Neoadjuvant Systemic Chemotherapy in the Management of Extensive Eyelid Sebaceous Gland Carcinoma: A study of 10 Cases

Swathi Kaliki, M.D., Anuradha Ayyar, M.D.*, Akshay G Nair, M.D.*, Dilip K Mishra, M.D.†, Vijay Anand P Reddy,*, and Milind N Naik, M.D.**

**Institute for Eye Cancer; and †Ophthalmic Pathology Service, L V Prasad Eye Institute, Hyderabad, India*

Purpose: To report the efficacy of neoadjuvant systemic chemotherapy in the management of eyelid sebaceous gland carcinoma (SGC).

Methods: Retrospective study of 10 patients that received neoadjuvant systemic chemotherapy (Cisplatin/Carboplatin and 5-Fluorouracil) for eyelid SGC.

Results: 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 males. The mean tumor basal diameter was 36 mm (median, 31 mm, range, 20 to 65 mm), with orbital tumor extension in 9 cases. On the basis of TNM Classification, the tumors were classified as T3 (n = 10), N1 (n = 6), and M1 (n = 2). The mean number of cycles of neoadjuvant systemic chemotherapy per patient was 3 (median, 3; range, 3 to 4). The mean percentage reduction of tumor basal diameter after neoadjuvant chemotherapy was 74% (median, 80%; range, 30% to 100%). None of them had any major systemic side-effects of neoadjuvant chemotherapy. Postchemotherapy, surgical treatment for residual tumor was performed in 7 cases. Five cases underwent excision biopsy and 2 cases with residual orbital component underwent eyelid-sparing orbital exenteration. No tumor recurrence was noted in any of the 7 cases at a mean follow-up period of 18 months (median, 14 months; range, 3 to 63 months). One patient died due to systemic metastasis.

Conclusion: Neoadjuvant systemic chemotherapy is effective and safe in the management of eyelid sebaceous gland carcinoma.

(*Ophthal Plast Reconstr Surg* 2015;XX:00–00)

Sebaceous gland carcinoma (SGC) is a potentially aggressive malignancy arising from the sebaceous glands. The head and neck region, particularly the eyelid is the most common site of SGC owing to the high density of sebaceous glands.[1] Sebaceous gland carcinoma is the most common eyelid malignancy in the Asian Indian population accounting for 28% to 60% cases,[2–4] while it is relatively uncommon in the western population accounting for only 4% to 5% of eyelid malignancies.[2]

Accepted for publication December 8, 2014.

The authors have no financial or conflict of interest to disclose.

Support provided by Operation Eyesight Institute for Eye Cancer (SK) and Hyderabad Eye Research Foundation (SK), Hyderabad, India. The funders had no role in the preparation, review or approval of the manuscript.

Address correspondence and reprint requests to Swathi Kaliki, M.D., Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad-500034, India. E-mail: kalikiswathi@yahoo.com

DOI: 10.1097/IOP.0000000000000398

The management of eyelid SGC depends on the tumor location, tumor extent, and the systemic status of the patient. Treatment options include wide excision biopsy under frozen section or Mohs microsurgery control and subsequent eyelid reconstruction for relatively small and well-defined lesions, cryotherapy and/or topical mitomycin-c for pagetoid tumor invasion of the conjunctiva, external beam radiotherapy for extensive eyelid lesions, orbital exenteration for those with orbital tumor extension or extensive involvement of the conjunctiva by pagetoid tumor spread, and observation for terminally ill patients with extensive systemic metastasis.[5–12] The use of systemic chemotherapy for eyelid SGC is sparsely described in the literature as isolated case reports.[13–16] Hereby, we describe our experience with the use of systemic intravenous chemotherapy in the management of eyelid SGC in 10 patients.

