

Role of gender in the survival of surgical patients with nonsmall cell lung cancer

Nóris C. Scaglia, José M. Chatkin, José A. Pinto, Maria T. R. Tsukazan, Mário B. Wagner, Adriana F. Saldanha

Department of
Respiratory Diseases,
Hospital São Lucas da
Pontifícia Universidade
Católica do Rio Grande
do Sul, Porto Alegre,
Brazil

Address for correspondence:

Dr. José Miguel Chatkin,
Department of Respiratory
Diseases, Hospital São
Lucas da Pontifícia
Universidade Católica
do Rio Grande do Sul,
Av. Ipiranga 6690, Porto
Alegre-90610 000, Brazil.
E-mail: jmchatkin@puccrs.br

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Abstract:

PURPOSE: There are reports of greater survival rates in nonsmall cell lung cancer (NSCLC) patients of female gender. The objective of this study was to evaluate the role of gender in survival of NSCLC patients treated surgically with curative intent (stage I/II).

METHODS: In a retrospective cohort design, we screened 498 NSCLC patients submitted to thoracotomies at the hospital São Lucas, in Porto Alegre, Brazil from 1990 to 2009. After exclusion of patients that did not fit to all the inclusion criteria, we analyzed survival rates of 385 subjects. Survival was analyzed using the Kaplan-Meier method. The Cox regression model was used to evaluate potential confounding factors.

RESULTS: Survival rates at 5 and 10 years were 65.3% and 49.5% for women and 46.5% and 33.2% for men, respectively ($P = 0.006$). Considering only stage I patients, the survival rates at 5 and 10 years were 76.2% and 55.1% for women and 50.7% and 35.4% for men, respectively ($P = 0.011$). No significant differences in survival rates were found among stage II patients.

CONCLUSIONS: Our results show female gender as a possible protective factor for better survival of stage I NSCLC patients, but not among stage II patients. This study adds data to the knowledge that combined both genders survival rates for NSCLC is not an adequate prognosis.

Key words:

Gender, lung cancer mortality, nonsmall cell lung cancer surgery, nonsmall cell lung cancer survival

Lung cancer is one of the most common malignant neoplasms, being the main cause of death due to malignant neoplasm in males and also very frequent among females.^[1] In Brazil, it is not different and the estimated risk of new cases of lung cancer to be diagnosed in 2012 is 18/100,000 men and 10/100,000 women.^[2]

Although there is evidence that the smoking epidemic is stabilizing or even in decline in several regions or countries of the world, the lung cancer epidemic is still an import public health problem in many countries.^[2,3]

This neoplasm is related to elevated mortality, with 5-year survival rates being around 8%-15%, taking all stages into consideration.^[4,5] Patients with less advanced nonsmall cell lung cancer (NSCLC) have better survival when submitted to surgical resection. However, although presumably curative, resection presents 5-year survival rates of 60%-80% for stage I patients and 40%-50% for stage II patients.^[4,5]

Studies have associated female gender with improved survival in this type of neoplasm, with survival increasing by approximately one and a half times, when compared to males.

Accordingly, female gender is now considered by some authors as a predictor of better survival in NSCLC patients. Women are more likely to survive lung cancer at all stages of the disease; however, this survival advantage over men is greater for local disease.^[6-11]

In 2004, we reported significant differences in survival according to gender in stage I NSCLC patients, with improved rates among women and such effect remained after adjusting for confounding factors (age, tumor histology, smoking, tumor size, serum hemoglobin levels, and postoperative complications).^[12]

The current study extended the analysis of the role of gender in NSCLC patients treated surgically with curative intent (stages I and II) at the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul São Lucas Hospital (HSL-PUCRS) between 1990 and 2009. The main reasons of this paper is to confirm previous results, now following the patients over a long period of time and add data to a possible future meta-analysis in this issue.

Methods

In a retrospective cohort design, NSCLC patients

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of both sexes of any age were included when treated surgically with curative intent between January 1990 and December 2009, at the Hospital São Lucas, in Porto Alegre, Brazil. Subject should be at stage I or II.

Exclusion criteria were patients with tumor-node-metastasis (TNM) staging more than equal to III,^[13] those submitted to any kind of chemotherapy or palliative surgery, those who died within 30 days after surgery and those who died from causes unrelated to the tumor.

