



# From Scalpel to Syringe: Intralesional Interleukin-2-Based Therapy is Effective for Locally Advanced Periocular Cutaneous Squamous Cell Carcinoma

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## ABSTRACT

**Introduction:** Cutaneous squamous cell carcinoma (cSCC) is a common eyelid malignancy that is typically treated by surgical excision. Locally destructive periocular cSCC may not be amenable to surgery in cases where extensive resection would result in structural or functional compromise.

**Methods:** We report the first series of biopsy-confirmed periocular cSCC cases treated with intralesional interleukin-2 (IL-2)-based therapy.

**Results:** Treatment courses for five patients are summarized, with one representative case detailed here. A 74-year-old man presented with

a large, painful, centrally pedunculated mass on the left upper eyelid, measuring 5.5 cm by 2.5 cm. Mass excisional biopsy and reconstruction revealed moderately differentiated invasive SCC involving deep and peripheral margins. Given the risks associated with further resection, the patient opted to pursue local immunotherapy. He received five doses of intralesional IL-2 every 2 weeks. The lesion was completely clinically cleared at 6 weeks, and there was no recurrence noted at 15-month follow-up.

**Conclusion:** Local intralesional IL-2-based therapy may be a treatment option for periocular cSCC in cases that may result in significant functional or aesthetic compromise, or in those who have failed prior standard of care.

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### Key Summary Points

Locally invasive cutaneous squamous cell carcinoma (cSCC) in anatomically sensitive sites and high-risk patients may render surgical excision impractical.

To our knowledge, this is the first case series reporting the use of intralesional interleukin-2 (IL-2) specifically for periocular cSCC.

Among five patients treated, three achieved complete clinical response and one achieved partial response, resulting in an overall response rate of 80%.

Intralesional IL-2 was well tolerated, with only mild and self-limited side effects such as local discomfort and flu-like symptoms.

These findings support intralesional IL-2 as a promising local immunotherapy option in select periocular cSCC cases and warrant further investigation in larger studies.

## INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most prevalent eyelid malignancy after basal cell carcinoma (BCC), comprising 5–10% of all eyelid skin cancers [1]. SCC tend to exhibit more aggressive invasion and metastasis than BCC [2]. The current gold standard treatment for SCC is surgical excision with reconstruction [3]. Surgical resection can be challenging in periorbital areas with intricate structural, functional, and aesthetic requirements. Locally invasive SCC presents unique concerns, particularly when characterized by multiple lesions, a large tumor size, or when located in difficult-to-treat areas such as the eyelid margin or lacrimal apparatus. In addition, certain patients may not be suitable for surgical intervention because of advanced age or significant comorbidities. Herein, we present a series of cases of cSCC of the eyelid being treated with intralesional interleukin-2 (IL-2)-based therapy and use a representative case to highlight the potential benefit of this treatment in management of periocular cSCC.

## METHODS

### Patient Selection

Patients with locally invasive cSCC of the head, neck, and periocular region who have failed prior therapies or have technically challenging disease in anatomically sensitive areas are referred to our local immunotherapy program through dermatology, otolaryngology, or ophthalmology services. All of these patients were biopsy confirmed and deemed by their prior care team to have failed standard treatment modalities without salvage, or refused major functionally impacting operations. All patients presenting between 2012 and 2024 inclusive with cSCC of the periocular region had their charts reviewed, and clinical, photographic, and radiographic data was collected.

