Overall Long-Term Survival in Lung Cancer Analyzed in 610 Unselected Patients

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INTRODUCTION AND OBJECTIVES: Many studies of lung cancer survival are carried out in patients selected for certain features that usually influence prognosis favorably. The objective of this study was to assess the overall survival of unselected patients with a diagnosis of lung cancer in our practice.

PATIENTS AND METHODS: We studied 610 patients for whom survival information was available, a population comprising 88% of the 694 with lung cancer diagnosed in our hospital from 1991 through 1998. The variables analyzed for their correlation with survival were age, sex, histology, tumor-node-metastasis (TNM) stage, treatment, and time of diagnosis (with patients grouped by 2-year periods).

RESULTS: The cases of 596 men and 14 women with a mean age of approximately 67 years were studied. Small cell tumors were found in 141, non-small cell tumors in 447, and other tissue types in 22. Surgical excision was carried out on 118 (19.3%), and treatment was confined to control of symptoms for 6.4% of the patients with small cell tumors and 40.5% of those with non-small cell cancer. Symptomatic treatment alone was more common for patients older than 70 years (52.5%) and less common during the last 2 years of the study period (1997-1998: 19%). Overall 5-year survival was 7.9% (2.8% in small cell cancer and 9.4% in non-small cell cancer). Survival rates were lower in patients over 70 years of age. Significant differences in survival were seen for successive TNM stages, with the exception of IIIA and IIIB. The 1997-1998 period saw better survival rates, at 40.8% after 1 year and 11.2% after 5 years.

CONCLUSIONS: The survival rates in lung cancer patients in our hospital practice are low because the rate of surgical resections is low owing to the high percentage of cases found in advanced stages. Our observations are similar to those reported from other European countries.

Key words: *Lung cancer. Overall survival. Unselected patients.*

Supervivencia global a largo plazo en el cáncer de pulmón. Análisis de una serie de 610 pacientes no seleccionados

INTRODUCCIÓN Y OBJETIVOS: Muchos estudios sobre la supervivencia en el cáncer de pulmón se refieren a subgrupos de pacientes seleccionados por diferentes criterios que suelen influir favorablemente en la estimación del pronóstico. El objetivo de este trabajo es conocer la supervivencia global de los pacientes diagnosticados en nuestro medio.

PACIENTES Y MÉTODOS: De 694 pacientes diagnosticados de cáncer de pulmón en nuestro centro en el período 1991-1998, se incluyó en el estudio a 610 (88%) con datos de supervivencia. Se analizaron la edad, el sexo, la estirpe histológica, estadios, tumor, nódulos, metástasis (TNM), tratamiento aplicado bienio diagnóstico y su relación con la supervivencia.

RESULTADOS: Se incluyó en el estudio a 596 varones y a 14 mujeres, con una mediana de edad de 67 años. En cuanto a la estirpe del cáncer de pulmón, 141 eran microcíticos, 447 no microcíticos y 22 de otra estirpe. Se operó a 118 pacientes (19,3%). El 6,4% de los casos de cáncer de pulmón microcítico y el 40,5% de los no microcíticos recibieron sólo tratamiento sintomático. Éste fue más frecuente en mayores de 70 años (52,5%) y menos habitual durante el último bienio (1997-1998; 19%). La supervivencia a los 5 años del grupo total fue del 7,9% (del 2,8% para los microcíticos y del 9,4% para los no microcíticos). Los mayores de 70 años tuvieron peor supervivencia. Hubo diferencias significativas entre los sucesivos estadios TNM clínico, salvo entre IIIA y IIIB. Los diagnosticados en el período 1997-1998 tuvieron mejor supervivencia (un 40,8% al año y un 11,2% a los 5 años).

CONCLUSIONES: La supervivencia observada, similar a la de otros países europeos, es pobre porque la tasa de resecciones quirúrgicas es baja dado el alto porcentaje de estadios avanzados.

Palabras clave: *Cáncer de pulmón. Supervivencia global. Pacientes no seleccionados.*

Introduction

Lung cancer, the main cause of cancer deaths among men in Western countries, was responsible for 8.16% of all male deaths and 1.1% of female deaths in 2000 in Spain.[1] Increased worldwide and Spanish mortality due to lung cancer is predicted over the next 20 years,[2] attributable to the likely rise in mortality among women.[3,4] The predictions are based on the probability of a higher rate of new cases as well as on the ominous prognosis for lung cancer in most cases.

