

# Histopathological and patient-related characteristics of basal cell carcinomas of the head and neck influencing therapeutic management

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## Abstract

The authors hypothesize that histopathological characteristics of basal cell carcinomas of the head and neck (BCCHN) have changed over time and the correlation of BCCHN localization and histological tumour type can help improving the number and quality of necessary therapeutic interventions. Information of 222 patients with 344 BCCHN was gained. Descriptive measures were compared to prior studies to prove whether or not characteristics of basal cell carcinomas or patients have changed over time. Afterwards descriptive measures were correlated with number of conducted operations to evaluate if tumour localization, histological tumour type and number of operations depend on one another. Aggravating factors which lead to a higher number of operations were older age, greater size of BCCHN, adjacent elastosis, the localizations eye, ear and nose and histological tumour types *morpheaform* and *nodular-ulcerated*. In comparison to earlier studies characteristics of BCCHN and patients showed positive developments because of grown awareness of BCCHN. Furthermore, our correlations demonstrate that therapeutic results of BCCHN treatment are continuously improving. Nevertheless, treatment of aggressive morpheaform BCCHN in combination with distinctive patient characteristics still needs improvement.

## Introduction

Basal cell carcinomas (BCC) account for approximately 75% of all skin malignancies in humans.<sup>1</sup> Incidences rise on a daily basis worldwide.<sup>2</sup> The major risk factor for development of BCC is the ultra-violet radiation of the sun.<sup>3</sup> Therefore, BCC are predominantly localized in sun-exposed body regions of the head and face, *i.e.* ears,

forehead, nose, lips, cheeks and neck.<sup>2</sup> Though mortality is rare, BCC abundance and therapy is costly for the regional health-care system. Hence, they pose a popular investigational approach in many studies. BCC are slow growing, non-destructive and seldomly metastasize. There is no agreement on whether BCC derive from dysplastic stem-cells of the hairbulb or precursor-cells of the interfollicular epidermis.<sup>4</sup> There are several different histopathological structures of BCC. The World Health Organization (WHO) classifies BCC in i) nodular, ii) superficial and iii) infiltrating types.<sup>5</sup> Types rarely encountered are micronodular, fibroepithelial, basosquamous, keratotic and BCC with adnexal differentiation.<sup>5</sup>

Therapy of choice is surgical excision with a recurrence rate of approximately 3%.<sup>6</sup> Alternative treatment modalities are chemotherapy, kryotherapy, photodynamic therapy and radiotherapy with the disadvantage of no available sample for subsequent microscopic examination and a recurrence rate of about 10%.<sup>7</sup>

Several studies tried to analyse the correlation of specific histopathological types and anatomical localization of BCC. With 42-90% nodular BCC represent the most common BCC in the head and neck region, whereas superficial types occur mainly on the trunk of the body.<sup>8</sup> Many studies found a male predilection for the development of BCC.<sup>9</sup> Mean age in patients with first time BCC occurrence is 63-72 years.<sup>8</sup> Incomplete BCC excisions were most commonly found at the nose, ear and eyelids.<sup>10</sup> The number of necessary operations and the amount of incomplete excisions correlate with BCC size.<sup>11</sup>

To date no correlation between the histological type and the localization of BCC could be determined. Also, there is no consensus on whether BCC histology, size, age, body region or sex taken together correlate in any way with one another. In terms of early screening tests for people with BCC predisposing factors these findings could be highly relevant for prognosis and recurrence rate.

In general, correlation of BCC localization with BCC histological types is important to give patients an outline of the therapeutic approach they can expect.

