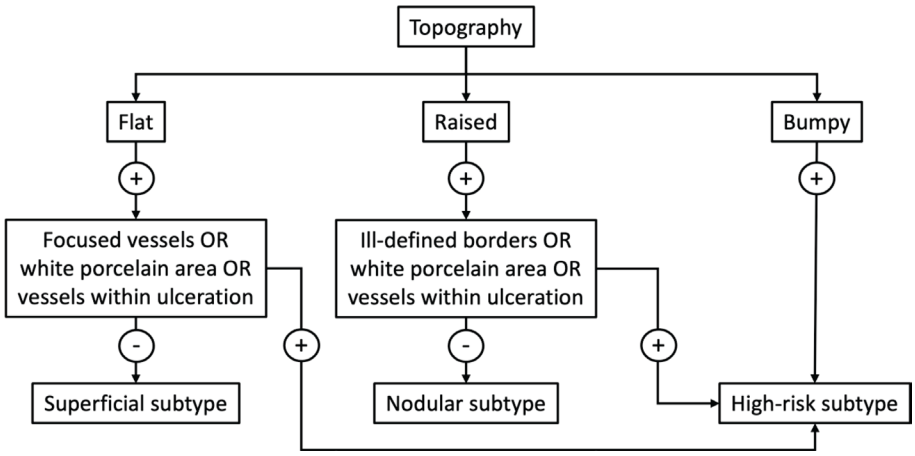

Figure 3. Proposed diagnostic algorithm for predicting the potential need for a biopsy in facial basal cell carcinomas to exclude a high-risk histopathological subtype.

description of these combinations using the term 'bumpy' topography. Whether this will improve the identification of high-risk BCCs preoperatively remains to be determined. Several authors have previously described a flat topography in 71.4-100% of superficial BCCs, an 'elevated'/'infiltrated' or nodular topography in 75.0-92.5% of nodular BCCs and a flat or 'elevated'/'infiltrated' topography in 53.7-100% of high-risk BCCs [25-28].

We found that nodular BCCs were associated with well-defined clinical and dermoscopic borders, which aligns with several previous publications. Conforti et al. observed well-defined edges in 77.8% of nodular BCCs [29]. In our study, ill-defined clinical and dermoscopic borders were associated with both superficial and high-risk BCCs. Conforti et al. observed ill-defined edges in 82.5% of sclerodermiform BCCs, but only in 30.5% of superficial BCCs [29]. Recently, Kamimura et al. reported an interobserver agreement of 86% among 47 dermato-oncologists when assessing whether the clinical borders of 79 BCCs were well-defined or ill-defined [30].

Importantly, our study pinpoints the importance of differentiating between focused and unfocused vessels. Several authors observed arborizing vessels (i.e., focused vessels) in 75-86% of nodular BCCs and 50-76% of high-risk BCCs, but only in 7-21% of superficial BCCs. These studies also reported short-fine telangiectasias (i.e. unfocused vessels) in 60-75% of superficial BCCs, but only in 20-46% of high-risk BCCs and 3-18% of nodular BCCs [17, 18, 28]. Conforti et al. classified vessel morphology differently but noted that only 2.1% of 95 superficial BCCs presented with 'classical' arborizing vessels [29].

The presence of a white porcelain area was associated with high-risk BCCs and this was observed in 39% of the cases. Camela et al. recently observed white porcelain areas in 30.4% of 115 high-risk, micronodular and morpheaform BCCs [21]. Conforti et al. described 'pink-white areas' (depicted to be similar to what we define as white porcelain areas) in 84.5% of 97 sclerodermiform BCCs [29].

The presence of vessels within ulceration is a novel observation, which showed a statistically significant association with high-risk BCCs. Although only present in 27.5% of all high-risk BCCs, vessels within ulceration may also be an important clue to high-risk histopathological subtype in lesions with an otherwise raised topography and well-defined borders mimicking a more indolent nodular BCC (Figure 4).

Superficial BCCs in this study were associated with ≥4 erosions but this was also an infrequent observation (7% of superficial BCCs). 'Multiple small erosions' have previously been observed in 38.6-47.1% of superficial BCCs [17, 26-28]. Moreover, any blue pigment was associated with nodular BCCs and the frequency of this finding was 17% in such tumors. Other authors have observed blue-gray ovoid nests in 27-55% of nodular BCCs as compared to 9-21% of superficial BCCs and 5-21% of high-risk BCCs [17, 27, 28].

