



Original Article

Lung Cancer in Women: a Comparison with Men and an Analysis of Cases Diagnosed in Ourense (Spain) 1999-2006

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ABSTRACT

Introduction and objective: To analyse the frequency, characteristics and survival of women with lung cancer (LC), compared with male patients.

Patients and methods: A retrospective study was performed in patients with LC diagnosed by histocytology from 1999 to 2006. Survival was estimated by the Kaplan-Meier method. The chi-squared test was used to compare variables.

Results: A total of 1,290 patients were diagnosed; 190 (14.7%) of them were women, with a mean age of 67 ± 13 . The percentage of smokers was 17%. Histological types included: adenocarcinoma 53%, small cell 21%, epidermoid carcinoma 13%. Surgery was performed (20%) in a higher percentage of women than in men. There were no differences in survival between the two groups.

Conclusions: Of the total cases diagnosed, 14.7% were women, with a lower percentage of smokers. Adenocarcinoma was the most common histological type. There were no differences in survival compared to men.

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Cáncer de pulmón en mujeres, comparativo con hombres: análisis de los casos diagnosticados en el Complejo Hospitalario de Ourense entre 1999 y 2006

RESUMEN

Introducción y objetivo: Analizar la frecuencia, las características y la supervivencia de las mujeres con cáncer de pulmón (CP), comparándolas con los pacientes varones.

Pacientes y métodos: Estudio retrospectivo de pacientes diagnosticados de CP mediante citohistología del 1999 al 2006. Se estimó la supervivencia por el método de Kaplan-Meier. Para estimar la relación entre las variables se usó la prueba de chi-cuadrado.

Resultados: Se diagnosticaron 1.290 pacientes, el 14,7% mujeres. En el grupo de mujeres la edad media (\pm desviación estándar) fue de 67 ± 13 años. Eran fumadoras el 17%. Según la citohistología, el 53% eran adenocarcinomas, 21% célula pequeña y 13% epidermoide. Se realizó cirugía (20%) en mayor porcentaje que en los varones. No hubo diferencias de supervivencia con el grupo de los hombres.

Conclusiones: El 14,7% de los casos fue diagnosticado en mujeres, siendo el porcentaje de fumadoras menor. La estirpe histológica más frecuente es adenocarcinoma. No hubo diferencias de supervivencia con el grupo de los hombres.

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Introduction

Lung cancer (LC) is currently the most frequently diagnosed cancer in the world.¹ In Spain alone, an estimated 18,500 new cases are diagnosed each year.² Since the beginning of the LC epidemic, incidence has been higher in men than in women, but in recent years there is a growing tendency in women. In fact, in countries such as the United States, the male/female ratio is close to 1.^{3,4} In Spain, this rate continues to be high, although less so than in years past.⁵ This is due to the fact that, while the incidence in men has decreased, in women it has remained stable, or has even increased.^{6,7}

Moreover, LC mortality in European women has increased steadily in recent years, with an annual growth rate of 4.6%.⁸ In our country, mortality has also increased,^{5,9} and is currently third only to breast and colon cancer.

Given the growing incidence and mortality of LC in women, the aim of our study was to analyze the frequency, clinical characteristics and survival of women diagnosed with LC in our health-care area, comparing these with data from men.

Patients and Methods

Ours is an observational, retrospective study of a cohort of LC patients diagnosed from 1 January, 1999 to 31 December, 2006 at the Complejo Hospitalario in Ourense, Galicia, Spain. Included for study were all those patients with primary LC diagnoses, confirmed by cytology and/or histology. Patients were included at the moment of diagnosis and data were compiled from the Clinical Documentation Service database and the Bronchoscopy and Pathological Anatomy files.

We designed a database using the SPSS 15.0 program, establishing a data collection protocol that included: identification, age, sex, tobacco habit, symptoms, comorbidity, bronchoscopic findings, diagnostic tests, stage, definitive diagnosis, treatment and date of death. For the histological classification, we followed the World Health Organization (WHO) classification.¹⁰ For the study of tumor extension, we used the classification by Mountain.¹¹ Date of death was taken from the medical files; if it was not included, we confirmed this data by a phone call to the listed place of residence or to the Galicia Death Registry. We established the censor (last day of the study) as 30 September, 2009. Never-smokers were defined as those patients who had smoked less than 100 cigarettes over the course of their lives; ex-smokers were defined as those who had quit smoking at least 6 months before.

