Prognostic value of chronic obstructive pulmonary disease in 2994 cases of lung cancer

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Abstract

Objective: Given the frequent association between chronic obstructive pulmonary disease (COPD) and lung cancer (LC), the objective of this paper is to analyse the prognosis of this comorbidity. Methods: Multicenter prospective study compiling 2994 consecutive cases of surgically treated LC (1993–1997), the population with non-small cell lung cancer and complete resection was selected for the prognostic study of COPD. COPD is defined when the FEV1/FVC is <0.7 (n=1370; 46%). Overall and conditional survivals (survival likelihood when alive at 2, 3 or 5 years after treatment) as well as the degree of severity (FEV1% percentiles) were calculated to establish prognosis. Results: Although the overall survival is similar whether or not COPD is present (Log-rank: 0.34), the conditional survival analysis is different in every stage at 60 months (Log-rank: 0.02) and different in stage pI at 24–36 months (Log-rank: 0.04). In LC (stage pI) with COPD, the presence of a worst pulmonary function (last FEV1% percentile vs first FEV1% percentile) is a bad prognostic factor (Log-rank: 0.002). Conclusions: The analysis of conditional survival at 24 months shows that COPD can be considered as a prognostic factor and that there is a clear relationship between the severity of the condition (FEV1%) and survival.

Keywords: Lung cancer; Chronic obstructive pulmonary disease; Prognosis; Conditional survival analysis; Comorbidity; Surgery

1. Introduction

Given the well known role that tobacco plays in the development of chronic obstructive pulmonary disease (COPD), and the higher risk to suffer from lung cancer (LC) in the presence of COPD [1,2], the association between COPD and LC is clinically frequent [3].

In some cases, the functional impairment caused by COPD renders the patient inoperable [4] or makes it necessary for the surgeon to perform smaller resections, with a lower cure rate [5]. Comorbidity as a possible independent prognostic factor in surgically treated LC (SLC) [6-9] has not been analysed as frequently.

The aim of this paper is to analyse patient characteristics with and without COPD and the possible prognostic value of this comorbidity using a sample of 2994 cases of SLC.

2. Material and methods

2.1. Study subjects

All the patients included in the study had LC and thoracotomy and had been recruited from hospitals pertaining to the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). We prospectively included all patients treated surgically from October 1993 to September 1997 in hospitals participating in the GCCB-S. The annual cumulative number of cases was almost 50% of all surgical cases occurring in Spain. The participating GCCB-S centres had a wide variety of activities, including a representative range in the number of beds, teaching or research activities (university and non-university hospitals), public and private ownership, and the number of interventions per year (from 8 to 100 interventions were performed in participating centres for this disease). The sample was complete, as verified by the inclusion of all patients undergoing surgery in the registry, including incomplete resections and exploratory thoracotomy.

Operative mortality was understood to include all deaths directly related with the surgical procedure, regardless of...
when they occurred. The final number of cases included in this study was 2994.

For the objectives of this paper in terms of analysing the characteristics of surgically treated LC cases with and without COPD, the entire population was selected (n = 2994). The prognostic analysis excluded cases presenting the most potent prognostic factors (microubicotic type, no resection or incomplete resection) or factors that might confound the prognostic study (operative mortality, induction therapy). In line with several other studies on the prognosis of non-small cell lung cancer (NSCLC) that excluded these characteristics from analysis [10], our study also excluded cases with operative mortality. The number of cases for this prognostic analysis is 2051.

2.2. Methods

The same criteria for the functional operability of the patients and the oncological operability of the tumour were used in all the GCCB-S hospitals [11].

The degree of certainty of the TNM-stages classification depends on the diagnostic methods used; according to some international organizations, post-mortem study yields the maximum certainty factor and the clinical findings yield the minimum certainty factor [12].

By consensus among the members of the GCCB-S coordinating group (two thoracic surgeons and a pneumologist), we established the methods for affirming maximum classificatory certainty for each component (maximum possible clinical certainty adjusted for affirming maximum classificatory certainty for each problem) [13,14]. Lymph node categories (N) were evaluated using different diagnostic criteria of classificatory certainty. To confirm a cN0 classification, there had to be no lymph node enlargement at all or lymph node enlargement of less than 1 cm in diameter as confirmed by computed tomography in lymph node areas 4, 7 and 10 [15]. Furthermore, there had to be no lymph node enlargement in the aorto-pulmonary window or in the anterior mediastinal area (areas 5 and 6), if the LC was left-sized (superior lobule or main left bronchus). If these criteria were not met, negative mediastinoscopy- Mediastinotomy or negative fine-needle aspiration biopsy (transbronchial, transthoracic or transesophageal) of these areas was required. The cN1 classification was confirmed by cytohistological evidence (transbronchial fine-needle biopsy, hiliscopy). To confirm a cN2 classification, cytohistological evidence was required (mediastinoscopy, mediastinotomy, fine-needle aspiration biopsy using any approach).

