Master thesis

Factors influencing the basal cell carcinoma's morphologic universe

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Dr. Anna-Sophie Bamer
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Declaration of honor

I hereby confirm on my honor that I personally prepared the present academic work and carried out myself the activities directly involved with it. I also confirm that I have used no resources other than those declared. All formulations and concepts adopted literally or in their essential content from printed, unprinted or Internet sources have been cited according to the rules for academic work an identified by means of precise indications of source.
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Pyhra, 8th of July 2022

Abstract

Background:

Basal cell carcinoma is the most frequent human malignant neoplasm worldwide and poses a tremendous burden on health care systems. The incidence of this type of non-melanoma skin cancer is constantly increasing. Dermoscopy is a non-invasive diagnostic tool that increases the accuracy of basal cell carcinoma detection, due to the presence of specific dermoscopic features, and may also be used for the monitoring of treatment outcomes. So far, several factors influencing the dermoscopic morphology of basal cell carcinomas have been described in the existing literature but were not linked together. These factors might have the potential to predict the morphology of basal cell carcinomas to facilitate their detection and diminish misdiagnosis.

Objectives:

To identify and demonstrate the different factors influencing the basal cell carcinoma's dermoscopic aspect, to link them together, and to point out the resulting morphologic changes, as well as to conclude from these findings a possible prediction.

Methods:

This thesis is a literature review. The research was performed using the online database PubMed. Inclusion criteria: retro- and prospective studies and case reports, case series, as well as case-control studies with a focus on dermoscopic description, and the possible influence of extrinsic and intrinsic factors. 69 publications were included in the main part of this thesis.

Conclusion:

The histologic subtype and the anatomical location exert a great influence on the dermoscopic morphology of basal cell carcinoma. Further, an individual's pigmentary traits were strongly influencing the basal cell carcinoma's dermoscopic features.

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Table of frequently used abbreviations

5-FU	5-fluorouracil
ASIP	agouti signaling protein
BCC	basal cell carcinoma
BDCS	Bazex-Dupré-Christol syndrome
BMI	body mass index
CSL	collision skin lesion
etc.	et cetera
Fig.	Figure
HH	Hedgehog pathway
HHI	Hedgehog pathway inhibitors
HPV	human papillomaviruses
HIV	human immunodeficiency viruses
i.e.	id est = that is
ICD-10	International classification of diseases, 10th revision
IRF4	interferon regulatory factor 4
LASER	light amplification by stimulated emission of radiation
MC1R	melanocortin-1 receptor
MM	malignant melanoma
mm	millimeter
NBCCS	nevoid basal cell carcinoma syndrome
NMSC	non-melanoma skin cancer
PTCH1	Protein patched homolog 1
PTCH2	Protein patched homolog 2
RCM	reflectance confocal microscopy
SCC	squamous cell carcinoma
SHH	Sonic hedgehog
SMO	smoothened gene
SNP	single nucleotide polymorphism
SOC	skin of color
SOTR	single-organ transplant recipients
SUFU	suppressor of fused homolog
TYR	tyrosinase gene
U.K.	United Kingdom
U.S.A.	United States of America
UV	ultraviolet
XP	Xeroderma pigmentosum

I Introduction

1. Epidemiology

Basal cell carcinoma (BCC) represents the most frequently occurring form of skin cancer (1), particularly in the fair-skinned population.(2) The estimation of the rates of occurrence of this type of cancer vary in the literature. It accounts for between 70% (3) and 75% (1) of all skin cancers and approximately 85% of non-melanoma skin cancers.(4) For a light-skinned individual the lifetime risk of developing a BCC is about 30%.(5) Men are slightly more often affected, and metastasizing is extremely rare with less than 0,55%.(6)

Gaining access to accurate epidemiological data is often hindered due to various circumstances. First and foremost, cancer registries find themselves confronted with a great many cases. Furthermore, not all BCCs are excised or sent for a histopathological examination (1) and most cancer registries only use histologically confirmed diagnoses.(7) These issues complicate a proper routine recording. Moreover, some national cancer registries still use the ICD-10 version of 2019, in which the BCC is classified as C44 – “other malignant neoplasms of the skin”. However, other types of skin cancer are included in this definition, like the SCC, the Merkel cell carcinoma and other non-melanoma skin cancers.(8) Therefore, a precise subsequent sorting out for statistical purposes is almost impossible. For example, Austria’s official Federal Statistical Office, namely “Statistik Austria”, provides a lot of up-to-date information on the epidemiology of melanoma but none on BCC.(9) However, valid data can be obtained from Germany, which is akin to Austria in its geographical position and its demography. According to the German center of cancer registries, namely “Zentrum für Krebsregisterdaten”, 200.000 people were diagnosed in 2018 with NMSC for the first time, and about 75% (in numbers 150.000) were BCCs.(10) This institution also showed a 2,4-fold increase of BCCs in the years 1998 to 2010 in Germany.(11)

Finland’s incidence rates of BCC are the lowest compared to other European countries.(5) Between the years 1993 to 1998 in Italy, the Trentino Skin Cancer Registry reported an incidence of 88/100.000.(1) In comparison, the BCC incidence rates in 1994 in Slovakia was only 38/100.00 person-years. In 2003, the female and male combined incidence rate in the Netherlands was 87,5/100.000. During the period from 2000 to 2006 in England an incidence rate of 76,21/100.000 person-years was

registered. Over the last 40 years the incidence rates in Europe show a similar rate of increase, by approximately 20/100.000 person-years every 15 years.(2)

North America shows altogether higher incidences than Europe. In the Canadian province of Manitoba, incidence rate of BCC in the year 2000 accounted for 93,9/100.000 person-years for male individuals; and in Alberta in 2006, 147/100.000 person-years. Several studies in the U.S.A. have shown widespread differences in the BCC incidence rates according to the latitude. Northern states like Minnesota and New Hampshire reported an incidence of 170/100.000 person-years in 1980, whereas states in the South-West, like New Mexico and Arizona, showed a significantly higher incidence rate of approximately 935,9/100.000 person-years in 1996. Different studies after standardization showed that the incidence rates of BCC in the U.S.A. increased at the same rate of 2% per year.(2, 12-14)

Australia is reported to be the country and continent with the highest incidence worldwide, having rates almost 10 times higher than Germany, the U.K. and Canada. Queensland is the Australian state that had the highest incidence rates, with twice the national average in the year 1990.(15) Nevertheless, in 2017, with 1355/100.000 person-years lower numbers were registered.(16) A national study in 2002 registered a rate of 884/100.000 person-years, and in 2014 a decrease to 770/100.000.(15)

Africa appears to have the lowest BCC incidence rates in the world, with less than 1/100.000 person-years, however only limited data on this issue is available.(2)

In 2019 the South African National Cancer Registry reported an incidence rate of 21,93/100.000 (world standard population).(17) Non-systematic research revealed only several small cohort studies. For example, a uni-centered prospective study was performed in Morocco from 2010 to 2012 on dermoscopy in 100 patients with BCC.(18) A study in Togo in 2019 included 294 people with albinism and 31 cases of BCCs were diagnosed.(19)

In summary, the global incidence of BCC varies broadly, with Australia reported to have the highest incidence rates, followed by the U.S.A. and Europe. Significant regional variations are reported within countries and continents due to registration systems, degrees of latitude and study periods.(5) Overall, an increase in BCC incidence rates is reported. Furthermore, the total number of BCC cases is presumably severely underestimated by reason of the incidence of skin cancer not always being registered properly.(7)

2. A short glimpse into history and terminology

Skin lesions matching the description of a BCC were recorded a long time before its present-day definition. For example, non-healing ulcers were already identified in ancient Egypt, but cannot be indicated with certainty as skin cancers. In ancient Greece, Hippocrates described ulcers that could either be cured with a knife or cautery or were incurable. In ancient Rome, Celsus reported, in his famous “De Re Medicina”, carcinomas that were most commonly found on the face and surrounded by “tortuous veins”.(20) These fit the concept of a BCC very well.

In 1827, a paper on BCC was published by Arthur Jacob, a surgeon at Sir Patrick Dunn’s Hospital in Dublin. He described its clinical appearance, especially the extraordinarily slow growth and bizarre features of the ulcer’s edges.(20) He provided the first description of such ulcers. As a result, ophthalmologists used the term “Jacob’s ulcer” in the 19th and (beginning of the) 20th century as a synonym for BCCs that occur in proximity to the eye.(21) In 1875, Ferdinand Ritter von Hebra and his son-in-law, Moriz Kaposi, depicted in their book – “Lehrbuch der Hautkrankheiten” – the microscopic appearance of an ulcus rodens.(20) However, it was Edmund Krompecher (in Hungarian, Ödön Krompecher), an Austro-Hungarian pathologist, who characterized BCC by its cytological features and coined the term “carcinoma basocellulare”, which we still use today.(22) Notably, the BCC is still called “Krompecher’s tumor” (in Hungarian Krompecher-daganat) at the Pathology Institute of the Semmelweis University in Budapest.(23)

The origin of dermoscopy can be traced back to the 17th century. It developed from the technique of capillary microscopy.(24) When dermoscopy was discovered for the inspection and evaluation of melanocytic nevi and melanoma in the 1950s (24), the dermoscopy of BCC also gained traction.(25) In 2000, Menzies *et al.* proposed the dermoscopic criteria for BCC, which are widely used today in daily dermatological practice.(26)

In contrary to the English term “basal cell carcinoma”, in German-speaking regions the term “basalioma” (Basaliom) is often used.(6) Several authors in German literature distinguish between a localized “basalioma” and a metastasized “basal cell carcinoma”, though the wordings nowadays are used synonymously.(27) Yet the term “basalioma” diminishes the aggressive potential of this skin cancer and is therefore not recommended anymore.(6) Another German phrase for the BCC is “semi-malignant”,

to describe the fact that while the BCC grows slowly, is locally infiltrating and destructive, it metastasizes extremely rarely.(27) This term is scarcely used in the English literature.

3. Pathogenesis

3.1. Etiology and genetics

With 65 mutations per megabase, BCC is one of the most mutated human tumors.(28, 29) The molecular pathogenesis of BCCs is a complex process involving an interdependence of inherited genetic susceptibility (30) and sporadic somatic mutations. Sporadic mutations often induce carcinogenesis via the Hedgehog signaling pathway.(31) The many variants causing the inherited susceptibility include germline single nucleotide polymorphisms (SNP), genetic traits as well as inherited syndromes and disorders.(30)

3.1.1. Inherited predisposition

Familial studies in Nordic countries like Norway and Finland have shown that the probability of inheriting a BCC or SCC is 43%. (32) According to a study that utilized data from the U.K. Biobank it is estimated that 17% of BCCs are caused by inherited SNPs.(33)

a. Genetic syndromes

Due to the inheritance of highly penetrant mutations in the germline, some individuals are confronted with a higher risk of developing a BCC than the general population. A total of 19 syndromes, most of them very rare, arise from these mutations. Some of them are listed below (30):

- Gorlin-Goltz syndrome
- Bazex-Dupré-Christol syndrome
- Rombo syndrome
- Happle-Tinschert syndrome
- Muir-Torre syndrome
- Brooke-Spiegler syndrome
- Cowden syndrome
- Cartilage-hair hypoplasia
- Schimmelpenning syndrome
- Xeroderma pigmentosum
- Werner syndrome
- Rothmund-Thomson syndrome
- Schopf-Schulz-Passarge syndrome
- Epidermoplasia verruciformis
- Oculocutaneous albinism
- Hermansky-Pudlak syndrome

Obviously more than a half of the names of the above listed syndromes are eponyms, honoring the physicians who played a major part in identification and description of the syndromes.

The Gorlin-Goltz syndrome (OMIM 109400) is also called nevoid basal cell carcinoma syndrome (NBCCS), and it approximately 1:60.000 more frequently prevalent than the others listed above. 1 out of 200 patients with BCCs suffer from this syndrome, even though in 15% of the cases no BCCs arise. The causing mutations are either on the PTCH1 gene (on chromosome 9q22), the PTCH2 gene (on chromosome 1p32) or the SUFU gene (on 10q24-q25). The NBCCS is inherited via an autosomal dominant pattern, with a high degree of penetrance, although the phenotype is variable. Individuals suffering from NBCCS develop nevoid BCCs already in their youth or even during childhood, and its development accelerates with increasing age.(34) The BCCs are situated typically on sun-exposed areas, like the face and trunk, and seem to grow slower than sporadic BCCs, sometimes even staying superficial and stable in growth and growing in a less invasive manner.(27) Apart from the first BCC occurring before the age of 20 other major criteria are odontogenic keratocysts also before the age of 20, palmar or plantar pitting, calcification of the dural folds, medulloblastoma and a first degree relative with NBCCS.(35) Some facial characteristics are also common, such as macrocephaly, hypertelorism with or without strabismus, broad nasal bridge and sometimes affected individuals are mentally disabled. Associated neoplasms are for example medulloblastoma, ovarian cancer, cardiac fibromatosis, fibrosarcoma and rhabdomyosarcoma; while melanoma, meningioma and craniopharyngioma are less frequently reported.(34)

The most frequent mutation causing NBCCS is a germline loss of function affecting the earlier mentioned PTCH1 gene, which is a tumor suppressor gene as the receptor of Sonic hedgehog (SHH). It encodes a 7-transmembrane protein that inhibits the translocation of a protein, called “smoothened” (SMO), which signals cell proliferation. The SHH signaling pathway is activated when the Sonic hedgehog morphogen binds to the PTCH, and SMO is released.(36) The theorem of “two-hit hypothesis” for recessive oncogenes states that “healthy cells require two separate mutagenic hits to produce carcinoma”. This means that individuals with an inherited cancer syndrome, like NBCCS, already have in one of their two copies of a tumor suppressor gene, like PTCH1, a preexisting germline mutation, which alone is not enough to induce

malignancy. For a cancer to occur a second somatic mutation is required, leading to the loss of the second copy of the tumor suppressor gene and further to tumorigenesis.(37)

