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Neoadjuvant chemotherapy for advanced eyelid and periocular sebaceous gland carcinoma: a study of 25 cases

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Purpose To report the outcomes of platinum-based neoadjuvant chemotherapy (NACT) for eyelid and periocular sebaceous gland carcinoma (eSGC). **Methods** Retrospective study of 25 patients. **Results** The mean age at presentation of eSGC was 59 years. The mean tumor basal diameter was 46 mm. By the 8th edition of AJCC classification, tumors belonged T2 (n = 2, 8%), T3 (n = 6, 24%), and T4 (n = 17, 68%); N1 (n = 12, 48%); and M1 (n = 1, 4%). NACT with 5-fluorouracil (5-FU) and cisplatin/carboplatin was administered in 21 (84%)/4 (16%) patients, respectively. The mean number of cycles of neoadjuvant systemic chemotherapy per patient was 2 (median, 3). The mean percentage reduction of tumor basal volume after neoadjuvant chemotherapy was 65% (median, 60%). After NACT, 12 (48%) patients underwent surgical treatment, 6 (12%) patients underwent EBRT, and 4 (8%) underwent adjuvant chemotherapy. A total of 11 (44%) patients were lost to follow-up during the course of treatment, of whom 3 died from metastatic disease. In 16 patients followed up for ≥ 3 months, complete tumor control was achieved in 11 (69%) patients, local tumor control in 14 (88%), and globe salvage in 7 (44%) at a mean follow-up of 25 months (median, 7 months; range, 3 to 110 months). No tumor recurrence was seen in any case. One (4%) serious adverse event of cardiotoxicity was noted. **Conclusion** Platinum-based NACT is a suitable option for eSGC with advanced tumors and locoregional metastasis. Adverse events are rare and in patients compliant with treatment, NACT-based combination therapy offers globe salvage and systemi

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Neoadjuvant chemotherapy for advanced eyelid and periocular sebaceous gland carcinoma: a study of 25 cases

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Abstract

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3 died from metastatic disease. In 16 patients followed up for ≥ 3 months, complete tumor control was achieved in 11 (69%) patients, local tumor control in 14 (88%), and globe salvage in 7 (44%) at a mean follow-up of 25 months (median, 7 months; range, 3 to 110 months). No tumor recurrence was seen in any case. One (4%) serious adverse event of cardiotoxicity was noted.

Conclusion Platinum-based NACT is a suitable option for eSGC with advanced tumors and locoregional metastasis. Adverse events are rare and in patients compliant with treatment, NACT-based combination therapy offers globe salvage and systemic tumor control.

Keywords Eye · Tumor · Eyelid · Sebaceous carcinoma · Neoadjuvant chemotherapy · Platinum-based

Introduction

Eyelid and periocular sebaceous gland carcinoma (eSGC) is the most common eyelid malignancy in most Southern and Southeast-Asian countries such as India, Sri Lanka, Nepal, and Japan [1–4]. It is the 2nd most common malignant eyelid tumor after basal cell carcinoma in China and Korea [6–8], and the 3rd most common in Caucasians [9]. It is a complex disease to treat owing to its propensity for pagetoid spread, locoregional extension, lymph node

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Table 1 Neoadjuvant chemotherapy for inoperable eyelid and periocular sebaceous gland carcinoma: Demographics

Feature	N (%)
Age at presentation (years)	59 (60, 36–78)
Mean (median, range), (years)	
Sex	
Male	8 (32)
Female	17 (68)
Eye affected	
Right eye	10 (40)
Left eye	15 (60)
Duration of symptoms (months)	32 (24, 2 to 240)
Mean (median, range)	
Symptoms	
Mass	24 (96)
Eyelid deformity	13 (52)
Pain	7 (28)
Decreased vision	7 (28)
Protrusion of the eye	7 (28)
Watery	7 (28)
Ptosis	6 (24)
Discharge	6 (24)
Redness	2 (8)
Prior intervention (Excisional biopsy)	3 (12)
Referral diagnosis	
Sebaceous gland carcinoma	5 (20)
Squamous cell carcinoma	2 (8)
Basal cell carcinoma	1 (4)
Carcinoma	1 (4)
Granuloma	1 (4)
Lag time from symptom onset to first treatment (months)	15 (12, <1 to 65)
Mean (median, range)	
Lag time from diagnosis of SGC to referral (months)	9 (3, <1 to 26)
Mean (median, range)	

