ORIGINAL RESEARCH

Margin Status Predicts Outcome In Patients With Cutaneous Squamous Cell Carcinoma of The Scalp: The Westmead Hospital Experience

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ABSTRACT

Background: An involved or close resection margin in the setting of cutaneous SCC (cSCC) is associated with the risk of developing recurrence. The scalp poses unique anatomical challenges when obtaining adequate resection margins and further treatment may be required. We aimed to investigate the risk of recurrence in patients with scalp cSCCs and the role of adjuvant radiotherapy.
Methods: Eligible patients with cSCC of the scalp treated with curative intent at Westmead hospital, Sydney, were identified and patient, tumor and treatment factors analyzed. Patients were categorized based on margin status and analyzed in terms of treatment delivered, local recurrence and survival.
Results: In total, 114 patients with a median age of 70 years with the majority (81%) male, were identified with a median follow up of 5.6 years. Following surgery, 52 patients (46%) had clear margins, 62 (54%) had close (≤2mm) or involved margins, with a significant difference in the 5-year disease specific mortality of 20% and 35%, respectively (p=0.05). Twenty-eight patients (25%) underwent surgery and adjuvant radiotherapy, most with a close/involved margin. There was no significant difference in the risk of developing local recurrence between the group of patients in whom a clear margin was obtained and the group in whom the margin was close/involved (p=0.23).
Conclusion: Margin status had a significant impact on disease specific mortality, but was not associated with the risk of developing local recurrence. The addition of adjuvant radiotherapy in select high-risk patients may improve outcome although this was not demonstrated in our study.

INTRODUCTION

Non melanoma skin cancer (NMSC) comprising basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) is the most common malignancy in Australia with a rising incidence.[1] While most are cured by excision alone, there is a subset of patients with cSCC who develop locoregional recurrence.[2] Pathological risk factors for recurrence in the setting of cSCC include: margin status, tumor thickness, invasion beyond subcutaneous fat, the presence of perineural invasion (PNI), diameter >20mm and poor differentiation[3] in addition to immunosuppression and recurrent tumors.[4]

The relevance of margin status in cSCC both in terms of treatment recommendations and patient outcome remains unclear with limited high-level evidence. As such, clinicians are

reliant on the results of lower-level institutional observational cohort studies and underlying oncological principles. Margin status (clear *vs* involved) has been shown to have an impact on survival,[4] and this benefit persists when comparing outcomes by margin status in patients undergoing adjuvant radiotherapy.[5] In light of emerging evidence, incomplete excision has been proposed as an additional high-risk feature for a poor outcome in a review article assessing the different definitions of high-risk features and the evidence supporting these.[6]

The incidence of incomplete excisions of cSCC is reported as between 7.6-9.4% across a range of clinical settings[7,8] and in the majority of cases (up to 78%) the deep excision margin is involved, suggesting that using wider peripheral resection margins may be of limited benefit.[8,9] A close or positive margin following resection of cSCC is associated with a recurrence risk of up to 37%,[10] and further treatment is often recommended, which may involve a wider more complex resection or local adjuvant radiotherapy.

Managing patients with cSCC of the scalp poses site specific issues in terms of anatomical restrictions limiting further resection, pathologically aggressive behavior of the tumor, and the potential of adjuvant scalp radiotherapy associated with skin graft loss and osteoradionecrosis of the underlying skull in occasional patients.[11] The relatively thin soft tissue components have implications for obtaining a negative deep margin, which may require removal of periosteum or the outer table of the skull.[9] There are limited data documenting outcomes of patients with scalp cSCCs with close or involved margins following surgical resection.

We aimed to analyze our institution's outcomes for patients treated with cSCC of the scalp in order to investigate the association of margin status with the patient outcomes and to analyze the effect of treatment options on the risk of developing local recurrence and on disease specific mortality.

METHODS

Patients with a primary scalp cSCC with documented margin status were identified from a prospectively maintained computer database of patients diagnosed with metastatic cSCC to parotid and/or cervical lymph nodes. Relevant demographic data and the characteristics of the primary tumor were recorded including tumor grade, PNI, lymphovascular invasion (LVI) and treatment details. Many patients had initial scalp treatment elsewhere and were referred to our service after developing locoregional recurrence. Follow up data including disease related outcomes and status at last review were recorded with follow up calculated from the completion of treatment of the scalp primary.

