Acral melanoma: a retrospective cohort from the Brazilian National Cancer Institute (INCA)

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Acral melanoma (AM) is a rare subtype of melanoma arising on the palms, soles and subungual areas. In the Brazilian and Latin American populations, the sociodemographic and clinical-pathologic features of AM are unclear. AM tends to be more advanced at presentation because of delayed diagnoses, with poor survival. This study reports on a retrospective AM cohort from the Brazilian National Cancer Institute. We reviewed a database of 529 patients presenting with AM from 1997 to 2014 and analysed the sociodemographic and clinical-pathologic features of AM associated with overall survival and relapse-free survival. All patients were Brazilian, ranging in age from 19 to 101 years (mean 65.4; median 67.0). Two hundred and ninety-four (55.8%) patients were women. The Breslow primary lesion thicknesses ranged from 0.0 to 65.0 mm (mean 8.3 mm; median 5.0 mm). Of these patients, 43.3% had the acral lentiginous histologic subtype. Plantar was the most frequently involved site (68.5%), and ulcers and mitosis were present in 79.0 and 86.4% of these cases, respectively. Multivariate analysis results found that Breslow thickness of 1.03 (95% confidence interval: 1.01–1.05; $P = 0.01$) and ulceration of 2.70 (95% confidence interval: 1.00–7.06; $P = 0.05$) were poor prognostic indicators of overall survival. AM tumours were thick on diagnostic tests and were associated with poorer survival outcomes. Unfavourable prognosis likely derives from the delayed diagnosis compared with other melanoma subtypes. *Melanoma Res* 28:458–464 **Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Cutaneous melanoma (CM) can develop in any region of the body. When it appears on the palm, plantar or subungual surfaces, it is known as acral melanoma (AM) [1]. In the USA, as in White populations, AM is rare and accounts for ~2–3% of all cases of melanoma [2]. Asian, Hispanic, African [3–5] and Latin American populations [6–10] show higher proportions of AM compared with those of White origin.

The prognosis of AM is poor compared with non-AM. Because of the advanced presentation stage, some studies suggest that the poor survival is related to delayed diagnosis, although others suggest that AM presents a more aggressive biological behaviour [11].

In Brazil and Latin America, AM studies are scarce, and this study evaluates the clinical and sociodemographic aspects associated with overall survival (OS) and relapse-free survival (RFS) in a single-institution cohort of a cancer reference centre in the city of Rio de Janeiro.

Patients and methods

We carried out a retrospective study of patients with AM treated at the Brazilian National Cancer Institute (INCA) between 1997 and 2014. Of 3878 patients with CM, 529 had AM. All patients who presented for evaluation at INCA had their specimens pathologically reviewed at the time of presentation to confirm the diagnosis, pathologic stage and histologic features. AM was defined by anatomic location as melanoma on the palmar, plantar or subungual sites. Patients younger than 18 years of age were excluded. For the survival analysis, six (1.3%) patients with melanoma 'in-situ' were excluded, and the patient cohort until December 2014 was evaluated. The remaining 415 patients were described as the initial study population. Sociodemographic and clinicopathological factors included age, sex, race, socioeconomic status (SES), anatomic site, tumour thickness, ulceration, mitoses, surgery type, margin status, sentinel lymph node biopsy (SLNB) and positive SLNB. The socioeconomic variable of choice was education (>9 vs. ≤9 years of school attendance). Age and thickness were evaluated as continuous variables. OS and RFS were defined as the times from pathological diagnosis to the time of death or relapse, respectively, or the last follow-up. Univariate Cox regression was used to examine the associations of clinical and pathologic variables with OS and RFS. Characteristics significant in the univariate analysis with a P value of 0.10 were entered into a multivariate Cox proportional hazards model. For patients who underwent SLNB, a multivariate Cox proportional hazard model was used to examine the effect of a positive SLNB on OS and

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RFS, adjusting for known confounders such as Breslow thickness and ulceration. Statistical analysis was carried out using the free software R, version 3.2.4 (2016–03–10) (*www.R-project.org/*). This study was approved by the institutional review board.

