

Master Thesis

Site and Gender Specific Distribution of Different Subtypes of Basal Cell Carcinoma

submitted by

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Statutory declaration

I declare that I have written this work independently and without assistance other than those specified sources, and have not used sources or means without declaration in the text. Any thoughts from others or literal quotations are clearly marked. The Master Thesis was not used in the same or in a similar version to achieve an academic grading or is being published elsewhere.

Prior to this study the approval of the Ethics Committee of the University Hospital Charité Berlin, the approval of the Research Department of the German Military/Bundeswehr and of the Data Protection Supervisor of the Bundeswehr Hospital Berlin were obtained.

Berlin, 17.10.2022

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List of abbreviations

BCC	basal cell carcinoma
PTCH1 gene	Protein patched homolog 1 gene
SMO gene	Smoothened gene
TP53	Tumor suppressor protein 53
EpCAM	epithelial cell adhesion molecule

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1. Abstract

Background: Basal cell carcinoma is the most common and frequent form of human neoplasms in Central Europe. It is classified as a keratinocyte carcinoma, it grows locally, is destructive to neighbouring tissues and has a very low tendency for metastasis. Most forms of BCC are remediable and cause minor damage when detected and treated early. This tumour appears in several histopathological and clinical subtypes and, according to literature, male individuals appear to have a higher predisposition to BCC than the female counterpart.

Objective: The aim of this study is to detect a correlation between subtypes of BCC and the distribution on body sites as well as a predisposition to appear within a certain sex.

Materials and methods: This retrospective study analyses 66 BCC treated hospitalisation cases (24 female, 42 male) at the Bundeswehr Hospital in Berlin from 2018 to 2019. Site specific and sex specific differences were analysed for all 7 common subtypes: nodular, micronodular, superficial, sclerosing, ulcerated, pigmented and fibroepithelial. Mixed subtypes in one BCC lesion were counted individually to consider 126 histopathological cases.

Results: The study showed the following occurrences of BCC, broken down by subtype: 43% in nodular, 22% in micronodular, 13% in superficial, 12% in sclerosing, 8% in ulcerated, 1% in pigmented and 1% in fibroepithelial BCC lesions. The calculated correlation and the significant test result suggest that a meaningful predictor for the BCC subtype has been found in the body site. This statement cannot be made for the variable sex.

Conclusion: The results show site specifics in distribution of BCC subtypes. Site specific distribution could be found for nodular, micronodular and sclerosing BCC predominantly on the face whereas sclerosing BCC have more tendencies to occur on the torso. The male sex shows a higher BCC prevalence as the female sex. Sex specific prevalence in certain BCC subtypes are not proven by this study.

2. Introduction

Basal cell carcinoma is the most common and frequent form of human neoplasms in middle Europe¹. The clinical appearance in early stages can be easily misdiagnosed by general physicians and not every state reports BCC cases to the administrative centre for cancer registry date therefore estimated numbers of unknown cases are likely to be high. BCC is classified as a keratinocyte carcinoma, it grows locally, is destructive to neighbouring tissues and has a very low tendency for metastasi². It can appear anywhere on the skin's surface but is rarely detected on the mucous membranes or palmoplantar³. BCC appears in several histopathological and clinical subtypes. Mixed subtypes can occur as well. Male individuals appear to have a higher predisposition to BCC than the female counterpart⁴.

Most forms of BCC are remediable and cause minor damage when detected and treated early. The first line therapy is the surgical excision. Other therapy regimes may include radiation therapy, local therapy with Imiquimod 5% or 5-Fluorouracil 5% or systemic therapy with Hedgehog-inhibitors⁵.

2.1. Objective

The aim of this study is to detect a correlation between subtypes of BCC and the distribution on body sites as well as the preponderance of occurrences based on sex.

2.2. Epidemiology

The incidence lies at 200 per 100.000 inhabitant per year in Germany^{4,6,7}.

The lifetime prevalence for people of central and northern European ethnicity is estimated at 10%⁸. Both sexes are affected whereas the male sex shows a higher incidence⁴.

2.3. Risks of developing BCC

The underlying mechanisms of oncogenesis are mostly genetic mutations in the PTCH1 or SMO gene. These mutations lead to pathological activation of the Hedgehog signal pathway. The Hedgehog signal pathway is contributing in embryonal development and is physiologically deactivated. 85% of all BCC show mutations in this signal pathway. A third, less common mutation involves the alteration of the TP53 gene. This is a tumour suppressor gene, which detects DNA damages and inhibits affected cells from replicating their DNA⁵.

The risk of mutations and thereby the development of BCC is dependent on genetic and environmental factors². Ultraviolet radiation is the highest risk factor^{2,3,9}. UV radiation can produce mutations in the TP53 gene¹⁰. Both chronic sun exposure and intermediate sunburns are detected as risk factors^{11,12}.

Within the generations beyond 60 years protective measures against UV radiation from the sun were not that commonly understood as nowadays. Therefore, a rise in incidences of BCC could be postulated.

Certain genetic syndromes such as the Gorlin-Goltz syndrome, Bazex-Dupré-Christol syndrome, Rombo syndrome, Xeroderma pigmentosum and albinism are associated to higher risks of developing BCC. Other risk factors are immunosuppression, arsenic poisoning, the male sex, Fitzpatrick skin types I and II and ionizing radiation⁵.

2.4. Diagnosis

Dermoscopic examination continues to be readily accessible, expedient, low cost method to evaluate a lesion for malignancy. The results achieve 93,3 % in sensitivity and 91,8 % in specificity in the detection of BCC¹³. Even early stages of BCC can be better detected via dermoscopy¹⁴. Other examination methods can be performed with confocal laser microscopy or optical coherence tomography. But beyond these current technological innovations, histopathological examination of lesions prevails as gold standard. Whereas punch biopsies may not be reliable in their accuracy due to inhomogeneous distribution patterns of mixed subtypes in one lesion, a whole excision is recommended for evaluation^{15,16}.

