SEBACEOUS CARCINOMA

Thesis submitted for the degree of Master of Philosophy

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Abstract

Sebaceous carcinoma (SC) is a rare skin cancer which usually occurs on the head and neck, and has a propensity for metastasis. It is easily mistaken for benign conditions, resulting in inappropriate management. Thus, it is important to maintain a high index of suspicion for SC, to avoid delay in diagnosis and worsening of prognosis. Due to its poor prognosis and tendency to occur on cosmetically sensitive areas, the primary treatment of SC should be margin control surgery, preferably Mohs micrographic surgery. Chapter 1 is a comprehensive review on cutaneous SC, discussing its epidemiology, clinical features, histologic features, pathogenesis and management.

There has been significant uncertainty about the demographics and anatomical distribution of SC. Of particular note, it has frequently been assumed that SC occur more commonly in Asians than whites; however, data to support this are limited. Chapter 2 investigates these uncertainties by comparing the previously published incidence rates of SC in various countries. However, the incidence rates could not be compared accurately as different studies focused on different anatomical sites, and adjusted to different standard populations. To facilitate a more accurate comparison of incidence rates and further clarify the uncertainties about the epidemiology of SC, Chapter 3 presents new data obtained from cancer registries of the United States, England, Norway and Taiwan, and calculates incidence rates with uniform age-adjustment.

Chapter 4 reports a case of eyelid SC in situ that presented atypically as a haemorrhagic cyst. Chapter 5 describes an unusual case of SC with lacrimal sac involvement, presenting with clinical features of nasolacrimal duct obstruction.

The optimal management of SC remains uncertain, due to its rarity and thus limited data on which to base recommendations. Areas of uncertainty include whether to investigate for subclinical metastasis and other malignancies of Muir-Torre Syndrome, whether to perform sentinel lymph node biopsy and conjunctival map biopsies, and whether to use intraoperative histologic margin control and if so which method (e.g. frozen section, paraffin section, or Mohs). In Chapter 6, the management preferences of different groups of clinicians in different countries are surveyed (Australian Mohs surgeons, and Australian, New Zealand, and Japanese oculoplastic surgeons). This may provide a foundation to develop Asia-Pacific consensus guidelines.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Albert Wu
2020

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Chapter 1: Cutaneous sebaceous carcinoma (comprehensive review)

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Statement of authorship

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Albert Wu   2020

Author contributions

Principal author (AW) contribution: 80%

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Abstract

Cutaneous sebaceous carcinoma (SC) occurs almost exclusively on the head and neck, and has a significant propensity for recurrence and metastasis. It is easily mistaken for benign conditions, resulting in inappropriate management. Thus, it is important to maintain a high index of suspicion for SC. This is a comprehensive review on cutaneous SC using PubMed, discussing its epidemiology, clinical features, histologic features, pathogenesis and management. Despite previous reports, SC may occur with similar frequency in Asians and whites. Recent genetic data suggest there are multiple mutational groups of SC, paving the way for targeted treatment. After a diagnosis of SC, investigations for staging and for Muir-Torre syndrome should be considered. The available evidence on the treatment options for SC are discussed, and specific recommendations for management are made.

Introduction

The cutaneous malignancy sebaceous carcinoma (SC) can occur anywhere on the skin but most often presents on the head and neck.[1] It is the second or third most common eyelid malignancy depending on geographic area, and is frequently misdiagnosed.[2,3] SC has a propensity to recur and metastasise, particularly if treated inadequately.[4] This article aims to comprehensively review its epidemiology, clinical features, histologic features, pathogenesis and management. The PubMed database was searched to October 2019 using the search string "(sebaceous OR meibomian) AND carcinoma". Relevant English-language articles were identified by reviewing titles and abstracts.

Epidemiology

<u>Age</u>

SC most frequently occur in the age range 60 to 79 years but cases have been reported from 15 to 105 years.[1-3,5]

<u>Gender</u>

A higher proportion of all SC occurs in males than females (58-60%), whereas a higher proportion of ocular SC occurs in females (51-70%).[1,3,5,6]

<u>Incidence and ethnicity</u>

US data found a higher incidence rate for whites (0.23 per 100,000 person-years) than blacks (0.07 per 100,000, $p<0.01$).[1]

It has been postulated that SC occur more commonly in Asians than whites. However, registry-based data do not support this claim, and show Asians and whites have similar incidences.[6] Incidence rate of all SC in the predominantly white populations of US and Netherlands ranged from 0.1 to 0.23 per 100,000 person-years.[1,5,6] Given ocular SC accounts for 26-27% of all SC, the incidence rate of ocular SC could be estimated to range from 0.03 to 0.06.[1,6] Consistent with this, incidence rate of ocular SC in the UK was 0.04 per 100,000 person-years.[3] Similarly, the incidence rate of ocular SC in the predominantly Chinese populations of Taiwan and Singapore was 0.02-0.05 per 100,000 person-years.[2,6] The incidence rate of all SC has not been reported using prospective registry-based data from large Asian populations.

Clinical features

Anatomical location

SC are often classified by anatomical location, as ocular and extraocular. According to US and Dutch data, 26-27% of SC are ocular, 55-69% occur elsewhere on the head and neck, and 5-18% elsewhere on the body.[1] These figures correspond to the density distribution of sebaceous glands on the skin. Ocular SC arise mainly from Meibomian glands of the tarsus or Zeis glands of the eyelashes, and can also arise from sebaceous glands of the caruncle and eyebrow. They occur more commonly in the upper lid than lower lid.[3,7-9] Some SC have been described to be 'multicentric'; however, it is uncertain whether SC truly arise from separate foci, or whether there is failure to identify intervening tumour, or whether the intervening tumour had regressed.[10]

Presentation and differential diagnosis

SC commonly presents as a solitary pink or yellow nodule (Figure 1), or diffuse thickening (Figure 2).[7] A high proportion (85-94%) of ocular SC in Asians may present as a nodule or mass,[7,8,11,12] whereas a higher proportion of cases in Caucasians present as eyelid thickening.[9] Due to the non-specific presentation, ocular SC are frequently mistaken for benign conditions such as chalazion or blepharoconjunctivitis, causing considerable delay in diagnosis and potential worsening of prognosis.[3,13] An index of suspicion should be maintained for presumed chalazion or blepharoconjunctivitis that do not respond to usual management or that have atypical features. Other common differential diagnoses are basal cell carcinoma (BCC), which occurs more commonly on the lower lid, and squamous cell carcinoma (SCC).[14] BCC and SCC are also histologic differential diagnoses, and immunohistochemical stains can be useful for differentiation as discussed below.

Muir-Torre syndrome (MTS)

MTS is a genetic condition characterised by predisposition to develop sebaceous neoplasms and visceral malignancies, the most common being colorectal adenocarcinoma.[15] Other sites of visceral malignancy include the genitourinary tract, breast, brain, lung, and small bowel. The inheritance pattern may be autosomal dominant or recessive. MTS is diagnosed clinically, and genetic testing is used to support the diagnosis. In a patient with newly-diagnosed SC, MTS may be diagnosed if there is a history of visceral malignancy, or colorectal tumour with microsatellite instability. Patients with SC should be asked about a personal or family history of visceral malignancy. Referral to a genetics service, and workup for further

malignancies should be considered in appropriate patients. Whether sebaceous neoplasms should be universally screened for MTS with immunohistochemistry is a debated area. In addition to relevant clinical examination, investigations to consider arranging include colonoscopy, endometrial biopsy, and urine cytology.[15]

<u>Association with hereditary retinoblastoma and radiation therapy</u>
An association between hereditary retinoblastoma and ocular SC has been reported, but ocular SC may be caused by radiotherapy for retinoblastoma rather than the mutation itself.[16] Aberration in the RB1 gene in SC is discussed below.

<u>Association with immunosuppression</u>
In a study of US patients with AIDS (n=497,192), the risk of SC was significantly increased.[17] However, SEER registry data did not demonstrate an increased incidence of SC among a large cohort with CLL (n=28,964) or non-Hodgkin lymphoma (n=94,967).[18] There may be an increased risk of SC in solid organ transplant recipients.[19]

Histologic diagnosis
Histologically, SC can sometimes be difficult to differentiate from other skin neoplasms, including BCC and SCC. On haematoxylin and eosin (H&E) stain, sebaceous differentiation is suggested by multilocular cytoplasmic vacuolation and scalloped nuclei, which can be sparse (Figure 3).[20]

For diagnosis of ocular SC, full-thickness eyelid biopsy (including skin, tarsus and conjunctiva) is recommended.[21] On a small superficial eyelid biopsy, it can be difficult to differentiate intraepithelial SC from Bowen's disease.[20]

Lipid stains have previously been used in the diagnosis of SC, however this technique is now uncommonly used (used in 4% of UK ocular cases), due to impracticality as fresh or non-routinely processed tissue is required.[3,20]

Immunohistochemistry can be used to support the diagnosis (used in 49% of UK ocular cases).[3,20] An immunohistochemical panel can differentiate SC from BCC and SCC. One proposed panel consists of adipophilin, androgen receptor (AR), EMA, CK7 and BerEP4 (Table 1) (Figures 4 and 5).[20]

<u>Intraepithelial spread</u>

SC can display intraepithelial spread, which can be pagetoid or bowenoid in pattern (Figure 6). This makes complete resection more difficult and is associated with poorer prognosis.[10,22,23] Ocular SC show intraepithelial spread in 8%-51% of cases, possibly occurring less frequently in Asians than whites.[3,8,9,24] SC is occasionally confined to the epithelium, a phenomenon called 'SC in situ'.[25]

Pathogenesis

As understanding of the pathogenesis of SC improves, targeted therapy may become a treatment option.[16,26,27] Recent genetic studies suggest that SC arises from multiple distinct mechanisms and not a single pathway (Table 2).[26]

Investigations

Investigations are performed to establish the diagnosis (diagnostic biopsy), to determine local extent of tumour (conjunctival map biopsy discussed below, CT/MRI orbit), or to search for subclinical or suspected metastasis. Investigations for metastasis can include CT/MRI/PET (head and neck, systemic), ultrasound of regional lymph nodes +/- biopsy, chest X-ray, ultrasound abdomen, liver function testing, and sentinel lymph node biopsy (discussed below).[4,7,11,24] Investigations for workup of MTS are listed above.

<u>Conjunctival map biopsy</u>

Conjunctival map biopsy describes a technique of sampling conjunctiva away from the clinically appreciable ocular SC to determine the extent of tumour and pagetoid spread. The rationale is to identify potential tumour involvement in macroscopically normal areas. These results are used to plan definitive treatment.

Studies of white patients whose SC typically present as diffuse eyelid thickening have produced data to support map biopsies. In a series of 60 eyelid SC, conjunctival involvement was identified in 28 cases.[9] Of these 28 cases, the superior tarsal and forniceal conjunctivae were involved in all cases, even when the presumed origin was the lower lid. In another series of 45 ocular SC which underwent map biopsies, in cases of upper lid SC, the superior and inferior conjunctivae were similarly likely to have positive map biopsy (31-36%).[28] However, this study was retrospective and map biopsies may have been targeted to clinically suspicious areas which would produce a higher positive rate than if all cases underwent routine lower lid map biopsies. Despite these findings, many centres do not perform map biopsy routinely,

with 20% of UK cases undergoing the procedure and some centres only performing the procedure for clinically suspected cases.[3,7,8] Routine map biopsy may have a lower yield in Asian patients who may have a lower rate of pagetoid spread.[8]

Different biopsy sites and numbers of biopsies per eye (10-23) have been proposed. The palpebral conjunctiva of any lid may be sampled two (medial and lateral) to three (nasal, central, temporal) times with or without tarsus. Bulbar conjunctivae may be sampled six times (nasal, central and temporal, each superiorly and inferiorly). If corneal involvement is suspected, four limbal biopsies may be taken (superior, inferior, nasal and temporal).[9,29,30] Other suggested sites include medial and lateral canthus when the tumour is in close proximity to these areas, and caruncle.[13,28] Biopsy diameter of approximately 4 mm can be used.[28,30]

Careful handling of map biopsy tissue is important to avoid non-diagnostic biopsies (artefactual loss or damage of epithelium), which can occur in up to 15% of biopsies. Cases with extensive pagetoid disease have a higher proportion of non-diagnostic biopsies than cases with less extensive pagetoid disease (37% compared to 10%, respectively). This may be because infiltrating tumour cells disrupt adhesion of epithelium to basement membrane, leading to artefactual loss of epithelium. As non-diagnostic biopsy may occur due to conjunctival involvement, a repeat biopsy is recommended when the result is inconclusive.[31]

Sentinel lymph node biopsy (SLNB)
The utility of SLNB for SC remains uncertain, due to the paucity of data on its effectiveness. In two studies that performed SLNB, sentinel nodes were involved in 5/30 and 1/17 cases, respectively. During follow-up, 2/10 and 0/16 cases with negative sentinel nodes developed nodal metastasis during median follow-up durations of approximately 24.5 and 28 months, respectively.[22,24,32-34] These results show SLNB has the potential to identify subclinical and sub-radiological nodal metastasis, but a negative result does not preclude subsequent nodal metastasis.

