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## Long-Term Lung Cancer Survival in a Province of Spain

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### Abstract

**Introduction and aims:** To analyze the characteristics and long-term survival of patients diagnosed with lung cancer (LC), small cell and non small cell, in our hospital.

**Patients and methods:** Retrospective study of patients with a cytohistological diagnosis of LC between 1999 and 2004. Survival was estimated using the Kaplan-Meier method. The chi-squared test was used to assess possible associations between different variables.

**Results:** In this time period, 996 cases were diagnosed, 85.6% in males and 14.4% in females. A total of 80.6% of the patients were smokers. Squamous cell carcinoma was the most frequent in males and adenocarcinoma in females; 20.4% of the tumours were at an early stage (I and II) at the time of diagnosis and only 16.8% were amenable to surgery. Overall survival was 7.9% at 5 years and the LC-specific survival was 14%. Survival was significantly worse in advanced stages and in patients that did not receive active treatment.

**Conclusions:** Overall 5-year survival in our series was low, but similar to that described in other Spanish registries. This may be related to the low number of patients diagnosed in early stages and who could be treated surgically.

### Introduction

Lung cancer (LC) is the most frequently diagnosed type of cancer around the world [1] and the most frequent cause of cancer-related death. The incidence of LC in Spanish males is 74.8 cases/100,000 inhabitants and in females 9.7 cases/100,000 inhabitants [2]. Overall, 20,327 people die each year due to LC in Spain [3]. LC is the first cause of cancer-related death in males and the third in females, following breast and colon cancer [4]. The high rate of smoking, the difficulty to devise a screening programme and the scarce advances in the treatment of non-surgical tumours can partially explain the present high mortality associated with this tumour.

The epidemiological features of LC in Spain are similar to other countries. However, there are differences in certain aspects, for example the percentage of women, which is higher in the American series [5], or in the histology lineage distribution. While in our country, the most common histological type is the squamous cell carcinoma, overall the world, the most common subtype is the adenocarcinoma [6]. Therefore, epidemiological and clinical characteristics, diagnostic and therapeutic resources used in the LC vary between countries, regions and health centers, and this could influence their prognosis. In Spain there are very few reports analyzing the long-term survival in large series of patients and the latest published reports include patients that were diagnosed more than 10 years ago [7,8]. The main objective of the present study was therefore to determine the overall and specific long-term survival of the patients diagnosed with LC in our hospital as well as the possible association between survival and histological type, age, sex, tumour stage and type of therapy.

### Patients and Methods

A retrospective observational cohort study was carried out of patients diagnosed with LC between January 1, 1999 and December 31, 2004 at the Ourense Hospital Complex (second-level hospital care). We enrolled all patients diagnosed with LC for the first time and confirmed cytologically and/or histologically. Clinical data were collected from the database of the Clinical Documentation Department, Bronchoscopy and Surgical Pathology archives.

We designed a study database and created a protocol for data collection, which included identification, age, sex, tobacco smoking, symptoms, comorbidities, fibrobronchoscopic findings, results of diagnostic tests, stage, definitive diagnosis, therapy and date of death.

The histological classification of the tumours was made according to the World Health Organization (WHO) classification [9]. The tumour staging studies were those used in the sixth edition TNM LC [10]. The date of death was either obtained from the clinical records of the patients or, if unavailable, by telephoning the patient's family or by consulting the official Mortality Registry in Galicia. The last day of the study was January 1, 2010. Never-smokers were defined as patients who had smoked less than 100 cigarettes in their entire life and former smokers as those who had quit smoking at least 6 months before diagnosis.

### Statistical analysis

We performed a descriptive analysis of the data, expressing the results for quantitative variables as mean  $\pm$  standard deviation (SD) or median and 95% confidence interval (CI), as required. Qualitative variables were expressed as absolute frequencies and percentages. The chi-squared test was employed to test possible associations between the variables. Survival was estimated using Kaplan-Meier curves. Subsequently, we performed a multivariable analysis based on the Cox proportional hazards model to identify which factors were independently associated with death. The LC-specific survival was also measured (a survival analysis in which a death event was considered to be only a death directly related to LC). A follow-up was performed of all the patients enrolled and at the end of the study 79 were alive. A p-value of 0.05 was considered statistically significant. The statistical analysis was performed using SPSS 15.0 statistical package.

