Master of Science in Dermoscopy and Preventive Dermato-Oncology

Master Thesis title:
Body site differences of basal cell carcinoma

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Declaration of Authorship:

I hereby declare that the thesis submitted is my own unaided work. All direct or indirect sources used are acknowledged as references.

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1. Abstract

Basal cell carcinoma (BCC) is the commonest type of skin cancer affecting primarily fair skinned individuals. Although the incidence of basal cell carcinoma in the UK is not well established due to the lack of documented epidemiological data, the estimated incidence is approximately 200 cases/100,000 population (1) making BCC the commonest type of skin cancer and one of the most common cancers amongst all cancers. Treatment options for the management of primary BCC are mainly surgical with Mohs micrographic surgery being the most effective treatment modality. However, other treatment options are available and their efficacy depends on both the tumour characteristics but also the body site location of the tumour. Dermoscopy has been developed over the past decade and is proven to be a very useful aid for the diagnosis of basal cell carcinomas. The aim of this project is to summarize and review the current literature delineating the current evidence of body site related differences of both the clinical and dermoscopic characteristics of basal cell carcinomas.

2. Introduction

The skin in the largest human organ and is fundamental for a variety of different functions. Those include acting as a physical and chemical barrier, thermoregulation, antigen presentation (2) but also sensory transduction (3) and immune regulation (4). It consists of the epidermis, dermis, adipose tissue and adnexal structures. The epidermis consists of multi-layered stratified epithelium (Figure 1) containing keratinocytes, melanocytes and Langerhans cells.

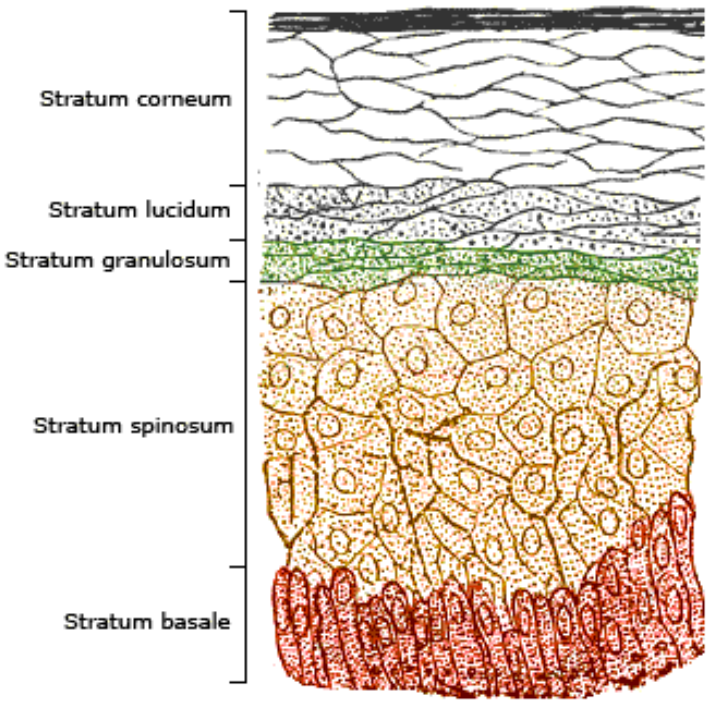

Figure 1: *Layers of normal epidermis (Adapted from Gray's epidermal layer, 1918)*

The epidermis is supported by the dermis which is composed of two layers, the more superficial papillary dermis and the deeper reticular dermis. The papillary dermis primarily consists of connective tissue containing capillaries, elastic fibers, reticular fibers, and some collagen whereas the reticular dermis consists

of dense connective tissue containing larger blood vessels, elastic fibers and coarse collagen bundles. The dermis also contains the nerves innervating the skin and provides blood supply to the epidermis.

The subcutaneous fat plays a protective but also supporting role in skin function (5). One of the subcutaneous fat's main functions is thermoregulation and body temperature stabilization in extreme conditions. However, apart from the mainly supportive role of subcutaneous fat, recent evidence supports a more regulatory role in skin function. A recent paper by Ezure et al highlights the interaction between increased number of adipose cells and a reduction in the proliferating capability of dermal fibroblasts (6), indicating a secretory and not purely structural role of the subcutaneous fat in skin function.

In summary, the skin has a complex and important role in human biology and serves a variety of functions ranging from providing an interface between the external environment and the human and therefore a barrier between the body and the outside environment (7).

2.1 Basal cell carcinoma

Cutaneous basal cell carcinoma (BCC) is the commonest form of skin cancer in the Caucasian population. Although the incidence of BCC in the UK is not well established, as it is often omitted from healthcare statistics because of the large number of cases reported and low mortality, the world wide incidence of BCC is rising (8).

2.1.1 Causes and risk factors for BCC

Although the exact origin of BCC is not yet established, BCC is traditionally felt to be a result of a combination of cumulative ultraviolet (UV) light exposure and intermittent UV exposure (9). UV radiation (UVR) causes DNA damage and genomic alteration with UVB being more carcinogenic compared to UVA (10). UVB causes characteristic point mutations in p53 which is commonly found in both BCC and other forms of non-melanoma skin cancer. The UVR- associated mutations also seem to cooperate with the age-related declining DNA repair mechanisms and the combination of UVR and defective DNA repair lead to an increase in the estimated risk of BCC by at least 5-fold (11) which could explain the clinical observation that BCC is a disease primarily of the elderly.

