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Original Research

Time-to-treatment initiation for cutaneous melanoma reflects disparities in healthcare access in Brazil: a retrospective study

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ABSTRACT

Objectives: This study aimed at identifying the sociodemographic and first treatment characteristics affecting time-to-treatment initiation (TTI) of patients with cutaneous melanoma assisted by the Brazilian Unified Health System (SUS).
Study design: Retrospective observational study using cutaneous melanoma cases recorded in the Brazilian Hospital-Based Cancer Registries (HBCR).
Methods: A total of 12,783 cutaneous melanoma cases were included in the analysis. Based on the legislation, TTI in Brazil is 60 days; therefore, the cohort was dichotomized into TTI within 60 days and over. The association among variables was evaluated through the Chi-squared test. Kaplan–Meier method and log-rank hypothesis test were used to determine the probability of initiating treatment within 60 days. Cox proportional hazards regression model was used for multivariate analysis.
Results: Median TTI was 28 days (95% CI, 25–29). First treatment in SUS provided more than 60 days after diagnosis (34.8%) was associated with females; low level of formal education; living or getting treatment in northern Brazil; being diagnosed in SUS and treated at different healthcare facilities, in addition to starting treatment with radiotherapy or systemic therapy. There were no significant differences in access to health care before and after the enactment of the 60-day law.
Conclusion: Increased TTI for cutaneous melanoma is associated with sociodemographic and first treatment characteristics in Brazil; approximately one-third of cases did not have access to first treatment within the period established by law. Receiving the diagnosis and treatment at different healthcare facilities (transitions in care) is the main independent factor associated with TTI longer than 60 days.
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Introduction

Cutaneous melanoma is the most lethal skin cancer. Patients diagnosed in the early stages present a specific disease survival rate higher than 78% within 5 years; however, this value drops to 40% in advanced cases.[1] The standard treatment is surgery, and a long delay in undergoing this procedure makes patients' cases worse.[2] Diagnosis of cutaneous melanoma at its advanced clinical stages (III and IV) in Brazil is almost four times higher than that recorded for populations in developed countries.[3–5] It was also observed that, for the most advanced cases, melanoma treatment is more expensive in both the public (SUS) and private Brazilian health systems.[6]

Time-to-treatment initiation (TTI) is crucial for the best prognosis of several cancer types,[7–10] including cutaneous melanoma.[2] Recent studies have shown that different sociodemographic and health assistance characteristics, such as healthcare system type and provided treatment,[9,11,12] transitions in care between health institutions,[8,11–13] education level,[9,11] race,[9,11,14] sex and distance from the hospital where treatment is offered,[9] are related to increased TTI. Although the worse prognosis in cutaneous melanoma correlates with several demographic, socio-economic, and health care access variables,[15] heretofore, race is the only known parameter associated with longer TTI.[14]

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The time limit from diagnosis to first treatment (60 days) is established by law in Brazil since 2013;[16] however, it is known that, unfortunately, this is not what happens. The access to the most suitable treatments is not always available in many parts of the country.[17] Therefore, the impact of sociodemographic characteristics and first treatment with TTI for cutaneous melanoma in cases assisted in SUS was evaluated.

Methods

Ethical aspects

The Brazilian National Health Council's Resolution n. 510 — from April 07, 2016, states that research using data collected from public databases, without the identification of individuals, does not need to be reviewed by research ethics committees.

Data source

A retrospective observational study was conducted in the public database of the Brazilian Hospital-Based Cancer Registries (HBCR), available at https://irhc.inca.gov.br/RHCNet/. The Brazilian HBCR integrator is a WEB system managed by the Brazilian National Cancer Institute (INCA, Ministry of Health), and fed by SUS hospitals that are qualified in oncology.

