Original Article

Malignant tumors of the eyelid in India: A multicenter, multizone study on clinicopathologic features and outcomes

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Purpose: To analyze data on eyelid malignancy in India, clinical and pathologic features, and outcomes. **Methods:** A multicentre study, from oculoplastic practices in four geographic zones in India. The centers perform similar documentation and protocol-based management for eyelid tumors. Clinical features, pathology, American Joint Committee on Cancer (AJCC) class, management, and the outcomes were analyzed. **Results:** The study included 129 patients, with slight female preponderance and mean age 62.7 years. The median delay to the consultation was 9 months. Rural patients traveled a mean distance of 115.2 km; there was no difference between the city and outstation patients in the delay to consultation or follow up. Pathology included 55/129 (42.6%) sebaceous gland carcinoma (SGC), 47/129 (36.4%) basal cell carcinoma (BCC), squamous cell carcinoma (SCC) in 15 (11.6%), and 12 (9.3%) other tumors. Commonest AJCC class was T2b/T3a in 80/111 (72%), invasion of the orbit was present in 16 (12.4%). Surgery with margin clearance was performed in 103. With a mean follow-up of 21.44 months, local recurrence and/or metastasis were seen in 12%. The diagnosis of SGC was strongly associated with adverse outcomes (odds ratio: 7.36). On multiple logistic regression analysis, diagnosis of SGC (P = 0.011) was significant in having adverse outcomes. **Conclusion:** The multicenter Indian data shows the highest prevalence of SGC, with the commonest AJCC class T2b. Most tumors were locally resectable at presentation. The histopathologic diagnosis of SGC is the factor strongly associated with adverse outcomes.

Key words: Basal cell carcinoma, eyelid malignant tumors, India, sebaceous gland carcinoma, squamous cell carcinoma

Basal cell carcinoma (BCC) is held to be the commonest eyelid malignancy worldwide.[1,2] Sebaceous gland carcinoma (SGC) is seen more frequently in the Asian and Asian Indian population and known to have the second-worst prognosis among eyelid malignancies.[3,4]

The outcome of eyelid malignancies depends on the histopathologic diagnosis and the extent. The American Joint Committee for Cancer (AJCC) classification is used for documentation of disease severity. The Indian literature on eyelid malignancies includes several series with contradictory data. No reporting of the extent of disease or AJCC classification of eyelid malignancies in India is available.

In a country with a large geographic extent and diverse population, there is a need for representative data on clinicopathologic features and outcomes on eyelid malignancy in India. This study presents data on eyelid malignancies in India across zones (North, East, West, and South).

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Methods

The study was a retrospective interventional multicenter study, from five centers located in four geographic zones in India. All the participating ophthalmologists are trained similarly in principles of oculoplastic surgery and ocular oncology. At the time of this study, they had experience between 10 to 15 years and had single-surgeon sub-specialty practices. The duration of the series included in the study ranged from 5 to 12 years; the shortest from 2014–2019, longest from 2008–2019. All authors practice protocol-based management of eyelid malignancies. Only patients with biopsy-proven malignancy were included in this study.

All authors follow similar criteria for clinical diagnosis: Unexplained, rapidly progressive mass lesion, ulceration, loss of lid margin architecture and madarosis, unexplained unilateral blepharoconjunctivitis. The greatest dimension and perpendicular are measured, and a clinical photograph is documented [Fig. 1a-d]. Orbital imaging is advised when the posterior margin of the tumor cannot be determined on clinical examination, presence of proptosis, ptosis, or

limitation of ocular movement [Fig. 1d]. Draining lymph nodes are examined clinically. The authors also follow a similar procedure for excision—minimal touch technique with 5 mm margins, margins sent for histopathology marked for orientation, and map biopsy in all SGC. The pathologist confirms the diagnosis and absence of tumor on the margins, and the defect is reconstructed.

Histopathology included hematoxylin–eosin stain on tissue embedded in paraffin sections. The patients from the East zone underwent Oil Red O stain on fresh tissue when there was a suspicion of SGC. Patients underwent immunohistochemistry for other tumors such as eccrine carcinoma, lymphoma, mucinous carcinoma, and so on.

All patients were managed by surgical excision with tumor-free margins verified on histopathology, either on frozen or on the permanent section. Orbital exenteration was performed for orbital extension of the tumor or for SGC with an extensive pagetoid spread. The excision was followed by reconstruction. All patients had a pathologist confirm the diagnosis on permanent section histopathology, and were reviewed at 1 week, 6 weeks, and advised reviews 3 monthly for the first year, and after that yearly.

