

# Demographic, Clinical, and Pathologic Features of Patients With Cutaneous Melanoma: Final Analysis of the Brazilian Melanoma Group Database

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## abstract

**PURPOSE** National epidemiologic data on melanoma are scarce in Brazil. The current work presents final demographic, clinical, and pathologic results from the Brazilian Melanoma Group database to detail how patients with melanoma present at diagnosis.

**METHODS** The online database includes patients diagnosed between 1982 and 2015 and evaluated at their centers of origin between 2001 and 2016. The primary objective was to describe the demographic, clinical, and pathologic characteristics of the patients, and secondary objectives were to investigate the association between clinical and pathologic variables of interest.

**RESULTS** A total of 1,596 patients were included. Median age was 52 years, 57% were women, and the majority were identified as white. Invasive melanoma was diagnosed in 1,297 patients, mostly localized, whereas 299 (19%) had in situ disease (TisNOM0). Only 165 patients had initial lymph node involvement. Fitzpatrick skin types I or II were slightly more frequent with in situ melanoma (73%) than with invasive disease (67%;  $P = .054$ ). The median Breslow thickness was 0.95 mm, Clark levels 2 and 3 comprised nearly 70% of cases, and ulceration was present in 18% of patients. The mitotic rate was significantly associated with the presence of ulceration and both vascular and perineural invasion but not with margin positivity, whereas histologic regression was associated with both intratumoral and peritumoral inflammatory infiltrates.

**CONCLUSION** Despite the limitations of an observational, registry-based study, the current results provide a general profile of patients with cutaneous melanoma in Brazil at the time of diagnosis.

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## INTRODUCTION

The incidence of melanoma has increased over the past three decades, and its mortality rate increases faster than that of several other malignancies in some countries.<sup>1,2</sup> Although cutaneous melanoma is amenable to early diagnosis and curative surgical resection, in the United States, more than 12,000 people are expected to die as a result of invasive melanoma each year, and approximately 87,000 new cases of in situ melanoma of the skin are expected each year.<sup>3</sup> In Brazil, national epidemiologic data on melanoma are scarce,<sup>4,5</sup> and reported studies are often restricted to regional series, something that is insufficient for a multi-ethnic continental-sized country.<sup>6-9</sup> Nationwide estimates from the Brazilian National Cancer Institute indicate that slightly more than 6,000 new cases of

melanoma occur each year,<sup>10</sup> but the real incidence is likely to be higher; moreover, there is evidence of an increased incidence of cutaneous melanoma in Brazil,<sup>11</sup> a country with a diverse ethnic composition and socioeconomic structure.

Founded in 1996, the Brazilian Melanoma Group (GBM)<sup>12</sup> is a multidisciplinary team that comprises surgical and medical oncologists, dermatologists, plastic surgeons, pathologists, nurses, and other professionals with interest in the management of patients with melanoma. In November 2000, the GBM initiated a database to collect nationwide clinical and pathologic information on cutaneous melanoma. The results after 14 years of data collection have been published and have confirmed the absence of tumor-infiltrating lymphocytes to be a risk factor for sentinel

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Melanoma epidemiologic data in Brazil are relevant data. In considering a continental country from equatorial to subtropical climate with a large multi-ethnic population, it is important to publish how patients with melanoma present at diagnosis.

### Knowledge Generated

Different medical specialties are responsible for different steps at melanoma diagnosis, and according to these multidisciplinary teams and the available resources in each country, melanomas are diagnosed at diverse stages of the disease. The data related to the melanoma stage at diagnosis for Brazilian patients can provide to health professionals and decision-makers in health care specific clinical and pathological tools. These tools can be relevant in a country where the health care system has limited availability of diagnostic and therapeutic options that can lead to losses in terms of efficiency of early melanoma diagnosis, reverberating in a significant financial impact.

### Relevance

Knowing how patients with melanoma present at diagnosis in Brazil is essential to establish national programs of awareness and education, and define the target population. It is also essential to better prepare institutions and medical teams according to the stage of the disease.

lymph node metastasis.<sup>13</sup> The current work presents final demographic, clinical, and pathologic results from the GBM database. It is hoped that this sizeable nationwide series will contribute to increasing knowledge about cutaneous melanoma in Brazil, serve as a tool to estimate the impact of interventions, and guide value-based frameworks.