All the surgical procedures and clinical evaluations were performed by the same respirologists and thoracic surgeons. Both teams decided on the type of surgery, but all subjects were submitted to mediastinoscopy previously to any pulmonary resection. Neoplasm staging was performed according to the TNM system.^[13]

From the review of medical records, demographic characteristics were collected, including gender, age, tumor histology, after-surgery TNM staging, type of surgery, hemoglobin concentration (used as an indirect marker of the performance index,^[14]) smoking habit, tumor size, and postoperative complications. Histological confirmation was obtained for all patients.

Follow-up and patient survival information was obtained by researching death registrations in the Health Information Center of the state of Rio Grande do Sul, Brazil or by an active searching, contacting patients, or family members by telephone.

Survival time was calculated as the period from the date of surgery to the date of death, or to the end of the study observation period or lost of follow-up.

Statistical analyses

The quantitative variables were described by means and standard deviations and their comparison by the Student's *t*-test. Categorical variables were described by counts and percentages with their significance determined by the Chi-squared test.

The survival estimates were obtained by the Kaplan-Meier method comparing both genders, using stratification by staging. The univariate comparisons within the groups were based on the log rank test. The strength of association was evaluated by the relative risk obtained from the proportional hazards model, expressed as hazard ratio (HR) with its respective confidence interval (CI) of 95%.

The median follow-up times for this cohort, overall, by gender and by stage were calculated by the reverse censoring method.^[15]

To evaluate the impact of potential confounding factors and adjust for their effects in the comparison between genders, the Cox proportional hazards regression model was used. The inclusion of the variables in the model was based on their clinical relevance. The female gender HR obtained in the Cox proportional-hazards regression model was adjusted for age, smoking, histological type, tumor size, postoperative complications, anemia, and surgical type. The significance level was set at $\alpha = 0.05$.

The data were processed and analyzed with the SPSS for Windows program, version 17.0 (SPSS Inc., Chicago, IL, USA).

The Ethics and Research Committee of this University considered the written consent not necessary, since this is a retrospective analysis including patients since 1990. The project was approved under the number 1259/10. All procedures followed were in accordance with the ethical Brazilian standards and with Helsinki Declaration of 1975, as revised in 2000.

Results

We evaluated 498 thoracotomies performed with curative intent on NSCLC patients between January 1990 and December 2009. Of these patients, 113 (22.7%) were excluded from the study. We excluded 93 subjects due to staging TNM more than equal to III, 15 due to death occurring during the first 30 days after surgery and 5 due to unrelated deaths (3 due to chronic obstructive pulmonary disease complications and 2 due to external causes). In total, 385 patients were included for the analyses [Figure 1].

The majority of the patients were males ($n = 266$, 69.1%), with a mean (\pm SD) age of 64.9 (\pm 10.0) years, ranging from 32 to 91 years old. Serum levels of hemoglobin indicated anemia in almost half of the participants ($n = 165$, 42.9%). In stage I patients, only 1.9% of the men and 13.4% of the women never smoked. However, regarding to smoking habits no significant difference among subjects of stage II was found. About the frequency of current smokers, there was no statistically significant difference between the genders. There was also no significant difference between the frequencies of the histological types of the neoplasms among stage I patients. Among stage II patients, the most common histological types were squamous cells in men and adenocarcinoma in women ($P = 0.003$). The most common surgical resection performed was lobectomy ($n = 306$, 79.5%). The main characteristics of the patients are listed in Table 1.

At the end of five and 10 years of follow-up after surgery, the overall survival rates were 65.3% and 49.5% and 46.5% and

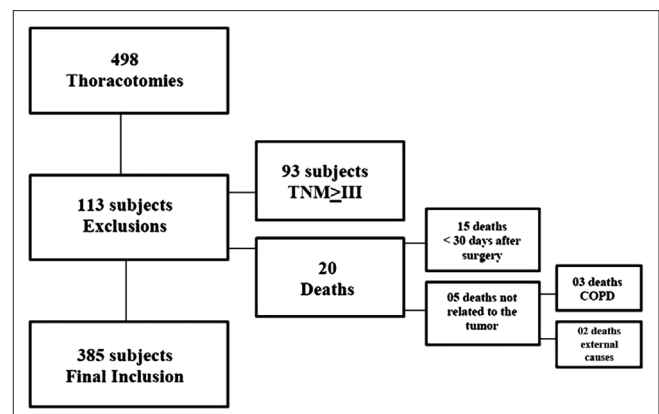


Figure 1: Flowchart showing inclusion of NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, during the period 1990-2009, $n=385$

33.2%, respectively for women and men. The median survival time of the overall sample was 99.4 and 53.8 months for females and males, respectively ($P = 0.006$). The median follow-up for all subjects was 30.8 months (range: 0.03-183.7). The median follow-up time was 55.7 and 56.1 months for females and males, respectively ($P = 0.562$) [Figure 2].

