DERMATOLOGY PRACTICAL & CONCEPTUAL
www.derm101.com

The dermatoscopic universe of basal cell carcinoma

Aimilios Lallas[1], Zoe Apalla[2], Giuseppe Argenziano[2], Caterina Longo[1], Elvira Moscarella[1], Francesca Specchio[1], Margaritha Raucci[1], Iris Zalaudek[3]

1 Skin Cancer Unit, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, Italy
2 Dermatology Unit, Medical Department, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
3 Department of Dermatology, Medical University of Graz, Austria

Keywords: basal cell carcinoma, diagnosis, dermoscopy, dermatoscopy, non-melanoma skin cancer, management

Citation: Lallas A, Apalla Z, Argenziano G, Longo C, Moscarella E, Specchio F, Raucci M, Zalaudek I. The dermatoscopic universe of basal cell carcinoma. Dermatol Pract Concept. 2014;4(3):2. http://dx.doi.org/10.5826/dpc.0403a02.

Received: January 7, 2014; **Accepted:** March 8, 2014; **Published:** July 31, 2014

Funding: Study supported in part by the Italian Ministry of Health (RF-2010-2316524).

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

Corresponding author: Aimilios Lallas, M.D., Skin Cancer Unit, Arcispedale Santa Maria Nuova IRCCS, Viale Risorgimento 80—42100 Reggio Emilia, Italy. Email: emlallas@gmail.com

ABSTRACT Following the first descriptions of the dermatoscopic pattern of basal cell carcinoma (BCC) that go back to the very early years of dermatoscopy, the list of dermatoscopic criteria associated with BCC has been several times updated and renewed. Up to date, dermatoscopy has been shown to enhance BCC detection, by facilitating its discrimination from other skin tumors and inflammatory skin diseases. Furthermore, upcoming evidence suggests that the method is also useful for the management of the tumor, since it provides valuable information about the histopathologic subtype, the presence of clinically undetectable pigmentation, the expansion of the tumor beyond clinically visible margins and the response to non-ablative treatments. In the current article, we provide a summary of the traditional and latest knowledge on the value of dermatoscopy for the diagnosis and management of BCC.

Introduction

Following the first descriptions of the dermatoscopic pattern of BCC that go back to the very early years of dermatoscopy, gradually gathering evidence significantly enriched our knowledge on the topic [1-12]. Up to date, the value of dermatoscopy in improving the diagnosis of BCC has been extensively demonstrated, while the method continuously gains appreciation as a useful tool in the management of the tumor [1,9,13-17].

Dermatoscopy for diagnosis of BCC

The list of dermatoscopic criteria associated with BCC has been several times updated and renewed. An analytic description of the BCC-related dermatoscopic criteria and their histopathologic correlation is quoted in Table 1, while a characteristic example of each one of them is presented in Figures 1 and 2 [1,9,12,18,19]. Figure 3 illustrates representative examples of histopathologic alterations corresponding to BCC-related dermatoscopic criteria.

The dermatoscopic variability of BCC is a result of different combinations of these criteria, depending on several factors. Apart from the histopathologic subtype, which represents the most important determinant of the dermatoscopic pattern of BCC, there is upcoming evidence that the dermatoscopic aspect of the tumor is influenced also by factors related to the patient, such as gender, age and pigmentary

TABLE 1. Definition and histopathologic correlation of the dermatoscopic criteria of basal cell carcinoma. [Copyright: ©2014 Lallas et al.]

Dermatoscopic criteria	Definition	Histopathologic correlation
Arborizing vessels	Stem vessels of large diameter, branching irregularly into finest terminal capillaries. Their color is bright red, being perfectly in focus due to their location on the surface of the tumor	Dilated vessels in the dermis, representing the supportive neovasculature of the tumor cells
Superficial fine telangiectasia	Short, fine, focused linear vessels with very few branches	Telangiectatic vessels located in the papillary dermis
Blue-gray ovoid nests	Well circumscribed, confluent or near confluent pigmented ovoid or elongated configurations, larger than globules and not intimately connected to pigmented tumor body	Large well-defined tumor nests with pigment aggregates, invading the dermis
Multiple blue-gray globules	Numerous, loosely arranged round to oval well-circumscribed structures, which are smaller than the nests	Small, roundish tumor nests with central pigmentation, localized to the papillary dermis and/or reticular dermis
In-focus dots	Loosely arranged well-defined small gray dots, which appear sharply in focus	Free pigment deposition along the dermo-epidermal junction, and/or melanophages and/or small aggregates of pigmented neoplastic cells in the papillary and reticular dermis
Maple leaf-like areas	Translucent brown to gray/blue peripheral bulbous extensions that never arise from pigmented network or from adjacent confluent pigmented areas	Multifocal tumor nests containing pigment aggregates, connected to each other by lobular extensions. They are mainly localized in the epidermis and less frequently in the papillary dermis
Spoke wheel areas	Well-circumscribed radial projections, usually tan but sometimes blue or gray, meeting at an often darker (dark brown, black, or blue) central axis	Tumor nests arising and connected to the epidermis, characterized by finger-like projections and centrally located pigmentation
Concentric structures	Irregularly shaped globular-like structures with different colors (blue, gray, brown, black) and a darker central area. They possibly represent variations or "precursors" of the spoke wheel areas	Small tumor nests arising and connected to the epidermis with centrally located pigmentation
Ulceration	One or more large structureless areas of red to black-red color	Loss of the epidermis, usually covered by hematogenous crusts
Multiple small erosions	Small brown-red to brown-yellow crusts	Thin crusts overlying superficial loss of the epidermis
Shiny white-red structureless areas	Translucent to opaque white to red areas	Diffuse dermal fibrosis or fibrotic tumoral stroma
Short white streaks (chrysalis)	Orthogonal short and thick crossing lines seen only with polarized dermoscopy	Presence of collagenous stroma and fibrosis in the dermis

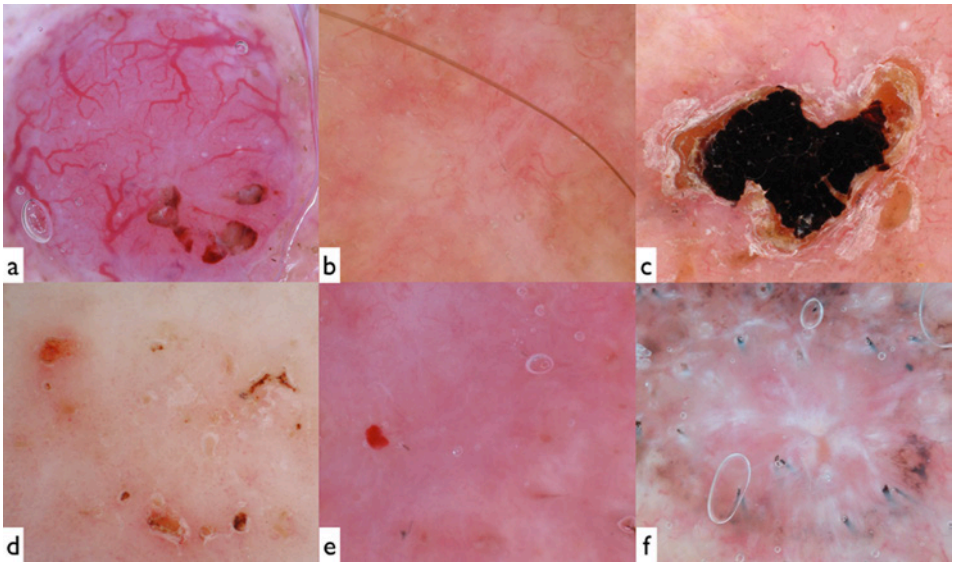

Figure 1. The dermatoscopic criteria of non-pigmented BCC: (a) arborizing vessels, (b) superficial fine telangiectasia, (c) ulceration, (d) multiple small erosions, (e) shiny white-red structureless areas and (f) short white streaks. [Copyright: ©2014 Lallas et al.]