This retrospective study was an extension of an already implemented treatment protocol at our institution. We treated all patients in this cohort (i.e., those who had failed prior therapies or anatomically sensitive disease) with intralesional IL-2 and/or topical imiquimod. Dosing of IL-2 is based on previously determined institutional guidelines derived from well-defined melanoma literature, with standard dosing ranging from 0.1 to 1.0 mL (500,000–4,000,000 units), delivered every 2 weeks at 0.1 mL/mm<sup>2</sup>. Clinical responses were evaluated at each visit using RECIST 1.1 criteria. For patients with suboptimal responses or signs of progression, we added topical imiquimod at the physician's discretion. Imiquimod (5% cream, Aldara) was applied once daily, 5 days per week, following manufacturer guidelines, and administered in parallel with IL-2. In cases where response could not be assessed clinically with confidence, we performed targeted biopsies to confirm histological regression. All histopathology was reviewed by board-certified dermatopathologists with expertise in cutaneous malignancies.

### Ethical Approval

This study was performed in accordance with the Helsinki Declaration. All subjects provided

informed consent to study participation and publication. Collection and evaluation of protected patient health information were HIPAA compliant. Ethics committee approval was not required, as this was a retrospective study using an already established treatment protocol for cSCC in non-periocular regions at our institution.

## RESULTS

### Baseline Characteristics

Between 2012 and 2024, we identified five patients with periocular cSCC through our

intralesional immunotherapy program who have been treated with intralesional IL-2-based therapy. The average age of this cohort was 72.2 years (61–78, Table 1). Two patients were treated with IL-2 alone, while one patient had imiquimod added after a partial response to IL-2. One patient was treated with adjuvant cemiplimab and went on to have progressive disease necessitating orbital exenteration. One patient had no response to IL-2 and went on to undergo radical orbital exenteration. All patients are alive as of the time of writing this manuscript.

The mean number of IL-2 treatments was 6 (3–9, Table 1). The mean treatment duration was 3.9 months (1.5–7, Table 1). Mean progression-free survival, defined as time alive from initial therapy to last follow-up or disease-progression,

**Table 1** Patient characteristics and treatment responses of patients with periocular cutaneous squamous cell carcinoma (cSCC) treated with intralesional IL-2

ID Current age/ gender	Site of cSCC	Number of intralesional IL-2 treatments	Additional thera- pies	Treatment duration (months)	Type of response <sup>a</sup>	Progres- sion-free survival <sup>b</sup>
Patient 1 77 M	Left upper eyelid and left temple	5	–	2	CCR	8
Patient 2 61 M	Right lower eyelid	8	–	7	CCR	48
Patient 3 74 M	Right lower orbital rim	9	Imiquimod added after two treat- ments	5	PR	42
Patient 4 78 M	Lateral canthus, invading into right orbit and lateral rectus	5	Cemiplimab added after PR to IL-2; progressed on cemiplimab, underwent orbital exentera- tion	4	PR	4
Patient 5 71 M	Left lower eyelid, extending into fornix and caruncle	3	Salvage radical excision after no response	1.5	NR	1.5

<sup>a</sup>CCR complete clinical response, PR partial response, NR no response

<sup>b</sup>Progression-free survival measured as months alive since beginning intralesional therapy, to last follow-up or disease progression (requiring alternative therapy)

was 20.7 months (1.5–48, Table 1). All patients tolerated the injections well, with only grade 1 adverse events consisting of local injection site pain, flu-like illness not longer than 24 h, and malaise not longer than 24 h.

### Clinical Response

In this cohort of five patients, we observed two complete clinical responses to IL-2 alone, and one complete response after additional imiquimod, representing a complete response rate of 40% to IL-2 alone. One patient had a partial response that required adjuvant cemiplimab and then further surgery, yielding a partial response rate of 40%, and thus yielding an overall response rate of 80%. Partial response was defined as a reduction in tumor size without complete clearance of the visible tumor. Mean progression-free survival, defined as time alive from initial therapy to last follow-up or disease progression, was 20.7 months (1.5–48, Table 1). As a result of the prospective nature of this data, some responders continue to be followed clinically. Below, we provide a detailed overview of patient 1.

