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Basal Cell Carcinoma. Analysis of 395 cases localized in the neck, ear and nose region

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SUMMARY

Background and objectives. To test if there are different outcomes in basal cell carcinoma for lesion size, histopathology, localization, and recurrence rates.

Materials and methods. A total of 395 patients with BCC localized in the neck, nose and ear regions who were surgically treated in Latvian Oncology Centre between 2006-2011 were analyzed retrospectively. The data were analyzed using modified classification based on Clarks *et al.* (2014) and McKenzie *et al.* (2016).

Results. Three hundred and ninety-five cases of BCC that were surgically treated in head and neck region were reviewed. Results were tabulated in four categories: anatomical region, histopathology, lesion size, and recurrence rates. Classification by anatomical region: 228 cases in the nose region, 82 cases in the neck region, 82 cases in the ear region. Classification by histopathology: 259 cases presented as low risk BCC [nodular, pigmented, adenoid, keratotic and cystic], 21 cases presented as superficial, 94 cases presented as mixed, and 21 cases presented as high-risk BCC (metatypical, morphea form). Mann-Whitney U test was used to compare recurrent BCC cases to non-recurrent cases. Significantly higher recurrence rates were observed if BCC at the time of the excision was ≥ 10mm ($p<0.001$). Significance was also noted in cases where histopathology was mixed BCC and in cases where mixed BCC was localized to the nose region ($p<0.001$).

Conclusion. More attention should be brought to assessing classification and clinical treatment synergy. Higher recurrence rates are observed when lesions occur in high risk anatomical region (H zone), when lesion size reaches or exceeds 20 mm in diameter, and when lesion is subtyped as mixed BCC. It is crucial to evaluate risk factors such as BCC subtype and localization, as these are associated with a higher rate of recurrence when present in a single lesion. These risk factors, together with pre-treatment lesion evaluation will enable formulation of better treatment plan and prognostic aspects in each case.

Key words: basal cell carcinoma, recurrence, head and neck oncology, non-melanoma skin cancer.

INTRODUCTION

Basal cell carcinoma (BCC) is the most frequent malignant skin tumor and rates of incidence are increasing (1-5). It originates from interfollicular epidermal stem cells that simulate keratinocyte characteristics (6-12). The main risk factor is believed to be the UV radiation-induced mutations in the PTCH1 gene which causes the upregulation of hedgehog (HH) signaling pathway, but other gene pathways have been reported to have a significant role in BCC development (6-10). BCC is characterized as a locally invasive, slow-growing carcinoma, with infrequent rate of metastasis (0.0028-0.5%) (11). Though BCC may present as benign, it is well described for its invasiveness involving local anatomical structures (12).

BCC is commonly classified by three main parameters: anatomical location, histopathology, and lesion size. Dandurand *et al.* classified BCC according

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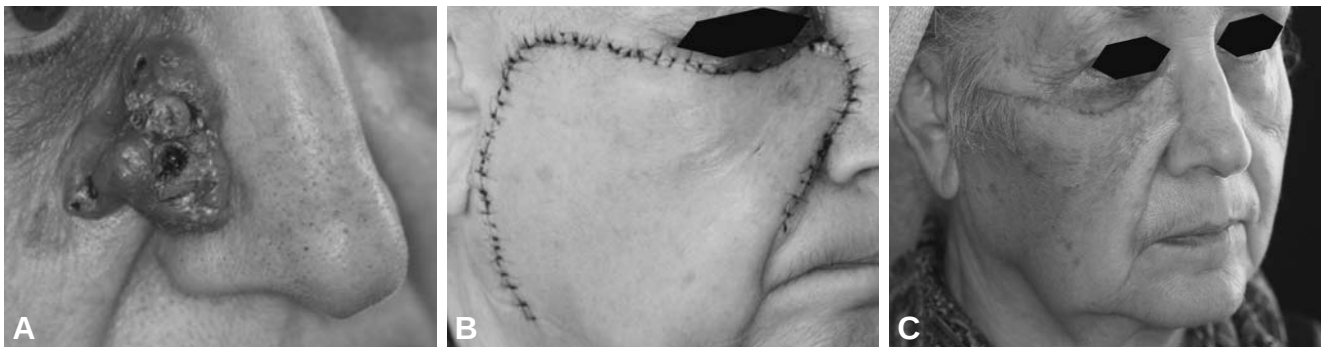

Fig 1. A – case classified as Group IV or mixed BCC histology subtype, larger than 20 mm and located in the nose region. B – the patient was treated with WE method and margins were stated as clean. C – after 4 months no recurrence was detected.

