Evolution of Lung Cancer in the North of the Province of Castellón, Spain, 1993-2002

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OBJECTIVE: To investigate the changes in lung cancer incidence, histological type, and survival in patients in the north of the province of Castellón, Spain, during a follow-up period of 10 years, and to compare the findings with other national and international studies.

PATIENTS AND METHOD: All patients diagnosed with lung cancer between January 1, 1993 and December 31, 2002 were included in this prospective, observational study. Disease was confirmed by biopsy or suspected from clinical, radiological, and/or bronchoscopic findings.

RESULTS: In the study period, 271 patients were diagnosed with lung cancer (239 men and 32 women), with a mean (SD) age of 66.8 (11.8) years. The age-adjusted incidence rate standardized to the world population was 20.42 cases per 100 000 population. Smokers or ex-smokers comprised 88.1% of the study population, and 72.6% of patients were over 60 years old. Biopsy confirmation was obtained in 262 cases (96.7%). Squamous cell carcinoma predominated (46.5%) but the proportion of adenocarcinoma increased (23.6%). Surgery was possible in only 22% of the patients. Mean overall 5-year survival was 15.7 months.

CONCLUSIONS: In the north of the province of Castellón, the incidence of lung cancer continues to increase in men but has decreased slightly in women. Squamous cell carcinoma is the most common type, but the incidence of adenocarcinoma has clearly increased. Overall, survival did not improve during the 10 years of follow up despite advances in treatment.

Key words: *Lung cancer. Incidence. Treatment. Survival.*

Evolución del carcinoma broncopulmonar en el norte de la provincia de Castellón, 1993-2002

OBJETIVO: Conocer la evolución de la incidencia, tipos histológicos y supervivencia del carcinoma broncogénico en el norte de la provincia de Castellón, en un período de seguimiento de 10 años, y comparar los resultados con los de otros estudios nacionales e internacionales.

PACIENTES Y MÉTODO: Se ha realizado un estudio prospectivo y observacional, en el que se incluyó a todos los pacientes diagnosticados de carcinoma broncogénico desde el 1 de enero de 1993 hasta el 31 de diciembre de 2002. Se exigió la confirmación citohistológica o la sospecha basada en datos clínicos, radiológicos y/o broncoscópicos.

RESULTADOS: En el período estudiado se diagnosticó de carcinoma broncogénico a 271 pacientes (239 varones y 32 mujeres), con una edad media (± desviación estándar) de 66,8 ± 11,8 años. La tasa de incidencia ajustada a la población mundial fue de 20,42 casos por 100.000 habitantes. El 88,1% eran fumadores o ex fumadores, y el 72,6% de los pacientes tenía más de 60 años. Se obtuvo confirmación citohistológica en 262 (96,7%) casos. Predominó el tipo epidermoide (46,5%) pero con un ascenso del adenocarcinoma (23,6%), y sólo se pudo realizar tratamiento con cirugía en el 22% de los casos. La supervivencia media global a los 5 años ha sido de 15,7 meses.

CONCLUSIONES: En el norte de la provincia de Castellón la incidencia de carcinoma broncogénico sigue aumentando en los varones y ha disminuido ligeramente en las mujeres. Predomina el carcinoma epidermoide pero con un ascenso claro del adenocarcinoma. A pesar de los avances del tratamiento, desde una visión global, la supervivencia no ha mejorado en los 10 años de seguimiento.

Palabras clave: *Carcinoma broncogénico. Incidencia. Tratamiento. Supervivencia.*

Introduction

Lung cancer (LC) causes more deaths among men in developed countries and among women in the United States than any other malign tumor.[1] In Spain, mortality due to LC is much higher among men, although it has leveled off in the last year, whereas mortality among women has increased.[2] National cancer registries have detected an increase in the incidence of LC related to an increase in smoking, particularly among women.[3] Incidence rates have to be obtained indirectly from mortality rates, as few countries have tumor registries that include extensive geographic regions. Moreover, the incidence of LC and associated mortality are similar because of low survival rates associated with late diagnosis of the disease. Nevertheless, it is important to collect data on incidence

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Figure 1. Mortality curves and incidence.

because of the widely recognized problems arising from analysis of death certificates.

Few long-term studies on LC have assessed changes in incidence, histological type, stage at the time of diagnosis, treatment, and survival, though this information is very important to ensure optimal and effective management of the disease in each health care area.

