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# Previous tumour is a prognostic factor in Stage I Non-small Cell Lung Cancer

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**ABSTRACT Objective:** To evaluate the presence of co-morbidity as an independent prognostic factor in lung cancer. **Population and methods:** Data on 2,991 consecutive cases of lung cancer was gathered prospectively from 19 Spanish hospitals between 1993 and 1997 by the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). To evaluate the survival impact due to the existence of co-morbidity, 1,121 cases of non-small-cell lung cancer (NSCLC) in pathological stage I with complete resection were selected, excluding operative mortality. At the time of thoracotomy, the presence of specific co-morbidities was registered prospectively. **Results:** In Cox regression, strata of tumoral size (0-2, 2-4, 4-7, > 7 cm)(HR 1.45 [95% confidence intervals (95% CI) 1.08-1.95], 1.86 [95% CI 1.38-2.51], 2.84 [95% CI 1.98-4.08]), previous tumour (present – absent) (HR 1.45 [95% CI 1.17-1.79]) and age (HR 1.02 [95% CI 1.01-1.03]) showed a significant prognostic association with survival. These study exclude the presence of visceral pleural involvement or other co-morbidities as an independent variable. **Conclusion:** The presence of a previous tumour is an independent prognostic factor in pathological stage I NSCLC with complete resection, increasing the probability of death 1.5 times at 5 years. It is independent from other co-morbidities, TNM classification and age.

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## INTRODUCTION

The presence of other associated diseases (co-morbidity) occurs in 68% of all lung cancers included in a population registry [1], and in 73% of surgical cases of lung cancer from a Spanish prospective study. [2]

Co-morbidity has been considered as a prognostic factor in cancer in general [1] [3] and in the initial stages of surgically treated lung cancer. [4] Specifically, the association between lung cancer and chronic obstructive pulmonary disease (COPD) is frequent [2], the latter being an independent aetiological factor from smoking. If we evaluated COPD by means of a conditional survival analysis, it could behave as a late onset prognostic factor after the second or third year from the date of surgery. [5] The presence of a past history of aerodigestive or bladder tumours is frequent in patients with lung cancer [6][7][8][9], and is an additional risk to develop lung cancer. This frequent association has been reported as a result of the field cancerization of these tumours that could facilitate their multiple presence with possible explanatory genetic mechanisms. [10]

The aim of this paper is to evaluate prospectively the prognostic value of co-morbidity in a series of consecutive patients surgically treated for lung cancer in 19 Spanish hospitals between 1993 and 1997.

## MATERIAL AND METHODS

### Population

All patients with bronchogenic carcinoma who underwent thoracotomy from October 1993 to September 1997 in hospitals participating in the GCCB-S were registered prospectively in a homogeneous way. The sample was complete, as verified by the inclusion in the registry of all patients undergoing surgery, including incomplete resections and exploratory thoracotomy.

Operative mortality was understood to include all deaths directly related with the surgical act, regardless of time of occurrence. The initial number of cases included in this study was 2,994. After a new evaluation of the entire series, 3 registry entries were excluded. When the pathology was reviewed, a case was carcinosarcoma. The other two registry entries corresponded to the same person who had been operated on due to two different tumours, one on each side, in 1994 and in 1996; this was known when the confidentiality of the data was disclosed in order to determine long-term survival. Thus, the final number of patients is 2,991. Given that the last case of this series underwent operation on the 30th of September 1997, we now have available (March 2005) a mortality experience or real survival rates of over 7 to11 years of follow-up.

The population with pathological stage I non-small cell lung cancer (NSCLC) with adequate mediastinal pathological staging was selected to carry out survival multivariate analysis, excluding those patients with operative mortality, with induction treatment, or those without resection or with incomplete resection (R1-R2). In total 1,121 patients.

### Methods

The 1997 TNM classification was used. [11] Clinical staging is understood to be a classification obtained by any means, even surgical, before applying the definitive therapeutic procedure.

