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Recurrence rate of corneal squamous cell carcinoma in dogs undergoing superficial keratectomy surgery

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ABSTRACT

Background: Corneal squamous cell carcinoma (cSCC) is a rare neoplasm of dogs that can be treated with various modalities, principally by superficial keratectomy (SK) surgery. It is common to treat cSCC with multiple adjunctive therapies, but this may not always be practical for clinicians, clients, or patients.

Aim: This retrospective study describes the signalment of affected dogs, concurrent medical therapy, and success rate of surgical treatment of cSCC with SK surgery alone or in combination with adjunct therapy.

Methods: Eligible dogs undergoing SK surgery for histologically confirmed cSCC were selected from medical records (2009-2024) of Animal Eye Care, Melbourne. Records were examined for cSCC recurrence at follow up.

Results: Between January 2009 and August 2024, 16 eyes from 14 dogs (5 male; 35.7% (37.5% eyes), 9 female; 64.3% (62.5% eyes) had a confirmed histopathological diagnosis of cSCC following SK surgery. All cases were diagnosed within the last 9 years. There was a notable predilection of brachycephalic breeds (85.7% of dogs; 81.3% of eyes) with pugs the most overrepresented (42.9% of dogs; 37.5% of eyes). The average age at diagnosis was 8.7 years (range 2.1–13.8). Tumor recurrence occurred in two cases following incomplete excision, with no tumor recurrence reported following a second SK surgery. Adjunctive therapy was used in four cases and included cryotherapy and topical interferon alpha-2a. At the time of diagnosis, 12 out of 16 eyes had been treated previously with topical immunomodulatory therapy. Prevalence data varied but peaked in 2021 with 0.14% of total patients and 0.82% of all brachycephalic patients diagnosed with cSCC.

Conclusion: Complete excision of cSCC by SK surgery is effective for preventing the recurrence of cSCC in dogs, even in the absence of adjunctive therapies. Dogs with chronic corneal inflammatory conditions, particularly brachycephalic breeds, are at higher risk for developing cSCC. Corneal SCC should be suspected in middle-aged brachycephalic dogs presenting with proliferative, raised, or hyperaemic corneal lesions.

Keywords: Canine, Eye, Immunomodulatory, Tacrolimus, Tumor.

Introduction

Ocular squamous cell carcinoma (SCC) is a rare tumor of the eye of dogs and humans (Gelatt *et al.,* 2021). It is seen most commonly in cattle and horses (Dubielzig, 2016; Gelatt *et al.,* 2021), uncommonly in cats and sheep (Wilcock, 1993), and has been reported in goats (Marà *et al.,* 2005), reindeer (Gonzalez-Alonso-Alegre *et al.,* 2013), and other species (Wilcock 1993; Valentine and Martin, 2007). Publications about corneal SCC (cSCC) in dogs are sparse and are mostly limited to single case reports.

In cattle and horses, risk factors for ocular SCC include increased exposure to ultraviolet (UV) radiation (Heeney and Valli, 1985; Tsujita and Plummer, 2010), light pigmentation (Anderson, 1963; Dugan *et al.,* 1991), and breed (Knickelbein *et al.,* 2019, 2020). In the dog proposed risk factors for the development of cSCC include the use of topical immunomodulatory therapies (Dreyfus *et al.,* 2011), hereditary predisposition (Bernays *et al.,* 1999), chronic corneal inflammation (Dreyfus *et al.,* 2011), prior trauma (Latimer *et al.,* 1987), and UV light exposure induced cellular damage (Montiani-Ferreira *et al.,* 2008; Dreyfus *et al.,* 2011) including P53 tumor suppressor gene mutation (Montiani-Ferreira *et al.,* 2008) and papilloma viral infection (Bernays *et al.,* 1999).

The incidence of cSCC in dogs appears to be increasing (Dreyfus *et al.,* 2011). Proposed contributors to this increased incidence include the rising popularity of brachycephalic breeds that are prone to conditions causing chronic corneal inflammation and the increasing use of topical immunomodulatory therapies including cyclosporin and tacrolimus in veterinary medicine.

The mainstay of treatment of cSCC is surgical excision of affected tissue, most often with superficial

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keratectomy (SK) (Busse *et al.,* 2008; Montiani-Ferreira *et al.,* 2008; Takiyama *et al.,* 2010). In humans (Yeoh *et al.,* 2022) and animals, specific adjunctive therapies have been utilized alongside SK. These include topical mitomycin C (Karasawa *et al.,* 2008), 5-flurouracil (Overton *et al.,* 2015; Dorbandt *et al.,* 2016), or interferon alpha-2b (Martabano *et al.,* 2024), strontium-90 beta irradiation (Plummer *et al.,* 2007; Nevile *et al.,* 2015), carbon dioxide laser photoablation (Michau *et al.,* 2012), radiofrequency hyperthermia (Fischer *et al.,* 2002), and cryotherapy (Schoster, 1992). It is possible that veterinary clinicians may not always have access to adjunctive therapies, or the ongoing cost may be prohibitive for some owners. It has been reported that in uncomplicated cases surgical excision with wide margins carries a good prognosis (Peiffer *et al.,* 1978) and it, therefore, would not be unreasonable to consider treatment with SK alone.