Reliable, accurate data on postoperative survival have been available for lung cancer for many years for

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North American and Japanese populations, and also for Spain thanks to the work of the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-SEPAR).[5] Patients who undergo surgery account for only a small percentage of all lung cancer cases, however, and the more favorable prognosis for such patients is not representative of all those who have the disease.

Reports on overall survival of lung cancer are characterized by marked differences, even among European countries with very similar social and economic situations,[6] possibly attributable in part to differences in inclusion criteria. Studies of long-term survival in large patient series in Spain are scarce and the few published reports do not usually offer much information on patient characteristics or inclusion criteria.[7]

The aim of this study was to determine the short- and long-term survival rates for patients diagnosed with lung cancer in our hospital from 1991 through 1998.

Patients and Methods

This was a retrospective study of patients diagnosed and treated for lung cancer in our service from 1991 through 1998, although many of the patients were also enrolled in prospective studies of various types. Patients diagnosed after 1998 were excluded so that the follow-up period during the study would be sufficiently long. The shortest follow up was 54 months and 94% of the patients were followed for over 60 months.

During the study period our hospital served a predominantly rural community with a population of 188 431 in which geographic mobility was low. Our respiratory medicine department diagnoses, treats, and monitors patients with lung cancer. Candidates for surgery were referred to other hospitals for treatment, as our hospital does not offer this surgical specialty.

From the records of patients diagnosed during the study period (1991-1998), the following information was gathered:

– Date of diagnosis, referring physician, age, and sex.

– Tumor histology. Although surgical patients could be diagnosed by studying the excised tumor, most cases were classified by bronchial biopsy and/or brushing and/or aspirate obtained during fiberoptic bronchoscopy, such that only a cytology sample was available. For a small number of patients (Table 1) microscopic confirmation of the diagnosis was not obtained in spite of tests performed. Other reasonable diagnoses had been ruled out for such patients.

– Tumor–node–metastasis (TNM) stage (1997 classification adopted by SEPAR[8]). Patients were classified by clinical procedures (clinical TNM), although a pathologist's TNM diagnosis was also available for surgical patients (see Results section). Small cell tumors were classified as usual in one of two groups: *a)* limited disease, when lesions were confined to a single hemithorax, including ipsi- and contralateral mediastinal lymph nodes, and *b)* extensive disease, if cancer had spread beyond the aforementioned limits. A computed tomography scan of the thorax and abdomen was available for most patients, excepting those whose tumors were not staged and whose clinical situation precluded diagnostic testing. Among stage IIIA and IIIB patients who did not undergo surgery, N2 staging often could not be confirmed by cytology or histology (transtracheal puncture biopsy or mediastinoscopy). Remote metastasis was established by imaging except in 10 patients with skin and/or liver metastasis, who were diagnosed clinically.

TABLE 1
Patient Characteristics

Sex	
Men	596
Women	14
Age, years	
Mean, range	65.2 (35-91)
Median	67
<40	8
40-49	37
50-59	113
60-69	229
70-79	198
>80	25
Histology, n (%)	
Small cell	141 (23.1)
Non-small cell	447 (73.3)
Squamous	245 (40.7)
Adenocarcinoma	116 (19.0)
Bronchoalveolar	2 (0.3)
Mucosal-squamous	2 (0.3)
Undifferentiated large cell and/or non-small cell	82 (13.4)
Not typed	18 (3.0)
Unconfirmed	4 (0.7)

– Treatment type. Treatment groups were as follows: *a)* surgery, with or without associated chemotherapy and/or radiotherapy and with or without chemotherapy upon recurrence; *b)* chemotherapy alone; *c)* radiotherapy alone; *d)* combined chemo- and radiotherapy; and *e)* symptomatic treatment alone.

– Date of death. When the date of death could not be determined based on records, the family was contacted or the municipal records of the patient's place of residence were consulted. Survival time was calculated from the time of start of treatment, except when no treatment had been provided, in which case the date of diagnosis was used as the starting point.

