Title: Acral lentiginous melanoma: clinicopathologic and survival differences according to tumour location.

Running title: Acral lentiginous melanoma and location

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Abstract

Background/Objectives: Acral lentiginous melanoma (ALM) is a melanoma subtype associated with atypical locations on the hands and feet and advanced disease at diagnosis. There is a limited understanding of whether the survival is similar for nail, non-nail, lower limb and upper limb ALM patients. We therefore explored clinicopathologic characteristics and melanoma specific survival (MSS) of ALM patients according to tumour location.

Methods: A prospectively collected cohort study was performed of all primary invasive cutaneous nodular melanomas with known thickness and tumour location reviewed at a tertiary referral centre over 21 years.

Results: 101 ALM patients were reviewed from 1994 until 2016. The majority of cases (82/101) occurred on the feet. Hand ALMs were thicker and more likely to be ulcerated than feet ALMs ($P=0.05$ and 0.02 respectively), however survival was not statistically different between these two groups (univariate HR 0.48 $P=0.11$, 95% CI 0.20-1.17; multivariate HR 0.67 $P=0.40$, 95% CI 0.27-1.69 respectively). Non-nail ALM patients had longer survival when compared to nail ALM on univariate analysis (HR 0.40, 95% CI, 0.17 to 0.90) which was accounted for by Breslow thickness and ulceration (multivariate HR 0.56, 95% CI, 0.24 to 1.34).

Conclusions: The reduced MSS in nail ALM patients was likely due to their greater thickness and ulceration. Although hand ALMs are thicker and more frequently ulcerated, this is likely due to the higher proportion of nail ALMs present in this location.

Keywords: acral lentiginous melanoma, histologic subtype, tumour location, survival, clinicopathologic, ALM, nail melanoma

Abbreviations:

ALM- acral lentiginous melanoma

MSS- melanoma specific survival

HR- Hazard ratio

CI- Confidence interval

AJCC- American joint committee on cancer

VMS- Victorian Melanoma Service

NMSC- non-melanoma skin cancer

HPF-high powered field

VCR- Victorian Cancer Registry

MICE- Multiple imputation using chained equations

Introduction

Acral lentiginous melanoma (ALM) characteristically affects the volar surfaces of the hands and feet as well as the nail apparatus¹. It is a less frequent subtype in Caucasians than other melanoma subtypes, but ALM comprises a much higher percentage of all melanoma in Hispanic, Asian and African populations where there is a lower proportion of UV related subtypes²⁻¹⁰. In keeping with the typical locations affected by ALM, its epidemiology is unusual with a lack of association to either ultraviolet radiation, total non acral or acral naevi counts and distinct mutational profiles compared to other subtypes¹¹⁻¹⁴.

The acral locations diagnosed with ALM have an interesting distribution. The majority of ALM are diagnosed in the lower extremities, where most are located on the plantar sole and relatively few occur in the toenail apparatus^{5, 15-17}. Conversely, most upper limb ALMs are associated with the fingernail apparatus^{15, 17}. There is conflicting evidence whether clinicopathologic variables differ between upper and lower limb ALM¹⁸ and between nail and non-nail ALM^{13, 19}. Consequently, it is unclear whether survival differs according to ALM location¹⁹ and whether clinicopathologic prognostic factors influence this comparison.

The aim of the study therefore was to evaluate the impact of tumour location on ALM survival in greater detail than has previously been possible.

Materials and Methods

Institutional ethics approval was obtained from the Hospital and University HRECs for this study. All invasive cutaneous primary melanoma cases reviewed at the Victorian Melanoma Service (VMS) from the commencement of the service in 1994 until January 2016 with known Breslow thickness and location were included. The VMS is a multidisciplinary tertiary referral service located at the Alfred Hospital in Melbourne. It reviews approximately one quarter of total new diagnoses of melanoma in the Australian state of Victoria.

