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Lung Cancer and COPD: a Common Combination

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ABSTRACT

Background and objective: To analyse frequency, characteristics and patient survival with lung cancer (LC) and Common Obstructive Pulmonary Disease (COPD), comparing them with patients that do not have COPD.
Material and methods: A retrospective study, of patients diagnosed by means of cytohistology. Survival was estimated by the Kaplan-Meier method. Statistical analysis was carried out using SPSS 15.0.
Results: A total of 996 patients were diagnosed, 39.8% with COPD. Mean age70±9.19 years. GOLD stages: I 18.2%, II 53.6%, III 24%, IV 4.2%. The histological types: squamous cell carcinoma 48.2%, adenocarcinoma 22%, and small cell carcinoma 22.5%. Survival was longer in the COPD group.
Conclusions: LC and COPD are combined in 39.8%. Squamous cell type is more frequent and survival was longer in the COPD group.
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Cáncer de pulmón y EPOC: una asociación frecuente

Palabras clave:
Cáncer de pulmón
EPOC
Epidemiología
Supervivencia

RESUMEN

Introducción y objetivo: Analizar la frecuencia, las características y la supervivencia de los pacientes con cáncer de pulmón (CP) y enfermedad pulmonar obstructiva crónica (EPOC), comparándolas con las de pacientes sin EPOC.
Material y métodos: Se ha realizado un estudio retrospectivo de pacientes diagnosticados de CP mediante citohistología. Se estimó la supervivencia por el método de Kaplan-Meier. El análisis estadístico se realizó con el programa SPSS 15.0.
Resultados: Se diagnosticó de CP a 996 pacientes, el 39,8% con EPOC. La edad media (± desviación estándar) de estos últimos era de 70 ± 9,19 años. En cuanto a los estadios GOLD, el 18,2% se encontraba en estadio I, el 53,6% en estadio II, el 24% en estadio III y el 4,2% en estadio IV. Según la citohistología, el 48,2% de los CP eran escamosos, el 22% adenocarcinomas y el 22,5% microcíticos. La supervivencia fue mayor en el grupo con EPOC.
Conclusiones: El CP y la EPOC se asocian en un 39,8% de los casos. La estirpe más frecuente del CP es la escamosa y la supervivencia es mayor en el grupo con EPOC.
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Introduction

Lung cancer (LC) is at present the most frequently diagnosed cancer worldwide and the first cause of death by cancer in men.[1] 18,500 new LC cases are yearly[2] recorded in Spain.

Chronic obstructive pulmonary disease (COPD) is the fourth cause of death,[3,4] preceded by cancer and cardiovascular and cerebrovascular diseases. It is the only increasing cause; it is estimated that it will become the third cause of death in 2020. Its prevalence in Spain is of 9.1% in the age group ranging from 40 to 69 years.[5]

Causal association between active smoking and LC is firmly established.[6] Smoking is also the most important risk factor in the development of COPD.[3,4] It is well known that tobacco smoke stimulates both local and systemic inflammation, and it has been pointed out that inflammation may play a causal role in both LC and COPD.[7]

On the other hand, LC frequently occurs in patients with COPD.[8-11] Although tobacco is an aetiologic factor both in LC and COPD,[12] some authors have argued that reduced lung function is another important risk factor stimulating LC.[8,13,14] LC and COPD, therefore, share risk factors in common, amongst which smoking, genetic predisposition, and environmental exposure are included, and through these, similar pathogenic mechanisms may also be shared.[3,7,5]

Consequently, the objective of our study has been to analyse frequency, clinical characteristics and survival in patients diagnosed with LC and COPD, and compare these against the same indications in no-COPD LC patients (suffering LC but not COPD).

Material and methods

This is an observational retrospective study over a cohort of patients diagnosed with LC from 1 January 1999 until 31 December 2004 in the Hospital Complex of Ourense. All patients diagnosed with LC for the first time by cytology and/or histology were included. Data collection was done by consulting with the data base of the clinical documentation service, the archive of bronchoscopy and pathological anatomy.

