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Clinical and sociodemographic profile of patients with cutaneous melanoma attended at an oncology referral hospital in Florianópolis between 2013 and 2017

Perfil clínico e sociodemográfico de pacientes com melanoma cutâneo atendidos em um hospital de referência em oncologia de Florianópolis entre 2013 e 2017

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ABSTRACT

Introduction: Cutaneous melanoma is the most lethal skin cancer and its incidence has significantly increased in recent years. In particular, Florianópolis is the Brazilian capital with the highest incidence of the disease. **Objective:** To investigate the clinical and sociodemographic profile of patients with cutaneous melanoma treated at a public oncology referral hospital in Florianópolis from 2013 to 2017. **Methods:** This is a descriptive and cross-sectional study carried out at the Santa Catarina Oncology Research Center (*Centro de Pesquisas Oncológicas - CEPON*). It included 468 patients diagnosed with melanoma skin cancer (ICD-O, 3rd edition C44 - skin melanoma) evaluated between 2013 and 2017. Data collection was performed by accessing the hospital cancer registry and electronic and physical medical records. The data were plotted in a *Windows Excel* spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS) software. **Results:** There was a slight predominance of females, white-skinned, with a mean age of 54.3 years old at the time of diagnosis. The most prevalent primary tumor site was the trunk. Superficial spreading melanoma was the most frequent condition, and ulceration was absent in most cases. Clinical stage IV was the most common, and lungs and bronchi were the main metastasis sites. The most performed treatment was wide local excision and the most widely used systemic therapy was chemotherapy. **Conclusion:** This study characterized the sociodemographic and clinical profile of patients diagnosed with cutaneous melanoma and treated at a referral hospital in the Brazilian capital with the highest skin cancer rates.

Keywords: Melanoma; Skin neoplasms; Health profile.

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RESUMO

Introdução: O melanoma cutâneo é o câncer de pele mais letal e sua incidência tem aumentado significativamente nos últimos anos. Em particular, Florianópolis é a capital brasileira com maior incidência da doença. **Objetivo:** Investigar o perfil clínico e sociodemográfico dos pacientes com melanoma cutâneo atendidos em um hospital público de referência em oncologia de Florianópolis, no período de 2013 a 2017. **Métodos:** Trata-se de um estudo descritivo e transversal realizado no Centro de Pesquisas Oncológicas de Santa Catarina (Centro de Pesquisas Oncológicas - CEPON). Foram incluídos 468 pacientes com diagnóstico de câncer de pele melanoma (CID-O, 3ª edição C44 - melanoma de pele) avaliados entre 2013 e 2017. A coleta de dados foi realizada por meio do acesso ao registro hospitalar de câncer e prontuários eletrônicos e físicos. Os dados foram plotados em planilha do *Windows Excel* e analisados no software Statistical Package for the Social Sciences (SPSS). **Resultados:** Houve discreta predominância do sexo feminino, de cor branca, com média de idade de 54,3 anos no momento do diagnóstico. O sítio de tumor primário mais prevalente foi o tronco. O melanoma de disseminação superficial foi a condição mais frequente e a ulceração esteve ausente na maioria dos casos. O estágio clínico IV foi o mais comum, sendo os pulmões e os brônquios os principais sítios de metástase. O tratamento mais realizado foi a excisão local ampla e a terapia sistêmica mais utilizada foi a quimioterapia. **Conclusão:** Este estudo caracterizou o perfil sociodemográfico e clínico dos pacientes diagnosticados com melanoma cutâneo e atendidos em um hospital de referência da capital brasileira com as maiores taxas de câncer de pele.

Descritores: Melanoma; Neoplasias da pele; Perfil de saúde.