Statistical Analysis

The statistical analysis was carried out by means of a descriptive analysis, where the results of the quantitative variables are expressed as mean \pm standard deviation or as median and 95% confidence interval (CI), depending on the case. The qualitative variables are expressed as absolute frequencies and percentages. To determine the paired associations, the χ^2 test was used. We estimated survival with the Kaplan-Meier method, and the curves obtained were compared using the Mantel-Haenszel test (log rank). Multivariate analyses were carried out to identify factors related to death in women with LC, based on the Cox proportional hazard estimation model (variables included were age, smoking, histological type, stage and treatment received). The level of statistical significance (p) was set as 0.05. The statistical software used was SPSS 15.0.

Results

Demographic Characteristics

In the study period, 1,290 patients were diagnosed with LC, 190 of which (14.7%) were women. The main patient characteristics, differentiated by sex, are shown in table 1.

Table 1

Patient characteristics, according to sex

	Women	Men	p
Age (years)	67.41 \pm 13	68.16 \pm 10.8	0.39
Smoking history	17%	95%	< 0.001
Packs/year	36.7 \pm 18	61.7 \pm 29.7	< 0.001
Stage I, II	18.4%	20.1%	0.027
Stage IIIA, IIIB	34.7%	43.1%	0.028
Stage IV	46.8%	36.8%	0.04
Surgery	20%	14.4%	0.032
Chemotherapy	54.3%	57.9%	0.19
Radiotherapy	32.4%	34.5%	0.32
Palliative	28.1%	26.8%	0.39
Survival	11%	9.3%	0.4

Table 2

Associated comorbidities in female and male patients

	Women	Men	p
Arterial hypertension	31.7%	20.2%	0.000
Cardiopathy	12.6%	18.7%	0.051
Previous neoplasia	11.1%	10.6%	0.899
Diabetes	10.5%	12.5%	0.053
Previous pneumonia	8.9%	10.7%	0.052
Digestive	8.9%	13.7%	0.08
Psychiatric	7.4%	2.9%	0.005
Neurological	7.4%	7.4%	1.000
COPD	5.8%	45.5%	0.000

COPD: chronic obstructive pulmonary disease.

Clinical Characteristics

In the group of women with LC, the most frequent associated comorbidities were arterial hypertension (31.7%) and cardiopathy (12.6%). In men, these were chronic obstructive pulmonary disease (COPD) (45.5%) and arterial hypertension (20.2%) (table 2). The main symptoms were cough and general syndrome in both sexes (table 3). All women underwent bronchoscopy, and direct or indirect signs of neoplasia were found in 121 (63.7%). In the group of women, the cyto-histological diagnosis was adenocarcinoma in 101 patients (53.2%), small-cell in 41 (21.6%), epidermoid in 25 (13.2%) and others in 23 (12.1%). Table 4 shows the comparative analysis for sex and tobacco habit related with histological type, stage and treatment.

Survival

Overall survival at the end of the study for the entire study group was 9.6% (mean 8.5 months; 95% CI, 7.7-9.3). Survival in the group of women was 11% (mean 7.9 months; 95% CI, 6.18-9.61), while in the group of men it was 9.3% (mean 8.6 months; 95% CI, 7.8-9.4). There were no significant differences for survival between the two groups (log rank = 0.691; p = 0.4) (fig. 1).

