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Research Article

Prognostic Factors Associated with Lung Cancer Survival: A Population-Based Study in Southern Spain

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ABSTRACT

Purpose: Lung cancer is the leading cause of cancer death worldwide. The objective was to analyze survival for lung cancer in Granada, and to identify the factors influencing survival.

Methods: Data were obtained from the population-based cancer registry in Granada (Spain). All cases of newly diagnosed primary lung cancer in 2011-2012 (n=685) were included. One and two-year relative survival was estimated.

Results: Of our population, 65% of the patients were over 65 years of age, and 83% were men. 74% of patients had good performance status (PS); 81% of the tumors were microscopically verified; and 81% were non-small cell lung cancer. Overall, 16% were stage I-II, whereas 57% were stage IV. Radiotherapy was administered in 28% of cases, chemotherapy in 45%, whereas 23% of patients were operated. The two-year survival rate was 18% (67% and 5% for stage I and IV). Survival was higher among women (29%), <75 years of age (21.6%), and those with good PS (23%). Microscopic verification and surgery led to higher survival rates of 23.4% and 69%, respectively.

Conclusions: Since the factors affecting survival were PS, stage, and surgery, efforts should target the early diagnosis of lung cancer since this would improve treatment options and outcomes.

Purpose

Survival of cancer patients is one of the main quality indicators of the health care system since it reflects the extent to which cases are diagnosed at a potentially curable stage and also measures the effectiveness of the therapeutic procedure. A population-based cancer survival analysis thus provides valuable information that can be used to assess healthcare performance in patients diagnosed with malignant tumors. This survival analysis is estimated from all incident cases within a cancer registry area over a certain time period and provides a valid measure of cancer care performance. According to the EUROCARE-5 [1] study, the European mean age-standardized 5-year survival for lung cancer (LC) was the poorest of the ten index cancers (13%, 95% CI 12.9-13.1) with a higher percentage for women than for men.

Despite efforts to improve management, prognosis of LC patients remains unsatisfactory. Non-surgical treatment options, such as radiotherapy, chemotherapy, and targeted therapy, have been studied in order to determine whether they prolong overall survival. The moderate progress achieved with these therapies has led to research on whether there are certain subgroups of LC patients that would benefit more from specific treatment strategies [2, 3].

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There are numerous proposed causes for its development and increasing mortality, but the primary cause remains tobacco smoking [4]. Several reports have also regarded smoking as a significant prognostic factor. Studies have shown that the clinical characteristics and prognosis of LC in non-smokers are substantially different from those in smokers [5]. However, this association has not been observed in all studies [6]. These controversial results may be attributed to potentially confounding factors such as a different definition of smoking status, age, gender, and histology. Other factors, such as gender and histological type, seem also to play an important role in prognosis, but not all studies have found them to be prognostic factors [7, 8]. Because of these differing results from previous studies, we conducted a study analyzing the prognostic significance of various factors for the survival in LC in Granada (southern Spain).

Material and method

I Population, data source, and data collection

The study population came from the Granada Cancer Registry, a population-based cancer registry in Southern Spain. Created in 1985, it covers a population of approximately 920,000 inhabitants (2011 intercensal population estimates. Source: National Statistical Institute (INE, in Spanish) (http://www.ine.es). Granada Cancer Registry is a member of the European Network of Cancer Registries and collaborates in the EUROCARE study [9]. From 1 January 2011 to 31 December 2012, 685 patients in the province of Granada were diagnosed with an invasive primary LC (new cases). LCs were defined as codes C33–34, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [10]. Life status follow-up was uniformly updated until April 2015 for all LC cases.