Interestingly, findings suggest that dark-skinned individuals with NBCCS are less likely to develop BCCs. This represents an example of the interplay between genetic factors in carcinogenesis like pigmentation and epigenetic factors like UV sensitivity.(38)

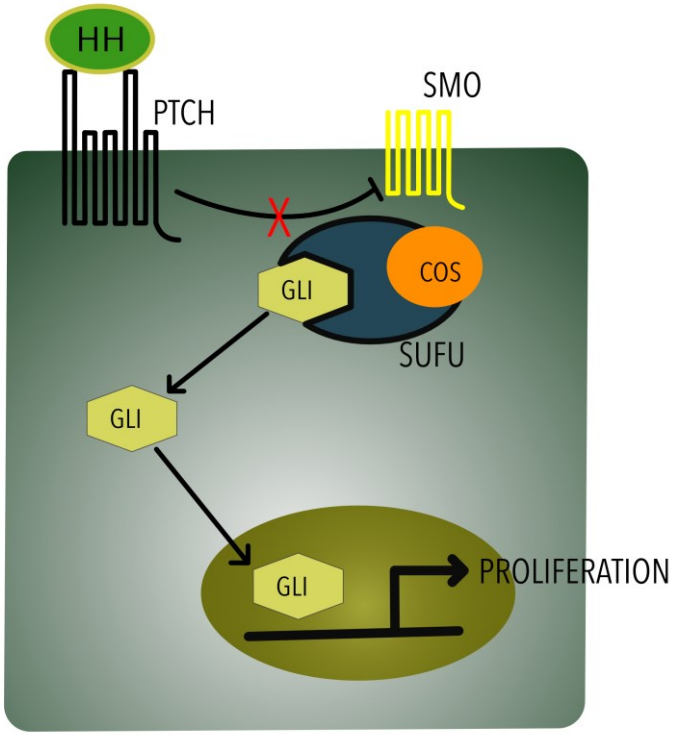


Fig. 1 The Sonic-Hedgehog-Pathway

Physiologically, the SHH cascade is essential for both the determination of tissue patterning and the cell's fate during the early embryogenesis. Per this signaling pathway, pluripotent cells (i.e. stem cells) differentiate into cells of the neural tube, skin cells, muscle cells etc.(27, 39) During evolution, this pathway has been highly conserved.(39) In the skin, the SHH pathway bears responsibility for the adherence of stem cells and controls the hair follicles' development and the sebaceous gland's development.(31) However, the question arises as to how the SHH pathway works exactly? The Hedgehog signaling is activated by its ligand binding the 7-transmembrane complex built by PTCH and its coreceptor SMO. As described above, if PTCH is not bound to the Sonic hedgehog morphogen, it inhibits the release of SMO, thus reducing the hedgehog signaling. But the amalgamation of PTCH and HH leads to their degradation in the cell's lysosomes and thus a liberation of SMO. Subsequent

upregulation of the signaling cascade occurs via several proteins, among others SUFU. The cascade results in the formation of the transcription factor GLI (glioma associated protein) (31, 37, 39), the main power unit “which transcribes genes involved in cell renewal, fate, survival as well as angiogenesis”.(31) In summary hyperactivation of the SHH signaling pathway is the fuel for the BCC’s tumorigenesis.(40-42)

The Bazex-Dupré-Christol syndrome (BDCS) (OMIM 301845) is a very rare disorder with a prevalence of less than 1:1.000.000.(35) Its inheritance pattern is X-chromosome-linked dominant. The characteristic triad of symptoms are the following: basal cell neoplasms (including nevoid BCCs), congenital hypotrichosis and atrophoderma vermiculata (especially dorsa of hand and feet).(43) The pathogenesis is also linked to the hedgehog signaling pathway, and the gene responsible for the aberrant activation is the ACTRT1 gene.(35, 43, 44)

The Rombo syndrome (OMIM 180730) shows similar features in comparison to the BDCS, and therefore it is hard to distinguish them from each other. The hallmarks are extreme rareness, an early onset, usually before the age of 10, and an autosomal dominant inheritance pattern.(35, 45)

Inherited BCC susceptibility also occurs in syndromes that are not linked to a hyperactivation of the SHH signaling pathway, for example Xeroderma pigmentosum. The pathogenesis of this autosomal recessive disorder lies in the malfunction of DNA-nucleotide excision repair of mostly UV-induced damage. The consequence is skin cancer like BCC and others. There is no causal therapy apart from the lifelong avoidance of UV-radiation.(46)

b. Phenotypic traits

Inherited phenotypic traits such as a fair skin type are associated with a higher risk of developing NMSCs in general due to a lack of protective pigment. Overall pigmentation represents a polygenic attribute with high heritability.(47) This results in a greater hereditary propensity to photodamage-induced carcinogenesis and thus increased rates of BCCs. Especially affected are the Fitzpatrick skin types I and II with northern European ancestry, fair skin, childhood freckling, light-colored eyes (like blue, green or hazel), light-colored hair (red and blonde) and the inability to tan.(48) The Fitzpatrick skin type I with red hair and fair skin, which burns easily but does not tan, has a two-fold increased risk of developing a BCC.(49)

Interestingly, photoprotection has also been recommended for people with skin of color (SOC), even though further studies need to examine the correlation between UV-radiation and skin cancer in SOC individuals.(69)

c. Germline polymorphisms

Some traits associated with an increased BCC risk are frequently concomitant with a susceptibility to UV-radiation-induced damage, and are also heritable in terms of genetic polymorphism. Those genetic polymorphisms are controlled by a single genetic locus. In genome-wide association studies 33 different loci were identified as being linked with a higher predisposition for a BCC's development. These loci account for 10.98% of heritable BCCs.(37, 50-53) Below, examples are proposed.

The melanocortin-1 receptor (MC1R) is a polymorphism affecting pigmentary traits and therefore modulates the BCC predisposition. Its upregulation leads to darker pigmentation and subsequently raises UV resistance.(54) Several variants of the MC1R come with a significantly higher risk for BCC, and it has been suggested that some of these variants even raise the risk independently of the pigmentation process.(55) Other examples for polymorphisms influencing genes associated with pigmentation and with a significantly increased risk of BCC are the TYR and ASIP genes. Melanin is produced through the oxidation of tyrosine. TYR encodes the responsible enzyme named tyrosinase. The agouti signaling protein is coded by ASIP and suppresses melanin production.(56) Further loci with an increased risk are IRF4, LPP, EXOC2 and RALY. Loci reported as having a decreased risk are SLC45A2, BNC2 and HERC2.(50)

Mutations in the tumor suppressor gene P53 are highly significant for the BCC. The functions of P53 are mainly to exercise control over the cell cycle regulation and apoptosis, and its mutation leads to tumor formation.(57) Furthermore, the expression of P53 is related to the BCC's aggressiveness.(58) Other important tumor suppressor genes involved in the tumorigenesis of BCC are CDKN2A and CDKN2B. They encode for the cyclin D kinase inhibitors and function as a cell cycle regulator.(59)

As a matter of course, polymorphisms in genes involved in epidermal differentiation and cytoskeletal organization may lead to an increased predisposition to develop BCCs. The KRT5 gene is responsible for the production of K5, an important protein in the cytoskeleton network of basal keratinocytes.(59) This network has been deemed

to be “vital for the basal layer’s structural integrity”.(37) The substitution namely G138E in the KRT5 gene may lead to a higher susceptibility of developing BCC.(59)

Polymorphisms in the NOTCH signaling pathway end in skin cancer and other skin abnormalities. It is an important pathway for the proliferation of keratinocytes and their differentiation (60), and its suppression leads to a BCC. Adding a NOTCH signaling peptide to a BCC leads to an apoptosis of the tumor cells.(61)

Further important polymorphisms are found in genes regarding the telomere maintenance, the DNA repair as well as cutaneous immunity.(37) Important genes affected in terms of telomere maintenance are TERT (59, 62) and OBFC1.(50) TERT encodes for telomerase, which is an enzyme necessary for the attachment of protective repeating sequences on the telomeres (59, 62), while OBFC1 is important for the regulation of the length of telomeres.(50) Aberrant function of these two genes is associated with chromosomal instability and therefore with carcinogenesis, through subsequently better adaptation and survival of BCC cells.(37) The prevention of malignancy by sufficient DNA repair is crucial, as a result polymorphisms affecting these mechanisms lead to an increased propensity to develop BCCs. It was shown that if the genes MUS81 and NABP2 are mutated, they increase the risk of BCC development.(63)

The risk of skin cancer, along with BCC, can also be increased by downregulation of the immune system, including the cutaneous immunity. This happens either by iatrogenic immunosuppression after a solid organ transplantation or infectively acquired via HIV. Furthermore, an association has been reported between a higher propensity of BCCs and polymorphisms in the genes HLA and IRF4.(30) The CT60 GG genotype of CTLA4 seem to play a protective role in the development of BCCs. It was demonstrated in a cohort study of fair-skinned subjects in New Hampshire that this genotype goes hand in hand with a diminished risk of developing BCC. The CT60 GG polymorphism decreases the UV induced immunosuppression due to lesser T-regulatory cell function. Reciprocally, these individuals showed an increased risk for several autoimmune diseases.(64)

3.1.2. Somatic mutations

While germline polymorphisms lead to a heritable susceptibility to BCC, sporadic mutations are required for carcinogenesis. The most frequently mutated pathogenic genes in BCC are DPH3-OXNAD1, TERT, MYCN, LATS1, LATS2, PTPN14, TP53,

SUFU, SMO and PTCH1/2. The last three are HH related. Both LATS and PTPN14 are Hippo-Yap signaling pathway related. 90% of these mutations were identified to be characteristic UV signature mutations.(1, 37, 65)

3.2. Histogenesis

BCC is a neoplasm that derives from epidermal cells on hair-bearing, sun-exposed skin without any preceding precancerous lesion.(6) Its precise cytological origin has been discussed for a long time, but until now its mystery has not yet been fully solved. In the past, the consensus was that BCCs arose from the basal or germinal layer of the epidermis due to the histologic resemblance.(22, 27) This was on account of several studies showing notably different results, but still two assumptions remained the most plausible. One hypothesis stated that BCCs arose from the stem cells located in the hair follicle, precisely the upper and lower bulge, isthmus as well as a region called the touch dome epithelia. Supporting this assertion, Peterson *et al.* demonstrated in a mouse model the association of tumorigenesis with the loss of PTCH1.(66) The other hypothesis indicated that BCCs arose from long-term resident progenitor cells located in the interfollicular epidermis and upper infundibulum. This observation concerned SMOM2-induced BCC-like cancers also in a mouse model.(67) Regardless of which mutation one considers, a subsequent forced activation of the HH signaling pathway leads to BCC-like tumors in mice from both earlier mentioned cell origins.(68)

In immunohistochemical analyses the cells of a BCC expressed the markers Keratin 5 and 14, which were characteristic features of the basal layer of the epidermis, and Keratin 19, which was expressed in epidermal stem cells. BCC cells also expressed EpCAM, a diagnostic marker that could be used to exclude SCCs in the diagnostic process.(27)

In summary, depending on the carcinogenic mutation involved, either stem cells from the hair follicle or from the interfollicular epidermis, including infundibulum, generated a BCC. Moreover, cells from a BCC were remarkably hard to cultivate, since exact environmental and cytologic factors for optimal proliferation needed to be determined.(1)

3.3. Growth and metastasizing

In most of the cases, the growth of BCCs was reported to be very slow. Van Winden *et al.* showed in all small-cohort study on watchful waiting that less than 50% of the BCCs increased in size, and that growth depends on the tumor's subtype rather than size and anatomical location. The median increase in tumor diameter was 4,46mm in 1 year for micronodular or infiltrative BCCs, while other subtypes – like superficial or nodular subtypes – grew 1,06mm.(69) Sykes *et al.* demonstrated a growth rate of between 0,72 and 0,84 mm per year in diameter, and a total surface area growth of 11,5 mm² per year in superficial BCCs. Furthermore, male individuals were reported to have larger BCCs than females.(70)

With indolent, slow progression and eventual local destruction, the outcome of developing a BCC is usually not lethal if treated properly and in time (1, 71), but due to its growth being boundless towards anatomical borders, vital structures may be invaded, for example arrosion of vessels, or consecutive bleeding of the tumor leading to life-threatening situations.(72) Locally advanced BCCs may also infiltrate intracranially or show perineural invasion.(35) Immunohistochemical staining revealed that more aggressive BCCs expressed less CTGF.(71)

Occasionally it happens that excised BCCs reoccur. A recurrence may appear even three years or more after the initial excision.(71) Risk factors for this are: histologically tumor free margins of less than 1 mm (both lateral and deep), special localizations like nasolabial fold, nasal, orbital and auricular, a micronodular, infiltrative as well as a sclerodermiform growth pattern (1, 71) and the basosquamous subtype of BCC.(73, 77) Basosquamous is a histopathologic term.(107)

In most cases, the conventional BCC lacks severe malignant potential and seldomly metastasizes. The numbers reported for metastasizing were far less than 1% (0,0028%-0,55%) (74) but may be approximately 2% if the tumor's diameter is more than 3cm.(78) However, the BCC's basosquamous subtype showed a greater likelihood of metastasizing, with a rate between 5-8,4%.(72, 77) The BCC spread primarily to the regional lymph nodes and lungs (73, 75) and later to muscles and bones.(35) With a median survival time of 24 months (hematogenous spread) to 87 months (isolated lymphatic spread), metastatic BCC comes with a poor prognosis.(76)

3.4. Environmental risk factors

The inherited risk factors contributing to the susceptibility to BCC have already been discussed elaborately in section 3.1., but the environmental factors leading to carcinogenesis of skin tumors in general are not less significant. On the contrary, they go hand in hand.