METHODS

A computerized database search was conducted for patients with a diagnostic coding of "eyelid sebaceous gland carcinoma (SGC)" from January 1, 2000 to April 30, 2014 at the Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India. Institutional Review Board approval was obtained. All medical records were reviewed to assess the primary treatment for SGC at our institute in each case. The patients who received neoadjuvant chemotherapy included those with extensive eyelid sebaceous gland carcinoma with/without orbital extension, the complete treatment of which would require orbital exenteration or more than 75% loss of eyelid tissue, and those with intact globe and useful vision. The patients who were fit for systemic chemotherapy with normal blood profile and renal function tests were selected for treatment with neoadjuvant chemotherapy. Neoadjuvant chemotherapy was given to avoid an orbital exenteration or allow an eyelid sparing orbital exenteration. All patients who received neoadjuvant systemic chemotherapy for SGC with follow-up visit for clinical evaluation during each cycle of systemic chemotherapy and on its completion were included in this study. The patients who were lost to follow up during the course of neoadjuvant chemotherapy were excluded.

The demographic data and details of history retrieved from the medical records included age at presentation (years), gender, affected eye, referral diagnosis, history of prior intervention, presenting complaints, and duration of symptoms (months). Best-corrected visual acuity was recorded. Tumor details including tumor epicenter (upper eyelid, lower eyelid, caruncle, only conjunctival), extent of tissue involvement by the tumor (eyelids, canthus, caruncle, conjunctiva, orbit, lacrimal system, para nasal sinuses, intracranial extension), gland of tumor origin (meibomian gland, Glands of Zeiss, sebaceous glands of caruncle, ectopic), largest tumor dimension (mm), lesion morphology (nodular, noduloulcerative, diffuse eyelid thickening, diffuse conjunctival lesion, fungating mass), and associated features (loss of eyelashes, intrinsic vascularity, overlying skin and underlying conjunctival changes) were noted. Photographic documentation was done in all cases. In those cases

TABLE 1. Neoadjuvant systemic chemotherapy for sebaceous gland carcinoma in 10 patients

Patient	Age (years)/ Gender	Tumor epicenter (eyelid)	Maximum basal dimension (mm)	Orbital tumor extension	TNM staging*	Indication of neoadjuvant chemotherapy	Chemotherapy regimen	Number of cycles of chemotherapy	Response to chemotherapy	Surgical intervention post-chemotherapy	Residual tumor on HPE	Adjuvant treatment	Final outcome at last follow up	Follow-up duration (months)
1	70/M	Upper	45	Yes	T3bN1M0	Group 2	Car+5-FU	4	Moderate	None†	na	None	Alive	4
2	55/F	Lower	30	Yes	T3bN1M0	Group 2	Car+5-FU	3	Moderate	Eyelid sparing orbital exenteration	Yes	EBRT-1	Alive	28
3	50/M	Upper	65	Yes	T3bN1M1	Group 2	Cis+5-FU	3	Moderate	None‡	na	EBRT-1	Dead	22
4	55/M	Upper	31	No	T3aN1M0	Group 1	Cis+5-FU	3	Good	Excision biopsy with local flaps/ grafts	No	EBRT-1	Alive	3
5	70/F	Upper	20	Yes	T3bN0M0	Group 2	Cis+5-FU	3	Good	Excision biopsy with local flaps/ grafts	Yes	EBRT-1	Alive	6
6	72/M	Upper	30	Yes	T3aN1M1	Group 2	Cis+5-FU	4	Good	None§	na	None	Alive	63
7	45/F	Lower	39	Yes	T3bN0M0	Group 2	Cis+5-FU	3	Moderate	Eyelid sparing orbital exenteration	Yes	EBRT-2	Alive	15
8	55/F	Upper	50	Yes	T3bN0M0	Group 2	Cis+5-FU	3	Good	Excision biopsy with local flaps/ grafts	Yes	None	Alive	5
9	50/F	Lower	30	Yes	T3bN0M0	Group 2	Cis+5-FU	3	Good	Excision biopsy with direct closure	Yes	EBRT-2	Alive	12
10	59/F	Lower	20	Yes	T3bN1M0	Group 2	Cis+5-FU	3	Good	Excision biopsy with direct closure	No	EBRT-1	Alive	18

*Based on American Joint Cancer Committee (AJCC) classification;

†Patient was advised orbital exenteration, but was lost to follow up.

‡ Patient was advised orbital exenteration but refused surgery and eventually died due to systemic metastasis.

