Characteristics of Lung Cancer in a Region in Northern Spain

M.A. Alonso-Fernández, M. García-Clemente, and C. Escudero-Bueno, for the Asturian Society of Respiratory Disease (ASTURPAR) Lung Cancer Working Group (GACP)

OBJECTIVE: To gather information on the disease characteristics and survival rate of patients diagnosed with bronchogenic carcinoma in the respiratory medicine departments of hospitals in Asturias, Spain.

PATIENTS AND METHODS: This was a retrospective observational study carried out using a standardized data collection protocol. All cases of lung cancer diagnosed during 2001 were included provided there was cytologic or histologic confirmation or they fulfilled a series of clinical, radiological, and/or endoscopic criteria consistent with such a diagnosis.

RESULTS: Standard incidence rates adjusted to the world population were 22.4, 42.6, and 4.6 per 100 000 population for the whole population, men, and women respectively. The mean (SD) age was 67 (10.9) years, and 92% of the patients were men. Overall, 98% of the men and 44% of the women were smokers. Diagnosis was confirmed by cytologic or histologic findings in 92% of patients, and the majority were non-small cell tumors (81.4%). At the time of diagnosis, 65% of the patients had advanced disease, with distant metastasis in 26.6% of the non-small cell cancers and 52.8% of the small cell cancers. Patients received surgical treatment in 21.3% of cases, chemotherapy alone or combined with radiation therapy in 43.1%, and radiation therapy alone in 9.3%. In 26.2% of patients only palliative care was given. Overall, median survival in weeks was 36.4 (95% confidence interval [CI], 29.4-43.4). Median survival by treatment type was as follows: 69.3 (95% CI, 49-9.5) for surgery; 39.6 (95% CI, 31.2-48) for chemotherapy alone or with radiation therapy; 30 (95% CI, 15.4-44.6) for radiation therapy alone; and 13.3 (95% CI, 5.9-20.6) for patients who received palliative care alone ($P < .05$).

CONCLUSIONS: The findings with respect to age, sex, incidence, histology, extent of tumor, and smoking status of patients with bronchogenic carcinoma in our region do not differ significantly from those reported for other areas of Spain. Current smoking is the primary cause of the high prevalence of this disease. Twenty-six percent of patients received only palliative care. The percentage of patients treated with surgery was low.

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

Características del carcinoma broncopulmonar en una región del norte de España

OBJETIVO: Conocer las características y supervivencia del carcinoma broncogénico (CB) diagnosticado en las unidades de neumología del Principado de Asturias.

PACIENTES Y MÉTODOS: Se ha realizado un estudio observacional retrospectivo en el que se ha empleado un protocolo común de recogida de datos. Se incluyeron los CB diagnosticados en el año 2001 con confirmación citohistológica o por concordancia basada en datos clínicos, radiológicos y/o endoscópicos.

RESULTADOS: Las tasas de incidencia estándar para toda la población, varones y mujeres, ajustadas a la población mundial fueron de 22,4, 42,6 y 4,6/100.000 habitantes, respectivamente. El 92% era varón; la edad media (± desviación estándar) fue de 67 ± 10,9 años. Tenía hábito tabáquico el 98% de los varones y el 44% de las mujeres. Se alcanzó confirmación citohistológica en el 92% y la mayoría era CB no microcíticos (81,4%). En el momento del diagnóstico el 65% de los pacientes tenía enfermedad avanzada, con metástasis a distancia en el 26,6% de los CB no microcíticos y en el 52,8% de los de células pequeñas. Se trató con cirugía el 21,3% de los casos, con quimioterapia sola o asociada a radioterapia el 43,1%, con radioterapia exclusivamente el 9,3% y recibió tratamiento paliativo el 26,2%. La mediana de supervivencia global, en semanas, fue de 36,4 (intervalo de confianza [IC] del 95%, 29,4-43,4) y para los distintos tratamientos fue la siguiente: para la cirugía, 69,3 (IC del 95%, 49-9,5); para la quimioterapia sola o asociada a radioterapia, 39,6 (IC del 95%, 31,2-48); para la radioterapia sola, 30 (IC del 95%, 15,4-44,6), y para el paliativo, 13,3 (IC del 95%, 5,9-20,6) ($p < 0,05$).