Surgical-pathological N0 was classified by radical mediastinal lymph node dissection or sampling of at least four lymph node areas (2 only in right LC), 4, 7 and 10 on the same side as the tumour), especially in pT3 [14]. This criterion is similar to that defended in recently proposed guidelines, such as the six hilarmediastinal enlarged lymph nodes in the international tumoral classification [12].

Internal and external audits were made to survey the ratio between the number of patients undergoing surgery and the cases included in the registry (standard over 95%) as well as to determine the presence and validity of the data recorded for each case (standard over 70%), including the consistency of tumoral staging [13]. The criterion used to assess the validity of the survival data was the existence of a known follow-up for 85%, or more, of the cases registered in each hospital. In the hospitals that did not meet these conditions, the cases corresponding to the period of at issue were excluded. Finally, correct data transmission by a single central office from the paper record to the computer database was verified. These procedures were designed to control the selection biases of surgical cases, of registered cases out of the total number of surgical cases, sample size, type of hospital, prognostic migration due to the prolonged period of case recruitment, classification with low or deficient degrees of certainty, contamination by data from incomplete series or erroneous data and loss of long-term follow-up.

COPD is defined when a compatible clinical picture exists, when there is a chronic obstruction to the air flow and when other conditions with similar symptoms are ruled out. Obstruction to the air flow was confirmed when the post-bronchodilator FEV1/FVC was <0.7 [16]. All functional data were subjected to quality control audits conducted at the GCCB-S between 1993 and 1997.

The performance status (PS) scale (ECOG) was: 0, normal activity or asymptomatic; 1 symptomatic, completely ambulatory; 2 symptomatic, restrained to bed less than 50% of day time; 3 symptomatic restrained to bed more than 50%; 4 restrained to bed 24 h (100% of the time).

2.3. Analysis

To compare the frequency of presentation of the characteristics amongst the different populations, we used either the Pearson χ² technique or the Fisher’s exact test for qualitative variables and the T student test and the Levene test, when required, for quantitative variables. The difference is considered significant when P < 0.05.

In this study, overall survival was used to evaluate the prognosis, considering exitus from any cause as an event. We hypothesised that with this comorbidity (COPD), and in the presence of a disease as severe as NSCLC, we could only ascertain its prognostic value after the annual death load due to NSCLC had been reduced after the 2nd or 3rd year of progress following therapeutic treatment. Because of this, besides calculating the actuarial survival (Kaplan-Meir test) in the presence or in the absence of COPD and its comparison (Log-rank test), the conditional survival at 2, 3 or 5 years from surgery was also calculated. Data were obtained by determining the accumulated probability to be alive at 5 years, with the condition to be alive at 2 or 3 years, or survival at 8 years, if alive after 5 years.

Lastly, using the most widely accepted test (post-bronchodilator FEV1%) and a comparison of its most extreme quartiles, the functional severity of COPD was considered as a logical prognostic factor.

3. Results

All consecutive cases of thoracotomy performed for LC in the 10 hospitals participating in the GCCB-S were prospectively included in this study covering the period from 1st October 1993 through 31st September 1997, making a total
of 2994 cases. In 278 tumours, identification of the pathological stage (exploratory thoracotomy, poor nodal classification) was not possible. The distribution per stages of the remaining 2716 cases was as follows: hidden stage or ‘in situ’ 6, IA 290, IB 997, IIA 43, IIB 401, IIIA 524, IIIB 413, IV 42.

In 2928 cases (98%), primary data on FEV1 and FVC were available and, thus, the FEV1/FVC relation known; of these 2928 cases, 1370 patients (46%) had COPD. The FEV1% values were: mean 70.6 (SD 16.2); median 70.6. The FEV1/FVC values were: mean 0.61 (SD 0.8); median 0.62. Classification, according to the severity of COPD [16], was: stage I, 371; stage IIA, 836; stage IIB, 137; stage III, 5. In 21 cases the FEV1 value was not available in a percentage of the theoretical value.