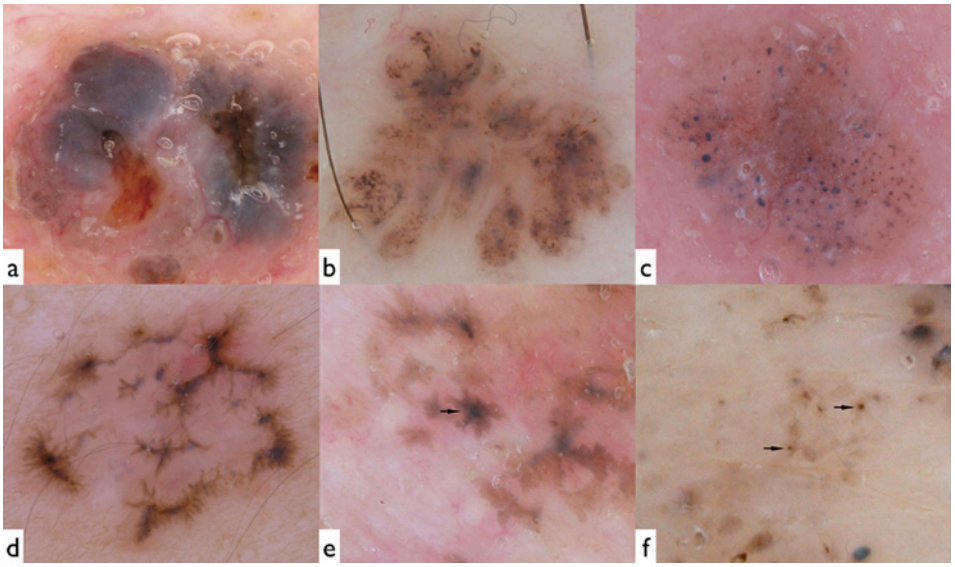

Figure 2. Pigmented BCC may display, in addition to the criteria shown in Figure 1, one or more of the following features: (a) blue-gray ovoid nests, (b) multiple blue-gray dots/globules, (c) in-focus dots, (d) maple leaf-like areas, (e) spoke wheel areas (arrow) and (f) concentric structures (arrows). [Copyright: ©2014 Lallas et al.]

trait. Studies report on a higher frequency of superficial BCC (sBCC) on the trunk and lower legs of women, whereas the majority of nodular BCC occur on the head and neck of men [20,21]. Pigmentation is present in more than 50% of the tumors in skin of color, whereas less than 10% of BCCs in fair skinned individuals are pigmented (Figure 4) [22-26]. Furthermore, the concept of the signature pattern of BCC has been recently introduced, referring to the observation that multiple BCCs in an individual usually display a repetitive dermatoscopic pattern [27].

Dermatoscopy improves the clinical diagnosis of BCC, enabling its detection even at an early stage, when the tumor is still clinically inconspicuous (Figure 5). Dermatoscopy has also been assessed as a valuable method to differentiate BCC from other skin tumors and inflammatory skin diseases [1,9,13]. The reported diagnostic accuracy of dermatoscopy for BCC diagnosis has been reported to range from 95% to 99%, depending on BCC subtype and the set of diseases included in the control group [1,9,12,13]. Indeed, various entities constitute the differential diagnosis of different BCC sub-types. For example, the classical nodular non-pigmented BCC has to be discriminated from squamous cell carcinoma (SCC), amelanotic melanoma and other non-pigmented tumors, while heavily pigmented variants have to be differentiated mainly from melanoma and nevi. Instead, the differential diagnosis of superficial BCC includes both skin

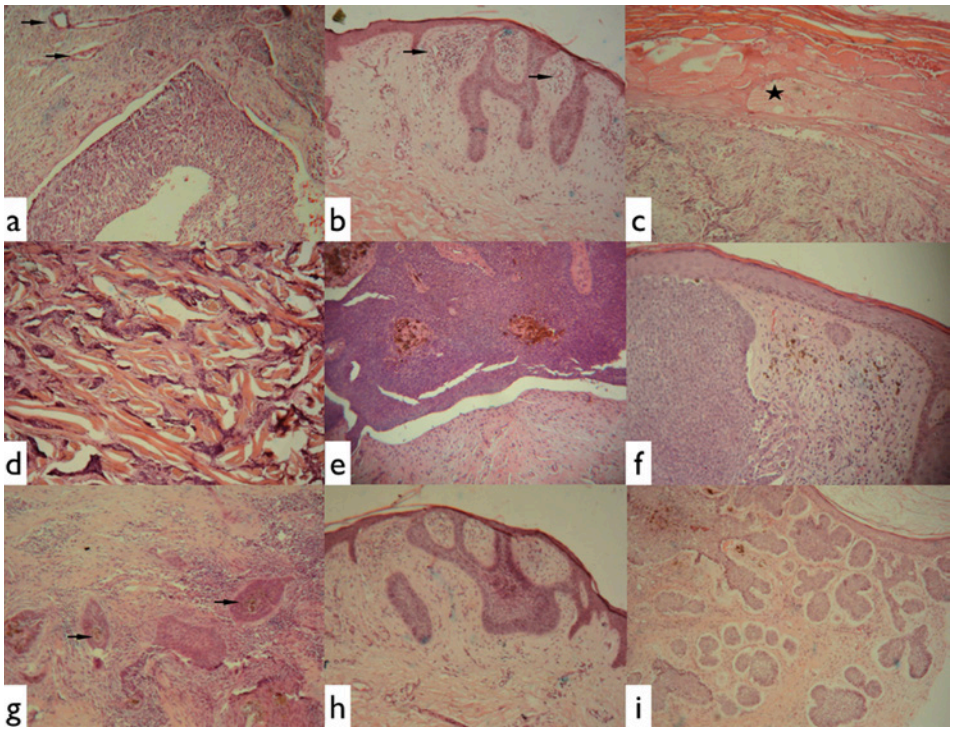

Figure 3. (a) Large dilated vessels in the dermis, corresponding to the arborizing vessels seen in dermatoscopy; (b) fine telangiectatic vessels located in the papillary dermis in a sBCC, dermatoscopically seen as superficial fine telangiectasias; (c) thick hematogenous crust overlying ulceration, dermatoscopically seen as structureless area of black-red color; (d) strands of neoplastic cells in the background of a collagenous fibrotic stroma, corresponding to shiny whitish areas in dermatoscopy (e) large well-defined tumor nests with pigment aggregates, invading the dermis, recognized as blue-gray ovoid nests in dermatoscopy; (f) multiple melanophages in the papillary and reticular dermis, dermatoscopically seen as blue-gray dots; (g) small, roundish tumor nests with central pigmentation localized in the dermis, dermatoscopically corresponding to multiple blue-gray globules; (h) tumor nests arising and connected to the epidermis, characterized by finger-like projections and centrally located pigmentation, that represent the histopathologic correlate of spoke-wheel areas; and (i) multifocal tumor nests containing pigment aggregates, connected to each other by lobular extensions, evoking the dermatoscopic criterion of maple leaf-like areas. [Copyright: ©2014 Lallas et al.]

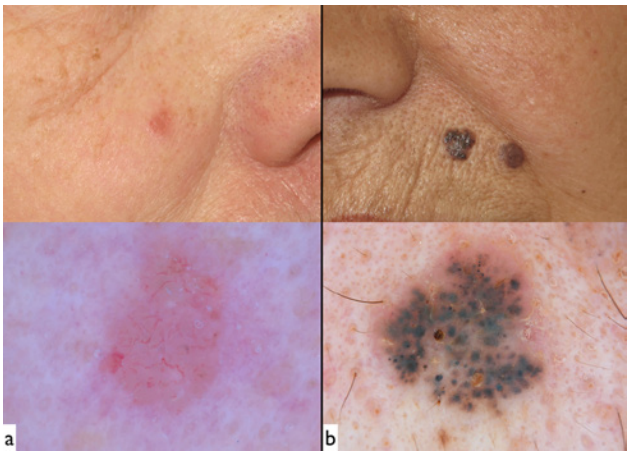

Figure 4. The clinical and dermatoscopic aspect of BCC is influenced by the pigmentary trait of the patient. Fair skin individuals usually develop non-pigmented tumors (a), while the frequency of pigmented variants is much higher in patients with darker skin (b). [Copyright: ©2014 Lallas et al.]