The most important environmental risk factor for BCC development is UV radiation, more precisely UVB at a wavelength of 280 to 315nm.(79, 80) The risk of developing a BCC is increased by sun exposure that was episodic as well as intense with resulting severe sunburns.(48) Xiang *et al.* reported that approximately 82% of BCCs were ascribable to such excessive exposure.(81) Indoor tanning significantly increased the risk of skin cancer. Especially sunbeds have been shown to have a distinct association with BCCs. Due to their tanning behavior, younger women were particularly affected.(82) The strong association between skin cancer (primarily melanoma) and commercially used, artificial tanning devices led to their ban in Australia in 2015.(83) The most important circumstances concerning UV radiation leading to BCCs were moderate to severe sunburns during childhood and adolescence.(84) The mechanisms leading to UV-induced carcinogenesis were inflammation, immune suppression and direct DNA damage.(85) Migration studies showed that the closer fair-skinned individuals lived to the equator, the greater the probability to develop a BCC due to the higher UV radiation to which they were exposed to.(5) This could be explained that such individuals were exposed to more cumulative UV doses than those of which their genetics prepared them.(103)

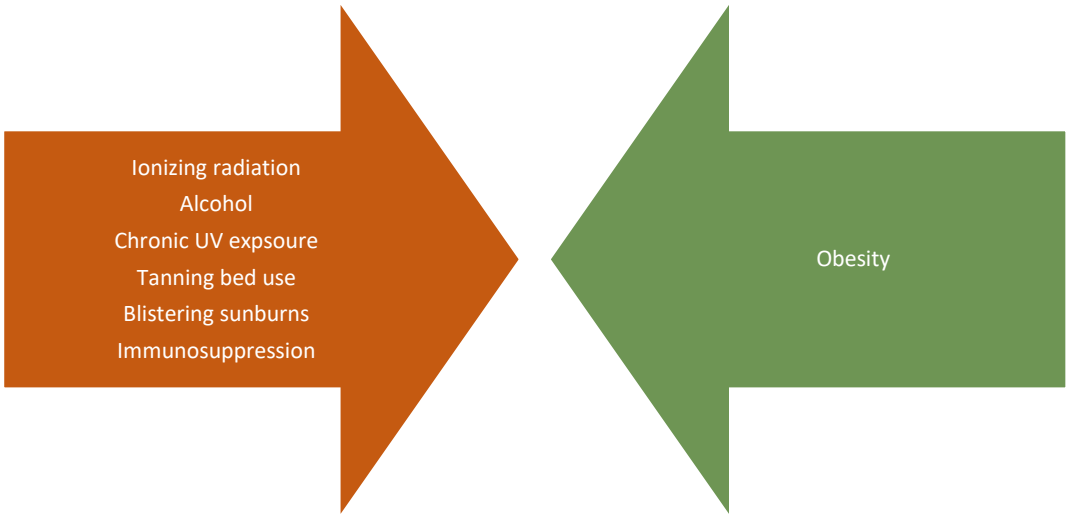


Fig. 2: Environmental risk factors for BCC development. Orange: Risk factors; Green: protective factors

Ionizing radiation also leads to an increased risk of BCCs. Ionizing radiation may originate for medical purposes like radiotherapy, x-rays and total body irradiation; or may be caused by other reasons, like occupational exposure or even as a consequence of atomic bombs. This form of radiation caused carcinogenesis via cell apoptosis, genomic instability and direct DNA damage.(86) Preston *et al.* suggested that the risk of developing a BCC in atomic bomb survivors was directly connected with the age of an exposed individual and the dose of radiation exposure. The younger an individual was at the initial radiation exposure, the higher the risk of developing a BCC.(87)

Comorbidities, like chronic immunosuppression also affected the risk of BCC, but to a lesser extent than SCC. An individual may suffer from immunosuppression, either medically induced by organ transplant medications or caused by an illness like chronic leukemias, lymphomas or an HIV infection.(88, 89) In solid organ transplant receivers the risk of NMSC was increased, but they develop rather SCCs than BCCs.(90) Brewer *et al.* showed that patients suffering from chronic lymphatic leukemia tended to have not only a higher risk of BCCs (and SCCs) but that these tumors were also more aggressive.(91) No significant correlation between HIV infection and susceptibility of BCCs was found.(30)

Interestingly, obesity seems to have a protective impact on both SCC and BCC. Overweight individuals have been shown to be less likely to develop NMSCs compared to individuals of normal weight. This finding was more apparent in women.(92-94) The protective impact of a higher BMI might be explained by less outdoor sport activities and therefore less UV-radiation.(93) While this has not yet been fully explained (93), the protective effect of higher estrogen levels caused by obesity has been demonstrated in mouse models.(95)

As already stated above, iatrogenic immunosuppression via immunosuppressants, for example for single-organ transplant recipients (SOTR), have been associated with an increased the occurrence of skin tumors.(97) Population-based studies were able to report a 6-to-16-fold higher risk for SOTR to develop a BCC. The risk was even higher in patients with a kidney transplant.(105, 106)

Several vitamins also seemed to have an effect. Oral intake of nicotinamide, well-known as vitamin B3, decreased the risk of new BCC development by 20%.(99) High

intake of vitamin D supplements led to a slightly increased risk for BCC development.(98)

Alcohol consumption seemed to demonstrate a positive association with the risk of developing BCC in a non-linear, dose-dependent manner.(100)

While current, and even heavy smoking, was positively associated with SCC risk, it seemed to decrease the risk of BCC as well as MM. Former smoking seems to have no correlation with the risk of developing any skin cancer.(101)

The association between arsenic and increased skin cancer risk is well known.(30) Arsenic-induced BCCs distinguish themselves from BCCs that occur due to UV radiation through their frequent occurrence in non-sun-exposed areas.(102)

No significant correlation could be demonstrated between chronic skin inflammation, HPV infections, HIV infections or dysbiosis of the skin's microbiome, on the one hand, and an increased risk of developing a BCC, on the other hand.(30)

Age also seems to be a risk factor. Usually, the BCC is a tumor occurring most frequently in elderly patients and is – at a ratio of 2:1 – more common in men.(104)

4. Clinical appearance and classification

Clinically, BCCs appear firstly as a skin-colored or pinkish papule, with only a few millimeters in size. Arising only from skin bearing hair follicles, the palms of the hand and the soles of the feet, as well as the mucosa, are not affected. In the first stages, the small BCC nodule presents itself as a shiny, almost pearly aspect and grows for several years without aggressive tendencies.(1, 27, 107, 108) The slow growth of the BCC has already been illustrated in section 3.3. The pinkish nodule grows into a plaque or becomes ulcerated. Often vessels in the form of surface telangiectasia can be seen. Over 26 different subtypes have been reported in the literature (108), but only certain clinical subtypes based on the BCC's appearance are widely acknowledged, such as the nodular, the superficial, the morpheaform (or also known sclerodermiform) and ulcerated BCC.(1, 27, 107, 108) Another rare subtype, the Fibroepithelioma of Pinkus is tremendously uncommon. It arises as an indolent pedunculated papulonodule on the trunk.(107) BCCs can also appear pigmented, even to the extent that they mimic melanoma.(109, 110, 131)

The nodular subtype is the most common one, accounting for 50 to 80% of BCCs. Arising frequently on sun-damaged skin of the head and neck, it appears, as mentioned

before, as a shiny papule or nodule and later rolled borders and small arborizing vessels. If not treated early enough, this subtype advances and becomes larger, and may ulcerate and become a so-called ulcus rodens (107) or terebrans.(111) In advanced stages, vital structures might be invaded and destroyed.(107) Melanin in nodular BCCs is more commonly seen in dark-skinned or SOC individuals.(108)

The superficial subtype accounts for approximately 10 to 30% of BCCs. The superficial BCC arises most commonly on the skin of the trunk and legs and less commonly on the head and neck. Appearing often as an erythematous and scaly lesion or thin plaque, it might be hard to distinguish from an inflammatory lesion, like eczema and psoriasis, or a SCC in situ.(107, 108)

The sclerodermiform (also called morephaform, sclerosing or desmoplastic) subtype is the least common subtype, accounting for less than 10% of BCCs. This variant stands out as an infiltrated, scar-like plaque, with ill-defined borders and subclinical extension and a predilection for occurrence on the skin of the head and neck. It is often hard to distinguish this subtype from a morphea plaque or a scar.(107, 108) The sclerodermiform subtype is more aggressive with a high risk of reoccurrence and local invasion.(112)

Some BCCs may have a highly polymorphic aspect and therefore cannot be classified easily into one of the above-mentioned standard subtypes.(1)

The vague term “locally advanced” is still used as much in the literature as in practice. It is used for BCCs in advanced stages. Firstly, it is used for BCCs with a long growth time span but without any treatment. Secondly, it is utilized sfor BCCs with extensive destruction of the surrounding tissue. Thirdly and lastly, it is used for BCCs so thoroughly progressed that they have become too difficult or even impossible to cure. In daily practice it is useful to distinguish between easy-to-treat and difficult-to-treat BCCs.(1)

The WHO classified the following histologic subtypes of the BCC as lower-risk: nodular, superficial, pigmented, infundibulocystic and fibroepithelial. These are considered as higher-risk: basosquamous carcinoma, sclerodermiform, infiltrating, micronodular and BCCs with a sarcomatoid differentiation.(133)

The anatomical location of a tumor also gives hints as to the possibility of recurrence. The “H-zone” on the face includes the periorbital region, the eyelids and eyebrows, the nose, the angles of the jaw, the temples, ears, and the pre- and postauricular regions. Interestingly, those zones marked on the face produce the letter “H”, although this “H”

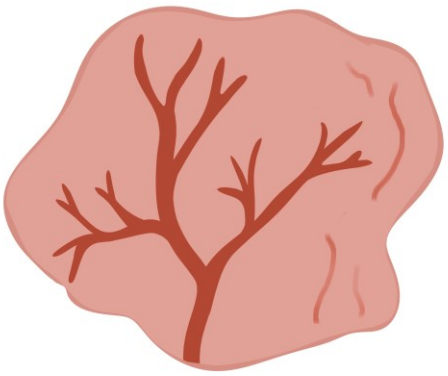
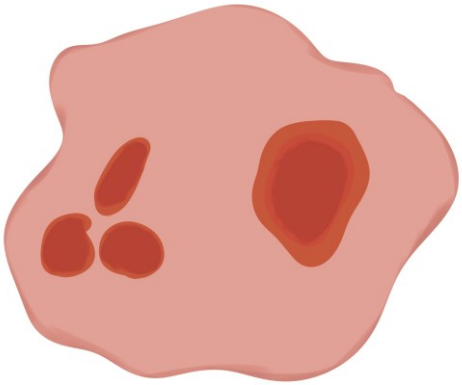
stands for high risk. Further parts of the body that are high risk zones are the genital regions as well as the hands and feet.(6, 134)

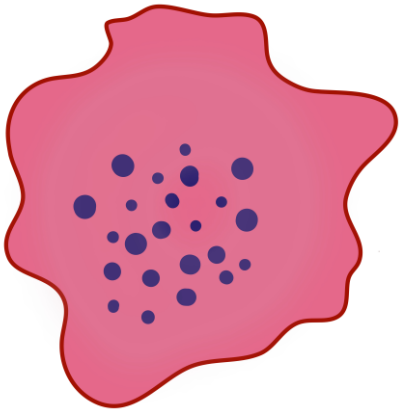
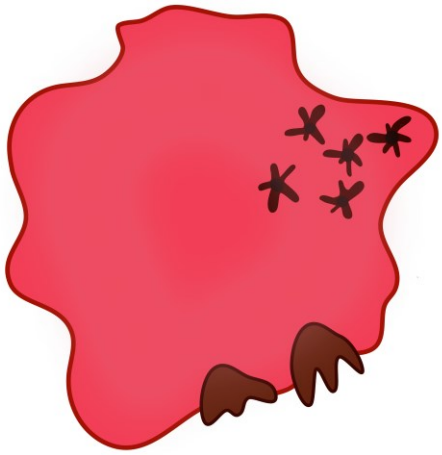
5. Dermoscopy of the BCC

In the diagnosis of BCCs dermoscopy increased the specificity to 91,2% and the sensitivity to 95% due to specific dermoscopic features. Of course, the sensitivity is higher when dermoscopy is performed by an expert and even further when it is performed on the patient (analogue) and not digitally on photographs or in the form of teledermatology.(1) The sensitivity has also been reported as being higher for pigmented BCCs than for non-pigmented ones.(1, 131)

Dermoscopy can also be used preoperatively for the characterization of BCCs into one of the above-mentioned subtypes and furthermore it is useful for the evaluation of the BCC's response to topical treatment.(113, 114) However, in lesions with inconclusive features dermoscopy cannot replace histopathology for a definitive diagnosis.(115)

The dermoscopic criteria for BCCs are the following (116, 117, 118, 119):

Linear and branching vessels, often referred to in the literature as "arborizing vessels" or "arborizing telangiectasias" Fig. 3	 Fig. 3
Erosions and ulceration Fig. 4	 Fig. 4

Bluish-grey clods variable in size, referred to in the literature as "ovoid nests, globules and also focused dots" Fig. 5	 Fig. 5
Radial brown lines arising from a central clod or dot, often referred to in the literature as "**spoke-wheel areas**" **Maple leaf-like areas** Fig. 6	 Fig. 6

In pigmented BCC, the colors vary between light brown and blue. The bluish-grey ovoid nests can appear as oval or elongated large areas that are well-circumscribed. If the pigment is aggregated in smaller cohorts, it appears in smaller bluish-grey globules or dots. While the dots represent histologically dermal melanophages, the ovoid nests and globules correspond histologically to basaloid neoplastic cells in the dermis.(131) Another dermoscopic clue for BCC is clods in clods as concentric structures, this arrangement is rarely visible and is believed to be an early stage of spoke-wheel areas. Nonetheless, the most important feature that differentiates a BCC from a melanocytic lesion is the absence of brown reticular lines (the so-called pigment network).(116, 117) If the uncommon case of pigment network in a BCC occurs, it is usually in a collision of a BCC with a solar lentigo or nevus.(120)

Below, the specific dermoscopic features of different subtypes are listed.

