

Ocular sebaceous gland carcinoma in Northern India: Clinico-pathological features and treatment outcome

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Abstract

Purpose: The objective of this study was to analyze clinical presentation, histopathological spectrum and outcome of ocular sebaceous gland carcinoma in a teaching hospital.

Materials and Methods: This prospective study was carried out at the Ocular oncology and Oculoplasty Unit, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi from March 2014 to February 2016. 34 patients with suspected sebaceous gland carcinoma were enrolled from outpatient department. All patients were admitted to ward and underwent detailed history, clinical, radiological evaluation and necessary laboratory investigations. In each case incisional/excisional biopsy were taken to study the histopathological characteristics. All patients were treated either surgically or non-surgically by single ocular oncologist. Pre and post treatment clinical photographs were taken to compare structural outcome and for purpose of documentation. Data were recorded in predesigned proforma and analyzed for demographic profile, clinico-pathological characteristics and outcomes by using SPSS 16 program.

Results: Out of total 34 patients of SGC, 73.53% were females. The age range of patients was 46–82 years. The mean age of presentation was 55 years. Most frequent site of origin was the eyelid (94.12%) followed by cruncle (5.88%). Upper eyelid was the most frequently affected site (41.18%) followed by lower lid (29.41%). The medial canthus and lateral canthus were the least involved (11.76% each). Maximum duration of lesion was more than three years. The most common clinical presentation was painless mass, nodular type (82.35%) and ulcero-nodular type (17.65 %). Severe degree of mechanical ptosis was observed in 29.41% cases. Regional lymph node were involved in 20.59% patients. In 8.82% cases preauricular lymph nodes were involved in the post-excisional period. The distant metastasis was observed in three cases. 23.53% patients had tumor diameter <10 mm, 47.06% had 10 to 20 mm while in 29.41% cases tumor diameter exceeded 20mm. Histopathologically majority were well differentiated type (44.12%) however 29.41% were poorly/ undifferentiated type. 35.29% patients underwent primary surgical excision with plastic reconstruction and 23.53% received neoadjuvant systemic chemotherapy followed by surgical excision while three patients of advanced stage refused surgery and were treated by palliative chemotherapy/ radiotherapy. There was recurrence in 23.53% cases. Three patients died due to distant metastasis.

Conclusion: Sebaceous gland carcinoma is slow growing malignancy, commonly occurring in upper eyelid. Nodular type is the most common presentation and well sebaceous differentiation was the commonest histopathological pattern. Its treatment is essentially surgical. Duration of lesion, tumor diameter and histological differentiation are important prognostic factors.

Keywords: Lid reconstruction, Mebomian gland carcinoma, Metastasis, Pagetoid spread, Pre auricular lymph node, Sebaceous carcinoma.

Introduction

Sebaceous gland carcinoma (SGC) are relatively rare and slow growing but aggressive and most lethal/dangerous eyelid tumor due to its capability to mimic inflammatory conditions such as chalazion, blepharitis or chronic conjunctivitis and leading to delay in diagnosis, high incidence of metastasis, difficulty in delineating tumor margins because of multi-centric origin / pagetoid spread.

SGC was first described by Allaire (1891), it accounts for less than 1% of all cutaneous malignancies.⁽¹⁾ 3/4th of all SGC occur in periocular area.^(2,3) SGC usually arises from Mebomian gland, gland of Zies and sebaceous glands of eyelid and other periocular structures such as caruncle, conjunctiva, eyebrow and lacrimal gland.⁽⁴⁻⁶⁾ It has predilection for upper eyelids and more commonly seen in women around 6-7th decades.^(7,8) SGC is a disease of unknown etiology but reported risk factors includes advanced age,

women, ethnicity of population, Muir-Torre Syndrome (MTS), previous irradiation to head and neck, HIV, HPV, RB and p⁵³ mutation.⁽⁹⁻¹²⁾ Incidence rate of SGC is higher in Asian population (Chinese 39%, Japanese 37.5%, Indian 31.5% and Singapore 10.2%) than Caucasians (1-5.5%).^(7,13-17) The demonstration of overexpression of p⁵³ protein suggests a possible role of UV radiation and tumorigenesis.⁽¹⁸⁾