Pathological staging is understood to be a classification obtained through findings observed upon thoracotomy with an examination of the excised specimen, together with the data obtained through the clinical staging. [11]

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In accordance with the initial design of this study, the case recruitment period was short. The same criteria for the functional operability of patients and oncological operability of the tumour were used in all the GCCB-S hospitals. [12]

Surgical-pathological N0 was classified by radical mediastinal lymph node dissection or systematic sampling of at least four lymph node areas (2 [only in right lung cancer], 4, 7, and 10 on the same side as the tumour). [13][14] Moreover, no nodes must be present in the aortopulmonary window nor in the anterior mediastinal areas (areas 5 and 6), if the SLC is left-sided (upper lobe or main left bronchus). In order to classify the presence or absence of mediastinal lymph node involvement, a randomized study demonstrated that systematic sampling had a similar value to that of radical mediastinal lymph node dissection. [15]

Internal and external audits were made to survey the ratio between the number of patients undergoing surgery and the patients included in the registry (standard over 95%), the presence and validity of the data recorded for each case (standard over 70%), including the consistency of tumoral staging. [16] The criterion for the validity of the survival data was established as the existence of a known follow-up for 85%, or more, of the cases registered in each hospital. 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, 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.

**Study variables**

Pathological tumour size in prognostic strata [17], visceral pleural involvement, distal infiltration of a main bronchus, the presence of atelectasis and pneumonitis of less than the entire lung, have all been considered the basic primary variables of stages IA and IB. [11] Age and co-morbidity have also been considered as variables. For the evaluation of co-morbidity, there is a prospective data registry covering all clinical scenarios and associated diseases registered just before thoracotomy for all cases of the GCCB-S. These data refer to the following parameters: body mass index (BMI), FEV1 in percentage of the theoretical value (FEV1%), ischemic heart disease, peripheral vascular disease, systemic arterial hypertension, diabetes mellitus, COPD and a history of previous tumour.

**Analysis**

Prognostic data are expressed in survival probability at 5 years, with 95% confidence intervals (95% CI) and in median (months) using the life – table method of Kaplan-Meier, considering as an event death by any cause. Time cero is the date of the operation. The log rank or Breslow test was used for the comparison of survival times. A statistically significant difference was considered when $p < 0.05$.

The multivariate analysis (Cox proportional hazard analysis) is performed adjusting the basic primary variables for stages IA and IB [11], which are tumoral size in prognostic strata [17], involvement of the visceral pleura, distal infiltration of the main bronchus, the presence of atelectasis – pneumonitis involving less than the entire lung (with bivariate

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prognostic significance); and also, the age in years and the presence or absence of different specific co-morbidities. The variable considered as a dependent variable was "time to the event", censuring those values with a survival over the 5 year period. Stepwise selection was used for the selection of variables. The SAS® statistical program (SAS Institute Inc. SAS Circle. Box 800. Cary NC 27512-8000) was used in this study.

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## RESULTS

**Descriptive data of the series for analysis** (n=1.121)

The mean age was 65 years (SD 8.8), and median 66 years (range: 38-89 years). The interquartile range is 60-72. Table 1 shows some of the population characteristics under study.

**Table 1 CHARACTERISTICS OF STUDY POPULATION**

| | n | % |
|---|---|---|
| Gender male | 1033 | 92 |
| Stage pIA | 250 | 22 |
| pIB | 871 | 78 |
| Histological types | | |
| Squamous | 664 | 59 |
| Adenocarcinoma | 290 | 26 |
| Large-cell carcinoma | 73 | 7 |
| Bronchioloalveolar | 48 | 4 |
| Non-specified | 46 | 4 |
| Involvement (pathological) | | |
| Visceral pleura | 286 | 26 |
| Pneumonitis – atelectasis < entire lung | 273 | 24 |
| Main bronchus > 2 cm from carina | 72 | 6 |

The tumoral size in the surgical specimen over 1,110 (99%) cases in which this datum was collected with certainty was on average 4.3 cm (SD 2.2), median 4 cm (interquartile range 2.7-5). By prognostic strata, in tumoral size between 0,1 and 2 cm there were 159 (14%) cases, between 2.1 and 4 cm 493 (44%) cases, between 4.1 and 7 cm 363 (33%) cases and over 7 cm 95 (9%) cases.

