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Growth of Periocular Basal Cell Carcinoma

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Introduction

Basal cell carcinomas have traditionally been considered slow-growing tumours. Scrutiny of earlier research on growth of basal cell carcinomas reveals data that was published up to 70 years ago, data based on small sample sizes, questionable study designs and retrospective studies with no description of the tumour site or histological type.[1-4]

New Zealand has one of the highest incidences of skin cancers in the world.[5-7] Several factors contribute to this high incidence. The two most important are the high prevalence of Fitzpatrick Class I or II skin type and chronic sun exposure in an environment where ultraviolet radiation index commonly exceeds 14 during summer. Practising dermatologists in the Southern hemisphere have often observed basal cell carcinomas growing rapidly (over several months), particularly at sites such as the head and neck.

The objective of this study is to determine the growth rate of basal cell carcinomas at a high risk site – the periocular region. Clinical and tumour characteristics associated with the rate of tumour growth were also examined.

Materials and Methods

Study design and population

A prospective, observational analysis was performed from September 2010 to March 2012. This study was approved by Northern Y Ethics Committee, New Zealand (HREC: NTY/10/EXP/024). Clinical trial number ACTRN12610000542099.

Consecutive patients were recruited from an ophthalmic sub-specialist oculoplastic clinic at a tertiary hospital and from a private oculoplastic clinic with referral populations of over 800,000 people. Consenting patients had their tumour size measured and completed a questionnaire at their first specialist appointment (FSA) with the oculoplastic surgeon. The following data was obtained from the questionnaire: basic demographic details, Fitzpatrick skin type, referral source, previous skin cancer, smoking status, immune suppression and primary or recurrent cancer. In this study, immunosuppression referred to use of medications such as corticosteroids, inherited or acquired diseases (eg. Agammaglobulinaemia or HIV) and conditions such as malnutrition, underlying malignancy or splenectomy.

All patients had a shave or incisional biopsy of the tumour performed by the initial referrer or at the FSA. The histological type of BCC was recorded.

Exclusion criteria were patients with histopathology that was later confirmed as squamous cell carcinomas or non-basal cell carcinomas, patients who had incomplete questionnaires, those with incomplete tumour measurement on follow-up and those patients who underwent urgent treatment for clinically aggressive periocular BCC (pBCC) that were judged to be a high risk to vision.

Measurement of tumour size

Tumour size was measured with a combination of clinical and epiluminescent microscopy (Dermatoscopy – Dermlite ProHRII 3Gen, Inc., San Juan Capistrano, CA) to assess as accurately as possible tumour margins. Rulers with 1-mm gradations were used. Macroscopic digital images were obtained with (Canon EOS 550D, Canon New Zealand, Wellington, NZ).

The patient was then placed on a waiting list for Mohs Micrographic Surgery. A repeat measurement of tumour size was performed on the day of Mohs Micrographic Surgery. Second measurements were obtained with investigators (one of three Mohs surgeons at random) blinded to the initial dimensions. No changes were made to the routine operating schedules.

The difference in tumour size at the time of Mohs Micrographic Surgery was compared to the size at FSA. The surface area was estimated using the formula for an ellipse A =1/4 πwh where w represented width (minor radius) and h represented height (major radius).

Statistical Analysis

The central tendency was reported either as median (for waiting time) or mean (for tumour dimension, area, and the 30-day tumour growth). The difference in tumour size was assessed using paired Student's t-test.

To characterise factors associated with the rate of tumour growth, multiple regression analyses were performed to examine which clinical and tumour characteristics (age, gender, immunosuppression, tumour recurrence, initial size, previous surgery, and the location of the index lesion) were associated with the accelerated growth rate. In addition, multivariate logistic regression models were fitted to examine characteristics associated with tumour regression. The association between histologic type of the tumour and growth rate was assessed by Fisher's exact test.