Nodular BCC

In dermoscopy the nodular subtype of the BCC shows as characteristic features large, bright red arborizing vessels over the lesion's surface upon a homogenous white to

pinkish background.(117) White streaks or shiny white lines may also be visible in polarized light, namely chrysalis or crystalline structures. Furthermore, ulceration can also be observed in nodular BCCs and presents as structureless orange-red, reddish-brown, reddish black or as blood.(121) In lesions with erosion or ulceration, the “sticky fiber sign” may also be visible. It occurs when serum or blood dries and textile fibers from clothes stay adherent to dried serum crusts.(122) If pigment is present in a nodular BCC, it often appears as blue-grey globules or ovoid nests, only seldomly in the form of spoke-wheel or leaflike areas.(26, 130) Special anatomical sites may lead to a different dermoscopic appearance. For example, a nodular BCC may appear peculiarly on the lower leg. Instead of the classic arborizing vessels other vessel structures like hairpin and coiled vessels can be seen (117), but this will be further explored in the main part of this thesis.

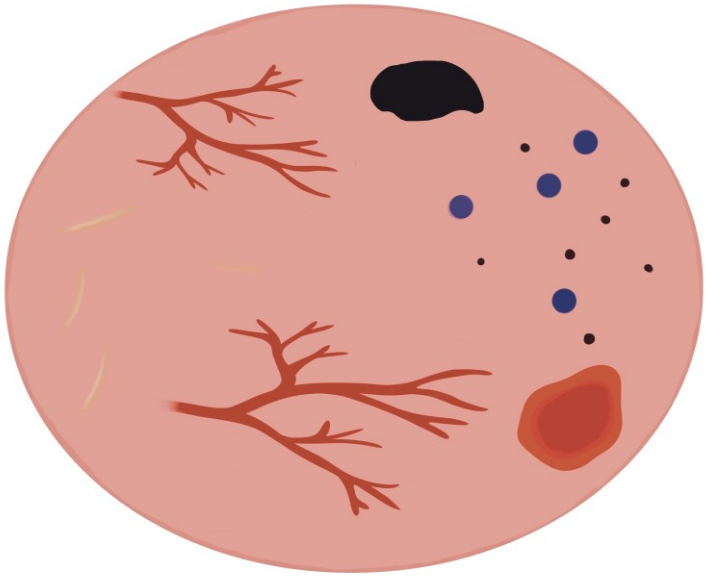


Fig. 7: Dermoscopic features of a nodular BCC summarized in a picture

Superficial BCC

Dermoscopy can be useful to differentiate between a superficial BCC and other diagnoses. Since clinically this subtype appears as an erythematous macule or patch, the possible differential diagnoses are actinic keratosis, Bowen’s disease, lichen planus-like keratosis, Tinea corporis and several inflammatory lesions.(117)

The dermoscopic features of a superficial BCC are fine vessels that appear barely branched on a pinkish background. In the existing literature, they are referred to as “microarborizing vessels”. Erosion or ulceration may be visible as well.(123) Polarized light enables one to observe the above-mentioned shiny white structures in some

lesions. Salerni *et al.* have published cases where these chrysalis structures were the only dermoscopic clues indicating superficial BCCs.(124) Pigmentation patterns may appear, as mentioned above, in the form of spoke-wheel areas, leaflike areas and ovoid nests.(117) However, the pigment may also be visible as hub like areas, which are believed to be the early appearance of leaflike and spoke-wheel areas. They consist of a brown dot surrounded by a lighter brown halo, thus forming a concentric pattern.(125)

Fig. 8: Dermoscopic features of a superficial BCC summarized in a picture

Sclerodermiform BCC

In the terms of dermoscopic features, the sclerodermiform BCC reveals itself as a pinkish to white structureless, scar-like background with fine vessels on it. The vessels are less branched than in the other two above-mentioned subtypes. The borders of the lesion are ill-defined.(117). It has been suggested that the whiter (and less pinkish) the tumors appear in dermoscopy the more aggressive they are.(126)

Fibroepithelial BCC – Fibroepithelioma of Pinkus

This uncommon subtype has been reported to appear on the lumbosacral region of elderly individuals. The dermoscopic findings are fine arborizing vessels and whitish streaks or even septal lines. Like in the sclerodermiform subtype, the vessels have been described with less ramifications than in the nodular or superficial subtype.(127)

In addition, orange-red or brown erosions and ulcerations can be seen as well.(117) Pigment is present in the form of structureless areas of brown to grey, or as blue-grey, dots.(127)

Infundibulocystic BCC

The infundibulocystic BCC is rather a histopathologic than a clinical or dermoscopic subtype. Often found in patients with NBCCS, it resembles clinically benign lesions such as a nevus or skin tag.(117) Dermoscopically arborizing or fine elongated vessels, blue-grey ovoid nests and blue-grey globules can be observed. No leaflike areas, spoke-wheel areas or ulceration were reported.(128)

Basosquamous BCC

The metatypical basosquamous carcinoma (BSC) is an uncommon subtype of the BCC, displaying the clinical and histological features of a BCC as well as a SCC.(117) In dermoscopy the features of both BCC and SCC can be observed. Arborizing vessels, with a predilection of the lesion's periphery, ulceration, blood crusts and ill-defined blue-grey clods are visible features of a BCC. Multiple brown dots and leaflike areas have also been reported. The SCC-related dermoscopic findings are surface scaling, keratin masses, white structureless areas and white circles around follicles. Vessel formations typical for SCC are dotted, hairpin and irregular linear vessels.(129) At least one feature specific to each of the entities must be present for a proper dermoscopic diagnosis of BSC.(125, 129)

6. Therapy and treatment

The BCC's treatment options are either surgical or non-surgical, depending on its subtype and state of advancement. The more probable that recurrence seems, the more aggressive the treatment must be. Of course, the gold standard therapy is the surgical approach, with subsequent microscopical examination of the margins, but not all subtypes need such a radical intervention.(1, 71) The surgical approach is associated with a low recurrence rate, of less than 2 to 8% in the first 5 postoperative years, which is an effective concept of primary treatment.(131) With a subsequent histological examination, not only can the diagnosis be confirmed but also the radicality of the excision can be quantified. The aim is to eliminate the clinically visible tumor, as

well as its microscopic and therefore subclinical extensions. In that regard, a circumferential excision with a peripheral safety margin of several millimeters should be performed.(1) According to the current guidelines, the suggestion for safety margins depends on the risk of recurrence. For low-risk BCCs, a margin range of 2 to 5mm is suggested, and for high-risk BCCs a range of 5 to 15 mm is recommended.(132) It has been reported that the tumor's size was a hint for possible subclinical extension.(1) The threshold was 20mm in diameter: in 95% of the cases a safety margin of 4mm was enough for a complete excision of a BCC with a diameter of less than 20mm.(134) Recurring BCCs should always be excised with a subsequent histological examination, because recurrence is a sign of subclinical spread and therefore needs a proper monitoring.(131, 135) If a BCC is completely excised from the clinical-macroscopic aspect and still a residuum was found histologically, the rate of recurrence was approximately 26 to 41% in a follow-up of 2 to 5 years, which is not that high.(136)

The decision to pursue a therapeutic approach with topical treatment needs to be made carefully. Topical treatment may be successful in patients with a low-risk BCC, especially a superficial BCC. Inoperability as well as other patient-related factors may lead to this decision, like age, comorbidities, logistic difficulties and some others.(1)

Several topical, non-surgical treatment options are available.

Topical imiquimod is approved for the treatment of superficial BCCs as well as actinic keratosis and genital warts. The treatment plan for superficial BCCs is a cream with 5% of the active ingredient applied once daily for 5 times a week over a period of 6 continuous weeks.(137) Imiquimod has been reported as being superior to methyl aminolevulinate photodynamic therapy (MAL-PDT) and 5-fluorouracil (5-FU) for the treatment of superficial BCCs in a follow-up study over a period of 5 years.(138) Treatment failure could not be predicted by a superficial BCC's thickness or adnexal extension (139), but dermoscopic clues were found to predict a response and non-response to imiquimod in superficial BCCs. While lesions with focused grey dots and multiple small erosions responded well, lesions with ulceration, shiny white-red structureless areas, chrysalis structures, as well as blue-grey ovoid nests and arborizing vessels were reported to be poorly responsive. Rainbow-pattern and areas of a blue-white veil were only found in non-responsive lesions.(158) Compared to excision, topical imiquimod led, in 84 to 98% of the cases, to a successful treatment in low-risk BCCs.(140) On the effectiveness of topical imiquimod for the nodular BCC type, unfortunately only limited evidence is available. Depending on the treatment plan,

cure rates varied between 42 and 81%.(141) The combination of carbon dioxide laser, diclofenac 3% and imiquimod 5% has been reported as effective, even for high-risk BCCs.(142) Imiquimod has also been reported as an effective cure for nodular BCCs of the eyelid.(143) In summary imiquimod is an effective alternative to surgical excision in the treatment of low-risk BCCs, whether they appear as single or multiple BCCs, if they are superficial. A biopsy pre-treatment is recommended.

Another topical treatment alternative is 5% 5-FU. The approved treatment plan for the superficial BCC is an application twice daily for 2 to 4 weeks.(1) Its effectiveness has been mentioned above. A carbon dioxide laser-assisted combination of 5-FU and cisplatin has been reported as being effective for the treatment of superficial low-risk BCC.(144)

Other topical, but semi-surgical, interventions include shaving or curettage, electrocauterization, cryotherapy and laser ablation. The advantage of shaving over the other destructive options is the subsequent histological examination. As mentioned above, laser combined with another topical treatment option led to a more effective outcome.(1) Several studies used laser pre-treatment before photodynamic therapy.(145) Aside from carbon dioxide lasers, also erbium yittrium aluminium garnet lasers have also proven to be efficient as destructive treatment options. Tissue was ablated via vaporization of tissue water.(146) The success of a destructive form of topical treatment depended greatly on the executor’s skills, the anatomical site and the characteristics of the BCC.(147)

The photodynamic therapy with 5-aminolevulinic acid or its methyl ester (MAL-PDT) should not be used as a treatment for high-risk variants of BCC like the sclerodermiform and pigmented types. It also should not be used in the afore-mentioned H-zone of the face, where the risk of deep tumoral penetrations, and tumor survival and recurrence, are more likely.(1) It is preferably used as a treatment for nodular or superficial BCCs with a tumor thickness of less than 2mm, and if surgical intervention is contraindicated due to patient-related factors, such as age, medication, comorbidities etc.(148) The MAL-PDT leads to a cure of superficial BCCs in 92 to 97% of the cases studied, with a recurrence rate of 22% after 5 years post-treatment, and the cosmetic outcome was reported to be superior compared to surgical treatment.(149)

If surgery or radiotherapy is not indicated a systemic medication for locally advanced BCC is still available. The Hedgehog inhibitors vismodegib and sonidegib are approved

by the FDA as well as the EMA for the treatment of locally advanced BCCs. For the treatment of the metastasizing BCCs, only vismodegib is approved.(1, 76) The class-specific adverse drug reaction of both HHI that have been reported were hair loss, muscle spasms, fatigue, dysgeusia and consecutive weight loss. Most patients reported these adverse drug reactions, and in a third of the cases they led to an interruption of the treatment.(150) With vismodegib, a response rate of 60,3% for locally advanced BCC and 48,5% for metastasized BCC was observed. 20 out of 60 patients had a total response of their locally advanced BCC, while only a partial response was reported in patients with a metastasized BCC. A median survival rate of 33,4 months was observed in patients with metastasized BCC.(151)

Immunotherapy has been reported as being successful in the treatment of either treatment-refractory or treatment-naïve patients with locally advanced or metastasized BCC (1), since BCCs held a high burden of mutation, and checkpoint-inhibitors were designed for that.(153) That is a good option for patients who cannot tolerate the adverse drug reactions of HHI or “display primary or secondary resistance to HHI”.(6) Cemiplimab, nivolumab and pembrolizumab were reported as being efficient in a review of case reports.(153) A phase II study (NCT03132636) is ongoing, in order to research the efficiency of the PD1 antibody cemiplimab in patients with locally advanced or metastasized BCC. According to the scheme of inoperable or metastasized SCC, 350mg of cemiplimab were administered intravenous at an interval of 3 weeks.(154) The preliminary data has been auspicious, so the FDA approved cemiplimab for the treatment of locally advanced BCC after a previous HHI therapy and treatment failure or interruption due to adverse drug reactions. It was also approved as a second line-treatment for metastatic BCC.(155, 156) Further studies need to be conducted for the above-mentioned antibodies.

Radiation therapy is a treatment option for locally advanced BCC when R0 excision is impossible or the tumor is inoperable. It might also be considered as the primary treatment option. It has also been reported as a good treatment option for the perineural invasion of a BCC. Patient-related factors, like comorbidities and logistics, need to be taken in account. It has proven to be a good treatment option when the patient refused the surgical approach. It was usually well tolerated. An adverse effect could be radiodermatitis, which presents itself acutely as an erosive and chronically hypopigmented lesion with telangiectasis.(1)

In summary several treatment options for the different BCC types are available and need to be chosen individually and in consultation and agreement with the patient.

