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RESEARCH ARTICLE

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Subungual melanoma: A retrospective cohort of 157 cases from Brazilian National Cancer Institute

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Abstract

Background: Subungual melanoma (SM) is rare. The lesions are thick at the time of diagnosis. Few studies have evaluated SM in Brazil.

Objective: The objective of this study was to investigate the factors associated with the survival of SM patients from the Brazilian National Cancer Institute.

Methods: One-hundred and fifty-seven patients diagnosed with SM were included in this study. We evaluated the epidemiologic, clinical, and histopathological data. Overall survival (OS) and relapse-free survival (RFS) curves were computed using the Kaplan-Meier method. Multivariable analyses were conducted using the Cox proportional hazard regression model.

Results: Among the 157 patients, 87 (55.4%) were female. The median age was 68 years old. Median tumor depth was 6.0 mm. Lesions were ulcerated in 94 (59.9%). OS and RFS rates for 5 years were 61.0% and 41.8%, respectively. Median follow-up time was 28 months. The factors associated with OS were Breslow thickness and ulceration, and for RFS, they were the anatomical site, Breslow thickness, and ulceration.

Conclusion: This is the largest series of SM patients. The 5-year OS and RFS rates were low (61.0% and 48.2%, respectively), and the main prognostic factors for OS were Breslow thickness and ulceration.

KEYWORDS
prognosis, subungual melanoma, survival

1 | INTRODUCTION

Subungual melanoma (SM) is rare and represents only 1% to 3% of all melanomas.[1-3] Little is known about the risk factors, and ultraviolet radiation is unlikely to be a determinant factor of its appearance. Some authors suggest that trauma may be a risk factor.[4] Classical treatment is amputation; however, functional surgery has been realized in superficial lesions.[5-7] SM prognosis has not been studied much and seems to be associated with the same survival determinant factors as cutaneous melanoma (CM).[8] The objective of this study was to evaluate the factors associated with SM survival.

2 | METHODOLOGY

A cohort of patients with SM was evaluated at the Brazilian National Cancer Institute (INCA). All patients diagnosed with SM between January 1, 1997 and December 31, 2014, with ages equal to or greater than 18 years old, were included in the study for descriptive analysis. For survival analysis, the cohort of 103 SM patients diagnosed between January 1997 and December 2011 was evaluated. 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,

TABLE 1 Sociodemographic, clinical, and histopathological characteristics of patients diagnosed with subungual melanoma, in an oncological reference center, Rio de Janeiro, Brazil (N = 157)

Age, y	
Range (average ± SD)	19-94 (64.4 ± 15.8)
Median	68.0
Gender, n (%)	
Male	70 (44.6)
Female	87 (55.4)
Skin color, n (%)	
White	102 (65.0)
Nonwhite	54 (34.4)
Unknown	1 (0.6)
Diagnoses first location, n (%)	
Public hospital	40 (25.5)
Private hospital	52 (33.1)
INCA	56 (35.7)
Unknown	9 (5.7)
Anatomical site, n (%)	
Foot	100 (63.7)
Hand	57 (36.3)
Histological type, n (%)	
Acrolentiginous	40 (25.5)
Nodular	36 (22.9)
Superficial dissemination	11 (7.0)
Others	4 (2.5)
Unknown	66 (42.1)
Breslow depth, mm	
Mean	8.7
Median	6.0
Depth (Breslow) (T)	
Tis	2 (1.2)
T1	15 (9.6)
T2	13 (8.3)
T3	20 (12.7)
T4	78 (49.7)
Unknown	29 (18.5)
Clark, n (%)	
I	2 (1.3)
II	11 (7.0)
III	18 (11.5)
IV	45 (28.7)
V	51 (32.5)
Unknown	30 (19.0)
Ulceration, n (%)	
Yes	94 (59.9)
No	24 (15.3)
Unknown	39 (24.8)
Mitosis, n (%)	
Yes	71 (45.2)
No	15 (9.6)
Unknown	71 (45.2)
Margins, n (%)	
Negative	140 (89.2)
Positive	13 (8.3)
Unknown	4 (2.5)
Sentinel lymph node biopsy, n (%)	
Yes	61 (38.9)
No	96 (61.1)
Interferon	
Yes	13 (8.3)
No	144 (91.7)
Sentinel lymph node, n (%)	
Positive	16 (26.2)
Negative	45 (73.8)
5-y overall survival, %	61.0
5-y relapse-free survival, %	48.2
Median follow-up, mo	28
Follow-up < 6 mo	9 (5.7)