SGC = sebaceous gland carcinoma

metastasis, and distant metastasis [10, 11]. Greater than 50% of the tumors in India present beyond the T2 stage (8th edition of AJCC classification). [1, 2]

The management becomes challenging when tumors are not amenable to resection, when the surgical morbidity is high, and in the presence of locoregional or systemic metastasis. Options for patients with advanced tumors and locoregional metastasis are limited to anthracycline or platinum-based neoadjuvant chemotherapy (NACT), external beam radiotherapy (EBRT), and immunotherapy with PD-1 inhibitors [1, 2, 9]. Traditionally considered radioreistant, the role of EBRT for large eSGC is equivocal

[12–14]. Immunotherapy with pembrolizumab has shown promise in reports from Caucasian populations with eSGC [15, 16], but the cost and availability limit its use in developing countries. Thus, the most feasible options narrow down to NACT. Although initial evidence on NACT for eSGC dates back to 1985 [17], there have been sparse subsequent reports in this field over the last five decades [18–22]. Our initial experience in 10 cases has shown promising results with the use of NACT in extensive eSGC [21]. Herein, we present an extended series of 25 patients treated with NACT and discuss the outcomes and challenges with treatment.

Table 2 Neoadjuvant chemotherapy for inoperable eyelid and periocular sebaceous gland carcinoma: Clinical features

Feature	n = 25 n (%)
Tumor epicenter	
Upper eyelid	14 (56)
Lower eyelid	8 (32)
Medial canthus	2 (8)
Lateral canthus	1 (4)
Tissues involved	
Upper eyelid	19 (76)
Lower eyelid	16 (64)
Both eyelids	10 (40)
Lateral canthus	11 (44)
Medial canthus	6 (24)
Caruncle	8 (32)
Lid margin	22 (88)
Conjunctiva	25 (100)
Tumor morphology	
Nodular	15 (60)
Noduloulcerative	4 (16)
Fungating	3 (12)
Cystic	2 (8)
Diffuse	1 (4)
Tumor diameter (mm)	46 (45, 20 to 100)
Mean (median, range)	
Associated features	
Loss of lashes	17 (68)
Meibomian gland orifice effacement	16 (64)
Tarsal fixity	22 (88)
Skin fixity	14 (56)
Multicentricity	5 (20)
Orbital extension	21 (84)
T stage	
T2	2 (8)
T3	6 (24)
T4	17 (68)
N	
N0	13 (52)
N1	12 (48)
M	
M0	24 (96)
M1	1 (4)

T =Tumor; N=lymph node; M=distant metastasis

Methods

This was a retrospective interventional study approved by the Institutional Review Board. The study adhered to the tenets of the Declaration of Helsinki. An electronic medical record search was performed to identify patients of eSGC between June 2002 and January 2018. Digital records and copies of physical records were reviewed to identify patients who were treated with NACT. Patients who were treated with NACT or EBRT a priori were excluded.

Demographics, clinical features, treatment, and outcomes were reviewed. Demographic details included age, gender, laterality, symptoms, previous interventions, and referral diagnosis. Data on clinical features such as tumor epicenter, tissues involved, eyelid changes, extension to adjacent structures, and details of radiological imaging were extracted from the records. The 8th edition of the American Joint Committee for Cancer (AJCC) stage [23], treatment modalities administered, their chronological sequence, and adverse effects were reviewed for all patients.

NACT was recommended for patients with advanced tumors and/or with lymph node and distant metastasis. The indications included (i) tumors with orbital extension (8th edition, AJCC T4 stage) where an eyelid-sparing orbital exenteration could not be performed without using a free flap for socket reconstruction, (ii) tumors with orbital extension where patients declined orbital exenteration, (iii) tumors with massive eyelid involvement where wide local excision would leave a tissue defect too large for reconstruction with local myocutaneous flaps (8th edition, AJCC T3 stage) and (iv) tumors of any T stage in the presence of metastatic disease. Broadly, the treatment protocol constituted NACT for 3- 4 cycles followed by surgical resection (tumor excision/ orbital exenteration) of residual disease. EBRT was recommended in the presence of orbital or regional extension at presentation, residual disease following surgical resection, and for lymph node metastasis. Adjuvant chemotherapy for three cycles was advised based on the extent of residual, lymph node and systemic disease.