A data base was designed using SPSS 12.0 application, setting out a protocol for data collection that included: personal details, age, sex, smoking, symptoms, comorbidity, fibrobronchoscopy findings, diagnostic tests, staging, final diagnosis, treatment, and date of death. Diagnosis and COPD classification were performed in compliance with Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] guidelines. In absence of spirometry, COPD was ratified when this diagnosis was entered in the patient's case history, when the patient had been a smoker, and if he/she received bronchodilator treatment. The classification from World Health Organization (WHO) was followed for the histologic classification. Mountain[17] classification was followed for the tumoral extension study. Date of death was taken from the clinical history and, when this was not recorded, by telephone contact or through the death registry of Galicia. The last day for the study was established on 31 September 2006. Non smokers were defined as those persons who had smoked fewer than 100 cigarettes throughout their lifetime, and ex-smokers as those who had quit 6 months earlier or longer.

Statistical analysis

The statistical analysis was performed by a descriptive analysis, where the results from quantitative variables are expressed as mean ± standard deviation or as mean and confidence interval (CI) of 95%, depending on the case. Qualitative variables are expressed as absolute frequencies and percentages. To determine the association between quantitative and qualitative variables χ^2 Test was employed. Survival was estimated by Kaplan-Meier method and the curves obtained were compared by Mantel-Haenszel tests (log rank). Multivariate analyses were performed to identify factors related to death, based on the proportional hazard Cox's model. Statistical significance was set at 0.05. SPSS 15.0 was the application used.

Results

Demographic characteristics

LC was diagnosed in 996 patients of whom 396 (39.8%) had COPD. Mean age (± standard deviation) of patients with COPD was 70 ± 9.19 years (range: 42-90), being 54.4% older than 70 years. 387 (97.7%) were men and 9 (2.3%) women. 96.6% were smokers, 50.7% ex-smokers, and the mean packs/year was 67 ± 30.37. COPD stage was established according to GOLD classification in 380 patients, of whom 69 (18.2%) staged I, 204 (53.6%) staged II, 91 (24%) staged III, and 16 (4.2%) staged IV; forced expiratory volume mean in the first second (FEV_1) was 1,628 ± 598ml, and FEV_1% 62 ± 19. No functional study was available in 16 cases.

Clinical characteristics

The following are amongst the associated co-morbidities (table 1): cardiovascular disease 19.2% (table 2), high blood pressure 17.2%, and previous neoplasia 10.4%, being larynx and bladder neoplasias the most frequently associated. The most frequent symptoms (table 3) were cough (55.1%) and weight loss (41.7%). Fibrobronchoscopy performed in all the patients showed direct or indirect signs of neoplasia in 295 (74.5%) patients. Cytohistological diagnosis showed squamous cell carcinoma in 191 (48.2%) patients, adenocarcinoma in 87 (22%), microcytic carcinoma in 89 (22.5%), and others in 29 (7.3%). Diagnosis was established at early stages (I and II) in 112 patients (28.3%), localised regional stage (IIIA and IIIB) in 179 patients (45.2%),

Table 1
Co-morbidities associated in COPD patients and no-COPD patients

	COPD	No-COPD	P
Cardiovascular	19.2%	16.3%	U
High blood pressure	17.2%	23.5%	0.020
Diabetes	14.6%	14.8%	U
Previous pneumonia	14.6%	8.2%	0.001
Digestive	13.4%	14%	U
Previous neoplasia	10.4%	10.2%	U
Neurological	7.1%	8.2%	U
Hepatic	5.6%	4.5%	U

Table 2
Cardiovascular co-morbidity in COPD patients and no-COPD patients

	COPD	No-COPD
No cardiopathy	321 (81%)	502 (83.7%)
Ischemic heart disease	44 (11.1%)	46 (7.6%)
Arrhythmia	21 (5.3%)	27 (4.5%)
Valvular cardiopathy	3 (0.8%)	10 (1.7%)
Hypertensive cardiopathy	3 (0.8%)	10 (1.7%)
Other cardiopathy	4 (1%)	5 (0.8%)
Total	396 (100%)	600 (100%)

