DOI: 10.1590/1413-81232022273.02992021

Factors associated with time to initiate lung cancer treatment in Minas Gerais, Brazil

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Abstract *The aim was to verify the association of individual factors and healthcare system characteristics with time to initiate treatment of lung cancer by the Brazilian National Health System, in Minas Gerais state. A retrospective cohort study, with patients who initiated treatment for lung cancer by the SUS, from 2008 to 2015. Sociodemographic and clinical characteristics of patients, besides organizational variables of the healthcare system were selected. The logistic regression model evaluated the association of selected explanatory variables with the outcome of initiating treatment within 60 days after diagnosis. Odds ratio (OR) and respective 95% confidence interval were used to measure the power of association. Most treatments for lung cancer in the state of Minas Gerais initiated within 60 days after diagnosis. However, being male and diagnosed as stage IV increased the likelihood of starting treatment within 60 days. On the other hand, the patient's age, radiation therapy as first treatment, and the place of residence decreased such chance. Time to initiate treatment is associated with individual characteristics and provision of services in macroregions, and the observed inequalities possibly raised from the better or worse access of the population to the services provided by SUS.*

Key words *Lung cancer, Time-to-treatment, Regional Health Planning, Health status disparity*

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Introduction

In 2018, lung cancer ranked second as most frequent cancer worldwide, after non-melanoma skin cancer. It was also the most common type of cancer in men and the third most common in women[1]. In Brazil, it is estimated that 30,200 new cases of lung cancer will occur per year, between 2020 and 2022, ranking it as the third most common cancer in men and the fourth, in women. In Minas Gerais, lung cancer was the second leading cause of cancer-related death in men and women between 2014 and 2018[3], and 2,990 new cases were estimated to occur in 2020[2].

Lung cancer is divided into small cell (SCLC) and non-small cell (NSCLC) lung cancer for therapeutic and prognostic purposes. These are both highly aggressive and lethal cancers with low cure and survival rates. Mean cumulative five-year survival rates in developed and developing countries range from 13% to 21%, and 7% to 10%, respectively[4]. In a Brazilian nationwide study, 45% and 16% of affected patients survived less than 1 and more than 5 years, respectively, with higher disease-specific survival in patients in stages 0, I and II, relative to patients in stages III and IV cancer[5]. Tumors diagnosed at early stages have a better prognosis[6,7]. Delayed lung cancer management increases the chances of disease progression and hinder curative treatment[8].

Time to lung cancer treatment varies widely across the globe[9]. In England, 96% of patients initiated cancer treatment within one month of diagnosis, between 2019 and 2020[10]. In Canada, at least 97% of patients underwent radiation therapy within 28 days and 50% started treatment within 9 days of diagnosis, between 2015 and 2019[11]. In Brazil, approximately 70% of patients diagnosed with lung cancer between 2013 and 2019 started treatment within 60 days of diagnosis. However, rates differed between regions, with lower percentages in the north region of the country[12].

Associations between time to treatment and patient characteristics, such as level of education, race, skin color, income and place of residence have been examined in international studies. Treatment tends to be delayed in patients with characteristics associated with social vulnerability[9]. A Brazilian nationwide study with secondary data, conducted between 2000 and 2004, revealed longer time to initiate lung cancer treatment in female patients[13]. In a different study based on hospital data for cancer, from 2000 to 2011, time from diagnosis to treatment initiation was longer in patients aged 70 years or older. However, this difference was not statistically significant[14]. In a Brazilian study on female breast cancer, factors associated with delayed treatment varied between regions according to skin color, level of education, marital status, staging, year of diagnosis and referral to SUS[15]. Inaccessibility to treatment, especially in the north of the country, and evidence of insufficient care even in regions with greater availability of services, have been reported[16].

In November 2012, Law no. 12.732[17] was published in an effort to reduce delays in treatment. According to this law, treatment must be initiated within 60 days of diagnosis, in compliance with the National Policy for Prevention and Control of Cancer, which holds the States, the Federal District and Municipalities accountable for oncologic care and referral flow management, in order to ensure access to care within the established time frame[18].

Regionalization of health care, the backbone of the Unified Health System (SUS), plays a major role in the orchestration of medium and high complexity health care flow. Health regions defined according to territorial division are used to inform physical and financial planning. In this manner, municipalities are able to manage supply and demand, according to their respective profiles and needs[19].

Minas Gerais has 853 municipalities, most of them small (up to 25,000 inhabitants in 84% of cases). These are grouped into 13 health macroregions (*Center, South Center, Jequitinhonha, East, East South, West, South, Southeast, North, Northeast, Northwest, Northern Triangle, Southern Triangle*), and comprise 31 licensed specialized oncology hospital services in the period spanning 2008 to 2015. These services were not equally distributed across macroregions: *Jequitinhonha* and *Northeast* lacked licensed services, *Center* and *East South* offered only chemotherapy, and *Northwest* only chemotherapy and radiation therapy[20].

Lung cancer is a public health problem requiring timely diagnosis and treatment. This study set out to examine associations between individual factors and initiation of lung cancer treatment within 60 days of diagnosis, in patients using Unified Health System services from 2008 to 2015.