Staging
Of risk factors for worse prognosis, AJCC staging has most consistently been shown to be useful.[35] Kaliki et al. found that compared to AJCC7 eyelid T2 tumours, T3 and T4 were five and 26 times more likely to have nodal metastasis respectively, six and 60 times more likely to have distant metastasis respectively, and nine and 75 times more likely to die of the disease respectively.[4] Similarly, higher AJCC8 eyelid T

staging has been associated with local recurrence, nodal metastasis, distant metastasis, and death from disease. AJCC8 eyelid stage N1 had a higher risk of distant metastasis and worse disease-specific survival than N0.[12,22]

Other independent poor prognostic factors may include involvement of both upper and lower lids, multicentric origin, presenting as diffuse disease (as opposed to nodular), greater tumour size, greater age, perineural invasion, lymphovascular invasion, orbital invasion, poor differentiation, highly infiltrative pattern, and pagetoid invasion.[7,22,23,36,37]

Treatment and outcomes

The following discussion on treatment and outcomes draws from evidence in series containing >5 SC cases from 1985 onward that report follow-up duration in the English-language literature. This provides a higher likelihood of accurate diagnosis of SC (due to improved diagnostic techniques), outcome based on more current treatments, and reduced likelihood of reporting bias. Population-based data such as from SEER can be limited by underreporting of treatment and outcome measures.

Primary surgery

Despite the lack of randomised controlled trials, recommendations for primary surgery can be made based on the available data. These recommendations are outlined in Table 3 and discussed below.

The primary treatment of SC is surgery, either excision with margin control or Mohs micrographic surgery (MMS). The majority of case series that report treatment outcomes focus on ocular SC rather than extraocular SC, and use excision rather than MMS (Table 4). Studies that used excision reported risks of recurrence 0-40%, nodal metastasis 0-25%, distant metastasis 0-14%, and death due to disease 0-12%, during average follow-up of 12-72 months. There may be a trend to better outcomes over time, due to improved recognition and management of SC. Studies that used MMS reported risks of recurrence of 0-16%, nodal metastasis 0-13%, and death due to disease 0-5%, during average follow-up of 3-60 months. It may be preferable to use MMS rather than excision to reduce the risk of recurrence and maximise conservation of normal tissue. This is especially important on the eyelid which is a cosmetically sensitive area. An oculoplastic surgeon can assist with eyelid reconstruction.

Margin control can be achieved using paraffin or frozen sections. Use of frozen sections, due to technical and interpretative issues, can potentially result in misdiagnosis of margin clearance and miss pagetoid spread.[21] However, in one centre experienced in the use of intraoperative frozen sections for SC, frozen and paraffin sections were concordant in 265 (99%) slides from 75 cases, with only two (<1%) false negatives and two (<1%) false positives. There was one recurrence at median follow-up of four months, in a case with clear margins on frozen and paraffin sections and 15 negative map biopsies.[38] When paraffin section margin control is used, reconstruction will be delayed.

Among studies that reported excision of ocular SC, clinical margins of 3-5mm have most commonly been used. If margins were involved, one study using frozen section control resected further 1mm margins until clearance was achieved, while another study using paraffin section control resected further 5mm margins.[7,11] Margins used for extraocular SC have ranged from 5mm to beyond 20mm. Narrower margins are used for ocular SC to conserve healthy tissue in this cosmetically and functionally sensitive area.

In cases of ocular SC with orbital invasion or extensive conjunctival involvement, orbital exenteration may be required.[39,40] The outcome of locally advanced ocular SC undergoing exenteration can be poor. In one series of 13 cases, seven had locoregional recurrence within two years.[40] However, in another series of ten cases with median follow-up of 15 months, one developed nodal metastasis and another died of disease.[39]

In cases of nodal metastasis for radical treatment, lymph node dissection is performed. For ocular SC, this involves neck dissection +/- parotidectomy +/- adjuvant radiotherapy.

Adjuvant radiotherapy
Adjuvant radiotherapy can be delivered following excision with close/incomplete margins, exenteration, or lymph node dissection. It can be delivered to the primary site or the nodal basin.[39,40]

Primary radiotherapy
As surgery is the mainstay of treatment, data on the use of radiotherapy as the primary treatment are limited.[41-43] SC has previously been considered radioresistant;

however, this may have been due to use of insufficient radiation dose.[42] One large study used radiotherapy for 83 eyelid SC, of which 65 cases underwent primary radiotherapy.[43] Median dose was 60 Gy with ≥5 mm margin. At median follow-up of 92 months, 43% of cases recurred, 20% developed neck node metastasis, 6% developed distant metastasis, and 5% died of disease.[43] Primary high dose rate (HDR) brachytherapy has also been used for eight eyelid SC with total dose 39 Gy in six fractions.[41] The cosmetic outcome was acceptable, and there were two recurrences at median follow-up of approximately 39.5 months.[41] Based on these data, primary radiotherapy may be considered when surgery is refused or is unsuitable.

Topical mitomycin C (MMC)

Topical MMC is used infrequently as primary or adjuvant treatment of ocular SC. The usual regimen is 0.04% topical MMC four times daily, 1-3 weeks on, 1-3 weeks off, in repeated cycles (total duration of actual MMC treatment may be 3-6 weeks).[44-46] Common short-term adverse effects include allergy/lid swelling, hyperaemia, keratoconjunctivitis, epiphora, and superficial punctate keratopathy. Long-term adverse effects included ongoing keratoconjunctivitis, corneal epithelial changes due to limbal stem cell deficiency, epiphora due to punctal stenosis, corneal pannus, and recurrent corneal abrasion.[44-46] Concurrent topical steroids and lubricants may be used to alleviate some of these complications.[44] When used post-operatively, it may be started after wound healing and within one month of surgery.[45] Medication intolerance can necessitate treatment cessation.[45,46] Two series administered a whole course of primary topical MMC in three cases each, with very different outcomes. In one study, 3/3 recurred at mean follow-up of approximately 29 months; and in the other study, 0/3 recurred at median follow-up of 10 months.[44,46] The few series that use topical MMC as adjuvant treatment report low rates of recurrence; however, the specific contribution of MMC to the outcome is uncertain.[44,45] Based on limited data, MMC is an unreliable primary treatment for SC, but can delay disease progression. It may be used as an adjuvant treatment; however, its efficacy is uncertain.

Cryotherapy

Cryotherapy is not widely reported in the literature (Table 4). However, it has been used extensively by at least one group.[9] Following excision, cryotherapy may be delivered to remaining bulbar and palpebral conjunctiva to treat pagetoid spread, or

to surgical margins when there is concern about recurrence.[9,29,45] The specific contribution of this adjuvant treatment to outcomes is uncertain.

Chemotherapy

Neoadjuvant chemotherapy can be used for eyelid SC to reduce tumour volume, and potentially avoid exenteration or allow for eyelid-sparing exenteration. One series used three or four cycles of cisplatin/carboplatin and 5-fluorouracil for ten cases of extensive SC which would otherwise have required exenteration or removal of more than 75% of eyelid (nine cases had orbital invasion, six had nodal metastasis, two had distant metastasis), resulting in median 80% reduction of tumour diameter without any major systemic adverse effects. Seven cases underwent subsequent surgery. Of these, five had wide local excision and two had eyelid-sparing exenteration. Adjuvant external beam radiotherapy was delivered to orbit +/- regional lymph nodes in seven cases. There was no local recurrence at median follow-up of 14 months. One case died of disease.[47]

Systemic chemotherapy can help to control disease in cases of metastatic SC, particularly platinum-based agents (cisplatin/carboplatin), 5-fluorouracil and paclitaxel.[48]

Immunotherapy

Anti-PD1 checkpoint inhibitor pembrolizumab has had anecdotal success in two cases of metastatic SC.[49,50]

Consensus guidelines

North American consensus guidelines on the diagnosis and management of SC were published after the date of literature search for this review.[58,59] The recommendations in those guidelines are consistent with this review. The guidelines recommended deep diagnostic biopsy, special histologic stains, primary surgery with margin control, and conjunctival map biopsy. In addition, radiotherapy can be considered for cases with lymph node involvement or when surgery is unsuitable.[58,59]

Conclusion

SC favours the age group 60-79 years. More males develop SC overall but more females develop ocular SC. Despite previous reports, ocular SC may occur with similar frequency in Asians and whites. Recent genetic data suggest there are multiple mutational groups of SC, potentially paving the way for future personalised

medicine and targeted treatment. Given its propensity for metastasis, close nodal surveillance is required for all ocular SC. Conjunctival map biopsy may be a useful procedure, but is not routinely performed in all centres. Surgery with margin control remains the primary treatment of choice. Paraffin sections may be preferred to frozen sections.

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Tables

Table 1: Immunohistochemical panel for diagnosis of SC*

	SC	BCC	SCC
Adipophilin	+	-	-
EMA	+	-	+
AR	+	+/-	-
CK7	+	+/-	+/-
BerEP4	+/-	+	-

*modified from Iacobelli et al.[20]

Table 2: Postulated mechanisms of SC pathogenesis

Mechanism	Notes
DNA mismatch-repair	Extraocular SC may be associated with DNA repair mutations more than ocular SC.[16,26]
Ultraviolet radiation	[26]
Pauci-mutational	This group of SC has low numbers of mutations. Ocular SC may tend to belong to this group.[26]
PI3K pathway	One study suggested trialling PI3K inhibitors in SC, particularly mTOR inhibitors.[16]
TP53 and RB1	These tumour suppressor genes were commonly mutated in ocular SC but not extraocular SC.[16,27]
HER2	SC and breast cancer may share overlapping biologic characteristics. Use of trastuzumab (a monoclonal antibody HER2 blocker) has been suggested.[51]
HPV	[27,52]

Table 3: Recommendations for primary surgery of SC

Margin control surgery should be used, preferably Mohs micrographic surgery.
Paraffin sections are preferable to frozen sections unless the pathologist/Mohs surgeon has extensive experience in examining frozen sections of SC.
When performing excision, clinical margins of 3-5mm for ocular SC, and ≥5mm for extraocular SC can be used, with further resection performed until margins are clear.
Consider involving an oculoplastic surgeon for eyelid reconstruction.
Consider orbital exenteration for ocular SC with orbital invasion or extensive conjunctival involvement.

