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EXCISION MARGINS AND SENTINEL LYMPH NODE STATUS AS PROGNOSTIC FACTORS IN THICK MELANOMA OF THE HEAD AND NECK: A RETROSPECTIVE STUDY

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ABSTRACT

Background: Recommended margins for thick cutaneous melanoma (Breslow thickness >4mm, T4) have decreased over recent decades. Optimal margins and sentinel node biopsy in thick head and neck melanoma remain controversial.

Methods: A single-centre review of patients treated between 2002 and 2012 assessing the impact of excision margins, and sentinel node status, on loco-regional recurrence and melanoma specific survival.

Results: One-hundred and eight patients were identified. Median age was 71.1years and median Breslow thickness 6.0mm. Median follow up was 40 months. Loco-regional recurrence occurred in 27% and there was no significant reduction in recurrence with margins ≥2cm (p=0.17). Increasing margins did not improve survival (p = 0.58). Fifty-nine patients (55%) underwent sentinel node biopsy, 27% were positive. There was a trend towards longer survival for patients who were sentinel node negative (p=0.097).

Conclusions: Wider margins do not significantly improve loco-regional recurrence or melanoma-specific survival. Sentinel node involvement reflects a poor prognosis.

INTRODUCTION

The incidence of melanoma is increasing worldwide and makes up a significant proportion of the overall cancer burden [1,2]. Australia and New Zealand have the highest melanoma rates in the world, and they are rising. It is estimated that in 2015 in Australia 12,960 new cases of melanoma will be diagnosed, making up 10.2% of all new cancer diagnoses and a projected 1,675 Australians will die from the disease[2]. In the United States, the estimated number of melanoma diagnoses in 2013 was 76,690 with 9840 deaths[3].

Up to 25% of all cutaneous melanomas are located in the head and neck (H&N) [4,5]. Tumour thickness is the most important prognostic factor for early stage melanoma[6,7]. Thick tumours defined as ≥4mm or T4, according to the American Joint Committee on Cancer (AJCC) staging system, have a 5-year survival of approximately 50%[8]. Several studies have reported that melanomas located in the H&N have a worse prognosis compared to melanomas at other sites[9,10].

Guidelines such as the National Comprehensive Cancer Network (NCCN) and Australian Cancer Network recommend a 2cm excision margin for thick melanomas[11]. This is based on limited data from two randomised controlled studies of patients with T4 melanomas[12,13]. A 2cm margin may be easily achieved for lesions located on the extremities and trunk, but for lesions of the H&N such a margin may be associated with significant functional and

cosmetic disability and require complex reconstructive procedures with increased hospital stay and cost.

The importance of sentinel node biopsy (SNB) in staging patients with cutaneous melanoma is now accepted for patients with intermediate thickness melanoma (1 – 4 mm thick) but debate remains about it's role in thick melanomas. Sentinel node biopsy in the H&N may also present technical issues, as the nodes are small relative to other sites and the lymphatic drainage is complex often with multiple lymph node sites involved.

This single centre retrospective study aimed to investigate margins of excision and sentinel node biopsy on loco-recurrence (LRR) and melanoma-specific survival (MSS) in patients with T4 melanomas of the H&N.

MATERIALS AND METHODS

All patients diagnosed with T4 melanoma of the H&N who underwent definitive treatment at Peter MacCallum Cancer Centre (PMCC) in Melbourne, Australia, between January 1st 2002 and December 31st 2012, were identified from a pre-existing database. The database contained all patient demographics, melanoma characteristics (site, Breslow thickness, ulceration, mitotic count, satellitosis, Clark level, lymphovascular invasion, perineural invasion, tumour invading lymphocytes and regression) as well as details and timelines of treatment and follow up. Ethics approval was granted by the Peter

MacCallum Cancer Centre Human Research Ethics Committee (Study Number 14/123R).