Another risk factor of the development of BCC is skin type I/II. Clinical observation highlight an association between skin type I (never tans, always burn) with an increased risk of all types of skin cancer including BCC (12). BCC development is also associated with increased UV exposure in childhood (13) with an increased risk of BCC in children living in sunny climates. Along these lines, there is also an increased risk of BCCs in individuals with increased occupational UVR exposure. A systematic review published in 2011 by Bauer et al has highlighted the association between occupational UV exposure and increased risk of BCC (14). However, a more recent study has indicated a more protective role of natural UV radiation. This was only limited, though, to lighter skinned individuals (15). Taken into account these data suggest that the role of occupational UV radiation is not yet well established and further research delineating the effect of UV radiation in specific patient subgroups will need to take place.

Another risk factor for the development of BCC is immunosuppression. Patients on immunosuppressive agents have a higher risk for the development of non-melanoma skin cancer, primarily squamous cell carcinoma (SCC) (16), but also BCC. BCC seem to present with a modest increase of approximately 10 fold in patients on systemic immunosuppression (17). The underlying mechanism contributing to the development of non-melanoma skin cancer in immunosuppressed patients differs between the commonly used immunosuppressive medications. Azathioprine use leads to an increase in p53-mutant foci were found in the skin of azathioprine-treated and also associated with a decreased DNA repair activity in azathioprine-exposed keratinocytes (18). In the case of calcineurin inhibitors, the mechanisms leading to increased risk of skin cancer is very complex and multifactorial. Although their use is primarily associated with an increase in SCC by modifying the skin's immunological profile by impacting on the number and functional capacity of Langerhans cells (19), dendritic cells and T cell signaling, it is speculated that the mechanism leading to the development of BCC lies also within the same etiological factors.

One of the major risk factors for the development of BCC is genetic disorders that carry a significant risk for the development of multiple BCC's and usually from an early age. Gorlin's syndrome is a rare autosomal dominant condition in which patients develop multiple basal cell carcinoma, pitting of the palms and the soles of the feet, jaw cysts and calcification of the falx cerebri, and cataracts (20). Gorlin's syndrome is caused by mutations in the *PTCH1* gene *and BCCs* most often they appear between puberty and 35 years of age with the mean age of onset at about 25 years of age.

Another significant genetic risk factor for the development of BCC is xeroderma pigmentosum (XP). XP is an autosomal recessive disorder characterized by extreme sensitivity to UVR and more than a 1,000-fold increase in the risk of cutaneous malignancy, including BCC (21). A number of rarer genetic conditions have been reported to be associated with an increased incidence of BCC like albinism, Gardner's syndrome and Bazex syndrome.

2.1.2 Cell of origin

Over the past few decades the cell BCCs originate from have been a field of intense research and controversy. Lever was the first one to attempt to delineate the origin of BCCs proposing a follicular origin and supporting that BCC originates from incompletely differentiated cells of the epithelial hair germ (22). However, few years later, Zachkeim suggested an interfollicular origin of BCC (23). Latest research in murine models highlight the potential role of long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum and the potential role of skin resident stem cells in BCC development (24).

One of the major breakthroughs in BCC research is the identification of the hyper activation of the hedgehog pathway and its role in both sporadic and germline BCC. The hedgehog pathway is fundamental in embryonic development but the deregulated pathway is associated with a number of cancers including BCC (25) and medulloblastoma (26). What has revolutionised the management of BCC in the past couple of years is the introduction of specific hedgehog inhibitors to treat BCC but this will be further discussed in chapter 3.3.

Taken this evidence into account it is fair to say that although significant amount of research has been devoted to the understanding of the development of BCC but there is still a long way before we have a more robust understanding of the origin of this cancer type and the implications that might have in targeted therapies and management of this common cancer type.

3. Clinical variants and BCC subtypes

3.1 Clinical variants

BCCs can demonstrate different clinical and histological characteristics. These usually depend on the body location of BCC, the background or not of significant UV exposure and the presence of pre-existing inflammatory skin disease or trauma.

As a general guide, BCCs present as pearly pink or skin colored papules or nodules. A clinical characteristic of BCC is the presence of surface telangiectasia and typically the presence of a 'rolled border'. Their more aggressive counterparts can present with larger nodules, which are frequently ulcerated or crusted.

Traditionally BCCs have been clinically subcategorized as nodular, superficial and morpheaform BCC.

Nodular BCCs are the most common clinical subtype and accounts for approximately 50% of all lesions. Clinical characteristics include erythematous or skin colored papules or nodules which characteristic pearly appearance and surface telangiectasia (Figure 2a). These lesions can present with bleeding after minor trauma or spontaneously and frequently become ulcerated. Nodular BCCs usually present on the head and neck area and approximately 90% of nodular BCCs present on the head.

Superficial BCCs are the second most common clinical subtype and accounts for approximately 15% of all cases. Lesions typically present as well circumscribed, scaly, pink, red or skin colored macule, patch, thin papule or plaque (Figure 2b). These lesions can also have rolled pearly edges or central crust. Superficial BCCs favor the trunk and extremities, in contrast to nodular BCCs, which favor the head and neck area. Superficial BCCs are sometimes challenging to diagnose as they could be mistaken for inflammatory dermatoses and most commonly psoriasis or discoid eczema.

Finally, morpheaform BCCs is an uncommon subtype, which accounts for approximately 5% of all cases (27). Lesions typically present as pink or ivory-white, shiny, scar-like, indurated plaques with ill-defined borders. Frequently,

there is associated atrophy. The terminology of this BCC subtype derives from the resemblance of these lesions with the atrophic and indurated plaques of morphoea. Morpheaform BCC is usually more aggressive than nodular and superficial BCC as it tends to exhibit subclinical spread with the potential for extensive local destruction.