Clinical features of each patient collected by the reviewing clinician included: age, sex, date of diagnosis (biopsy date) and tumour location coded utilising a body map of 232 areas differentiating anterior from posterior, left from right and midline structures, as developed by the Pigmented Lesion Study Group)²⁰. Other clinical features recorded included: clinical hypomelanosis, hair colour, previous history of non-melanoma skin cancer and family history of melanoma. Patients were subsequently examined by reviewing clinicians to determine total naevi count. Independent pathology review of each melanoma case was undertaken by an expert melanoma dermatopathologist. Histologic features that were assessed included: tumour subtype according to World Health Organization guidelines (in order to verify each case was acral lentiginous melanoma)²¹, Breslow thickness, ulceration status, mitotic rate (mm^2), neurotropism, lymphovascular invasion, satellite metastasis, regression and tumour invading lymphocytes. As mitotic rate was recorded in per 10 high powered field (HPF) prior to 2005, reporting pathologist's conversion factors were utilised to convert to per millimeter squared.

Survival information for all patients in the study was obtained by linkage with the Victorian Cancer Registry (VCR), a population-based cancer registry that collects data on all cancer diagnoses and mortality for residents in the state of Victoria, Australia. Patient vital status was current as of 31st

December 2015. For patients diagnosed with more than one primary cutaneous melanoma, the melanoma with the greatest Breslow thickness was retained for our analysis²²

After exclusion of insitu cases (n=23 ALMs), non-registry linked cases (n=4 ALMs), unknown Breslow thickness (n=3 ALMs), non cutaneous melanoma (n=4 for total cohort) and multiple melanomas (n=334 for total cohort), 101 invasive acral lentiginous melanoma cases were available for analysis out of 3570 cutaneous invasive melanoma patients in total (2.8% of total melanoma cases).

Differences in clinicopathologic data between groups of interest were compared using the Wilcoxon rank tests (for continuous variables) and chi-squared tests (for categorical variables) or fisher exact tests (for categorical variables when values were less than 5). Analysis of MSS for association between ALM tumour locations was performed using Cox proportional hazards models. Given a skewed distribution for Breslow thickness, a log transformation was applied with the transformed version included in models as a continuous variable. Age at diagnosis was dichotomised for analysis at the median age of the total cohort of 65 years. Mitotic rate was categorised into five strata to allow discrimination and create similar strata to observed survival differences in AJCC data²². Multiple imputation using chained equations (MICE) method was used to impute values in place of missing data for ulceration(see Table 1 legend for the number of missing values for each variable)²³. There were no missing values for location, thickness, age, sex and previous history of melanoma. Pre and post imputation diagnostic checks led to assumption of missing at random.

The Nelson-Aalen estimate of cumulative hazard generated from univariate analysis and the censor indicator variable were included in the imputation model²⁴. Ten data sets (cycles) with imputed values for each missing value were generated and results of analysis applied to all ten sets were combined according to Rubin's rules²⁵. All statistical analyses were performed using Stata (Version 14.3, StataCorp, College Station, TX). Results were considered statistically significant if the P value was less than 0.05.

Results

Acral lentiginous melanoma tumour location

Most cases of ALM were on the feet (82/101 cases, 81% of ALMs) with 19/101 cases on the hands (19%, Table 1). There were sixteen fingernail ALM diagnosed on the right hand versus ten on the left hand, with the thumbnail the most common site (11/16 of total fingernail ALM, Figure 1). Palmar ALM was uncommon, with only three cases in a total of 19 hand ALMs. Twenty of 82 ALM of the feet occurred under the toenails, with equal frequency on left and right sides (10 each). Thirty five ALM occurred on the plantar soles.

Median Breslow thickness and ulceration rates did differ significantly between upper and lower limb ALM (2.3mm, 1.5mm, $P=0.05$ respectively; with 63% of upper limb ALM ulcerated, and 34% of lower limb ALM ulcerated, $P=0.02$ each, Table 1). Sixteen from 23 ALM specific deaths occurred in cases on the feet. The 82 patients with ALM on the foot had longer survival than the 19 patients with ALM on the hand although this did not reach statistical significance (univariate HR 0.48 $P=0.11$, 95% confidence interval (CI) 0.20-1.17; multivariate (adjusted for Breslow thickness and ulceration) HR 0.67 $P=0.40$, 95% CI 0.27-1.69 respectively).