### Results

During the study period, LC was diagnosed in 996 patients. Of

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these, 853 (85.6%) were males and 143 (14.4%) were females, with a male:female ratio of 5.9:1. The mean age was 68 years (SD ± 11.15; range 35-97) and 507 patients (51%) were older than 70 years. A total of 80.6% of patients were present or former smokers and the mean cigarette consumption was 60.52 (SD + 29.13) packs/year. Table 1 shows the epidemiological and clinical characteristics of the patients, both overall and according to sex. Table 2 shows the therapies employed in these patients.

Overall cumulative survival for all of the patients at the end of the study (January 1, 2010) was 7.9% and the median survival time was 8.3 months (95% CI: 7.7-9.4). Figure 1 shows the survival at 1, 3 and 5 years. LC-specific survival was 14% with a median survival time of 8.9 months (95% CI: 8.09-9.84). The median follow-up time in our series was 7.9 ± 1.7 years. LC was the cause of death in 93.5% of our patients and the remaining 6.5% died due to other concurrent diseases (Table 3). Survival differences were found according to clinical stage ( $\chi^2 = 170$ ;  $p < 0.001$ ) (Figure 2), histological type ( $\chi^2 = 11.7$ ;  $p = 0.008$ ) and therapy (Figure 3) ( $\chi^2 = 300$ ;  $p < 0.001$ ). There were no statistically significant sex-related differences in survival ( $p = 0.248$ ). Survival was lower in patients older than 70 years ( $\chi^2 = 27.8$ ;  $p < 0.001$ ) (Table 4).