This report presents an analysis of cases of confirmed cSCC presenting to a referral veterinary ophthalmology clinic (Animal Eye Care, Melbourne, Australia) over a 15-year period (January 2009—August 2024). The aims of this study were to retrospectively review the clinical records to assess the efficacy of SK as a treatment for cSCC and to identify the signalment patterns of cSCC.

Materials and Methods

Case selection

A retrospective case series study was performed. An electronic search of medical records at a specialist veterinary ophthalmology clinic (Animal Eye Care, Melbourne, Australia) was performed using the keywords "squamous cell carcinoma", "SCC", "squamous", and "carcinoma", to identify cases of SCC between 1 January 2009 and 31 August 2024. Cases were excluded if minimal follow-up data were available (less than 4 months), if SK surgery was not performed, or if no histopathological diagnosis was available. Data collected from medical records included breed, sex, age, surgeon, surgery details, adjunctive therapies used (if any), date of tumor recurrence (if any), and date of most recent follow-up. Prevalence data were collected by searching medical records for both total initial canine cases seen per year and total initial brachycephalic breed cases seen per year.

Presurgical evaluation and treatment

A complete ophthalmic examination was performed at the initial consultation. Each case was examined by a veterinary ophthalmologist before surgery.

A presumptive diagnosis was made on the clinical presentation. No cytology or biopsy was performed at the time of consultation.

Surgical technique and post-surgical evaluation

Surgery was performed by one of four surgeons, including two veterinary ophthalmologists, an ophthalmology resident under direct supervision by a veterinary ophthalmologist and who later became a third veterinary ophthalmologist and a special interest practitioner in ophthalmology under the direct supervision of a veterinary ophthalmologist.

Dogs were premedicated with either acepromazine or medetomidine, in combination with either butorphanol or methadone. Anesthesia was induced with alfaxalone (Alfaxan®, Jurox Animal Health, NSW, Australia), and all dogs were intubated and maintained on isoflurane inhalational anesthetic. Patients were given intravenous fluids. The cornea was anesthetized with topical 0.5% proxymetacaine hydrochloride (Alcaine®, Alcon Laboratories Australia Pty Ltd, NSW, Australia). The cornea, conjunctiva, and eyelids were disinfected with 1% povidone-iodine solution. The cornea was regularly irrigated with either a balanced salt solution or the iodine solution during surgery.

Using a corneal disc knife (Alcon Laboratories (Australia) Pty Ltd, NSW, Australia), SK surgeries were performed to approximately 20%–50% of the corneal stromal depth with visually clear margins of at least 2 mm, under the magnification of an operating microscope (Topcon OMS-85, Topcon Healthcare Solutions Australia & New Zealand, SA, Australia). At the completion of the surgeries, lateral temporary tarsorraphy sutures were placed using 4/0 nylon (Nylene® N405, Dynek Sutures, South Australia).

Excised masses were fixed with 10% neutral buffered formalin and submitted for histopathology (Australian Specialised Animal Pathology Laboratory, Victoria, Australia).

Patients were discharged on the day of the procedure. Medical therapies used immediately postoperatively varied at the surgeon's discretion. Treatments included topical antibiotic therapy (chloramphenicol 0.5% (Chlorsig® Eye Drops, Aspen Australia, NSW, Australia), Ofloxacin 0.3% (Ocuflox® Eye Drops, Allergan Australia, NSW, Australia), or 10,000 IU/g Polymyxin B sulfate, 500 IU/g Bacitracin zinc, 5 mg/g Neomycin sulfate triple antibiotic ointment (Tricin® Eye and Ear ointment, Jurox Animal Health, NSW, Australia)), topical immunomodulatory therapy with calcineurin inhibitors (2 mg/g cyclosporin (Optimmune® Ophthalmic Ointment, MSD Animal Health, NSW, Australia), 0.02% Tacrolimus (Bova Aus, NSW, Australia)) or peginterferon alfa-2a 3MIU in 0.5 ml solution (Roferon-A, Roche Products Pty Ltd, NSW, Australia) diluted to 5,400IU/ml in Blink® Contacts Eye Drops (AMO Australia Pty Ltd, NSW, Australia), an oral anti-inflammatory (carprofen (Rimadyl®, Zoetis, Australia) or 1.5 mg/ml meloxicam suspension (Loxicom, Norbrook Laboratories Australia Pty Ltd, VIC, Australia), systemic antibiotics (doxycycline (Doxy 50/100 Antibiotic Tablets, Dechra Veterinary Products (Australia) Ptd Ltd, NSW, Australia), and gabapentin (WP Gabapentin, Medtas Pty Ltd, NSW, Australia).