and follow-up data were collected. Comparisons of categorical variables were made using t test and χ^2-test. Continuous variables were presented as an average with standard deviation 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 the Cox proportional risk model to evaluate the associations between independent variables and OS or relapse-free survival (RFS). $P < 0.05$ 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.

3 | RESULTS

The sociodemographic, clinical, and histopathological characteristics are summarized in Table 1. The median age was 68 years old, 55.4% were female and 65.0% had fair skin. Of the tumors, 63.7% were in the foot, with a 6.0 mm median depth. The acrolentiginous (ALM) type was the most frequent (25.5%). A large proportion of patients in this series lacked documentation of the presence of ulceration (24.8%), and mitotic index (42.5%). However, when documented, many of these characteristics were unfavorable: 59.9% of tumors were ulcerated and 42.5% had mitoses. Positive margins were seen in 8.3% of patients. SLNB was conducted in 61 patients and was positive in 16 (26.2%) (Table 1). There were no significant differences in the clinical or pathologic characteristics between hand and foot subungual sites. Only 13 (8.3%) patients were treated with interferon.

The cohort of 103 SM patients diagnosed between January 1997 and December 2011, with follow-ups for up to 60 months, presented a median follow-up time of 33.0 months (mean of 35.1 months, ranging from 0 to 60 months). The OS and RFS rates for 5 years were 61.0% and 48.2%, respectively.

It is observed in Figure 1 by Kaplan-Meier analysis of the OS curve that ulceration and tumor depth are important prognostics factors. The OS curve differences of ulceration ($P = 0.006$) and tumor

depth ($P = 0.0002$) are statistically significant by the log-rank test. The RFS curve differences are also statistically significant when the variables are either anatomical site ($P = 0.002$), ulceration ($P = 0.0007$) and tumor depth ($P = 0.002$) (Figure 2).

The factors associated with 5-year OS are presented in Table 2. Univariate analysis showed that Breslow thickness ($P = 0.001$), the Clark level ($P = 0.01$), ulceration ($P = 0.05$), status nodal and metastasis in SLNB were associated with a worse 5-year OS. Age, race, gender, lesion site, and mitosis were not associated with worse OS. Multivariate analysis showed that Breslow thickness and ulceration were independent risk factors to the 5-year OS, adjusted by the Clark level, ulceration, and Breslow thickness.

The factors associated with a 5-year RFS are presented in Table 3. Univariate analysis showed that anatomical site ($P = 0.003$), the Clark level ($P = 0.01$), Breslow thickness ($P = 0.001$), ulceration ($P = 0.01$) and a positive SLNB ($P = 0.05$) were associated with a worse 5-year RFS. Age, gender, race, place of diagnosis, and mitotic rate were not associated with worse RFS. Multivariate analysis by the Cox proportional risk model, using the model that included variable anatomical sites, the Clark level, Breslow thickness, and ulceration, demonstrated that Breslow depth, 1.04 (95% CI, 1.01 to 1.07; $P = 0.04$), ulceration, 10.14 (95% CI, 1.34 to 76.81; $P = 0.02$) and SM located on the foot, 2.26 (95% CI, 1.08 to 4.70; $P = 0.03$), are independent risk factors.

4 | DISCUSSION

Melanoma is known as acral melanoma (AM) when located in the palmar, plantar, or subungual region. SM is rare and represents 2% to 3% of CM in the Caucasian population and approximately 20% of the melanomas among Afro-descendants and Asians.[1,9-11] 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.[12] In these countries, the AM ratio is also high and similar to other continents, lesions are deep at the time of diagnosis, and the prognosis is worse.[13,14]

In this study, the mean age was 64.4, ranging from 19 to 94 years old, and the median was 68 years old. As in other studied series, the age was advanced at the time of diagnosis.[11,14-17] The time between onset of symptoms and diagnosis ranged from 1.4 to 2.2 years.[11,16-18] 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 SM.

