Int Ophthalmol (2019) 39:1187–1197
https://doi.org/10.1007/s10792-018-0925-z

REVIEW

Ocular sebaceous gland carcinoma: an update of the literature

Maria Vittoria Cicinelli · Swathi Kaliki

Received: 9 December 2017 / Accepted: 13 April 2018 / Published online: 25 April 2018

Abstract
Purpose To review and summarize the newest update on ocular sebaceous gland carcinoma (SGC) focusing on diagnosis and treatment.
Methods A PubMed search was carried out using the terms "Sebaceous Carcinoma", "Meibomian Gland Carcinoma", "Sebaceous Cell Carcinoma", and "Sebaceous Gland Carcinoma". All studies published in English up to October 2017 were included in this review.
Results Globally, the overall incidence of SGC is increasing making it the third most common eyelid malignancy after basal cell carcinoma (BCC) and squamous cell carcinoma. The mainstay of treatment of ocular SGC is wide surgical resection under frozen section or Moh's micrographic surgery control followed by eyelid reconstruction. Based on histopathological features, SGC can be classified according to growth pattern, cell type, and cytoarchitecture. Based on the growth pattern, they can be classified as trabecular, lobular, papillary, and BCC-like. The cell type can be classified as basaloid, basosquamous, and epidermoid. The SGC cytoarchitecture presents either as a nodular or as an infiltrative lesion. Based on immunohistochemistry, the overexpression of ZEB2, BAG3, androgen receptor, and C-erbB-2 oncoprotein is associated with poor prognosis. The tumor is associated with systemic metastasis in 8–14% and death in 10–30%.
Conclusion Ocular SGC is an aggressive tumor associated with poor prognosis. Early identification and appropriate treatment may help improve the prognosis. New insight into its pathogenesis and the immunohistochemical profile may lead to the development of new effective treatment strategies, along with traditional therapies.

Keywords Eye · Eyelid · Tumor · Sebaceous gland carcinoma · Meibomian gland carcinoma · Eyelid tumor · Ocular oncology

M. V. Cicinelli · S. Kaliki (✉)
The Operation Eyesight, Universal Institute for Eye Cancer (MVC, SK), L V Prasad Eye Institute, Hyderabad 500034, India
e-mail: kalikiswathi@yahoo.com

Introduction

First described by Allaire in 1891, sebaceous gland carcinoma (SGC) is a highly malignant and potentially lethal tumor of sebaceous glands [1, 2]. High recurrence rates and tendency for local spread and distant metastases make correct diagnosis and prompt appropriate treatment extremely important for these patients [3]. Mean delay from onset of the lesion to diagnosis still ranges from 1 to 2.9 years [4]. However, progressive education about this disease has reduced the mortality rate from 50% to around 2–10%, according to more recent reports [5, 6]. The aim of

this review is to give the newest update on this disease entity, focusing on diagnosis and treatment.

Literature search

A PubMed engine search was carried out using the terms "Sebaceous Carcinoma", "Meibomian Gland carcinoma", "Sebaceous Cell Carcinoma", and "Sebaceous Gland Carcinoma". All studies published in English up to October 2017, irrespective of their publication status, were included in this review.

Epidemiology

SGC represents 1–3% of all malignant tumors and 0.6–10.2% of eyelid tumors [7]. Such a large range is explained by the different prevalence of SGC among different ethnicities. SGC is more common in the Chinese and Japanese, followed by the Indian and Singapore population [8–13]. In India, SGC represents nowadays the most common malignant ocular lesion (37%), followed by SCC (21%) [14]. On the contrary, SGC accounts only for less than 1–5.5% of eyelid malignancies in Caucasians [1, 15].

The overall incidence of SGC is increasing significantly. In 2012, it was 3.2 (male) and 1.6 (female) per 1 million person/years, versus 1–2 cases per 1 million individuals/year estimated in 2009, making it the third most common eyelid malignancy after basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) globally [15, 16].

Clinical presentation

The tumor typically arises in the sixth–seventh decade of life (57–72 years), but cases in younger age groups have also been described [17, 18]. History of periocular irradiation represents a documented risk factor, while gender predilection is still an object of debate [5, 12, 19, 20]. Clinical associations with Muir–Torre syndrome (MTS) [21], immunosuppression [22], familial retinoblastoma [23], human immunodeficiency virus, and human papilloma virus infection have also been reported [24, 25].

According to the Surveillance, Epidemiology, and End Results (SEER) study from 2002 to 2012, SGC can be classified into two groups: ocular type and extraocular type [26]. Extraocular sites account for only a quarter of the cases of SGC, predominantly located in areas of skin covered by hair, such as the head, trunk, and genitalia [27, 28]. The analysis of extraocular phenotype is beyond the scope of this review.

Ocular SGC arises mainly from the Meibomian glands of the upper eyelid (39–50% of cases), due to the presence of a greater number of glands compared to the lower eyelid [15, 29]. It can also arise from the glands of Zeis of the eyelid margin (10%), at the caruncle (< 10%), or in the skin of the eyebrow; around 12% were multicentric with no obvious source of origin [30, 31]. The clinical appearance of ocular SGC is highly heterogeneous; it often mimics other ocular benign conditions, such as chalazion, posterior blepharitis, superior limbic keratoconjunctivitis, keratitis [32, 33]. SGC can be confused also with other malignancies, including SCC, BCC, or Merkel cell tumors.

Classically, this lesion appears as a firm, painless, indurated thickening of the eyelid, with a yellow hue due to the high concentration of intracellular lipids [34]. Upon eyelid eversion, the lesion appears as a multinodular protruding or fungating mass. Madarosis, unilateral blepharoconjunctivitis, forniceal shrinkage due to diffuse infiltration of the palpebral or the bulbar conjunctiva, and invasion of the cornea are generally associated with the intraepithelial spread of tumor cells.

Multiple SGCs represent a common feature of the MTS, an autosomal dominant condition characterized by sebaceous tumors (sebaceous adenoma, basal cell epithelioma with sebaceous differentiation, and sebaceous carcinoma) associated with gastrointestinal, endometrial, and urologic malignancies [21, 35, 36].

Tumor staging is assessed using the TNM (tumor node metastasis) definitions as provided by the American Joint Committee on Cancer (AJCC) recommendations [37]. The recent staging of SGC based on the eighth edition of AJCC classification is listed in Table 1 [37].