Statistical Analysis

Margin status was categorized into two patient groups: A high-risk group (HRG) comprising patients with an involved or close margin (≤2mm); a low-risk group (LRG) having a clear margin (>2mm). These two groups were compared in terms of treatment delivered, risk of local recurrence (LR), and disease specific mortality, with multivariate analysis performed to identify prognostic factors for both LR and disease specific mortality. Methods incorporating competing risks were used in the analysis of LR, and disease specific mortality.[12,13]

This study was conducted with approval from the Western Sydney Local Health District's Human Research Ethics Committee.

RESULTS

A total of 114 patients met the inclusion criteria with a median age of 70 years (range 34-91), most were male (81%), and the median follow up was 5.6 years. The majority of cSCC were moderately (n=42, 37%) or poorly (n=45, 40%) differentiated (Table 1). Fifty-four patients (47%) had primary cSCC ≥2cm, and tumor size data was missing in 19. A total of 52 patients (46%) had clear excision margins (LRG) and 62 (54%) had close (≤2mm) or involved margins (HRG). A total of 28 patients (25%) were treated with surgery and adjuvant radiotherapy with most 24/28 (85%) from the HRG (Figure 1). The majority of patients in the LRG (92%) were treated with surgery alone.

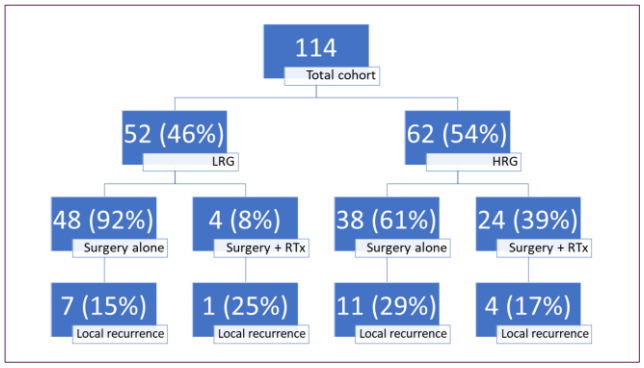

Figure 1. Flow diagram of treatment (surgery +/- adjuvant radiotherapy) and local recurrence rates by margin status (Low risk group (LRG): >2mm; High risk group (HRG): ≤2mm)

Within our cohort 23 patients (20%) experienced local recurrence. There was no significant difference in LR rates between the LRG (8 patients, 15%) and HRG (15 patients, 24%), (p= 0.23, see Figure 2). Multivariate analysis was performed including patient factors (age, sex, immunosuppression, treatment) and tumor factors (grade, PNI, vascular invasion, margin status) and there were no significant factors that predicted for LR including margin status or the addition of adjuvant radiotherapy. Within the HRG, the LR rate for those undergoing surgery alone was 29% (11/38) compared with 17% (4/24) for those treated with surgery and adjuvant radiotherapy (Table 2); as the difference in the LR rate between the LRG and HRG was not significant, testing within the subgroups was not performed.

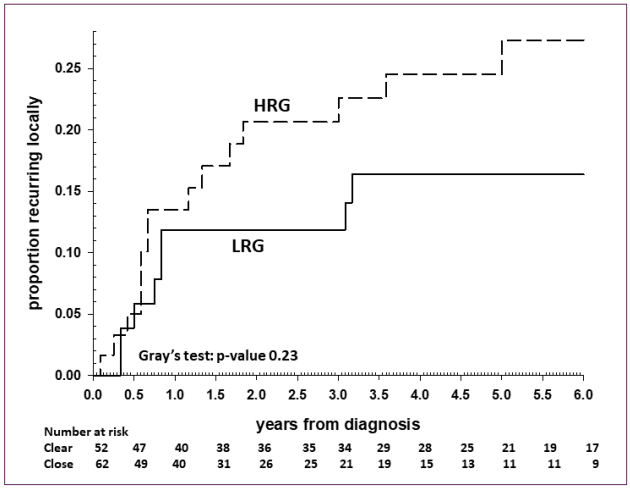

Figure 2. Local recurrence by margin status (Low risk group (LRG): >2mm; High risk group (HRG): ≤2mm)

The 5 year disease specific mortality (Figure 3) was 20% in the LRG compared to 35% in the HRG (p=0.05), and on multivariate analysis no additional significant factors impacting on disease specific mortality were identified.