Ethical approval

This study describes the findings of a clinical and diagnostic investigation of clinical cases in a private

practice setting with non-experimental privately owned animals under the Guidelines for Ethical Research in Veterinary Ophthalmology. Therefore, ethical approval from a committee was not required for publication.

Results

A total of 31,233 new canine patients including 5,002 of brachycephalic breed presented to Animal Eye Care, Melbourne between 1 January 2009 and 31 August 2024. Corneal SCC was suspected in 30 eyes from 28 dogs. Fourteen eyes were excluded from the study because surgery was not pursued (6/14), the eye was enucleated (3/14), histology was not performed following SK surgery (4/16), the eye was lost to follow up 2 months following SK surgery, and histologic confirmation of cSCC (1/14) (Table 1). Corneal SCC was confirmed by histopathology following SK in 16 eyes from 14 dogs, 5 males and 9 females (Table 2). The mean (± standard deviation) age of patients at SCC diagnosis was 9.3 years (± 2.8) with a range of 2.1–13.7 years. In case 8, recurrence was noticed at the original site after 1.5 years (Fig. 1). Case 9 was the youngest dog affected (Fig. 2). The left eye was affected in 8 dogs, the right eye in 4 dogs, and both eyes were affected in 2 dogs.

Complete excision of cSCC was confirmed by histology in 7/16 eyes (43.8%). Incomplete excision was suspected in 9/16 eyes (56.2%). 14 out of 16 eyes had no recurrence of tumor after a mean follow-up time of 2 years (± 1.8) with a range of 0.4–7.3 years (Table 3). There was no recurrence of any completely excised tumors.

Of the nine cases with suspected incomplete excision, two patients (Case 8 and Case 10) had suspected tumor recurrence (22.2%). The clinical presentation and location of the lesion were the same as in the initial presentation. This case was treated with a second superficial keratectomy although this sample was not submitted for histopathology. In case 10, recurrence was suspected at 2.8 years following initial SK, and repeat SK with adjunct strontium 90 plesiotherapy was performed at 3.1 years. Histopathology confirmed carcinoma *in situ* with complete excision. There was no recurrence in the remaining 7 cases with suspected incomplete excision after at least 1 year of follow up.

Two patients had cSCC diagnosed in both eyes. A Jack Russell Terrier was diagnosed in both eyes simultaneously at 9.7 years of age and a Cavalier King Charles Spaniel was diagnosed in the left eye at 5.1 years of age and in the right eye at 8.2 years of age (Table 2).

All study cases were diagnosed within the past 9 years (Table 2). Within this period (January 2016—August 2024), the prevalence ranged from 0% to 0.14% of total canine cases (Table 4). The prevalence among brachycephalic breeds ranged from 0% to 0.82%. In 2009, a total of 179 new brachycephalic patients were seen, or 8.7% of total new cases. In the first 8 months of 2024, a total of 279 new brachycephalic patients were seen, or 21.4% of total new cases.

Brachycephalic breeds—Pugs, Bulldogs, and Cavalier King Charles Spaniels, were overrepresented accounting for 81.3% (13/16) of study cases (Table 2). Of note, Pugs accounted for 37.5% (6/16) of all cases, the most prevalent breed diagnosed with cSCC.

Table 1. Details of suspected cSCC cases excluded from study and reason for exclusion.

Year cSCC suspected	Breed	Sex	Reason for exclusion
2009	Pug	MN	Eye enucleated at referring vet
2010	Staffordshire Bull Terrier	MN	SK performed, histopathology confirmed cSCC, lost to follow up after 2 months
2010	King Charles Spaniel	MN	Eye enucleated at referring vet
2014	Bichon Frise X	FS	SK performed, histopathology not available
2014	Pug	M	SK performed, histopathology not available
2014	Pug	MN	Eye enucleated after histopathology confirmed cSCC
2019	Cavalier King Charles Spaniel	MN	Died soon after cSCC suspected
2019	Pug	M	SK not performed, started 5-flurouracil then lost to follow up
2019	Pug	F	SK performed, histopathology not available
2019	British Bulldog	FS	SK performed, histopathology not available
2021	French Bulldog	FS	SK not performed
2021	Golden Retriever	FS	SK not performed
2021	British Bulldog	MN	SK not performed, started 5-flurouracil then lost to follow up
2024	British Bulldog	M	SK not performed

Table 2. Signalment of dogs included in study.