Histopathology

An eyelid biopsy should be executed in every suspected case of SGC, especially when associated with recurrent chalazion, eyelid thickening, lash loss, mass on lid eversion, or ulceration of the eyelid is present. The histopathological diagnosis of SGC is

Table 1 Definitions of TNM for eyelid carcinoma, AJCC cancer staging manual, eighth edition *Source*: [37]

Primary tumor (T), lymph node (N), systemic metastasis (M)	Definition
TX	Cannot assess the primary tumor
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor $\leq$ 10 mm in greatest dimension
T1a	No invasion of tarsal plate or eyelid margin
T1b	Tumor invades the tarsal plate or eyelid margin
T1c	Tumor involves full thickness of the eyelid
T2	Tumor $>$ 10 but $\leq$ 20 mm in greatest dimension
T2a	No invasion of tarsal plate or eyelid margin
T2b	Tumor invades the tarsal plate or eyelid margin
T2c	Tumor involves full thickness of the eyelid
T3	Tumor $>$ 20 but $\leq$ 30 mm in greatest dimension
T3a	No invasion of tarsal plate or eyelid margin
T3b	Tumor invades the tarsal plate or eyelid margin
T3c	Tumor involves full thickness of the eyelid
T4	Tumor invading ocular, orbital, or facial structures
T4a	Tumor invading ocular or intraorbital structures
T4b	Tumor with erosion of bony orbital walls, or those with paranasal sinus extension, or those invading lacrimal sac or nasolacrimal duct, or those invading the brain
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Lymph node tumor extension involving a single ipsilateral regional lymph node but $<$ 3 cm in greatest dimension
N1a	Metastasis based on clinical evaluation or imaging
N1b	Histopathology-proven metastasis
N2	Lymph node tumor extension involving a single ipsilateral regional lymph node but $>$ 3 cm in greatest dimension or involving bilateral or contralateral lymph nodes
N2a	Metastasis based on clinical evaluation or imaging
N2b	Histopathology-proven metastasis
M0	No distant metastasis
M1	Distant metastasis

challenging, and this lesion has been often misinterpreted as poorly differentiated SCC or BCC [3, 38].

SGC encompasses a broad variety of different features, ranging from well-differentiated sebaceous neoplasms to highly undifferentiated tumors. Foamy sebocyte-like cells with vacuolization of the cytoplasm represent the hallmark of well-differentiated lesions; these cells are mainly located in the center of the lobules with an outer zone of non-vacuolated, basaloid cells. On the contrary, poorly differentiated tumor cells are characterized by basophilic pleomorphic cells with prominent nucleoli, high number of mitotic figures, and degree of apoptosis. "Squared-off" or angulated nuclei, and so-called appliqué pattern, made of solid aggregations of necrotizing neoplastic cells in the periphery of the tumor, have also been described in 100 and 32% of periocular SGC, respectively [39].

Morphologically, SGC can be classified according to growth pattern, cell type, and cytoarchitecture. Four morphological patterns can be recognized at low magnification: trabecular, lobular, papillary, and

BCC-like; a combination of two or more of these patterns can be seen in a single lesion [40]. The lobular pattern, with variable size of lobules within the same tumor, is the most common [4, 40]. The lobules display no evidence of differentiating arrangements (i.e., the formation of lumens), and some of them surround areas of central necrosis (comedonecrosis), which correspond to foci of exaggerated holocrine secretion rather than true necrosis [42].

The three main cell types encountered in SGC are: basaloid, epidermoid, and basosquamous [41]. The basaloid type originates from the outer germinal cells of the secretory alveoli and shows a high nuclear-to-cytoplasmic ratio; it is the most common cell type in infiltrative lesions and the percentage of basaloid cells is inversely correlated with the level of differentiation. The epidermoid cell type displays scattered dyskeratotic cells or nonkeratinizing cellular whorls; the basosquamous cell type shows intermediate cytoplasmic features of the basaloid and epidermoid types.

Based on cytoarchitecture, SGC presents either as a nodular or as an infiltrative lesion [43–45]. The infiltrative spread, called "pagetoid", is characterized by malignant cells diffusion to the adjacent epithelium apparently separated from main tumor [6, 46].

Special stains and immunohistochemistry

Traditional stains, such as Oil Red O, Sudan IV, and Leu-m1, help in confirming the diagnosis of SGC. The major limitation of Oil Red O is that it relies on the availability of fresh frozen tissue, as intracellular lipids are dissolved during standard preparation of paraffin-embedded sections. Moreover, the Oil Red O staining is often negative in poorly differentiated lesions [38]. Based on these major flaws, immunostaining on paraffin-embedded sections has being looked at as a potential resource, especially in more undifferentiated tumors or in case of pagetoid spread (Table 2) [47–49].

SGC specific immunophenotype

Sebaceous lineage cells are related to the production of lipids (mainly triglycerides). The positivity of SGC for three proteins associated with lipid droplets, such as adipophilin (ADP), perilipin, and TIP47/PP17, has demonstrated high specificity (around 100%) and moderate sensitivity (8.3–77%) [50]. These molecules localize in the phospholipid monolayer membrane surrounding the intracytoplasmic triglyceride droplets. ADP detection seems to be the best method of proving sebaceous differentiation, while perilipin appears to be more specific but less sensitive [50, 51]. Positive reaction is defined by a vacuolar, vesicular-rimming pattern, while granular staining is considered non-specific. ADP staining intensity may vary throughout the different areas of the tumor, depending on cell differentiation grade, from fine non-vacuolar granular staining to complete immunonegativity [52].

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor family and are important mediators in epidermal growth, differentiation, and lipid metabolism. In a study of 31 SGC cases, immunohistochemical evaluation revealed nuclear overexpression of PPAR-γ in 87% of cases, with an inverse correlation between the degree of expression and tumor differentiation [53].

While perforin has shown contradictory results [54], nuclear factor XIIIa (AC-1A1) has been proved to be a sensitive and specific marker for sebaceous differentiation, with diagnostic utility exceeding that of ADP [55]. On the contrary, given to the ubiquity of cytokeratin (CK) in epithelial malignancies, attempts to employ these markers in SGC have not shown high reliability in the differential diagnosis [56–59].