A thematic map was designed in ArcGIS 10.5 software to assess the spatial distribution of HBCRs at a nationwide level, based on the Graphic Semiology systematized by Bertin.[18] The map was elaborated using data provided by INCA's Population Research Division and by the Brazilian Institute of Geography and Statistics (IBGE).[19]

Study population

Cutaneous melanoma cases were selected based on morphological codes set for this cancer type, as described in the International Classification of Diseases for Oncology (ICD-O): 8720/2, 8720/3, 8721/3, 8722/3, 8723/3, 8730/3, 8740/3, 8742/3, 8743/3, 8744/3, 8745/3, 8761/3, 8770/3, 8771/3, 8772/3. Cases registered between 2009 and 2017 were included in the study to evaluate the effectiveness of the '60-day law' (Federal Law number 12.732/12, May 3, 2013) upon observing a 5-year period before and after the law's enactment. Data from each analyzed year were downloaded on April 4, 2020, and subsequently, entered into a single database created in Stata software (version 15).

Of the 34,433 registered cutaneous melanoma cases, 22,978 received no treatment before their registration at HBCR; those were selected for the study. The first treatment provided to 2665 cases was neither surgery, systemic therapy nor radiotherapy; therefore, they were not considered in the cohort. Another 205 cases were also excluded because patients were younger than 18 years, older than 109 years, or were of indigenous race. Cases among the indigenous population ($n = 10$) were left out owing to the lack of definition for 'indigenous'. For example, in Brazil, some registries only include indigenous people who have no racial mixture, and others consider those with any indigenous ancestry.[20]

It was not possible to calculate the time from diagnosis to treatment initiation of cases with missing information about the dates of diagnosis or/and treatment initiation ($n = 371$). Inconsistent dates and/or typing mistakes were factors taken into consideration in the exempted cases because (i) the dates were not in the format adopted in Brazil (day, month, year), (ii) the time from diagnosis to first treatment was longer than 365 days, and (iii) the cases in which the first treatment was provided before the histopathological diagnosis ($n = 665$). The application of the exclusion criteria resulted in 19,072 eligible cutaneous melanoma cases.

Variables presenting 30% or more missing values were not included in the statistical analysis. The final cohort comprised 12,783 cases recording 100% data regarding variables sex, age, formal education, Federative Unit (FU) of residence and treatment, type of healthcare system in which the diagnosis was established (SUS or non-SUS), transitions in care between health institutions and first form of treatment.

Statistical analysis

The absolute and relative frequencies of categorical variables were calculated to evaluate the characteristics associated with TTI for cutaneous melanoma cases. Continuous variables were expressed as mean values followed by 95% confidence intervals (95% CI).

The Chi-squared test was used to analyze differences between patients who started treatment within 60 days and those who started it thereafter. The average time from diagnosis to first treatment, and its respective 95% CI, were calculated through survival analysis; cutaneous melanoma diagnosis was the onset event in this analysis and cutaneous melanoma treatment was the occurrence in this analysis.

The Kaplan–Meier method, followed by the log-rank hypothesis test, was applied to estimate the probability of starting treatment within 60 days of diagnosis. Semiparametric Cox proportional hazards regression model was used to assess the hazard ratio (HR) of TTI within 60 days. Variables for which *P*-value was <0.02 in the bivariate analysis were included in the multivariate comparison, and all variables included therein were adjusted for confounders (sex, age group, formal education, region of treatment, healthcare unit at diagnosis, transition in care and first treatment). The category that featured the highest frequency was the criterion of choice for the baseline in the model. Statistical analyses were carried out in Stata software (version 15), and *P*-value <0.05 was considered to be statistically significant.

Results

The number of registered hospitals per 100,000 inhabitants in each Federative Unit (FU) in Brazil is shown in Fig. 1. HBCRs are observed in all regions of the country, and 46.6% of them are concentrated in southeastern Brazil. The southern and northeastern regions account for 21.0% and 19.3% of these hospitals, respectively. The midwestern and northern regions, in turn, have the lowest concentration of registered hospitals: 8.7% and 4.4%, respectively.

Among cutaneous melanoma cases registered in Brazil between 2009 and 2017 included in the analysis, 65.2% started treatment within 60 days after diagnosis (Table 1). Melanoma frequency was similar in both sex groups, and the 50–69 years age group represented 45.3% of cases. Almost half of our cohort did not complete elementary school. Regarding the region of residence, southeastern Brazil accounted for the highest percentage of cases, whereas the northern and midwestern regions had the lowest percentages.

