LUNG CANCER

Previous tumour as a prognostic factor in stage I non-small cell lung cancer

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Thorax 2007;**62**:386–390. doi: 10.1136/thx.2005.051615

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Received 15 August 2005
Accepted 23 January 2006
Published Online First 31 January 2006

Objective: To evaluate the effect of comorbidity as an independent prognostic factor in lung cancer.
Method: Data on 2991 consecutive cases of lung cancer were collected 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 effect of comorbidity on survival, 1121 patients with non-small cell lung cancer (NSCLC) in pathological stage I who underwent complete resection were selected, excluding operative mortality. The presence of specific comorbidities at the time of thoracotomy was registered prospectively.
Results: Cox regression analysis showed that tumour size (0–2, 2–4, 4–7, >7 cm) (HR 1.45 95% CI 1.08 to 1.95), 1.86 (95% CI 1.38 to 2.51), 2.84 (95% CI 1.98 to 4.08)), the presence of a previous tumour (HR 1.45 (95% CI 1.17 to 1.79)) and age (HR 1.02 (95% CI 1.01 to 1.03)) had a significant prognostic association with survival. This study excluded the presence of visceral pleural involvement or other comorbidities as independent variables.
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 by 1.5 times at 5 years. It is independent of other comorbidities, TNM classification and age.

The presence of other associated diseases (comorbidity) has been reported 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] Comorbidity is considered to be a prognostic factor in cancer generally[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 conditional survival analysis, it could be considered a late onset prognostic factor 2–3 years after surgery.[5] The presence of a past history of aerodigestive or bladder tumours is frequent in patients with lung cancer,[6–9] and is an additional risk for developing the disease. This association is thought to be a result of field cancerisation of these tumours that facilitate their multiple presence in aerodigestive epithelium, possibly due to genetic mechanisms.[10]

A study was undertaken to evaluate prospectively the prognostic value of comorbidity in a series of consecutive patients surgically treated for lung cancer in 19 Spanish hospitals between 1993 and 1997.

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 manner. The sample was complete, as verified by inclusion in the registry of all patients undergoing surgery including incomplete resections and exploratory thoracotomy.

Operative mortality included all deaths directly related to surgery, regardless of when it occurred. The initial number of cases included in the study was 2994. However, after further evaluation, three registry entries were excluded: one was found to have carcinosarcoma and the other two corresponded to the same person who had been operated on for two different tumours (one on each side) in 1994 and in 1996; this was established when the confidentiality of the data was disclosed in order to determine long-term survival. Thus, the final number of patients included in the study was 2991. Given that the last case of this series underwent surgery on 30 September 1997, mortality and survival rates are available for 10–14 years of follow-up.

Patients with pathological stage I non-small cell lung cancer (NSCLC) with adequate mediastinal pathological staging were selected for multivariate analysis of survival. Patients with operative mortality, those who underwent induction treatment and those without resection or with incomplete resection (R1–R2) were excluded. The total number of patients included in the analysis was 1121.

Study design

The 1997 TNM classification was used.[11] Clinical staging is a classification obtained by any means, even surgical, before applying the definitive therapeutic procedure. Pathological staging is a classification obtained from findings observed at thoracotomy and examination of the excised specimen, together with the data obtained from clinical staging.[11]

In accordance with the initial design of the study, the 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

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; 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

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 or in the anterior mediastinal areas (areas 5 and 6) if the lung cancer was left-sided (upper lobe or main left bronchus). In order to classify the presence or absence of mediastinal lymph node involvement, a randomised study has shown that systematic sampling has 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 transmission of data 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 comorbidity have also been considered as variables. For the evaluation of comorbidity 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), forced expiratory volume in 1 s as a percentage of the theoretical value (FEV_1%), ischaemic heart disease, peripheral vascular disease, systemic arterial hypertension, diabetes mellitus, COPD and a history of previous tumour.

Analysis of data

Prognostic data were expressed as survival probability at 5 years (with 95% CI) and as median (months) using the Kaplan-Meier life table method, considering death from any cause as an event. The date of the operation was time 0. The log rank or Breslow test was used for comparison of survival times.

Table 1 Characteristics of study population

	N (%)
Male	1033 (92)
Pathological stage	
IA	250 (22)
IB	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)

A statistically significant difference was considered when $p<0.05$.

Multivariate analysis (Cox proportional hazard analysis) was performed, adjusting for the following basic primary variables for stages IA and B:[11] tumour size,[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 prognostic significance), and also age in years and the presence or absence of different specific comorbidities. 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 analysis was performed using the SAS statistical program (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Characteristics of the series for analysis (n = 1.121)

The mean (SD) age of the patients included in the analysis was 65 (8.8) years and the median age was 66 years (range 38–89; interquartile range (IQR) 60–72). Table 1 shows some of the characteristics of the study population.

The mean (SD) tumour size in the surgical specimens from 1110 cases (99%) in which this measurement was taken with certainty was 4.3 (2.2) cm, median 4 cm (IQR 2.7–5). When stratified by tumour size, there were 159 cases (14%) with tumours of 0.1–2 cm, 493 (44%) with tumours of 2.1–4.0 cm, 363 (33%) with tumours of 4.1–7 cm, and 95 (9%) with tumours of >7 cm.

