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Correlation of Basal Cell Carcinoma Variables with Operation Variables: Which Factors can Improve Patients` Treatment Burden?

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Abstract

Background: The burden of Basal Cell Carcinomas (BCCs) for the health care system is high and prevention and therapy need to be perfected.

Methods: Information of 222 patients with 344 BCCs was collected. Descriptive measures were compared with other studies to prove if the characteristics of BCCs or the patients' characteristics have changed over time. Then the descriptive measures were correlated with "operation variables" to evaluate if there are points to improve concerning the therapy. Therefore, among others the ANOVA, t-test, Chi square test and Fisher's exact test were used. The p value was set at 0.05.

Results: The ratio of men to women was 1.4:1 ($p<0.05$). The mean age of patients was 72.59 years. The mean size of BCCs was 0.85 cm. Aggravating factors in relation to the "operation variables", like the number of operations, e.g., were a higher age, a greater size of BCCs, adjacent elastosis, the localizations eye, ear and nose and the histologies morpheaform and nodular ulcerated.

Conclusion: In comparison to earlier studies the characteristics of BCCs and patients show positive developments due of the awareness of BCCs. Furthermore, the correlations demonstrate an actual encouraging state of therapy with only a few things to improve, for example the treatment of aggressive morpheaform BCCs.

Keywords: Basal cell carcinomas; Morpheaform; Operation variables

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Introduction

It is important for people to know facts about Basal Cell Carcinomas (BCCs) and their therapy possibilities because they account for about 75% of all skin malignancies with an increasing tendency [1,2]. Up to now, there are no studies, which compare the distribution of characteristics like histology, tumor size, e.g., of today with the one of former studies. This can for example show if the ratio of aggressive histologies has changed to more non aggressive histologies or if the tumors are smaller today.

Furthermore, BCCs occasion high costs for the health care system. There are many different options to treat a BCC. Among them are cryotherapy, cremes, radiotherapy, photodynamic therapy, laser therapy and intralesional chemotherapy [3,4].

The gold standard still remains surgery [5], due to the lowest recurrence rates [6] and the possibility of histological control [4]. The recurrence rates for surgery account for about three percent [7-10] with the lowest recurrence rates for Mohs micrographic surgery [3] and for the other treatment options about ten percent [11-17]. The crèmes achieve cure rates of around 80% [18,19]. Even if surgery is the gold standard, the methods are not perfected up to now. There are studies that correlate the number of operations and the amount of incomplete excisions with the tumor size [20-22]. Other studies deal with the amount of incomplete excisions and the localizations [21-25], the histology in relation to the number of Mohs stages [10,26] or the amount of incomplete excisions [20-22,27,28]. However, there are also studies considering abnormal tissue findings other than bcc on the ground of BCCs in connection with incomplete excisions [21,22].

In general, the correlation of operation variables of BCCs with characteristics of BCCs is important to give the patients an idea of the therapy they have to expect according to the histology or the localization of their BCC. Additionally, it can be found for which kind of BCCs the therapy

Table 1: Descriptive measures (patients and BCC characteristics).

No. of BCCs No. of patients	**1 BCC 159 (71.62%)**	**2 BCCs 35 (15.77%)**	**3 BCCs 15 (6.76%)**	**4 BCCs 7 (3.15%)**	**5 BCCs 3 (1.35%)**	**7 BCCs 1 (0.45%)**	**10 BCCs 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 [a] 94 (42.34%)				
Age of diagnosis	Ø 72.59 y SD=10.90 y							
Size	Ø 0.85 cm SD=0.89 cm							
Localisation	Nose[a] 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%)	Neck 9 (2.6%)	Rest 4
Histology	Nodular[a] 152 (46.3%)	Superficial 50 (15.2%)	Morpheaform 24 (7.3%)	Nodular, morpheaform 13 (4.0%)	Nodular, superficial 28 (8.5%)		Nodular, ulcerated 26 (7.9%)	Rest 35
Adjacent tissue	Normal skin 153 (45%)			Adjacent elastosis or keratosis 187 (55%)				

[a] p<0.05 in the binominal test

Table 2: Operation variables.

Number of Operations	**Ø 2,36 Operations (SD=1,12)**		
Number of further resections (fr)	Ø 0,55 further resections (SD=0,77) 0 fr: 191 (56,85%); 1 frs: 118 (35,12%); 2 frs: 17 (5,06%); 3 frs: 8 (2,38%); 4 frs: 1 case; 5 frs: 1 case		
Biopsy	Yes 152 (45,51%)		No 182 (54,49%)
Anaesthesia	Local anaesthesia* 459 (72,06%)	Local anaesthesia with analgosedation 26 (4,08%)	General anaesthesia 152 (23,86%)
Hospitalisation	Ambulatory 247 (43,72%)[a]		Hospitalisation 318 (56,28%)
Days of hospital stay	Ø 4,05 days		
Wound closure	Primary wound closure 170 (55,56%)	Secondary wound closure 123 (40,20%)	Free granulation 13 (4,25%)

*30,07% of the ambulatory operations were biopsies; [a]46,96% of these were biopsies

should be improved.