### Case Presentation

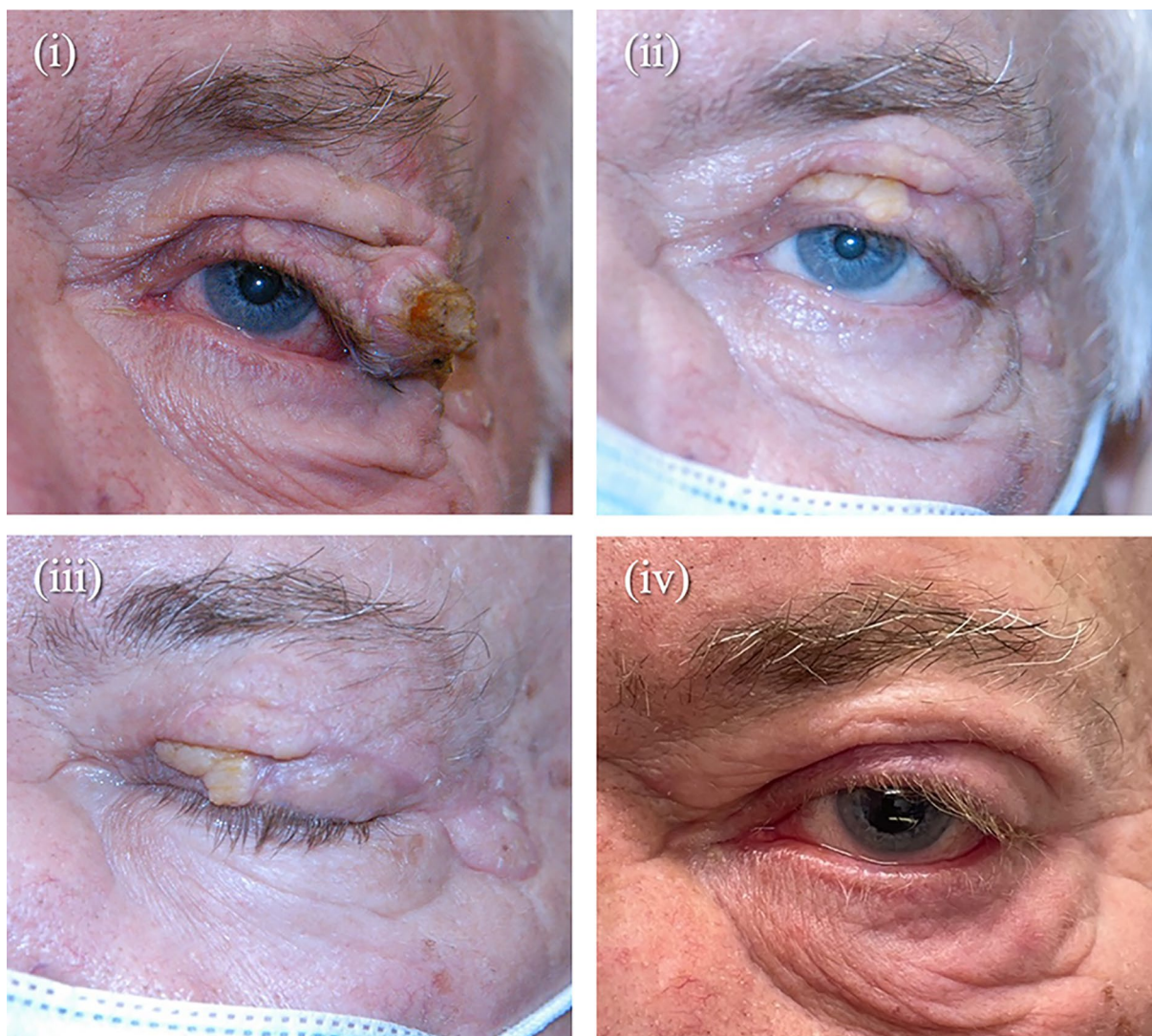
A 74-year-old man presented with a 12-month history of left upper eyelid growth accompanied by pain, irritation, and tearing. He had no history of skin cancer, blistering sunburn, immune compromise, or previous eyelid surgery. Liquid nitrogen therapy of the lesion had been tried in the past with no benefit. Ocular history was only positive for a cataract in the right eye. His past medical history included gastroesophageal reflux disease and respiratory issues thought to be related to COPD or underlying asthma. Systemically, he was treated with pantoprazole, Advair inhaler, and salbutamol inhaler.