Patients were grouped based on anatomical site of their melanoma; 1) scalp, 2) face (including ear, pre-auricular and post-auricular regions), and 3) neck. All patients had a diagnosis of melanoma prior to definitive surgery either by a partial biopsy or complete excision. Margin excision widths were obtained from the medical records and the narrowest transverse histological margin was calculated. For specimens containing melanoma, we used the narrowest margin as measured in the pathology report. For those containing scar only (where prior excisional biopsy had been performed), margins were calculated as half of the narrowest diameter of the specimen as stated in the pathology report. If patients underwent successive excisions of the same melanoma in order to achieve appropriate margins, the margins from each excision were added.

There was no formal selection process for patients who underwent SNB but lymphatic mapping was performed for all patients who did, (using technetium antimony sulphide), and commonly SPECT / CT imaging in addition to intra-operative patent V blue dye.

Locoregional recurrence (LRR) was defined as a recurrence of melanoma within or close to the site of the original melanoma, an in-transit recurrence or cervical lymph node recurrence. Time to recurrence was calculated from the date of melanoma diagnosis. Cumulative incidence curves were used to

generate recurrence and survival statistics and curves compared with the log rank test. Competing risks regression analyses were used to test for association between candidate prognostic factors and each of LRR and MSS. p-values for association between anatomical site and patient characteristics were calculated using the Fisher's exact test for categorical characteristics and using the Kruskal-Wallis test for ordinal ones. Results were summarised graphically using cumulative incidence curves.

RESULTS

A total of 108 patients were identified. Patient demographics and melanoma characteristics are shown in Table 1 and have been stratified by anatomical site: scalp, face and neck. For the entire cohort, median Breslow thickness was 6.0mm and 99 (94%) melanomas had an elevated mitotic count (one or more mitoses per mm^2 with a mean of 8 per mm^2). Characteristics for each anatomical site were similar with no significant difference in gender (p=0.077), age (p=0.105), Breslow thickness (p=0.134) or ulceration (p=0.349). There were, however, differences between excision margins for each anatomical site (p=0.002): the highest rates of widest margins (>2cm) occurred in the scalp (37%), and the highest rates of narrow margins (<1cm) occurred in the face (36%), which included sensitive anatomical sites, such as the lip and periorbital area. The rate of SNB was similar between the anatomical sites (p = 0.677).

Fifty-nine patients (55%) underwent a SNB, 16 (27%) of whom were node positive. Only one patient underwent SNB in the first year of data collection

(2002), and almost half of the SNBs occurred in the last two years (2011-2012). Patient and tumour information by performance of SNB is shown in Table 2. Patients in the non-SNB group were older (median age 79 vs 65 years). The median Breslow thickness was greater, but not significantly, in the SNB group (6.25mm vs 5.5mm, p = 0.924). Fourteen of the 16 patients who were SNB positive underwent a completion cervical lymphadenectomy (88%), six of whom had further positive non-sentinel nodes (43%). Tumour ulceration was present in 27 (55%) and 30 (52%) patients in the non-SNB and SNB groups, respectively. Median excision margins were also similar, (1.1 and 1.5 cm), respectively.

After a median follow up of 40 months, 50 patients (46.3%) developed a recurrence. This included 29 patients (27%) with a local, in transit or regional recurrence, and 21 distant recurrences (19%), predominantly lung. There was a weak association between scalp and face melanomas and LRR (p=0.059), and a significant difference between face and scalp (p=0.044, Table 3). Wider excision margins did not significantly reduce LRR rates (p=0.17).

There was no significant difference in LRR between patients who underwent a SNB and those who did not (p=0.49, Table 3). Sentinel node status (positive or negative) was also not associated with LRR (p = 0.8, Table 3). For patients who underwent a SNB there was a trend towards improved survival in the SNB negative compared to the SNB positive group (p = 0.097, Table 4).

Twenty-three patients (21%) died from their disease. On univariate analysis, survival was poorer in patients who had lymphovascular invasion or the

presence of satellitosis (Table 4). Anatomical site did not significantly impact on MSS (p=0.37 for scalp versus face, and p=0.17 for face versus neck (Table 4). Overall, margin size was not found to be a predictor of survival (Figure 2, Table 4).

