Lung Cancer in Never-Smoker Subjects: Epidemiological, Clinical and Survival Patterns based on Gender

Câncer de Pulmão em Indivíduos não Fumantes: Padrões Epidemiológicos, Clínicos e de Sobrevida baseados no Gênero

Cáncer de Pulmón en Individuos no Fumadores: Patrones Epidemiológicos, Clínicos y de Supervivencia basados en el Género

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Abstract

Introduction: Tobacco smoke is the predominant risk factor for the development of lung cancer (LC). However, a recent increase of LC in never-smokers is prominent in some countries. **Objective:** Our aim was to verify epidemiological and survival characteristics in never-smoker LC patients. **Method:** A historical cohort of never-smoker subjects with LC diagnosed from 2000 to 2009. Overall survival was compared using Log-rank test, and Cox regression analysis was used to identify independent prognostic factors. **Results:** A total of 254 never-smoker LC patients were studied (median age: 65.5 years; 66.5% women). The most common histological type was adenocarcinoma (65.7% in women and 60.0% in men), being that the majority of the patients had advanced staging (III-IV) (79.6% in women and 92.8% in men). According to treatment, 9.9% of the patients were treated with surgery (13.1% in women and 3.6% in men). The overall 1-year, 3-year and 5-year survival rates were, respectively: 37.2%, 14.2%, and 9.5%. The median overall survival was 8.3 months. Women had a better survival than men (9.6 vs. 6.9 months; p=0.023). Non-surgical treatment (p<0.001), performance status 2-4 (p=0.038), and stage III-IV (p<0.001) were associated with a poorer overall survival. **Conclusions:** We found a higher occurrence of adenocarcinoma, of advanced staging, and of non-surgical treatment. Women had a better survival than men. Due to a low overall survival, these data underscores the importance of early diagnosis of LC in never-smoker patients.

Key words: Tobacco Smoke Pollution; Lung Neoplasm; Survival; Prognosis.

Resumo

Introdução: O tabagismo é o fator de risco predominante para o desenvolvimento do câncer de pulmão (CP). Contudo, um aumento recente de CP em não fumantes é proeminente em alguns países. **Objetivo:** O objetivo deste estudo foi verificar as características epidemiológicas e de sobrevida em não fumantes com CP. **Método:** Coorte histórica de não fumantes com CP diagnosticados de 2000 a 2009. A sobrevivência global foi comparada usando o teste Log-rank e a análise de regressão de Cox foi usada para identificar fatores prognósticos independentes. **Resultados:** Um total de 254 pacientes com LC não fumantes foram estudados (mediana de idade: 65,5 anos, 66,5% de mulheres). O tipo histológico mais comum foi o adenocarcinoma (65,7% nas mulheres e 60,0% nos homens) e a maioria tinha estadiamento avançado (III-IV) (79,6% nas mulheres e 92,8% nos homens). Um total de 9,9% dos pacientes foi tratado com cirurgia (13,1% em mulheres e 3,6% em homens). As taxas de sobrevida global de 1, 3 e 5 anos foram, respectivamente: 37,2%, 14,2% e 9,5%. A sobrevida global mediana foi de 8,3 meses. As mulheres tiveram melhor sobrevida do que os homens (9,6 vs. 6,9 meses, p=0,023). O tratamento não cirúrgico (p<0,001), o *performance status* 2-4 (p=0,038) e os estádios III-IV (p<0,001) foram associados com uma sobrevida global pior. **Conclusão:** Encontrou-se uma maior ocorrência de adenocarcinoma, estadiamento avançado e tratamento não cirúrgico. As mulheres tiveram uma sobrevida maior do que os homens. Em razão da baixa sobrevida global, esses dados reforçam a importância do diagnóstico precoce do CP em não fumantes.

Palavras-chave: Poluição por Fumaça de Tabaco; Neoplasias Pulmonares; Sobrevivência (Saúde Pública); Prognóstico.

