Sentinel Lymph Node Biopsy in Patients With Acral Melanoma: Analysis of 201 Cases From the Brazilian National Cancer Institute

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BACKGROUND Sentinel lymph node biopsy (SLNB) is the most powerful predictor of relapse-free survival (RFS) and overall survival (OS). No studies have evaluated survival of acral melanoma (AM) undergoing SLNB in Brazil.

OBJECTIVE The objective of this study was to investigate the factors associated with the survival of patients with AM undergoing SLNB.

MATERIALS AND METHODS Patients diagnosed with AM and submitted to SLNB were included in this study. We evaluated the epidemiologic, clinical, and histopathological data. Overall survival and RFS curves were estimated using the Kaplan–Meier method. Multivariable analyses were conducted using the Cox regression model.

RESULTS Among the 201 patients, 117 (58.2%) were female. The median age was 64 years old. Median tumor depth was 5.0 mm. Lesions were ulcerated in 134 (66.7%). Five-year OS and RFS rates were 44.6% and 38.6%, respectively. Median follow-up time was 39 months. The factors associated with OS were Breslow thickness, ulceration, and SLNB status, and for RFS, they were Breslow thickness and SLNB status.

CONCLUSION This is the largest series of AM submitted to SLNB. The 5-year OS and RFS rates were low (44.6% and 38.6%, respectively), and the main prognostic factors for OS were Breslow thickness, ulceration, and the status of SLNB.

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Sentinel lymph node biopsy (SLNB) is a minimally invasive and low-morbidity procedure for regional melanoma staging. It was introduced in the early 1990s to identify the presence of occult regional metastatic disease.[1–3] Because the sentinel node is the initial site of regional metastasis, its tumor status accurately predicts the tumor status of other nodes in the lymphatic basin.[4] Although it has been shown to provide important prognostic information in cutaneous melanoma (CM) of nonacral localization, few studies have evaluated SLNB in patients with acral melanoma (AM).[5–7] The objective of this study was to investigate the factors associated with the survival of patients with AM submitted to SLNB from the Brazilian National Cancer Institute (INCA).

Materials and Methods

A cohort of patients with AM submitted to SLNB was evaluated at Brazilian National Cancer Institute (INCA). All patients diagnosed with AM submitted to SLNB between January 1, 2000, and December 31, 2014, with ages equal to or greater than 18 years old, were included in the study. Patients were identified from the Pathology Division database, and data were extracted by means of reviewing the records and consulting histopathological reports. Demographic, socioeconomic, primary lesion, staging, treatment, and follow-up data were collected. Comparisons of categorical variables were made using *t*-test and chi-square. Continual variables were presented as mean

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TABLE 1. Sociodemographic, Clinical, and Histopathological Characteristics of Acral Melanoma Submitted a Sentinel Lymph Node Biopsy, in an Oncological Reference Center, Rio de Janeiro, Brazil (*N* = 201)

Age, yrs	
Range (average ± SD)	19–89 (62.71 ± 11.7)
Median	64.0
Sex, *N* (%)	
Male	84 (41.8)
Female	117 (58.2)
Skin color, *N* (%)	
White	110 (54.7)
Nonwhite	91 (45.3)
Anatomical site, *N* (%)	
Plantar	135 (67.2)
Palmar	5 (2.5)
Subungual hand	29 (14.4)
Subungual foot	32 (15.9)
Histological type, *N* (%)	
Acrolentiginous	135 (67.2)
Nodular	5 (2.5)
Superficial dissemination	29 (14.4)
Unknown	32 (15.9)
Breslow depth, mm	
Mean	12.2
Median	5.0
Depth (Breslow) (T)	
Tis	2 (1.0)
T1	12 (6.0)
T2	22 (10.9)
T3	48 (23.9)
T4	107 (53.2)
Unknown	10 (5.0)
Clark, *N* (%)	
I	2 (1.0)
II	8 (4.0)
III	34 (17.0)
IV	86 (42.8)
V	50 (24.9)
Unknown	21 (10.3)
Ulceration, *N* (%)	
Yes	134 (66.7)
No	36 (17.9)
Unknown	31 (15.4)
Mitosis, *N* (%)	
Yes	106 (53.0)
No	18 (9.0)
Unknown	76 (38.0)
Margins, *N* (%)	
Negative	189 (94.0)
Positive	12 (6.0)
Interferon	
Yes	21 (10.4)
No	180 (89.6)
Sentinel lymph node, *N* (%)	
Positive	60 (29.9)
Negative	141 (70.1)
Nonsentinel lymph node, *N* (%)	
Positive	27 (45.0)
Negative	33 (55.0)
Median 5-year overall survival (%)	44.6
Median 5-year relapse-free survival (%)	38.6
Median follow-up (mo)	39
Follow-up <6 mo	10 (5.0)