Treatment outcomes included local tumor control, local recurrence, systemic disease control, chemotherapy-related adverse effects, development of new metastasis, and death. Data was entered in Microsoft

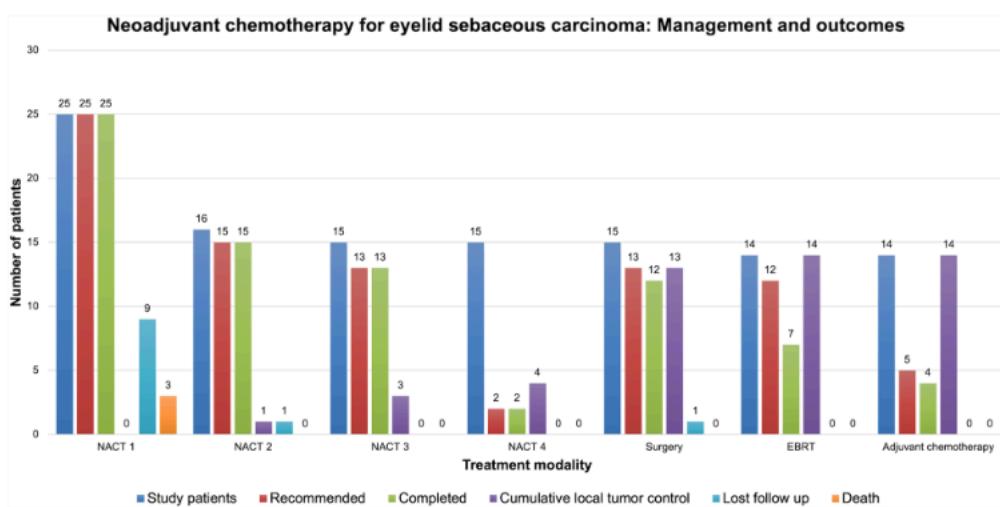


Fig. 1 Neoadjuvant chemotherapy for sebaceous gland carcinoma: management and outcomes. NACT = neoadjuvant chemotherapy; EBRT = external beam radiotherapy

Excel for Mac. Continuous data was expressed as mean, median, and range, and categorical data was expressed as proportions.

Results

Twenty-five patients were included in the study. The mean age at presentation was 59 years (median, 60 years; range, 36 to 78 years). The male-to-female ratio was 8:17. The right eye was affected in 40% and the left in 60%. The most common symptom was eyelid mass ($n=24$, 96%), and the mean duration of symptoms was 32 months (median, 24 months; range, 2 to 240 months). Three patients had recurrent tumors after prior surgical excision, and the rest were all primary tumors. The mean lag time from onset of symptoms to first treatment was 15 months (median, 12 months; range, <1 to 65 months). The demographic details are summarized in Table 1.

The most common tumor epicenter was the upper eyelid ($n=14$, 56%). The mean basal diameter of tumors was 46 mm (median, 45 mm, range, 20 to 100 mm). Tumors involved the upper eyelid, lower eyelid, both eyelids, lateral canthus, medial canthus, caruncle, lid margin, and conjunctiva in 76%, 64%,

40%, 44%, 24%, 32%, 88%, and 100% of the cases, respectively. Involvement of conjunctiva, orbit, lacrimal drainage system, and maxillary sinus was noted in 25 (100%), 20 (80%), 1 (4%), and 1 (4%) patients, respectively. By the 8th edition of AJCC classification, tumors belonged to T2 ($n=2$, 8%), T3 ($n=6$, 24%), and T4 ($n=17$, 68%) categories. At presentation, locoregional lymph node metastasis was present in 12 (48%) patients and systemic metastasis in 1 patient (Table 2). Both patients who belonged to stage T2 had lymph node metastasis, hence NACT was preferred to wide local excision. Histopathology was consistent with sebaceous gland carcinoma in all cases (100%), which was well differentiated in 28%. The most common histomorphology was the lobular pattern (64%).