Table 3
Symptoms at the moment of presentation

Symptoms	N	%
Cough	218	55.1
Weight loss	165	41.7
Haemoptysis	129	32.6
Dyspnoea	124	31.3
Thoracic pain	99	25
Expectoration	79	19.9
Fever	42	10.6
Extra-thoracic pain	36	9.1
Neurological symptoms	24	6.1
Asymptomatic	27	6.8

Table 4
Comparative analysis between COPD patients and no-COPD patients

	COPD	No-COPD	p
Age (years)	70	66.7	0.000
Sex			
Male	97.7%	77.7%	
Female	2.3%	22.3%	0.000
Smoker	96.6%	74.4%	0.000
Packs/year	67	54.9	0.000
Out-patient handling	54.2%	39%	0.000
Dyspnoea	31.3%	24.8%	0.025
Haemoptysis	32.5%	20.6%	0.000
Expectoration	19.9%	14.3%	0.020
Atelectasis and/or post-obstructive pneumonitis	35.3%	27.6%	0.010
Pleural effusion	7.3%	15.8%	0.000
Squamous	48.2%	35.3%	0.000
Adenocarcinoma	21.9%	31.8%	0.000
Stage			
Early	28.3%	15.2%	
Advanced	26.5%	40.8%	0.000

and advanced stage (IV) in 105 (26.5%). Surgery was performed in 70 patients (17.6%), chemotherapy in 192 (49%), radiotherapy in 133 (33.6%) (with curative intention in 67 and palliative in 66) and palliative treatment in 92 (23.5%).

When performing a comparative analysis against the group of patients without COPD, significant differences were observed between groups (table 4). There were no significant differences regarding the treatment received.

Survival

Final survival for all the patients was 9.6% (mean: 8.5 months; CI 95%, 7.8-9.3), with a follow-up mean of 8.6 months. Survival of COPD patients yearly was 41.4% and at the end of the study 9.3% (mean: 9.8 months; CI 95%, 8.6-10.9), whereas in the no-COPD group was 9.4% (mean: 7.6 months; CI 95%, 6.6-8.6) Survival of COPD patients surgically treated was 31% (mean: 47.9 months; CI 95%, 23.9-71.8).

Survival was significantly higher in COPD patients (log rank = 5.87; p = 0.016) (fig. 1). Significant differences in survival were observed in the COPD patients depending on their histology (log rank = 18.80; p = 0.000), GOLD stages (log rank = 8.02; p = 0.045), clinical stages (log rank = 87.52; p = 0.000) and treatment (log rank = 92.77; p = 0.000). No differences appeared in survival of COPD and no-COPD patients surgically treated (log rank = 0.228; p = 0.633) (fig. 2).

In the regression multivariate Cox's analysis, risk of death was significantly higher at stages IIIB and IV, and in absence of surgery and chemotherapy.

Discussion

LC is the first cause of death by cancer worldwide, and tobacco smoking is associated with it in 90% of the LC cases.[6] Tobacco is also the most important risk factor for COPD. LC and COPD, therefore, share a risk factor in common, tobacco smoking, through which they can also have similar pathogenic mechanisms.[3,7]

COPD diagnosis has been associated with a higher rate of LC.[8,9,14] On the other hand, several studies have shown that a common cause of death between those affected with COPD is LC, mostly so when COPD is mild and moderate.[18,19] Furthermore, other studies[8,14] have shown that airway obstruction is associated with an increment 4 to 6 times in the risk to develop LC, independently of tobacco smoking history.