Definitive diagnosis of SGC is only by histopathology.⁽¹⁹⁾ Primary, wide surgical excision (at least 4mm healthy margin) with intraoperative Frozen section or Moh's microscopic surgery with lid reconstruction by various surgical techniques, is recommended for localized SGC. Orbital exenteration, chemotherapy and radiotherapy may be required for extensive lesions. In case of lymph node metastasis radical neck dissection is necessary.⁽²⁰⁻²³⁾ The overall mortality rate in SGC is reported to be 5-10%.⁽²⁴⁾ Recurrence are seen in 9-36% cases⁽²⁵⁻²⁷⁾ while

metastasis (14-28%) occurs in lymph nodes and hematogenous spread in liver, lung, brain and bone.^(4,28,29) The factors associated with poor prognosis include long duration of lesion (>6months), involvement of both eyelids, large tumor (>10mm), lymphovascular infiltration, orbital invasion, multicentric origin, intraepithelial /pagetoid spread and poorly differentiated carcinoma.⁽⁴⁾

This was a prospective, interventional and non-comparative study, conducted over a period of two years, in a teaching hospital. This study is focused on clinical and pathological presentation and treatment outcome of SGC in this part of country.

Materials and Methods

This prospective, interventional clinical study was carried out at the unit of Ocular Oncology and Oculoplasty, Department of ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi from March 2014 to February 2016. All consecutive cases of ocular SGC that reported to eye out patient department of SS Hospital were included in this study. Some patients were referred from dermatology OPD. Ethical clearance was obtained from Institute Ethical Committee. A total 34 patients, who gave informed consent and completed the study with complete examination, biopsy proven and under regular follow up to six months were included in the study. The patients whose biopsy was not conclusive, left against medical advice, lost to follow up or never reported back after referral were excluded from the study. The selected patients were admitted to eye ward for detailed workup.

In each case a complete medical and surgical history was taken, ocular examination including location, extent and clinical appearance of the lesion was done. The routine haematological investigations (complete blood check-up, platelet count, blood urea, serum creatinine, LFT), radiological investigations like X-ray PNS, CT Scan /MRI were performed as per need. Diagnosis was confirmed preoperatively by excisional/ incisional biopsy (histopathology), imprint cytology or fine needle aspiration cytology of lymph node. Patients were staged according to TNM staging classification. A preoperative photograph was taken.

Treatment of SGC involved a multimodal approach, using primary wide surgical excision, keeping a safe margin of 2-4 mm normal and lid reconstruction with help of grafts/ flaps, radiotherapy and chemotherapy (5FU + Cis platinum). Post treatment follow-up was done at one week, one months every three month for one year and six monthly thereafter to assess the functional and cosmetic outcome and complications / recurrence.

All data were recorded for each patient on a prevalidated proforma and statistical analysis was performed on computer using SPSS -16 program where

data were analyzed for sex distribution, age of presentation, location, size and appearance of tumor and clinical staging, histological grading, treatment procedure and outcome and complications/ recurrence.

Results

A total of 34 patients were recruited in this study, out of which 25 (73.53%) were females and rest 9 (26.47%) were males. The mean age of presentation was 58 years (range: 46-82 years). The mean age amongst male and female was almost the same. There was no evident left-sided or right sided preference amongst tumors. Location wise distribution of ocular SGC indicates eyelid as the most common site being affected (N=32, 94.12%) followed by caruncle (N=2, 5.88%)[Fig. 1]. Upper eyelid was the most frequently affected site (N=14, 41.18 %) [Fig. 2] followed by lower lid (N=10, 29.41%). The medial canthus and lateral canthus were the least involved (N=4, 11.76% each) [Table 1 & Fig. 3]. The mean duration of symptom was 9 months (range 4-38 months).Maximum duration of lesion was more than three years. The most common clinical presentation was painless mass, nodular type (N=24, 82.35%) followed by ulcero-nodular type (N=6, 17.65%) and diffuse lid thickening (N=4, 11.76%) [Fig. 1]. Severe degree of mechanical ptosis was observed in 10 (29.41%) cases [Table 1]. Other associated complaints included itching, discharge from eye and local redness. At the time of diagnosis, 23.53% patients had tumor diameter <10 mm, 47.06% had 10 to 20 mm while in 29.41% cases the tumor diameter exceeded 20 mm[Table 2]. On histopathological examination, majority were well differentiated type (44.12%) however 29.41% were poorly/ undifferentiated type [Table 3]. Regional lymph nodes were involved in 20.59% patients[Fig. 4]. In 8.82% cases preauricular lymph nodes were involved in the post-excisional period. The distant metastasis was observed in three cases. 35.29% patients underwent primary surgical excision with plastic reconstruction and 23.53% received neoadjuvant systemic chemotherapy [Fig. 5] followed by surgical excision while three patients of advanced stage refused surgery and were treated by palliative chemotherapy/ radiotherapy [Table 4]. Surgical methods used included wide excision with lid reconstruction either by direct closure or by using cutler beard/ tarso-conjunctival flap/ tanzel rotational flap technique [Fig. 6]. The rate of follow-up was 76.47% at 6 months, 17.65% at 1 year and 5.88% at 2 years. 76.47% patients had complete response. There was recurrence in 23.53% cases. Three patients died due to distant metastasis [Table 5].

