Periocular Basal Cell Carcinoma: 20-Year Experience at a Tertiary Eye Care Center of South India

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Abstract:

**PURPOSE:** To study the clinical profile and management outcomes of periocular basal cell carcinoma (BCC).

**MATERIALS AND METHODS:** A retrospective analysis of all histopathologically proven cases of BCC between 1995 and 2015 was done. The demographic data, clinical presentation, histopathological subtype, and management outcomes were analyzed.

**RESULTS:** We had a total of 185 malignant eyelid tumors during the study period, out of which 37 (20%) were BCC. Thirty-two (86.5%) out of 37 cases were primary BCC. The mean age was 63.3 years. Pigmented ulcerative lesion (14, 38%), lower eyelid (19, 51%), and nodular BCC (15, 40%) were the most common presentation, periocular site, and histological subtype, respectively. 28 patients underwent excision under frozen section with an average tumor-free margin of 3.5 mm. Mean follow-up period was 18.78 months. Recurrence rate of 0% and 3.1% was noted in primary and recurrent BCC, respectively.

**CONCLUSION:** Periocular BCC commonly presents as pigmented ulcerative lesion in the lower lid. Excision biopsy under frozen section with an average tumor-free margin of 3.5 mm offers cure in most cases.

**Keywords:** Basal cell carcinoma, frozen section, periocular

Introduction

Basal cell carcinoma (BCC) is a locally invasive malignant neoplasm causing significant morbidity when affecting the ocular adnexa. It is the most common skin cancer in the western population.\(^1\,^2\,^3\) 80% of them arise from the head-and-neck region, of which 20% affect the eyelids and periocular region.\(^3\) It is the second most common eyelid malignancy in the Indian subcontinent, following sebaceous gland carcinoma (SGC).\(^5\) BCC is commonly seen in the elderly fair-skinned individuals with chronic exposure to sunlight,\(^4\,^5\) chemicals such as arsenic,\(^7\) ionizing radiation,\(^8\) and on immunosuppressives.\(^9\) Successful management of BCC is facilitated by thorough knowledge of the epidemiology, clinical spectrum, associated risk factors, and existing management options. Mohs micrographic surgery (MMS) is a method of tumor excision with margin assessment by frozen section method,\(^10\) which has an overall 5-year cure rate of 99% for primary BCC and 94% for recurrent BCC.\(^11\) However, the facility for Mohs is not available at many of the developing countries.

This study was carried out to determine the epidemiological profile, clinical
characteristics, and management outcomes of periocular BCC in the Indian subcontinent.

**Materials and Methods**

A retrospective, noncomparative, interventional case series of patients with periocular BCC in a tertiary eye care center in Chennai was carried out between 1995 and 2015. Institutional review board clearance was obtained, and the study strictly adhered to the tenets of Declaration of Helsinki. Histopathology laboratory records were analyzed, and all histologically proven cases of periocular BCC were included in the study. The parameters analyzed were patients’ demographics, duration of symptoms, presenting features, location, size and extent of the tumor, amount of tumor-free margin, number of frozen section levels to obtain histologic clearance, histopathological subtype, adjuvant therapy, and recurrence.

Statistical analysis was done by Chi-square tests using SPSS software (version 14, IBM, Armonk, New York. U.S.A).

**Results**

Between 1995 and 2015, there were a total of 185 malignant eyelid tumors. The proportion of the three most common malignant eyelid tumors namely SGC, BCC, and squamous cell carcinoma (SCC) was 57.8% (n = 107), 20% (n = 37), and 10.8% (n = 20), respectively. Thirty-seven consecutive patients of histologically proven BCC were identified. Among them, 19 (51%) were males and 18 (49%) were females, with a mean age of 63.3 ± 12.5 years (median, 65; range 37–90). Seven patients (46%) and 20 patients (54%) had involvement of the right and left eye, respectively [Table 1].

**Clinical presentation**

Fourteen out of 37 patients (38%) presented clinically as pigmented ulcerative lesion followed by 10 patients (27%) who presented as nonpigmented ulcerative lesion, 6 patients (16%) presented as pigmented nodular growth, 5 patients (13%) as nonpigmented nodular mass, and 1 patient each (3%) as wart and scar [Figure 1]. Pigmented lesion was more common (20 patients, 54%) as compared to nonpigmented lesions (17 patients, 46%). Two patients had Gorlin–Goltz syndrome.