On exam, the patient had a best corrected visual acuity (BCVA) of 20/50 in the right eye (OD) with no pinhole improvement and 20/25 in the left eye (OS). Intraocular pressures were 10 mmHg OD and 11 mmHg OS. Pupil exam and extraocular movements were within normal limits. There was a large centrally pedunculated

mass on the left upper eyelid, measuring 5.5 cm horizontally by 3.5 cm vertically (Fig. 1i). The mass caused an S-shaped deformity of the lid, significant laxity, and mechanical ptosis. There was associated thickening of the eyelid medial to the main mass, also extending temporally. The cornea was clear, but the conjunctiva was injected temporally from mechanical exposure. The remainder of the anterior segment exam and fundoscopic exam were otherwise unremarkable. There was no posterior extension on the eyelid or onto the globe, and the orbit clinically appeared to be uninvolved. Ophthalmic nerve (cranial nerve V1) function was intact. There was a right palpable neck lymph node, which was referred for further investigation.

The clinical differential diagnosis included keratoacanthoma, SCC, seborrheic keratosis, and keratin horn. Punch biopsies were taken from multiple sites on the left upper eyelid mass, revealing verruca vulgaris medially and actinic keratoses centrally and laterally. No clear malignant process was identified at this time. As a result of the symptomatic nature of this mass, including ocular irritation and ptosis, the patient underwent a mass debulking approximately 2 months following his initial presentation. This involved an excisional biopsy and reconstruction via upper eyelid advancement myocutaneous flap with free full-thickness skin graft from the right postauricular area (Fig. 1ii, iii). A shave biopsy was also performed on a separate lesion from the left temple at this time, which showed SCC in situ (SCCIS). There were no complications.

Histopathological analysis of the excisional biopsy from the eyelid revealed a well- to moderately differentiated squamous neoplasm, in keeping with invasive SCC with a background of SCCIS and verruca-like areas (Fig. 2). Specifically, low magnification showed striking verruca-like features comprising an exo-endophytic architecture with zones of hyperkeratosis, areas of parakeratosis, hypergranulosis, and intracorneal hemorrhage (Fig. 2i). Increased and dilated capillaries in the dermal papillae were also present. These changes suggest that the SCC may have arisen in association with a pre-existing verruca vulgaris. Medium magnification demonstrated acanthosis of the epidermis with full thickness