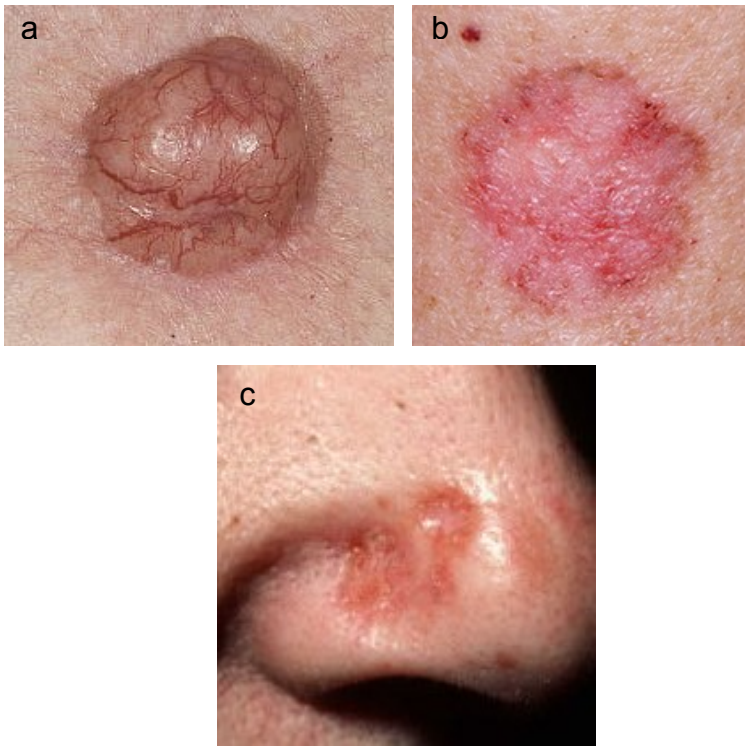

Figure 2: Clinical appearance of the most common BCC subtypes. 2a) Nodular BCC, 2b) superficial BCC and 2c) Morphoeic BCC

3.2 Histological variants of BCC

A number of histological subtypes of BCC have been reported. However the only histologically confined determinant of tumour aggressiveness is the histological pattern of invasion. Generally, BCCs are subcategorized histologically in two broad groups, the undifferentiated and differentiated. I will now briefly describe some of the histological subtypes of BCC and their implications in management and patient prognosis.

Nodular BCCs are histologically characterized by discrete large or small nests of basaloid cells in either the papillary or reticular dermis. Nodular BCCs can exhibit any of the differentiated elements (eccrine, sebaceous, etc). As nodular BCCs commonly present in sun-exposed areas, this can be histologically visible by the presence of concomitant solar elastosis. A significant number of nodular BCCs can demonstrate a variable degree of adnexal, superficial or micro nodular morphologies histologically (28).

Superficial BCCs characteristically demonstrate proliferation of atypical basaloid cells that are located parallel to the epidermal surface. Tumour cells are often apparent in the hair follicle and there is variable degree of pigmentation, giving rise to the not very infrequent phenomenon of pigmented superficial BCCs. Also of note frequently there is histologically a dense, band-like lymphocytic infiltrate present, which could prompt to the diagnosis of a superficial type of BCC (28).

Morphoeic BCCs are usually characterized by basaloid cells, which are arranged in columns and embedded in a densely collagenised abnormal fibroblast containing stroma. Mitotic activity is usually present and brisk and tumour cells are generally invading into the reticular dermis and subcutaneous tissue.

Infiltrative growth pattern BCCs are regarded the higher risk and most difficult to manage. These are characterized by irregularly sized and shaped nests of tumor cells exhibiting frequent mitotic activity and individual cell necrosis. Approximately one-third of infiltrative BCCs demonstrate the presence of a nodular component (29). Resembling the morphoeic variant, infiltrative BCCs, tumors are poorly circumscribed and may demonstrate invasion in subcutis and adjacent muscular and other structures but also perineural infiltration.

Other more uncommon BCC types include the differentiated BCCs, which demonstrate specific cell lineage differentiation features that do not impact prognosis. I will now briefly mention the most common types of differentiated BCCs.

Pleomorphic BCC is a subtype of BCCs that exhibit tumour cells with enlarged giant hyperchromatic nuclei with amorphous nucleoplasms. Characteristically these giant nuclei are either scattered individually through tumor lobules or show clustering indicating that their origin might be of a similar clone. The

presence of these large cells harbours no prognostic significance and do not demonstrate any additional biological aggressive behavior (30).

Fibroepithelioma of Pinkus (FEP) was first described by Hermann Pinkus in 1953 and it is recognized as a rare subtype of BCC. These lesions typically present as skin colored or erythematous papules or nodules and characteristic anatomic locations are the lower abdomen or the extremities (31). Several variants of FEP, including cystic, pleomorphic and giant variants have been documented in the literature. The differential diagnoses include intradermal and compound melanocytic nevi, fibroma, granuloma, hemangioma, and seborrheic keratosis. The definitive diagnosis is reached by histopathological examination. Histologically FEP is characterized by elongated basaloid epithelial strands embedded in a myxoid matrix or a background of proliferating spindle cells with abundant collagen (29). Treatment in mainly by surgical excision and recurrence rates are similar to those of other BCC subgroups.