All statistical analyses were performed by using R v.2.15.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics and characteristics

There were 112 patients (54 female, 61 males) and 115 basal cell carcinomas (Table 1). Six patients were excluded because of incomplete data/ tumour measurement at FSA or at time of Mohs Micrographic Surgery. Eleven squamous cell carcinomas and one mucinous carcinoma was excluded. One patient was excluded as urgent surgery had to be performed due to rapid tumour growth and potential threat of vision. A further two intra-orbital basal cell carcinomas and three intraorbital squamous cell carcinomas were excluded as they required exenteration.

All patients have listed their primary ethnicity as European with predominantly Fitzpatrick Type I and II skin type (Type I = 41, Type II = 74). Most of the cases were operated in the tertiary hospital (62.6%) and the remainder at the private clinic (37.4%). Primary tumours were the most common presentation (89 cases, 62.6%). There were 37.4% (26) recurrent tumours.

Half of the patients had more than 1 previous skin cancer surgery (n=56, 49.6 %), with a mean of 3 previous surgeries previously). There were 7 cases (6.3%) who were immunosuppressed at the times of assessment (Table 1).

Most of the tumours were located on the lower lid (55%) followed by the medial canthus (31%) and other peri-orbital areas (Table 1).

Rate of pBCC growth

We observed a mean increase of 41.9mm^2 from the FSA to the Mohs Micrographic Surgery. The mean growth of pBCC was 11.1 mm^2 per 30-days, with large variations between individuals (95% C.I. -54.6—76.7 mm^2) (Table 2) (Figure 1).

Growth of pBCC between assessments

Comparing the difference between two measurements, we observed a mean increase in area of 40.7 mm^2 between assessment (FSA: 68.5±138.8 mm^2, time of surgery 109.2±194.7 mm^2, mean ± standard deviation, $p<0.001$, paired t-test). A median delay between FSA and surgery of 115 days was also found (IQR: 68 - 168 days). We found no differences between female and male patients with respect to differences in the tumour size at the two measurements ($p=0.451$, linear mixed effect model).

There was also a consistent difference when using the longest dimension of tumour (length of the lesion). The mean growth of peri-orbital BCC was observed to be 0.75 (95% CI: -3.54—5.04) mm per 30 days; an average increase of 2.36 (95% CI: 1.3—3.4) mm was found from FSA to the time of surgery ($p<0.001$, paired t-test).

Patient characteristics associated with tumours that regressed after FSA

Thirty percent of lesions regressed between FSA and time of surgery (n=34). Female sex was significantly associated with the regression of tumour (OR: 3.2, 95% CI: 1.04—9.83), taking into account age, immunosuppression status, recurrent cancer, previous surgery, initial tumour size and the location of the pBCC (Table 3). The lesion sizes at the time of FSA were not significantly different between the tumours that regressed and those that did not regress (73.1 vs. 58.2 mm^2, $p=0.43$, unpaired t-test). All biopsies were performed at FSA. The time at which the biopsy was performed did not affect the regression of the tumour ($p=0.315$, Mann-Whitney U test).

Patient characteristics associated with tumour growth rate

Two tumour characteristics (tumour recurrence and the size at FSA) were significantly associated with accelerated tumour growth. The recurrent tumours were associated with an increased rate of growth of 22.1 mm^2 per 30 days (95% CI: 5.4—38.8 mm^2/30-day, $p=0.01$) (Table 4). The tumour size at FSA was also positively associated with the rate of growth: each mm^2 of pBCC at FSA was associated with an increased rate of growth of 0.047 mm^2 per 30-days, (95% CI: 0.003—0.091 mm^2/30-day, $p=0.037$) (Table 4). When the data was stratified into fast-growth BCC versus slow-growth BCC, male sex was related to a faster growth (OR: 3.84, $p=0.02$).

Tumour growth & pBCC histological sub-type

The most common histological sub-type of pBCC was nodular (30 cases, 26%), followed by infiltrative (19 cases, 16%) and superficial (19 cases, 16%).The authors defined non-aggressive BCCs as nodular or superficial type and aggressive BCCs as infiltrative, micronodular, metatypical or mixed type. [3-4,8-14]

Aggressive BCCs accounted for 49 % (57 cases) of all types of which micronodular was the most common type (30%, 19 cases). There was no association between aggressive BCCs and significant growth (p= 0.84, Fisher's exact test).