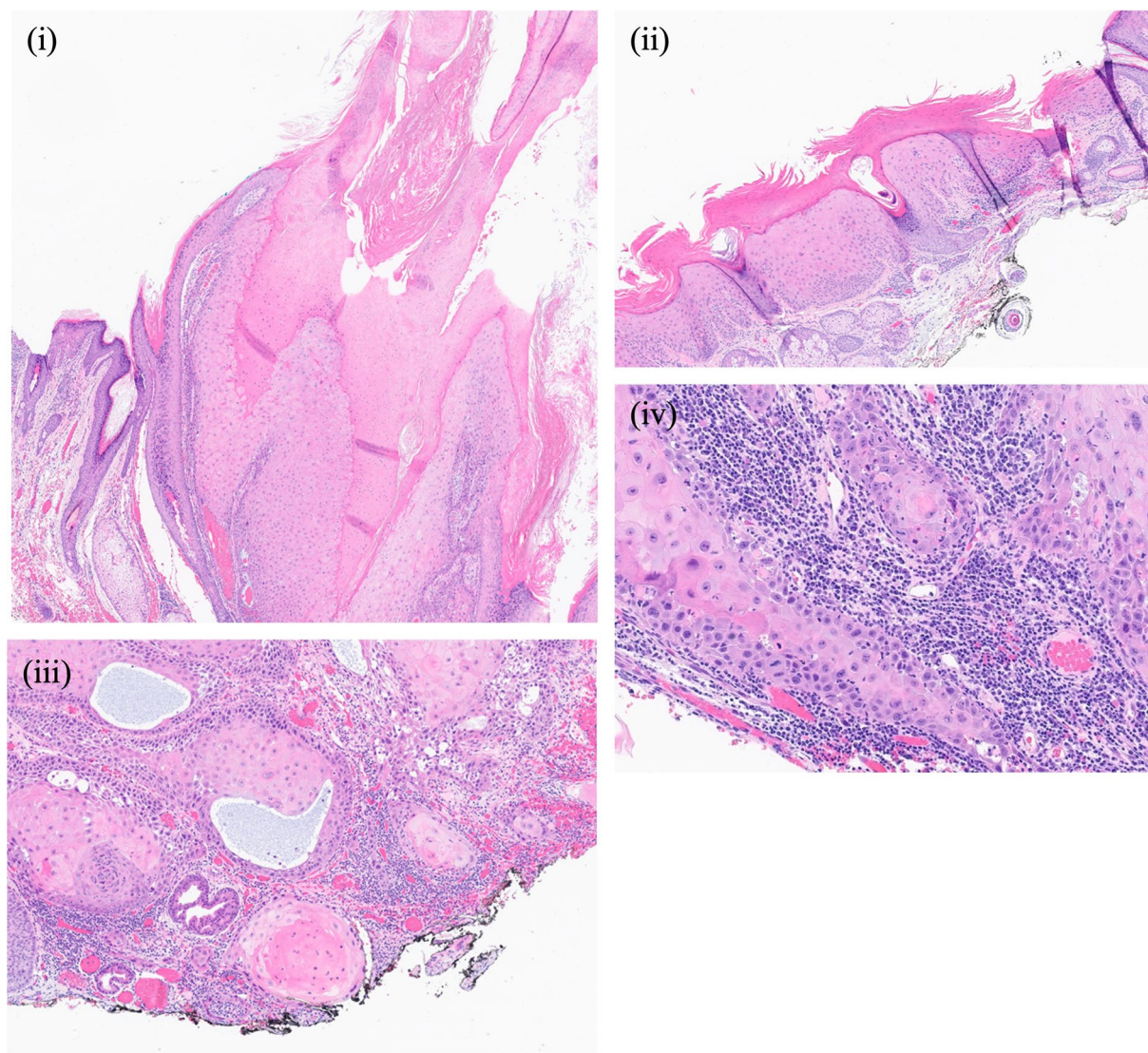
**Fig. 1** Photos of the eyelid mass on presentation (i), following mass excisional biopsy (ii, iii), and subsequent intralesional IL-2 treatment at 15 months (iv)

dysplasia consistent with SCCIS (Fig. 2ii), extending to inked peripheral margins. Finally, small sized nests of atypical, well- to moderately differentiated keratinocytes were identified, infiltrating the dermis and extending to the ink at the deep specimen margin, consistent with invasive elements (Fig. 2iii). A brisk lymphoplasmacytic inflammatory infiltrate was noted, bordering the tumor interface (Fig. 2iv).

Further surgical intervention of the involved margins would have required resection of large areas of the upper lid, brow, and temple in addition to reconstruction with potential ocular

compromise. This case was discussed with the surgical oncology team. Given the recent success at our institution with intralesional treatment for cSCC and melanoma, the patient was referred for consideration of local immunotherapy with combined imiquimod and IL-2 [4].