2.5. Clinical and histopathological specifics of basal cell carcinoma

Clinically BCC may present as pinkish- to redish-coloured nodes, plaques or ulcerations. The clinical aspect is dependent on the localisation, subtype and age of the lesion. Most common characteristics are telangiectasia, a raised rolled border with translucent or pearly appearance. Ulceration and pigmentation may also occur.¹⁷

Histopathologically aggregated basaloid cells are characteristic. Cells palisading in the periphery can be detected. The cells are often poor in cytoplasm with round to oval dark nuclei and can be coloured with antibodies against EpCAM. EpCAM is a transmembrane protein which plays an important role in embryogenesis and oncogenesis which is not detected in squamous cell carcinoma.

There are several subtypes of BCC. This study refers to the 7 most common:

2.5.1. nodular

The nodular subtype of BCC is characterized by nodules and plaques and can have ulcerations in larger lesions.

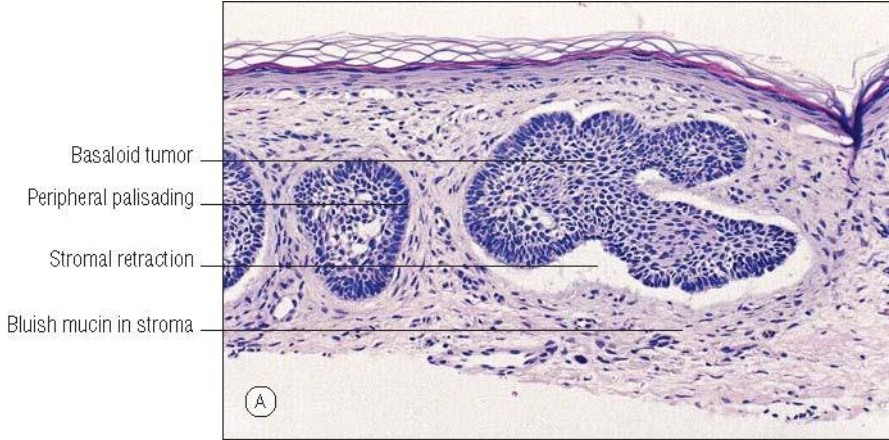


Figure 1: Clinical nodular BCC²² with raised rolled border, telangiectasia, sunken centre and pearly appearance



Figure 2: Dermoscopy nodular BCC²² with arborizing vessels

Histopathologically this subtype shows multiple nests of basaloid cells with peripheral palisading whereupon the centre of nests show haphazard nuclei and apoptosis^{3,19}.

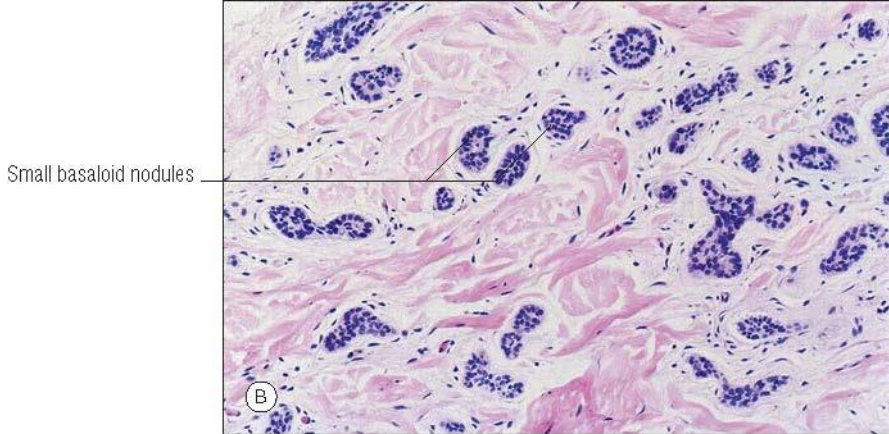


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Figure 3: Histopathological nodular BCC¹⁹

2.5.2. micronodular

The micronodular subtype of BCC is characterized clinically with rather flat nodules and plaques. Histopathologically this subtype is similar to the nodular subtype except for its smaller (<0,15mm in diameter) nests of basaloid cells. These nests can reach down to the subcutaneous fat and show a greater risk of local recurrence^{3,19}.



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Figure 4: Histopathological micronodular BCC¹⁹

2.5.3 superficial

The superficial subtype of BCC is characterized clinically as flat plaques.



Figure 5: Clinical superficial BCC²³ on the dorsal torso as a flat erythematous plaque with peripheral pigmentation