3.1. Characteristics of the patients with and without COPD

No statistically significant differences were found between both groups when assessing the presence of previous tumor, ischemic cardiopathy, systemic arterial hypertension or diabetes mellitus. Likewise, no differences were found in the peripheral or central localization of the SLC, or in the presence of weight loss ≥ 10%, as compared to baseline figures. In relation to the extension of the resection, no differences were found in the frequency of pneumonectomy between the group with COPD (38%; 28%) and the group without COPD (46%; 30%), or in the frequency of lobectomy–bilobectomy (49 and 50%, respectively). Lesser resections were more frequent in the COPD group (8.8 vs 5%). No differences were found in the values of haemoglobin, total leukocyte count, percentage of polymorphonuclear cells or in the tumoral pathological size. However, differences were found in relation to FEV1 (%), FEV1 (liters) and FEV1/FVC. Obviously, by definition, the values were lower in the COPD group. Table 1 shows the variables that presented significant differences. There are also significant differences (P<0.001) in smoking between patients with COPD (mean, 54.5 pack-years) and the group without COPD (46 pack-years).

Pathological stages were determined using adequate criteria of classificatory certainty [14] in 91% of both groups (with and without COPD). Stage pI was significantly higher (625/1243) (50%) in the group with COPD than in the group without COPD (632/1411) (45%) (P<0.01), and opposite for stage pIII (32 vs 37%, respectively) (P<0.01).

3.2. COPD as a prognostic factor

To evaluate the possible prognostic value of COPD in NSCLC, a sequence of the results obtained is presented. Two analyses were performed on the selected population to study the prognostic value of COPD: an initial analysis on the overall survival and then a second analysis studying temporary conditional survival at 2, 3 and 5 years (Table 2). The analysis of conditional survival at 2, 3 or 5 years from surgery was performed determining the accumulated probability to be alive at 5 years, with the condition to be alive at 2 or 3 years, or survival at 8 years, if alive after 5 years. The overall survival at 5 years is not different between

<table>
<thead>
<tr>
<th>Patient characteristics depending on the presence or absence of COPD</th>
<th>COPD</th>
<th>%</th>
<th>No COPD</th>
<th>%</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1370</td>
<td>1558</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>1336</td>
<td>98</td>
<td>1379</td>
<td>89</td>
<td>0.0001</td>
</tr>
<tr>
<td>PS (ECOG) ≥ 3</td>
<td>31</td>
<td>2</td>
<td>16</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>165</td>
<td>12</td>
<td>141</td>
<td>9</td>
<td>0.008</td>
</tr>
<tr>
<td>Squamous</td>
<td>859</td>
<td>63</td>
<td>812</td>
<td>52</td>
<td>0.001</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>311</td>
<td>23</td>
<td>416</td>
<td>27</td>
<td>0.05</td>
</tr>
<tr>
<td>Complete surgery</td>
<td>1128</td>
<td>82</td>
<td>1228</td>
<td>79</td>
<td>0.05</td>
</tr>
<tr>
<td>Absence pN1</td>
<td>763</td>
<td>56</td>
<td>793</td>
<td>51</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>447</td>
<td>33</td>
<td>583</td>
<td>37</td>
<td>0.007</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>62</td>
<td>5</td>
<td>108</td>
<td>7</td>
<td>0.005</td>
</tr>
<tr>
<td>Perioperative transfusion</td>
<td>389</td>
<td>28</td>
<td>391</td>
<td>25</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Percentages over the total number of cases with information for that variable.

a Pearson χ² or Fisher’s exact test.

b See degree for the PS (performance status) index in Material and methods.

Table 2 Overall and conditional prognostic value of COPD in NSCLC

<table>
<thead>
<tr>
<th>COPD</th>
<th>No COPD</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Survival 5 years</td>
<td>Median</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>970</td>
<td>0.43</td>
</tr>
<tr>
<td>Conditional survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive at 24 months</td>
<td>621</td>
<td>0.67</td>
</tr>
<tr>
<td>Alive at 36 months</td>
<td>507</td>
<td>0.79</td>
</tr>
<tr>
<td>Conditional survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive at 60 months</td>
<td>344</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Analyses conducted on a selected population: NSCLC, complete resection, excluding operative mortality and cases with induction therapy.
the groups under analysis (COPD/no COPD). However, the overall survival is in fact different when the conditional survival at 36 months is considered.

A third analysis, which evaluated only those cases in stage pI with overall and conditional survival, was carried out to assess the tumoral pathological stage, another first-line prognostic factor (Table 3) (Figs. 1 and 2). The effect described above is more clearly detected when the population presenting a lower tumoral load (stage pI) is evaluated. In higher stages (pII, pIII), such effect of different conditional survivals is not identified. When evaluating cases with pneumonectomy or with lobectomy, in any given stage, the presence or absence of COPD did not present any prognostic differences in the conditional survival analysis.