CONCLUSIONES: En nuestra región, las características del CB en cuanto a edad, sexo, incidencia, histología, extensión tumoral y tabaquismo no difieren significativamente de las halladas en otras áreas del ámbito nacional. El tabaquismo activo es la causa fundamental de su alta prevalencia. Se ofreció solamente tratamiento de soporte al 26%. El porcentaje de pacientes quirúrgicos es bajo.

Palabras clave: *Cáncer de pulmón. Incidencia. Supervivencia.*

Introduction

There is no doubt whatsoever that lung cancer is the leading cause of death due to neoplastic disease in western countries.[1] In Spain, lung cancer mortality continues to be higher in men than in women[2] although changes in smoking habits have resulted in a trend towards similar rates in both sexes.[3] Notwithstanding improved accuracy in diagnosis and staging, advances in treatment have not resulted in any substantial modification of the poor survival rates associated with this disease.[4] Data concerning the incidence and importance of lung cancer is available for most provinces in Spain from the records and mortality rates published by the Spanish National Institute of Statistics

Correspondence: Dr. M.A. Alonso-Fernández.
Servicio de Neumología I. Hospital Universitario Central de Asturias.
Dr. Bellmunt, s/n. 33006 Oviedo. Asturias. España.
E-mail: migu67@separ.es

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(Instituto Nacional de Estadística). In Asturias, data for the years 1990 through 1993 are also available from the Asturian Health Authority (Consejería de Sanidad del Principado de Asturias).[5,6]

The aim of this study was to determine the incidence of bronchogenic carcinoma in Asturias, and to gather information on the treatments used and survival rates achieved. To this end, the Asturian Society of Respiratory Disease (ASTURPAR) created a working group representing the respiratory medicine and thoracic surgery departments of all the public and private hospitals in the region. This group has collected data on all cases of lung cancer diagnosed in 2001.

Patients and methods

This was a regional and retrospective observational multicenter study. A standardized data collection protocol was designed and subsequently discussed and accepted by all members of the group. The data reviewed in this study were as follows: personal details, age, sex, smoking status, type of sample used for diagnosis (cytologic, histologic, or both). Tumors were classified into 5 types according to the histologic classification published by the World Health Organization in 1999[7]: squamous cell carcinomas, adenocarcinomas, and large cell anaplastic carcinomas, which are classified together as non-small cell lung cancer (NSCLC); and small cell lung cancer (SCLC). The fifth group, designated as "undetermined" tumors, comprised samples with the characteristics of NSCLC that the pathologist was unable to type. TNM staging followed the guidelines proposed by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)[8] and was based on radiographic studies (conventional radiography and computed tomography) and endoscopic findings. The results of ultrasound, magnetic resonance imaging, and cranial computed tomography were used to determine the extent of disease by investigating the presence of distant dissemination. The treatment received in each case and the clinical follow-up of each patient were also reviewed. Date of death was ascertained from patient records, public vital records or, when necessary, by way of a phone call.

All patients normally resident in the region with a cytohistologic diagnosis of primary lung cancer between January 1 and December 31 of 2001 were included in the study. Even when disease had not been confirmed cytohistologically, patients were included in the study if the clinical, radiographic, and/or endoscopic findings were consistent with a diagnosis of lung cancer and all other possible diagnoses could be reasonably ruled out.[9] Mean follow-up was 3 years (range, 2.5-3.5 years), and the study ended on June 30, 2004.

Statistical Analysis

The reference population used to calculate incidence rates was the municipal census for Asturias in 1999. Standard incidence rates adjusted to the world population were calculated using the direct adjustment method. The data was entered into a computerized database and then analyzed using a licensed copy of the SPSS 6.0 software package (SPSS, Chicago, Illinois, USA). First, descriptive statistics were compiled by obtaining percentages for the qualitative variables and means with confidence intervals (CI) or ranges for the quantitative variables. The Kaplan-Meier method was then used to analyze survival. The survival curves obtained were compared using the Mantel-Haenszel or log-rank test. A value of *P* less than .05 was considered statistically significant.

