Management of Periocular Basal and Squamous Cell Carcinoma: A Series of 485 Cases

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PURPOSE: To analyze the outcome of management of patients with basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) in a tertiary referral eye center in Sydney, Australia.

DESIGN: Retrospective case series.

METHODS: Review of medical records of 485 consecutive cases (469 patients) with confirmed eyelid cancer.

INTERVENTION PROCEDURES: Surgical excision with 3- to 5-mm clinically clear margins and histologic confirmation of the surgical margins. Frozen section histology or Mohs' micrographic surgery (MMS) was used for incompletely excised cases, and those located in the medial canthus or close to the lacrimal drainage system. Standard reconstruction techniques were employed.

MAIN OUTCOME MEASURES: Survival period free of tumor, incomplete excision, recurrences, type of closure, and complications.

RESULTS: Excision was initially incomplete in 25.4% of all tumors. Morpheaform type of BCC ($\chi^2 P < .001$), and medial canthus location BCCs ($\chi^2 P < .05$) were associated with a higher incomplete resection rate. A 35.9% incomplete excision rate was associated with a significantly higher recurrence rate compared with complete excision (8.4% and 4.6%, respectively, $\chi^2 P < .05$). Twenty-seven patients (5.6%) had a recurrent tumor. After incomplete excision, there was no recurrence with MMS, but 4.7% recurrence rate when frozen section technique was used ($P < .05$). Local postoperative complications occurred in 41 patients (8.5%).

CONCLUSIONS: In the setting of a tertiary referral center, incomplete primary resection of an eyelid skin cancer is the main risk factor for recurrence. Incomplete resection is significantly associated with medial canthus location and morpheaform type of BCC and with moderately differentiated SCC. MMS is the safer technique after incomplete tumor excision. (Am J Ophthalmol 2006;142:293–297. © 2006 by Elsevier Inc. All rights reserved.)

IT HAS BEEN REPORTED THAT 5% TO 10% OF ALL SKIN cancers occur in the periocular region, with eyelid malignancies representing more than 90% of all ophthalmic tumors. Although the mortality from eyelid skin cancer is very low, the morbidity is significant. The aim of treatment is total tumor eradication with the smallest recurrence risk, employing the most cost-effective method that is acceptable to the patient.

The aim of this study is to analyze the outcome of management of patients with periocular basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) treated over a 15-year period in Sydney Eye Hospital, a tertiary referral center in Sydney, Australia.

METHODS

WE REVIEWED CASE NOTES AND HISTOPATHOLOGY FROM a consecutive series of patients with periocular BCC and SCC between 1990 and 2004 at the Sydney Eye Hospital, a tertiary referral center. Computerized medical records were used for the diagnosis of skin cancer confirmed by histopathologic examination in all cases. The medical records were reviewed for demographic and clinical data, which were transcribed onto a computerized table. Histologic records from the ocular pathology department servicing Sydney Eye Hospital in Sydney were reviewed noting the histopathologic findings. The study and data accumulation were carried out with approval from the Institutional Review Board. The primary outcome measures were: survival period free of tumor, completeness of tumor excision, local recurrences, type of closure, and complications.
The subtypes of BCC were classified as nodular and morpheaform, and those of SCC by the histologic differentiation. (well, moderately, and poorly differentiated).

There were some variations in surgical techniques according to the individual surgeon’s preferences, but most of the surgical procedures were performed as follows: clinically clear margins were marked around the tumor by noting the transition in surface contour, vascularization, skin color, and surface texture by light reflection. The deep extent of the tumor was judged by the lesion’s mobility over the underlying tissues and macroscopic features of the excision plane.

Margins of 3 mm for BCC and 5 mm for SCC were marked with the skin under tension. Local anesthesia was obtained with infiltration of a 50/50 mixture of bupivacaine 0.5% and lignocaine 0.1%: with adrenaline one in 100,000, which was injected beneath and around the area marked for excision and subsequent reconstruction, and ocular amethocaine (tetraacaine hydrochloride 1%) (topical use of drops).