Knowledge regarding the level of interobserver agreement can be used to refine the core teaching methods for identifying high-risk facial BCCs [22]. Overall, the interobserver concordance for the clinical and dermoscopic findings was fair to substantial, with the highest agreement observed for ulceration/erosion, presence of classic pigmented features, white porcelain areas, the predicted clinical diagnosis and well-defined or ill-defined borders. The topography (which may be more challenging to assess through images than in real-life) and predominant vessel types demonstrated fair interobserver agreement. We consider this to be an acceptable agreement considering previous investigations, the number of readers from different parts of the world as well as the relatively high number of possible answer combinations for several of the assessed features. Di Meo *et al*. showed κ-values of 0.55 for arborizing vessels, 0.40 for ulceration and

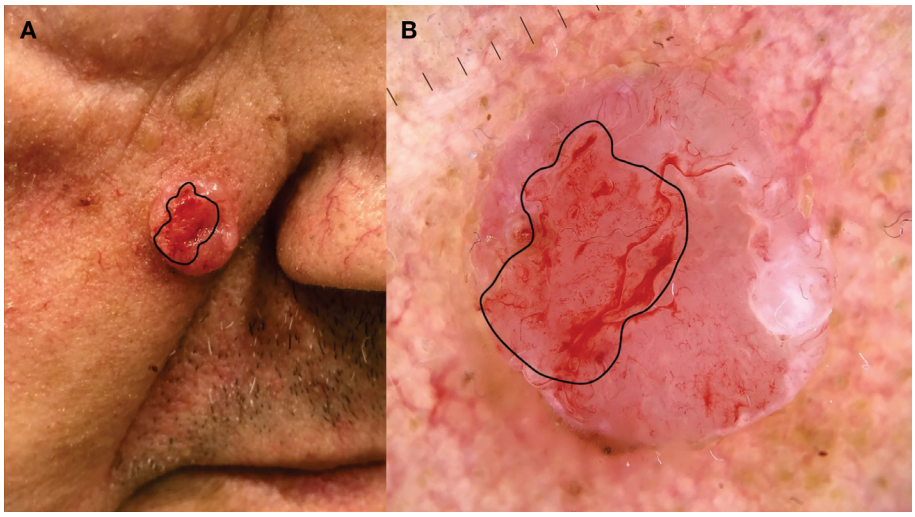

Figure 4. High-risk basal cell carcinoma with (A) raised topography and well-defined borders clinically, but (B) vessels within ulceration (black outlined areas) observed with dermoscopy.

0.27-0.42 for classic pigmented features using 4 observers assessing small BCCs [31]. Peris *et al.* observed κ-values of 0.72 for arborizing vessels and 0.49 for ulceration, 0.26-0.85 for classic pigmented features with 5 observers assessing pigmented BCCs [32].

In regards to the prediction of the histopathological BCC subtype, Nedved et al. showed a lower κ-value of 0.30 using 6 observers as compared to 0.53 in our study [33]. Popadic et al. observed κ-values of 0.85 for superficial BCCs, 0.62 for nodular BCCs, but only 0.13 for superficial BCCs in regards to agreement between the dermoscopic findings and the histopathological subtype with 2 observers [34].

Our proposed diagnostic algorithm for predicting BCC with a high-risk subtype resulted in relatively high sensitivity and specificity. The sensitivity improved significantly when adding the dermoscopic features to the clinical topography while maintaining relatively high specificity. During its construction, we used an "inverse approach" to exclude superficial and nodular subtypes despite the suggestive topography. In the future, we intend to test the proposed algorithm on consecutive and prospectively collected cases from different centers.

One limitation of our study is that we only included facial BCCs. However, treatment for BCCs on other anatomical areas is less challenging in terms of incomplete excisions or recurrence risks. Another limitation is the fact that it was a retrospective analysis conducted in a single center. Furthermore, the histopathological reports were not reviewed by separate pathologists, and we relied on the Swedish histopathological classification system for BCCs, which is not accepted internationally. Moreover, the majority of the BCCs occurred in fair-skinned patients and we did not record patient skin type. Finally, all invited readers were aware that the analyzed tumors represented BCCs and were presented with a prespecified set of criteria. Inclusion of other keratinocyte tumors would most likely have yielded a different distribution of dermoscopic features.

When assessing facial BCCs, integration of both clinical as well as dermoscopic features are essential to improve subtype prediction. This decision provides important guidance for when a preoperative biopsy may be necessary. Increasing correct predictions for high-risk facial BCCs may lead to less frequent incomplete excisions of BCCs with traditional surgery and avoidance of inappropriate destructive or topical treatments leading to difficult-to-treat recurrences.

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