The information in the cancer registry came from a wide range of sources (inpatient and outpatient files, mortality files, etc.), which were used to reconstruct the patient history. Sources of patient data were medical and treatment records from the pneumology, thoracic surgery, medical oncology, and radiotherapy oncology departments of hospitals in the province of Granada. The list of patients was obtained from the Granada Cancer Registry through the Hospital Cancer Registry and the Minimum Basic Data Set (MBDS) of hospital discharges. Topography and morphology were coded according to the International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3) [11]. Both microscopically verified and unverified LC cases were included. Those cases whose diagnosis was only based on the death certificate or autopsy were also included. Age at diagnosis was categorized as 15-44, 45-54, 55-64, 65-74, and ≥75 years. Stage at diagnosis was based on the 7th edition of the TNM manual [12]. The following five stage categories were selected: stage I (T1-2aN0M0); stage II (T2b-T3N0M0, T1-T2N1M0); stage IIIA (T4N0M0, T3-T4N1M0, T1-T3N2M0); stage IIIB (T4N2M0, T1-T4N3M0); and stage IV (M1).

Method of diagnosis was categorized as clinical/instrumental only, cytological, or histological (including histological diagnosis of metastasis). If diagnosis was based on cytological or histological evaluation, the disease was considered to be microscopically verified and was further classified by morphology as small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), or not otherwise specified (NOS). Surgery, chemotherapy, radiotherapy, targeted treatment, and diagnostic examinations were marked as *done*, *not done* or *unspecified/unknown*. Chemotherapy and radiotherapy schemes were also taken into account. Information regarding the timeliness of the treatment was <1 month in curative treatment or< 1 week in palliative treatment. Furthermore, our study included information pertaining to diagnostic examinations: chest X-ray, computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), bronchoscopy, endobronchial ultrasound guided bronchoscopy (EBUS), and mediastinoscopy. Also considered were 19 items for co-morbidities at diagnosis (Charlson index), performance status, PS (Karnofsky, ECOG/WHO), smoking habit (*yes, currently*; *yes, former*; *no never*) and Body Mass Index (BMI) [13-15].

II Statistical analysis

This study generally focused on the distribution of cases by age, sex, method of diagnosis, stage, morphology, comorbidities, and treatments. It also analyzed the percentage of patients who received specific diagnostic examinations. Another important feature was the time between the diagnosis of the disease and the onset of the first treatment (delays), more specifically, a delay in palliative treatments of > 7 days and a delay in curative treatment of >30 days [16]. Monitoring was based on the National Death Index (NDI; NDI is an information system that contains personal data of each of the deaths that have been inscribed in the Civil Registries of all the State obtained through the INE.), on the Mortality Statistics by Causes of Andalusia which provides quarterly and annual information on the mortality produced in Andalusia according to the cause of the death by sex and age, and active searches of hospital medical records.

The one and two-year relative survival (RS) was estimated by using the Pohar-Perme model for population-based cancer survival [17]. This is the ratio of survival observed in cancer patients and the survival that would have been expected if they had experienced only the all-cause death rates (background mortality) of the general population where they lived. Background mortality rate data were obtained from INE. RS is interpretable as survival from the cancer after adjustment for other causes of death. It is required for international comparisons because it removes differences in the survival of cancer patients, which are unrelated to their cancer. To study the combined contribution of factors for both the patient and tumor, the risk of death was modeled with a generalized linear model with a Poisson error structure, based on collapsed data using exact survival times. Relative excess risks (RERs) of death with 95% confidence intervals (CIs) were estimated using the maximum likelihood method. Predictor variables included in the multivariate model were sex, age, PS, histology, smoking, previous lung disease stage, and treatment. A sensitivity analysis was carried out of the variables with many missing values. For this purpose, more than one model was made of those variables that showed differences in the magnitude and direction of associations. Two multivariate models were evaluated. The first model (n=558) included all predictor variables except PS because of the high number of missing values (18.5%), whereas the second model (n=685) included the PS variable [18].

The IBM SPSS Statistics, version 12, software application was used for analysis. The R Package Survival and Results (R version 3.2.0), was

used to estimate and model RS, respectively. The significance level was 0.05.

Table 1: Lung cancer cases diagnosed in 2011–2012 with distribution by sex, performance status, lung disease, smoking habit, stage and method of diagnosis.