We observed in our study that 39.8% of LC patients have COPD. This is a proportion similar to that described by other authors.[20] Although COPD and LC are usually together, their aetiologic relation is controversial. In order to clarify whether COPD is a risk factor for LC, Skillrud et al[8] prospectively studied 113 COPD patients and 113 control individuals, and observed that COPD constitutes a risk factor for LC after adjusting for sex, age, tobacco and occupation. Tockman et al[14] observed an increased risk to develop LC along with an obstruction degree increment, and that smokers with obstruction have a higher risk to develop LC than no-obstruction smokers. Mannino et al[9] researched into new cases of LC in a 5,402 patient cohort with lung function measures and observed that the presence of moderate to acute COPD was associated with a risk increase to develop LC during the follow-up period. The Lung Health Study[19] contributed with more evidence on LC risk amongst airway-obstruction patients. Amongst 6,000 smokers with mild to moderate obstruction, LC was the most common cause of death at the end of a 5-year follow-up.

In our patients diagnosis was mostly established at GOLD stages II and III. In some studies[10,14,21] it has been observed that reduced FEV_1 is associated with risk increase of LC. Purdue et al[22] have recently studied 834 LC cases in a 174,000 Sweden construction workers cohort. They found LC incremented rates for mild airway-flow-obstruction (relative risk = 1.5) and moderate/acute (relative risk = 2.2) compared against normal lung function. On the other hand, Kuller et al[13] evaluated the ratio between FEV_1 and LC in smokers participating in the Multiple Risk Factor Intervention Trial (MRFIT). FEV_1 predicted independently of LC in that study.

Wasswa-Kintu et al[23] carried out a systematic revision and meta-analysis of population studies over the lung function and LC risk ratio. They concluded that, regardless of tobacco smoking history, a reduced FEV_1 increases LC risk over the general population. Furthermore, the ratio depends on acuteness, so that individuals showing the worst lung function run the highest risk. The potential clinical implication is that both in smokers and ex-smokers FEV_1 can provide a criterion, beyond age and tobacco smoking intensity, to identify those smokers with an increased risk to develop LC.

COPD-group patients are older than no-COPD-group patients. Longevity increases co-morbidity risk and LC. Apart from classical co-morbidity, it has been described that these patients have a higher risk of presenting with cardiovascular diseases. Smoking, apart from being independently related to cardiovascular disease, also associates with an increment in figures for high blood pressure.[24] 96.6% of the COPD patients had been smokers, particularly heavy smokers, whereas in no-COPD patients this proportion is reduced to 75%, which might otherwise be explained by genetic predisposition or

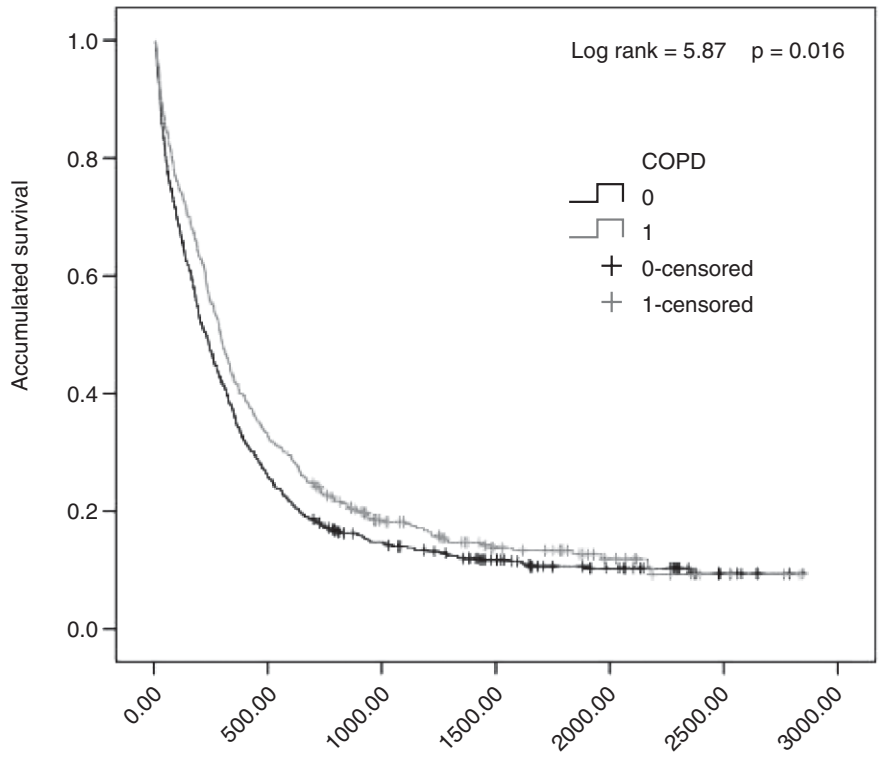

Figure 1. Survival estimation curves in COPD patients and no-COPD patients.