Results

Patient sociodemographic and primary tumour characteristics are shown in Table 1. AMs constituted 13.6% of all melanomas in this population. The median age at diagnosis was 67.0 years. Most patients in this series were women (55.8%), and race was auto-referred as White (56.8%). Only 99 (18.9%) had higher education. The sociodemographic and clinicopathologic characteristics distributed by school attendance are shown in Table 2. Age, sex and the hospital where the diagnosis was made were associated with SES. Of the 527 patients, 370 had volar lesions (i.e. on palmar or plantar surfaces) and 157 had subungual lesions. The median thickness was 5.0 mm. Many patients in this series lacked documentation of ulceration (21.3%) and mitotic index (48.2%); however, when documented, many of these characteristics were unfavourable: 79% of the tumours were ulcerated and 86.4% had mitoses. Clinical or pathologic characteristics between volar and subungual melanomas

Table 1 Sociodemographic, clinical and histopathological characteristics of patients diagnosed with acral melanoma in an oncological reference centre, Rio de Janeiro, Brazil (*N* = 529)

Age (years)	
Mean ± SD	65.41 ± 14.2
Median	67.0
Sex [*n* (%)]	
Male	233 (44.2)
Female	294 (55.8)
Skin colour [*n* (%)]	
White	299 (56.8)
Non-White	227 (43.2)
SES [*n* (%)]	
Low	424 (81.1)
High	99 (18.9)
Anatomical site [*n* (%)]	
Volar	370 (70.2)
Subungual	157 (29.8)
Histological type [*n* (%)]	
Acrolentiginous	143 (44.3)
Nodular	133 (41.2)
Superficial dissemination	35 (10.8)
Others	12 (3.7)
Breslow's depth (mm)	
Range (mean ± SD)	0–65 (8.3 ± 9.4)
Median	5.0
Stage AJCC (2009)	
I	51 (12.28)
II	184 (44.3)
III	147 (35.4)
IV	16 (3.8)
NE	17 (4.1)
Distant metastasis	177 (33.4)
Multiples sites	68 (38.4)
Lung	63 (35.6)
Central nervous system	16 (9.0)
Bone	7 (4.0)
Others	12 (6.8)
Ulceration [*n* (%)]	
Yes	328 (79.0)
No	87 (21.0)
Mitosis [*n* (%)]	
Yes	236 (86.4)
No	37 (13.6)
Margins [*n* (%)]	
Negative	450 (89.1)
Positive	55 (10.9)
Sentinel lymph node biopsy [*n* (%)]	
Yes	154 (43.1)
No	203 (56.9)
Therapeutic modalities	
Surgery	477 (9.2)
Imunotherapy	51 (9.6)
Chemotherapy	81 (15.3)
Radiotherapy	93 (17.6)
Sentinel lymph node [*n* (%)]	
Positive	45 (29.2)
Negative	126 (70.8)
Median follow-up (months)	28.0

SES, socioeconomic status.

Table 2 Clinical and sociodemographic characteristics of patients diagnosed with acral melanoma, in an oncological reference centre, 1997–2014, Rio de Janeiro, Brazil (*N* = 529)

	SES		
Variables	Low	High	*P*-value
Sex (%)			
Male	32.9	11.1	0.005
Female	48.2	7.8	
Age			
Mean	67.0	58.0	< 0.001
Median	68.0	60.0	
Skin colour (%)			
White	43.8	12.8	0.08
Non-White	37.3	6.1	
Stage (%)			
0	0.6	0.2	0.34
I	8.7	3.2	
II	36.8	8.2	
III	29.9	6.6	
IV	5.2	0.6	
Histologic type (%)			
ALM	36.2	8.4	0.95
Nodular	33.0	7.8	
SSM	8.7	2.2	
Others	3.1	0.6	
Topography (%)			
Plantar	58.5	10.1	0.08
Subungual foot	13.6	5.2	
Palmar	1.3	0.4	
Subungual hand	7.6	3.3	
Hospital of diagnostic			
INCA	36.9	6.2	0.08
Public hospital	19.4	2.6	
Private hospital	25.1	9.8	
Breslow thickness			
Mean	8.5	6.9	0.11
Median	5.2	5.0	
Ulceration (%)			
Present	65.1	14.0	0.60
Absent	16.5	4.4	
Mitosis			
Present	70.1	16.2	0.19
Absent	9.6	4.1	
SLN biopsy (%)			
Yes	35.2	8.2	0.74
No	47.0	9.6	
SLN status (%)			
Positive	19.3	7.0	0.26
Negative	60.8	12.9	

ALM, acrolentiginous melanoma; INCA, Brazilian National Cancer Institute; SES, socioeconomic status; SLN, sentinel lymph node; SSM, superficial spreading melanoma.