The aim of this study was to investigate the change over time in these parameters, and in other clinical and epidemiological aspects of interest, in Health Care Area 01 of the province of Castellón (Spain) during a period of 10 years. Our objective was also to compare our findings with those of other Spanish and international studies.

Patients and Method

This was an observational prospective epidemiological study, carried out in the north of the province of Castellón, Spain. The area has a population of 67 669 inhabitants (33 330 men and 34 339 women). The population is densest in the costal area. Inland districts have a more elderly population and, for many years, these areas have been affected by substantial environmental pollution in the form of acid rain from the Andorra thermal power station in the neighboring province of Teruel. This pollution is, however, currently under control. The whole region corresponds to Health Care Area 01 of the Autonomous Community of Valencia.

The study included all patients diagnosed with LC between January 1, 1993 and December 31, 2002 in the Internal Medicine Service and the Pulmonology and Pathology Unit of the referral hospital. Patients diagnosed in any hospital, whether in Health Care Area 01 of the Autonomous Community of Valencia or not, were also included provided he or she had been resident in the study region for at least one year before the start of the study.

All patients first diagnosed by cytology or histology were included in accordance with usual recommendations[4] using histological typing of the World Health Organization.[5] Patients could also be included if clinical, radiological, or bronchoscopic suspicion existed without cytologic and histologic confirmation. Three study investigators assessed such cases and considered them appropriate for inclusion when all other reasonable diagnoses had been discarded. During the study, all personnel involved in the study met annually to assess progress in data collection. Patients with benign lung tumors, pleural tumors, and lung metastases were excluded.

Information was gathered according to the same protocol as a previous study.[6] The crude incidence rates and those standardized to the world population were calculated using the municipal census from 1996 and directly adjusted with the Epidat 1.0 program. The clinical stage at the time of diagnosis was determined according to the Mountain classification,[7] which is accepted by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[4] In the study of disease spread to detect metastasis, cytology and histology were only performed when the adrenal gland was swollen and skin lesions were present. The patients, once diagnosed, were admitted to the referral hospital to complete their examination and undergo surgery if indicated, or receive chemotherapy or radiotherapy.

Statistical Analysis

The results were analyzed on a personal computer with the commercially available statistical package, SPSS 9.0 (SPSS Inc., Chicago, Illinois, United States of America). The Kaplan-Meier test was used to calculate survival.

TABLE 1
Annual Incidence Rates by Age Group and Sex

Age Group (Years)	Men	Women	Both Sexes
30-39	9.93	2.01	6.00
40-49	42.07	7.47	25.30
50-59	112.60	8.40	61.03
60-69	169.78	7.11	86.34
70-79	261.15	39.80	138.43
≥80	199.43	32.02	97.49

Results

Demographic Characteristics

LC was diagnosed in 271 patients during the 10-year study period. Of these, 239 were men (88.2%) and 32 were women (11.8%), yielding a ratio of men to women of 7.46/1. The mean (SD) age of all patients was 66.8 (11.8) years (range: 32-92 years; mode: 78 years). The percentage of patients aged over 60 years at the time of diagnosis was 72.6%. The mean age of women was 69.8 (14.0) years and that of men was 66.4 (11.5) years—the difference was not statistically significant. Smokers or ex-smokers accounted for 234 of the 271 patients, 34 patients had never smoked (7 men and 27 women), and smoking status was not available for 3 patients. Ex-smokers were defined as those who had not smoked in at least 6 months. No data on passive exposure to cigarette smoke were collected.

Incidence

The average annual crude incidence rate over the 10 years of the study was 40.04 cases/100 000 inhabitants, and the rate standarized to the world population was 20.42/100 000 inhabitants. Table 1 shows the annual age- and sex-adjusted incidence rates. The mortality curve for lung, bronchial, and tracheal carcinoma (1987-2001) and

TABLE 2
Diagnostic Technique and Histological Type*

	Total	Men	Women
Diagnostic Technique			
Bronchoscopy	183 (67.5)		
FNA biopsy	68 (25.1)		
Clinical/radiological	9 (3.3)		
Others	11 (4.1)		
Type			
Epidermoid	126 (46.5)	121 (50.6)	5 (15.6)
Adenocarcinoma	64 (23.6)	51 (21.3)	13 (40.6)
Small cell	41 (15.1)	37 (15.5)	4 (12.5)
Nonsmall cell	19 (7)	15 (6.3)	4 (12.5)
Unknown	9 (3.3)	6 (2.5)	3 (9.4)
Others	12 (4.4)	9 (3.7)	3 (9.4)

*Data presented as numbers with percentages between parentheses.
FNA indicates fine-needle aspiration.

