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Epidemiology of Lung Cancer in Spain and Forecast for the Future

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Lung cancer, a steadily growing problem, ranks as the first cause of tumor-related deaths in developed countries. The relation between lung cancer and smoking makes it a potentially avoidable disease. Found mainly in men, it has made alarming gains among women. The main prognostic factor is the possibility of receiving curative surgery; however, in real practice the diagnosis usually comes when the disease has reached an advanced stage, when only 20% can be treated surgically. Nonsurgical treatments based on chemo- and radiotherapy have not advanced appreciably in recent years, and 5-year survival is poor, estimated at only around 7% to 12% in Spain. Attempts must be made to improve preventive measures and early diagnosis in order to improve the prognosis for lung cancer patients.

Key words: *Cancer. Lung. Spain.*

Situación epidemiológica y pronóstica del cáncer de pulmón en nuestro medio

El cáncer de pulmón es una enfermedad en permanente crecimiento, es la primera causa de muerte de origen tumoral en los países desarrollados. Su asociación con el tabaco hace de ella una enfermedad potencialmente evitable, presenta un claro predominio en varones, pero con un alarmante incremento en mujeres. Su principal factor pronóstico es poder recibir un tratamiento quirúrgico con intentos curativos; sin embargo, la realidad nos dice que el diagnóstico se suele realizar en fases avanzadas de la enfermedad, cuando sólo un 20% de los casos puede ser intervenido. Con los tratamientos no quirúrgicos, basados en quimioterapia y radioterapia, no se han observado significativos avances en los últimos años. Presenta una pobre supervivencia a los 5 años, que en nuestro medio se encuentra en un escaso 7-12%. Deberemos intentar mejorar las medidas de prevención y su diagnóstico precoz para mejorar el pronóstico final de esta enfermedad.

Palabras clave: *Cáncer. Pulmón. España.*

Introduction

Lung cancer has the sad distinction of being the most prevalent neoplastic disease in developed countries and the first cause of tumor-related deaths. Although lung cancer predominates in men, it ranks as the first cause of death from neoplastic diseases among women in the United States of America. Poor progress in the reduction of smoking addiction worldwide, the rise in the number of female smokers, the difficulty of implementing effective early detection programs, and scarce progress in treating patients ineligible for surgery do not allow us to forecast a particularly hopeful future in relation to this disease.

In Spain, as in other countries, lung cancer is the most common tumor, still found mainly in men, and the one with the highest mortality.[1] According to data published by the Spanish National Institute of Statistics, lung cancer is clearly advancing, shown by mortality rates that have now doubled since the 1980-1982 period and by a 15% increase in comparison with the decade of the 1990s (Table 1).[2] Furthermore, although the prevalence has started to decrease among men in countries like the United States, it is still rising in Spain. Even though smoking has decreased appreciably here in recent years, particularly among men, we will have to wait more than a decade before the prevalence of lung cancer will start to decline. Furthermore, the rising incidence expected in women means that the overall short- and medium-term prevalence rates will rise.

Incidence Rates for Lung Cancer in Spain

The incidence of lung cancer in Spain varies somewhat among the series described in the literature, but a steady increase is evident (Figure 1). Although figures may be skewed in some cases because of problems with data source reliability (tumor registers versus medical death certificates) or lost or unavailable data, particularly for patients transferred to other hospitals or health care regions, the rates tend toward similarity. Moreover, figures gathered systematically by some authors or for certain areas based on similar case

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finding methods[3-5] yield similar annual incidence rates that are consistent with those reported for other regions. The overall message conveyed by published data is that the passing years have seen a gradual increase in the number of patients diagnosed with lung cancer.[3-5]

As in other countries, the percentage of male lung cancer patients is high in Spain. The rate is always above 85% and sometimes exceeds 90% to 95%.[6-10] Recent analyses have detected a clear trend toward a higher incidence in women.[4,5]

Age at onset of symptoms is similar in all series at 63 to 67 years.[3-10] It is noteworthy that in all reports the disease presents at an older age in men than in women and the difference is significant in some series.[7] Also noteworthy in some studies is a high percentage, around 50% (range, 42%-52%) of patients over the age of 70 years.[5,6]