II Main part

1. Materials and methods

This thesis is a literature review – especially for the main part. For the review, a broad search was performed using the online database PubMed. For this part of the thesis the key terms used for the research were “BCC AND dermoscopy” and the results were screened for relevance according to the research question: What factors are influencing the BCC’s morphologic universe?. Other key terms used were “influencing BCC morphology”, and the following were added to the main search term “BCC AND dermoscopy”: “growth”, “age”, “anatomic location”, “skin photoype”, “gender”, “topical treatment” and “tattoo”. The findings of this search were screened for inclusion. Inclusion criteria were as follows: retro- and prospective studies and case reports, case series, as well as case-control studies with a focus on dermoscopic description, and the possible influence of extrinsic and intrinsic factors. If the title of studies was promising, the abstract was further examined for inclusion. If no abstract was available, the paper was still read and analyzed for possible inclusion. Studies and case reports without dermoscopic analysis, ex vivo dermoscopy and automated detection were excluded. A total of 2.889 publications were identified based on the selected search terms and 69 were included in the main part of this thesis, and further data was extracted according to its relevance.

This thesis has limitations. It is mostly dependent on the quality and quantity of already published content. Furthermore, in some of the included papers, dermoscopy was used as a mean to draw other conclusions or was used in comparison with other imaging techniques.

2. Problem statement: factors influencing the BCC’s dermoscopic morphology

The BCC, being the most common malignant skin cancer, with increasing incidence rates, poses a tremendous burden on health care systems. Dermoscopy has proven itself as an inexpensive and fast device to aid in the non-invasive diagnosing process and treatment outcomes. So far, several factors influencing the dermoscopic morphology of BCCs have been described in the existing literature but were not linked together. However, these factors might have the potential to predict the morphology of BCCs to facilitate diagnosis for experts, as well as non-experts on dermoscopy and

diminish misdiagnosis. Furthermore, possible primary prevention and treatment plans might be deducted from the results of this thesis.

Based on the concept of “signature nevi” (158) Zalaudek *et al.* have observed a “signature pattern” of multiple BCCs.(159) This term was formed to mirror the widely acknowledged term “signature nevus pattern”, which describes the predominant dermoscopic pattern in individuals with multiple nevi.(158, 159) Individuals with multiple superficial BCCs display similar dermoscopic features of their BCCs as a repetitive pattern. Interestingly, the similarity of dermoscopic features were even more striking when more BCCs were found on the same anatomical site of one patient.(159) It should be mentioned, that in line with these considerations, a “signature pattern” of actinic keratoses was also suggested.(160) The fact that lesions, and in this thesis first and foremost BCCs, tend to express the same or similar dermoscopic features in the same individual leads to the questions as to why and how this happens, and what factors influence the dermoscopic morphology of BCCs? The research question of this thesis is to find different factors influencing the BCCs dermoscopic aspect, to link them together, and to point out the resulting morphologic changes, as well as to conclude from these findings a possible prediction. In the following sections, these factors are outlined.

3. The skin phototypes

In this thesis’ introduction, the pigmentary traits as UV-protection and the subject of pigmentation were already touched upon. Furthermore, it was shown that ethnicity – and therefore an individual’s phenotype – seem to have an impact on the BCC’s morphology. Not many studies or case reports dealing with this subject were found. One of the reasons may be that BCCs are rare in people with darker skin phototypes.(161)

A retrospective observational study in South India was conducted to point out the dermoscopic features in people with SOC. It was stated that most descriptions of dermoscopic traits were investigated and therefore described for Caucasian skin types, namely skin phototypes I to III. In that study, non-polarized contact dermoscopy was used to observe BCCs in patients with skin phototypes IV and V. While pigmented BCCs have a low prevalence of approximately 10% in Caucasian individuals, this study revealed a prevalence of 95% pigmented BCCs in dark-skinned patients. An exception

was one patient with oculo-cutaneous albinism, who was included and his BCCs were lacking pigmented structures. The pigmented features most frequently observed were those with 61,7% maple leaf-like areas and with 53,4% blue-white veils. While the maple leaf-like areas were associated with superficial BCCs, the blue-white veils were associated with the nodular subtype.(162) “BCC-associated pigmented structures correlate with the presence of melanin both within and outside the tumor lobes”.(162, 163) Behera *et al.* concluded, that the dominant dermoscopic patterns in the BCCs of dark-skinned patients were pigmented structures and further that the blue-white veil should be considered as an important diagnostic clue in the diagnosis of BCCs in dark-skinned individuals.(162)

Another retrospective study was conducted to compare pigmented and non-pigmented BCCs via dermoscopy and reflectance confocal microscopy (RCM) in individuals with skin phototypes I and II. Although the study’s focus was not on pointing out the dermoscopic features characteristic of a certain skin type, an interesting finding was made. 3 individuals with a skin phototype I and 18 with skin type II were included in the study. 11 pigmented and 10 non-pigmented BCCs were observed. In the study, the presence of blue globules was strikingly significant for pigmented BCCs. The presence of other features linked to pigmentation were grey or blue ovoid nests and leaf-like structures, but they were not statistically significant.(164)

Another study that linked skin phototypes to dermoscopic examination of BCCs together was a unicentered study in Morocco. In that study, the skin type I was not represented, and the skin types II and V were quite underrepresented, with only 5,9% of participants having skin types II and 5,9% of participants having skin type V. At 51,5% of participants, the skin phototype III was the most examined, followed by skin type IV at 36,6%. The investigated lesions were classified into 22% non-pigmented and 78% pigmented BCCs, which were further sub-classified into lightly (29%), medium (16%) and heavily pigmented (33%) BCCs. Classic dermoscopic features linked to pigmentation were ovoid nests (52%) and with grey-blue globules (38%). Leaf-like structures were only found in 7% of participants. Only in the lighter skin types, namely II and III, were non-pigmented BCCs found. The BCCs observed in the darker skin types, namely IV and V, were all pigmented. In fact, 73,3% of the BCCs observed in darker skin types were heavily pigmented, while only 26% of the BCCs in lighter skin types showed heavy pigmentation. Thus Soughi et al. were able to confirm a relation between skin phototypes and the extent of pigment in BCCs. The authors also noted,

that the more pigmented a BCCs was, the harder was the discrimination between melanoma and BCC via dermoscopy.(18)

The fact that dermoscopy of heavily pigmented BCCs is more difficult and challenging has already been reported by Altamura *et al.* in 2010. The authors conducted a retrospective study to analyze the reliability of dermoscopic criteria of BCC in Austria, Italy and Australia. According to that publication, heavily pigmented BCCs showed in 40,6% of dermoscopic features that were suggestive of a melanocytic lesion, like brown and black dots and globules, blue-white veil-resembling structures and vascular patterns that were dotted, comma, hairpin and linear irregular vessels. Furthermore, the correlation between heavy pigmentation in BCCs and the frequency of melanocytic patterns increased in a linear manner: the more pigmented a BCC was, the more melanocytic patterns were visible. Therefore, heavily pigmented BCCs are hard to distinguish from both melanomas and melanocytic nevi. (165)

No description of dermoscopic features of BCCs in Australia's indigenous population was found, although NMSC in this population was described as an underrated health care problem. In a study of indigenous people in Sydney, 19 of 22 individuals had a skin phototype III, although in this population a darker skin type was expected. 11 BCCs, were detected without any further description of dermoscopic features.(166)

Fair-skinned populations suffer from BCCs displaying less pigmentation or non-pigmented BCCs. Ahnlide *et al.* conducted a prospective study in Sweden to predict preoperatively the histological subtype of BCCs. A major part of the cohort in this study was fair skinned, with skin type II being the most represented. 431 BCCs were histologically confirmed. 99,3% of those were found in individuals with skin phototypes I to III, and 90% on the skin phototypes I and II. Only a few pigmented BCCs were reported, although a direct comparison between skin phototypes and amount of pigment in the BCCs was not executed. It was concluded that the best predictive features for superficial BCCs in fair-skinned population were a flat surface, multiple erosions, and the absence of both ulceration and arborizing vessels.(167)

In Nigeria, a cross-sectional study was conducted to investigate the prevalence of skin cancer in 90 patients with oculocutaneous albinism. The skin was examined with the unaided eye as well as dermoscopy. Dermoscopic features that were detected that led to the diagnosis of BCCs were arborizing telangiectasia, blue-grey ovoid nests, leaf-like structures, spoke-wheel areas as well as shiny white blotches and ulceration. 58 malign lesions were biopsied from 30 patients. In relation to 37,9% of the lesions BCCs

were verified, but no further details on the dermoscopic features were given. According to the BCC features listed, pigmented structures were also observed. (168)

4. Tattooed skin

BCCs arising from tattooed skin were rare, or at least rarely documented. Only 14 such cases have been published until now (as of April 17, 2022).(169) Unfortunately, it was not mentioned specifically in the relevant publications if dermoscopy was performed, although it was speculated that the same dermoscopic features of BCCs in tattoo-free skin could also be found in tattooed skin: arborizing vessels and telangiectasias, blue-grey ovoid nests and globules and ulceration. The color from which BCCs originated in tattoos were mostly black (7 patients) and blue (4 patients).(170) It should be mentioned that the dermoscopic features of tattoos have been described as forming a nonspecific homogenous pattern, lacking sharp borders at the periphery.(171) The occurrence of a BCC in a tattoo could be interpreted as a coincidence, since the prevalence of tattoos is increasing and accordingly to that the possibility of a BCC occuring on body parts with a tattoo was also expected to increase. However, since the number of tattooed individuals is steadily increasing, the incidence of BCCs originating in tattoos should be higher than they were reported.(170, 172) Still, the pathogenesis of BCCs arising from tattooed skin has not yet been discovered. Pigment toxicology and the skin's metabolism supposedly played a major role in this.(170)

5. The BCC in collision tumors

The coexistence of two (or more) independent and unrelated types of lesions in direct anatomical proximity is called a collision tumor and results in an atypical appearing lesion. It has been reported to be relatively uncommon.(173, 174)

It was already stated in the introduction that a pigment network provides a dermoscopic hint to melanocytic lesions, like nevi and melanoma, and does usually not occur in BCCs. However, a pigment network might be present in BCCs in the case of a collision tumor. Gulia *et al.* conducted a retrospective analysis of 412 dermoscopic pictures that were histologically proven BCCs. In 14 cases, a pigment network was present. 9 of these lesions exhibited a "peripheral brown to black, regularly meshed and narrowly spaced reticular structure, thinning out in the periphery".(120) The network was either localized on the edge of the lesions, surrounding nearly the entire lesions or covering

the surface of the whole lesion. In 9 of these cases the BCC's pigment network resulted from the direct proximity to another skin neoplasm, like nevus, actinic keratosis and solar lentigo. One even lacked any dermoscopic features characteristic of a BCC, and only a pigment network was observed. 3 of the 14 lesions exhibited short linear irregular structures, resulting in a pattern resembling a network. The authors stated in their conclusion that the presence of a pigment network represents a pitfall in finding the correct diagnosis via dermoscopy.(120)

Blum *et al.* conducted a retrospective study of 77 histologically proven collision skin lesions (CSL) from 75 patients. 45,5% of the CSL had a BCC component. CSL with a BCC component were more often found on the head and neck area, in individuals with a median age over 60 years and in males. In absolute numbers, 35 CSL with a BCC component were found. 18 were composed of seborrheic keratoses; 5 with angiomas; 5 with dermatofibromas; 2 with actinic keratoses; 2 with hyperplasia of sebaceous glands; and 1 with a clear cell acanthoma, a keratoacanthoma and a solar lentigo. The authors detected that epidermal-epidermal combinations of CSL were found more often in older individuals. Several CSLs were listed as examples. A lesion composed of a BCC and a lentigo maligna showed pigmented follicles, destroyed follicles with a patchy pigmentation, as well as arborizing vessels and blue-grey globules. Another lesion with blue grey ovoid nests, brown fat fingers, pseudo horn cysts and sulci was identified as the collision of a BCC and a seborrheic keratosis. The presence of red lacunas, arborizing vessels and blue-grey globules was diagnosed as a collision of a BCC and an angioma. Arborizing vessels surrounded by a central white patch with shiny white lines and post-inflammatory peripheral hyperpigmentation, were diagnosed as the collision of a BCC with a dermatofibroma. The collision of three different specific patterns, namely arborizing vessels and blue-grey globules, dotted vessels in a line and brown fingerprint structures was histologically confirmed as the collision of a BCC, a clear cell acanthoma and a seborrheic keratosis. The authors concluded that dermoscopy was helpful in finding the diagnosis.(174)

The collision of a BCC and a seborrheic keratosis has been reported by Ferrara *et al.*, amongst other. Diffuse bluish homogenous areas forming huge ovoid nests at the periphery, and comedo-like openings with a milia-like cysts were described. Furthermore, it was suggested by the authors that the collision of seborrheic keratoses and BCCs might easily be underdiagnosed if the progressive growth of the BCCs

destroys the seborrheic keratosis or if the features of the seborrheic keratosis were simply overlooked.(175)

De Giorgi *et al.* published a case report of a collision tumor consisting of a melanocytic nevus, a BCC and a seborrheic keratosis on the hip of a 38-year-old woman. In this case, dermoscopy did not enhance the diagnostic accuracy compared to simple clinical inspection with the unaided eye. Using dermoscopic algorithms like the ABCD-rule of dermoscopy and the 7-point checklist revealed a suspicious lesion, hinting towards melanoma. The lesion lacked any BCC-specific criteria, like arborizing vessels and maple leaf-like structures. Furthermore, pointed vessels and pigment network were hints that a melanocytic lesion, i.e. melanoma, was present. Pseudo horn cysts and blue-grey ovoid nests were also described. The final diagnosis was found via histological examination. The authors concluded that, in cases like this, dermoscopy could mislead.(176)

The collision of a BCC and a melanoma was reported to be rare. In a case report of Savas *et al.*, a tumor dermoscopically examined revealed an atypical dark brown network, with irregularly pigmented follicles and a homogenous white structureless area. Dermoscopy needed the support of RCM to identify this lesion as the collision of a melanoma and a BCC, since specific criteria of the latter were absent. The diagnosis was histologically confirmed.(173)

Martorella *et al.* published a case report of a CSL arising from the scar of a melanoma in situ, excised 4 years previously. The lesion exhibited criteria for melanoma (black and blue round structures, irregular whitish areas on a blue-grey background), as well as BCC (arborizing vessels, erosion) and scales.(177)

Medeiros *et al.* reported a CSL on the frontal region of a 60-year-old male individual. According to the authors, the clinically already suspect lesion revealed under the dermoscope according to the authors a multi-component pattern consisting of an atypical vascular pattern, multiple blue-grey spots, shiny white streaks, a hypochromic area and an amorphous area. Based on the dermoscopic findings, a melanoma was expected. The histological examination revealed the collision of a melanoma and an infiltrative type of BCC with transition to a basosquamous carcinoma. Therefore, this represented another case in which dermoscopy failed to diagnose a BCC.(178)

Alves *et al.* reported an interesting case of a CSL. A red plaque of 3 years duration on the nose of an 85-year-old female showed the following dermoscopic features: ulceration, small telangiectatic vessels on the surface and maple leaf-like structures.