Table 4: Case series that primarily use excision or Mohs surgery

	n, site	Treatment (n)	Outcome (n, %)	Median follow-up (months)
Dogru 1986-1994	14 ocular	Excision, frozen +/- paraffin control, margin 1/3/5mm (14) Treatment of recurrence: Excision, margin 5mm (3) Exenteration + neck dissection + RT (2)	Nodal metastasis (2, 14%)	24
Callahan 1987-1996	9 ocular	Excision, frozen and paraffin control, margin 5mm (9) Treatment of recurrence: Exenteration (2)	Local recurrence (2, 22%) Died of disease (1, 11%)	54
Yoon 1999-2004	24 ocular	Excision, frozen control (22) Exenteration (2) Adjuvant RT (7)	Local recurrence (6, 25%) Distant metastasis (2, 8%) Died of disease (2, 8%)	43 (mean)
Izumi 1993-2006	30 ocular	Excision, paraffin control (26) Node dissection (14) Parotidectomy (11) Excision of multiple salivary glands (1) Adjuvant RT (1)	Local recurrence (2, 7%) Nodal metastasis (3, 10%) Died of disease (1, 0%)	66 (mean)
Gaskin 1994-2008	31 ocular	Excision, frozen (22) and paraffin (7) control Map biopsy if SC suspected	Local recurrence (1, 3%) Died of disease (1, 3%)	72 (mean)
While 2003-2010	17 ocular	Excision, paraffin control, margin 3mm (17) Map biopsy (13)	Local recurrence (2, 12%) Nodal metastasis (1, 6%) Distant metastasis (1, 6%) Died of disease (2, 12%)	60 (mean)
Muqit 2008-2010	51 ocular	Excision, mode margin 4mm (31) MMS (4) Exenteration (5) Node dissection (2) Parotidectomy (1) Adjuvant RT (4) Mitomycin C (6)	Nodal metastasis (7, 14%) Distant metastasis (2, 4%) Died of disease (1, 2%)	12

Choi 1999-2011	40 ocular	Surgery, frozen control, margin 3-4mm (40) Neck dissection (2) Adjuvant RT (1) Cryotherapy (2)	Local recurrence (4, 10%) Nodal metastasis (10, 25%) Distant metastasis (1, 3%)	52 (mean)
Kaliki 1995-2013	186 ocular	Excision, frozen control (147) Exenteration (21) Neck dissection (13) Neoadjuvant systemic chemotherapy (16) Adjuvant RT (31) Adjuvant systemic chemotherapy (9) Mitomycin C (2) Treatment of recurrence: Excision (31) Exenteration (10) Cryotherapy (6) Mitomycin C (3)	Nodal metastasis (41, 23%) Distant metastasis (26, 14%) Died of disease (19, 10%)	20
Park 2001-2014	13 ocular 16 extraocular	Ocular: excision, margin 5-6mm (12) Extraocular: excision, margin 5-6mm (7); MMS, margin 2mm (9)	Ocular: recurrence (0, 0%), metastasis (0, 0%) Extraocular: recurrence (0, 0%), nodal metastasis (1, 6%)	Ocular: 24 Extraocular: 29
Haber 1995-2015	24 patients 3 ocular, 25 extraocular	Excision (28), margin 5-6mm (9), 10mm (12), ≥20mm (5)	Local recurrence (4, 14%) Distant metastasis (1, 4%) Died of disease (0, 0%)	36
Hsia 2000-2015	63 ocular	Excision, frozen control (57) Exenteration (6) Adjuvant RT (7) Treatment of recurrence: Excision (9) Exenteration (7) Treatment of nodal metastasis: Node dissection (7)	Local recurrence (15, 24%) Nodal metastasis (14, 22%) Distant metastasis (1, 2%) Died of disease (4, 6%)	46

		RT (13)		
Lam 2001-2015	22 ocular	Excision, frozen control, margin 5mm. Involved margins resected with 1mm margins until clear (20) Exenteration (2) Mitomycin C (1)	Local recurrence (3, 14%) Nodal metastasis (3, 14%) Died of disease (1, 5%)	69 (mean)
Takahashi 2006-2015	34 ocular	Excision, paraffin control, margin 5mm. Involved margins resected with 5mm margins until clear (34)	Recurrence/metastasis (4, 12%)	44 (mean)
Raza Rizvi 2009-2015	24 ocular	Excision, frozen control, margin 5mm (19) Map biopsy when pagetoid spread suspected Exenteration (5) Node dissection (1) Adjuvant RT	Nodal metastasis (1, 4%) Distant metastasis (1, 4%) Died of disease (1, 4%)	30 (mean)
Zhou 1991-2017[53]	360 ocular	Excision, no control (245) MMS, frozen control (115) Conjunctival map biopsy for diffuse growth pattern	Excision Local recurrence (97, 40%) Metastasis (38, 16%) Died of disease (21, 9%) MMS Local recurrence (18, 16%) Metastasis (9, 8%) Died of disease (6, 5%)	60
Sa 1999-2017	100 ocular	Excision (85) Exenteration (14) Adjuvant RT (9) Mitomycin C (6) Chemoradiation (3)	Local recurrence (6, 6%) Nodal metastasis (21, 21%) Distant metastasis (7, 7%) Died of disease (6, 6%)	31.5
Yount 1986-1990	8 ocular	MMS, paraffin control (6) MMS, frozen control (1) MMS, frozen and paraffin control (1)	Recurrence (1, 13%) Nodal metastasis (1, 13%) Died of disease (0, 0%)	53.5
Spencer 1988-1998[54]	18 ocular	MMS, frozen +/- paraffin control (18) Conjunctival map biopsy (18)	Local recurrence (2, 11%) Nodal metastasis (1, 6%)	26

			Died of disease (0, 0%)	
Snow 1985-2001[55]	7 ocular	MMS, frozen (7) and paraffin (3) control Conjunctival map biopsy	Recurrence (0, 0%)	36
Hou 1992-2012[56]	52 patients 7 ocular, 66 extraocular	Excision (26) MMS (35) Biopsy only (7)	Recurrence (3, 7%) Nodal metastasis (1, 2%) Died of disease (0, 0%)	12
Flohil 2008-2012	6 head or neck	MMS, frozen control (6)	Recurrence (0, 0%)	3 (mean)
Brady 2001-2013[57]	37 patients 6 ocular, 39 extraocular	MMS, frozen (44) and paraffin (1) control Paraffin section of final stage (8)	Recurrence (0, 0%) Nodal metastasis (0, 0%) Distant metastasis (0, 0%) Died of disease (0, 0%)	43 (mean)

MMS, Mohs micrographic surgery; RT, radiotherapy
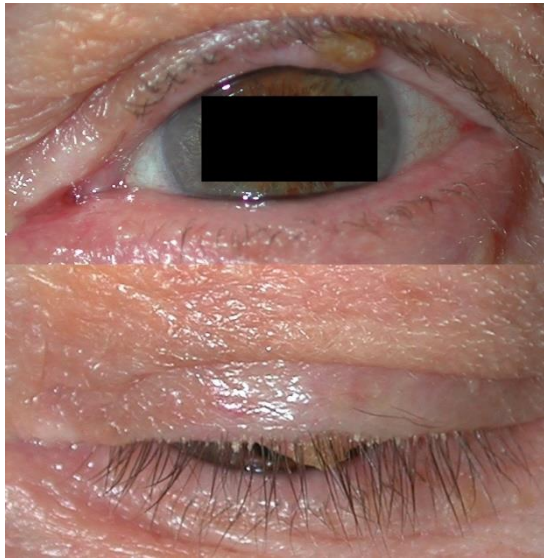
Figures

Figure 1: Crusted yellowish papule on central upper eyelid margin. Eye open above and closed below

Figure 2: Yellowish eyelid plaque and thickening with loss of eyelashes, involving entire lateral upper lid
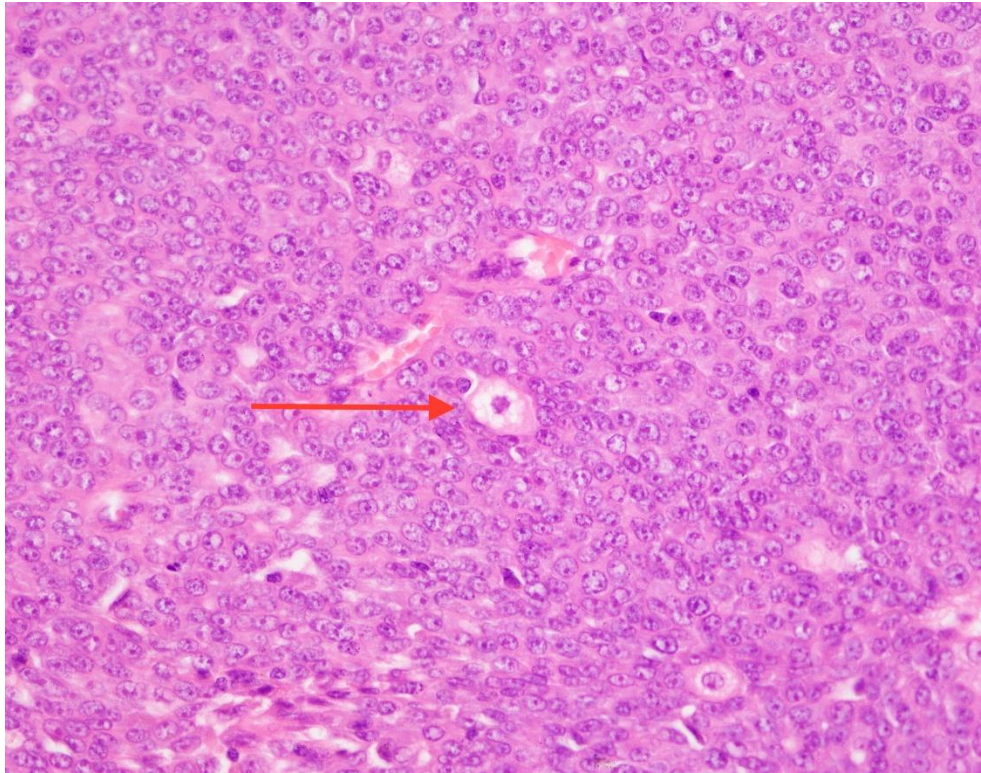
Figure 3: Prominent nucleoli in atypical seboblasts and characteristic multivacuolated pleomorphic sebocytes with scalloped nuclei (arrow), H&E ×400