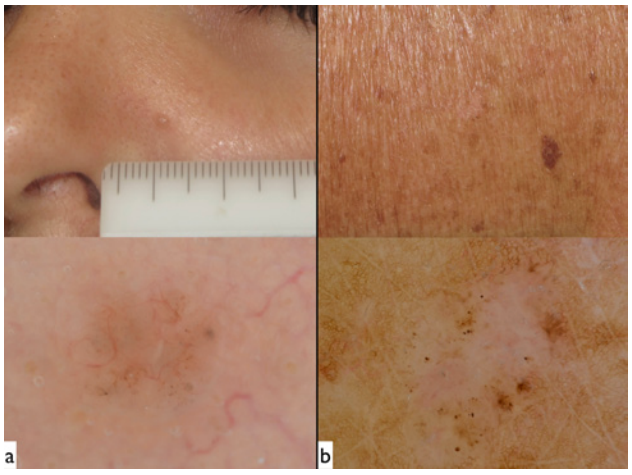

Figure 5. (a) A 2 mm clinically incospicuous papule can be easily interpreted as BCC with dermatoscopic examination. (b) dermatoscopy of this shuttle hypopigmented macule on sun-damaged skin reveals short fine telangiectasia, blue-gray dots and peripheral maple leaf-like areas, allowing a straight-forward diagnosis of BCC. [Copyright: ©2014 Lallas et al.]

tumors, like actinic keratosis or Bowen's disease (BD), and inflammatory skin diseases, such as psoriasis or dermatitis.

The diagnostic accuracy of dermatoscopy has been mainly tested in the field of pigmented BCC, with the well-known Menzies method achieving a sensitivity of 97% and a specificity of 92% and 93% for differentiating pigmented BCC from melanoma and nevi, respectively (Figure 6) [1]. According to the latter model, the diagnosis of pigmented BCC is based on the dermatoscopic absence of pigment network and the detection of one of six positive criteria: arborizing vessels, ulceration, large blue-gray ovoid nests, maple leaf-like areas, spoke wheel areas or multiple blue-grey dots/globules [1]. The substantial reproducibility of these criteria has been appropriately assessed, with arborizing vessels, maple leaf-like areas and large blue-gray ovoid nests representing the most robust and reliable BCC specific parameters [9]. Altamura et al. recently validated Menzies method in a study including more than 600 BCCs, 96.5% of which exhibited at least one

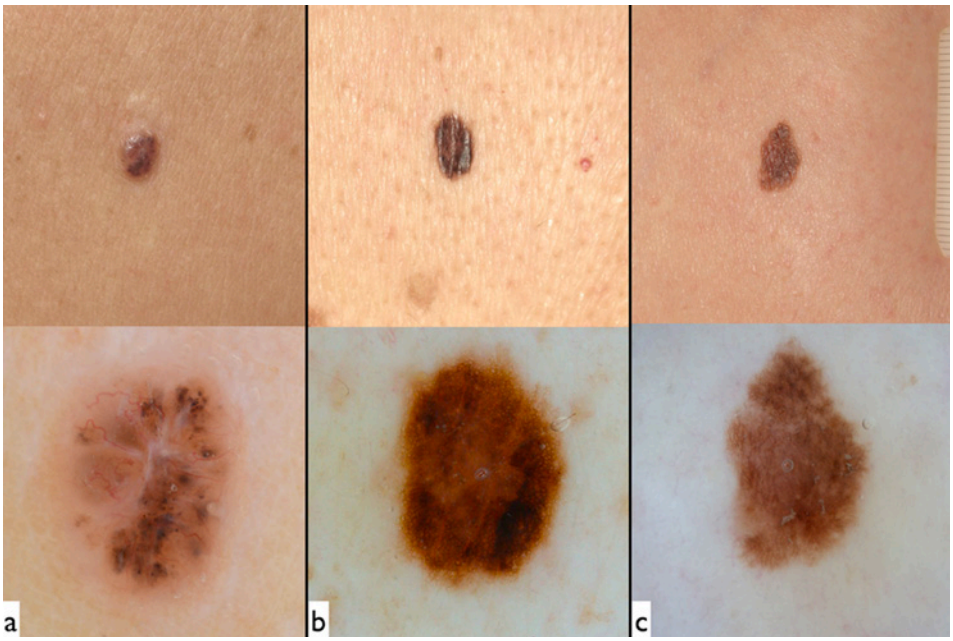

Figure 6. Pigmented nodular BCC has to be discriminated from melanoma and nevi. The diagnosis of BCC (a) is based on the absence of pigment network and the presence of at least one of the BCC-related criteria (in this case arborizing vessels, blue-gray ovoid nests and multiple blue-gray dots). In contrast melanoma (b) and nevi (c), as a rule, exhibit an atypical or a typical pigment network, respectively. [Copyright: ©2014 Lallas et al.]

of the six positive dermatoscopic criteria [9]. Of interest, 40% of the BCCs in the latter study displayed criteria suggestive of melanocytic lesions, including dots/globules, blue-whitish veil and vascular structures. The frequency of the latter criteria linearly increased with pigmentation, highlighting the diagnostic challenge in differentiating heavily pigmented BCC from melanocytic tumors (Figure 7). However, even heavily pigmented BCCs were diagnosed with a high accuracy based on the aforementioned absence of pigment network and presence of at least one positive criterion [9].

Although the diagnostic accuracy of dermatoscopy for non-pigmented nodular BCC has not been assessed up to date, several lines of evidence suggest that the detection of arborizing vessels is highly predictive of the diagnosis of BCC, enabling its differentiation from SCC and other non-pigmented skin tumors (Figure 8). In the study by Altamura

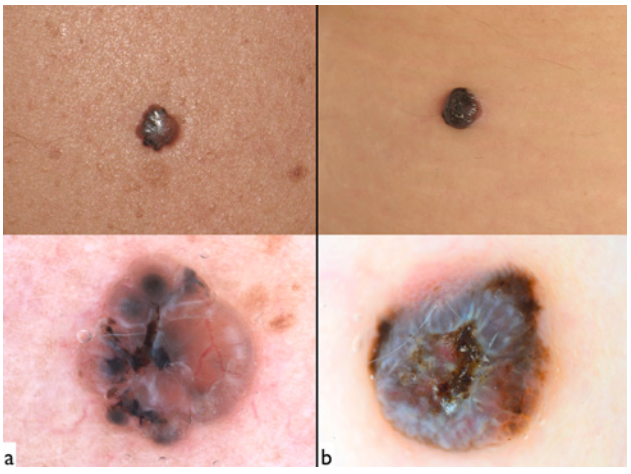

Figure 7. Two clinically similar pigmented nodular tumors. The BCC can be dermatoscopically recognized by the absence of pigment network and the presence of arborizing vessels and blue-gray ovoid nests (a). Although nor the second nodule displays a pigment network, it exhibits dotted vessels and its pigmented structures are irregular brown/black globules and irregular peripheral streaks, in contrast to the well-circumscribed large blue-gray ovoid nests of the BCC. As strongly suggested by its dermatoscopic pattern, the second tumor is a nodular melanoma (b). [Copyright: ©2014 Lallas et al.]

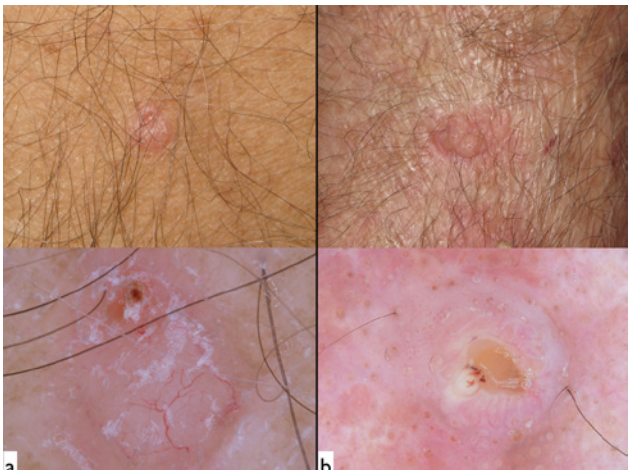

Figure 8. The differential diagnosis of non-pigmented nodular tumors includes BCC, SCC and other less frequent entities. Dermatoscopically, the first nodule exhibits focused arborizing vessels, highly predictive of the diagnosis of BCC (a). Dermatoscopy of the second tumor reveals dotted and linear irregular vessels, keratin masses and perifollicular white circles, overall suggestive of the diagnosis of SCC (b). [Copyright: ©2014 Lallas et al.]