– Other aspects relevant to prognosis, such as the Eastern Cooperative Oncology Group (ECOG) score, weight loss, analytical findings, etc, which were only recorded for some patients, were not entered into analysis in this study.

Kaplan-Meier survival curves were constructed and logarithmic ranges were used for comparisons, although the graphs have been presented in simplified form to show only survival percentages from year to year (ECOG). A χ^2 test was used to compare percentages.

Results

Lung cancer was diagnosed in 694 patients during the 1991 through 1998 study period. Survival time could not be verified for 84 patients, such that only 610 (88% of the total) were entered into analysis. The characteristics of those patients are shown in Table 1. Because only cytology was available for many patients, and that sample is unreliable for diagnosing histological type, we

TABLE 2
Staging*

All Cases		No. (%)
Small cell		
Limitated		54 (38.3)
Extensive		82 (58.2)
Unknown		5 (3.5)
Non-small cell and others† (TNMc)		
Stages I and II		123 (26.2)
Stage IIIA		41 (8.7)
Stage IIIB		127 (27.8)
<Stage IV (unspecified)		9 (1.9)
Stage IV		106 (22.6)
Unknown		53 (11.3)
Non-Small Cell, Not Excised	**TNMc, No. (%)**	**TNMsp, No. (%)**
Stages I and II	97 (82.9)	86 (73.5)
Stage III A	9 (7.7)	22 (18.8)
Stage IIIB	2 (1.7)	8 (6.8)
<Stage IV (unspecified)	9 (7.7)	–
Stage IV	–	1 (0.4)

*TNM indicates tumor–node–metastasis; TNMc, TNM determined by clinical procedures; TNMsp, TNM determined by pathological examination of the surgically excised tumor.
†Others are cases in which type was unknown or unconfirmed.

TABLE 3
Treatment Distribution

	No. (%)
Small cell (n=141)	
Surgery*	1 (0.7)
Chemotherapy only	104 (73.8)
Chemo- and radiotherapy	27 (19.1)
Symptomatic treatment	9 (6.4)
Non-small cell and others† (n=469)	
Surgery*	117 (24.9)
Chemotherapy only	97 (20.7)
Chemo- and radiotherapy	43 (9.2)
Radiotherapy only	22 (4.7)
Symptomatic treatment	190 (40.5)

*Twelve patients also received chemotherapy before and/or after surgery, 10 received postoperative radiotherapy, and 18 received chemotherapy upon recurrence.
†Others are cases in which type was unknown or unconfirmed.

grouped those cases together as undifferentiated large-cell tumors with no further specification. The results of staging are shown in Table 2 for both small and non-small cell tumors. The series is also broken down by surgical and non-surgical treatment type, and by clinical and pathological TNM classification. The TNM classification of the 9 surgical patients had not been determined by clinical diagnosis, although they were believed to be in stages lower than IV.

Table 3 shows the treatments applied. Some surgical patients also received other therapeutic modalities (neoadjuvant and/or adjuvant chemotherapy, post-operative radiotherapy, and/or chemotherapy during recurrence).

Distribution by age and by 2-year diagnostic period, as well as by extension (percentage in the earliest stages: TNM I and II for non-small cell cancers and limited or extensive disease for small cell tumors) and the percentage of unstaged tumors are shown in Table 4. A significantly larger percentage of unstaged cases were observed in the older age group ($P<.001$).

Table 5 gives the type of treatment by age and 2-year diagnostic period. Significantly more cases of exclusively symptomatic treatment were found among older patients ($P<.001$). Symptomatic treatment alone was also used significantly less often during the last 2-year period ($P<.001$).

There was a tendency during the last 2-year diagnostic period (1997-1998) for fewer patients to receive only palliative care ($P<.001$).

Figure 1 shows the percentages of survivors after 1, 2, 3, 4, and 5 years. When patients were stratified in 3 age groups (less than 50 years old, from 50 to 69, and 70 years or older), survival was found to be shorter for older patients ($P<.001$; Figure 2).

