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Predicting incomplete basal cell carcinoma excisions – a large multidisciplinary retrospective analysis in a tertiary centre

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ABSTRACT

INTRODUCTION Surgical treatment of basal cell carcinomas is often performed by physicians with different surgical backgrounds. Collecting data from different surgical departments would better reflect their real-life surgical management.

OBJETIVES To identify the rate, recurrence risk and predictive factors accordingly to their relative contribution for an incomplete basal cell carcinoma excision in a large multidisciplinary real-life setting

METHODS Retrospective cohort study of 2305 surgically treated lesions in different departments of a tertiary center

RESULTS There was a rate of incomplete excisions (15%) and a recurrence rate (35.5% vs 6.8% in incomplete vs complete excisions ($p < 0.001$)) A third of incompletely excised BCCs will recur over time. Stratified by relevancy, high-risk histological subtypes (micronodular (OR 5.10 – $p < 0.001$) and morpheaform (OR 5.42 - $p<0.001$), smaller specimen sizes (<0.5 cm or 0.5 to 1 cm, OR 3.99 and 2.49, respectively, $p<0.001$) high-risk locations (OR 3.06 on the nose, OR 2.77 on the eyelids, $p < 0.001$) and recurrent BCCs (OR 1.72, $p<0.001$). are the best predictors of an incomplete excision.

CONCLUSIONS Acknowledging the rate, recurrence risk and predictive factors for incomplete excisions may be beneficial for optimal preoperative planning and to prevent unwarranted re-interventions, morbidity and healthcare costs

INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignancy worldwide and its incidence is steadily rising (1). Despite an exceedingly low metastatic potential, BCC tends to behave as a locally aggressive tumour which may result in significant functional and cosmetic impairment as well as high healthcare costs (2,3). Despite the myriad of available treatment modalities, surgery remains the preferred contemporary treatment strategy for most BCCs as it allows for histologic margin assessment and very high cure rates when a complete excision is achieved. Incomplete excisions, however, appear to be fairly frequent (7-25%)(4), leading to a higher relapse risk, despite the disagreement in the reported recurrence rates(26-67%)(4). Some authors attempted to identify which factors could predict an incomplete BCC resection (5,6) and several characteristics, including tumour location, size, and histological subtype were pointed out. However, most studies are old, small sample-sized and potentially biased towards high-risk tumours in Plastic Surgery departments. To our knowledge, few studies have been performed on a multidisciplinary, real-life setting. Henceforth, our aim is to identify the rate, predictive factors and recurrence risk for incomplete BCCs excisions on a large tertiary hospital setting. Through a statistical model, the predictive risk factors were further stratified according to their relative contribution for an incomplete excision.

METHODS

Study design and subjects

A retrospective cohort study was performed in a major tertiary centre in Lisbon, Centro Hospitalar Universitário de Lisboa Central (CHULC). All electronic medical records and pathology reports of histopathological-proven BCCs between January 2008 and December 2014 were captured through database searching tools hosted at the institution. Data were then extracted and reviewed by independent physicians. Patients were considered eligible if they were aged 18 years or older, submitted to a complete or incomplete surgical excision (SE) of one or more primary or recurrent BCCs at one of the Medical Departments of CHLC (Dermatology, Plastic and Reconstructive Surgery, Oral and Maxilofacial Surgery, General Surgery and Ophthalmology). Patient files were then retrospectively reviewed, beginning on the 3rd month after surgery, for a biopsy-confirmed BCC recurrence. Recorded variables included patient age, gender, department of the treating physician, number of primary and recurrent lesions per patient and their location, number of excisions per patient in the same operative time, excised specimen size (measured as the distance from the distal or external margin to the proximal or internal margin of the excised specimen), histopathologic BCC subtype, histological report of complete or incomplete excision (the latter defined as the presence of tumour at the lateral or deep margin of the resected specimen), and time until recurrence (if any). BCC risk was further categorized per anatomic location in high (H area), medium (M area) and low-risk (L area), according to the latest NCCN guidelines (National Comprehensive Cancer Network, Version 1.2016)(7). Exclusion criteria included medically-treated BCCs; tumors subjected to any other surgical procedure (Mohs micrographic surgery

(MMS), punch, curettage and shave biopsies) or treatment modality (ablative laser, photodynamic therapy, electrodesiccation and curettage) other than SE; a follow up shorter than 24 months for the recurrence study; or incomplete clinical data.

