Oncological treatment in Brazil: a gender and region are associated to starting the therapeutics

Tratamento oncológico no Brasil: um risco associado ao início da terapêutica

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ABSTRACT

Introduction: Malignant neoplasms are a major public health problem, being the second leading cause of death in the world. In 2012, the Ministry of Health (BR) instituted Law No. 12,732, which grants cancer patients the right to obtain, from the anatomopathological diagnosis, access to the first treatment in the Brazilian Healthcare System - Sistema Único de Saúde (SUS), within up to sixty days. The change in the patient's prognosis is the aim of this program. Objective: To evaluate the panorama of the time to start cancer therapy in Brazil. Methods: This is a cross-sectional and analytical study on the time for the establishment of the beginning of cancer treatment in Brazil, in the period from 2013 to 2019. The data were extracted from the PANEL-Oncology of the informatics department of Unified Health System. Chi-square and Fisher’s exact tests were used to analyze proportions and risk ratios, respectively. Results: The percentage of malignant neoplasms that had the longest delay in starting therapy (>60 days) in the country were prostate (59.6%) and cervix (50.9%). As for sex, the delay was present in 36.9% of men and 33.3% of women (p<0.05). Differences in the rates of cancers with and without delay for the institution of treatment are also evident in the Brazilian macroregions (p<0.05). Assessing the odds ratio for delayed cancer treatment, the male gender is shown to be a risk factor (p<0.05) in all regions, except in the North of the country. The risk for delayed treatment differs depending on the type of cancer. Conclusion: Cancers that have a longer delay in starting therapy are those that have health policies aimed at their screening.

Keywords: Oncology; Therapeutics; Risk factors.
INTRODUCTION

Malignant neoplasm (MN) are cells with abnormal proliferation and it represents a worldwide public health problem.\[^1,2\] The MN is the second cause of death in the world and it has been related with several risk factors, especially, those associated to socioeconomic conditions and aging.\[^3-5\] Therefore, strategies to reduce cancer rates were made and, one of them, is a better understanding of the mechanisms that induce the formation of MN. In regard to that, the ability of the MN cells to: self-sufficiency, avoidance of cell death, development of an own angiogenesis system, invasion of local tissues, spreading to distant sites\[^1,2,6\] are determined by TNM staging system and it has been done to assist in determining therapy; predicts the patient’s prognosis; helps to limit therapy and it has be done to assist in determining therapy; determines the elapsed time between the diagnosis and establishment of the cancer therapy leads to better prognosis and increase the proportions of cure.\[^9,10\]

The Brazilian Ministry of Health (MH) through Ordinance No. 874 of May 2013\[^8\] instituted the National policy for the prevention and control of cancer determines the elapsed time between the diagnosis and establishment of the cancer therapy leads to better prognosis and increase the proportions of cure.\[^9,10\] The establishment of the Law No. 12,732: “all patients with malignant neoplasm must be submitted to the first treatment, from the confirmation of the diagnosis, within up to 60 (sixty) days”, recognizes that the early access to the treatment is effective against cancer and it guides the physicians decision.\[^11,12\]

Thus, we aim to analyze the time of the start of the oncological therapy in Brazil, through the data contained in the PANEL-Oncology (DATASUS). As well, identify the most delayed MN in Brazil, between all the demographic regions and verify how the sex variable acts a risk factor for the delay in the establishment of the oncological treatment.

METHODS

This study is a cross-sectional and analytical study with secondary data, based on time to the establishment of the oncological treatment in Brazil, between the years 2013 to 2019. The data were extracted from the “time until the beginning of the oncological treatment - PANEL-Onco of the informatics department of Unified Health System” (DATASUS). The time to start the treatment was stratified in two stages (up to 60 days and more than 60 days), following the Brazilian recommendations (Law No. 12,732/2012). The evaluated variables were sex, age and staging in different regions: North, Northeast, Midwest, Southeast, and South of Brazil. The study included the CID often MN that takes longer to be treated in Brazil based in DATASUS information. In the group of ten MN, CIDs were selected, common to all regions; resulting in eight MN to be analyzed.