TABLE 3
Staging at Time of Diagnosis of Lung Cancer

Stage	Nonsmall Cell	Small Cell
I-A	21	0
I-B	61	2
II-A	3	1
II-B	7	2
III-A	26	6
III-B	41	7
IV	62	22

the incidence data (1993-2002) are plotted in Figure 1. Figure 2 displays the number of cases by year of the study.

Diagnosis by Histological Type

Table 2 presents the techniques used for diagnosis and histological typing. Clinical and radiological findings were used for diagnosis in 9 cases (3.3%). Diagnosis was made solely from cytologic examination in 27.3% of the patients, whereas the remaining patients had histological samples with or without cytology. The most widely used diagnostic technique was fiberoptic bronchoscopy (67.5%).

Stage at Time of Diagnosis

The stage at the time of diagnosis is presented in Table 3. Staging could not be performed in 2 patients. Stages III-B and IV accounted for 49% of the patients.

Treatment

Table 4 shows the treatment applied once diagnosis was complete (the table excludes 3 patients for whom follow up was not possible). Surgery was performed in 22% of all patients and in 25.5% of the patients with nonsmall cell LC. Chemotherapy and radiotherapy were applied to all patients, as both a curative and palliative treatment.

Survival

Mean overall survival after 5 years was 15.78 months (95% confidence interval [CI], 13.5-18.03 months). Table 5 shows survival according to main histological

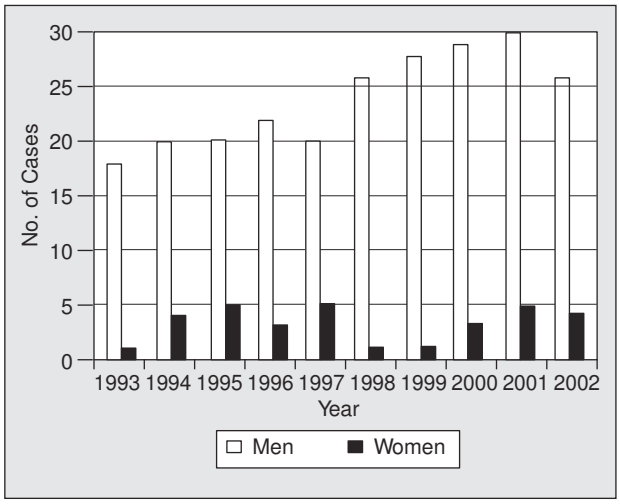

Figure 2. Annual distribution of cases.

type. There were no significant differences between men and women. The survival analysis according to histological type also showed no differences in terms of small cell versus nonsmall cell LC. Significant differences were found among the different clinical TNM stages—survival was better for patients diagnosed in the earlier stages. The type of treatment had a marked effect. Patients who underwent surgery survived much longer—the difference was highly significant. Thus, mean survival in patients who underwent surgery was 37.7 months (95% CI, 29.9-45.5 months), compared to 11.8 months (95% CI, 10-13.5 months) in the remaining patients. In stage IV patients, if we adjusted survival according to whether they received chemotherapy treatment, significant differences in favor of treatment were seen. The probability of surviving for 5 years after diagnosis of LC was 7.2% (Figure 3).

TABLE 4
Treatments Applied

Treatment	No. of Cases (%)
Chemotherapy	76 (28.4)
Radiotherapy	40 (14.9)
Surgery	43 (16.0)
Chemotherapy + radiotherapy	19 (7.1)
Surgery + radiotherapy	5 (1.9)
Surgery + chemotherapy	4 (1.5)
Chemotherapy + surgery	7 (2.6)
Palliative	74 (27.6)

TABLE 5
Survival by Histological Type and Overall Survival*

Type	Survival (Months)	
	Median (95% CI)	Mean (95% CI)
Epidermoid	16.54 (13.32-19.77)	8 (5.48-10.52)
Adenocarcinoma	15.24 (10.58-19.90)	8 (5.37-10.63)
Small cell	11.37 (7.57-15.17)	10 (7.59-12.41)
Nonsmall cell	14.79 (6.18-23.40)	7 (3.14-10.86)
Overall	15.78 (13.54-18.03)	8 (6.36-9.64)

*CI indicates confidence interval.