INTRODUCTION

Melanoma is the most lethal skin cancer, with increasing incidence rates.[1] It is estimated that 7% of the new cases in 2019 are cutaneous melanoma, according to the American Cancer Society.[2] In addition, it is currently the fifth most prevalent tumor in American men and women.[2]

The Brazilian National Cancer Institute (*Instituto Nacional de Câncer* – INCA) estimated the total incidence rate of cutaneous melanoma at 4.03 per 100,000 men and at 3.94 per 100,000 women in 2020. The highest incidence rates are found in the South region, with 6.49/100,000 men and 6.61/100,000 women. In addition, Santa Catarina is the state with the highest adjusted incidence of cutaneous melanoma in the country. Specifically, its capital Florianópolis presents the highest rates, with 14.82 cases per 100,000 in men and 12.22 cases per 100,000 in women.[3]

Many risk factors for melanoma have been established, such as exposure to ultraviolet (UV) radiation; Fitzpatrick skin types I and II (skin that easily burns and does not tan or tans with difficulty, respectively);[4] frequent sunburn; presence of dysplastic nevi; artificial tanning; family history of melanoma and previous history of melanoma.[5] Recent studies suggest that UV radiation can be one of the main risk factors for the onset of cutaneous melanoma. It presents a high level of mutation, and most of its cases are typically caused by exposure to UV rays.[6-8] In this sense, approximately 86% of the melanoma cases are directly attributed to UV exposure.[9]

The population of Santa Catarina, a state mainly composed of white-skinned inhabitants (83.97%),[10] has high sun exposure mainly related to economic and cultural habits linked to fishing, agriculture and beaches, having high exposure to risk factors for cutaneous melanoma. Due to the high incidence of the disease, some studies have already been conducted in Santa Catarina seeking to understand the profile of patients who develop melanoma, as well as the histopathological characteristics of the lesions, as observed in the cities of Blumenau,[11] Brusque[12] and Florianópolis.[13,14]

The ABCDE rule is a useful tool for the investigation of suspected cutaneous melanoma.[1] Therefore, it is mandatory for the diagnosis to perform an excisional biopsy followed by margin enlargement and to associate or not the sentinel lymph node survey according to the Breslow index.[15] With these data, it is possible to classify the disease in clinical stages (CS) and define which tests are still needed for staging, thus favoring planning and treatment (according to the American Joint Committee on Cancer (AJCC), 8th edition, available since January 2018).[16]

The treatment options for melanoma are based on current knowledge of tumor biology and are chosen according to the individualized clinical assessment and to the disease stage. It is important to note that chemotherapy was the standard treatment for the metastatic disease until 2010. During this period, the use of alpha interferon as adjuvant therapy in early-stage diseases was questionable, with high toxicity as a limiting factor.[17]

Fortunately, this scenario changed with the advent of immunotherapy, with melanoma being a pioneer in relation to other neoplasms. In addition to immunotherapy, there is evidence of target drugs such as BRAF and MEK inhibitors[18] serving as an option for BRAF gene mutation (present in approximately 50% of the cases).[19]

For adjuvant treatment, the available options are immunotherapy and targeted drugs. In addition to immunotherapy and target therapy for metastatic melanoma, the patient can be treated with chemotherapy and radiotherapy.[20]

The Oncological Research Center (CEPON) is the reference public service in the macro-region of Florianopolis/Santa Catarina for oncological treatment. During the study period, it was the state reference for melanoma among the entire state of Santa Catarina, being the only center that performed sentinel lymph node biopsy. CEPON is involved in clinical research throughout the country, allowing patients in the public system access to various treatment modalities not yet included in the therapeutic arsenal of the Brazilian unified health system.

In this sense, it is essential to identify the clinical and sociodemographic profile of patients with cutaneous melanoma, considering the high exposure to risk factors for the disease and the incidence in the state of Santa Catarina and its capital city. Thus, this study aims at characterizing the clinical and sociodemographic profile of patients with cutaneous melanoma treated at a public oncology referral hospital in Florianópolis from January 2013 to December 2017.

METHODS

This is a cross-sectional and descriptive study carried out at the Santa Catarina Oncological Research Center (CEPON), located in Florianópolis, Santa Catarina. The institution plays an important role in cancer treatment in the mesoregion of Florianópolis, is a referral hospital for melanoma treatment in the State of Santa Catarina (until 2018), and a reference for palliative medicine, according to the World Health Organization (WHO). The study included patients diagnosed with melanoma skin cancer (ICD-O, 3rd edition C44 - skin melanoma) treated at CEPON between January 2013 and December 2017. The sociodemographic information was obtained from the CEPON's Hospital Cancer Registry (HCR) database, whereas the clinical characteristics and treatments were verified by accessing electronic and physical medical records.