**Duration of symptoms**

The average duration of symptoms was 6.8 ± 7.3 years (median, 4 years; range, 5 months to 40 years).

**Periocular site**

The most common site of involvement was the lower eyelid (19, 51%). Lower eyelid lesions were predominantly seen in female gender (11, 58%), which was statistically significant (P = 0.0468). Eight patients (22%) had involvement of more than one periocular site of which five patients (62.5%) were females. A statistically significant correlation (P = 0.045) was observed between female gender and lesions affecting more than one periocular site. Five patients (14%) had upper eyelid involvement of which four patients (80%) were males. Upper eyelid lesions were more common in men with a statistically significant correlation (P = 0.014) [Table 2]. Three patients (8%) had medial canthus involvement and two patients (5%) had lateral canthus affection.

Majority of lower eyelid lesions were of nodular type (12, 63%), and 80% (4 patients) of the upper eyelid lesions were of pigmented type. A very strong association

| Table 1: Epidemiological profile of the patients |
| **Parameters** | **Numbers and Percentages** |
|----------------|-----------------------------|
| Mean age (years) | 63.3±12.5 (range 37–90) |
| Male: female | 1:1 |
| OD: OS | 1:1.7 |
| Primary BCC (%) | 32 (86.5) |
| Recurrent BCC (%) | 5 (13.5) |
| Lost to follow-up | 4 (3 refused any further intervention after diagnosis and 1 with metastasis did not report after being advised palliative therapy) |
| BCC with systemic syndromes (%) | 2 (5) |
| Mean duration of symptoms | 6.8±7.3 years (range 5 months to 40 years) |
| Median duration of recurrence | 5 years |
| Mean duration of follow-up | 18.78±30.5 months (range 2 months to 8.5 years) |
| Treatment (n=33) | Excision under frozen section (n=28), n (%) |
| Hughes flap | 16 (48.5) |
| Direct closure | 5 (15.2) |
| Glabellar flap | 4 (12.1) |
| Mustarde cheek rotation flap | 2 (6.1) |
| Tenzel flap | 1 (3) |
| Exenteration (%) | 4 (12.1) |
| Observation (%) | 1 (3) |

BCC: Basal cell carcinoma, OS: Oculus sinister, OD=Oculus dexter

| Table 2: Correlation between periocular site involvement and gender |
| **Periocular site** | **Male, n (%)** | **Female, n (%)** | **P** |
|-----------------|-----------------|-----------------|---|
| Upper eyelid | 4 (80) | 1 (20) | 0.0147 |
| Lower eyelid | 8 (42) | 11 (58) | 0.0468 |
| Medial canthus | 2 (67) | 1 (33) | 0.268 |
| Lateral canthus | 2 (100) | 0 | 0.0593 |
| >1 site | 3 (37.5) | 5 (62.5) | 0.045 |

Upper eyelid lesions were significantly more common in males with a P value of 0.0147. Lower eyelid lesions were more common in females with a statistically significant correlation (P=0.0468). A statistically significant correlation (P=0.045) was observed between female gender and lesions affecting more than one periocular site.
between tumor site and histopathological type was observed (Cramer’s V value = 0.393); however, the correlation was statistically insignificant.

**Histological subtype**
Nodular BCC was the most common histological subtype (19 patients, 51%) followed by pigmented subtype (13 patients, 35%) [Figure 2]. Infiltrative subtype was seen in only 5 patients (14%) [Table 3]. No significant correlation was noted between the duration of symptoms and the histological subtype.

**Lesion size**
The average size of the lesion was 17.5 ± 9.4 mm × 10.8 ± 8.3 mm (range, 6–40 mm [vertical diameter]; 3–45 mm [horizontal diameter]). Patients with infiltrative BCC had larger lesions measuring 23.2 mm × 16.8 mm (range, 7–45 mm × 5–45 mm).