Smoking is also the main risk factor for lung cancer in Spain. The percentage of smokers among these patients is extremely high: over 95% of male lung cancer patients smoke and the rate reached nearly 100% in the 1992-1993 series for the city of Avila.[5] The rate is lower in female patients, although it has increased markedly in recent series (to 23.08%, 38.4%, and 44% in different series[5,6,8]) in comparison with an older series (6.1%).[3] Recent years have seen smoking addiction decline considerably in Spain, but based on the lag time observed in other countries between a fall in the rate of smoking and the start of a reduction in the incidence of lung cancer, we must still expect the rates to continue rising for at least 10 to 15 years longer. Only after that, and if the prevalence of smoking addiction falls, will we see a reduction in the incidence of lung cancer. From the current perspective, we will probably first detect the reduction in men, while the incidence rises in women. Later, the fall in incidence rates will also reach women.

No detailed analyses of the influence of other environmental or occupational factors besides smoking are available. Nevertheless, studies have found that 16.3% of patients report workplace exposure to carcinogenic substances in Extremadura,[11] and overall incidence rates for shoe industry workers have been estimated for Alicante.[12] This issue is important, given that occupational exposure to substances such as arsenic, asbestos, or polyaromatic hydrocarbons is related to nearly 18% of lung cancer cases. It would be very useful, therefore, to collect information systematically on work history and exposures to substances and known carcinogens both for the purpose of properly assessing their influence on the development of the disease and for implementing complementary measures to reduce the number of new cases.

Histologic Characteristics of Lung Cancer in Spain

Unlike the United States, where the most common histologic type of cancer is now adenocarcinoma,[13] Spain continues to see more cases of squamous cell cancer. A significant decrease in the rate of epidermoid carcinomas has been noted in recent years, however, and there may also be a fall in the prevalence of small cell cancers as the rate of adenocarcinoma rises. It has been suggested that this trend may be due to the decline of smoking among men, as there is a stronger correlation between smoking and squamous cell or small cell cancers. Furthermore, the systematic use of low-nicotine and filtered cigarettes has led to changes in the pattern of tobacco consumption, as those products are associated with deeper inhalation by smokers wanting to achieve high nicotine levels. As a consequence, carcinogenic substances reach deeper areas of the lung. Moreover, as women have become smokers, the higher rate of adenocarcinoma in this population has contributed to a higher incidence of this tumor.[14] This new trend has already been confirmed in both Europe and the United States.[15,16] In the parts of Spain where the incidence rates have been studied systematically,[3-6] these trends for squamous cell carcinoma and adenocarcinoma can also be discerned (Figure 2).

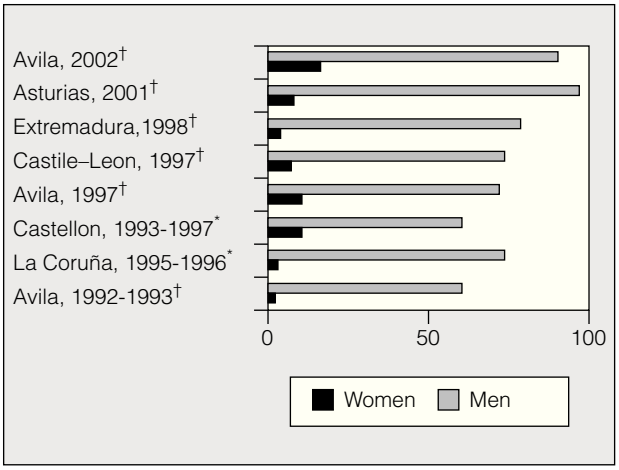

Figure 1. Incidence rates published for the different areas of Spain (crude rate per 100 000 population). Data collection: *, hospital records[3,4,7]; and †, provincial or Spanish autonomous community records.[5,8,9,11] Data are ordered by year when data collection was funded.