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Table 3 Series comparison of variables by subungual melanoma and volar melanoma, 1997–2014, in an oncological reference centre, Rio de Janeiro, Brazil ($N = 157$)

	Acral melanoma		
Variables	Volar	Subungual	*P*-value
Age (years)			0.30
Mean	65.8	64.4	
Median	66	68	
Sex (%)			0.98
Male	30.9	13.3	
Female	39.3	16.5	
Skin colour (%)			0.01
White	37.4	19.4	
Non-White	32.8	10.3	
Staging (%)			0.29
Stage 0	0.4	0.4	
Stage I	7.7	4.1	
Stage II	31.4	13.6	
Stage III	27.8	8.5	
Stage IV	4.1	1.8	
Histological type (%)			0.9
Acrolentiginous	31.9	12.4	
Nodular	30.0	11.1	
Superficial dissemination	7.4	3.4	
Others	2.5	1.3	
Diagnosis location (%)			0.18
INCA	21.4	0.6	
Public hospital	31.5	3.4	
Private hospital	41.3	1.8	
Breslow's depth (mm)			0.61
Mean	8.3	8.8	
Ulceration (%)			0.94
Yes	56.2	22.6	
No	15.4	5.8	
Mitosis (%)			0.28
Yes	60.4	26.0	
No	8.1	5.5	
SLNB (%)			
Yes	27.0	11.6	0.99
No	43.3	18.2	
SLNB status (%)			0.55
Positive	20.1	6.8	
Negative	50.9	22.2	

INCA, Brazilian National Cancer Institute; SLNB, sentinel lymph node biopsy.

did not differ significantly, except for race (Table 3). Positive margins were found in 10.9% of patients, most of whom underwent re-excision. Distant metastasis occurred in 177 (33.4%) and 154 (43.1%) patients underwent SLNB, 45 (29.2%) of which were positive (Table 1).

Survival analysis

Factors associated with OS and RFS are shown in Table 4. On univariate analysis, sex ($P = 0.04$), SES ($P = 0.04$), melanoma site ($P = 0.04$), histologic type ($P = 0.02$), stage ($P < 0.001$), Breslow thickness ($P < 0.001$), mitosis ($P < 0.001$), positive margin status ($P < 0.001$), SLNB positivity ($P < 0.002$) and ulceration ($P < 0.001$) were all associated with reduced 5-year OS. Age, race and melanoma site were not associated significantly with OS in this series. The Cox proportional hazard model showed that Breslow thickness [hazard ratio (HR) 1.03, 95% confidence interval (CI): 1.03–1.05] and ulceration (HR 2.70, 95% CI: 1.00–7.06) are independent risk factors for OS. Given that SLNB status is an important prognostic factor associated with survival, a multivariate analysis was carried out on the AM patient subset who underwent SLNB ($n = 154$). These results are reported in the multivariate section of Table 4. A positive SLNB was associated significantly with OS (HR 2.91, 95% CI: 1.55–5.45) even after adjusting for age, sex, SES, Breslow thickness and ulceration.

Discussion

In Brazil and Latin America, studies on AM are scarce, and most, similar to the present study, are of single-hospital series [7–9,12]. This study represents the largest series from Brazil, with 527 cases of AM, enrolled in an oncology reference centre. In addition to the descriptive analysis of the sociodemographic and clinicopathologic data, it addressed OS and RFS determinants.

Some differences were noted in this cohort's sociodemographic characteristics (Table 1). Although the male–female ratio of 1 : 1.26 is comparable with other authors' data [2,13–16], the mean age at diagnosis (65.4 years) was older than that of other series [6,7,11,14, 16,17]. Sex differences were also present in the SES distribution. Women had statistically significantly lower SES rates than men (Table 2). Although the female melanoma survival advantage is well established, little information exists on this sex effect for AM. However, our results showed that the OS estimation by Kaplan–Meier was greater for women than men, but when adjusted by other variables, such as Breslow thickness, ulceration, and mitotic index, it was not significant. Other studies are needed to clarify this (Fig. 2a).