Considering only stage I patients, the survival rates at 5 and 10 years were 76.2% and 55.1% and 50.7% and 35.4% for females and males, respectively. The median survival time for these patients was 146.0 and 62.6 months for women

and men, respectively ($P = 0.011$). The median follow-up time was 55.7 and 61.6 months for females and males, respectively ($P = 0.688$) [Figure 3].

For stage II patients, the difference was not statistically significant, with a survival rate for women of 39.5% and 39.3% at 5 and 10 years. The survival rate among men was 40.9% and 36.3% at 5 and 10 years. The median survival time was 46.7 and 32.1 months for women and men, respectively ($P = 0.288$). The median follow-up time was 48.7 and 40.9 months for females and males, respectively ($P = 0.173$) [Figure 4].

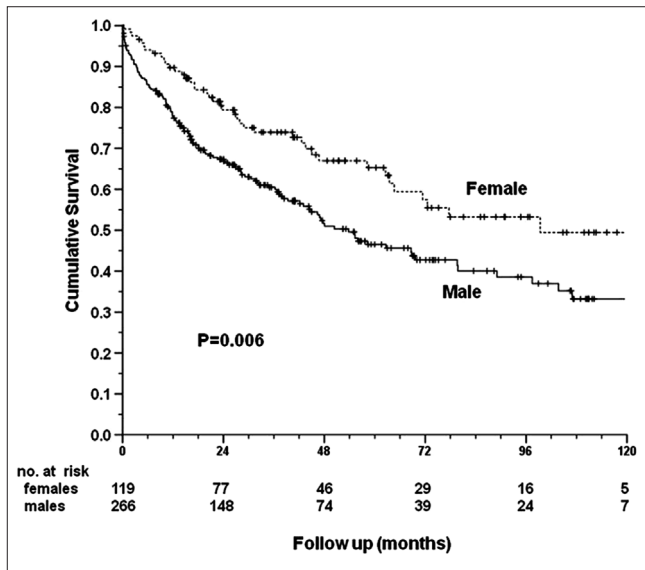


Figure 2: Kaplan-Meier curve for survival in NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, according to gender, during the period 1990-2009, n=385

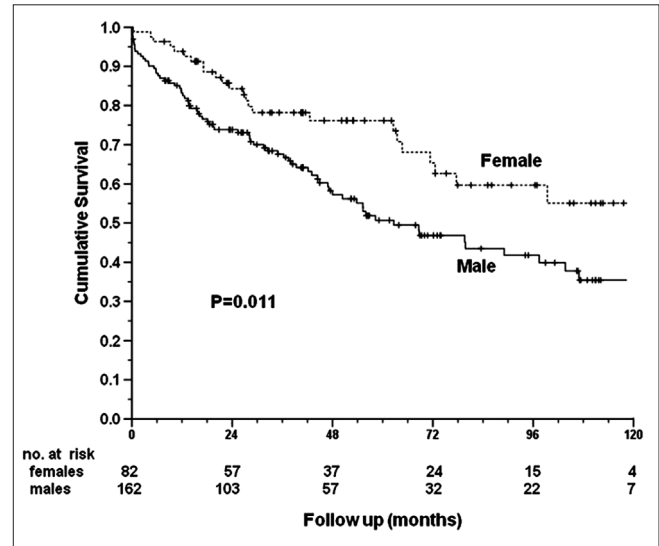


Figure 3: Kaplan-Meier curve for survival in stage I NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, according to gender, during the period 1990-2009, n=385

Table 1: Characteristics of the NSCLC patients treated surgically with curative intent at the HSL-PUCRS hospital, during the period 1990-2009, n=385

