Review Article

Lung Cancer in Spain. Current Epidemiology, Survival, and Treatment

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ABSTRACT

In 2005, 19 115 people died of lung cancer in Spain. In spite of the increase in absolute mortality rates since 1950, the adjusted rate for men has declined. The incidence among women is lower in Spain than in other countries but it has increased (with a ratio of 1 woman for every 8.5 men). More than 50% of the patients are over 70 years of age. While the proportion of adenocarcinomas relative to other histological types has increased worldwide, squamous cell carcinoma still predominates in Spain (ranging from 24%-50.5%). The number of patients treated by surgical resection has not increased (14.8% in Spain in 2003). Operative mortality is 6.8%. Between 25% and 50% of patients receive only palliative medication. Absolute overall survival in patients with lung cancer is under 10% in many countries. The 5-year survival rate among patients treated surgically has increased slightly, with stage IA rates ranging from 58.3% to 68.5% and stage IIIA from 28.3% to 35.8%.

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El cáncer de pulmón en España. Epidemiología, supervivencia y tratamientos actuales

RESUMEN

En 2005 fallecieron 19.115 personas por cáncer de pulmón en España. Pese al aumento de las cifras absolutas de mortalidad desde 1950, las tasas ajustadas en varones han disminuido. La incidencia en mujeres, inferior a la de otros países, ha aumentado (1 por cada 8,5 varones). Más del 50% de los pacientes tienen más de 70 años. La proporción de adenocarcinomas ha aumentado en el mundo, aunque en España la estirpe epidermoide es predominante (24%-50,5%). Las resecciones quirúrgicas (14,8% en España, en 2003) no han aumentado. La mortalidad operatoria es del 6,8%. Un 25-50% de los pacientes recibe sólo medicación paliativa. La supervivencia absoluta global del cáncer de pulmón es menor del 10% en muchos países. Entre pacientes resecados, la supervivencia a los 5 años (estadio IA: 58,3-68,5%; estadio IIIA: 28,3-35,8%) ha aumentado ligeramente.

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Table 1
Lung Cancer Deaths in Spain, Evolution 1980-2005

<table>
<thead>
<tr>
<th>Region or Province</th>
<th>Study Period</th>
<th>Men</th>
<th>Gross Rate</th>
<th>Women</th>
<th>Standardized Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>La Coruña</td>
<td>1995–1996</td>
<td>73.7</td>
<td>3.0</td>
<td>37.1</td>
<td>12.1</td>
</tr>
<tr>
<td>Vinaroz (Castellón)</td>
<td>1993–2002</td>
<td>71.7</td>
<td>9.3</td>
<td>40.0</td>
<td>13.3</td>
</tr>
<tr>
<td>Asturias</td>
<td>2001</td>
<td>96.3</td>
<td>7.6</td>
<td>53.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Avila</td>
<td>2002</td>
<td>89.9</td>
<td>15.9</td>
<td>39.8</td>
<td>14.9</td>
</tr>
<tr>
<td>Orense</td>
<td>2003</td>
<td>105.9</td>
<td>23.4</td>
<td>38.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Torrelavega (Cantabria)</td>
<td>2003</td>
<td>85.7</td>
<td>11.2</td>
<td>43.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Extremadura</td>
<td>2003</td>
<td>107.3</td>
<td>4.5</td>
<td>61.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Source: Instituto Nacional de Estadística. 1

*Number of deaths and percent increase with respect to the total number of deaths in the year shown in the preceding column.

Introduction

Lung cancer still ranks as the leading cause of tumor-related death in the world and is one of the respiratory diseases with the highest mortality. In recent years, changes have been observed in certain basic epidemiological parameters, such as distribution by age, sex, and histological type. Other aspects, such as clinical presentation, treatment strategy, the risks of surgery, overall survival, and waiting times for treatment, have changed very little, although there are still marked differences between studies and authors, in large part attributable to differences in the study methods used. The aim of the present review was to summarize in numbers the variations observed which included hospitals in 9 regions in Spain. Studies like these confirm the increased lung cancer incidence among women, a trend that is already very pronounced in some areas.