The excision specimen was marked with a suture to provide orientation. Well-demarcated tumors were treated with primary repair, and the excision specimen was submitted for histologic confirmation of the diagnosis and examination for clearness of the surgical margins. Immediate examination of frozen tissue was used in cases of primary incomplete excision or recurrence when the tumor was located in the medial canthral region. Mohs’ micrographic surgery (MMS) technique was used in some cases of primary incomplete excision or recurrences in the medial canthus or when the tumor was close to the lacrimal drainage system. Cases that did not undergo primary repair were dressed with a nonsticky dressing after the application of chloramphenicol ointment to the surgical defect while awaiting confirmation or orientation of histologic clearance.

Reconstruction was performed with direct closure where possible, or with cantholysis, flaps, or grafts if required. After suture removal, follow-up in the hospital clinic was carried out at one to three months for the first year, and thereafter every six to 12 months for five years. In cases of incompletely excised tumors (on histology), there was discussion with the patient about subsequent management. In some cases of extensive tumor, the patient had the option of excision to achieve histologically clear surgical margins or radiation therapy.

Associations between categorical variables were analyzed using \( \chi^2 \) tests. Comparison of normally distributed variables among groups was performed using \( t \) tests and analysis of variance. Exact 95% confidence intervals (CIs) were calculated for the recurrence rates.

**RESULTS**

IN ALL, 469 PATIENTS HAD 485 RECENTLY DIAGNOSED MALIGANT EYELID BCC AND SCC. All patients were Caucasian, with men showing a slight predominance to women (56.7% versus 43.3%). Ninety-five were smokers (20.3%), most of them being males (84%). The mean follow-up was 33 months (range three to 125 months).

The mean age at diagnosis was 68.3 ± 14.6 years (range 14 to 95 years). In both BCC and SCC groups, most of the patients were older than age 70 years (53% and 51%, respectively). The incidence rates for the eyelid malignancies are: BCC 86% (n = 417) and SCC 14.0% (n = 68).

The lower eyelid was the most frequent location for both BCC and SCC (62.6% and 54.4%, respectively). More malignant tumors were diagnosed on left eyelids (53.5%) than the right (46.5%). The location distribution of the malignant tumors is summarized in Table 1.

Forty-four (9.1%) patients (35 BCC and 9 SCC) had a history of previous skin cancers (at least one) being excised from other parts of the body.

At the time of diagnosis, 16 cases of BCC and SCC tumors (3.3%) showed invasion into adjacent bone or orbital structures, and spread to regional lymph nodes. One case had spread to regional lymph nodes (SCC), eight had spread to adjacent bone (seven cases of BCC and one case of SCC), and seven tumors had spread into the orbit (five of BCC and two of SCC).

Excision was initially incomplete in 25.4% (123 cases) of all tumors. Those patients were given the option of reexcision or radiation therapy. A total of 104 (84.6%) of

| TABLE 1. Periocular Location Distribution of Basal and Squamous Cell Carcinomas |
|-----------------|------------------|------------------|------------------|------------------|------------------|
| Location        | BCC (n = 417)    | SCC (n = 68)     |                  |                  |                  |
|                 | Morphea (n)      | Nodular (n)      | Well Dif (n)     | Moderate Dif (n) | Total n (%)      |
| LL              | 21               | 240              | 33               | 4                | 298 (61.4%)      |
| MC              | 15               | 77               | 8                | 3                | 103 (21.2%)      |
| UL              | 2                | 42               | 14               | 1                | 59 (12.2%)       |
| LC              | 1                | 19               | 4                | 1                | 25 (5.2%)        |
| Total           | 39 (8.0%)        | 378 (77.9%)      | 59 (12.2%)       | 9 (1.9%)         | 485              |
| BCC = basal cell carcinoma; SCC = squamous cell carcinoma; LL = lower lid; MC = medial canthus; UL = upper lid; LC = lateral canthus; Dif = differentiated.
these patients had reexcision (guided by frozen section or MMS), and 10.6% (13 cases) had radiation therapy. Six of those patients (4.9%) had no additional procedure and continued to be clinically followed in the clinic.