NACT with 5-fluorouracil (5-FU) and cisplatin was administered in 21 (84%) patients, and 5-FU with carboplatin in 4 (16%) patients. The patients received a mean number of 2 cycles (median, 3; range, 1 to 4) of neoadjuvant systemic chemotherapy, and the mean percentage reduction of tumor volume after neoadjuvant chemotherapy was 65% (median, 60%; range, 20% to 100%). Following NACT, adjuvant therapy was warranted in the form of wide local excision with margin clearance by frozen sections in 7 (28%) patients, orbital exenteration in 5 (20%), 6 (12%)

Table 3 Neoadjuvant chemotherapy for inoperable eyelid and periocular sebaceous gland carcinoma: Pathology, management and outcomes

Feature	n (%)
Tumor differentiation	
Well differentiated	7 (28)
Moderately differentiated	2 (8)
Poorly differentiated	4 (12)
Growth pattern	
Lobular	16 (64)
Comedo	2 (8)
Mixed	4 (16)
Papillary	1 (4)
Pagetoid spread	9 (36)
Perineural invasion	1 (4)
Perivascular invasion	1 (4)
NACT regime	
5 FU and cisplatin	21 (84)
5 FU and carboplatin	4 (16)
Number of NACT cycles	2 (3, 1–4)
Mean (median, range)	
% reduction in tumor volume	64 (60, 20–100)
Mean (median, range)	
Adjuvant treatments	
Wide local excision under frozen section control	7 (28)
Orbital exenteration	5 (20)
External beam radiotherapy, orbit	4 (16)
External beam radiotherapy, neck	3 (12)
Adjuvant chemotherapy	4 (16)
Adverse effects of NACT	
Anemia	1 (4)
Pancytopenia	3 (12)
Cardiomyopathy	1 (4)
Outcomes (n=25)	
Mean duration of follow up (median, range) (months)	4 (16, 1 to 110)
Local tumor control	14 (56)
Globe salvage	9 (36)
Systemic tumor control	11 (44)
Tumor recurrence	0 (0)
Metastasis	1 (1)
Disease-related death	3 (12)
Outcomes (n=14, follow up ≥ 3 months)	
Mean duration of follow up (median, range) (months)	25 (11, 7 to 110)
Local tumor control	14 (88)
Globe salvage	7 (44)
Systemic tumor control	11 (69)
Tumor recurrence	0 (0)
Metastasis	1 (7)
Disease-related death	0 (0)

NACT = neoadjuvant chemotherapy; 5 FU = fluorouracil

patients underwent EBRT, and 4 (8%) underwent adjuvant chemotherapy (Fig. 1).

Notably, a total of 11 (44%) patients were lost to follow-up during the course of treatment (Fig. 1). Of these, three were confirmed to have succumbed to the disease. All these 3 patients had metastatic disease at presentation. However, among the patients ($n=16$) who were followed up for ≥ 3 months, a complete response of the local tumor and metastatic disease was achieved in 69%, a complete response of local tumor alone in 88%, and globe salvage in 44% (Table 3) patients. Among 12 patients with lymph node metastasis at presentation, clinical regression of the nodes was seen in 8, 3 died from disease, and one was lost to follow-up after two cycles of NACT (Supplemental Table 1). Of the three patients with recurrent eSGC, tumor control was achieved in 2 (67%), and one patient was lost to follow-up after one cycle of chemotherapy.

One (4%) serious adverse event of cardiotoxicity and reversible myocardial ischemia was noted. The patient was treated in conjunction with an internist, and coronary angiography subsequently showed normal cardiac perfusion. He refused further chemotherapy and was treated with orbital exenteration in view of progressive disease (Fig. 3). Other less serious adverse effects included anemia and pancytopenia, which warranted blood transfusions, and patients recovered well subsequently.

Discussion

The introduction of chemotherapy for the treatment of cancer in the late twentieth century rendered cancer a ‘curable’ disease, in stark contrast to the previously popular treatments such as surgery and radiotherapy, for which cure rates never rose beyond a third of treated patients [24]. Over the years, the horizons of chemotherapy expanded from being an adjuvant treatment modality to the primary treatment modality in advanced cancers of the breast, cervix, colon, esophagus, stomach, lung, nasopharynx, ovary, pancreas, prostate and the head and neck [24]. NACT has become the norm in advanced head and neck cancers, and the practice is spilling over into the management of advanced periocular cancers, including eSGC. [25]

The use of NACT for advanced eyelid sebaceous cell carcinoma has been explored to a limited extent,

with initial reports demonstrating its use in rendering inoperable tumors amenable to exenteration [17–19]. Subsequent reports depict globe salvage and excellent aesthetic outcomes in addition to tumor control due to the remarkable reduction in tumor size [20–22]. The sparsity of reports on the NACT for eSGC can be explained in part by a survey conducted by Cheung et al. on the practice patterns of oculoplastic surgeons treating SGC. In this survey, only 22% preferred to attempt globe salvage with NACT in patients with advanced eSGC, 11% preferred primary NACT for locally advanced non-metastatic eSGC, and 8% opted for NACT for recurrent tumors. Surgical treatment was the most common preferred primary modality for locally advanced eSGC and recurrent eSGC.