## METHODS

### Database Structure and Data Collection

The database includes patients diagnosed between 1982 and 2015 and evaluated at the participating centers between 2001 and 2016. Data collection was approved by the Research Ethics Committee at A.C. Camargo Cancer Center, São Paulo, Brazil, and patients were identified only by study-specific identity codes, with the suppression of additional protected personal information. Data were entered using an online tool by each participating institution and stored in a temporary database, which was periodically reviewed by an attending physician and, if required, sent back to the center of origin to clarify queries. Demographic, clinical, and pathologic variables were collected, including age, sex, race, family history, lesion location and staging, histologic type, Breslow thickness, Clark level, presence of ulceration and regression, growth phase (radial or vertical), mitotic rate, vascular invasion, perineural invasion, tumor-infiltrating lymphocytes, peritumoral inflammatory infiltration, sentinel lymph node status, and general treatment information. Staging of cutaneous melanoma was reported using the seventh edition of the TNM staging system.<sup>14</sup> Pathologic specimens were assessed locally at each participating center.

### Objectives and Outcomes of Interest

For the current analysis, the primary objective was to describe the main demographic, clinical, and pathologic characteristics of the registered patients. Secondary objectives

were to investigate the association between clinical and pathologic variables of interest.

### Statistical Analysis

Descriptive statistics summarized continuous and categorical variables. Except for staging information, for which there were categories with very few cases, all presented percentages have been rounded for simplicity. The Kolmogorov-Smirnov test was used to evaluate the distribution pattern of the numerical variables in the sample, and continuous variables with non-normal distribution were compared between groups of interest using the Mann-Whitney test. Categorical variables were compared using the Fisher's exact or the  $\chi^2$  test, as appropriate. Odds ratios (ORs) and their 95% CIs were computed for selected cases in which an association was sought between 2 categorical variables. As a rule, significance levels of 5% were used as indicative of a statistically significant difference, and there was no imputation of missing values. All analyses were performed using MedCalc version 11.3.3.0 software (MedCalc, Mariakerke, Belgium).

## RESULTS

### Patient Demographics and Characteristics

A total of 1,596 patients from eight participating centers were registered in the database. [Table 1](#) lists the baseline demographic and skin characteristics of the patients analyzed. Ages ranged from 2 to 93 years (median, 52 years), and there was a slight female predominance (57%). The majority of patients had no personal or family history of melanoma, 91% were identified as white, and Fitzpatrick skin types I or II were reported for approximately two thirds of patients. Moreover, light-colored hair and light-colored eyes were reported for 32% and 35% of patients, respectively, and actinic skin damage was present in 40%. Information collected on cutaneous nevi indicated that

**TABLE 1.** Baseline Demographic and Clinical Features

Characteristic	No. (%)
Age, years	
Range	2-93
Median (IQR)	52 (40.5-64.0)
Sex	
Female	906 (57)
Male	690 (43)
Skin color	
White	1,455 (91)
Other	141 (9)
Family history of melanoma	
No	1,456 (91)
Yes	138 (9)
Personal history of melanoma	
No	1,506 (94)
Yes	90 (6)
Fitzpatrick skin type I or II	
No	512 (32)
Yes	1,074 (68)
Actinic skin damage	
No	960 (60)
Yes	637 (40)
Light-colored hair	
No	1,084 (68)
Yes	507 (32)
Light-colored eyes	
No	1,024 (64)
Yes	565 (36)

NOTE. Totals for each characteristic < 1,596 indicate missing values, with percentages computed only with nonmissing data.

Abbreviation: IQR, interquartile range.

most patients had no history of atypical or congenital melanocytic nevi, but 23% had multiple melanocytic nevi. Of note, melanoma during pregnancy was described in 25 patients.

### Clinical Features of Cutaneous Melanoma

The final disease stage upon an initial evaluation of each patient, according to the TNM classification, is listed in Table 2. In situ melanoma (defined as TisNOM0) was present in 299 patients (19%), whereas 1,295 patients had invasive disease; for 2 patients, information with regard to the final TNM stage was not available. Only 165 patients had lymph node involvement. The majority of patients had no distant metastasis described at initial presentation. Signs that suggested clinical regression of the primary lesion were described as present in 59 patients (4%) and absent in 886 (56%), but it was unknown in approximately 41%. Compared with invasive disease, there was no significant