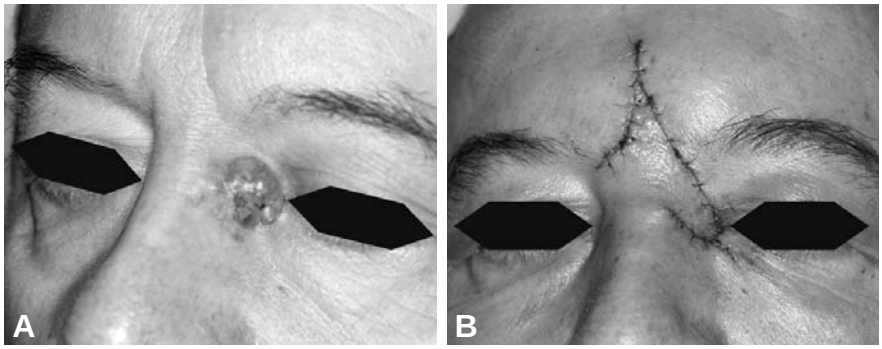

Fig 2. A – a case classified as Group II or low-risk BCC histology subtype, from 10 to 20 mm in size and located in the nose region. B – the patient was treated with SE method and margins were stated as clean and no recurrence after follow up was detected.

to three anatomical locations based on tumor recurrence risk (13). Body and limbs are separated as being a part of the low-risk region; forehead, cheek, chin, scalp, and neck are regarded as medium-risk regions; nose, perioral, and periocular areas are considered as a high-risk region. Clark *et al.* classified BCC by anatomical location, histopathology, lesion size, and recurrence parameters into low- and high-risk groups (14) (Table 1).

Clark *et al.* and McKenzie *et al.* both suggest classifying superficial BCC as low-risk histopathology (14, 15).

Table 1. BCC classification based on size, location, histopathology, and recurrence

Parameters	Low risk	High risk
Location/size	L<20 mm	L≥20 mm
	M<10 mm	M≥10 mm
	H<6 mm	H≥6 mm
Histological subtype	Nodular, superficial	Demonstrating an aggressive growth pattern – morphea form, fibrosing, perineural, metatypical, sclerosing, mixed infiltrative or micronodular features
Primary vs. recurrent	Primary lesion	Recurrent lesion

Low-risk area (L) – trunk and extremities. Medium-risk area (M) – cheeks, forehead, neck, jawline, scalp, peri-tibial surface. High-risk area (H) – mask areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermillion], chin, mandible, pre-auricular and post-auricular, temple, and ear, genitalia, hands, feet, nail units, ankles, nipples/areola. Table according to Clark *et al.* (14).

It is not clear how to clinically distinguish between "high risk" BCC and BCC with relatively benign growth (9, 16-18). In addition, there are opposing views on the biological nature, clinical course, and the recurrence rates of superficial and mixed BCC, encouraging researchers to seek evidence-based classification whether superficial BCC belongs to 'low risk" or a "high risk" histopathological groups (16-18).

The aim of this retrospective study was to analyze data of surgically treated patients in Riga East Clinical University Hospital, Latvian Oncology Centre (LOC), Department of Head and Neck BCC between 2006 to 2011.

METHODS

Selection of patients

Patients' data were included in the present study if they complied with the following criteria: the tumor was histologically proven as BCC; localization of BCC was either in nose, neck or ear region (since these localizations represent high and low risk anatomical regions) (13); the tumor was excised between year 2006 to 2011 (inclusive); there was histopathological information about size, histological subtype and TNM classification (T-tumor size, N-lymph node metastasis, M-distant metastasis).