The lowest quartile of body mass index (BMI) was 23 (n = 272) and the highest quartile was 27.8 (n = 267). For FEV_1%, the lowest quartile was 68.3 (n = 271) and the highest quartile was 94.4 (n = 270). Ischaemic cardiac disease was present in 97 cases (9%), 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%). Table 2 indicates the site of previous tumours, with laryngeal cancer and bladder cancer occurring most frequently, followed by skin tumours, tumours of the female genital tract, and gastric and breast cancers. The number of deaths due to any cause was 603 (54%).

Univariate prognostic data of sex, age, comorbidity and pT parameters (size, visceral invasion, etc)

Univariate analysis gave a hazard ratio (HR) for gender of 0.89 (95% CI 0.64 to 1.24) and for age of 1.02 (95% CI 1.01 to 1.03).

Table 3 shows that only three of the eight comorbidities evaluated had a significant effect on prognosis. Increasing tumour size had an increased prognostic association with survival (table 4). Involvement or non-involvement of the visceral pleura had no effect on survival. However, given the constant presence of this variable in the definition for T2 disease and its controversial prognostic value reported in the literature, this condition was maintained for multivariate analysis. Involvement or non-involvement of the distal area of the main

Table 2 Site and frequency of previous tumours

Site	No (%) of cases with previous tumours (n = 192)
Larynx	48 (25)
Bladder	36 (19)
Lung	17 (9)
Colon and rectum	16 (8)
Head and neck	14 (7)
Lymphoma/leukaemia	11 (6)

Table 3 Univariate analysis of effect of comorbidities on prognosis

Parameters	HR (95% CI)
Previous tumour (present/absent)	1.44 (1.16 to 1.78)
Systemic arterial high blood pressure (present/absent)	1.30 (1.06 to 1.59)
FEV_1 as % of theoretical value (extreme quartiles)	1.00 (0.99 to 1.01)
Peripheral vascular disease (present/absent)	1.24 (0.96 to 1.59)
BMI (extreme quartiles)	1.15 (0.94 to 1.41)
COPD (present/absent)	1.13 (0.80 to 1.59)
Ischaemic heart disease (present/absent)	0.98 (0.73 to 1.32)
Diabetes mellitus (present/absent)	1.17 (0.89 to 1.54)

FEV_1, forced expiratory volume in 1 s; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

bronchus and the presence of atelectasis-pneumonitis involving less than the entire lung had no effect on prognosis.

Multivariate analysis of prognosis

Table 5 shows the results of Cox regression, the highest HR corresponding to the largest tumour size. This confirms that involvement of the visceral pleural is not a prognostic factor. The only significant comorbidity selected for the final model, together with tumour size and age, is a history of previous tumour (HR 1.45). No colinearity or interaction between the selected variables was found.

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

DISCUSSION

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

In the initial stages of NSCLC (pathological stages IA and B) with complete resection (R0), the presence of specific comorbidity (previous tumour) is an independent prognostic factor for survival, increasing the probability of death from any cause by 1.5 times in the 5 years following surgery.

The prognostic factors most studied in lung cancer are those related to the extent of the tumour (TNM).[19] In our study, univariate analysis showed that, of all the TNM parameters that define involvement in stages IA and B, only tumour size was a prognostic factor. It has previously been reported that, in small tumours, the presence of distal involvement of the main bronchus or of the visceral pleura are not prognostic factors.[20] Nevertheless, given that there are consistent reports in the literature on the prognostic value of involvement of the visceral pleura,[21–23] this variable was taken into account in our multivariate analyses. However, Cox regression showed that involvement of the visceral pleura was not significant and it was therefore discarded.

Tumour size was stratified, taking into account the greater prognostic discrimination observed with this strategy[17] in relation to the T1–2 dichotomous system in size ($\leqslant$3 cm vs >3 cm).[24] Another selected variable used in the multivariate analysis was age. It is known that the frequency of comorbidity is directly related to age,[2] and our study has confirmed it to be an independent factor.

Comorbidity can have several clinical consequences on NSCLC in potentially resectable stages IA–B. The most studied repercussion is the one relating to the risk of lung resection.[25–27]

Table 4 Univariate prognostic analysis of parameters (T1–T2)

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

One aspect that has not been studied in much depth is comorbidity as a survival prognostic factor. When recent revisions concerning prognostic factors in NSCLC are considered, the factors relating to the patient that are most frequently mentioned are weight loss and performance status.[19 28] In our series of resected patients with NSCLC pathological stages IA and B, only 7% had "weight loss" with no effect on prognosis ($p = 0.73$, log rank). A comparison of patients in grades 1 and 2 of the ECOG scale (99% of patients were in these two categories) showed no significant difference in prognosis between the two grades ($p = 0.40$, log rank). Other studies have reported that performance status and comorbidity are independent prognostic factors.[29]

The indices used to measure comorbidity[28–31] include a wide spectrum of diseases ranging from ischaemic heart disease caused by a history of myocardial infarction to the presence of another metastatic tumour or AIDS.[28] In patients undergoing resection for NSCLC, many of these conditions are not present as they would be considered exclusion criteria for surgery. In our study we considered a series of diseases that are frequently seen in patients with lung cancer resected in our setting.[2] These diseases, with a precise definition, were collected prospectively in the GCCB-S registry as being present or absent just before thoracotomy. This registry procedure reduces both the underdiagnosis and overdiagnosis of comorbidity. Of the eight conditions or clinical situations used to evaluate comorbidity in our study, three were found to have a prognostic value on univariate analysis. Each of these clinical situations has biological plausibility from a prognostic point of view.

