Vascular patterns in basal cell carcinoma: Dermoscopic, confocal and histopathological perspectives (Review)

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Received August 20, 2018; Accepted December 13, 2018

DOI: 10.3892/ol.2019.10070

Abstract. Basal cell carcinoma (BCC) is the most prevalent skin cancer in the Caucasian population. A variety of different phenotypic presentations of BCC are possible. Although BCCs rarely metastasize, these tumors commonly destroy underlying tissues and should therefore be treated promptly. As vascular formation and angiogenesis are indicators of tumor development and progression, the presence of blood vessels, their morphology and architecture are important markers in skin lesions, providing critical information towards pathogenesis and diagnosis. BCC commonly lacks pigmentation, therefore it is important to emphasize the usefulness of vascular feature detection, recognition, quantification and interpretation. To answer the question of whether vascular patterns observed on dermoscopy, reflectance confocal microscopy (RCM) and histopathology might reflect the biologic behavior of BCCs, we undertook this review article. Several studies have sought, by various means, to identify vascular features associated with the more aggressive BCC phenotypes. Dermoscopic vascular pattern assessment can facilitate diagnostic discrimination between BCC subtypes, more aggressive BCCs displaying less or no pink coloration and a relative absence of central tumor vessels. RCM, a novel, non-invasive imaging technique, allows for the quantification of blood vessel size, density, and flow intensity in BCCs. BCCs are distinguished on RCM chiefly by vessels that branch and intertwine between neoplastic aggregates, a pattern strongly reflecting tumor neo-angiogenesis. The analysis of these vascular morphological and distribution patterns can provide further support in the diagnosis, assessment, or monitoring of BCCs. Histopathology shows significantly higher microvessel densities in the peritumoral stroma of BCCs, when compared to normal skin or benign tumors. This angiogenic response in the stroma is associated with local aggressiveness, therefore the quantification of peritumoralmicrovessels may further assist with tumor evaluation. How dermoscopy and RCM vascular patterns in BCC correlate with histopathological subtype and thus help in discriminating aggressive subtypes definitely deserves further investigation.

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Key words: dermoscopy, carcinoma, basal cell, microscopy, confocal reflectance, microvessels, biomarkers, histology

1. Introduction

The skin is the site most frequently affected by neoplasia, and basal cell carcinoma (BCC) is the most prevalent of all cancers in fair-skinned individuals. Epidemiologic data reveal that worldwide prevalence and incidence rates of non-melanoma skin cancer (NMSC) are increasing, especially in the young population, most likely due to a combination of ozone depletion, increased recreational outdoor activities, and changes in

clothing style (1), therefore turning BCC into a growing public health problem (2).

Even though BCCs are usually indolent, these tumors may also have an aggressive evolution, infiltrating deep structures, destroying the underlying tissues and in rare instances metastasizing (3). BCC should therefore be treated at the earliest possible stage. Moreover, numerous studies were directed at identifying risk factors associated with more aggressive phenotypes (4).

Vascular structures play a substantial role in the pathogenesis of malignant skin tumors. Hence, investigation of vascular structures in skin lesions using non-invasive techniques such as dermoscopy and reflectance confocal microscopy (RCM) and evaluation of their morphology and architectural arrangement on histopathological examination could provide valuable clues for the diagnosis and prognosis of BCC (5,6).

BCC is characterized by a large variety of clinical and dermoscopic traits (7) owing to a large number of combinations of histologic features, thus making the diagnosis of BCC not always easy. Dermoscopy is usually helpful in identifying BCC and, with the help of several dermoscopic criteria, discriminating it from other skin cancers, still the majority of dermoscopic studies have been carried out mainly on pigmented BCCs. However, BCC lesions often prove difficult to diagnose due to the lack of pigmented structures. Thus, detection and quantification of lesion vasculature may provide critical information for diagnosis and prognosis (8).

Furthermore, in the case of these ulcerated BCCs the clinician simply lacks the means to correctly diagnose a BCC, and is therefore driven towards other entities such as melanoma or squamous cell carcinoma (SCC) resulting in an increased patient psychological distress and increased burden of urgent surgical removals (9). In these cases, other *in vivo* imaging techniques, such as RCM, could provide additional information regarding the tumor vascular pattern, increasing diagnostic accuracy and reducing moral and financial burdens.

BCC's ability of local invasion but rarely metastasis may be connected to its microvasculature, suggesting that histopathological and immunohistochemical studies of microvessels counts and angiogenic factors expression could provide a more detailed account of the vascular mechanisms supporting its evolution.

This review article plans to take you on a journey through the vascular aspects of BCCs, starting with anatomical observations, observable with the naked eye, through dermoscopy, *in vivo* RCM, and ending with the physiopathological and histological foundations of BCC vasculature development and evolution.

2. Gross anatomy of the relation between BCC and blood vessels

Recent clinical observations have led to possible paradigm shifting hypotheses concerning risk factors for BCC development. Heckmann *et al* (10) suggest that ultraviolet radiation (UV) exposure may not be the only factor for NMSC localization. The authors found no correlation between BCC and areas of chronic UV exposure alone, reporting a higher incidence of BCC in the preauricular crest compared to helix, and in the medial orbital quadrant compared to the lateral quadrant. Others have proposed that localized tissue changes such as reduced dermal thickness via disturbed cell matrix interactions may promote NMSC development in specific regions of the face (11,12). Altogether, these observations imply the existence of additional NMSC risk factors, other than chronic UV exposure.

Recently, the question has been raised, whether the facial arterial network may influence NMSC localization. Studying NMSC arterial colocalization in the fronto-temporal area by means of echo-Doppler ultrasonography and histopathology, Kuonen *et al* (13) found BCC arterial colocalization in 59% of tumors, a significantly higher proportion than that of random arterial colocalization in adjacently distributed 175 mm^2 surface areas (32%). Combining both echo-Doppler and microscopic analyses revealed that 82% of tumors colocalized with an arterial branch. The authors reported similar rates of colocalization for the frontal versus temporal regions (78 vs. 85%) as well as in BCC versus SCC (83 vs. 80%). Taken together, these findings suggest that BCCs of the fronto-temporal area are preferentially localized in the close proximity of the facial arterial blood vessels (13). However, the study only took into account high-caliber arterial vessels of the cutaneous and subcutaneous layers of the skin detected by echo-Doppler ordefined by a diameter greater than 300 μm on histopathology, which is an arbitrary restriction and may very well underestimate the actual tumor-artery colocalizations.

3. Angiogenesis and BCC

The skin's vascular supply is provided through a deep dermal plexus and a superficial, subpapillary plexus. Dermal blood vessel growth primarily occurs during embryogenesis and, as discovered since the 1980s, is regulated by several soluble factors of angiogenesis and antiangiogenesis (14). Among these, vascular endothelial growth factor (VEGF) is recognized as the main proangiogenic factor, and thrombospondin 1 and 2 as main antiangiogenic factors. Blood vessel shape and size remain constant as long as there is a balance between pro- and anti-angiogenic stimuli (15). Angiogenesis, a process stimulated by hypoxia and inflammation (16,17), has been thought of as essential for tumor growth since 1971 (18).

