ORIGINAL ARTICLES

Risk Factors in Bronchogenic Carcinoma Surgery

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OBJECTIVE: To analyze the factors that determine the risk of morbidity and mortality associated with lung resection in patients with bronchogenic carcinoma.

PATIENTS AND METHODS: Prospective multicenter study conducted between October 1, 1993 and September 30, 1997 in the 19 hospitals that make up the Bronchogenic Carcinoma Cooperative Group. During the study period, 2994 patients with bronchogenic carcinoma underwent surgery. The morbidity and mortality data at 30 days from all centers were recorded in a single registry.

RESULTS: Major resection was performed in 2491 patients, whereas 212 underwent minor resection. The resection had to be extended in 296 and exploratory thoracotomy was carried out in 291.

Postoperative complications were reported in 1057 patients (35.2%). Complications directly related to surgery were the most common (22.9%), followed by respiratory (19.5%) and cardiovascular (10.7%) complications. Of the patients with complications, 654 patients (21.8%) had only 1, whereas 403 (13.4%) had more than 1. After classification of complications, 21% were found to be minor and 14.2% were major.

Mortality at 30 days was 6.8% (204 patients), and strongly linked to the presentation of major complications—40.8% of those with such complications died.

CONCLUSIONS: Surgical treatment of bronchogenic carcinoma in Spain is associated with high morbidity and mortality. The morbidity reported in the present study lies in the middle of the ranges found in the literature, whereas mortality lies at the high end of the range. The presence of major complications and/or multiple complications should be considered as strong risk factors.

Key words: *Bronchogenic carcinoma. Risk factors. Morbidity. Mortality.*

Parámetros de riesgo en la cirugía del carcicoma broncogénico

OBJETIVO: Analizar la morbilidad y mortalidad asociadas a la cirugía de exéresis pulmonar por carcinoma broncogénico, como parámetros definitorios del riesgo inherente a este tratamiento.

PACIENTES Y MÉTODOS: Estudio prospectivo y multicéntrico, realizado en los 19 hospitales integrantes del Grupo Cooperativo de Carcinoma Broncogénico entre el 1 de octubre de 1993 y el 30 de septiembre de 1997. En este tiempo fueron sometidos a toracotomía 2.994 pacientes con carcinoma broncogénico. La morbilidad y mortalidad a los 30 días se recogieron mediante un registro de datos unificado para todos los hospitales.

RESULTADOS: Se practicaron 2.491 exéresis mayores y 212 menores. Se precisó resección extendida en 296 pacientes, mientras que en 291 se efectuó toracotomía exploradora.

En 1.057 pacientes (35,2%) se objetivaron complicaciones postoperatorias, de las que las más frecuentes fueron las relacionadas directamente con la intervención quirúrgica (22,9%), seguidas por las respiratorias (19,5%) y las cardiovasculares (10,7%). En 654 casos (21,8%) las complicaciones fueron de carácter único, mientras que 403 (13,4%) presentaron más de una. Atendiendo a su categoría, el 21% de las complicaciones fueron menores, en tanto que las complicaciones mayores sucedieron en el 14,2% de los casos.

El análisis de la mortalidad en los 30 primeros días mostró una incidencia del 6,8% (204 pacientes), y estuvo notablemente vinculada con la aparición de complicaciones mayores (40,8%).

CONCLUSIONES: En nuestro medio el tratamiento quirúrgico del carcinoma broncogénico genera una morbilidad y una mortalidad elevadas, en el rango de las habitualmente referidas en relación con la morbilidad y en el límite alto cuando se considera la mortalidad. La presencia de complicaciones mayores y/o su multiplicidad deben considerarse elementos sustancialmente moduladores del incremento del riesgo.

Palabras clave: *Carcinoma broncogénico. Parámetros de riesgo. Morbilidad. Mortalidad.*

Introduction

Bronchogenic carcinoma is currently one of the leading causes of death. Surgical resection is still the treatment of choice when the disease is in its early stages. The outcome depends on both an accurate disease assessment and careful overall perioperative decisions to ensure patients receive the most appropriate postoperative care

and to prevent the complications associated with this type of surgery.[1-3]

We must also bear in mind that the presence of complications associated with surgery determines the survival prognosis for these patients too. Thus, some variables that determine surgical risk also strongly influence the outcome. Essentially, when making surgical decisions, we consider variables such as the possibility of morbidity or complications and mortality, although the future quality of life of the patients is a third aspect to take into account.[4]

The surgical risk is itself influenced by a number of factors of an exacerbating nature (age, comorbidity, functional status, type of treatment, etc) that may intervene and alter the relative importance of the aforementioned factors, in turn altering the probability of complications or death.[5,6]

The objective of our study was to assess risk factors in this clinical setting, that is, to analyze the incidence of morbidity and mortality associated with this type of surgery in Spain.