The inferior quartile of the BMI had a value of 23 (n=272) and the superior quartile 27.8 (n=267). In relation to FEV1%, the inferior quartile is 68.3 (n=271) and the superior quartile 94.4 (n=270). Ischemic cardiac disease is present in 97 (9%) cases, peripheral vascular disease in 129 (11%), arterial high blood pressure in 224 (20%), diabetes mellitus in 109 (9,6%), COPD in 544 (48%) and the presence of previous tumour in 192 (17%) cases. Table 2 indicates the most frequent previous tumours, ranking among the first larynx carcinoma and bladder carcinoma. Skin tumours, tumours of the female genital tract, and gastric and breast cancers followed in frequency.

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**Table 2 ORIGINAL SITE OF THE MOST FREQUENT PREVIOUS TUMOURS**

| Site | Number of cases with previous tumours (n=192) | Percentage (%) |
|---|---|---|
| Larynx | 48 | 25 |
| Bladder | 36 | 19 |
| Lung | 17 | 9 |
| Colon – rectum | 16 | 8 |
| Head – neck | 14 | 7 |
| Lymphoma – leukaemia | 11 | 6 |

The number of mortality events due to any cause was 603 (54%).

**Univariate prognostic data of gender, age, co-morbidity and pT parameters**

The univariate prognostic study of the gender is HR 0.89 (95% CI 0.64 – 1.24); of the age is HR 1.02 (95% CI 1.01 – 1.03).

Table 3 shows that only 3 of the 8 comorbidities evaluated present a significant prognostic difference.

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**Table 3 UNIVARIATE PROGNOSTIC ANALYSIS PARAMETERS OF CO-MORBIDITY**

| **Parameters** | HR [95% confidence intervals] |
|---|---|
| Previous tumour (present / absent) | 1.44 [1.16-1.78] |
| Systemic arterial high blood pressure (present / absent) | 1.30 [1.06-1.59] |
| FEV1 in percentage on the theoretical value (extreme quartiles) | 1.00 [0.99-1.01] |
| Peripheral vascular disease (present / absent) | 1.24 [0.96-1.59] |
| Body mass index (extreme quartiles) | 1.15 [0.94-1.41] |
| Chronic obstructive pulmonary disease (present / absent) | 1.13 [0.80-1.59] |
| Ischemic heart disease (present / absent) | 0.98 [0.73-1.32] |
| Diabetes mellitus (present / absent) | 1.17 [0.89-1.54] |

Table 4 shows that tumour size presents, in its 4 strata, an elevated prognostic value for survival. The involvement or non involvement of the visceral pleura does not make a difference for survival. However, given the constant presence of this variable in the definition for T2 and its controversial prognostic value reported in the literature, this condition was maintained for multivariate analysis. In the involvement or non involvement of the distal area of the main bronchus or the presence of atelectasis - pneumonitis involving less than the entire lung, no prognostic differences are found.

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**Table 4 UNIVARIATE PROGNOSTIC ANALYSIS PARAMETERS pT (pT1-T2)**

| Parameters | | 5-year survival | HR [95% confidence intervals] |
|---|---|---|---|
| Tumoral size | 0-2 cm | 65% | - |
| | 2-4 cm | 57% | 1.42 [1.06 – 1.91] |
| | 4-7 cm | 48% | 1.86 [1.38 – 2.50] |
| | > 7 cm | 38% | 2.78 [1.93 – 3.99] |
| Visceral pleural involvement | Yes | 53% | 1.07 [0.88 – 1.30] |
| | No | 54% | |
| Involvement of main bronchus >2 cm from carina | Yes | 48% | 1.21 [0.80 – 1.84] |
| | No | 53% | |
| Pneumonitis – atelectasis < entire lung | Yes | 57% | 0.97 [0.79 – 1.18] |
| | No | 52% | |

**Multivariate analysis of the prognosis**

Table 5 shows the results yielded by Cox regression, the highest hazard ratio (HR) corresponds to the largest tumoral size. It is confirmed that the involvement of the visceral pleural does not behave as a prognostic factor. The only significant co-morbidity selected for the final model, together with the strata of size and age, is the history of previous tumour with an HR of 1.45. It is not possible to identify collinearity or interaction among the selected variables.