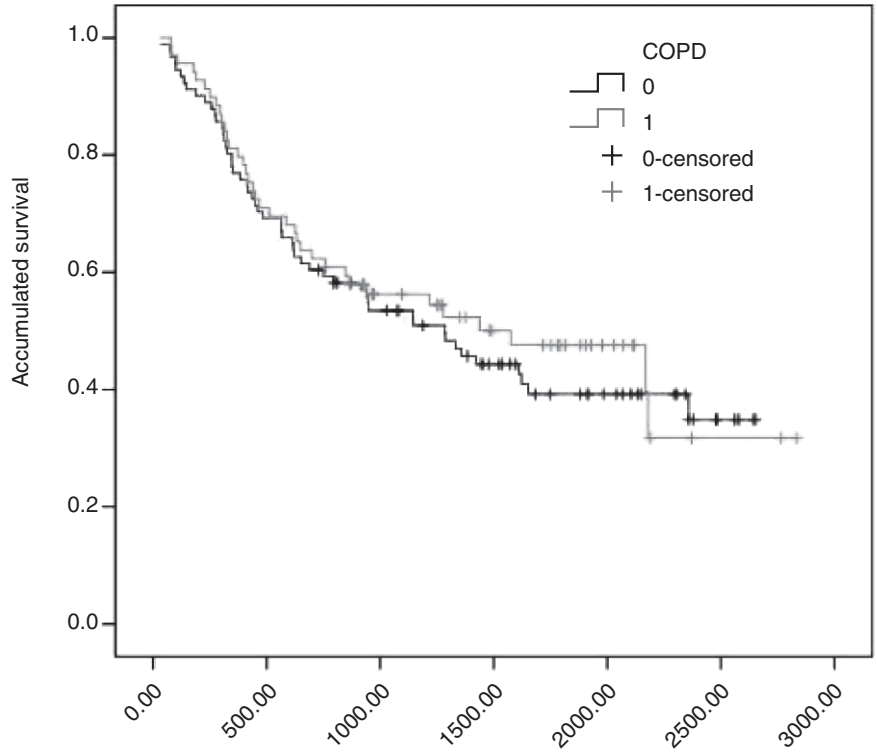

Figure 2. Survival estimation curves in COPD patients and no-COPD patients surgically treated.

passive tobacco smoking, risk factors that have not been analysed being this a retrospective study. In our series, women still represent a very small percentage of COPD patients, probably due to having started smoking later in life.

As opposed to other series[25] where a tendency toward a cytohistological diagnosis of adenocarcinoma is observed, in our population we keep observing squamous cell carcinoma with increasing frequency. Although tobacco smoking is a risk factor for any histological type of LC, association is closer for squamous cell carcinoma, microcytic carcinoma, and in large cell carcinoma than for adenocarcinoma.[26] Papi et al[12] observed in patients operated on LC that COPD increased 4 times the risk of developing histological subtype of squamous cell carcinoma. Other authors[10] also observed a closer association of reduced lung function with squamous cell carcinoma and microcytic carcinoma than with adenocarcinoma.

Survival of LC to 5 years varies between 6% to 16% in Spanish[27,28] and international[29] series. In our study, final survival was 9.6%, but it is more surprising the fact that survival was higher in COPD patients, and, additionally, with significant difference in survival depending on the GOLD stages. However, it is worthy of note that co-morbidity has such an important impact on LC patients. Several studies[30] investigating co-morbidities in LC patients have observed that COPD is a strong survival predictor. Authors such as Kuller et al[13] and Eberly et al[21] have also observed that FEV_1 measure is a significant mortality predictor for LC. We believe that our results may be due to the fact that COPD patients are diagnosed in earlier stages than no-COPD patients.