## Materials and Methods

The present study was performed at Düsseldorf University Hospital, Germany. Comprised in this study were 222 patients with a total number of 344 basal cell carcinomas of the head and neck (BCCHN). All

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patients were either treated at the Department of Oral and Maxillofacial Surgery or Dermatology between the years 2010 and 2014. In retrospect, the following patient and BCC data were collected from the surgery report program *Medico Release 19.00* (Cerner, Idstein, Germany): sex, age at time of diagnosis, tumour size, histological tumour type, tumour localization and the type of tumour surrounding stroma (presence or absence of adjacent elastosis or actinic keratosis). Furthermore, surgical variables, number of operations, conducted biopsies, type of anaesthesia, outpatient treatment and number of days hospitalised were listed. Additionally, operations necessary for secondary wound closure were assessed. If a patient had multiple BCCHN, variables were collected for each BCC separately. Tumour size and histological tumour type data were collected from histopathological reports. For determination of the histological tumour type classification of the WHO from 2006<sup>5</sup> was used. Mixed histological tumour types were considered separately.

The count of conducted operations included biopsies, primary resection, further resections if necessary and, if applicable, secondary wound closure. Patients who cancelled the therapy or consulted another

hospital were excluded from the study. Further, patients with Gorlin-Goltz Syndrome or Xeroderma Pigmentosum were excluded from the study.

SPSS Version 22 (IBM, Armonk, USA) was used for a statistical analysis. Distributions of one variable were tested with the binominal test. Furthermore, the variables were correlated with each other. Correlations were statistically evaluated with ANOVA, Student's t-test, Chi-square or Fisher's exact-test. If Levene-test was significant Brown-Forsythe or Welch-test was used instead of ANOVA. P-value<0.05 was considered statistically significant and P-value>0.05 and <0.10 was considered marginally significant. If ANOVA or Chi-square test was significant each subcategory was compared with the rest of the category by means of Student's t-test or Fisher's exact-test. Variables with significant or marginally significant correlations were divided into improving or aggravating factors. Improving factors were defined as factors that lead to a lower number of operations, a higher amount of outpatient treatment or more operations which could be conducted under local anaesthesia. Aggravating factors resulted in a higher number of operations, a higher number of hospitalisations or a higher amount of operations conducted under general anaesthesia. Because all variables were correlated with

each other, possible overlaps could be shown, resulting in an improved overview.

## Results

Significantly more men than women with BCCHN were found in this study (ratio 1.4:1). The mean age of patients at first diagnosis was 72.59 years (SD 10.90; median 74 years); the youngest patient was 42 years old and the oldest 102. Average tumour size was 0.85 cm (SD 0.89 cm). Tumour sizes between 0.1-0.5 cm and 0.6-1.0 cm were represented significantly more often. The most common histological tumour type was nodular with 46.3%. Superficial BCC (15.2%) and BCCs with mixed histological tumour types (31.1%) were also often found. The amount of morpheiform BCC, which belong to the aggressive growing BCCs, was the lowest with 7.3%. The localizations could be assigned to the following eight main localizations: nose (25.2%), temple (14.5%), eyes (14.5%), ear (14.2%), forehead (12.8%), cheek (9.8%), lips (2.6%) and neck (2.6%). 45.9% of the BCCs showed healthy underlying tissue with the remaining 54.1% showing abnormal underlying tissue like elastosis (48.8%) or actinic keratosis (2.6%) (Table 1). Mean number of operations was

2.36 (SD 1.12). In most cases patients underwent 2 operations (P<0.01). In 152 (45.51%) cases the patients had a biopsy before tumour resection. The mean number of post-resections was 0.55 (SD 0.77). In 191 (56.85%) of the cases patients had only one resection and 118 (35.12%) patients needed two resections until tumour-free margins were reached. In 170 (55.56%) BCCHN operations primary wound closure could be performed and in 123 (40.20%) cases the surgeons needed an additional operation for secondary wound closure (13 (4,24%) cases of free granulation). Most operations (72.06%) were performed under local anaesthesia. In 56.28% of cases patients had to stay in the hospital and the mean length of stay was 4 days (Table 2).