Materials and Methods

The study was performed at the Heinrich-Heine-University hospital of Düsseldorf in Germany. The cohort sample consisted of 222 patients with 344 BCCs who were treated at the centre of maxillofacial surgery or dermatology in the years 2010 to 2014. From each patient, the following variables were extracted retrospectively from the surgery report program, Medico Release 19.00 (Cerner, Idstein, Germany) and collected in Excel Version 2003 (Microsoft Corporation, Redmond, USA): Sex, age of diagnosis, tumor size, tumor histology, tumour localization and type of peritumoral stroma (presence or absence of adjacent elastosis or actinic keratosis). Furthermore, the operation variables, number of operations, further tumour resections, presence of biopsy, kind of anaesthesia, outpatient treatment and the days of stay if hospitalization was needed, were listed. Besides, extra operations for wound closure were quoted. If one patient had multiple BCCs, the variables were collected for each BCC. Size and histology of the tumour were extracted from histopathological reports. For histological classification the classification of WHO (world health organization) from 2006 [29] was used and the mixed histologies were considered separately. The localizations of the head and the neck were divided into ten almost equal parts in which the left and the right side of the head were combined. In doing so, only the most frequent histologies and localizations were considered and the other ones were only included when one subcategory was compared with the rest. The number of operations was the result of biopsy, first resection, further resections and if done, the extra operation for wound closure. Patients who cancelled the therapy or preceded it at another hospital were excluded from the study. Further, patients with diagnosed Gorlin-Goltz Syndrome or Xeroderma pigmentosum were abstracted.

Statistical methods

Data was transferred to SPSS, Version 23 (IBM, Armonk, USA) for a statistical analysis. Distributions of one variable were tested with the binominal test. Furthermore, the variables were correlated with each other. In doing this, depending on one chosen main variable the occurrence of the operation-variables was tested. Each of the collected variables was sometimes considered as the main variable. The correlations were statistically evaluated by ANOVA (analysis of variance), Student's t test, Chi square or Fisher's exact test. If Levene's test was significant Brown Forsythe or Welch test was used instead of ANOVA. A p value less than 0.05 was considered as statistically significant and a p value greater than or equal to 0.05 and less than 0.10 was considered as a trend. If ANOVA or Chi square test were significant each subcategory was compared with the rest of the category wherein Student's t test or Fisher's exact test was finally used. The variables which lead to significant correlations or trends were divided into improving or aggravating factors. Improving factors were defined as factors that lead to a lower number of operations, a lower number of further resections, a higher amount of outpatient treatment or more operations which could be done in local anaesthesia. Aggravating factors were factors that resulted in a higher number of operations, a higher number of further resections, and a higher number of hospitalizations or a higher amount of operations in general anaesthesia. Because all variables were correlated with each other, possible overlaps could be recognized, resulting to a better overview.

Results

The descriptive measures are presented in Table 1. There were significantly more men than women with BCCs in the study (ratio 1.4:1). The mean age of patients at first diagnosis was 72.59 years ± 10.90 years standard deviation. The median was 74 years; the youngest

Table 3: Improving factors.

	Age ↓ (years)	Diameter ↓ (cm)	Cheeck	Neck	Forehead	Nodular BCC	Superficial BCC	Nodular-morpheaform BCC
Number of operations ↓		+	+			+		
Number of further resections ↓				+		+	+	
Number of ambulatory treatments ↑	+ (72,38)	+ (0,70)	+					
Amount of operations in local anaesthesia ↑		+ (0,79)			+		+	+

+ = $p<0.05$ in Fishers' exact test or $p<0.05$ in student's t-test in comparison to the rest.
Same coloured fields: $p<0.05$ or $0.05\leq p<0.1$ in Fishers' exact test or $p<0.05$ or $0.05\leq p<0.1$ in student's t-test in comparison to the rest.

Table 4: Aggravating factor.