Epidemiology

Mortality in Spain

In 2005, 19,115 people (16,445 men and 2,670 women) died of lung cancer in Spain. Although there has been a transient increase in absolute mortality, the downward trend is evidenced by the decline in the percent increase from 29.4% in the 5-year period between 1980 and 1985 to 5.1% in the period between 1995 and 2000 (Table 1). The slight upturn (+10%) during the last 5-year period (2000-2005) must be viewed in the context of the sizeable and rapid increase in the Spanish population caused by massive immigration. Taking recent demographic trends into account (the rapid aging of the indigenous population and the increase in the overall population caused by the recent large scale incorporation of immigrants), it can be easily determined that the adjusted incidence rates—which correlate closely with mortality rates—have begun to decline, at least in men. This phenomenon is reflected in some of the recent studies carried out in Spain. 2-4 It appears, therefore, that the uninterrupted increase in the incidence of lung cancer that started in the middle of the last century has finally come to an end and that Spain has now, although with some delay, joined the group of Western countries (USA, Canada, United Kingdom, Sweden, etc) that some years ago were the first places where the incidence of lung cancer first stabilized and then started to decline.

Incidence

The results of various studies on the incidence of lung cancer in Spain have recently been reported. Most of these studies were regional or provincial in scope, 4-6 with the exception of the EpicliCP-2003 study, 7 which included hospitals in 9 regions in Spain. Some of the variations observed can be attributed to differences in the characteristics of the studies themselves, but the results also revealed discrepancies between the regions even when the same methods were used (Table 2). Studies like these confirm the increase in lung cancer among women, a trend that is already very pronounced in some areas.

Age and Sex

While incidence has always been lower among women since the start of the lung cancer epidemic, the worldwide trend in recent years has been towards convergence, and the current male-to-female ratio in the USA is close to 1. 10 A number of statistical analyses and interpretations of large databases of cases of lung cancer have recently been published. It is clear that, in the non-smoking population, the incidence of lung cancer is higher among women, 11-13 Moreover, recent findings also suggest that women may be somewhat more susceptible to the carcinogenic effect of tobacco, 14,15 although this remains a matter of debate. 16-21 In Spain, the ratio of males to females with lung cancer is still high, although less so than in the...
past. In terms of mortality, the male-to-female ratio has been declining since 1995 (Table 1). With respect to incidence, the authors of a recent Spanish multicenter epidemiological study (EpicliCP-2003) found marked differences between regions in this ratio, probably attributable to small differences in the timing of the massive incorporation of women into the smoking population. The male-to-female ratio is still substantially higher in males in several European countries, accounting for 37% in France, 44% in Poland, and 45% in Holland in the period between 1993 and 1997. In Spain, squamous cell carcinoma is still the most common subtype: 37.7% on average in the EpicliCP-2003 study and percentages varying between 24% and 50.5% in local and regional registries. Nonetheless, small cell lung cancer still accounts for some 20% of cases in most Spanish registries.

### Clinical Presentation

#### Asymptomatic Patients. Trends

In the first place, we must specify that in this section we are not talking about patients whose lung cancer is diagnosed in the course of population screening, in which case, ideally, 100% would be asymptomatic. We are referring to patients undergoing tests for a variety of reasons (preoperative examinations, suspected cardiac or respiratory disease, etc), who may have symptoms that the physician who diagnoses the lung cancer does not attribute to this disease. In such cases, the cancer is diagnosed fortuitously, usually as a result of the discovery of an abnormality in a chest radiograph. In such cases, it should be remembered that, although the lung cancer may be classified as clinically silent or asymptomatic, this is in general a diseased population or a population with comorbidities and a very different cohort to the healthy population that typically participates in population screening programs. The percentage of patients with no symptoms on diagnosis (5% in the USA in 1985 and 1.3% in Caceres, Spain in 1987) has increased substantially. In a study carried out in 2000 to compare 2 European regions, in England and 1 in Italy, lung cancer was asymptomatic in 7% and 21% respectively of the patients diagnosed. A steady increase in this percentage has been observed in the Extremadura region of Spain, where it has gone from 1.3% in 1985 to 11.5% in 1998 and 18.1% in 2003. This trend probably reflects a more active diagnostic approach characterized by the performance of more tests, especially chest radiographs, particularly in older patients. However, it is impossible to rule out the possibility that this trend may be influenced by the more indolent progression of the disease in an older population.