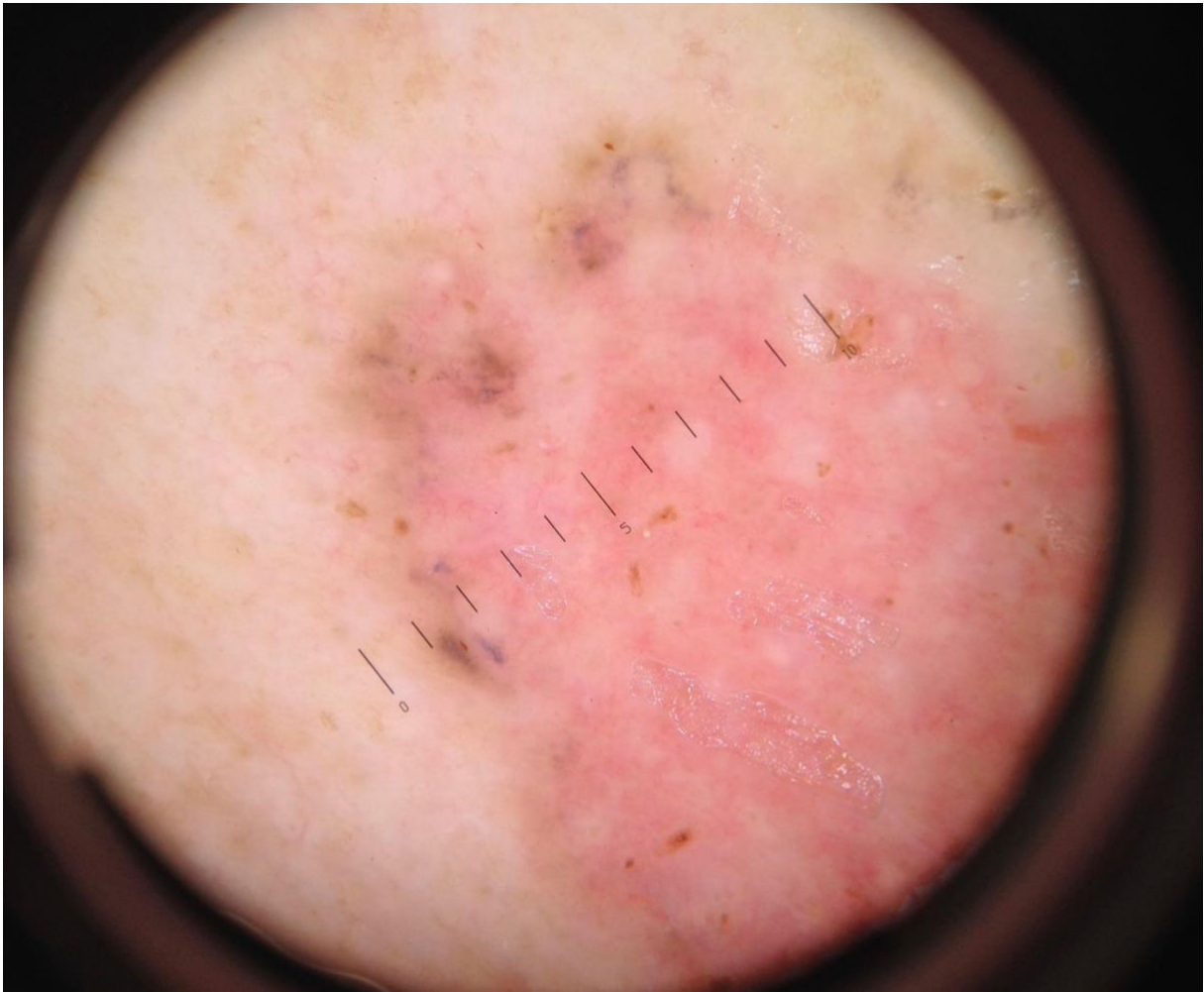


Figure 6: Dermoscopy superficial BCC²³ with multiple peripheral blue-gray areas, maple leaf-like areas and tiny ulceration

Histopathologically this subtype shows basaloid cells that are connected to the epidermis or slightly descending from it^{3,19}.

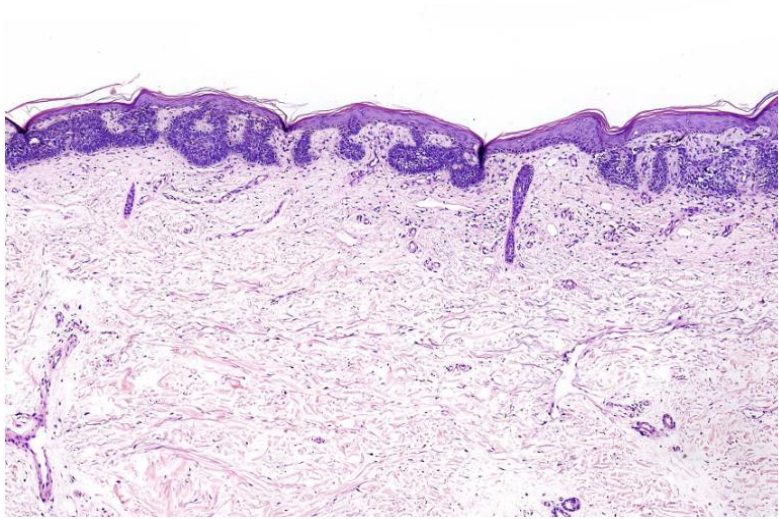
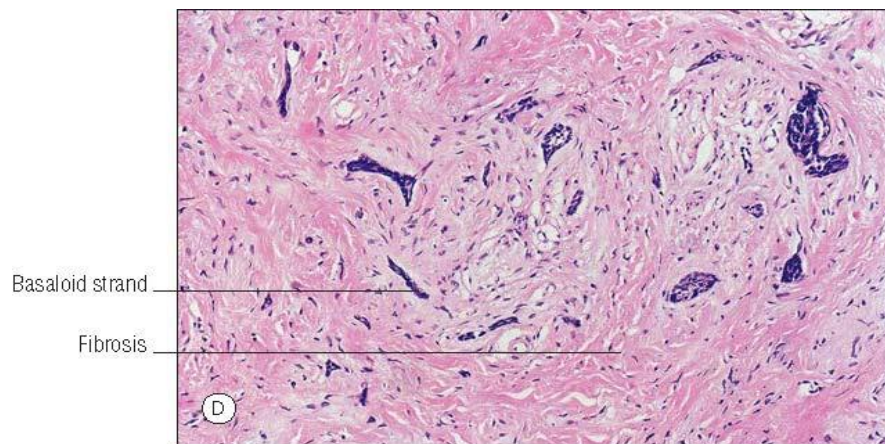


Figure 7: Histopathological superficial BCC²⁰

2.5.4. sclerosing

The sclerosing subtype of BCC is characterized clinically in a scar like appearance. Histopathologically this subtype shows thin cords of basaloid cells with dense sclerotic collagenous stroma. The tendency for invading the dermis and perineural invasion is high^{3,19}.



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Figure 8: Histopathological sclerosing BCC¹⁹

2.5.5. ulcerated

The ulcerated subtype of BCC is characterized clinically by the presence of ulceration.



Figure 9: Clinical ulcerated BCC²² with raised rolled border, telangiectasia and pearly appearance