TABLE 1
Incidence Rates and Distribution by Age, Sex, and Smoking Status for the Patients Studied

	Number of Patients, %		Mean (SD) Age, Years
Sex			
Men	478 (92)		67.4 (10.9)
Women	43 (8)		63.9 (13.4)
Age >70 years	219 (42)		
Smoking status	489 (94)		
Men	470 (98)		
Women	19 (44)		
Incidence Rate (Number of Cases/100 000 Population)	**Overall**	**Men**	**Women**
Crude rate	50.16	96.34	7.62
Adjusted to Spain*	41.98	80.43	6.54
Adjusted to Europe*	40.04	72.33	6.56
Adjusted to world population*	22.43	42.61	4.6

*Adjusted to the population in 1999.

Results

The population of Asturias in 1999 was 1 084 314. A total of 521 cases were studied. Table 1 shows incidence rates and the patient characteristics in terms of age, sex, and smoking status.

Only 32 patients (6%) had never smoked: 1.6% of the men and 55.8% of the women. Mean (SD)

TABLE 2
Diagnostic Method, Histologic Type, Staging, and World Health Organization (WHO) Functional Score in 521 patients*

	Number of Patients, %
Diagnostic method	
Cytohistologic	478 (92)
Clinical and radiographic	43 (8)
Histologic type	478 (92)
SCLC	89 (18.6)
Limited disease	42 (47.2)
Extended disease	47 (52.8)
NSCLC	389 (81.4)
Squamous cell carcinoma	226 (58.1)
Adenocarcinoma	114 (29.3)
Large cell carcinomas	19 (4.9)
Undetermined	30 (7.7)
Staging of NSCLC	
IA	35 (9)
IB	69 (18)
IIA	2 (0.5)
IIB	26 (7)
IIIA	48 (12)
IIIB	90 (23)
IV	119 (30.5)
WHO functional score	
0	167 (32)
1	182 (35)
2	89 (17)
3	57 (11)
4	26 (5)

*NSCLC indicates non-small cell lung cancer; and SCLC, small cell lung cancer.

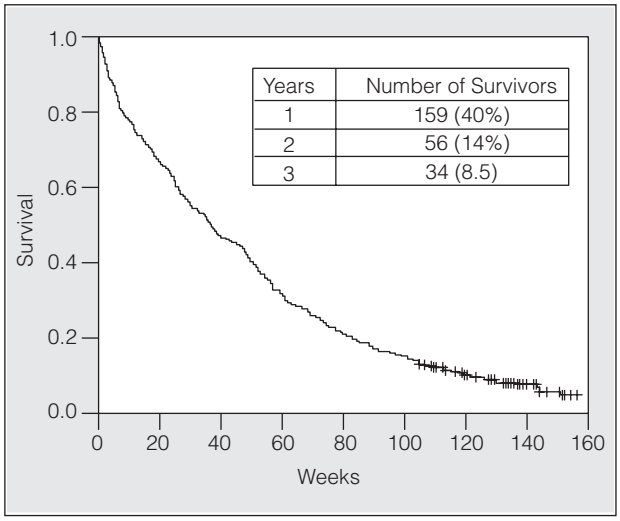

Figure 1. Overall survival calculated by the Kaplan-Meier method.

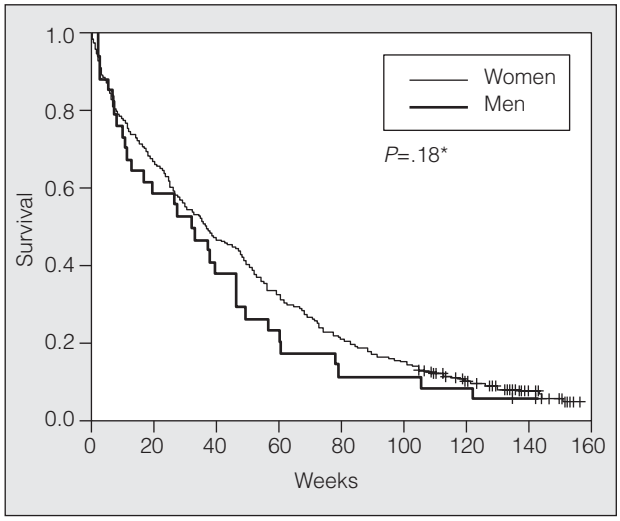

Figure 2. Survival by sex calculated with the Kaplan-Meier method. *P value by the Mantel-Haenszel test.