§Patient was advised excision biopsy but the patient refused surgery because there was no clinical evidence of persistent tumor.

mm, millimeters; Group 1, to facilitate minimally invasive eyelid surgery; Group 2, to avoid orbital exenteration; HPE, histopathology examination; M, male; F, female; Mei, Meibomian gland; T, tumor size; N, lymph node; M, systemic metastasis; Car, carboplatin; Cis, cisplatin; 5-FU, 5-fluoro uracil; na, not applicable; EBRT-1, external beam radiotherapy to the orbit and regional lymph nodes; EBRT-2, external beam radiotherapy to the orbit.

with no visualization of posterior extent of tumor, CT of the orbit was performed. Locoregional lymph node examination was performed and in those cases with palpable lymph nodes, fine needle aspiration cytology was performed. Systemic metastatic workup was done with chest x-ray, ultrasound abdomen, and liver function tests. All tumors were retrospectively classified by TNM staging (Tx, 0, is, 1, 2, 3, or 4; N0 or 1; M0 or 1) based on 7th edition of American Joint Cancer Committee Classification.[17]

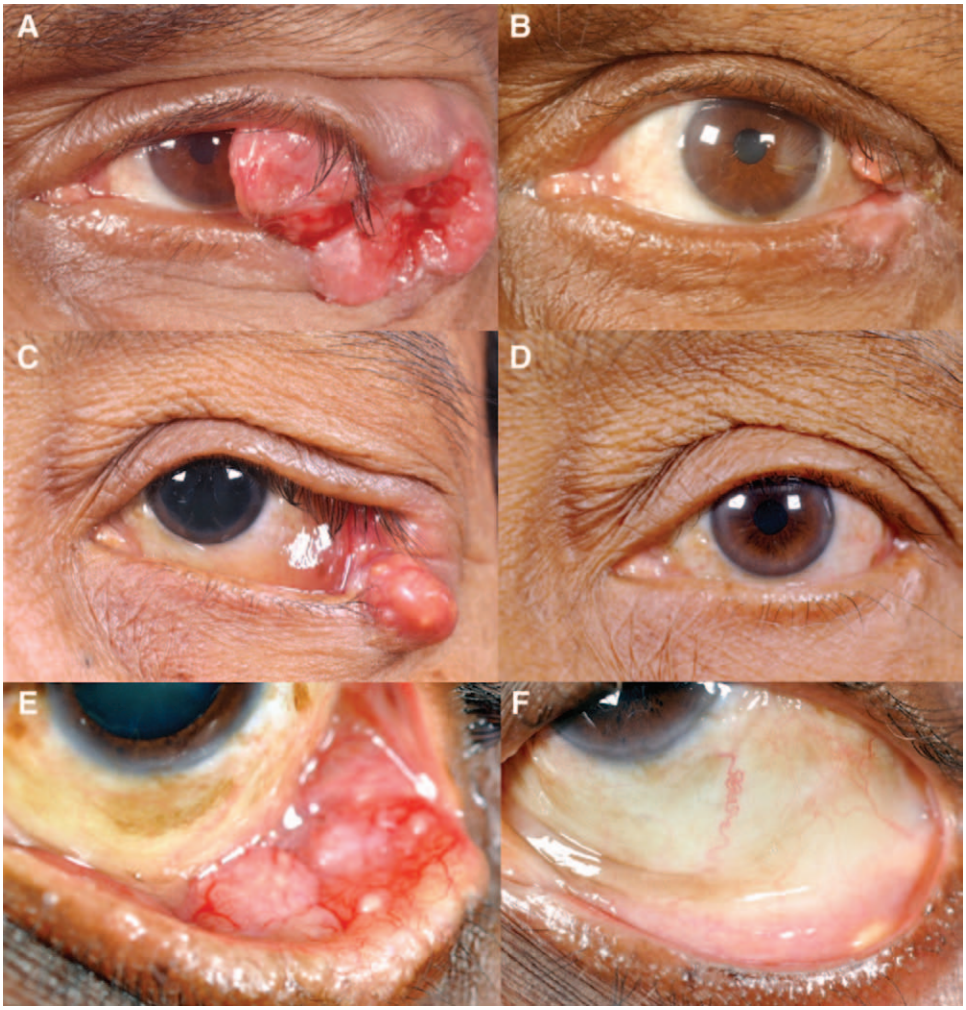
Prior to systemic intravenous chemotherapy, incisional biopsy from the tumor was performed to confirm the diagnosis of SGC by histopathology. Treatment details regarding systemic intravenous chemotherapy drugs, number of cycles, interval between each cycle (weeks), and side effects of chemotherapy were recorded. After each cycle of systemic chemotherapy, tumor details including largest tumor dimension (mm) and extent of tissue involvement by the tumor were noted. On the basis of the response to treatment, the tumor response was classified as good response (>75% reduction in tumor size and 100% reduction in orbital component), moderate response (50% to 75% reduction in eyelid tumor size and <100% reduction in orbital component), or poor response (<50% reduction in eyelid tumor size and <100% reduction in orbital component) to treatment. Cases with good response to neoadjuvant systemic chemotherapy were advised eyelid excision biopsy with wide margins under frozen section control, and those with moderate/poor response were advised orbital exenteration. Details of adjuvant treatment (external beam radiotherapy, radical neck dissection, adjuvant systemic chemotherapy) were noted.