When TTI was compared between males and females, the frequency of men who have received first treatment within 60 days was higher than that of women. Concerning TTI, age distribution among cases did not vary substantially, although it was statistically significant. It may be because large data are linked to a fallacy of a large sample size,[21] that is, extreme statistical significance despite small or even trivial effect sizes.[21,22] However, with respect to formal education, 54.8% of patients with TTI longer than 60 days did not complete elementary school. Residence region also influenced TTI; the frequency of residents in northern Brazil who have initiated treatment more than 60 days after diagnosis was almost two

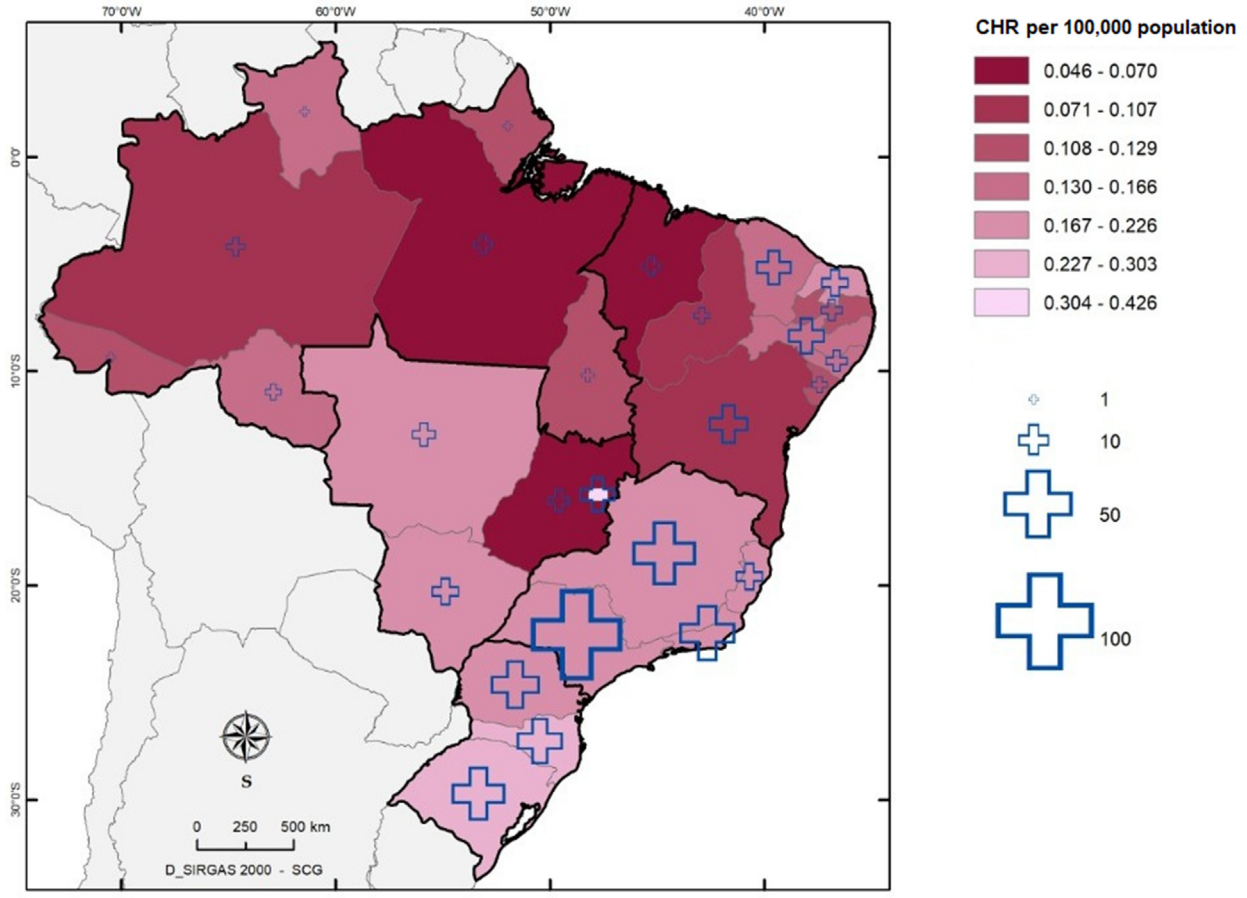

Fig. 1. Hospital units composing the integrated system of Hospital-Based Cancer Registries (HBCRs) per 100,000 inhabitants in Brazil. + Corresponds to the Proportional Geometric Figure method, which points out the number of healthcare units comprised in the HBCR per 100,000 inhabitants in each Federative Unit (FU) of Brazil.