	N (%)
Sex	
Male	572 (83.5%)
Female	113 (16.5%)
Performance status ECOG	
ECOG 0-1	413 (74%)
ECOG ≥ 2	145 (26%)
* Unknown	127 (18.5%)
Lungdisease	
Yes	245 (36.4%)
No	428 (63.6%)
*Unknown	12 (1.8%)
Smoker	
Currently	254 (42.5%)
Former	262 (43.8%)
Never	82 (13.7%)
*Unknown	87 (12.7%)
Stage	
I	73 (10.8%)
II	33 (4.9%)
IIIA	71 (10.6%)
IIIB	109 (16.2%)
IV	387 (57.5%)
*Unknown	12 (1.8%)
Diagnosis	
Clinical	131 (19.1%)
Histological	554(80.9%)

* Percentages were only calculated with the known data

Results

A total of 685 population-based LC cases were included in the analysis. As shown in (Table 1), over 83.5% were men, with a male-to-female ratio of 5.3. In 35.3% of the cases, the patients were older than 75. The percentage of patients with PS ≥ 2 was 26%. Patients with chronic obstructive pulmonary disease (COPD) were 36.4%. According to the data, 42.5% of the diagnosed cases of LC were current smokers, with a higher prevalence in men (44.2%) than in women (34.3%). When current and former smokers were taken into account the percentage was much higher, 86.3%. Only 10.7% of cases were stage I whereas 57.5% of cases were stage IV. Generally speaking, 2% of the cancers had an unspecified (unknown or not assessed) stage at diagnosis. Over 81% of the cases were histologically verified. In only 19% of the cases, the diagnosis was based on clinical or instrumental methods though, this 19% was not evenly distributed. Relevant factors were patient age and PS. More specifically, the percentages were 40.1% for patients ≥ 75 years though only 7% for those patients younger than 75. Similarly, this was the case for 32% patients with a PS ≥ 2, but only for 12% with a good PS. The most common morphological category was NSCLC (81%) in comparison to the remaining 19% that were SCLC. Morphology was unspecified in 2.3% of cases. For both sexes, the median age at diagnosis was 69 years. In regard to men (Table 2), 69.6% of the new LC patients were over 65. The incidence rate was highest in men older than 75. For women, the peak incidence was between the ages of 45 and 54. In both sexes, incidence was low in the15-44 age range. LC incidence by histologic type (Table 2) also shows gender-related differences. In women, adenocarcinoma was the most frequent histologic type (68.5%). In contrast, the most frequent types in men were squamous cell carcinoma (37%) and adenocarcinoma (35%). SCLC was the second most frequent type in women (15.2%) and the third most frequent in men (19.7 %,). In previous work, we highlighted that LC incidence in females increased in 1985-2012 by +4.2% per year (95 % CI 3.1–5.4). This trend was mainly due to patients in the 55–64 age range (annual percentage change (APC) = +7%) and to adenocarcinoma incidence in women (APC = +6.8%) [19]. Regarding patients that underwent main diagnostic examinations (Table 3), 87.5% had a chest X ray and 95.6% had a CT. These categories are not mutually exclusive. Patients who had a chest x-ray and a CT for diagnosis were 83.6%. Over 63.2% of cases received a bronchoscopy, but only 29.8%, an EBUS. In 52.4% of cases, a PET was given. Other diagnostic examinations (MRI, mediastinoscopy) were performed in less than 12% of cases.

Table 2: Lung cancer incidence (%) by sex, age and histological type, Granada 2011–2012.

	Men	Women
Age		
15-44	10 (1.7%)	6 (5.3%)
45-54	46 (8.1%)	34(30.1%)
55-64	118 (20.6%)	27 (23.9%)
65-74	187(32.7%)	15 (13.3%)
≥ 75	211 (36.9%)	31 (27.4%)
Histologic type		
Non-microscopic verification	114 (19.9%)	17 (15.2%)
Microscopic verification	459 (80.1%)	95 (84.8%)
ADC	156 (35%)	63 (68.5%)
SCC	165 (37%)	9 (9.8%)
LCC	13 (2.9%)	1 (1.1%)
SCLC	88 (19.7%)	14 (15.2%)
Others	24 (5.4%)	5 (5.4%)
Total	446 (100%)	92 (100%)
NOS	13 (2.3%)	3 (2.7%)

ADC adenocarcinoma, SCC squamous cell carcinoma, LCC large cell carcinoma, SCLC small cell lung carcinoma, NOS not otherwise specified