Histopathology features (degree of differentiation, growth pattern, pagetoid spread, mitosis, perineural and/or perivascular invasion) were noted. The final outcome at last follow up (alive with disease, alive with no evidence of disease, dead due to disease, dead due to other causes) was recorded.

RESULTS

Of the 191 cases with eyelid SGC, 16 patients were advised neoadjuvant systemic chemotherapy. Of these 16 cases, only 10 cases were included in this study based on our inclusion criteria (Table 1).

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 males.



Neoadjuvant systemic chemotherapy for eyelid sebaceous gland carcinoma. A, A 55-year-old male with eyelid sebaceous gland carcinoma (SGC) involving both eyelids and lateral canthus (Case no. 4, Table 1). **B,** Tumor regressed following 3 cycles of neoadjuvant systemic chemotherapy facilitating wide excision biopsy of the lesion. There was fibrosis and lipogranuloma with no evidence of residual tumor on histopathology. **C,** A 50-year-old female with sebaceous gland carcinoma at lateral canthus extending into the orbit (Case no 9, Table 1) (**D**) showed good response to 3 cycles of neoadjuvant systemic chemotherapy with complete regression of orbital component. Excision biopsy of the residual lesion showed poorly differentiated SGC. **E,** A 59-year-old female with sebaceous gland carcinoma of the lower eyelid (Case no 10, Table 1) (**F**) showed good response to 3 cycles of neoadjuvant systemic chemotherapy with complete tumor regression. Excision biopsy of the suspected residual tumor revealed no evidence of residual tumor on histopathology.

The most common presenting complaint was appearance of an eyelid mass (n = 10). The mean duration of symptoms was 18 months (median, 17 months; range, 5 to 26 months). There was a previous history of excision biopsy in 6 cases. In these 6 cases, the time interval between prior excision biopsy and tumor recurrence was 11 months (median, 13 months; range, 1 to 26 months). All cases had massive eyelid lesion (largest tumor basal diameter ≥ 20 mm) on presentation with a mean tumor basal diameter of 36 mm (median, 31 mm, range, 20 to 65 mm). Tumor epicenter was located in upper (n = 6) or lower (n = 4) eyelid. Orbital tumor extension was evident in 9 cases. There were associated features of loss of eyelashes (n = 8), overlying skin fixation (n = 5), and underlying conjunctival involvement (n = 8). On the basis of TNM Classification, the tumors were classified as T3 (n = 10), N1 (n = 6), and M1 (n = 2).