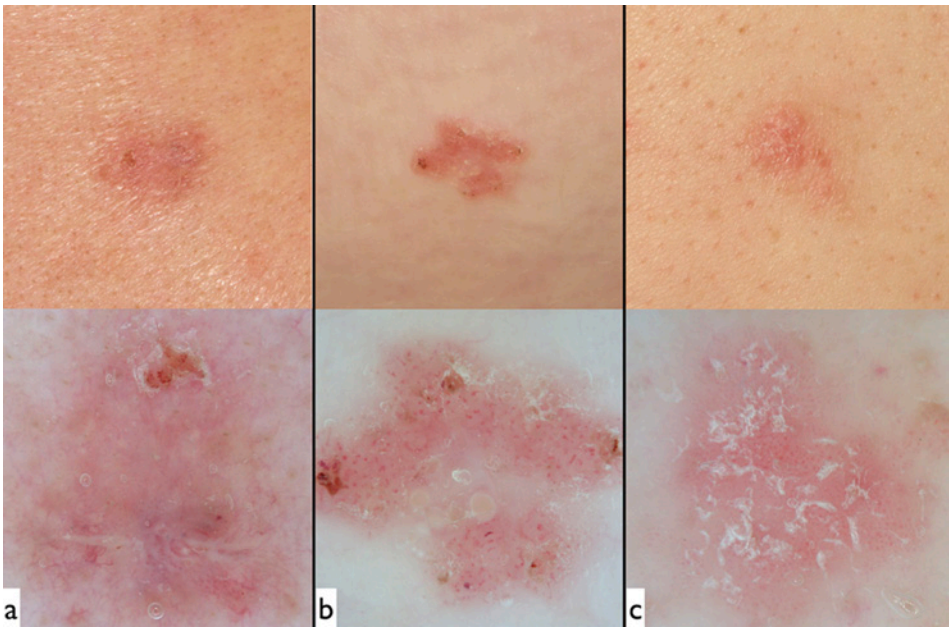

Figure 9. Three clinically similar erythematous and slightly scaly flat lesions. Dermatoscopy of the first case reveals superficial fine telangiectasia and few blue-gray dots, suggestive of the diagnosis of superficial BCC (a). The second lesion dermatoscopically displays dotted and glomerular vessels and yellow crusts, which indicate the diagnosis of Bowen's disease (b). Dermatoscopy of the third plaque reveals the typical pattern of psoriasis, consisting of regularly distributed dotted vessels and white scales (c). [Copyright: ©2014 Lallas et al.]

et al, the characteristic vascular pattern of BCC and the presence of ulceration or erosions were the most useful criteria for the diagnosis of non-pigmented BCC [9]. Rosendahl et al investigated the dermatoscopic pattern of SCC in a study that included a large set of non-pigmented skin tumors with 20 different diagnoses. In addition to their primary findings, the authors found a strong association between the presence of arborizing vessels and the diagnosis of BCC [28].

Superficial BCC has to be differentiated from other skin tumors (mainly in-situ SCC) and inflammatory skin diseases (Figure 9). The clinical discrimination between sBCC and BD can be enhanced by dermatoscopy, which typically reveals shiny white/red structureless areas and superficial fine telangiectasia in the former and glomerular vessels in the latter [13]. Recently, Pan et al assessed the diagnostic accuracy of dermatoscopy for differentiating among sBCC, BD and solitary psoriatic plaques and found the following criteria to be associated with BCC: scattered vascular pattern, arborizing microvessels, telangiectatic or atypical vessels, milky-pink background and brown dots/globules. The authors reported a diagnostic probability of 99% if four of these six features were identified [13]. The dermatoscopic diagnosis of pigmented sBCC is usually straightforward even in small and clinically inconspicuous lesions (Figure 10). This is because pigmented sBCC displays dermatoscopic criteria corresponding to dermo-epidermal melanin deposition (maple leaf-like areas, spoke wheel areas, concentric structures), which are highly specific for the diagnosis of BCC.

In contrast to its usefulness for discriminating BCC from keratinocyte skin cancer, dermatoscopy seems insufficient to differentiate between BCC and adnexal tumors [29]. The latter group comprises sebaceous, follicular, eccrine and apocrine neoplasms, several of which have been characterized as dermatoscopic "mimickers" of BCC [30]. Trichoblastoma, trichoepithelioma, pilomatrichoma, cylindroma and eccrine poroma are only some of the entities reported to dermatoscopically exhibit linear branching vessels and blue-gray globules, similar to those seen in BCC [29,31-35]. In this context, it has been suggested that the differential diagnosis might be facilitated by the observation that the vessels of adnexal tumors are usually less focused, or by the detection of whitish or yellowish structures that have been associated with follicular and sebaceous tumors, respectively [29]. However, the validity and usefulness of the latter dermatoscopic clues and the possible value of dermatoscopy for differentiating between BCC and adnexal tumors require further elucidation.

Dermatoscopy for management of BCC

In addition to its well-documented value for the diagnosis of BCC, dermatoscopy continuously gains an essential role in the management of the tumor. In our era, the therapeutic armamentarium of clinicians for BCC includes several surgical methods as well as non-surgical modalities [36]. The

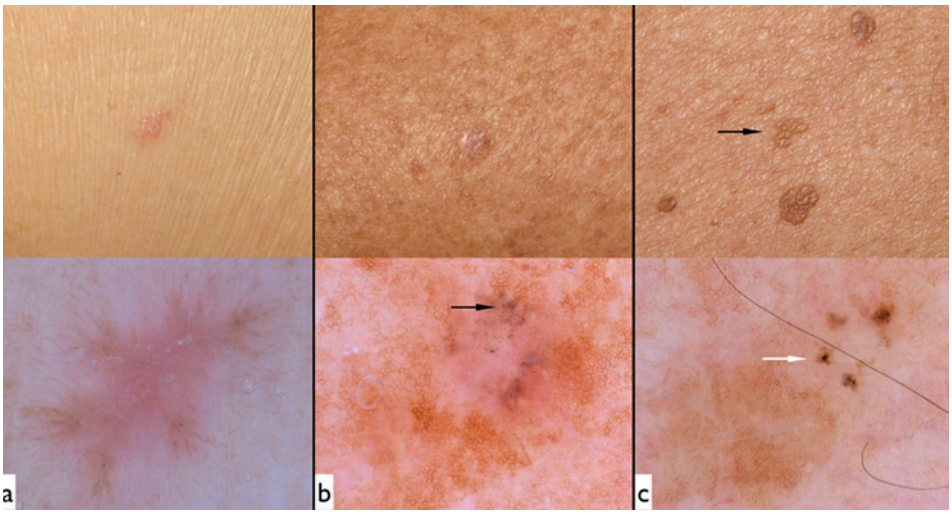

Figure 10. Pigmented superficial BCC can be dermatoscopically recognized at an early stage, based on the characteristic morphology of the dermo-epidermal pigmented structures. (a) Although typical maple leaf-like areas have not been formed yet, the brown peripheral projections of this slightly pigmented sBCC can be easily recognized. (b) A pigmented sBCC arising within a solar lentigo, dermatoscopically typified by small blue-gray dots (black arrow). (c) Another collision of a solar lentigo and a small pigmented sBCC, the latter dermatoscopically exhibitng spoke wheel areas (white arrow). [Copyright: ©2014 Lallas et al.]

choice of the appropriate treatment depends on several factors including the histopathologic subtype, the presence of pigmentation or ulceration, the tumor depth, the anatomical site and the presence of residual disease or recurrence [36,37]. Dermatoscopy has been shown to provide valuable information for several of the aforementioned parameters.

Dermatoscopy for predicting the histopathologic subtype

The histopathologic subtype is the most crucial factor influencing the treatment choice for BCC [36,38]. This is because the response rates of different tumor subtypes to a given treatment modality vary significantly. Superficial BCC, despite of its overall indolent physical course, has been classified in the past among high-risk subtypes, on the basis of its high recurrence rates after surgery [38-40]. This can be explained by the natural tendency of the tumor to expand peripherally beyond clinically visible margins, which often results in incomplete surgical excision and subsequent recurrence. In the recent years, sBCC has been shown to respond perfectly to non-ablative treatments such as imiquimod or photodynamic therapy, prompting experts to recommend the latter modalities as first-line therapeutic options for this subtype [41-46]. In contrast, nodular BCC is associated with high response rates to surgery (up to 98%), while non-surgical treatments are much less effective [36,47-49]. Management of infiltrative and sclerodermiform BCC are more troublesome, since they are characterized by considerable recurrence rates following surgery (up to 40%) while they respond poorly to non-surgical modalities [36,45,47-49]. Mohs' surgery is suggested as the treatment of choice for the latter subtypes [50,51].