There is a great body evidence highlighting the importance of aberrant angiogenesis in the pathogenesis of cancer. Growing tumors feed on newly formed capillaries, and continuity between the tumor and the host's vascular system is dependent on this microvascular bed (19). Without angiogenesis, a tumor cannot grow beyond a size of ~1-2 mm^3 and cannot metastasize (14,20,21).

Moreover, it has been shown that the angiogenic phenotype sets the boundary line between hyperplasia and neoplasia (20), and that even though vascular patterns vary significantly in solid tumors, there is a certain relationship between tumor growth and the degree of vascularization (22).

The term ‘angiogenic switch’ refers to the predominance of proangiogenic factors, resulting in formation of new blood vessels (20,23). Higher microvessel densities (MVD) measured in histologic specimens of tumors and in areas adjacent to the tumor-stroma interface, have been linked to adverse prognosis in a variety of tumor entities (21,22,24-35).

Expression of VEGF, the main proangiogenic factor, has been found increased in BCCs when compared to normal

skin, although to a lesser degree than in cutaneous SCC (36). Studies suggest that VEGF in BCCs is correlated to MVD (37). Angiogenesis must, in turn, be supported by extracellular matrix remodeling (38). Proteomic studies have identified biomarkers such as COX-2, matrix metallopeptidase-9 (MMP-9), and Maspin to play important roles in the promotion of angiogenesis and neovascularization in BCCs (39,40). Moreover, a correlation between COX-2 overexpression and increased levels of vascular endothelial growth factor-A, regulators of apoptosis Mcl-1 and Bcl-2, and CD31 positive vessels has been suggested by previous studies (41). In contrast, tissue inhibitors of metalloproteinases (TIMPs) exert anti-angiogenic activities through inhibition of MMP-dependent angiogenesis (42).

There is sufficient evidence suggesting that angiogenesis is crucial for the metastasis of vascular tumors. The immaturity of new microvessels promotes the local shedding of neoplastic cells into the tumoral venous stream (30,43), thereby consolidating the expansion of metastatic colonies (23).

What about tumors that can invade but do not metastasize? It is hypothesized that differences in the microvasculature associated with various types of epidermal-derived tumors might account for these differences in tumor behavior. BCCs are a perfect example of epidermal-derived tumors that have potential for local invasion but in which metastatic spread is rare, with incidences ranging from 0.0028 to 0.55% (44,45).

4. The dermoscopic perspective on BCC vasculature

The skin has a layered structure, its different color components being determined by the presence of different pigments. Out of all these pigments, melanin and hemoglobin are the most dominant, the latter being responsible for the color red.

Dermoscopy is an *in vivo* skin examination technique that has proven helpful in differentiating BCC from other malignancies, such as SCC and melanoma (46-49). Dermoscopic diagnostic criteria for BCC include leaf-like areas, large blue-grey ovoid nests, short white streaks/chrysalis, spoke-wheel areas and multiple blue-gray dots and globules (7,50,51). In addition to these pigmentary criteria, specific vascular patterns may prove useful for BCC diagnosis, particularly when the above-mentioned structures are missing (6,52-54). Relatively superficial blood vessels are readily accessible to dermoscopic investigation, thus a number of vascular patterns have been described in BCCs (Fig. 1), all the while keeping in mind that skin pigmentation due to melanin can sometimes occlude the visibility of blood vessels.

Dermoscopic global vascular patterns in BCC. Global vascular patterns helpful in the dermoscopic diagnosis of BCC have been outlined by several authors. These patterns include either clustered (vessels with similar morphology closely gathered together), scattered (vessels with irregular and diffuse distribution), homogenous (densely aligned symmetrical vessels), or avascular (no vessels can be seen). Trigoni *et al* (55) found that the most consistent global vascular pattern in all BCC subtypes is the scattered pattern (96%), while Pan *et al* (56) also found the scattered pattern to be the most frequent (97%) in superficial BCC (sBCC). In contrast, the avascular global pattern was noted in only 3% of nodular BCCs and 7% of sBCCs (55).

Dermoscopic local vascular patterns in BCC

Arborizing vessels. Arborizing vessels are the most impressive vascular pattern seen in BCC. Because in many instances clinical assessment of telangiectasia does not account for the particular structure of the vessels, many tumors are misdiagnosed as BCCs just because telangiectasias are visible. As Staindl and Lametschwandtner perfectly pointed out, blood vessels in BCC are located on the surface, just below the epidermis, regularly traversing the whole lesion (57). This accounts for their perfect visibility and sharp focus, even in heavily pigmented tumors. Furthermore, arborizing vessels in BCC have stem vessels of >0.2 mm in diameter and wind in a strange fashion, branching irregularly into fine capillaries. These vessels are bright red, as opposed to normal pink vessels in the dermal plexus, which are always slightly blurry, never being depicted as crisp (Fig. 1A). There are a few tumors (nodular melanoma, blue nevi, and syringomas) which display similar vascular structures at first glance. Looking closer, their vessels appear to branch more regularly and orderly than BCC vasculature and they can be differentiated easily by morphologic measuring techniques (53).

Arborizing vessels have been described in all BCC subtypes with different frequencies. Giacomel and Zalaudek (58) report their presence in 63% (retrospective study; n=24) of all BCC subtypes analyzed, Liebman *et al* (59) place that figure between 18.8-38.3% (retrospective study; n=149) deeming arborizing vessels as one of the main vasculature types, as do Micantonio *et al* (54) with 60.7% presence (retrospective study; n=504), and Popadic which places this feature as second most frequent after the milky-red background (prospective observational study; n=151) (48). This pattern is constantly described in nodular BCC (nBCC) and cicatricial BCC (53), whereas in superficial BCC (sBCC) they are harder to detect (54,55), probably as a result of the greater vascular need in the nodular type compared with sBCC. In a retrospective observation study Pan *et al* (56) note that arborizing vessels were more likely to be observed in a sample of 150 sBCC than in other cutaneous malignancies or inflammatory skin diseases, such as intraepidermal carcinoma or psoriasis. According to Kreusch and Koch, the sensitivity and specificity of the arborizing vessels pattern for BCC is very high, at 96.1 and 90.9% (n=84), respectively (60). Thus, even though the data comes mainly from retrospective studies, it is clear that arborizing vessels is one of the most important dermoscopic criteria in BCC evaluation.