**TABLE 2.** Stage of Cutaneous Melanoma, Reported as Final Upon an Initial Evaluation of Each Patient, Using the Seventh Edition of the TNM Staging System<sup>14</sup>

Category	No. (%)
<b>T</b>	
T0	1 (0.1)
Tx	17 (1.1)
Tis	305 (19.1)
T1a	644 (40.4)
T1b	36 (2.3)
T2a	227 (14.2)
T2b	47 (2.9)
T3a	104 (6.5)
T3b	79 (4.9)
T4a	51 (3.2)
T4b	83 (5.2)
Not available	2 (0.1)
<b>N</b>	
N0	1,409 (88.3)
Nx	16 (1.0)
N1a	81 (5.1)
N1b	13 (0.8)
N2a	22 (1.4)
N2b	9 (0.6)
N2c	7 (0.4)
N3	33 (2.1)
Not available	6 (0.4)
<b>M</b>	
M0	1,540 (96.5)
Mx	11 (0.7)
M1a	19 (1.2)
M1b	8 (0.5)
M1c, normal LDH	10 (0.6)
M1c, elevated LDH	3 (0.2)
Not available	5 (0.3)
<b>TNM</b>	
TisNOM0	299 (18.7)
T1aNOM0	621 (38.9)
T1b or T2aNOM0	222 (13.9)
T2b or T3aNOM0	120 (7.5)
T3b or T4aNOM0	72 (4.5)
T4bNOM0	46 (2.9)
Other categories <sup>a</sup>	214 (13.4)
Not available	2 (0.1)

Abbreviation: LDH, lactic dehydrogenase.

<sup>a</sup>Categories that were more advanced than T4bNOM0, but could not be precise in consideration of the information available.

association (all  $P > .10$ ) between the presence of in situ melanoma and age, sex, or reported skin color, whereas Fitzpatrick skin type I or II was slightly more frequent with in situ melanoma (73%) than with invasive disease (67%;  $P = .054$ ).

### Pathologic Features of Cutaneous Melanoma

The most frequent histologic subtype was superficial spreading melanoma reported in 902 patients (57% of all patients, and 72% when patients with in situ disease were excluded). Melanoma histology was in situ for 350 patients, including 49 whose histologic subtype was classified as lentigo maligna melanoma. One hundred three patients (6.5% of the 1,596) had acral lentiginous melanoma, 153 had nodular melanoma, and the remainder had melanoma not otherwise classified or information not available. Growth phase was reported as radial in 25% and vertical in 75% of patients with available information on this feature (20% of patients overall had no information on growth phase). The distributions of Breslow thickness, Clark level, and presence of ulceration are listed in Table 3. Breslow thickness

**TABLE 3.** Distributions of Breslow Thickness, Clark Level, and the Presence of Ulceration Among Patients With Cutaneous Melanoma

Characteristic	No. (%)
No. with Breslow thickness available	1,267
Breslow thickness, mm	
Range	0.1-72
Mean $\pm$ SD	1.86 $\pm$ 3.28
Median (IQR)	0.95 (0.50-2.00)
Not applicable or not available	329
Breslow thickness categories, mm	
$\leq 1$	677 (42)
$> 1$ and $\leq 2$	275 (17)
$> 2$ and $\leq 4$	185 (12)
$> 4$	130 (8)
Not available	329 (21)
No. with Clark level available	1,272
Clark level	
1	16 (1)
2	367 (23)
3	521 (33)
4	311 (20)
5	57 (4)
Not available	324 (20)
Ulceration	
Absent	1,037 (65)
Present	232 (18)
Not available	327 (20)

NOTE. Percentages may not total 100% because of rounding. Abbreviations: IQR, interquartile range; SD, standard deviation.

was not available in 323 patients, including all 299 with in situ disease (TisNOMO). In considering the 1,267 patients with available Breslow thickness, the median was 0.95 mm (range, 0.1-72 mm). Likewise, Clark level was not available in 324 patients, again including all those with in situ disease. Clark levels 2 and 3 comprised nearly 70% of patients with available information. Finally, no data