Discussion

Periocular BCC in this study grew at a rate of 11.1 mm^2/month or 0.75 mm /month. Factors that were related to a faster growth were large initial tumour size, male sex and recurrent tumours. Despite 30% of the pBCC regressing after the FSA, the majority grew. This is particularly significant considering a punch or incisional biopsy was performed at FSA removing a portion of the tumour and reducing its diameter.

Initial tumour size was also a significant factor in that larger tumours grew faster and were less likely to regress compared with smaller tumours.

In 30% of cases, there was a reduction in the size of the basal cell carcinomas. Alcalay et. al. assessed residual basal cell carcinoma after shave biopsy with Mohs Micrographic surgery.[15-16] In 22-25% the biopsy was curative and no residual basal cell carcinoma was found.[15-16] A related retrospective analysis of 910 excisions for basal cell carcinoma or squamous cell carcinomas revealed 24% of cases showed no evidence of residual skin cancer.[17] This was more likely following shave biopsy rather than punch biopsy and was more common in squamous cell carcinomas than basal cell carcinomas. These authors postulated that the inflammation and process of wound healing played a role in tumour regression. Although in none of our cases was there clearance of tumour, in one third the tumour shrank. Female sex was associated with a greater likelihood of regression of tumour. In a study by Grelck et. al., male sex was more likely associated with a positive residual basal cell carcinoma after biopsy.[18]

The mean age of patients in our study was 69.3 years with nearly half (49%) of cases being of aggressive histology. In a retrospective study of histological types of basal cell carcinoma in the Veterans Affairs population, the investigators noted a high frequency of aggressive basal cell carcinomas (morpheaform, infiltrative and micronodular types).[19]

Two studies from the United Kingdom have studied the impact of waiting time on the growth of basal cell carcinomas.[20-21] The incentive for these studies was the requirement by the U.K. government for all cancers to be seen by a specialist within two weeks. Gordon et. al. retrospectively assessed case records from 162 patients with basal cell carcinomas in the head and neck region.[20] They noted a slow growth of basal cell carcinomas where reducing the referral interval from a mean of 10.7 weeks to 2 weeks would equate to a size difference in BCC of 0.7mm. However, this study was limited by its retrospective nature and aspects of the reference points for time interval were unclear (the authors used patient self reported duration but then reported two other time intervals as well – time to hospital outpatient assessment and time to surgery). It was unclear how tumour size was assessed and who measured the tumour subsequently. No specific sites within the head and neck region were specified.

In another smaller study, the investigators assessed the growth of primary basal cell carcinomas in fifty patients. [21] A mean increase of 0.5mm over a mean interval of 70 days was noted. The median change in area was 4.71mm^2. In four patients, the BCC enlarged by >2mm and these patients were older with mean age of 71.8 years. Aggressive histological types were rare. By comparison, the percentage of aggressive histological types (infiltrative, metatypical, micronodular and desmoplastic) in our group was 49% with the most common aggressive type being micronodular. The distribution of types of BCC in this study similar to a large study from South Australia with the exception of a larger proportion of aggressive BCCs. [22]

At a high risk site such as the periocular area, a small increase in size of pBCC may have a significant impact on morbidity as larger tumours may require more complex reconstructive surgery. In our study, it is unknown whether the true growth pattern of periocular BCC is linear, exponential or logarithmic growth as only two time-point measurements were used. The authors are not aware of any studies that specifically address this issue.

Our study is limited by its smaller sample size and hence formal power calculations were not possible. Assessment of cancer growth was performed visually with the aid of a dermatoscope. An ideal measurement would microscopically and non-invasively assess the volumetric growth of the tumour with precise margins but the technology does not exist at the time of writing. Confocal microscopy or Optical Coherence Tomography is being investigated as tools for assessing tumour margins but each have their limitations. [23-24]

The type of biopsy could affect regression of tumour. Although this effect was not specifically assessed in this study, most biopsies were performed via incisional biopsy with a smaller proportion performed via shave biopsy. The type of biopsy could affect regression of tumour but a more interesting point is that tumours increased in size in spite of most biopsies being incisional; potentially removing more tumour than a shave biopsy.