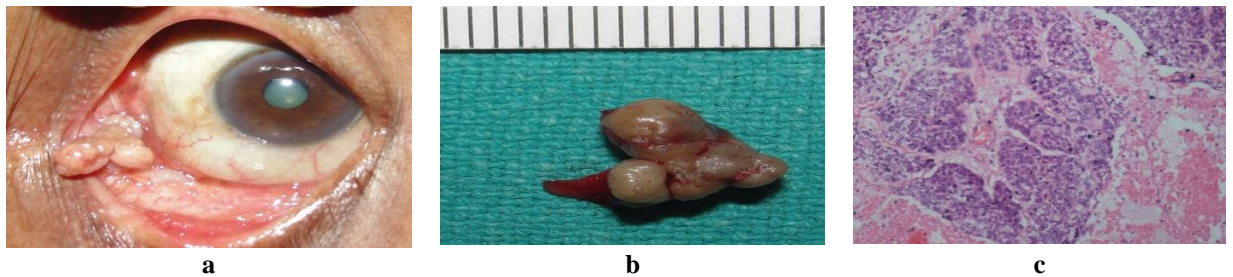


Fig. 1: (a) Photograph showing SGC of Caruncle (b) Macroscopic appearance of tumor (c) Microphotograph (100X, H&E staining) showing monomorphic malignant cells with sebocytic differentiation

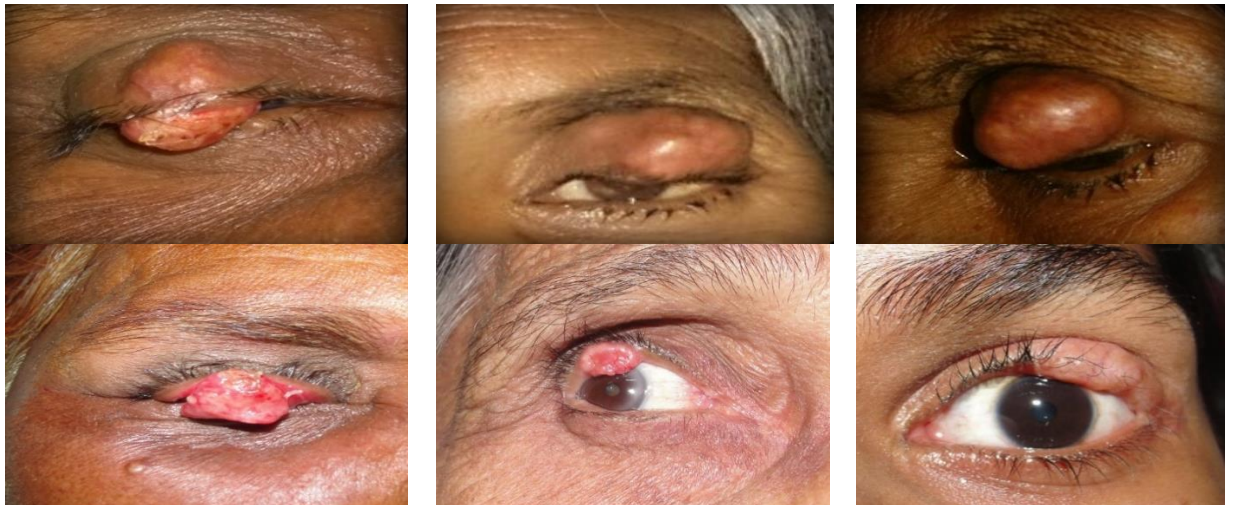


Fig. 2: Photographs showing upper eyelid Sebaceous gland carcinoma. Nodular type (upper rows), Ulcero-nodular type (left two, lower row) and Diffuse thickening type (right, lower row)