Methods

A retrospective cohort study based on data extracted from National Oncology Database (Base

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ONCO15), a nationwide cohort comprising records of all patients undergoing oncologic treatment provided by SUS, between 2000 and 2015, and aimed to enable cohort follow-up. Base ONCO15 is a patient-centered subset database derived from National Health Database. This database was created using binding techniques to integrate data from primary SUS Information Systems: Outpatients Information System (SIA), Hospital Information System (SIH) and Mortality Information System (SIM), from 2000 to 2015[21].

The study population comprised patients initiating lung cancer treatment at SUS, between January 2008 and October 2015, who met the following criteria: residence in the state of Minas Gerais at the time of first treatment; 19 years of age or older; no previous treatment for any other type of cancer; and complete medical records (date of diagnosis, date of first treatment and staging upon diagnosis). The period spanning 2008-2015 was thought to provide the most recent and complete data. Also, as of 2008, outpatient and inpatient procedure codes were unified, facilitating the identification of treatments provided. Therefore, this time period was selected.

Exclusion criteria were as follows: patients undergoing only surgical treatment (since staging and date of diagnosis are not informed in the Hospital Admission Authorization (AIH); patients with missing staging data or stage 0 (possibly a medical record error); history of treatment for other types of cancer (since, in these cases, it was not possible to determine the primary cancer); and missing data regarding date of diagnosis and initiation of treatment (for these pieces of data would have direct impacts on the response variable). Eligibility criteria adopted in this study are shown in Figure 1.

The response variable (time from diagnosis to treatment) was defined as the number of days between the date of diagnosis (histopathologic confirmation, regardless of histologic type) and date of cancer treatment initiation (surgery, chemotherapy, or radiation therapy) and categorized into ≤60 and ≥61 days, according to Law no. 12.732, which provides oncologic treatment should be initiated within 60 days of diagnosis[17].

The following explanatory covariates were included in this study: I) Sociodemographic: sex, age, age range, macroregion of residence. II) Clinical: cancer staging, first treatment received, treatments received over the course of the experimental period, and respective combinations, goal of chemotherapy, goal of radiation therapy, surgical interventions, comorbidities, death over the course of the experimental period and if related to lung cancer, follow-up time, and time of diagnosis. III) Health system organization: health macroregion at the time of first treatment, and health care flow. Use of an administrative database precluded the analysis of variables such as histologic type, smoking, years of education and skin color, and introduced a limitation in the analysis of the reported phenomena.

Chemotherapy was classified as palliative (improved quality of survival) and non-palliative (curative, adjuvant, neoadjuvant or prior). Radiation therapy was categorized into palliative (treating the tumor with no impacts on survival) or non-palliative (neoadjuvant or cytoreductive, adjuvant or curative)[20].

Lung cancer-related surgical procedures were defined according to the first 6 digits of the Sigtap code 041205 (surgical procedures, thoracic surgery, lung). These procedures include lobectomy, wedge resection, open tumorectomy/lung biopsy and pneumonectomy.

Retrospective analysis of ICD-10 codes listed in patient records in the National Health Database was used to calculate the number of comorbidities (0, 1-3, ≥4). The lookback period was extended to the earliest date in database records (01/01/2000).

Staging data were extracted from High-complexity Outpatient Procedures (APAC), even in patients receiving surgical treatment first. Health macroregions were defined according to *Minas Gerais, diagnóstico e diretrizes para o plano da rede de atenção em oncologia 2015*[20].

Descriptive data analysis was based on distribution of absolute and relative frequencies for qualitative variables, and measures of central tendency (median) and variability (interquartile range) for continuous variables. Differences in proportions between categorical variables were investigated using the Pearson's chi-square test. Continuous variables were compared using parametric (Student's *t* test) and non-parametric (Mann-Whitney U test) approaches. Numerical variables were tested for normality using the Shapiro-Wilk test.

A diagram representing patient origin-destination flow was used to illustrate commuting of patients at the time of first treatment. This diagram shows the number of people traveling from place of residence (origin) to place of treatment (destination)[16]. Health macroregions were defined as the geographical unit. Origin-destination flow was represented by simple connections