SGC versus BCC and SCC

Poorly differentiated SGC can be distinguished from BCC and SCC by staining epithelial antigens. The two epithelial markers considered to be most useful in the differential diagnosis of SGC are the epithelial membrane antigen (EMA) and Ber-Ep4 [49, 60]. EMA is a cell membrane-associated glycoprotein first isolated in breast carcinoma cells, expressed in glandular structures and squamous epithelium, but not in follicular structures. EMA is prominently expressed in SGC and SCC, while being predominantly negative in BCC. Ber-Ep4 is a monoclonal antibody directed toward the epithelial cell adhesion molecule, expressed in the secretory portion of eccrine glands and follicular germinative cells in normal skin and eyelids. SGC and SCC are negative for Ber-Ep4 in 74–94 and 100% of cases, respectively, and, BCC shows immunostaining in 70–100% of cases [47, 48]. More recently, the terminal deoxynucleotidyl

Table 2 Immunoreactivity of sebaceous gland carcinoma

Author(s), year of publication	Sample size	CK	EMA	Perforin	Adipophilin	BerEP-4	AR	Factor XIIIa	Cam5.2
Ansai et al. [48, 58]	35	na	+	na	+	–	+	na	na
Jakobiec et al. [60, 73]	12	na	+	na	+	na	+	na	na
Mulay et al. [69, 74]	56	+	+	na	+	–	+	na	na
Plaza et al. [49]	27	na	+	na	+	–	±	–	na
Mittal et al. [54]	11	+	+	+	+	+	na	na	na
Schmitz et al. [52]	4	+	+	±	+	na	+	na	+
Tjarks et al. [55]	30	na	na	na	+	na	na	+	na

CK cytokeratin, *EMA* epithelial membrane antigen, *AR* androgen receptor, *na* not applicable, + positive reaction, ± weak reaction, − negative reaction

transferase (TdT), a DNA polymerase expressed in immature, lymphoid, or haematopoietic neoplastic cells and in neuroendocrine carcinoma, has been found only in cells with sebaceous cell differentiation, in comparison to BCC or SCC cells [61].

Genetic immunomarkers and prognostic implications

Recently, some authors have investigated the role of genetic aberrations as immunomarkers of SGC. The p53 transcription factor, which induces apoptosis when DNA damage occurs, is encoded by the onco-suppressor gene p53. Approximately 67% of SGC tumors harbor missense or nonsense mutations in this gene, and immunoreactivity has been reported in 50–100% of SGC cases [62, 63]. P53 overexpression has been advocated as a diagnostic clue in the differential diagnosis of SGC from benign sebaceous proliferation (11%), BCC (20%), and SCC (50–60%) [64–67]. Similar role has been attributed to p16 [67].

The fraction of Ki-67-positive tumor cells (called Ki-67 proliferation index, PI) of SGC has been estimated as 38–72%, a slightly higher value compared with other solid malignancies (25–50%) [68]. High Ki-67 PI correlates with a poor clinical outcome concerning tumor recurrence and regional lymph node metastasis [69].

High levels of the Bcl-2-associated athanogene 3 (BAG3) and ZEB2/SIP1 have been detected in SGC cases [70]. ZEB2 is a transcription factor related to the epithelial to mesenchymal transition phenomenon that represses the E-cadherin gene expression [71]. The presence of immunohistochemical overexpression of ZEB2, as well as loss of E-cadherin and CDH1 promoter methylation, has been correlated with major risk of lymph node metastasis, orbital invasion, large tumor size, advanced stage, and poorest survival. Multivariate analysis has shown that ZEB2 is the best poor prognostic indicator for eyelid SGC. Similarly, the overexpression of BAG3 has been related to the development of cancer, invasiveness, metastasis, angiogenesis, tumor adhesion, migration, and resistance to chemotherapy [72].

Hormonal immunophenotype

Hormonal panel has revealed immunostaining for estrogen, progesterone, and androgen receptors (AR), in 43, 26, and 81% of cases, respectively [73–75]. Immunoreactivity for these proteins provides a possible therapeutic opportunity for SGC in the future. Positive staining for AR has been found in a variable nuclear or cytoplasmic pattern of SGC cell, in particular in those tumors featuring a pagetoid spread [52]. This marker can be of particular help when differentiating SGC from SCC (predominantly negative, 90–100%) and BCC (occasionally positive, 50–86%) [73, 76]. Recently, it has been shown that a high AR score carries a greater risk of cancer recurrence after excision [69, 74]. Similarly, C-erbB-2 oncoprotein, an important oncogene in breast carcinoma, has been shown to be overexpressed in 85% cases of SGC, mostly associated with ERBB2 amplification detected by fluorescence in situ hybridization [77, 78].

Immunophenotype in syndromic SGC

The immunohistochemical screening for mismatch repair proteins (MMRP) aberration is an easy and convenient way to diagnose MST [79, 80]. This syndrome is caused by an autosomal dominant inherited defect in one of the genes encoding for MMRP, resulting in genomic microsatellite instability. A second hit somatic mutation or methylation suppression of the remaining functioning allele invariably leads to carcinogenesis [81]. Deficient immunohistochemical expression of MLH1, MSH2, MSH6, and PMS2 suggests an urgent counseling for hereditary neoplasia.

In conclusion, a panel of immunohistochemical stains is recommended in the diagnosis of SGC, as a specific combination of markers characterizes this entity. A potential stain panel to discriminate SGC from BCC is presented by EMA, Ber-Ep4, AR, and adipophilin, while to distinguish SGC from SCC, the expression of AR and adipophilin should be tested. Two other useful markers for the differential diagnosis are p53 and erb-b2, both of which will be predominantly immunopositive in SGC (Table 3).

Treatment

The mainstay of treatment of SGC is surgical resection followed by eyelid reconstruction [31, 82]. Careful analysis of the margins may be carried out with wide local excision (WLE) and frozen section or Mohs' micrographic surgery (MMS), although it might occasionally be complicated by the multifocal nature of the tumor [83–87]. A surgical margin of 5–6-mm in WLE and a 2-mm margin in MMS are recommended [88]. In the setting with no frozen section or MMS control, another useful management protocol for SGC is excision with 3- to 5-mm surgical margins, paraffin section control, and delayed reconstruction [29, 89, 90].