The data entry was done from medical records, clinical drawings, and clinical photographs. A common data collection form was used, which included the following: Age, gender, referral diagnosis, distance to the clinic, laterality, involvement of upper lid/lower lid/canthus/margin/contiguous conjunctiva, orbital extension, regional lymph nodes, pathology details, AJCC class, treatment, both planned and performed, and outcome (whether recurrence, locoregional spread, or metastasis).

We included all patients with available histopathologic diagnoses for the classification and categories of tumors. This also included patients who did not undergo definitive treatment. For outcome analysis, we included only patients with a follow-up of 3 months or greater.

AJCC 7th edition classification was applied retrospectively based on the recorded dimensions and extent. Some patients had undergone partial excision elsewhere and were categorized as Tx.

Analysis

Descriptive data were compiled using MS Excel (MS Office 2018). Statistical analysis was done using MedCalc v19.0.5. We assessed clinical and pathologic features as risk factors for locoregional spread and recurrence, using odds ratio and logistic regression analysis.

Patients from the city and outstation patients were compared for the delay to diagnosis and duration of follow-up using the Student's T-test.

Results

The final analysis included a total of 129 patients, with 68 (52.3%) female patients. The mean age of patients was 62.7 years (range 5–92 years). From the first appearance of signs, the median delay to the first consultation was 9 months (mean 17.26 months, range 1–120). The mean distance from home to hospital was 115.2 km (range 0–738 km). Forty-eight patient records showed a referral diagnosis, of which nine (18.7%) had been misdiagnosed as benign. Thirty-one (24%) patients had a history of intervention elsewhere, including incision biopsy, incision and curettage, or excision without margin clearance.

Table 1 shows the clinical characteristics of the tumors. Among the clinical features, 120/129 (93%) patients presented with a mass lesion, 6/55 (10.9%) of the SGC patients presented with blepharoconjunctivitis, 25/129 (19.3%) of all patients had bleeding on presentation, and 17/129 (13%) patients presented with ptosis. One patient who presented with an orbital extension of SGC had a history of treatment for 'ocular cicatricial pemphigoid' for 8 years.

Histopathology revealed [Table 2] SGC to be the commonest. The distribution included BCC, squamous cell carcinoma (SCC),
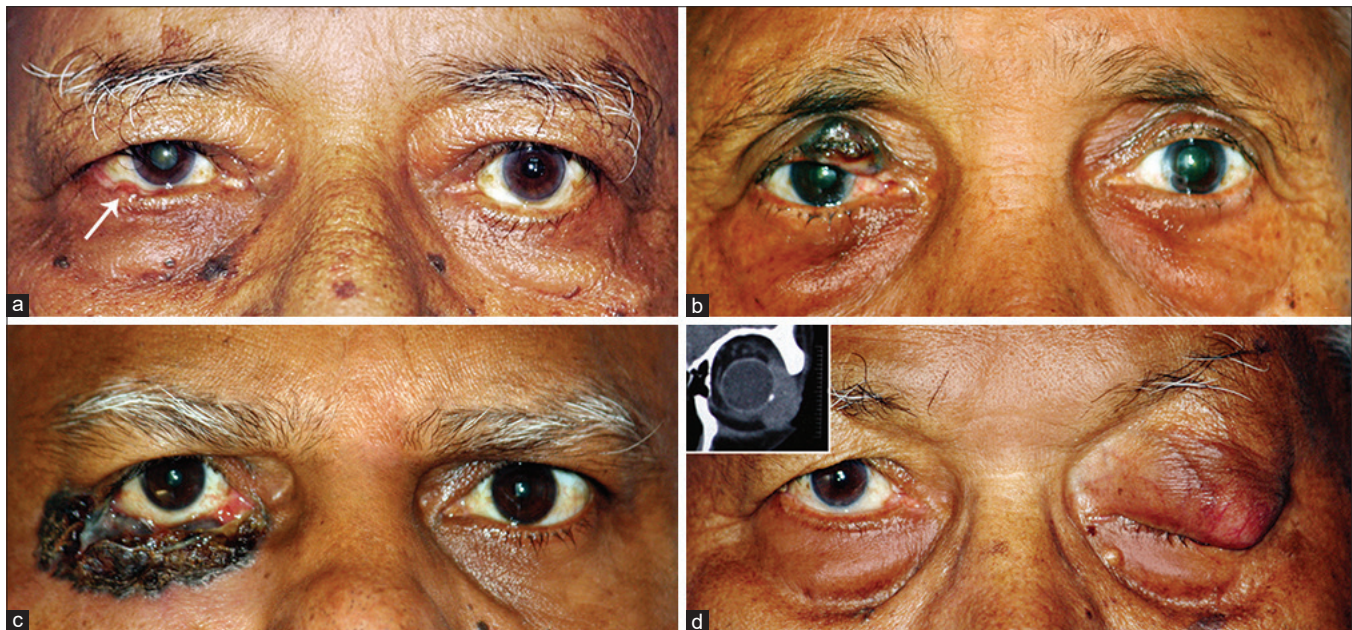
Figure 1: (a) Sebaceous carcinoma (white arrow), stage T2a. (b) Basal cell carcinoma, stage T2b. (c) Basal cell carcinoma, stage T3a. (d) Sebaceous carcinoma, stage T3b. Inset: Computed tomography shows the orbital extension