Following discussion of the risks and benefits of IL-2 versus combined IL-2 and topical imiquimod, the patient opted for IL-2 monotherapy given the risks of corneal irritation associated with imiquimod. Under the joint care of the surgical oncology and ophthalmology teams, the patient received five doses of intralesional IL-2



**Fig. 2** Photomicrographs of eyelid mass histology. Low power magnification of verruca-like features including hypergranulosis, hyperkeratosis, dilated capillaries (i). Medium magnification showing full thickness epidermal

dysplasia consistent with SCCIS (ii). Invasive SCC characterized by small aggregates of atypical keratinocytes infiltrating the dermis, involving black inked deep margin (iii). Associated brisk lymphoplasmacytic infiltrate (iv)

injections approximately every 2 weeks, starting at nearly 5 months following initial presentation. Significant clinical reduction was noted within 2 weeks following the first injection. The lid lesion continued to recind throughout the treatment course without ulceration. During this time, the patient reported only grade 1 adverse events, consisting of mild flu-like symptoms of fatigue and soreness lasting 2–3 h after treatment, which resolved with acetaminophen.

At 6 weeks, the lesion had clinically completely cleared after receiving three doses of immunotherapy. There was only minimally raised tissue irregularity on the lateral canthus, which was thought to be residual surgical changes. At 8 weeks, a slight irregular plaque appeared at the left lateral canthus, suspected to be residual actinic keratosis, along with a lesion on the left cheek, likely a BCC. Both responded to further treatment. Complete resolution was achieved at

15 weeks, and there was no recurrence noted at 15 months since starting the treatment (Fig. 1iv). The patient also underwent uncomplicated cataract surgery in the left eye during this period.

## DISCUSSION

In this case series, we present five cases of locally advanced periocular cSCC that were treated with intralesional IL-2 with or without adjuvant imiquimod. This treatment was overall well tolerated with good clinical response. The illustrative case reported here demonstrated a complete response with minimal complications.

The first use of IL-2 in human cancer treatment was documented in 1984, when a 33-year-old woman with treatment-resistant metastatic melanoma received systemic infusion of high-dose recombinant IL-2 (rIL-2) and autologous lymphokine-activated killer (LAK) cells [5]. Her tumors completely regressed within months, and she remained disease-free during the following 29 years [6]. Following clinical trials, high dose rIL-2 became the first cancer immunotherapy approved by the US Food and Drug Administration (FDA) for the treatment of metastatic renal cell carcinoma and metastatic melanoma in 1992 and 1998, respectively [6]. Subsequent randomized clinical trials demonstrated that the anti-tumor effects were attributable to IL-2 alone, leading to the discontinuation of LAK cells in future studies [7]. These landmark papers sparked interest in developing further IL-2-based immunotherapies for cancer and autoimmune disease [8].

Despite its lasting effects, high-dose systemic IL-2 is effective only in a small subset of patients, and its therapeutic potential is limited by severe adverse effects, including capillary leak syndrome, hypotension, hypoxia, lymphopenia, thrombocytopenia, and impaired neutrophil chemotaxis [9]. This has prompted researchers to explore more targeted local and regional approaches. Intralesional IL-2 has been extensively studied in metastatic and in-transit melanoma [10, 11]. Since 2016, it has been recognized by the National Comprehensive Cancer

Network (NCCN) clinical practice guidelines as an effective treatment for in-transit, non-resectable melanoma [12]. Although the exact mechanism of action is not fully understood, this pleiotropic cytokine is thought to promote anti-tumor activity by stimulating effector T cells and natural killer (NK) cells [4]. Intralesional injections of IL-2 restore local immunity by delivering high doses of IL-2 directly to the tumor site to maximize effectiveness, while minimizing systemic side effects. It is generally well tolerated, with common side effects including local injection site inflammation and systemic flu-like symptoms (nausea, fatigue, chills, stomach pain, and headache), like those experienced by our patient. These are typically mild and respond to over-the-counter analgesics [12].