**Differences between primary and recurrent basal cell carcinoma**
Out of 37 patients, 32 patients (86%) presented as primary BCC and remaining 5 (14%) presented as recurrent cases. Among the five patients with recurrent BCC, two patients had lesions involving lower eyelid, one patient had isolated medial canthus involvement, and two patients had combined lower eyelid and medial canthus affection. Patients with lower eyelid and medial canthus involvement had 2.4 times (odds ratio) more chances of developing recurrence. 80% (4 out of 5) of patients with recurrent BCC had infiltrative subtype on histopathology, with a statistically significant correlation of \( P < 0.005 \) [Table 3]. All patients with recurrent BCC had undergone only excision biopsy without a frozen section assessment of the margins previously. The median duration of recurrence was 5 years. There was no statistically significant correlation between age, gender of patient, and recurrence. One out of five recurrent cases developed re-recurrence and received adjuvant radiotherapy.

**Local and distant spread**
Of 37 patients, four patients (11%) had orbital invasion of which two patients each (50%) had infiltrative and nodular subtype of histopathology. One patient had enlarged cervical lymph nodes with distant metastasis to lung and was referred for palliative therapy. Thereafter, the patient was lost to follow-up.

**Management**
Complete excision under frozen section control followed by eyelid reconstruction was done in 28 patients and exenteration in four patients. Remaining five patients did not undergo any surgery (3 patients were lost to follow-up, 1 patient had distant lung metastasis and was referred for palliative radiotherapy, and 1 patient was under close follow-up for a suspicious scarred area).

An average tumor-free margin of 3.5 mm was sent on frozen section. Eight out of 32 patients (25%) required two levels of margin clearance on frozen section.

The various reconstructive techniques adopted were Hughes flap in 16 patients (43%), direct closure in 5 patients (14%), glabellar flap in 4 patients (11%), Mustarde cheek rotation flap in 2 patients (5%), and Tenzel flap in 1 patient (3%) [Table 1].

Two of the patients received adjuvant external beam radiotherapy.

**Follow-up**
The average period of follow-up was 18.78 months (range 2 months–8.5 years). Four patients were lost to follow-up. Rest all patients who underwent treatment as primary BCC (32, 100%) were free of tumor and alive at the last follow up.

**Discussion**
BCC is the second most common eyelid malignancy in the Indian subcontinent following SGC, and we noticed a similar pattern in the present study too.[13] Out of 185 malignant eyelid tumors which we analyzed, 57.8% were SGC which was followed by BCC (20%). SCC accounted for 10.8% of all the malignant eyelid tumors treated at our center. Because of the rarity of BCC in the Indian subcontinent, there are not much studies available from this part of the world and the present study would fill up that lacunae.

BCC is a slow-growing tumor that rarely metastasize.[12] Usually, their growth is confined to the area of origin. However, some forms of BCC tend to infiltrate the surrounding structures in a three-dimensional pattern, leading to subclinical tumor spread, making it difficult to clinically assess the margins of the lesion at the time of excision.[13] If left untreated or inadequately treated, the tumor can extensively destroy the periorcular tissues, thus complicating its management. There are conflicting reports on the recurrence rates of the eyelid BCC possibly due to difference in the technique adopted
for tumor excision and therefore the adequacy of it.\[^{[14]}\] BCC may remain static without any growth for years, or it may grow rapidly. Thus, early prompt treatment is mandatory to minimize the morbidity associated with the tumor as well as its management.

The mean age of 63 ± 12.5 years was consistent with other published data. BCC was found to be commonly seen in the 6th to 7th decade of life as reported in other studies.\[^{[15‑19]}\] Our study did not show any gender preponderance (49% females vs. 51% males). Chalfin and Putterman\[^{[14]}\] and Conway \ et al.\[^{[13]}\] also reported similar equal gender distribution in their studies. However, Kale \ et al.\[^{[19]}\] and Pfeiffer \ et al.\[^{[20]}\] reported female preponderance of 57.14% and 64.5%, respectively. On the contrary, Malhotra \ et al.\[^{[15]}\] reported male preponderance of 54% in their study. This difference in the reported gender distribution may be attributed to the difference in geographical distribution and patient selection.

On assessing the correlation between gender and periocular site, we found that lower eyelid was more commonly affected in females and upper eyelid in males, and this difference was found to be statistically significant. Malhotra \ et al.\[^{[15]}\] reported that lower eyelid and medial canthal affection was more common in males and females, respectively (\(P = 0.0008\)).