Statistical analysis

Categorical variables were summarized by relative and absolute frequencies of each excision type (complete and incomplete). To account with the clustered nature of the data (multiple excisions for the same subject), the comparison between complete and incomplete excisions was performed using the Donner's adjustment of the chi-squared test.

To analyze the relationship between incomplete excisions and tumor characteristics, Generalized Estimating Equations (GEE) were applied with binomial logit link function and exchangeable working correlation structure, to examine factors associated with the tumor characteristics, while considering repeated excisions on the same patient. Crude Odds Ratio (OR) and a 95% Confidence Interval (CI) was reported for each tumor characteristic. For all tumor characteristics, the category with higher representation was selected as the reference. All variables identified as statistically significant in the univariate analysis, considering p-value ≤ 0.2, were included in a final adjusted model.

To estimate the impact of each variable in the final adjusted model, each variable's proportion of explained outcome variability was calculated through iteration of the marginal R2 using the LMG method. A significance level of 0.05 was considered throughout the analysis. All statistical analysis was performed using R Statistical Software version 3.4.3.

Results

This study included a total of 2305 BCCs, corresponding to surgically treated 1371 patients between 2008 and 2014. Other 194 BCCs were excluded according to the exclusion criteria. Approximately half of the patients were female (n = 693, 50.5%). The mean age at the time of treatment was 73.8 ± 12.1 years and mean follow-up was 29.4 ± 25.0 months. By treating department, 2052 (89%) were surgically treated in the Dermatology and Venereology department, 210 (9.1%) in the Plastic and Reconstructive Surgery department, and 43 (1.9%) in other specialties (Ophthalmology, Oral and Maxillofacial Surgery, and General Surgery).

Eighty-five percent (n = 1958) of the BCCs had a complete excision and 15% (n = 347) had an incomplete excision. There were significant differences between histological subtype, NCCN location, anatomical location, and specimen size in the complete excision group compared to the incomplete excision group ($p < 0.001$ in all categories, Table 1). There were more incomplete excisions if the tumor was located in a H area, of the micronodular, morphearform or infiltrative subtypes and specimen size less than 1cm ($p < 0.001$ in all categories). Recurrent lesions were more prone to incomplete excisions (30.1%) comparatively to primary cases (13.6%, $p<0.001$). Of the tumors with at least 24 month follow up, more than one-third (35.5%) of the 234 incompletely excised BCCs had a recurrence, compared to 6.8% of the 1175 completely excised cases ($p < 0.001$). The median recurrence-free time for incomplete excisions was 64 months.

Univariate and adjusted analysis were used to evaluate the factors associated with an incomplete excision of a BCC (Table 2). In the present study, both age group at treatment and gender were not associated with incomplete excisions. On the other hand, a histologically-proven BCC was 1.62 times more likely to have an incomplete

excision, although this was not statistically significant in the multivariate analysis. Moreover, there were significant associations between an incomplete excision and three histological BCC subtypes, namely superficial (adjusted OR 2.41), micronodular (adjusted OR 5.10), or morpheaform (adjusted OR 5.4). Within the risk stratified location (NCCN location), the M and L areas were less likely to have an incomplete excision (adjusted OR 0.61 or 0.42, respectively). Additionally, in the univariate analysis, there was an increased risk of incomplete excision in several anatomical locations, ranging from 3.06 times on the nose (a high-risk area) to 1.70 times on the cheeks. Furthermore, a smaller specimen size, namely <0.5 cm or 0.5 to 1 cm, was 3.99 times and 2.49 times more likely to have an incomplete excision, respectively. Finally, recurrent lesions were 1.72 times more likely to be incompletely excised.