Table 1
Sociodemographic characteristics and time-to-treatment initiation for cutaneous melanoma (Brazil, 2009–2017).

Sociodemographic characteristics	Total		Time-to-treatment initiation				*P*-value[a]
			Within 60 days		More than 60 days		
	n	%	*n*	%	*n*	%	
Total	12,783	100.0	8335	65.2	4448	34.8	n.a.
Sex							
Male	6306	49.3	4215	50.6	2091	47.0	<0.001
Female	6477	50.7	4120	49.4	2357	53.0	
Age (years)							
20–39	1437	11.2	974	11.7	463	10.4	0.032
40–49	1882	14.7	1215	14.6	667	15.0	
50–59	2765	21.6	1767	21.2	998	22.4	
60–69	3033	23.7	2001	24.0	1032	23.2	
70–79	2395	18.7	1524	18.3	871	19.6	
80 or +	1271	9.9	854	10.2	417	9.4	
Formal education							
Illiterate	1151	9.0	700	8.4	451	10.1	
Incomplete elementary school	5068	39.6	3081	37.0	1987	44.7	<0.001
Complete elementary school	2476	19.4	1665	20.0	811	18.2	
Complete high school	2595	20.3	1771	21.2	824	18.5	
College degree	1493	11.7	1118	13.4	375	8.4	
Region of residence							
South	3966	31.0	2662	31.9	1304	29.3	<0.001
Southeast	6162	48.2	4010	48.1	2152	48.4	
Midwest	337	2.6	224	2.7	113	2.5	
Northeast	2019	15.8	1282	15.4	737	16.6	
North	299	2.3	157	1.9	142	3.2	

[a] Corresponds to the *P*-value in the Chi-squared test, n.a.: does not apply.

Table 2
First treatment characteristics and time-to-treatment initiation for cutaneous melanoma (Brazil, 2009–2017).

Health assistance characteristics	Total		Time-to-treatment initiation				*P*-value[a]
			Within 60 days		More than 60 days		
	n	%	*n*	%	*n*	%	
Total	12,783	100.0	8335	65.2	4448	34.8	n.a.
Region of treatment							
South	3987	31.2	2683	32.2	1304	29.3	<0.001
Southeast	6336	49.6	4101	49.2	2235	50.2	
Midwest	226	1.8	162	1.9	64	1.4	
Northeast	1985	15.5	1261	15.1	724	16.3	
North	249	1.9	128	1.5	121	2.7	
Healthcare unity at diagnosis							
SUS	6815	53.3	4001	48.0	2814	63.3	<0.001
Non-SUS	5968	46.7	4334	52.0	1634	36.7	
Transition in care							
Yes	5322	41.6	1714	20.6	3608	81.1	<0.001
No	7461	58.4	6621	79.4	840	18.9	
First treatment							
Surgery	11,510	90.0	7703	92.4	3807	85.6	<0.001
Radiotherapy	460	3.6	226	2.7	234	5.3	
Systemic therapy	813	6.4	406	4.9	407	9.2	
Registration							
Before the 60-day law	5589	43.7	3619	43.4	1970	44.3	0.345
After the 60-day law	7194	56.3	4716	56.6	2478	55.7	

SUS: Brazilian Unified Health System (Sistema Único de Saúde, SUS).
[a] Corresponds to the *P*-value in the Chi-squared test. n.a.: does not apply.

times higher than that recorded for the ones who have started it within 60 days.

Table 2 shows the impact of the first treatment characteristics on TTI. The analysis of the region of treatment showed a 33% loss of cases in the midwest region compared to residents in this region over the same period (Table 1). Cutaneous melanoma cases diagnosed in SUS accounted for the majority of TTI spanning more than 60 days. Treatment at the same institution where the diagnosis was made (i.e. no transition in care between health institutions[8]) was registered in higher rates for cases of TTI within 60 days. The first treatment was surgery in most cases. The 60-day law did not influence the ratio of patients who have started the treatment within this period.