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**Table 5 MULTIVARIATE ANALYSIS COX REGRESSION (Hazard Ratio (HR))**

| Variable | Hazard ratio | 95% HR confidence limits |
|---|---|---|
| Tumoral size > 7 cm | 2.84 | 1.98 – 4.08 |
| Tumoral size 4.1-7 cm | 1.86 | 1.38 – 2.51 |
| Tumoral size 2.1-4 cm | 1.45 | 1.08 – 1.95 |
| Previous tumor | 1.45 | 1.17 – 1.79 |
| Age | 1.02 | 1.01 – 1.03 |

The presence of a previous tumour represents an increased risk of mortality at 5 years in this population of lung cancer (resected stage pI) of 1.5 (95% CI 1.17-1.79). The prognostic value of a history of tumour is independent from the pT parameter significant for survival (pathological size) and age.

## DISCUSSION

This study was conducted in a large series of patients collected in a short, recent time interval. The study was multi-institutional and representative of the cases of NSCLC treated surgically in Spain, with an initial design conceived to control the usual biases in prognostic and/or therapeutic studies.

In this paper, in the initial stages of NSCLC (pIA-IB) with complete resection (R0), the presence of specific co-morbidity (previous tumour) is an independent prognostic factor for survival, increasing 1.5 times the probability of death due to any cause in the 5 years following surgical treatment.

The most studied prognostic factors in lung cancer are those related to the tumour extension (TNM). [19] In our study, and upon univariate analysis, of all the TNM parameters that define the involvement in stages IA and IB only the tumoral size behaves as a prognostic factor. In other experiences it was already detected that in small tumours, the presence of distal involvement of the main bronchus or of the pleural viscera were not prognostic factors. [20] Nevertheless and given that the literature is very consistent on the prognostic value of visceral pleural involvement [21][22][23], this variable was taken into account in our multivariate analyses. In Cox regression, the involvement of the visceral pleura was not significant, and was, consequently, discarded.

Tumoral size was evaluated in different strata, taking into account the greater prognostic discrimination observed with this strategy [17], in relation to the T1-T2 dichotomic system in size (equal or below 3 cm versus greater than 3 cm). [24] Another

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selected variable at multivariate analysis was age. It is known that the frequency of co-morbidity is directly related to age. [2] Our study identifies its independent value.

Co-morbidity can have several clinical repercussions on NSCLC in potentially resectable stages IA-B. The most studied repercussion is the one relating to the risks of surgery with lung resection. [25][26][27] An aspect that has not been looked at that much in depth is the consideration of co-morbidity as a survival prognostic factor. When recent revisions concerning prognostic factors in NSCLC are considered, the factors relating to the patient that are mentioned the most are weight loss or the performance status. [19] [28] In our series of NSCLC cases resected in stages pIA-IB there was only a 7% of cases with “weight loss”, without identification of a prognostic effect (long-rank: 0.73). Comparison between grade 1 and 2 of the ECOG scale (99% of the total number of cases fell in these categories) presented no significant difference in prognosis (long-rank: 0.40). Other studies have identified that the performance status and co-morbidity are independent prognostic factors. [29]

The indexes used to measure co-morbidity [28] [30][31] consider a wide spectrum of diseases: from the presence of ischemic heart disease caused by a history of myocardial infarction to the presence of another metastatic tumour or AIDS. [28] In the population with resection due to NSCLC many of these conditions are not present as they would meet the exclusion criteria for surgery.

Our study has considered a series of diseases that are frequently seen in the population with lung cancer resected in our setting. [2] These diseases, with a precise definition, were collected prospectively in the GCCB-S registry as present or absent just before thoracotomy. This registry procedure decreases both the under as well as the overdiagnosis of the co-morbidity. Of the 8 conditions or clinical situations to evaluate co-morbidity in this study, 3 behaved as prognostic values upon univariate analysis. Each and one of these clinical situations have biological plausibility from a prognostic point of view.