Greater median Breslow thickness and rates of ulceration for nail ALM over non-nail ALM appear the likely reason for this survival difference (median Breslow thickness 2.2mm and 1.5mm respectively; $P=0.09$, 19/36 (53%) nail ALM were ulcerated compared to 21/65 (32%) non-nail ALM, $P=0.02$).

Right-sided nail ALM had a greater median thickness than left-sided nail ALM (3mm versus 1.7mm, $P=0.04$). Melanoma specific survival was compared between patients with nail ALM and those with non-nail ALM. In univariate analysis, non-nail ALM patients had improved survival compared to those with nail apparatus ALM (HR 0.40, $P=0.03$, 95% CI 0.17-0.90). This was accounted for by for adjustment with Breslow thickness and ulceration (multivariate HR 0.56, $P=0.19$, 95% CI 0.24-1.34).

Discussion

This study describes survival outcomes of a prospectively collected Australian ALM cohort with respect to location. Patients with nail ALM had worse univariate survival than non-nail ALM. This was due to nail ALM being thicker and more often ulcerated than non-nail ALM. Patients with ALM on the foot had longer survival than the patients with ALM on the hand although this did not reach statistical significance. This may have been due to the higher proportion for fingernail ALM in the upper limb in contrast to the lower limb and therefore also due to more advanced disease observed in nail ALM.

With respect to ALM survival based on upper or lower limb location, a previous study did not demonstrate a significant difference in survival between hand and feet ALM¹⁸. The hallux and thumbnails were the most common locations for nail ALM in our cohort similar to previous data (Figures 2-3)²⁶. However, our data were in contrast to the previous suggestion that the right hand is more commonly affected than the left for upper limb ALM¹⁹. There are varying results on whether ALM is more common on weight bearing portions of the foot prone to trauma^{19, 27, 28}. Out of the 82 ALM of the feet, 34 occurred on weight bearing areas of the foot (Figures 4-5), with another 20 within the toenail apparatus. Cases of dorsal foot melanoma were validated as acral lentiginous melanoma by independent dermatopathologist review, the majority extended from the lateral or

medial edge of the plantar sole on glabrous skin and all shared lentiginous pattern without evidence of significant solar damage.

Two previous survival comparisons between nail and non-nail ALM were identified in literature: one did not detect a survival difference¹⁹, another demonstrated reduced multivariate overall survival in patients with hypopigmented nail melanoma, however not all patients were exclusively acral lentiginous subtype²⁹. Previous studies have reported higher rates of ulceration in nail ALM, similar to our findings. However we found an increased Breslow thickness¹⁹ of nail ALM in comparison to non-nail ALM, in contrast to other studies^{20, 48}. As nail ALM is often misdiagnosed for infection or trauma, delayed diagnosis rather than rapid growth may explain the pathological differences between nail and non-nail ALM^{30, 31}. Greater thickness in right compared to left sided nail ALM mirrored the findings from another study³² and this has been suggested to be due to either more rapid growth or due to greater risk of mechanical stress given high frequency of right hand dominance in the population³².

The proportion of ALM in our cohort was similar to other Caucasian cohorts reporting ALM incidence between 2-3%^{4, 5, 33}. Predominance of ALM in the feet, women and older patients was also consistent with several previous reports^{5, 9, 16}. Other studies support the finding of the thumb and the hallux as the most common subsites for nail ALM³¹ and the hand to have a predominance of nail rather than acral ALM¹⁵.

There were limitations to our study, including potential for referral bias given the tertiary nature of our service. This means patients with difficult to treat sites (ie. Nail ALM) are more likely to have been referred to our institution. Molecular testing was introduced relatively recently hence mutational status was not assessed because it was incomplete for older cases.