From the data obtained in DATASUS, tables were built using Microsoft Excel, version 2019, and the proportions related to the delay for each variable under study were tested by Fisher’s exact test, using the GraphPad Prism program, version 8.4.3, p-value less than 0.05 was considered significant and finally, the odds ratio (OR) was calculated and the forest plot was elaborated - with a 95% confidence interval, to ascertain the possibility of an association between the delay in the cancer treatment. This study uses
secondary data from Brazilian Government without patient identification and it was not necessary to apply informed consent term, but still in compliance with the resolution of the National Health Council (CNS/BR) No. 196, of October 10, 1996.

RESULTS

After obtaining the data, we evaluated the MN which takes more time to start the therapy; for that, the time to start the treatment was stratified in “up to 60 days” and “more than 60 days” (as recommended by Brazilian Law No. 12,732/12). The cancers that presented high percentages in “more 60 days” were: secondary from other locations/metastases (n=21,159; 64.0%), prostate (n=110,289; 59.6%), breast (n=120,456; 48.8%), rectum (n=20,426; 46.6%), stomach (n=16,962; 32.5%), colon (n=23,230; 30.6%), bronchi and lungs (n=17,388; 26.8%), and these proportion were significant (p<0.01). The sex rate of individuals who initiate cancer treatment after sixty days were 36.9% (n=286,311) and 33.3% (n=293,755) for males and females, respectively (p<0.01).

However, regarding to age, younger patients were associated with early treatment, with a progressive decrease in the percentage of each age group as to the start of treatment within 60 days (p<0.01).

In terms of staging, there are a predominance of “not applicable” (n=307,170; 85.5%) and “ignored” (n=85,614; 18.1%) within up to 60 days; however, it is verified in stage 2 (about 121 thousand cases) with a high rate of delay when compared to the other groups in the segment (p<0.05) (Table 1).

Investigating the five demographic regions, the data depicted a different distribution of percentages between “up to 60 days” and “more 60 days” in age (p<0.01); the same difference are depicted in terms of staging (p<0.01). The Northern region was the only macro-region to present non-differences in sex between delayed treatment in comparison with another regions (p=0.43). In other hand, sex was homogeneous between all another regions (Table 2).

Verifying the panorama of treatment between Brazilian regions, we analyzed the risk to delay the treatment according to the sex. Therefore, the Northern region of the country was the only region with a non-significant p-value (p-value=0.43). This finding demonstrates the variable sex is not different between “up to 60 days” and “more 60 days” for initiating cancer treatment. Despite that, the differences in others regions presented the female sex as a protective factor against the delay in establishing cancer therapy, while males represents a risk, by calculating the odds ratio (OR). The

Table 1. Rate of time until the beginning of the treatment of malignant neoplasms in Brazil, considering the variables sex, age and staging (2013 to 2019); DATASUS: Oncological Panel.

| TYPE OF CANCER, n (%) | UP TO 60 DAYS | MORE THAN 60 DAYS | Does not report | Value p |
|----------------------|--------------|------------------|-----------------|---------|
| C50 – Malignant neoplasm of the breast | 119.307 (48,3) | 120.456 (48,8) | 7.093 (2,9) | <0.001 |
| C61 – Malignant prostate cancer | 59.235 (32,0) | 110.289 (59,6) | 15.570 (8,4) |
| C53 – Malignant neoplasm of the cervix | 34.721 (44,3) | 39.910 (50,9) | 3.798 (4,8) |
| C18 – Colon malignancy | 44.747 (59,0) | 23.230 (30,6) | 7.843 (10,3) |
| C79 – Secondary malignant neoplasm from other locations | 9.915 (30,0) | 21.159 (64,0) | 1.963 (5,9) |
| C20 – Malignant neoplasm of the rectum | 20.355 (46,4) | 20.426 (46,6) | 3.058 (7,0) |
| C34 – Malignant neoplasm of bronchi and lungs | 43.132 (66,4) | 17.388 (26,8) | 4.403 (6,8) |
| C16 – Malignant neoplasm of the stomach | 26.670 (51,1) | 16.962 (32,5) | 8.513 (16,3) |
| Other malignant neoplasms | 384.414 (45,0) | 210.246 (24,0) | 276.693 (31,1) |

| SEX, n (%) | <0.001 |
|-----------|---------|
| Male | 347.411 (44,8) | 286.311 (36,9) | 141.183 (18,2) |
| Female | 405.085 (45,9) | 293.755 (33,3) | 183.751 (20,8) |