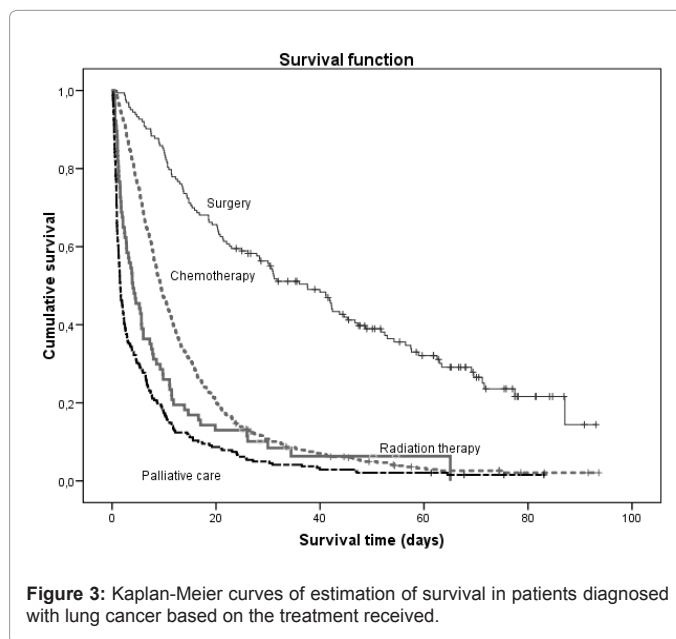
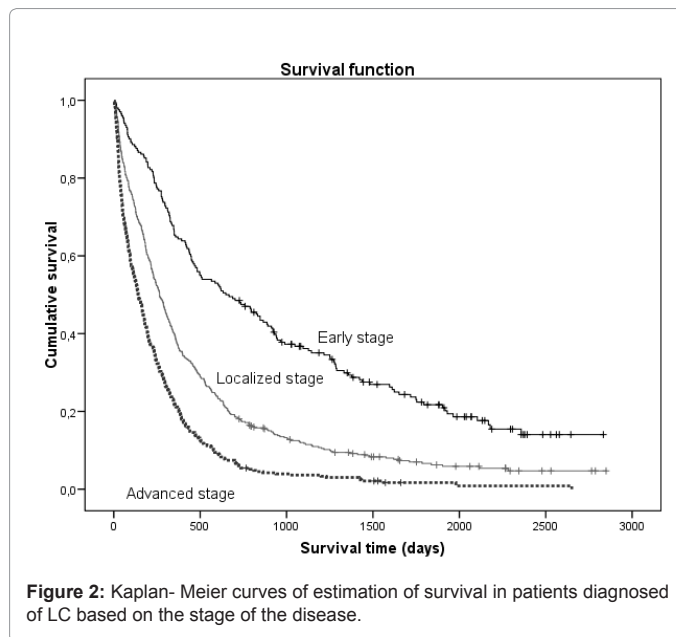
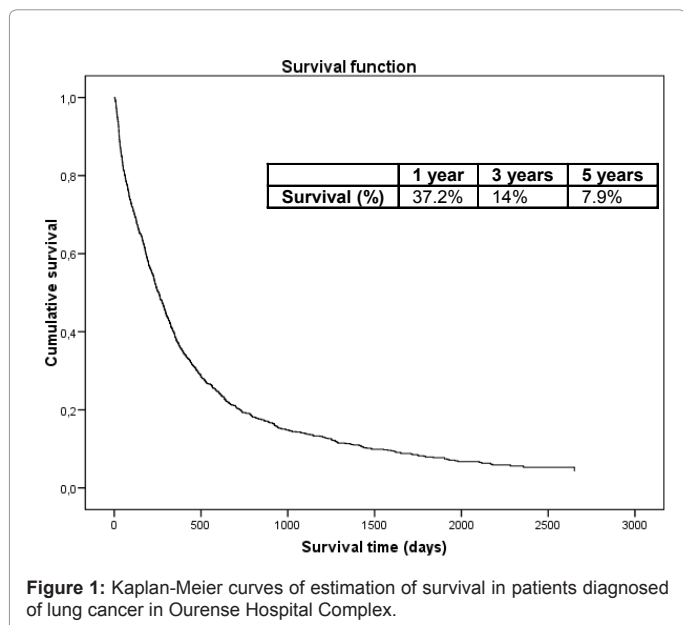
	Males	Females	Overall	p *
Age (mean±SD)	68.17±10.7	67.41±13	68±11	0.44
Smoking	95%	16%	80.6%	<0.001
Packs/year	61.3±29.1	36.18±18.9	60.52±29	<0.001
Histology				
Adenocarcinoma	24%	50.3%	27.9%	<0.001
Squamous cell	45.4%	11.6%	40.5%	
Small cell	23%	23.1%	22.9%	
Others *	7.6%	15.4%	8.7%	
Stage				
I,II	20.5%	18.9%	20.4%	0.009
IIIA,IIIB	46.2%	35%	44.5%	
IV	33.3%	46.2%	31.1%	

\* SD: standard deviation

\* p: statistical significance for the comparison between the two sexes

\* Others: adenosquamous, large cell, undifferentiated, carcinoid

Table 1: Overall and sex-related epidemiological and clinical characteristics of the patients.



Multivariable Cox regression analysis estimated that the factors independently associated with the risk of death were advanced stage ( $p < 0.001$ ) and lack of active treatment ( $p < 0.001$ ) (Table 5).

## Discussion

LC is the malignant tumour that has increased the most in recent decades [11]. Overall survival of these patients remains poor, with variations related to the geographic area. Regional registries reflecting data of the incidence, clinical approach and survival can be used to define the present epidemiological situation for this tumour.

In our series we found that squamous cell carcinoma was the most frequent histological type of tumour, although there were marked differences in histological diagnosis between the sexes. In females there was a preponderance of adenocarcinoma (50.3%), while in males squamous cell carcinoma predominated (45.4%). These results are