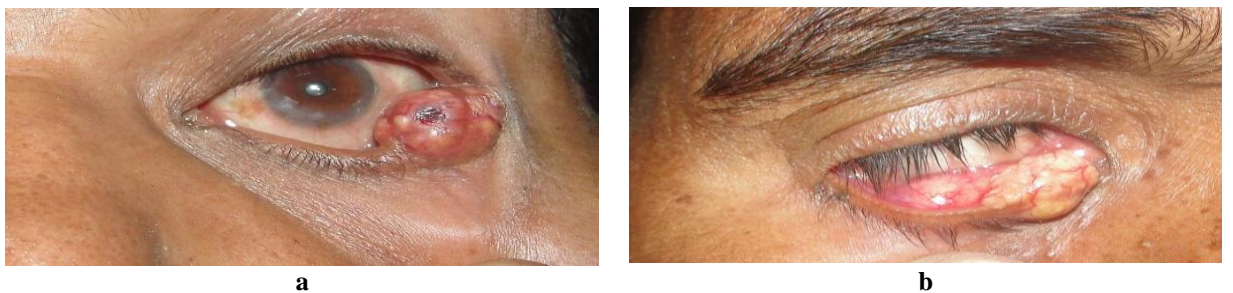


Fig. 3: Photographs showing SGC involving lateral canthus (a) and medial canthus (b)



Fig. 4: Photographs of 55 years female patient showing nodular type SGC of right eye lateral canthus with submandibular lymph node metastasis