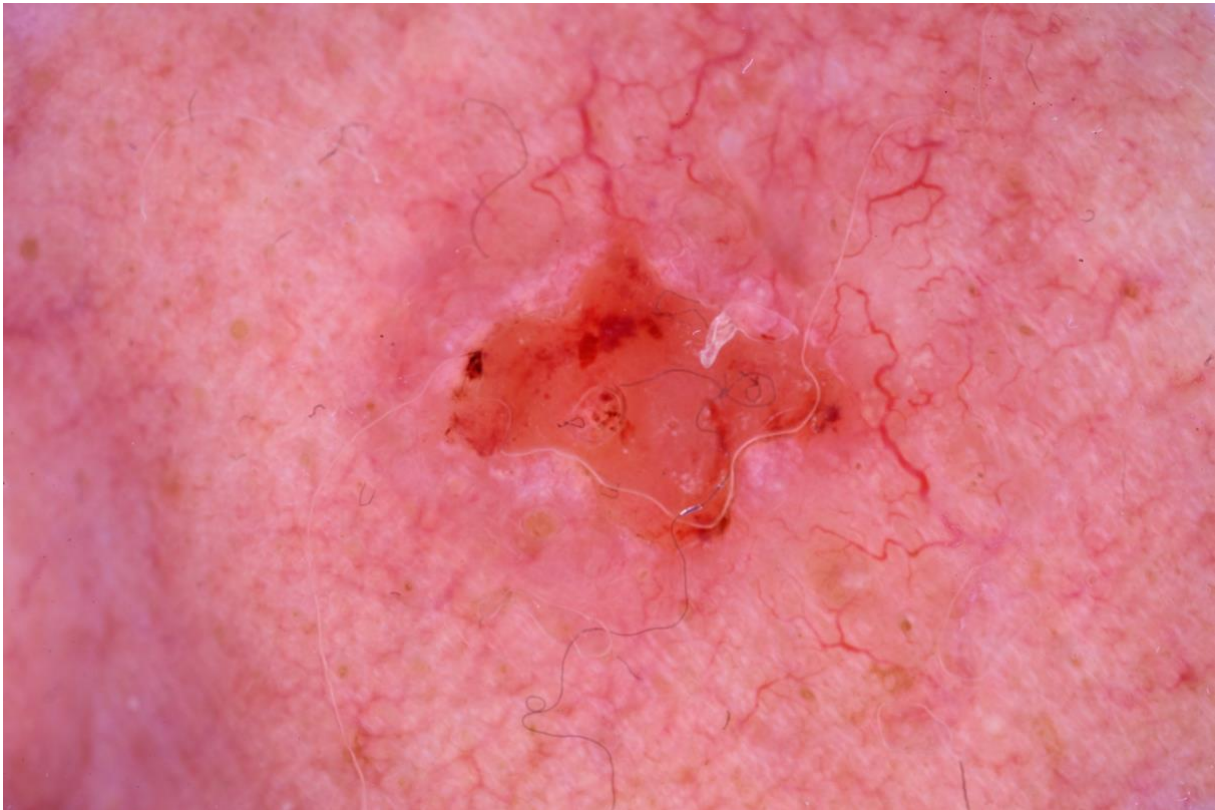


Figure 10: Dermoscopy ulcerated BCC²² with central ulceration and arborizing vessels

Histopathologically this subtype shows signs of epidermal ulceration^{3,19}.

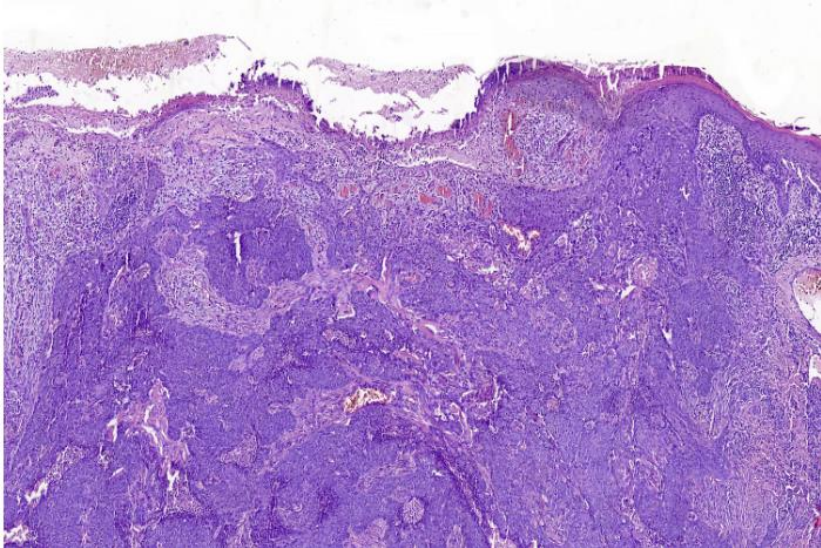


Figure 11: Histopathological ulcerated BCC²⁰

2.5.6. pigmented

The pigmented subtype of BCC shows brown to black pigmentation. The dermoscopic image of the lesions shows absence of pigment network and the detection of one of the following positive criteria: large blue-gray ovoid nests, maple leaf-like areas, spoke wheel areas or multiple blue-grey dots/globules¹⁸.

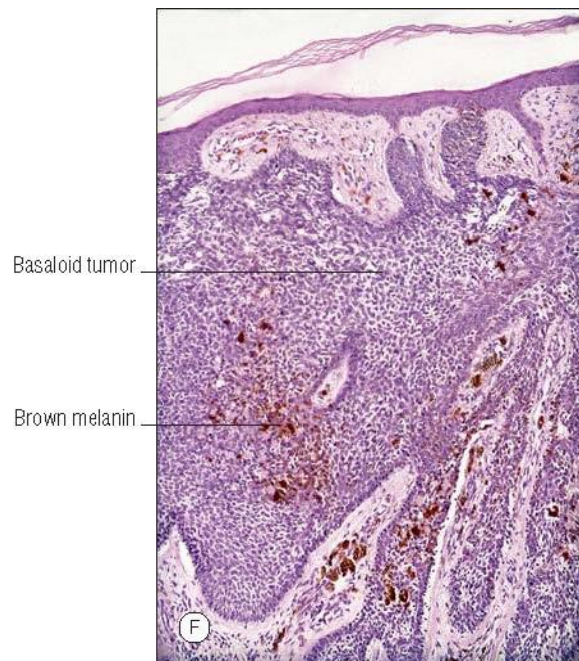


Figure 12: Clinical pigmented BCC²² with brown to black areas.



Figure 13: Dermoscopy pigmented BCC²² with spoke wheel areas

Histopathologically this subtype shows melanocytes and melanin admixed with the tumor cells^{3,19}.



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Figure 14: Histopathological sclerosing BCC¹⁹

2.5.7. fibroepithelial

The fibroepithelial subtype of BCC is characterized clinically by a fibroma-like appearance. The lesions are skin coloured and present soft nodules.

Histopathologically this subtype shows aggregation of basaloid cells surrounded by fibrous stroma^{3,19}.