Although co-morbidity has been enunciated for a long time now as a prognostic factor in initial NSCLC, it has just been given some attention in these past few years. [1] [4] [31][32] In a study on NSCLC, co-morbidity is considered as an independent prognostic factor upon multivariate analysis in stage pI together with the performance status, the histological type and the intensity of smoking. [31] In another recent paper of multivariate analysis on NSCLC in stage pI-II age, the T1-T2 classification and the treatment are the selected variables, ruling out gender, type and co-morbidity. [32] However, the latter participates independently as a prognostic factor upon multivariate analysis if the variable “treatment” [33] is not included in such analysis. Battafaro et al. published a study on 451 cases of NSCLC in stage pIA-B using for the measurement of co-morbidity, a modification of the Kaplan-Feinstein index. [4] Their results show a survival probability of 86% at 3 years in the absence of co-morbidity and between 69 and 75% depending on the different degrees of its presence. Adjusting (Cox) by age, gender, pT and histology, the HR of co-morbidity was 1.44 if it was medium degree, 2.28 if it was moderate, and 1.94 if such co-morbidity was severe; the 95% CI range between 0.89 and 3.70 (medium degree). [4]

In our study the presence of a previous tumour had an independent prognostic value. 192 (17%) cases had had a previous tumour, similar to the 11% reported in one recent series composed of 8,363 cases of lung cancer. [34] In our series, the most frequent sites of previous tumour had already been described in other experiences (head and neck, bladder and previous lung cancer). [6][7][8][9] We have not excluded patients with non-melanoma skin cancer, given its possible prognostic significance. [35] In the Kaplan-Feinstein co-morbidity index, the presence of malignancy within co-morbidity is considered in two grades of severity [30]: grade 3 would be “uncontrollable malignancy” and grade 2 would be “controlled malignancy” (i.e. successful previous resection or other therapy)”. This last description is the most equivalent to the “presence of previous tumour”

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in our study.

In our work, the HR of co-morbidity (Cox) was 1.45 with a very narrow 95% CI [1.17-1.79], and this was so exclusively due to the presence of previous tumour given that the other co-morbidities, in this population of NSCLC-pI-RO, did not express an independent prognostic value. In another recent paper, HR for overall moderate to severe co-morbidity was 1.78 (95% CI 1.44-2.20). [1] Consequently, in general terms, and based on all these experiences, it appears that co-morbidity increases the probability to die for any cause between 1.5 and 1.8 times between 3 and 5 years after the surgical treatment in the initial stages of NSCLC.

The implications that these data bear can be relevant. NSCLC occurs in patients that contribute with their own loads of annual mortality risk, irrespectively of the lung cancer they may have (among these, co-morbidity). The consideration of all these factors is extremely important for the prognostic estimation in these patients.

In therapeutic trials in initial stages of lung cancer (neoadjuvant or co-adjuvant to surgery), this co-morbidity must be measured to determine if it is distributed homogenously between both arms, to make sure there is no bias in the selection for patients.

The study here presented has some limitations. The evaluation of the co-morbidity performed only discriminates in the presence or absence of diseases associated with a certain prognostic sense, without establishing degrees. Furthermore, this type of studies shows that co-morbidity does not explain too much the prognostic variability. The stage of the LC has been supposedly explains a 25% of that variability and co-morbidity only a 6%. [32] Other studies report a 3% as the proportion of the survival variance that is explained by the co-morbidity in localised NSCLC. [1]

In conclusion, this study identified that the presence of a previous tumour increases 1.5 times the probability to die for any cause in patients with NSCLC in stage pIA-B that have undergone complete resection. This increase is irrespective of the tumor size, age and the presence of other co-morbidities. Given these findings, a past history of a previous tumour should be considered as an independent variable for prognostic studies on co-morbidity.

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**Abbreviations:**

95CI: Confidence intervals at 95%; GCCB-S: Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; SLC: surgical lung cancer.

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## Appendix

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