Table 3

Presentation symptoms in male and female patients

	Women	Men	p
Cough	58.4%	52%	0.059
Weight loss	40%	43.3%	0.154
Dyspnea	32.1%	26%	0.050
Chest pain	21.1%	27.1%	0.047
Extrathoracic pain	13.7%	11.9%	0.279
Hemoptysis	11.6%	28.9%	0.000
Expectoration	11.1%	15.4%	0.072
Asymptomatic	9.5%	5.8%	0.045
Fever	7.9%	8.2%	0.515
Neurological symptoms	6.8%	6.6%	0.508

Table 4
Comparative analysis for sex and tobacco habit

	Women		Men	
	Smokers, n (%)	Never-smokers, n (%)	Smokers, n (%)	Never-smokers, n (%)
Early stage	4 (12.5%)	31 (19.9%)	202 (20.3%)	10 (19.2%)
Localized/regional stage	11 (34.4%)	54 (34.6%)	433 (43.4%)	22 (42.3%)
Advanced stage	17 (53.1%)	71 (45.5%)	362 (36.3%)	20 (38.5%)
Epidermoid	2 (8.7%)	14 (11.7%)	359 (46%)	15 (36.6%)
Adenocarcinoma	9 (39.1%)	63 (52.5%)	182 (23.3%)	14 (34.1%)
Small cell	9 (39.1%)	24 (20%)	181 (23.2%)	7 (17.1%)
Other	3 (13%)	19 (15.8%)	58 (7.4%)	5 (12.2%)
Surgery	4 (18.2%)	26 (22.2%)	127 (16.6%)	6 (14.6%)
Chemotherapy	14 (63.6%)	48 (41%)	402 (52.4%)	19 (46.3%)
Radiotherapy	0 (0%)	11 (9.4%)	63 (8.2%)	1 (2.4%)
Paliative	4 (18.2%)	32 (27.4%)	175 (22.8%)	15 (36.6%)

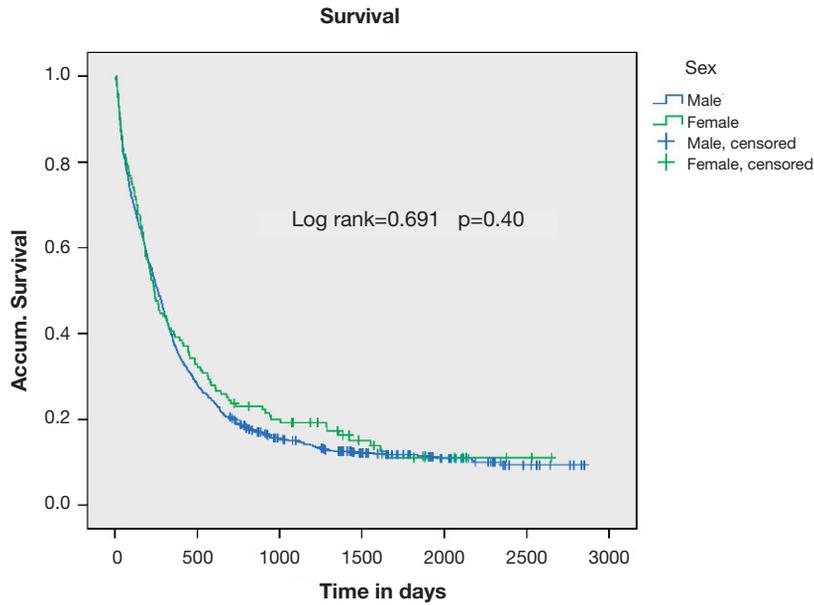


Figure 1. Survival estimation curves, according to sex.

In the women, there were significant differences in survival depending on stage (log rank = 28.31; $p < 0.001$) (fig. 2) and treatment, and was significantly better in patients who received surgical

treatment (log rank: 37; $p < 0.001$); the same was true in the group of men (fig. 3). There were no significant differences in survival between sexes regarding smoking (log rank = 6.96; $p = 0.073$) (fig. 4).