The collision of a BCC and a melanoma was suspected, and the lesion was excised. The histological and immunohistochemical examination enabled the diagnosis of a BCC and an atypical fibroxanthoma. A case like this was reported for the first time in this publication, and the difficulties of finding the diagnosis via dermoscopy was indicated.(179)

6. The Anatomical site

It has already been stated in this thesis that the BCCs may arise on any site of the body with hair-bearing skin. Mostly sun-exposed areas are affected, like the head, neck and trunk (1, 6, 174), but does the anatomical location of the tumor also influence its morphology?

Suppa *et al.* stated in their monocentric retrospective study of 2015 that “particular dermoscopic criteria are independently associated with clinical type and anatomic location of BCC”.(180) 501 dermoscopic pictures of histologically proven BCCs were evaluated. The patients had the skin phototypes I to III, and the median age was 62 years. The majority were either non-pigmented (23,5%) or scarcely pigmented (35,9%). The BCCs were further categorized into lightly, moderately and heavily pigmented BCCs. 491 of the 501 tumors showed at least one BCC-associated pattern under dermoscopic examination, resulting in 98%. Arborizing vascular structures were more frequently detected in nodular BCCs; while leaf-like areas, short and fine telangiectasias, small erosions, spoke-wheel areas, and other concentric structures were more likely to be found in superficial BCCs. Interesting differences were found regarding the dermoscopic morphology compared to the anatomical location. In comparison with BCCs on other parts of the body, pigmented structures were more frequently observed in BCCs of the scalp and significantly less in BCCs of the face. In BCCs of the scalp blue-grey ovoid nests, leaf-like areas, multiple brown or black dots and globules as well as blue-white veil-like structures and a melanocytic pattern were more likely to be observed than in other body sites. Arborizing vessels were more frequently observed in facial BCCs. In BCCs of the trunk the features of superficial BCCs and further different vascular structures like dotted, linear-irregular, glomerular and polymorphous vessels were observed. BCCs on the scalp usually showed no more than one vascular pattern. Nodular BCCs were found to occur more regularly on the face, and superficial BCCs were more often found on the trunk. However, Suppa *et al.*

were able to demonstrate that specific dermoscopic patterns can be found independently of the histological type, but depending on the anatomical location of the BCC. Arborizing vessels were more frequently associated with facial BCCs; while short and fine telangiectasias, small erosions and spoke-wheel areas were more frequently associated with BCCs of the trunk. The authors proposed, as a possible explanation, that not only the different anatomy on various parts of the skin but also varying sorts of sun exposure on different body parts lead to dermoscopic patterns of the BCC prone to their anatomical location. The sun exposure on the trunk was intermittent, while on the face it was chronic but on the scalp variable. There was no association between polarized light structures, like shiny white lines, rosettes and rainbow pattern, on the one hand; and anatomical location, on the other hand, but these patterns were found in nodular BCCs more often than in superficial BCCs.(180)

Fagotti *et al.* concentrated in their retrospective analysis of BCCs and SCCs on the head. They divided the face and scalp into 16 anatomical regions that were further summarized into macro-areas: fronto-nasal, the scalp, periauricular, perioral and periorbital. The authors were able to affirm that nodular tumors with arborizing telangiectasias occurring on the fronto-nasal macro-area were mostly nodular BCCs. On the contrary, tumors of the periauricular area with short and fine telangiectasias, whitish-red structureless areas and white streaks are mostly sclerodermiform BCCs.(181)

Wolner *et al.* were able to categorize 392 histologically proven BCCs in their location on the body as well as their status of pigmentation. Using polarized as well as non-polarized light, the full range of dermoscopic attributes of the BCCs were observed. 43,1% of the lesions were found on the head and neck, 32,9% on the trunk, 13,8% on the lower limbs and 10,2% on the upper limbs. Pigmented lesions were most frequently located on the upper extremities and less frequently on the head or neck. Compared to BCCs on other body sites, BCCs of the leg arborizing telangiectasias were less likely to be observed, but they showed more often polymorphous or thin serpentine vessels as well as shiny white blotches, white strands, erythema, and lastly erosions and ulcers.(182) BCCs of the legs displayed an association with a young age at diagnosis, female sex and a superficial subtype.(182, 183) Further, their dermoscopic features were strikingly different compared to BCCs on other body sites with polymorphous vessels, ulcerations and erosions, as well as shiny white structures visible in polarized light.(183)

Liopyris *et al.* conducted a retrospective study to further dermoscopically examine and characterize facial BCCs that displayed as clinically unsuspicious small white lesions. All the participants had fair skin phototypes I and II with severe photodamage. Pigmented features were rare in this cohort. Dermoscopy revealed a prevalence of arborizing telangiectasias in 66,7% of participants, shiny white structures in 55,6%, short and fine vessels in 35,6%, and in 28,9% or participants the classical dermoscopic features of BCCs were missing. The lesions were ulcerated in only 4,4% of cases. The authors concluded that for white unsuspicious lesions on an extensively sun damaged face, BCCs should be included as a differential diagnosis. Helpful dermoscopic criteria are arborizing vessels and shiny white structures.(184)

The localization of a BCC on the face may result dermoscopically in a pseudonetwork pattern, which is known to be a primary feature of both non-melanocytic and melanocytic lesions located on the skin of the face or the vulva. Gulia *et al.* noticed this pseudonetwork in 2 out of 14 BCCs on the face in their retrospective study. The authors stated in their conclusion that a pigment network may result in a BCC due to the anatomical localization on photodamaged skin.(120)

A retrospective study was conducted by Conforti *et al.* to point out the dermoscopic differences between BCCs and dermal nevi of the face since they may easily be confused during simple clinical examination. 118 BCCs and 77 dermal nevi were examined. While BCCs were predominantly located on the lateral site of the forehead and on the nose, dermal nevi were most frequently found perorally, on the cheeks and the scalp. No face-site-specific features were identified for BCCs.(185)

BCCs located on the lower limbs have already been mentioned in this thesis in the introduction. Peculiar features might be observed via dermoscopy in this localization. In a retrospective study, Lombardi *et al.* examined 81 BCCs of the lower extremities. Concerning dermoscopy, these BCCs had – in 22% of the cases examined – a benign-looking aspect, and in 78% of the cases examined they had a malignant-looking aspect. In their study, the authors noted that most BCCs did not arise from photodamaged skin. Of the 63 malignant-looking lesions, 24 were immediately identified as BCCs, but 23 mimicked SCCs, 2 mimicked Kaposi-sarcoma and 9 mimicked a melanoma. 5 lesions exhibited nonspecific dermoscopic patterns. The most reported feature of benign- as well as malignant-looking lesions was ulceration. The 18 benign-looking BCCs mimicked, in 11 cases, seborrheic keratoses and in 7 cases dermatofibromas. In the absence of pigmented structures, the existence of

vessels and their morphology was significant for the dermoscopic diagnosis of BCCs. However, the localization on the lower limbs may have led to a different formation of vessels. In only 45% of the BCCs in that study, the characteristic arborizing vessels or short and fine vessels were observed. Glomerular vessels were found in 26% of the cases and in 19% of the cases polymorphic vessels were found. This high percentage of BCC atypical vessels found in the lower extremities may have been the reason why BCCs in this localization often mimic other lesions and – in the study referred to above – mostly Bowen's disease and SCCs. The authors suggested in their conclusion that due to this finding all lesions that display ulceration and atypical vessels should have been excised.(186)

Regarding the BCCs' localization on the lower extremities Suppa *et al.* described the morphology of the BCCs as glomerular and polymorphous (180) while Wolner *et al.* reported polymorphous and thin serpentine vessels.(182) Other dermoscopic findings of the nodular BCC on the lower leg were reported as hairpin and coiled vessels, as well as further ulceration, whitish striae and blue-grey globules or ovoid nests.(117)

A study conducted in Mexico reported 32 cases of blue-white BCCs. The cases were gathered retrospectively over a duration of 10 years. The skin phototypes were not pointed out. These BCCs were, in 75% of cases, located on the face, in 19% of cases on hairy skin (scalp), and in 6% of cases they were located on the trunk. Ulceration was most frequently found in two thirds of the lesions. Clinically the BCCs were black-bluish tumors and, under dermoscopy, they revealed in a striking majority of 97% of cases a homogenous blue structureless area, which is not a classical BCC criterion. The authors also suggested that the few cases on BCCs published in the literature, on the subject of BCCs appearing as blue-white tumors, may have been due to underdiagnosis or misdiagnosis, because of mistaking these lesions with possible differential diagnoses like seborrheic keratosis, melanoma or blue nevus.(187) It has been proposed that heavy pigmentation may disguise any vascular pattern.(180)

Vaccari *et al.* reported a retrospective case series of 16 histologically confirmed BCCs located on the eyelid margin. Clinically, the aspect of plaques with ill-defined borders or erythematous patches were reported. 15 of the 16 cases were on the inferior eyelid, 10 were on the lateral half of the eyelid and 12 individuals had madarosis. Dermoscopic examination revealed arborizing telangiectasias, or perpendicularly and parallelly arranged linear vessels. Healthy skin did not show such vessels. These perpendicular vessels were also found at the borders of BCCs of the eyelid margin. In addition,

curved and linear-irregular vessels were detected. Arborizing vessels were found more frequently in nodular BCCs. Pigmented BCCs revealed small dots or globules, or a cobble stone pattern. The authors suggested perpendicular vessels as a hint for BCCs of the eyelid margin.(188)

Cinotti *et al.* conducted a study of 165 tumors located on the eyelid margin, of which 48 were BCCs. The authors stated how hard the clinical discrimination was between a BCC and a dermal nevus of the eyelid margin. Macroscopically, BCCs displayed themselves as papulonodular and amelanotic tumors. Dermoscopy revealed in these BCCs intense structureless yellow and pink colors. The yellow color originated from crusts on erosions. Linear thin vessels were also reported. Further, the authors reported that arborizing vessels were indeed more often observed in BCCs than in dermal nevi, but interestingly were not found specifically for BCCs.(189)

Williams *et al.* reported 21 cases of BCCs on the eyelid margin. These BCCs were more frequently located on the anterior margin of the lower eyelid. The dermoscopic attributes observed were irregular surfaces, madarosis and arborizing vessels on a skin-colored to pink background. However, the arborizing vessels were reported to be specific for BCCs in general and not specific for the location on eyelid margins.(190)

The vulvar BCC accounts for approximately 2% of all BCCs. Interestingly this location is usually not exposed to sun light. The BCCs are reported to be less pigmented in this location. The authors concluded that misdiagnosis of psoriasis, eczema or an infectious dermatosis may have led to inappropriate treatment and delayed surgery.(191) De Giorgi *et al.* published a case report of a vulvar BCC on the right labium minus of a 65-year-old woman. Dermoscopic features that led to the diagnosis of a BCC were the absence of features typical for melanocytic lesions, and the presence of blue ovoid nests and telangiectasis. The dermoscopic diagnosis was histologically confirmed as a multifocal superficial subtype.(192)

A similar case report concerned a tumor found on the right labium maius of a 63-year-old female. Polarized digital contact dermoscopy revealed leaf-like areas, ulceration and fine telangiectasias. The sticky-fiber-sign was highlighted as providing evidence of a long-lasting ulcer. Shiny white structures were observed all over the lesion. A BCC was histologically confirmed.(193) Although located on mucosal skin, the dermoscopic features of vulvar BCCs were the same as those found on other sites of the body.(191-193)

A single case report by Kitamura *et al.* gave details of a rare site for the occurrence of a BCC. A 65-year-old man presented clinically with black macule next to one of his areolas, which are physiologically more pigmented areas. Under dermoscopic examination, an atypical, thick black network of a brown to dark brown color was observed. On the part of the lesion towards the areola, shiny white structures were observed; and in the periphery of the lesion leaf-like structures, spoke-wheel areas and arborizing telangiectasias. On the healthy part of the areola, dermoscopy revealed a light-colored network originating from the mammary ductal glands. The authors named the atypical, partly black network “large black web”. Further, the authors mentioned 2 cases in which they observed a partial network-like structure, like this “large black web”. In histology, the tumor cells forming this pattern were not found in the follicular areas. The authors concluded that this finding was site-specific.(194)

7. Time and growth

Due to growth over time, BCC’s appearance might change. Sykes *et al.* conducted a retrospective review on the dermoscopic behavior of 100 clinically diagnosed BCCs in 70 individuals over a time period of two years. Only superficial BCCs were included in the study. 69% of the patients had a skin phototype I or II. In males, the BCCs were in located on their backs (58%), while in females the majority was to be found on their extremities (54%).(70) A similar distribution was reported in relation to melanoma: the primary melanoma was more likely to be found and on their back (in case of men), and on their lower extremities (in case of women). A possible explanation was proposed, namely to be the clothing style.(195) Area growth rates were reported to be 0,96 mm² per month or 11,5 mm² per year. Multivariable analysis showed a slightly different outcome with 0,81 mm² per month or 9,7 mm² per year. A positive correlation was revealed between the long axis size and shiny white structures, brown clods and blue concentric structures, while a negative association was revealed between the size of the long axis and short and fine vessels. A positive association was reported between shiny white structures, brown clods, concentric blue structures, blue small clods and micro-erosions with the short axis measurement. The surface area was positively associated with shiny white structures, brown clods, concentric blue structures, blue small clods and ulceration. The most striking change in dermoscopic features over time was that superficial BCCs with surface area extending larger than 41,9 cm² increased

their shiny white structures. Superficial BCCs smaller than the above-mentioned threshold did not show any notable change in their dermoscopic features. The authors proved that the superficial BCC is a slow growing tumor, which grows at a rate of approximately 1 mm² per month. Moreover, they concluded that the dermoscopic signs of dermal involvement, being shiny white structures, increased with size.(70)