Table 3 Patterns of immunostaining of sebaceous gland carcinoma

	EMA	ADP	BerEP-4	AR	p53	ERBB2
SGC	+	+	−	+	+	+
BCC	−	−	+	±	±	−
SCC	+	−	−	−	±	−

SGC sebaceous cell carcinoma, *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma, *EMA* epithelial membrane antigen, *ADP* adipophilin, *AR* androgen receptor, + positive reaction, ± weak reaction, − negative reaction

Map biopsies should be taken from 17 sites: four clock hours of the limbus, three from the upper and lower forniceal conjunctiva, three from upper and lower tarsal conjunctiva, and one from the caruncle [91, 92]. After a complete review of all biopsies, pagetoid disease can be addressed with cryotherapy, mitomycin-C in cases with limited involvement and in cases with diffuse pagetoid spread or associated orbital involvement, and orbital exenteration may be indicated [93]. Obtaining clear margins is an important goal of orbital exenteration; clear margin status, however, is not always associated with lower risk of recurrence in patients with SGC and orbital invasion [94].

Different non-invasive imaging techniques have been used in the attempt to precisely localize the lesion, to exclude a potential orbital spread, to follow its progression, or some combination of these. Computed tomography is well tolerated, can be rapidly obtained at most medical centers, and gives clues to the specific diagnosis. Magnetic resonance imaging (MRI) signal intensity and pattern of contrast enhancement allow to distinguish between similar appearing lesions [95, 96]. Recently, advanced imaging techniques such as MRI diffusion-weighted imaging (DWI), 18-FDG-PET CT, and MRI PET are being used in the pre-therapeutic workup and monitoring of patients with eyelid and orbital malignancies, including SCG [97–99]. The DWI technique aids in the distinction of benign and malignant lesions by quantifying different apparent diffusion coefficient (ADC) thresholds and represents a promising tool in the correct staging of the disease [100].

Due to the tendency to give locoregional lymph node metastasis, the use of sentinel lymph node biopsy (SNLB) as a part of tumor staging has been advocated for this malignancy [101]. SLNB allows for the identification of micrometastases and influences the AJCC stage of the tumor as well as the treatment approach. The procedure is effective, reliable, and associated with very low risk (e.g., temporary weakness of the marginal mandibular branch of the facial nerve) [102].

SNLB or at least strict regional lymph node surveillance is recommended in patients with tumors

of 10 mm or more in greatest dimension. Radical neck dissection is indicated in SGC patients with regional lymph node metastases, followed by radiation therapy [103].

Radiation (50–66.6 Gy) administered as a primary treatment on the tumor site is effective in achieving a prolonged survival, a better tumor control, and a more cosmetic preservation of the eyelid, or as an adjuvant treatment following orbital exenteration [104, 105]. Adjuvant reirradiation with modest doses (30–45 Gy) may be considered in tumor recurrences to provide disease control and long-term survival [106, 107]. In very advanced cases with or without locoregional lymph node metastasis, neoadjuvant chemotherapy with 5-fluorouracil and carboplatin/cisplatin may allow local resection of advanced tumors otherwise requiring more invasive procedures [108, 109].

Finally, recent studies on expression of estrogen, progesterone, and androgen receptors may suggest a potential role of hormonal therapy in the treatment of SGC. Future larger-scale studies are needed to evaluate their utility in locally advanced or metastatic disease.

Prognosis

The overall mortality rate of SGC is 5–10%, being as high as 29% in certain populations, owing to early recurrence and metastatic spread [110]. A recurrence rate of 11–36% in 5 years and an 18–30% 5-year mortality has been reported with WLE of 5–6-mm margins, and 38% of these recurrences are locally invasive [76]. On the contrary, MMS has been shown to be associated with lower rate of recurrence (7%), with a metastatic rate of 4% [30].

Snow and colleagues have reported an overall metastasis rate of 8% (4/49) in a review up to 2002; the higher risk is carried by advanced tumor [111]. Metastatic sites include lung, regional lymph nodes, liver, brain, and bone. The time from diagnosis of ocular SGC to metastasis may range from 0 to 62 months [103]. According to a recent study published by our group, locoregional lymph node metastasis was noted in 23% of patients, while systemic metastasis in 14% and death due to metastasis was 10% over a mean follow-up period of 29 months [12].

Clinical prognostic risk factors include medial canthal involvement, location at both upper and lower eyelids, multicentric origin, orbital invasion, duration of symptoms > 6 months, and tumor size > 10 mm [11, 12, 90, 112]. The T category, as defined by the AJCC, and a prolonged interval from symptoms appearance to the correct diagnosis have also a role in the overall prognosis [37, 113, 114]. Histopathologically, a pagetoid infiltrative pattern of the skin and conjunctiva [76, 108], vascular or lymphatic invasion, non-lobular growth pattern [90], and poor differentiation [115] is associated with worse prognosis. Human telomerase RNA (hTR) has been shown to be a marker of undifferentiated disease [116].

On the contrary, tumors originating from the glands of Zeis and those associated with MTS have a better prognosis [30, 110]. The factors predictive of locoregional lymph node and systemic metastasis are medial canthal involvement, lateral canthal involvement, tumor basal diameter > 10 mm, and perivascular invasion [12, 114]. The factors predictive of death due to metastasis are medial canthal involvement and tumor basal diameter > 10 mm [12, 114].

Conclusion

Ocular SGC is an uncommon, aggressive tumor associated with poor prognosis. Early identification of negative prognostic factors may help to eradicate the lesion before locoregional and systemic metastasis. New insight into its pathogenesis and the immunohistochemical profile may lead to the development new effective treatment strategies, along with traditional therapies.

Funding Support was provided by The Operation Eyesight Universal Institute for Eye Cancer and Hyderabad Eye Research Foundation, Hyderabad, India.