Short fine telangiectasia. With a presence of 92% (n=24), one retrospective study (58) found short, fine telangiectasias (SFTs) to be a dermoscopic hallmark of sBCC (Fig. 1B and C). This finding is supported by a larger retrospective study, Liebman *et al* (59) documenting the presence of SFTs in 73.8-82.6% (n=149) of all nodular, superficial, and infiltrative BCCs. On the other hand, Popadic (48), in her prospective observational study, mentions a much lower frequency of SFTs in BCC (19.9%) (n=151), although accompanied by a positive predictive value (PPV) of 100%, thus suggesting that the presence of this feature is highly evocative of the diagnosis.

Arborizing microvessels. Arborizing microvessels, seen at routine ten-fold magnification as short, linear straight, linear serpentine vessels of small diameter and relatively few branches (Fig. 1A and B), are more likely observed in

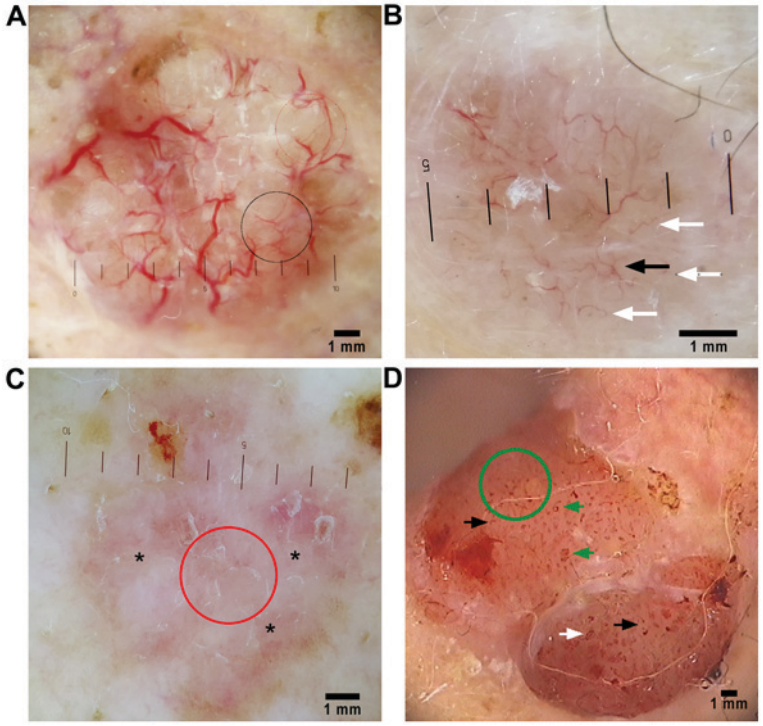

Figure 1. Dermoscopic vascular features in BCC. (A) Arborizing vessels, arborizing microvessels (black circle). (B) Arborizing microvessels (black arrow) and short fine telangiectasia (white arrow). (C) Milky-pink background (black asterisks) and short fine telangiectasia (red circle). (D) Dotted (green circle), hairpin (white arrow), comma (black arrows) and glomerular vessels (green arrows).

sBCC than in nBCC, cystic BCC (6). According to Popadic's prospective observational study with a sample of 151 tumors, arborizing microvessels were more frequent than large vessels (49 vs. 35%) in BCCs, but had a slightly lower diagnostic value (PPV=97 vs. 98%) (50).

Milky-pink background. Milky-pink background, often described as a white-red, translucent to opaque structureless area (Fig. 1C) has been found by many authors, with various degrees of frequency ranging from 41.6 to 100%, in superficial BCCs (55,56,58,59,61). Popadic found milky-red background, out of all studied vascular patterns, to have the highest sensitivity value for BCC diagnosis. However, because this dermoscopic feature simply correlates to lesion vascularization and is also present in several non-BCC lesions such as actinic keratoses, SCC, Bowen's disease, seborrheic keratoses, and angiomas, it has a low specificity (48%) and does not have significant diagnostic value for BCC (50).

Comma vessels. Comma vessels (Fig. 1D) are reported by some authors as minor vascular patterns found in less than 10% (retrospective study; n=504) of BCC lesions (54) while others have observed them in 45% of all BCC subtypes, reaching 93% presence in superficial BCCs (retrospective study; n=138) (55).

Glomerular vessels. While glomerular vessels, defined as frequently clustered, tortuous capillaries (Fig. 1D), are archetypical of Bowen's disease (52,53,62), they have been described as a minor vascular pattern (frequency of 0-2.7% for all subtypes) of BCC in non-polarized dermoscopic studies (n=531 and n=150, respectively) (52,56).

Loop vessels. The next two patterns, pinpoint or dotted vessels and hairpin vessels are merely variants of the same vascular structure, loop vessels. Vascular loops are seen in many lesions, primarily in keratinizing tumors and melanoma. In order for these patterns to be useful in discriminating keratinizing tumors from melanoma, the criteria of 'keratinization' have been introduced by Kreusch (53).

In thin tumors, the short capillary loops appear dermoscopically as small red dots, of 0.01-0.02 mm in diameter (Fig. 1D). When observed at higher magnifications (30-fold or more) it becomes obvious that these dots are the tips of short capillary loops. Dotted vessels are to be considered tumoral vessels only when supplying a solid tumor whose borders can be recognized on clinical inspection.

Although dotted vessels may be observed in nevi, melanoma (52,53) and many keratinizing tumors with low vertical diameters such as warts, actinic and seborrheic keratoses, Bowen's disease (59), and SCC (52,53), they have been reported, to some extent, in every BCC subtype (59). Some authors have found these subtle, sparse, and focally distributed vessels in >50% of lesions (n=149) across all dermoscopic BCC types (59) while larger studies report them as a minor vascular pattern, found in <10% of lesions (n=504) (54).

In thicker tumors, vascular loops are longer and can be seen as such, sometimes twisting and bending. However, their diameter of ~0.01-0.03 mm remains constant along the entire course of the vessel. This pattern in frequently encountered in the same types of lesions as mentioned for dotted vessels, but only in lesions of greater vertical thickness. Several studies mention the presence of hairpin vessels in BCCs as a minor vascular feature, with a wide range of frequency, between 2.6 and 18% (46,52,56,58,63).

As stated by Kreusch, blood vessels in all keratinizing tumors are surrounded by a whitish halo representing vital keratinocytes supplied by that particular vessel. This white

area gradually merges into a zone of yellow keratin. The amount of keratin is dependent on the degree of cell differentiation as it can be missing in poorly differentiated SCC or as a consequence of scratching or keratolytic treatment of a lesion. This whitish halo is absent in all melanocytic lesions, which can show pinpoint or hairpin vessels, depending on their vertical diameter, in various arrangement patterns (53).

It now becomes obvious how helpful global and local vascular patterns can be to the clinician during the dermoscopic examination of a skin lesion suspected to be a BCC. While not all patterns have high diagnostic values and there is great variability in reported sensitivities and specificities, the presence of arborizing vessels or short fine telangiectasia can be of significant value in the differential diagnosis. If vascular patterns are easily observed through the dermoscope in intact lesions, the situation changes with ulcerated or completely ulcerated and heavily pigmented lesions.