Overall, there are distinct differences in clinicopathological features and frequency in locations diagnosed with ALM. Differences in ulceration and potentially thickness between nail and non-nail ALM in our data were observed, which likely accounted for both the univariate decreased MSS of nail ALM patients as well as the difference in hand versus foot ALM MSS that approached significance. Further research is required to establish why nail ALM is diagnosed with advanced features compared to volar ALM.

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Figures

Figure 1: Detailed body map demonstrating distribution of acral lentiginous melanoma per anatomical subsite (n=101)

Figure 2: a 1.2mm Breslow thickness nail acral lentiginous melanoma

Figure 3: a 6mm Breslow thickness nail acral lentiginous melanoma

Figure 4: a 4.8mm Breslow thickness non nail acral lentiginous melanoma

Figure 5: an 8.5mm Breslow thickness non nail acral lentiginous melanoma

Tables

Table 1: Baseline clinicopathologic characteristics of 101 individuals with invasive acral lentiginous melanomas, P values for differences in distribution of clinicopathologic characteristics according to location

Clinicopathologic factor	Upper limb, n=19	Lower limb, n=82	P- value ^a	Nail, n=36	Non-nail, n=65	P- value ^a
Female Sex, n (%)	6 (31%)	50 (61%)	0.02	17 (47%)	39 (60%)	0.22
Age, y, median (IQR)	65 (57-75)	67.5 (56-79)	0.63	67 (61-75)	70 (54-80)	0.88
Breslow thickness, mm, median (IQR)	2.3 (1.65-4.2)	1.5 (0.75-3.0)	0.05	2.2 (1.2-4.1)	1.5 (0.7-3.3)	0.09
Ulceration, n (%)	12 (63%)	28 (34%)	0.02	19 (58%)	21 (33%)	0.02
Mitotic rate, per mm ² , n (%)			0.34			0.64
<1	3 (20%)	23 (30.3%)		8 (28%)	18 (29%)	
1-4	7 (47%)	40 (53%)		13 (45%)	34 (55%)	
5-9	3 (20%)	7 (9%)		4 (14%)	6 (10%)	
10-19	1 (7%)	5 (7%)		3 (10%)	3 (5%)	
>20	1 (7%)	1 (1%)		1 (3%)	1 (1%)	
Regression, n (%)	2 (13%)	6 (8%)	0.62	4 (13%)	4 (7%)	0.44
Lymphovascular invasion, n (%)	2 (13%)	7 (9%)	0.64	4 (13%)	5 (8%)	0.48
Neurotropism, n (%)	2 (13%)	4 (5%)	0.26	3 (10%)	3 (5%)	0.34
Satellite metastases, n (%)	0	0		0	0	
Previous melanoma, n (%)			1			1
0	17 (89%)	71 (87%)		32 (89%)	56 (86%)	
1	2 (11%)	10 (12%)		4 (11%)	8 (12%)	
≥2	0	1 (1%)		0	1 (2%)	
Previous history NMSC, n (%)			1			1
0	16 (84%)	62 (82%)		30 (86%)	48 (80%)	