Lung Cancer Diagnosis in Spain

The diagnostic technique used in most studies is bronchoscopy. However, there is a trend toward greater use of computed-tomography–guided transthoracic

TABLE
Number of Cases and Annual Incidence Rates by Sex

	1980-1982	1992	2001
Men			
Mean age, y	66.48	67.57	69.22
Cases	8193*	13 636	16 218
Rate per 100 000 population†	44.24	71.39	82.29
Women			
Mean age, y	68.55	70.35	68.68
Cases	1164*	1395	1948
Rate per 100 000 population†	6.06	7.01	9.48

*Yearly average
†Estimated annual crude rate per 100 000 standard population Source, Spanish national statistics institute and statistical bulletins on death records Code CIE-10, C33-C342

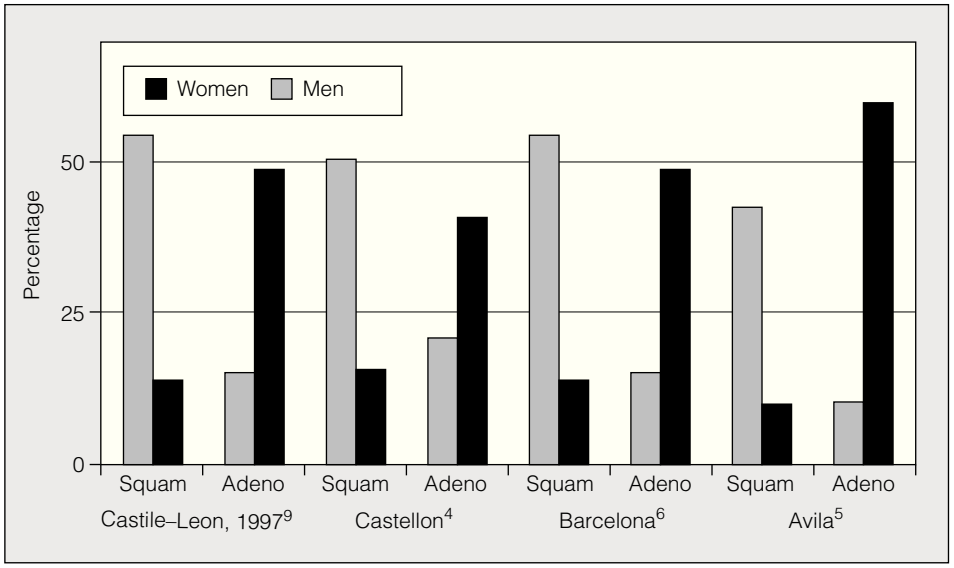

Figure 2. Relation between sex and histologic type (squamous cell carcinoma [Squam] and adenocarcinoma [Adeno]).

needle aspiration. As pneumologists, we must insist on the advantages of bronchoscopy, as it provides more precise information about central involvement when surgery is under consideration. Moreover, bronchoscopy gives more precise information about the degree of response to local chemo- and radiotherapies. Whereas needle biopsy obtains cytology samples, bronchoscopy provides tissue samples for histology, which can help with more precise decisions regarding certain recent chemotherapies. It is also more widely available, reducing diagnostic delay.

The percentage of patients with a diagnosis of lung cancer unconfirmed by histology or cytology is somewhat variable in Spain. The figures change according to type of study or data collection method. Circumstances as diverse as the role played by the pneumologist in diagnosing the disease, the age of the patient,[5] or the presence of active comorbidity can affect the rate of unconfirmed diagnosis. If we analyze findings for our practice setting, we see no significant change in the percentage of diagnoses based on clinical and radiologic evidence since the end of the 1990s (7.8%-13.7%)[7,9,11] through the first years of this decade (3.3%-13.2%).[4-6] Our percentages are lower than those published for other European countries,[16-18] although they are higher than those for some series from the United States.

One of the most important prognostic factors is stage at the time of diagnosis. The stage of the disease has a decisive influence on curative operability and, therefore, a chance at longer survival. Stage of disease is also an important determining factor when considering a palliative treatment, particularly when the patient is elderly or has severe concomitant disease.

Twenty-two percent of patients with non-small cell lung cancer had only localized disease in a study by Santos-Martínez et al[6]; that percentage was unchanged from historical data. On the other hand, regional involvement increased from 11.7% in the historical series to 35.7% and there was a significant decrease in the percentage of patients with disseminated disease (from 65.9% to 42.5%). Recent studies seem to show a rise in the number of cases with localized disease in comparison with the frequencies found by Santos-Martínez and colleagues. Thus, the frequency of stage I disease found was 27% in a study by Alonso-Fernández et al[8] and 37.1% in data published by Miravet et al,[4] although Sánchez de Cos Escuín et al[10] reported that only 26.2% of non-small cell cancers were found to be in stages I or II in their series. The rate of metastasis at the time of diagnosis has ranged from 22.6% in Cáceres[10] to 42.5% in Barcelona.[6] If non-small cell carcinomas are grouped together with locally extended tumors and disseminated disease (IIIB), variation is less, ranging from 46.6% to 53.5%.[4,8,10] More than half the cases of small cell carcinoma are disseminated at the time of diagnosis.[4,10]