TABLE 3
Treatment Received Overall and by Histologic Type*

Type of Treatment	Overall (n=515)	NSCLC (n=389)	SCLC (n=89)	Clinical and Radiographic (n=37)
Surgery	110 (21.3)	109 (28)	1 (1.1)	0
Chemotherapy†	222 (43.1)	143 (36.7)	79 (88.8)	0
Radiation therapy	48 (9.3)	48 (12.3)	0	0
Palliative care	135 (26.2)	89 (22.9)	9 (10)	37 (100)

*Data are expressed as number of patients (%). NSCLC indicates non-small cell lung cancer; and SCLC, small cell lung cancer.
†Alone or combined with radiation therapy.

consumption among the smokers was 54.7 (24.6) pack-years (range, 4-150), and 93% had a history of 20 pack-years or more. Table 2 shows distribution by diagnostic method, histologic type, staging, and functional score on the World Health Organization scale. In our study, 36% of patients had distant metastasis at the time of diagnosis; disease had reached advanced stages (IIIB and IV) in 53.5% of NSCLC patients and 52.8% of those with SCLC had extended cancer. Analysis of the treatment the patient received was possible in 515 cases (98.8%) (Table 3).

Survival was analyzed 3.5 years after the start of the study (June 30, 2004), mean follow-up was 3 years, and information on survival was obtained for 427 (82%) of the 521 patients. Median survival overall was 36.4 weeks (95% CI, 29.4-43.4) (Figure 1) and was similar in men (36.7 weeks; 95% CI, 28.6-44.8) and women (31.7 weeks; 95% CI, 16.5-47.1) (Figure 2). Figure 3 shows survival curves for patients with SCLC and NSCLC

TABLE 4
Median Survival Rates for Each Histologic Group and Stage*

Type	Weeks	95% CI	Difference
SCLC			*P*<.001†
Limited disease	53.9	28.5-79.2	
Extended disease	24.3	19.2-29.4	
NSCLC			*P*<.001†
Stage I (IA and IB)	63.3	(39.4-73.2)	
Stage II (IIA and IIB)	51.6	(27.6-75.8)	
Stage III (IIIA and IIIB)	44.7	(27.1-49.8)	
Stage IV	20.9	(9.7-24.5)	

*Median survival rates by type and tumor size calculated with the Kaplan-Meier method. CI indicates confidence interval; SCLC, small cell lung cancer; and NSCLC, non-small cell lung cancer.
†*P* value by the Mantel-Haenszel test.

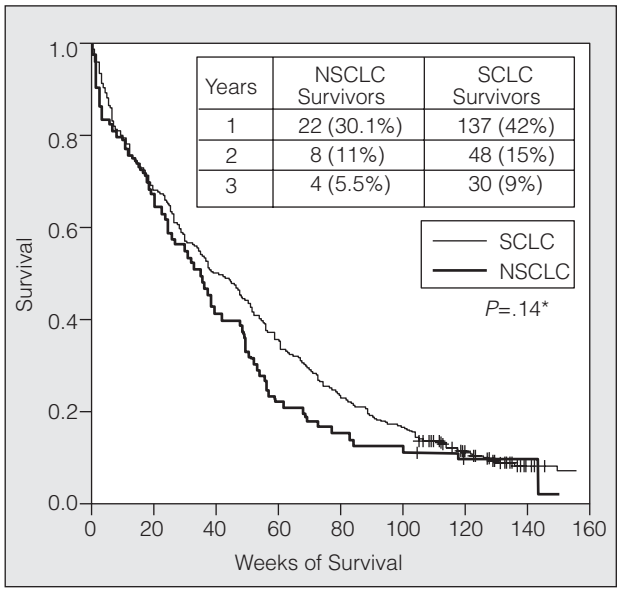

Figure. 3. Survival by histologic group calculated with the Kaplan Meier method. NSCLC indicates non-small cell lung cancer; and SCLC, small cell lung cancer. *P value by the Mantel-Haenszel test.

respectively, excluding clinical diagnoses. Four hundred cases were analyzed (327 NSCLC and 73 SCLC). Median survival was longer in the NSCLC patients (39.7 weeks; 95% CI, 32.6-46.8) than among those with SCLC (35.1 weeks; 95% CI, 23.8-46.4), although the differences were not statistically significant.