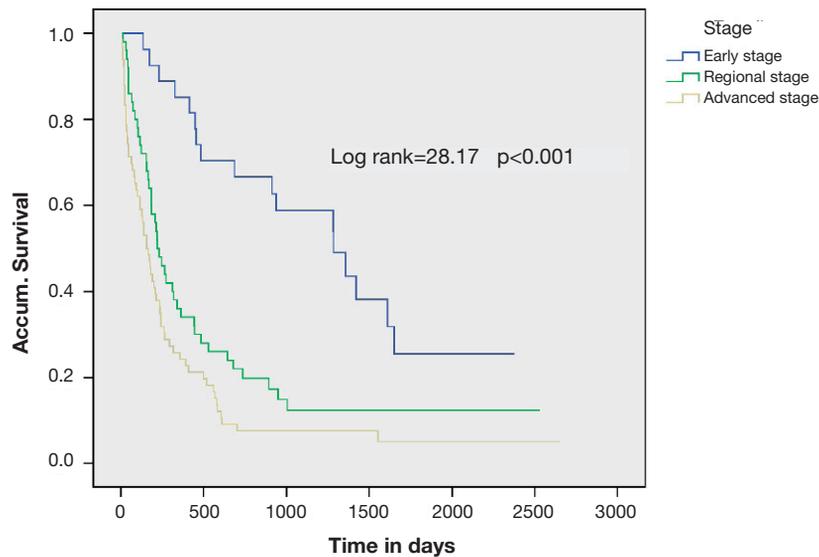


Figure 2. Survival curves in women, according to clinical stage.

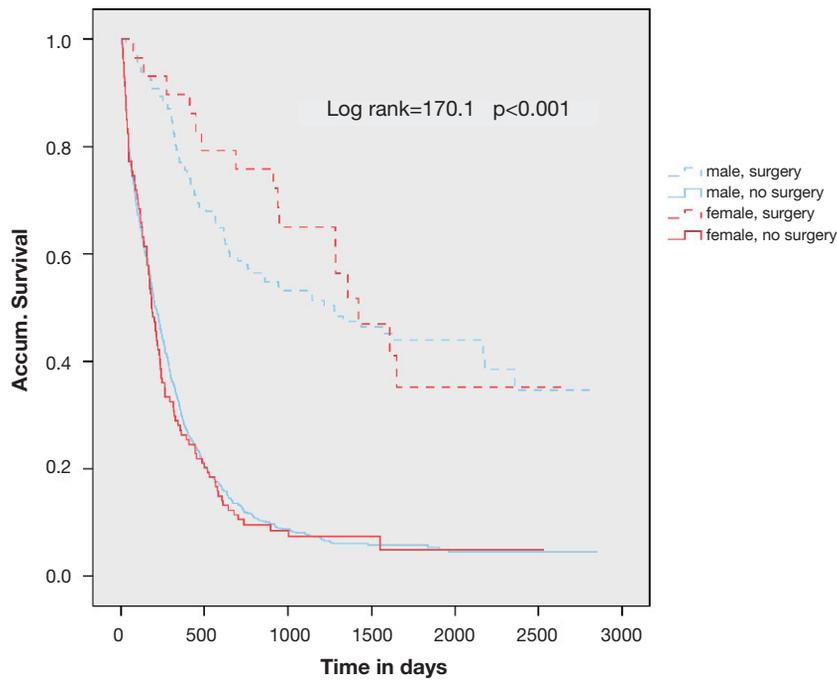


Figure 3. Survival estimation curves, according to sex and surgical treatment.

In the Cox multivariate regression analysis, the risk of death in women was significantly higher with older age, the epidermoid subtype and advanced stages.

Discussion

In recent years, there has been a rising trend in lung cancer rates in Spanish women.⁹ In our study, we have observed 14.7% of LC cases in women, a percentage similar to articles in other regions of Spain. These include the publications of Hernández et al.⁶ with 13% in Castilla-León and Cantabria, and Miravet et al.¹² with 15.3% in the province of Castellón.

LC is the main cause of death by cancer in the world and smoking is the most important risk factor for its development, involved in 90% of cases.^{13,14} In our study we observed 17% of women who smoked compared with 95% of male smokers. Lung cancer in non-smokers is more frequent in women than in men. In a review article by Sun et al.¹⁵ in non-smoker LC cases, a higher proportion of women was observed in Europe as well as in the United States (21% in Europe and 15% in the US). The high percentage of non-smoker women could be explained by genetic predisposition, second-hand smoke or environmental factors.¹⁶ We did not analyze these risk factors as ours is a retrospective study.