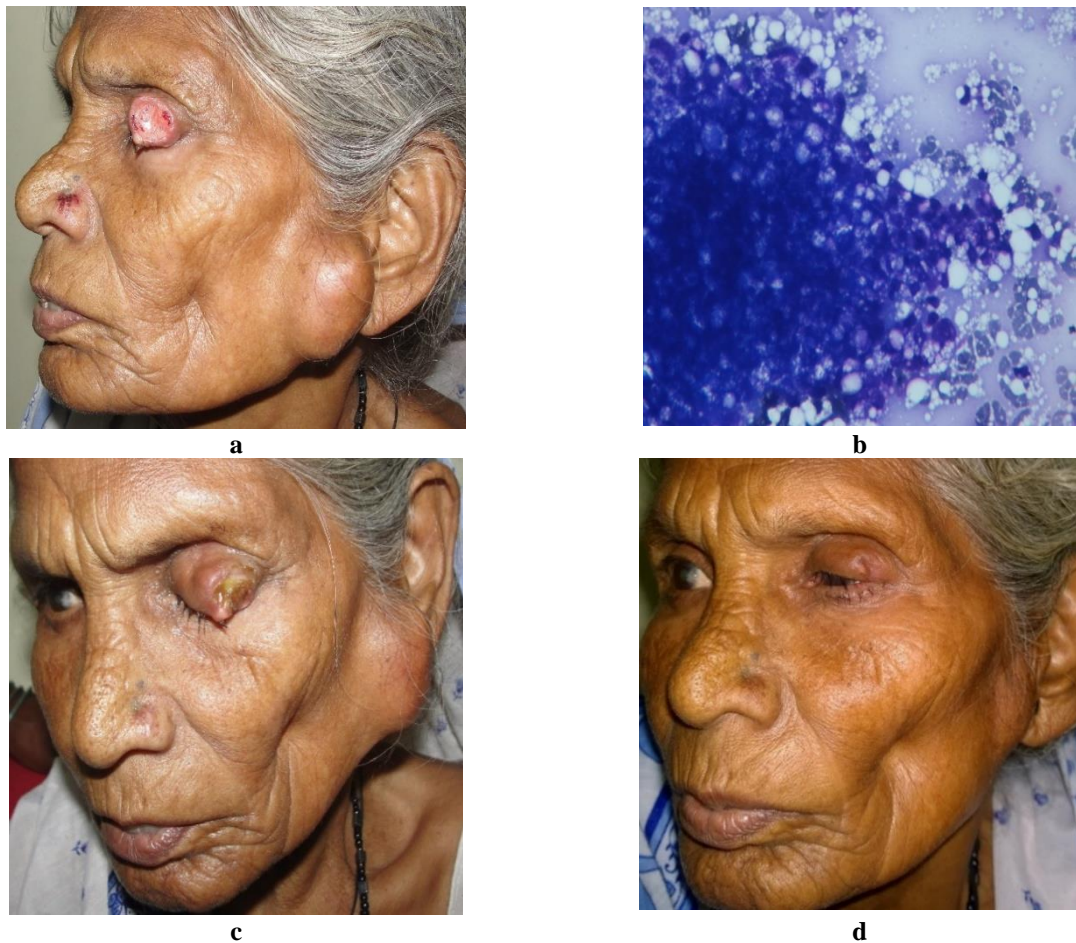
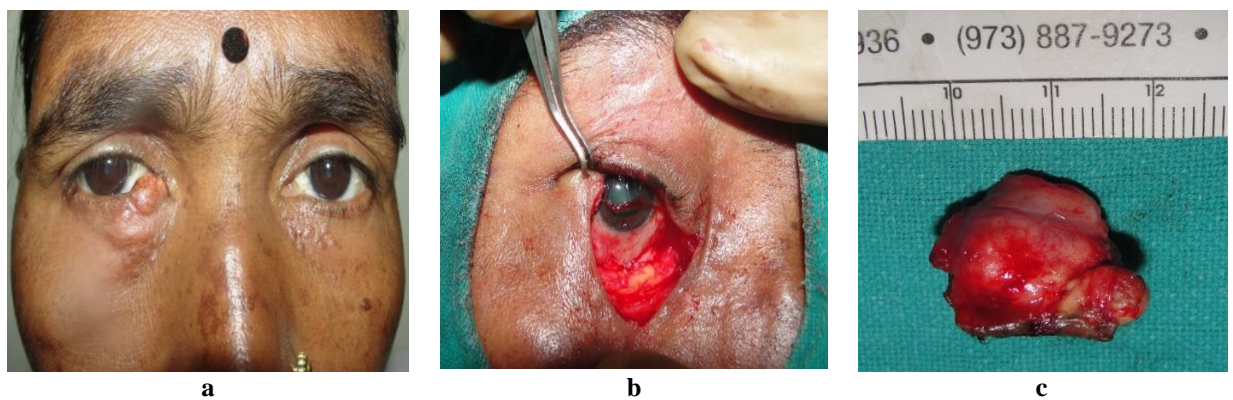


Fig. 5: (a) Clinical photograph of 80 years female patient showing ulcero-nodular type SGC of left upper eyelid with preauricular lymph node metastasis (b) Microphotograph of FNAC specimen of sebaceous cell carcinoma showing monomorphic malignant cells with sebocytic differentiation at places (100X, Giemsa stain) (c & d) Post Chemotherapy (Cis-Platinum + 5FU) photograph after 1st cycle (c) and after 2nd cycle (d).