Inter-observer variability in measuring tumour dimensions is inherently present in this study - the investigator that measured the tumour size at FSA differed from those who measured it at time of Mohs micrographic surgery. However, the investigators who performed the second measurement were blinded to the baseline measurements done at the FSA. Furthermore, in spite of several different investigators and measurements at two different time points, the overall tumour size was noted to have increased (and in a small proportion, a decrease in size was noted).

Only one site was assessed and hence generalisability of this study is restricted to BCCs in the peri-orbital area. In addition, the population in New Zealand consists predominantly of individuals with fairer skin type (Fitzpatrick Type I and Type II skin) and thus the pattern of growth could be different in individuals with darker skin types.

In spite of the limitations, this is the largest prospective study to date assessing the growth of basal cell carcinomas at a high risk site. The follow-up of patients was excellent, allowing for accurate longitudinal assessment of tumour growth. Until the technology exists for accurate volumetric

growth of skin cancers, this study provides a platform for future studies on growth rates of basal cell carcinomas.

In conclusion, pBCC can grow rapidly, and many have aggressive histological sub-types. Rapid growth is more likely in larger tumours, in men, and in recurrent tumours.

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Table 1. Patient Demographics and Lesion Characteristics

Characteristic		% or Interquartile range (IQR)		
Patient characteristics				
Number of patients	112			
Age	73	(61—79)	(mean: 69.3)	years
Female Sex	54	(46%)		
Skin type				
Fitzpatrick Class I	41	(35.7%)		
Fitzpatrick Class II	74	(64.3%)		
Immunosuppressed	7	(6.1%)		
Funding - Public hospital	72	(62.6%)		
Lesion characteristics				
Number of lesions	115			
Recurrent lesion	26	(22.6%)		
Numbers of previous skin surgeries (median)	1	(0—3)	(mean: 3.0)	
Dimension of lesion				
At the FSA				
Length (median)	8	(6—12)	(mean: 9.9)	mm
Width (median)	6	(4—8)	(mean: 6.8)	mm
Area (median)	35.3	(22.0—71.5)	(mean: 68.5)	mm^2
At the time of surgery				
Length (median)	10	(7—15)	(mean: 12.22)	mm
Width (median)	6	(5—10)	(mean: 8.4)	mm
Area (median)	50.3	(27.5—122.5)	(mean: 109.2)	mm^2
Aggressive histology types	56	(48.7%)		
Location of the lesion				
Lower lid	63	(54.8%)		
Medial canthus	36	(31.3%)		
Lateral canthus	12	(10.4%)		

Upper lid	2	(1.7%)
Eyebrow	1	(0.9%)
Bridge of nose	1	(0.9%)

Abbreviations: FSA: First specialist assessment

Table 2. Growth rate of BCC

Thirty-day tumour growth	Mean ± SD		Median
All lesion (n=115)			
Length (mm)	0.75 ± 2.19	0.39	(IQR: -0.14—1.22)
Width (mm)	0.43 ± 1.86	0.19	(IQR: -0.18—0.83)
Area (mm^2)	11.1 ± 33.5	2.87	(IQR: -0.7—14.3)
Tumours that grew in size (by area, n=80)			
Length (mm)	1.46 ± 2.13	0.75	(IQR: 0.20—1.88)
Width (mm)	1.06 ± 1.68	0.59	(IQR: 0.21—1.30)
Area (mm^2)	22.1 ± 32.6	10.7	(IQR: 2.9—24.4)

NB: SD: Standard deviation; IQR: Interquartile range

Table 3. Relative odds of tumours that regress in size by multivariate logistic regression analysis

Variable	(n=115)		p value
	Odds ratio	C.I. 95%	
Age	0.97	(0.93—1.01)	0.20
Female sex * (Reference: male)	3.2	(1.04—9.83)	0.04
Immunosuppression			
No	1	(Reference)	
Yes	3.71	(0.467—29.4)	0.22
Recurrent cancer?			
No (Primary)	1	(Reference)	
Yes (Recurrent)	0.28	(0.0544—1.41)	0.12
Previous surgery			
Yes	1	(Reference)	
No	0.39	(0.121—1.25)	0.11
Location (Reference: Other sites)			