The incidence in females was slightly higher, at 87 (55.4%). The F:M ratio was 1.23:1.00. Although in this series, the SM occurrence in females was higher than in males, and this ratio has also been found in other series,[11,15-19] it seems there was no difference in the occurrence rates related to gender. In the study of Bradford et al,[20] the only

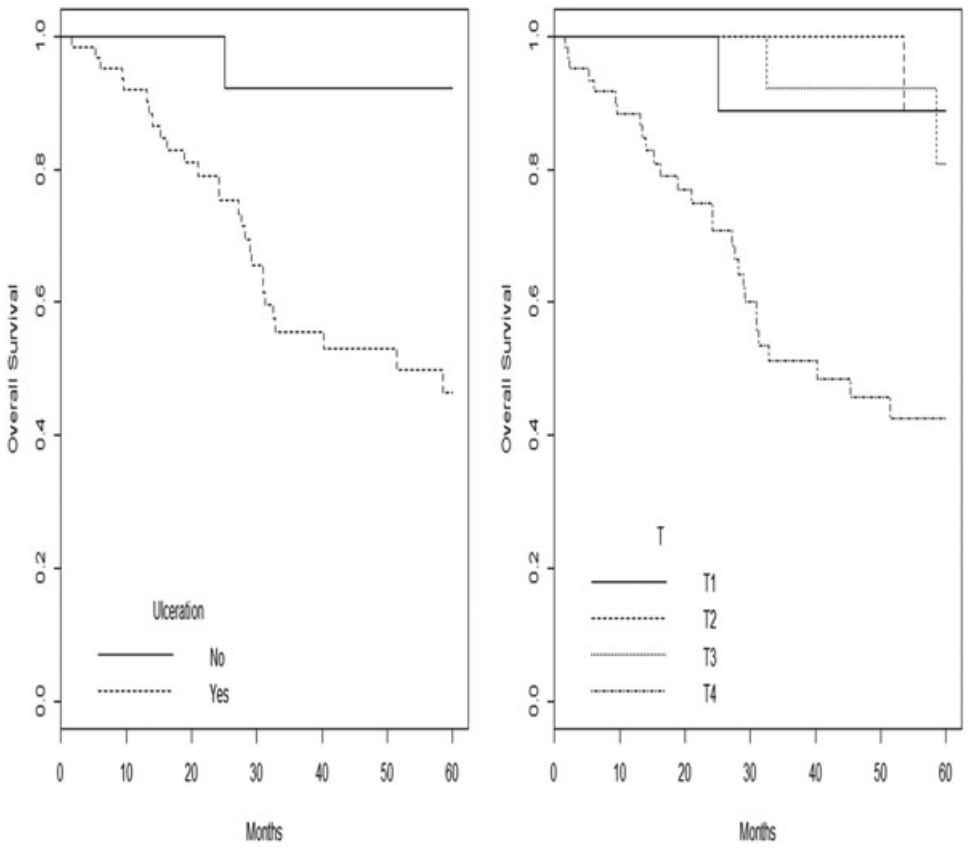

FIGURE 1 Kaplan-Meier overall survival curves for subungual melanoma by ulceration and depth