**TABLE 4.** Distribution of Key Pathologic Features of Cutaneous Melanoma

Characteristic	No. (%)
Margins	
Negative	1,268 (79)
Positive	292 (18)
Not available	36 (2)
Mitotic rate	
In cells/10 HPF	1,243
Range	0 to 52
Mean $\pm$ SD	3.2 $\pm$ 5.3
Median (IQR)	1 (0 to 4)
Not available	353
Categories, cells/10 HPF	
0	394 (25)
1-5	625 (39)
$\geq 6$	224 (14)
Not available	353 (22)
Vascular invasion	
Absent	1,208 (76)
Present	56 (4)
Not available	332 (21)
Perineural invasion	
Absent	1,222 (77)
Present	41 (3)
Not available	333 (21)
Intratumoral inflammatory infiltrate	
Absent	870 (54,5)
Present	389 (24,4)
Not available	337 (21,1)
Peritumoral inflammatory infiltrate	
Absent	543 (34)
Present	748 (47)
Not available	305 (19)
Regression	
Absent	1,068 (67)
Present	199 (13)
Not available	329 (21)

NOTE. Percentages may not total 100% because of rounding. Abbreviations: HPF, high-power field; IQR, interquartile range; SD, standard deviation.

were available or applicable with regard to the presence of ulceration for 327 patients, including those with in situ melanoma. In considering only the 1,269 patients with available data, ulceration was present in 18%.

**Table 4** lists the distributions of key pathologic features of cutaneous melanoma. There was information on margins of resection for 98% of patients; margins were reportedly negative in 81% of these patients and positive in the remaining 19%, which includes incisional biopsy. In considering only the 1,243 patients with available information, the median mitotic rate was 1, with a range of 0-52 mitotic cells/10 high-power fields; the 353 patients without an available mitotic rate included those with in situ disease according to the TNM staging (TisNOMO). Vascular and perineural invasion were reported infrequently, but an intratumoral inflammatory infiltrate was present in 31% of patients with available information. All patients with in situ disease are accounted for in the categories with missing data for these three features. Peritumoral inflammatory infiltrate was present in 58% of patients.

#### Association Between Clinical and Pathologic Variables

The presence of ulceration was significantly associated with the Breslow thickness and with the mitotic rate (**Table 5**). The median mitotic rate was 1 (interquartile range [IQR], 0-2) among patients with no ulceration and 5.5 (IQR, 2-10) among those with ulceration ( $P < .01$ ). This significant difference was also observed when mitotic rate was analyzed as categories. Among the 222 patients with ulceration who had data available for mitotic rate, 208 (94%) had a mitotic rate different from 0.

There was a statistically significant association between vascular and perineural invasion, with only 85 of 1,262 patients with available data having a discrepancy between the results for these two features ( $P < .01$ ). Likewise, the mitotic rate was significantly associated with the presence of both vascular and perineural invasion. The median mitotic rate was 1 (IQR, 0-3) among patients without vascular invasion and 5 (IQR, 1.25-11.75) among those with vascular invasion ( $P < .01$ ), 1 (IQR, 0-4) among patients without perineural invasion and 2 (IQR, 1-6.5) among those with perineural invasion ( $P = .02$ ), and 2 (IQR, 0-4) among patients with negative margins and 1 (IQR, 0-4) among those with positive margins ( $P = .58$ ). Finally, ORs were computed for the associations between histologic regression and the presence of intratumoral and peritumoral inflammatory infiltrates. In both cases, the association was statistically significantly positive, with an OR of 2.13 (95% CI, 1.56 to 2.91;  $P < .01$ ) for intratumoral infiltrates and 3.19 (95% CI, 2.20 to 4.60;  $P < .01$ ) for peritumoral infiltrates.

#### DISCUSSION

The key findings from the study are a slight predominance of female patients, the increased prevalence compared with expected distributions in Brazil of white skin color and fair complexion features, and significant associations among selected pathologic variables. Moreover, the results provide an overview of the staging profile of patients with cutaneous melanoma in Brazil. Of note, our study also shows the feasibility of conducting nationwide registries in a country where the absence of compulsory, efficient notification, inefficient registration, and low prioritization by

**TABLE 5.** Association Among Breslow Thickness, Mitotic Index, and the Presence of Ulceration

Variable	Ulceration, No. (%)		P
	Present	Absent	
No. with Breslow thickness available (n = 1,262)	230	1,032	
Breslow thickness category, mm			
≤ 1	19 (3)	654 (97)	< .01
> 1 and ≤ 2	48 (18)	226 (83)	
> 2 and ≤ 4	79 (43)	106 (57)	
> 4	84 (65)	46 (35)	
No. with mitotic rate available (n = 1,242)	222	1,020	
Mitotic rate, cells/10 HPF			
Range	0-52	0-40	
Median (IQR)	5.5 (2-10)	1.0 (0-2)	< .01
Mitotic rate category, cells/10 HPF			
0	14 (6)	380 (37)	
1-5	97 (44)	527 (52)	< .01
≥ 6	111 (50)	113 (11)	