Surgery prolongs survival in LC early stages. In our series 17.6% of the patients were operated. COPD sets forth serious problems when it comes to setting non-tolerable limits for resection. A rigorously careful selection of patients, together with advances in surgery and anaesthesia, will result in surgical intervention with low frequency of complications to provide for most patients with limited lung function.[31-33]

Global survival to 5 years of complete resection surgery is 30-40%. However, great differences exist depending on tumoral staging.[17] Survival for our COPD patients surgically treated was 31%, but, as opposed to other authors, we did not find significant differences against the no-COPD group. López-Encuentra et al[34] analysed the characteristics of COPD and no-COPD patients and possible prognostic value of this co-morbidity over a sample of 2,994 LC no-microcytic cases surgically treated, in hospitals participating in the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). This study shows that such association may have deleterious prognostic value in patients presenting with both diseases. The effect is observed after 2 years from surgical resection and COPD is directly related to functional acuteness (FEV_1%). Sekine et al[31] and Battafarano et al,[35] who also investigated co-morbidity impact over no-microcytic resected LC, found a mortality rate higher in COPD patients against no-COPD patients. As opposed to the studies cited above, especially López Encuentra et al that is prospective, multicentre and with a large number of patients, ours is limited by being retrospective, performed in a single centre and over a smaller number of patients.

To conclude, our study shows that LC and COPD frequently associate (39.8%) and that patients are more advanced in age and have tobacco smoking antecedents. They are more frequently diagnosed with squamous cell carcinoma in early stages and GOLD II and III stages. Survival is higher in COPD patients than in no-COPD patients.