Patients with non-small cell cancer survived longer (9.4% alive at 5 years vs 2.8% alive for small cell cancer patients; $P<.05$; Figure 3). Figure 4 shows survival for non-small cell cancer patients according to TNM stage. Patients in stages I and II are grouped together, and we have also included an "unstaged"

TABLE 4
Extension (Clinical TNM Stage or Limited/Extensive Disease Classification) by Age Groups and Main Histologic Type and by 2-Year Diagnostic Period and Main Histologic Type*

	Non-Small Cell or Others,† No. (%) Stages I and II‡	Small Cell (% Limited Disease)§	Total (% Stage Unknown)
Age groups			
< 50 years	8 (23.5)	1 (9.1)	4 (8.9)
50-69 years	78 (30.0)	33 (40.2)	19 (5.6)
≥70 years	37 (21.1)	20 (41.7)	36 (16.1)‖
2-year diagnostic period			
1991-1992	25 (22.7)	13 (35.1)	13 (8.8)
1993-1994	23 (34.8)	14 (36.8)	9 (8.6)
1995-1996	38 (26.9)	18 (46.1)	25 (13.9)
1997-1998	37 (24.3)	9 (33.3)	12 (6.7)

*TNM indicates tumor–node–metastasis.
†Others are cases in which type was unknown or unconfirmed.
‡Percentage of all patients with non-small cell carcinoma.
§Percentage of all patients with small cell carcinoma.
‖$P<.001$.

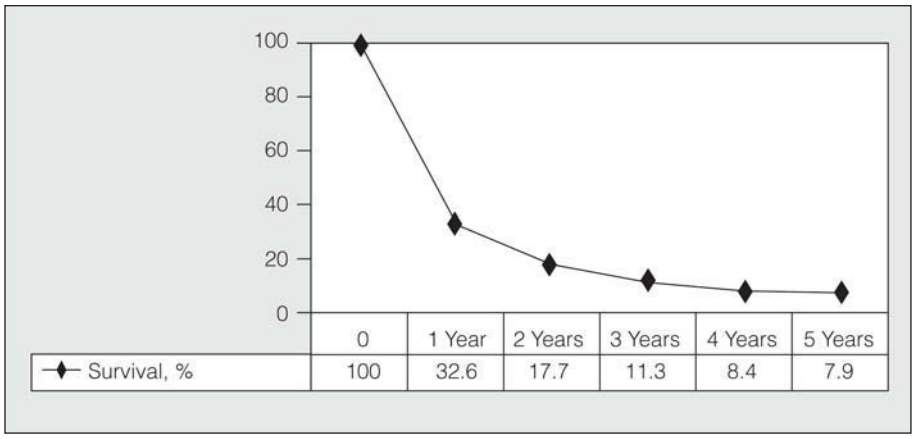

Figure 1. Overall survival, all patients.

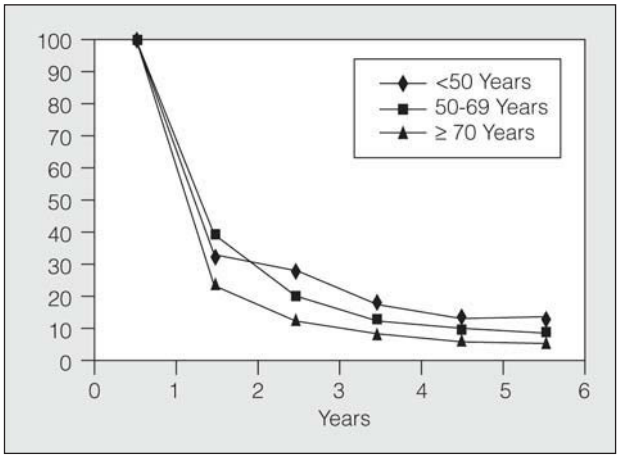

Figure 2. Survival by age groups (overall *P*<.0005; between group 2 [50-69 years] and group 3 [≥70 years], *P*<.001).

group, in which the prognosis can be seen to be worse. All differences between groups were highly statistically significant, with the exception of the distinction between groups IIIA and IIIB.