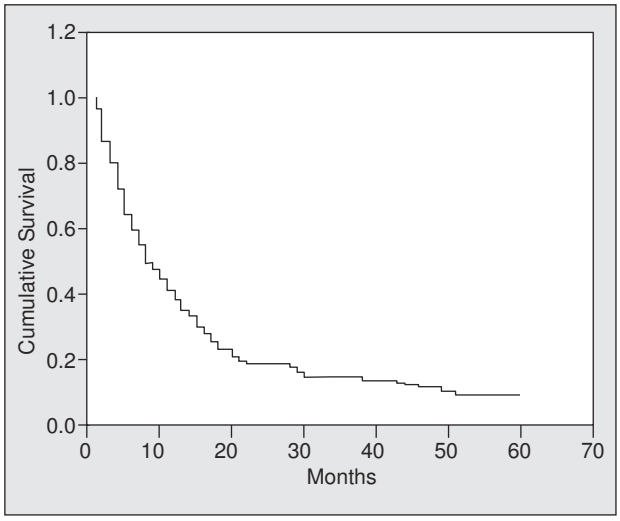

Figure 3. Overall survival.

Discussion

LC is the type of malignant tumor whose incidence has increased most in Spain over the last decade.[8] Mortality data are obtained from death certificates. Tumor registries are another important source of information, but only a few provinces in Spain keep such records.[3] The correlation between incidence rates and mortality is well known given the short life expectancy of patients with LC in general, and our health care area is no exception (Figure 1). Nevertheless, both incidence and mortality should be studied to avoid erroneous conclusions. Studies of incidence, mortality, and survival are very important to assess the impact of therapeutic advances in this disease.

The province of Castellón does not keep a registry of tumors, so the importance of LC had to be determined indirectly from the mortality rates. The annual standardized incidence rate in Health Care Area 01 was 17.4/100 000 world population (31.2/100 000 men and 4.5/100 000 women).[6] At present, the overall annual standardized incidence rate has increased (20.4/100 000 population) due to an increase in incidence in men (38.08/100 000 men) that more than compensates for the decreasing rate in women (3.90/100 000 women). These rates are lower than overall Spanish rates (51.7/100 000 men and 4/100 000 women)[9] and European rates (55.6/100 000 men and 10.3/100 000 women).[9] A comparison of our results with those reported in recent years for other Spanish autonomous communities shows the incidence rate in men is well below that found in La Coruña (73.7/100 000 men),[10] the Basque Country, Asturias, and Majorca (60/100 000 men),[11] Extremadura,[12] Granada, Murcia (50/100 000 men),[11] and Castile-León (41.5/100 000 men).[13] Despite the decrease in new cases in women, the incidence rate is still one of the highest in Spain, along with the incidence rates in Minorca, Asturias,[11] and Castile-León.[13] The incidence of LC is therefore increasing in men in our health care area, even though mortality rates in other autonomous communities have tended to stabilize.[2,11] In women, we see a slight decrease and still no evidence of the increase predicted by some Spanish studies[2,11] and corroborated by other studies.[1,9] A crude incidence rate greater than that of mortality, the study duration of 10 years, and the inclusion of cases diagnosed in other hospitals of the province or outside the province suggest that the incidence rate we report should be close to the true one. Other possible causes for underestimation are difficult to assess and, in any case, we think they are negligible. Incidence remains lower in inland districts than in costal districts, so we assume that environmental pollution in the form of acid rain—the worst of which occurred long enough ago for any potential impact to become apparent—seems not to have affected LC incidence in the area.