The following variables were considered in the study: sociodemographic variables (gender, age, ethnicity, schooling, working outdoors during sun exposure, and origin according to state region); treatment variables (first treatment received at the hospital); and clinical characteristics (histological type, primary tumor location, Breslow index, presence of ulceration in the primary tumor, tumor staging, presence of metastasis, and metastasis sites).

The data were inserted in a *Windows Excel* spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS) program, version 18.0 (Chicago, SPSS Inc., U.S., 2009). The qualitative data were presented as simple and relative frequencies and the quantitative data as mean and standard deviation (SD).

This research was conducted according to Resolution No. 466/2012 of the National Health Council, approved by the Research Ethics Committees of the University of Southern Santa Catarina and of CEPON under CAAE registration numbers 26476019.0.3002.5355 and 26476019.0.0000.5369. The researchers declare no conflicts of interest.

RESULTS

The total number of cutaneous melanoma cases per year is shown in Table 1. Data from medical records and from the HCR revealed 468 cases of cutaneous melanoma between January 2013 and December 2017. An annual increase in the number of cases was observed, ranging between 68 cases in 2013 and 106 in 2017.

Table 1. Cases of cutaneous melanoma per year.

Year	n	%
2013	68	14.53
2014	90	19.23
2015	100	21.37
2016	104	22.22
2017	106	22.65

The sociodemographic characteristics of the evaluated subjects are shown in Table 2. The patients' mean age was 54.3 years old (SD=14.852), with the youngest subject being 18 years old and the oldest, 89. The most affected age groups were those between 61 and 70 years old (24.14%) and between 51 and 60 years old (22.65%), in addition to the age group between 41 and 50 years old (19.02%). In addition, the female gender was slightly predominant (51.07%), and 458 patients were white-skinned (97.9%).

The most prevalent topographies of primary tumors are shown in Table 3. The trunk was the most common site with cutaneous melanoma, with similar incidence in both genders (39.32%). However, the second most frequent site was different between the genders, affecting the upper limbs (13.97%) in men and the lower limbs in women (23.85%). In addition to that, it was not possible to classify the location of 54 tumors according to the HCR.

Regarding the histological classification, 35.68% of the tumors were melanoma or melanoma NOS (no other specifications). In addition, the most frequent histological subtypes were superficial spreading (35.26%), followed by nodular melanoma (20.51%). Furthermore, 35.8% of the lesions in primary tumors presented ulceration.

Table 2. Patient's sociodemographic characteristics.

Variables	n	(%)
Gender (n=468)		
Female	239	51.07
Male	229	48.93
Age (n=468)		
11 to 20	1	0.21
21 to 30	24	5.13
31 to 40	71	15.17
41 to 50	89	19.02
51 to 60	106	22.65
61 to 70	113	24.15
71 to 80	49	10.47
81 to 90	15	3.2
Race (n=468)		
Yellow	2	0.43
White	458	97.87
Brown	4	0.85
Black	4	0.85
Education (n=436)		
None		
17		
3.9		
Incomplete primary education	170	39.0
Primary education	72	16.51
High school education	99	22.7
Incomplete undergraduate education	16	3.67
Undergraduate education	62	14.22
Working outdoor (sun exposure) (n=425)		
Yes	152	35.76
No	273	64.24
Origin (State region) (n=457)		
Greater Florianópolis	340	74.5
North	5	1.0
West	28	6.1
Mountain region (“Serra”)	9	2.0
South	30	6.6
Itajái Valley	43	9.4
Other States	2	0.4

Table 3. Primary tumor location in both genders.