Table 1: Clinical details of eyelid malignancies

Clinical Feature	Number (%)
Laterality	Right 75 (58.1%)
	Left 52 (40%)*
Eyelid	Upper 62 (48%)
	Lower 51 (39.5%)**
Canthus involvement (medial/lateral)	13 (10%)
Eyelid margin involvement n=127	89 (70%)
Involvement of contiguous conjunctiva	54 (41.8%)
Orbital extension	16 (12.4%)
Mean diameter in mm (widest area and perpendicular)	16.6 and 12.2
Lymphadenopathy at presentation	4 (3.1%)

*One patient had bilateral disease, total in the table does not add up to 100%. **Others could not be localized to upper or lower lid, total in the table does not add up to 100%

Table 2: Histopathologic diagnosis and AJCC classification

Histopathologic classification (n=129)	Number	Percent
Basal cell carcinoma	47	36.4% (CI 28.2-45.4)
Sebaceous carcinoma	55	42.6% (CI 34.0-51.6)
Squamous cell carcinoma	15	11.6% (CI 6.8-18.7)
Others	12	9.3% (CI 5.1-16.0)

AJCC classification (n=111)*	SGC	BCC	SCC
T1	0	3	0
T2a	10	4	2
T2b	24	28	8
T3a	10	9	1
T3b	8	1	3

*Rest other tumors or Tx

Table 3: Distribution of tumor diagnoses in the different zones of India

Zone	BCC	SGC	SCC	Others
North (n=44)	15 (34%)	21 (47.7%)	3 (6.8%)	5 (11.3%)
East (n=33)	16 (48.4%)	14 (42.4%)	3 (9%)	0 (0%)
West (n=23)	5 (21.7%)	10 (43.5%)	5 (21.7%)	3 (13%)
South (n=29)	11 (37.9%)	10 (34.4%)	4 (13.8%)	4 (13.8%)

BCC: Basal cell carcinoma ;SGC: Sebaceous gland carcinoma; SCC: Squamous cell carcinoma

Table 4: Management and outcome, n=98 for outcome

Management and outcome	Number
Excision biopsy with free margins and eyelid reconstruction (direct/flap/graft)	103
Orbital exenteration	9
Margin clearance for excision biopsy	Frozen section 56 (54.3%)
	Permanent section 47 (45.6%)
Followup duration	Mean 21.44 months
Disease-free at last follow-up	82/94 (87.2%)
Metastasis to lymph nodes/systemic*	9/94 (9.5%)
	BCC 0/47, SCC 1/15 (6.6%), SGC 8/55 (14.5%)
Local recurrence in eye and orbit*	5/94 (5.3%)
	BCC 0/47, SCC 0/15, SGC 5/55 (9%)

*Two patients with sebaceous carcinoma had both local recurrence and lymph node metastasis

and others. Among the SGC, 22.7% were well-differentiated, 54.5% were moderately differentiated, and 22.7% were poorly differentiated. Pagetoid spread was seen in 23 (41%) patients of SGC. The miscellaneous tumors included 6 (4.6%) cases of eccrine carcinoma and mucinous carcinoma of sweat gland, 2 (1.5%) cases of lymphoma, 1 case of embryonal rhabdomyosarcoma, 1 case of angiosarcoma , 1 case of adenoid cystic carcinoma, and 1 case of adenosquamous carcinoma. Table 3 shows the comparative distribution of the different malignancies in the various zones of the country.