The mean age of onset of LC (66.8 [11.8] years) has decreased with respect to the previous study[6] (67.01 [12.3] years) and is similar to the age of onset in the majority of patients in other parts of Spain[10,12,13] and Europe.[14] However, there is a striking difference between the age of onset in women in our study and the very low age of onset found in the study published by Montero et al[13] in La Coruña. The proportion of patients aged under 60 years has decreased slightly, but it remains similar to that found in other studies.[12,13]

It is well known that the main risk factor for LC is smoking. In our study, 97% of the men and 15.6% of the women were smokers or ex-smokers. Women, in particular, are now smoking more—cigarette consumption has increased 3-fold compared to the previous study.[6]

The most used diagnostic technique was fiberoptic bronchoscopy (in 67.5% of the patients) but use of transthoracic fine-needle aspiration biopsy and computed axial tomography has increased. The percentage of patients with cytologic and histologic confirmation —96.7%—is very high compared to other studies,[12,13] and patients diagnosed by clinical, radiological, and bronchoscopic suspicion account for only 3.3%—a rate that is lower than rates in other studies.[10-13] This difference is probably related to the characteristics of the referral hospital.

The main histological type in the 262 patients with cytologic and histologic diagnoses was squamous carcinoma—seen mainly in men—followed by adenocarcinoma and small cell LC. In women, adenocarcinoma continues to be the main histologic type, in agreement with other national and European studies.[3,10,12-14] Overall, we found a decrease in squamous carcinomas and an increase in adenocarcinomas, in line with the findings of the Spanish study by Rezola and Sanzo[15] and in accordance with results from the United States, where adenocarcinoma is the main histological type.[16] The percentage of patients with an initial diagnosis of nonsmall cell LC in stages III-B and IV fell to 44.9%. Overall, it was only possible to operate on 59 patients (25.5%)—a similar percentage to that reported in other studies,[10,14] so despite a decrease in the number of patients with advanced stages of the disease, the percentage of those undergoing surgery has fallen by 1.4%.

Cancer survival studies aim essentially to determine treatment efficacy, but they usually investigate populations who undergo surgery.[17,18] Such studies offer

a very biased view of the disease because younger patients with smaller tumors, less comorbidity, and a better general state of health tend to be included. Therefore studies such as the present one are important because they provide an overall view.

In our study, the mean survival rate after 5 years for all types of LC was 7.2%, slightly lower than the previous study (7.6%)[6] and very much lower than the survival rates in the United States (14%),[16] Europe (15%),[19] and the province of Guipúzcoa in Spain (12.6%).[15] The survival rate is, however, greater than that reported by Arias et al[20] for the province of Saragossa and similar to the that of the area of La Coruña.[10] With regard to histological type, survival tended to be worse in small cell LC, although there are no significant differences compared to nonsmall cell LC, in line with the findings of other authors.[10,15] Mean survival has increased slightly for all histological types. Patients who were eligible for surgery clearly survived longer.[10,17,18] For patients with stage III-B and IV tumors, we saw a small but statistically significant improvement in the survival of those who received chemotherapy compared to those who received palliative treatment. The authors of other studies that assessed the efficacy of chemotherapy in patients with extensive disease have reported similar findings, and the longer survival has even been associated with a good quality of life.[21-23] Unfortunately, we did not measure quality of life, but it would be very interesting to compare the quality of life of patients receiving chemotherapy with that of patients receiving palliative treatment because the increase in survival, although small, is statistically significant. Few studies have investigated overall survival and survival by histological type. The period covered should be taken into account when comparing such studies because differences could be partly explained by the type of treatment applied.[15] The findings from these studies point to the generally poor survival in LC, which continues to be diagnosed in advanced stages such that the number of patients who can benefit from surgery is small. Other treatments have managed to achieve only minimal improvement in survival. Perhaps the most sensible approach is therefore to campaign against smoking and to try to diagnose the disease in its early stages while we await new and effective therapeutic treatment strategies.[23]

In conclusion, we report that the incidence of LC among men in Health Care Area 01 of the Autonomous Community of Valencia continues to increase, but it remains far below the national incidence rate. Even though the incidence rate in women has decreased, it remains among the highest in Spain. Squamous carcinoma continues to be the main histological type of LC, but a clear increase in the incidence of adenocarcinoma is evident. Despite advances in treatment, the overall survival of patients with LC has not improved during the 10-year study period.