Regarding treatments (Table 3), surgery was performed on 15.2% of the patients (23.4% of the NSCLC cases, with 85.7% for stage I and stage II NSCLC, and 33.3% for stage III-A). A total of 302 patients (45%) received chemotherapy with marked differences between stages mainly in advanced stages (49.3% in stage IIIA; 56.5% in stage IIIB; and 47.4% in stage IV). A total of 189 patients (28%) received radiotherapy, 46.4% curative treatment, and 53.5% palliative treatment, with differences between stages. Patients in advanced stages had the highest percentages (22% in stage IIIB; and 53% in stage IV). Nevertheless, approximately 38% of the cases did not receive chemotherapy, radiotherapy, or surgery. For a small percentage, there was no available information regarding

chemotherapy (1.5%) and radiotherapy (1.3%). Only 4.5% of patients received a target treatment with EGFR inhibitor. Two-year RS was 18%, but as shown in Table 4, varied markedly with age (25% in 15–44 years; 11.2% in ≥75 years), sex (15.8% in men; 28.9% in women), and PS (23% PS<2 vs 1.8% PS ≥2). Two-year RS also decreased as the stage advanced: 5.4% for stage IV. Data for operated patients showed that of the 72 stage I cases, about 86% were NSCLC and 92% underwent surgery. Two-year RS for these operated cases was 76%. Of the 33 stage II cases, approximately 81.8% were NSCLC, and 70.4% underwent surgery. Two-year RS for these operated cases was 52.6%. Of the 71 stage IIIA cases, roughly 63.4% were NSCLC, and 37.8% underwent surgery. Two-year RS for these operated cases was 83%. Data were also obtained for stage IIIB cases treated with chemotherapy and radiotherapy. Approximately 58% of the 109 stage IIIB cases were NSCLC, and 23% were SCLC. Of these cases, 63.4% were treated with concomitant chemo-radiotherapy and 22%, with sequential chemo-radiotherapy. Two-year RS for these cases was 27.5% and 22%, respectively. Table 5 shows the results, depending on sex, age, and histological type.

Table 3: Diagnostic examinations and treatments carried out for lung cancer cases diagnosed in 2011–2012.

Diagnostic examinations	**N (%)**
Chest X-ray	
Yes	590 (87.5%)
No	84 (12.5%)
*Unknown	11 (1.6%)
CT	
Yes	646 (95.6%)
No	30 (4.4%)
*Unknown	9 (1.3%)
PET	
Yes	352 (52.4%)
No	320 (47.6%)
*Unknown	13 (1.9%)
MRI	
Yes	73 (11%)
No	592 (89%)
*Unknown	20 (2.9%)
Bronchoscopy	
Yes	429 (63.2%)
No	250 (36.8%)
*Unknown	6 (0.9%)
Mediastinoscopy	
Yes	67 (10%)
No	606 (90%)
*Unknown	12 (1.8%)
Treatments N (%)	
Surgery	
Done	104 (15.2%)
Not done	581 (84.8%)
*Unknown	0 (0%)
Radiotherapy	
Done	189 (28%)
Not done	486 (72%)
*Unknown	10 (1.5%)
Chemotherapy	
Done	302 (44.7%)
Not done	374 (55.3%)
*Unknown	9 (1.3%)
Targeted treatment	
Done	30 (4.5%)
Not done	641 (95.5%)
*Unknown	14 (2%)

*Percentages were only calculated with the known data

The multivariate analysis with all predictor variables (Table 6) showed a statistically significant association with smoking, previous lung disease, PS, stage, and treatment. In the model in which all variables except PS were taken into account, despite adding the PS variable (18.5% of missing values), all the coefficients of the remaining variables were modified though the trend of significant association remained the same. In this model, the sex variable was also significant, but when the PS variable was added, it was no longer significant. However, the other variables remained statistically significant. In the model where all the predictor variables were taken into account, the PS variable was significantly associated with survival. This meant that patients with an ECOG PS ≥ 2 had a 2.19 greater risk of dying than those with a good PS.