Compliance with ethical standards

Conflict of interest No conflicts of interest.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

References

1. Kass LG, Hornblass AU (1989) Sebaceous carcinoma of the ocular adnexa. Surv Ophthalmol 33:477–490

2. Prieto-Granada C, Rodriguez-Waitkus P (2016) Sebaceous carcinoma of the eyelid. Cancer Control 23:126–132
3. Yeatts RP, Waller RR (1985) Sebaceous carcinoma of the eyelid: pitfalls in diagnosis. Ophthal Plast Reconstr Surg 1:35–42
4. Nelson BR, Hamlet KR, Gillard M, Railan D, Johnson TM (1995) Sebaceous carcinoma. J Am Acad Dermatol 33:1–15
5. Shields JA, Demirci H, Marr BP, Eagle RC Jr, Shields CL (2004) Sebaceous carcinoma of the eyelids: personal experience with 60 cases. Ophthalmology 111:2151–2157
6. Muqit MM, Foot B, Walters SJ, Mudhar HS, Roberts F, Rennie IG (2013) Observational prospective cohort study of patients with newly-diagnosed ocular sebaceous carcinoma. Br J Ophthalmol 97:47–51
7. Yin VT, Merritt HA, Sniegowski M, Esmaeli B (2015) Eyelid and ocular surface carcinoma: diagnosis and management. Clin Dermatol 33:159–169
8. Jahagirdar SS, Thakre TP, Kale SM, Kulkarni H, Mamtani M (2007) A clinicopathological study of eyelid malignancies from central India. Indian J Ophthalmol 55:109–112
9. Mak ST, Wong AC, Io IY, Tse RK (2011) Malignant eyelid tumors in Hong Kong 1997–2009. Jpn J Ophthalmol 55:681–685
10. Lim VS, Amrith S (2012) Declining incidence of eyelid cancers in Singapore over 13 years: population-based data from 1996 to 2008. Br J Ophthalmol 96:1462–1465
11. Watanabe A, Sun MT, Pirbhai A, Ueda K, Katori N, Selva D (2013) Sebaceous carcinoma in Japanese patients: clinical presentation, staging and outcomes. Br J Ophthalmol 97:1459–1463
12. Kaliki S, Ayyar A, Dave TV, Ali MJ, Mishra DK, Naik MN (2015) Sebaceous gland carcinoma of the eyelid: clinicopathological features and outcome in Asian Indians. Eye (Lond) 29:958–963
13. Gupta P, Gupta RC, Khan L (2017) Profile of eyelid malignancy in a Tertiary Health Care Center in North India. J Cancer Res Ther 13:484–486
14. Gupta Y, Gahine R, Hussain N, Memon MJ (2017) Clinico-pathological spectrum of ophthalmic lesions: an experience in tertiary care hospital of central India. J Clin Diagn Res 11:9–13
15. Dasgupta T, Wilson LD, Yu JB (2009) A retrospective review of 1349 cases of sebaceous carcinoma. Cancer 115:158–165
16. Tripathi R, Chen Z, Li L, Bordeaux JS (2016) Incidence and survival of sebaceous carcinoma in the United States. J Am Acad Dermatol 75:1210–1215
17. Keskinaslan I, Pedroli GL, Piffaretti JM, Meyer P, Kunz C, Haefliger IO (2008) Eyelid sebaceous gland carcinoma in a young Caucasian man. Klin Monbl Augenheilkd 225:422–423
18. Sung D, Kaltreider SA, Gonzalez-Fernandez F (2011) Early onset sebaceous carcinoma. Diagn Pathol 6:81
19. Lemos LB, Santa Cruz DJ, Baba N (1978) Sebaceous carcinoma of the eyelid following radiation therapy. Am J Surg Pathol 2:305–311
20. Rundle P, Shields JA, Shields CL, Eagle RC Jr, Singh AD (1999) Sebaceous gland carcinoma of the eyelid seventeen years after irradiation for bilateral retinoblastoma. Eye (Lond) 13:109–110
21. Gauthier AS, Campolmi N, Tumahai P, Kantelip B, Delbosc B (2014) Sebaceous carcinoma of the eyelid and Muir-Torre syndrome. JAMA Ophthalmol 132:1025–1028
22. Landis MN, Davis CL, Bellus GA, Wolverton SE (2011) Immunosuppression and sebaceous tumors: a confirmed diagnosis of Muir-Torre syndrome unmasked by immunosuppressive therapy. J Am Acad Dermatol 65:1054–1058
23. Kivela T, Asko-Seljavaara S, Pihkala U, Hovi L, Heikkonen J (2001) Sebaceous carcinoma of the eyelid associated with retinoblastoma. Ophthalmology 108:1124–1128
24. Gonzalez-Fernandez F, Kaltreider SA, Patnaik BD et al (1998) Sebaceous carcinoma: tumor progression through mutational inactivation of p53. Ophthalmology 105:497–506
25. Yen MT, Tse DT (2000) Sebaceous cell carcinoma of the eyelid and the human immunodeficiency virus. Ophthal Plast Reconstr Surg 16:206–210
26. Tryggvason G, Bayon R, Pagedar NA (2012) Epidemiology of sebaceous carcinoma of the head and neck: implications for lymph node management. Head Neck 34:1765–1768
27. Bailet JW, Zimmerman MC, Arnstein DP, Wollman JS, Mickel RA (1992) Sebaceous carcinoma of the head and neck: case report and literature review. Arch Otolaryngol Head Neck Surg 118:1245–1249
28. Bouraoui S, Khaddar RK, Mokni M, Badri T, Azaiez MY, Dhahri AB (2006) Extrapalpebral sebaceous carcinoma. Ann Dermatol Venereol 133:165–167
29. Song A, Carter KD, Syed NA, Song J, Nerad JA (2008) Sebaceous cell carcinoma of the ocular adnexa: clinical presentations, histopathology, and outcomes. Ophthal Plast Reconstr Surg 24:194–200
30. Rao NA, Hidayat AA, McLean IW, Zimmerman LE (1982) Sebaceous carcinomas of the ocular adnexa: a clinicopathologic study of 104 cases, with five-year follow-up data. Hum Pathol 13:113–122
31. Shields JA, Demirci H, Marr BP, Eagle RC Jr, Shields CL (2005) Sebaceous carcinoma of the ocular region: a review. Surv Ophthalmol 50:103–122
32. Ha A, Kim N (2016) Sebaceous gland carcinoma of tarsus can be misdiagnosed as intratarsal keratinous cyst. Can J Ophthalmol 51:99–101
33. Knackstedt T, Samie FH (2017) Sebaceous carcinoma: a review of the scientific literature. Curr Treat Options Oncol 18:47
34. Satomura H, Ogata D, Arai E, Tsuchida T (2017) Dermoscopic features of ocular and extraocular sebaceous carcinomas. J Dermatol. https://doi.org/10.1111/1346-8138.13905
35. Cohen PR, Kohn SR, Kurzrock R (1991) Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. Am J Med 90:606–613
36. Cohen PR, Kohn SR, Davis DA, Kurzrock R (1995) Muir-Torre syndrome. Dermatol Clin 13:79–89
37. Esmaeli B, Dutton JJ, Graue GF et al (2017) Eyelid carcinoma. In: Edge SB, Greene FL, Byrd DR et al (eds)