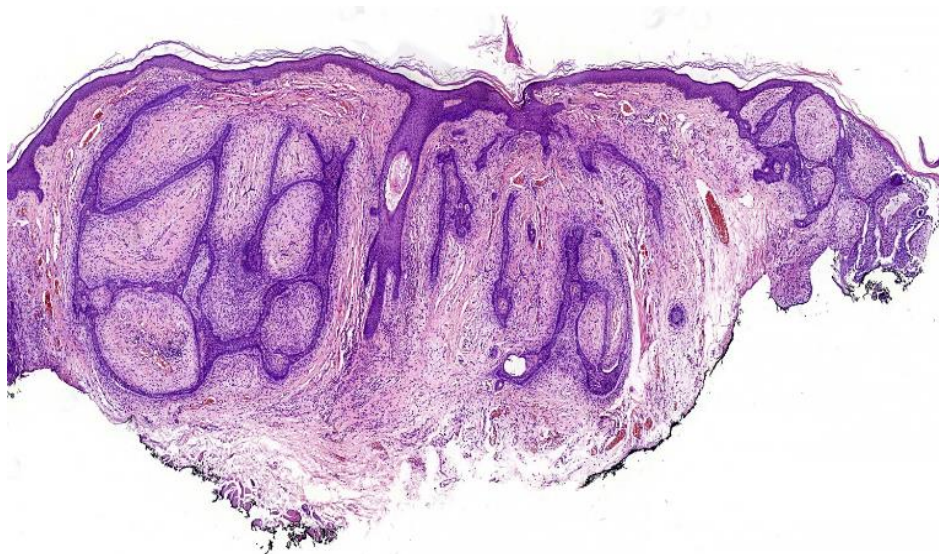


Figure 15: Histopathological fibroepithelial BCC²⁰

3. Materials and Methods

3.1. Data collection

This retrospective study analyses 66 BCC treated hospitalisation cases at the Bundeswehr Hospital in Berlin from 2018 to 2019. The data was collected by searching for all patients who were hospitalised for excision of BCC via KIS Nexus System. Included were all patients with following BCC subtypes: nodular, micronodular, superficial, sclerosing, ulcerated, pigmented and fibroepithelial. The dermatohistopathologist of the pathology section of the Bundeswehr Hospital in Berlin described up to 4 subtype specific characteristics in some lesions in her pathological findings. Thus mixed subtypes in one BCC lesion were counted individually to consider 126 histopathological cases. A standardized histopathological examination was supported by committing the specimen to the own pathological section of the hospital. General anatomic regions (face, scalp, neck, frontal torso, dorsal torso, upper extremities, lower extremities) were chosen as shown in figure 1 for displaying the selected distribution pattern.

Data analysis was conducted with Microsoft® EXCEL® Version 2016 MSO, Microsoft Cooperation Inc., California, USA and RStudio® Version 07.2022, Boston, USA. Statistical analysis was done by empirical analysis (sum, Chi-squared, Cramer's V).