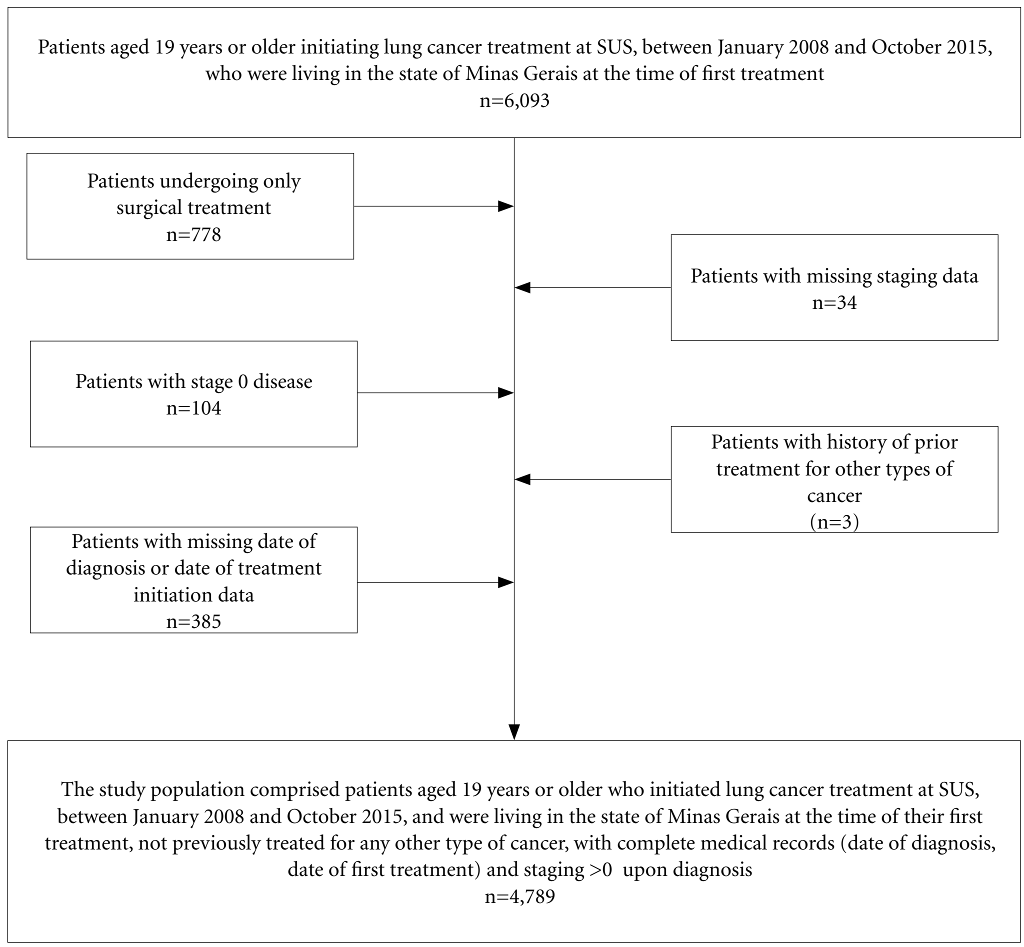

Figure 1. Patient selection flowchart according to inclusion and exclusion criteria.

Source: Authors.

between macroregion of residence and macroregion of treatment, both belonging to the same level.

Logistic regression was used to examine associations between the response variable (treatment initiation within 60 days of diagnosis) and selected explanatory covariates (sex, age, staging, first treatment received, macroregion of treatment, health care flow, comorbidities, and macroregion of residence). Odds ratios (OR) were used to measure the power of associations detected. Respective confidence intervals (95% CI) were provided. Univariate models were used to examine associations between explanatory covariates and the response variable. Covariates with $p < 0.20$ were eligible for inclusion in the multivariate model. Comorbidities and health care flow were excluded. The significance criterion for retention of covariates in the multivariate model was $p < 0.05$. Macroregion of treatment was excluded. The possible interactions between variables were investigated using logistic regression, and they were non-significant. The goodness of fit of the final model was examined using the Hosmer-Lemeshow test ($p > 0.05$). Explanatory variables were tested for multicollinearity using variance inflation factors. Statistical procedures were carried out using a free software environment (R version 3.3.4, R Foundation).

This study was conducted in compliance with standards and guidelines for research with human beings, provided in Resolution 466, of December 12, 2012. The study was approved by the Research Ethics Committee (COEP) of *Universi-*

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dade Federal de Minas Gerais, on May 12, 2015, under protocol CAAE: 44121315.2.0000.5149.

Results

This sample comprised 4,789 patients. Most patients were males, median age of 63 years (range of 56 to 72 years), and diagnosed as stage III or IV lung cancer. Chemotherapy was the first treatment in 80.8% of cases. In this sample, 43.2% of patients received only chemotherapy, and 37.7% received a combination of chemotherapy and radiation therapy. Palliative and non-palliative radiation therapy indication differed by only 1.5%. Lobectomy accounted for 31.9% of 119 surgical procedures performed as first treatment. Most patients (90.8%) had at least one comorbidity. In this sample, 3,563 patients died during over the course of follow-up. Of these, 53.3% died within 6 months of treatment initiation, 24.6% within 6 months to 1 year, and 22.1% after 1 year of treatment. Overall, 79.6% of deaths were due to lung cancer. Approximately 60% of patients were followed up for 6 months (longest follow-up time, 88 months). In this sample, 82.2% of patients received their first treatment in their macroregion of residence, and 73.4% were seen prior to enforcement of Law 12.732/2012. (Table 1).

In 81.9% of cases, treatment was initiated within 6 months of diagnosis; median waiting time was 1 month, regardless of modality of first treatment (surgery, chemotherapy, or radiation therapy). Chemotherapy was the most common therapeutic modality in patients treated within 6 months of diagnosis (82.8%), followed by radiation therapy (76.0%) and surgery (75.6%) (data not shown in tables).