Lastly, the prognostic value of different pulmonary functions (FEV1% in extreme quartiles) was assessed in the selected population and in the patient population with an initial stage (pI) and COPD (Table 4).

For the populations analysed in Table 2, and based on the last conditional survival (over 60 months), no differences were found between both groups (COPD vs no COPD) in the frequency of peripheral vascular disease, perioperative transfusion, PS≥2, body mass index or age. The difference (P=0.05) between histological types was maintained (P=0.05) with a higher frequency of squamous tumors in the COPD group (66 vs 57%). Slightly decreased values of serum albumin were found in the COPD group (4 vs 4.15) (P=0.02).

For the same population, but in stage pI (Table 3), only the age was higher in the group with COPD (65 vs 63.5) (P=0.05).

Lastly, when the patients in the COPD group were divided according to the extreme values of FEV1% (Table 4), no differences were noted between the two groups in any of the mentioned variables.

4. Discussion

This multicentre study was conducted using a large series of cases compiled in a short period of time and is representative of LC cases treated surgically in Spain, with an initial design conceived to control the usual biases in prognosis.

The results of the study show that LC cases with COPD occur most frequently in males and the tumour is of a squamous type. This higher rate in gender and type has also been reported in other studies [7]. None of the other various variables analysed presented any differences with regard to frequency in the group with COPD, and when they did, their clinical significance was low. In terms of prognosis, COPD comorbidity can present a possible prognostic value in stage pI NSCLC when it is analyzed using conditional survival.

### Table 3
Overall and conditional prognostic value of COPD in NSCLC-stage pI

<table>
<thead>
<tr>
<th>COPD</th>
<th>No COPD</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Survival 5 years</td>
<td>Median</td>
</tr>
<tr>
<td>Overall</td>
<td>Overall survival</td>
<td>542 0.54</td>
</tr>
<tr>
<td>Conditional</td>
<td>Alive at 24 months</td>
<td>411 0.70</td>
</tr>
<tr>
<td></td>
<td>Alive at 36 months</td>
<td>352 0.79</td>
</tr>
</tbody>
</table>

Analyses conducted on a selected population: NSCLC, complete resection, excluding operative mortality and cases with induction therapy.
The functional severity of COPD (FEV1%) has its own prognostic gradient within the COPD group.

The functional criteria for the diagnosis of COPD obviates, to a large extent, the problem raised by the use of clinical criteria or by the use of the administrative date on the discharge form. With these last procedures, cases of COPD could be underdiagnosed in the presence of a severe disease such as LC [17,18]. In our study, a database was initially designed (1993) for the prospective compilation of the preoperative value of FEV1 (liters) and FVC (liters). These two values were retrieved in 98% of the total 2994 number of cases and were also the subject of external audits. The definition of COPD used in this paper is different to that published in other studies, which can in turn lead to a different measurement of disease frequency [19].

The number of probable or possible prognostic factors in LC is very high [20]. Unfortunately comorbidity has not been studied in depth in LC [21,22] and even less in surgical LC (COPD) have also shown its prognostic value to determine overall survival [6] and the mortality caused by other late intercurrent conditions after 3 years of follow-up [7].

Given that the most severe form of COPD rendered some patients inoperable (4), the analysis subject of this study was performed using a selected population with mild or moderate COPD with a FEV1/FVC spectrum between the 25 percentile of 0.56 and the 75 percentile of 0.67. Despite this restrictive range of functional pulmonary alteration in COPD, the comparison between extreme percentiles of FEV1% in COPD with stage pl NSCLC still detects a significant prognostic gradient (Table 4). This value is in accordance with all the data available on COPD [25].

This paper presents some limitations, such as the functional definition of COPD, without taking into consideration other spirometric or clinical criteria [19]. It is, thus, possible that other studies with different diagnostic criteria for COPD may fail to reproduce the results yielded by this study. Moreover, the possible volume reduction effect of some resections in patients with emphysema [4] was not studied either in this paper. Lastly, only the overall survival, which takes into account death for any cause (cancer or other causes), was studied in this paper.

The future implications of the prognostic value of this frequent comorbidity relate to the manner in which this COPD variable must be used in multivariate models for the prognostic analysis of surgical LC. A more specific knowledge of its value and the way in which it impacts on patient prognosis will help us manage this comorbidity variable more efficiently. If these data were to be confirmed by independent studies, the comorbidity of NSCLC with COPD should be taken into account when elaborating multiparametric prognostic indexes.

In summary, this study on COPD comorbidity in SLC shows that this association can be of deleterious prognostic value in patients who present both diseases. The effect is observed after 2 years of resection surgery and in COPD it is directly related with the degree of functional severity (FEV1%).

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References


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