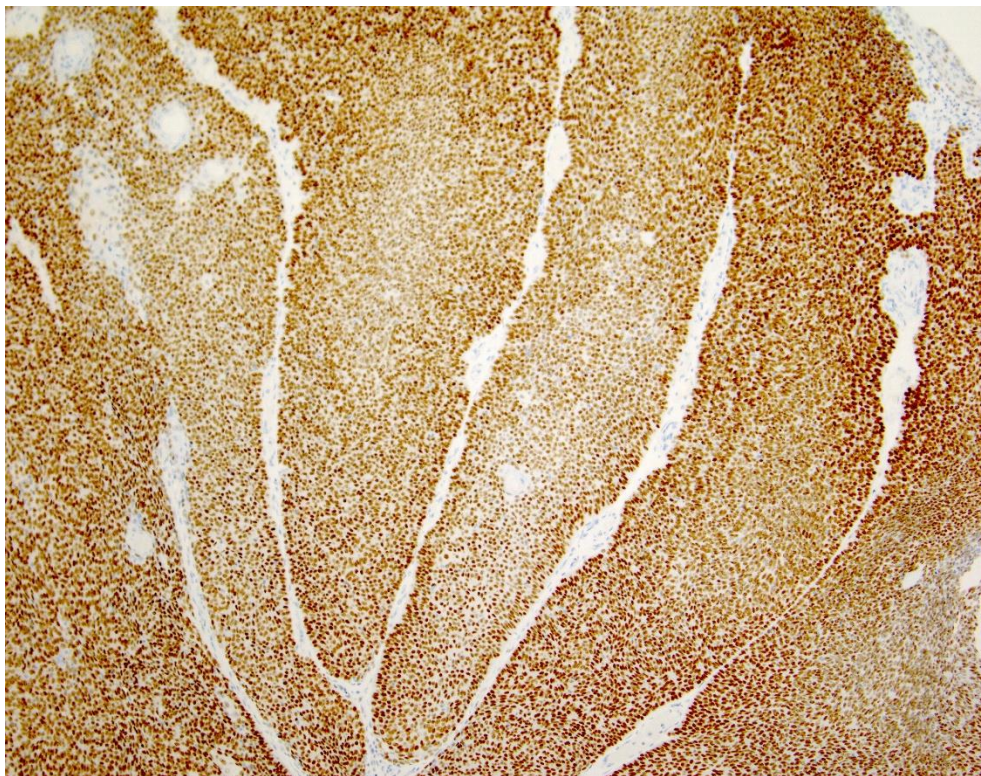Figure 4: Strong androgen receptor staining in >95% of tumour cells, ×100
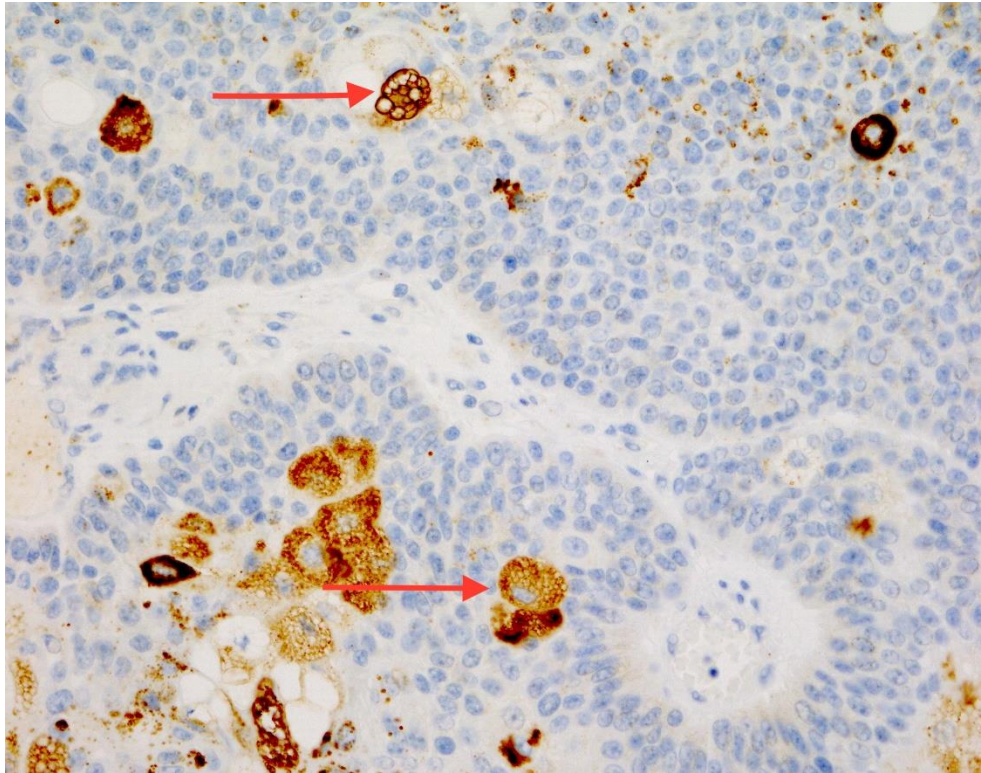
Figure 5: Characteristic cytoplasmic lipid vacuolar staining of tumour cells with adipophilin (arrows), contrasting with non-specific granular staining, ×200
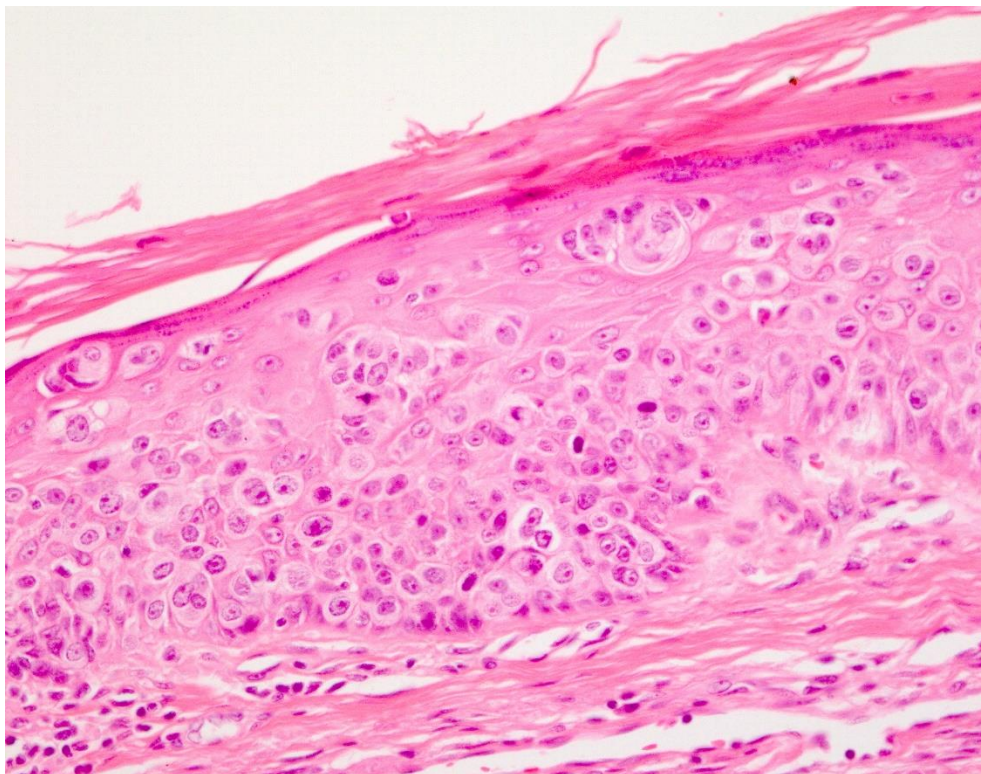

Figure 6: Pagetoid pattern in situ sebaceous carcinoma. Tumour cells are distributed at all levels of the epidermis in clustered and single cell 'buckshot' pattern, H&E ×200

Chapter 2: Re-evaluating the epidemiology of cutaneous sebaceous carcinoma

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<u>Statement of authorship</u>

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

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Introduction

Cutaneous sebaceous carcinoma is most commonly found on the head and neck, and has a propensity for metastasis.[1] It is the third most common eyelid malignancy, but has been reported to be the second most common in some Asian studies.[2,3] There is uncertainty in regard to its gender predilection, with conflicting data in different studies.[1,3] There is also significant uncertainty in regard to its ethnic predilection. It is thought that sebaceous carcinoma is more common among Asians than whites.[4] However, strong evidence to support this is limited. This assumption may have arisen because some Asian studies showed that sebaceous carcinoma accounted for a high proportion of eyelid malignancies (27-39%) even rivalling basal cell carcinoma (BCC) (30-48%).[5] However, this may reflect a lower incidence of BCC and squamous cell carcinoma (SCC) in these populations, and additionally these results are not consistently shown in Asian populations, with registry-based studies finding that BCC accounted for 65-82% of eyelid malignancies and sebaceous carcinoma for 8-11%.[2,6] US data have conversely shown higher incidence of sebaceous carcinoma in whites (2.03 per million) than Asians (1.07 per million, p=0.0001).[7] However, the merging of Asian and Pacific Islander groups in these data could have confounded results.

Methods

This is a review, using the PubMed database, of prospective registry-based data to clarify the uncertainties in regard to the gender and ethnic predilection of sebaceous carcinoma. Inclusion of prospective registry-based data in large populations reduces the selection bias of single-centre case series and increases the accuracy of incidence rates of this rare entity. We include the most recent study from each country reporting on incidence rate, and extract data on gender and incidence rate. The proportion of sebaceous carcinoma occurring in each gender in different studies are compared. Incidence rates in different studies are modified to have the same units of measurement and to describe the same anatomical location, to facilitate comparison.

Results

Studies were identified from the US, Canada, UK, Netherlands, Taiwan and Singapore.[1-3,6,8-10] In these studies, among sebaceous carcinoma overall, the male proportion was higher than the female proportion (range 58-60%); while the female proportion was higher among eyelid sebaceous carcinoma (range 51-70%).[1-3,6,8-10]

In the predominantly white populations of US and Netherlands, age-adjusted incidence rates of all sebaceous carcinoma were 0.23 and 0.1 per 100,000 person-years.[1,9] Ocular sebaceous carcinoma accounts for 26-27% of all sebaceous carcinoma in US and Dutch studies. Therefore, a simple calculation suggests that incidence rates of ocular sebaceous carcinoma would have been approximately 0.06 and 0.03.[1,10] Consistent with this, the UK crude incidence rate of ocular sebaceous carcinoma was 0.04 per 100,000 person-years.[3] Canadian data were not included, as the reported incidence rates were altered by modelling.[8] In the predominantly Chinese populations of Taiwan and Singapore, the incidence rates of ocular sebaceous carcinoma were similar to the white studies. In Taiwan, the incidence rate of ocular sebaceous carcinoma was 0.02-0.03 per 100,000 person-years.[6] In Singapore, the incidence rate for ocular sebaceous carcinoma fluctuated about 0.05 per 100,000 person-years during a 13-year period.[2]

Discussion

Our review consistently showed that more sebaceous carcinoma occur in males overall, and more ocular sebaceous carcinoma occur in females. The apparently conflicting data in the literature was the result of different studies investigating sebaceous carcinoma on different anatomical locations, with most case series focusing on ocular sebaceous carcinoma.[1,3]

In addition, we found similar incidence rates of ocular sebaceous carcinoma in Asians (or at least Chinese) and whites, contrary to popular belief. Our comparison of incidence rates has limitations. Firstly, the different studies used different methods of age adjustment (the US study adjusted to 2000 US standard population, the Dutch studies adjusted to European standard population, and the Chinese studies adjusted to 2000 world population).[1,2,6,9] However, the incidence rates were consistent between multiple studies from different populations, supporting the comparison. Secondly, it is not possible to definitively conclude that Asians and whites have similar incidences of all sebaceous carcinoma, as registry-based data on the anatomical distribution of sebaceous carcinoma in Asians are lacking.

In summary, there has been uncertainty about the gender and ethnic predilection of sebaceous carcinoma. On re-evaluation of the data, we found that more sebaceous carcinoma occur in males overall, but more ocular sebaceous carcinoma occur in females. Also, the incidence of ocular sebaceous carcinoma appears to be similar

between Asians and whites. This knowledge will allow clinicians to better understand the risk factors for sebaceous carcinoma.

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Chapter 3: Epidemiology of cutaneous sebaceous carcinoma

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<u>Statement of authorship</u>

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

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Abstract

Background: There has been uncertainty about the demographics and anatomical distribution of cutaneous sebaceous carcinoma (SC). Incidence rates in different countries and ethnicities have been difficult to compare as different studies focused on different anatomical sites, and adjusted to different standard populations. This study aims to investigate these uncertainties by analysing data from various countries.

Methods: Data were obtained from cancer registries of the United States, England, Norway and Taiwan, and incidence rates were calculated with uniform age-adjustment.

Results: SC were more commonly male than female in white populations, whereas the inverse was true in Taiwan. Ocular SC were more commonly female than male in all populations, despite male predominance of SC overall in white populations. The majority of SC (approx. 70-90%) occurred on head and neck in Asians and whites. Age-adjusted incidence rate (to the 2000-2025 WHO World Standard Population) ranged from 0.07 to 0.18 per 100,000 person-years, and was not higher in Taiwan than white populations.

Conclusion: Overall, the gender and anatomical distributions of SC in whites and Asians show similar patterns, with some differences. SC are not more common in Asians than whites. This knowledge will allow clinicians to better understand the risk factors for SC.

Introduction

Cutaneous sebaceous carcinoma (SC) is a cancer with a propensity for recurrence and metastasis.[1,2] While registry-based data have provided insights into the epidemiology of SC, there remain uncertainties in regard to: 1) the relative incidence in white and Asian populations, 2) gender predilection, and 3) anatomical distribution in Asian populations.[1-10]

To investigate each of these areas, we analyse new data from the cancer registries of several countries.

Methods

The following data on cutaneous SC were extracted from cancer registries: age group, gender and anatomical distribution. Institutional review board approval was obtained.

Data from the United States (US) in 2006-2015 were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 18 database, which covers over 28% of the US population.[1,11] SEER*Stat software version 8.3.5 was used.[12]

Data from England in 1997-2016 were obtained from the National Cancer Registration and Analysis Service (NCRAS). Reporting of cancer cases is required of National Health Service (NHS) hospitals and pathology laboratories, and recommended to private care providers.[13]

Data from Norway in 1987-2016 were obtained from Cancer Registry of Norway. Clinicians, pathologists, radiologists and other laboratory physicians are required to report cancer cases.[14] Cases without histopathologic confirmation were excluded.

Data from Taiwan in 1987-2016 were obtained from Taiwan Cancer Registry (TCR), which requires hospitals with ≥50 beds to report cancer cases.[8] The completeness of the TCR database is greater than 98%, and the TCR is among the highest quality cancer registries in the world.[15]

Data from Singapore were obtained from a Singapore Cancer Registry report. This Registry obtains data reported by doctors, and from pathology reports, hospital records and death certificates.[16]

Anatomical site was categorised using topography codes from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) and ICD-10. Cases of cutaneous SC were identified by the morphology code 8410/3 and topography code C44.

Incidence rates were calculated using the most recent decade of data 2007-2016 (2006-2015 was used for US). Incidence rates were age-adjusted to the 2000-2025 WHO World Standard Population, using five-year age groups as well as 85+ years.

Results

Table 1 shows cutaneous SC cases in each country in 2007-2016 by age group. Table 2 shows cases by gender and anatomical site. Table 3 shows cases by laterality and anatomical site.

In the US, England, Norway and Taiwan, SC occurred most frequently in age groups greater than 60 years.

In US, England and Norway, SC were more commonly male than female (ratio 1.2-1.7 to 1). However in Taiwan, SC were more commonly female (ratio 1.3 to 1). Eyelid SC were more commonly female in all of these countries (ratio 1.3-1.7 to 1).

In Taiwan, head and neck SC (including ocular SC) accounted for 91% of SC, and over half of all SC occurred on the eyelid (the most common site) in both males and females. In US, England and Norway, head and neck SC made up 71-79% of cases due to a higher proportion of SC on trunk/limbs, and approximately half of all SC were non-eyelid head and neck (the most common site).