Center was the macroregion with the largest percentage of resident patients undergoing first treatment, followed by *South* and *Southeast*, whereas *Jequitinhonha* and *Northeast* had the smallest proportions. At least 64.5% of resident patients initiated treatment within the established time frame in all macroregions, with largest percentages in *Southern Triangle, North* and *Southeast* (Table 2).

Origin-destination flow according to health macroregion is shown in Figure 2. The stripes illustrate the commuting of patients from the column "origin" to the column "destination" at the time of first treatment. Overall, 62% of treatments were provided in macroregions *Center*, *Southeast* and *South* . Patients living in macroregion *Center* traveled least. This macroregion received the largest number of patients from other regions. *Center, Souteast* and *North* were the macroregions with the lowest density of commuting, whereas *Jequitinhonha* and *Northeast* had the highest density. The latter regions lacked licensed oncologic services at the time. Therefore, residents had to seek treatment in other macroregions. Approximately 70% of patients living in macroregions *South, East South* and *Northwest* received treatment in other macroregions. Patients living in *East South* tended to travel to macroregion *Southeast* (54.1%), and those living in *South Center* tended to travel to macroregion *Center* (64.8%), whereas 35.8% of patients living in macroregion *Northwest* traveled to other states. Of 338 patients initiating treatment in other states, 86.7% were treated in the state of São Paulo. Of these, 82.2% lived in macroregions *Northern Triangle, Southern Triangle* and *South.*

Male patients had a 22% higher odds of receiving treatment within 60 days relative to female patients (multivariate logistic regression). The odds of initiating treatment within the established time frame decreased as patient age increased, as did the odds of receiving radiation therapy as first treatment relative to chemotherapy. In contrast, patients with stage IV were 1.32 times more likely to initiate treatment within 6 months relative to those with to stage I cancer. Macroregion of residence was associated with time to oncologic treatment. Patients living in *Jequitinhonha* were 74% less likely to initiate treatment within 60 days relative to those living in macroregion *Norte* (reference). The following macroregions had (statistically significant) lower odds ratios relative to reference (*North*): *Northeast* (0.34), *East South* (0.38), *Center* (0.41), *East* (0.44), *West* (0.53), and *Jequitinhonha* (0.26). In remaining macroregions with lower or higher odds ratios relative to the *North* macroregion, differences were not statistically significant (Table 3).

The Hosmer-Lemeshow test revealed appropriate goodness of fit of the model (p= 0.27). No evidence of multicollinearity between explanatory variables was found.

Discussion

In Minas Gerais, most lung cancer patients initiated treatment within 60 days of diagnosis. However, male sex and stage IV cancer increased the odds of receiving treatment within 60 days. Factors associated with lower odds of initiating

Table 1. Demographic and clinical characteristics of lung cancer patients initiating treatment at the Unified Health System. Minas Gerais. 2008-2015.

Variable	Total number of patients		Treated within 60 days of diagnosis			
			No		Yes	
	n=4,789	100% (95%CI)	n=887	18.1% (95%CI)	n=3,902	81.9% (95%CI)
Sex						
Female	1,759	36.7 (25.4:38.1)	356	40.1 (36.9:43.3)	1,403	36.0 (34.4:37.5)
Male	3,030	63.3 (61.9:64.6)	531	59.9 (56.6:63.1)	2,499	64.0 (62.5:65.6)
Age						
Mean (standard deviation)	63.4	(11.1)	64.6	(11.5)	63.1	(11.0)
Median (interquartile range)	63.0	(56:72)	66.0	(57:73)	63.0	(56:71)
Age range						
19 to 49 years	513	10.7 (9.8:11.6)	92	10.4 (8.4:12.6)	421	10.8 (9.8:11.8)
50 to 59 years	1,288	25.7 (24.4:26.9)	199	22.4 (19.7:25.3)	1,029	26.0 (25.0:27.8)
60 to 69 years	1,543	32.2 (30.9:33.6)	269	30.3 (27.3:33.5)	1,274	32.6 (31.2:34.1)
70 years +	1,505	31.4 (30.1:32.8)	327	36.9 (33.7:40.1)	1,168	30.2 (28.8:31.7)
Staging						
I	84	1.7 (1.4:2.2)	26	2.9 (1.9:4.3)	58	1.5 (1:1.9)
II	324	6.8 (6.1:7.5)	87	9.8 (7.9:12.0)	237	6.1 (5.3:6.9)
II	1,824	36.7 (25.4:38.1)	361	40.7 (37.4:44.0)	1,463	37.5 (36.0:39.0)
IV	2,557	53.4 (52.0:54.8)	413	46.6 (43.2:49.9)	2,144	54.9 (53.4:56.5)
First Treatment						
Chemotherapy	3,870	80.8 (79.7:81.9)	666	75.1 (72.1:77.9)	3,204	82.1 (80.9:83.3)
Radiation therapy	800	16.7 (15.7:17.8)	192	21.6 (19.0:24.5)	608	15.6 (14.5:16.8)
Surgery	119	2.5 (2.1:3.0)	29	3.3 (2.2:4.7)	90	2.3 (1.9:2.8)
Treatment and Treatment Combinations Over the Course of the Experimental Period						
Only chemotherapy	2,067	43.2 (41.8:44.6)	401	45.2 (41.9:48.6)	1,666	42.7 (41.1:44.3)
Chemotherapy + radiation therapy	1,808	37.7 (36.4:39.1)	275	31.0 (28.0:34.2)	1,533	39.3 (37.8:40.8)
Radiation therapy	451	9.4 (8.6:10.3)	135	15.2 (12.9:17.8)	316	8.1 (7.3:9.0)
Surgery + chemotherapy + radiation therapy	210	4.4 (3.8:5.0)	30	3.4 (2.3:4.8)	180	4.6 (4.0:5.3)
Surgery + chemotherapy	206	4.3 (3.7:4.9)	(31)	3.5 (2.4:4.9)	175	4.5 (3.0:5.2)
Surgery + radiation therapy	47	1 (0.7:1.3)	15	1.7 (0.9:2.8)	32	0.8 (0.6:1.2)
Goal of Chemotherapy in First Treatment						
Palliative	2,448	63.3 (61.7:64.8)	401	61.5 (57.6:65.3)	2,047	63.6 (61.9:65.3)
Non-palliative	1,422	36.7 (35.2:38.3)	251	38.5 (34.7:42.4)	1,171	36.4 (34.7:38.1)
Goal of Radiation therapy in First Treatment						
Palliative	394	49.2 (45.7:52.8)	321	52.4 (48.3:56.4)	73	39.0 (32.0:46.4)
Non-palliative	406	50.7 (47.2:54.3)	292	47.6 (43.6:51.7)	114	61.0 (53.6:68.0)