Primary tumor location	Male		Female	
	n	%	n	%
Face	19	8.3	13	5.44
Scalp and neck	23	10.04	14	5.86
Trunk	101	44.11	83	34.72
Upper limb	32	13.97	51	21.34
Lower limb	21	9.17	57	23.85
Not specified	33	14.41	21	8.79

The Breslow index and clinical-pathological staging were grouped according to the 8th edition of the AJCC.[16] Tumors with thickness less than 0.8mm represented 15.60% of the samples, although the most frequent tumors were between 1 and 2mm thick (17.95%). However, the most frequent CS at diagnosis was stage IV (27.92%), and the most frequent metastases sites were located in the lungs and bronchi (19.64%), non- regional lymph nodes (17.35%) and central nervous system (CNS) (13.70%). It is important to note that 48.72% of the patients diagnosed with CS IV had synchronous metastases. The results regarding tumor histology, Breslow index, staging and topography of the metastases are described in Table 4.

Regarding the first treatment, 41.67% of the patients received only one modality at the first moment, 39.1% underwent more than one modality and 19.23% were not subjected to any treatment (16.67% due to follow-up loss).

Margin enlargement surgery was performed in 58.49% of the patients in CS 0, standing out among the indicated treatments. However, it is important to note that another 32.08% of the patients directly initiated clinical follow-up as they were operated on in other institutions.

Margin enlargement surgery was also the most frequent treatment for patients with CS IA (80.36%). However, sentinel lymph node biopsy (SLB) was performed in 62.5% of the cases with CS IB in addition to enlargement surgery. One patient in this group was subjected to lymphadenectomy associated with margin enlargement surgery as initial treatment (1.39%).

The patients with CS IIA, IIB, and IIC who underwent enlargement surgery associated with SLB for initial treatment accounted for approximately 92.10%, 80%, and 82.35%, respectively. Two patients with CS IIC were subjected to lymphadenectomy (11.76%).

This initial therapeutic scenario was similar for patients with CS III. Enlargement surgery associated with SLB was the most used procedure for patients with CS IIIA, IIIB and IIIC (60%, 40%, and 40.9%, respectively). However, it is important to note that other treatments were also applied, especially lymphadenectomy, performed in 20% of the patients with CS IIIA, 30% of those with CS IIIB, 27.27% with CS IIIC and 25% with CS IIID. Adjuvant interferon was used in three patients (6.39%) with unspecified CS III. Radiotherapy was used in 13.64% of the patients with CS IIIC and 25% with CS IIID. Only one patient with CS IIIC received chemotherapy (4.54%).

Chemotherapy (dacarbazine alone or carboplatin associated with paclitaxel) was used in 29.06% of the cases with CS IV melanoma, with 3.42% of these being associated with radiotherapy. The second most used treatment for this group of patients was radiotherapy, used alone in 19.09% and in combination with other therapies in 5.98% of the subjects. Importantly, target therapy (vemurafenib) was the first choice for 8.55% of the cases.

Table 4. Histological classification, Breslow, staging and metastasis site.

Variables	n	%
Histology (n = 468)		
Melanoma (no other specifications)	167	35.68
Superficial spreading	165	35.26
Nodular	96	20.51
Malignant lentigo	12	2.56
Acral	18	3.85
Other	10	2.14
Breslow (n = 468)		
Tis		
53		
11.33		
<0.8mm	73	15.60
0.8-1mm	36	7.69
>1-2mm	84	17.95
>2-4mm	65	13.89
>4mm	61	13.03
No information*	96	20.51
Staging (n = 419)		
0		
53		
12.65		
IA	56	13.37
IB	72	17.18
IIA	38	9.07
IIB	20	4.77
IIC	17	4.06
IIIA	10	2.39
IIIB	10	2.39
IIIC	22	5.25
IIID	4	0.95
IV	117	27.92
Metastasis site (n = 117)**		
Lung and bronchi	43	19.64
Non-regional lymph nodes	38	17.35
Bones	18	8.22
Central nervous system	30	13.70
Subcutaneous tissue	14	6.39
Liver	20	9.13
Adrenal	8	3.65
Skin	7	3.20
Peritoneum/retroperitoneum	11	5.02
Other	20	13.70

Technical note: *79 of these (82.3%) presented evidence of metastasis; **57 of these (48.72%) had more than one site of metastasis.