Lung Cancer Treatment in Spain

Currently, medical oncologists and oncologic radiotherapists are the specialists who treat most nonsurgical cancer patients in Spain. While pneumologists diagnose and stage the disease, they do not often take part in therapeutic decision-making or follow-up. It is surprising that only slightly more than half (51%) of pneumology departments or units show interest in taking a more comprehensive approach to lung cancer treatment, including administration of chemotherapy. Even more surprising, only 17 respiratory medicine departments in Spain administer chemotherapy.[19] Studies have shown that patients benefit when pneumologists take a prominent role in diagnosing lung cancer,[17,20,21] and their participation can perfectly well be extended to all aspects of treatment and follow-up of our patients. It is worth noting that most of these patients are smokers and they often have associated respiratory diseases. Furthermore, respiratory

complications will almost certainly present at some time during the course of lung cancer, and the pneumologist's perspective should be sought. For these reasons, it is the pneumologist who should play the most active role in hospitals where specialists who usually treat lung cancer are not present, as it is unusual to find patients transferring from primary or secondary level care to tertiary level hospitals for nonsurgical treatment. Likewise, it would be desirable for pneumology departments to play a wider role in therapeutic decision-making and follow-up after diagnosis in those hospitals where oncology units are available.

Surgery

The treatment of choice for lung cancer is surgery, but only a small percentage of patients—between 21% and 25%—are so treated. This may be one of the most important prognostic factors related to 5-year survival. The most recent 5-year survival figures in selected, nonsurgical series in Spain are around 7%,[4,10] very much lower than in the United States.[15]

Patients undergoing surgery in the period 1985-1995 accounted for 27% of cases in the US, whereas European rates were slightly lower.[22,23] The percentages in Spain exceed those of other nearby countries and approach the US figures: 17% in La Coruña,[7] 19.5% in Asturias,[8] 23% in Castellon,[4] and 24.9% in Caceres.[10] We can say that around 20% of diagnosed lung cancers are treated surgically and in the case of non-small cell carcinomas, where surgery is most strongly indicated, the percentage operated ranges from 23% to 25% in some series[7,10] to 31.4% in a more recent one.[5] Survival in different surgical series depends largely on patient selection,[24] mainly based on staging at the time of operation. Thus, 5-year survival rates of 78.63% have been described for stage I cancers[25] and 39.8% for stage II.[26] Series reports do not always describe whether the cause of death was tumor-related or due to other events not directly related, however, and other causes can account for as many as 40% of deaths.[25] The most common causes of death for patients treated surgically at early stages are related to the development of metastasis or a second carcinoma.

Surgical teams continue to debate certain issues,[27] such as the practice of systematic radical lymph node dissection in early stages of disease, segmenal resection in stage IA, the use of adjuvant chemotherapy in stages I and II, and finally, neoadjuvant treatment and postoperative adjuvant treatment in stage III.[28-31] The prognosis in surgical cases has been correlated with invasion of more than 1 lymph node, a non-squamous cell tumor, and tumor size[25,32,33] in early stages. In the always controversial and heterogeneous stage III tumors prognosis has been linked to response to induction chemotherapy.[29,30]

Chemotherapy

Experience tells us that most patients with lung cancer are not candidates for surgery at the time of diagnosis, whether because the tumor has spread locally or because disease is disseminated. Alternative treatments must be considered in such cases, though the chances of survival are lower.