Resumen

Introducción: El tabaquismo es el factor de riesgo predominante para el de cáncer de pulmón (CP). Sin embargo, un aumento reciente de CP en no fumadores es prominente en algunos países. **Objetivo:** El objetivo de este estudio fue verificar las características epidemiológicas y de sobrevida en no fumadores con CP. **Método:** Cohorte histórica de no fumadores con CP diagnosticados de 2000-2009. La supervivencia global fue comparada usando análisis de Log-rank y el regresión de Cox para identificar factores pronósticos independientes. **Resultados:** Uma muestra totalizando 254 pacientes no fumadores con CP fue estudiada (mediana de edad: 65,5 años, 66,5% de mujeres). El tipo histológico más común fcorrespondió a adenocarcinoma (65,7% en las mujeres y el 60,0% en los hombres) y la mayoría en estadio avanzado (III-IV) (79,6% en las mujeres y el 92,8% en los hombres). Un total de 9,9% de pacientes fueron tratados con cirugía (13,1% en mujeres y 3,6% en hombres). Las tasas de supervivencia global de 1, 3 y 5 años fueron, respectivamente, el 37,2%, el 14,2% y el 9,5%. La supervivencia mediana global correspondió a 8,3 meses. Fue observada una mejor sobrevida en mujeres que em hombres (9,6 frente a 6,9 meses, p=0,023). El tratamiento no quirúrgico (p <0,001), el estado de equilibrio del estado 2-4 (p=0,038) y los estadios III-IV (p <0,001) se encontraron asociados con una peor sobrevida global. **Conclusiones:** Se encontró una mayor ocurrencia de adenocarcinoma, estadificación avanzada y tratamiento no quirúrgico. Las mujeres mostraron una sobrevida meyor que los hombres. En función de la baja sobrevida global, estos datos refuerzan la importancia del diagnóstico precoz del CP en no fumadores.

Palabras clave: Contaminación por Humo de Tabaco; Neoplasias Pulmonares; Supervivencia (Salud Pública); Pronóstico.

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INTRODUCTION

Lung cancer (LC) is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths) worldwide[1]. Globocan 2018 estimates that there will be 2.1 million new cases of LC worldwide in 2018, closely followed by female breast cancer (2.09 million), colorectal cancer (1.85 million), and prostate cancer (1.27) for incidence. The number of predicted deaths by LC in 2018 is 1.8 million, representing close to 1 in 5 cancer deaths. [(1)] In men, LC is the most commonly diagnosed cancer and the leading cause of cancer death, followed by prostate and colorectal cancer for incidence, and liver and stomach cancer for mortality. Among females, lung cancer is the leading cause of cancer death in 28 countries[1].

In the United States, LC causes as many deaths as the next 4 most deadly cancers combined (breast, prostate, colon, and pancreas)[2]. The 5-year relative survival rate for LC in the United States for the period of 2003-2009 was 17.5%[3].

Estimated number of new LC cases in Brazil for 2019 was 18,740 among men and 12,530 among women. In Brazil, LC is the leading cause of death from cancer among men and the second leading cause of cancer death among women[3]. In Brazil, the estimated number of new LC cases corresponds to a risk of 18,16 new cases/100,000 men and 11,81 new cases/100,000 women[3]. The LC incidence rates in a given country reflect the tobacco consumption. The median survival estimate for LC was 14% for males and 18% for females[4]. A Brazilian household survey revealed that the prevalence percentage of current users of tobacco products ranged from ranged from 13.4% in the Northern Region to 16.1% in the Southern Region[5]. The Brazilian incidence of LC has increased lately and mortality remains high, similar to the rest of the world[3].

Many causes of LC have been identified, including active cigarette smoking, exposure to second-hand cigarette smoke, pipe and cigar smoking, occupational exposure to agents such as asbestos, nickel, chromium, and arsenic, exposure to radiation, including radon gas, and exposure to indoor and outdoor air pollution[6]. Despite the identification of this constellation of well-established causal risk factors, the global epidemic of LC is primarily caused by a single factor: cigarette smoking[7]. The attributable risk of smoking as a causative agent of lung cancer is higher than 90.0% in Brazil[8,9]. The LC prevalence in never-smokers is increasing according to some authors[10-15]. Global estimates indicate that about 300,000 LC deaths annually are not due to tobacco use[10]. Even though this estimate represents a minority of the LC burden, its incidence in never-smokers ranges from 4.8 to 20.8 per 100,000 among individuals aged 40 to 79 years[16]. Although genetic risk remains to be discovered in LC, identification of genes involved in the cause of disease could contribute to further understanding of the underlying mechanisms, and eventually lead to additional prevention strategies and targeted treatments[17]. A family history of lung cancer is associated with a 1.5 to 4-fold increased risk of lung cancer after adjustment for the clustering of smoking in families[17]. Large, collaborative genome-wide association studies have identified three separate loci that are associated with lung cancer (5p15, 6p21, and 15q25) and that include genes regulating nicotinic acetylcholine receptors and telomerase production[6].

