CLINICAL SCIENCE

Squamous cell carcinoma of the eyelids

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Aim: To review the clinical features, management, and outcomes of surgical treatment of eyelid squamous cell carcinoma (SCC).

Methods: A retrospective review of all eyelid SCCs treated between 1992 and 2001.

Results: 51 cases were identified in 50 patients. Patient ages ranged from 26 to 93 years, with a mean age of 65 years. 33 patients were male and 17 were female. The lesion was found on the lower lid in 31 cases, upper lid in five cases, lateral canthus in six cases, and medial canthus in nine cases. Perineural invasion was found in four patients, and orbital invasion in three patients. Recurrence occurred in one patient. Treatment was by complete excision with histological confirmation of clear margins. Exenteration was required in three patients. No patients developed lymph node or distant metastases. One patient, who declined treatment, died as a result of the tumour. Mean follow up was 31.1 months.

Conclusions: Eyelid SCC is a relatively uncommon, but potentially fatal disease. However, if detected early and treated adequately, the prognosis is generally excellent. Treatment by complete excision with histological confirmation of tumour clearance is recommended. Perineural spread is an adverse prognostic sign, which may require postoperative radiotherapy. Orbital invasion is a rare complication but, if recognised early, can be treated effectively with exenteration. Because presentation varies and histological examination is required for accurate diagnosis, any suspicious lesion occurring on the eyelids should be excised or biopsied. All patients with eyelid SCC should be advised of the risk of recurrent or new tumours and encouraged to attend lifelong follow up. Prevention remains of prime importance in minimising the morbidity and mortality of these lesions.

Squamous cell carcinoma (SCC) is an invasive epithelial malignancy showing keratinocytic differentiation. It is the second most common malignant neoplasm of the eyelids,¹ comprising 5–10% of all eyelid malignancies. The incidence for eyelid SCC has been reported to be between 0.09 and 2.42 cases per 100 000 population.² Extrinsic risk factors include ultraviolet light/actinic damage and exposure to arsenic, hydrocarbons, radiation, or immunosuppressive drugs.³ Intrinsic risk factors include albinism, pre-existing chronic skin lesions and genetic skin disorders such as xeroderma pigmentosum and epidermodysplasia verruciformis.

Because of the significant morbidity of these lesions and in order to better define the clinical features and treatment outcomes, and to make management recommendations, we conducted a review of all eyelid SCCs treated over a 9 year period.

METHODS

A retrospective medical record review was conducted of all eyelid squamous cell carcinomas seen in the practice of one of the authors (TJS) in the 9 years from 1992 to 2001. Cases were identified by searching the practice records of the author and hospital and pathology laboratory computerised databases. Included were all lesions originating on the eyelids or canthi with a pathologically confirmed diagnosis of SCC. Exclusion criteria included lesions outside the orbital margin, primary conjunctival lesions, ocular surface squamous cell neoplasia, and cases with less than 3 months of follow up.

Each patient underwent a thorough history and clinical examination, and all follow up was performed by the senior author. The majority of lesions were treated with excision, while some were biopsied by the referring practitioner before definitive excision. Frozen section examination of surgical margins was used to ensure adequate excision in cases where the edge of the lesion was indistinct, to maximise preservation of normal tissue in cases with large lesions, and in all cases of recurrent disease.

Frozen section examination of tissues received at the time of operation involves the following key steps. First it is ideal for the pathologist to discuss the case in theatre with the surgeon before the removal of the lesion. In this way, margins of most concern can be identified. Witnessing the removal of the lesion guarantees proper orientation of the specimen by the pathologist. The specimen is then represented in diagrammatic form and sections are taken from the specimen, with the location of the sections being indicated on the diagram. Critical margins are best sampled using an en face or tangential section technique to ensure the entire margin is sampled, thereby minimising the risk of a false negative report at the time of frozen section. Examples include the medial and lateral margins of eyelid resections, margins adjacent to canaliculi and conjunctival surfaces, and clinically suspicious margins. Less critical areas can be sampled using transverse sections. The sections are then mounted in mounting medium, frozen in liquid nitrogen, sectioned at approximately 5 µm, and stained with haematoxylin and eosin. The tumour is then classified and the extent of the lesion mapped onto the original diagram with any areas of margin proximity or involvement indicated. This is then presented to the surgeon and, following a discussion between surgeon and pathologist, a joint decision is made as to the need for further excision and the site for any required excision. Re-excised margins are best sectioned with the en face technique.