The marginal R2 of the multivariate GEE model and the LMG method were used to obtain an estimation of the percentage of variation explained by the model for each tumor characteristic. The marginal R2 obtained for the full multivariate model was 11%, where 47% was devoted to the histological subtype, 27% to the specimen size, 16% to the NCCN location, 8% to the recurrent BCC, and 2% to the type of diagnosis. Specific anatomical location was not included in the multivariate analysis to preclude from a duplication of the same factor (NCCN location).

DISCUSSION

This present study presents a large analysis of 2305 surgically-treated BCCs which were managed by different medical specialities, emulating the real-life treatment setting of these tumours. There was a 15% rate of incomplete excisions, of which 35.5% led to a clinical detectable recurrence. This agrees agrees with previous published data (4). However, the management of incompletely excised BCCs remains

a matter of debate. It is still not totally understood if a positive margin really imply tumour persistence, as only 33% (7-45%) of immediate re-interventions identify residual tumour(8). Moreover, there is also the low-grade malignant nature of most BCCs, which may advocate a conservative approach, especially in frailer patients. Nonetheless, it is our opinion that a recurrence rate as high as 35.5%, as presented in the current analysis, should promptly justify a re-intervention at first opportunity in most cases.

We also sought to stratify BCCs characteristics by their relative contribution to an incomplete excision. Nearly half (47%) of the contribution is attributable to the histopathological subtype, being the non-nodular subtypes associated with a higher rate of incomplete resections. This finding highlights the importance of a cutaneous biopsy and proper preoperative planning, especially if a nodular BCC subtype is not clinically evident. Specimen size and NCCN location are the following strong predictors in terms of importance, which account, respectively, 27% and 16% to the relative contribution for incomplete excisions. It is surprising that it was the smaller tumours which led to incomplete excisions more frequently, even after adjusting for confounders in the multivariate analysis. This suggests that surgeons may be more radical when addressing larger, "scarier" tumoral masses. Moreover, time-constrains and limited reconstructive experience may push towards exceedingly conservative margins to prevent complex reconstructions. Tumour location is another well-established risk factor for incomplete SE (10,11). Again, cosmetically sensitive areas such as the nose and eyelids may influence surgeons into smaller surgical margins. This, however, can jeopardize the desired and primary outcome in oncologic surgery: the complete removal all neoplastic tissue. The first surgical intervention is always the easier to achieve a complete SE, and surgical margins should not be sacrificed entirely

for better cosmesis or easier closures. Generalisation of techniques allowing for intraoperative comprehensive surgical mapping such as MMS (12) would be helpful in this regard.

We found no association between incomplete excisions and gender or age. Other studies, such as the one by Codazii *et al*, reported advanced age as a risk factor(6). Nevertheless, their study was limited to a Plastic Surgery department, which tends to create a bias towards high-risk lesions, as shown by their prevalent use of flaps (60%) for defect closure. Since older people are commonly inadequate candidates for extensive surgical procedures, the chosen approach was probably on the conservative side and henceforth less potentially curative.

Unsurprisingly, recurrent tumours had almost a third of incomplete excisions. A more aggressive behaviour of this tumours, combined with technical difficulties due to scar tissue from earlier interventions can compromise a full tumoral excision.

Our study has several strengths, such as its large sample size and the collected real-life data comprising a wide spectrum of independent departments which perform cutaneous surgery at a large hospital complex. Thus, our study best represents the BCCs management in a tertiary setting. Nevertheless, it also has limitations. Its retrospective design implies intrinsic risks, such as missing data and investigator bias. Some analysis, such as operator-relator outcomes, were impossible to perform with this design. The surgical margins were defined by the physician preoperatively and unavailable in the records. Interdisciplinary prospective trials are warranted to ascertain our findings.