Recurrent BCC accounts for approximately 10% of all BCC and is generally regarded as higher risk. Usually recurrence follows a conventional management approach like excision, curettage and cautery or non-invasive techniques like 5-FU and Imiquimod. The recurrence rates following BCC treatment approach depend of the choice of treatment approach selected but also the histological variant of BCC, with infiltrative tumours demonstrating a higher recurrence rate. The recurrence rates also depend on anatomic location with higher recurrence rates being reported in lesions on the head and neck and particularly on the nose and ears (32). While the majority of BCC recurrences appear within the first 3 years of initial treatment, recurrences have been reported to present up to 20 years following the original treatment (32). Histologically, recurrent BCCs present with a more aggressive histological pattern, which reflects the more aggressive nature of these tumours (28). Treatment approach for these tumours is usually surgical and patients are generally followed up for a longer period of time to identify new recurrences.

4. Treatment options for BCC

BCC is a very common type of skin cancer and thousands of patients are treated each year in the UK. A number of treatment options are available for the management of BCC and these can be tailored to each patients and each tumour specific characteristics. In this chapter I will briefly summarize the most widely used treatment modalities.

4.1 Surgical excision, curettage and cautery and Mohs Micrographic Surgery

Surgical excision is felt to be the gold standard of treatment amongst dermatologists. The aim of surgical excision is to completely remove the tumour but also allow for the pathologist to examine the lesion in its entity and confirm the surgical margin clearance. Surgical excision is traditionally quoted to give cure rates of as high as 95% and generally allow for an acceptable cosmetic outcome.
To ensure adequate tumour free rates, normally a 4mm normal skin margin is sacrificed. There has been a lot of debate over the years about the necessary clinical margins for the excision of BCCs but it is widely accepted that a 4mm margin is necessary for the eradication of 95% of BCCs (33).

Curettage and cautery is a destructive method for the management of BCC. The aim is not to completely remove the tumour but to remove the visible part of the tumour and destroy any remaining tumour cells by heat. One of the main disadvantages of curettage and cautery is the fact that there is great histological difficulty to assess the completeness of the removal of the tumour which makes curettage and cautery not very attractive when treating BCCs especially in cosmetically important areas like the head and neck. On balance, though, curettage and cautery can be used for low grade tumours with good clearance rates of up to 90% (34).

Mohs micrographic surgery (MMS) is the most effective surgical method of complete removal of skin tumours (35). Mohs micrographic surgery is felt to be able to provide superior clearance rates and lower recurrence rates compared to surgical excision. However, given the fact that Mohs surgery is both time and resource consuming certain standards have been introduced to allow for the selection of subgroups of patients in which Mohs surgery will be appropriate. Indications for Mohs surgery include tumours with poorly defined borders, tumours on high risk sites or sites where the clinical margins should be minimized (like nose, eyelids, lips, cheek, ears), large tumours and tumours with aggressive histological characteristics (like infiltrative or morpheiform pattern on histology).

Overall surgery and Mohs surgery are regarded as the most effective methods for the management of BCC but other methods can be used and will be discussed in subsequent sectors.

4.2 Cryosurgery

Cryosurgery is another technique that can be used for the management of selective BCCs. Cryosurgery uses liquid nitrogen to freeze the clinically apparent tumour and leads to the destruction of the tumour cells when thawing. Although there are historical data supporting the use of cryosurgery for the management of BCC with up to 92% clearance rates at 5 year follow up (36), its routine clinical use is limited to selected patients with low grade BCCs.

4.3 Imiquimod

Imiquimod is a toll-like receptor-7 agonist enhancing both the innate and acquired immune response and it is effective by activating the production of a number of inflammatory compounds, including IFN-α, IL-1, -6, -8, -10, -12, and TNF-α, stimulates natural killer cells and the proliferation of B-cells (37). These functions which lead to alteration of the immune responses have been used to manage certain subsets of BCC. Several studies have been published over the past few years indicating that imiquimod can be used 5/week for 6 weeks with

good results in managing BCC and indicate a histologically proven clearance rate of approximately 75% (38). However, Imiquimod is only used in selected patients as its use can be restricted by side effects which include erythema, oedema, pruritus and burning sensation.

4.4 Photodynamic therapy (PDT)

Photodynamic therapy has been used for the management of low risk BCC. Recently, MAL is more widely used compared to ALA which was used in the past as it demonstrates superior tumour selectivity. Recent studies demonstrate a clearance rate of approximately 75-85% with recurrence rates of 20% when MAL-PDT was used in a selected group of patients (39). However PDT can only be used in a subset of patients given the high rate of side effects which results to poor compliance.

4.5 Radiotherapy

Radiotherapy has been extensively used the in past for the management of difficult to treat or recurrent BCC. Nowadays it can be used for surgically recurrent BCC or patients who are unable to tolerate surgery and are not suitable to undergo any other treatment options. Radiotherapy can also be used in the adjuvant setting for patients with high risk tumours and incomplete or narrow excision margins. In the past radiotherapy was felt to lead to poor cosmetic outcomes and high recurrence rates but this has significantly improved with the novel equipment and techniques used. Radiotherapy is also more difficult to be used in certain body areas like eyelids and lower leg as these areas tend to have a greatest rate of radio necrosis and lead to chronic wound formation. In terms of efficacy, radiotherapy has been shown to provide good control in selected patients, with cure rates of up to 91% at 5 years post treatment (40).

4.6 Hedgehog inhibitors

A number of studies have attempted to delineate the molecular mechanisms driving the development of BCC. Groundbreaking studies, which were initially studied in Drosophilla, characterized the importance of the patched gene. The hedgehog pathway plays a fundamental role in embryonic development and its deregulation is responsible for the development of a number of tumour types including BCC and medulloblastoma (41). Genetic studies have highlighted the presence of genetic alteration in the hedgehog pathway in almost all BCCs, which results in deregulation of the pathway and tumour cell proliferation and survival. These mutations most commonly cause a loss of function of the patched homologue 1 (PTCH 1) whose normal function is to inhibit the signaling activity of smoothened (SMO) and therefore lead to hyper activation of the pathway (25) (Figure 3).