Variable	Total n=385	Stage I		P	Stage II		P
		Men n=162	Women n=82		Men n=104	Women n=37	
Age, years	64.9±10.0	65.4±9.6	63.5±10.7	0.158	65.1±9.7	65.4±11.2	0.915
Smoking				<0.001			0.391
Current smoker	284 (73.8)	124 (76.5)	64 (78)		73 (70.2)	23 (62.2)	
Exsmoker	81 (21.0)	35 (21.6)	7 (8.5)		28 (26.9)	11 (29.7)	
Never smoked	20 (5.2)	3 (1.9)	11 (13.4)		3 (2.9)	3 (8.1)	
Histology				0.186			0.003
Epidermoid	173 (44.9)	72 (44.4)	30 (36.6)		61 (58.7)	10 (27.0)	
Adenocarcinoma	171 (44.4)	76 (46.9)	39 (47.6)		35 (33.7)	21 (56.8)	
Other ^(*)	41 (10.6)	14 (8.6)	13 (15.9)		8 (7.7)	6 (16.2)	
Tumor size, cm	4.4±2.5	4.0±2.4	3.9±2.0	0.755	5.5±2.9	4.3±2.3	0.026
PO complications	63 (16.4)	33 (20.4)	7 (3.5)	0.030	19 (18.3)	4 (10.8)	0.426
Anemia ^(†)	165 (42.9)	77 (47.5)	21 (25.0)	0.002	56 (53.8)	11 (29.7)	0.020
Surgery				0.643			0.015
Lobectomy	306 (79.5)	133 (82.1)	70 (85.4)		72 (69.2)	31 (83.8)	
Pneumonectomy	41 (10.6)	9 (5.6)	3 (3.7)		27 (26.0)	2 (5.4)	
Bilobectomy	19 (4.9)	11 (6.8)	3 (3.7)		2 (1.9)	3 (8.1)	
Segmentectomy	19 (4.9)	9 (5.6)	6 (7.3)		3 (2.9)	1 (2.7)	

The data is presented as mean±standard deviation or percentage, NSCLC = Nonsmall cell lung cancer; PO = Postoperative, ^(*)Includes adenosquamous, bronchialalveolar, and large cell carcinomas; ^(†)Serum hemoglobin <13.0 g/dL for men and <12.0 g/dL for women; P = Statistical significance (%), HSL-PUCRS = Hospital são lucas da pontificia universidade católica do rio grande do sul são lucas hospital

Females in stage I presented greater survival compared with males even after adjustment for potential confounding factors using Cox regression ($P = 0.047$). Such difference between genders was not observed in stage II ($P = 0.322$) [Tables 2 and 3].

Discussion

In this study, the role of gender as a protective factor for survival of NSCLC patients treated surgically with curative intent was confirmed, showing greater survival among women in relation to men, a finding that remained in stage I patients even after adjusting for various confounding factors.

Previously, in the analysis of 253 cases of NSCLC patients treated surgically by the same medical group in this hospital, in a 10-year follow-up period (1990-2000), greater survival was demonstrated among women compared to men.^[12] Now, the

period of observation is expanded from 1990 until the day of death of the subject as registered in the death certificates or accomplished by direct or telephone contact with the patients themselves or family members. All patients were treated at the same institution by the same clinician and surgeon, ensuring the uniformity of diagnostic and therapeutic procedures. We had no losses and we could get information of all included patients.

Such findings are consistent with other several studies, which also demonstrated the advantage of female gender in survival of NSCLC patients.^[6,8-12,16-21]

Johnson *et al.*,^[22] in 1988 published that female patients with small cell lung cancer live longer than male patients. A few years later, Ferguson *et al.*, first in 1990^[23] and subsequently in 2000,^[17] reported that female patients with lung cancer presented better survival rates, even after adjusting for possible

Table 2: Occurrence of death according to gender and TNM stage I in NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, 1990-2009 (n=244, 102 deaths)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Female gender	0.56 (0.36-0.88)	0.012	0.57 (0.35-0.95)	0.029
Age	1.03 (1.01-1.05)	0.002	1.03 (1.01-1.05)	0.009
Smoking status				
Never	1		1	
Former	2.08 (0.46-9.51)	0.343	1.23 (0.26-5.81)	0.793
Current	4.14 (1.02-16.8)	0.047	2.24 (0.53-9.41)	0.271
Histological type				
Adenocarcinoma	1		1	
Epidermoid	1.95 (1.29-2.95)	0.002	1.64 (1.05-2.56)	0.029
Others	1.15 (0.55-2.38)	0.717	1.45 (0.68-3.10)	0.340
Tumor size	1.09 (1.01-1.18)	0.039	1.06 (0.99-1.15)	0.232
PO complications	4.57 (2.99-6.98)	0.001	3.68 (2.34-5.79)	0.001
Hemoglobin	0.85 (0.76-0.95)	0.003	0.87 (0.78-0.98)	0.018
Surgical type				
Lobectomy	1		1	
Pneumonectomy	0.98 (0.40-2.43)	0.961	0.86 (0.34-2.16)	0.748
Bilobectomy	0.98 (0.36-2.20)	0.801	1.04 (0.41-2.61)	0.940
Segmentectomy	2.51 (1.30-4.84)	0.006	1.15 (0.56-2.38)	0.704