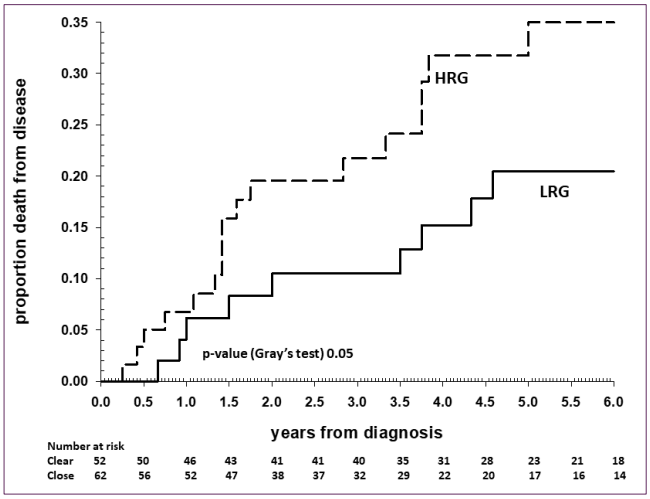

Figure 3. Disease specific mortality by margin status (Low risk group (LRG): >2mm; High risk group (HRG): ≤2mm)

DISCUSSION

The optimal management of patients with inadequately excised cSCC of the scalp is unclear as is an accepted definition of an adequate excision margin, with variability within global guidelines, ranging from 4mm to 10mm, and based on primary tumor risk derived from tumor size, thickness, differentiation and subsite.[14,15] In a systematic review of 21,569 cases of cSCC, the overall incidence of incomplete excisions was only 9.4% ,[8] and a series of 633 cSCCs managed across four regional plastic surgery departments documented an incidence of involved margins of 15% with an overall recurrence rate of 6.7% at 5 years, the majority (96%) occurring within 2 years.[7] In comparison, in our study, over half of the patients (54%) had tumors excised with close/involved margins, which may reflect the high risk nature of the cSCC in the study population and our arbitrary definition of a close margin as 2mm.

Using wider peripheral resection margins may not reduce the proportion of incomplete excisions as often the deep margin is primarily involved[8], with a scalp specific retrospective review documenting deep margin failure in 32 of 41 cases (78%) with involved margins.[9]

Most of our patients were older males, many with an extensive history of NMSC treated over the years. We consider cSCC of the scalp a high-risk cutaneous sub-site, comparable to the lower lip and external ear in terms of risk of developing parotid/cervical nodal metastases,[16] and as such they represent ~10% of cases with metastatic nodal disease in our own previously published data.[17] Unlike in BCC where a patient with a close or involved margin is at risk of local relapse and observation with expectant treatment (i.e. radiotherapy or surgery) is an accepted option in many, further treatment is generally recommended for an involved or close cSCC margin due to the increased risk of developing local recurrence which in turn increases the risk of subsequent nodal metastases.[10] Many patients developing local recurrence of scalp cSCC are not always candidates for surgical salvage. Anatomical restrictions of the scalp need to be carefully considered as further resection of an involved or close deep margin may necessitate either more complex reconstruction or even skull resection, and adjuvant radiotherapy can be associated with risks including late graft loss with subsequent bone exposure, as well as osteoradionecrosis of the skull.[11]

Table 1. Patient Characteristics

		LRG	HRG	Total
Gender	Male	43 (46.7%)	49 (53.3%)	92
	Female	9 (40.9%)	13 (59.1%)	22
Immunosuppression	Yes	5 (45.5%)	6 (54.5%)	11
	No	47 (45.6%)	56 (54.4%)	103
Grade	Well differentiated	7 (46.7%)	8 (53.3%)	15
	Moderately differentiated	20 (47.6%)	22 (52.4%)	42
	Poorly/Undifferentiated	20 (43.5%)	26 (56.5%)	46
	Unknown	4 (40%)	6 (60%)	10
Perineural invasion	Yes	4 (16.7%)	20 (83.3%)	24
	No	17 (42.5%)	23 (57.5%)	40
	Unknown	31 (62%)	19 (38%)	50
Vascular invasion	Yes	0	7 (100%)	7
	No	24 (46.2%)	28 (53.8%)	52
	Unknown	28 (50.9%)	27 (49.1%)	55