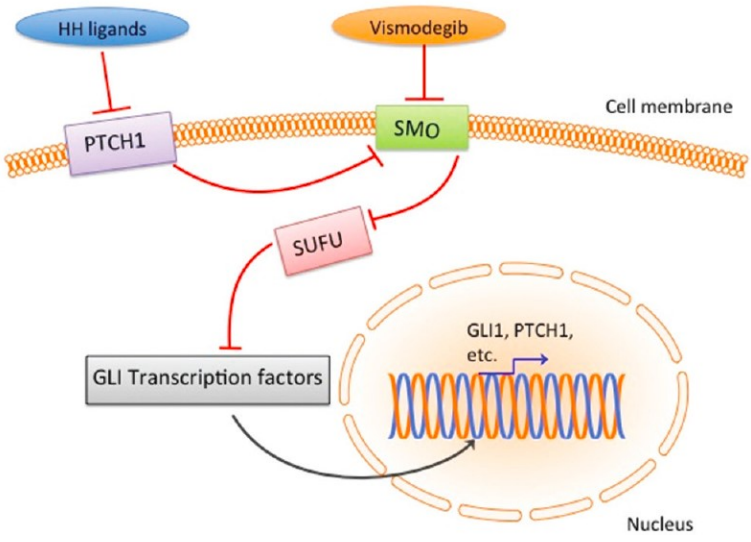

Figure 3: Schematic of the hedgehog-signaling pathway: Hedgehog binds to patched 1, leading to suppression of smoothened. Smoothened then promotes glioma-associated oncogene transcription factors (taken from Booms et al, Annals of Maxillofacial surgery, 2015 (42))

Vismodegib has been developed to target the abnormal smoothened and therefore lead to switching back off the pathway and therefore resulting to tumour shrinkage. There is recent compelling evidence from clinical trials reinforcing the efficacy of Vismodegib in patients with inoperable locally advanced or metastatic BCC (43). Clinical trial results demonstrate a 58% response rate and a median duration of response of approximately 12.8 months (same as before). Overall Vismodegib is a viable option for patients with advanced, inoperable or metastatic BCCs and has been approved in the UK for these indications but also for patients with Gorlin's syndrome in an attempt to reduce the frequency and number of BCCs.

5. Dermoscopy of bcc

5.1 Dermoscopy

Dermoscopy is a non-invasive technique used for the microscopic examination of pigmented and non-pigmented skin lesions. Although a lot of interest has concentrated in the aid of dermoscopy to the diagnosis of pigmented skin lesions, recent data suggest an emerging and significant role of dermoscopy in the diagnosis and management of non-pigmented skin lesions, inflammatory skin diseases but also skin infestations. Emerging evidence also highlights the use of dermoscopy in following up tumour clearance following surgical and non-surgical or destructive treatment methods (44). Dermoscopy also improves the diagnostic accuracy and discriminates pigmented BCCs from malignant melanoma which is indeed challenging to differentiate macroscopically. Although the diagnostic accuracy using dermoscopy is significantly higher compared to clinical examination alone, the usefulness of dermoscopy heavily relies on clinical training and experience of the user. A number of dermoscopic characteristics for the diagnosis of BCC have been described and I will summarize some of them in section 5.2.

5.2 Dermoscopic characteristics of BCC

A number of studies have described in detail the dermoscopic characteristics of BCC and subcategorized their findings according to clinical subtypes.
Menzies et al were the first group to describe the dermoscopic characteristics of BCCs and introduce specific criteria for the recognition of these tumours (45). In this paper the proposed model followed the below criteria: the absence of a pigment network, and the presence of one or more of the 6 positive features mentioned below (Figure 4).

- large gray-blue ovoid nests
- multiple gray-blue globules
- maple leaflike areas
- spoke wheel areas

- ulceration
- arborizing "treelike" telangiectasia

In this study, the presence of these criteria has created a model with a sensitivity of 97% for the diagnosis of pigmented BCCs and a specificity of 93% for invasive melanoma diagnosis (45) and therefore it is providing a useful tool for the differential diagnosis between a pigmented BCC and a malignant melanoma which can be clinically challenging.