Correlation of BCC and patient characteristics with *surgical variables* lead to the following factors: improving factors (Table 3) were a lower age (mean 72.38 years) at time of first diagnosis, smaller BCCHN size, localizations cheek, neck and forehead and BCC with the histological types superficial, nodular and nodular-morpheiform. The number of operations was lower for smaller BCC, BCC on the cheek and nodular BCC. Since nodular BCC were significantly smaller than the rest, it could be assumed that both factors as a combination were responsible for the lower number of operations. The number of post-resections

**Table 1. Descriptive measure.**

Category	Severity								
No. of BCCs	1 BCC	2 BCCs	3 BCCs	4 BCCs	5 BCCs	7 BCCs	10 BCCs		
No. of patients	159 (71.60%)	35 (15.77%)	15 (6.76%)	7 (3.15%)	3 (1.35%)	1 (0.45%)	2 (0.90%)		
Time between first and further diagnoses	50.82% of the patients Same time					Rest of the patients Ø 2.62 years after first diagnosis			
Sex	Male* 128 (57.66%)					Female 94 (42.34%)			
Age of diagnosis	Ø 72.59 y SD=10.90 y								
Size	Ø 0.85 cm SD=0.89 cm								
Localization	Nose* 86 (25.2%)	Temple 50 (14.5%)	Eye 50 (14.5%)	Ear 49 (14.2%)	Frontal 44 (12.8%)	Cheek 33 (9.8%)	Lips 9 (2.6%)	Cervikal 9 (2.6%)	Rest 4
Histology	Nodular* 152 (46.3%)	Superficial 50 (15.2%)	Morpheiform 24 (7.3%)	Nodular, morpheiform 13 (4.0%)		Nodular, superficial 28 (8.5%)	Nodular, ulcerated 26 (7.9%)	Rest 35	
Adjacent tissue	Normal skin 158 (45,9%)			Adjacent elastosis or keratosis 186 (54,1%)					
Further malignancies	51 patients with further 78 malignancies 28 patients had 45 SCCs 6 patients had 6 MMs								
Operated precancerous lesions	Patients: 81				Lesions: 173 Elastosis: 60 Keratosis: 81				

BCC, basal cell carcinoma; SCC, Squamous cell carcinoma; MM, Malignant melanoma. \*P<0.05 in the binominal test.

was significantly lower for BCCs on the neck, nodular BCCs and superficial BCCs. Neck BCC localization significantly correlated with superficial BCC type. Therefore, it could not be distinguished to what extent these two factors contribute to the lower number of post-resections. The amount of outpatient treatments was higher for younger patients (mean age 72.38 years), for smaller BCCs (mean size 0.70 cm) and for BCCs localized on the cheek. The amount of operations that could be performed under local anaesthesia was significantly higher for BCCs with a smaller size (mean 0.79 cm), for those on the forehead, superficial and nodular-morpheaform BCCs. BCCs on the forehead were also significantly correlated with superficial BCCs.

Aggravating factors (Table 4) were older age at the time of first diagnosis, a bigger size of BCCs, localizations near the eye, on the nose, on the ear, histological types morpheaform and nodular-ulcerated as well as BCCs with adjacent abnormal tissue. The number of operations was significantly higher for patients with bigger BCCs, BCCs localized on the nose and morpheaform BCCs. The number of post-resec-

tions was significantly higher for BCCs near the eye and morpheaform BCCs. The number of hospitalisations was significantly higher for patients with older age at the time of first diagnosis (mean 75.22 years), for bigger BCCs (mean size 0.94 cm), for BCCs near the eye and the ear. For patients with nodular-ulcerated BCCs the length of hospitalization was significantly longer. General anaesthesia was performed significantly more often in patients with bigger BCCs (mean size 1.41 cm), BCCs on the ear, nodular-ulcerated BCCs and BCCs with adjacent abnormal tissue. BCCs on the ear (P=0.096) and nodular-ulcerated BCCs (P=0.059) were also correlated with a bigger size of BCCs.