Commonest AJCC classes were T2b and T3a, accounting for 80/111 (72%) lesions. Positron emission tomography (PET) scan was advised at the time of diagnosis to all patients of SGC, all orbital extension, and patients other than BCC [Table 2]. However, due to financial constraints, it was performed in 21 patients, and one showed positive lesions elsewhere in the body at initial assessment. None of our patients underwent sentinel node biopsy. None underwent pre-emptive lymphatic dissection.

Surgery with tumor-free margin was done in 112 eyes, with other patients lost to follow-up after advice [Table 4]. The mean follow-up was 21.44 months, with metastasis and/or recurrence in 14 patients (11.3%). All the recurrences were SGC or SCC. SGC patients showed a 9% recurrence and 14.5% metastasis in spite of histopathologic margin clearance at surgery [Table 4]. One patient underwent neoadjuvant chemotherapy and orbital exenteration and was lost to follow-up.

There was no difference between metro (37%) and outstation (63%) patients in the mean delay to first consultation (18.73 months versus 18.74 months) or the loss to follow-up (22% versus 26%).

Analysis of adverse outcome (distal metastasis, lymphatic spread, or recurrence) was performed for 98 patients with more than 3 months of follow-up after surgical excision. This included both cases with eyelid lesion excision with clear margins, and with orbital exenteration [Table 4]. On logistic regression analysis [Table 5], the diagnosis of SGC was more likely to have an adverse outcome such as recurrence or metastasis (odds ratio 7.36, P = 0.0115). The involvement of canthus, greatest dimension, and duration of disease did not seem to affect the outcome. On further analysis of SGC versus other tumors, the mean greatest dimension was similar in both categories: 17.3 mm in SGC, 16.5 mm in others, P value = 0.82. The duration of disease was significantly more in non-SGC tumors (mean 12.9 months in SGC, 25.8 months in others, P = 0.05). Involvement of canthus was significantly less in SGC (34% in SGC versus 54.6%, P = 0.02).

Discussion

BCC is the commonest eyelid malignancy worldwide. Studies from Japan and China show an equal incidence of SGC and BCC [Table 6].[3,4] It has long been the impression that the pattern of eyelid malignancies in India differs from that in the Western population. However, the Indian reports have been variable, with different studies describing different distributions of tumors.[7-11]

Table 5: Analysis of factors influencing adverse outcome (recurrence, lymph node metastasis or distant metastasis)

	Odds ratio	Confidence Interval	P
Sebaceous carcinoma vs others	7.36	1.49-36.19	0.01
Permanent section vs frozen section	0.50	0.11-2.23	0.36
Canthal involvement	1.73	0.25-11.95	0.57
Largest diameter >20 mm	0.30	0.07-1.28	0.10
Outstation patient	1.34	0.32-5.62	0.68
Duration >9 months	1.30	0.31-5.55	0.7

Table 6: Comparative proportion of eyelid malignancies in various studies

	Location	BCC (%)	SGC (%)	SCC (%)	Comments
Deprez (n=894)[2]	Switzerland	86	3	7	
Takamura (n=38)[3]	Japan	39.5	28.9	10.5	
Ni (n=1144)[4]	China	37.6	31.7	18.9	
Lee (n=325)[5]	Singapore	84	10		
Ho (n=28)[6]	Hong Kong	43	7	18	
Jahagirdar (n=27)[7]	India	44	37	15	Plastic surgery unit, central India
Abdi (n=85)[8]	India	38.8	27.1	22.4	Pathology unit north India
Kale (n=85)[9]	India	48	31	13.7	Plastic surgery unit
Sihota (n=178)[10]	India	29.8	32.6	28	Referral center north India
Kaliki (n=536)[11]	India	24	53	18	Referral center south India
This study (n=129)	India	36.4	42.6	11.6	Multicenter multi zone

Of the Indian studies, three are from plastic surgery or pathology services.[7-9] All three find BCC to be the commonest eyelid malignancy. They may not reflect the picture seen by ophthalmologists. There are two studies from referral eye institutes.[10,11] These differ significantly in the distribution of the different diagnoses. Sihota *et al.* found BCC, SCC, and SGC to be almost equally common, whereas Kaliki *et al.* found SGC to vastly outnumber BCC.[10,11] Due to these contradictory results, one cannot generalize about eyelid malignancy patterns in India from the previous reports. A recent editorial on ocular oncology elaborates on the pitfalls of drawing conclusions for eyelid malignancy for the entire country from retrospective data of a single referral center.[12] Our study aims to address the need for a data set, which is more truly representative of the country.