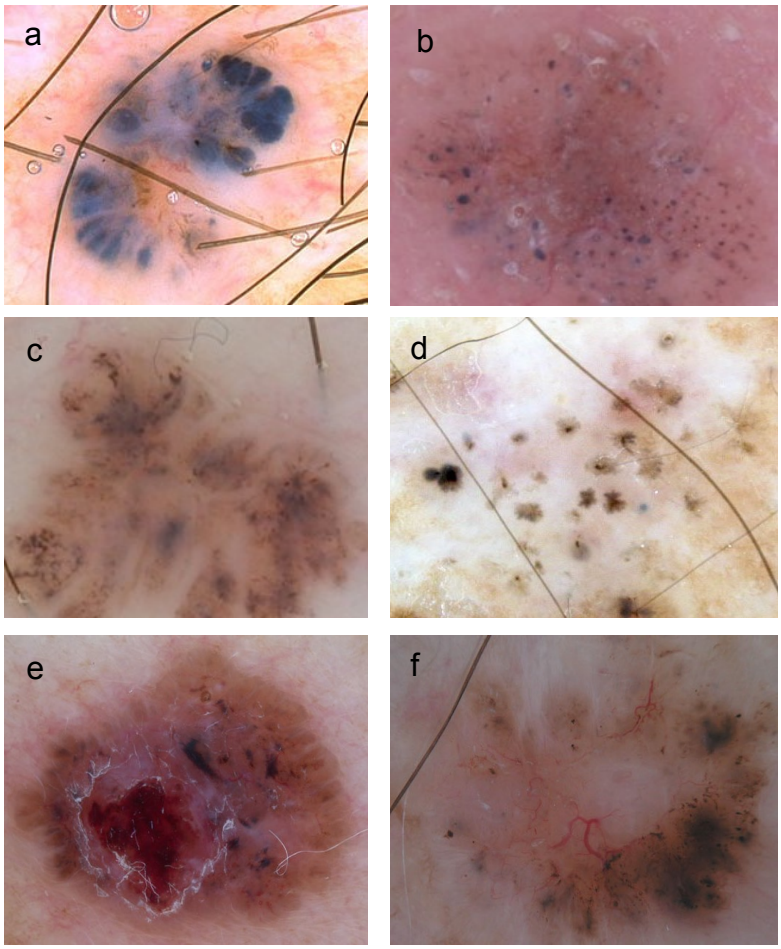

Figure 4: Dermoscopic characteristics for BCC as initially described by Menzies et al. 4a) large gray-blue ovoid nests, 4b) multiple gray-blue globules, 4c) maple leaflike areas, 4d) spoke wheel areas, 4e) ulceration, 4f) arborizing "treelike" telangiectasia (Photos 4a, 4e, 4f taken from Dermnetnz.org (46) and photos 4b,4c,4d taken from Lallas et al (44))

Following these initial observations a number of studies have further delineated the role of dermoscopy in the diagnosis of both pigmented and non-pigmented BCCs. Initially BCCs are subcategorized by the presence of pigmentation into three different categories, the non-pigmented BCCs which demonstrate complete lack of pigmentation, scarcely pigmented BCCs demonstrate surface pigmentation in <25% of the total surface and lightly pigmented BCCs which demonstrate pigmentation which is involving 25-50% of the lesion's surface and heavily pigmented BCCs in which the pigmentation involves >75% of the lesions surface. Altamura et al have published an in depth description of the dermoscopic characteristics of BCCs according to the presence of classic or more unusual characteristics and further subcategorized them according to the degree of surface pigmentation (47). Some of the main characteristics which were highlighted in this paper are listed in the table below (Table 1).

	Dermoscopic characteristics	**Non pigmented**	**Lightly pigmented**	**Heavily pigmented**
Classic BCC pattern	Arborizing vessels	84%	63%	32%
	Large blue/gray ovoid nests	0%	49%	58%
	Ulceration	49%	46%	20%
	Multiple blue/grey globules	0%	38%	36%
	Leaflike areas	0%	22%	25%
	Spoke-wheel areas	0%	49%	80%
Melanocytic pattern	Multiple brown to black dots/globules	0%	33%	25%
	Blue/white veil like structures	0%	17%	62%
	Non arborizing vessels	12%	10.4%	3.6%
	Radial streaming/pseudopods	0%	0.8%	1.8%
Non classical pattern	Short fine superficial telangiectasia	14%	5.8%	1.8%
	Multiple small erosions	7.6%	6.5%	9.1%
	Concentric structures	0%	8.1%	7.3%

Table 1: Common dermoscopic features in BCCs categorized according to the degree of pigmentation and the presence or absence of any classical features as described by Menzies et al (Adapted from Altamura et al (47)).

Other studies like the one published by Suppa et al have concentrated on the dermoscopic characteristics and differences between nodular and superficial subtypes of BCC (48). In this study arborizing vessels were found primarily in nodular BCCs whereas short fine telangiectasias, small superficial erosions, leaf-like areas and concentric structures were a feature mainly of the superficial BCCs. Nodular BCCs were also characterized by blue veil-like structures and white shiny areas. These characteristics could be reflecting the tumour burden and need for neo angiogenesis which is a lot more prominent in bulky and more nodular BCCs.

These observations were also documented in another paper by Lallas et al. This study aimed to delineate the dermoscopic characteristics of superficial BCCs compared to other clinical subtypes. In this study, dermoscopic characteristics like maple leaf-like areas, superficial fine telangiectasias, multiple superficial erosions and shiny white areas were most predictive of superficial BCCs whereas arborizing vessels, blue-gray ovoid nests and ulceration were strong predictors of non-superficial types of BCC and most likely nodular BCC(49).

In conclusion, a number of different dermoscopic characteristics for the diagnosis of BCC have been proposed. The classical dermoscopic features have been initially proposed by Menzies and since then further subcategorization has been made for the clinical subtypes of BCC and a lot of work has concentrated on the dermoscopic characteristics of the nodular versus superficial subtypes.

6. Materials and methods

This Master thesis aims to delineate and summarize the body site differences of basal cell carcinoma. To this aim, appropriate bibliography has been sourced from Pubmed and articles were summarized.

7. Results

As already mentioned in section 3.1 BCCs exhibit a number of different clinical subtypes and these have a certain predilection in different parts of the body and also demonstrate variable dermoscopic features.

The observed differences in BCCs clinical characteristics depends not only on anatomical location but also on the patient's age. There is a growing body of evidence demonstrating the prevalence of BCCs on different anatomical sites depending on patient's age. The presence of BCCs on the head and neck area significantly increases with age (34% in patients <40 years old versus 64% in patients >90 years old). Similarly there seem to be an inverse correlation in the presence of BCCs on the body according to age with 62% of BCCs in patients <40 years old to be present on the body compared to 23% of patients >90 years old (50, 51). This phenomenon supports the speculation that nodular BCCs are more commonly related to cumulative chronic sun exposure compared to their other counterparts (Table 2).