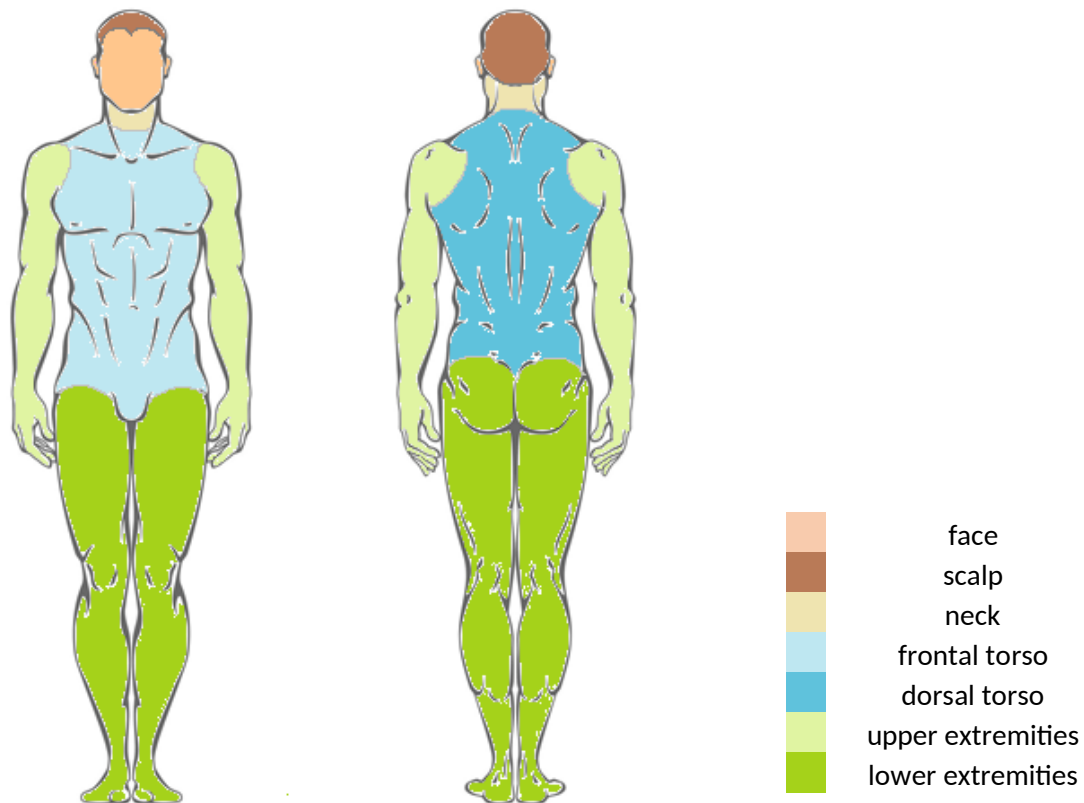


Figure 16: Selected areas for BCC distribution

3.2. Study population

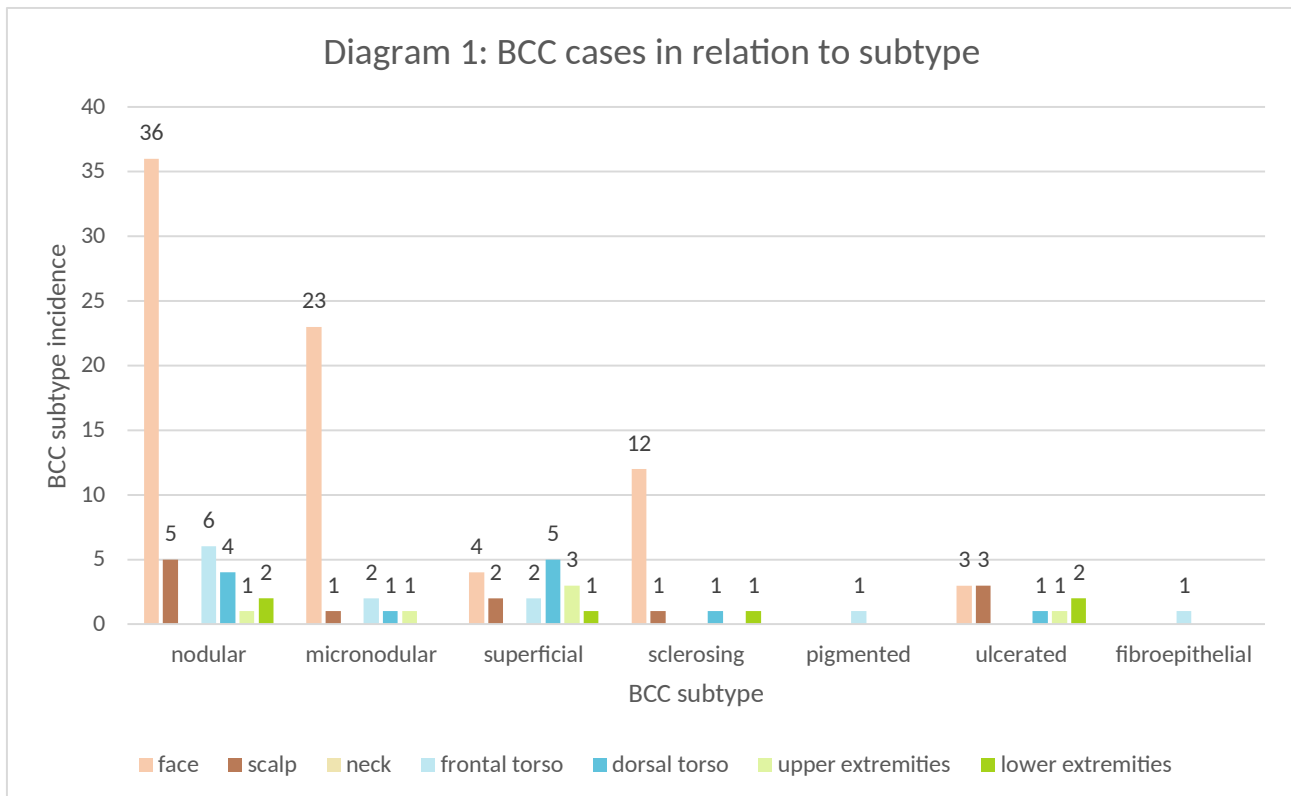
Concluded in this study are patients of an age range from 31 to 93 years with a mean age of 73 years. The collective is composed of 24 female patients as well as of 42 male patients.

The age range of female patients is from 36 to 88 years with an average age of 73 years. The age range of male patients is from 31 to 93 years with an average age of 73 years.

4. Results

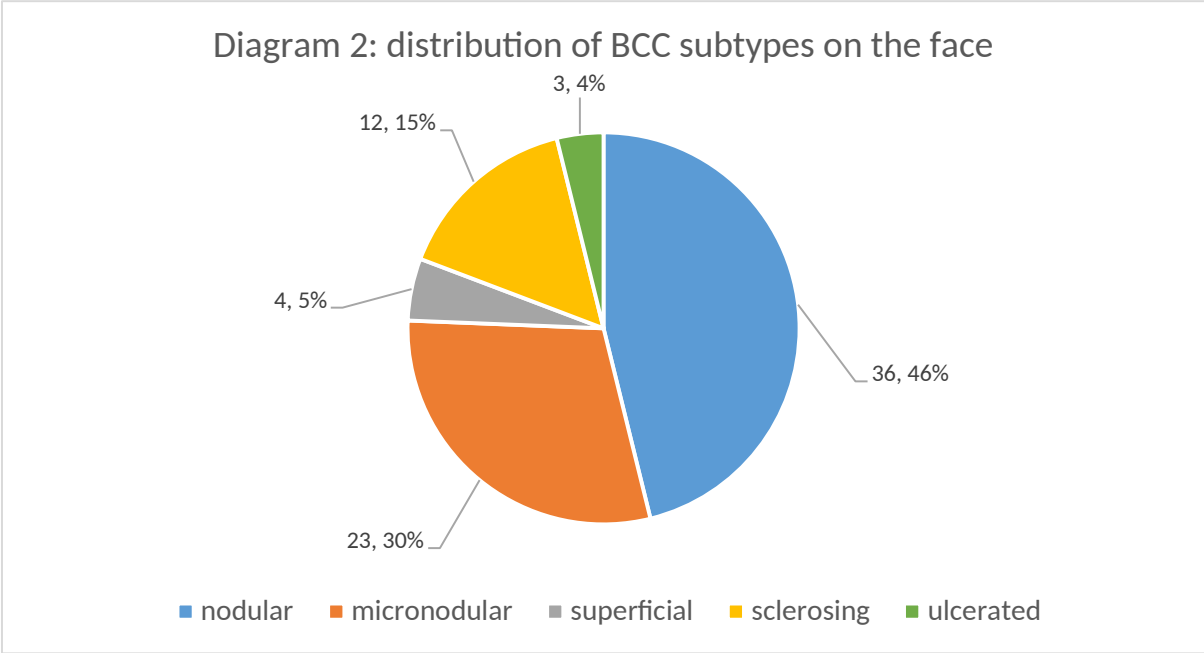
4.1. site specific results

Diagram 1 presents the histological subtype in comparison to its site of incidence. The face stands out as a main location for BCC.



This study shows within the selected population high incidences of nodular, micronodular and sclerosing BCC predominantly on the face whereas superficial BCC has more tendencies to occur on the dorsal torso. The incidence of the nodular BCC is the highest in this study as this subtype comprises 60-80% of BCC cases in general¹⁷.

Diagram 2 presents the main localization of BCC incidence. 78 of the 126 cases occurred on the face with incidences of 46% in nodular, 30% in micronodular, 15% sclerosing, 5% in superficial and 4% in ulcerated. In general, the nodular subtype occurs predominantly on the skin of the head¹⁷.