In this study, we evaluated SES by patient education level. The association between education and health is well established [18]. Education may help individuals recognize the signs and symptoms that necessitate prompt medical care. Our results found that patients with higher education levels were less likely to present advanced ages at AM diagnosis than those with lower education levels, although the difference between Breslow thicknesses was not significant. The SES was low in 86% of the population, and this may partly explain the thicker lesions at diagnosis and the worse prognosis in these patients (Table 2). Although SES is widely accepted as an important prognostic factor in predicting CM patient outcomes [9,19,20], it has not been studied in AM. The data presented here show that low SES yields worse outcomes than high SES. Kaplan–Meier curves showed that high SES had better outcomes than low SES (Fig. 2b). Univariate analysis showed a significant difference in OS between high and low SES levels (0.63; 95% CI: 0.63–0.99; $P = 0.04$), but this was not significant in multivariate analysis. Although this study could not ascertain the reason for this association, it is consistent with the association of education levels with late cancer presentation. Melanoma thickness at presentation is associated significantly with education level and other

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Table 4 Analysis of factors associated with overall survival and relapse-free survival in the acral melanoma cohort

	RFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.00 (0.99–1.01)	0.82	–	–	1.00 (0.99–1.01)	0.54	–	–
Sex								
Female	1.00	0.10	–	–	1.00	0.04	–	–
Male	1.25 (0.95–1.64)				1.37 (1.01–1.87)			
Skin colour								
White	1.00	0.21	–	–	1.00	0.18	–	–
Non-White	1.18 (0.9–1.56)				1.24 (0.91–1.69)			
SES								
Low	1.00	–	–	–	1.00	0.04	–	–
High	0.71 (0.48–1.03)				0.63 (0.40–0.99)			
Localization								
Volar	1.00	–	–	–	1.00	0.04	–	–
Subungual	0.83 (0.61–1.12)				0.68 (0.47–0.99)			
Histologic type								
ALM	1.00	0.02	–	–	1.00	0.02	–	–
NM	1.36 (0.96–1.92)				1.25 (0.86–1.84)			
SSM	0.37 (0.17–0.81)				0.32 (0.13–0.81)			
Other	0.33 (0.08–1.35)				0.75 (0.27–2.09)			
Stage								
I	1.00	–	–	–	1.00	< 0.001	–	–
II	3.54 (1.71–7.34)				4.85 (1.76–13.37)			
III	7.66 (3.72–15.77)				12.12 (4.44–33.10)			
IV	17.90 (7.46–42.93)				41.88 (13.59–129.10)			
Breslow (mm)	1.04 (1.03–1.05)	< 0.001	1.03 (1.01–1.05)	0.001	1.05 (1.04–1.06)	< 0.001	1.03 (1.01–1.05)	0.01
Clark level								
II/III	1.00	< 0.001	–	–	1.00	0.04	–	–
IV/V	3.12 (1.86–5.24)				1.60 (1.03–2.49)			
Ulceration								
Absent	1.00	0.001	1.00	0.001	1.00	0.02	1.00	0.05
Present	3.12 (1.86–5.24)		2.57 (1.46–4.55)		2.98 (1.18–7.56)		2.70 (1.00–7.06)	
Mitosis (n/mm^2)	1.00 (0.99–1.01)	0.19			1.06 (1.03–1.10)	< 0.001		
Margin								
Positive	1.00	–	–	–	1.00	< 0.001	–	–
Negative	0.42 (0.29–0.61)				0.39 (0.25–0.61)			
SLNB status		< 0.001		< 0.001		< 0.002		< 0.001
Negative	1.00		1.00		1.00		1.00	
Positive	2.23 (1.33–3.74)		2.56 (1.47–4.45)		2.46 (1.38–4.41)		2.91 (1.55–5.45)	

Adjusted for age, sex, education, Breslow thickness and ulceration.
ALM, acral lentiginous melanoma; LMM lentigo maligno melanoma; NM nodular melanoma; OS, overal survival; PFS, progression-free survival; RFS, relapse-free survival; SES, socioeconomic status; SLNB, sentinel lymph node; SSM superficial spreading melanoma.

SES measures [9]. Public health education efforts should focus on identifying new strategies that specifically target those subgroups of the population who have thick melanomas at diagnosis. In addition, professional educational efforts are needed to improve physician communication to lower SES individuals about early detection and to increase physician skin screening in this group [19,21–23].

In Brazil, and particularly in the city of Rio de Janeiro, miscegenation is common, thus, people with fair skin is not common. In this study, we classified race as a dichotomous variable, self-reported as White or non-White, and most were White 299 (56.8%), which was statistically significant, $\chi^2 = 9.85$ ($P = 0.001$). AM's distribution by ethnicity is curious because it affects large proportions in Afro-descendant and Asian populations in which the incidence of CM of non-acral location is low. Incidence rates by ethnic group do not appear to differ, and the difference in the proportion of AM among groups is because of the low CM incidence in these groups with higher AM proportions [3]. Previous reports of outcomes in patients with melanoma have been conflicting, with Reintgen *et al.* [24] reporting differences in stage-specific melanoma outcomes between African Americans and Whites, and Hemmings *et al.* [25] reporting no differences in outcomes in non-White versus White patients who were stratified by stage at initial diagnosis. As in the latter study, our results showed no differences in OS 1.24 (0.91–1.69) between White and non-White patients.