Case number	Year of diagnosis	Breed	Sex	Age at diagnosis (years)	Eye affected
1*	2016	Cavalier King Charles Spaniel	MN	5.1	Left eye
2	2016	Pug	MN	9.2	Right eye
3	2017	Bulldog	F	8.0	Left eye
4	2018	Cavalier King Charles Spaniel	MN	10.4	Left eye
5	2018	Pug	FS	13.8	Left eye
6	2019	British Bulldog	FS	8.7	Left eye
7*	2019	Cavalier King Charles Spaniel	MN	8.2	Right eye
8	2020	Bulldog	F	8.0	Left eye
9	2021	British Bulldog	M	2.1	Left eye
10	2021	Golden Retriever	FS	9.5	Left eye
11	2021	Pug	M	10.5	Right eye
12	2021	Pug	FS	12.1	Left eye
13	2022	Pug	FS	13.1	Right eye
14$^{\Delta}$	2023	Jack Russell Terrier	FS	9.7	Left eye
15$^{\Delta}$	2022	Jack Russell Terrier	FS	9.7	Right eye
16	2022	Pug	FS	10.4	Right eye

* = same dog, $^{\Delta}$ = same dog.

The majority of eyes (15/16) featured a chronic inflammatory condition or prior chronic irritation (Table 5). All Pugs and Cavalier King Charles Spaniels included in the study displayed concurrent pigmentary keratitis making this the most prevalent pre-existing condition in this series. Five dogs had pre-existing keratoconjunctivitis sicca (KCS). One of three non-brachycephalic eyes in the study, a 9.5-year-old Golden Retriever (case 10), had no pre-existing keratitis or KCS recorded, however, had sustained trauma to the eye as a puppy.

Most eyes (13/16) included in the study were being treated with long-term topical immunomodulatory or anti-inflammatory therapy prior to SCC diagnosis (Table 6). The most common treatment was tacrolimus (10 eyes), with an average duration of therapy of 4 years prior to a diagnosis of cSCC.

Following SK for the confirmed cSCC, adjunctive therapy was used in 4 of the 15 cases (Table 3). Three cases received topical interferon alpha-2a either 2 months before SK surgery (case 16), or following SK surgery (day 1 case 13, day 13 case 10). One of these cases (case 10) had tumor recurrence suspected at 2.8 years postoperatively. Two cases received cryotherapy at the time of surgery and had no recurrence.

Discussion

Our study found that 87.5% (14/16) of cases had no tumor regrowth after a mean follow-up time of 2 years (± 1.8). Published reports of canine cSCC in the veterinary literature are increasing but remain relatively rare. In a large-scale retrospective study looking at samples submitted to the Comparative Ocular Pathology Lab of Wisconsin, Dreyfus *et al.,* (2011) found that 10 out of 26 SCC tumors removed by SK recurred at the original site of removal. These authors noted that 7 out of the 10 recurrent cases had incomplete margins after the first keratectomy; however, information regarding the surgical approach was not provided. In our analysis, both cases recur and were incompletely excised based on histology. Interestingly, seven other cases were suspected to have had incomplete excision but had no tumor regrowth during a mean follow-up time of 1.6 years (± 1.2).

Corneal SCC has been demonstrated to infiltrate the deep stroma in horses (Kafarnik *et al.,* 2009) and can invade the anterior chamber and periocular tissues in cattle (Martins, 2021). There is only one report of a highly invasive canine cSCC in the literature which demonstrated both exophytic growth and extension deep into the stroma (María Del Mar *et al.,* 2019). Conservative surgical treatment for canine cSCC should always be considered as most published reports indicate that tumors remain exophytic on the surface of the cornea or involve only the superficial stroma, facilitating surgical excision (Karasawa *et al.,* 2008; Takiyama *et al.,* 2010; Dreyfus *et al.,* 2011; Nevile *et al.,* 2015; Dorbandt *et al.,* 2016).

Several authors have reported success in treating cSCC with SK alone. Busse *et al.,* (2008) found no recurrence of tumour 25 weeks after SK in a Border Collie with cSCC. Takiyama *et al.,* (2010) reported on two cSCC cases, a pug that after initially having tumor regrowth had no recurrence 18 months after a second