DISCUSSION

This study reports the largest single institution study of thick, (> 4mm, T4), primary cutaneous melanomas of the head and neck. In summary, we found that neither locoregional recurrence nor overall survival were compromised when the margin of excision was at least 1cm. SNB was performed in over half of patients and the presence of melanoma within the SLN identified patients at a greater risk of death from melanoma.

The evidence guiding the width of excision of primary cutaneous melanoma is limited. A Cochrane review from 2009 did not demonstrate a statistically significant difference in overall survival according to margin status and concluded that insufficient data existed to address optimal excision margins[14]. Multiple international guidelines recommend a minimum 2cm margin for thick melanoma[15]. These recommendations are based on two randomised studies which included patients with thick melanoma. The UK – Scottish study randomised patients with melanomas ≥2mm to margins of 1cm or 3cm[13]. Almost half of the 769 patients had T4 melanomas, however none were located on the head and neck and the authors did not specifically discuss the role of margins in <4mm versus >4mm melanomas. Tumour thickness was noted to be the strongest predictor of both LRR and death, and narrower

margins (1cm) significantly increased the risk of LRR (p=0.05), but not true local or regional recurrence, or survival. The recent Swedish study randomised 936 patients with melanomas > 2 mm to either a 2cm or 4cm margin[12]. Only two of these patients had H&N melanomas, both located on the neck. Long term follow up revealed excision margins did not impact significantly on recurrence (p=0.96) or survival (p=0.69).

A number of studies have found that H&N melanomas carry a poorer prognosis compared to those of other anatomical sites, having increased rates of LRR and poorer survival[9,10]. Anatomic site within the H&N may also be independently related to mortality, with a three-fold increase in disease-specific mortality for scalp melanomas compared with those located on the face.[16]

Unfortunately there are very few reports which address the issue of excision margins for melanomas of the head and neck[17-19]. In summary these studies vary from reports of cutaneous melanoma around the body with a small proportion located on the H&N, or small retrospective series of H&N melanomas most of which are not T4 lesions. This can probably be explained by the relative rarity of this group of patients and a lack of consensus on the most appropriate management. Furthermore, the head and neck presents specific and varying technical challenges for lesions such as those found on the lip, ear and eyelids. Patients with thick melanomas are at significant risk of dying from the disease with survival at five years reported to be from 39% to 53%[8]. To date, evidence is lacking to show that increasing excision

margins improves these survival statistics. The current study reports the largest experience of T4 melanoma of the H&N and does not demonstrate a significant improvement in survival with wider margins, (Figure 2), supporting the limited literature available[12,9,14]. The presently accruing Australia and New Zealand Melanoma Trials Groups (ANZMTG) sponsored MelMarT study (clinicaltrials.gov NCT02385214) compares 1cm versus 2cm margins for primary melanomas greater than 1mm thick and includes lesions located in the H&N. Whether this study will accrue sufficient numbers of patients with H&N lesions due to the difficulties of potentially performing 2 cm margin remains to be seen. Nevertheless the current study supports a trial of narrower margins for T4 melanomas of the H&N and in most cases a margin of at least 1cm may be adequate.

The role for sentinel node biopsy in patients with cutaneous melanoma has been clarified recently by the final results from the Multicentre Selective Lymphadenectomy Trial 1 (MSLT1) reported by Morton and colleagues[20]. These results and others confirm that the status of the sentinel node is the most powerful prognostic factor in early-stage melanoma, similar to the findings of a recent meta-analysis along with other reports [16,20-24]. It should be noted that melanomas of the H&N were excluded from the MSLT1 study and T4 melanomas were a relatively small subgroup and reported separately. Lymphatic drainage patterns of the H&N skin can be unpredictable, with lymph nodes located close to the index lesion or within the parotid gland, making preoperative lymphoscintigraphy potentially less accurate and unlike other cutaneous melanoma sites multiple pathways and sentinel nodes may