This study showed that the most frequent AM localization was on the plantar surface (68.5%), and it is rare on palmar surfaces (1.7%) (Table 1). These data are similar to those of other series [26–28]. Volar melanomas are of interest because they arise in areas unexposed to UV radiation [29]. Because of their anatomical locations, it has been suggested that trauma could be a risk factor for AM, which is supported by the AM distribution related to plantar region subsites [30]. Mechanical stresses such as plantar pressure and shear stress are higher on the front and rear areas than on other areas of the sole [31]. The most frequent

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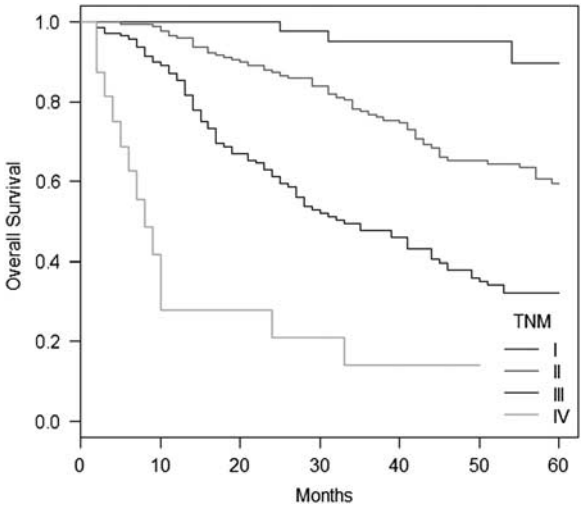
histopathologic type was ALM (44.3%). Kuchelmeister *et al.* [17] reported that all melanomas originating on palmoplantar and subungual regions were of the ALM histopathologic type, but all melanomas originating on the dorsal hands and feet were of the SSM type. However, other studies have generally reported that although ALM is a distinct histopathologic type on the palmoplantar and subungual sites, other subtypes can occur, with survival rates not significantly different between ALM and other histopathologic types at acral sites [32,33].

Fig. 1

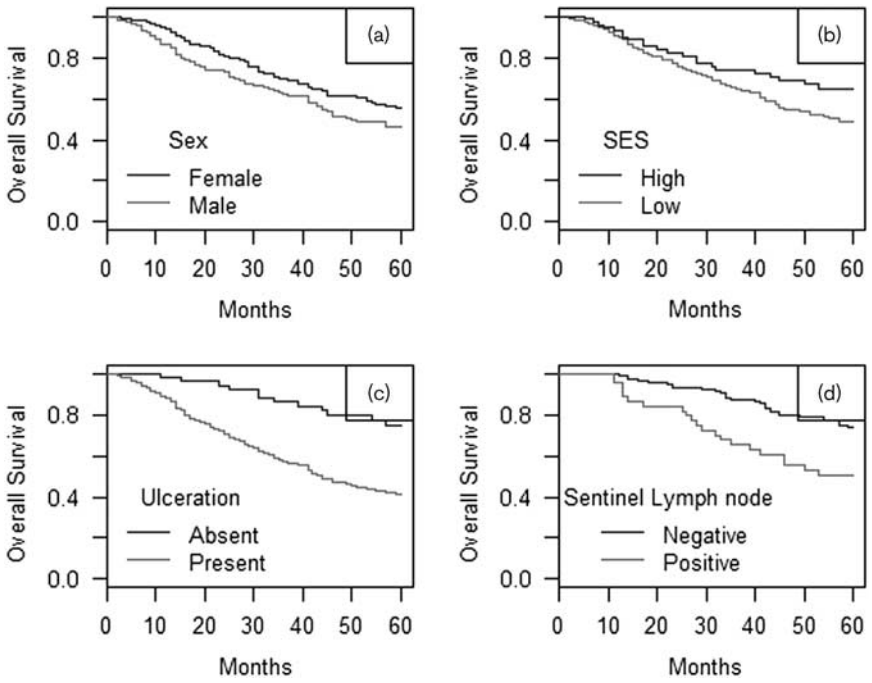


Kaplan–Meier overall survival curves for acral melanoma by stage.