Dermatoscopy has been shown to provide valuable information for the pre-operative classification of BCC, since several lines of evidence suggest that different histopathologic subtypes exhibit different dermatoscopic patterns (Table 2, Figure 11) [1,4,7,9,11,12].

The latter observation is reasonable, since the dermatoscopic criteria of BCC correspond to underlying histopathologic alterations [18,19].

Dermatoscopy of non-pigmented nodular BCC, which is the commonest subtype, typically reveals a translucent pinkish tumor. Arborizing vessels represent the dermatoscopic hallmark of nodular BCC, while ulceration is also a common finding. Pigmented nodular BCC is dermatoscopically typified by blue-grey ovoid nests or multiple blue-gray dots/globules, usually associated with arborizing vessels. Structures corresponding to dermo-epidermal pigmentation, including maple leaf-like areas, spoke wheel areas and concentric structures are less frequently observed in nodular tumors, being typically distributed at the peripheral, more superficial part of the lesion [1,9,11].

Infiltrative and sclerodermiform BCC also display branching vessels under dermatoscopy. However, they are usually finer, more scattered and show fewer branches compared to the classic vessels of nodular BCC. In addition, in contrast to the global translucent pinkish color of nodular BCC, infiltrative BCC often exhibits white/red structureless areas, while the underlying fibrosis of sclerodermiform BCC results in a dermatoscopically whitish background [11,12].

In contrast, superficial BCC usually lacks the classic arborizing vessels, typically displaying superficial fine telangiectasia with relatively few ramifications. Multiple small erosions

TABLE 2. Dermatoscopic criteria of basal cell carcinoma according to subtype.

Dermoscopic criteria	Definition
Superficial Pigmented	Superficial fine telangiectasia Multiple small erosions Shiny white-red structureless areas Maple leaf-like areas Spoke wheel areas Concentric structures Multiple blue-gray dots In-focus dots ^ detection of blue-gray ovoid nests excludes the diagnosis of superficial BCC
Nodular Pigmented	Arborizing vessels Ulceration Short white streaks^^ Blue-gray ovoid nests Multiple blue-gray dots In-focus dots Maple leaf-like areas* Spoke wheel areas* Concentric structures* ^^ seen only with polarized dermoscopy * typically detected at the peripheral, superficial parts of the lesion
Morpheaform Pigmented	Arborizing vessels** Ulceration Whitish background Blue-gray ovoid nests Multiple blue-gray dots In-focus dots **usually finer, more scattered and with fewer branches comparing to the vessels of nodular BCC
Infiltrative Pigmented	Arborizing vessels^^^ Ulceration White-red structureless areas Blue-gray ovoid nests Multiple blue-gray dots In-focus dots ^^^usually finer, more scattered and with fewer branches comparing to the vessels of nodular BCC
Fibroepithelioma of Pinkus	White-pinkish background Fine arborizing vessels in the center Dotted vessels at the periphery
Basosquamous carcinoma Pigmented	Arborizing vessels Keratin masses White structureless areas Superficial scale Ulceration/blood crusts Blood spots in keratin masses Blue-gray ovoid nests Multiple blue-gray dots

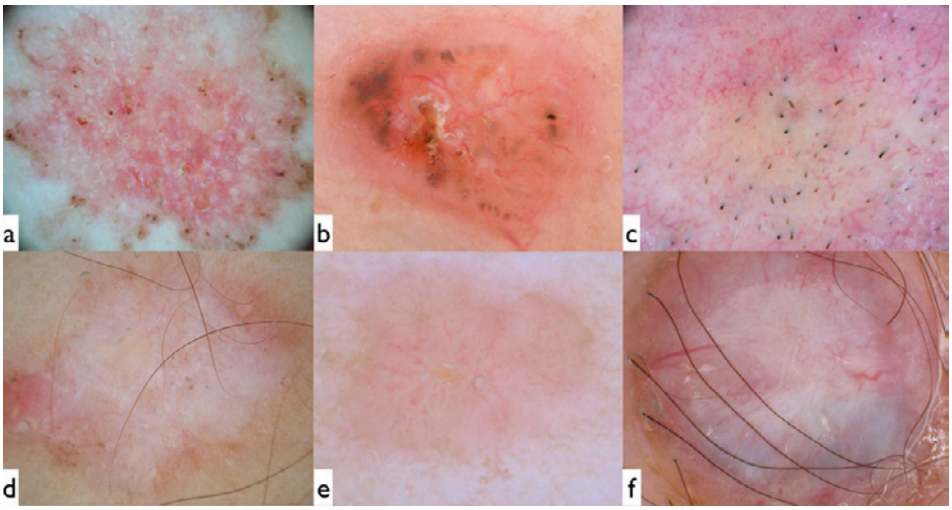

Figure 11. Representative examples of the dermatoscopic pattens of different BCC subtypes: (a) superficial, exhibiting superficial fine telangiectasia, multiple small erosions and maple leaf-like areas; (b) nodular, displaying arborizing vessels, ulceration, blue-gray ovoid nests and multiple blue-gray dots; (c) infiltrative, showing a yellowish-red background and arborizing vessels with small calliber and few ramifications and; (d) morpheaform, exhibiting a whitish backround, few fine arborizing vessels and multiple brown dots. (e) Fibroepithelioma of Pinkus, typified by the combination of fine arborizing vessels in the center and dotted vessels at the periphery; and (f) basosquamous carcinoma characterized by unfocused, peripheral arborizing vessels, a large whitish structureless area in the center and blue-gray ovoid nests at the lower part. [Copyright: ©2014 Lallas et al.]

and shiny white/red structureless areas represent common additional dermatoscopic criteria of non-pigmented superficial BCC. When pigmentation is present in superficial tumors it is located at the level of dermo-epidermal junction, being dermatoscopically seen as translucent light brown to grayish concentric structures, spoke-wheel areas or maple leaf-like areas. Instead, detection of blue-gray ovoid nests signifies the presence of dermal pigmented basaloid nests, indicating that the tumor is not superficial [4,7,12].

Fibroepithelioma of Pinkus is an uncommon variant of BCC, dermatoscopically typified by a white-pinkish background color with fine arborizing vessels in the center and dotted vessels at the periphery [52,53].

Basosquamous carcinoma (BSC) was traditionally described as an uncommon aggressive variant of BCC. However, its biologic course and some clinical and epidemiologic data are rather similar to SCC. Heretofore, BSC is considered to represent a complex of tumors characterized by both basaloid and squamoid differentiation, in an apparent continuum between BCC and SCC [54-56]. The dermatoscopic characteristics of BSC have been recently reported to mirror its peculiar histopathology, since the tumor shares dermatoscopic criteria of both BCC and SCC [57]. In detail, the most frequent dermatoscopic criteria of BSC are unfocused (peripheral) arborizing vessels, keratin masses, white structureless areas, superficial scale, ulceration or blood crusts, blue-grey blotches and blood spots in keratin masses. Notably, nearly all BSC were reported to exhibit at least one BCC-related plus one SCC-related dermatoscopic feature [57].

Nevoid BCC is an uncommon variant of the tumor, typically associated with patients with Gorlin-Golz syndrome. Although dermatoscopy of nevoid BCC may show brown pigmentation similar to the one seen in nevi, it also typically reveals blue-gray dots, globules or nests, often combined with arborizing vessels. In the context of Gorlin-Goltz syndrome, dermatoscopy facilitates also the recognition of the characteristic palmar pits, by revealing lineary arranged dotted vessels (Figure 12).

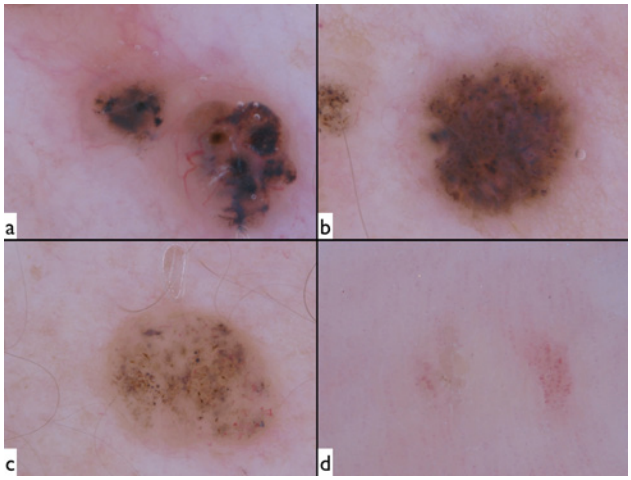

Figure 12. Dermatoscopy of nevoid basal cell carcinomas (a-c) and palmar pits (d) in patient with Gorlin-Goltz syndrome. Although the brown pigmentation is similar to the one seen in nevi, the diagnosis of BCC can be based on the presence of blue-gray nests and arborizing vessels (a), multiple blue-gray globules (b), and multiple blue-gray dots and superficial fine telangiectasia (c), respectively. Dermatoscopy of the palmar pits reveals linearly arranged dotted vessels (d). [Copyright: ©2014 Lallas et al.]