	Age ↑ (years)	Diameter ↑ (cm)		Eye	Ear	Nose	Morpheaform BCC	Nodular-ulcerated BCC	Adjacent elastosis/ keratosis
Number of operations ↑		+				+	+		
Number of further resections ↑				+			+		
Amount of hospitalisation ↑	+ (75,22)	+ (0,94)		+	+				
Days of hospitalisation ↑								+	
Amount of operations in general anaesthesia ↑		+ (1,41)	+ (1,41)		+			+	+

+ = $p<0.05$ in Fishers' exact test or $p<0.05$ in student's t-test in comparison to the rest.
Same coloured fields: $p<0.05$ or $0.05\leq p<0.1$ in Fishers' exact test or $p<0.05$ or $0.05\leq p<0.1$ in student's t-test in comparison to the rest.

patient was 42 years old and the oldest 102. The average tumour size was 0.85 cm with a standard deviation of 0.89 cm. The groups of 0.1 cm to 0.5 cm big BCCs and 0.6 cm to 1.0 cm big BCCs were represented significantly often. The most common histology was the histology nodular with 46.3%. Superficial BCCs (15.2%) and BCCs with mixed histologies (31.1%) were also well represented among the histologies. The amount of morpheaform BCCs, 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%), neck (2.6%). 46% of the BCCs had "normal" underlying tissue and the rest was growing on abnormal underlying tissue like elastosis (48.8%) or actinic keratosis (2.6%).

The "operation variables" resulted in the following descriptive findings (Table 2): The mean number of operations was 2.36 with a standard deviation of 1.12. Most patients underwent 2 operations ($p<0.01$). 152 (45.51%) of the patients had a biopsy before the resection of the tumour. The mean number of further resections after the first resection was 0.55 with a standard deviation of 0.77. 191 (56.85%) of the patients had only one resection and 118 (35.12%) patients needed two resections until tumour-free margins were reached. At 170 (55.56%) BCCs a direct wound closure was done and in 123 (40.20%) cases the surgeons needed an extra operation for wound closure. Most operations (72.06%) were performed in local anaesthesia. In 56.28% of the cases the patients had to stay in the hospital and the mean length of stay was 4 days.

Correlation of BCC and patient characteristics with "operation-variables" lead to the following factors: Improving factors (Table 3) were a lower age (mean 72.38 years) at the first diagnosis, a smaller BCC, the localizations cheek, neck and forehead and BCCs with the histologies superficial, nodular and the mixed histology nodular morpheaform. The number of operations was lower for smaller BCCs, BCCs on the cheek and nodular BCCs. Since nodular BCCs were significantly smaller than the rest, it could be assumed that both factors as a combination were responsible for the lower number of operations (dark green colored fields in Table 3). The number of further resections was significantly lower at BCCs on the neck, nodular BCCs and superficial BCCs. BCCs on the neck were also correlating significantly with superficial BCCs so that it could not be said, to what extent the two factors were responsible for the lower number of further resections (bright green colored fields in Table 3). The amount of ambulatory treatments was higher for younger patients (mean age 72.38 years), for smaller BCCs (mean size 0.70 cm) and for BCCs on the cheek. The amount of operations that could be performed in local anaesthesia was significantly high for BCCs with a smaller size (mean 0.79 cm), for BCCs on the forehead, superficial BCCs and nodular morpheaform BCCs. BCCs on the forehead were also significantly correlated with superficial BCCs (bright green colored fields in Table 3).

Aggravating factors (Table 4) were a higher age at the first diagnosis, a bigger size of the BCCs, BCCs near the eye, BCCs on the nose, BCCs on the ear, morpheaform BCCs, nodular ulcerated BCCs and BCCs with adjacent abnormal tissue. The number of operations was significantly higher for patients with bigger BCCs, BCCs on the nose and morpheaform BCCs. The number of further resections was significantly higher for BCCs near the eye and morpheaform BCCs. The number of hospitalizations was significantly higher for patients with a higher age at the first diagnosis (mean 75.22 years), for bigger BCCs (mean size 0.94 cm), for BCCs near the eye and for BCCs on the ear. The length of hospital stay was significantly higher for patients with nodular ulcerated BCCs. The amount of operations in general anaesthesia was significantly higher for patients with bigger BCCs (mean size 1.41 cm), for BCCs on the ear, for nodular ulcerated BCCs and for 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 (colored fields in Table 4).

Discussion

The incidence of BCC is steadily increasing worldwide so that it is important to improve the prevention and therapy [2]. There are a lot of studies in which the descriptive measures are pointed out. But

there are no studies yet, which compare them with measures from earlier studies, to establish a development. The operation-variables are also considered in a few studies. A further check is necessary to find regularities that can help the patient and the therapist. Furthermore, the regularities can help to highlight factors the therapists can do better.