RESULTS

Fifty one cases meeting the inclusion criteria were identified in 50 patients. Thirty three of the patients were male (66 %) and 17 were female (34 %). Patient ages at the time of surgery ranged from 26.8 to 93.5 years (mean 65.2, median 67.9 years). The mean age of male patients was 66.8 years, and the mean age of female patients was 63.0 years. One patient was younger than 30 years (age 26 years), but the majority were

Figure 1 Patient age distribution.

aged > 60 years (Fig 1). Three patients had predisposing factors, including arsenic exposure in one patient, and immunosuppression after organ transplantation in two patients (one heart, one lung). None of the six patients less than 40 years of age had predisposing risk factors. There were no patients with a predisposing genetic skin disorder.

Fourteen patients had recurrent eyelid lesions, previously treated elsewhere. The previous treatment was surgical excision in six cases, cryotherapy in four cases, curettage in two cases, and radiotherapy in two cases. It is difficult to know for certain whether these lesions represent recurrence of the original lesion, or the development of a metachronous lesion, although the former would seem to be more likely.

Thirty two patients (64.0 %) had previously had skin lesions excised from other parts of the body. These included SCC in 17 patients, basal cell carcinoma in 21 patients, intraepidermal carcinoma in 12 patients, and melanoma in two patients. Tumour location was on the right side in 28 patients and on the left side in 23 patients. This difference was however not statistically significant ($p = 0.48$). The sites of the lesions are detailed in Table 1.

The preoperative clinical diagnosis was squamoproliferative lesion in 32 patients (25 SCC, four intraepidermal carcinoma, three keratoacanthoma), basal cell carcinoma in 15, tricholemmoma in one, granuloma in one, and not specified in one patient. In 13 cases, the lesions were biopsied by the referring practitioner before definitive excision. In 10 of these cases, the biopsy demonstrated squamous cell carcinoma, in two cases it demonstrated intraepidermal carcinoma and in one case it showed poorly differentiated carcinoma of unknown type.

Lesion size ranged from 3 mm to 30 mm with a mean of 9.7 mm and median of 7.0 mm.

Management used in this series is detailed in Table 2.

Frozen section examination of margins was used in 36 patients. The frozen section diagnosis was confirmed on

paraffin section in 32 of these patients. In three cases, invasive SCC was not seen on the frozen section specimen; however, in these cases the frozen section was used only to confirm that surgical margins were clear of tumour, and not to obtain a histological diagnosis of tumour type. In one case the frozen section diagnosis of "probable basal cell carcinoma (BCC)" was changed to basaloid SCC on paraffin section. Histological examination of paraffin sections revealed no cases with tumour involvement of surgical resection margins. The classic histological appearance of one of the lesions is depicted in Figure 2E and F.

In 11 cases (21.6 %) tumour arose within foci of intraepidermal carcinoma. In 14 cases (27.5%) tumour arose within solar keratoses, three of which were among the 11 specimens that contained foci of intraepidermal carcinoma.

The presence of perineural or orbital invasion significantly complicates the management of an eyelid SCC. These problems often coexist; however, owing to their importance in determining prognosis and treatment, they are discussed separately.

Microscopic perineural invasion was found within the lesion in four cases (7.8%). Two of these patients had recurrent lesions without orbital invasion. They were treated with excision and postoperative prophylactic radiotherapy and both were recurrence free at last follow up, of 9 and 24 months respectively. The other two patients had extensive lesions with orbital invasion at presentation. One was treated with primary exenteration followed by radiotherapy. He is recurrence free at 43 months. The fourth patient presented to us with a recurrent tumour with orbital invasion, 2 years after the original excision. She was treated with radiotherapy and exenteration, and is recurrence free 5 years after exenteration.

Orbital invasion was seen in three cases (5.9%). Two of these patients also had perineural spread and are described above. The third patient had an extensive lesion with orbital exenteration at presentation. He declined exenteration and was treated with palliative radiotherapy. He died in his sleep 1 month after presentation. The mean age at diagnosis of orbital invasion was 67.3 years.

Orbital exenteration was required in three patients. Two of these patients had orbital invasion and are described in the previous paragraph. The third patient had known perineural spread but no evidence of orbital invasion. He was treated with surgical excision and graft repair with postoperative radiotherapy. He developed flap and graft failure resulting in intractable exposure problems, requiring exenteration. It is likely that the graft failure was a result of postoperative radiotherapy, rather than a complication of the surgical repair. Exenteration was offered to one additional patient, mentioned earlier, who declined surgery.

Recurrence occurred in only one patient (2.0%). He presented with a recurrent lesion in a field of intraepidermal carcinoma, 6 years after excision of a well differentiated SCC without perineural invasion and with clear surgical margins. He was treated with further excision, and is recurrence free 1 year later. He has, however, required surgery for excision of further intraepidermal carcinoma.

Lymph node or distant metastasis was not observed in any patients. One patient died as a direct result of complications of orbital invasion, as described above.