be identified on lymphatic mapping. A systematic review of SNB in H&N melanoma[22], which included 3442 patients in a total of 32 studies published between 1990 and 2009 concluded that, despite a high identification rate of the sentinel node (93.4%), there is also a higher false negative rate in H&N melanoma (20%) compared with non-H&N sites, reflecting the technical challenge and anatomical variation of lymph drainage in this region. Data from the Melanoma Institute of Australia showed that a common cause of false negative SNB was failure to remove all nodes identified on lymphatic mapping[25]. The addition of SPECT imaging to standard lymphoscintigraphy appears to significantly increase the identification of sentinel nodes[26.] The meta-analysis reported by de Rosa[22] noted an increased likelihood of recurrence in SN positive patients without a clear survival benefit of completion lymphadenectomy. For most patients with further positive nodes at completion node dissection, these nodes are located in the same lymph node group as the SLN[27].

The largest study of SNB in patients with T4 melanoma by Yamamoto et al[28] included 571 patients with thick melanoma located around the body without clinical lymph node involvement, and found significant improvement in recurrence, disease-specific and overall survival in SN-negative patients ($p<.0001$). This current study highlights the important prognostic significance of sentinel node status in T4 melanoma (HR=2.54, p=0.097).

Limitations of this study include the retrospective nature of the study and the relatively small sample size. The calculation of margin width from the

pathology reports is a different methodology to that employed in prospective studies where clinical margins were used, however the technique was standardised and all the definitive procedures and pathology were performed at the Peter MacCallum Cancer Centre.

In conclusion, this report is the largest single centre experience of T4 melanoma of the head and neck. We found that wider margins (≥2cm) offered no extra benefit in recurrence rates or melanoma specific survival over a margin of at least 1 cm and that SNB identifies patients at high risk of death from melanoma in these advanced tumours. These results support and contribute to the growing body of literature on the surgical management of primary melanoma in the modern era. To date there have been no reported randomised trials including T4 head and neck melanomas and this should be a consideration for future trial design.

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TABLES AND FIGURES

Table 1: Patient and tumour characteristics

Variable	Statistic	All groups	Scalp (n=30)	Face (n=59)	Neck (n=19)
Gender (p=0.077)	Female Male	31 (29%) 77 (71%)	4 (13%) 26 (87%)	21 (36%) 38 (64%)	6 (32%) 13 (68%)
Age at diagnosis (years) (p=0.105)	Median [range]	71.1 [22.2-100.8]	67.3 [24-88.8]	74.2 [30.9-100.8]	57.6 [22.2-93.2]
Melanoma type (p=0.84)	SSM NM LM DM Other	17 (16%) 53 (49%) 12 (11%) 18 (17%) 8 (7%)	4 (13%) 15 (50%) 3 (10%) 7 (23%) 1 (3%)	11 (19%) 29 (49%) 7 (12%) 7 (12%) 5 (8%)	2 (11%) 9 (47%) 2 (11%) 4 (21%) 2 (11%)
Breslow thickness (mm) (p=0.134)	Median [range]	6.0 [4-26]	6.95 [4-12]	5.4 [4-16]	6.5 [4-26]
Margin categories (p=0.002)	0-1cm 1-2cm 2-3.5cm Median[range]	27 (25%) 61 (56%) 20 (19%) 6 [4-26]	2 (7%) 17 (57%) 11 (37%) 6.95 [4-12]	21 (36%) 30 (51%) 8 (14%) 5.4 [4-16]	4 (21%) 14 (74%) 1 (5%) 6.5 4-26]
Mitosis (p=0.725)	0 ≥1	6 (6%) 99 (94%)	2 (7%) 28 (93%)	4 (7%) 53 (93%)	0 (0%) 19 (100%)
Ulceration (p=0.349)	No Yes	50 (47%) 57 (53%)	12 (40%) 18 (60%)	27 (46%) 32 (54%)	11 (61%) 7 (39%)
Satellites (p=0.003)	No Yes	87 (93%) 7 (7%)	23 (79%) 6 (21%)	49 (100%) 0 (0%)	15 (94%) 1 (6%)
Lymphovascular invasion (p=0.043)	No Yes	90 (88%) 12 (12%)	22 (76%) 7 (24%)	52 (95%) 3 (5%)	16 (89%) 2 (11%)
Sentinel lymph node biopsy (p=0.677)	Number (%)	59 (55)	18 (60)	30 (15)	11 (58)

SSM = superficial spreading melanoma, NM = nodular melanoma, LM = lentigo maligna, DM= desmoplastic melanoma, LVI = lymphovascular invasion.