4.2. sex specific results

Diagram 3 presents the relation between BCC subtype incidences with the sex related subtypes. While a sex-specific subtype could not be proven, the overall occurrence of BCC in this study displays the proportion of incidences male to female at 82 to 44, which displays a higher incidence within men related to women via factor 2.

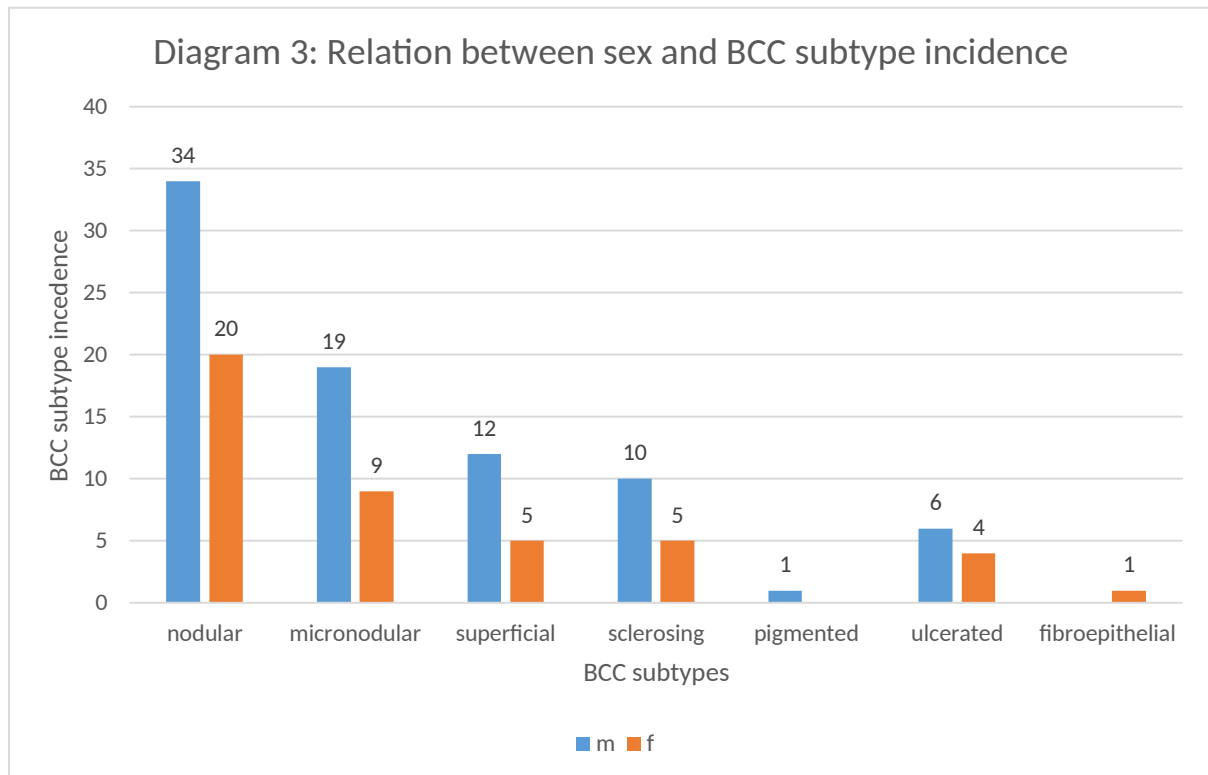
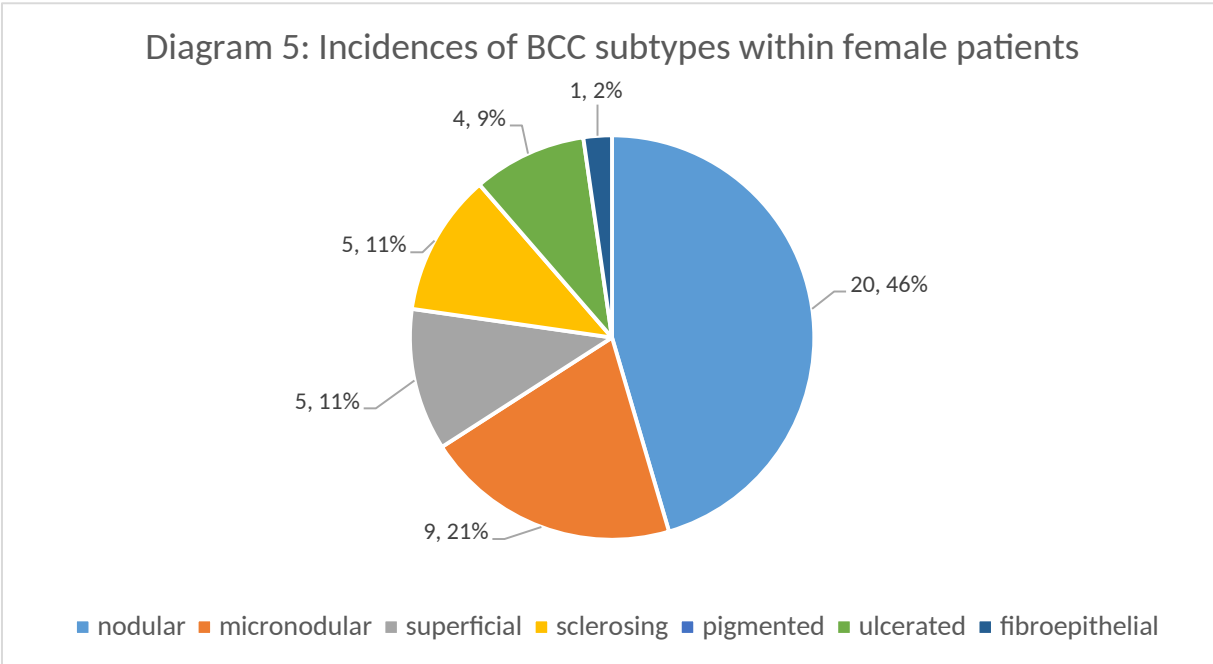
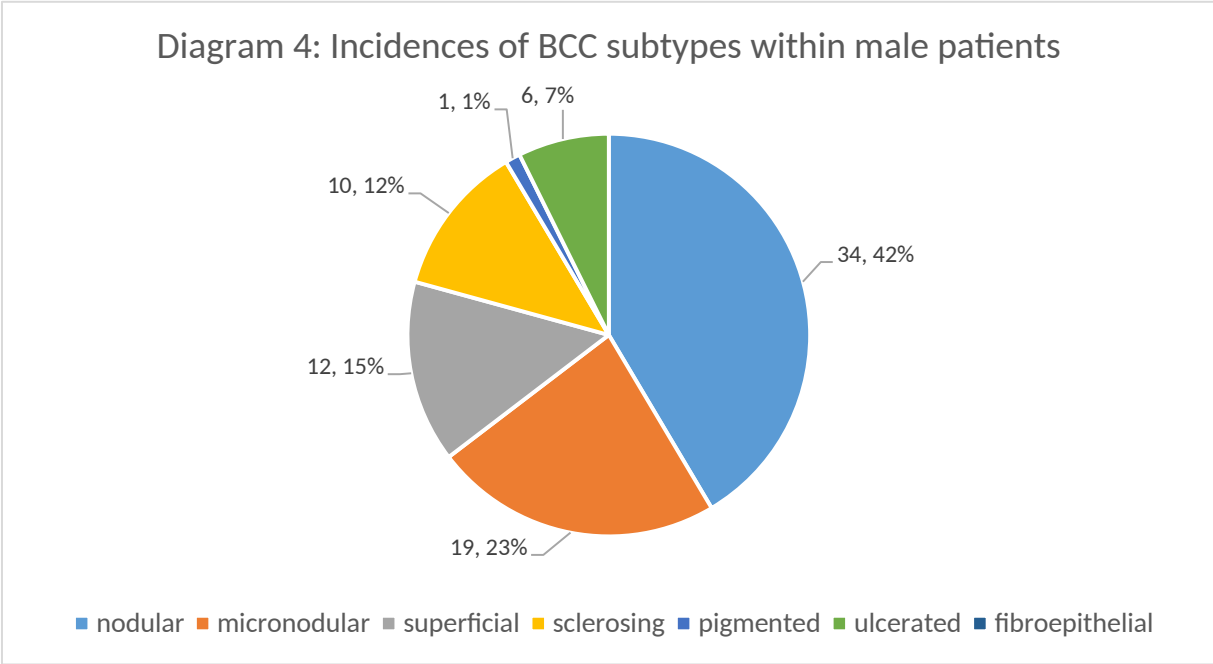