The purpose of neoadjuvant chemotherapy was to facilitate minimally invasive eyelid surgery in 1 case (Fig. A) and to avoid orbital exenteration in 9 cases. All patients received a combination of cisplatin/carboplatin and 5-fluorouracil as neoadjuvant systemic chemotherapy every 3 weeks. On the basis of extrapolation of data from head and neck cancers, 3 cycles of neoadjuvant chemotherapy were planned in all cases, but the number of cycles was modified based on tumor response. The mean number of cycles of neoadjuvant systemic chemotherapy per patient was 3 (median, 3; range, 3 to 4). All patients except 2, received planned 3 cycles of neoadjuvant chemotherapy. Two patients received 4 cycles of chemotherapy as the tumor showed minimal tumor residue with 3 cycles, and the fourth cycle was given to achieve near total tumor regression with chemotherapy. The mean percentage reduction of tumor basal diameter after neoadjuvant chemotherapy was 74% (median, 80%; range, 30% to 90%). All patients had transient side-effects (nausea, vomiting, pancytopenia) with quick recovery, and none of them developed any major side-effects due to systemic chemotherapy. Postchemotherapy, surgical treatment for residual tumor was performed in 7 cases, while 3 cases were lost to follow up after neoadjuvant chemotherapy. Of these 3 patients lost to follow up, 1 patient had good response and was advised excision biopsy of the residual tumor, and 2 had moderate response and were advised orbital exenteration. Of those who underwent surgical treatment postchemotherapy, 5 cases had good response to treatment and underwent eyelid excision biopsy with wide margins under frozen section control and eyelid reconstruction (n = 5) and 2 cases with moderate response to treatment with residual orbital component underwent eyelid-sparing orbital exenteration (n = 2). Histopathology revealed residual tumor in 5 cases with tumor-free margins and 2 cases had no evidence of residual tumor. External beam radiotherapy to the orbit and/or regional lymph nodes was performed in 7 cases as adjuvant treatment. No tumor recurrence was noted in any patient at a mean follow up period of 18 months (median, 14 months; range, 3 to 63 months). Of the 3 cases with no surgical intervention, 1 case had good response, 1 had moderate response, and 1 had poor response to treatment. In this series, 1 patient with metastasis at presentation died due to systemic metastasis 19 months after completion of neoadjuvant chemotherapy.

DISCUSSION

Neoadjuvant chemotherapy for eyelid SGC could facilitate eyelid and globe preservation by significant tumor volume reduction, spare the patient from radical neck dissection in those with regional lymph node metastasis, lower the risk of systemic metastasis, and prolong the disease-free survival period. Neoadjuvant systemic chemotherapy downstages the disease and provides significant benefits of organ preservation, locoregional tumor control, lower risk of distant metastasis, and prolonged overall survival period.[18–22]

The standard chemotherapy agents used in the management of head and neck cancers are platinum-based agents (cisplatin/carboplatin) and 5-fluorouracil.[20,23–27] The other chemotherapy agents with beneficial effect in head and neck cancers include docetaxel, paclitaxel, leucovorin, and panitumumab.[20,23–30] With the encouraging results of the use of neoadjuvant systemic chemotherapy in the management of head and neck squamous cell carcinoma, similar treatment has been used for locally advanced eyelid and/or extraorbital SGC.[13–16,31,32] In our study, a combination of platinum-based agents (cisplatin/carboplatin) and 5-fluorouracil was used in all cases. The overall response rate following neoadjuvant chemotherapy in our series ranged from 30% to 100% with a complete response (with no evidence of tumor on histopathology) in 2 cases.

Several previous single case reports describe effective use of neoadjuvant chemotherapy in patients with advanced sebaceous carcinoma of eyelid (Table 2). In a previous report published in 1985 by Paschal and Bagley,[13] a combination of surgery, radiotherapy, and sequential combination chemotherapy was used to achieve complete tumor regression in a 48-year old patient. In another report by Priyadarshini et al.,[15] neoadjuvant

TABLE 2. Published reports on neoadjuvant chemotherapy for eyelid sebaceous gland carcinoma