With respect to staging and survival (Table 4), patients with disease at localized stages survived longer in both the NSCLC (Figure 4) and SCLC (Figure 5) groups. A higher median survival was observed in patients treated surgically (69.3 weeks; 95% CI, 49-89.5), followed by those who received chemotherapy (39.6 weeks; 95% CI, 31.2-48), and radiation therapy (30 weeks; 95% CI, 15.4-44.6). Survival among patients who received only palliative care was 13.33 weeks (95% CI, 5.9-0.6), and while no statistically significant differences were found between radiation therapy alone and chemotherapy, significant differences were found between the other groups (P<.001) (Figure 6).

Discussion

Lung cancer continues to be an important health problem. The inaccuracy of data on mortality related to lung cancer obtained from death certificates is to a large degree compensated by population-based tumor records. A standardized register of cancer cases based on information from death records is available for the region of Asturias, Spain.[6] The present study was the first one to be carried out in Asturias by pulmonologists. While it is likely that a review of patient records obtained exclusively from respiratory medicine departments could lead to an underestimation of the real incidence of lung cancer, we believe, nonetheless, that any omission of data on patients diagnosed in primary care facilities or internal medicine departments must have been slight given the presence of respiratory specialists in all areas of the health service.

The mean age of patients in our study coincides with most of the case series studied in western countries[10,11] and is similar to that observed in other regions of Spain.[12-15] As would be expected, analysis of distribution by sex reveals that lung cancer continues to affect mainly men (92% of the patients in our study) and smokers (94%).

Incidence rates for the entire population and by sex in Asturias (Table 1) are slightly higher than those found in Castile-León,[12] Castellón,[14] and La Coruña,[15] and lower than those reported for Extremadura.[13] Our results are also in line with the figures reported by Morote et al[5,6] for the 1990s, indicating that our data collection procedure was valid.

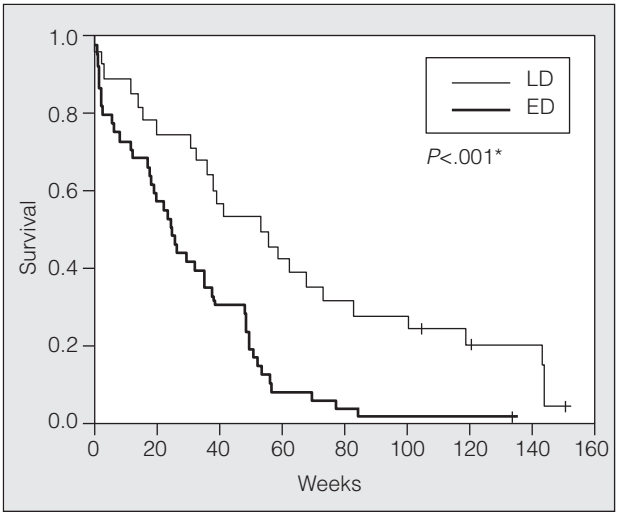

Figure 5. Survival of patients with small cell lung cancer by tumor extension calculated with the Kaplan-Meier method. LD indicates limited disease; and ED, extended disease *P value by the Mantel-Haenszel test.

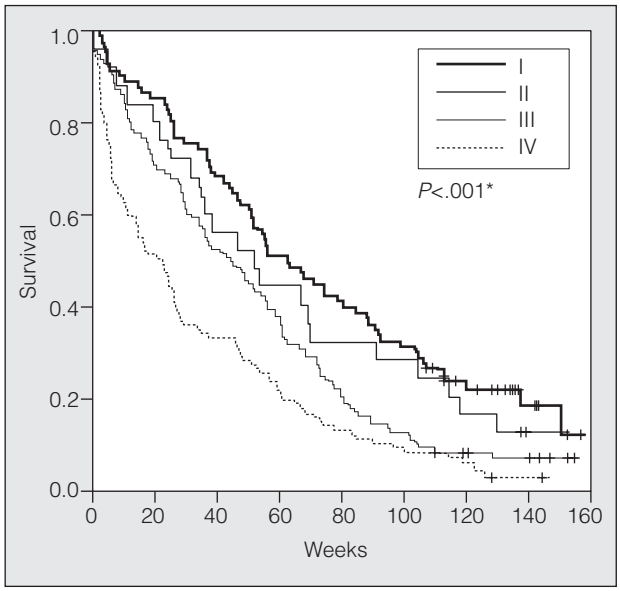

Figure 4. Survival by staging of non-small cell lung cancer calculated with the Kaplan Meier method. *P value by the Mantel-Haenszel test.