Similarly, regional IL-2 therapy has been well studied in head and neck squamous cell carcinoma (HNSCC) using various delivery methods, ranging from intralesional injections into tumors and lymph nodes, to synthetic gene delivery [13–15]. Randomized trials have shown that local low-dose perilymphatic IL-2 injections, when combined with traditional surgery and radiotherapy, can improve survival rates in patients with SCC of the oral cavity or oropharynx [16]. However, research on cSCC remains limited. Two of five patients in this case series achieved complete clinical regression after intralesional IL-2. These preliminary results suggest that IL-2 could be a promising therapeutic option, warranting further evaluation in larger, controlled studies.

Although the literature on periocular SCC immunotherapy remains limited, numerous bovine studies have shown that intralesional IL-2 can lead to clinical regression of bovine ocular SCC (BOSCC) [17, 18]. A study examining 70 BOSCC tumors treated with different doses of peritumoral IL-2 found that 200,000 U IL-2 resulted in better long-term outcomes compared to 5000 U or 20,000 U [19]. After 9 months, complete regression was observed in 89% of tumors treated with 5000 U IL-2, 80% with 20,000 U, and 67% with 200,000 U. After 20 months, complete regression rates were 35%, 31%, and 67%, respectively, for the same treatments [19]. Higher doses of IL-2 appear to have lower clinical regression rates in the short term

but result in better long-term maintenance. A similar trend was observed by Stewart et al., who treated 174 BOSCC tumors of varying sizes with daily IL-2 injections for 10 days [20]. The IL-2 doses ranged from 5000 to 2 million U, and all doses significantly improved clinical outcomes compared to the control solvent group. Whilst higher doses (greater than 500,000 U) showed less effectiveness at 9 months, responses were better maintained at 20 months. However, no statistically significant difference was found between the different doses [20]. Interestingly, tumors on the third eyelid and corneal limbus, which were the fastest growing, were most responsive to IL-2 therapy [20]. Furthermore, IL-2 monotherapy has been shown to be more effective than combination therapy with IL-12. In a study randomly assigning 25 cows to a 5-day treatment with 200,000 U IL-2, 0.5 µg/day IL-12, or a combination of IL-2/IL-12, the results at 20 months showed 63% complete regression in the IL-2 group, 38% in the combination group, and 0% in the IL-12 group [21].

Whilst a few studies have examined the effects of intralesional IL-2 in cSCC, to our knowledge, none have investigated its use in periocular cSCC. Recently, Vidovic and colleagues demonstrated that combined intralesional IL-2 and topical imiquimod can effectively clear recurrent, aggressive, multifocal facial cSCC lesions in a double organ transplant patient. In this case, lesions were clinically cleared after only 6 weeks of immunotherapy despite exhibiting many high-risk features of poor differentiation, lymphovascular invasion, and positive margins [4]. By restoring local immunity, immunomodulators can serve as an effective treatment for premalignant and malignant cSCC in immunosuppressed transplant patients, who face a 65- to 250-fold increased risk of cSCC [22].

It is worth noting that patients 4 and 5 (Table 1) had either partial or no response to the treatment. Patient 4 had deep invasion of the cSCC into the zygoma and orbit (Table 1). Prior to undergoing orbital exenteration, the overlying skin lesion had appeared necrotic. Patient 5 had no response to the skin or conjunctival lesions and subsequently underwent a keratectomy and lid excision. It is possible that SCC with orbital and conjunctival involvement

may behave and respond differently to treatment compared to purely cSCC.

Studies have shown that cSCC responds well to immune checkpoint inhibitors (ICI) such as cemiplimab and pembrolizumab [23, 24]. This responsiveness is likely due to its high tumor mutation burden from UV-induced DNA damage and an inherently immunogenic microenvironment [25]. Although data on conjunctival and orbital SCC remain limited, recent case series suggest ICI may benefit some locally advanced tumors, warranting further clinical trials [26]. Emerging evidence indicates conjunctival SCC can also harbor elevated mutation burdens [27]. However, a recent report of five patients with conjunctival SCC treated with ICI found only the patient with a bulbar lesion responded, while those with palpebral or tarsal lesions did not—possibly reflecting lower UV exposure and mutation rates in these sites; additional clinical data are needed to confirm this hypothesis [27].