Carcinoma of the eyelid. AJCC cancer staging manual, 8th edn. Springer, New York, pp 779–785
38. Wolfe JT 3rd, Yeatts RP, Wick MR, Campbell RJ, Waller RR (1984) Sebaceous carcinoma of the eyelid: errors in clinical and pathologic diagnosis. Am J Surg Pathol 8:597–606
39. Broekaert SM, Flux K, Kyrpychova L et al (2017) Squared-off nuclei and "Applique" pattern as a histopathological clue to periocular sebaceous carcinoma: a clinicopathological study of 50 neoplasms from 46 patients. Am J Dermatopathol 39:275–278
40. Park SK, Park J, Kim HU, Yun SK (2017) Sebaceous carcinoma: clinicopathologic analysis of 29 cases in a Tertiary Hospital in Korea. J Korean Med Sci 32:1351–1359
41. Pereira PR, Odashiro AN, Rodrigues-Reyes AA, Correa ZM, de Souza Filho JP, Burnier MN Jr (2005) Histopathological review of sebaceous carcinoma of the eyelid. J Cutan Pathol 32:496–501
42. Ansai SI (2017) Topics in histopathology of sweat gland and sebaceous neoplasms. J Dermatol 44:315–326
43. Shields CL, Naseripour M, Shields JA, Eagle RC Jr (2002) Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid sebaceous gland carcinoma. Ophthalmology 109:2129–2133
44. Shet T, Kelkar G, Juvekar S, Mistry R, Borges A (2004) Masquerade syndrome: sebaceous carcinoma presenting as an unknown primary with pagetoid spread to the nasal cavity. J Laryngol Otol 118:307–309
45. Leibovitch I, Selva D, Huilgol S, Davis G, Dodd T, James CL (2006) Intraepithelial sebaceous carcinoma of the eyelid misdiagnosed as Bowen's disease. J Cutan Pathol 33:303–308
46. Barsegian A, Shinder R (2017) Eyelid sebaceous gland carcinoma with extensive pagetoid spread. Ophthalmology 124:858
47. Sinard JH (1999) Immunohistochemical distinction of ocular sebaceous carcinoma from basal cell and squamous cell carcinoma. Arch Ophthalmol 117:776–783
48. Ansai S, Takeichi H, Arase S, Kawana S, Kimura T (2011) Sebaceous carcinoma: an immunohistochemical reappraisal. Am J Dermatopathol 33:579–587
49. Plaza JA, Mackinnon A, Carrillo L, Prieto VG, Sangueza M, Suster S (2015) Role of immunohistochemistry in the diagnosis of sebaceous carcinoma: a clinicopathologic and immunohistochemical study. Am J Dermatopathol 37:809–821
50. Muthusamy K, Halbert G, Roberts F (2006) Immunohistochemical staining for adipophilin, perilipin and TIP47. J Clin Pathol 59:1166–1170
51. Boussahmain C, Mochel MC, Hoang MP (2013) Perilipin and adipophilin expression in sebaceous carcinoma and mimics. Hum Pathol 44:1811–1816
52. Schmitz EJ, Herwig-Carl MC, Holz FG, Loeffler KU (2017) Sebaceous gland carcinoma of the ocular adnexa–variability in clinical and histological appearance with analysis of immunohistochemical staining patterns. Graefes Arch Clin Exp Ophthalmol 255:2277–2285
53. Jayaraj P, Sen S, Bhattacharya T et al (2016) Clinical relevance of cyclooxygenase 2 and peroxisome proliferator-activated receptor gamma in eyelid sebaceous gland carcinoma. Histopathology 69:268–275
54. Mittal R, Araujo I, Czanner G, Coupland SE (2016) Perforin expression in eyelid sebaceous carcinomas: a useful and specific immunomarker for the differential diagnosis of eyelid carcinomas. Acta Ophthalmol 94:325–330
55. Tjarks BJ, Pownell BR, Evans C et al (2017) Evaluation and comparison of staining patterns of factor XIIIa (AC-1A1), adipophilin and GATA3 in sebaceous neoplasia. J Cutan Pathol. https://doi.org/10.1111/cup.13037
56. Murata T, Nakashima Y, Takeuchi M, Sueishi K, Inomata H (1993) The diagnostic use of low molecular weight keratin expression in sebaceous carcinoma. Pathol Res Pract 189:888–893
57. Heyl J, Mehregan D (2008) Immunolabeling pattern of cytokeratin 19 expression may distinguish sebaceous tumors from basal cell carcinomas. J Cutan Pathol 35:40–45
58. Ansai S, Arase S, Kawana S, Kimura T (2011) Immunohistochemical findings of sebaceous carcinoma and sebaceoma: retrieval of cytokeratin expression by a panel of anti-cytokeratin monoclonal antibodies. J Dermatol 38:951–958
59. Kawachi Y, Fujisawa Y, Furuta J, Nakamura Y, Ishii Y, Otsuka F (2011) Superficial epithelioma with sebaceous differentiation: immunohistochemical study of keratinocyte differentiation markers. Eur J Dermatol 21:1016–1017
60. Jakobiec FA, Mendoza PR (2014) Eyelid sebaceous carcinoma: clinicopathologic and multiparametric immunohistochemical analysis that includes adipophilin. Am J Ophthalmol 157:186–208
61. Tzorakoleftheraki SE, Iliadis A, Kostopoulos I, Koletsa T (2017) TdT expression in normal and neoplastic sebaceous cells. Histopathology. https://doi.org/10.1111/his.13304
62. Kiyosaki K, Nakada C, Hijiya N et al (2010) Analysis of p53 mutations and the expression of p53 and p21WAF1/CIP1 protein in 15 cases of sebaceous carcinoma of the eyelid. Invest Ophthalmol Vis Sci 51:7–11
63. Shalin SC, Sakharpe A, Lyle S, Lev D, Calonje E, Lazar AJ (2012) p53 staining correlates with tumor type and location in sebaceous neoplasms. Am J Dermatopathol 34:129–135
64. Cabral ES, Auerbach A, Killian JK, Barrett TL, Cassarino DS (2006) Distinction of benign sebaceous proliferations from sebaceous carcinomas by immunohistochemistry. Am J Dermatopathol 28:465–471
65. Mateoiu C, Pirici A, Bogdan F (2011) Immunohistochemical nuclear staining for p53, PCNA, Ki-67 and bcl-2 in different histologic variants of basal cell carcinoma. Rom J Morphol Embryol 52:315–319
66. Athanassiadou AM, Lazaris AC, Patsouris E, Tsipis A, Chelidonis G, Aroni K (2013) Significance of cyclooxygenase 2, EZH-2 polycomb group and p53 expression in actinic keratosis and squamous cell carcinomas of the skin. Am J Dermatopathol 35:425–431
67. Bell WR, Singh K, Rajan KdA, Eberhart CG (2015) Expression of p16 and p53 in intraepithelial periocular sebaceous carcinoma. Ocul Oncol Pathol 2:71–75