In the US, England, Norway and Taiwan, the age-adjusted incidence rates per 100,000 person-years were 0.18, 0.10, 0.07 and 0.12, respectively.

In the US, England and Taiwan, among cases with known laterality, there was no strong predilection for either side.

In England in 2007-2016, reported non-melanoma skin cancers included basal cell carcinoma (BCC) (n=808,180 or 77%), squamous cell carcinoma (SCC) (n=236,336 or 23%) and SC (n=1,076 or 0.1%).

In US in 2006-2015, there were 71 cases of skin SC in situ (26 eyelid, 35 non-eyelid head and neck, 10 trunk/limbs). In Taiwan in 1987-2016, there were four cases, three of which occurred on the eyelid. Thus, the ratio of skin SC in situ to skin SC in US and Taiwan were 1:34 and 1:185, respectively.

Singapore

There were 47 skin SC in Singapore's resident population from 2003 to 2012.[16] In contrast, there were 2,800 BCC and 1,102 SCC. Thus among these neoplasms, SC accounted for 1% of cases. The calculated crude incidence rate is 0.13 per 100,000 person-years.

Discussion

The gender predilection of SC has been uncertain, with conflicting data in previous registry-based studies.[1-3,5-7] In addition, the gender predilection of all SC in Asian populations has been uncertain, as Asian registry-based data tended to focus on ocular SC (showing a higher female proportion on the eyelid).[3,4,8] Our data show a male predilection of all SC in white populations, but a female predilection in Taiwan.

Gender predilection varies depending on anatomical site. Our data show that eyelid SC were more commonly female than male in both white and Asian populations. This was despite a strong male predominance of SC overall in white populations. The reason for this is unknown, but it may reflect differences in the nature or density of sebaceous glands on the eyelid between males and females.

The anatomical distribution of Asian SC has been uncertain as previous Asian registry-based data tended to focus only on the ocular region.[3,4,8] Our data show a difference in anatomical distribution of SC between white and Asian populations. In Taiwan, the most common site of SC was the eyelid. In contrast in the white populations of US, England and Norway, the most common site was non-eyelid head and neck. Also, the vast majority of SC occurred on the head and neck, with a higher proportion in Asians (approximately 90% of SC) than whites (approximately 70-80%). These differences may be due to different biological characteristics of SC in whites and Asians. Asians and whites have differing presentations (Asians tend to present as a nodule rather than eyelid thickening), and intraepithelial spread may be less common in Asians.[17,18] Genetic studies may help to elucidate any biological underpinnings for these ethnic differences.

It is frequently assumed that SC occur more commonly in Asians than whites; however, data to support this are limited.[3,19] It may be a perception based on high proportions of SC (accounting for up to 39% of eyelid malignancies) compared to BCC in Asian studies, rather than a true difference in incidence.[20-25] Asian registry-based data do not support these studies and show proportions of 8-11%.[4,8] In a US centre, SC accounted for 2% of eyelid malignancies.[20] We found SC accounted for 0.1% of all BCC/SCC/SC in England, and 1% in Singapore. However, good quality registry-based data on BCC and SCC are scarce, making it more difficult to investigate the relative proportions of non-melanoma skin cancers.

Ethnic variation in incidence has previously been difficult to analyse as rates were age-adjusted to different standard populations and Asian registry-based data focused on ocular SC only.[1,3-9] We perform this analysis, age-adjusting rates to a common standard population. Age-adjusted incidence rate was 0.12 per 100,000 person-years in Taiwan, and ranged from 0.07 to 0.18 per 100,000 person-years in the white populations. These data do not support a higher incidence in Taiwan than white populations, but further studies are required to determine incidence in other Asian populations, particularly Japan where high numbers of cases are anecdotally reported.

Potential underreporting is a limitation of any registry-based data. However, the different registries had similar findings and incidences, supporting the validity of the data. Another limitation is that only one Asian registry was included. This is a large registry but findings may differ in other Asian populations.

Using data from various countries, we found a male predilection of SC in white populations, but a female predilection in Asians. In both white and Asian populations, there was a strong female predilection of ocular SC. SC occur most commonly on the eyelid in Asians and on non-eyelid head and neck in whites. The vast majority of SC occurs on the head and neck, with a higher proportion in Asians. There was no clear difference in age-adjusted incidence between Asians and whites.

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Tables

Table 1: Sebaceous carcinoma cases by age group in most recent decade (2007-2016)

Age group (y)	SEER 18[a]	England	Norway	Taiwan
0-19	4 (0%)	1 (0%)	0 (0%)	0 (0%)
20-39	28 (1%)	6 (1%)	1 (1%)	7 (2%)
40-59	441 (18%)	135 (13%)	8 (10%)	77 (19%)
60-79	1162 (49%)	532 (49%)	27 (35%)	202 (50%)
80+	759 (32%)	402 (37%)	42 (54%)	122 (30%)
Total	2394	1076	78	408

[a]SEER 18 data are from 2006-2015

Table 2: Sebaceous carcinoma cases by subsite and gender

	SEER 18 (2006-2015)		England (1997-2016)		Norway (1987-2016)		Taiwan (1987-2016)	
Site	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Eyelid	221 (15)	279 (31)	242 (26)	327 (42)	14 (15)	20 (36)	170 (53)	289 (69)
Head and neck, excluding eyelid	818 (55)	412 (46)	476 (52)	293 (38)	45 (49)	24 (44)	115 (36)	94 (22)
Trunk and limbs	447 (30)	197 (22)	175 (19)	142 (18)	21 (23)	5 (9)	23 (7)	25 (6)
Total[a]	1500	894	924	780	91	55	320	418

[a]Includes 'overlapping subsites, and unspecified subsite'

Table 3: Sebaceous carcinoma cases by laterality

	SEER 18 (2006-2015)			England (1997-2016)			Taiwan[b] (1987-2016)		
Site	Left	Right	Other[a]	Left	Right	Other[a]	Left	Right	Other[a]
Eyelid	238	257	5	262	280	27	107	154	198
Head and neck, excluding eyelid	458	411	361	206	217	346	34	36	139
Trunk and limbs	271	272	101	71	57	189	13	13	22
Overlapping subsites, and unspecified subsite	3	1	16	3	2	44	3	5	14

[a]Includes midline and unknown; [b]Laterality only reported after 2007

Chapter 4: Eyelid sebaceous carcinoma in situ presenting as haemorrhagic cyst

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<u>Statement of authorship</u>

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Albert Wu   2020

<u>Author contributions</u>

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Data analysis: AW, MS, SO

Literature review/study results interpretation: AW, MS, SO, SH, DS

Final manuscript draft/editing: AW, MS, SO, SH, DS

Michelle T Sun   2020   Shyamala C Huilgol   2020

Sophia Otto   2020   Dinesh Selva   2020

Introduction

Sebaceous carcinoma (SC) is the second or third most common eyelid malignancy. It has a propensity for metastasis, and has a five-year disease-related mortality rate of 19%.[1] We describe the first case of eyelid SC presenting as a haemorrhagic cyst and the seventh case of ocular SC in situ since the year 2000.

Case

A 64-year-old Asian woman presented with a well-defined, dark purple, painless cyst, 5mm in diameter, in the left superior tarsus (Figure 1). The lesion had been present for 6 months but rapidly increased in size over the preceding 2 weeks. She reported some mild epiphora and occasional irritation. The clinical appearance was consistent with a haemorrhagic cyst or a pigmented chalazion. There were no palpable lymph nodes. An incisional biopsy was performed, and the lesion was found to be cystic and contained blood. The biopsy showed poorly differentiated carcinoma, but the cellular differentiation could not be confidently established. There was positive immunolabelling for the squamous cell markers (P40, P63, CK5/6, EMA), a basal cell carcinoma marker BerEp4, and androgen receptor which is a sensitive marker of SC.

She underwent left upper eyelid excision with frozen-section control, along with map biopsies of the bulbar and palpebral conjunctivae. Reconstruction was performed with a sliding tarso-conjunctival flap and V-Y subcutaneous island pedicle skin flap. Histology revealed expansion of sebaceous glands and involvement of the conjunctival epidermal junction by mitotically active malignant cells. The cells had large vesicular nuclei, a high nuclear/cytoplasmic ratio, and vacuolated foamy cytoplasm. The findings were consistent with SC with intraepithelial involvement, also known as Pagetoid spread. The margins were clear with no invasive component identified (Figure 2). Immunohistochemistry showed normal expression of mismatch repair gene proteins MLH1, MSH2, MSH6 and PMS2. The patient made an uncomplicated recovery and at one month follow-up the eyelid was in a good position with no lagophthalmos or entropion.

Discussion

Eyelid SC are notorious for masquerading as benign conditions, delaying diagnosis and worsening prognosis. A previously reported SC was clinically diagnosed as an intratarsal keratinous cyst, and this presented as a non-tender blue-greyish firm nodule fixed to tarsus.[2] Our patient is the first reported case presenting atypically as a haemorrhagic cyst. The cystic presentation may be due to sebaceous carcinoma

cells colonising the lining epithelium of sebaceous units, resulting in cystic dilatation. Although the lesion appeared clinically benign, the history of recent rapid growth was suspicious, prompting a biopsy. It is important to maintain a high index of suspicion to allow prompt diagnosis and management.

Our case is a 'SC in situ', a term which describes non-invasive SC confined to the epithelium, including epidermis, glands and ducts (AJCC8 Tis).[3,6] This is a very rare entity. To our knowledge, this case is the seventh ocular SC in situ to be described in the literature since the year 2000.[4] The same treatment as for invasive SC (excision) is recommended, due to its potential for aggressive behaviour.[5]

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Figures

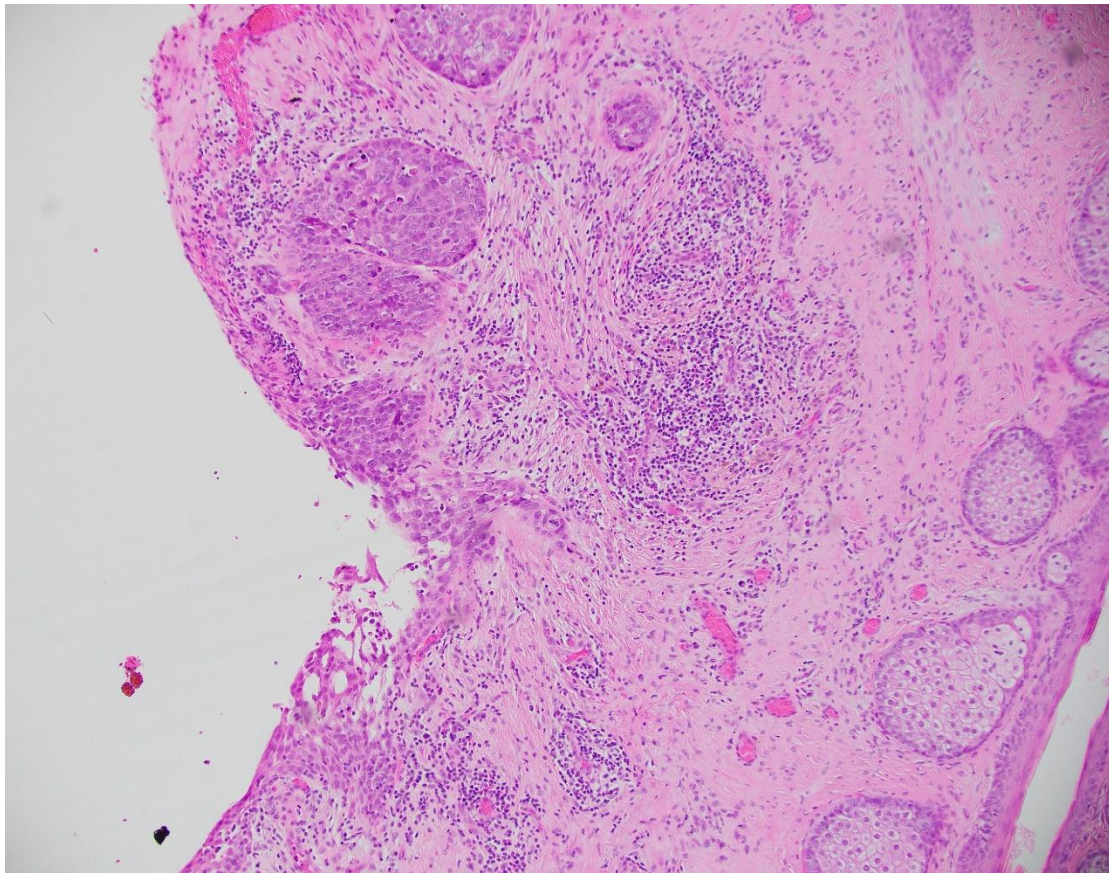Figure 1: Left upper lid sebaceous carcinoma clinically resembling a haemorrhagic cyst

Figure 2: Invaginating tongues of neoplastic cells with full thickness epithelial involvement (H&E, ×10)

Chapter 5: Nasolacrimal duct obstruction secondary to lacrimal sac involvement by sebaceous carcinoma

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Statement of authorship

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Albert Wu   2020

Author contributions

Principal author (AW) contribution: 70%

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Data analysis: AW, DC, RM

Literature review/study results interpretation: AW, DC, RM, DS, GD

Final manuscript draft/editing: AW, DC, RM, DS, GD

David S Curragh   2020   Dinesh Selva   2020

Rebecca Morrow   2020   Garry Davis   2020

Abstract

Sebaceous carcinoma (SC) is the third most common eyelid malignancy in Australia, and is potentially fatal. It usually presents as a nodule or diffuse eyelid thickening, and is commonly misdiagnosed. We describe a case of SC with lacrimal sac involvement, presenting with clinical features of nasolacrimal duct obstruction. At the time of endoscopic dacryocystorhinostomy (DCR), nasal endoscopy revealed a polypoid mass of the opened lacrimal sac. Biopsy of the mass showed poorly differentiated SC. The lacrimal drainage apparatus was later excised via a combined external and endoscopic approach. Conjunctival map biopsies showed extensive intraepithelial disease, which was treated with topical mitomycin C. At three-month follow-up, there was no evidence of residual disease on nasal endoscopy or repeat conjunctival biopsy.