Xu *et al.* conducted a unicentered, retrospective study of 98 BCCs, to point out the differences in dermoscopic features of BCCs according to their size. BCCs were divided according to their size into 2 groups: BCCs larger than 1cm (≥1 cm) and smaller than one cm (<1 cm) in diameter. In larger BCCs blue-grey dots, arborizing telangiectasias, short white chrysalis like structures, ulceration and large structureless, blue-grey areas were more likely to be found than in the smaller ones. Furthermore, the BCCs were divided according to their pigmentation status: lightly pigmented (< 30% pigmentation), medium pigmented (30-70%) and heavily pigmented (>70%) BCCs. In the medium pigmented subgroup, arborizing telangiectasias and large structureless blue-grey areas were more frequently observed in larger BCCs. In the heavily pigmented subgroup, larger BCCs more frequently showed large structureless blue-grey areas, ulceration and short white chrysalis structures. The large structureless blue-grey areas were proposed by the authors to be a fusion of large blue-grey ovoid nests and could be an important clue of large pigmented BCCs. The authors further pointed out that the growth of the BCC also influenced several dermoscopic features that mirrored the tumorigenesis. The tumor's vascularization was displayed by arborizing vessels; the fibrosis was displayed by short white chrysalis structures; and the pigmentation was displayed by blue-grey dots and large structureless blue-grey areas.(196)

By contrast with these findings, Popadić *et al.* analyzed 151 BCCs to investigate dermoscopic difference in small and large BCCs, and obtained different results. The tumors were divided according to their size in 2 groups: smaller tumors (≤1 cm in diameter) and larger tumors (>1 cm in diameter). No difference was noticed in the 2 groups regarding their pigmentation status. However, multiple small erosions, arborizing vessels and short and fine telangiectasias, were more likely to be found in BCCs with a diameter larger than 1 cm. Mirroring the tumor's development these findings corresponded with tissue destruction and angiogenesis.(197)

Emiroglu *et al.* conducted a study of 98 BCCs, in order to analyze the connection between dermoscopic features and histologic subtypes. Although the actual focus of

the study lay elsewhere, the authors indicated that the larger the diameter of a BCC, the more frequently were blue-grey ovoid nests observed.(198)

Takahashi *et al.* conducted a retrospective study to analyze the dermoscopic features of small pigmented BCCs. The tumors were divided into 2 groups, in order to compare their morphology according to their size. One group included BCCs smaller than 3 mm and the other included BCCs with a diameter between 4 and 6 mm. Dermoscopy revealed in BCCs smaller than 3 mm in diameter no arborizing telangiectasias, no spoke-wheel or leaf-like areas, no erosion and ulceration and further no shiny white areas. However, large blue-grey ovoid nests and multiple blue-grey globules were observed. In the groups of BCCs with a diameter ranging from 4 to 6 mm, the dermoscopic findings were multiple those of blue-grey globules, large blue-grey ovoid nests, shiny white areas, erosions and ulcerations, leaf-like areas, arborizing telangiectasias, and spoke-wheel areas. The authors drew conclusions regarding the usefulness of dermoscopy even in small-sized pigmented BCCs. The main features detected in both groups were multiple blue-grey globules and blue-grey ovoid nests.(199)

Similar findings were reported by Longo *et al.* In their study, 87 BCC smaller than 5 mm were compared to the same number of BCCs larger than 5mm in diameter. Compared to the large ones, the smaller BCCs were positively associated with an anatomical location of the head and neck. The dermoscopic features mostly observed were multiple blue-grey dots, in 95% of cases, and large blue-grey ovoid nests also in 95% of cases. Therefore, the authors concluded that these features should be considered as predictors of small pigmented BCCs. Furthermore, BCCs with a diameter less than 5 mm were 3,5 times more likely to be of a nodular subtype than larger BCCs.(200)

8. Topical treatment

The variety of topical treatment options has already been outlined in the introduction of this thesis. Interestingly, dermoscopic features may change during treatment, whether it was successful or not.

Ablative laser treatment is not recommended for malignant skin tumors but may come in useful when such lesions are misdiagnosed as benign, for example misdiagnosed as seborrheic keratosis. Kim *et al.* reported 55 patients with a history of previous laser

treatment of a pigmented BCC. The findings were compared to a control group without previous ablative laser treatment. The study group displayed in 92,7% of cases at least one classic BCC criteria, while 100% of the control group displayed more than one. The most common dermoscopic feature present in the lasered group were multiple blue-grey globules (58,2)% and arborizing vessels (54,6%). Other detected features were in large blue-grey ovoid nests in 38,2% of cases, ulceration in 36,4% of cases and leaf-like areas in 9,1% of cases. Spoke-wheel areas were not found in any individuals in the study group. Non-classical BCC criteria were almost twice as likely more likely to be found in the group of previous laser ablation. The authors suggested a careful inspection of a pigmented lesion before treating it with an ablative laser.(201)
Imiquimod is licensed for the topical treatment of superficial BCCs. Dermoscopy can be used to evaluate the therapeutic response. In a prospective study, Husein-ElAhmed *et al.* dermoscopically examined 20 pigmented BCCs in week 4 and week 8 of topical imiquimod treatment. In 80% of the cases examined, the BCCs displayed large blue-grey ovoid nests, in 50% of the cases multiple blue-grey globules, and in 30% of the cases examined they displayed leaf-like areas. None of the lesions displayed spoke-wheel areas. In the first evaluation after 4 weeks of treatment, 17 of the 20 lesions showed a response, and there was complete elimination of the lesion in the follow-up after 8 weeks. 2 of the 20 lesions were already eliminated at the first inspection. The disappearance of large blue-grey ovoid nests occurred in one lesion after 4 weeks and in 14 out of 16 lesions after 8 weeks of treatment. One lesion remained stable. Blue-grey globules responded more quickly. 5 out of 10 such lesions showed a full dermoscopic clearance after 4 weeks and the rest after 8 weeks. Regarding leaf-like areas, 1 out of 6 lesions disappeared within 4 weeks, the rest were gone after 8 weeks. In addition, most arborizing telangiectasias were eliminated. Ulceration was not observed anymore in the first follow-up after 4 weeks. In summary, ulceration and vascularization were the first dermoscopic BCC features to disappear. The first pigmented structures to disappear were blue-grey globules. The authors concluded that dermoscopy was useful to evaluate imiquimod's therapeutic success.(202)
In a single case report by Roldán-Marín *et al.* the usefulness of imiquimod for treating incompletely excised BCCs was analyzed. A papule on the nose of a 92-year-old woman was suspected to be a BCC, due to the arborizing vessels and telangiectasias exhibited in the dermoscopic examination. Histopathology confirmed an incompletely excised BCC of the infiltrating nodular subtype. The patient and her family refused any

further surgical approach, so imiquimod 5% cream was applied for 8 weeks. 3 weeks after establishing this therapy an “appropriate response to the topical treatment characterized mainly by erythema and mild ulceration” was observed. A follow-up after 12 months revealed no dermoscopic signs of a BCC, and after 23 months the total eradication of the lesion was confirmed by the consistent lack of BCC criteria. Therefore, the authors concluded that dermoscopy is a helpful tool in evaluating treatment response and success.(203)

Diluvio *et al.* reported a case series of successful use of a topical solution composed of 0,5% 5-FU and 10% salicylic acid on pigmented BCCs. The lesions were dermoscopically examined before and after treatment. The earlier observed BCC specific criteria – being blue-grey dots, concentric structures, spoke-wheel areas, maple leaf-like areas and shiny whitish-red structureless areas – disappeared in both cases after a treatment of 6 weeks’ duration. Skin discoloration was the only remnant found dermoscopically as well as macroscopically.(204)

Another form of local treatment for BCCs is radiotherapy. To describe the changes engendered by this therapy, a study was conducted by Navarrete-Dechentet *et al.* For the foregoing study, BCCs and their surrounding skin were examined via dermoscopy and other techniques for in vivo imaging. In summary, 41 dermoscopic images were observed. After the treatment BCC, specific criteria were less likely to be observed in the follow-ups, especially arborizing telangiectasias. The colors orange and white were increasingly noticed in the follow-ups after 6 weeks, 3 and 12 months. The emergence of white features dermoscopically corresponded in RCM with fibrosis. The authors concluded that RCM was superior to dermoscopy in monitoring the treatment efficacy of radiotherapy in relation to BCCs.(205)

Krzysztofiak *et al.* conducted a prospective study on the effects of high dose rate brachytherapy on the dermoscopic features of BCCs. 23 patients with high-risk BCCs, that were inoperable, or who were otherwise disqualified from surgical excision, were included in this study. 16 BCCs were localized on the central region of the face, 4 on the lateral parts of the face, 1 on the scalp and 2 on the neck. The treatment protocol was 9 fractions of 5 Gy aimed at the tumor with a margin of 5 mm. Thus, the cumulative dose delivered was 45 Gy over a period of 3 weeks. Dermoscopic images were taken before every treatment session, and were scanned for the presence or absence of BCC specific patterns. During treatment dermoscopically observed erosions became ulcerations of the radiated area, corresponding to destruction of tumor masses. In

addition, a reduction of white shiny structures and white structureless areas, which corresponded to fibrosis, was obtained. A possible adverse effect of high dose rate brachytherapy was radiodermatitis, which was observed in 10 patients in a more severe form, ranging from grade 2 to grade 4. Dermoscopic features of non-tumorous, but radiodermatitis affected, skin were displayed, at a severity of grade 2 diffuse scaling. In that publication, dermoscopic pictures were provided, showing the gradual disappearance of BCC specific patterns. The authors concluded that high dose rate brachytherapy led to a decrease in typical dermoscopic BCC features. Further, this was more likely to be observed in older patients.(206)

Tognetti *et al.* conducted a placebo-controlled study of 38 BCCs and their dermoscopic changes during long-term intermittent treatment with vismodegib. In the study, 6 patients with a mean age of 67 years and multiple BCCs were included. The treatment regimen for all patients was 150mg vismodegib per day for 24 weeks, followed by a placebo for 8 weeks in 3 cycles and 8 weeks of 150mg vismodegib per day. Biopsies were taken before starting and 72 weeks after ending the therapy regimen. Clinical and dermoscopic pictures were taken before starting the therapy, at week 32 and week 72. For the dermoscopic structures, a scoring system of 14 specific features was established to quantify treatment success. The BCCs which responded best to the treatment with vismodegib were superficial non-pigmented BCCs with an average diameter smaller than 1,2cm, since in these BCCs the dermoscopic features decreased significantly during the treatment. The authors concluded that the combination of clinical and dermoscopic examination is a useful approach to monitor vismodegib treatment.(207)

Villani *et al.* published a case report of a 62-year-old woman with a locally advanced BCC, which was successfully treated with vismodegib. A complete remission was reported after 40 weeks of treatment, and thus the medication was discontinued. In a follow-up after 5 months, dermoscopy revealed blue-grey globules and short-fine telangiectasias in the scar, strongly resembling a recurring BCC in the scar. The lesion was surgically removed, and subsequently a recurrent BCC was histologically confirmed. The authors' conclusion was that dermoscopy and RCM were useful to identify recurrent BCCs, but further studies with a larger sample size still needed to be conducted.(208)

9. Genetic syndromes

As previously described in the introduction, rare genetic syndromes may lead to the accumulation of BCCs in an individual. Malvehy *et al.* described the case of two siblings suffering from Xeroderma pigmentosum and the dermoscopic morphology of their BCCs. The patients were 17 and 19 years of age, and together had 26 BCCs. The authors pointed out that the presence of generalized actinic lentigo with light to dark brown pigmented network around BCCs and overlaying BCCs often lead to mistaking these for melanocytic tumors. Furthermore, they described the difficulty of differentiating between telangiectasias resulting from poikiloderma and arborizing vessels of BCCs. Vessels of BCCs were clearly shorter and arborizing in comparison to the elongated vessels of poikilodermic skin. No further BCC features like ulceration, spoke-wheel areas, blue globules, maple leaf-like structures or large ovoid nests were found in skin affected by poikiloderma.(209) Then again, the BCCs in patients with Xeroderma pigmentosum showed the same features as in patients without this genetic disease. The main difficulty was differentiating these from benign sun damaged skin.(209, 210)

Kolm *et al.* were the first to publish a paper on dermoscopy in patients with NBCCS, i.e. Gorlin-Goltz syndrome. They summarized their findings in a case series of 5 patients. Only one patient at the age of 16 did not develop any BCCs yet at the date of the paper's publication. As expected, the patients had multiple nevoid BCCs with a typical pearly aspect. The dermoscopic examination revealed pigmented BCCs with multiple grey-brown globules and dots. The lesions did not exceed a diameter of several millimeters. Some lesions also revealed dermoscopically arborizing telangiectasias. The authors' conclusion was that dermoscopy was useful for the identification of early nevoid BCCs and subclinical pits, and thus helped to identify patients with NBCCS.(211)

Casari *et al.* published a case report of a 21-year-old woman with Gorlin-Goltz syndrome. The dermoscopical examination revealed lesions of only several millimeters in size, resembling BCCs multiple grey-blue dots and structureless areas. Suspicious palmar pits with a spread of 2 x 1 mm appeared under dermoscopy as pigmented spots with grey-blue dots, which was confirmed under RCM rather as BCCs than palmar pits. The authors concluded that dermoscopy as well as RCM are useful to identify tumors in their early stages.(212)

Patients with Gorlin-Goltz syndrome often have BCCs that clinically assemble skin tags. In the publication of Feito-Rodriguez *et al.*, these lesions were mostly located on the upper back. The BCC associated features, like multiple grey globules, arborizing telangiectasias as well as small blue grey ovoid nests, fine elongated telangiectasias and further isolated blue grey globules were described. The authors concluded that these dermoscopic findings in lesions clinically appearing as skin tags facilitated an early diagnosis and therefore also an early treatment of BCCs.(128)

In summary, in NBCCS, the most frequent findings were dots and globules that were either blue, grey, brown or a combination of these colors. These dots and globules were characteristic of nevoid BCCs. No other distinct findings were reported.(128, 210-212).