Patients' data without follow-up control were excluded.

Surgical methodology

Standard conventional surgical protocol was used for excision of the BCC (19).

Based on clinical guidelines, surgeon's experience, and tumor manifestation, standard excision method (SE, 3 mm indention in the healthy soft tissue surrounding the tumorous growth) or wide excision method (WE, 5 mm indention in the healthy soft tissue surrounding the tumorous growth) was used. The intraoperative frozen section was used for all cases. If necessary, a free flap or rotational flap was used to close the wound to achieve a better aesthetic result. Mohs surgical protocol (microscopically controlled surgery) was not used in this study (Fig. 1, 2) (19).

Classification

Modified classification of Clarks *et al.* (2014) and McKenzie *et al.* (2016) was used for analysis in this study (14, 15).

BCC was divided into 4 main groups: anatomical location, histopathology, lesion size, or recurrence. Anatomical location was classified as follows: neck, nose, or ear region. Histopathology was divided into 4 subgroups: group I nodular, pigmented, adenoid, keratotic, or cystic BCC; group II consisted of superficial BCC; group III of mixed BCC and group IV consisted of morphea form, or metatypical BCC. Based on Clarks *et al.* (2014) and McKenzie *et al.* (2016) classification, group I may otherwise be approached as low risk group, whereas group IV is a high-risk group. Lesions were also categorized into three subgroups by the following intervals of lesion diameter: <10 mm, 10-20 mm, >20 mm (Table 2).

Each subgroup was further compared according to the recurrence or non-recurrence of the lesion.

Data description

Number labels were assigned to enable anlaysis of data using IBM SPSS Software. To assess tumor characteristics as numbered data (Table 2), each histological subtype, size and recurrence was labelled accordingly. Histological subtype: low risk (label: 1), superficial (label: 2), mixed (label: 3), high risk (label: 4). Size: <10 mm (label: 1), 10-20 mm (label: 2), >20 mm (label: 3). Recurrence: recurrent (label: 1), non-recurrent (label: 2).

Statistical Analysis

Data were analyzed in IBM SPSS Software. The Kolmogorov–Smirnov test was used to establish the normality of the data. If the data were ≥0.05, parametric approach was used, however if the data were p<0.05, non-parametric approach was indicated and

Table 2. Distribution of BCC categories.

Histology group	Neck				Nose				Ear				
	I	II	III	IV	I	II	III	IV	I	II	III	IV	IV
Cases (n)	56	4	21	4	155	10	53	10	48	7	20	7	
Recurrence count (n)	0	1	2	0	1	3	5	2	0	2	3	1	
Total of cases (n)	85				228				82				
Total of all recurrences (n)	3				11				6				
Recurrence rates (%)	3.53				4.82				7.32				

Histology is divided by histological subgroups: group I – nodular, pigmented, adenoid, keratotic and cystic; group II – superficial; group III – mixed, group IV – morphea form, metatypical. Anatomical distribution is divided into three anatomical locations: neck, nose, and ear. Recurrence rates were calculated as total recurrences divided by total cases. n – number of cases.

Table 3. Distribution of recurrent and non-recurrent BCC by tumor size, histology group, and anatomical location.

Region	Recurrence			Non-recurrence			P value*
	n	Med (25%; 75%)	KS sig. level	n	Med (25%; 75%)	KS sig. level	
Histology							
Ear	6	3.00 (2.00; 3.25)	0.272	76	1.00 (1.00; 3.00)	<0.001	0.009
Neck	3	3.00 (2.00; 3.00)	0.766	82	1.00 (1.00; 3.00)	<0.001	0.042
Nose	11	3.00 (2.00; 3.00)	0.178	217	1.00 (1.00; 3.00)	<0.001	<0.001
Total	20	3.00 (2.00; 3.00)	0.082	375	1.00 (1.00; 3.00)	<0.001	<0.001
Size							
Ear	6	2.00 (2.00; 3.00)	0.748	76	1.00 (1.00; 2.00)	<0.001	0.041
Neck	3	3.00 (2.00; 3.00)	0.766	82	2.00 (1.00; 2.00)	<0.001	0.057
Nose	11	3.00 (2.00; 3.00)	0.469	217	2.00 (1.00; 2.00)	<0.001	0.005
Total	20	2.50 (2.00; 3.00)	0.035	375	2.00 (1.00; 2.00)	<0.001	<0.001