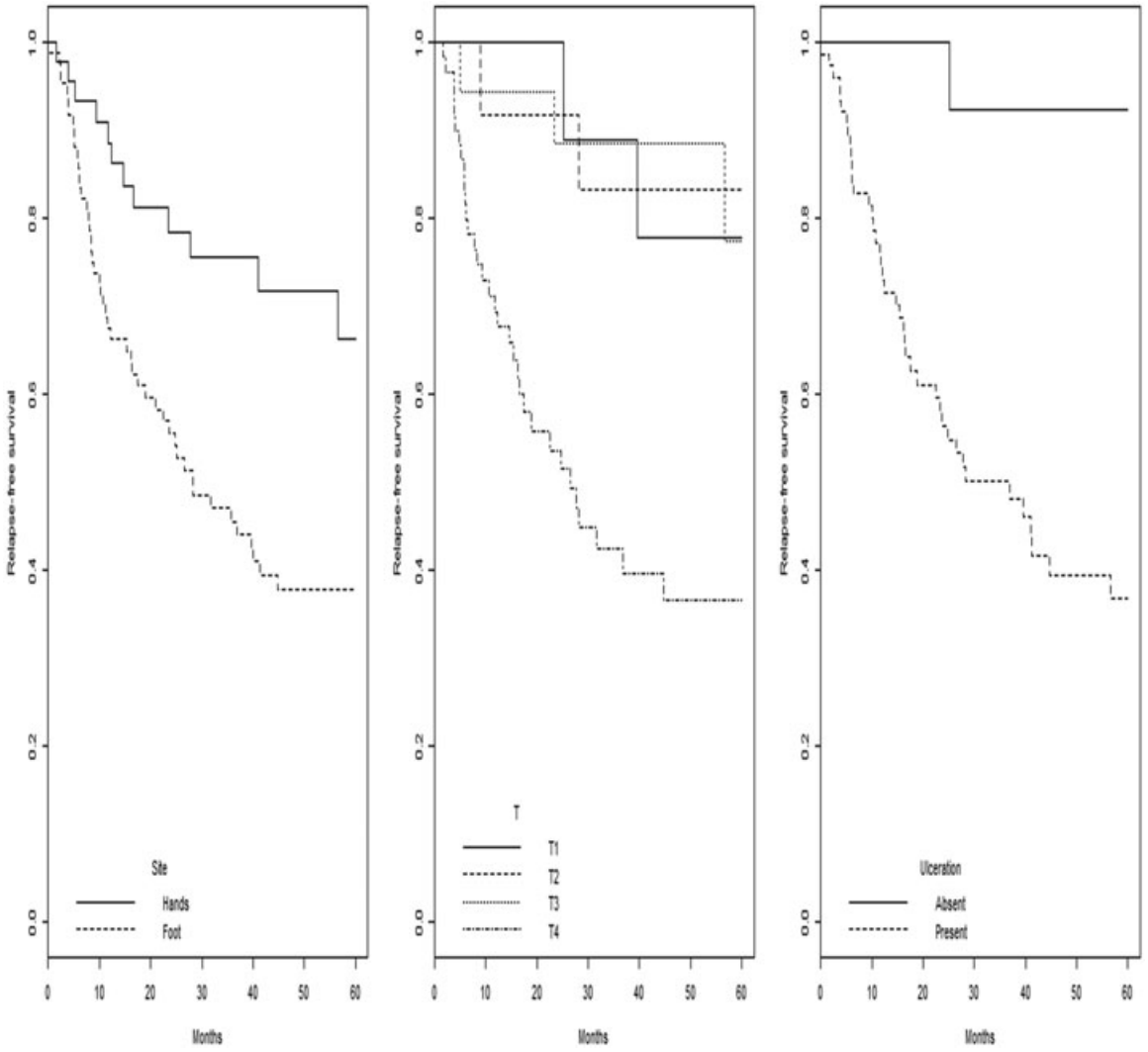

FIGURE 2 Kaplan-Meier relapse-free survival curves for the subungual melanoma by anatomical site, ulceration and depth

population-based and largest study (N = 1413 cases) up until the present date, the occurrence rate of AM was similar among men and women (1.9 and 1.8 of 1 000 000 people per year, respectively); furthermore, in other studies about SM, the occurrence in men was even higher.[16,17]

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 102 (65.0%). SM 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 SM ratio difference among the groups is due to the low occurrence of CM in these groups.[21]

Information about the hospital where the diagnosis was made was available for 146 cases. Most were in INCA, 56 (35.7%), followed by private hospitals, 52 (33.1%), and public hospitals, 40 (25.5%) (Table 1). No relation was observed between the hospital of initial diagnosis and survival, 0.74 (0.31 to 1.80). Hospital of diagnosis had not been studied yet as a prognostic factor, and although we have not observed differences in survival, other studies should be made to determine whether there are any differences when these patients are initially addressed at reference oncologic centers.