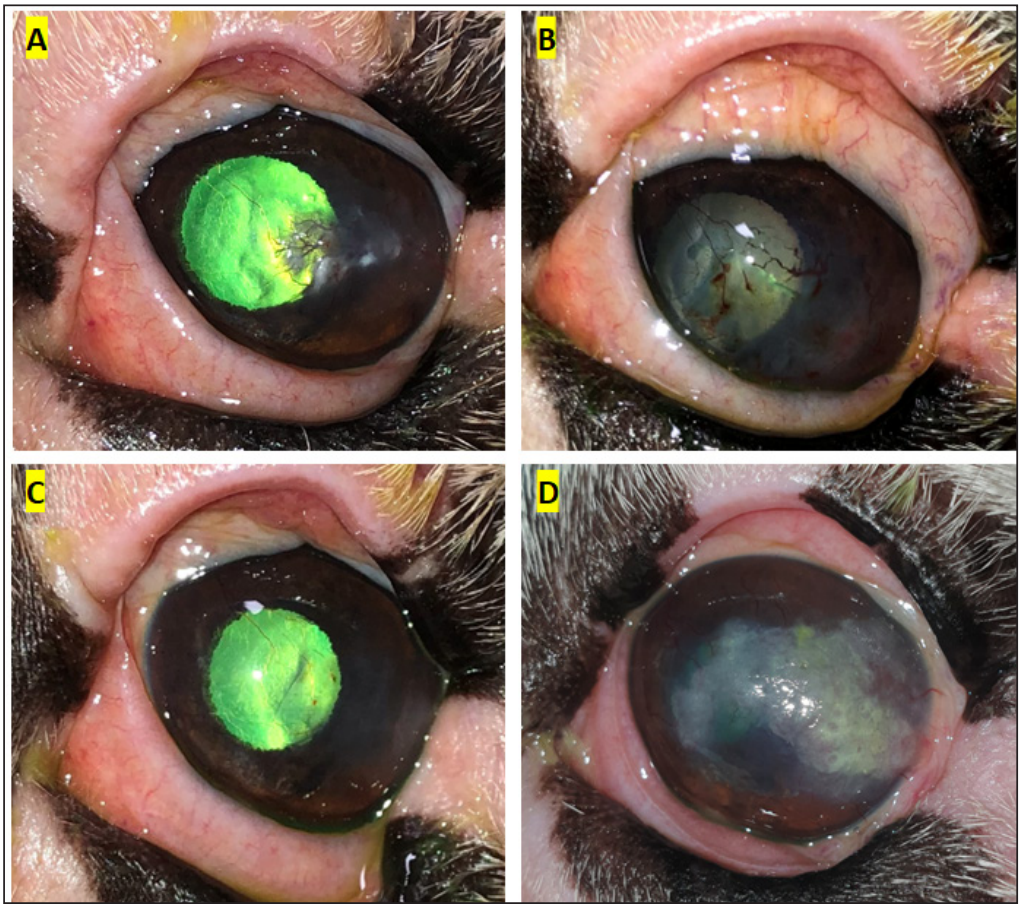

Fig. 1. Clinical progression of case 8. (A) raised opacities with associated vascularisation were seen 7 months prior to initial SK surgery. (B) 8 days following initial SK surgery, the surgical site was epithelialized with prominent corneal vascularisation present. (C) 1 month following initial SK surgery the cornea was clear and only very faint vascularisation remained. (D) 1 year 7 months following initial SK, recurrence of the incompletely excised cSCC was demonstrated. Repeat SK was performed 1 month later.

SK, and a toy poodle that had no tumor regrowth 15 months after SK. It has previously been reported that in uncomplicated cases of canine cSCC surgical excision with wide margins carries a good prognosis without the use of adjunctive therapies (Peiffer *et al.,* 1978). In humans, the gold standard of ocular surface squamous neoplasia has historically been excision alone (Alvarez *et al.,* 2021), with favorable success rates in uncomplicated cases (Galor *et al.,* 2012). It has been suggested that when human corneal tumors are removed with 2 mm margins adjuvant treatment with cryotherapy is unnecessary (Yan *et al.,* 2011). In contrast, some more recent studies in human medicine show an increasing move toward medical management with chemotherapeutic drugs and immunomodulatory agents (Yeoh *et al.,* 2022).

In this study, most cases did not receive adjunctive therapy to treat cSCC. Specific adjunct therapies previously utilized in dogs include strontium-90 beta irradiation (Nevile *et al.,* 2015), topical chemotherapy with 5-flurouracil (Overton *et al.,* 2015) or mitomycin C (Karasawa *et al.,* 2008), and cryotherapy (Ward *et al.,* 1992). Topical 5-flurouracil has been used successfully as a monotherapy to treat a small cSCC in a pug (Dorbandt *et al.,* 2016), and topical mitomycin C has recently been used as a monotherapy to treat cSCC in a cat (Delgado, 2020). Cryotherapy has been utilized to treat ocular surface neoplasms in humans (Galor *et al.,* 2012) and has been used alongside SK surgery in dogs (Latimer *et al.,* 1987; Schoster, 1992; Ward *et al.,* 1992). Topical interferon has the advantage of being well tolerated by the eye (Ghaffari *et al.,* 2021), minimally invasive yet treating the whole cornea (Wilson *et al.,* 2001; Schechter *et al.,* 2002), non-toxic to the ocular surface (Boehm and Huang, 2004), and relatively readily available and affordable. In humans, interferon alpha-2b is used following surgical excision, and topical or perilesional interferon is increasingly being used as a sole therapy (Boehm and Huang, 2004; Ghaffari *et al.,* 2021). Intralesional interferon alpha-