| AGE, n (%) | <0.001 |
|-----------|---------|
| 0 to 24 years | 44.067 (61,5) | 10.596 (14,8) | 16.953 (23,7) |
| 25 to 35 years | 37.451 (48,7) | 18.769 (24,4) | 20.607 (26,8) |
| 35 to 44 years | 73.481 (46,5) | 49.867 (31,6) | 34.582 (21,9) |
| 45 to 54 years | 134.733 (46,1) | 104.358 (35,7) | 53.354 (18,2) |
| 55 to 64 years | 193.236 (45,1) | 159.072 (37,1) | 76.153 (17,8) |
| 65 to 74 years | 169.309 (42,9) | 152.308 (38,6) | 73.247 (18,5) |
| ≥ 75 years | 99.360 (41,8) | 88.612 (37,3) | 49.457 (20,8) |

| STAGING, n (%) | <0.001 |
|---------------|---------|
| 0 | 25.676 (49,0) | 26.716 (51,0) | 0 (0,0) |
| 1 | 35.686 (36,3) | 62.675 (63,7) | 0 (0,0) |
| 2 | 66.058 (35,4) | 120.494 (64,6) | 0 (0,0) |
| 3 | 105.931 (44,9) | 130.192 (55,1) | 0 (0,0) |
| 4 | 126.361 (50,4) | 124.598 (49,6) | 0 (0,0) |
| Not applicable | 307.170 (85,5) | 52.072 (14,5) | 0 (0,0) |
| Unknown | 85.614 (18,1) | 63.319 (13,4) | 324.934 (68,6) |
# Table 2. Rate of time until the beginning of treatment of malignant neoplasms in the Brazilian demographic regions, considering the variables gender, age and staging (2013 to 2019); DATASUS: Oncological Panel.

| Type of Cancer, N (%) | MIDWEST | NORTHEAST | NORTH | SOUTHEAST | SOUTH |
|-----------------------|---------|-----------|-------|-----------|-------|
|                       | Up to 60 Days | More Than 60 Days | P-Value | Up to 60 Days | More Than 60 Days | P-Value | Up to 60 Days | More Than 60 Days | P-Value | Up to 60 Days | More Than 60 Days | P-Value |
| C16 – Malignant neo- | 1.159 (63.9) | 859 (36.1) | <0.0001 | 6.670 (61.8) | 4.118 (38.2) | <0.0001 | 1.125 (49.1) | 1.167 (50.9) | <0.0001 | 10.842 (42.6) | 8.057 (57.4) | <0.0001 |
| plasm of the stomach |         |           |       |           |         |       |           |           |       |         |           |       |
| C18 – Colon malignancy | 3.031 (71.4) | 1.213 (28.6) | 6.955 (64.7) | 3.787 (35.3) | 746 (53.1) | 660 (46.9) | 21.487 (37.5) | 12.892 (37.5) | 12.528 (27.2) | 4.678 (72.2) |
| C20 – Malignant neo- | 1.265 (50.9) | 1.218 (49.1) | 3.436 (51.2) | 3.281 (48.8) | 477 (38.0) | 779 (62.0) | 9.673 (46.2) | 11.260 (53.8) | 5.504 (58.6) | 3.888 (41.4) |
| plasm of the rectum |         |           |       |           |         |       |           |           |       |         |           |       |
| C34 – Malignant neo- | 2.592 (72.5) | 983 (27.5) | 8.246 (73.0) | 3.049 (27.0) | 1.128 (63.6) | 646 (36.4) | 17.371 (32.6) | 8.419 (32.6) | 13.795 (32.6) | 4.291 (23.7) |
| plasm of the stomach |         |           |       |           |         |       |           |           |       |         |           |       |
| C50 – Malignant neo- | 7.344 (53.7) | 6.323 (46.3) | 28.023 (48.0) | 3.876 (44.9) | 4.760 (55.1) | 51.770 (62.1) | 28.294 (54.6) | 21.330 (43.0) | 7.584 (57.1) | 5.692 (42.9) |
| plasm of the breast |         |           |       |           |         |       |           |           |       |         |           |       |
| C53 – Malignant neo- | 2.717 (51.9) | 2.520 (48.1) | 10.772 (52.6) | 2.190 (30.9) | 4.907 (69.1) | 11.458 (14.8) | 7.584 (56.4) | 5.692 (42.9) | 7.584 (57.1) | 5.692 (42.9) |
| neoplasm of the cervix |         |           |       |           |         |       |           |           |       |         |           |       |
| C61 – Malignant prostatic cancer | 3.189 (34.0) | 6.188 (66.0) | 13.595 (65.1) | 2.146 (29.2) | 4.034 (70.8) | 29.208 (65.8) | 11.577 (61.6) | 18.563 (61.6) | 5.874 (61.6) | 4.291 (32.6) |
| C79 – Secondary malignant neoplasm from other locations | 242 (20.8) | 919 (79.2) | 1.917 (28.6) | 4.780 (71.4) | 260 (19.7) | 1.057 (80.3) | 4.418 (32.5) | 9.176 (67.5) | 3.078 (37.1) | 5.227 (62.9) |
| Other neoplasms | 24.463 (68.7) | 12.213 (33.3) | 86.331 (68.4) | 46.141 (36.6) | 11.476 (55.1) | 9.337 (44.9) | 162.860 (64.7) | 100.031 (38.1) | 109.284 (75.9) | 42.504 (29.5) |