In our study, lower eyelid was more commonly affected (51%) followed by multisite involvement (22.5%), upper eyelid (13.5%), medial canthus (8%), and lateral canthus (5%). Cook \ et al.\[^{[21]}\] also reported lower eyelid (43%) as the most commonly affected periocular site. However, medial canthus was the second most common site (26%) in their study, whereas medial canthus was most commonly affected (48.3%) in the study conducted by Malhotra \ et al.\[^{[15]}\]

There are no standard histopathological subclassifications for BCC. The most important histopathological feature of BCC is the presence of circumscribed or infiltrative growth pattern, which has prognostic value in the surgical treatment of BCC.

Circumscribed BCC clinically corresponds to nodular/nodulocystic BCC type whereas infiltrative variety corresponds to morphea type.\[^{[10]}\] A third pattern of growth referred to as superficial BCC has multicentric origin. Based on the cellular differentiation, BCCs may also show sebaceous, eccrine, apocrine, pilar, or basosquamous differentiation of which the last type has a very aggressive behavior and hence are highly recurrent and have metastatic potential.\[^{[22]}\]

The most common histological growth pattern seen in our study was nodular (19.51%). Nodular BCC exhibit spaces in between due to mucin accumulation. Infiltrative BCCs are locally aggressive subtype with high risk of recurrence and are characterized by irregular groups of tumor with spiky appearance and presence of stromal fibrosis.\[^{[23]}\] Patients with infiltrative BCC had larger lesions in our study (23.2 mm × 16.8 mm), which confirms the locally aggressive nature of this histological subtype. This was consistent with the results of The Australian Mohs Database, Part I wherein infiltrative BCCs had significantly larger tumor size and consequently larger defect sizes.\[^{[18]}\]

Recurrent BCCs have more chances of re-recurrence and assume more aggressive histological subtype even after MMS.\[^{[10]}\] In our study, recurrent lesions were predominantly infiltrative with larger tumor size. Out of the five cases who presented to us as recurrent BCC, 4 (80%) had infiltrative type on histopathological examination, which showed a statistically significant correlation of \(P < 0.005\). Ho \ et al.\[^{[18]}\] recorded a recurrence rate of 3.8% in primary morpheaform BCC. This is consistent with previous studies which showed the margin for complete tumor excision for recurrent BCC to be twice than that required for primary BCCs. Hamada \ et al.\[^{[15]}\] reported a recurrence rate of 4.35% in patients with infiltrative BCC as compared to 1.6% in patients with noninfiltrative BCC treated with 4 mm surgical margin, indicating the inadequacy of surgical margin in the aggressive types of BCCs. In the study conducted by Pieh \ et al.\[^{[17]}\] a recurrence rate of 5.36% was observed after primary surgery which increased to 14.7% and 50% after the second and third surgery, respectively. Robins \ et al.\[^{[24]}\] observed recurrence rates twice as high for medial canthal lesions as for other periocular sites (9.5% vs. 4.5%) after Mohs surgery. Similarly, Pieh \ et al.\[^{[16]}\] concluded from their study that recurrences are higher in medial canthal BCCs. In our study, we found that recurrent BCC was twice more common in the lower eyelid and medial canthus as compared to other periocular site (odds ratio = 2).

Orbital invasion was seen in 4 patients (11%) in our study. All of them underwent exenteration with frozen section control of which two patients showed positive margins on frozen section and were hence referred for adjuvant external beam radiotherapy. Among these four patients, 50% had morpheaform on histopathology. Howard \ et al.\[^{[25]}\] studied the clinical characteristics associated with orbital invasion of cutaneous basal cell tumors of eyelid in 11 patients and observed that all 11 patients exhibited aggressive histological behavior.