with SD and median. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. An evaluation of survival was made by means of Cox proportional risk model to evaluate the associations between independent variables and overall survival (OS) or relapse-free survival (RFS). p-value <.05 was adopted as significant. Free software R version 3.2.4 was used for the statistical analysis. This study was submitted and approved by the INCA Ethics and Research Committee.

Results

The sociodemographic, clinical, and histopathological characteristics are summarized in Table 1. The median age was 64 years old, 58.2% were female, and 54.7% had fair skin. Of the tumors, 67.2% were located in plantar region, with a 5.0-mm median depth, 2 (1.0%) were in situ, 12 (6.0%) T1, 22 (10.9%) T2, 48 (23.9%) T3, 107 (53.2%) T4, and 10 (15.9%) were unknown; 1.0% were Clark I, 4.0% Clark II, 17.0% Clark III, 42.8% Clark IV, 24.9% Clark V, and 10.3% were unknown. A total of 15.9% did not present information about histological type, and acrolentiginous (ALM) was the most frequent (67.2%). A large proportion of patients in this series lacked documentation of the presence of ulceration (15.4%) and mitotic index (38.0%). However, when documented, many of these characteristics were unfavorable: 66.7% of tumors were ulcerated, and

TABLE 2. Correlation of the SLNB Status With Sociodemographic, Clinical, and Histopathological Factors in 201 Patients With Acral Melanoma From Brazilian National Cancer Institute (INCA)

	SLNB Status		
	Negative	*Positive*	p
Age (yrs)			.45
<60	47	24	
≥60	94	36	
Sex			.62
Female	80	37	
Male	61	23	
Skin color			.30
White	81	29	
Nonwhite	60	31	
Anatomical site			.37
Plantar	93	42	
Palmar	2	3	
Subungual hand	22	7	
Subungual foot	24	8	
Breslow thickness (mean), mm	10.3	16.7	.07
Clark			.09
I	2	0	
II	7	1	
III	29	5	
IV	60	26	
V	29	21	
Unknown	14	7	
Breslow (T)			.04
In situ	2	0	
T1	12	0	
T2	19	3	
T3	34	14	
T4	68	39	
Unknown	6	4	
Ulceration			.04
No	31	5	
Yes	87	47	
Unknown	23	8	
Mitosis			.15
Negative	16	2	
Positive	74	32	
Unknown	50	26	
Margins			.95
Negative	132	57	
Positive	9	3	

SLNB, sentinel lymph node biopsy.

53.0% had mitoses. Positive margins were seen in 6.0% of patients. Sentinel lymph node biopsy was conducted in 201 patients and was positive in 60 (29.9%). Non-SLNB was positive in 27/60 (45.0%) (Table 1). Breslow thickness and ulceration were associated with sentinel lymph node (SLN) metastasis, and it was significant (Table 2). Only 21 (10.4%) patients were treated with interferon. Median

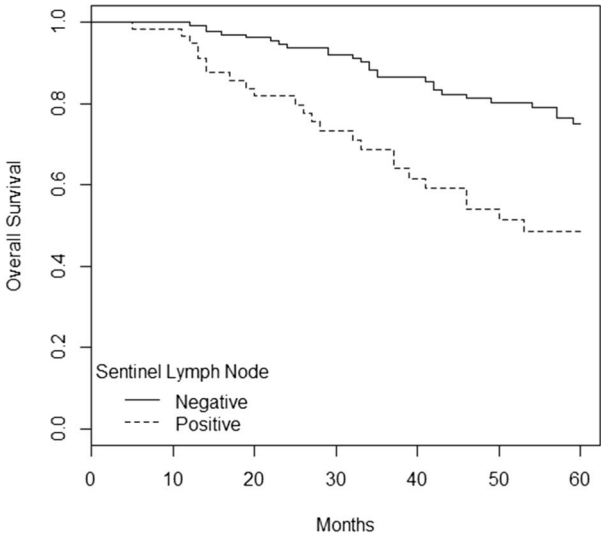

Figure 1. Kaplan–Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of sentinel lymph node.