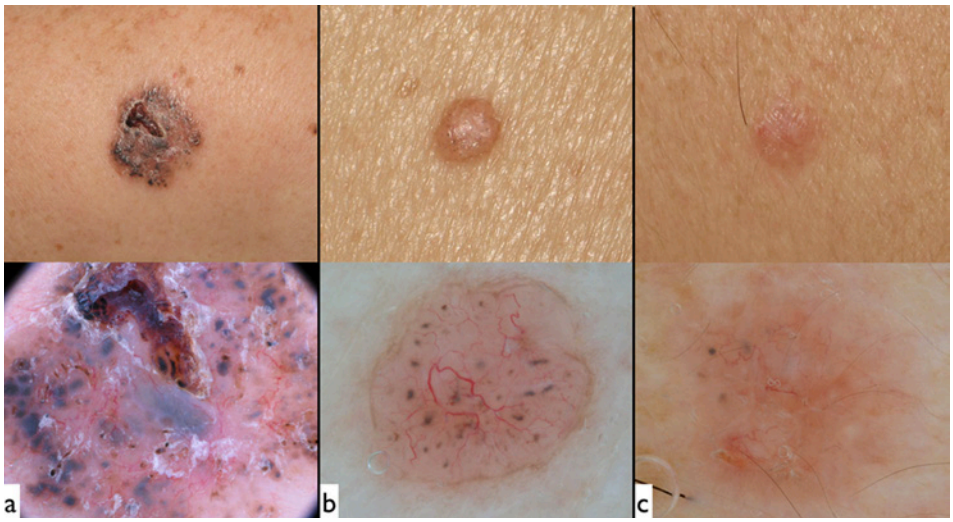

Figure 13. (a) The presence of pigmentation in this BCC is both clinically and dermatoscopically evident. (b) Macroscopically, a few pigmented dots can be hardly seen in this BCC. Dermatoscopy reveals clear-cut pigmented structuress, namely blue-gray globules and nests. (c) On clinical grounds, this BCC is judged as non-pigmented. Dermatoscopy reveals clinically undetectable pigmentation (blue-gray dots/globules). [Copyright: ©2014 Lallas et al.]

A recent study investigated the accuracy of dermatoscopic criteria for discriminating superficial from the other subtypes of BCC [58]. This is particularly relevant in clinical practice, since the possible misinterpretation of a nodular or infiltrate tumor as superficial BCC could lead the clinician to the inappropriate choice of a non-surgical treatment modality. According to the results of the latter study, the presence of short fine telangiectasia, multiple small erosions and structures corresponding to dermo-epidermal pigmentation predict the superficial subtype. In contrast, detection of ovoid nests should lead clinicians to exclude the diagnosis of superficial BCC, while arborizing vessels and large ulcerations are also suggestive of nodular, sclerodermiform or infiltrative tumors. The sensitivity and specificity of this algorithm for the diagnosis of superficial BCC were 81.9% and 81.8%, respectively [58].

Dermatoscopy for assessing the presence of pigmentation

The frequency of pigmentation in BCC varies significantly among different races, since pigmented BCC accounts for less than 10% of BCCs in Caucasians, while the majority of BCCs in Hispanics and Asians and virtually all BCCs in black individuals are pigmented [22-26]. Notably, histopathological studies found trace amounts of pigment in a considerable percentage of clinically non-pigmented BCCs [24]. This is explained by the fact that when only scarce foci of pigmentation are present, they might be insufficient to result in clinically evident pigmentation.

The presence of pigmentation is not routinely reported in histopathologic reports, since in the past it was not considered to influence the management and prognosis of the tumor [38,39]. However, the induction of PDT in BCC treatment restored the importance of pigmentation, since its presence was shown to influence the tumor's response. In detail, case series studies reported a poor response of pigmented BCC to PDT, compared to non-pigmented variants (14% versus 62-100%) [43,59]. This was incorporated in recent guidelines on the use of PDT, suggesting that the method is generally not recommended for pigmented tumors [43,60]. The low efficacy of PDT in pigmented tumors has been attributed to melanin, which appears to act as a competitive light-absorbing pigment, decreasing response rates.

Effectively, the presence of clinically undetectable pigmentation might represent a diagnostic pitfall for clinicians, forcing them to apply an ineffective treatment on a subset of BCCs. This problem seems to be, at least partially, solved by the application of dermatoscopy, which was recently shown to reveal clinically undetectable pigmentation in approximately 30% of macroscopically non-pigmented BCCs, enhancing clinicians to better select tumors potentially sensitive to PDT and minimize treatment failures (Figure 13) [61].

Dermatoscopy for assessing excision margins

Positive surgical margins represent the most potent predictor of BCC recurrence [62,63]. Incomplete surgical excision usually follows removal of tumors located on the face, while recurrence is also associated with BCC subtypes that are characterized by a tendency to expand beyond clinically-visible margins [36,63]. The most reliable method to overcome the problem of positive surgical margins is Mohs' surgery, which is suggested as the optimal treatment for aggressive tumor subtypes (e.g, morpheaform BCC) and for BCCs located on the face [50,51]. However, with the exception of highly

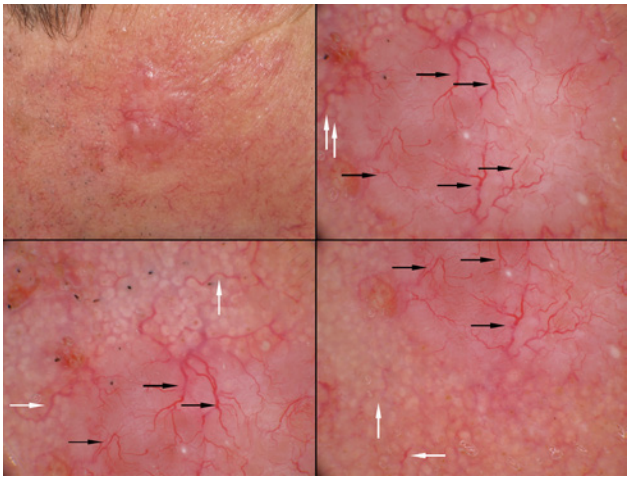

Figure 14. Defining the surgical margins of this BCC developing on telangiectatic, sun-damaged skin is troublesome. Dermatoscopy facilitates the determination of tumor margins, by enhancing the discrimination between tumoral vessels and telangiectasia of the healthy skin. Specifically, the BCC vessels are bright red, appear sharply in focus and exhibit evident ramifications to finer capillaries (black arrows). Instead, the telangiectatic vessels of the surrounging skin are more blurred, unfocused and show few, if any, branches (white arrows). [Copyright: ©2014 Lallas et al.]

specialized clinical settings, the traditional surgical excision remains the choice treatment in the majority of BCCs. Using the recommended lateral excision margins of 3mm, the conventional surgery has been associated with recurrence rates up to 17% [48,49,62].

Dermatoscopy, by providing a more accurate assessment of the true extension of the tumor, allows a more precise estimation of the required surgical margins, helping to minimize the recurrence rate. Specifically, Carducci et al. suggested that the margins of the perilesional healthy skin can be defined by the absence of the well-known dermatoscopic criteria of BCC [14]. The discrimination of BCC vessels from the dermal plexus vasculature of the surrounding healthy skin can be based on the blurred appearance and dark red-to-purple color of the surrounding sun-damaged skin, in contrast to the bright-red and focused vessels of the tumor (Figure 14) [12,14]. While the diagnostic significance of pigmented structures, such as blue-gray ovoid nests, blue-gray globules or maple leaf-like areas is unquestionable, the usefulness of vascular structures in defining the surgical margins is controversial. Mun et al. suggested that arborizing vessels and superficial fine telangiectasia do not directly correspond to BCC cells, but represent feeding vessels of the tumor and may extend also to the perilesional skin [64]. Subsequently, if vessels are considered helpful in defining excision margins, there is the risk of unnecessarily removing healthy skin surrounding the BCC [64]. Although Mun's hypothesis seems reasonable, it was supported by only one published case and, accordingly, the question whether vascular structures should be considered for defining surgical margins of BCC remains to be further elucidated.