**SEX, n (%)**

| SEX, n (%) | MIDWEST | NORTHEAST | NORTH | SOUTHEAST | SOUTH |
|------------|---------|-----------|-------|-----------|-------|
| Male | 20.861 (56.1) | 16.332 (43.9) | 71.003 (54.0) | 60.490 (46.0) | 9.896 (45.8) | 11.700 (54.2) | 151.899 (51.7) | 141.858 (48.3) | 93.752 (62.6) | 55.931 (37.4) |
| Female | 25.501 (61.3) | 16.104 (38.7) | 94.942 (58.3) | 67.916 (41.7) | 13.048 (45.5) | 15.647 (54.5) | 167.188 (54.2) | 141.085 (45.8) | 104.406 (66.3) | 53.003 (33.7) |

**AGE, n (%)**

| AGE, n (%) | MIDWEST | NORTHEAST | NORTH | SOUTHEAST | SOUTH |
|------------|---------|-----------|-------|-----------|-------|
| 0 to 24 years | 3.341 (83.2) | 673 (16.8) | 12.227 (82.0) | 2.676 (18.0) | 2.013 (65.7) | 1.053 (34.3) | 17.379 (79.5) | 4.427 (20.5) | 9.139 (84.6) | 1.659 (15.4) |
| 25 to 35 years | 2.650 (69.5) | 1.163 (30.5) | 9.676 (66.7) | 4.833 (33.3) | 1.617 (50.9) | 1.557 (49.1) | 14.193 (64.3) | 7.892 (35.7) | 9.378 (74.6) | 3.199 (25.4) |
| 35 to 44 years | 5.275 (62.5) | 3.163 (37.5) | 19.003 (60.0) | 12.672 (40.0) | 3.174 (46.4) | 3.672 (53.6) | 28.168 (56.4) | 21.740 (43.6) | 18.029 (68.3) | 8.386 (31.7) |

