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
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).

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location/size</td>
<td>L&lt;20 mm</td>
<td>L≥20 mm</td>
</tr>
<tr>
<td>M&lt;10 mm</td>
<td>M≥10 mm</td>
<td></td>
</tr>
<tr>
<td>H&lt;6 mm</td>
<td>H≥6 mm</td>
<td></td>
</tr>
<tr>
<td>Histological subtype</td>
<td>Nodular, superficial</td>
<td>Demonstrating an aggressive growth pattern – morphea form, fibrosing, perineural, metatypical, sclerosing, mixed infiltrative or micronodular features</td>
</tr>
</tbody>
</table>

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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.
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 analysis 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

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### Table 2. Distribution of BCC categories.

<table>
<thead>
<tr>
<th>Histology group</th>
<th>Neck</th>
<th>Nose</th>
<th>Ear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>56</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>155</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>IV</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Recurrence count (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total of cases (n)</td>
<td>85</td>
<td>228</td>
<td>82</td>
</tr>
<tr>
<td>Total of all recurrences (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>228</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>82</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>82</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Recurrence rates (%)</td>
<td>3.53</td>
<td>4.82</td>
<td>7.32</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Region</th>
<th>Recurrence</th>
<th>Non-recurrence</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Med (25%; 75%)</td>
<td>KS sig. level</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>6</td>
<td>3.00 (2.00; 3.25)</td>
<td>0.1272</td>
</tr>
<tr>
<td>Neck</td>
<td>3</td>
<td>3.00 (2.00; 3.00)</td>
<td>0.6766</td>
</tr>
<tr>
<td>Nose</td>
<td>11</td>
<td>3.00 (2.00; 3.00)</td>
<td>0.1787</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>3.00 (2.00; 3.00)</td>
<td>0.082</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>6</td>
<td>2.00 (2.00; 3.00)</td>
<td>0.748</td>
</tr>
<tr>
<td>Neck</td>
<td>3</td>
<td>3.00 (2.00; 3.00)</td>
<td>0.7666</td>
</tr>
<tr>
<td>Nose</td>
<td>11</td>
<td>3.00 (2.00; 3.00)</td>
<td>0.469</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>2.50 (2.00; 3.00)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

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 due to the lack of information on TNM classification by size, 3 cases due to the lack of information on lesion dimensions, 3 cases due to the lack of information on 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).

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, 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).

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).

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-
Fig 3. 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.
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 (morphoeform and metatypical) 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 reasonably 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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