Risk of death two years after diagnosis (Table 6) was significantly higher than the RERs of death in men than women (1.79, 95% CI 1.19 – 1.90). In addition, risk of death increased with advancing age, ≥ 75 years (2.05, 95% CI 1.49-2.64 vs. 45-54 years (reference)), poor PS (2.19, 95% CI 1.61.45 – 2.99), diagnosis of COPD (1.33, 95% CI 1.61-2.99) and stage at diagnosis (9.70, 95% CI 5.10 – 14.86 for stage IV vs. stage I (reference)). Compared to NSCLC (reference), risk of death was greate for SCLC (1.44, 95% CI 1.04 – 1.65), unspecified morphology (1.40 95% CI 0.82 – 2.39), and non-microscopically verified cancers (3.83 95% CI 2.63 – 3.97). Risk of death at 2 years showed a greater differenc between males and females, with better outcomes for women of all age except for the 55-64 age group. For these patients (55-64 years), the risk of death among women was 1.5 times greater than among men. Patients who had not been operated had risk of death that was 8.68 times higher (significant) than patients who underwent surgery. Delays in treatments increased risk of death (1.12, 95% CI 0.86 – 1.44), although it was not statistically significant.

Table 4: One and two-year relative survival (with 95% confidence intervals) according to age, sex, smoking habit, lung disease, performance status, morphology, stage, surgery, radiotherapy, chemotherapy, and targeted treatment for lung cancer patients diagnosed in 2011–2012.

	One-year RS (95% CI)	**Two-year RS (95% CI)**
Age		
15-44	37.5 (20.9-67.5)	25.0 (11.5-54.5)
45-54	42.4 (32.8-54.8)	23.2 (14.9-36.3)
55-64	43.5 (36.2-52.4)	24.2 (17.4-33.6)
65-74	36.6 (30.4-44.0)	19.1 (14.0-25.9)
≥75	22.4 (17.5-28.6)	11.2 (7.5-16.6)
Sex		
Men	31 (27.4-35.2)	15.8 (12.8-19.7)
Women	47.6 (39.1-57.9)	28.9 (21.2-39.4)
Smoker		
No	53.1 (43-65.6)	32.7 (23.2-46.1)
Yes	32.0 (28.1-36.4)	16.8 (13.6-20.8)
Lungdisease		
No	38.1 (33.6-43.1)	20.9 (17-25.6)
Yes	28 (22.8-34.4)	14.0 (9.9-19.8)
Performance status		
ECOG<2	43.5 (38.9-48.7)	23 (18.8-28.1)
ECOG ≥ 2	11.5 (7.2-18.3)	1.8 (0.6-5.9)
Morphology		
NSmCC	43.4 (38.9-48.5)	23.4 (19.3-28.4)
SmCC	27.8 (20.3-38.0)	12.4 (7.1-21.5)
Non-microscopic verification	7.6 (4.1-14.0)	4.1 (1.7-9.9)
Stage		
I	89.7 (82.1 – 97.9)	66.5 (54.3 – 81.5)
II	62.0 (47.4 – 81.1)	44.1 (29.4 – 66.1)
III	41.4 (34.6 – 49.6)	21.1 (15.3 – 29.2)
IV	16.8 (13.4 – 21.0)	5.4 (3.5 – 8.4)
Surgery		
Done	89.2 (82.9 – 96.0)	69.0 (59.1 – 80.6)
Not done	23.8 (20.5 – 27.6)	9.2 (6.9 – 12.2)
Radiotherapy		
Done	46.4 (39.7 – 54.3)	23.1 (17.2 – 31.0)
Not done	29.0 (25.2 – 33.4)	16.0 (12.8 – 20.1)
Chemotherapy		
Done	43.1 (37.8 – 49.1)	20.1 (15.7 – 25.9)

Not done	26.2 (21.9 – 31.2)	16.1 (12.4 – 20.9)
Targeted treatment		
Done	67.8 (52.8 – 87.0)	27.7 (15.3 – 50.1)
Not done	31.9 (28.4 – 35.9)	17.8 (14.7 – 21.4)

RS relative survival, CI confidence intervals, NSmCC non-small cell carcinoma, SmCC small cell carcinoma

Table 5: One and two-year relative survival (with 95% confidence intervals) according to sex by age and histological type for lung cancer patients diagnosed in 2011–2012.