The average TTI for cutaneous melanoma in Brazil was 28 days (95% CI, 25–29); it did not change much due to the enactment of the aforementioned law. Median time for the assessed variables corroborated with the reported findings (Supplementary Table 1).

The probability of TTI within 60 days for cutaneous melanoma in Brazil was estimated at 64.8% — unchanged after the promulgation of the 60-day law. Men were more likely to start treatment within 60 days than women. The age groups encompassing the youngest and oldest patients presented the highest probability of TTI within 60 days. The likelihood of TTI within 60 days increases as formal education level increases (Table 3).

HR is a useful measure to quantify the risk or chance of experiencing an event, such as a clinical outcome, at a given point in time. The male sex presented an HR 5% higher for TTI within 60 days in the multivariate analysis. Formal education level has significantly influenced HR; it was 10% higher for patients who have completed elementary and high school than for the ones who did not complete elementary school. This rate reached 26% among patients who had higher formal education level. Cases treated in all other regions, rather than in the southeast, showed greater HR for TTI within 60 days; this difference was quite remarkable in the midwest region. The HR for TTI within 60 days was 34% higher among cases diagnosed in the non-SUS healthcare system; it was approximately 600% higher among cases with no transition in care between health institutions. Treatment initiated by radiotherapy or systemic therapy decreased HR for TTI within 60 days by 34% and 30%, respectively (Table 4).

Discussion

Cancer treatment must be available as soon as possible to improve survival rates;[2,7–10,23] therefore, TTI has proven to be an important tool to identify potential weaknesses in the cancer care network.[9,11,12,24] Recent studies have shown that curative surgery performed within 90 days after diagnosis, in stages I, II (localized) and III (regionally spread) of cutaneous melanoma patients, rules out adverse outcomes in this population.[2,25] On the other hand, significant mortality risk was found in TTI longer than 30 days in stage I patients when they were stratified by clinical stage.[2]

Melanoma affects individuals from all ethnic groups, but the incidence is higher in European descents.[26,27] Some particularities should be considered in the Brazilian setting as it is a mixed population country. According to INCA, the southeast and south regions represent 80.5% of the melanoma cases.[28] Although they have the lowest rates of ultraviolet radiation,[29] these two regions include 56.3% of the Brazilian population,[19] and the proportion of individuals with European ancestry are the highest in the country.[30] In agreement with these data, the southeast and south regions account for 79.2% of the cases in our cohort.

In Brazil, TTI for oncological patients is set by law since 2013; therefore, treatment must start 60 days after diagnosis. However, the experimental design of our study made it possible to conclude that the 60-day law did not change the rate of cases assisted within this period at SUS. Paulino and colleagues[16] carried out a study based on a 4-year time lapse before and after this law was enacted using the HBCR database. They showed that the 60-day law did not expand the access to first treatment for patients with gynecological cancer. Apparently, this regulation remains an aspiration for many.

Moreover, our results identified sociodemographic and first treatment characteristics related to longer TTI. Sex and age lightly influenced longer TTI in our research, as well as in other similar studies.[8,11,12] The higher the level of education, the greater the access to first treatment for cutaneous melanoma within 60 days.

Table 3
Probability of time-to-treatment initiation within 60 days for cutaneous melanoma (Brazil, 2009–2017).