Finally, Figure 5 shows how survival evolved over the course of the study (1991-1998) with patients grouped by 2-year diagnostic period. Survival was significantly longer for those diagnosed in the last 2-year period (1997-1998) and the group differences were particularly evident in the analysis of 1-year survival (40.8% for those diagnosed in the last 2-year period vs 28.8%, 27.6%, and 28.8% for the 3 previous periods), although the advantage for those in the last period was still clear in the analysis of 5-year survival (11.2% for patients diagnosed in 1997-1998 vs 7.5%, 5.7%, and 6.1% for those in the earlier 2-year periods; *P*<.01).

TABLE 5
Treatments by Age Groups and by 2-Year Diagnostic Period*

	Surgery†	CT and/or RT	Symptomatic Only
Age			
<50 years	11 (24.4)	28 (63.8)	6 (13.3)
50-69 years	76 (22.2)	190 (55.5)	76 (22.2)
≥70 years	31 (13.9)	75 (33.6)	117 (52.5)‡
2-year diagnostic period			
1991-1992	23 (15.8)	58 (39.7)	65 (44.5)
1993-1994	13 (12.4)	52 (49.5)	40 (38.1)
1995-1996	38 (21.1)	82 (45.5)	60 (33.3)
1997-1998	44 (24.6)	101 (56.4)	34 (19.0)‡

*Results are shown as numbers of patients, with percentages of the total in each age group or diagnostic period between parentheses. CT indicates chemotherapy; RT, radiotherapy.
†With or without CT and/or RT.
‡*P*<.001

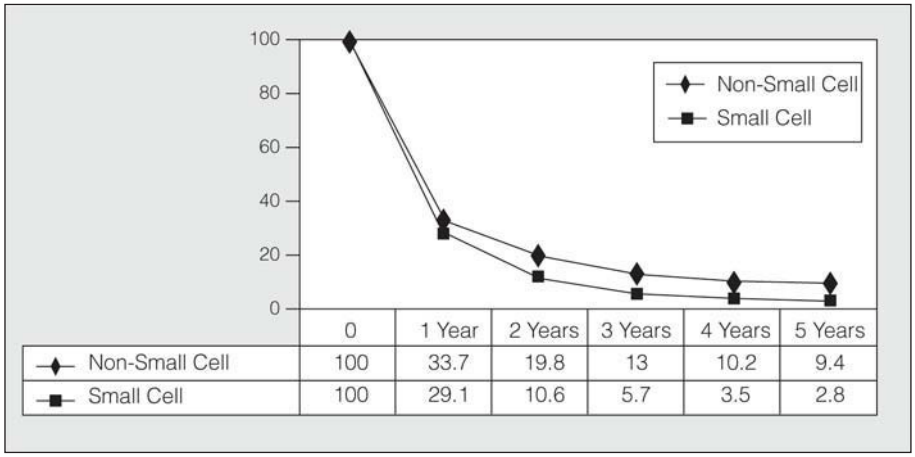

Figure 3. Survival by histologic type (*P*<.05).

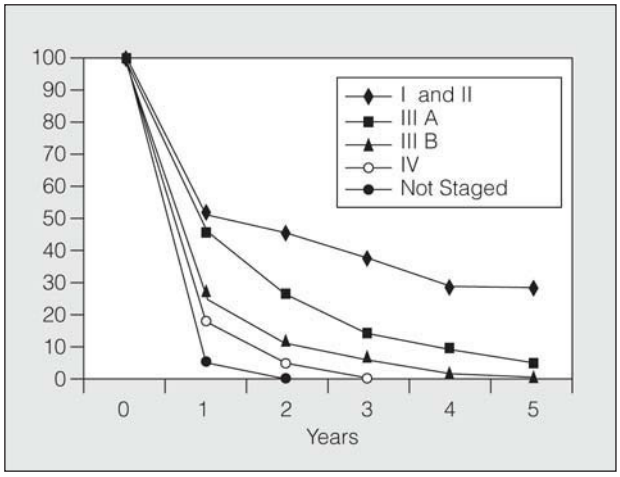

Figure 4. Non-small cell carcinoma. Survival by tumor–node–metastasis (TNM) staging. (overall *P*<.00001; between I+II and IIIA, *P*<.0001; between IIIA and IIIB, not significant; between IIIB and IV, *P*<.0001; between IV and cases not staged, *P*<.001).