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| Group            | n   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|------------------|-----|---------|---------|---------|---------|---------|
| 45 to 54 years   | 8,900 | 1.523 (58.0) | 3.257 (55.0) | 2.668 (45.0) | 312 (57.6) | 230 (42.4) | 14,521 (45.1) | 17,648 (54.9) | 6,063 (45.5) | 5,065 (45.5) |
| 55 to 64 years   | 11,390 | 1.373 (28.4) | 3.469 (71.6) | 7.407 (63.1) | 12,668 (61.7) | 766 (27.6) | 2,008 (72.4) | 12,893 (30.2) | 29,770 (69.8) | 13,247 (47.3) | 14,760 (52.7) |
| 65 to 74 years   | 9,530 | 3.446 (36.9) | 5.888 (63.1) | 18,226 (38.3) | 29,381 (61.7) | 2,502 (26.3) | 7,005 (73.7) | 26,811 (31.8) | 57,466 (68.2) | 15,073 (42.1) | 20,754 (57.9) |
| ≥ 75 years       | 5,276 | 6.653 (47.3) | 7.405 (52.7) | 28,944 (44.6) | 35,929 (55.4) | 3,750 (35.9) | 6,710 (64.1) | 40,597 (41.1) | 58,285 (58.9) | 25,987 (54.3) | 21,863 (45.7) |
| 0                | 8,583 | 3.513 (53.1) | 7.586 (49.6) | 26,581 (50.6) | 25,953 (49.4) | 3,472 (35.7) | 5,270 (60.3) | 53,060 (46.5) | 60,966 (53.5) | 34,665 (58.3) | 24,823 (41.7) |
| Not applicable   | 19,285 | 3.212 (14.3) | 61,614 (88.7) | 7,848 (11.3) | 8,857 (75.5) | 2,871 (24.5) | 134,008 (81.7) | 29,896 (18.3) | 83,406 (91.1) | 8,155 (8.9) |
| Ignored          | 5,199 | 3.771 (40.7) | 19,916 (58.8) | 13,959 (41.2) | 3,285 (50.2) | 3,253 (49.8) | 37,197 (56.3) | 28,822 (43.7) | 19,717 (56.3) | 13,514 (40.7) |
minimum risk was archived by Northeast region with 1.1 times (95%CI: 1.174-1.209) and the higher South region with 1.3 times (95%CI: 1.158-1.193) (Figure 1).

Sex has been shown as an important risk factor for the delay in the start of cancer treatment in Brazilian regions. Based on that, we stratify the cases considering the CID of neoplasm, once the MN occurs with different incidence between the sexes. Thus, in the Midwest region, the risk of delay in starting cancer therapy was 5.5 (95%CI: 4.8-6.4) times for secondary from other locations/metastases and 3.1 (95%CI: 3.0-3.3) times for prostate malignancy; in the Northeast, malignant breast cancer, cervix, malignant neoplasm of the rectum, malignant prostate cancer or secondary malignant neoplasm from other locations is associated with greater risk for delay in the establishment of cancer therapy; in the north of the country, the neoplasm considered as a risk factor for delay in starting cancer treatment are those of the rectum (OR = 1.3/95%CI: 1.2-1.5), prostate (OR = 2.2/95%CI: 2.0-3.5) and secondary from other locations/metastases (OR = 3.5/95%CI: 3.0-4.1); breast and metastases are the main ones associated with the risk, which can vary from OR = 1.3 (95%CI: 1.2-1.3) in rectum to OR = 2.4 (95%CI: 2.4-2.4) in prostate cancer, in the Southeast region; the South region has the risk of delaying the start of cancer treatment, the identification of: secondary from other locations/metastases (OR = 3.1/95%CI: 3.0-3.3), malignant prostate cancer (OR = 3.3/95%CI: 3.2-3.3), malignant breast cancer (OR = 1.4/95%CI: 1.4-1.4) and malignant neoplasm of the rectum (OR = 1.2/95%CI: 1.2-1.3). On the other hand, in all regions, malignant tumors of the colon ([Midwest OR = 0.5/95%CI: 0.5-0.5], [Northern OR = 0.4/95%CI: 0.4-0.5]), (Northeast OR = 0.6/95%CI: 0.6-0.7), (Southwest OR = 0.6/95%CI: 0.6-0.6), (South OR = 0.6/95%CI: 0.6-0.6)], bronchi ([Midwest OR = 0.5/95%CI: 0.4-0.5], (Northern OR = 0.4/95%CI: 0.4-0.5), (Northeast OR = 0.4/95%CI: 0.4-0.4), (South OR = 0.5/95%CI: 0.5-0.5]), and lungs ([Midwest OR = 0.5/95%CI: 0.4-0.5], (Northern OR = 0.4/95%CI: 0.4-0.5), (Northeast OR = 0.4/95%CI: 0.4-0.5), (South OR = 0.4/95%CI: 0.4-0.4), (Southwest OR = 0.4/95%CI: 0.4-0.4), (South OR = 0.5/95%CI: 0.5-0.5)]. The socioeconomic disparities reflect the health of the population and the access to existing health services, even though the SUS tries to mitigate the unfavorable outcomes.\[17-22\]

