Cutaneous squamous cell carcinoma: predictors of positive and close margins and outcomes of re-excision in Northland, New Zealand

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ABSTRACT

BACKGROUND: Non-melanoma skin cancer (NMSC) is the most commonly diagnosed and costly cancer in Australasia. Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 25% of NMSC. A better understanding of predictors of close and positive margins following surgical excision will help guide treatment.

METHODS: A retrospective study was carried out of all primary cSCC histologically diagnosed in Northland, New Zealand in 2015. The cohort was identified by searching the regional pathology database. The primary outcome of interest was positive and close (≤1mm) margin rate following surgical excision and factors influencing them. Secondary outcomes of interest were outcomes of re-excisions.

RESULTS: A total of 1,040 cSCC were identified in 890 unique patients and 825 lesions were surgically excised. Increased odds of positive margin on surgical excision was found with increased tumour thickness (OR 1.56, 95% CI 1.24–1.96), tumours from the head and neck (OR 2.78, 95% CI 1.33–5.80) and those excised in primary care (OR 2.20, 95% CI 1.07–4.52). Increased odds of close margins was found in females (OR 2.01, 95% CI 1.3–3.2) and excision in primary care (OR 2.44 95% CI 1.5–3.98). Residual tumour was present in 13 (31.7%) patients with positive margins and 0 patients with close margins.

CONCLUSIONS: Lesions of the head and neck, those removed in primary care and with increased tumour thickness were more likely to have positive margins following surgical excision. Close margins were associated with excision in primary care and female gender. The value of re-excising tumours with close margins remains uncertain.

Non-melanoma skin cancers (NMSC) are the most commonly diagnosed malignancies in the world. Rates vary internationally, with the highest incidence rates seen in Australasia.[1] They consume significant healthcare resources, costing over $700 million dollars in Australia and over $50 million dollars in New Zealand per annum; around 9% of total cancer costs.[1–3] Cutaneous squamous cell carcinoma (cSCC) accounts for between 20–30% of NMSC, with the remainder being predominantly basal cell carcinoma.[3,4] cSCC is however considered more dangerous due to its ability to metastasise and cause significant morbidity and mortality.[4,5]

The standard treatment of the majority of cSCC is surgical excision with histological margin assessment, however disease burden extends beyond the capacity of sole management in secondary care. Therefore in Australasia, lesion excision is commonly performed in primary care too. To reduce recurrence and avoid re-excision, complete tumour excision with histologically clear margins is recommended. Patients with positive margins commonly undergo re-excision, but the treatment of patients with close margins (tumour within 1mm of margin) is not well defined. Current guidelines advise consideration of re-excision or radiotherapy.[6]

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Many series have reported rates of positive margins, including factors associated with positive margins.[7–13] Most commonly size, thickness and anatomical location are implicated. However, a majority of studies are limited by not considering compounding factors through use of multivariate analysis. The pathological outcomes in re-excisions of these lesions have also been reported[9] but no previous studies have examined rates and factors leading to close margin rates. Greater understanding of the factors influencing close margin rates and outcomes of re-excisions is critical in improving treatment in patients with cSCC. This knowledge will aid effective decision making in both primary and secondary care with the intent to increase success of surgical excision to avoid costly reoperations, which can increase patient morbidity.[8] We have previously reported the basic demographics and outcomes in our large cohort of patients from both primary and secondary care.[14]

The aim of this study was to define the rate of positive and close margins following primary excision of cSCC, examine outcomes of re-excisions and investigate predictive factors for inadequate excision using multivariate analysis.

Methods

A 12-month retrospective study was carried out of all primary cSCC diagnosed in Northland for one year commencing 1 January 2015. Patients undergoing primary surgical excision were identified and these formed the primary cohort for this study.