The incidence of cutaneous cancers has been associated with skin color, sun exposure, or a location closer to the equator. The Indian mainland spans 8°4′N to 37° 6 ′N latitudes and a wide variety of climate. The Indian population also shows diversity in skin pigmentation.[13-15] Thus, a multizone study such as ours yields the most representative data on eyelid malignancies in India.

The AJCC classification [Table 7] is increasingly commonly used. In SGC and SCC, higher T grading in the AJCC classification is predictive of nodal metastasis, systemic metastasis, and mortality.[16-18] These existing studies use the AJCC 7th edition. Our series also uses AJCC 7th edition classification in a retrospective fashion and allows comparison to current literature. The largest number of patients presented to the oncology service with tumor Group 2a to Group 3a, permitting surgical resection and sparing the globe.[19] The AJCC 8th edition is in use from January 2018. It will be useful to prospectively stage eyelid malignancies as per the 8th edition.

SGC is known for aggressive behavior, with 12–40% loco-regional spread and mortality.[20,21] Our study shows that the prevalence of SGC is the commonest in Indian population. We also see an Odds ratio of 7.36, that SGC will lead to a worse outcome than non-SGC.

Canthal involvement and the greatest dimension of tumor were not found significant for adverse outcomes. We did not analyze the greatest dimension and AJCC classification separately since the latter incorporates the size of the tumor. Delay from the onset of disease to diagnosis was not significant for adverse outcomes [Table 5]. These results are unexpected since each of these factors has been shown to influence prognosis. We hypothesize that this result comes from a combined analysis of the different kinds of tumors. The SGC outcomes were much worse compared to any other tumor. SGC had a significantly shorter duration of disease than others and fewer canthal involvement. The greatest dimension of SGC was similar to that of other categories, but with worse outcomes. Overall, the prognosis of SGC was so serious as to supersede the other known risk factors in this series.

When comparing the use of frozen section versus permanent section for margin clearance, we found no significant difference in the outcome. The authors emphasize that tumor-free margins must be obtained on the excision of an eyelid malignancy, whether by frozen section or by permanent section [Table 5]. A permanent section histopathology may require the surgeon to excise more tissue at a second sitting before reconstruction is done. A recent study shows that while the frozen section closely approximates the results of the permanent section, the sensitivity of the permanent section is better than that of the frozen section in SGC.[22] There is also data to show that delayed reconstruction after paraffin section margin clearance gives good results.[23] However, wherever the facility is available, a single-stage procedure with on-table frozen section margin clearance and reconstruction would be preferable.

Table 7: AJCC TNM classification of eyelid malignancies

Class	Specification
Tx	Cannot assess primary tumor
T0	No primary tumor
T1	Size less than/equal to 5 mm, tarsal plate/eyelid margin not involved
T2a	Size 5 to 10 mm, or any tumor less than/equal to 10 mm with tarsal plate/lid margin involvement
T2b	Size 10 to 20 mm, or any tumor with full-thickness eyelid involvement
T3a	Tumor >20 mm, or tumor involving adjacent orbital tissues
T3b	Total tumor removal is possible only with enucleation, exenteration
T4	Unresectable tumor due to extension into craniofacial structures or brain
N0	No lymph node metastasis
N1	Lymph node metastasis present
M0	No metastasis
M1	Metastasis present

Logistic and financial difficulties are a hurdle in seeking timely help for malignancies. Before referral to subspeciality practitioners, there had been misdiagnoses in 19% and inappropriate management in 24%. We found that the delay to first consultation and loss to followup were similar in patients from within the city versus out-station patients. Patients were motivated to travel a mean of 115.2 km for specialty treatment. This knowledge can help future planning of subspecialty services in ophthalmology.

The strength of the study is that it is a multi-zonal, multicentric study, including both urban and rural patients, and including AJCC classification. The authors follow similar patterns of evaluation, documentation, management, and follow-up protocol as mentioned in the methods section. This permits homogeneity in data collection. The weakness of the study is that the pathologic evaluations of the tumors were performed at different locations, and may not have been uniform. This study is a retrospective, hospital-based study, and subject to the limitations of design. We cannot comment on the incidence or prevalence of the disease conditions from this study. In future, a national registry of ocular oncology-pathology may help in a prospective study of such disease.

Conclusion

In conclusion, this study offers a representative look at the mix of eyelid malignancies in India, the severity of presentation and outcome. The proportion of SGC is high, and this is the single largest risk factor for poor outcome.

Conflicts of interest

There are no conflicts of interest.

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