Therefore, individuals in unfavorable socioeconomic conditions are the portion of the Brazilian population with the highest rates of MN and, consequently, represent the majority of individuals who have a delay to begin the cancer therapy. Staging, on the national and regional levels, has not been shown to have a major impact on delaying the cancer treatment, although it is proven the treatment for

**DISCUSSION**

Most of the Brazilian population (about 160 million individuals) depend on the assistance offered by Brazilian Healthcare System - Sistema Único de Saúde (SUS), and it needs to be discussed\[12,13\] Since the treatment is not standardized, with several therapeutic approaches to the same neoplasm depending in the location of the treatment center or even on demand\[14\] The rates for delayed to initiate the cancer treatment in Brazil reflex the characteristics of the Brazilian regions\[11,15,16\] The socioeconomic disparities reflect the health of the population and the access to existing health services, even though the SUS tries to mitigate the unfavorable outcomes.\[17-22\]
most tumors occurs in advanced stages. This fact is linked to the precariousness of the provision of diagnostic services in the oncological sphere. [12,14,19,20] The scarce investment in the elaboration and/or to implement actions in primary healthcare, is linked to the prevention in the most prevalent types of cancers in the Brazil.[3,18] The delay to start the cancer treatment for MN of the breast and cervix are probably related to the screening policies recommended by the MH, which generate a large number of diagnoses for these cancers.[12-25] Rodrigues et al. (2015),[26] evaluate the breast cancer, using the campaign for active screening of this cancer and found an elevation in the identification. The prostate cancer is the second most common cancer in men in the country and there is a preventive campaign called “Blue November” that campaign was elaborated nationwide, which increases the number of diagnosed for that cancer in Brazil [3,5,27,28] it is noted that the screening policies, despite contributing to the diagnosis of MN in early stages.[9-11,25] Wherever, the early diagnoses are not correlated with treatment within sixty days. The malignant tumors of the cervix is potentially preventable and it is the third most common type of cancer in the female population.[23,25] The MH is acting improving the vaccination campaigns against human papilloma virus (HPV),[23,25,29-33] but it does not seems to be enough to reduce the high mortality generated by this cancer.[30] This situation is related with the social and economic differences between regions, which results in an uneven distribution of care centers for cancer patients and a delay in establishing the therapy for this type of malignant tumor.[12,14,16,17,20]

The colorectal cancer presents several risk factors, like: male gender, black ethnicity, inflammatory bowel diseases, age over 50 years, smoking, and eating habits.[34,35] Brazilian demographic regions have similar socioeconomic patterns to developed countries, such as the southern region of Brazil express a higher incidence of this cancer.[34] Poor Brazilian regions such the Northeast region of the country, also express a higher prevalence of this type of neoplasm and due to a poor healthcare system, culminating in the delay to start the cancer therapy. In the North, unlike the other regions, there was no risk relationship between sex and the delay in starting the establishment of cancer treatment. On the other hand, being male in the other regions (Midwest, Northeast, South and Southeast) is a risk factor for delay the cancer treatment. According to Rodrigues et al. (2015),[26] the North region, especially the state of Amazonas, has higher incidence and mortality rates due to cancer, it is explained by socioeconomic inequalities and low accessibility to services for the prevention.[12,14,16,18,26]

The physiopathology mechanisms of MN include intrinsic (genetic predisposition) and extrinsic factors, which are directly linked to the individual’s time of exposure to a certain type of agent (biological, physical or chemical).[2,4] When analyzing this finding, it is concluded that the sex of the subject and a distinct ways to treat the different type of cancers are risk factors for the delay the cancer treatment.[2]

This study has limitations for using secondary data from the PANEL-Oncology/DATASUS. DATASUS is an administrative-based reimbursement system and sub notifications are not archived in this study, although it, this study still innovative measuring the delay to treatment and the risk associated with this delay, giving evidence in which cancer the MH needs a more informative approach.

CONCLUSION

Several cancers are associated with the delay to start the treatment and it is influenced by Brazilian regions. The male gender is considered a risk factor for delayed initiation of treatment in all demographic regions, except in the North. Several cancers are a risk to start the treatment and it is different between Brazilian regions. Our study was tried to associate the risk of some cancer to start the treatment urging for the implementation of individualized and standardized public policies able to handle the differences in geographic areas.

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