Sociodemographic and health assistance characteristics	Probability of time-to-treatment initiation within 60 days		
	P_{60}	95% CI	*P*-value[a]
Global	64.8	64.0–65.6	n.a.
Registration			
Before the 60-day law	64.5	63.2–65.8	0.606
After the 60-day law	65.1	64.0–66.2	
Sex			
Male	66.6	65.4–67.7	<0.001
Female	63.2	62.0–64.4	
Age (years)			
20–39	67.5	65.0–69.9	<0.001
40–49	63.9	61.7–66.0	
50–59	63.6	61.8–65.4	
60–69	65.8	64.1–67.5	
70–79	63.3	61.3–65.2	
80 or +	66.8	64.2–69.4	
Formal education			
Incomplete elementary school	60.5	59.3–61.7	<0.001
Complete elementary school	66.7	64.9–68.6	
Complete high school	68.0	66.2–69.8	
College major degree	74.4	72.1–76.5	
Region of treatment			
South	67.0	65.5–68.4	<0.001
Southeast	64.3	63.1–65.5	
Midwest	71.7	65.7–77.4	
Northeast	63.2	61.1–65.3	
North	51.4	45.4–57.7	
Healthcare unity at diagnosis			
SUS	58.3	57.1–59.5	<0.001
Non-SUS	72.3	71.2–73.5	
Transition in care			
Yes	31.5	30.3–32.8	<0.001
No	88.6	87.9–89.3	
First treatment			
Surgery	66.5	65.7–67.4	<0.001
Radiotherapy	48.7	44.2–53.3	
Systemic therapy	49.6	46.2–53.0	

CI: confidence interval; SUS: Brazilian Unified Health System (Sistema Único de Saúde, SUS).
[a] Corresponds to the *P*-value in the Log-rank test.

Table 4
Multivariate analysis adjusted for covariates to estimate the hazard ratio of time-to-treatment initiation within 60 days for cutaneous melanoma (Brazil, 2009–2017).

Sociodemographic and health assistance characteristics	Adjusted model[a]	
	HR	95% CI
Sex		
Female	1.00	–
Male	1.05	1.01–1.10
Age (years)		
20–39	1.07	0.98–1.15
40–49	1.01	0.93–1.08
50–59	0.97	0.90–1.03
60–69	1.00	-
70–79	0.93	0.86–0.99
80 or +	0.99	0.91–1.07
Formal education		
Incomplete elementary school	1.00	–
Complete elementary school	1.10	1.03–1.17
Complete high school	1.11	1.04–1.18
College major degree	1.26	1.17–1.35
Region of treatment		
Southeast	1.00	–
South	1.30	1.23–1.37
Midwest	1.73	1.47–2.03
Northeast	1.22	1.14–1.30
North	1.20	1.01–1.44
Healthcare unity at diagnosis		
SUS	1.00	–
Non-SUS	1.34	1.27–1.42
Transition in care		
Yes	1.00	–
No	6.09	5.76–6.44
First treatment		
Surgery	1.00	–
Radiotherapy	0.66	0.59–0.76
Systemic therapy	0.70	0.64–0.78

HR: hazard ratio; CI: confidence interval; SUS: Brazilian Unified Health System (Sistema Único de Saúde, SUS).
[a] Model adjusted by sex, age group, formal education, region of treatment, healthcare unit at diagnosis, transition in care and first treatment.

Education level can be a determining factor for access to health care services, once it is related to understanding medical instructions that are provided during the confirmation of the diagnosis.[31] The lower the educational level, the longer the TTI in cancer patients,[8,9,11,12] as well as worsening their survival rates.[7–10,23] Lower education was related to cutaneous melanoma diagnosis at its most advanced stages in Sweden, but it did not influence the time from biopsy to curative surgery among stage I and II patients.[31]

Brazil has a continental territory and clear social inequalities that are highlighted in studies focused on comparing social and sanitation indicators recorded for different regions in the country.[17,32] The rate of TTI cases longer than 60 days was almost two times higher in the northern region. A study carried out with data from the HBCR integrator about breast cancer evidenced similar outcomes.[33] According to our study, the increased HR to start the first treatment within 60 days recorded for this region can be explained by the difference between the two categories in these sampling groups, as the average time recorded for the southeastern region was almost half of that recorded for the northern region (Supplementary Table 1). The low registration rates shown in the northern region reflect the health care weaknesses therein, such as reduced number of hospitals and physicians,[17,32] as well as the lower incidence of melanoma in this region, 2.3%.[28] The health care shortcoming in this region is reflected by most FUs in the northern region having low HBCR density per 100,000 inhabitants, as illustrated in Fig. 1.