Anatomical location	**Histological subtype**		
	Nodular	**Superficial**	**Morpheiform**
Sun exposed	86%	38%	91%
Photoprotected	13%	61%	8%

Table 2: Incidence of different BCC subtypes according to the anatomical location and sun exposure (Adapted from Scrivener et al (52))

Interestingly in a study of 4960 tumours, there seems to be a clear predilection for nodular BCCs to present on the scalp and head compared to superficial BCCs that tend to present mainly on the trunk and extremities (51, 52) (Table 3 and Figure 5).

Body site	Superficial BCC	Nodular BCC	Infiltrative BCC
Scalp	0.8%	2.2%	2.1%
Face	18%	45%	54%
Neck	5%	6%	7%
Upper extremities	17%	14%	8%
Trunk	25%	9%	8%
Lower exremities	12%	10%	9%

Table 3: Body site distribution of BCCs of different histological subtypes (data pooled and adapted from Raasch et al (51))

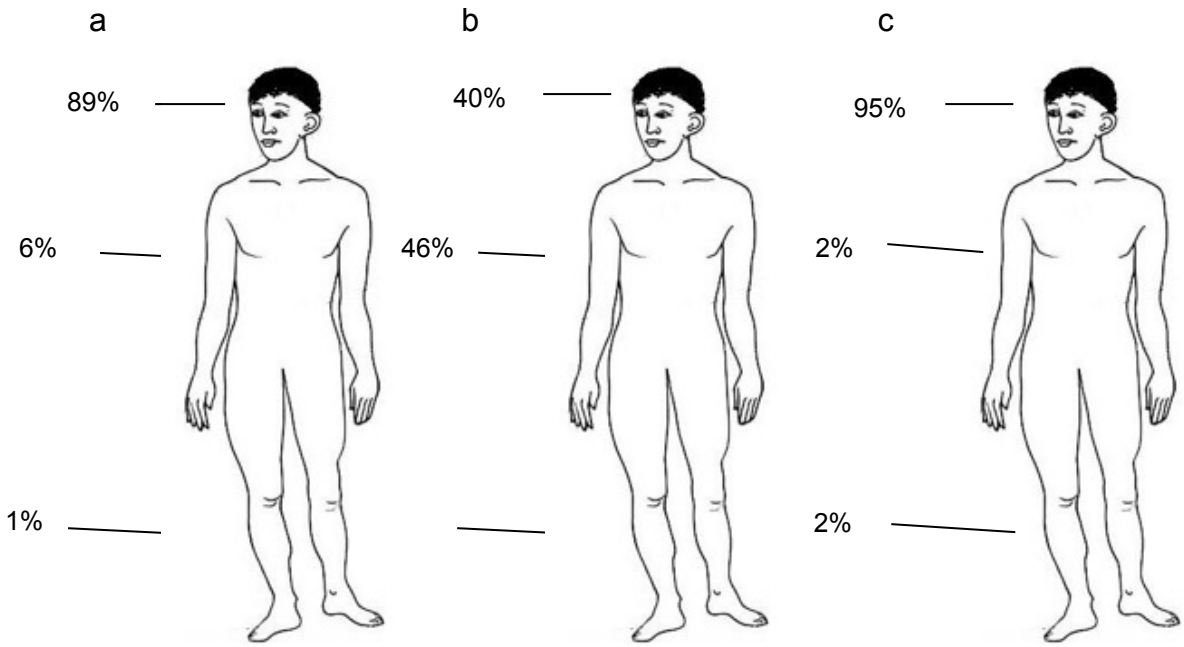

Figure 5: Anatomical distribution of nodular BCC (5a), superficial BCC (5b) and morpheiform BCC (5c). Adapted from Scrivener et al (52).

Interestingly, the anatomical distribution of BCC is also gender dependent. BCCs on the head and neck area are more commonly found in women than in men and this observation was independent of the histological subtype (52). The most striking gender dependent difference is observed in superficial BCCs which are usually found on the head and neck area in women and primarily on the trunk in men. In this study the superficial variant is found in almost equal frequency in both men and women, The male to female ratio in this study was 1.02 for nodular, 0.96 for superficial and 0.73 for morpheic BCC. This study highlights the differences in histological characteristics of BCCs in men and women.

As we have already discussed in previous sections, different histological subtypes of BCC demonstrate different dermoscopic features and certain subtypes have a predilection for a certain body site. As a result, it is not surprising that BCCs appearing on different anatomical locations also demonstrate different dermoscopic features. In this section I will review the literature on this topic and report the results on an anatomical location-based manner.

7.1 Dermoscopic features of BCCs on head and neck compared to the trunk

Suppa et al have recently published their work looking at the dermoscopic differences of BCCs according to anatomic location and degree of palpability and pigmentation (48). This study included 501 histologically proven BCCs and investigated the dermoscopic variability according to anatomic location. This study has highlighted a strong association between the presence of arborizing telangiectasias and ulceration with facial BCCs. Specifically, arborizing telangiectasia was present in 73% of facial BCCs ($p<0.001$) and ulceration was present in 44% of all cases ($p<0.001$) whereas arborizing telangiectasia was present in only 41% of truncal BCCs and ulceration in only 31% accordingly.

Interestingly the scalp demonstrates slightly different dermsocopic characteristics compared to the head and neck area. Pigmentation has been significantly more prominent on scalp BCCs compared to facial BCCs. Scalp BCCs also demonstrated more blue-grey ovoid nests, leaf-like areas , blue-white veil structures and melanocytic patterns compared to BCCs located in other parts of the body, indicating that BCCs located on the scalp demonstrate unique clinical and dermoscopic appearances.