it continues

treatment within 60 days were age, indication of radiation therapy as first treatment, and place of residence.

Most patients in the sample were males. Similar findings have been reported in other Brazilian studies[7,22,23]. Differences in lung cancer distribution between sexes is related to exposure to tobacco, which is traditionally more common among males, in spite of increasing smoking rates among women[24,25].

As in a prior investigation[22], approximately 80% of lung cancer treatments were initiat-

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Table 1. Demographic and clinical characteristics of lung cancer patients initiating treatment at the Unified Health System. Minas Gerais. 2008-2015.

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			No		Yes	
	n=4,789	100% (95%CI)	n=887	18.1% (95%CI)	n=3,902	81.9% (95%CI)
Surgeries Performed						
Lobectomy	38	31.9 (23.7:41.1)	8	27.6 (12.7:47.2)	30	33.3 (23.7:44.1)
Multiple, Sequential Surgeries	36	30.2 (22.2:39.3)	8	27.6 (12.7:47.2)	28	31.1 (21.8:41.7)
Pneumonectomy	24	20.2 (13.4:28.5)	10	34.5 (17.9:54.3)	14	15.6 (8.8:24.7)
Wedge resection	12	10.1 (5.3:17.0)	3	10.3 (2.2:27.4)	9	10.0 (4.7:18.1)
Others	9	7.6 (3.5:13.9)	0	0 (0.0:11.9)	9	10.0 (4.7:18.1)
Comorbidities						
None	439	9.2 (8:4:10)	92	10.4 (8.4:12.6)	347	8.9 (8.0:9.8)
1 to 3	2,181	45.5 (44.1:47.0)	417	47.0 (43.7:50.4)	1,764	45.2 (43.6:46.8)
4 or more	2,169	45.3 (43.9:46.7)	378	42.6 (39.3:45.9)	1,791	45.9 (44.3:47.5)
Death Over the Course of the Experimental Period						
Yes	3,563	74.4 (73.1:75.6)	282	31.8 (28.7:35.0)	944	24.2 (22.9:25.6)
No	1,226	25.6 (24.4:26.9)	605	68.2 (65.0:71.3)	2,958	75.8 (74.4:77.1)
Death per Period (n=3,563)						
Within 6 months	1,898	53.3 (51.6:54.9)	271	45.9 (41.8:50.0)	1,627	54.7 (52.9:56.5)
Between 6 months and 1 year	877	24.6 (23.2:26.1)	169	28.6 (25.0:32.4)	708	23.8 (22.3:25.4)
More than 1 year	788	22.1 (20.8:23.5)	151	25.5 (22.1:29.3)	637	21.4 (20.0:23.0)
Lung Cancer-related Death (n=3,563)						
Yes	2,836	79.6 (78.2:80.9)	465	76.9 (73.3:80.9)	2,371	80.2 (78.7:81.6)
No	727	20.4 (19.1:21.8)	140	23.1 (19.8:26.7)	587	19.8 (18.4:21.3)
Follow-up time						
Up to 6 months	2,864	59.8 (58.4:61.2)	541	61.0 (57.7:64.2)	2,323	59.5 (58.0:61.1)
Between 6 months and 1 year	1,002	20.9 (19.8:22.1)	164	18.5 (16.0:21.2)	838	21.5 (20.2:22.8)
More than 1 year	923	19.3 (18.2:20.4)	182	20.5 (17.9:23.3)	741	19.0 (17.8:20.3)
Treatment flow						
Same macroregion	3,936	82.2 (81.1:83.3)	716	80.7 (78.0:83.3)	3,220	82.5 (81.3:83.7)
Different macroregion	853	17.8 (16.7:18.9)	171	19.3 (16.7:22.0)	682	17.5 (16.3:18.7)
Date of diagnosis (prior to/after 60-day law)						
Prior	3,517	73.4 (72.2:74.7)	701	79.0 (76.2:81.7)	2,816	73.4 (72.2:74.7)
After	1,272	26.6 (25.3:27.8)	186	21.0 (18.3:23.8)	1,086	26.0 (25.0:27.8)

