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Acral lentiginous melanoma: differences in survival compared to other subtypes.

Running title: acral lentiginous melanoma survival analysis

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Conflict of interest:

The authors have no conflicts of interest to declare

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Dear editor, acral lentiginous melanoma (ALM) is typically diagnosed at an advanced stage which may be due its unique presentation¹. Studies have evaluated whether the ALM subtype is an independent prognostic factor with conflicting results^{2,3}. Previous reports have been limited by small numbers and lacked adjustment for confounders¹⁻³. Therefore, the aim of this study was to compare melanoma specific survival (MSS) of ALM with other subtypes.

Institutional ethics approval was obtained for this cohort study. All invasive cutaneous primary melanoma cases reviewed at the Victorian Melanoma Service from 1994 until January 2016 underwent independent pathology review by an expert melanoma dermatopathologist. Survival information was obtained by linkage with the Victorian Cancer Registry. For patients with multiple melanomas, the case with the greatest thickness was retained. After exclusion of insitu cases (n=1329), non-registry linked cases (n= 317), unknown thickness (n= 44), and multiple melanomas (n= 334), 2951 invasive superficial spreading, acral lentiginous and nodular melanoma cases were available for analysis.

Differences in clinicopathologic data were compared using the Kruskal-Wallis test (continuous variables) and chi-squared test (categorical variables). Analysis of MSS for subtype was performed using multivariable Cox proportional hazards models and multiple imputation using chained equations (MICE) method with 10 data sets to impute values in place of missing covariate data. There were no missing values for age, sex, Breslow thickness or survival. Cause-specific hazard ratios for MSS were estimated by these models since patients were censored at the time of death from the competing risk of other causes of death. All statistical analyses were performed using Stata (Version 14.3, StataCorp, College Station, TX). Statistical significance was determined at $P \leq 0.05$. Clinicopathologic variables were included in the multivariable analysis if the overall P-value from a univariable Cox proportional hazards model was ≤ 0.1 . Age was included due to known importance as a prognostic factor⁴. As a result, five variables were included in the multivariable model (thickness, ulceration, mitotic rate, age and sex).

Table 1 describes the baseline characteristics. There were 101 ALMs, 2,272 superficial spreading melanomas (SSM) and 578 nodular melanomas (NM). ALM was more common in females. NM had higher median Breslow thickness and rate of ulceration than ALM. The median mitotic rate was fourfold higher in ALM cases than SSM. Other adverse pathological features such as lymphovascular invasion and neurotropism were more apparent in ALM than the other two melanoma subtypes. Rates of hypomelanosis were greater in ALM than SSM but were low in comparison to NM. Median follow-up (12.5% survival time) was 4.6 (2.4) years for ALM patients, 4.8 (2.4) years for NM patients and 8.0 (14.8) years for SSM patients with mortality rates of 22.7%, 32.4% and 5.4% respectively.

In an unadjusted analysis of the three subtypes, SSM patients had significantly improved MSS (HR 0.30, 95%CI 0.19-0.46, $P < 0.001$) compared to ALM and survival was similar between NM and ALM patients (HR 0.94, 95%CI 0.60-1.47, $P = 0.79$). Adjustment for the five aforementioned clinicopathologic variables accounted for most of the difference between SSM and ALM (adjusted HR 0.70, 95%CI 0.44-1.11, $P = 0.13$) and revealed significantly improved survival in NM patients compared to ALM (adjusted HR 0.50, 95%CI 0.32-0.80, $P = 0.004$). Using complete case analysis, the adjusted hazard ratios were similar (SSM v ALM HR 0.64, 95%CI 0.40-1.03, $P = 0.07$; NM v ALM HR 0.48, 95%CI 0.29-0.77, $P = 0.003$).

Hence, in this study of a prospectively collected Australian ALM cohort, multivariable subtype survival comparisons demonstrated a significantly longer adjusted survival for NM patients compared to ALM. Our findings of poorer adjusted survival of ALM patients compared to NM

suggest that ALM may have more high risk biology, in keeping with the higher rate of lymphovascular invasion in our study and another series⁵.