#### Comorbidity

Although there are reasons to suppose that comorbidity has increased, it is difficult to analyze trends or to compare the results of different studies because of differences in the way the data were collected and recorded. Some authors supply incomplete details...
about concomitant diseases and conditions and others limit themselves almost exclusively to reporting cardiac and respiratory disease. Furthermore, while some report concomitant disease in detail, others use scores that summarize comorbidity by way of a point scale (such as the Charlson index). In the Epiclip-2003 study, 81.7% of the patients diagnosed had comorbid disease, a somewhat higher percentage than that reported in other European registries (Table 3). In all registries, cardiorespiratory diseases were the most common comorbidities.

### Lung Cancer Screening

Unlike the case of other common cancers, there is still no evidence to support the usefulness of screening to reduce lung cancer mortality. Current evidence does not support the usefulness of screening with chest radiography or sputum cytology, and the results of large randomized trials assessing the effectiveness of low-dose radiation computed tomography have not yet been published. An observation of interest with respect to the many (mostly nonrandomized) studies that have analyzed the results of screening with computed tomography is the high percentage of images giving rise to a positive finding or a suspicion of malignancy (between 5% and 51% of imaging studies) (Table 4) although the percentage of confirmed cases of lung cancer (prevalence) following this initial examination is in the region of 1%. Incidence (cases detected during follow-up) was somewhat lower. Bach et al calculated the incidence per 1000 person-years to be between 10.3 and 20.4. Most of the cases of lung cancer detected during screening are in the early stages and are resectable. However, there is no evidence to date of any decrease in lung cancer mortality in screened populations, and the practical problems involved include the high rate of false positives (between 22% and 36% of the patients who undergo thoracotomy procedures)

### Treatment Strategy

#### Resection Rate

While the proportion of patients diagnosed with lung cancer who undergo surgery is an important statistic for assessing the quality of health care systems and patient care, it is very difficult to obtain reliable data because many authors still fail to provide sufficient detail. Comparisons between different countries and regions are affected by the so called “denominator problem,” a difficulty identified some time ago. The SEER (Surveillance, Epidemiology, and End Results) data in the USA exclude patients whose diagnosis was not confirmed by cytology or histology. Consequently, the high resection rate reported in the USA (27%) cannot be compared with the rate obtained using population-based studies in the European countries that try to include all patients diagnosed with lung cancer irrespective of such confirmation (Table 5). The resection rates for Holland (20%), Finland (20%), and Scotland (10%) probably offer a more reliable picture of the true situation. In a recent population-based study that analyzed data from 2 small European regions (1 in Italy and 1 in England) using identical methodology, the rates were 24% and 7%, respectively. The resection rate was 14.8% in the Spanish Epiclip-2003 study, which included all patients irrespective of whether diagnosis was confirmed by histology or cytology and all histological types (small cell and non-small cell lung cancers). Although it is difficult to identify trends because of the methodological differences mentioned above, it appears that the resection rate has not only failed to increase in comparison to previous years, but may in fact have decreased. In some areas of Spain, the rate has decreased slightly, a trend that could be attributed to the high comorbidity associated with advanced age and, perhaps, to the more selective criteria currently used by thoracic surgeons to select candidates for surgery.