CI = Confidence interval, HR = Hazard ratio obtained in the Cox proportional-hazards regression model adjusted for age, smoking, histological type, tumor size, postoperative complications, anemia, and surgical type, NSCLC = Nonsmall cell lung cancer, P = Statistical significance; TNM = Tumor-node-metastasis system, HSL-PUCRS = Hospital são lucas da pontificia universidade católica do rio grande do sul são lucas hospital

Table 3: Occurrence of death according to gender and TNM stage II in NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, 1990-2009 (n=141, 71 deaths)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Female gender	0.74 (0.43-1.29)	0.291	0.78 (0.41-1.46)	0.431
Age	1.01 (0.98-1.03)	0.675	1.03 (1.00-1.06)	0.045
Smoking status				
Never	1		1	
Former	0.45 (0.17-1.23)	0.118	0.39 (0.14-1.12)	0.082
Current	0.57 (0.23-1.43)	0.231	0.59 (0.22-1.61)	0.304
Histological type				
Adenocarcinoma	1		1	
Epidermoid	0.96 (0.58-1.57)	0.861	0.85 (0.50-1.45)	0.551
Others	0.78 (0.34-1.78)	0.555	0.45 (0.17-1.15)	0.097
Tumor size	1.02 (0.94-1.12)	0.613	1.01 (0.91-1.21)	0.846
PO complications	2.95 (1.74-5.02)	0.001	3.99 (2.16-7.39)	0.001
Hemoglobin	0.91 (0.80-1.02)	0.115	0.88 (0.77-1.01)	0.059
Surgical type				
Lobectomy	1		1	
Pneumonectomy	2.09 (0.75-5.84)	0.159	2.16 (0.69-6.73)	0.184
Bilobectomy	0.43 (0.06-3.13)	0.406	0.22 (0.03-1.80)	0.158
Segmentectomy	0.79 (0.42-1.48)	0.466	0.77 (0.39-1.51)	0.443

CI = Confidence interval, HR = Hazard ratio obtained in the Cox proportional-hazards regression model adjusted for age, smoking, histological type, tumor size, postoperative complications, anemia, and surgical type, NSCLC = Nonsmall cell lung cancer, P = Statistical significance, TNM = Tumor-node-metastasis system, HSL-PUCRS = Hospital são lucas da pontificia universidade católica do rio grande do sul são lucas hospital

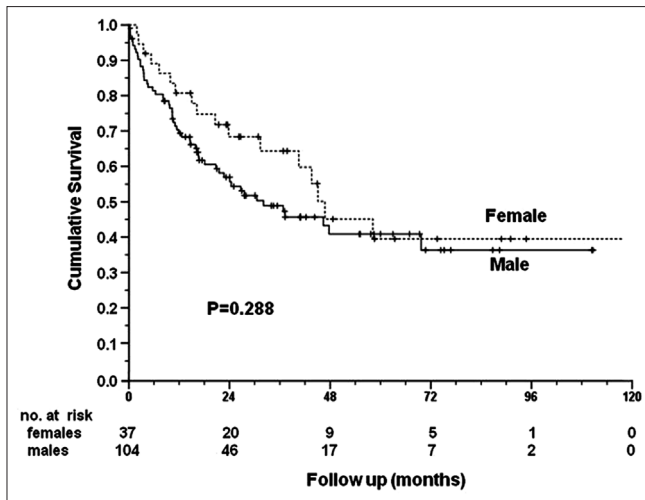


Figure 4: Kaplan-Meier curve for survival in stage II NSCLC patients treated surgically with curative intent at the HSL-PUCRS Hospital, according to gender, during the period 1990-2009, n=385

confounding factors (staging, age, and histological type). Similarly, in 1999, Bouchardy *et al.*,^[16] evaluating the survival at 10-year follow-up period of 428 lung cancer patients, found better results for women adjusting for age, socioeconomic status, extent of the surgical resection, and tumor histology.