Med – median, 25% – first quartile, 75% – third quartile; n – count; P value – significance level 0.05. KS sig. level – Kolmogorov Smirnov test significance level 0.05. Size: <10 mm (labelled: 1), 10-20 mm (labelled: 2), >20 mm (labelled: 3). Histology: low risk – group I (labelled: 1), superficial – group II (labelled: 2), mixed – group III (labelled: 3), high-risk – group IV (label: 4). As all of the data were non-parametric (KS sig.<0.001), the Mann-Whitney U test was used for assessing significance of difference in recurrence and non-recurrence by histology group or tumor size.

Mann-Whitney U test was used. Significance was accepted at $p<0.05$ and all values are expressed as median (25% – first quartile; 75% – third quartile) for the data. Results from Kolmogorov-Smirnov test and Mann-Whitney U test were summarized in Table 3.

RESULTS

From 2006 to 2011, 905 operated BCC cases in LOC, Department of Oral and Maxillofacial Surgery. The average age was 62.2 (min. 21 y., max. 95 y.) and sex of the patients were distributed as follows: 321 males, 584 females. Anatomical locations of BCC lesions were distributed as follows: 113 cases in the frontal region, 93 cases in the orbital region, 186 cases in the cheek region, 283 cases in the nose region, 132 cases in the ear region and 98 cases in the neck region. From 905 cases, 395 cases were selected based on exclusion criteria as follows: 392 cases were excluded due to the anatomical location, 86 cases due to the lack of information on specific subtype of BCC, 18 cases due to the lack of information on lesion dimensions, 3 cases due to the lack of information on TNM classification. Three hundred and ninety-five cases (99 males, 296 females) were selected based on selection criteria. The average age was 62. 5 (min. 21 y., max. 95 y.).

Cases were divided as shown in Table 2. There were 5. 1% (n=20) recurrent cases out of a total of 395 BCC cases. Two hundred and twenty-eight cases (57.7%) were located in the nose region. The neck region was affected in 21.5% (n=85) cases and ear region in 20.8% (n=82) cases. Low risk (group I) BCC was found in 65.6% (n=259) cases, superficial (group II) BCC was identified in 5.3% (n=21) cases, mixed (group III) BCC was identified in 23.8% (n=94) cases and high risk (group IV) BCC was diagnosed in 5.3% (n=21) cases. The flowchart shown in Figure 3 illustrates the case distribution between BCC characteristics [total number of cases → divided per anatomical region → histopathological classifications by group in each anatomical region → lesion classification by size].

The distribution of recurrent cases according to location: nose region 55% (n=11); ear region 30% (n=6); neck region 15% (n=3). Group III (mixed BCC) reoccurred in 50% (n=10) of all cases whereas group II (superficial BCC) in 30% (n=6), group IV (morphea form, metatypical BCC) in 15% (n=3) and group I (nodular, pigmented, adenoid, keratotic and cystic BCC) in 5% cases (n=1).

In Table 3 recurrent cases were compared with non-recurrent cases. The Kolmogorov Smirnov test was used to assess the data normality. As all of the data were non-parametrical (<0.001), the Mann-Whitney U test was used to determine the significance of the difference between groups according to histological and size parameters. The mixed BCC subtype dominated in terms of recurrence (50th quartile mixed BCC/$p<0.001$). The statistical median for the size characteristic was larger than 20 mm in the neck and nose region and 10-20 mm in the ear region (Table 3).

In non-recurrent cases, all of the anatomical regions were observed with the low-risk histopathological subtype. In the neck and nose region, the statistical median size was 10-20 mm, but in the ear region, it was less than 10 mm in diameter (Table 3).

Significantly higher recurrence rates were observed if BCC at the time of the excision was 10-20 mm or larger ($p<0.001$). Significance was also noted for mixed BCC histopathology and for cases where mixed BCC was localized in the nose region (Table 3, $p<0.001$).