To date, there is limited literature focusing clinical, epidemiological and survival patterns exclusively in never-smoker LC patients, especially in Brazil. The main objective of this study was to verify the clinical, epidemiological, laboratory and survival characteristics in a sample of Brazilian never-smokers LC patients referred to a tertiary hospital of general oncology.

METHOD

Study design

This study protocol was approved by the Research Ethics Committee of the *Instituto Nacional de Câncer José Alencar Gomes da Silva* and informed consent was waived because it was a retrospective review. It was conducted at the in a tertiary referral center for general oncology, in Rio de Janeiro State, Brazil, that is accessible to patients from all socioeconomic status, although the majority of patients seen are from lower social classes. A retrospective analysis of a prospective LC database was done of patients with LC diagnosed during the period from January 1, 2000 to December 31, 2009. All tumors were histopathologically proven, corresponds to all events registered in Chapter IDC-10: C-34 to C-39 in Malignant Neoplasm in the SUS.

Collection of patient data

Eligibility requirements included a pathologically proven LC with negative history of current tobacco use, age >18 years, the absence of anticancer treatment, medical charts indicating epidemiologic characteristics, the treatment given and no previous or other concomitant malignant disease except basal cell carcinoma. Never-smokers were those indicating that they had smoked <100 cigarettes in their lifetime and were not current smokers. The patients had their medical charts reviewed for demographic data, disease stage, histology and treatment. The variables included in the study were: gender, age, race, histology (non-small-cell lung cancer [NSCLC]

subtypes), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-4), disease extent (advanced or non-advanced), distant metastases (negative or positive), treatment regimen, number of chemotherapy (CT) cycles and dose of thoracic radiotherapy (RT).

The clinical PS was evaluated according to the ECOG scale[18]. Histological diagnosis was made according to previous guidelines for NSCLC[15-20]. The stage was defined in accordance to the 7th edition of tumor-node-metastasis (TNM)[21]. Staging of the tumor was based on the results of physical examination, chest radiography, fiberoptic bronchoscopy with biopsy and cytologic examination, computed tomography of the chest and the brain, ultrasonography or computed tomography of the abdomen, radionuclide bone scanning, positron emission tomography-computed tomography scans, and other tests as needed and registered in the medical records. The advanced disease included patients with stages IIIa, IIIb, and IV; non-advanced disease included the stages Ia, Ib, IIa, and IIb. Treatment status was stratified into two categories: a) surgical treatment and non-surgical treatment (including the best treatment support). Medical charts were also evaluated for pre-treatment laboratory parameters: hemoglobin, white blood cell count, platelets count, urea, creatinine, sodium, aspartate aminotransferase, alanine aminotransferase, bilirrubin, alkaline phosphatase, gamma-glutamyltranspeptidase, albumin, calcium, lactate dehydrogenase, and glucose.

In addition, waiting times (recorded in months) were defined as follows: a) specialist's delay as time between first visit to specialist in our institution and LC diagnosis and b) treatment delay as time between LC diagnosis and initial treatment.

Statistical analysis

A statistical analysis was performed using a statistical software package (SPSS for Windows, version 17.0; SPSS; Chicago, IL). The data were expressed as median and inter-quartile range to summarize continuous data. The categorical variables were reported as percentages of the population. Comparisons between groups were performed using the chi-square-test for dichotomous variables, Student's *t*-test for normally distributed continuous variables and the Mann-Whitney *U*-test for not normally distributed continuous variables. The endpoint of this study was overall survival. It was measured as the duration from the date of diagnosis to the date of death or the last contact date. Survival rates were estimated using the Kaplan-Meier method and compared between the groups by the Log-rank test. Unadjusted hazard ratio (HR) with 95% confidence interval (CI) was calculated by univariate Cox regression. Additional multivariate analysis was done adjusting for those known prognostic factors and potential confounders that were significant in the univariate analysis ($p<0.10$). Correlation was evaluated using the Spearman rank correlation coefficient (r_s). A two-sided p value <0.05 was considered to be statistically significant.