In addition to these treatments, immunotherapy (nivolumab or pembrolizumab) was the therapy of choice for 5.13% of the patients. Direct referral to the palliative care team occurred in 6.84% of the cases. Other approaches were also indicated as first treatment, such as margin enlargement surgery associated with SLB (4.27%), metastasectomy (1.71%), lymphadenectomy (7.69%) and three patients (2.56%) underwent the trilogy (vemurafenib, cobimetinib associated with atezolizumab or placebo) research protocol. Finally, 20 patients with CS IV did not receive any treatment (17.09%). Among the reasons are follow-up loss, treatment options at another institution, and death before the scheduled treatment.

DISCUSSION

Cutaneous melanoma is a prevalent neoplasm in Santa Catarina, especially in Florianópolis, when compared with other Brazilian cities. In this sense, the current study was conducted at CEPON, the referral hospital for the treatment of melanoma in the state of Santa Catarina.

This research involved 468 patients, 239 women and 229 men, with a slight predominance of female cases with cutaneous melanoma. These findings corroborate with other publications in the area. In a study conducted in São Paulo by Melo et al. (2018),[21] a slight predominance of cases was found among females (51.9%). Furthermore, in 2020, Wainstein et al.[22] showed a majority of cases among women (57%), in addition to studies carried out in Brusque, SC[12] and Curitiba, PR[23] that also detected predominance of women (56.6% and 58.9%, respectively).

Regarding age at diagnosis, 79.49% of the patients were over 40 years old, corroborating Paulson et al.,[24] who demonstrated in 2019 that melanoma was widely associated with patients over 40 years of age in the United States. The predominance of cases in this age group was also found in a retrospective study conducted at the Federal University of São Paulo by Ferreira et al., in 2018.[25]

The present study identified that 97.87% of the subjects with cutaneous melanoma were white-skinned, similar to studies carried out in the country by Wainstein et al. (2020)[22] (91%) and Costa et al. (2019)[26] (93.1%). In addition, the strong association of fair skin with the development of cutaneous melanoma has already been identified in other works, as in the prospective study by Olsen et al. (2019).[27] Regarding this topic, the ethnic characteristics of the Santa Catarina population also stand out, since 83.97% of the inhabitants are white-skinned.[10]

It was observed that 3.9% of the patients had no schooling and 39% presented incomplete primary education. On the other hand, 57.1% had completed primary, high school, or undergraduate education. These data are similar to those found by the 2010 Brazilian National Demographic Census concerning the Santa Catarina population's schooling levels. According to the census, 32.07% had no school education or incomplete primary school, whereas 58.05% had finished primary school or more.[10]

Most of the population treated at CEPON due to cutaneous melanoma diagnoses came from the Greater Florianópolis region (74.5%). Moreover, there were patients from all other five macro-regions of Santa Catarina (25.1%). Another 0.4% of the patients were from other states. It is important to note that CEPON was the state reference center for the disease until 2018. The institution performed sentinel lymph node biopsy, serving patients from all state regions, justifying the wide coverage of care.

Sun exposure, mainly through intermittent exposure and sunburn, has a strong association with the development of melanoma. Despite this relationship, the present study identified only 35.76% of patients working under high sun exposure, a result similar to that observed by Ferreira et al. (2018),[25] evidencing 26.6% of workers subjected to high sun exposure. It was also noticed that 35.26% of the tumors were classified as the superficial spreading melanoma subtype, the most common in the literature[28] and, in the present study, also being more related to seasonal sun exposure.

Regarding tumor histology, spreading superficial melanoma was also the most frequent subtype observed in Brazilian studies, as reported by Wainstein et al. (2020)[22] (91%) and Costa et al. (2019)[26] (35.1%). Similar data were also found in southern Brazil by Naser (2011)[11] in a retrospective study carried out in Blumenau (53%). However, concerning tumor histology, 35.68% of them were classified as melanoma NOS. This can be explained by the incidence of *in situ* melanoma, which in many cases was not classified according to the histological subtype. In addition, tumor diagnosis was only defined through immunohistochemistry, making it difficult to define the histological subtype. Melanoma NOS was the most frequently classified among 78.1% of the tumors in a Brazilian study conducted by Melo et al. (2018).[21] Another relevant factor was the ulceration status found in 35.8% of the lesions, reflecting a prognosis that is part of the AJCC.[16]