Although comorbidity has been proposed as a prognostic factor in initial NSCLC for some time, attention has only been given to it in the past few years.[1 4 31 32] In a study of NSCLC, comorbidity was considered to be an independent prognostic factor on multivariate analysis in patients with pathological stage I together with performance status, histological type and

Table 5 Multivariate analysis (Cox regression)

Variable	HR (95% CI)
Tumour >7 cm	2.84 (1.98 to 4.08)
Tumour 4.1–7 cm	1.86 (1.38 to 2.51)
Tumour 2.1–4 cm	1.45 (1.08 to 1.95)
Previous tumour	1.45 (1.17 to 1.79)
Age	1.02 (1.01 to 1.03)

smoking intensity.[31] In another recent paper of multivariate analysis of patients with pathological stage I–II NSCLC, age, T1–2 classification and treatment were the selected variables, ruling out gender, type and comorbidity.[32] However, the comorbidity performs independently as a prognostic factor in multivariate analysis if ''treatment'' is not included in the analysis.[33] Battafarano *et al*[4] published a study of 451 cases with NSCLC pathological stage IA–B using a modification of the Kaplan-Feinstein index as the measurement of comorbidity. Their results showed a survival probability of 86% at 3 years in the absence of comorbidity and of 69–75% in the presence of different degrees of comorbidity. After adjusting (Cox regression analysis) by age, gender, pT and histology, the HR of comorbidity was 1.44 (95% CI 0.89 to 3.70) for medium comorbidity, 2.28 for moderate comorbidity, and 1.94 for severe comorbidity.[4]

In our study the presence of a previous tumour had an independent prognostic value. One hundred and ninety-two cases (17%) had had a previous tumour, similar to the 11% reported in a recently published series of 8363 cases of lung cancer.[34] In our series, the most frequent sites of previous tumour were in agreement with other reports (head and neck, bladder and previous lung cancer).[6–9] We did not exclude patients with non-melanoma skin cancer, given its possible prognostic significance.[35] In the Kaplan-Feinstein comorbidity index, the presence of malignancy within comorbidity is considered in two grades of severity:[30] grade 3 which is ''uncontrollable malignancy'' and grade 2 which is ''controlled malignancy'' (ie, successful previous resection or other treatment). This last description is the nearest equivalent to the ''presence of previous tumour'' in our study.

The HR for comorbidity (Cox regression analysis) in our study was 1.45 with a very narrow 95% CI (1.17 to 1.79), and this was exclusively due to the presence of previous tumour given that the other comorbidities in this population of NSCLC-pI-R0 did not have an independent prognostic value. In another recent paper the HR for overall moderate to severe comorbidity was 1.78 (95% CI 1.44 to 2.20).[1] It therefore appears that comorbidity increases the probability of death from any cause by 1.5–1.8 times 3–5 years after surgery in the initial stages of NSCLC.

The implications of these findings are of relevance. NSCLC occurs in patients with annual mortality risks in addition to lung cancer (including comorbidity). Consideration of all these factors is extremely important when estimating the prognosis in these patients. Comorbidity should therefore be measured in therapeutic trials performed in patients in the initial stages of lung cancer (neoadjuvant or co-adjuvant to surgery) to determine whether it is distributed homogenously between both arms and to make sure there is no bias in patient selection.

Our study has some limitations. The evaluation of comorbidity only determined the presence or absence of diseases associated with prognosis without establishing degrees. Furthermore, this type of study shows that comorbidity does not explain the prognostic variability. The lung cancer stage has been reported to explain 25% of that variability compared with 6% for comorbidity.[32] Other studies have found the proportion of survival variability explained by comorbidity in localised NSCLC to be 3%.[1]

In conclusion, this study has shown that the presence of a previous tumour increases by 1.5 times the probability of death from any cause in patients with pathological stage IA–B NSCLC who have undergone complete resection. This increase is irrespective of tumour size, age and the presence of other comorbidities. Given these findings, a past history of a previous tumour should be considered as an independent variable for prognostic studies on comorbidity.

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This study was partly financed by FIS grant 97/0011, FEPAR-2000 grant, RTIC-03/11-ISCIII-Red-Respira grant, RTIC-03/090-ISCIII-Red MBE, FIS grant 03/46 and financial aid from Castilla-León regional government and Menarini Foundation. None of the supporting organisations participated in the study design or in analysis of the data or its interpretation. The authors had full access to all the data in the study and were ultimately responsible for submitting the paper for publication.

Competing interests: None.

A complete list of GCCB-S members is given in Appendix A.

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