RESULTS

Demographic characteristics

Between January 1, 2000 and December 31, 2009, 279 consecutively never-smoker LC patients were enrolled in a single institution. Of these, 20 were excluded due to incomplete demographic and/or survival data and 5 were excluded due to small cell lung cancer diagnosis. Therefore, 254 NSCLC subjects were studied (median age: 65.5 years; 66.5% women). Based on diagnosis, the most used diagnostic method was transthoracic needle aspiration or biopsy in 91 subjects (35.8%), followed by flexible fiberoptic bronchoscopy in 72 (28.3%), thoracentesis with or without closed pleural biopsy in 27 (10.6%), exploratory thoracotomy in 26 (10.2%), peripheral lymph nodes biopsy in 15 (5.9%), mediastinoscopy in 5 (2.0%), and others diagnostic tests in 18 subjects (7.2%). According to Table 1, women when compared to men were older (p=0.040). The majority of the patients had advanced staging (III-IV) at diagnosis: 79.6% in women and 92.8% in men; p=0.005. A total of 148 subjects (58.2%) were classified as metastatic disease (stage IV). Family history of cancer was positive in 36.8% (44.2% in women and 23.8% in men; p=0.001). According to laboratory tests, women showed in relation to men, a lower value of hemoglobin (p<0.001), of urea (p=0.003), of creatinine (p=0.001), of alanine aminotransferase (p=0.004), and of lactate dehydrogenase (p=0.027). Conversely, the values of albumin and of sodium were higher in women than men (p=0.004 and p=0.026, respectively).

Treatment offered

Based on Table 2, in all patients evaluated, 9.9% of the patients were treated with surgery (13.1% in women and 3.6% in men; p=0.015). The most common type of treatment was CT alone, which was offered to 35.0% of the patients. A total of 221 patients (87.0%) were treated and 33 patients (13.0%) were followed with palliative care. Of the treated patients, 25 patients received surgical treatment, 127 patients received CT, and 111 patients received RT. Among patients treated with CT (83 women and 44 men), the most frequent chemotherapeutic regimens were platinum-based regimens (88.6%). Of total of patients treated with CT, 32 patients received two cycles, 21 patients received three cycles, 64 patients

Table 1. Demographic and laboratory characteristics of the patients

Variables	n	Total (n=254)	Men (n=85)	Women (n=169)	P value
Demographic Variables					
Age (years)	254	65.5 (54.0-74.0)	62.0 (50.0-73.5)	67.0 (57.0-74.0)	0.040
Race (%)					
White	193	76.1	86.1	71.4	0.044
Non-white	61	23.9	13.9	28.6	
Histology (%)					
Adenocarcinoma	162	63.8	60.0	65.7	0.606
Squamous cell carcinoma	33	13.0	17.6	10.7	
Non-typed NSCLC	31	12.2	14.1	11.2	
Carcinoid tumor	15	5.9	4.7	6.5	
Large cell carcinoma	8	3.1	2.4	3.5	
Non-classified carcinoma	5	2.0	1.2	2.4	
Stage (%)					
I-II	41	16.0	7.2	20.4	0.005
III-IV	213	84.0	92.8	79.6	
PS (%)					
0-1	180	70.9	67.5	72.6	0.256
2-4	74	29.1	32.5	27.4	
Familiar history of cancer (%)					
Negative	146	63.2	76.2	55.8	0.001
Positive	85	36.8	23.8	44.2	
Blood Tests Variables					
Hemoglobin (g/dL)	233	12.9 (11.7-13.8)	13.8 (13.1-14.2)	12.9 (11.4-13.6)	<0.001
WBC count (x 10^3/mm^3)	231	8.7 (6.5-11.8)	11.0 (8.1-14.2)	7.7 (5.7-9.9)	0.056
Platelets count (x 10^3/mm^3)	231	294.0 (241.0-368.5)	289.0 (238.0-376.0)	298.0 (247.0-373.5)	0.976
Urea (mg/dL)	226	30.0 (25.0-38.0)	33.0 (25.2-39.0)	29.0 (23.7-37.0)	0.003
Creatinine (mg/dL)	231	0.8 (0.7-1.0)	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.001
Sodium (mEq/L)	221	140.0 (138.0-142.0)	139.0 (137.0-141.7)	141.0 (139.0-143.0)	0.026
AST (U/L)	167	20.0 (16.0-28.0)	22.5 (17.2-28.7)	19.0 (15.7-22.5)	0.056
ALT (U/L)	165	19.0 (14.0-31.0)	22.0 (13.0-40.0)	14.0 (12.0-20.2)	0.004
Bilirrubin (mg/dL)	119	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.897
Alkaline phosphatase (U/L)	183	156.5 (96.2-269.0)	176.0 (104.0-337.0)	146.0 (92.5-265.0)	0.087
GGT (U/L)	160	37.0 (23.0-77.0)	42.5 (26.7-117.5)	33.5 (20.0-46.7)	0.061
Albumin (g/dL)	157	4.1 (3.7-4.4)	4.0 (3.7-4.1)	4.1 (3.8-4.4)	0.004
Calcium (mg/dL)	176	9.4 (9.1-9.8)	9.4 (9.1-9.9)	9.6 (9.0-10.0)	0.892
LDH (U/L)	168	386.0 (329.5-496.0)	414.0 (350.0-598.2)	344.0 (302.7-444.7)	0.027
Glucose (mg/dL)	227	100.5 (92.2-112.0)	101.0 (89.0-117.2)	99.5 (92.0-107.2)	0.468