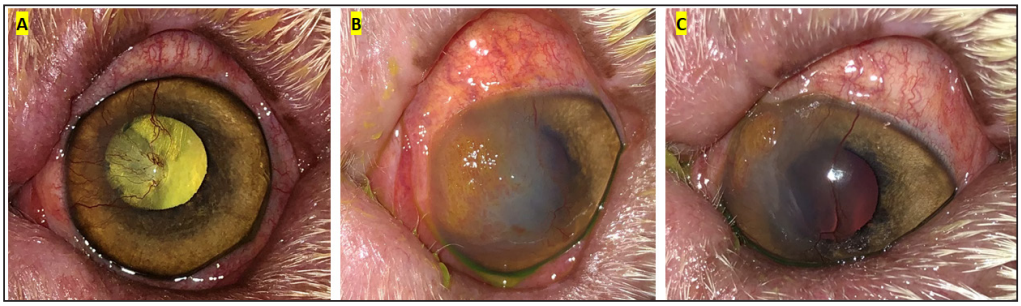

Fig. 2. Clinical progression of case 9. (A) vascularisation and scarring of the dorsomedial cornea were seen 1 year prior to SK surgery. (B) increased opacification and dense, raised vascularisation with an irregular cobblestone appearance was noted a year later, 2 weeks prior to SK surgery. (C) improved corneal clarity and a more discrete, localised, irregular, raised, pink growth was seen 7 days later, 7 days prior to SK surgery, following treatment with topical dexamethasone, topical Polymixin B sulfate/Bacitracin zinc/ Neomycin sulfate triple antibiotic ointment, systemic doxycycline and systemic carprofen.

Table 3. Treatment and outcome data of included cSCC cases.

Case number	SK excision	Perioperative adjunctive therapy	Outcome
1*	Complete	None	No recurrence after 7 years, 4 months
2	Incomplete	None	No recurrence after 3 years, 10 months
3	Incomplete	None	No recurrence after 1 year, 1 month
4	Incomplete	None	No recurrence after 1 year, 5 months
5	Incomplete	None	No recurrence after 10 months
6	Incomplete	None	No recurrence after 11 months
7*	Complete	None	No recurrence after 4 years, 2 months
8	Incomplete	None	Recurrence after 1 year, 6 months. Second SK performed at 1 year 8 months and subsequently lost to follow up.
9	Incomplete	Cryotherapy	No recurrence after 4 months
10	Incomplete	Topical interferon	Recurrence after 2 years, 9 months, interferon in tears restarted. Second SK performed at 3 years 1 month with adjunctive strontium 90 and topical interferon. Histopathology confirmed complete excision.
11	Complete	None	No recurrence after 2 years, 6 months
12	Complete	None	No recurrence after 1 year, 4 months
13	Complete	Cryotherapy, topical interferon	No recurrence after 1 year
14$^{\Delta}$	Complete	None	No recurrence after 1 year, 1 month
15$^{\Delta}$	Incomplete	None	No recurrence after 1 year, 1 month
16	Complete	Topical interferon	No recurrence after 5 months

* = same dog, $^{\Delta}$ = same dog.

2b has recently been used with some success to treat periocular SCC in horses (Martabano *et al.,* 2024). In general, there is a paucity of data on the use of adjunct therapy in treating canine cSCC. Most publications are single case reports or limited case series and therefore inferences on the efficacy of adjunct treatments are difficult to determine. The only existing published large retrospective analysis on canine cSCC did not report on the use of adjunctive therapy following SK (Dreyfus *et al.,* 2011). The current study represents the largest number of confirmed canine cSCC cases known to be successfully treated with SK alone (11/12 eyes) or in combination with adjunctive therapy (3/4 eyes) reported in the literature to date.

Table 4. Cases seen at Animal Eye Care from 1 January 2009–31st August 2024.