† Low risk group (LRG): >2mm ‡ High risk group (HRG): ≤2mm

Table 2. Patterns of recurrence (following treatment of nodal disease)

	No Recurrence	Local	Regional or Distant	Total
LRG†	35 (67%)	8 (15%)	9 (17%)	52
HRG‡, Surgery alone	12 (32%)	11 (29%)	15 (40%)	38
HRG‡, Surgery + adjuvant Radiotherapy	9 (38%)	4 (17%)	11 (46%)	24

† Low risk group (LRG): >2mm ‡ High risk group (HRG): ≤2mm

In a review of 235 patients treated for cSCC of the scalp at the Peter MacCallum Cancer Centre, Melbourne, an incomplete excision rate of 24% was reported. In total, 22 patients (9%) experienced local recurrence with margin status reported in 11/22, with 4 involved. Of note most that recurred (16/22) did not receive adjuvant radiotherapy.[9] In a series of scalp cSCCs 60% (3/5) of patients with an involved pericranium margin experienced local recurrence, and of those with a close (≤2mm) deep margin 8% (3/37) experienced local recurrence.[18] No patients received adjuvant radiotherapy and because of the low rate of local recurrence in patients with a close but clear deep margin the authors suggested that close observation may be appropriate.

Radiotherapy is an effective modality in both the definitive and adjuvant setting in patients with cSCC and also in patients who are not optimal candidates for surgery (or more extensive re-excision surgery).[19] A clear role and benefit of adjuvant radiotherapy for improving local control and survival in the setting of close or involved margins in cSCC has not been well investigated and remains contentious. Many patients are at competing risks of developing regional and distant relapse or an intervening co-morbid medical event and establishing a benefit can be difficult. In a series of 11 patients all with locally advanced cSCCs undergoing adjuvant radiotherapy for positive excision margins, but without gross residual disease, the majority (82%) had poor outcomes including 4 developing local recurrence, 7 developing nodal metastases and 2 with distant metastases.[20] This study confirms the importance of aggressive surgical management to achieve negative margins whenever feasible and is consistent with our findings of a survival advantage for those with clear resection margins.

A case matched study investigating patients with high risk cSCC treated with surgery alone, compared to surgery and adjuvant radiotherapy, included patients with clear surgical margins and did not identify a significant difference in outcomes including local recurrence, distant metastases or disease specific survival. A sub-group analysis of 33 patients with large caliber PNI (≥0.1mm), 16 treated with surgery and adjuvant radiotherapy and 17 treated with surgery alone, identified no significant difference in outcomes, although all 3 local recurrences occurred in patients undergoing surgery alone.[2] Within our study only 4 patients in the LRG underwent adjuvant radiotherapy so we were unable to draw any conclusions about the benefit of additional treatment in patients with clear margins. A recent meta-analysis reported that margin status, PNI and immunosuppression were all factors associated with a significant reduction in OS, and that adjuvant radiotherapy improved OS.[4] Based on this limited published evidence, we suggest that margin status is relevant in making a decision regarding adjuvant radiotherapy.

In our study, having a close/positive margin was associated with an increasing risk of developing LR (24 *vs* 15%) and the addition of adjuvant radiotherapy showed a trend towards improved outcomes for this HRG (LR of 17% vs 29% for surgery alone). We found that margin status had a significant effect on disease specific mortality with a survival benefit for those in the LRG and postulate that an involved margin may be an indicator of aggressive, infiltrative tumor biology and associated with worse outcomes.

We acknowledge the weaknesses of our study which include its retrospective methodology, although the analyzed computer database has been prospectively maintained by the senior author for over 20

years. There is also selection bias as all patients had been referred to a major teaching hospital with metastatic cSCC to the parotid and/or cervical lymph nodes, thus the primary tumors in our patient population were high-risk, which may account for the high number in the HRG. As most (80-85%) developed metastatic lymph nodes following scalp treatment (12-24 months) we don't believe this detracts from the issues regarding the management and outcome of the scalp cSCC.

CONCLUSION

Margin status had a significant impact on disease specific mortality, but did not appear to be associated with the risk of developing local recurrence. The addition of adjuvant radiotherapy in select high-risk patients may improve outcome although this was not demonstrated in our study.

Conflict of Interest Disclosures: None

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