CONCLUSIONS

It is expected that nearly a third of incompletely excised BCCs will recur over time. Stratified by relevancy, high-risk histological subtypes, smaller specimen sizes, high-risk locations and recurrent BCCs are the best predictors of an incomplete. Acknowledging these risk factors may be beneficial for optimal preoperative planning and to prevent unwarranted re-interventions, morbidity and healthcare costs.

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FIGURE LEGENDS

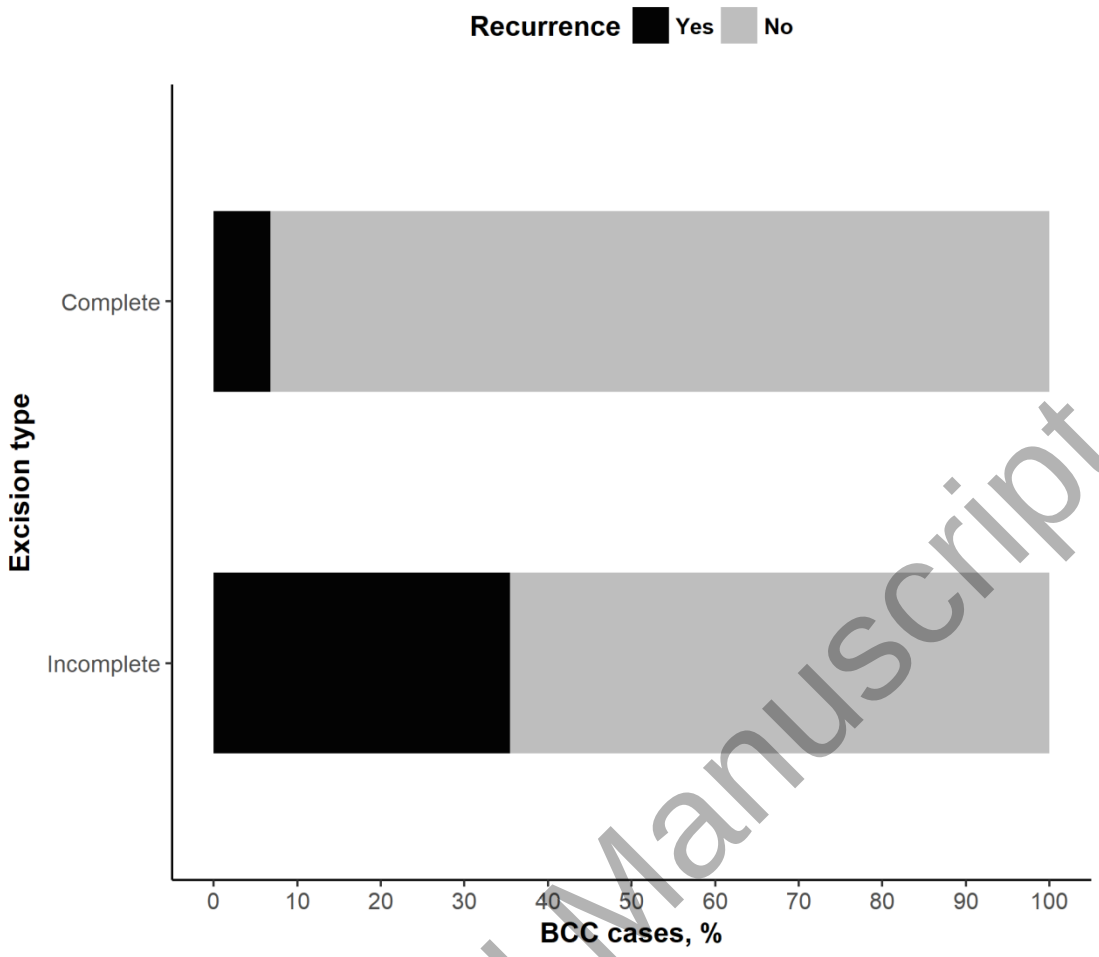

Figure 1 – Recurrence rate by BCC excision outcome

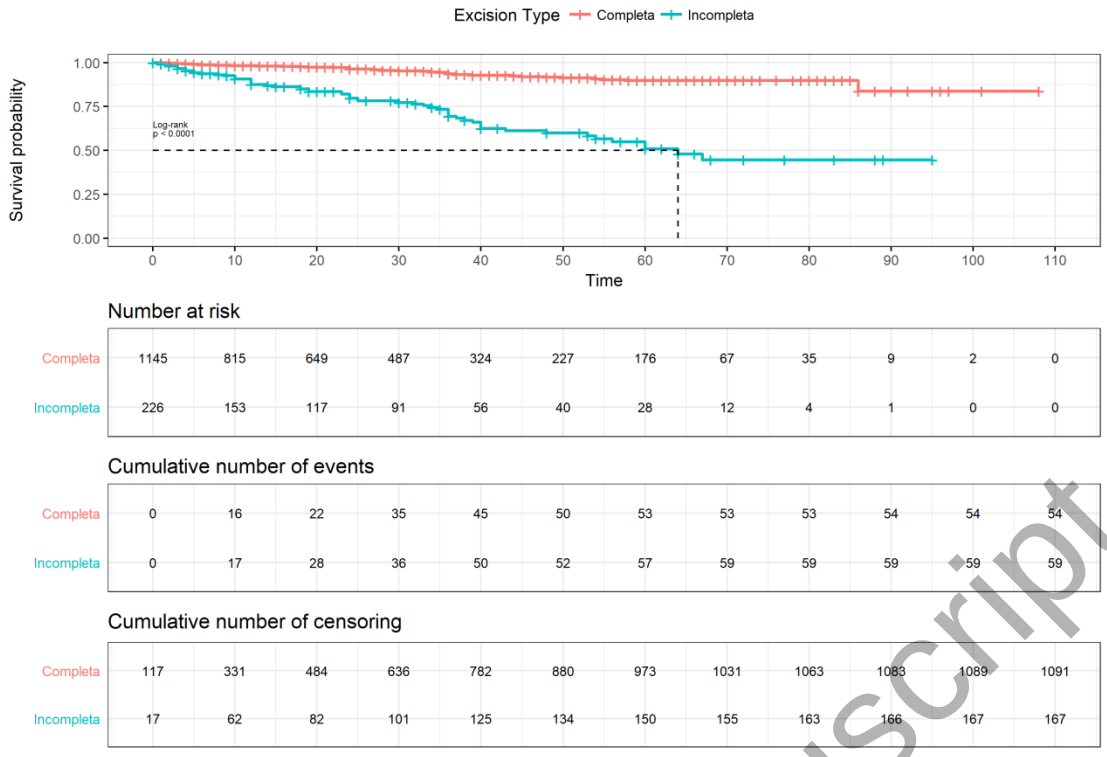

Figure 2 – Time-to-recurrence by BCC excision outcome

TABLES

Table 1 – Characteristics of the basal cell carcinoma cases with complete and incomplete excisions