The superficial subtype was the second most recurrent subtype in this study. In the Mann-Whitney U test, the superficial subtype appeared in every anatomical region in 25th quartile. No significant difference was found between recurrent and non-recurrent cases when excisions were carried out on other BCC subtypes (Table 3).

DISCUSSION

It is essential to assess the quality of life of the patient in the relationship to oncological radicalism with functional and aesthetic surgery approach (20). Although recurrence rates of treated BCC have decreased, some studies still report rates reaching up to 15% (6, 8). Since BCC is most commonly located in the facial region, aesthetical and functional expectations may influence the surgical approach. Current classifications that are determined by lesion characteristics such as location, histopathology, and lesion size, must be taken into account so that the primary treatment goal of reducing recurrence rates might be achieved (9, 19, 21, 22).

Our study has significantly lower male to female ratio than other studies in the literature. We cannot directly address the cause of this bias in our study, but variation in sex ratios are not uncommon. In some reports, the higher incidence of BCC in men versus women (1. 5:1 (23), 1. 4:1 (24), 1. 3:1 (25), 1. 1:1 (26)) is explained by the higher use of protective sunscreens by women or by the higher frequency of outdoor physical work (higher sun exposure) for men. In other reports, the incidence of BCC is either more equally distributed between men and women (1. 1:1 (26), 1. 1:1 (27)) or the incidence is higher in wom-

en (1:1.1 (9), 1:1.3 (28), 1.1:1 (29), 1:1.6 (30), 1:1.4 (31)). Before applying the exclusion criteria, the male to female ratio was 1:1.81; after the exclusion criteria were applied, the male to female ratio was 1:2.99. The largest portion of excluded patients (80% of total excluded) was due to the anatomical location of the BCC. Ghanadan *et al.* (2014) found that males had a higher frequency of BCC on the scalp than females (32). Scrivener *et al*. (2002) attributes such male to female ratio with increasing female predominance to age- and sex-dependent mortality; pathologies such as cardiovascular and internal oncology occur earlier in men.

Average age was not different after application of exclusion criteria (62.2 yrs. before, 62.5 yr.) and according to Eurostat, the cardiovascular and oncology related mortality in men was almost 3-fold higher than for women for the population 65 yrs. old and younger (33). A study evaluating almost 30 years of data gathered in Netherlands report BCC incidence in woman increasing with a faster rate than in man and even higher increase in incidence for younger woman (<50 yrs.) (2). Several studies have also reported clinically observed BCC significantly higher in men aged between 70-79 yrs. , whereas other studies report an increase of incidence in women aged 40-49 or aged 60-79 (23, 34). These studies report