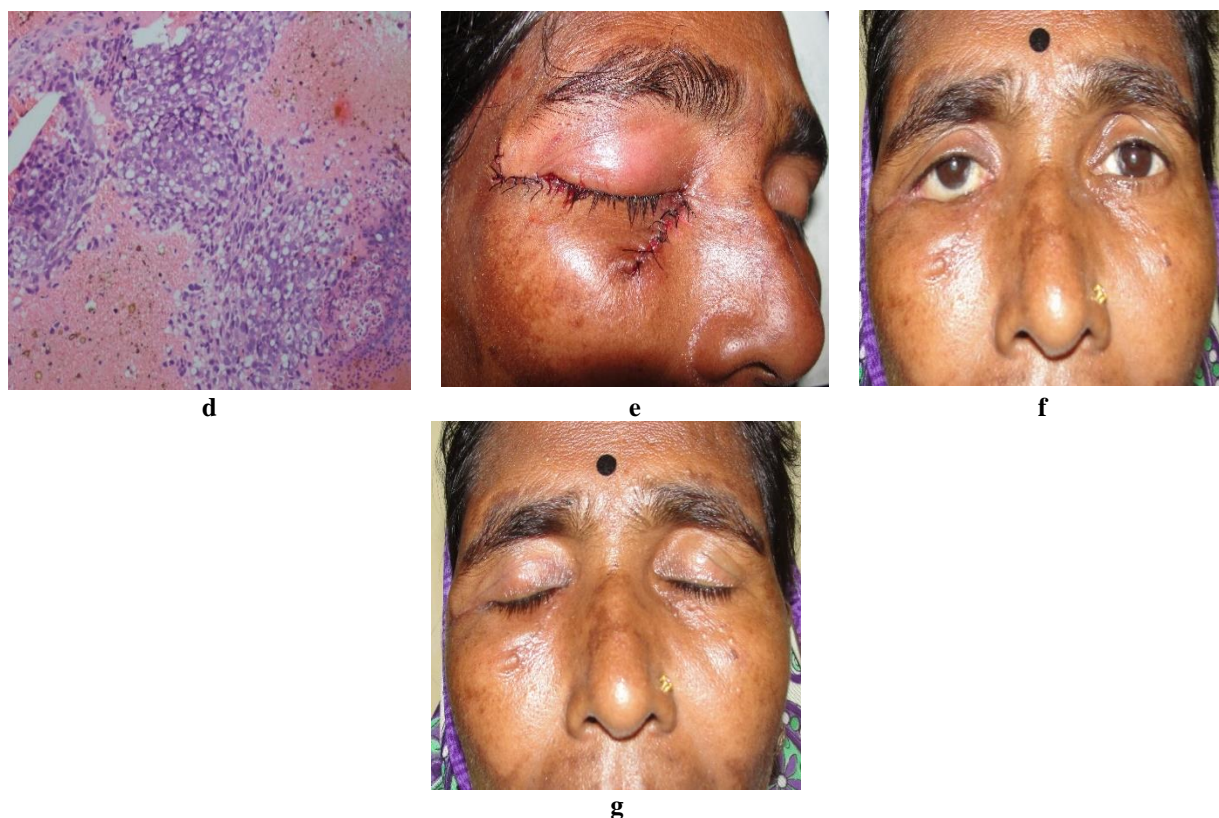


Fig. 6: (a) Preoperative clinical photograph of 48 years female showing large nodular type of SGC of right eye lowerlid involving medial canthus (b) Primary surgical excision, defect showing loss of 2/3rd eyelid (c) Macroscopic appearance of tumor showing nodular surface (d) Microphotograph of sebaceous cell carcinoma showing monomorphic malignant cells with sebocytic differentiation at places.(200 X, H&E staining)(e) Immediate post operative picture showing lid reconstruction was done by tanzel rotational flap.(f & g) Clinical photograph one month after operation

Table 1: Characteristics of the patient

Characteristics	No	%
Gender		
Male	9	26.47
Female	25	73.53
Age Group (Yrs)		
46-55	4	11.76
56-65	6	17.65
66-75	14	41.18
76-85	10	29.41
Laterality		
RE	18	52.94
LE	16	47.06
BE	Nil	-
Tumor Location		
Upper Lid	14	41.18
Lower Lid	10	29.41
Medial Canthus	4	11.76
Lateral Canthus	4	11.76
Caruncle	2	5.88
Presenting Signs		
Nodular mass	24	70.59
Ulcer-nodular	6	17.65

Diffuse Lid Thickening	4	11.76
Mechanical ptosis	10	29.41
Loss of eyelashes	28	82.35

Table 2: Distribution according to Size of Tumor

Largest Diameter of Tumor	No	%
< 10 mm	8	23.53
10-20mm	16	47.06
>20mm	10	29.41

Table 3: Distribution According to Degree of Differentiation

Type of Histological Differentiation	No	%
Well Differentiated type	15	44.12
Moderately Differentiated type	9	26.47
Poorly/ Un Differentiated	10	29.41

Table 4: Primary Management

Primary Treatment	No	%
Primary Surgical Excision	12	35.29
Neoadjuvant Chemotherapy + Surgery	8	23.53
Surgical debulking + Chemotherapy	6	17.65
Surgical debulking + Chemotherapy + EBRT	5	14.71
Palliative Chemotherapy + EBRT	3	8.82