68. Ohara M, Sotozono C, Tsuchihashi Y, Kinoshita S (2004) Ki-67 labeling index as a marker of malignancy in ocular surface neoplasms. Jpn J Ophthalmol 48:524–529
69. Mulay K, Shah SJ, Aggarwal E, White VA, Honavar SG (2014) Periocular sebaceous gland carcinoma: do androgen receptor (NR3C4) and nuclear survivin (BIRC5) have a prognostic significance? Acta Ophthalmol 92:681–687
70. Bhardwaj M, Sen S, Sharma A et al (2015) ZEB2/SIP1 as novel prognostic indicator in eyelid sebaceous gland carcinoma. Hum Pathol 46:1437–1442
71. Jayaraj P, Sen S, Sharma A et al (2012) Epigenetic inactivation of the E-cadherin gene in eyelid sebaceous gland carcinoma. Br J Dermatol 167:583–590
72. Yunoki T, Tabuchi Y, Hayashi A (2017) Expression of anti-apoptotic protein BAG3 in human sebaceous gland carcinoma of the eyelid. Anticancer Res 37:1931–1934
73. Jakobiec FA, Werdich X (2014) Androgen receptor identification in the diagnosis of eyelid sebaceous carcinomas. Am J Ophthalmol 157:687–696
74. Mulay K, White VA, Shah SJ, Honavar S (2014) Sebaceous carcinoma: clinicopathologic features and diagnostic role of immunohistochemistry (including androgen receptor). Can J Ophthalmol 49:326–332
75. Na HY, Choe JY, Shin SA et al (2016) Proposal of a provisional classification of sebaceous carcinoma based on hormone receptor expression and HER2 status. Am J Surg Pathol 40:1622–1630
76. Asadi-Amoli F, Khoshnevis F, Haeri H, Jahanzad I, Pazira R, Shahsiah R (2010) Comparative examination of androgen receptor reactivity for differential diagnosis of sebaceous carcinoma from squamous cell and basal cell carcinoma. Am J Clin Pathol 134:22–26
77. Cho KJ, Khang SK, Koh JS, Chung JH, Lee SS (2000) Sebaceous carcinoma of the eyelids: frequent expression of c-erbB-2 oncoprotein. J Korean Med Sci 15:545–550
78. Kwon MJ, Shin HS, Nam ES et al (2015) Comparison of HER2 gene amplification and KRAS alteration in eyelid sebaceous carcinomas with that in other eyelid tumors. Pathol Res Pract 211:349–355
79. Plocharczyk EF, Frankel WL, Hampel H, Peters SB (2013) Mismatch repair protein deficiency is common in sebaceous neoplasms and suggests the importance of screening for Lynch syndrome. Am J Dermatopathol 35:191–195
80. Boennelycke M, Thomsen BM, Holck S (2015) Sebaceous neoplasms and the immunoprofile of mismatch-repair proteins as a screening target for syndromic cases. Pathol Res Pract 211:78–82
81. Ponti G, Longo C (2013) Microsatellite instability and mismatch repair protein expression in sebaceous tumors, keratocanthoma, and basal cell carcinomas with sebaceous differentiation in Muir-Torre syndrome. J Am Acad Dermatol 68:509–510
82. Chang HH, Suh E, Fortes BH, Zheng F, Cheng AM (2017) Forehead galeal pericranial flap for single-staged total upper eyelid reconstruction in sebaceous gland carcinoma excision. Int Med Case Rep J 10:309–312
83. Arora A, Barlow RJ, Williamson JM, Olver JM (2004) Eyelid sebaceous gland carcinoma (SGC) treated with 'slow' Mohs' micrographic surgery. Eye (Lond) 18:854–855
84. Spencer JM, Nossa R, Tse DT, Sequeira M (2001) Sebaceous carcinoma of the eyelid treated with Mohs micrographic surgery. J Am Acad Dermatol 44:1004–1009
85. Hou JL, Killian JM, Baum CL et al (2014) Characteristics of sebaceous carcinoma and early outcomes of treatment using Mohs micrographic surgery versus wide local excision: an update of the Mayo Clinic experience over the past 2 decades. Dermatol Surg 40:241–246
86. Tolkachjov SN (2017) Adnexal carcinomas treated with Mohs micrographic surgery: a comprehensive review. Dermatol Surg 43:1199–1207
87. Brady KL, Hurst EA (2017) Sebaceous carcinoma treated with Mohs micrographic surgery. Dermatol Surg 43:281–286
88. Tan KC, Lee ST, Cheah ST (1991) Surgical treatment of sebaceous carcinoma of eyelids with clinico-pathological correlation. Br J Plast Surg 44:117–121
89. While B, Salvi S, Currie Z, Mudhar HS, Tan JH (2014) Excision and delayed reconstruction with paraffin section histopathological analysis for periocular sebaceous carcinoma. Ophthal Plast Reconstr Surg 30:105–109
90. Takahashi Y, Takahashi E, Nakakura S, Kitaguchi Y, Mupas-Uy J, Kakizaki H (2016) Risk factors for local recurrence or metastasis of eyelid sebaceous gland carcinoma after wide excision with paraffin section control. Am J Ophthalmol 171:67–74
91. Putterman AM (1986) Conjunctival map biopsy to determine pagetoid spread. Am J Ophthalmol 102:87–90
92. McConnell LK, Syed NA, Zimmerman MB et al (2017) An analysis of conjunctival map biopsies in sebaceous carcinoma. Ophthal Plast Reconstr Surg 33:17–21
93. Shields JA, Saktanasate J, Lally SE, Carrasco JR, Shields CL (2015) Sebaceous carcinoma of the ocular region: the 2014 Professor Winifred Mao Lecture. Asia Pac J Ophthalmol 4:221–227
94. Gerring RC, Ott CT, Curry JM, Sargi ZB, Wester ST (2017) Orbital exenteration for advanced periorbital nonmelanoma skin cancer: prognostic factors and survival. Eye (Lond) 31:379–388
95. Khan SN, Sepahdari AR (2012) Orbital masses: CT and MRI of common vascular lesions, benign tumors, and malignancies. Saudi J Ophthalmol 26(4):373–383
96. Mafee M, Karimi A, Shah J et al (2005) Anatomy and pathology of the eye: role of MR imaging and CT. Neuroimaging Clin North Am 15:23–47
97. Kapur R, Sepahdari AR, Mafee MF, Putterman AM, Aakalu V, Wendel LJ, Setabutr P (2009) MR imaging of orbital inflammatory syndrome, orbital cellulitis, and orbital lymphoid lesions: the role of diffusion-weighted imaging. AJNR Am J Neuroradiol 30(1):64–70
98. Krishna SM, Finger PT, Chin K, Lacob CE (2007) 18-FDG PET/CT staging of ocular sebaceous cell carcinoma. Graefes Arch Clin Exp Ophthalmol 245:759–760
99. Zhao X, Wang GF, Zhao K, Cui HG, Ding W (2015) Value of (18)F-FDG-PET/CT in ocular sebaceous adenocarcinoma: a case report and literature review. Int J Clin Exp Med 8:19524–19529
100. Sepahdari AR, Politi LS, Aakalu VK, Kim HJ, Razek AA (2014) Diffusion-weighted imaging of orbital masses: multi-institutional data support a 2-ADC threshold model