Diagram 4 and 5 present the relation between the two sexes separately and BCC subtype incidences.



4.3. Results of the calculation of correlation

After the descriptive presentation of the distributions, the chi-square independence test and Cramer's V are used to obtain a measure of the correlation.

The chi-square test measures whether there is a significant relationship between two discrete variables. A p-value of 0.001142 was calculated for the association between body site and the BCC subtype that occurred. Thus, the association is significant at a 95% significance level. The same test was performed for the variables sex and BCC subtype. Here, the test yielded a p-value of 0.814. Thus, this relationship is not significant.

In the next step, the correlation coefficient in the form of Cramer's V was calculated for both correlations. Cramer's V takes values between 0 (no correlation) and 1 (perfect correlation). For the correlation between body site and BCC subtype, the value was 0.3066. Thus, the correlation can be classified as medium strong. For the correlation between sex and BCC subtype, only a value of 0.1532 could be calculated. This is to be interpreted as very weak, so there is no correlation here.

In conclusion, it can be said that the calculated correlation and the significant test result suggest that a meaningful predictor for the BCC subtype has been found in the body site where the subtype may occur. This statement cannot be made for the variable sex.

5. Discussion

In this monocentric retrospective observational study, the correlation between BCC subtypes in relation to specific body sites and sex is described.

The data was collected from the in house dermatohistopathologist to the Bundeswehr Hospital in Berlin and therefore a standardisation of the histopathological examination is given. The collective in this study is too small to state results with high significance. Nonetheless this study reinforces results that are found in medical literature.

The mean age of first diagnosis in BCC patients in Germany 2014 was at 72 years, whereas 52% of these patients were male ⁴. This correlates to the mean age of the collective of this study.

This study presents within the selected population high incidences of nodular, micronodular and sclerosing BCC predominantly on the face whereas superficial BCC has more tendencies to occur on the dorsal torso. These findings correlate to the impressions in the clinical environment of a dermatologist and literature⁴. As indicated by this study the body site may be a meaningful predictor for the BCC subtype. This comes in handy in preoperative assessment of lesions. For example, as described under 2.5.4. sclerosing BCC can be difficult to be assessed in its tumour spread and therefore might need larger safety margins. Amongst specific dermatoscopic findings, the factor body site might be taken in consideration when assessing the BCC subtype of a lesion.

The main locus of BCC in this study is the face. As described in this thesis, UV radiation is a major risk for developing BCC ^{2,3,9}. The face is one of the body sites with a great sun exposure. One factor that might increase the BCC incidence on the face in this study is that all these patients were hospitalised for the excision of BCC. In general BCC excisions are performed in an outpatient setting, only large and anatomically complicated lesions are treated in a stationary setting. The occurrence of BCC on the face is a contributing factor for hospitalisation as excisions on the face are more

complicated due to anatomical specifics like lesions on the eye lids, nose, lips etc. Therefore, the incidences of BCC on the face could be biased by this factor.

A sex specific incidence of a certain BCC subtype could not be proven. The proportion of incidences male to female is 2:1. Due to a relatively low case number (n=126) the significance of this finding can be biased. A factor that might bias the sex proportion in favour of the male sex in this study is that soldiers and veterans are predominantly treated in military hospitals, even though the Bundeswehr Hospitals are open to the public. The percentage of female soldiers in 2018 was at 12,1%¹. Theoretically for this research the study population could have been divided into soldiers and civilians to better assess the aforementioned bias, but veterans cannot be detected via the hospital information system, therefore this approach would have been too vague.

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22. Pictures with kind allowance by Prof. Dr. Hofmann-Wellenhof, Clinic of Dermatology and Venerology, University Clinic of Graz

23. Pictures of the Clinic of Dermatology and Venerology, Bundeswehrkrankenhaus Berlin