Table 5: Tumor outcomes in 34 patients with Sebaceous carcinoma

Tumor Outcomes		No	%
Local Outcome	Complete Regression	26	76.47
	Recurrence	8	23.53
Regional Outcome	No Lymph node Metastasis	27	79.41
	Lymph node Metastasis	7	20.59
Systemic Outcome	No distant Metastasis	31	91.18
	No distant Metastasis	3	8.82
Final Outcome	Alive	31	91.18
	Death due to metastasis	3	8.82

Discussion

Majority of our patients were females similar to other major reviews^(3,4,26,30) in contrast to Dasgupta T et al who reported slight male predominance.⁽¹⁹⁾ Doxanos et al also reported male predominance in his review of 40 cases.⁽²⁸⁾ Jameel A et al reported a case of lower eyelid SGC in young male patient.⁽³¹⁾ In our study about 70% patients were above 65 years which is supportive of other studies who reported tumor in advanced age.⁽³⁾ SGC arises two to three times more frequently in upper than in lower eyelid due to abundant meibomian glands in upper eyelid. Several authors reported SGC in lower eyelid.⁽³¹⁻³³⁾ In our study upper lid was the most frequently affected site (48.18%) followed by lower eyelid (29.41%). The medial canthus and lateral canthus were least involved (11.76% each). This mimics most of the studies.^(4,34) SGC has varied clinical presentation and often misdiagnosed as inflammatory benign condition. One must always suspect SGC in a case of recurrent chalazion with loss of eye lashes, superior limbic kerato conjunctivitis and unilateral blpharitis/blepharoconjunctivitis not responding to treatment. The most common clinical presentation of SGC is insidious onset, very slow growing, painless erythematous/yellowish nodular or ulceronodular mass. The nodular type of SGC appears as hard, discrete, immobile multiple nodules. In our study nodular type (70.59%) was the

commonest clinical type followed by noduloulcerative type (17.65%) and third commonest presentation was blepharoconjunctivitis type (diffuse thickening with loss of eyelashes) in 11.76%.

SGC is an aggressive and locally invasive tumor. Though the tumor histopathologically mimics with BCC and SCC but unlike single origin of other tumors, SGC has multicentric origin. In order to determine the extent of the disease, conjunctival map biopsy are advocated, due to its tendency of patchy epithelial involvement with skip areas.⁽³⁵⁾ Unlike radial spread of BCC and SCC, superficial intraepithelial spread or pagetoid infiltration of conjunctival epithelium or skin epidermis are the histopathological hallmarks of SGC. Pagetoid infiltration results loss of eye lashes, eyelid deformity or distortion. SGC may be mistaken for carcinoma in-situ.^(20,36) Pagetoid invasion is one of the important prognostic factor. Other poor prognostic factors are local and distant metastasis, tumor diameter >10mm and poor histological differentiation.⁽⁴⁾ Bonuik and Zimmerman reported local metastasis in 17% cases.⁽³⁷⁾ Carcinoma can spread through direct, lymphatic or hematogenous route. Most common site of local metastasis are orbit, preauricular lymph nodes, parotid, submandibular and cervical lymph nodes.⁽³⁸⁾ Nunery et al reported rare local metastasis in parotid salivary gland.⁽³⁹⁾ Common site of distant metastasis are liver, lung, skull and brain.^(30,35,37) In our study majority (76.47%) of patients had tumor diameter >10mm. Review of literature shows metastasis rate between 14-25%.^(4,28,29) We observed lymph node metastasis in 20.59% cases and poor histopathological differentiation in 29.41% cases. Rao et al reported that poor histopathological differentiation was associated with high mortality rate. Worse prognosis was associated with advanced stage tumor (TNM stage III to IV). Esmali B et al reported five year disease specific survival rate between 79 to 97%.⁽⁴⁰⁾

Conclusion

Sebaceous gland carcinoma is slow growing malignancy, commonly occurring in upper eyelid. Nodular type is the most common presentation and well sebaceous differentiation was the commonest histopathological pattern. Its treatment is essentially surgical. Duration of lesion, tumor diameter and histological differentiation are important prognostic factors. Another study with a larger sample size and longer follow up period may validate these results.

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