	Men		**Women**	
	One-year RS (95% CI)	**Two-year RS (95% CI)**	**One-year RS (95% CI)**	**Two-year RS (95% CI)**
Age				
15-44	30.0 (12.8 – 70.4)	10.0 (2.3 – 42.8)	50.0 (24.6 – 100)	50.0 (24.6 – 100)
45-54	31.2 (20.4 – 47.8)	15.2 (6.8 – 34.2)	57.7 (43.3 – 76.9)	33.7 (20.7 – 54.9)
55-64	44.2 (36.1 – 54.1)	23.0 (15.6 – 33.8)	40.9 (26.3- 63.5)	28.7 (16.0 – 51.5)
65-74	33.9 (27.6 – 41.5)	17.3 (12.4 – 24.4)	71.8 (52.3 – 98.7)	40.8 (21.9 – 75.8)
≥ 75	21.1 (16.0 – 27.7)	10.7 (6.9 – 16.4)	30.0 (17.7 – 51.0)	14.5 (5.9 – 35.7)
Histologic type				
ADC	39.4 (32.3 – 48.0)	17.0 (11.6 – 25.0)	54.3 (43.3 – 68.0)	37.5 (26.8 – 52.4)
SCC	42.5 (35.4 – 50.9)	24.7 (18.2 – 33.7)	50.2 (26.7 – 94.4)	18.9 (5.3 – 66.8)
LCC	34.4 (16.7 – 71.0)	0 (0 – 0)	100 (100 – 100)	0.3 (0 – 2.1)
Others	12.9 (8.4 – 19.8)	7.6 (4.1 – 14.1)	29.1 (16.0 – 52.9)	25.5 (12.8 – 50.9)
SmCC	25.4 (17.7 – 36.2)	13.9 (7.9 – 24.2)	43.2 (24.4 – 76.3)	7.2 (1.6 – 32.1)

CI confidence intervals, ADC adenocarcinoma, SCC squamous cell carcinoma, LCC large cell carcinoma, SmCC small cell carcinoma

Table 6: Relative excess risks of death, with 95% confidence intervals according to age, sex, smoking habit, lung disease, performance status, morphology, stage, surgery, radiotherapy, chemotherapy, targeted treatment and delays in the treatment for lung cancer patients diagnosed in 2011–2012.

	RER	**(95% CI)**	**p**
Age			
45-54	1(ref)		-
15-44	1.17	(0.61-2.04)	0.620
55-64	1.03	(0.74-1.40)	0.855
65-74	1.27	(0.96-1.74)	0.116
≥75	2.05	(1.49-2.64)	0.001
Sex			
Women	1(ref)		-
Men	1.78	(1.19-1.90)	0.06
Smoker			
No	1(ref)		-
Yes	1.88	(1.16-1.97)	0.001
Lungdisease			
No	1(ref)		-
Yes	1.33	(1.06-1.50)	0.001
Performance status			
ECOG<2	1(ref)		-
ECOG ≥ 2	2.19	(1.61-2.99)	0.001
Histology			
NSmCC	1(ref)		-
SmCC	1.44	(1.04-1.65)	0.002
Non-microscopic verification	3.83	(2.62-3.97)	0.001
Stage			
I	1(ref)		-
II	2.51	(1.18-5.34)	0.01
III	4.23	(2.43-7.37)	0.001
IV	9.70	(5.10-14.86)	0.001

Surgery			
Done	1(ref)		-
Not done	8.68	(4.44-9.65)	0.001
Radiotherapy			
Done	1(ref)		-
Not done	1.55	(1.26-1.83)	0.001
Chemotherapy			
Done	1(ref)		-
Not done	1.59	(1.34-1.88)	0.001
Targeted treatment			
Done	1(ref)		-
Not done	2.21	(1.19-2.70)	0.001
Delays			
No	1 (ref)		
Yes	1.12	(0.86-1.44)	0.38