95%CI: confidence interval (estimated by Pearson's chi-square, Student´s t test and Mann-Whitney U test)

Source: Authors.

ed within 60 days of diagnosis in Minas Gerais. Women were less likely to start treatment within 60 days than men. Similar findings (i.e., longer waiting time among women) have been reported in a national study with secondary data, conducted between 2000 and 2014[13]. According to another study with oncologic patients receiving treatment at SUS, women were 16% less likely to be admitted and spent 2% less time at hospital[26]. A temporal trend analysis of lack of access to health care in Brazil, between 1998 and 2013, revealed women tend to seek care more often, yet have poorer health outcomes.[27] This trend is supported by data from the 2019 National Health Survey[28]. These differences may reflect social organization and gender stratification, and emphasize the impacts of historical gender inequality on health care provision to male and female patients[29].

Table 2. Macroregion of residence and percentage of treatment within 60 days of diagnosis, in patients living in Minas Gerais at the time of first treatment. Unified Health System, Minas Gerais, 2008-2015.

	Total number of patients		Treated within 60 days of diagnosis			
			No		Yes	
	N	%	N	%	N	%
Center	1,151	24.0	277	24.1	874	75.9
South Center	159	3.3	28	17.7	131	82.4
Jequitinhonha	31	0.6	11	35.5	20	64.5
East	310	6.5	73	23.5	237	76.5
East South	172	3.6	46	26.7	126	73.3
Northeast	55	1.1	15	27.3	40	72.7
Northwest	134	2.8	22	16.4	112	83.6
North	246	5.1	29	11.8	217	88.2
West	279	5.8	58	20.8	221	79.2
Southeast	705	14.7	92	13.0	613	87.0
South	796	16.6	132	16.6	664	83.4
Northern Triangle	416	8.7	73	17.5	343	82.5
Southern Triangle	335	7.0	31	9.3	304	90.7
Total	4,789	100	887	18.1	3,902	81.9

Source: Authors.

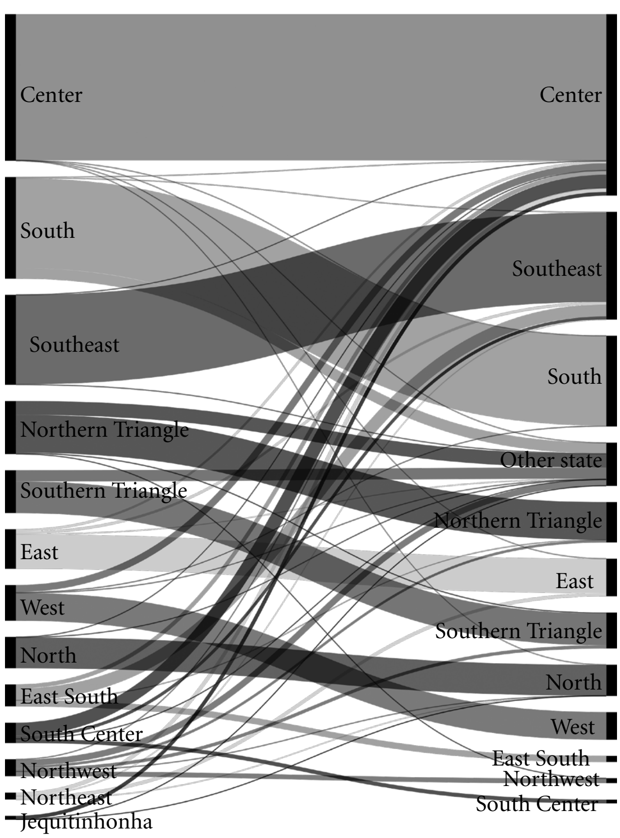

Figure 2. Graphic representation of origin-destination flow according to macroregion of residence and macroregion of treatment in lung cancer patients initiating treatment at SUS. Minas Gerais. 2008-2015.

Source: Authors.

Men are thought to engage less in self-care and, hence, would be expected to have poorer health outcomes. Data presented suggested institutional mechanisms responsible for wider access of male patients to care must be discussed.

Patients aged over 60 years prevailed in this sample. This finding is consistent with the fact that lung cancer affects primarily older adults[7,22-24]. The inverse relation between likelihood of initiating treatment within 60 days and age was strongly associated with the response variable. Similar evidence was provided by a British study[30] and a national investigation[14]. In both cases, older age tended to be associated with undertreatment in lung cancer patients. As other researchers, the authors of this study believe age should not be a crucial factor in determining lung cancer treatment provision, and that barriers to treatment of older adults must be understood and overcome.

Most cases of lung cancer are diagnosed at stages III and IV of disease (i.e., advanced stages)[23,31]. Lower rates of late diagnosis have been reported in a Brazilian study[22]. Nonetheless, the sample in that study comprised only patients undergoing surgical treatment.