1	2 (11%)	9 (12%)		4 (11%)	7 (12%)	
2-5	1 (5%)	4 (5%)		1 (3%)	4 (7%)	
6-10	0	1 (1%)		0	1 (2%)	
Pre-existing naevus, n (%)	0	10 (13%)	0.2	31 (94%)	54 (87%)	0.49
Clinically hypomelanotic, n (%)	4 (21%)	6 (7%)	0.09	2 (6%)	8 (13%)	0.74
Number of family members with history of melanoma, n (%)			1			0.72
0	17 (89%)	68 (83%)		32 (89%)	53 (82%)	
1	2 (11%)	11 (13%)		3 (8%)	10 (15%)	
≥2	0	3		1 (3%)	2 (3%)	
Tumour invading lymphocytes, n (%)			0.05			0.02
Absent	9 (60%)	40 (54%)		18 (60%)	31 (53%)	
Minimal/mild	4 (27%)	30 (41%)		7 (23%)	27 (46%)	
Moderate	0	4 (5%)		3 (10%)	1 (2%)	
Severe	2 (13%)	0		2 (7%)	0	
Previous severe sunburns, n (%)			0.22			0.67
0	10 (53%)	34 (44%)		18 (52%)	26 (43%)	
1-5	8 (42%)	32 (42%)		13 (37%)	27 (43%)	
6-10	0	7 (9%)		2 (6%)	5 (8%)	
10-20	0	4 (5%)		1 (3%)	3 (5%)	
>20	1 (5%)	0		1 (3%)	0	
Total naevi count, n (%)			0.68			0.54
<50	11 (69%)	45 (63%)		20 (71%)	36 (60%)	
50-100	3 (19%)	12 (8%)		3 (11%)	8 (13%)	
100-200	1 (6%)	12 (17%)		2 (7%)	11 (18%)	
>200	1 (6%)	7 (10%)		3 (11%)	5 (8%)	
Eye colour, n (%)[#]			0.55			0.58
Blue	12 (63%)	32 (43%)		17 (50%)	27 (46%)	
Green	1 (5%)	8 (11%)		2 (6%)	7 (12%)	
Light brown/hazel	2 (11%)	15 (20%)		8 (24%)	9 (15%)	

Brown	4 (21%)	19 (26%)		7 (21%)	16 (27%)	
Hair colour, n (%)			0.84			0.54
Blonde	3 (16%)	10 (14%)		4 (12%)	9 (16%)	
Red	0	5 (7%)		0	5 (9%)	
Light brown	6 (32%)	22 (31%)		11 (33%)	17 (29%)	
Brown	7 (37%)	28 (39%)		14 (42%)	21 (36%)	
Black	3 (16%)	7 (10%)		4 (12%)	6 (10%)	
AJCC²² Breslow thickness categories per subtype and melanoma specific deaths, n (cases), n (deaths)						
T1 (≤1mm thickness)	3 (16%)	28 (34%)		8 (22%)	23 (35%)	
T2 (1.01-2mm thickness)	5 (26%)	17 (21%)		9 (25%)	13 (20%)	
T3 (2.01-4mm thickness)	6 (32%)	26 (32%)		10 (28%)	22 (34%)	
T4 (>4mm thickness)	5 (26%)	11 (13.4%)		9 (25%)	7 (11%)	

IQR= interquartile range, ALM= acral lentiginous melanoma, NMSC= non melanoma skin cancer, AJCC=

a P-value for difference between ALM locations from Wilcoxon rank test (for continuous variables) and chi squared tests/Fisher exact tests (for categorical variables).

Number of missing values, n (% of observed) for ALM: ulceration 5 (5%), mitotic rate 10 (9%), Previous history NMSC 6 (5%), Previous severe sunburns 5 (5%), eye colour 8 (8%), hair colour 10 (10%), naevi count 13 (13%), satellite 9 (9%), lymphovascular invasion 9 (9%), tumour invading lymphocytes 12 (12%), regression 12 (12%), pre-existing naevus 6 (6%), neurotropism 11 (11%).

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Lymphovascular invasion, n (%)	2 (13%)	7 (9%)	0.64	4 (13%)	5 (8%)	0.48
Neurotropism, n (%)	2 (13%)	4 (5%)	0.26	3 (10%)	3 (5%)	0.34
Satellite metastases, n (%)	0	0		0	0	
Previous melanoma, n (%)			1			1
0	17 (89%)	71 (87%)		32 (89%)	56 (86%)	
1	2 (11%)	10 (12%)		4 (11%)	8 (12%)	
≥2	0	1 (1%)		0	1 (2%)	
Previous history NMSC, n (%)			1			1
0	16 (84%)	62 (82%)		30 (86%)	48 (80%)	
1	2 (11%)	9 (12%)		4 (11%)	7 (12%)	
2-5	1 (5%)	4 (5%)		1 (3%)	4 (7%)	
6-10	0	1 (1%)		0	1 (2%)	