Vascular dermoscopic patterns in particular BCC subtypes

Ulcerated versus non-ulcerated BCC. In some cases, BCCs clinically present as ulcerated nodules or papules, and therefore their clinical differential diagnosis is difficult. In these instances, the dermoscopic appearance of vascular patterns can significantly improve diagnostic accuracy.

In a very recent retrospective blinded study including 139 lesions, Arpaia *et al* (9) addressed the issue of vascular dermoscopic patterns in ulcerated BCCs. The authors found that ulcerated BCCs presented with annular, peri-ulcerous, distributed telangiectatic vessels and hypopigmentation, both of which had high diagnostic values (annular telangiectasias, PPV=95%; annular hypo-pigmentation, PPV=100%). In the ulcerated areas, the comma vascular pattern was significantly associated with the presence of pigmentation (P=0.001) and blue-grey ovoid nests (P=0.027). In the non-ulcerated areas, milky-pink background was associated with leaf-like areas, and blue-white veil. However, the absence of blue-white veil was strongly associated with the presence of arborizing vessels. An inverse association was also observed between the presence of hairpin vessels and the presence of at least one of the classic BCC patterns. Through logistic regression analysis, their analysis shows that the vascular features influencing the correct diagnosis the most were: the presence of arborizing vessels in ulcerated areas (100%), absence of the dotted pattern in non-ulcerated portions, and absence of hairpin and glomerular patterns in the ulcerated areas, the latter two being more commonly associated with either melanoma or SCC.

Regarding completely ulcerated lesions, authors found dotted and linear-irregular dermoscopic patterns to be the most frequent, with a presence of 88.2 and 70.6%, respectively. Comma and polymorph patterns occurred in ~35% of lesions and other patterns (hairpin and glomerular) were rare (9).

These observations support the earlier findings of Popadic (48), which have found arborizing vessels (Sn=57.1%), arborizing microvessels (Sn=66.7%), annular hypopigmentation (Sn=66.7%), milky-red background (Sn=76.2%), and annular distribution of telangiectatic vessels (Sn=90.5%) to be the most frequent vascular structures in their sample of 21 ulcerated BCCs. Out of all these, arborizing vessels, annular distribution of telangiectatic vessels, and annular hypopigmentation were found to be highly significant (P<0.001) for ulcerated BCC, while arborizing microvessels and milky-red background were only significantly (P<0.05) present in these lesions.

Also of importance, translucency was absent in ulcerated BCCs, whereas it commonly appears in combination with other dermoscopic features in non-ulcerated BCCs (48).

Pigmented versus non-pigmented BCC. As stated before, dermoscopy has been primarily used in the study of pigmented skin lesions, therefore, in our opinion, a comparison between vascular patterns in pigmented versus non-pigmented BCC merits attention.

After being initially described in 52% (n=142) of pigmented BCCs (63) and in 57.1-82% of BCCs in subsequent studies (n=609) (46,64) that included both nBCC and sBCC, in a much smaller study (n=42) arborizing vessels have been identified in 14.3% of superficial pigmented and non-pigmented BCCs (65). It is possible that the BCC subtypes (nodular and/or superficial) included in different studies may account for the great variability in percentages reported so far (54).

Four dermoscopic features regarding vessel morphology, have been identified as the most valuable in the differentiation between non-pigmented and pigmented BCCs. These criteria include telangiectasias, arborizing vessels, red dots and globules. In their statistical analysis Trigoni *et al* (55) reveal that arborizing vessels were more often found in pigmented (74%) rather than non-pigmented (31%) BCCs (n=138; P<0.0001), suggesting that this criterion may prove of value in differential diagnosis. This observation had already been mentioned in the literature, Micantonio *et al* reporting a highly significant difference in arborizing vessels frequency between superficial pigmented versus superficial non-pigmented BCCs, while no difference was found in pigmented vs. non-pigmented nBCC lesions (n=504) (54).

In contrast to other investigators, Altamura *et al* (46) noted a high frequency of arborizing vessels in non-pigmented BCCs. This inconsistency might very well be the result of the subdivision of lesions into several groups, based on the degree of observable pigmentation. Opposed to other studies (46,63,66,67), Trigoni *et al* (55) found atypical vessels to be more common in all categories of BCCs. Furthermore, the authors (55) reported telangiectasias to be less frequent compared to the high percentages reported by Micantonio *et al* (54), which subdivided telangiectatic vessels into arborizing telangiectasia and SFTs. Further regarding SFTs, Giacomel and Zalaudek (58) found SFTs in 92.0% (n=24) of exclusively non-pigmented sBCCs, and Scalvenzi *et al* (65) described SFTs in 66.6% (n=42) of superficial pigmented and non-pigmented BCCs. This great variability in reported percentages might be attributed to lesion selection in these cases.

Fibroepithelioma of Pinkus. Zalaudek *et al* (68) reported fine arborizing vessels, either alone or associated with dotted vessels were predominant in fibroepithelial BCC (fibroepithelioma of Pinkus). It appears that even though the vessels seen in fibroepithelioma of Pinkus are arborized and in sharp focus, they differ from the arborizing telangiectasias of nodular BCC, lacking stem vessels of large diameter and having fewer ramifications (6).

Taken together, these data show that it is significantly more difficult to diagnose a BCC solely on clinical appearance or dermoscopy if the tumor is completely ulcerated or very

heavily pigmented. In such instances, BCCs are often mistaken for SCCs or melanomas, leading to more aggressive treatments and, as a consequence, an increased healthcare burden.

Dermoscopy of aggressive BCC. Few studies investigate the dermoscopic vascular features of individual BCC subtypes and, while superficial (56,58,65) and nodular BCC dermoscopic vascular features have widely been reported, aggressive BCC subtypes have been relatively neglected. These so-called 'aggressive-growth' subtypes are distinguished by a poorly circumscribed infiltrative growth pattern with a tendency towards perineural and perivascular invasion, leading to difficult surgical excision and consequent high recurrence rates (69). A recent study that investigated the correlation of dermoscopic criteria with different BCC histotypes showed that dermoscopy had a low sensitivity to identify risk of recurrence (70).

In everyday practice, it is pink in the lesion area of BCC that commonly attracts attention during clinical examination. Superficial BCCs have been observed to display pink in more than half of the tumor area in 84.9% of cases, a useful clue to identifying this tumor (71). In contrast to this, the same authors have shown (71) that aggressive BCC subtypes display absent or less pink in the tumor area than other subtypes. Pink represents increased localized vascular perfusion and is more conspicuous in polarized non-contact dermoscopy (59). The former authors (71) postulate that prominent collagen in the tumoral stroma of infiltrating and morphoeic BCC may correlate with the reduced pink areas. Although not formally analyzed in the study, the non-pink tumor areas where observed to be dominated by white structureless areas, seen more frequently in BCC through contact dermoscopy compared to polarized non-contact dermoscopy (59). It is yet unknown to what extent these pink areas relate to the associated lichenoid response in the papillary dermis, or to more specific tumor factors (71).