Genetic differences between ALM and NM may underpin distinct tumour biology and clinicopathologic differences^{6,7}. Previous matched and adjusted analyses have demonstrated poorer survival of ALM patients compared with non-ALM^{3,8} however this was not corroborated in other large prognostic studies². Nevertheless, in contrast to our study, the studies demonstrating difference lacked adjustment for ulceration and mitotic rate^{1,3} which differed significantly between NM, ALM and SSM in our patients and another report¹. This significant change in chance of survival between unadjusted and adjusted associations for subtypes demonstrates that univariable models can be misleading as they do not take into account clinicopathologic differences between subtypes.

There were limitations to our study, including potential for referral bias given the tertiary nature of our service. Molecular testing was introduced relatively recently hence mutational status was not assessed because it was incomplete for older cases.

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Abbreviations:

ALM- acral lentiginous melanoma

SSM- superficial spreading melanoma

NM- nodular melanoma

MSS- melanoma specific survival

HR- Hazard ratio

CI- Confidence interval

MICE- Multiple imputation using chained equations

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Conflict of interest:

None to declare

Table 1: Baseline clinicopathologic characteristics of 101 individuals with invasive acral lentiginous melanomas, P values for differences in distribution of clinicopathologic characteristics compared to 2,272 superficial spreading melanomas and 578 nodular melanomas

Clinicopathologic factor	ALM N=101	SSM N=2272	NM N=578	P- value ^a
Female Sex, n (%)	56 (55.4%)	1158 (51.0%)	222 (38%)	<0.001
Age, y, median (IQR)	67 (57-78)	61 (50-71)	70 (22)	<0.001
Breslow thickness, mm, median (IQR)	2 (0.9-3.3)	0.8 (0.5- 1.4)	2.8 (1.8- 4.5)	<0.001
Ulceration, n (%)	40 (41.7%)	244 (11.8%)	267 (48.6%)	<0.001
Missing values, n (% of observed)	5 (5.2%)	196 (9.4%)	29 (5.2%)	
Mitotic rate, per mm ² , n (%)	2 (0-3)	0.5 (0-2)	5 (2-10)	<0.001
0 per mm2	26 (28.6%)	959 (51.2%)	32 (6.5%)	
1-4 per mm2	47 (51.7%)	691 (36.9%)	211 (42.9%)	
5-9 per mm2	10 (11.0%)	142 (7.6%)	106 (21.5%)	
10-19 per mm2	8 (8.8%)	83 (4.4%)	143 (29.0%)	
Missing values, n (% of observed)	10 (10.1%)	397 (21.2%)	86 (17.5%)	
Regression, n (%)	8 (9.0%)	426 (22.6%)	51 (10.3%)	<0.001
Missing values, n (% of observed)	12 (13.5%)	388 (20.6%)	81 (16.3%)	
Lymphovascular	9 (9.8%)	50 (2.6%)	38 (7.7%)	<0.001

invasion, n (%)				
Missing values, n (% of observed)	9 (9.8%)	381 (20.1%)	82 (16.5%)	
Neurotropism, n (%)	6 (6.7%)	24 (1.3%)	17 (3.4%)	<0.001
Missing values, n (% of observed)	11 (12.2%)	384 (20.3%)	82 (16.5%)	
Satellite metastases, n (%)	0 (0%)	16 (0.9%)	23 (4.7%)	<0.001 ^b
Missing values, n (% of observed)	9 (9.8%)	389 (20.7%)	83 (18.7%)	
Previous melanoma, n (%)				0.15
0	88 (87.1%)	2017 (88.8%)	506 (87.5%)	
≥1	13 (12.9%)	255 (11.3%)	72 (12.5%)	
Pre-existing naevus, n (%)	10 (10.5%)	703 (34.6%)	860 (26.7%)	<0.001
Missing values, n (% of observed)	6 (6.3%)	238 (11.7%)	51 (9.7%)	
Clinically hypomelanotic, n (%)	10 (9.9%)	110 (4.8%)	135 (23.4%)	<0.001

IQR= interquartile range, ALM= acral lentiginous melanoma, NM= nodular melanoma, SSM= superficial spreading melanoma

^a P-value for difference between ALM, NM and SSM subtypes from Kruskal-Wallis H tests (for continuous variables) and chi squared tests (for categorical variables).

^b P-value for difference between ALM, NM and SSM subtypes obtained from Fisher exact test for satellite metastasis.

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