10. Examination technique

At the beginning of the dermoscopy era, only the non-polarized modality in contact dermoscopy was available. Nowadays, further modalities, like polarized contact dermoscopy and polarized non-contact dermoscopy are in use. Liebmann *et al.* published a study comparing 149 BCC in consideration of the 3 mentioned modalities. It was stated that “the 3 types of dermoscopy provide complementary information highlighting different lesion attributes.” Only under polarized are light bright shiny white structures like shiny white lines, shiny white areas and rosettes are visible. Shiny white lines are also called chrysalis or crystalline structures and can also be observed in dermatofibromas, Spitz nevi and melanomas as their histopathologic equivalent is supposed to be collagenous stroma and fibrosis located in the dermis. Furthermore, the lack of pressure using non-contact polarized dermoscopy made striking vascular blush and vascular structures more visible. The authors concluded that vascular structures could have been better observed under non-contact dermoscopy and that shiny white structures that are only visible under polarized light should have been considered as an auxiliary criterion for the diagnosis of BCCs.(213)

Lupu *et al.* concluded in their review that vascular features become decisive in BCCs lacking pigmented structures. Further emphasis lay on the optimal performance, since compression may have led to the abrupt cut-off of a blood vessel.(214)

11. Subtypes of BCCs

The BCC's type has great influence on its dermoscopic morphology and therefore holds the most predicting potential. This is due to the fact that underlying histopathologic changes of BCCs correlate with particular dermoscopic features.(215) According to Lallas *et al.*, dermoscopy was most "reliable for differentiating superficial BCCs from other subtypes". The presence of maple leaf-like areas and short fine superficial telangiectasias – while lacking arborizing vessels, ulceration and blue-grey ovoid nests – were significantly associated with the diagnosis of a superficial BCC. Regardless of the clinical presentation of a BCC, the presence of blue-grey ovoid nests should have led to the diagnostic exclusion of a superficial subtype. This should also have been applied when ulceration was detected.(216)

Navarrete-Dechent *et al.* conducted a retrospective study over a duration of 7 years. In this time, 656 lesions were examined, of which 291 were BCCs. In their study, they discovered a dermoscopic feature consisting of clusters arranged in "multiple aggregated yellowish to white globules" in non-pigmented BCCs, which were visible in polarized as well as non-polarized light. While in other tumors, similar features like milia-like cysts or shiny white structures might have been visible as well, these multiple aggregated yellow-white globules were only seen in BCCs. Histopathologically, these findings seemed to correlate with "isolated, round areas of dystrophic calcification in or around tumor nodules and with the presence of calcified keratocysts."(217) Furthermore, these features were not examined in superficial BCCs, and calcification was more frequently found in high-risk histologic subtypes. The authors concluded that multiple aggregated yellow-white globules should be added as a useful criterion to identify high-risk BCC subtypes.(217) It should be noted that yellow structures were already mentioned in the literature 6 years previously by Bellucci *et al.* in a retrospective analysis of 400 BCCs. They discovered, besides milia-like cysts, also other yellow structures and named them "yellow lobular-like structures". They also proved that they were more frequently occuring in the nodular – rather than in the superficial – subtype of BCCs. The authors thus concluded that the presence of these structures should not have led to the exclusion of a BCC as diagnosis.(218)

Pampena *et al.* conducted a retrospective observational study aiming to describe the dermoscopic features of the infiltrative subtype in comparison to the nodular and superficial subtype of BCCs. 481 BCCs were examined of which 14,8% were of the infiltrative subtype. Dermoscopically, this subtype exhibited most frequently ulceration

and arborizing as well as superficial fine telangiectasias. In polarized light, shiny white structures, like short white streaks and red and white structureless areas, were more frequently observed. Further, the infiltrative subtype was less pigmented than the nodular subtype. The authors concluded that, in infiltrative BCCs, arborizing and superficial fine telangiectasia frequently coexisted in the same lesion and recognizing this would improve presurgical identification of this subtype and therefore led to excision with broader safety margins, thus reducing the risk of recurrence.(219)

According to Popadić a milky-red background had the highest sensitivity value, at 85%, notwithstanding having a low specifity value of 48% for BCCs, and therefore had no diagnostic value. Multiple erosions, ulceration, short fine telangiectasias and spoke-wheel areas were the most specific features with the highest diagnostic value. Popadić concluded that, for the diagnosis of a BCC, the most reliable dermoscopic features were telangiectatic vessels and multiple small erosions; while spoke-wheel areas, multiple blue-grey globules, short fine telangiectasias, ulceration and translucency were merely important clues.(220)

In another publication by Lallas *et al.* the authors specified the role of dermoscopy in the accuracy of discriminating the histopathological BCC subtype.(221) The nodular, non-pigmented BCC exhibited arborizing vessels as a distinct feature, while ulceration was a frequent finding. In the case of nodular, pigmented BCCs, the arborizing vessels were usually accompanied by blue-grey globules or dots. Furthermore, in the peripheries of such a tumor, i.e. the superficial parts, spoke-wheel or maple leaf-like areas could be observed. The dermoscopic feature of branching vessels was also observed in the infiltrative and sclerodermiform subtype, although these vessels were more scattered, finer and with fewer ramifications in comparison to the classical arborizing vessels of the nodular BCC. Further, the infiltrative subtype of the BCC often displayed a whitish background.(125, 221) The pigmented, as well as the non-pigmented, superficial subtype of the BCC exhibited fine telangiectasias with few ramifications. In the case of a non-pigmented, superficial BCC, multiple small erosions and shiny white or red areas could be present. In the presence of pigment, spoke-wheel areas and maple leaf-like structures were observed.(216, 221) The Fibroepithelioma of Pinkus dermoscopically exhibited a white-pinkish background, while in the center arborizing vessels were observed, and in the periphery dotted vessels were to be seen.(221, 222) The BSC is characterized by the dermoscopic features of both the BCC and the SCC, mirroring its special histopathology. In almost

all BSC, at least one BCC-specific and one SCC-specific feature were present. These included peripheral arborizing vessels, white structureless areas, keratin masses and blood spots in keratin masses, superficial scaling, ulceration, blood crusts or blue-grey blotches.(221, 223) The authors concluded that dermoscopy has become “an irreplaceable part” of the daily dermatological examination and further that via differentiating the BCC’s subtype the management of tumor could be planned in a better manner.(221)

III Conclusion

The research question of this thesis was to find different factors influencing the BCCs dermoscopic aspect, to link them together, and to point out the resulting morphologic changes, as well as to conclude from these findings a possible prediction on its subtype and an efficient treatment plan. To the best of my knowledge, there has not yet been a paper published summarizing all influencing factors of the BCCs morphology and dealing further with this subject. What conclusions can be drawn from this thesis?

The skin phototype of an individual seems to play a major role in the pigmentation of BCCs. Although BCCs were reported to be rare in individuals with SOC (161), some publications adressing this subject were found. In a Moroccan, study all BCCs found in patients with skin phototypes IV and V were pigmented.(18) Similar findings confirming this showed that, in 95% of individuals with the skin phototypes IV and V, pigmented structures in their BCCs were observed under dermoscopy.(162) On the contrary, the BCCs with pigmented structures in fair-skinned individuals bearing the skin phototypes I and II were less frequently found (164) or not at all (167). The conclusion drawn from these findings in this thesis is that during dermoscopic examination, it is important to also have a patient's phototype in mind in order to evaluate the possible existence of pigment. This might be useful in differentiating BCCs from MMs. It is essential to add that studies on minorities were scarce, and in one way this lack of data regarding indigenous people could be interpreted to be the consequence of poor access to health institutions. Data acquisition on this could be helpful and may raise awareness.

Only a few publications pointed out the specific features of BCCs on tattoos. As mentioned before in the main part of this thesis, the occurrence of a BCC in a tattoo could have been interpreted as a coincidence, since higher numbers were expected.(170, 172) No proposition for a pathogenesis linking tattoos and BCCs together was found. However, since tattoos have become socially accepted, they have become more popular over the last years. While tattoos on an elderly patient is an exception today, this could become more frequent in the future. In my opinion, the colors used in a tattoo will have an impact on the dermoscopic appearance of a BCC. Dark colors, like blue or black, may even disguise BCC hallmarks – such as arborizing vessels or pigmented structures, like blue-grey ovoid nests or globules. Furthermore, individuals, who regret getting tattoos often undergo laser treatments. In the years to

come, tumors and especially BCCs arising from this former tattooed and laser treated skin could have an altered dermoscopic appearance. Dermoscopic studies on these subjects might play a role in future dermoscopy.

The section of this thesis addressing collision tumors with BCCs highlighted the importance of pattern analysis and the limits of dermoscopy. CSL were reported to be rare (173), thus in everyday dermatological work, they should not play a major role, although it was proposed that a CLS consisting of a seborrheic keratosis and a BCC were underdiagnosed.(175) Especially the presence of a pigment network misled the examiner.(120) The majority of the studies suggested that dermoscopy was not helpful in finding the right diagnosis. It can there be concluded from the CSL section of this thesis that every suspect lesion with specific dermoscopic clues hinting towards different diagnosis or even chaos should either be excised for histopathologic examination or at least followed by short-term monitoring, so that dermoscopy cannot mislead. Furthermore, in the future, the BSC might lose its entity as an independent subtype of the BCC as it is today depicted in literature, to be referred to as a collision tumor of a BCC and a SCC. Further, the pictures provided in the publication of Medeiros *et al.* (178) were of bad quality. The described features, for example an atypical vascular pattern, could not be observed properly. Secondly the mentioned amorphous pattern was neither marked nor could it be observed in the pictures. In line with the blurred pictures, a better description would have been light to dark brown pseudonetwork, grey and brown dots, pigment in follicular openings, structureless areas, and black-grey structureless areas.

According to the BCC's location, the tumor may reveal site-specific dermoscopic features and patterns. While arborizing vessels are more frequently observed on the face, the BCCs on the trunk exhibited more than one type of vascular pattern like short and fine telangiectasias or polymorphous vessels.(180) The proximity to structures like the areola led to the additional feature of reticular black lines.(194) The BCCs of the distal lower extremity displayed rather polymorphous than arborizing vessels.(117, 183)

All suitable studies focusing on the growth of BCCs and the resulting dermoscopic changes reported, apart from the obvious growth, an increase in pigmented structures, like blue-grey ovoid nests or globules.(70, 196-200) My conclusion is that this finding does not play a major role in the daily dermatological practice.

The different treatment options led to a decrease in dermoscopic features over time (201-208), which could be used to monitor a treatment's success.(205) Blue-grey globules, ulceration and arborizing vessels responded fastest to topical imiquimod.(202) Earlier laser treatment led to non-characteristic dermoscopic features of BCCs.(201) I conclude therefore that the anamnesis also needs to cover the administered treatments, so that dermoscopy does not mislead the diagnosis.

Generally, the section of this thesis regarding the BCC and genetic syndromes underlined the importance of examining the whole patient. Dermoscopy has not only proven itself useful to find BCCs but also in giving hints to diagnose unidentified syndromes.(128, 210-212)

It is in dermoscopy's nature that histopathologic changes correlate with dermoscopic findings (215). Thus, the greatest impact of a BCC's morphology lies in its subtype. Opposing this, stands the deduction of Suppa *et al.*, stating that specific dermoscopic patterns were found independently of the BCC's histological type but depending on its anatomical location. However, nodular BCCs are more frequently located on the face, while superficial BCCs are more likely to be found on the trunk.(180) The BCC's subtypes and their dermoscopic findings have been described in detail in this thesis' introduction and main part.(1, 113-129, 131, 215-223) The thorough research in this thesis has led me to the conclusion that dermoscopy has proven itself utterly useful for the prediction of the BCC subtype (198), and therefore the determination of its treatment as concluded by many authors before.(1,71)

What further studies could be interesting in this context in relation to the topic of this thesis? There was no publication found on dermoscopy of a BCC located on male genitalia. Although cases were reported, no dermoscopic features were published. This also counts for perianal BCC. Further, there was no publication found focusing on the subject of a patient's age influencing the dermoscopic morphology of a BCC. Although differences in dermoscopic appearance could be deducted by comparing case reports of geriatric patients with those of younger patients. Besides, the BCC is considered a tumor of elderly individuals (apart from genetic syndromes).

What can be predicted by the elaborated factors and features? During the dermoscopic examination of individuals with a darker complexion, more pigment in their BCCs compared to fairer individuals is to be expected.(18, 162, 164, 167) Status post insufficient local treatment may lead to an unusual appearance of the tumor (201) and should always be noted in the patient's medical history. Lesions that show several

characteristic patterns of different tumors should be excised to histopathologically confirm a CLS (173, 176-179) or to uncover an underlying genetic syndrome.(128, 211, 212)

This thesis might also provide the impetus for a study regarding the assumption of a “signature pattern” of multiple BCCs (159) and parts of it could be used in such a study. Finally, all these findings may help to increase the diagnostic confidence for the detection of BCCs through dermoscopy and to elaborate a fitting treatment plan individually designed for the patient.

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