Cases were identified by searching the Northland District Health Board pathology database and a database of outsourced pathological specimens using key terms. Together these databases contain all histological specimens processed in Northland; both public and private from primary and secondary care. The 15,719 pathology reports obtained from this search were manually screened to identify all cSCC that were excised by primary surgical excision. Demographic data was obtained from the district health board data warehouse, lesion characteristics and anatomical location data was extracted from the pathology report, and if excised in secondary care, this data was further supplemented by operation notes obtained from the hospital results reporting system CONCERTO. These variables were entered into a Microsoft Excel spreadsheet.

A positive margin was defined as tumour being present at the histological resection margin and a close margin was defined as tumour being present within one millimetre of the resection margin. Inadequate excision included both positive and close margins. Resection margin distances were defined as the shortest distance between resection margin and tumour cells.

The primary area of interest was the rate of positive and close margins as well as predictive factors on multivariate analysis, secondary area of interest was pathological outcomes following re-excision in those with positive and close margins.

Descriptive statistics were used to describe basic demographics and distributions were assessed for normality. Paired t-tests were used to ascertain differences between continuous data assumed to be normally distributed, Wilcoxon-Mann-Whitney was used as a non-parametric analog and Chi-squared test was used for categorical variables. Univariate analysis was used to determine statistically significant variables. If variables were clinically justifiable and exhibited significance at P of <0.10 in explanatory analysis it was entered into a multivariate logistic regression model. Statistical analyses were carried out using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided and P values less than 0.05 were considered statistically significant.

The data used in this study was collected as part of a service evaluation of patients referred with suspicions skin lesions to Northland District Health Board and was approved by locality assessment. Data collection was discussed with the Health and Disability Ethics Committee and an “out of scope letter” obtained on 29 March 2016.

Results

The patients and lesion characteristics of this patient cohort have been previously described in detail.[14]

Patient characteristics/ demographics

A total of 1,040 cSCC were identified in 890 patients. During this time period, 825 lesions were surgically excised in 701 patients. The

median enrolment age was 75.1 years old (SD 10.2). The cohort was made up of 432 men and 269 women.

Lesion characteristics

The median lesion diameter at study diagnosis was 6.1mm (IQR 4.0–9.5mm). The median histologic thickness was 2.4mm (IQR 1.7–3.5mm). In regards to anatomical location, 385 lesions (47%) were excised from the head and neck, 22% from the upper limb, 22% from the lower limb and 9% from the trunk.

Surgical characteristics

Surgical excision in primary care occurred for 54% of lesions. In secondary care, 38% of excisions were performed by an hospital contracted Medical Officer Special Scale (MOSS) or General Practitioner with Special Interest (GPwSI), the remaining lesions were excised by a consultant surgeon (25.5%), private specialist (19.5%) or surgical registrar (16.6%). Tumour size and thickness was recorded within pathology reports of 581 (70.9%) of excised specimens.

Surgical outcomes and predicting positive and close margins

On histologic examination following surgical excision, 78 of the 825 (9%) lesions were found to have a positive margin (Table 1). Of those, 53 had a positive deep margin, 42 had a positive radial margin and 14 lesions were positive in both deep and radial margins. When defined as having tumour cells within 1mm of excision margins, 139 (17%) lesions had close margins (Table 2). Combining these groups revealed that 26% of total excisions had tumour cells at or within 1mm of excision margins.

Table 1: Comparison of patient and tumour characteristics in lesions found to have positive and close (<1mm) compared to distant margins on surgical excision.

	Positive margins n=78	**Close margins n=139**	**Distant margins n=608**
Age, years			
Mean ± SD	76.4 ± 10.4	74.72 ± 10.2	75.0 ± 10.2
Sex, n (%)			
Male	49 (62.8)	77 (55.4)	449 (60.1)
Female	29 (37.2)	62 (44.6)*	295 (39.5)
Surgical characteristics, n (%)			
Excised in primary care	45 (57.7)	89 (64.0)**	399 (53.4)
Histologic characteristics, median (IQR)			
Tumour diameter	6.1 (5.0–11.0)**	5.6 (3.5–8.1)	5.6 (3.9–9.0)
Tumour thickness	2.9 (2.0–5.0)***	2.5 (1.8–3.5)	2.3 (1.6–3.2)
Tumour characteristics, n (%)			
Metastases	4 (5.1)**	0 (0)	7 (0.9)
Perineural invasion	4 (5.1)**	5 (3.6)**	7 (0.9)
Lymphovascular invasion	1 (1.3)	1 (0.7)	3 (0.4)
Anatomical location, n (%)			
Head and neck	48 (61.5)**	77 (55.4)**	337 (45.1)
Trunk	2 (2.6)*	12 (8.6)	71 (9.5)
Upper limb	16 (20.5)	35 (25.2)	166 (22.2)
Lower limb	12 (15.4)	14 (10.1)***	16.8 (22.5)