Although Nguyen et al[16] reported the hand as the major anatomical location of SM, most series show that lower limbs are more frequently affected,[2,15,17] and this difference was also observed in this study. In this series, as in other world series, the most frequent histologic type of SM was ALM, 40 (25.5%) (Table 1).[15,18]

SM studies in Brazil are scarce. Most of them are small, hospital-based series, and none of them have evaluated survival. In some international series, tumors are thick at the time of diagnosis (median 2.1 to 5.0 mm),[3,13-16] and 5-year OS rates are low (39.0% to 76.0%).[1-3,11,14,16,17] For CM, Breslow thickness was associated with OS and RFS.[22] In most SM series, the lesion was deep at the time of diagnosis (1.75 to 3.2 mm),[11,14-16,18] which could explain the worse prognosis compared to CM. In this series, the 5-year OS was 61.0%, which is similar to what Nguyen et al[16] reported (60.5%), but the 5-year RFS was lower than what they reported (48.2% × 57.1%) (Table 1). Mean and median thicknesses were 8.7 and 6.0 mm, respectively,

TABLE 2 Factors associated with 5-year overall survival in patients with subungual melanoma, 1997 to 2011, Rio de Janeiro, Brazil (N = 103)

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.00 (0.98-1.02)	0.988		
Gender				
Female	1.00			
Male	1.24 (0.66-2.32)	0.500		
Skin color				
White	1.00			
Nonwhite	0.71 (0.35-1.40)	0.320		
Place of diagnostic				
Public hospital	1.00			
Private hospital	1.01 (0.43-2.37)	0.977		
INCA	0.74 (0.31-1.80)	0.513		
Anatomical site				
Hand	1.00			
Foot	1.29 (0.65-2.55)	0.462		
Breslow thickness, mm	1.08 (1.05-1.11)	0.001	1.07 (1.03-1.10)	0.001
Clark		0.010		
II/III	1.00			
IV/V	7.43 (1.77-31.13)			
Ulceration		0.050		
No	1.00			
Yes	9.49 (1.29-70.00)		7.62 (1.03-56.70)	0.050
Mitosis	1.00 (0.99-1.01)	0.360		
Nodal status				
Negative	1.00	0.002		
Positive	4.58(2.27-9.25)			
SLNB*				
Negative	1.00			
Positive	3.72 (0.99-14.12)	0.050		

Abbreviations: INCA, Brazilian National Cancer Institute; SLNB, sentinel lymph node biopsy.
*Analysis of 61 patients.

showing that the diagnosis was also late (Table 1). As in other series,[8,11,14,22] Breslow thickness was associated with OS, 1.07 (95% CI, 1.03 to 1.10; $P = 0.001$), and RFS, 1.04 (95% CI, 1.01 to 1.07; $P = 0.04$) (Tables 2 and 3) (Figures 1 and 2).

In this study, as in other series, the diagnosis of SM was made when the disease was already advanced at the primary site.[11,15,16] Some authors in the past considered the Clark invasion level IV/V as a factor of worse prognosis for OS and RFS compared to invasion levels II/III.[23] Although the Clark level was not considered as an important variable in the eighth edition of the melanoma staging manual,[22] it is routinely described in histopathological records. In this series, it was informed in 81.0% of patients, and as in other series, most lesions (61.2%) were Clark IV/V, and multivariate analyses showed that there was no association with OS or RFS (Tables 1-3).[11,15]

Although the mitotic rate is not included in the T1 subcategory criteria of the eighth edition of the melanoma staging manual,[22] mitotic activity in T1 melanomas has also been associated with an increased risk of SLN metastasis.[24,25] In this series, the analysis was performed on those, only with complete data. The variable mitosis data were missing in 71 (45.2%) cases, and like other series of AM,[26] mitotic activity was not associated with OS or RFS (Tables 2 and 3).