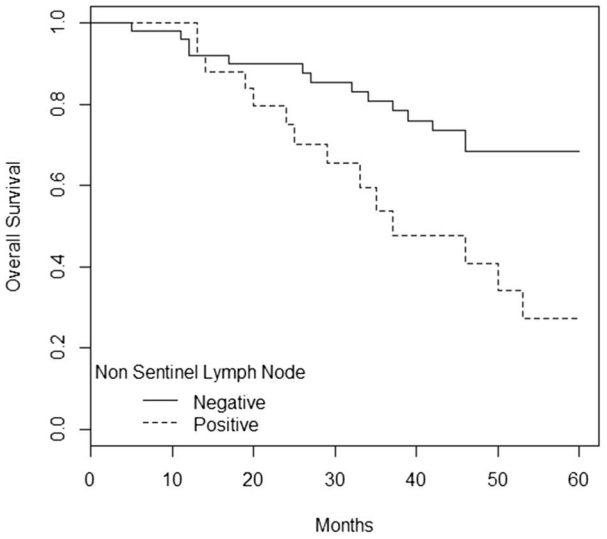

Figure 3. Kaplan–Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of nonsentinel lymph node.

follow-up time was 39.0 months. The OS and RFS rates for 5 years were 44.6% and 38.6%, respectively.

It is observed in Figures 1, 2, and 3 by the Kaplan–Meier analysis of the OS curve that status of SLNB, ulceration, and status of non-SLNB are important prognostics factors. The OS curve differences of positive SLNB (Figure 1) (p = .001), ulceration (Figure 2) (p = .002), and positive non-SLNB (Figure 3) (p = .0002) are statistically significant by the log-rank test. The RFS curve differences are also statistically significant when the variables are either status of SLNB (p = .002) (Figure 4), ulceration (p = .004) (Figure 5), and positive non-SLNB (p = .004) (Figure 6).

The factors associated with 5-year OS are presented in Table 3. Univariate analysis showed that Breslow thickness (p = .001), Clark's level (p = .05), ulceration (p = .05), mitosis (p = .001), positive SLNB (p = .05), and positive non-SLNB (p = .01) were associated with a worse 5-year OS. Age, race, sex, anatomical

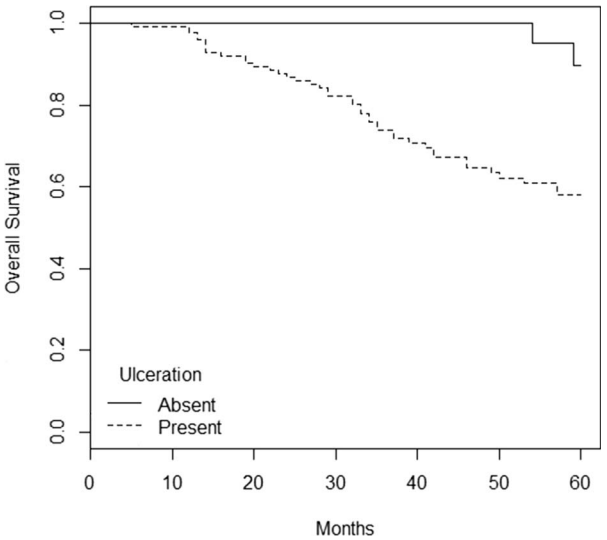

Figure 2. Kaplan–Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by ulceration.

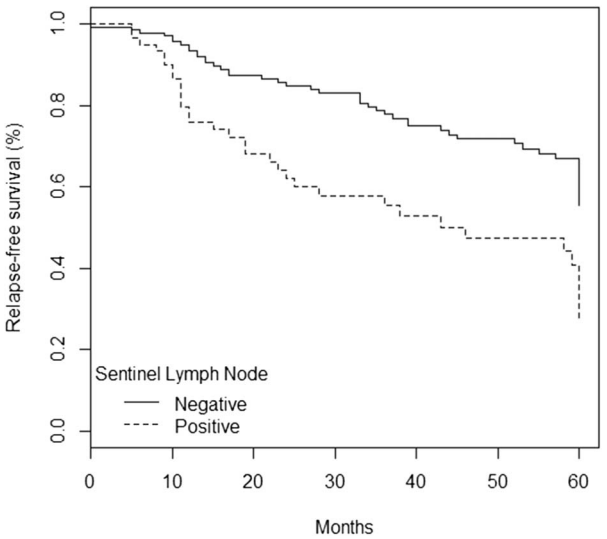

Figure 4. Kaplan–Meier relapse-free survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of sentinel lymph node.