The underlying reason for the advanced presentation of eSGC and the eventual need for NACT is the delay in diagnosis due to its seemingly innocuous presentation [26, 27]. This cohort of patients experienced symptoms for a mean duration of 15 months before seeking any form of treatment. Even after diagnosis of eSGC, the time to referral to our center was a mean of 9 months, accounting for a mean cumulative lag time of 24 months. Awareness about the disease among ophthalmologists and medical practitioners is crucial to reduce this lag time and facilitate early referral.

With extensive disease manifesting with multicentricity, orbital extension, and metastases, tumor control cannot be achieved with surgery alone. The primary advantage of NACT is low or no surgical morbidity, with globe preservation in some instances. It also has the hypothetical benefit of reducing micrometastasis and can also tackle systemic disease [17–22]. In our previous cohort of 10 patients treated with NACT for eSGC, 90% were alive, and globe salvage was possible in 70% at a mean follow-up period of 18 months. [21] Verma et al. reviewed 8 cases receiving NACT for eSGC and reported a survival rate of 70% and a globe salvage rate of 40% over 45 months follow-up period. [22]

In the current series, the local tumor control rate was 88%, with globe salvage at 44%. In 75% of cases with positive cervical lymph nodes at presentation, a regression of lymph node metastasis was seen, and an excellent response to NACT was noted in 66% cases with recurrent eSGC. Thus, NACT is beneficial in eSGC patients with advanced disease, tumor

Fig. 2 A 63-year-old lady presented with a nodulo-ulcerative sebaceous gland carcinoma with submandibular lymph node metastasis (A, B). Following three cycles of neoadjuvant chemotherapy, the tumor reduced to trace thickening of eyelid margin (C, D). The lymph node metastasis also regressed. A wide local excision with margin clearance by frozen section followed by Cutler-Beard reconstruction was performed, and histopathology revealed no evidence of a residual tumor. Globe salvage was achieved (E, F)



recurrence following surgical excision, and those with locoregional metastasis.

Notably, there was significant attrition during the course of treatment, and this was maximal after the first cycle of chemotherapy. Nine patients did not follow up after the first treatment, and only 14 adhered to the treatment until the resolution of the disease (Fig. 1). While this is a limitation of this study, it allows introspection into one of the disadvantages of NACT, which is poor tolerance to treatment that can lead to non-compliance or refusal for further treatment. Several factors contribute to adherence to cancer therapy, and these include treatment-related toxicity, taxing treatment regimes, socioeconomic status, travel, education, and understanding about the disease and treatments [28]. Given the study's retrospective nature, these parameters could not be assessed in our cohort but warrant attention, especially with challenging treatment modalities. In the patients who were followed up, however, serious adverse events were rare, with one patient developing cisplatin-induced

cardiotoxicity that was reversible. Cisplatin is known to cause cardiotoxicity in 7–32% of patients and, if not detected in time, can result in permanent vascular damage and myocardial ischemia [29]. Concurrent monitoring with an internist is therefore recommended. Our patient who developed cardiotoxicity had no identifiable systemic predisposing factors.

Among nine patients who did not follow up after the first NACT, three were confirmed to have died from disease. Poor outcomes with patients refusing cancer treatment are well known [30]. While untreated cancers are usually uniformly fatal, a delay in surgery in patients who respond poorly to NACT has also been associated with poor outcomes in head and neck cancers [31]. In one patient in this series who deferred treatment after reversible cardiotoxicity, disease progression was noted (Fig. 3), and he was adequately counseled about the need for orbital exenteration. The outcomes of NACT and multimodal treatments for advanced eSGC depend not only upon the stage of the disease and treatment regimens but