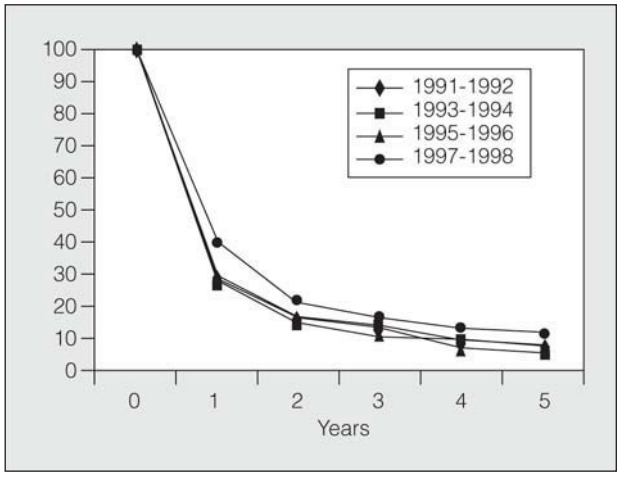

Figure 5. Survival by 2-year diagnostic period (overall *P*=.06; between 1991-1996 and 1997-1998, *P*<.01).

Discussion

The prognosis for a patient with lung cancer varies greatly in function of diverse factors. Overall survival is still very poor, however, although rates differ from study to study and by geographic area. In the United States of America, where there are epidemiologic records for most cases, the overall 5-year survival rate for patients diagnosed between 1985 and 1995 was 11% for men and 15% for women.[9] The EURO-CARE working group found clear geographic differences from one European country to another, the worst survival rate (6%) being found for men in Poland, Scotland, and Denmark, whereas the male survival rate in Holland, France, Spain, and Slovakia was 12%.[6] Survival figures for women were slightly better. The findings of the EURO-CARE study included full population statistics for some countries whereas only 20% of the data was available for others. It is therefore possible that discrepancies are due to differences in data collection methods.

More recently, a 3-year survival rate of 7% was reported for Scotland.[10,11] The authors of those studies emphasized the importance of early involvement by respiratory medicine specialists in lung cancer, and their opinion was seconded in an accompanying editorial[12] based on the argument that a pneumologist's involvement increases the likelihood of cytohistologic confirmation of disease, more precise staging, and increased survival.

Our aim has been to determine survival rates in a large series of unselected patients that we consider to be fairly representative of lung cancer cases in our region, although the number of cases lost (12%) and not included in the analysis might have changed the findings we report. We have been unable to gather sufficient data to determine whether the lost patients included a higher percentage of advanced-stage cases or patients with comorbidity, although it is reasonable to suppose that that was the case.

The overall survival of 7.9% we observed at 5 years, although quite poor, is within the range of figures mentioned above for other European countries. Small cell cancer had a clearly worse prognosis than non-small cell cancer (2.8% and 9.4%, respectively), undoubtedly in relation to the great differences between these two disease classifications with regard to possibility of surgical treatment (0.6% and 24.9%, respectively; Table 3). A study carried out in Asturias, Spain,[12] based on population registers of tumors, reported survival rates for small cell and non-small cell tumors of 6.4% and 11.2%, respectively. The better survival rate in the Asturian study in comparison with ours might be attributable to a difference in the percentage of cases lower than stage IV (classifiable mostly as limited disease), although the difference may also be attributable to the fact that the Asturian study was population-based, with the participation of many more hospitals, as well as to their exclusion of 25.7% of the registers because of missing information. Comparison is therefore difficult. Another study from Guipuzcoa, Spain, that was also based on tumor registers,[7] reported overall survival to be 12.5%, although that study focused mainly on incidence and histologic type, with no reporting of treatment type, follow up, or number of cases included in the survival analysis. In yet another Spanish study, of a series of 118 hospital cases in Castellón diagnosed between 1993 and 1997, Miravet et al[13] reported overall survival to be 7.6%, a figure that came close to our observations.