Author (year of publication)	Number of patients	Age (years)/ Gender	Chemotherapy regimen	Number of cycles of neoadjuvant chemotherapy	Response to chemotherapy	Tumor recurrence at last follow up	Final outcome at last follow up	Follow-up duration (months)
Paschal BR et al (1985)[13]	1	48/M	5-fluorouracil Doxorubicin Cisplatin Vinblastine	7	Complete response*	No	Alive	4
Murthy et al (2005)[14]	1	55/F	Carboplatin 5-fluorouracil	3	Partial response	No	Alive	26
Priyadarshini et al (2010)[15]	1	35/M	Cisplatin 5-fluorouracil	1	Complete response	No	Alive	18
Gogia et al (2013)[16]	1	48/M	Cisplatin 5-fluorouracil	3	Partial response	No	Alive	10
Current study (2015)	10	58†/6F, 4M	Cisplatin/ Carboplatin 5-fluorouracil	3‡	Partial response (N=8) Complete response (n=2)	No	Alive (n = 9) Dead (n = 1)	18§

*Complete response was achieved after 2 sequential courses of chemotherapy and surgical intervention between the 2 courses of chemotherapy;
†Mean age at presentation;
‡Mean number of chemotherapy cycles;
§Mean follow-up period.

chemotherapy was used in a 64-year-old patient with recurrent SGC and regional lymph node metastasis who had complete response to 1 cycle of neoadjuvant chemotherapy without the need for surgical excision of eyelid tumor. Another report by Gogia et al.[16] described the use of neoadjuvant chemotherapy in a 48-year-old patient with eyelid SGC infiltrating the lateral rectus muscle, in which a lesser mutilating surgery could achieve tumor control, and thus avoiding orbital exenteration. Similarly, Murthy et al.[14] described the use of neoadjuvant chemotherapy in a 55-year-old patient with recurrent SGC and regional lymph node metastasis, which caused significant tumor volume reduction making eyelid-sparing orbital exenteration possible and sparing the patient from radical neck dissection. In our series of 10 cases, significant tumor volume reduction was achieved in all cases, facilitating a less mutilating surgery. Of the 10 cases who received neoadjuvant chemotherapy, 6 cases were suitable for eyelid excision biopsy (60%) and 4 cases for eyelid-sparing orbital exenteration (40%). However, only 5 cases underwent surgical excision biopsy and 2 cases underwent eyelid-sparing orbital exenteration. A tumor-free margin was achieved in all the 7 cases. Radical neck dissection for lymph node metastasis could be avoided in all those cases with preexisting lymph node metastasis (n = 6). Possible microscopic residual tumor in the orbit and lymph nodes was treated by adjuvant external beam radiotherapy. In our case series, neoadjuvant chemotherapy could potentially salvage eyelid, globe, and orbital contents in 60% cases and downstage the regional lymph node metastasis in 100% cases.

In this series, there was no evidence of tumor recurrence in any case, and disease-related mortality occurred in only 1 case. However, the follow-up duration is short with a mean follow-up period of 18 months, and 4 patients had a follow-up duration of less than a year. Long-term results in a larger group of patients are warranted.

In summary, neoadjuvant chemotherapy is a promising and safe treatment strategy for patients with locally advanced eyelid SGC providing adequate tumor volume reduction with additional benefit of locoregional tumor control. Additional studies with long-term results in a large cohort will assist in further defining the role and limitations of neoadjuvant chemotherapy in the management of eyelid SGC.