Characteristics	Total (N = 2305, 100%)	BCC cases, No. (%)		p-value
		Complete excision (N = 1958, 85%)	Incomplete excision (N = 347, 15%)	
Age at treatment				
>70 years	1607	1370 (85.3)	237 (14.7)	0.581
≤70 years	698	588 (84.2)	110 (15.8)	
Gender				
Male	1269	1078 (84.9)	191 (15.1)	0.997
Female	1036	880 (84.9)	156 (15.1)	
Type of diagnosis				
Clinical	1410	1199 (85.0)	211 (15.0)	<0.001
Histological	410	320 (78.0)	90 (22.0)	
Unknown/Not defined	485	439 (90.5)	46 (9.5)	
Histological subtype				
Nodular	1774	1564 (88.2)	210 (11.8)	<0.001
Superficial	182	154 (84.6)	28 (15.4)	
Micronodular	95	50 (52.6)	45 (47.4)	
Mixed	52	43 (82.7)	9 (17.3)	
Morpheaform	49	30 (61.2)	19 (38.8)	
Infiltrative	36	28 (77.8)	8 (22.2)	
Other	20	14 (70.0)	6 (30.0)	
Unknown/Not defined	97	75 (77.3)	22 (22.7)	
NCCN location[a]				
H area	863	681 (78.9)	182 (21.1)	<0.001
M area	684	598 (87.4)	86 (12.6)	
L area	634	574 (90.5)	60 (9.5)	
Unknown/Not defined	124	105 (84.7)	19 (15.3)	

Anatomical localization				
Trunk and extremities[b]	634	574 (90.5)	60 (9.5)	<0.001
Nose	436	331 (75.9)	105 (24.1)	
Cheeks	223	189 (84.8)	34 (15.2)	
Forehead	171	145 (84.8)	26 (15.2)	
Pre/postauricular sulci	150	124 (82.7)	26 (17.3)	
Temple	133	123 (92.5)	10 (7.5)	
Eyelids	99	77 (77.8)	22 (22.2)	
Other	408	349 (85.5)	59 (14.5)	
Unknown/Not defined	51	46 (90.2)	5 (9.8)	
Specimen size[c]				
<0.5 cm	77	51 (66.2)	26 (33.8)	<0.001
0.5-1 cm	340	266 (78.2)	74 (21.8)	
1-2 cm	1109	961 (86.7)	148 (13.3)	
2-3 cm	534	459 (86.0)	75 (14.0)	
3-4 cm	164	151 (92.1)	13 (7.9)	
>4 cm	81	70 (86.4)	11 (13.6)	
Recurrent BCC[d]				
No	2099	1814 (86.4)	285 (13.6)	<0.001
Yes	206	144 (69.9)	62 (30.1)	

BCC, basal cell carcinoma; NCCN, National Comprehensive Cancer Network

[a] Anatomical regions according to the NCCN guidelines for basal cell skin cancer, Version 1.2016.

[b] Excluding pretibial, hands, feet, nail apparatus, and ankles.

[c] Defined as the distance from the distal or external margin to the proximal or internal margin of the excised specimen.

[d] First excision versus previously excised tumors.

Table 2 – Factors associated with incomplete excision of basal cell carcinomas

Characteristics	Univariate analysis				Adjusted analysis[a]			
	N	n (%)	OR (95% CI)	p-value	N	n (%)	OR (95% CI)	p-value
Age at treatment								
>70 years	1607	237 (14.7)	1 [Reference]	-	-	-	-	-
≤70 years	698	110 (15.8)	1.08 (0.83-1.41)	0.552	-	-	-	-
Gender								
Male	1269	191 (15.1)	1 [Reference]	-	-	-	-	-
Female	1036	156 (15.1)	1.00 (0.78-1.29)	0.990	-	-	-	-
Type of diagnosis								
Clinical	1410	211 (15.0)	1 [Reference]	-	1281	189 (14.8)	1 [Reference]	-
Histological	410	90 (22.0)	**1.62** (1.22-2.14)	<0.001	325	71 (21.8)	1.25 (0.87-1.80)	0.225
Histological subtype								
Nodular	1774	210 (11.8)	1 [Reference]	-	1281	167 (13.0)	1 [Reference]	-
Superficial	182	28 (15.4)	1.40 (0.92-2.14)	0.124	133	25 (18.8)	**2.41** (1.41-4.13)	0.001
Micronodular	95	45 (47.4)	**6.59** (4.21-10.32)	<0.001	66	31 (47.0)	**5.10** (2.82-9.22)	<0.001
Mixed	52	9 (17.3)	1.58 (0.74-3.36)	0.234	43	8 (18.6)	1.47 (0.74-2.93)	0.274
Morpheaform	49	19 (38.8)	**4.77** (2.64-8.62)	<0.001	39	18 (46.2)	**5.42** (2.68-10.96)	<0.001
Infiltrative	36	8 (22.2)	2.04 (0.88-4.71)	0.096	28	6 (21.4)	1.64 (0.62-4.34)	0.322
Other	20	6 (30.0)	**3.23** (1.24-8.41)	0.017	16	5 (31.2)	2.63 (0.79-8.83)	0.117
NCCN location[b]								
H area	863	182 (21.1)	1 [Reference]	-	623	143 (23.0)	1 [Reference]	-
M area	684	86 (12.6)	**0.54** (0.39-0.75)	<0.001	503	69 (13.7)	**0.61** (0.42-0.88)	0.008
L area	634	60 (9.5)	**0.39** (0.27-0.54)	<0.001	480	48 (10.0)	**0.42** (0.28-0.65)	<0.001
Anatomical localization								
Trunk and extremities[c]	634	60 (9.5)	1 [Reference]	-				