References

1. Ahmedin JA, Tiwari RC, Murray T. Cancer statistics. CA Cancer J Clin. 2004; 54:8-29.
2. López-Abente G, Pollán M, Aragoneses N, Pérez B, Hernández V, Lope V, et al. Situación del cáncer en España: incidencia. Anales Sis San Navarra. 2004;27:165-73.
3. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163:1256-76.
4. Peces-Barba G, Barberá JA, Agustí A, Casanova C, Casas A, Izquierdo JL, et al. Guía clínica SEPAR-ALAT de diagnóstico y tratamiento de la EPOC. Arch Bronconeumol. 2008;44:271-81.
5. Sobradillo V, Miravitlles M, Gabriel R, Jiménez CA, Villasante C, Viejo JL, et al. Geographical variations in prevalence and underdiagnosis of COPD. Results of the IBERPOC multicentre epidemiological study. Chest. 2000;118:981-9.
6. Bach P, Ginsberg RJ Epidemiology of lung cancer. In: Ginsberg RJ, editor. Lung Cancer. Hamilton: BC Decaer; 2002. p. 1–10.
7. Barreiro E. EPOC y cáncer de pulmón. Arch Bronconeumol. 2008;44:399-401.
8. Skillrud DM, Oxford KP, Millar RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med. 1986;105:503-7.
9. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data from First National Health and Nutrition Examination Survey follow-up. Arch Intern Med. 2003;163:1475-80.
10. Nomura A, Stemmermann GN, Chyou PH, Marcus EB, Buist S. Prospective study of pulmonary function and lung cancer. Am Rev Respir Dis. 1991;144:307-11.
11. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. JAMA. 1994;272:1497-505.
12. Papi A, Casoni G, Caramori G, Guzzinati I, Boschetto P, Ravenna F, et al. COPD increases the risk of squamous subtype in smokers who develop non-small cell lung carcinoma. Thorax. 2004;59:679-81.
13. Kuller LH, Ockene J, Meilahn E, Svendsen KH. Relation of forced expiratory volume in one second (FEV1) to lung cancer mortality in the multiple risk factor intervention trial (MRFIT). Am J Epidemiol. 1990;132:265-74.
14. Tockman MS, Anthonisen NR, Wrigh EC, Donithan MG. Airways obstruction and the risk for lung cancer. Ann Intern Med. 1987;106:512-8.
15. Cohen BH, Diamond EL, Graves CG, Kreiss P, Levy DA, Menkes HA, et al. A common familial component in lung cancer and chronic obstructive pulmonary disease. Lancet. 1977;2:523-36.
16. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. Eur Respir J. 2001;18:1059-68.
17. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest. 1997;111:1710-7.
18. Sin DD, Anthonisen NR, Soriano JB, Agustí AGN. Mortality in COPD: role of comorbidities. Eur Respir J. 2006;28:1245-57.
19. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233-9.
20. Montero C, Rosales M, Otero I, Blanco M, Rodríguez G, Peterga S, et al. Cáncer de pulmón en el Área Sanitaria de A Coruña: incidencia, abordaje clínico y supervivencia. Arch Bronconeumol. 2003;39:209-16.
21. Eberly LE, Ockene J, Sherwin R, Yang L, Kuller C. Pulmonary function as a predictor of lung cancer mortality in continuing cigarette smokers and in quitters. Int J Epidemiol. 2003;32:592-9.
22. Purdue MP, Gold L, Järvholm B, Alavanja MCR, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. Thorax. 2007;62:51-6.
23. Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Din DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax. 2005;60:570-5.
24. Izquierdo JL. Nuevos parámetros clínicos en la EPOC. Arch Bronconeumol. 2008;44:4-10.
25. Santos-Martínez MJ, Curull V, Blanco ML, Macià F, Mojal S, Vila J, et al. Características del cáncer de pulmón en un hospital universitario. Cambios epidemiológicos e histológicos en relación con una serie histórica. Arch Bronconeumol. 2005;41:307-12.
26. Wang SY, Hu YL, Wu YL, Li X, Chi GB, Chen Y, et al. A comparative study of the risk factors for lung cancer in Guangdong, China. Lung Cancer. 1996;14:S99-S105.
27. Miravet L, Paradís A, Peláez S, Arnal M, Cabadés F. Evolución del carcinoma broncopulmonar en el norte de la provincia de Castellón, 1993–2002. Arch Bronconeumol. 2004;40:553-7.
28. Sánchez de Cos J, Disdier C, Corral J, Riesco JA, Sojo MA, Masa JF. Supervivencia global a largo plazo en el cáncer de pulmón. Análisis de una serie de 610 pacientes no seleccionados. Arch Bronconeumol. 2004;40:268-74.
29. Nacional Cancer Institute. SEER. Cancer Statistics Review 1975–2001, Bethesda, 2005, Disponible en, http://www.statecancerprofiles.cancer.gov.
30. López-Encuentra A, Bronchogenic Co-operative Group. Comorbidity in operable lung cancer:a multicenter descriptive study on 2992 patients. Lung Cancer. 2002;35:263-9.

31. Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. Lung Cancer. 2002;37:95-101.
32. Grupo Cooperativo de Carcinoma Broncogénico de SEPAR (GCCB-S). Cirugía del carcinoma broncogénico en España. Estudio descriptivo. Arch Bronconeumol. 1995;31:303-9.
33. Gómez G, Güell R, González A, Fibla JJ, Estrada G, León C. Influencia de un programa de rescate en la decisión quirúrgica en pacientes con carcinoma broncogénico y EPOC. Arch Bronconeumol. 2007;43:262-6.
34. López-Encuentra A, Astudillo J, Cerezal J, González-Aragoneses F, Novoa N, Sánchez-Palencia A. Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Prognostic value of chronic obstructive pulmonary disease in 2,994 cases of lung cancer. Eur J Cardiothorac Surg. 2005;27:8-13.
35. Battafarano RJ, Piccirillo JF, Meyers BF, Hsu HS, Guthrie TJ, Cooper JD, et al. Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2002;123:280-7.