In recent years, chemotherapy for lung cancer has changed only very little, mainly with regard to better tolerance and a lower rate of side effects. Progress in long-term survival has been unremarkable. In spite of very modest outcomes, there has been a tendency to use chemotherapy more often in lung cancer patients, particularly after the 1995 publication of a meta-analysis demonstrating the clinical benefits of chemotherapy or other treatments in comparison with conservative approaches.[34] In a study by Hernández Hernández et al,[5] the percentage of patients receiving only chemotherapy or chemotherapy associated with radiotherapy doubled between 1992 (18.5%) and 2002 (43.6%). Published reports of the use of chemotherapy show that rates currently range from 32% to 44.4%.[4,5,7,8,10] These figures underline the need for Spanish pneumologists to update their knowledge in this respect, and in fact, the management of chemotherapy has been included in the new curriculum for residents in our specialty. Only with such knowledge can the pneumologist achieve a more complete, active approach to lung cancer treatment. We consider that such a change would be beneficial for both patients and pneumologists and their departments. Some Spanish respiratory medicine departments have been systematically administering chemotherapy for lung cancer for several years with good results, similar to those reported by other authors and with full acceptance by patients. According to Sampablo and Izquierdo,[19] over half of pneumology departments surveyed were willing to initiate chemotherapy for lung cancer with protocols provided and recommended by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Although chemotherapy has become less toxic, its application requires knowledge of indications, pharmacological characteristics of the drugs, and their potential side effects as with any other drug treatment.

Radiotherapy

Induction radiotherapy with intent to cure is the modality least often applied in lung cancer. Its use ranges from 3.6% to 14% in different series.[4,5,10] Induction radiotherapy is often used in combination with chemotherapy, concurrently or sequentially, usually administered as standard or hyperfractionated irradiation. Combined treatment seems to improve disease-free survival, but not the incidence of metastasis.[35]

Palliative Treatment

The percentage of lung cancer patients receiving palliative treatment, including palliative radiotherapy, has been declining in recent years. In spite of factors such as age, the stage of disease upon diagnosis, and the

presence of comorbidity, palliative treatments have declined significantly. In successive studies of a single public health care area, the reduction has exceeded 30%.[5] The rates of palliative treatment in Spain range from 26%[7] to 32.6%[10] and are clearly lower than those observed in some European studies.[17] The variables that are most highly associated with palliative treatment are advanced age, the presence of active concomitant disease, and a diagnosis based on clinical or radiologic signs[5,7,18] rather than confirmation of locally advanced or disseminated disease at the time of diagnosis. There has therefore been a clear trend in the last 10 years toward active treatment of these patients with lung cancer who are not surgical candidates: underlying the trend is evidence for the usefulness of combined treatments[34] and a change in physicians' attitudes.

Lung Cancer Survival in Spain

Overall long-term survival depends on curative operability, implying early clinical or radiologic stages and more favorable patient characteristics (age, lung function, and comorbidity). Survival differs in different studies; certain surgical series include selected patients[24-26] whereas others are unselected.[10] Taken together, they allow us to form a picture of the real overall survival pattern for this disease. Surgical series have clearly superior survival rates in function of both disease stage and general patient condition. These reports provide only a partial view, according to spread of disease. Published 5-year survival rates of 81.4% for stage IA,[24] 78.6% for stage IA and IB together,[25] and 39.8% for stage IIIB[26] are similar to figures for other non-Spanish series.[27,36] Perioperative mortality ranges from 1.8% to 2.7% for selected patients.[24,26] Deaths from causes unrelated to the tumor for early stages range from 24% to 39.2%.[24,25] Tumor size, the involvement of more than 1 lymph node, and type other than squamous cell carcinoma have been associated with poorer survival.[26,37] In contrast with such promising statistics is the survival for unselected patient series, which include all stages and clinical characteristics. In such series, survival rates are lower. These series are also subject to biases and variations, such as in the percentages lost to follow-up or the percentages treated surgically or given active chemotherapy or radiotherapy in contrast with the percentage afforded palliative care. A study by Alonso-Fernández et al[8] found survival was 82% at 3 years and the median survival was 36.4 weeks. Those authors had a patient series in which 9% of cases were non-small cell carcinomas and 5.5% were small cell tumors. Studies extending follow-up to 5 years in unselected series have reported survival rates under 8% (7.2%-7.9%).[4,10] Those rates contrast with observations by Rezola Solaum et al[38] in Guipúzcoa and are clearly below those reported for other parts of Europe[39] or for the United States.[13] The factors that exercise the greatest influence on survival in these series are curative operability and disease stage at the time of diagnosis.

We can conclude that there are several aspects of lung cancer on which we should focus our effort: a steady and more effective fight against smoking with the aim of reducing the incidence of disease, implementation of more effective protocols and techniques leading to earlier detection so that the rate of curative surgery can improve, and a more active approach in locally advanced or disseminated disease where the pneumologist should undertake to integrate all treatment possibilities throughout the course of disease.

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