Table 2: Baseline characteristics of patients who did and did not undergo sentinel node biopsy

Variable		No SNB (number, total = 49)	No SNB (%)	SNB (number, total = 59)	SNB (%)
Gender	Male	34	69	43	73
	Female	15	31	16	27
Age at diagnosis (years)	Median [range]	79.2 [24-100.8]		65.7 [22-89.6]	
Site	Scalp	14	29	16	27
	Face	27	55	32	54
	Neck	8	16	11	19
Type	SSM	6	12	11	20
	NM	26	53	27	48
	LM	3	6	9	16
	DM	10	20	8	14
	Other	4	8	1	2
Breslow thickness (mm) (p=0.924)	Median [range]	5.5 [4-20]		6.25 [4-26]	
Mitosis	No	5	11	1	2
	Yes	42	89	57	98
	Median [range]	6 [0-24]		8 [0-34]	
Ulceration	No	22	45	28	48
	Yes	27	55	30	52
Satellites	No	36	90	51	94
	Yes	4	10	3	6
Lymphovascular Invasion	No	46	98	44	80
	Yes	1	2	11	20
Margins (cm)	Median [range]	1.1 [0-3.5]		1.5 [1-3.0]	
	[0-1]	19	39	8	14
	[1-2]	21	43	40	68
	[2-3.5]	9	18	11	19

Abbreviations: SNB= Sentinel node biopsy, SSM = superficial spreading melanoma, NM = nodular melanoma, LM = lentigo maligna, DM = desmoplastic melanoma.

Table 3. Univariate Analysis for Loco-regional Recurrence

Variable	Level	Number	HR	95% CI	p-value
Gender	Female	31	1		
	Male	77	1.03	[0.45, 2.36]	0.95
Age at diagnosis	Years	108	1	[0.97, 1.02]	0.76
Site	Scalp	30	1		
	Face	59	2.8	[0.96, 8.17]	0.059
	Neck	19	3.61	[1.04, 12.55]	0.044
Breslow thickness (mm)	per unit increase	108	0.97	[0.87, 1.08]	0.61
Margin (cm)	0-1	27	0.68	[0.39, 1.18]	0.17
	1-2	61			
	2-3.5	20			
Mitotic count	0	6	1.64	[0.31, 8,74]	0.56
	≥1	99			
	Missing	3			
Ulceration	Absent	50	1		
	Present	58	1.01	[0.49, 2.07]	0.98
Satellites	Absent	87	1		
	Present	7	0.53	[0.07, 3.75]	0.52
	Missing	14			
Lymphovascular Invasion	Absent	90	1		
	Present	12	1.15	[0.42, 3.13]	0.78
	Missing	6			
SN# Biopsy	No	49	1		
	Yes	59	0.77	[0.37, 1.60]	0.49
SN Status	Negative	10†	1		
	Positive	5†	1.15	[0.41, 3.22]	0.8