Introduction

Sebaceous carcinoma (SC) is the third most common eyelid malignancy in Australia.[1] It has a propensity to metastasise and is potentially fatal.[2] Ocular SC usually presents as a nodule or diffuse eyelid thickening.[3] These non-specific presentations frequently lead to misdiagnoses as chalazia or blepharoconjunctivitis.[1] Involvement of the lacrimal sac and presentation as nasolacrimal duct obstruction are uncommon.[4] We describe an unusual case of SC with these features.

Case

A 57-year-old Caucasian female presented with a 12-month history of right-sided epiphora and intermittent discomfort of the right eye. The lower canaliculus was irrigated with saline, resulting in complete reflux from the upper canaliculus, suggestive of nasolacrimal duct obstruction. Dacryocystography was performed but was of poor quality and not helpful diagnostically. The upper eyelid tarsal conjunctiva demonstrated papillae and inflammation (Figure 1), and the cornea had an irregular epithelial appearance. The caruncle appeared normal.

An endoscopic dacryocystorhinostomy (DCR) was performed. After opening the lacrimal sac, a polypoidal mass was seen obscuring the internal opening of the common canaliculus. Biopsy of the mass revealed a lobulated malignant basaloid tumour with diffuse infiltration of the submucosal stroma (Figure 2). The lesional cells showed nuclear atypia, and sebaceous differentiation in the form of clear cytoplasmic vacuoles indenting the nuclei. Mitoses were readily identified. On immunohistochemistry, the tumour showed positive labelling for AR, CK7, CD117 and adipophilin (Figure 3), supporting the morphological impression of a poorly differentiated SC. The SC extended to the deep margin at the base of the polyp. As sebaceous neoplasms can occur in Muir-Torre syndrome, immunohistochemistry for mismatch repair proteins was performed and showed no loss of nuclear labelling of MLH1, MSH2, MSH6 and PMS2. The lacrimal drainage apparatus was subsequently excised via a combined external and endoscopic approach, and conjunctival map biopsies were taken. From an endoscopic approach, the nasolacrimal duct was accessed by excising the anterior head of the inferior turbinate to free the nasolacrimal duct from its bony canal. Mucosal incisions were made around both the opening of the nasolacrimal duct in the inferior meatus and the residual opened lacrimal sac to free it from the nasal mucosal aspect. Subsequently, via an external incision, similar to that created for an external DCR, the lacrimal drainage apparatus was removed en bloc after freeing the canaliculi from the medial canthus. Histology

confirmed invasive SC in the lacrimal drainage apparatus, and extensive intraepithelial disease colonising the superior tarsal and bulbar conjunctiva (Figure 2). The AJCC 8th Edition category was T4b.[15]

Over a six-week period, three cycles (seven days each) of topical mitomycin C (MMC) 0.04% qid were applied to treat the conjunctival intraepithelial disease. She developed a moderate anterior uveitis which settled with topical steroid. Positron emission tomography (PET) scan revealed two enlarged cervical lymph nodes which were negative for carcinoma on fine needle aspiration biopsy. On repeat imaging with ultrasonography at two months, the nodes had decreased in size. At three-month follow-up, there was no evidence of recurrence on nasal endoscopy. Repeat conjunctival biopsies revealed benign inflammatory changes, with no evidence of residual SC (Figure 4).

Discussion

We describe a case of lacrimal sac SC with the unusual presentation of nasolacrimal duct obstruction. This is different to previous cases which presented primarily as masses (Table 1).[4-6]

The lacrimal sac is an unusual site for SC. Several mechanisms have been proposed to explain this phenomenon. One mechanism is contiguous epithelial spread of ocular SC to the lacrimal sac as described in a previous case.[6]

Another possible mechanism of spread is non-contiguous, with tumour cells being carried by tears and implanting in the lacrimal drainage apparatus (oncorrhoea). This may explain two previous cases of lacrimal sac SC that both occurred five years after excision of ocular SC.[4,5] In both cases, the site of the primary SC was not contiguous with the lacrimal sac. This mechanism of tumour seeding may explain the phenomenon of multicentric and skip lesions that has been postulated to occur in SC.[7] Due to this theoretical risk of tumour seeding, tumour cell dissemination should be minimised during surgery for SC.[4]

Other theoretical mechanisms for lacrimal sac SC without a history of ocular SC are the presence of ectopic sebaceous glands or sebaceous gland metaplasia of the lacrimal sac. One case of primary SC of lacrimal sac has been reported.[4]

Given that our case involved the tarsal conjunctiva, and ocular SC often arise from Meibomian glands of tarsus, the tumour likely arose from the superior tarsus and spread to the lacrimal sac where it developed into a mass.[3] To establish if spread was contiguous or non-contiguous, histological examination of the lacrimal canaliculi was attempted. Unfortunately, the mechanism of spread could not be confirmed due to ulceration of surface mucosa and distortion of normal architecture by tumour.

Treatment of primary malignancies of the lacrimal drainage apparatus often involves wide surgical resection with adjunctive radiation and/or chemotherapy.[8] En bloc tumour resection along with the surrounding bony structures can achieve tumour margin clearance and local tumour control.[9,10] Various alternative approaches with and without bony excision have been described via a combined external and endoscopic approach.[11,12]

Topical MMC is sometimes used as primary or adjuvant treatment for ocular SC. In our case, it was used for extensive intraepithelial disease which would be challenging to completely excise and reconstruct. Data on treatment outcomes following a full course of primary topical MMC have been limited and mixed. The recurrence rates in two series were 3/3 cases at 29-month follow-up, and 0/3 cases at ten-month follow-up, respectively.[13,14] Given these results, close follow-up is required to monitor for recurrence. Due to the significant risk of metastasis from SC in general, close nodal surveillance is also recommended.

This case demonstrates the need to maintain an index of suspicion for SC when a lacrimal sac lesion is found in the presence of chronic conjunctival disease. Diagnosis of the conjunctival disease prior to dacryocystorhinostomy would have led more appropriately to a lacrimal sac biopsy without breaching bone, with possible beneficial long-term consequences to the patient.

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Tables

Table 1: Cases of lacrimal sac SC

Age (y)	Gender	AJCC8	Treatment	Outcome
57	Female	T4b	Excision Topical mitomycin C	No recurrence at 3 months
74	Female	T4b	Excision Adjuvant RT	No recurrence at 2.5 years
85	Female	T4b	Exenteration Adjuvant RT	No recurrence at 3 years
70	Female	T4b	Excision Adjuvant RT	No recurrence at 13 months

Figures

<u>Figure 1</u>: Papillae and inflammation of upper eyelid tarsal conjunctiva
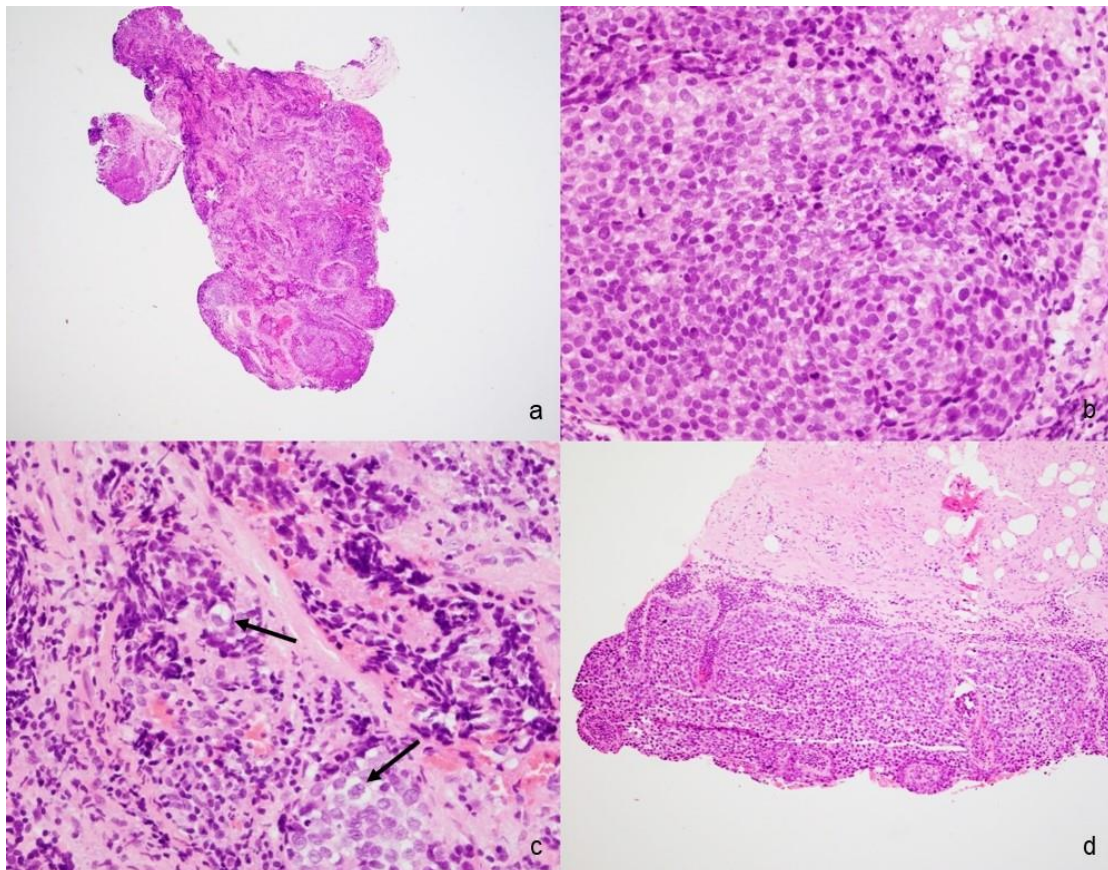
<u>Figure 2</u>: Lacrimal sac polyp demonstrating the infiltrative nested basaloid sebaceous carcinoma within the submucosal stroma, extending to the deep margin/stalk of the polyp, H&E ×10 (a). Sebaceous carcinoma nests composed of cells with multi-vacuolated clear cytoplasm which indent the nuclei (arrows), H&E ×40 (b, c). Subsequent tarsal plate biopsy showing sebaceous carcinoma colonising the surface epithelium, H&E ×20 (d).