Pre-existing naevus, n (%)	0	10 (13%)	0.2	31 (94%)	54 (87%)	0.49
Clinically hypomelanotic, n (%)	4 (21%)	6 (7%)	0.09	2 (6%)	8 (13%)	0.74
Number of family members with history of melanoma, n (%)			1			0.72
0	17 (89%)	68 (83%)		32 (89%)	53 (82%)	
1	2 (11%)	11 (13%)		3 (8%)	10 (15%)	
≥2	0	3		1 (3%)	2 (3%)	
Tumour invading lymphocytes, n (%)			0.05			0.02
Absent	9 (60%)	40 (54%)		18 (60%)	31 (53%)	
Minimal/mild	4 (27%)	30 (41%)		7 (23%)	27 (46%)	
Moderate	0	4 (5%)		3 (10%)	1 (2%)	
Severe	2 (13%)	0		2 (7%)	0	
Previous severe sunburns, n (%)			0.22			0.67
0	10 (53%)	34 (44%)		18 (52%)	26 (43%)	
1-5	8 (42%)	32 (42%)		13 (37%)	27 (43%)	
6-10	0	7 (9%)		2 (6%)	5 (8%)	
10-20	0	4 (5%)		1 (3%)	3 (5%)	
>20	1 (5%)	0		1 (3%)	0	
Total naevi count, n (%)			0.68			0.54
<50	11 (69%)	45 (63%)		20 (71%)	36 (60%)	
50-100	3 (19%)	12 (8%)		3 (11%)	8 (13%)	
100-200	1 (6%)	12 (17%)		2 (7%)	11 (18%)	
>200	1 (6%)	7 (10%)		3 (11%)	5 (8%)	
Eye colour, n (%)[#]			0.55			0.58
Blue	12 (63%)	32 (43%)		17 (50%)	27 (46%)	
Green	1 (5%)	8 (11%)		2 (6%)	7 (12%)	
Light brown/hazel	2 (11%)	15 (20%)		8 (24%)	9 (15%)	
Brown	4 (21%)	19 (26%)		7 (21%)	16 (27%)	
Hair colour, n (%)			0.84			0.54
Blonde	3 (16%)	10 (14%)		4 (12%)	9 (16%)	

Red	0	5 (7%)		0	5 (9%)	
Light brown	6 (32%)	22 (31%)		11 (33%)	17 (29%)	
Brown	7 (37%)	28 (39%)		14 (42%)	21 (36%)	
Black	3 (16%)	7 (10%)		4 (12%)	6 (10%)	
AJCC²⁰ Breslow thickness categories per subtype and melanoma specific deaths, n (cases), n (deaths)						
T1 (≤1mm thickness)	3 (16%)	28 (34%)		8 (22%)	23 (35%)	
T2 (1.01-2mm thickness)	5 (26%)	17 (21%)		9 (25%)	13 (20%)	
T3 (2.01-4mm thickness)	6 (32%)	26 (32%)		10 (28%)	22 (34%)	
T4 (>4mm thickness)	5 (26%)	11 (13.4%)		9 (25%)	7 (11%)	

IQR= interquartile range, ALM= acral lentiginous melanoma, NMSC= non melanoma skin cancer, AJCC=

a P-value for difference between ALM locations from Wilcoxon rank test (for continuous variables) and chi squared tests/Fisher exact tests (for categorical variables).

Number of missing values, n (% of observed) for ALM: ulceration 5 (5%), mitotic rate 10 (9%), Previous history NMSC 6 (5%), Previous severe sunburns 5 (5%), eye colour 8 (8%), hair colour 10 (10%), naevi count 13 (13%), satellite 9 (9%), lymphovascular invasion 9 (9%), tumour invading lymphocytes 12 (12%), regression 12 (12%), pre-existing naevus 6 (6%), neurotropism 11 (11%).

ajd_13310_f1.jpg

ajd_13310_f2.jpg

ajd_13310_f3.jpg

ajd_13310_f4.jpg

ajd_13310_f5.jpg

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