REFERENCES

1. Thomas WW, Fritsch VA, Lentsch EJ. Population-based analysis of prognostic indicators in sebaceous carcinoma of the head and neck. *Laryngoscope* 2013;123:2165–9.
2. Shields JA, Demirci H, Marr BP, et al. Sebaceous carcinoma of the ocular region: a review. *Surv Ophthalmol* 2005;50:103–22.
3. Abdi U, Tyagi N, Maheshwari V, et al. Tumours of eyelid: a clinicopathologic study. *J Indian Med Assoc* 1996;94:405–9, 416, 418.
4. Sihota R, Tandon K, Betharia SM, et al. Malignant eyelid tumors in an Indian population. *Arch Ophthalmol* 1996;114:108–9.
5. Dzubow LM. Sebaceous carcinoma of the eyelid: treatment with Mohs surgery. *J Dermatol Surg Oncol* 1985;11:40–4.
6. Harvey JT, Anderson RL. The management of meibomian gland carcinoma. *Ophthalmic Surg* 1982;13:56–61.
7. Snow SN, Larson PO, Lucarelli MJ, et al. Sebaceous carcinoma of the eyelids treated by mohs micrographic surgery: report of nine cases with review of the literature. *Dermatol Surg* 2002;28:623–31.
8. Tumuluri K, Kourt G, Martin P. Mitomycin C in sebaceous gland carcinoma with pagetoid spread. *Br J Ophthalmol* 2004;88:718–9.
9. Shields CL, Naseripour M, Shields JA, et al. Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid sebaceous gland carcinoma. *Ophthalmology* 2002;109:2129–33.
10. Shields JA, Shields CL, Demirci H, et al. Experience with eyelid-sparing orbital exenteration: the 2000 Tullos O. Coston Lecture. *Ophthal Plast Reconstr Surg* 2001;17:355–61.
11. Matsumoto CS, Nakatsuka K, Matsuo K, et al. Sebaceous carcinoma responds to radiation therapy. *Ophthalmologica* 1995;209:280–3.
12. Hata M, Koike I, Maegawa J, et al. Radiation therapy for primary carcinoma of the eyelid: tumor control and visual function. *Strahlenther Onkol* 2012;188:1102–7.
13. Paschal BR, Bagley CS. Sebaceous gland carcinoma of the eyelid: complete response to sequential combination chemotherapy. *N C Med J* 1985;46:473–4.
14. Murthy R, Honavar SG, Burman S, et al. Neoadjuvant chemotherapy in the management of sebaceous gland carcinoma of the eyelid with regional lymph node metastasis. *Ophthal Plast Reconstr Surg* 2005;21:307–9.
15. Priyadarshini O, Biswas G, Biswas S, Padhi R, Rath S. Neoadjuvant chemotherapy in recurrent sebaceous carcinoma of eyelid with orbital invasion and regional lymphandenopathy. *Ophthal Plast Reconstr Surg* 2010;26:366–8.
16. Gogia A, Pushker N, Sen S, et al. Avoidance of exenteration in orbital sebaceous gland carcinoma with neoadjuvant chemotherapy. *Graefes Arch Clin Exp Ophthalmol* 2013;251:2479–80.
17. Edge SB, Byrd DR, Compton CC, et al, eds. Carcinoma of the eyelid. In: AJCC *Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010:523–30.
18. Blanchard P, Baujat B, Holostenco V, et al.; MACH-CH Collaborative group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011;100:33–40.
19. Pignon JP, le Maître A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4–14.
20. Posner MR. Paradigm shift in the treatment of head and neck cancer: the role of neoadjuvant chemotherapy. *Oncologist* 2005;10 Suppl 3:11–9.
21. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;324:1685–90.
22. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091–8.
23. Lewin F, Damber L, Jonsson H, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: a randomized phase III study. *Radiother Oncol* 1997;43:23–8.
24. Dalley D, Beller E, Aroney R et al. The value of chemotherapy (CT) prior to definitive local therapy (DTL) in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). *Proc Am Soc Clin Oncol* 1995;14:297.
25. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst* 1994;86:265–72.
26. Domenge C, Lancar R, Coche-Dequeant B et al. Induction chemotherapy before radiotherapy in oropharyngeal carcinoma. *Eur J Cancer* 1995;31A (Suppl 5):S86.
27. Depondt J, Gehanno P, Martin M, et al. Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology* 1993;50 Suppl 2:23–7.
28. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol* 2013;14:697–710.
29. Parthan A, Posner MR, Brammer C, et al. Cost utility of docetaxel as induction chemotherapy followed by chemoradiation in locally advanced squamous cell carcinoma of the head and neck. *Head Neck* 2009;31:1255–62.
30. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006;24:2644–52.
31. el Nakadi B, Nouwynck C, Salhadin A. Combined therapeutic approach for extraorbital sebaceous carcinoma in a Torre's syndrome. *Eur J Surg Oncol* 1995;21:321–2.
32. Orcurto A, Gay BE, Sozzi WJ, et al. Long-term remission of an aggressive sebaceous carcinoma following chemotherapy. *Case Rep Dermatol* 2014;6:80–4.