Medial canthus	0.56	(0.157—2.00)	0.37
Lateral canthus	0.46	(0.071—3.00)	0.42
Histology			
Non-aggressive	1	(Reference)	
Aggressive	1.48	(0.531—4.12)	0.45

* Statistically significant at α = 0.05

Table 4. Multiple regression analysis on the rate of growth as the response variable of other clinical factors:

Variable	β coefficient	C.I.95%	P-value
(Intercept)	0.616	(-36.2—37.5)	0.97
Age	-0.166	(-0.70—0.37)	0.55
Male sex	12.4	(-0.19—25)	0.056
Immunosuppression	-7.6	(-32.8—17.6)	0.56
Recurrent tumour *	22.1	(5.4—38.8)	0.011
Initial size (mm^2) *	0.0474	(0.003—0.091)	0.037
No previous surgery	7.53	(-6.4—21.4)	0.29
Medial canthus BCC	10.9	(-2.9—24.8)	0.13
Lateral canthus BCC	19.9	(0.08—39.7)	0.052

* Statistically significant at α = 0.05

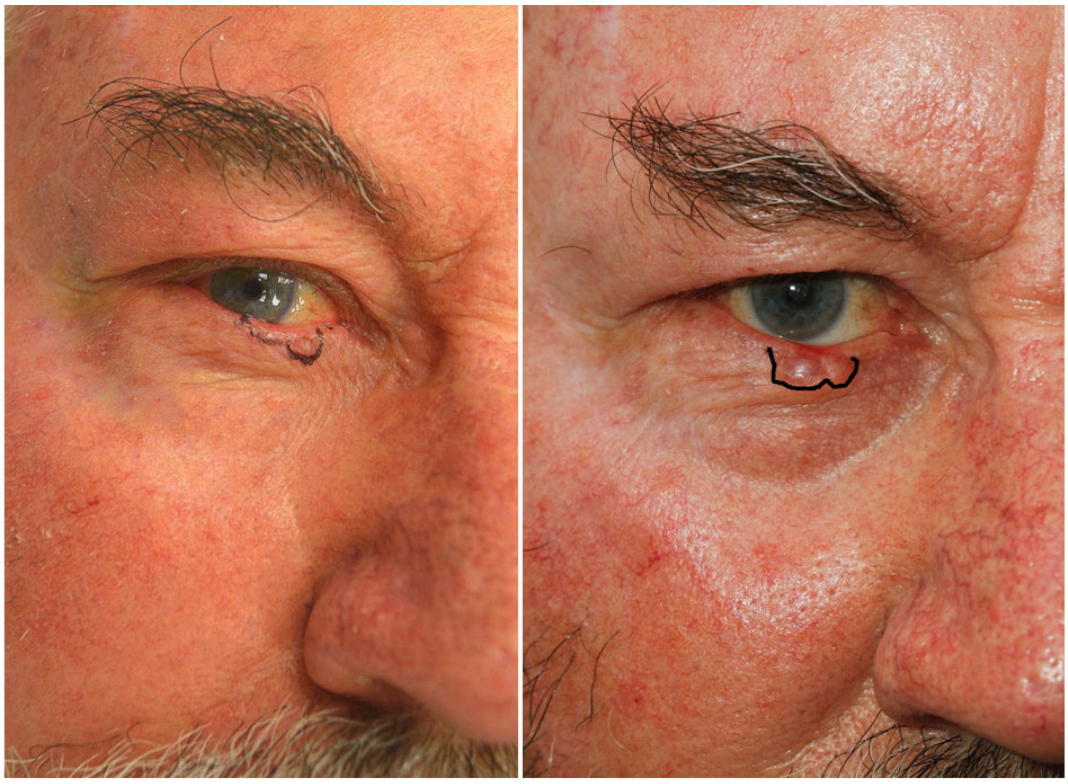

Figure 1a. Time at First Specialist Appointment (FSA)

Figure 1b. Time at Mohs Micrographic Surgery (8 months later)