While reduced or absent vessels in the central tumor area of aggressive subtypes has been observed, where 1 in 3 aggressive BCCs showed no central vessels (71), in aggressive BCC of the lower limbs, glomerular (81.0%), dotted (71.4%) and hairpin (66.7%) vessels were all more frequently observed than serpentine (57.1%) or branching (47.6%) vessels. In all BCC subtypes, at all other sites, branching and serpentine vessels predominate over glomerular, dotted and hairpin vessels. Therefore, the authors concluded that there is a shift towards SCC in the aggressive BCC vessel morphology profile (71).

Due to the fact that aggressive BCC is commonly found in combination with nBCC, the reported association between large diameter vessels and aggressive BCC may be result of the additional presence of nBCC in the same lesion (71).

A recent study focused on the dermoscopic features of aggressive BCC reported arborizing microvessels and milky-red background (100%), followed by SFTs, and white structureless areas (75%) to be the most frequently detected features in morphoeic BCC (72). The same study detected arborizing vessels and microvessels and white structureless areas in 66.7% of infiltrative BCCs, a finding supported by previous studies (70). Truncated vessels and globules have been reported as the main dermoscopic finding in micronodular BCC (70).

Regarding sclerodermiform BCC, branching vessels present in this variant tend to be finer, more scattered, and tend to show less branching compared to the classic arborizing vessels of nodular or cystic BCC. Moreover, the vessels of sclerodermiform BCC commonly occur on a whitish background with poorly defined borders, while the arborizing vessels of nodular or cystic BCC typically envelope a relatively well defined and translucent pink tumor (6).

These findings confirm that although dermoscopy is extremely useful in BCC detection, it has limited impact in discriminating aggressive histotypes from the non-aggressive ones.

Automatic BCC vessel detection and segmentation in dermoscopy images. Visual inspection, either clinical or through the dermoscope, suffers from subjectivity and a lack of precision. Furthermore, some vascular features are quite small and normally occluded by other structures making their detection a challenging task. Although studies in dermoscopy all concur on the importance and significant diagnostic value of vascular structures, very few studies exist on the quantitative and systematic analysis of blood vessels in dermoscopic images.

Several studies (73-75) have sought to solve these problems through machine learning using automatic vessel detection and segmentation algorithms. More recently, Kharazmi *et al* (8) presented a novel segmentation technique for feature extraction of cutaneous blood vessels in dermoscopy images that accounts for both the background color components of the skin and blood vessel shape. Compared to previous studies, this technique promises superior vascular feature extraction useful for BCC classification.

5. Reflectance confocal microscopy of BCC vasculature

Although dermoscopy has its indisputable place in the noninvasive diagnosis of skin lesions, even video-dermatoscopes that can display images enlarged 30- or even 70-fold do not show blood flow and cannot resolve microscopic details, sometimes needed if an accurate diagnosis is to be made. RCM is a novel imaging tool which provides horizontal optical sections of the skin at nearly histological resolution. In recent years it has become an established technique for noninvasive diagnosis in several skin disorders (76-78), especially in skin oncology (79-83).

Using RCM, cutaneous vascular structures and blood flow can be visualized in real-time. In the dermis, vessels appear as dark spaces transitioned by small, bright structures, representing blood cells. RCM examination of normal skin upper dermal vascular plexus shows horizontally oriented blood vessels. Vessels that run vertically and horizontally are seen as round or canalicular dark spaces, respectively (84,85). Blood flow can be observed due to fast moving bright particles inside the vessel lumina.

Various studies in this field have proposed specific confocal microscopic diagnostic criteria for nonpigmented skin tumors (86-89). RCM has the advantage of real-time observation of vascular morphology and distribution patterns, which can provide supplemental information for the diagnosis or monitoring of nonpigmented skin lesions.

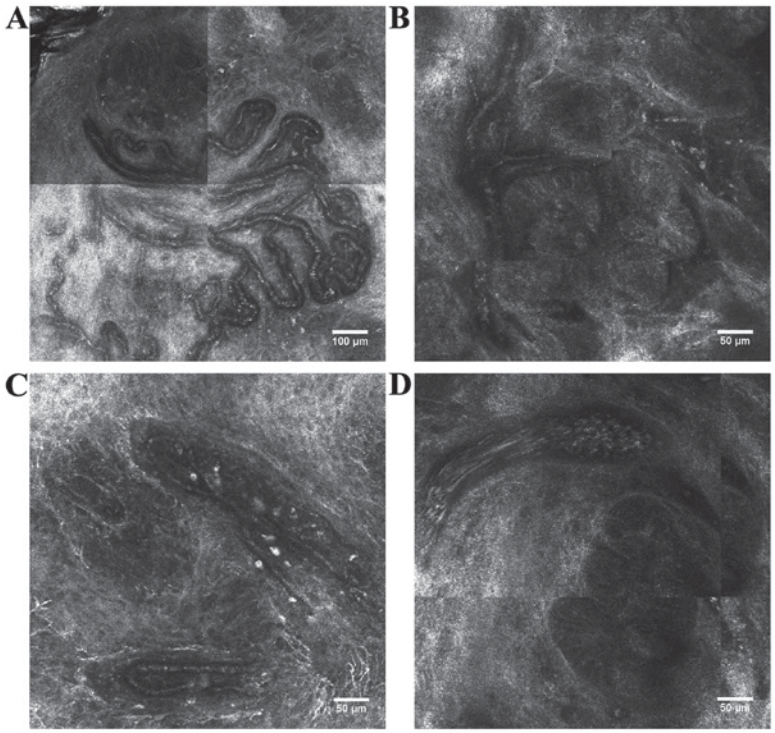

Figure 2. BCC vascular patterns by RCM. (A) RCM mosaic (1x1 mm) revealing horizontal, parallel oriented, tortuous, enlarged blood vessels with fast blood flow immediately beneath the surface in the tumoral area of a BCC. (B) RCM image (500x500 μm) showing blood vessels that surround tumor islands in a circular fashion in a nodular BCC. (C) RCM image (500x500 μm) of superficial, loop-like blood vessels with fast blood flow in the tumoral area of a BCC. (D) RCM image (500x500 μm) of a very large blood vessel located in the immediate proximity of BCC tumor islands.

A fair number of confocal microscopic vascular criteria for NMSC diagnosis have already been determined by previous research (79,85,90-93).