### Postoperative Mortality

In general, most authors define postoperative mortality as death occurring within 30 days of the surgical intervention. One broad review of global postoperative mortality reports percentages ranging from 1.3% in Japan to 8.6% in the USA. More uniform figures have recently been reported in analyses of large case series in various countries: 4.1% in the USA according to the American College Of Surgeons, 4.4% in Norway, and 6.8% in Spain according to the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (GCCB-SEPAR). However, as Duque et al indicated, postoperative mortality rates are closely associated with patient-related factors, especially preexisting comorbidity (although male sex and advanced age are also associated with a significant adverse prognosis), and the type of surgery undertaken—figures reported for postoperative mortality were between 3.2% and 16.7% for pneumonectomy and between 1.2% and 7% for lobectomy. In the GCCB-SEPAR study, postoperative mortality was 12.3% for pneumonectomy, 4.3% for lobectomy, and 2.5% for minor resection. The origin of the sample studied is also an important factor, since in national registries, such as that of Norway, interhospital mortality varied from 0% to 12%, percentages that coincide almost exactly with the figures reported in Spain by the
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coverage of registries), the inclusion criteria (particularly with respect to the inclusion or exclusion of cases not confirmed by cytology or histology), the percentage of cases lost to follow-up, and so on. Some authors provide details about the methods used.\textsuperscript{76-79} Table 5 summarizes data relevant to the correct interpretation of overall survival statistics. It is also worthwhile emphasizing the possible confusion that may arise from differences in the presentation of data: sometimes (particularly in very large national cancer registries) the figure reported is relative survival, a rate obtained by dividing the absolute survival of the patients with lung cancer by the survival for a group of the general population having a similar structure in terms of age and sex.\textsuperscript{10,29} Since lung cancer is a disease that particularly affects older people, the differences between absolute and relative survival can be considerable.\textsuperscript{77,78} Comparisons between hospitals and regions are rendered more difficult by all these differences in the methods used. However, it has been possible in some countries (USA),\textsuperscript{31} regions (Oulu, Finland),\textsuperscript{32} and hospitals (Hospital San Pedro in Caceres)\textsuperscript{33} to distinguish trends over time, and the trend observed in all of these studies has been an increase, albeit very slight, in the overall survival rate. As can be seen in Table 5, overall survival at 5 years, expressed in absolute terms, does not reach 15% in any country (the 15.7% rate cited for the USA refers to relative survival),\textsuperscript{30} and the absolute survival rate is less than 10% in many parts of Europe.\textsuperscript{24,28,30-32,54-58,79}

The life expectancy of patients who undergo surgery appears to have improved somewhat, although once again comparisons between hospitals are difficult owing to differences in the periods of time studied, the type of registry, and the data collection protocols used. Table 6 shows the results of 2 recent large case series (1 of regional scope in Germany, and the other a national study in Japan),\textsuperscript{80,81} together with the already classic and older results from Mountain (USA).\textsuperscript{34} The data on survival is shown by clinical and pathological TNM Stage.

### Table 6

<table>
<thead>
<tr>
<th>Stage</th>
<th>Overall Survival at 5 Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical TNM</td>
</tr>
<tr>
<td>I</td>
<td>61.0</td>
</tr>
<tr>
<td>II</td>
<td>36.0</td>
</tr>
<tr>
<td>III</td>
<td>34.0</td>
</tr>
<tr>
<td>IIIA</td>
<td>24.0</td>
</tr>
<tr>
<td>IIIB</td>
<td>13.0</td>
</tr>
<tr>
<td>IV</td>
<td>5.0</td>
</tr>
<tr>
<td>V</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*This percentage refers to 3-year survival.

The increase in the number of diagnostic or staging procedures and functional evaluations carried out in patients with lung cancer and the need for multidisciplinary coordination between different specialties (leading to the successive referral of patients) have contributed to more precise diagnoses, at the same time these changes have resulted in the multiplication of medical acts, undoubtedly contributing to often excessive delays in the start of treatment. Although waiting times can vary greatly—as can the ways they are measured—special importance has for many years been placed on the waiting time for surgery in candidates for such procedures. The GCCB-SEPAR\textsuperscript{83} recorded a mean waiting time of 35 days from confirmation of diagnosis to surgery in patients with stage I and II lung cancer. Cañizares et al\textsuperscript{10} recently reported a waiting time in Spain of 56.87 days between the date of first application for care and the eventual surgery. In a Manchester hospital, the median waiting time for surgery (after completion of the necessary tests) was 25 days.\textsuperscript{85} Although almost all of the studies agree that these waiting times have no effect on overall survival and that the primary factor determining survival is the innate biological behavior of the tumor,\textsuperscript{86} it is also generally agreed that it would be desirable to shorten, as far as possible, these waiting times, which at the very least cause considerable anxiety and anguish to patients and family members. In the United Kingdom, the National Cancer Plan has designated as acceptable the following maximum waiting times for lung cancer treatment: 14 days from referral by a general practitioner to first examination by a specialist; 31 days from the decision to treat to start of treatment; and 62 days from the initial referral by the general practitioner to the start of the first (or only) treatment. Researchers in the United Kingdom recently observed that while median times were similar to or shorter than the recommended targets when it was taken into account that the recommendations refer to maximum waiting times only some 50% of patients were treated within an acceptable time interval.\textsuperscript{86}

### References