*P≤0.05; **P≤0.01; ***P≤0.001; SD, standard deviation; n, number; IQR, interquartile range.
Note: Distant margin is defined as absence of tumour cells within 1mm of surgical margins.

Table 2: Multivariate binary logistic regression analysis demonstrating significant predictors of positive and close margins.

	Positive margins		**Close margins**	
	OR (95% CI)	**P Value**	**OR (95% CI)**	**P Value**
Age, years	1.00 (0.9–1.1)	0.588	1.02 (0.99–1.04)	0.205
Female sex	0.89 (0.4–1.9)	0.771	2.01 (1.3–3.2)	0.003**
Histologic tumour diameter, mm	0.92 (0.83–1.02)	0.128	0.95 (0.95–1.04)	0.433
Histologic tumour thickness, mm	1.56 (1.24–1.96)	**<0.001*** **	1.00 (0.85–1.18)	0.981
Excised from head and neck	2.78 (1.33–5.80)	**0.007****	1.11 (0.67–1.82)	0.691
Excised from trunk	0.41 (0.05–3.30)	0.401	N/A	N/A
Excised in primary care	2.20 (1.07–4.52)	**0.033***	2.44 (1.5–3.98)	<0.001***

*P≤0.05; **P≤0.01; ***P≤0.001; OR, Odds Ratio; CI, Confidence interval.

Table 2 describes the findings of multivariate analysis. Odds of positive margin on surgical excision was significantly increased with deeper tumours (OR 1.56, 95% CI 1.24–1.96), tumours from the head and neck (OR 2.78, 95% CI 1.33–5.80) and those excised in primary care (OR 2.20, 95% CI 1.07–4.52). On separate multivariate analysis, the odds of close margin on surgical excision was significantly increased in lesions excised in primary care (OR 2.44, 95% CI: 1.5–4.0) as well as lesions on females (OR 2.01, 95% CI: 1.3–3.2).

Outcomes of re-excisions

In patients with positive margins, 52.6% went on to have a surgical re-excision and in patients with close margins, 13.6% were re-excised. Residual tumour was present in 31.7% (13) patients with positive margins and no patients with close margins (Table 3).

Discussion

This study has demonstrated a high close margin rate despite an acceptable positive margin rate in a large cohort of patients undergoing primary excision of cSCC. Tumours of the head and neck, increased tumour thickness and surgical excision in primary care are significantly correlative with positive margin rate on multivariate analysis. Primary care excision and female sex were significantly associated with close margin rates. The rate of residual tumour in those with positive margins is similar to previous studies.

The burden of non-melanoma skin cancer in Australasia is significant, with Australia and New Zealand having the highest rates of cSCC in the world.[15–17] Despite effective methods to prevent cSCC, the incidence has been shown to continue to increase worldwide. Adequate treatment of patients with cSCC is imperative to improve outcomes, avoid unnecessary repeat procedures and reduce costs. Incomplete excisions are however likely to be inevitable as the decision between larger excisions needing greater expertise and possibly more reconstruction have to be balanced with the local resources constraints and consideration of cosmesis.

In contrast to other healthcare systems, the high rate of lesions in Australasia has led to NMSC being commonly treated in both primary as well as secondary care.[18,19] Surgical excision is usually curative, but adequate pathological margins are important for management. The intent is

Table 3: Surgical outcomes and residual cancer rate in lesions with positive and close margins.