Sauermann *et al* found numerous, horizontal, parallel oriented, enlarged blood vessels (diameter 10-105 vs. 10-14 μm in uninvolved skin) with very fast blood flow immediately beneath the epidermis (35 to 50 μm beneath the surface) in the tumoral region of BCCs. The authors found the same changes in fibrosing BCC (94). We could observe comparable vascular findings in RCM optical sections of BCCs (Fig. 2) (unpublished results).

One study conducted a comparative analysis of the RCM vascular features between several nonpigmented tumoral lesions which included 56 BCCs, 13 seborrheic keratoses (SKs), 11 SCCs, 8 actinic keratoses (AKs), 7 Bowen's Disease, 3 keratoacanthomas, and 24 other nonpigmented tumors (95). The authors (95) reported a strong association between vascular polymorphism and malignancy and a significantly ($P<0.05$) higher positive predictive value (72.1%) of branching vessels for BCC lesions than any other tumor groups analyzed. These findings are supported by others (95,96), who also reported BCC lesions to display vascular polymorphism on RCM examination, with at least two vascular morphologies as a result of bizarre angiogenesis. Moreover, they found that non-branching, high-diameter, straight linear and tubular vessels that surround tumoral islands have higher PPV for BCC compared with other nonpigmented lesions, a common finding in other confocal studies (96,97). Underpinning these *in vivo* observations, Grunt *et al* (98) histologically describe tumor cells beds in BCC as being enveloped by basket-like capillary plexus, and that telangiectatic but flattened capillaries run superficially, over long distances, across tumors. Among all the tumor types, BCC vasculature exhibited the largest vascular diameter (tubular vessels at 53.5 μm and branching vessels at 53 μm). Branching canalicular vessels have proved useful for differentiating BCC from AKs and SCC, which have different vascular patterns (96).

Abnormal blood flow is frequently observed in BCCs as a result of neoplastic angiogenesis (88). In one study (99), increased vasculature showed a sensitivity of 95.8% for BCC diagnosis. Although skin lesions with blood flow in opposite directions demonstrated a significantly higher chance of malignant potential (95), this feature was not found statistically significant in histopathology. A slight drawback of RCM is the fact that the technique cannot differentiate between preexisting blood vessels and the ones resulting from neoangiogenesis. Be that as it may, vascular polymorphism is associated with more complicated angiogenesis, thus it is highly suggestive of malignancy.

6. Histopathological view of BCC vasculature

Histopathology allows for the evaluation of microvessel densities, expression of various proangiogenic factors through immunohistochemistry, and the investigation of neovascularization heterogeneity, therefore creating a more detailed picture of tumor aggressiveness and prognosis.

Studies attempting to predict tumor behavior by quantifying MVD face a number of obstacles. First and foremost is the fact that there is no perfect vascular marker (100). Yet, in order to determine MVD, several endothelial cell index have been employed in immunohistochemical staining methods,

such as CD34 and VEGF in the study by Loggini *et al* (27), and platelet factor VIII in the study by Sari Aslani and Aledavood (101). However, the sensitivity and specificity of these indices are less than CD31 (102). Examining the relationship between vascular density of recurrent and non-recurrent lesions and mitosis, Yerebakan *et al* have used CD31 and Ki67 (103). Rasi *et al* (104) determined SCC and BCC vascular density using CD31, and Chin *et al* (25) used the same index to compare MVD in the body and stroma of BCC, SCC and trichoepitheliomas. Their results are briefly discussed below.

Immunohistochemical studies investigating MVD and VEGF expression using CD31 and VEGF antibodies have revealed that both these measures were higher in the morpheaform and nodular BCCs (average value of 28.3 vessels/mm^2) than in the superficial specimens (average value of 17.4 vessels/mm^2) (4), whereas Winter *et al* (35) have found no differences in MVD between nodular and morphoeic lesions but did note a highly significant ($P<0.0001$) difference between nBCC (24.7±6.7 peritumoral vessels/field), Pinkus' tumors (19.7±6.6 vessels/field) and trichoblastomas (15.3±5.1 peritumoral vessels/field). The latter authors noted generally low intratumoral MVD and higher values in peritumoral stroma with a strong correlation to tumor dignity (35), supporting previous studies (25-27). Therefore, both MVD and VEGF expression have been found to gradually increase from the noninvasive to the more aggressive lesions, defending earlier findings (28). Moreover, these results suggest that determination of peritumoral MVD might facilitate differential diagnosis.

A more recent study by Vuletic *et al* compared MVD and VEGF expression using CD34 and VEGF antibodies in 101 lesions, in relation to BCC histotypes and demographics. Superficial, nodular, cystic, keratinocytic, adenoid, infiltrative, and metatypical BCCs were included in the study. Their results show significantly higher MVD but no significant difference in VEGF expression in the infiltrative, adenoid, metatypical and nodular types. The lowest VEGF expression was found in superficial BCCs, while infiltrative and metatypical subtypes presented the highest values (105). Their results reinforce the fact that the angiogenic potential of BCC is related to lesion histotype. Our group could observe similar vascular findings in histopathological sections of BCCs (Fig. 3) (unpublished results).

Chin *et al* (25), using a multivariate model allowing for age, sex, and depth of tumor invasion, found higher MVD in SCC than BCCs and trichoepitheliomas (TE), although no difference in MVD was noted between nodular and morphoeic BCCs. Even though they found vessels in the body of SCC but not in nodular BCC or TE, the authors could not demonstrate a correlation between MVD and the depth of invasion in neither SCC, BCC, nor TE. Blood vessels in direct contact with tumor cells could not even be found in morphoeic BCC.

Contrary to Staibano *et al* (28) who reported neovascularization heterogeneity in BCCs, Chin *et al* (25) did not reach this result, even when staining for PDGF-Rβ, PDGF-B, Factor VIII, VEGF-receptor 2, and smooth muscle actin. However, the former authors describe the presence of intense inflammation which might have led to difficulties in microvascular evaluation. There is also a problem in methodology in Chin's study, as studied tumors were located on the head and neck and control skin was obtained from the breast, thus controls were poorly matched for age, sex, and most importantly, body site. Despite these limitations, these results are similar to previous studies, proving increased MVD in both BCC and SCC (26).

The absence of a proven correlation between vascular density and depth of invasion in BCCs is consistent with the existing concept of a stromal angiogenic switch that precedes the onset of invasive behavior. Chin *et al* (25) easily found intra-tumoral blood vessels in SCCs, but not in TEs or BCCs. This difference in the microvasculature would, therefore, explain how increased MVD can account for both invasiveness and metastatic potential. Perhaps the best possible test for this hypothesis would be to examine those rare instances of BCCs that have undergone metastatic spread. The prediction would be that blood vessels would be found in the body of such tumors. Carbone *et al* (4) did just that, and measured MVD in several primary superficial BCCs in a patient with BCC lung metastases obtaining a value of 55.5 vessels/mm^2, a value higher than both morpheaform and nodular BCCs examined in the same study (4), again confirming the strong relation between tumor vascularization and aggressiveness (28,36,106).