Median TTI time after the 60-day law enactment increased by almost eight times in the midwest region. Because the variation between the two periods was significant, both the global probability and the HR to start the first treatment within 60 days were the most significant in the country. Based on the *Cancer Surveillance Newsletter n.7*, published by INCA[34] in 2020, there was an intense flow (~33.4%) of patients with skin cancer who lived in the midwestern region, to look for treatment in São Paulo State, southeastern Brazil, between 2012 and 2016. Out of those, 63.3% of cases in Goiás State (GO), 30.5% of cases in Mato Grasso do Sul State (MS), 29.6% of cases in Mato Grosso State (MT) and 10.2% of cases in the Federal District (DF). This finding has highlighted the long routes taken by patients living in these regions to start the first treatment; consequently, it makes TTI longer. Changes in oncological care services implemented in this region may account for the lengthened time to first cancer treatment after the '60-day law' was enacted, and such fact deserves further analysis in subsequent studies.

Health care in Brazil is provided in three different settings: Public Unified Health System (SUS), health insurance coverage or direct private payment. Differences between the assistance given by the public and non-public healthcare systems — with emphasis on the advantages of non-public assistance — were evidenced in international[7,9–12,23,35] and Brazilian[24,36,37] studies about cancer care and survival. Lima and colleagues[36] have shown that most colon and rectum cancer cases registered in HBCR between 2006

and 2015 — with TTI longer than 60 days were assisted by SUS since the diagnosis.

Lesion biopsy is the golden standard for cutaneous melanoma diagnosis. It was possible to observe higher probability and HR of starting treatment within 60 days among cases with diagnosis and treatment in the same health institution. Diagnosis and treatment in different health institutions causes remarkable increase in TTI.[8,11–13] All Brazilian FUs have at least one hospital qualified in oncology, where it is possible to carry out the whole range from diagnosis to the most complex treatment protocols.[13,16] However, owing to health centralization, patients oftentimes experience care provided by different health institutions during their treatment.[16,38] Furthermore, Balmant and colleagues[13] attributed such longer time of treatment to the fact that, in some cases, the diagnosis needs to be confirmed by a pathologist from the qualified oncology hospital.

Surgery was the first treatment most frequently used in cases comprising our cohort; it presented the highest probability and HR of receiving first treatment within 60 days after diagnosis. On the other hand, the low ratio between cases initially treated with radiotherapy, or with systemic therapy, and the worst indicators observed for these treatments showed the difficulty to access them. Soft tissue sarcoma[12,39] and breast cancer[40] patients who did not start treatment by surgery are also related to longer TTI. Access to, and availability of, radiotherapy is limited in most low- and middle-income countries.[41] The average time to start the treatment by radiotherapy in Brazil is ~50 days.[42,43] Systemic cancer treatment is also a barrier in the country, for example, patients with non-SUS health assistance have more access to last-generation breast cancer therapies than SUS users.[37] SUS spends 90 times less with systemic therapy for melanoma cases than the private health system, whose treatment options for advanced disease range from cheaper chemotherapy agents to expensive monoclonal antibodies.[6] In August 2020, monoclonal antibodies that target immune checkpoints were added to the list of treatments available at SUS.[6] It represents a great advancement for Brazilians with metastatic melanoma, as these therapies are very expensive and, consequently, have a negative impact on the survival rates of patients facing the worst socio-economic conditions.[15,44]

The major limitation of this study lies on incomplete records and on likely lack of standardization of the variables since we used a secondary database. Information about race, marital status, clinical status at diagnosis and histological aspects were not included in the models to avoid selection biases. Despite these limitations, our data provided substantial information about first treatment of cancer in SUS; the findings can help designing more effective public health policies and enable resource allocation decisions focused on early cancer treatment, in general.

In conclusion, several sociodemographic and first treatment characteristics were related to longer TTI for cutaneous melanoma; moreover, the '60-day law' did not have an impact on access to melanoma treatment at SUS in the herein assessed period. The transition between health care institutions stood out as the greatest independent factor for longer TTI. Despite the structural problems of the system, which are barriers to cancer care in Brazil, the wide propagation of legal rights for patients with cancer could help minimizing the aforementioned disparities, in the short term.

Author statements

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Ethical approval

The Brazilian National Health Council's Resolution n. 510 — from April 07, 2016, states that research using data collected from public databases, without the identification of individuals, does not need to be reviewed by research ethics committees.

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Competing interests

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.06.006.

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