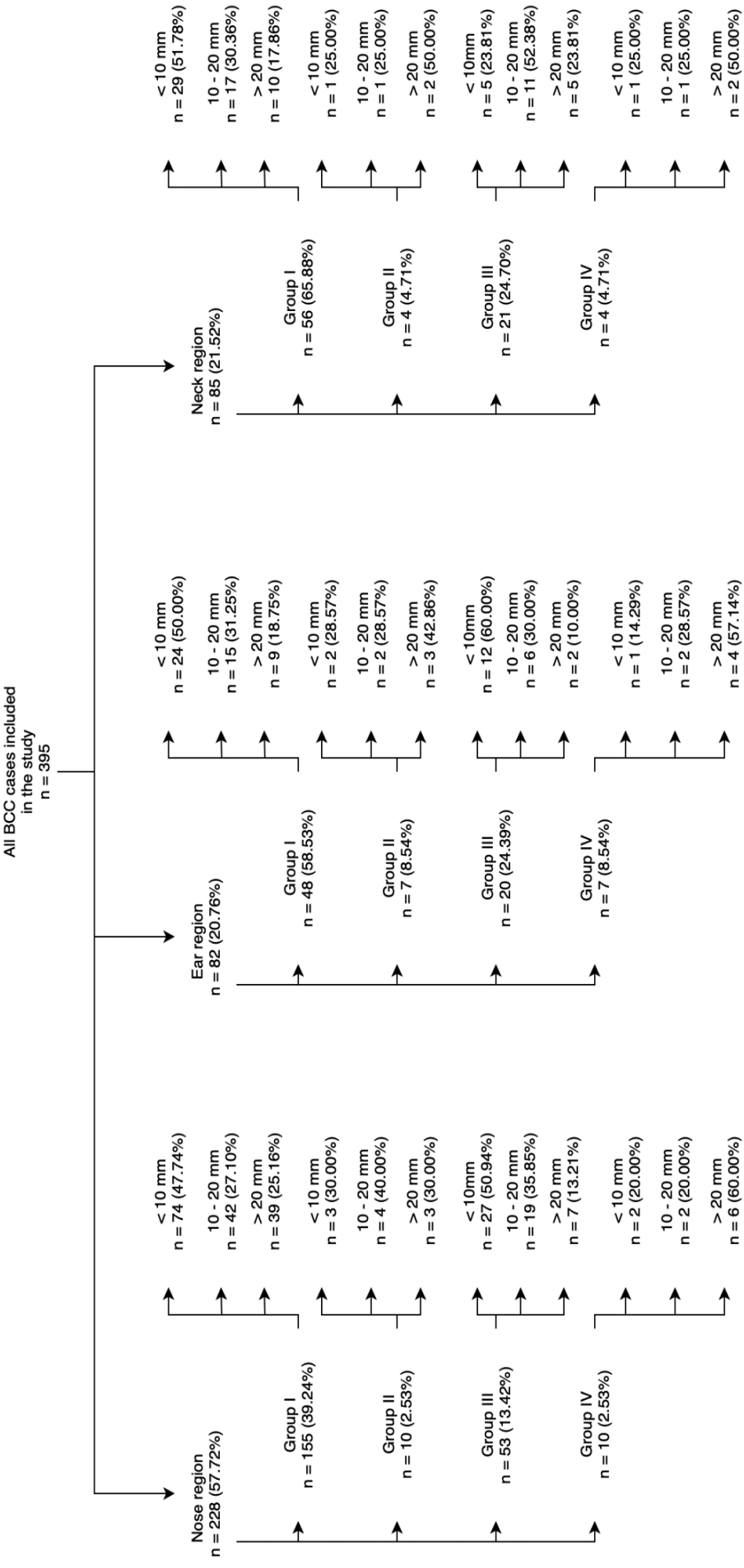

Fig 3. Histology is divided by histological subgroups: group I - nodular, pigmented, adenoid, keratotic and cystic; group II - superficial; group III - mixed, group IV - morpbea form, metatypical. Anatomical distribution is divided into three anatomical locations: neck, nose, and ear.

a tendency of clinical diagnosis made in men later in their age compared to women. One could surmise that either men are predisposed to BCC at an older age than woman or woman are more attentive to the anatomical changes in the head and neck region (or both). The current analysis does not include sex as a variable as we have too small a sample size to sufficiently address this along with the variables examined. We can offer some speculation based on the reports in other studies cited here that if the male to female ratio would been closer to 1:1, we would expect to have observed more large lesion sizes and higher recurrence rates. It is possible that our study population has resulted in an underestimation of some associations of variables to recurrence outcomes because of the low male: female ratio.

A significant difference was observed between recurrent and non-recurrent cases when comparing differences in lesion size ($p<0.005$, Table 3). This may suggest that most of the recurrent cases were diagnosed when the tumor was larger than 10 mm ([10-20;>20] mm, $p<0.001$, Table 3) where as non-recurrent cases did not reach size above 20mm. Significantly higher recurrence rates in cases of a tumor larger than 10 mm is in disagreement with Demirseren *et al.* (2014) reporting no connection between size and sex with recurrence rates (35). Some studies have proposed excision guidelines for BCC with larger healthy tissue indentations if the lesion is at least 20 mm in diameter (19). Most of the recurrent cases in the present study were observed in the high risk (H) zone. In fact, significantly higher recurrence was observed when mixed subtype was localized in the nose region (50th quartile mixed, localization: nose, $p<0.001$, Table 3). It is more likely that characteristics such as size and histopathology, in addition to the early recognition and treatment of zones of particular aesthetic concern, may have influenced the associations in this study, as they have in others (36).