What does the scarcity of small blood vessels within the body of nodular BCCs compared to the abundance in the peritumoral stroma mean biologically? Some studies link intratumoral vessel formation to metastatic potential of SCC in contrast to BCC (27), while others consider the high peritumoral MVD are attributed to local aggressiveness (25,26,28,107). The scarcity of blood vessels in the body of nBCC provides a good explanation for their ulcerated appearance, while the stromal angiogenic response would explain the appearance of telangiectasia surrounding the tumor. The lack of intra-tumoral blood vessels would account for the absence of metastatic potential leading to the obvious hypothesis that those BCCs that do metastasize contain intratumoral vessels. Opposite to this, SCCs which arise from a similar cell type, do generate an angiogenic response in the tumor body and frequently metastasize.

The forming picture shows that the angiogenic response takes place in the peritumoral stroma, at the edge of these tumors. Microvessels counts have frequently been reported to be highest at the tumor periphery (35,108) and it is here, in the tumor periphery, that the greatest endothelial cell proliferation occurs (109). The invasive potential of these tumors would then be explained by the presence of stromal angiogenesis. This course of reasoning suggests that it is the vasculature in the body of the tumor that is involved in the haematogenous dissemination of neoplastic cells. Usually, but not perfectly, invasive and metastatic potentials are correlated. Supporting these arguments, Staibano *et al* (28) found that the angiogenic process is especially noticeable at the border line between tumor and stroma, right at the invasive front of lesions, and between the sheets of invasive neoplastic cells, even at a significant distance from the main tumoral body. These authors also suggest that the weak angiogenesis at the peripheral border of non-aggressive BCCs, resembling the vascularization of preinvasive solid tumors (22), accounts for their indolent biological behaviour. Unfortunately, this study by Staibano *et al* had a major drawback: the immunohistochemical technique used could not distinguish between preexisting vessels and newly

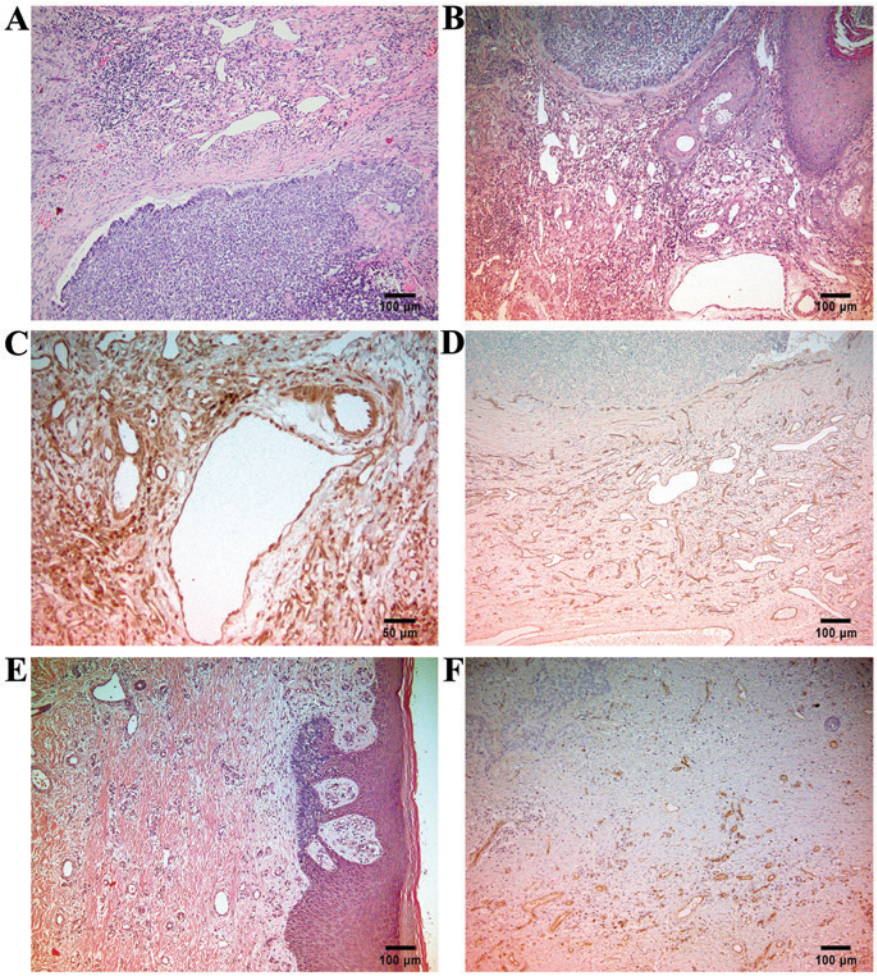

Figure 3. Microvascular architecture in basal cell carcinomas. (A and B) Nodular basal cell carcinoma. Numerous vessels branched and/or dilated in the vicinity of the tumor (H&E, x200). (C) Numerous peritumoral vessels in the vicinity of the tumor (VEGF, x400). (D) High density of vessels of variable calibers in peritumoral location (CD34, x200). (E) Superficial basal cell carcinoma. Fewer peritumoral vessels than in nodular basal cell carcinoma (H&E, x200). (F) Microvascular density in the periphery of a superficial basal cell carcinoma is lower than that in nodular basal cell carcinoma (CD34, x200).

formed ones, thus implying the need for studies concerning the production of angiogenic factors by tumor cells.

Considering the hypothesis that the event granting metastatic potential is the development of intra-tumoral angiogenesis we may wonder why not all studies show a correlation between MVD and prognosis. The observation that vessel density diminishes as one progresses from the periphery towards the center of a tumor has two possible explanations. It could be that as the tumor grows, the blood vessels do not, resulting in a more widely spaced vascular network. The second scenario is that blood vessel regression occurs within the tumor. Either model implies that angiogenesis takes place at the tumor edge and therefore, blood vessels enter the tumoral mass by co-option, a phenomenon thoroughly described in a rat glioma xenograft model (110). This second framework is supported by findings in intermediate-thickness cutaneous melanoma, where authors (22,111) have found significant higher vascularity associated with metastasis, independent from thickness. In the case of BCCs, where MVDs are low, only the second possibility can hold. It is believed that, through an unknown mechanism, there is a zone between the stromal angiogenesis and the leading edge of the tumor where blood vessels undergo complete regression. It is well known that tumors can generate antiangiogenic factors. A number of such factors, including angiostatin (112), were discovered through the phenomenon of tumor interference, by which the presence of one tumor implanted into an animal inhibits the growth of a second. The antiangiogenic agent involved in BCC blood vessel regression would have to have a short range of action compared with proangiogenic factors (25).