In the present study, staging acted as an "accelerator" of treatment. This effect has been widely reported. Findings of several studies suggested interventions other than palliative treatment tend to be delayed[8,9,32].

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Table 3. Odds ratios for treatment within 60 days of diagnosis (univariate and multivariate models). Unified Health System. Minas Gerais. 2008-2015.

Variable	Univariate model		Multivariate model	
	Crude OR (95%CI)	p value	Adjusted OR (95%CI)	p value
Sex		0.02		0,011
Female	1	-	1	-
Male	1.19 (1.03 - 1.39)		**1.22 (1.05 - 1.42)**	
Age (continuous)	0.99 (0.98 - 0.99)	<0.001	**0.99 (0.98 - 0.99)**	<0,001
Staging		<0.001		<0,001
I	1	-	1	
II	1.22 (0.72 - 2.06)		1.22 (0.71 – 2.09)	
III	1.82 (1.13 - 2.93)		**1.67 (1.02 - 2.72)**	
IV	2.33 (1.45 - 3.74)		**2.32 (1.42 - 3.77)**	
First Treatment		<0.001		<0,001
Chemotherapy	1	-	1	-
Radiation therapy	0.66 (0.55 – 0.79)		**0.66 (0.54 – 0.79)**	
Surgery	0.65 (0.42 – 0.99)		0.83 (0.53 – 1.29)	
Macroregion of Residence		<0.001		<0,001
North	1		1	
Center	0.42 (0.28 – 0.64)		**0.41 (0.27 – 0.62)**	
South Center	0.63 (0.36 – 1.1)		0.60 (0.34 – 1.05)	
Jequitinhonha	0.24 (0.11 – 0.56)		**0.26 (0.11 – 0.61)**	
East	0.43 (0.27 – 0.69)		**0.44 (0.27 – 0.70)**	
East South	0.37 (0.22 – 0.61)		**0.38 (0.23 – 0.64)**	
Northeast	0.63 (0.36 – 1.1)		**0.34 (0.17 – 0.70)**	
Northwest	0.68 (0.37 – 1.24)		0.69 (0.38 – 1.27)	
West	0.51 (0.31 – 0.83)		**0.53 (0.32 – 0.86)**	
Southeast	0.89 (0.57 – 1.39)		0.96 (0.51 – 1.51)	
South	0.67 (0.44 – 1.03)		0.67 (0.44 – 1.04)	
Northern Triangle	0.63 (0.40 – 1.0)		0.71 (0.44 – 1.13)	
Southern Triangle	1.31 (0.77 – 2.24)		1.34 (0.78 – 2.29)	
Treatment flow		0.206	-	
Same macroregion	1	-	-	
Different macroregion	0.89 (0.74 - 1.07)		-	
Comorbidities (continuous)	1.02 (0.99 – 1.05)	0.229	-	-
Macroregion of Treatment		<0.001		
Southern Triangle	1	-	-	
Center	0.26 (0.17 - 0.41)		-	
South Center	0.35 (0.13 - 0.95)		-	
East	0.28 (0.17 – 0.46)		-	
East South	0.25 (0.11 – 0.54)		-	
Northwest	0.25 (0.11 – 0.59)		-	
North	0.58 (0.33 – 1.04)		-	
West	0.36 (0.21 – 0.63)		-	
Other states	0.96 (0.51 – 1.51)		-	
Southeast	0.52 (0.32 – 0.84)		-	
South	0.41 (0.26 – 0.66)		-	
Northern Triangle	0.36 (0.22 – 0.61)		-	

OR (95%CI): Odds ratio (95% confidence interval). Reference category: treatment initiation within 60 days of diagnosis.

Source: Authors.

In this study, chemotherapy was the most common modality of first treatment provided within six months of lung cancer diagnosis. Likewise, in a British study, patients undergoing chemotherapy were more likely to initiate treatment in a timely manner compared to those assigned to other treatment modalities[30]. The fact that chemotherapy was more widely available (with the exception of macroregions *Jequitinhonha* and *Northeast*[19]) may have contributed to this outcome.

As in other studies[9,30], surgery was the least common type of treatment in patients initiating treatment within six months of diagnosis. The distance between patient place of residence and specialized services is a limiting factor in access to potentially curative surgical treatment. Surgical intervention rates vary according to health regions and geographical variations have been reported[16,32]. Surgery was not available in macroregions *South Center, Northwest, East South, Jequitinhonha* and *Northeast*[20]. However, this variable was non-significant in the final model.

Associations between radiation therapy and the response variable revealed patients receiving radiotherapy as first treatment were 34% less likely to initiate treatment within 6 months relative to those assigned to chemotherapy. The fact that radiation therapy is not widely available in Brazil has negative impacts on waiting time and there are waiting lists for radiotherapy[33]. Similar limitations apply to the state of Minas Gerais, where radiation therapy services are lacking in the *South Center, East South, Jequitinhonha* and *Northeast* macroregions[20]. Studies have shown patients undergoing radiotherapy are less likely to receive treatment within the established time frame[34], since these services are concentrated in a few locations due to the complex infrastructure involved[16].