Due to low metastatic potential, the main focus of treatment is on the local tumor control. Treatment of BCC can be surgical or nonsurgical. Surgical modalities include curettage and electrodesiccation, cryosurgery, surgical excision under frozen section control, and MMS.
Curettage and electrodesiccation or cryosurgery is suitable for low-risk lesions that are less than 2 cm, well-defined primary lesions with less aggressive histological subtype.\textsuperscript{[1,26]}

Several studies have evaluated the efficacy of topical imiquimod 5% in the treatment of low-risk superficial BCC and have been found to achieve histological clearance in 80% of the patients with once daily application for 6 weeks.\textsuperscript{[27]}

However, MMS remains the gold standard treatment modality of choice to achieve improved cure rates and reduce the need for subsequent re-surgeries. The 5-year recurrence rate for primary and recurrent BCCs treated with MMS is reported as 0% and 7.8%, respectively.\textsuperscript{[11]}

Further, the recurrence rate of 0% has been observed in patients with previous incomplete excision of the tumor treated with MMS, as compared to 4.7% recurrence rate in patients treated with frozen section technique as noted by Nemet \textit{et al.}\textsuperscript{[28]} Muller \textit{et al.}\textsuperscript{[29]} observed that MMS is superior to conventional surgical excision in terms of outcomes based on tissue sparing. However, due to nonavailability of MMS facilities widely, time-consuming nature of procedure, and expertise required in carrying out this technique, intraoperative frozen section control provides an equally better option for margin control in such cases.

In our study, an average tumor-free margin of 3.5 mm achieved nil recurrence in the primary BCCs and only one patient in the recurrence group had re-recurrence. In the study conducted by Doxanas \textit{et al.},\textsuperscript{[30]} 126 patients underwent excision without margin clearance by frozen section, of which 26.9% had positive margin histologically and 5.5% of them recurred. Kale \textit{et al.}\textsuperscript{[19]} reported a recurrence rate of 1.9% in patients treated with wide local excision with a margin of as large as 5–10 mm. Hamada \textit{et al.}\textsuperscript{[17]} reported a recurrence rate of 4.35% with a 4-mm surgical margin done without frozen section control.

As compared with other studies, our study achieved complete tumor excision with an average margin of 3.5 mm under intraoperative frozen section control in all primary cases.

Various inherited conditions such as Basal cell nevus syndrome, Gorlin–Goltz syndrome, Xeroderma pigmentosum, albinism, and Bazex syndrome have been reported to predispose to BCC.\textsuperscript{[10]} Two patients in our study had Gorlin–Goltz syndrome.

| Figure 1: (a) External photograph showing right lower eyelid basal cell carcinoma, (b) external photograph after excision biopsy and eyelid reconstruction, (c) external photograph showing left upper eyelid basal cell carcinoma, (d) postoperative photograph after excision biopsy and eyelid reconstruction, (e) external photograph showing extensive periocular basal cell carcinoma, (f) External photograph after excision biopsy and eyelid reconstruction, (g) external photograph showing basal cell carcinoma involving left forehead with orbital involvement, (h) external photograph after excision biopsy, exenteration, and reconstruction |
| Figure 2: (a) Photomicrograph showing lobules of basal cell carcinoma with peripheral palisading pattern consistent with nodular type of basal cell carcinoma (H and E stain), (b) photomicrograph showing tumor lobules with scattered numerous melanophages in the stroma consistent with pigmented basal cell carcinoma (H and E stain), (c) photomicrograph showing the basal cell carcinoma of the eyelid with thin elongated cord like tumor cells arising from the basal layer and infiltrating the dermis consistent with morphea like or infiltrating type of basal cell carcinoma (H and E stain) |
Metastasis often arises from lesions in the face and usually spreads to regional lymph nodes followed by bone, lung, and liver.[61] In our study, one patient had cervical lymphadenopathy with distant metastasis to the lung. The patient was advised palliative therapy under the care of an oncologist.

**Conclusion**

BCC is the second most common eyelid malignancy in the Indian subcontinent, and the present series is the second largest study on management outcomes of eyelid BCC from India. This study has found a significant correlation between gender and the periocular site of affection of BCC and has also analyzed the most common histopathological variant among the primary and recurrent BCC. Lower eyelid was the most common periocular site of affection while nodular BCC was the most common histopathological type. Females had involvement of more than one periocular site more commonly than males. Lesions in the medial canthus and infiltrative type of BCCs behave aggressively, leading to recurrence. An average tumor free margin of 3.5 mm along with intraoperative frozen section control helps in achieving complete tumor eradication with nil chance for recurrence. Skin cancer screening programs is the need of the hour for early diagnosis and prompt management of suspicious lesions, thereby reducing the morbidity associated with them. Studies with larger sample size and longer follow-up period from the Indian subcontinent are essential for improving the management outcomes.

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**Conflicts of interest**

There are no conflicts of interest.

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