This study has also highlighted the strong association between the dermoscopic presence of leaf-like areas, short fine telangiectaisas, small erosions, concentric structures and spoke wheel areas with truncal bcc whereas these dermoscopic characteristics were not frequently observed in facial BCCs (48) (Table 4).

In summary, these data is in line with previous observations indicating that the nodular subtype is the most common histological subtype of BCCs on the face and therefore demonstrates the most common dermoscopic characteristics of nodular BCCs which include arborizing telangiectasia and ulceration. On the other hand, the superficial subtype is the most histological subtype of BCCs on the trunk and therefore truncal BCCs are associated with the most common dermoscopic characteristics of superficial BCCs including leaf-like areas, short

fine telangiectasia, small erosions, concentric structures and spoke-wheel areas.

BCC associated pattern	Face	Trunk	Scalp
Arborizing telangiectasia	73%	41%	38%
Blue grey ovoid nests	31%	39%	49%
Ulceration	43%	30%	27%
Leaf-like areas	13%	36%	47%
Blue-grey globules	23%	30%	29%
Short fine telangiectasia	9%	39%	23%
Small erosions	4%	19%	7%
Concentric structures	5%	12%	10%
Spoke wheel areas	4%	13%	10%

Table 4 : Dermoscopic differences of BCCs of different anatomical location (data adapted from Suppa et al (48))

7.2 Melanocytic and vascular patterns in BCC

The presence of melanocytic patterns in BCCs was positively associated with the degree of pigmentation with the frequency of >1 melanocytic pattern was present in 30% of non-pigmented BCC compared to 87% in heavily pigmented BCCs (48). In terms of anatomic location, 41% of scalp BCCs exhibited multiple brown/black dots compared to 19% of facial and 27% of truncal BCCs. Also of note, 28% of scalp BCCs demonstrated blue-white veil like structures compared to only 12% of facial and 11% of truncal BCCs, indicating that scalp BCCs demonstrate a high level of pigmentation and unique dermoscopic features.

In this study by Suppa et al, diverse vascular structures were also studies and compared according to the anatomic location of BCC. Generally, facial and scalp BCCs demonstrated very few dermoscopic vascular patterns compared to truncal BCCs in which dotted vessels were present in 15%, polymorophous vessels in 12% and linear/irregular vessels in 9%. These data indicate that

although arborizing vessels in the hallmark or nodular facial BCCs, their truncal counterparts demonstrate a variety of vascular structures with atypical vascular formations.

8. Discussion

BCCs are the most common types of skin cancer and have a rising worldwide incidence. Although BCCs are not typically regarded as an aggressive tumour type, they carry significant morbidity and can be difficult to both diagnose and manage especially in the case of neglected tumours.

A number of treatment modalities are available for the management of BCCs and the choice of treatment option varies and depends on the tumours characteristics, the patient's preference but also the clinician's experience.

Treatment options range from pharmacological treatments like 5 FU cream and imiquimod to surgical excision and Mohs micrographic surgery. Recently the introduction of specific Hedgehog pathway inhibitors have revolutionized the management of patients with inoperable and metastatic BCC.

Dermoscopy has been developed to aid the diagnosis of both pigmented and non-pigmented skin tumours but also to help the clinicians to differentiate between benign and malignant tumours. Dermoscopy has been extensively studied in the context of both diagnosis of BCC and follow up of patients following different treatment modalities. Dermoscopy has been shown to aid the clinicians in the diagnosis of BCC and is routinely used in clinical practice.

This Master thesis aimed to summarize the clinical and dermoscopic characteristics of BCCs on different anatomic location. For this purpose I have mainly concentrated on the clinical and dermoscopic differences mainly on the scalp, head and neck area and trunk.

Different clinical and histological BCC subtypes demonstrate a predilection to certain body areas. Nodular BCCs are more common on the scalp, head and neck area whereas superficial BCCs tend to present more commonly on the body. Similarly morpheic BCCs also tend to have a predilection for the head and neck area.

Dermoscopicaly it comes as no surprise that different dermoscopic patterns are more commonly observed on different body areas. Arborizing vessels and ulceration, which are some of the dermoscopic hallmarks of BCC, are more commonly seen on the head and neck and are primarily features of nodular tumours. On the other hand, leaf-like areas, short fine telangiectasia, small

erosions, concentric structures and spoke wheel areas are primarily seen in truncal BCCs.

Several studies have also looked into other, non-typical dermoscopic BCC characteristics like the presence of pigmentation, the presence of other vascular structures and the presence of melanocytic patterns. Results to these demonstrate that scalp BCCs are more commonly pigmented and therefore demonstrating some of the melanocytic dermoscopic features and truncal BCCs more commonly demonstrate atypical vascular structures compared to the nodular BCCs, which are more commonly found on the head and neck, and are characterized primarily by large tortuous arborizing vessels.

Dermoscopy has proven that has a significant role in the diagnosis of BCC and its utility is not just limited to diagnosis and differential diagnosis between malignant and benign tumours but also could help with patient follow up following treatments for BCC. There is increasing role for non-surgical treatment for BCC but their use is limited by the slightly higher recurrence rates compared to surgical excision. Dermoscopy could be a useful tool to monitor these patients and detect early recurrence. This provides that there is good documentation of the demoscopic characteristics of the tumours prior to treatment and there is adequate material for accurate follow up. There is no doubt that the role of dermoscopy in the management of bot skin tumours and inflammatory skin diseases could shed light to the natural history of these diseases and is an undoubtedly helpful tool for the clinicians.

In summary, this Master thesis has summarized the clinical and histological subtypes of BCC, summarized the current treatment options and clinical and dermoscopic characteristics depending on anatomical location.

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