Eight patients experienced complications after their treatment. Two patients developed epiphora, which was expected because of tumour involvement of the canaliculus, requiring excision. One patient developed symptoms and signs of corneal exposure requiring tarsorrhaphy. Two patients developed minor wound infections, one of whom required needle drainage of a small collection. One patient with a prominent tissue fold after a flap repair was unhappy with the cosmetic result of surgery. Two patients developed complications due to postoperative radiotherapy—retinopathy and neovascular glaucoma in one and severe corneal exposure in the other. This

Table 1 Site of lesion of 51 cases of periocular SCC

Site	No of cases
Lower lid	31 (60.8%)
Medial canthus	9 (17.6%)
Lateral canthus	6 (11.8%)
Upper lid	5 (9.8%)

Table 2 Management options used

Treatment	No of cases
Excision with direct closure	13 (25.5%)
Excision with flap repair	25 (49.0%)
Excision with graft repair	9 (17.6%)
Exenteration	3 (5.9%)
Radiotherapy	1 (2.0%)

Figure 2 (A) Small well circumscribed SCC. (B) Poorly circumscribed, scaly erythematous SCC arising in patch of intraepidermal carcinoma. (C) Large, ulcerated SCC. (D) Histopathological appearance of SCC. Haematoxylin and eosin $\times 20$. (E) Haematoxylin and eosin $\times 100$. (F) Haematoxylin and eosin $\times 400$.

patient, previously irradiated with a recurrent lesion, had breakdown of his flap repair. He was found to have perineural involvement and subsequently underwent exenteration.

Mean follow up was 31.1 months, with a range of 3 months to 9 years.

DISCUSSION

This study highlights the difficulties in the clinical diagnosis of SCC. Lesions demonstrate a broad spectrum of clinical appearances at presentation, including small erythematous scaly patches, large ulcerated lesions, and small nodular or papillomatous lesions (Fig 2A–D) The edge of the lesion may be well circumscribed in some cases, and ill defined in others.

The wide variation in clinical appearances presents great difficulty in differentiating squamous cell carcinoma from basal cell carcinoma, and indeed 15 of the lesions were thought to be basal cell carcinoma preoperatively. Thirty two lesions (62.7%) were correctly identified as squamoproliferative lesions preoperatively. Numerous studies have confirmed the inaccuracy of preoperative clinical diagnosis, by even experienced observers.^{4–6} In one study the clinical diagnosis of SCC of the skin was confirmed in 51% of cases.⁴ Clinical diagnosis of BCC affords better results, with Kersten *et al*⁷ obtaining a diagnostic accuracy of 92.8%. This is perhaps to be expected, given that eyelid BCC is up to 10 times more common than SCC. These figures demonstrate the considerable difficulty associated with the clinical diagnosis of eyelid lesions, and highlight the importance of histological confirmation, preferably by excisional biopsy, for all suspicious eyelid lesions.

Eyelid SCC may develop *de novo* in relatively normal skin,⁷ or within areas of widespread actinic skin damage. Develop-

ment of ultraviolet radiation induced SCC occurs in a multistage process, with a progression of increasing severity from solar keratosis, through intraepidermal carcinoma, to invasive SCC. Solar keratoses have a risk of malignant transformation to SCC of less than 1%.^{7–8} SCC developing in a solar keratosis is less likely to metastasise,^{4,9} and in the absence of additional ultraviolet damage, may regress in up to 25% of cases.⁸ Intraepidermal carcinoma represents full thickness involvement of the epidermis by neoplastic epithelium with a relatively high risk of progression to invasive SCC. A recent study showed development of SCC in six of 31 patients (19%) with intraepidermal carcinoma of the eyelid.¹⁰

The mean age of patients in this series was 65.2 years, with male patients being slightly older than female patients (66.8 v 63.0 years). The majority of patients (72%) were 60 years of age or older. Given that Queensland has the highest incidence of cutaneous SCC in the world,¹¹ (2400 per 100 000) we had expected the average age of our patients to be younger than that reported in the literature. These figures are however very similar to other series.^{12–13} The distinct male predominance (64.7 % v 35.3 %) may represent increased occupational sunlight exposure by males, rather than a genetic predisposition.

Sixty four per cent of patients had a past history of other skin lesions requiring surgical excision. Numerous studies have documented an increased risk of additional non-melanoma skin cancers among those with cutaneous squamous cell carcinoma.¹⁴ Patients with a past history of cutaneous SCC have been shown to have a three times relative risk of developing another SCC compared to those who have not had previous SCC.¹⁵

Squamous cell carcinoma is the second most common eyelid malignancy. It is much less common than basal cell carcinoma, with the reported relative incidence ranging from 1:40¹⁶ to 1:11.¹⁷ Over the corresponding 9 year period, other eyelid lesions excised at our institutions included 653 BCCs,¹⁸ 37 intraepidermal carcinomas,¹⁰ 11 malignant melanomas, 9 sebaceous cell carcinomas, 10 keratoacanthomas,¹⁹ one Merkel cell carcinoma, and one angiosarcoma. The relative incidence of BCC to SCC is therefore approximately 13 to 1.