NSCLC: Non-small cell lung cancer; PS: Performance status; WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltranspeptidade; LDH: Lactate dehydrogenase.
Continuous variables are presented as median (inter-quartile range) and categorical variables are presented as percentages.

received four cycles, and 10 patients received six cycles. One hundred eleven subjects received chest RT with a median radiation dose of 30.0 Gy (range: 6-66 Gy). In relation to gender, the median radiation dose of RT did not differ among them: men with 30.0 Gy (range: 8-66 Gy) and women with 45.0 Gy (range: 6-65 Gy); p=0.265.

Survival

The authors also looked at wether blood tests, dichotomized by median, could be important factors on survival. Based on this, subjects with white blood cell count [x 10^3/mm^3] <8.7 (vs. ≥8.7), platelets count [x 10^3/mm^3] <294.0 (vs. ≥294.0), sodium [mEq/L] ≥140 (vs. <140), gamma-glutamyltranspeptidade [U/L] <37.0 (vs. ≥37.0), and albumin (g/dL) ≥4.1 [vs. <4.1] had a higher overall survival (in months). Despite of this, when these variables were studied by multivariate tests, this difference was not significant (data not shown).

According to Table 3, women showed in relation to men, similar overall survival rates at 1-year, 3-year and

Table 2. Characteristics of the patients related to treatment offered

Treatment offered	Total (n=254)	Men (n=85)	Women (n=169)
Surgical	25 (9.9)	3 (3.6)	22 (13.1)
Surgery alone	16 (6.3)	2 (2.4)	14 (8.3)
Surgery plus CT	5 (2.0)	-	5 (3.0)
Surgery plus RT	2 (0.8)	-	2 (1.2)
Surgery plus CTRT	2 (0.8)	1 (1.2)	1 (0.6)
Non-surgical	229 (90.1)	82 (96.4)	147 (86.9)
CT alone	89 (35.0)	37 (43.5)	52 (30.8)
RT alone	76 (29.9)	19 (22.4)	57 (33.7)
CTRT	31 (12.2)	6 (7.1)	25 (14.8)
Supportive care	33 (13.0)	20 (23.4)	13 (7.6)

CT: Chemotherapy; RT: Radiotherapy; CTRT: Chemoradiotherapy. Data presented as n (%).

5-year, but with a trend toward better survival in women, in relation to the opposite gender, mainly in 3-year and 5-year (p=0.058 and p=0.072; respectively). The overall 1-year, 3-year and 5-year survival rates were, respectively: 37.2%, 14.2%, and 9.5%. The median overall survival was of 8.3 months. Women had a better median survival than men (9.6 vs. 6.9 months; p=0.023). Figure 1 shows the Kaplan-Meier curves of overall survival for all patients classified according to PS, histology, stage, and treatment offered. The difference found was statistically significant in all situations: p<0.001 (for PS, stage and treatment offered) and p=0.017 (for histology).

According to Table 4, in the univariate analysis, PS, stage, and treatment offered were important variables for survival with p <0.001, p=0.035, and p<0.001; respectively. Multivariate analysis was built with these three variables plus the variable race (white vs. non-white). According to this Table, the treatment offered, PS and stage were independent variables for survival in never-smokers patients with NSCLC. The adjusted HR for non-surgical treatment (vs. surgical) was 9.009 (95% CI: 3.289-24.390), PS 2-4 (vs. 0-1) was 2.016 (95% CI: 1.440-2.816), and stage III-IV (vs. I-II) was 1.801 (95% CI: 1.031-3.144).