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REFERENCES

1. Greenlee RT, Hill-Harmon MB, Murray T, Thum M. Cancer statistics. CA Cancer J Clin 2001;51:15-36.
2. Villalbí JR, Pasarin MI, Nebot M, Borrell C. Mortalidad por cáncer de pulmón: inicio del declive en los varones de Barcelona. Med Clin (Barc) 2001;117:727-31.
3. Izarzugaza Lizarraga I. El cáncer de pulmón en España. Revisión epidemiológica. Arch Bronconeumol 1992;28:311-20.
4. Rami Porta R, Duque Medina JL, Hernández Hernández JR, López Encuentra A, Sánchez de Cos Escuin J. Normativa actualizada (1998) sobre el diagnóstico y estadificación del carcinoma broncogénico. Recomendaciones SEPAR. Arch Bronconeumol 1998;34:437-52.
5. World Health Organization. The World Health Organization histological typing of lung tumors. Second edition. Am J Clin Pathol 1982;77:123-36.
6. Miravet L, Peláez S, Paradís A, Arnal M, Cabadés F. Estudio epidemiológico del cáncer de pulmón en el norte de la provincia de Castellón. Arch Bronconeumol 2001;37:298-301.
7. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710-7.
8. Fernández E, Borrás JM, Levi F, Schiaffino A, García M, Vecchia C. Mortalidad por cáncer en España, 1955-1994. Med Clin (Barc) 2000;114:449-51.
9. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075-107.
10. Marzo Castillejo M, Mercadé F. Estadísticas. Cáncer. Jano 1999;56:2478-82.
11. Grupo de estudio del carcinoma broncopulmonar de la SOCALPAR. Incidencia del carcinoma broncopulmonar en Castilla-León durante el año 1997. Estudio multicéntrico de la Sociedad Castellano-Leonesa de Patología Respiratoria (SOCALPAR). Arch Bronconeumol 2000;36:313-8.
12. Sánchez de Cos Escuin J, Riesgo Miranda JA, Antón Martínez J, Díaz Santamaría P, Márquez Pérez L, Medina Gallardo JF, et al. Incidencia del carcinoma broncopulmonar en Extremadura durante el año 1998. Arch Bronconeumol 2000;36:381-4.
13. Montero C, Rosales M, Otero I, Blanco M, Rodríguez G, Peterga G, et al. Cáncer de pulmón en el área sanitaria de A Coruña: incidencia, abordaje clínico y supervivencia. Arch Bronconeumol 2003;39:209-16.
14. Mäkitaro R, Pääkkö P, Huhti E, Bloigu R, Kinnula VL. An epidemiological study of lung cancer: history and histological types in a general population in northern Finland. Eur Respir J 1999;13:43640.
15. Rezola Solaum R, Sanzo Ollakarizketa JM. Incidencia, tendencia y supervivencia del cáncer de pulmón, por tipo histológico, en Guipuzkoa (1993-1992). Rev Clin Esp 1999;199:208-14.
16. Travis WD, Travis LB, Devessa SS. Lung cancer. Cancer 1995; 75:191-202.
17. Padilla J, Calvo V, García A, Pastor J, Blasco E, París F. Pronóstico tras resección quirúrgica del carcinoma broncogénico no anaplásico de células pequeñas según la nueva normativa de estadificación: análisis de 1.433 pacientes. Arch Bronconeumol 1999;35:483-7.
18. Grupo Cooperativo de Carcinoma Broncogénico de la Sociedad Española de Neumología y Cirugía Torácica (GCCB-S). Available at: htpp://www.separ.es/
19. Bonino F, Capocaccia R, Esteve J, Gatta G, Hakulinen T, Micheli A, et al. Survival of cancer patients in Europe: the EUROCARE-2 study. IARC Scientific Publications no. 151. Lyon: IARC, 1999.
20. Arias J, de Gregorio MA, Alfonso ER, Conget F, Abós MD, Matarredona A. Cáncer de pulmón en la provincia de Zaragoza (1980-1985). Arch Bronconeumol 1992;28:212-6.
21. Cullen MH, Billingham L, Woodroffe C, Chetiyanardana A, Gower N, Joshi R. Mitomicyn, ifosfamide and cisplatin in unresectable non-small cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999;17:3188-94.
22. Vansteenkiste JF, Vandebroek JE, Nackaerts KL, Weynants P, Valcke YJ, Verresen DA, et al. Clinical-benefit response in advanced non-small-cell lung cancer: a multicentre prospective randomised phase III study of single agent gemcitabine versus cisplatinvindesine. Ann Oncol 2001;12:1221-30.
23. Sánchez de Cos Escuin J. Nuevas dianas terapéuticas en el cáncer de pulmón. Arch Bronconeumol 2002;38:386-91.