Descriptive measures

If one compares descriptive measures of earlier studies with the descriptive measures of this study and other recent studies, one can see some developments. The gender distribution resulted in no difference between earlier studies and this study. In most studies the amount of men was higher [2,8,30-32]. There were only a few studies with more female than male patients [6,33]. It has been suggested that the reason is that men are in the sun more often [23,34] and that they do not use sun cream so often [35,36]. Furthermore, women often wear makeup with sun protection factor [37]. The age of diagnosis was similar in most studies as in the present study [31-33]. In the studies of Heckmann et al. [30] and Niederhagen et al. [8] the patients were 10 years younger. A reason for this might be that the life expectancy was lower at that time. The most common localizations of BCCs in other studies corresponded with the most common one in this study [6,30,31,33]. The nose was the most affected localization [6,8,30,31]. The distribution of histologies has changed over time. In earlier studies the ratio of superficial BCCs was lower than in this study [6,8,33] and the amount of morpheaform BCCs was higher [6,8,30,33]. If the theory of a progression of BCCs from superficial over nodular to morpheaform BCCs is considered [28], this pointed towards an earlier detection of BCCs in this study. Furthermore, the assumption that the growth of superficial BCCs is triggered by intermittent sun exposure [38], pointed towards a better sun protection in these days. In current studies the distribution of histologies was like the distribution in the present study [7,21,23,35]. The ratio of the mixed histologies was also created by an early detection of the BCC, because the most diagnosed histology was the histology nodular-superficial. This corresponded with the study of Kaur et al. [28]. In this study the amount of adjacent elastosis was lower than in other studies [21,39,40]. This also points towards a better protection of the skin nowadays. Furthermore, mean size of BCCs is lower than in earlier studies [6,33], which proves a higher alertness of patients and physicians in these days. To summarise looking at the descriptive measures there were many characteristics that showed a positive development compared to earlier studies.

Correlations with "operation variables"

A higher age was an aggravating factor, because it led to significantly more clinical stays and longer hospitalizations. This may be due to the very frequent multimorbidity. Due to the logically significantly higher amount of ambulatory treatments and treatments in 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 in the fact that significantly more often an extra operation for wound closure was needed. This suggests that surgeons "gave their best" to keep the number of operations low because in other studies the number of further resections increased with the rise of the tumour size [20-22].

Looking at the localizations the more complicated regions like the eye, ear and nose had an aggravating prognosis. In contrary the higher number of further resections around the eye could not be observed in other studies [21,23-25]. 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 hospitalizations of patients with BCCs on the ear was high as well. The reason for this might be that BCCs on the ear were bigger than BCCs in other regions of the head and the neck. Furthermore, for BCCs on the ear the amount of operations in general anaesthesia was higher, which also could have led to a higher number of hospitalizations. The significantly higher number of operations for BCCs on the nose resulted from the fact that the amount of extra operations for wound closure was significantly higher.

The histologies nodular, superficial and the mixed histology nodular morpheaform were improving factors and the histologies morpheaform and nodular-ulcerated were aggravating factors for the 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 the significantly higher number of primary wound closures. The significantly lower number of further resections in cases of nodular BCCs was confirmed by other studies [20-22,26]. Superficial BCCs were significantly more often operated in local anaesthesia, which can be explained by the significantly high amount of superficial BCCs on the forehead and the neck. These localizations can be easily anesthetized without general anaesthesia. Besides, superficial BCCs were more often operated without further resections, which could not be confirmed by other studies [10,21]. The aggressive histology morpheaform is an aggravating factor for the prognosis because the number of operations was significantly higher and there were further resections needed than for the rest of the histologies. In other studies, too [21,26-28] the number of incomplete excisions for the morpheaform BCCs was higher, too. Reasons for the significantly higher number of operations in this study were the significantly higher number of biopsies and extra operations for wound closure. The significantly higher number of operations in general anaesthesia for nodular ulcerated BCCs in this study could be explained by the fact that nodular ulcerated BCCs were on average bigger than the rest.

The amount of operations in 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.

Conclusion

Summarizing, the burden of BCCs and their therapies for the health care system is high. The present study showed that we are on a good way regarding prevention and therapy but there are a few things which can be improved. One factor is a qualified information policy in sun protection for all people and potentially protective factors like oral nicotinamids and retinoids for high risk patients [3].

All patients should further more receive education in self-examination and skin cancer prevention measures. Patients with recurrent or multiple BCCs should be offered annual reviews [4].

Concerning histopathological features, aggressive histologies like morpheaform BCCs (high risk patients) and the more complicated localizations should be operated with Mohs surgery/micrographic surgery with frozen section analysis whenever possible, in order to lower the number of surgical interventions/further resections.

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