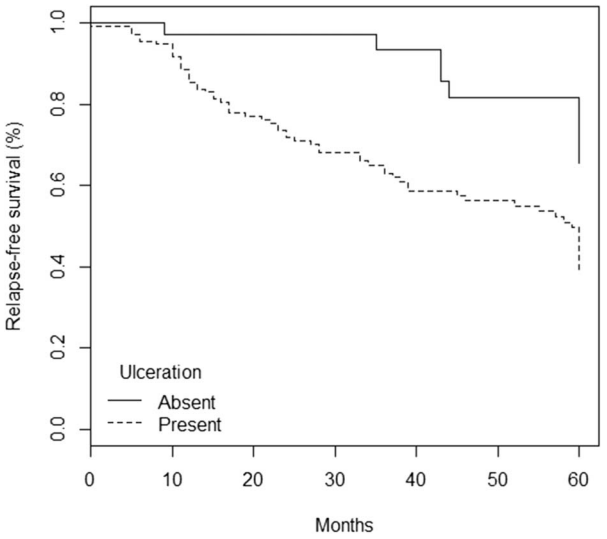

Figure 5. Kaplan–Meier relapse-free survival curves for acral melanoma submitted a sentinel lymph node biopsy by ulceration.

site, and mitosis were not associated with worse OS. Multivariate analysis showed that Breslow thickness, ulceration, and status of SLNB were independent risk factors to the 5-year OS.

The factors associated with a 5-year RFS are presented in Table 4. Univariate analysis showed that Breslow thickness (p = .001), Clark's level (p = .01), ulceration (p = .01), positive SLNB (p = .001), and a positive non-SLNB (p = .001) were associated with a worse 5-year RFS. Age, sex, race, place of diagnosis, anatomical site, non-SLNB, and mitotic rate were not associated with worse RFS. Multivariate analysis by Cox proportional risk model, using the model that included variable mitosis, Clark's level, Breslow thickness, non-SLNB, and ulceration, demonstrated that Breslow thickness, 1.05 (confidence interval [CI] 95% 1.03–1.07, p = .001), and positive SLNB, 2.12 (CI 95% 1.32–3.41, p = .01), are independent risk factors.

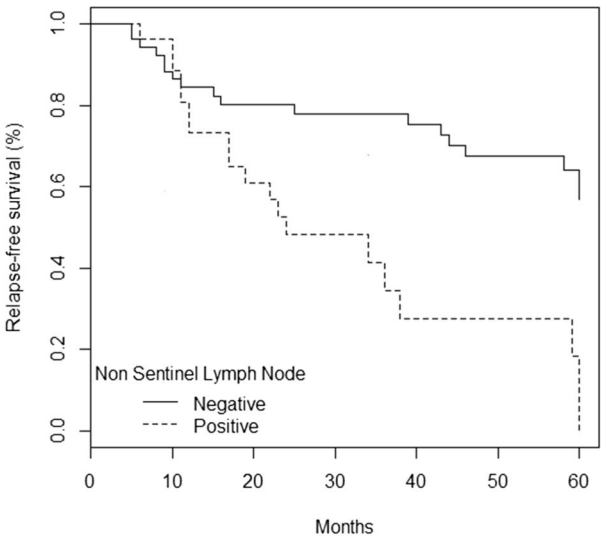

Figure 6. Kaplan–Meier relapse-free survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of nonsentinel lymph node.

Discussion

Sentinel lymph node biopsy was introduced in the management of CM by Morton in 1992.[1] Although its prognostic value is well established for CM Stage I and II,[4] few studies have evaluated its value in the management of AM.[5–7] Melanoma is known as AM when located in the palmar, plantar, or subungual region. Acral melanoma is rare and represents 2% to 3% of CM in the Caucasian population and approximately 20% of the melanomas among Afro-descendants and Asians.[4–6] In Latin America, the available data are mostly from hospital-based studies. There are few population-based cancer records in our continent, conferring a lack of accurate and reliable information to be analyzed and used for early diagnosis and preventive actions.[8] In these countries, the AM ratio is also high, and like other continents, lesions are deep at the time of diagnosis, and the prognosis is worse.[9,10]

In this study, the mean age was 62.7, ranging from 18 to 89 years old, and the median was 64 years old. As in other studied series, the age was advanced at the time of diagnosis.[9–12] The fact that the population, and even health professionals, lack awareness about rare diseases, coupled with the difficulties in mobilization and access to health services, may lead to a delay in the diagnosis of elderly patients with AM.