Figure 3: Immunohistochemistry. Cytoplasmic positive labelling with CK7 ×20 (a). Nuclear positive labelling with AR ×20 (b). Cytoplasmic 'droplet' pattern of positive labelling with adipophilin (arrows) ×40 (c).
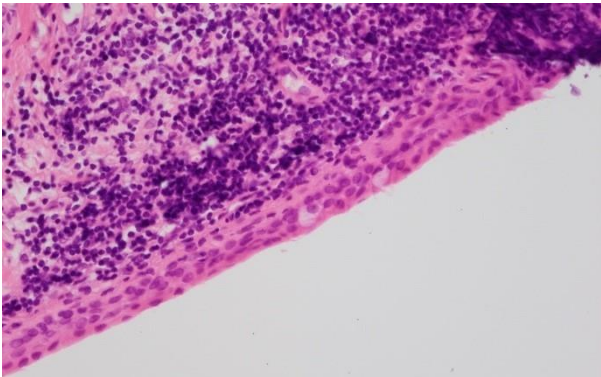
Figure 4: Post-treatment tarsal biopsy demonstrating benign conjunctival mucosa and underlying chronic inflammation, H&E ×40.

Chapter 6: Management of sebaceous carcinoma (survey of Mohs and oculoplastic surgeons)

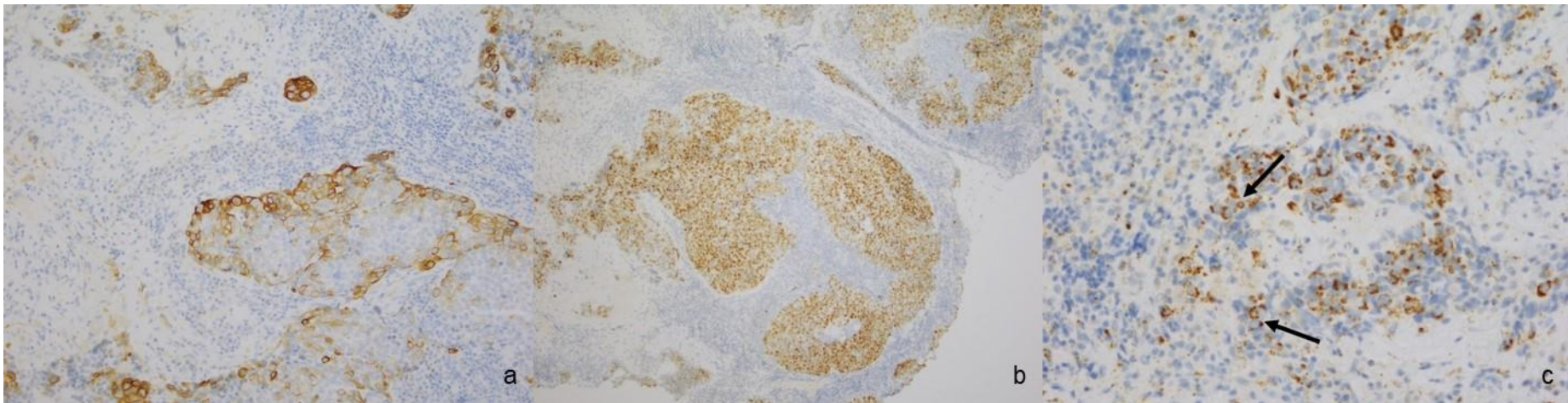This manuscript has been submitted to Clinical & Experimental Ophthalmology.

This work was presented at 52nd Annual Scientific Meeting of Australasian College of Dermatologists, Melbourne, 2019.

<u>Statement of authorship</u>

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Albert Wu   2020

<u>Author contributions</u>

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Abstract

Background: The optimal management of sebaceous carcinoma (SC) remains uncertain, due to its rarity and thus limited data on which to base recommendations.

Methods: Survey of the management preferences of Australian (AU) Mohs surgeons, and Australian and New Zealand (ANZ), and Japanese (JP) oculoplastic surgeons.

Results: There were 30 responses from AU Mohs surgeons, 16 from ANZ oculoplastic surgeons, and 28 from JP oculoplastic surgeons. AU Mohs surgeons were more likely (40%) to routinely investigate for other malignancies of Muir-Torre Syndrome than ANZ (7%) and JP (15%) oculoplastic surgeons. For ocular SC, AU Mohs surgeons most frequently used Mohs surgery with frozen section margin control (68%), while ANZ oculoplastic surgeons performed excision with paraffin section margin control (67%). In Australia/New Zealand, at least 16% of Mohs surgeons preferred to refer ocular SC to ophthalmology and 27% of oculoplastic surgeons preferred Mohs surgery. For extraocular SC, AU Mohs surgeons most frequently performed excision without margin control (53%), followed by Mohs surgery with frozen section margin control (27%). SC cases were usually followed up for up to five years or more.

Conclusion: This survey shows variation in management for SC between countries, between Mohs and oculoplastic surgeons, and between anatomical locations. This information may provide a foundation on which to develop Asia-Pacific consensus guidelines.

Introduction

Cutaneous sebaceous carcinoma (SC) occurs almost exclusively on the head and neck, and has a propensity for metastasis.[1-3] The optimal management of SC remains uncertain, due to its rarity and thus limited data on which to base recommendations.[4-10] Areas of uncertainty include whether to investigate for subclinical metastasis and other malignancies of Muir-Torre Syndrome, whether to perform sentinel lymph node biopsy and conjunctival map biopsies, and whether to use intraoperative histologic margin control and if so which method (e.g. frozen section, paraffin section, or Mohs).[4-6,9,10] We surveyed the management preferences of different groups of clinicians in different countries, which may provide a foundation to develop Asia-Pacific consensus guidelines. These groups of clinicians were Australian (AU) Mohs surgeons, and Australian and New Zealand (ANZ), and Japanese (JP) oculoplastic surgeons.

Methods

A survey was emailed to members of The Australasian College of Dermatologists Mohs surgeons' group, Australian and New Zealand Society of Ophthalmic Plastic Surgeons (ANZSOPS), and Japanese Society of Ophthalmic Plastic and Reconstructive Surgery (JSOPRS) between January and April 2019. The surveys for Mohs surgeons and oculoplastic surgeons were tailored for the respective subspecialty groups and were created using Qualtrics online survey software. Mohs surgeons were asked about cutaneous SC only, and oculoplastic surgeons were asked about ocular SC only. The 'ocular' region was defined superiorly by the superior margin of the eyebrow and inferiorly by the inferior orbital rim, and included the medial and lateral canthi. Survey questions were multiple choice asking for a single answer unless otherwise specified. It was mandatory to answer Q3 and Q4 (Table 1). Other questions were optional. Institutional review board approval was obtained from the Adelaide Surgicentre Medical Advisory Committee.

Results

From 62 AU Mohs surgeons, there were 34 responses, of which 30 were completed and analysed in this study (48%). From approximately 60 ANZ oculoplastic surgeons, there were 16 completed responses (27%), after excluding two incomplete ones. Of JP oculoplastic surgeons, there were 28 completed responses, after excluding seven incomplete ones.

Survey questions and answers are detailed in Tables 1-3.

For ocular SC, AU Mohs surgeons most frequently used Mohs surgery with frozen section margin control (68%), while ANZ oculoplastic surgeons most frequently performed excision with paraffin section margin control (67%) (Q14). JP oculoplastic surgeons most often performed excision with either paraffin section (41%) or frozen section margin control (48%).

For extraocular SC, AU Mohs surgeons most frequently performed excision and direct reconstruction without margin control (53%), followed by Mohs surgery with frozen section margin control (27%) (Q15).

ANZ and JP oculoplastic surgeons used similar surgical margins (median 5mm, range 2-10), and accepted a similar minimum pathological margin (median 3-3.5mm, range 1-5) (Q17-18). When performing non-Mohs excision, AU Mohs surgeons used a median margin of 5.5mm (range 3-10), and accepted a median minimum pathological margin of 3.75mm (range 1-10).

The proportion of SC cases discussed at a multidisciplinary team meeting was variable, with some surgeons discussing all cases and some discussing none (Q19). AU Mohs surgeons were least likely to discuss cases at a multidisciplinary team meeting.

Topical mitomycin C was almost never (95%) used by AU Mohs surgeons, but was used by 53% of ANZ and 26% of JP oculoplastic surgeons for ocular SC (Q20). Most AU Mohs surgeons (100%) and ANZ oculoplastic surgeons (80%) did not use cryotherapy for ocular SC (Q21). In contrast, 48% of JP oculoplastic surgeons used it in at least some cases. The majority of AU Mohs surgeons (96%) and ANZ oculoplastic surgeons (60%) did not refer SC for radiotherapy, while 74% of JP oculoplastic surgeons referred at least some cases for radiotherapy (Q22).

Discussion

This survey demonstrates considerable variation in the management preferences for SC between different groups of clinicians. Areas that varied between the groups included whether to investigate for other malignancies of Muir-Torre Syndrome, whether to perform conjunctival map biopsies, and which method of intraoperative margin control to use.

Some centres routinely obtain radiologic imaging to search for subclinical metastasis of SC.[9] The risks of nodal and distant metastasis from SC are up to 25% and 14%, respectively.[11,12] In our survey, a significant proportion of AU Mohs (64%) and ANZ oculoplastic (40%) surgeons did not obtain imaging to search for subclinical metastasis (Q5-6). JP oculoplastic surgeons were more likely to obtain routine imaging (48%). Imaging was more likely to be obtained for subclinical lymph node metastasis than distant metastasis.

Sentinel lymph node biopsy (SLNB) has the potential to identify subclinical and sub-radiological nodal metastasis, which helps with staging and treatment planning. Some researchers have recommended using it in SC cases at higher risk of developing nodal metastasis.[13] However, data on whether SLNB impacts on disease outcomes of SC are scant. In addition, its drawbacks include time and resource costs, and inter-operator variability.[10,14] Adverse effects include transient periocular blue discolouration, temporary ipsilateral face oedema, and temporary weakness of marginal mandibular nerve.[10,14] These may explain why only a quarter of the surveyed surgeons have used SLNB for SC (Q8).

Conjunctival map biopsies are used to identify tumour involvement in macroscopically normal areas, determine the extent of tumour, and plan definitive treatment. Of the limited evidence supporting this procedure, it was found that superior and inferior conjunctivae were similarly likely to have positive map biopsy (31-36%) even when SC originated from a single eyelid (upper lid).[15,16] We found that conjunctival map biopsy was used routinely by most ANZ oculoplastic surgeons (73%) (Q10). In contrast, most AU Mohs surgeons (100%) and JP oculoplastic surgeons (96%) used it in only some or none of their cases. The Mohs surgeons might have considered the procedure to be unnecessary as Mohs surgery allows examination of the entire margin. However, SC has been purported to exhibit skip lesions, that could theoretically be missed with Mohs surgery. Presumably to reduce this risk, a significant minority of Mohs surgeons (27%) removed an additional layer after a tumour-free plane was achieved (Q16). JP oculoplastic surgeons may have used conjunctival map biopsy less than ANZ oculoplastic surgeons as the yield may be lower in Asian cases which have a lower rate of intraepithelial spread.[17] This would be consistent with North American consensus guidelines which recommend considering conjunctival map biopsy for cases with pagetoid spread.[7,19] Conjunctival map biopsy was also used infrequently in the United Kingdom in 2008-2010, being used in 20% of all ocular SC treated by ophthalmologists.[6]

Surgeons perform conjunctival map biopsy in varied ways. Of ANZ oculoplastic surgeons who performed conjunctival map biopsy, 79% took samples from the entire conjunctiva, while 21% only sampled conjunctiva in close proximity to the clinically appreciable tumour (Q11). In contrast, JP oculoplastic surgeons who performed the procedure were most likely (42%) to only sample areas with clinical suspicion of involvement. Thus, JP oculoplastic surgeons tended to perform a less extensive form of the procedure than ANZ oculoplastic surgeons. This difference in practice may again reflect the lower rate of intraepithelial spread in Asian cases.[17]

When SC is diagnosed, the possibility of Muir-Torre Syndrome should be considered. There is uncertainty around which cases require specific investigations for other malignancies.[18,19] Various factors may influence this decision, such as personal and family history and tumour site. Investigations for other malignancies can include colonoscopy, endometrial biopsy and urine cytology.[18,19] AU Mohs surgeons were more likely (40%) to arrange investigations in all cases than ANZ (7%) and JP (15%) oculoplastic surgeons (Q12). Each surgeon group was more likely to arrange investigations in cases with a personal or family history of internal malignancy.