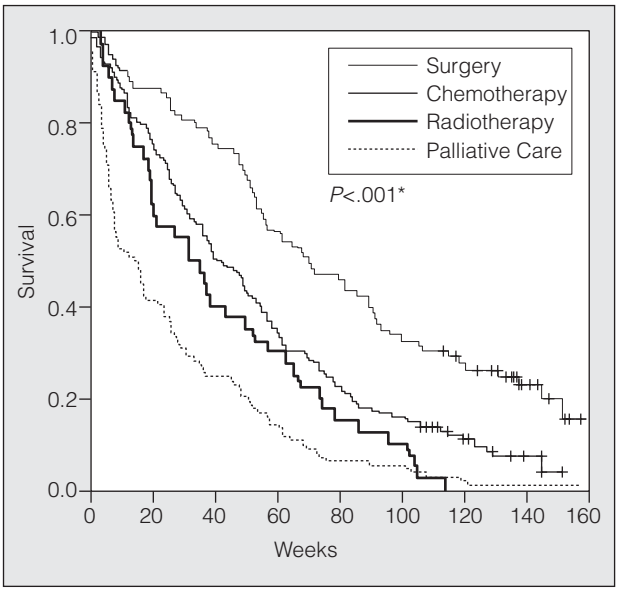

Figure 6. Survival in weeks by treatment type calculated with the Kaplan-Meier method. *P value by the Mantel-Haenszel test.

The chief risk factor for lung cancer is smoking, and the clear relationship between dose and effect is well known[16]; risk increases in relation to daily consumption, years of smoking, and earlier age of initiation. In this study, 98% of the men and 44% of the women were smokers. While the percentage for men is similar to figures published for other regions, prevalence was greater among female patients in Asturias than in Extremadura,[13] Castellón,[14] and Castile-León,[12] and similar to the figure reported for La Coruña.[15] In this respect, it is interesting to note that Hernández et al[17] report that smoking among women in the province of Avila increased over a 10-year period, rising to 23% in 2002, a clear indication of the increasing addiction of women to tobacco. This increase will, in turn, give rise to a gradual increase in the incidence of lung cancer among women.[18] The crude incidence rate among women in our study covering 2001 was 7.62 per 100 000 population. While this exceeds the rate found in a study carried out in Castile-León in 1997[12] (4 years earlier), it is lower than the incidence reported for 1 province in Castile-León in 2002.[17]

Cytohistologic confirmation was not obtained in 43 cases (8%). While this figure falls into an intermediate range with respect to the Spanish studies reviewed, it is lower than the percentages reported for studies by Gregor et al[19] in 1995 in Scotland (35.9%), by Mäkitaro et al[20] in Finland (14%), and by Brown et al[11] (26%) in the UK. The lower percentages found in Spain are probably due to a more aggressive approach to diagnosis on the part of pulmonologists. We compared the frequency of different histologic types with data from similar studies.[21] Our distribution—81.4% of NSCLC and 18.6% SCLC—falls within the ranges described elsewhere.[22] The frequency of squamous cell carcinoma (58.1%) in our study is comparable to that observed by other Spanish authors with the exception of Hernández et al.[17] That author reported a decline in this percentage from 59.4% to 38.1% over a 10-year period, a finding consistent with the trend observed in other European countries[20] and the United States of America.[23] There have been changes in histologic cancer type over recent decades. Adenocarcinoma is the most prevalent subtype among women and continues to increase[24]; in the USA, it is also the most prevalent type of carcinoma among men.[25] This shift could be explained by the hypothesis proposed by Wynder and Hoffman,[26] who attribute it to a higher consumption of low-nicotine filter tip cigarettes. They suggest that people consuming low nicotine cigarettes would tend to smoke more and inhale more deeply to obtain the desired concentration of nicotine (similar to the dose they would obtain smoking cigarettes without filters). The smoke of these filter tip cigarettes would therefore penetrate more deeply into the bronchial tree and reach areas where adenocarcinoma is more common.