Year	cSCC diagnoses	Total annual cases seen at clinic	SCC % of total cases	Total annual brachycephalic cases seen at clinic	Percentage of new cases that are brachycephalic	SCC % of brachycephalic patients
2009	0	2052	0.00	179	8.72	0.00
2010	0	2006	0.00	229	11.42	0.00
2011	0	1594	0.00	249	15.62	0.00
2012	0	1679	0.00	250	14.89	0.00
2013	0	1704	0.00	291	17.08	0.00
2014	0	1706	0.00	286	16.76	0.00
2015	0	1732	0.00	287	16.57	0.00
2016	2	1519	0.13	266	17.51	0.75
2017	1	1684	0.06	261	15.50	0.38
2018	2	1708	0.12	284	16.63	0.70
2019	2	2133	0.09	339	15.89	0.59
2020	1	2628	0.04	420	15.98	0.24
2021	4	2883	0.14	487	16.89	0.82
2022	2	2614	0.08	458	17.52	0.44
2023	1	2289	0.04	437	19.09	0.23
2024*	0	1302	0.00	279	21.43	0.00

* = January to August inclusive.

Most published cases of cSCC, including the dataset we present here, are recent diagnoses. We found that all included cases of cSCC, and 57.1% (8/14 eyes) of excluded cases were within the last 9 years (Table 2, Table 1). Dreyfus *et al.,* (2011) noted a similar pattern with 23/26 cases being recent diagnoses within 4 years of publication. These authors also reported the diagnosis of cSCC rising as a percentage of cases (0.08% in 2000 to 0.32% in 2007) and suggested a rise in disease prevalence. Whilst our data shows an increased prevalence of cSCC in the last 9 years compared to the prior, it does not show a year-on-year increase in prevalence within the last 9 years. There was no obvious trend observed when considering annual cSCC diagnoses against total annual cases seen (Table 4). While not the case in our data set, the apparent increase in diagnoses by Dreyfus *et al.,* (2011) may be due to more tumors being sent for histology after SK or excisional biopsy in recent years. The data set presented here may be too small to see the true change in the prevalence of cSCC in dogs. A much larger sample size is likely required to see an accurate representation of the rising prevalence of a disease so rare.

The number of brachycephalic dogs seen appears to be increasing over time, both in total number of cases and as a percentage of new cases at Animal Eye Care, Melbourne, Australia. The overrepresentation of brachycephalic breeds in this study is similar to that reported by Dreyfus et al. (2011). Most published case reports also involve brachycephalic breeds including Pugs (Takiyama *et al.,* 2010; Overton *et al.,* 2015; Dorbandt *et al.,* 2016), a Japanese Chin (Nevile *et al.,* 2015), an English Bulldog (Montiani-Ferreira *et al.,* 2008), a Lhasa Apso (Bernays *et al.,* 1999), a French Bulldog (María Del Mar *et al.,* 2019) and a Cavalier King Charles Spaniel (Nevile *et al.,* 2015). Brachycephalic breeds are predisposed to chronic inflammatory conditions such as KCS (Kaswan *et al.,* 1989) and pigmentary keratitis (Gelatt *et al.,* 2021; Sebbag and Sanchez, 2023), both of which have been suggested as risk factors for the formation of cSCC (Dreyfus *et al.,* 2011; Labelle and Labelle, 2013). Almost every case included in the current study displayed some form of chronic inflammation, with KCS and pigmentary keratitis featuring heavily (Table 5). The exact reason for the link between chronic keratitis and cSCC formation has not yet been fully explained, but increased cellular proliferation and inflammatory signals have been proposed as mechanisms for tumor development (Dreyfus *et al.,* 2011). It has also been suggested that corneal epithelial metaplasia accompanying pigmentary keratitis may represent a preneoplastic change (Bernays *et al.,* 1999). In line with previous reports, our results suggest that brachycephalic breeds are more at risk of developing canine cSCC (Dreyfus *et al.,* 2011), possibly as a result of their predisposition to chronic inflammatory conditions.

Table 5. Pre-existing conditions in cSCC cases.

Pre-existing condition	Cases exhibiting (total)
Pigmentary keratitis	1*,2, 5, 7*, 9, 11, 12, 13, 14$^{\Delta}$, 15$^{\Delta}$ (10)
Vascular keratitis	1*, 4, 6, 9, 10, 14$^{\Delta}$, 15$^{\Delta}$ (7)
Corneal scarring	2, 3, 5, 6, 8, 10, 12 (7)
Keratoconjunctivitis sicca	3, 6, 8, 11, 13 (5)
Entropion	8, 9, 11 (3)
Distichiasis	9 (1)

* = same dog, $^{\Delta}$ = same dog

Table 6. Topical medical treatment used prior to SK surgery and duration of therapy where known.

Topical therapy	Cases using (total)	Duration of therapy prior to SCC diagnosis (if known)
Tacrolimus	1*, 4, 7*, 8, 9, 11, 13, 14$^{\Delta}$, 15$^{\Delta}$, 16 (10)	Average = 4 years Range 0.1–10.1 years Based on 9 cases
Dexamethasone	4, 9, 11, 13, 14$^{\Delta}$, 15$^{\Delta}$ (6)	Average = 4.2 years Range 0.5–10.1 years Based on 5 cases
Prednisolone acetate	16 (1)	6.8 years Based on 1 case
Diclofenac Sodium	12 (1)	Insufficient data tocalculate duration average
Ketarolac tromethamine	9 (1)	Insufficient data tocalculate duration average
Cyclosporine	2, 6 (2)	Insufficient data to calculate duration average

* = same dog, $^{\Delta}$ = same dog.