		STAGE							
			IA	IB	IIA	IIB	IIIA	IIIB	IV
NSCLC	THERAPY	Surgery	n 31	38	0	3	4	4	2
			% 67.4%	39.6%	0.0%	8.8%	5.8%	1.6%	0.9%
		CT	n 0	8	0	4	17	81	68
			% 0.0%	8.3%	0.0%	11.8%	24.6%	32.7%	29.1%
		RT	n 2	11	0	2	6	17	30
			% 4.3%	11.5%	0.0%	5.9%	8.7%	6.9%	12.8%
		Palliative care	n 3	12	1	16	17	85	80
			% 6.5%	12.5%	50.0%	47.1%	24.6%	34.3%	34.2%
		Surgery+CT	n 4	7	0	4	3	4	3
			% 8.7%	7.3%	0.0%	11.8%	4.3%	1.6%	1.3%
		CT+RT	n 0	4	0	2	15	53	51
			% 0.0%	4.2%	0.0%	5.9%	21.7%	21.4%	21.8%
		Surgery+CT+RT	n 2	4	0	2	5	3	0
			% 4.3%	4.2%	0.0%	5.9%	7.2%	1.2%	0.0%
	Surgery+RT	n 4	12	1	1	2	1	0	
		% 8.7%	12.5%	50.0%	2.9%	2.9%	0.4%	0.0%	
SCLC	THERAPY	Surgery	n 0	1	0	1	0	1	0
			% 0.0%	14.3%	0.0%	14.3%	0.0%	1.1%	0.0%
		CT	n 0	1	0	1	10	31	52
			% 0.0%	14.3%	0.0%	14.3%	25.6%	33.3%	44.4%
		RT	n 0	0	0	0	1	1	9
			% 0.0%	0.0%	0.0%	0.0%	2.6%	1.1%	7.7%
		Palliative care	n 2	1	1	2	1	16	31
			% 66.7%	14.3%	100.0%	28.6%	2.6%	17.2%	26.5%
		Surgery+CT	n 0	2	0	0	1	0	0
			% 0.0%	28.6%	0.0%	0.0%	2.6%	0.0%	0.0%
	CT+RT	n 1	2	0	2	25	44	25	
		% 33.3%	28.6%	0.0%	28.6%	64.1%	47.3%	21.4%	
	Surgery+CT+RT	n 0	0	0	1	1	0	0	
		% 0.0%	0.0%	0.0%	14.3%	2.6%	0.0%	0.0%	

\*NSCLC: LC non small cell  
 \*SCLC: LC small cell  
 \*CT: chemotherapy.  
 \*RT: radiation therapy

**Table 2:** Percentage of patients receiving different therapies.

similar to those reported by other groups [12,13] and can be attributed to the differences in smoking between sexes (the women in our study smoked less), as well as to molecular or hormonal factors [14].

Overall survival in our series was 7.9% in accordance with other Spanish studies with similar features. In a series of 610 patients from Cáceres [7], overall survival was 7.9% and in another series of 118 patients from Castellón [8], 7.6%. However, neither of these reports analyzed the LC-specific survival, which in our series was estimated at 14%. This figure is similar to that reported in other European countries, with LC-specific survivals ranging from 9-20% [15]. One of the main limitations of our study is that it is a hospital-based series rather than being population-based, which can lead to bias due to patient selection. In our series, 6.5% of the patients died of causes unrelated to LC, mainly other malignant tumours and respiratory pathologies, including COPD. In the cases in which the cause of death could not be found in the patients' clinical records or by telephoning the families, it was obtained from the official death certificates, which presents certain limitations. Overall survival results were similar to those reported by other European registries [16,17]. A recently published study with data from different countries has found a 5-year survival of 12% [18,19]. This figure is lower than the 14% survival reported in series from the USA [20]. Another limitation to this study is related to those cases in

which we were not able to determine the cause of death after a thorough review of the clinical records or a telephone call to the relatives. We therefore searched for it using the Rexistro de Mortalidade de Galicia (The Galicia Mortality Registry), in which data are obtained from official death certificates. These results should therefore be interpreted with caution.

These poor survival data can be explained because, despite important advances in the medical therapy of LC, surgery remains the most effective therapeutic strategy. This might explain why LC survival is at least partially determined by the percentage of patients eligible for complete resection. This percentage is low in most European [16,17] and Spanish [7,8,21-24] registries, as also shown in the present series (16%). Series from the US, however, show higher percentages of surgical cases, nearing 27% [25], probably because the populations are highly selected. Non-surgical therapies were the most frequently employed in our series, which would explain the poor survival data.