Intraoperative histologic margin control increases the likelihood of complete clearance at the first procedure and helps conserve normal tissue.[1] Margin-controlled techniques are also recommended in North American consensus guidelines for ocular and extraocular SC.[7,19] The main methods of margin control are Mohs surgery, frozen section and fast paraffin. Frozen section analysis is highly technician and pathologist dependent, and has been thought to be unreliable for SC. However, it has produced good results in a centre experienced in using frozen sections for SC.[20] There remains uncertainty in regard to the optimal surgical method for combining tumour clearance, tissue conservation and patient tolerability. The wide variation in margin control methods found in this survey may reflect variable access to Mohs surgery (no access for 70% of JP oculoplastic surgeons, compared to readily available for 80% of ANZ oculoplastic surgeons) (Q13). AU Mohs surgeons were more likely to use margin control methods for ocular SC than extraocular SC (Q14-15), probably because eyelid defects represent a greater reconstructive challenge which makes tissue conservation more desirable.

Due to the risk of metastasis, close nodal surveillance has been recommended in the literature for high-risk ocular SC.[17] However, the optimal duration of follow-up is

uncertain. We found that surgeons usually followed up SC cases for up to 5 years or more (Q23).

JP oculoplastic surgeons treated more SC cases per surgeon than ANZ oculoplastic surgeons despite comparable duration of practice (Table 1). This may partly be due to a higher proportion of Australian cases being treated by Mohs surgeons instead. Another possibility is that the incidence of ocular SC is higher in Japan. To investigate this hypothesis, registry-based data from Japan are required and these are currently lacking.[21]

Limitations of this study include the response rate, and potential for recall bias. As the study was cross-sectional, management preferences may change over time. In addition, findings may not be generalisable to other countries.

In summary, this study presents the management preferences of AU Mohs surgeons, and ANZ and JP oculoplastic surgeons. This survey shows variation in practice for SC and may provide a foundation on which to develop Asia-Pacific consensus guidelines. Any consensus guideline needs to take into account significant differences in management between countries, between Mohs and oculoplastic surgeons, and between anatomical locations.

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Tables

Table 1: Profile

Question	Answer	Australian Mohs surgeons (n, %)	Australian/New Zealand oculoplastic surgeons (n, %)	Japanese oculoplastic surgeons (n, %)
1. For how many years have you been practising Mohs/oculoplastic surgery (including subspecialty training time)?	0-2	2 (7)	0 (0)	1 (4)
	3-5	3 (10)	0 (0)	3 (11)
	6-10	5 (17)	4 (25)	8 (29)
	11-20	11 (37)	7 (44)	10 (36)
	>20	9 (30)	5 (31)	6 (21)
2. What proportion of your dermatology clinical time is spent on Mohs surgery (consulting and operating)?	<10%	3 (10)		
	10-30%	14 (47)		
	31-50%	7 (23)		
	51-70%	3 (10)		
	71-90%	1 (3)		
	>90%	2 (7)		
3. In the last 10 years, how many cases of sebaceous carcinoma do you estimate you have treated?[a]	0	5 (17)	1 (6)	1 (4)
	1-2	11 (37)	0 (0)	0 (0)
	3-5	9 (30)	10 (63)	5 (18)
	6-10	4 (13)	3 (19)	4 (14)
	11-20	1 (3)	1 (6)	5 (18)
	21-30	0 (0)	1 (6)	6 (21)
	>30	0 (0)	0 (0)	7 (25)
4. Of these cases, how many were ocular?	All	10 (40)		
	Most	6 (24)		
	Some	3 (12)		
	None	6 (24)		

[a]If '0' was selected, the survey would end at this question

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Table 2: Investigations

Question	Answer	Australian Mohs surgeons (n, %)	Australian/New Zealand oculoplastic surgeons (n, %)	Japanese oculoplastic surgeons (n, %)
5. In the last 10 years, in how many sebaceous carcinoma cases did you obtain radiologic imaging to search for subclinical lymph node metastasis?	All	6 (24)	5 (33)	13 (48)
	Most	0 (0)	0 (0)	4 (15)
	Some	3 (12)	4 (27)	8 (30)
	None	16 (64)	6 (40)	2 (7)
6. In the last 10 years, in how many sebaceous carcinoma cases did you obtain radiologic imaging to search for subclinical distant metastasis?	All	2 (8)	2 (13)	11 (41)
	Most	0 (0)	2 (13)	5 (19)
	Some	4 (16)	5 (33)	8 (30)
	None	19 (76)	6 (40)	3 (11)
7. Do you have access to sentinel lymph node biopsy for sebaceous carcinoma?	No access	1 (4)	0 (0)	20 (74)
	Limited access	3 (12)	7 (47)	4 (15)
	Readily available	10 (40)	8 (53)	2 (7)
	Don't know	11 (44)	0 (0)	1 (4)
8. In the last 10 years, in how many sebaceous carcinoma cases did you perform/arrange sentinel lymph node biopsy?	All	0 (0)	0 (0)	0 (0)
	Most	0 (0)	1 (7)	0 (0)
	Some	1 (4)	3 (20)	5 (19)
	None	24 (96)	11 (73)	22 (81)
9. Would you consider performing/arranging sentinel lymph node biopsy for sebaceous carcinoma?	Yes	10 (42)	9 (82)	3 (14)
	No	14 (58)	1 (9)	19 (86)

10. In the last 10 years, in how many <u>ocular</u> sebaceous carcinoma cases did you perform/arrange conjunctival map biopsies?[a]	All	0 (0)	11 (73)	0 (0)
	Most	0 (0)	2 (13)	1 (4)
	Some	2 (11)	1 (7)	18 (67)
	None	17 (89)	1 (7)	8 (30)
11. Which of the following best describes how you performed conjunctival map biopsies for <u>ocular</u> sebaceous carcinoma in the last 10 years?[b]	Taking evenly distributed samples from the <u>entire</u> conjunctiva	0	11 (79)	4 (21)
	Taking samples from conjunctiva <u>in close proximity</u> to the clinically appreciable tumour	1	3 (21)	7 (37)
	Taking samples from areas with <u>clinical suspicion</u> of involvement <u>only</u>	0	0 (0)	8 (42)
	Other (please specify): Performed by oculoplastic surgeon	1		
12. In the last 10 years, in which sebaceous carcinoma cases did you arrange investigations for other malignancies (tick all that apply)?	All	10 (40)	1 (7)	4 (15)
	Family history of internal malignancy	9 (36)	7 (47)	5 (19)
	Personal history of internal malignancy	10 (40)	5 (33)	15 (56)
	Ocular location	2 (8)		
	Extraocular location	1 (4)		
	None	3 (12)	5 (33)	8 (30)
	Other (please specify): Referred on	2 (8)		
	Other (please specify): Concerning symptoms on systems review	1 (4)		

| | Other (please specify): Referral if Muir-Torre suggested by pathology | | 1 (7) | |
| | Other (please specify): Young age | | 1 (7) | |

[a]Mohs surgeons were asked this question if they had treated an ocular case in the last 10 years; [b]Mohs surgeons were asked this question if they had performed/arranged conjunctival map biopsies in the last 10 years

Table 3: Management

Question	Answer	Australian Mohs surgeons (n, %)	Australian/New Zealand oculoplastic surgeons (n, %)	Japanese oculoplastic surgeons (n, %)
13. Do you have access to Mohs micrographic surgery for ocular sebaceous carcinoma?	No access		2 (13)	19 (70)
	Limited access		1 (7)	5 (19)
	Readily available		12 (80)	1 (4)
	Don't know		0 (0)	2 (7)
14. In the last 10 years, which surgical method did you most frequently use/arrange for <u>ocular</u> sebaceous carcinoma?[a]	Mohs micrographic surgery		4 (27)	0 (0)
	Mohs micrographic surgery with paraffin section margin control	0 (0)		
	Mohs micrographic surgery with frozen section margin control	13 (68)		
	Excision with paraffin section margin control	0 (0)	10 (67)	11 (41)
	Excision with frozen section margin control	0 (0)	1 (7)	13 (48)
	Excision without margin control	0 (0)	0 (0)	3 (11)
	Mapped serial excision with paraffin sections	2 (11)		
	Other (please specify): Referral to ophthalmology	3 (16)		
	Other (please specify): Referred on	1 (5)		
15. In the last 10 years, which surgical method did you most frequently use/arrange for <u>extraocular</u> sebaceous carcinoma?[a]	Mohs micrographic surgery with paraffin section margin control	0 (0)		
	Mohs micrographic surgery with frozen section margin control	4 (27)		
	Excision with paraffin section margin control	2 (13)		

	Excision with frozen section margin control	0 (0)		
	Excision without margin control	8 (53)		
	Mapped serial excision with paraffin sections	1 (7)		
	Other (please specify):	0 (0)		
16. In the last 10 years, when performing Mohs micrographic surgery, did you ever remove an additional layer after a tumour-free plane was achieved in order to ensure complete removal of tumour?[b]	Yes	4 (27)		
	No	11 (73)		
17. In the last 10 years, when performing excision (non-Mohs), what surgical clinical margin did you most frequently use (mm)?[c]		Median 5.5 (range 3-10)	Median 5 (range 3-10)	Median 5 (range 2-10)
18. When performing excision (non-Mohs), what minimum <u>pathological</u> margin do you consider acceptable (mm)?[c]		Median 3.75 (range 1-10)	Median 3.5 (range 1-5)	Median 3 (range 1-5)
19. In the last 10 years, how many sebaceous carcinoma cases did you discuss at a multidisciplinary team meeting?	All	3 (12)	2 (13)	5 (19)
	Most	0 (0)	3 (20)	1 (4)
	Some	3 (12)	5 (33)	16 (59)
	None	19 (76)	5 (33)	5 (19)
20. In the last 10 years, for how many ocular sebaceous carcinoma cases did you use topical mitomycin C?	All		0 (0)	0 (0)
	Most		0 (0)	0 (0)
	Some		8 (53)	7 (26)
	Used	1 (5)		
	None/Not used	18 (95)	7 (47)	20 (74)

21. In the last 10 years, for how many ocular sebaceous carcinoma cases did you use cryotherapy?	All	0 (0)	0 (0)	1 (4)
	Most	0 (0)	1 (7)	3 (11)
	Some	0 (0)	2 (13)	9 (33)
	None	19 (100)	12 (80)	13 (48)
22. In the last 10 years, how many sebaceous carcinoma cases did you refer for radiotherapy?	All	1 (4)	0 (0)	2 (7)
	Most	0 (0)	0 (0)	1 (4)
	Some	0 (0)	6 (40)	17 (63)
	None	24 (96)	9 (60)	7 (26)
23. For how long do you follow up sebaceous carcinoma cases after surgery (pick the option that best describes your practice)?	No clinical follow-up	0 (0)	0 (0)	0 (0)
	Up to 6 months	0 (0)	1 (7)	0 (0)
	Up to 1 year	0 (0)	0 (0)	2 (7)
	Up to 2 years	0 (0)	0 (0)	3 (11)
	Up to 3 years	1 (4)	1 (7)	1 (4)
	Up to 5 years	9 (36)	6 (40)	14 (52)
	Up to 10 years	0 (0)	2 (13)	2 (7)
	Beyond 10 years	1 (4)	2 (13)	5 (19)
	Indefinitely	7 (28)	3 (20)	0 (0)
	Referring doctor to follow up the cases	7 (28)		

[a]Mohs surgeons were asked this question if they had treated an ocular/extraocular case in the last 10 years; [b]Mohs surgeons were asked this question if Mohs surgery was selected in Q14 or Q15; [c]Mohs/oculoplastic surgeons were asked this question if excision was selected in Q14 or Q15

Conclusion

Chapters 2 and 3 clarified the uncertainties about the demographics and anatomical distribution of cutaneous sebaceous carcinoma (SC). SC are more commonly male than female in white populations, whereas the inverse is true in Asians. Ocular SC are more commonly female than male in all populations, despite male predominance of SC overall in white populations. The majority of SC occur on head and neck in Asians and whites. Age-adjusted incidence rate (to the 2000-2025 WHO World Standard Population) ranges from 0.07 to 0.18 per 100,000 person-years. Contrary to a common assumption, SC are not more common in Asians than whites.

Chapters 4 and 5 described atypical presentations of SC. It is important to maintain an index of suspicion for SC when a presumed benign condition has atypical features or when a lacrimal sac lesion is found in the presence of chronic conjunctival disease.

Chapter 6 showed variation in management for SC between countries, between Mohs and oculoplastic surgeons, and between anatomical locations. For ocular SC, Australian Mohs surgeons most frequently use Mohs surgery with frozen section margin control, while Australian and New Zealand oculoplastic surgeons perform excision with paraffin section margin control. For extraocular SC, Australian Mohs surgeons most frequently perform excision without margin control. SC cases are usually followed up for up to five years or more. This information may provide a foundation on which to develop Asia-Pacific consensus guidelines.