The clinicopathologic characteristics of AM in this cohort indicated high ulcerative and mitotic rates 79.0 and 86.4%, respectively, and the median Breslow thickness was 5.0 mm, which might explain the lower 5-year survival rate (51.7%) (Table 1). This 5-year OS rate is similar to other Asian series, where AM was generally diagnosed at more advanced stages, with lower survival rates [13,17]. The 5-year AM survival rates reported in China and Japan, and CM in Hong Kong and Singapore, where ALM is the main type, were less than 50% [34–36].

Thickness and stage are important prognostic indicators of melanoma [37–41]. Overall, ~70% of CM were thin (0.01–1.00 mm) at diagnosis and 68% were stage I [2]. In contrast, in this study, only 8.9% of AM were classified as thin, and only 56.6% were stage I or II (Table 1). Figure 1 shows that OS by Kaplan–Meier curves and TNM AJCC staging (2009) are important factors in these patients' prognoses, and the stages are inversely proportional to survival. The differences between the survival curves were highly significant by the log-rank test ($P < 0.001$). Differences in survival curves were also statistically significant when covariates were sex ($P = 0.041$), SES ($P = 0.043$), ulceration ($P < 0.001$) or lymph node metastasis identified by SLB ($P < 0.001$) (Fig. 2a–d).

Fig. 2



Kaplan–Meier overall survival curves for acral melanoma population by (a) sex, (b) socioeconomic status (SES), (c) ulceration and (d) sentinel lymph node.

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Table 4 presents the factors associated with 5-year OS and RFS. Univariate analysis showed that sex ($P = 0.04$), SES ($P = 0.04$), lesion site ($P = 0.04$), histological type ($P = 0.02$), stage at diagnosis ($P < 0.001$), Breslow thickness ($P < 0.001$), ulceration ($P < 0.001$), mitotic index ($P < 0.001$) and surgical margin ($P < 0.00$) were associated with poor 5-year OS. Age, race and diagnosis location were not associated with poor OS. Table 4 presents the factors associated with 5-year RFS. Univariate analysis showed that histological type ($P = 0.02$), diagnostic stage ($P < 0.001$), Breslow thickness ($P < 0.001$), ulceration ($P = 0.001$) and surgical margins ($P < 0.001$) were associated with poor 5-year RFS. Age, sex, race, SES, diagnostic location, injury site and mitotic index were not associated with poor RFS. The Cox proportional risk model multivariate analysis, for the model that included age, sex, SES, ulceration and Breslow thickness, showed that Breslow thickness 1.03 (95% CI: 1.01–1.05, $P < 0.001$) and ulceration 2.70 (95% CI: 1.03–7.06, $P = 0.05$) were independent risk factors for 5-year RFS.

Nodal status, especially that of SLNB, is an important prognostic factor for CMs [42–44]. In this study, although increased Breslow thickness was an important factor in OS, SLNB status was the most predictive factor in patients with AM who underwent SLNB (Fig. 2d) (Table 4). This is the largest series to include AM with SLNB biopsy, thus confirming the prognostic significance of SLNB in AM patients. The SLNB positivity incidence was high (29.2%) for the entire cohort, consistent with other studies [11,26,45]. Thus, it appears that SLNB status in AM is an important prognostic factor.

This study had some limitations. Although AM is rare, and the series was relatively large, subpopulations were small, which limits the study's power. Considering that INCA is the main reference for cancer care in our state, and it is a reference for these patients for surgical or systemic treatment, selection bias may have been introduced. The study period was long, during which, the criteria were altered for staging patients with melanoma, which may have partially influenced the histopathologic reports. In addition, during this long period of study, SLNB for lymph node staging was introduced, thus altering the initial approach to AM.

This study also presents some strengths as this series of patients was relatively large and was the only study in Brazil and Latin America to analyse factors associated with AM patient survival. The differences between the survival curves for this AM cohort, by stages, were similar to those of AJCC (2009) for all CM. Because it was a hospital series, we collected follow-up data (sociodemographic, clinical and treatment) individually. In this cancer centre, the same group of professionals treated these patients with pre-established follow-up periods. The follow-up duration was long; thus, recurrences and deaths could be identified.

Conclusion

The present study showed that AM tumours were thick on diagnostic reports. The main prognostic factors for OS and RFS were Breslow thickness, ulceration and sentinel node biopsy status. Public health education efforts should focus on identifying new strategies that specifically target those subgroups of the population who have thick melanomas at diagnosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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