NOTE. Percentages refer to Breslow and mitotic index categories and may not total 100% because of rounding. Abbreviations: HPF, high-power field; IQR, interquartile range.

public health managers have been pointed out as barriers to a better understanding and control of this disease.<sup>5-7</sup>

The slight female predominance of cutaneous melanoma observed here was also reported in a study from the south of Brazil, in which 56.3% of 893 cases were reported in women.<sup>6</sup> An even higher imbalance was reported in a study of 364 patients from the city of São Paulo, with 40% more cases in women.<sup>8</sup> White people comprise 50.2% of the Brazilian population.<sup>5</sup> In the current study, the ethnicity/skin color distribution of patients with melanoma was 91.0% white. This discrepancy could be explained by European immigration, ancestry, and melanoma population distribution that is most prevalent in whites. There are also socioeconomic issues that reflect in better health care access to high-income Brazilians because the average per capita household income of the white population is more than double that of the black population.<sup>15</sup> On the other hand, the incidence rates for both in situ and invasive melanoma in the United States are approximately 60% higher in men than in women.<sup>1,16</sup> Of note, a nearly even sex distribution was reported in a large, nationwide study from Sweden,<sup>17</sup> whereas in Europe as a whole, the incidence of cutaneous melanoma is generally higher among women than among men.<sup>18</sup> The reasons for the apparent sex differences in melanoma incidence in different regions are not clear but may be related to biologic, occupational, and behavioral factors as well as to different referral patterns between women and men in different countries and cultures.

Melanoma in situ represented 19% of the sample, which suggests high melanoma awareness and early diagnosis. Among the 1,267 patients with available Breslow thickness, the median value was 0.95 mm (range, 0.1-72 mm). There are no data that compare the median value of Breslow thickness at the diagnosis of melanoma around the world; however, we believe that although 0.95 mm would refer to stage T1b, close to T2a, this value can be considered thin, which portends a good prognosis, with melanoma-specific survival of 99% and 96% at 5 and 10 years, respectively.<sup>19</sup>

The associations between several of the pathologic variables described here and long-term outcomes, such as recurrence-free and overall survival, have been the subject of extensive investigation in the literature.<sup>14,20</sup> Of note,

however, the association among several of these factors seems to have been reported less frequently. For example, in the current study, we have found a robust association between vascular invasion and perineural invasion; given that both were either concordantly present or absent in the majority of patients suggests that they reflect a shared propensity for the spread of the primary lesions. A similar association has been reported in a series of 519 patients with cutaneous melanoma.<sup>21</sup> Likewise, in our study, the mitotic rate was significantly associated with these two types of invasion and with the presence of ulceration, again which probably reflects the malignant potential of the disease in these patients. Of note, although no longer used for staging purposes in the eighth edition of the TNM classification,<sup>19</sup> the mitotic rate is a well-known prognostic factor in cutaneous melanoma,<sup>22,23</sup> and should continue to be recorded in individual patients.<sup>19</sup> Conversely, we found that histologic regression was associated with intratumoral and peritumoral inflammatory infiltrates, as reported by others,<sup>24</sup> which probably indicates a more effective immune response to these lesions.<sup>25</sup> It should be noted, however, that we had no phenotypic information on these infiltrating lymphocyte populations and were thus unable to ascertain the role of cytotoxic versus regulatory cells in this purported immune response.

This study has some limitations as a result of its observational nature, the fact that all cases were not reviewed by the same pathologist, and the fact that the patients registered represent an unknown percentage of contemporaneous patients with cutaneous melanoma in the participating institutions led by physicians committed to the study of melanoma and members of the GBM. This is due to the nature of data collection and our inability to ascertain the prevalence of nonregistered patients. Despite these limitations, the current study is a comprehensive picture of melanoma in Brazil with regard to how patients with cutaneous melanoma present at diagnosis.

In conclusion, the current results provide an overview of cutaneous melanoma at presentation and initial management in Brazil. Of note, our study also shows the feasibility of conducting long nationwide registries with highly motivated investigators.

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