Although further studies are required to more accurately describe the mechanisms behind VEGF overexpression in aggressive BCC subtypes, MVD and VEGF expression may prove to be useful prognostic factors to assess the risk of tumor invasiveness.

7. Discussion

The rapidly increasing incidence of NMSCs over the last decades (113) has led to the need for better prevention and treatment strategies, although this can only be achieved through a better biological understanding of NMSC development, involved tumor-promoting factors, risk factors (13), and markers for early diagnosis and aggressive subtype recognition.

Further studies are required to determine if the preferential development of BCCs close to high caliber arterial vessels

reflects a mutual functional influence between tumor and arterial blood flow. As already discussed, tumors promote vessel formation in their close proximity, due to angiogenic factors secreted due to hypoxia (114). However, angiogenesis usually promotes low-caliber vessels formation, therefore, tumor colocalization with high-caliber arteries hardly reflects tumor induced angiogenesis alone. The question that arises is whether arterial blood flow enhances the development of NMSCs. Recently, Polacheck *et al* (115) have shown that mechanical stresses may directly affect tumor progression. The finding of Shields *et al* (116) demonstrate a similar concept, according to which lymphatic flow could actually increase the lymphatic dissemination of neoplastic cells. Furthermore, the forces exercised by blood or lymphatic flow were shown to influence nuclear translocation and activation of transcription factors in vascular or lymphatic endothelial cells (117,118). More interestingly, laminar or oscillatory flow shear stresses have been shown to differently affect endothelial cells, inducing different transcription programs. Altogether, these findings suggest that physical blood flow impacts the tumor microenvironment in several ways (13). If this link were to be undeniably demonstrated, it would constitute a stepping stone for clinicians, a sort of unrefined map of danger areas when screening patients for skin malignancies.

Owing to the ubiquity of dermoscopy, establishment of specific dermoscopic criteria is essential for early and accurate diagnosis of BCC in its different variants. A great deal of studies involving BCCs have focused around defining dermoscopic criteria determined by melanin based structures such as blue-ovoid nests, only a few approaching the area of dermoscopically observable angioarchitecture. It is exactly in the most difficult cases, for example in poorly or non-pigmented tumors, that findings in blood vessels may provide additional information, much needed for a correct diagnosis. Several vascular features for BCC diagnosis have been described, yet the most reliable being considered sharply focused, superficial, typical, telangiectatic vessels (52,63,66,119-121). Still, with the help of machine learning algorithms we look forward to seeing quick and precise methods of vascular feature extraction and quantification, which could help in the differentiation of skin tumors.

In RCM, the vasculature of BCCs is characterized by relatively superficial and mainly horizontally orientated blood vessels that are increased in diameter and number and also irregularly shaped. Vessels parallel oriented can be observed side by side. Comparable changes in skin vasculature have not been described in this combination of features in other skin diseases with known angiogenic activity. In inflammatory conditions such as psoriasis or atopic dermatitis, the vessels are enlarged but orientated vertically (76,77,122). In SCC and melanoma the vascularization shows a more irregular vessel orientation and the leukocyte rolling phenomenon is not as marked as in BCC (79,94). Because angiogenesis might be a regulating factor for BCC aggressiveness, real-time imaging of BCC vasculature by RCM might also prove useful in studies on antiangiogenic therapy.

As already postulated by Rudolf Virchow in 1863 (123), and by Folkman *et al* in 1971 (18), angiogenesis is vital for tumor growth. Blood vessel density has been found to be correlated to tumor aggressiveness and prognosis in a variety of human cancers (124-127). Furthermore, the study of tumor blood vessels may help the therapeutic effort, as angiogenesis and tumor vasculature serve as targets for novel oncologic therapy regimens (128).

Histopathological determination of microvascular densities has been shown to serve as an aid for differential diagnosis. Moreover, VEGF, the main proangiogenic cytokine, has been found to have increased expression in BCCs when compared to normal skin, admitting to a lesser degree than in SCCs (36). Also, VEGF expression in BCCs has been shown to correlate to microvessel density (37). While some authors attribute intratumoral vessel development to metastatic capacity (27), peritumoral vessel density is seen as a trait of local aggressiveness (28,107), referring to BCCs.

Is the vascularization of BCC affected by the well-known pathogenic pathway of Smoothened/Gli activation due to the absence or reduction of PTCH signaling? Translocations or mutations characteristic of particular tumors have also been detected in stromal cells (129). The observation of Winter *et al* (35) made in regressed BCCs during oral treatment with a smo/gli pathway inhibitor that even in the absence of tumor cells, the vessel-containing tumor bed was still present, might disprove this theory in BCCs. The question as to whether fibroblasts in the stroma of BCCs carry the PTCH mutation is still, to the best of our knowledge, under investigation.

In conclusion, through the dermoscope, the pigmented structures in many BCCs, dermal nevi, and keratoacanthomas are visible with exceptional clearness, giving instant access to the diagnosis (130). However, vascular features may become decisive in poorly or non-pigmented lesions, when dermoscopy is correctly performed. Many dermoscopic images of tumors published in the literature show the abrupt ending of blood vessels, indicating a compression artifact. As a result, valuable information is lost (53). In contrast to dermoscopy, vascular structure identification and quantification in histopathology brings a smaller benefit for diagnosing these tumors, as the vertical sections of the tissue do not allow observation of the entire structure of the vasculature. It is, therefore, overwhelming, that most studies on skin tumor vascularization refer to statistical analyses of findings in histologic sections, such as microvessel density (131,132). RCM on the other hand, has the advantage of real-time observation of vasculature and blood flow. Furthermore, RCM optical sections are horizontal, parallel to the horizontalized blood vessels often encountered in BCCs, thus giving the examiner access to a bigger picture of the tumor's angioarchitecture. When factoring in time spent per lesion, RCM of a lesion takes, in our experience ~10 min and can easily be done bedside, while histology, even frozen sections, requires far more time, considering the time needed to obtain a skin biopsy. In conclusion, the emerging data in the literature have shown that while no single technique is perfect for tumor blood vessel evaluation, their complementary use can have an important clinical impact, despite their previously mentioned individual limitations.

Acknowledgements

Not applicable.

Funding

This study was partially supported by a grant of Romanian Ministry of Research and Innovation (Bucharest, Romania), CCCDI-UEFISCDI (project no. 61PCCDI/2018 PN-III-P1-1.2-PCCDI-2017-0341) within PNCDI-III.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ML, MIP and VMV contributed to references acquisition and design, analysis and systematization of data, manuscript drafting, and critical revision of it for important intellectual content. CC, SZ and DB were responsible for the analysis and systematization of data, manuscript drafting, and critical revision of it for important intellectual content. ML, CC and DB were involved in providing of dermoscopic and reflectance confocal microscopic images. SZ contributed to providing of histopathologic images. All authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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