In our analysis, the median delay from first specialist appointment to initial treatment was 1.48 months. The median delay from first visit to specialist to diagnosis was 0.56 months and it was not different between men and women (0.56 and 0.53 months, respectively; p=0.451). The median delay from LC diagnosis and initial treatment was 0.66 months. In a similar way, there was no difference in the treatment delay based on gender (men with 0.26 months and women with 0.90 months; p=0.589). The median overall survival (in months) was positively correlated with the time between initial appointment

Table 3. Differences on survival related to gender

Outcome	Total (n=254)	Men (n=85)	Women (n=169)	P value
Survival (%)				
1-year rates (%)	37.2	30.6	40.5	0.132
3-year rates (%)	14.2	8.2	17.3	0.058
5-year rates (%)	9.5	4.7	11.9	0.072
Survival in months				
Overall	8.3 (3.9-19.1)	6.9 (2.6-16.0)	9.6 (4.7-20.9)	0.023
Treatment offered¶				
Surgical	80.9 (46.3-97.3)	97.0 (84.3-109.7)	67.3 (32.6-94.1)	0.320
Non-surgical	7.7 (3.5-15.1)	6.5 (2.6-13.6)	8.3 (4.2-15.9)	
PS*				
0-1	9.9 (5.3-25.7)	8.0 (5.5-20.7)	11.9 (5.2-30.4)	0.076
2-4	5.0 (1.7-9.5)	2.3 (0.7-5.4)	6.8 (3.6-10.2)	
Stage#				
I-II	57.3 (9.7-85.6)	38.0 (8.1-88.6)	57.8 (10.2-86.8)	0.798
III-IV	7.5 (3.6-14.9)	6.2 (2.0-13.8)	8.2 (4.4-15.7)	
Histology§				
Adenocarcinoma	8.3 (3.9-19.1)	7.0 (2.7-16.9)	9.7 (4.6-19.2)	0.066
Non-adenocarcinoma	7.9 (4.1-19.1)	6.4 (1.4-15.7)	9.4 (5.0-41.9)	

PS: Performance status.
¶Surgical treatment showed better survival vs. non-surgical treatment in all patients and in both genders (all of them with p<0.001).
*PS 0-1 showed better survival vs. PS 2-4 in all patients (p<0.001), in men (p=0.011), and in women (p=0.001).
#Stage I-II showed better survival vs. stage III-IV in all patients, in men, and in women (all of them with p<0.001).
§Adenocarcinoma histology showed better survival vs. non-adenocarcinoma histology in all patients (p=0.017) and in women (p=0.012).
Survival in months is expressed as median (inter-quartile range).