Another factor that can explain the poor survival in LC is the high number of patients that are diagnosed with locally advanced or metastatic disease (stages IIIB or IV), which represented 75.6% of our series. This explains why palliative care alone was so frequently used in our patients, as also in other reports in the literature [12,21-24]. Our results show a trend towards more advanced stage at diagnosis in females, which may be due to the fact that there were fewer women

	n	%
<b>LC</b>	857	93.5%
<b>Other tumours</b>	27	2.9%
<b>Respiratory disease</b>	10	1.09%
<b>Heart disease</b>	7	0.76%
<b>Neurological disease</b>	6	0.65%
<b>Others</b>	10	1.09%
<b>Total</b>	917	100%

**Table 3:** Percentage of patients who died of LC and other causes.

	5-year survival	Median	p
<b>Sex</b>			
Males	7.3%	8.6 months	0.248
Females	11.9%	7.9 months	
<b>Age</b>			
Older than 70 years	4.7%	6.5 months	<0.001
Younger than 70 years	10.9%	10.4 months	
<b>Stage</b>			
I	23%	26 months	<0.001
II	13.6%	10.7 months	
III	7.4%	8.7 months	
IV	1.4%	4.6 months	
<b>Treatment</b>			
Surgery	36.20%	38.1 months	<0.001
Chemotherapy	7.79%	9.5 months	
Radiation therapy	4.23%	4 months	
Palliative care	2.07%	1.6 months	

**Table 4:** Percentage and median survival time according to sex, age, stage and treatment.

	B ·	p	HR ·	95% CI for HR	
				Lower	Upper
<b>Sex (female)</b>	-0.093	0.359	0.911	0.747	1.112
<b>Age (older than 70)</b>	0.048	0.517	1.049	0.908	1.211
<b>Histologic type (adenocarcinoma)</b>	0.034	0.694	1.034	0.875	1.223
<b>Histologic type (small cell)</b>	0.184	0.050	1.203	1.000	1.446
<b>Histology (others)</b>	-0.083	0.513	0.920	0.716	1.182
<b>Stage (localized)</b>	0.306	0.008	1.357	1.082	1.703
<b>Stage (advanced)</b>	0.727	0.000	2.068	1.641	2.605
<b>Surgery (yes)</b>	-1.083	0.000	0.339	0.246	0.465
<b>Chemotherapy (yes)</b>	-0.308	0.020	0.735	0.568	0.952
<b>Radiation therapy (yes)</b>	-0.261	0.002	0.770	0.652	0.910
<b>Palliative (yes)</b>	0.341	0.023	1.406	1.048	1.887

·HR: Hazard ratio

·B: Cox regression coefficient

**Table 5:** Multivariable analysis of the prognostic factors for LC.

smokers than men in the registry and they would not be routinely followed with imaging studies. However, this result was not found in prior studies [7,8,13]. Another finding was that 55.6% of our patients were treated with chemotherapy, a similar percentage to that reported in other national series. In the EPICLICB study [13], the percentage of patients receiving chemotherapy ranged from 42% to 68%. In recent years there have been many studies with new drugs targeting specific components of the tumour cells [14,26-28] and that might improve the survival of patients with recurrence or advanced stage tumours. In our series, none of the patients were treated with this kind of drug, since they were introduced after 2004, the last year for patient inclusion in our series. The struggle to improve survival from LC would undoubtedly benefit from achieving earlier diagnosis. Based on this, for many years there has been a search for effective screening programmes for LC. Recent reports have shown promising results using low-radiation chest computed tomography for screening and some reports have found an 80% 10-year survival [29]. The results of these ongoing studies are

awaited to confirm the effectiveness of these screening programmes [30].

Survival in our study was poorer for patients over 70 years. This can be attributed to the less aggressive therapeutic approach usually chosen in this population, both due to age itself and also the greater likelihood of comorbidities. In our series 40% of these older patients had COPD, a disease in which surgery is contraindicated in some cases. Prior studies in our country have shown similar results [7,13] the percentage of comorbidity even reached 81.7% in the EpiclicP 2003 study [13].

In short, we can conclude that 5-year overall and LC-specific survival in our series was low, although similar to other Spanish registries. This can be attributed to the low percentage of patients diagnosed at an early stage and that are eligible for surgical resection of the tumour. It seems reasonable to conclude that ongoing efforts to improve survival from LC should be centred on achieving an earlier diagnosis in our patients, while awaiting the development of the promising new targeted or individualized therapies.

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