In our study, we have found that women have less accumulated tobacco consumption than men, as observed in other studies.¹⁷

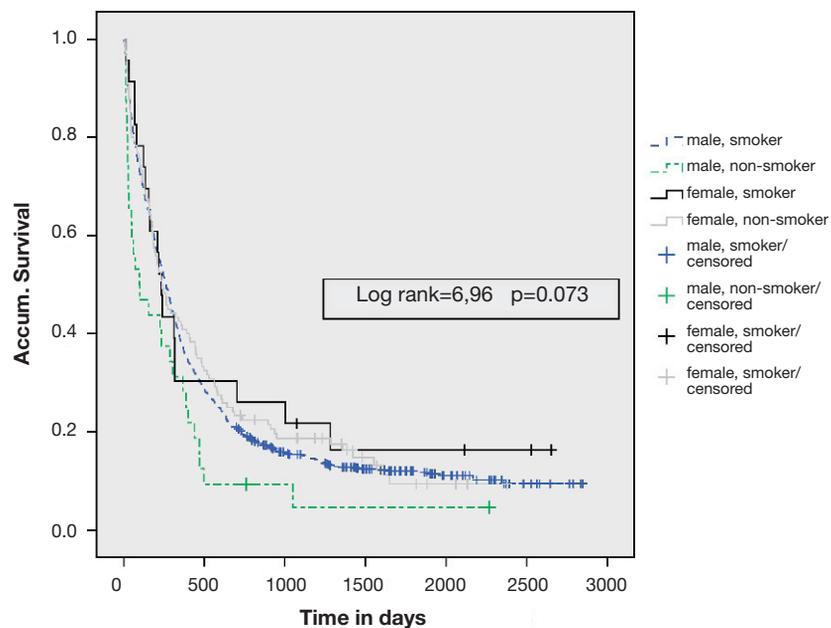


Figure 4. Survival curves, according to sex and tobacco habit.

Dresler et al.¹⁸ hypothesize that women are more susceptible to develop LC with the same level of exposure to tobacco smoke. Meanwhile, other authors, like Bain et al.,¹⁹ find that the risk for developing LC in men and women is similar for the same level of tobacco use.

In our series, the most frequent histological type was adenocarcinoma, the same as in other studies.^{6,7,14,20} Smoking is more closely associated with squamous, small-cell and large-cell carcinoma²¹ than with adenocarcinoma, which is more frequent in non-smokers. On the other hand, the change in the composition of cigarettes and the use of filters have also been related with the increase in adenocarcinoma.²² However, the differences in the histological distribution of LC cannot be explained by these data alone. Hormonal or molecular factors can influence the differences in histology observed between the sexes. Lynch et al.²³ observed that the mutation of the epidermal growth factor receptor (EGFR) is associated with adenocarcinoma and this mutation is more frequent in non-smoker women, which has implications in the current treatment with drugs directed at specific molecular targets.²⁴

The five-year survival of LC ranges from 6 to 16%.^{12,25-27} In our series, it was 11%, with no significant differences between men and women. Several authors have researched the influence of sex on the survival of LC with contradictory results. Some found that females were related to a better prognosis.²⁸ Nevertheless, previous studies²⁹ observed poorer survival and response to treatment in women. The differences in methodology of these studies make it difficult to compare the results and it is necessary to wait for future studies to evaluate similar populations in order to be able to establish the true influence of sex in the prognosis of LC.

Apart from this, surgery prolongs survival in the early stages of LC. In our series, 20% of the women underwent surgical treatment, which is a significantly higher percentage than in the group of men (14%). This is in spite of there being no significant differences between the sexes for the percentage of patients diagnosed in early stage. This may be due to the influence of comorbidity, since COPD poses serious problems to indicate this type of treatment,³⁰ and the percentage of patients with COPD is significantly greater in men than in women in our series.

In conclusion, 14.7% of the cases in our study were diagnosed in women. The percentage of smokers and the accumulated tobacco consumption in this group were less than in the group of male patients. Like other series, the most frequent histological diagnosis was adenocarcinoma. When compared with the group of men, no significant differences were found in survival.

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