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.[22] Some series showed an association between ulceration presence and SM survival, and the ulceration rate ranged from 30% to 34%.[11,15,18] Therein, ulcerated tumors presented lower survival. In this series, the ratio of ulcerated lesions, 94 (59.9%), was higher

TABLE 3 Factors associated with 5-year relapse-free survival in patients with subungual melanoma, 1997 to 2011, Rio de Janeiro, Brazil (N = 103)

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.00 (0.98-1.02)	0.853		
Gender				
Female	1.00			
Male	1.16 (0.70-1-93)	0.564		
Skin color				
White	1.00			
Nonwhite	0.62 (0.35-1.01)	0.100		
Place of diagnosis				
Public hospital	1.00			
Private hospital	0.91 (0.45-1.81)	0.783		
INCA	0.95 (0.48-1.88)	0.901		
Lesion site				
Hand	1.00			
Foot	2.57 (1.37-4.86)	0.003	2.26 (1.08-4.70)	0.03
Breslow depth, mm	1.05 (103-1.08)	0.001	1.04 (1.01-1.07)	0.04
Clark				
II/III	1.00	0.010		
IV-V	5.44 (1.95-15.22)			
Ulceration				
Absent	1.00	0.010	10.14 (1.34-76.81)	0.02
Present	13.71 (1.88-99.9)			
Mitosis				
Absent	1.00	0.100		
Present	6.24 (0.84-46.44)			
SLNB*				
Negative	1.00	0.05		
Positive	2.82 (0.96-8.22)			

Abbreviations: CI, confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.
*Analysis of 61 patients.

than in the published series, and ulceration presence was significant for OS, 7.62 (95% CI, 1.03 to 56.70; $P = 0.05$), and for RFS, 10.14 (95% CI, 1.34 to 76.81; $P = 0.02$) (Tables 2 and 3). We observed that the RFS curve for the nonulcerated patient is identical to the OS curve for that group of patients (Figures 1 and 2). The reduced number of nonulcerated tumors (24 patients) can explain the occurrence of only one death in that group. This subgroup of nonulcerated patients had a median follow-up time of 51 months, most were thin lesions (T1, 58.3%; T2, 8.3%; T3, 16.7%; T4, 16.7%) and the only recurrence was diagnosed at the same time of death due to loss of follow-up.

The surgical margin is an important predictive factor of AM survival. When positive, the re-excision is indicated. In this study, the margin was positive in the first surgical approach in 8.3% of the cases, similar to other reports in the literature.[27] In SM, even though there was no consensus in the literature regarding the choice between radical surgery and functional surgery, there was a trend of making conservative surgeries for more lesions having thin and intermediate depth. Studies, most of them on small series of cases, presented better aesthetic and functional results without affecting OS or RFS.[2,5,6,8,28-31]

The clinical condition of regional lymph nodes is considered an important prognostic factor for CM, especially when determined by SLNB.[22,24,32] In this series, 51 (32.5%) were stage III, 16 had a positive SLNB, and 35 had clinically evident metastasis. Few studies evaluated the role of SLNB in patients with AM. However, all of them revealed that biopsy positivity, as well as CM, are worse prognostic factors for both RFS and OS.[26,33,34] SLNB was performed for patients with performance status (PS) 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 SM series, 61 (38.9%) patients were submitted to SLNB and were positive in 16 (26.2%). Among those, 96 (61.1%) were not submitted, 35 (36.5%) were stage (III), 4 (4.2%) were stage IV, 10 (10.4%) did not meet characteristics for SLNB, 9 (9.4%) the radiolabeled colloid was not available, 17 (17.7%) PS was III or IV and 21 (21.8%) were diagnosed before the technique of SLNB was introduced in our center. It was introduced on June 15, 2000.

There are some limitations to 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 the main reference in oncologic assistance in the state, and patients with SM are referred for surgical treatment or for systemic therapy, there may have been an introduction of selection bias. Study time was long, and during this time, there were changes in the criteria for staging melanoma patients, which may have influenced anatomopathological reports. Moreover, a technology for lymph node staging (SLNB) was introduced, changing the initial SM approach.

However, this study presents some strengths, as this series of patients is relatively large and is the only one in Brazil and in Latin America that analyzes factors associated with SM survival. Being a hospital series, the data related to demographics, clinical treatment, and follow-up aspects were individually collected. In this oncologic center, the same group of professionals treated patients following a protocol with pre-established 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.

5 | CONCLUSION

This is the largest series of SM patients. The 5-year OS and RFS rates were low (61.0% and 48.2%, respectively). The main prognostic factors for OS were Breslow thickness and ulceration, and for RFS, they were anatomical location, Breslow thickness, and ulceration.

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