## Discussion

The incidence of BCCs is steadily increasing worldwide, hence, it is important to improve prevention and therapy. There are a lot of studies in which descriptive measures are pointed out. But there are no current studies that compare them with measures from earlier studies in order to overlook the latest trends in therapies. These relations may help to point out issues of BCC therapy needing improvement.

## Descriptive measures

Gender distribution resulted in no difference between earlier studies and this

**Table 2. Improving factors.**

	Female sex	Age of diagnosis ↓	Localization nose	
Occuring BCCs in general ↓	+			
Occuring mBCCs ↓	+	(+)	+	+
Occuring further malignancies ↓	+	+	+	+
		(Ø 71.26 y)		

mBCCs, multiple basal cell carcinomas. + = P<0.05 in Fisher's exact test or P<0.05 in Student's t-test in comparison to the rest. (+) = 0.05≤P<0.1 in Fisher's exact test or 0.05≤P<0.1 in Student's t-test in comparison to the rest.

**Table 3. Aggravating factors.**

	Male sex	Age of diagnosis ↑	Localization neck	Adjacent elastosis or keratosis	Operated precancerous lesions	mBCCs
Occuring BCCs in general ↑	+					
Occuring mBCCs ↑	+	(+)	+	+	+	
Occuring further malignancies ↑	+	+	+			+
		(Ø 77.04 y)				

mBCCs, multiple BCCs; + = P<0.05 in Fisher's exact test or P<0.05 in Student's t-test in comparison to the rest. (+) = 0.05≤P<0.1 in Fisher's exact test or 0.05≤P<0.1 in Student's t-test in comparison to the rest.

**Table 4. Further significant correlations and trends.**

Variable 1	Variable 2	P value
Male sex	Ear ↑	0.007
Male sex	Nodular ulcerated ↑	0.001
Male sex	Operated precancerous lesions ↑	0.022
Age of diagnosis ↑ (Ø 81.33 y)	Neck	0.001
Age of diagnosis ↑ (Ø 82.89 y)	Lips	0.012
Age of diagnosis ↓ (Ø 70.29 y)	Nose	0.001
Diameter ↑ (1.18 cm)	Ear	0.096
Diameter ↓ (0.63 cm)	Nose	0.001
Diameter ↓ (0.65 cm)	Nodular	0.001
Neck	Superficial ↑	0.021
Forehead	Superficial ↑	0.024
Neck	Nodular ↓	0.073
Morpheaform	Adjacent elastosis ↑	0.032
Superficial	Adjacent elastosis ↓	0.077
Superficial	Operated precancerous lesions ↑	0.008

The P value is the result of Fisher's exact.

study. In most studies the amount of men was higher.<sup>12</sup> There were only a few studies with more female than male patients.<sup>13</sup> It has been suggested that one reason might be that men are more often exposed to sunlight<sup>14</sup> and that they do not protect themselves by using sunscreen regularly.<sup>15</sup> Furthermore, women often wear makeup with sun protection factor.<sup>16</sup> The age at the time of diagnosis was similar comparing this study to former ones.<sup>17</sup> In the studies of Heckmann *et al.*<sup>9</sup> and Niederhagen *et al.*<sup>18</sup> patients were 10 years younger. A reason for this might be that life expectancy was lower at that time. The most common localizations of BCC in other studies corresponded with those in this study.<sup>19</sup> The nose was the most affected localization.<sup>20</sup> A change could be found in distribution of histological types. In earlier studies the ratio of superficial BCC was lower than in this study and the amount of morpheaform BCCs was higher.<sup>8</sup> If the theory of a progression of BCCs from superficial via nodular to morpheaform BCCs is considered,<sup>21</sup> this points towards an earlier detection of BCC in this study. Furthermore, the assumption that the growth of superficial BCC is triggered by intermittent sun exposure<sup>22</sup> points towards a better sun protection nowadays. In current studies distribution of histological types equals the distribution in the present study.<sup>23</sup> The ratio of mixed histological types was also created by an early detection of BCCs because the most frequently diagnosed histological type was nodular-superficial. This corresponds with the study of Kaur *et al.*<sup>12</sup> In this study the amount of adjacent elastosis was lower than in other studies.<sup>24</sup> This also points towards a better protection of the skin nowadays. Also of interest is that the mean size of BCC was lower than in earlier studies.<sup>25</sup> This proved a higher alertness of patients and physicians in these days. Looking at descriptive measures many characteristics could be found which showed a positive development compared to former studies. This demonstrates that the awareness for BCCs is already improving.