Nose	436	105 (24.1)	**3.06** (2.09-4.47)	<0.001	-	-	-	-
Cheeks	223	34 (15.2)	**1.70** (1.03-2.82)	0.038	-	-	-	-
Forehead	171	26 (15.2)	**1.79** (1.04-3.07)	0.035	-	-	-	-
Pre/postauricular sulci	150	26 (17.3)	**2.13** (1.26-3.60)	0.005	-	-	-	-
Temple	133	10 (7.5)	0.85 (0.41-1.76)	0.662	-	-	-	-
Eyelids	99	22 (22.2)	**2.77** (1.55-4.96)	<0.001	-	-	-	-
Other	408	59 (14.5)	**1.64** (1.08-2.49)	0.021	-	-	-	-
Specimen size[d]								
1-2 cm	1109	148 (13.3)	1 [Reference]	-	772	106 (13.7)	1 [Reference]	-
<0.5 cm	77	26 (33.8)	**3.28** (1.97-5.46)	<0.001	53	22 (41.5)	**3.99** (2.17-7.31)	<0.001
0.5-1 cm	340	74 (21.8)	**1.68** (1.20-2.34)	0.002	194	53 (27.3)	**2.49** (1.64-3.79)	<0.001
2-3 cm	534	75 (14.0)	1.03 (0.76-1.38)	0.867	391	61 (15.6)	1.17 (0.80-1.70)	0.422
3-4 cm	164	13 (7.9)	**0.44** (0.21-0.91)	0.027	133	11 (8.3)	0.54 (0.24-1.21)	0.134
>4 cm	81	11 (13.6)	1.00 (0.53-1.89)	0.996	63	7 (11.1)	0.61 (0.27-1.37)	0.231
Recurrent BCC[e]								
No	2099	285 (13.6)	1 [Reference]	-	1459	217 (14.9)	1 [Reference]	-
Yes	206	62 (30.1)	**2.57** (1.83-3.61)	<0.001	147	43 (29.3)	**1.72** (1.11-2.68)	0.016

BCC, basal cell carcinoma; CI, confidence interval; N, total number of BCC cases; n (%), number and percentage of BCC cases with an incomplete excision event; NCCN, National Comprehensive Cancer Network; OR, odds ratio.

Values in bold depict statistical significance.

[a] Adjustment for type of diagnosis, histological subtype, NCCN location, tumor size, and recurrent BCC.

[b] Anatomical regions according to the NCCN guidelines for basal cell skin cancer.

[c] Excluding pretibial, hands, feet, nail apparatus, and ankles.

[d] Defined as the distance from the distal or external margin to the proximal or internal margin of the excised specimen.

[e] First excision versus previously excised tumor