There was a slight preponderance of right versus left sided lesions (55.8% v 44.2%). One possible explanation for this is the increased sun exposure to the right hand side while driving. The difference was not statistically significant in this study; however, in a much larger study of 653 basal cell carcinomas at our institutions,¹⁸ a statistically significant predominance of right sided lesions was found (55%; $p = 0.0077$). The lower lid was the most common site of eyelid SCC by a considerable margin, accounting for almost 60% of lesions, while the upper lid was the least common site (9.6%). This differential between lower and upper lid lesions is considerably greater than the ratio of 1.4:1 that was found in the review by Reifler and Hornbliss.¹ Our figure of 6:1 is even higher than the ratio they described for basal cell carcinoma, of between 3:1 and 5:1.

Two patients developed their lesions after organ transplantation, a well known risk factor for the development of skin cancer. SCCs are more common than BCCs after renal transplantation, a reversal of the usual considerable predominance of BCCs.²⁰

Perineural spread is reported to occur in up to 14% of facial SCCs.²¹ The incidence in our study was 7.8%. All four cases were treated with postoperative radiotherapy and all are recurrence free after 9–60 months of follow up. Perineural invasion has been divided into two different populations,²² those with unexpected microscopic perineural invasion found on pathological review of resected lesions, and those with clinical signs or symptoms of perineural involvement. All four patients in our study were of the former group, which has a significantly better prognosis than those with clinical signs or symptoms. The risk of recurrence has been reported to be around 50%, in cases of head and neck SCC with perineural invasion treated by simple excision only.²¹ Postoperative radiotherapy is recommended in all patients with asymptomatic microscopic perineural invasion,²³ since the results of treatment are poor, once clinical signs or symptoms of perineural spread have developed.

Orbital invasion was seen in three cases (5.9%) This is a serious complication of aggressive or neglected lesions, which has been reported to occur in 2.5% of all eyelid basal and squamous cell carcinomas.²⁴ It usually presents with the characteristic signs of an ulcerated eyelid lesion associated with ocular motility restriction and requires orbital exenteration for cure. Three patients in this study required exenteration. All had a good result from surgery, and were recurrence free at 9, 42, and 87 months after surgery. This is in line with other studies which have demonstrated that recurrence after orbital exenteration is rare. In the series by Rathbun *et al*,²⁵ there were no recurrences in six cases of exenteration for SCC, with follow up ranging from 5 months to 13 years.

Reported rates of metastasis for eyelid SCC vary from 1–21%.²⁶ Rates for cutaneous SCC are better defined, and reported at 0.3–3.7%.²⁷ There were no cases of distant or lymph node metastasis in this series, which may be a result of the early treatment of the lesions, and the aggressive treatment of recurrent lesions. The reported incidence of lymph node metastasis from eyelid SCC has ranged from 0%¹ to as high as 21.4%.²⁸ However, the rate of 21.4% occurred in a small series of 14 patients, almost 40 years ago, and the true rate is almost certainly less than this.

There was one case of recurrence, which represents a recurrence rate of 2.0%. This compares favourably with the results

obtained by Mohs surgery, which has been reported to achieve a 5 year cure rate of 98.1%.²⁹

The tumour related mortality in this series was 2.0% (one patient). Mortality rates have been reported as high as 40%³⁰; however, once again, the true figure is almost certainly much lower in contemporary practice. Early diagnosis and treatment by surgical excision before lymph node metastasis or orbital invasion occur would be expected to significantly reduce mortality rates. Education campaigns targeting the public and general practitioners, encouraging early presentation may be responsible for the lower mortality rates in our community.

Eyelid SCC is a relatively uncommon, but potentially fatal disease. It is responsible for considerable morbidity; however, if detected early and treated adequately, the prognosis is generally excellent and death and disability can be reduced. The clinical presentation varies and histological examination is required for accurate diagnosis. Any suspicious lesion occurring on the eyelids should therefore be excised or biopsied. Perineural spread is an adverse prognostic sign, which requires consideration of postoperative prophylactic radiotherapy. Orbital invasion is a rare complication, but if recognised early can be treated effectively with exenteration and central nervous system dissemination can be prevented. All patients with eyelid SCC should be advised of the risk of recurrent or new tumours and encouraged to attend regular follow up examinations. Prevention by minimising sun exposure, especially in childhood and adolescence, remains of prime importance in minimising the morbidity and mortality of this disease.

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