The most frequent primary tumor site was located in the trunk in both genders (39.32%). It is possible to find divergent data in the literature regarding this variable. According to Lima et al. (2015)[12] and to Foiato et al. (2018),[23] the trunk was also the most common location of primary tumors in studies carried out in the cities of Brusque and Curitiba, respectively. In contrast, Vazquez et al. (2015)[29] demonstrated that the most prevalent location in Brazilian women was the lower limbs (36.3%). In addition, Tomizuka et al. (2017)[30] showed that the lower limbs were the most frequent topography for both genders (49.8%) in Japan. In contrast, Loria et al. (2020)[31] observed higher prevalence in men's trunk (37%) and in women's lower limbs (29%) in Argentina.

The Breslow index was grouped as suggested by the 8th edition of the AJCC.[16] The results showed a similar distribution between the groups according to their thickness. The group with tumor thickness between 1 and 2mm was the most frequent (17.95%). This result was different from other studies with a similar design, such as Lima et al. (2015),[12] Wainstein et al. (2020)[22] and Foiato et al. (2018),[23] showing prevalent tumor thickness smaller than 1mm (17.92%, 42%, and 32.1%, respectively).

Most diseases were staged at CS IV (27.92%) during diagnosis, characterized as metastatic and with a worse prognosis. Early diagnosis is considered difficult since the lesions are initially asymptomatic, delaying search for medical care. This result was also different from studies with a similar design in which CS IV was the least prevalent. According to Foiato et al. (2018),[23] only 3.4% of the patients presented metastatic disease, whereas Vazquez et al. (2015)[29] reported 15.7%. In contrast, almost half of the patients (43.2%) were diagnosed with early disease at CS 0, IA or IB, with an excellent prognosis. A similar scenario was observed by Melo et al. (2018),[21] in which 53.2% of the patients were diagnosed with melanoma at early CS. The most affected metastatic sites were located in the lungs and bronchi (19.64% of the lesions), followed by involvement of non-regional lymph nodes (17.35%) and of the central nervous system (13.70%).

The first treatment received at the hospital varied according to the patients' CS and was in accordance with the national recommendations.[20] Systemic treatments for melanoma have advanced in the last decade, promoting important changes in the context of adjuvancy, highlighting target therapy[15-18] and immunotherapy.[32-34] These options are still considered to be of high cost. Despite this limitation, it was observed that some patients had access to these therapies at CEPON, even as a free public health service.

These results can target primary and secondary prevention campaigns and policies for this population and reduce the high rate of metastatic disease diagnoses. In this sense, the present study highlights the increased prevalence of advanced melanoma and, thus, ratifies the need for improvement and access to better treatments in the public scenario. Therefore, we believe that the recent approval by the National Commission for the Incorporation of Technologies (*Comissão Nacional de Incorporação de Tecnologias*, CONITEC) in the unified health system of immunotherapy for advanced non-surgical and metastatic melanoma, according to ordinance SCTIE/MS No. 23, dated August 4th, 2020, will be a game-changer in this scenario.

The descriptive, cross-sectional and observational design has some limitations and biases. Selection bias may have occurred since only patients referred to the institution are treated. Many may not have been referred in the case of diseases with early diagnosis, underestimating the number of melanoma cases. It is also important to highlight the absence of some information in the database of this study. To minimize this bias, it was necessary to resort to physical medical records, although few relevant data have been found, representing a problem inherent to retrospective studies. In this same sense, the situation worsened with restricted access to the Institution due to the COVID-19 pandemic.

Thus, the sociodemographic data and the topography of the injuries could not be reviewed according to the medical records. Another limitation was related to the pathological skin analysis carried out by professionals from different institutions who, in some cases and for unknown reasons, did not describe the histological subtype in their reports, making it difficult to standardize the information.

CONCLUSION

In summary, it is concluded that the sociodemographic profile and the clinical characteristics (e.g., location of the primary tumor, histological subtype) were similar to those obtained by other national and international studies.

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