### Correlations with surgical variables

A higher age was an aggravating factor, because it led to significantly more clinical stays and longer hospitalisations. This may be due to frequent multimorbidity. Due to the significantly higher amount of outpatient treatments and treatments under local anaesthesia and the lower number of operations, patients with smaller BCCs had a better prognosis. The significantly higher number of operations for patients with bigger BCCs resulted from the fact that significantly more often an additional operation

for secondary wound closure was needed. This suggests that the surgeons gave their best to keep the number of operations low because in other studies the number of post-resections increased with the rise of tumour size.<sup>5,10</sup> Considering localizations, regions like eye, ear and nose had a poorer prognosis. In contrary a higher number of post-resections around the eye could not be observed in other studies.<sup>18</sup> A reason for the high number in this study might be that the surgeons were cautious not to damage anatomic structures unnecessarily. The number of hospitalisations of patients with BCCs at the ear was high as well. The reason for this might be that BCCs on the ear were bigger than those in other regions of the head and neck. Furthermore, for BCCs at the ear the amount of operations under general anaesthesia was higher, which could also have led to a higher number of hospitalisations. The significantly higher number of operations for BCCs on the nose resulted due to the fact that the amount of additional operations for wound closure was significantly higher.

The histological types nodular, superficial and nodular-morpheaform were improving factors and the histological types morpheaform and nodular-ulcerated showed a poorer prognosis. The improving properties of nodular BCCs can be explained by the fact that nodular BCCs were significantly smaller than the rest. The significantly lower number of operations was caused by a significantly higher number of primary wound closures. The significantly lower number of post-resections in cases of nodular BCCs was confirmed by other studies.<sup>5</sup> Superficial BCCs were significantly more often operated under local anaesthesia, which can be explained by a significantly higher amount of superficial BCCs on forehead and neck. These localizations can be easily anesthetized without general anaesthesia. Besides, superficial BCCs were more often operated without post-resections, which could not be confirmed by other studies. Aggressive morpheaform histological types counted as aggravating factors for prognosis because the number of operations was significantly higher. In other studies<sup>18</sup> the number of incomplete excisions of morpheaform BCC was higher. Reasons for the significantly higher number of operations in this study were the significantly higher number of biopsies and additional operations for secondary wound closure. The significantly higher number of operations under general anaesthesia for nodular-ulcerated BCC in this study could be explained by the fact that nodular-ulcerated BCC were on average bigger than the rest. The amount of

operations under general anaesthesia was significantly higher for BCCs with adjacent elastosis. One reason for this might be that these BCCs seemed to be larger because of the altered adjacent tissue.

### Conclusions

Summarizing, the burden of BCC treatment on the health care system is high. The present study shows that BCC-therapy is headed in the right direction regarding prevention and therapy but there are still a few issues which could be improved to reduce costs. On the one hand the information policy, especially for men, should be improved, so that BCC can be prevented or discovered earlier. In doing so, the mean size of BCC and the number of aggressive histological types could be reduced. As a result, the number of operations, operations under general anaesthesia and the number of hospitalisations could be reduced. This in turn would decrease the economic burden on our health care system. Furthermore, the aggressive histological type *morpheaform* and the more complicated localizations should be operated more often with Mohs surgery or micrographic surgery with frozen section analysis, in order to decrease the number of operations and further resections.

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