Dermatoscopy for monitoring response to non-ablative treatments

As mentioned above, non-ablative modalities have become very popular among dermatologists for the treatment of superficial BCC, achieving high response rates [46,65]. A common problem associated with non-ablative modalities is the post-treatment evaluation, since at the end of a treatment cycle, the clinical morphology of the lesion often does not allow a reliable estimation of the possible presence of residual disease. In this context, clinicians have to choose among the more conservative "wait and see" strategy, the safe option of performing a new diagnostic biopsy or the more aggressive approach of proceeding to a second therapeutic course or to another treatment modality. These scenarios are associated with the risk of under-treating a persisting tumor, over-treating a healed tumor and prolonging patient's morbidity and economic costs, respectively.

Dermatoscopy was recently shown to improve the post-treatment evaluation of BCC following non-ablative procedures; dermatoscopy facilitates the accurate assessment for the presence or absence of residual disease and minimizes the aforementioned risks of under- or over-treatment of BCC [66]. Specifically, the disappearance of the dermatoscopic criteria of BCC after treatment was shown to accurately predict histopathologic clearance, while the persistence or new appearance of some BCC criteria correlates well with persistence and relapse, respectively. According to the results of a recent study, the presence of arborizing vessels, ulceration or pigmented structures (e.g., blue-gray ovoid nests and maple leaf-like areas) accurately predicts residual disease, and should prompt the clinician to continue the treatment. Instead, red/white structureless areas and/or superficial fine telangiectasia might represent equivocal features, since they do not always correspond to residual disease [66]. Effectively, detection of the latter criteria warrants close monitoring to recognize a possible recurrence of the BCC (Figure 15). Of note, in a series of BCCs treated with imiquimod, arborizing vessels, maple leaf-like areas and spoke-wheel areas were reported to decrease in size and number at an early stage after treatment initiation, while ovoid nests and multiple blue-gray globules persisted for a longer period of time [17]. Detection of blue-gray globules has also been reported to be valuable for early diagnosis of disease recurrence.

Conclusion

While in the past dermoscopy was considered a second-level tool for evaluation of clinically equivocal skin tumors, in our era it represents an irreplaceable part of clinical examination.

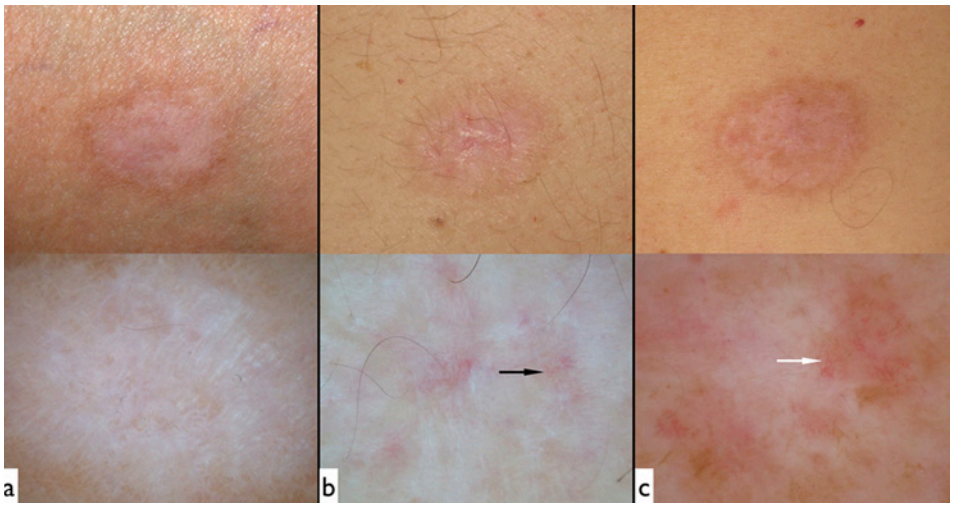

Figure 15. Three superficial BCCs after imiquimod treatment. The presence of residual disease can be neither confirmed nor excluded on clinical grounds. Dermatoscopically, the first lesion does not exhibit any BCC-related criterion, which is suggestive of complete histopathologic clearance (a). Dermatoscopy of the second lesion reveals a few superficial fine telangiectatic capillaries (black arrow), a finding whose significance for residual disease is not clear-cut (b); subsequently, this lesion should be closely monitored to detect disease recurrence. Dermatoscopy of the third lesion shows evident arborizing vessels (c); this finding is predictive of residual BCC, warranting further treatment. [Copyright: ©2014 Lallas et al.]

For BCC, dermoscopy not only augments the clinical differential diagnosis, but also seems to provide additional significant information for guiding the management of the tumor.

References

1. Menzies SW, Westerhoff K, Rabinovitz H, et al. Surface microscopy of pigmented basal cell carcinoma. Arch Dermatol. 2000;136:1012–6.
2. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48(5):679–93.
3. Argenziano G, Zalaudek I, Corona R, et al. Vascular structures in skin tumors: a dermoscopy study. Arch Dermatol. 2004;140:1485–9.
4. Giacomel J, Zalaudek I. Dermoscopy of superficial basal cell carcinoma. Dermatol Surg. 2005;31:1710–3.
5. Sanchez-Martin J, Vázquez-López F, Perez-Oliva N, et al. Dermoscopy of small basal cell carcinoma: study of 100 lesions 5 mm or less in diameter. Dermatol Surg. 2012;38:947–50.
6. Liebman TN, Jaimes-Lopez N, Balagula Y, et al. Dermoscopic features of basal cell carcinomas: differences in appearance under non-polarized and polarized light. Dermatol Surg. 2012;38:392–9.
7. Scalvenzi M, Lembo S, Francia MG, et al. Dermoscopic patterns of superficial basal cell carcinoma. Int J Dermatol. 2008;47:1015–8.
8. Micantonio T, Gulia A, Altobelli E, et al. Vascular patterns in basal cell carcinoma. J Eur Acad Dermatol Venereol. 2011;25:358–61.
9. Altamura D, Menzies SW, Argenziano G, et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol. 2010;62:67–75.
10. Fargnoli MC, Kostaki D, Piccioni A, et al. Dermoscopy in the diagnosis and management of non-melanoma skin cancers. Eur J Dermatol. 2012;22:456–63.
11. Zalaudek I, Kreusch J, Giacomel J, et al. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part II. Nonmelanocytic skin tumors. J Am Acad Dermatol. 2010;63:377–86–quiz387–8.
12. Lallas A, Argenziano G, Zendri E, et al. Update on non-melanoma skin cancer and the value of dermoscopy in its diagnosis and treatment monitoring. Expert Rev Anticancer Ther. 2013;13:541–58.
13. Pan Y, Chamberlain AJ, Bailey M, et al. Dermatoscopy aids in the diagnosis of the solitary red scaly patch or plaque-features distinguishing superficial basal cell carcinoma, intraepidermal carcinoma, and psoriasis. J Am Acad Dermatol. 2008;59:268–74.
14. Carducci M, Bozzetti M, Foscolo AM, et al. Margin detection using digital dermatoscopy improves the performance of traditional surgical excision of basal cell carcinomas of the head and neck. Dermatol Surg. 2011;37:280–5.
15. Peris K, Ferrari A, Fargnoli MC, et al. Dermoscopic monitoring of tazarotene treatment of superficial basal cell carcinoma. Dermatol Surg 2005;31:217–20.
16. Lacarrubba F, D'Amico V, Nasca MR, et al. Use of dermatoscopy and videodermatoscopy in therapeutic follow-up: a review. Int J Dermatol. 2010;49:866–73.
17. Micantonio T, Fargnoli MC, Piccolo D, et al. Letter: Changes in dermoscopic features in superficial basal cell carcinomas treated with imiquimod. Dermatol Surg. 2007;33:1403–5.
18. Demirtaşoglu M, İlknur T, Lebe B, et al. Evaluation of dermoscopic and histopathologic features and their correlations in pigmented basal cell carcinomas. J Eur Acad Dermatol. Venereol 2006;20:916–20.
19. Tabanlıoğlu Onan D, Şahin S, et al. Correlation between the dermatoscopic and histopathological features of pigmented basal cell carcinoma. J Eur Acad Dermatol .Venereol 2010;24:1317–25.
20. Bastiaens MT, Hoefnagel JJ, Bruijn JA, et al. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. J Invest Dermatol. 1998;110:880–4.

21. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Arch Dermatol. 1997;133:593–6.
22. Kikuchi A, Shimizu H, Nishikawa T. Clinical histopathological characteristics of basal cell carcinoma in Japanese patients. Arch Dermatol. 1996;132:320–4.
23. Cheng SY, Luk NM, Chong LY. Special features of non-melanoma skin cancer in Hong Kong Chinese patients: 10-year retrospective study. Hong Kong Med J. 2001;7:22–8.
24. Tan W-P, Tan AW-H, Ee H-L, Kumarasinghe P, et al. Melanization in basal cell carcinomas: microscopic characterization of clinically pigmented and non-pigmented tumours. Australas J Dermatol 2008;49:202–6.
25. Betti R, Gualandri L, Cerri A, et al. Clinical features and histologic pattern analysis of pigmented basal cell carcinomas in an Italian population. J Dermatol. 1998;25:691–4.
26. Bigler C, Feldman J, Hall E, et al. Pigmented basal cell carcinoma in Hispanics. J Am Acad Dermatol. 1996;34:751–2.
27. Zalaudek I, Moscarella E, Longo C, et al. The 'signature' pattern of multiple Basal cell carcinomas. Arch Dermatol 2012;148:1106.
28. Rosendahl C, Cameron A, Argenziano G, et al. Dermoscopy of squamous cell carcinoma and keratoacanthoma. Arch Dermatol. 2012;148:1386–92.
29. Lallas A, Moscarella E, Argenziano G, et al. Dermoscopy of uncommon skin tumours. Australas J Dermatol. 2014;55(1):53-62. Epub 2013 Jul 19 doi:10.1111/ajd.12074
30. Sgambato A, Zalaudek I, Ferrara G, et al. Adnexal tumors: clinical and dermoscopic mimickers of basal cell carcinoma. Arch Dermatol 2008;144:426.
31. Khelifa E, Masouyé I, Kaya G, Le Gal FA.. Dermoscopy of desmoplastic trichoepithelioma reveals other criteria to distinguish it from basal cell carcinoma. Dermatology. 2013;226(2):101-4. Epub 2013 Jan 30. doi:10.1159/000346246
32. Zaballos P, Llambrich A, Puig S, et al. Dermoscopic findings of pilomatricomas. Dermatology. 2008;217:225–30.
33. Lallas A, Apalla Z, Tzellos T, et al. Dermoscopy of solitary cylindroma. Eur J Dermatol. 2011;21:645–6.
34. Ferrari A, Buccini P, Silipo V, et al. Eccrine poroma: a clinical-dermoscopic study of seven cases. Acta Derm Venereol. 2009;89:160–4.
35. Nicolino R, Zalaudek I, Ferrara G, et al. Dermoscopy of eccrine poroma. Dermatology. 2007;215:160–3.
36. Telfer NR, Colver GB, Morton CA, British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. Br J Dermatol. 2008;159:35–48.
37. Sterry W, European Dermatology Forum Guideline Committee. Guidelines: the management of basal cell carcinoma. Eur J Dermatol. 2006;16:467–75.
38. Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8.
39. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol. 2003;148:195–202.
40. Bath-Hextall F, Bong J, Perkins W, et al. Interventions for basal cell carcinoma of the skin: systematic review. BMJ. 2004;329:705.
41. Wang I, Bendsoe N, Klinteberg CA, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol. 2001;144:832–40.
42. Soler AM, Warloe T, Berner A, et al. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. Br J Dermatol. 2001;145:467–71.
43. Christensen E, Warloe T, Kroon S, et al. Guidelines for practical use of MAL-PDT in non-melanoma skin cancer. J Eur Acad Dermatol Venereol. 2010;24:505–12.
44. Braathen LR, Szeimies R-M, Basset-Seguin N, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology. 2005. 2007. 125–43.
45. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2004;50:722–33.
46. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol. 2005;152:939–47.
47. Rhodes LE, de Rie M, Enström Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol. 2004;140:17–23.
48. Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? Br J Plast Surg 2005;58:795–805.
49. Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. Australas J Dermatol. 2006;47:1–12.
50. Smeets NWJ, Krekels GAM, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet. 2004;364:1766–72.
51. Smeets NWJ, Kuijpers DIM, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face—results of a retrospective study and review of the literature. Br J Dermatol 2004;151:141–7.
52. Longo C, Rajadhyaksha M, Ragazzi M, et al. Evaluating ex vivo fluorescence confocal microscopy images of basal cell carcinomas in Mohs excised tissue. Br J Dermatol. 2014 Apr 21. doi: 10.1111/bjd.13070. [Epub ahead of print].
53. Longo C, Lallas A, Kyrgidis A, et al. Classifying distinct basal cell carcinoma subtype by means of dermatoscopy and reflectance confocal microscopy. J Am Acad Dermatol. 2014 Jun 10. pii: S0190-9622(14)01425-X. doi: 10.1016/j.jaad.2014.04.067. [Epub ahead of print].
54. Reggiani C, Zalaudek I, Piana S, et al. Fibroepithelioma of Pinkus: case reports and review of the literature. Dermatology. 2013;226(3):207-11. Epub 2013 May 25. doi:10.1159/000348707
55. Zalaudek I, Ferrara G, Broganelli P, et al. Dermoscopy patterns of fibroepithelioma of pinkus. Arch Dermatol. 2006;142:1318–22.
56. Garcia C, Poletti E, Crowson AN. Basosquamous carcinoma. J Am Acad Dermatol. 2009;60:137–43.
57. Boyd AS, Stasko TS, Tang Y-W. Basaloid squamous cell carcinoma of the skin. J Am Acad Dermatol. 2011;64:144–51.
58. Betti R, Crosti C, Ghiozzi S, et al. Basosquamous cell carcinoma: a survey of 76 patients and a comparative analysis of basal cell carcinomas and squamous cell carcinomas. Eur J Dermatol. 2013;23:83–6.
59. Giacomel J, Lallas A, Argenziano G, et al. Dermoscopy of basosquamous carcinoma. Br J Dermatol. 2013;169:358–64.
60. Lallas A, Tzellos T, Kyrgidis A, et al. Accuracy of dermoscopic criteria for discriminating superficial from other subtypes of basal

cell carcinoma. J Am Acad Dermatol. 2014;70(2):303-11. Epub 20 November 2013. doi:10.1016/j.jaad.2013.10.003
61. Arits AHMM, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncol. 2013;14:647–54.
62. Apalla Z, Lallas A, Sotiriou E, et al. Effect of pigmentation on photodynamic therapy. Lancet Oncol. 2013;14:e339–40.
63. Lallas A, Argenziano G, Kyrgidis A, et al. Dermoscopy uncovers clinically undetectable pigmentation in basal cell carcinoma. Br J Dermatol. 2014 170(1):192-5. Epub 30 September 2013. doi:10.1111/bjd.12634
64. Kyrgidis A, Vahtsevanos K, Tzellos TG, et al. Clinical, histological and demographic predictors for recurrence and second primary tumours of head and neck basal cell carcinoma. A 1062 patient-cohort study from a tertiary cancer referral hospital. Eur J Dermatol. 2010;20:276–82.
65. Mueller CK, Nicolaus K, Thorwarth M, et al. Multivariate analysis of the influence of patient-, tumor-, and management-related factors on the outcome of surgical therapy for facial basal-cell carcinoma. Oral Maxillofac Surg. 2010;14:163–8.
66. Mun J-H, Jwa S-W, Song M, et al. Pitfalls of using dermatoscopy in defining surgical margins of basal cell carcinoma. Dermatol Surg. 2011;37:1704–5.
67. Morton CA, Szeimies RM, Sidoroff A, et al. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications—actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol. 2013;27:536–44.
68. Apalla Z, Lallas A, Tzellos T, et al. Applicability of dermoscopy for evaluation of patients' response to non-ablative therapies for the treatment of superficial basal cell carcinoma. Br J Dermatol 2013 *in press*.