The percentage of tumors with incomplete excision varied according to tumor location (Table 2). Patients with morpheaform-type BCC had a significantly ($P < 0.001$, $\chi^2 = 13.1$) higher rate of incomplete excision (43.6%) compared with nodular-type BCC (23.5%). The rate of incomplete excision was significantly higher at the medial canthal region compared with other tumor locations (35.9% and 25.4%, respectively, $P < .05$, $\chi^2 = 4.14$). Moderately differentiated SCC tumors showed higher, but not significant ($P = .14$) incomplete excision rates (44.4%) compared with well-differentiated SCC tumors (22.0%).

Reconstructive techniques used are outlined in the Figure. The overall recurrence rate in patients in whom reexcision was offered and executed was 5.6% with 27 recurrent tumors. The risk for recurrence was 5.5% per person-year for BCC (23 cases) and 5.9% for SCC (four cases). Recurrence was more common after initial incomplete excision (8.4%) than primary complete excision (4.6%) ($P < .05$). Tumor recurrence after complete and incomplete excision of periocular tumors is summarized in Table 3.

There was no recurrence in any of the 19 cases for which MMS technique was used after incomplete excision. Four of 85 cases (4.7%) in which frozen section was used after incomplete excision had a recurrence ($P = .05$).

The average time for recurrence was 32.17 months (range four to 81 months). The interval between the initial tumor excision and the recurrence was 34.15 months for BCC and 11.9 months for SCC.

The most common complication after reconstruction of the eyelids was ectropion, which was seen in 20 cases (4.1%), followed by trichiasis (8 cases), lagophthalmus (6 cases), ptosis (4 cases), and failed graft (3 cases).

**DISCUSSION**

In this study, there was initial incomplete excision in 25.4% of all tumors. (25.4% for BCC; 25% for SCC) Clinically clear margins evaluated by the transition in surface contour, vascularization, skin color, and surface texture may not ensure complete removal. Incomplete excision was more common for the morpheaform type BCC compared with the nodular type, for medial canthus location of BCC compared with other periocular locations, and for moderately differentiated SCC compared with well differentiated SCC.

In previous studies, the incidence of incomplete tumor excision is reported to be 16% to 40% when frozen section monitoring is not used,4-6 and it rises to 50% when the tumors are located on the lower lids and involve the lid margin.2

| TABLE 2. Incompleteness of Tumor Excision for Basal and Squamous Cell Carcinomas in Different Locations* |
| Location | BCC | SCC |
| Nodular | Morpheaform | Well Diff | Mod Diff |
| LL (n/total) | 47/240 (19.6) | 7/21 (33.4) | 9/33 (27.2) | 2/4 (50) |
| MC (n/total) | 25/77 (32.5) | 8/15 (53.3) | 2/2 (14) | 1/3 (33.3) |
| UL (n/total) | 12/42 (28.6) | 2/2 (100) | 2/14 (14.3) | 0/1 (—) |
| LC (n/total) | 5/19 (26.3) | 0/1 (—) | 0/4 (—) | 1/1 (100) |
| Total | 89/378 (23.5) | 17/39 (43.6) | 13/59 (22) | 4/9 (44.4) |

*Total cases of incomplete excision 123/485 (25.4%).

| TABLE 3. Tumor Recurrence Following Complete and Incomplete Excision of Periocular Tumors |
| Tumor | Recurrence |
| Total | Incomplete Excision | Complete Excision |
| BCC | 23 (5.5%) | 9/101 (8.9%) | 14/316 (4.4%) |
| SCC | 4 (5.9%) | 1/18 (5.6%) | 3/50 (6.0%) |
| Total | 27/485 (5.6%) | 10/119 (8.4%) | 17/366 (4.6%) |

BCC = basal cell carcinoma; SCC = squamous cell carcinoma; LL = lower lid; MC = medial canthus; UL = upper lid; LC = lateral canthus; well dif = well differentiated; mod dif = moderately differentiated.