Although some small progress has been made in lung cancer treatment, long-term survival rates still depend very much on the detection of surgically treatable cases in which the tumor can be fully resected. Geographic differences in the percentage of surgically treated cases are also marked, although bias from data collecting methods may be greater for this variable given that the

total number of patients on which percentages are calculated is subject to many conditions such as geographic area, type of population, nature of the treating hospital, and others, and these variables are not always explained in the published articles. In the United States, however, the rate of surgical resection held steady from 1985 through 1995 at 27% based on the National Cancer Data Base,[9] and that rate is clearly higher than the figures for European countries, where the rate of interventions has ranged from 10.7% in Scotland (1995)[10] to 20% in Finland (1990-1992).[14] Several recent Spanish series of unselected cases have reported surgical intervention rates to be 19.5% for non-small cell cancers (Asturias[15]), and for all lung cancers 23% (Castellón[13]) and 17% (including neoadjuvant treatments, in La Coruña[16]). Our hospital's rate of 19.3% for all cases and 24.9% for non-small cell cancers, although very similar to the rates of other Spanish areas and superior to the rates of some European countries, continues to be less than desirable. Increasing the treatment rate should be one of the priorities if the overall prognosis for lung cancer is to be improved.

Apart from patients undergoing surgery, whether associated or not with adjuvant treatments, many patients received chemotherapy, radiotherapy, or both (Table 3), although 32.6% of our patients were given only palliative care (6.4% of the cases with small cell cancer and 40.5% of those with non-small cell cancer. Other Spanish hospital studies have produced similar findings,[14,16] and the rates have been even higher when population databases have been used, such as in the Asturian study of 1992, where 49.4% of patients with non-small cell cancer and 23.5% of those with small cell cancer received only palliative care.[12] In Scotland, 43.2% of patients diagnosed in 1995[10] received no active or radical treatment. These data differ markedly from the 19% reported in the United States for the same year 1995.[9] It is useful to point out that after that year, which saw the publication of an extensive and detailed meta-analysis whose conclusions favored the use of chemotherapy,[17] the European approach became more active with regard to the medical treatment of lung cancer, particularly non-small cell cancers. Given that the effect of such treatments on survival is very modest overall, we should expect a slight increase in the percentage of short-term survivors (1 or 2 years). Our analysis of the trends in our case series over the 8 years of study allowed us to observe that survival improved for patients diagnosed in the last 2-year period (1997-1998), the effect was particularly evident for 1-year survival, which was 40.8% (in comparison with approximately 29% for the previous 2-year periods (Figure 5). This slight, though significant, improvement corresponded to more frequent application of active treatment.

We reported earlier on a trend for the average age of lung cancer diagnosis to increase,[3,4] and it can be foreseen that the trend will keep pace with the gradual aging of the Spanish population. In the present study we have seen that the older patients (>70 years) are diagnosed in early stages more often than young patients, especially in cases of small cell lung cancer. Nevertheless, they were less often treated using radical approaches, probably due not only to age per se but also to a much higher rate of severe comorbidity which was not analyzed in the present study. As lung cancer is usually the cause of death in patients who have the disease, the shorter survival of the elderly may be a result of the more conservative therapeutic approach as well as of other circumstances. In an earlier study we analyzed survival in patients with small cell lung cancer by age, finding that nearly all patients were treated with chemotherapy and the worst survival rates were seen for the youngest (<50 years).[18]

We have also analyzed the relation between TNM stage in non-small cell lung cancers and overall survival (Figure 4). In spite of the obvious limitations of the staging procedures (clinical TNM) and the fact that we studied a general series of patients that included a mixture of surgical and nonsurgical cases, the anatomical extension preserved a strong ability to discriminate and predict overall survival. Other authors who also used clinical TNM stages when analyzing a series of patients who had not been treated also reported the prognostic power of TNM stages.[19] As occurs in any study that attempts to include all patients, we also had to include a group in whom a sufficient number of tests had not been performed to give a minimally acceptable stage diagnosis. It is not surprising that survival was even worse for the patients for whom stage was unknown (Table 1) than it was for stage IV patients (Figure 4), given that such patients were generally very elderly, in poor general health, and had serious comorbidity.

In conclusion, overall long-term survival of lung cancer continues to be very low in spite of small advances that may have been registered for short-term survival with more generalized use of chemotherapy and radiotherapy. It would be very useful, in our judgment, for primary care physicians to increase their level of diagnostic suspicion with all smokers in the hope of detecting more cases in early stages and therefore to increase the number of surgical excisions.

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