It is interesting to note with respect to tumor size (Table 2) that at the time of diagnosis 65% of the patients had cancer in advanced stages (III-B and IV in the case of NSCLC) or had extended disease (in the SCLC patients). Our data reveal a serious shortcoming with regard to the chances of early detection, at stages that would permit surgical treatment.

The facts detailed above would explain the small number of patients with of NSCLC who are treated surgically (21.3%) and the high proportion who received only palliative care (26% of patients in this study, which corresponded to 23% NSCLC cases and 10% of SCLC cases). This rate of palliative care is similar to that observed by Montero et al[15] (26%) but is lower than the rate reported by other authors, such as Miravent et al[14] (29.8%) and Gregor et al[19] (43.2%). However, the once fatalistic attitude of many physicians is changing. This shift can be attributed to a greater awareness of ways to actively treat lung cancer made possible by advances involving the application of combined treatments.[27] In a study by Gregor et al,[19] only 8.2% of NSCLC patients and 62.5% of those with SCLC were treated with chemotherapy. Those authors suggest that this apparently fatalistic approach to the treatment of lung cancer in Scotland may be explained by the small percentage of patients studied by respiratory physicians. In contrast to the situation in Scotland, the proportion of patients receiving only palliative treatment in Spain is lower. In any case, the proportion of patients with NSCLC treated surgically is perhaps not rising in the short term. Data taken from the National Cancer Data Base in the USA shows that this figure remained at 27% from 1985 to 1995.[28]

Since our study did not evaluate survival over a 5-year period, our results cannot be compared with the epidemiological studies published in the USA[26] or the data reported by the EUROCARE group.[29] We analyzed survival in only 427 patients, so that it is possible that data not available for inclusion in this analysis may have affected the results. Of these patients, 159 (40%) were alive after 1 year, and 56 (14%) after 2 years. Median survival was 36.4 weeks, and sex was not a determining factor. Although the survival rate was lower in the SCLC patients, statistical analysis did not reveal any significant differences. Our findings differ from the results obtained by some authors[6,14,21,23,30] and agree with those of Montero et al.[15] In the latter study, and in ours, 90% of the patients with SCLC were treated with chemotherapy, and this may have contributed to their longer survival. Perhaps a larger number of patients with localized disease might explain these differences because in our study the survival of patients with limited disease was clearly higher (65.35 weeks) than that of patients diagnosed with extended disease (31.64 weeks).

On univariate analysis of the NSCLC patients, the variables that most significantly influenced survival were TNM staging and type of treatment received. Although the TNM staging used was clinical, there is no doubt about its utility for prognosis.[28,31]

In conclusion, the epidemiological characteristics of lung cancer in terms of age, sex, incidence, histology,

tumor extension, and smoking status do not differ in any noticeable way from those reported for other parts of Spain. Current smoking is the primary cause of the high prevalence of this disease. Since the percentage of patients treated surgically is low, survival rates are poor.

Addendum

Members of the ASTURPAR (Asturian Society of Respiratory Disease) Lung Cancer Working Group (GACP) in alphabetical order: M.A. Alonso Fernández (Neumología I, Hospital Universitario Central de Asturias [HUCA], Oviedo), E. Álvarez-Llaneza García (Neumología, Hospital Centro Médico de Asturias, Oviedo), T. Álvarez Sánchez (Neumología II, HUCA, Oviedo), F. Carro del Camino (Neumología II, HUCA, Oviedo), B. del Busto de Lorenzo (Neumología, Hospital de Jove, Gijón), C. Escudero Bueno (Neumología I, HUCA, Oviedo), J. Flórez Gutiérrez (Neumología, Hospital Comarcal Valle del Nalón, Sama de Langreo), M. García Clemente (Neumología, Hospital Comarcal Álvarez-Buylla, Mieres del Camino), M. García Marrón (Neumología, Hospital Comarcal San Agustín, Avilés), J. Gorostidi Pérez (Neumología, Hospital Comarcal de Jarrio), C. Orejas García (Neumología, Hospital Grande Covián, Arriondas), M.T. Pascual Pascual (Neumología, Hospital de Cabueñes, Gijón), B. Rodríguez Cocina (Neumología, Hospital Comarcal de Cangas de Narcea), J. Rodríguez Rodríguez (Cirugía Torácica, HUCA, Oviedo).

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