Although surgical intervention remains the gold standard treatment for malignant cSCC, local immunotherapy can serve a useful alternative modality, allowing for greater tissue preservation and improved functional and aesthetic outcomes. It can be particularly beneficial for patients who are unsuitable for surgery and in complex surgical cases involving substantial tumor size, aggressive tumor recurrence, or invasion of surgically challenging anatomical sites. In our patient, achieving negative resection margins would have conferred a significant defect with potentially challenging options for reconstruction, likely resulting in sequelae of exposure keratopathy and unwanted changes in cosmesis. In such select cases with structural and aesthetic concerns, intralesional treatment is a viable option to consider.

Immunotherapy has recently garnered increasing attention as a promising non-invasive and localized treatment approach for various cutaneous cancers. Although local immunotherapy shows great promise, its slow development for treatment of locally invasive periocular cSCC lesions is marked by critical considerations. Compared to other eyelid tumors, cSCC tend to be more aggressive with higher recurrence rates and require close follow-up. Currently, there is not enough robust evidence available to support

local immunotherapy as a monotherapy for invasive cSCC, and more trial data is required. Before conclusive results are made regarding monotherapy, immunomodulators may initially be used as a neoadjuvant for preoperative patients with long wait times.

Enhancing the targeting and efficacy of IL-2-based cancer immunotherapies is an active area of research. These include improving the stability of IL-2 by fusing it with molecules like PEG and Fc to extend its short half-life and increasing its specificity by attaching moieties that improve target delivery and binding to tumor cells [9]. Additionally, combining IL-2 with immune checkpoint inhibitors, such as anti-PD1 or anti-CTLA-4 antibodies, is being investigated to enhance the overall therapeutic effect [9]. While preclinical studies have shown promising results, further clinical evaluation is necessary. Moreover, there is ongoing research exploring other forms of targeted immunotherapy such as PD-1/PD-L1 inhibitors (e.g., cemiplimab and pembrolizumab) and epidermal growth factor receptor (EGFR) inhibitors. However, the data available for periocular cSCC remains limited [28].

This study has several limitations. The small sample size ( $n=5$ ) limits statistical power and generalizability, so observed responses may reflect case selection. The absence of a control group limits causal inference and direct comparison with standard therapies. Treatment regimens and adjunctive therapies were heterogeneous and follow-up durations varied. These caveats underscore the need for larger, prospective, controlled studies with standardized dosing and objective outcome measures.

## CONCLUSION

We have presented, to the best of our knowledge, the first cases of invasive periocular cSCC treated with intralesional IL-2 therapy. We propose a trial of intralesional IL-2 as a potentially effective alternative for patients like ours, who are at risk of potential surgical morbidity and functional compromise, or who have limited salvage options remaining. Systemic

immunotherapies may also be considered for those who have failed or cannot tolerate standard treatment with surgery or radiation therapy, at the risk of systemic toxicity. Further clinical data is required to evaluate the safety and effectiveness of this approach in a broader patient population.

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**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

### Declarations

**Conflict of Interest.** Sorayya Seddigh, Freddy Lee, Dejan Vidovic, Jennette R. Gruchy, Ahsen Hussain, and Carman Giacomantonio declare that they have no competing interests.

**Ethical Approval.** This study was performed in accordance with the Helsinki Declaration. All subjects provided informed consent to study participation and publication. Collection and evaluation of protected patient health information were HIPAA compliant. Ethics committee approval was not required, as this was a

retrospective study using an already established treatment protocol for cutaneous squamous cell carcinoma in non-periocular regions at our institution.

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