#Sentinel node, †number of loco-regional recurrences

Table 4. Univariate Analysis for Melanoma Specific Survival

Variable	Level	Number	HR	95% CI	p-value
Gender	Female	31	1		
	Male	77	0.68	[0.31, 1.53]	0.36
Age at diagnosis	Years	108	0.99	[0.97, 1.01]	0.38
Site	Scalp	30	1		
	Face	59	0.67	[0.28, 1.60]	0.37
	Neck	19	0.42	[0.12, 1.43]	0.17
Breslow thickness (mm)	per unit increase	108	0.97	[0.84, 1.11]	0.65
Margin (cm)	0-1	27	1.23	[0.59, 2.59]	0.58
	1-2	61			
	2-3.5	20			
Mitotic count	0	6	1.91	[0.46, 7.98]	0.38
	≥1	99			
	Missing	3			
Ulceration	Absent	50	1		
	Present	58	1.62	[0.71, 3.69]	0.25
Satellites	Absent	87	1		
	Present	7	5.97	[2.72, 13.13]	<0.001
	Missing	14			
Lymphovascular Invasion	Absent	90	1		
	Present	12	3.82	[1.64, 8.90]	0.002
	Missing	6			
SN[#] Biopsy	No	49	1		
	Yes	59	0.82	[0.35, 1.92]	0.65
SN Status	Negative (deaths)[†]	43 (5)	1		
	Positive (deaths)[†]	16 (6)	2.54	[0.84, 7.62]	0.097

[#]Sentinel lymph node, †deaths due to melanoma

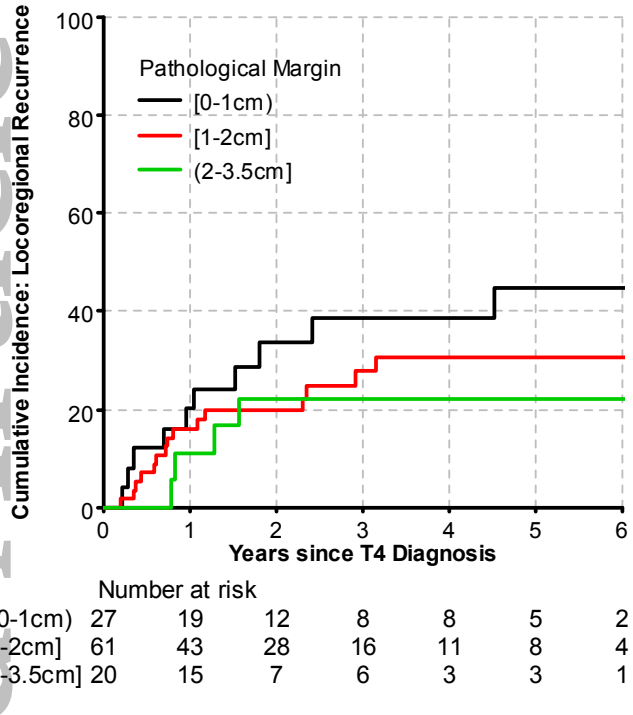

Figure 1: Cumulative incidence of Locoregional recurrence by excision margin

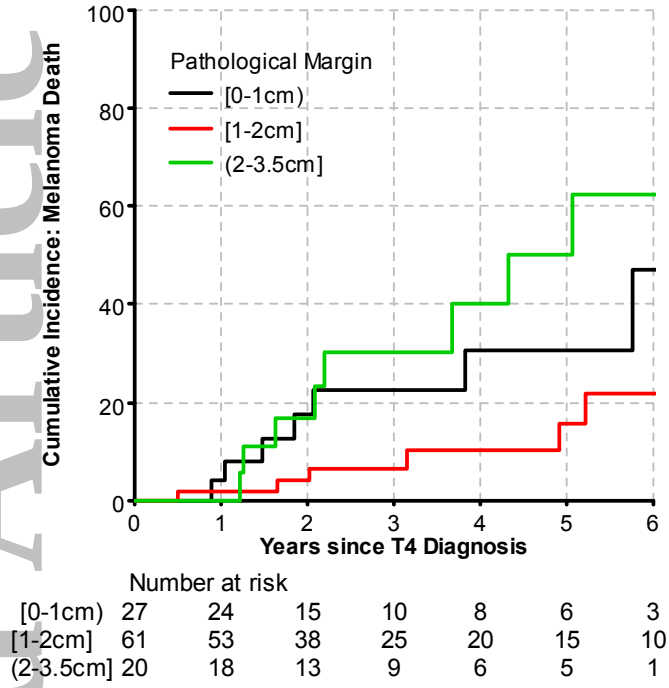

Figure 2: Cumulative incidence for melanoma-specific survival by excision margin