to categorize lesions as benign, malignant, or indeterminate. AJNR Am J Neuroradiol 35(1):170–175
101. Savar A, Oellers P, Myers J et al (2011) Positive sentinel node in sebaceous carcinoma of the eyelid. Ophthal Plast Reconstr Surg 27:4–6
102. Ho VH, Ross MI, Prieto VG, Khaleeq A, Kim S, Esmaeli B (2007) Sentinel lymph node biopsy for sebaceous cell carcinoma and melanoma of the ocular adnexa. Arch Otolaryngol Head Neck Surg 133:820–826
103. Husain A, Blumenschein G, Esmaeli B (2008) Treatment and outcomes for metastatic sebaceous cell carcinoma of the eyelid. Int J Dermatol 47:276–279
104. Hata M, Koike I, Omura M, Maegawa J, Ogino I, Inoue T (2012) Noninvasive and curative radiation therapy for sebaceous carcinoma of the eyelid. Int J Radiat Oncol Biol Phys 82:605–611
105. Deo SV, Shukla NK, Singh M, Jha D, Khanna P, Kallianpur A (2012) Locally advanced sebaceous cell carcinoma (T3) of eyelid: incidence and pattern of nodal metastases and combined modality management approach. Orbit 31:150–154
106. Kasperts N, Slotman BJ, Leemans CR, de Bree R, Doornaert P, Langendijk JA (2006) Results of postoperative reirradiation for recurrent or second primary head and neck carcinoma. Cancer 106:1536–1547
107. Sahai P, Shukla NK, Arora S, Mohanti BK (2016) Recurrent sebaceous carcinoma of the eyelid: outcome after postoperative reirradiation. Head Neck 38:16–19
108. Priyadarshini O, Biswas G, Biswas S, Padhi R, Rath S (2010) Neoadjuvant chemotherapy in recurrent sebaceous carcinoma of eyelid with orbital invasion and regional lymphadenopathy. Ophthal Plast Reconstr Surg 26:366–368
109. Kaliki S, Ayyar A, Nair AG, Mishra DK, Reddy VA, Naik MN (2016) Neoadjuvant systemic chemotherapy in the management of extensive eyelid sebaceous gland carcinoma: a study of 10 cases. Ophthal Plast Reconstr Surg 32:35–39
110. Wali UK, Al-Mujaini A (2010) Sebaceous gland carcinoma of the eyelid. Oman J Ophthalmol 3:117–121
111. Snow SN, Larson PO, Lucarelli MJ, Lemke BN, Madjar DD (2002) Sebaceous carcinoma of the eyelids treated by mohs micrographic surgery: report of nine cases with review of the literature. Dermatol Surg 28:623–631
112. Chao AN, Shields CL, Krema H, Shields JA (2001) Outcome of patients with periocular sebaceous gland carcinoma with and without conjunctival intraepithelial invasion. Ophthalmology 108:1877–1883
113. Choi YJ, Jin HC, Lee MJ, Kim N, Choung HK, Khwarg SI (2014) Prognostic value of clinical and pathologic T stages defined by the American Joint Committee on Cancer for eyelid sebaceous carcinoma in Korea. Jpn J Ophthalmol 58:327–333
114. Kaliki S, Gupta A, Ali MH, Ayyar A, Naik MN (2016) Prognosis of eyelid sebaceous gland carcinoma based on the tumor (T) category of the American Joint Committee on Cancer (AJCC) classification. Int Ophthalmol 36:681–690
115. Muqit MM, Roberts F, Lee WR, Kemp E (2004) Improved survival rates in sebaceous carcinoma of the eyelid. Eye (Lond) 18:49–53
116. Li B, Li N, Cheng G et al (2006) Correlation of the expression of telomerase RNA with risk factors for recurrence of sebaceous gland carcinoma. Graefes Arch Clin Exp Ophthalmol 244:480–484