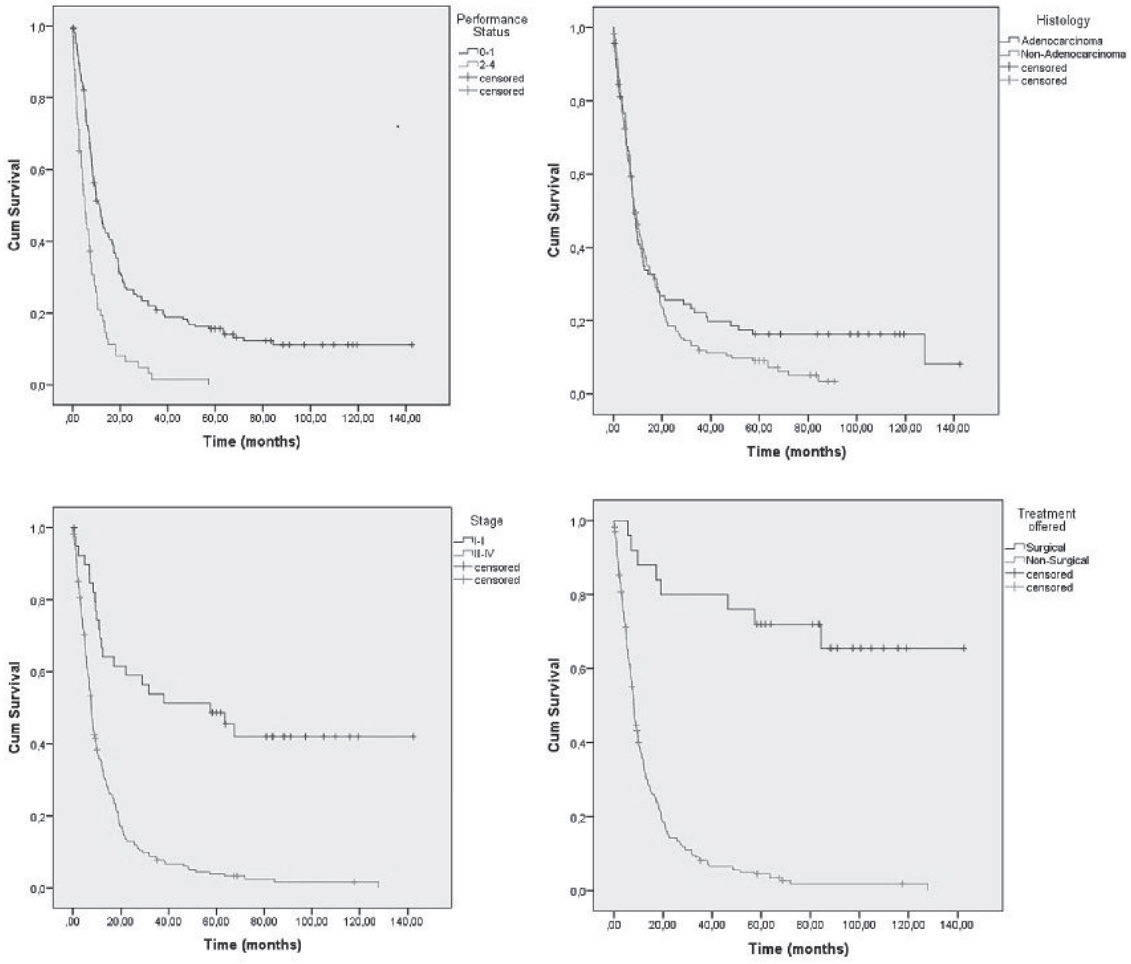

Figure 1. Kaplan-Meier curves of overall survival for lung cancer patients (n=254) classified according to performance status, histology, stage, and treatment offered. The difference found was statistically significant in all situations: p<0.001 (for performance status, stage and treatment offered) and p=0.017 (for histology)

and diagnosis (r_s=0.193; p=0.002), with the time between diagnosis and initial treatment (r_s=0.180; p=0.008), and with the time between initial appointment and initial treatment (r_s=0.407; p<0.001).

DISCUSSION

The overall 1-year, 3-year and 5-year survival rates were, respectively: 37.2%, 14.2%, and 9.5%. Our main finding was that in a sample of never-smokers patients with NSCLC, there was a better median survival in women *versus* men. Overall, there was a higher prevalence of women, of adenocarcinoma, and of advanced stage of disease, leading to a small proportion of patients who underwent surgery. These findings are consistent with previous studies that show that among non-smokers there is a clear predominance of women with adenocarcinoma[11,12,14,16,22]. In addition, the 5-year overall survival was 9.5%, which is lower than that found in Americans with LC (17.5%)[2]. Previous study[22], reported better survival in never-smokers compared with current smokers with adenocarcinoma, with a 5-year survival rate of 23% for never-smokers compared with 16% for current smokers (p=0.004). In general, never-smokers LC patients have better survival compared to LC patients with a positive smoking history (smokers and ex-smokers)[14,22]. Thus, our hypothetic overall survival (including patients with positive and negative smoking history) would be even lower. Unfortunately, our study did not compare never-smokers patients with patients with current or previous history of tobacco use. One explanation for our poor survival, even in never-smokers patients, could be the high proportion of patients with advanced stage in our sample.

Multivariate tests showed that the treatment offered, PS, and tumor stage were independent variables for the survival

Table 4. Univariate and multivariate analysis of the prognostic factors for overall survival

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Gender				
Women	1			
Men	1.267 (0.900-1.782)	0.174		
Age				
<50	1			
≥50	1.300 (0.863-1.959)	0.209		
Race				
White	1		1	
Non-white	1.417 (0.964-2.082)	0.076	1.272 (0.895-1.808)	0.179
PS				
0-1	1		1	
2-4	2.092 (1.453-3.003)	<0.001	2.016 (1.440-2.816)	0.038
Familiar history				
Negative	1			
Positive	1.032 (0.740-1.441)	0.851		
Histology				
Adenocarcinoma	1			
Non-adenocarcinoma	1.239 (0.878-1.748)	0.221		
Stage				
I-II	1		1	
III-IV	1.838 (1.042-3.236)	0.035	1.801 (1.031-3.144)	<0.001
Treatment offered				
Surgical	1		1	
Non-surgical	9.009 (3.067-26.315)	<0.001	9.009 (3.289-24.390)	<0.001