Some authors have suggested a possible association between canine cSCC development and treatment with topical immunomodulators (Ward *et al.,* 1992; Bernays *et al.,* 1999; Takiyama *et al.,* 2010; Dreyfus *et al.,* 2011). Most dogs in this study were being treated for chronic inflammatory conditions using topical immunomodulatory therapy (calcineuron inhibitors (tacrolimus or cyclosporine) and/or topical steroids (prednisolone acetate or dexamethasone sodium phosphate)) prior to cSCC diagnosis. This finding is consistent with Dreyfus *et al.* (2011) who found that 16 out of 21 dogs were being treated for KCS with long-duration tacrolimus or cyclosporine. In humans, long-term exposure to cyclosporine was associated with a higher risk of nonmelanoma skin cancer, especially SCC, in psoriasis patients (Paul *et al.,* 2003). Human transplant recipients receiving systemic tacrolimus treatment have been shown to be at higher risk of neoplasia (Rodríguez-Perálvarez *et al.,* 2022). However, more recent research has found no significant increase in the risk of cancer development with the use of topical tacrolimus (Arana *et al.,* 2021; Lam *et al.,* 2021) The authors cannot rule a potential influence of long-term immunomodulatory drug use in this study; however, firm conclusions are impossible to draw as this treatment is utilized for chronic inflammatory conditions that are also proposed risk factors for cSCC development. The study population presented here represents only a fraction of the cases that are treated with topical immunomodulatory therapies for ophthalmic conditions and therefore these findings should not be interpreted as a reason to alter the current standard of care.

Exposure to UV light has been shown to contribute to cSCC formation in horses and cattle (Wilcock 1993) and has been suggested as a contributing factor in canine cSCC formation in a case report from Brazil (Montiani-Ferreira *et al.,* 2008). Exposure to UV light can result in a mutation in the p53 tumor suppressor gene, resulting in overexpression frequently associated with ocular SCCs (Teifke and Löhr, 1996; Sironi *et al.,* 1999). The cases included in this study all originated in Melbourne, Australia where the ultraviolet index (UVI) ranges from low (1.8 UVI) in the winter to extreme (10.9 UVI) in peak summer (Australian Radiation Protection and Nuclear Safety Agency 2024). From November through to March UVI remains very high (>7.5 UVI). The anatomy of brachycephalic dog breeds frequently predisposes them to exophthalmos, macropalpebral fissures, and incomplete lid

closure which may result in greater cumulative UV exposure. The combination of high UVI and breed-specific morphology may have contributed to cSCC formation in the cases presented here. In Australia, brachycephalics dogs are predominantly kept inside during the hot summer months to minimize the risk of heat stroke. Unfortunately, not enough data were collected on the specific lifestyle of dogs included in this study to draw meaningful inferences, as indoor dogs have a reduced UV exposure risk. Additionally, immunohistochemistry was not performed in our series of cases, so no data on the expression of p53 tumor suppressor gene was available.

Interestingly case 10 was diagnosed with a pigmented cSCC with prominent papillomaviral induced cytopathy and papillomaviral PCR testing of the keratectomy sample confirmed concurrent canine papillomavirus 17 infection. Papilloma viral infection has been proposed as a risk factor for cSCC tumorigenesis (Bernays *et al.,* 1999). Pigmented cSCC has not been reported in any other animal in the veterinary literature and canine papillomavirus type 17 has only been reported in one other dog, and in that case was associated with oral SCC (Munday *et al.,* 2015).

Corneal SCC remains a seldom reported diagnosis in the veterinary literature and this study is one of only two larger scale retrospective analyses involving multiple cases. Although this study is inherently limited by its retrospective design, there is sufficient evidence to support the suggestion that the pathogenesis of canine cSCC may be influenced by chronic inflammatory conditions and the treatment thereof. This work highlights the importance of considering cSCC as a differential diagnosis in dogs with such conditions, particularly in middle-aged brachycephalic dogs.

Complete excision of canine cSCC appears to be curative, and recurrence rates are low even with suspected incomplete excision. This demonstrates the efficacy of SK surgery alone or in combination with adjunctive therapies for the treatment of cSCC in dogs.

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Authors' contributions

Helen Mather: Conceptualization, Methodology, Visualisation, Writing—original draft, Writing—review & editing. Robin G Stanley: Conceptualization, Writing—review & editing. Both authors contributed to the writing of, and have approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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