The incidence in females 117 (58.2%) was slightly higher. The F:M ratio was 1.39:1.00. Although in this series, the AM occurrence in females was higher than in males, and this ratio has also been found in other series,[13–17] it seems there was no difference in the occurrence rates related to sex.

TABLE 3. Factors Associated With 5-Year Overall Survival in Patients With Acral Melanoma Submitted a Sentinel Lymph Node Biopsy, in an Oncological Reference Center, Rio de Janeiro, Brazil (*N* = 201)

	Univariate		*Multivariate*	
	HR (95% CI)	p	*HR (95% CI)*	p
Age, yrs	1.00 (0.97–1.03)	.984		
Age, yrs				
<60	1.00			
≥60	0.96 (0.54–1.71)	.899		
Sex				
Female	1.00			
Male	0.89 (0.50–1.58)	.693		
Skin color				
White	1.00			
Nonwhite	1.50 (0.86–2.61)	.154		
Place of diagnostic				
Public hospital	1.00			
Private hospital	0.88 (0.43–1.84)	.740		
INCA	0.61 (0.29–1.82)	.190		
Anatomical site				
Subungual	1.00			
Volar	1.82 (0.89–3.75)	.103		
Breslow thickness, mm	1.07 (1.05–1.11)	.001	1.06 (1.02–1.09)	.001
Clark				
II/III	1.00			
IV/V	2.81 (1.19–6.65)	.050		
Ulceration				
No	1.00			
Yes	7.28 (1.76–30.13)	.010	4.77 (1.13–19.85)	.05
Mitosis	1.10 (1.04–1.15)	.001		
Sentinel lymph node status				
Negative	1.00			
Positive	2.82 (1.62–4.91)	.001	2.06 (1.13–3.78)	.05
Nonsentinel lymph node status				
Negative	1.00			
Positive	2.77 (1.31–5.88)	.010		

CI, confidence interval.

In our country, and particularly in the city of Rio de Janeiro, miscegenation is large, reducing the risk of having fair skin. In this study, we classified race as a dichotomous variable, as fair or colored skin, and most cases had fair skin 110 (54.7%). Acral melanoma distribution by ethnicity is interesting, in that it occurs in great proportions in groups with low occurrence of CM. As a matter of fact, it seems that there is no difference in the occurrence rates among ethnic groups, and the AM ratio difference among the groups is due to the low occurrence of CM in these groups.[18]

In some international series, tumors are thick at the time of diagnosis (2.1–4.7 mm),[3,10,13,14,19] and 5-year OS rates are low (39.0% to 76.0%).[2–4,10,13–15] For CM, Breslow thickness was associated with OS and RFS.[19] In most AM series, the lesion was deep at the time of diagnosis (1.75–3.2 mm),[10,14,16] which could explain the worse prognosis compared with CM. In this series, the 5-year OS and RFS rates were 44.6% and 38.6%, respectively (Table 1). Mean and median thicknesses were 12.2 and 5.0 mm, respectively, showing that the diagnosis was also late (Table 1). As in other series,[11,16,17] Breslow thickness was associated

TABLE 4. Factors Associated With 5-Year Relapse-Free Survival in Patients With Acral Melanoma Submitted a Sentinel Lymph Node Biopsy, in an Oncological Reference Center, Rio de Janeiro, Brazil (*N* = 201)

	Univariate		*Multivariate*	
	HR (95% CI)	p	*HR (95% CI)*	p
Age, yrs	1.00 (0.98–1.02)	.753		
Age, yrs				
<60	1.00			
≥60	1.00 (0.63–1.58)	.996		
Sex				
Female	1.00			
Male	1.16 (0.75–1.80)	.509		
Skin color				
White	1.00			
Nonwhite	1.25 (0.81–1.94)	.318		
Place of diagnostic				
Public hospital	1.00			
Private hospital	0.93 (0.52–1.66)	.800		
INCA	0.62 (0.34–1.12)	.115		
Anatomical site				
Subungual	1.00			
Volar	1.53 (0.91–2.59)	.11		
Breslow thickness, mm	1.06 (1.04–1.08)	.001	1.05 (1.03–1.07)	.001
Clark				
II/III	1.00			
IV/V	2.17 (1.19–3.97)	.050		
Ulceration				
No	1.00			
Yes	2.79 (1.33–5.82)	.010		
Mitosis	1.10 (1.06–1.14)	.001		
Sentinel lymph node status				
Negative	1.00			
Positive	2.33 (1.49–3.64)	.001	2.12 (1.32–3.41)	.01
Nonsentinel lymph node status				
Negative	1.00			
Positive	3.50 (1.77–6.94)	.001		