HR: Hazard ratio; 95% CI: 95% confidence interval; PS: Performance status

of LC patients with negative smoking history. Previous Brazilian studies have found similar results; in general, with a low overall survival and a high proportion of patients classified as advanced stage, and, consecutively, a low rate of patients treated, especially with surgical treatment[22-23]. Similarly, early disease diagnosis, treatment given and higher Karnofsky PS scores were also favorable, independent predictors of survival[22]. A retrospective study[24] of LC patients diagnosed between 1995 and 2002 was done with 352 patients (74.4% of men). The most common stages were stages IIIB and IV, in 45% and 21.5%, respectively. Of the total sample, 73.4% were submitted to treatment. Cumulative survival rates were low: 3-year survival was 6.5%, and 5-year survival was 3.5%. Other retrospective study[25] evaluated 240 LC patients (64% of men): only 131 patients (54.6%) were treated. Concerning staging, 34.4% presented stage IV and 20.6% presented stage IIIB. Five-year survival was of 65% for those in stage I. and for those in the remaining stages it was of 25%.

The etiology of LC in never-smokers is interesting and remains unclear. Its occurrence obviously suggests the existence of risk factors other than tobacco: secondhand smoking, occupational exposures, pre-existing lung diseases, diet, estrogen, human papillomavirus, and family history[22,24]. The causal relationship between environmental tobacco smoke and LC has been well established; however, the increasing rate of never-smoking NSCLC is inconsistent with the decrease in the smoking population in developed countries[26]. Never-smokers with LC may be genetically susceptible to carcinogen(s) or may be hereditarily predisposed to LC.[27] Previous studies support family history as an important risk factor for development of LC in never-smokers subjects[27-30]. Our study showed a considerable percentage of women with positive familiar history of LC in relation to men.

There is evidence suggesting that smoking exposure due to he involuntary inhaling of smoke is a poor prognostic factor in NSCLC patients[28]. Due to majority of never-smokers patients with NSCLC are female and have histology of adenocarcinoma, it is possible that the influence of both gender and histological types on survival may be attributed to the smoking status. In addition, more female patients and more adenocarcinoma patients are likely to be in the never-smoking group[12,29].

Another recent implication related to treatment is a good response to epidermal growth factor receptor

(EGFR)-tyrosine kinase inhibitors, such as gefitinib and erlotinib, whose is largely limited to never-smokers[27]. These mutations are found more frequently in women, particularly Asian women, with adenocarcinoma and especially never-smoker status[27,28]. Interestingly, the frequency of EGFR mutations has been shown to be inversely proportional to exposure to environmental tobacco smoke in never-smokers[27]. These findings suggest that EGFR-mutant tumors, which are closely linked to LC in never-smokers, occur by alternative mechanism other than the carcinogenic process induced by tobacco smoke[27-30].

Our study showed that there is no difference in the waiting times related to specialist and to treatment according to gender. Previous study[25] showed that median delay between the first specialist appointment and the final diagnosis was similar in both genders. The authors found a median delay from first specialist appointment to treatment of 41 days[25]. The main factor related to shorter delay was more advanced disease because these patients receive treatment more promptly due to severity of their signs and symptoms[30].

There were some limitations in our study. In the retrospective analysis, there was the possibility that our results are biased by patient selection (selection bias), by data collection (information bias) or by confounding. The selection bias was controlled using appropriate definition of the eligible population. We used a standard protocol (approved by our local ethics committee) in order to limit the information bias. Moreover, confounding was neutralized at the analysis by multivariate logistic model including all variables with $p<0.10$. Thus, we believe that the internal validity was not systematically compromised. Another limitation in our study was that there is no information about comorbidities, tumoral markers, environmental tobacco smoke, and molecular analyses of the tumors.

In conclusion, we believe that our study demonstrated that never-smokers patients are a specific group with proper demographic and survival characteristics. Our results highlight, due to a low overall survival, the importance of early diagnosis of LC in never-smoker patients. Further studies, mainly prospective, need to be conducted to better knowledge of these patients.

CONTRIBUTIONS

All the authors have contributed to a) the conception and design of the study; b) analysis and interpretation of data; and c) writing the article or revising it critically for important intellectual content. RLMD performed the statistical analysis and interpreted the results. MMZ prepared the first draft of the paper. RLMD and ASM were responsible for acquisition of clinical data and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

DECLARATION OF CONFLICTS OF INTEREST

The author Mauro Musa Zamboni declares potential conflict of interest due to being the Education Coordinator of INCA. The author Alessandra de Sá Earp Siqueira declares potential conflict of interest for being Associate Editor of the Brazilian Journal of Oncology. The other authors have no conflict of interest.

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