Margin status, n (%)		**Re-excised, n (%)**	**Tumour cells In re-excision**
Positive margin	78 (9.5%)	41 (52.6%)	13 (31.7%)
Close margin (<1mm)	139 (16.8%)	19 (13.7%)	0 (0%)

twofold; to ensure complete excision of the primary tumour and to remove in-transit micro-metastases around the tumour. There are several guidelines available worldwide. But in general, most advise surgical margins of 4–6mm depending on lesions characteristics, and margins of up to 10mm are recommended for high risk tumours.[20] Re-excision of tumours with positive margins is considered standard, but recommendations in patients with close margins are less clear. Current Australian guidelines advise consideration of re-excision or radiotherapy,[6] and one previous study has recommended re-excision in this group.[21] The surgical literature has previously concentrated on positive margin rate in cSCC and several papers have investigated factors associated with positive margins in squamous cell carcinoma, including two studies from New Zealand and one in Australia.[11–13] A large recent systematic review has calculated a pooled incomplete excision rate of 8.8% with simple surgical excision.[22] The majority of studies in this review considered an incomplete excision as one where tumour was present at the excised margin.[22] Only one study included tumour cells up to 1mm from the margin and reported an incomplete excision rate of 16%.[7] These findings are in keeping with our data where we report a 9% positive margin rate and a 17% close margin rate. This gives a potential incomplete excision rate of 26%, despite an acceptable positive margin rate. In studies that have assessed factors that can predict positive margins, the results have varied. In broad terms, tumours of the head and neck[8,12] and larger tumours[7,10] are more consistently associated with positive margins. Two studies have examined outcomes in primary and secondary care with variable results.[11,12] These previous studies are however limited, due to failure to take account of compounding variables through use of multivariate analysis. Our data has instigated anatomical location, tumour depth and excision in primary care being associated with a higher positive margin rate through these means. It is interesting to note that in our data tumour diameter was not a significant factor once multivariate analysis had taken place.

Close margin rates were also associated with excision in primary care and female gender. Secondary care physicians should continue to be encouraged to support primary care by facilitating local courses and opportunities to up skill. In addition, we recommend consideration of referring tumours of the head and neck as well as tumours that appear thicker to more specialist clinicians. It is unclear exactly why female gender affects close margin rates. It is known that there is variance in anatomic distribution of cSCC between genders, a phenomenon which has also been demonstrated in our study.[23,24] In addition, it has been suggested that cSCC of the lower limb represents a pathologically distinct lesion from cSCC elsewhere.[25] It is possible that this, together with other compounding factors such as a higher consideration of cosmesis, account for our observations.

Re-excision in patients with positive margins was associated with a 31% residual cancer rate, similar to that reported by Bovill te al.[9] Follow up from this UK study has shown that a positive re-excision was associated with higher rates of loco-regional recurrence and therefore extended follow-up was recommended.[21] Bovill et al[21] also demonstrated a 13% positive re-excision rate in patients with close margins and recommended re-excision in this group. This is in contrast to our data where no re-excisions in this small group of patients contained residual tumour. It is likely that larger studies are needed to determine the significance of a close surgical margin but in the interim, reporting of close margins and consideration of further treatment should be a minimum requirement for clinicians excising cSCC.

Despite its retrospective nature, this study has analysed a high number of consecutive cSCC excisions across primary and secondary care. All pathological reports were individually reviewed by the study team, and it is the first large study to consider patients with close margins. There was however, inconsistency in regional pathological reporting especially with regards to lesion size and thickness. It is also possible that a subgroup of patients went to another region to have a lesion re-excised, but it is likely that this number of patients is low.

In conclusion, this is the first study to report rates, predicting variables and outcomes of surgical excision in patients

with both positive and close margins following surgical excision for cSCC. It is recommended that referring tumours of the head and neck and those with increased clinical thickness to more specialist clinicians is considered. The need for re-excision in patients with close margins remains uncertain and larger studies are needed.

Competing interests:
Nil.

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