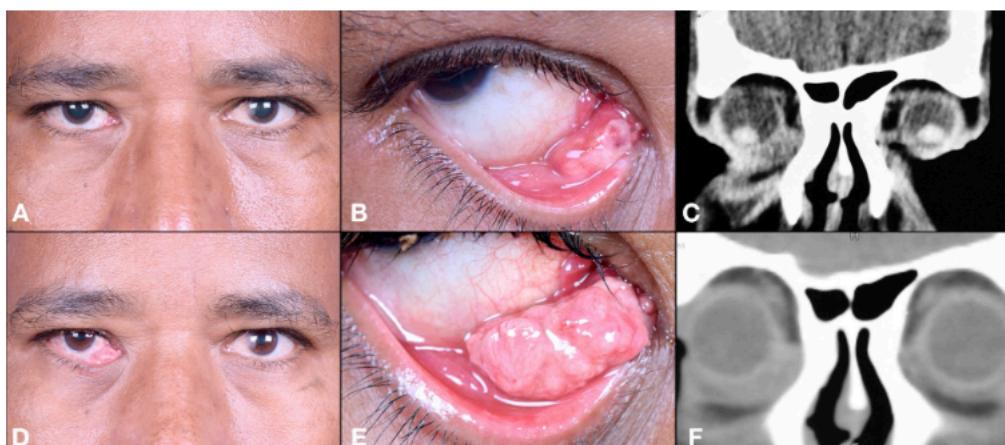


Fig. 3 A 50-year-old gentleman presented with a lesion on the medial aspect of the lower eyelid (**A, B**) with orbital extension (**C**) that revealed sebaceous gland carcinoma on incisional biopsy. Following one cycle of neoadjuvant chemotherapy, he developed cardiotoxicity and abandoned further treatment. He

returned with an enlarging tumor (**D, E**) with an orbital component (**F**). Orbital exenteration was performed, and adjuvant external beam radiotherapy was administered. He remained disease-free thereafter

also hugely upon treatment adherence, which can be a challenge.

In summary, the results of NACT for advanced eSGC are favorable in patients compliant with treatment. However, factors affecting attrition and refusal of treatment need to be further explored. Multicentric studies across the Asia–Pacific region where eSGC is a significant burden may offer additional insights into the outcomes and challenges with NACT.

Author Contribution Swathi Kaliki contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vijitha S. Vempuluru, Prema Sinha, Vishakha Tanna, and Yamini Maniktala. Vijay Anand Reddy Palkonda was involved with management of the cases. The first draft of the manuscript was written by Vijitha S. Vempuluru and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of LV Prasad Eye Institute.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the images in Figs. 2 and 3.

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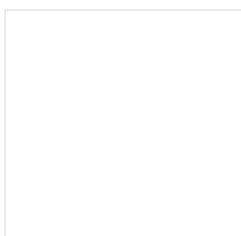
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There are sparse data on neoadjuvant systemic chemotherapy (NACT) in eyelid sebaceous gland carcinoma (SGC). The aim of this study was to evaluate efficacy and outcomes with NACT in eyelid SGC. We retrospectively analyzed 8 patients who received platinum-based NACT. The median number of cycles per patient was 4 (range, 3–5). The mean percentage reduction of tumor diameter after NACT was...

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To report the efficacy of neoadjuvant systemic chemotherapy in the management of eyelid sebaceous gland carcinoma (SGC). Retrospective study of 10 patients that received neoadjuvant systemic chemotherapy (Cisplatin/Carboplatin and 5-Fluorouracil) for eyelid SGC. The mean age at presentation of eyelid SGC was 58 years (median, 55 years; range, 45 to 72 years). There were 6 females and 4...

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A 40-year-old male presented with an orbital extension of conjunctival squamous cell carcinoma (SCC). The orbital mass was seen protruding outward from the left palpebral fissure overhanging the lower eyelid, completely obscuring the globe and lower lid. The patient gave a history of excision biopsy, which was histopathologically diagnosed as ocular surface squamous neoplasia. He also gave a history...

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Sebaceous carcinoma (SC) is an uncommon neoplasm manifesting itself either in the eyelid or extraocularly in the head and neck area. Surgery is the standard of care. Irradiation is rarely proposed as monotherapy but is frequently administered as an adjuvant regimen following surgical resection. There is no known strategy concerning chemotherapeutic treatment in highly aggressive recurrent - or...

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 Yasuyoshi Sato ·  Shunji Takahashi ·  Takashi Toshiyasu · [...] ·  Akihiro Homma

Eyelid squamous cell carcinoma is a major type of rare eyelid cancer, together with basal cell carcinoma and sebaceous gland carcinoma. It is a painless disease that progresses slowly and is often detected by the appearance of nodules or plaques. Risk factors include exposure to ultraviolet light, fair skin, radiation and human papillomavirus infection. The standard treatment is surgical removal, and in cases of...

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