The mixed histological subtype, by virtue of its name, consists of variety of BCC cell growth characteristics. Ghanadan *et al.* (2014) analyzed mixed BCC in terms of a combination of its components and classified each combination in terms of their occurrence rates (16). Their study shows the complexity of mixed BCC subtype and may explain the differences in results between studies due to skin type, genetics, and environment (21). Although such classifications may improve the understanding of mixed BCC subtype, it may be too clinically complex to assist in differential diagnosis, and it may not change the prediction of patients' post-surgical outcome.

In this study the histopathological difference was found to be significant between non-recurrent and recurrent cases. Low risk BCC was far more prevalent in non-recurrent cases (50th quartile low risk [25th low risk; 75th mixed], $p<0.001$, Table 3). However mixed BCC appeared significant in recurrent cases (50th quartile mixed [25th superficial, 75th mixed], $p<0.001$, Table 3). As this study did not include an evaluation of the infiltrative subtype of BCC, or the proportion of this subtype in the mixed subtype group, the only group that clearly resembles high risk histopathological characteristics is group IV or high-risk group (morpheaform and meatypical) based on Clarks *et al.* (2014) classification (14, 37). In this study, high risk BCC comprised only 15% of recurrent cases while mixed BCC comprised 50% of recurrence cases. We were unable to evaluate histopathological components for the mixed BCC subtype because the patient dataset did not include these components. This is a weak point in the present study as we cannot say for certain that high risk components in recurrent mixed BCC cases were present (10, 16, 24, 25). Two risk factors such as mixed subtype (if infiltrative or micronodular component is present) and H zone localization may explain the significant findings of recurrent cases in present study (38-41).

The rates of recurrence in this study were 5. 06% (20 cases of 395) which is in accordance with reported recurrence rates of 3.2% to 8.0% (19). The mixed histological subtype accounted for 50% of recurrent cases (10 cases of 395) which is also in agreement with many studies (12, 16, 25).

Clark *et al.* (2014) and McKenzie *et al.* (2016) suggest classifying superficial BCC as low risk subtype in histopathological terms (14, 15). Our study showed that in every anatomical group, superficial BCC reaches the 25th quartile of the median within recurrent cases and comprised 6 of the 20 recurrent cases. Why is superficial BCC (low risk) the second rank in recurrent cases? One explanation may be that the surgical excision procedure did not include the MOHS approach which is the accepted golden standard for the surgical treatment in BCC cases, thus excision margins could have been overlooked in cases of superficial subtype. As recurrence rates in this study do not differ much (or at all) from other studies reporting these rates in MOHS surgery, this may not contribute significantly to this observation. A randomized controlled trial and prospective randomized control trial with 5-year follow-up showed similar results achieving no significant difference between standard excision method and MOHS surgery (42, 43). High recurrence rates in superficial BCC have been reported previously (40). While this study found significant results in terms of cell growth patterns, anatomical location and lesion size, contradictory

results are still being reported in disagreement with current classifications (8, 18).

The analysis in this study was limited by sample size; this precluded the inclusion of sex as a variable in the analysis. The clinical records in our study did not include a description of the components of the mixed BCC subtype, which precluded an analysis of recurrence with the components (for example, with mixed BCC infiltrative or micronodular). As we evaluated more than 2 characteristics of BCC, one may suggest a multivariate analysis (per ex. MANOVA) that may help to identify new risk factors. We could not reasonable apply such an analysis given that the recommended sample size is not lower than n=50 for the results to be reliable (44).

CONCLUSIONS

Size, anatomical location and histopathological subtype were significant characteristics in recurrent cases in comparison with non-recurrent cases. Lesions that were 10 mm or larger in diameter, lesions found in nose region and lesions with mixed subtype characteristics were significant to recurrent cases. More attention should be focused on patients with such risk factors and pre-treatment lesion evaluation per classification (including a characterization of mixed BCC) should be done.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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