RER Relative excess risks, CI confidence intervals, ref reference, NSmCC non-small cell carcinoma, SmCC small cell carcinoma

Discussion

A registry study not only allows clinicians to accurately interpret the observed risk or incidence estimates of a disease in a population but also to apply this knowledge to the target population without potential biases, where the sampling bias is the most representative. Consequently, a good interpretation of a registry database provides a realistic picture of both the incidence and survival of the population and also helps to evaluate the quality of medical care given to patients. Compared to other studies, and based on age, sex, and histologic subtype, our population was similar to other populations, both nationally and internationally [20, 21]. Women had a better survival rate than men, who had a 78% excess risk of dying. Among the youngest patients, it was significant that relative two-year survival was 1.17 times higher in women than in men. This could reflect a more adequate care pattern in women as well as a lower co-morbidity.

The age-adjusted relative survival estimated by our study was close to those detected in Europe, where women under the age of 65 registered significantly higher survival rates than men. Similarly, we also had a man-to-woman ratio of 5.3 [22]. The age differences in our study are similar to those in the rest of Spain (with a man-to-woman ratio of 4) and more generally, around the globe (with a man-to-woman ratio of 2.7 and a higher ratio in southern European countries) [23-25]. In contrast, in the USA, this man-to-woman ratio was close to 1 [26]. The population in Granada is thus similar to other populations in Spain and in the Mediterranean countries of Europe. Differences between countries might be related to the population's exposure to smoking, since it has been estimated that 85%-90% of lung-cancer cases can be attributed to smoking [27]. Although smoking is the major risk factor for lung cancer, smoking cannot explain gender differences in LC, because about 25% of lung cancers occur in never smokers. However, over time, differences have been observed in regard to the association between tobacco smoke and histologic type of LC [28]. In the smoking-related LC epidemic, the most common type of cancer in smokers is squamous cell carcinoma, followed by SCLC, both of which are more frequent in men. Although recent studies have reported an association and dose-response relationship between tobacco smoke and all histologic types of LC, this association has nevertheless been historically weaker for adenocarcinoma, the most frequent histology in women [3, 29]. Apart from adenocarcinoma, which is more common among women, sex-related differences have been observed in survival [30]. Therefore, the fact that certain types of LC occur more frequently in men than in women would seem to explain at least part of the difference in survival. Furthermore, the higher adenocarcinoma incidence in females might be due to an inherent susceptibility to the carcinogenic effects of cigarette smoke or to the greater contribution of other risk factors. Alternatively, this could reflect the fact that twice as many women are never smokers and this difference increases with age [31]. LC also appears to be a biologically different disease in women. This difference in histological distribution (e.g. glandular differentiation is common in women) could be explained by differences in genetic, biologic, and hormonal factors [32]. Other factors that seem to influence survival are poor PS and lung disease, increasing the risk of death for both cases.

Cancer survival basically depends on early diagnosis and effective treatment [33]. Strikingly, the LC diagnoses of almost 20% of the population sample were not histologically verified. Moreover, this 20% was not randomly distributed, but was mostly composed of patients of advanced age and with a bad PS. The majority of LC guidelines stress the importance of having all cases histologically verified [34, 35]. However, here it is necessary to emphasize the non-adherence to medical guidelines, which are almost always based on populations that exclude patients with co-morbidities and bad PS. This non-adherence in regard to older patients is even more interesting since on the one hand there is no easy justification for it, and on the other, it was more frequent than in the case of patients with a poor PS (40.1% vs 32.0%, respectively). Another important medical tool that contributes to good staging and avoids unnecessary surgery is the use of a diagnostic PET test. In our population, more than 50% of patients had a PET test, a higher percentage than in other countries, where percentages ranged from 9% to a more acceptable 30% [36-38]. This was probably due to the easy access to this image test in our region, which is the main reason for the low percentage of mediastinoscopies.