High prevalence of comorbidities (more than 90% of patients) may have reflected the age range of the population[23]. Comorbid diseases may impact on provision of care and patient survival[6], but they were not significantly associated with time to initiate lung cancer treatment.

Death rates were considerably high. The fact that lung cancer was the primary cause of death emphasize the lethality, high mortality, and low survival rates of this disease[9,35]. In Brazil, mortality attributable to lung cancer is rising among women and declining among men. These trends are thought reflect interventions aimed to reduce the prevalence of smoking[25]. A recent Brazilian study revealed higher survival rates in women relative to men. The reasons behind such differences are not yet clear and conflicting data have been reported[36].

Median patient follow-up was 8.22 months. Similar follow-up time (7 months) has been reported in a different Brazilian study[22]. High mortality rates may explain the short follow-up time.

Macroregion of residence had a negative impact on the odds of initiating treatment within 60 days. Macroregions in which licensed oncologic services were lacking (*Jequitinhonha* and *Northeast*) had the lowest odds ratios. As in this study, other research has shown regional differences interfered not only with time to treatment, but also with outcomes[8,16,32,35,37,38]. Spatial fragmentation of therapeutic activities tend to decrease adherence to treatment, since patients must follow different flows to satisfy their needs[39]. According to a breast cancer study, the need to travel may introduce additional hurdles. Hence the significance of geographic access to treatment[16].

The distance to treatment centers has negative impacts on disease outcomes. Living in remote areas was associated with higher mortality rates in patients with different types of cancer in the United Kingdom[40]. In hierarchical health systems, the need to travel to have access to medium and high complexity health services is expected. However, unforeseen flows and long distances emphasize the need for improved planning and regulation of health care networks[41].

In this study, 62% of treatments were provided in macroregions *Center, Southeast* and *South.* In the state of Minas Gerais, 19 out of 31 licensed oncology services are located in these macroregions. The concentration of health care services in some locations and the lack of such services in others compromise access to care and results of care delivered.

Recent studies revealed regional inequalities in access to lung cancer treatment regarding timely diagnosis and treatment[42,43], as well as preventive and curative actions[44]. Diagnosis and treatment provision away from the place of residence have negative impacts on patient adherence to treatment and quality of life[45]. The need to travel long distances for hospital admission or therapy introduces additional treatment and postoperative recovery constraints[45].

A treatment center for several types of cancer located in a city in the state of São Paulo was the primary destination of patients living in macro-regions *Northern Triangle, Southern Triangle* and *South.* The proximity between these regions may explain this phenomenon. Also, this

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is a reference center and attracts patients from neighbor regions as well as all other Brazilian states[46]. Unforeseen flows may compromise existing health regionalization plans[41]. Given the three cancer treatment modalities are available in above mentioned macroregions, lack of services cannot justify this flow. The unveiling of causes behind this selective migration may contribute to understanding of non-regulated flow of patients through the health care network.

After completion of this study (2015), three novel oncology services were licensed in Minas Gerais. In 2019, the state *Rede de Atenção em Oncologia* comprised 34 licensed hospitals. Macroregion *Center* now has new chemotherapy and chemotherapy/radiation therapy services. In macroregion *Northeast*, previously lacking licensed services, chemotherapy in now available[47]. Licensing of new services in macroregion *Center*, which already had the highest number of treatment units, and the fact that macroregion *Jequitinhonha* still does not have any emphasize differences reported in this study and suggest inequalities persist.

This study has limitations. Patients receiving only surgical treatment could not be evaluated, since surgery is indicated for patients with initial stages of lung cancer. This omission may have reduced the proportion of patients diagnosed in these stages of the disease. It was not possible to determine the impact of application of the 6th and 7th editions of cancer staging on therapeutic decisions (and hence on patient prognosis), between 2008 and 2015. Finally, use of an administrative database precluded the analysis of covariates, such as histologic type, smoking, years of education and skin color, among others.

Data quality, validity and integrity are strong points of this study. Binding of APAC, AIH and SIM data allowed the inclusion of a wide range of patients who could otherwise not have been analyzed. This sample comprised an expressive number of records and findings may help inform future investigations.

Conclusion

This study revealed that most lung cancer patients initiate treatment within the timeframe determined by the 60-day law. However, time to treatment is associated with individual characteristics and factors related to service provision in macroregions.

Differences reported reflect the distribution of specialized oncology services. Lack of services in some regions and overload in others may have significant impacts on time to treatment. In conclusion, health care provision differs according to patient place of residence. Inequalities reported possibly stem from differences in access to health care services.

Collaborations

JAM Souza, HA Rocha and ML Cherchiglia contributed to study conception and design, data analysis and interpretation, in the writing and critical review of the manuscript and in the approval of the version to be published. MAC Santos contributed in the analysis and interpretation of the data, in the critical review of the manuscript and in the approval of the version to be published.

Acknowledgements

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (Fapemig).

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Article submitted 27/07/2020
Approved 18/02/2021
Final version submitted 20/02/2021

Chief editors: Romeu Gomes, Antônio Augusto Moura da Silva