In 2002, such improved prognosis for survival among women in comparison with men was also found in a study of 20,561 NSCLC cases.^[19] In a 15-year follow-up after surgery for NSCLC study, Batevik *et al.*,^[7] in 2005, demonstrated that female gender was one of the significant prognostic factors, predicting increased survival at 5, 10, and 15 years.

Later on, Cerfolio *et al.*,^[11] registered a better 5-year survival rate of women with NSCLC in stages I to III, studying a prospective cohort of lung cancer patients submitted to detailed evaluation that included positron emission tomography scans. In 2007, Hanagiri *et al.*,^[9] found similar results and, more recently, Agarwal *et al.*,^[6] presented an analysis of 519 patients, where, once again, men had worse 5-year prognosis in comparison to women (Relative Risk = 1.45, 95% CI 1.21 – 1.54, $P = 0.03$).

Our results were consistent with these studies since a protective effect was found in the analysis of the overall sample. However, when the patients were classified according to the stage of the disease, we observed that the effect remained only in stage I. The effect shown in the whole sample probably was probably influenced by the strong protective effect demonstrated in stage I patients but not existing in stage II patients.

The role of gender in lung cancer biology and in survival rates is not completely understood and at this time there is no full explanation for the longer survival of women with NSCLC. Women seem to be more susceptible to the development of lung cancer despite in general they smoke less and start later than men. When these factors are adjusted, the incidence rate of lung cancer emerges as greater in females than in males for the same tobacco intake.^[24,25] Hormonal factors may be involved, since the growth of tumor cells may depend on reproductive hormones.^[26,27] This hypothesis is supported by the finding that

the NSCLC cells have both estrogen receptors, ER and ER in abundant quantity, which differ among the various types of lung cancer and stages of the disease.^[28,29] In agreement with this perspective, new evidence suggest that hormone replacement therapy may increase the incidence of lung cancer in smoking women and may have an important role in the mortality rate differences between males and females. The carcinogenic effects of estrogens in lung cancer are being fully studied.^[30]

Several factors could interfere in our conclusions of better survival of women only at stage I. One of them could be the performance status of the patient at the moment of the surgery. Performance scales are efficient prognostic indicators in the preoperative period of NSCLC patients; although, these data are not always recorded for all patients, as in this retrospective analysis. Therefore, in an attempt to obtain information that could replace such performance scales, we used the level of hemoglobin as a preoperative predictor, as suggested by Jazieh *et al.*^[14] Lower values of hemoglobin in the preoperative period were shown to be a negative prognostic factor in our sample, for patients both in stages I and II but no difference was found when comparing genders, corrected to the reference values [Table 1]. These findings are consistent with the results obtained by other authors.^[14,26]

Regarding the other variables, we found that more advanced stages demonstrated worse survival, as expected.^[5,6,16] Larger tumor size, one of the items considered in the TNM system, analyzed here as a continuous variable, was also related to worse prognosis, that is, the greater the size of the tumor, worse was the survival period.

We found no correlation between the histological type with survival; however, since adenocarcinoma is usually associated with increased survival,^[17] further data will be required to clarify this possible discrepancy. In our sample, pneumonectomy was a negative prognostic factor only before adjustment for confounding factors, not maintaining statistical significance after the multivariate analysis. The presence of postoperative complication was also a factor associated with a worse prognosis in NSCLC patients in the overall sample.

One of the strengths of this study is that we could, over a long period of time, to follow all included cases, with no losses, from 1990 until the day of death as registered in the death certificates or accomplished by direct or telephone contact with the patients themselves or family members. All patients were treated at the same institution by the same clinician and surgeon, ensuring the uniformity of diagnostic and therapeutic procedures. Although we have used clinical staging of the disease in each subject, we have reallocated some patients according to the pathologic staging obtained after surgery. On the contrary, some of the limitations inherent to retrospective cohort studies were already presented.

Thus, in this study, it is shown that in the total group of NSCLC cases treated surgically with curative intent, the female gender was related to increased survival at 5 and 10 years, but not at 20 years in the survival timeline, information that we believe it is new. When gender was evaluated according to the staging of the neoplasm (stage I or II), the increased survival of females persisted only for stage I patients.

Many studies have analyzed the survival rate of lung cancer according to several prognostic factors, but several consider both sexes combined. Our results, in accordance with some other studies, confirm the point that combined gender rates do not provide an adequate prognosis index for women with NSCLC.

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