As medical technology advances, the diagnosis rate of LC is expected to gradually rise; however, an increase in the early diagnosis rate has yet to be observed [39, 40]. In this study, percentages of patients exhibiting

early-stage (stages I and II) were relatively low, whereas a significantly higher percentage exhibited advanced LC (stage IV; 57.5%). The majority of patients were in the late stages of LC at the time of initial diagnosis, and thus had missed the opportunity to receive surgery. Similar proportions of stage I cases have been reported in other population-based studies. Thus, an Italian study found that 10.1% of cancers were stage I [41]. A study of Chinese patients found that 3.9% of cases were stage I and 7.3% stage II [42]. In these studies, the proportions of stage II, III, and IV cases were similar to ours, with values between 75-80% for stages III and IV. One of the most promising advances could come from low dose-CT scan screening. Several trials have found that low dose CT screening is effectively at down staging LC cases and reducing lung mortality. Even though it is still not clear whether this new screening program is effective, there are currently some ongoing trials whose results will soon be published [43-45]. Our study also analyzed the timeliness of treatment because there is evidence that not having a treatment delay after diagnosis may improve survival [46]. Although the evidence is mixed in this subject [47-49]. However, in our population, treatment delays did not have a statistically significant association with a worse survival rate. Nevertheless, even if that were the case, treatment delays should be avoided it because they are still an unnecessary source of anxiety and stress for our patients.

In our population, 85.7% of patients with stage I or stage II NSCLC underwent surgery. Compared to percentages in other studies, this percentage was among the highest in Europe and clearly higher than the Spanish national mean (60%) [46]. This result is important because, as previously shown, there is a strong positive correlation between patients undergoing surgery and survival. More specifically, the RER of death for operated patients was 8.7 times lower than that of not operated patients. However, stage was the main factor influencing the decision of whether to perform surgery. This indicates that survival is associated with the stage of cancer, as surgery was generally a more feasible therapeutic option for patients with early-stage disease. Surgery, as well as any other treatment strategy, is also typically associated with the patient's general condition and age. Nevertheless, some studies on the role of surgery in older patients affirm that surgery should be offered to patients aged 80 years old or more [50, 51]. Another result worth discussing was the high percentage of patients undergoing surgery with III-A NSCLC, mainly 33.3% (82.4% of these patients also received another treatment besides surgery). This contrasts with the results of other research which obtained percentages of 12% or 15-26% [52, 53]. One possible explanation for our higher percentage might be the implementation in our medical centers of neoadjuvant chemotherapy prior to surgery for stage III-A LC, in contrast to other therapeutic options such as chemotherapy plus radiotherapy. Generally speaking, co-morbidities are also known to be a major reason why patients do not undergo surgery [54]. In all likelihood, co-morbidities prevented some stage I (or stage II) cases from undergoing potentially curable surgery or any other treatments although this is difficult to evaluate.

LC patients who were in generally poor condition, exhibited severe chronic complications, or were in the late stages of the disease, received only palliative treatment or no treatment at all. Thus, their prognosis was poor. In contrast, patients treated with targeted therapy in stage IV NSCLC showed an improved prognosis compared with those who only received chemotherapy. According to the literature, patients with epidermal growth factor receptor mutation-positive LC tend to have a good prognosis following treatment with targeted therapy [55]. During the period analyzed in this study (2011-2012), targeted therapy was just beginning to be used as a treatment option. Furthermore, the medical staff lacked information about it, and there was a long wait for EGFR test results. For all of these reasons, a low percentage of patients received this treatment and a higher percentage received first-line chemotherapy. However, now targeted therapies are well known in our region, and lack of knowledge is no longer an issue. As far as the wait for the EGFR test results, our study shows that this waiting time is subsequently well rewarded by a much better one-year and two-year survival, as well as a lower risk of death compared to those who did not benefit from this therapy (see table 4 and 6).

In conclusion, overall survival for LC is poor in this series becuse of PS, diagnosis in late stages, and the low percentage of cases that can be treated surgically. Therefore, our results indicate that efforts should be focused on early diagnosis since this would improve the effectiveness of treatments and thus the overall survival of LC patients. For this reason, it is necessary to have multidisciplinary teams, who would select the best treatment options for patients. This would also significantly enhance the quality of our health system.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical Approval

The study has been approved by the provincial Biomedical Research Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. For this type of study formal consent is not required. Details that might disclose the identity of the subjects under study have been omitted.

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