CI, confidence interval.

with OS, 1.06 (CI 95% 1.02–1.09; $p = .001$), and RFS, 1.05 (CI 95% 1.03–1.07; $p = .001$) (Tables 3 and 4).

The survival rate in patients with an ulcerated tumor is lower than in those with a tumor without ulceration at the same stage "T" and is equivalent to those with a nonulcerated tumor at a higher stage T.[20] Some series showed an association between ulceration presence and AM survival, and the ulceration rate ranged from 30% to 34%.[13,16,20] Therein, ulcerated tumors presented lower survival. In this series, the ratio of ulcerated lesions, 134 (66.7%), was higher than in the published series, and ulceration presence was significant for OS, 4.77 (CI 95% 1.13–19.85; $p = .05$) (Tables 3).

The clinical condition of regional lymph nodes is considered an important prognostic factor for CM, especially when determined by SLNB.[20–22] Few studies evaluated the role of SLNB in patients with AM. However, all of them revealed that biopsy positivity are worse prognostic factors for both RFS and

OS.[5,6,23] Sentinel lymph node biopsy was performed for patients with performance status 0–II who presented with SM larger than 1.0 mm or for those between 0.75 and 1.0 mm with other worse prognostic factors such as ulceration or a mitotic rate different from zero and without clinical evidence of distant metastasis. In the present series, 201 patients were submitted to SLNB and were positive in 60 (29.9%). Although the study population was not large, the incidence of SLNB positivity was high and consistent with other studies.[5,6,22] As in other studies, tumor thickness and ulceration were dominant independent predictors of SLN metastases[24] (Table 2). In the current study, 5-year OS rates in patients with SLNB negative versus positive were 75.1% and 48.7%, respectively. Similarly, 5-year RFS was significantly poorer in patients with positive SLNB (27.2%) (Figure 1, 4). Sentinel lymph node metastases was significantly associated with OS 2.06 (95% CI 1.13–3.78, $p = .05$) and RFS 2.12 (CI 95% 1.32–3.41, $p = .01$) after adjusted for Breslow thickness and ulceration (Tables 3 and 4). This is the largest series of AM with SLNB and confirms the prognostic value of SLN metastases in patients with AM.

Nonsentinel lymph node (NSLN) positivity is one of the most significant prognostic factors in patients with Stage III melanoma. Leung and colleagues suggested that subclassification of melanoma by NSLN tumor status should be considered for the American Joint Committee on Cancer staging system. Few studies have evaluated the status of NSLN at patients with AM. Like other series, the positive rate for additional metastatic lymph nodes by further CLND was high 45.0% (Table 1).[25] In the current study, 5-year OS rates in patients with NSLN negative versus positive were 68.4% and 27.2%, respectively. Similarly, 5-year RFS was significantly poorer in patients with positive NSLN (0%) (Figure 3, 6). This series confirms the prognostic value of NSLN metastases in patients with AM.

There are some limitations in this study. Although this series is relatively large, subpopulations are small and there are prognostic variables (mitosis, ulceration, and thickness) with missing data, limiting the power of the study. Considering that this center is a main reference in oncologic assistance and the unique that use the SLNB for staging melanoma in the state, there may have been an introduction of selection bias. Study time was long, and during this time, there were changes in the criteria for patients with staging melanoma, which may have influenced anatomopathological reports.

However, this study presents some strength, as it is the largest series that analyzes SLNB in a cohort of AM. Being a hospital series, the data related to demographics, clinical treatment, and follow-up aspects were individually collected. In this oncologic center, the patients were subjected to treatment by the same group of professionals after a protocol with preestablished follow-up periods. The follow-up term was long; thus, it was possible to identify relapses and deaths that occurred mostly in the first 2 years.

Conclusion

This is the largest series of AM submitted an SLNB. The 5-year OS and RFS rates were low (44.6% and 38.6%, respectively). Breslow thickness, ulceration, and positive SLNB were associated with poorer OS and RFS.

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