*Total cases of incomplete excision 123/485 (25.4%).
Our finding that incomplete excision of BCC and SCC is associated with a significantly higher recurrence rate after reexcision compared with complete excision at the primary procedure may be explained by the fact that those cases are more aggressive histologically (morphoeform type BCC and moderately differentiated SCC), and more of them are located at the medial canthal area compared with other tumor locations. Subclinical extension of BCC is known to be associated with aggressive histology (morphoeform) and is considered a risk factor for incomplete excision.\(^8\)\(^9\) Those in the medial canthal region\(^10\) have also been reported to have a high risk of recurrence after conventional treatment.\(^11\)\(^–\)\(^14\) Malhotra and associates reported that moderately differentiated SCCs were more likely to have significant subclinical extension with a larger difference in tumor and defect sizes.\(^15\) Moderately or poorly differentiated SCCs are also known to carry a significant risk of invasive spread, recurrence, or metastasis.\(^15\)\(^–\)\(^17\)

However, some of previous studies have shown that only a minority of patients with histologically documented positive margins will clinically experience a recurrence. Hamada and associates\(^4\) have recently reported that of those BCCs that were incompletely excised, histologically 53% contained no tumor at reexcision. Positive margin recurrence rates in other studies range from 35% to 67%.\(^18\)\(^–\)\(^20\) Specimen distortion of the narrow margins during fixing and sampling, making it difficult for the pathologist to confidently confirm clearance,\(^8\) and devitalized tumor cells at the operative site by surgery, may account for the lower than expected clinical recurrence rate after incomplete excision.\(^20\)

The reported recurrence rates for unmonitored surgical excision are in the range of 5% to 100%, and are related to the underestimation of the subclinical extension of BCC.\(^1\)\(^,\)\(^11\)\(^,\)\(^21\)\(^–\)\(^23\) Recurrence rates can be reduced if frozen section control or MMS are used at the time of the initial surgery.\(^8\)\(^,\)\(^24\)\(^,\)\(^25\) Frozen section is considered a safe method for clear margins. However, interpretation of standard frozen sections requires assumptions based on random sampling and is subject to skip areas large enough to allow residual tumor to remain undetected.\(^23\) Ghauri and associates found that 5% of tumors reported as having clear margins on frozen sections were seen later to have involved margins on permanent section.\(^26\) In our series, there were no documented cases of recurrence after MMS technique in incompletely excised BCCs, compared with 4.7% recurrence rate after frozen section after incomplete excision of BCCs.

Using MMS technique, Malhotra and associates found five-year recurrence rates of 0% and 7.8% for primary and recurrent periocular BCC, respectively. MMS is safer after incomplete excision and gives better results, as shown by the Australian MMS database and is the recommended treatment for periocular BCC.\(^27\)\(^,\)\(^28\) MMS also has the lowest reported recurrence rate (3.64%) of any treatment modality for periocular SCC.\(^15\) The five-year local recurrence rates for non-Mohs modalities in SCC are high and, depending on the site, vary between 3% and 23%.\(^16\)\(^,\)\(^17\)

Compared with frozen section technique, MMS examines en-face sections of the entire outer surface of excised tissue. However, it is time consuming and expensive and cannot replace the conventional, non-Mohs’ methods used to determine margin adequacy for most cases.\(^4\)

There was a longer interval between the initial tumor excision and the recurrences of BCC compared with SCC (34 months vs 11 months), which could be related to the aggressive nature of SCC. A significantly shorter interval for periocular SCC recurrence compared with BCC was also demonstrated in our orbital invasion tumors series (unpublished data).

Guideline safety margins were 3 mm for BCC and 5 mm for SCC. Margin-controlled excision of clinically involved tissue is important for periocular BCC and SCC management to minimize recurrence. However, the actual tumor edge may be difficult to determine clinically, and the result is an increased surgical tissue defect.

Two-millimeter margins have been shown to be adequate in preventing recurrences for nodular BCCs, and 4 mm for other types of BCC.\(^4\) For SCC,\(^21\)\(^,\)\(^23\) 4-mm margins were required to achieve a 95% clearance rate in low-risk SCC, and 6-mm margins were recommended to clear 95% of low-risk site SCCs of at least 2 cm size periocular SCCs and those with histologic grades 2 to 4.\(^29\)

The mean follow-up time in our study was 33 months (range three to 125 months). Longer term follow-up of five years is recommended for periocular tumors to exclude recurrences,\(^23\) especially for tumors that show large horizontal and depth extension.\(^10\)

All patients with eyelid tumors should be advised of the risk of recurrences or the development of new tumors and encouraged to attend regular follow-up examinations. Our findings further emphasize the importance of margin-controlled excision and accentuate the significance of histopathology and location of periocular tumors.

REFERENCES