Patients and Methods

This study is based on the prospective analysis of 2994 patients who underwent thoracotomy for bronchogenic carcinoma between the October 1, 1993 and September 30, 1997 in hospitals belonging to the Bronchogenic Carcinoma Cooperative Group (GCCB-S) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). All participating centers met the established quality controls. The GCCB-S includes 19 hospitals with thoracic surgery departments. The aim of the group is to study various aspects of bronchogenic carcinoma.

All hospitals in the group used the same case report form for recording information about the disease, its treatment, and the outcome of treatment. All preoperative variables known to have some prognostic influence and for which operational definitions were available were collected (including clinical, laboratory, functional, staging, and histologic information), along with the measurement methods for each variable in order to ensure the validity and reproducibility of the data.[7] For disease staging, the study used the TNM classification published in 1997 by the American Joint Committee on Cancer[8] whereas the Eastern Cooperative Oncology Group scale was used to determine the clinical state.

For perioperative variables, we recorded whether transfusions were done and the different types of surgery such as pneumonectomy, lobectomy, bilobectomy, and small resections (segmentectomies and excisions spanning more than one segment). A standard surgical procedure was defined as one in which the lung was resected with lymph node dissection, whereas extended procedures were considered as those that included resection of other structures invaded by the tumor, in addition to lung resection and lymph node dissection.

We assessed morbidity and mortality in the immediate postoperative period, defined as the first 30 days after surgery in accordance with the definition used in most studies. Morbidity was assessed by considering the complications reported. Eighteen types of complication were identified (see Appendix 1 for the operational definitions of these complications). For our analyses, these complications were divided into 4 main groups: a) surgical complications, b) respiratory complications, c) cardiovascular complications, and d) extrathoracic complications. In addition to the complications which might determine mortality (in our study, complications whose presence as a single complication was associated with an above average mortality rate) and which

we defined as major, we also collected data on minor complications (infection of the surgical wound or pleural cavity, etc) which may influence the postoperative quality of life.

Statistical Analysis

Statistical analysis of the data was carried out with SPSS, version 11.5. The descriptive statistics calculated were frequency distribution for qualitative variables and measures of central tendency and dispersion for quantitative ones. The association between 2 qualitative variables was determined with the χ^2 test. All hypotheses were tested with an α error of .05. For the analysis of the influence of all complications on mortality at 30 days, we used a binary logistic regression model, with the option to introduce variables and apply the indicator contrast method of comparison with the first category (0= no) as reference.

Results

The preoperative and perioperative variables describing the patient characteristics, histological diagnosis, and type of surgery are presented in Tables 1 and 2.

In total, 756 patients (25.2%) underwent a blood transfusion (10.6% perioperatively and 14.6% postoperatively). Of these patients, 2.5% required both perioperative and postoperative transfusions.

In the postoperative period, the cumulative incidence of morbidity was 35.2% (n=1057), with a range among the individual hospitals of the GCCB-S of 19.7% to 43.8%. A total of 1890 complications were reported, the most frequent being those related to surgery (22.9%), followed by respiratory complications (19.5%), and cardiovascular complications (10.7%).

The most common specific complication was arrhythmia, reported in 232 patients (7.8%). Extrathoracic

TABLE 1
Patient Characteristics*

Variable	No. of Patients	Percentage
Age, y		
<60	825	27.5
60-69	1199	40.0
70-79	906	30.2
>79	64	2.1
Sex		
Male	2771	92.5
Female	223	7.4
Smoking history		
Yes	2769	92.4
At present	1701	56.8
In the past	1068	35.6
No	225	7.5
Prior disease		
Yes	2529	84.4
No	463	15.4
General condition		
Not evaluable	12	0.4
Asymptomatic	620	20.7
ECOG 1	2312	77.2
ECOG 2	44	1.4
ECOG 3	6	2.0
ECOG 4	0	

*ECOG indicates the Eastern Cooperative Oncology Group scale.

TABLE 2
Tumor Classifications, Histology, and Surgical Reports

Variable	No. of Patients	Percentage
Histology		
Squamous	1774	59.2
Adenocarcinoma	759	25.3
Bronchoalveolar	84	2.8
Small cell	49	1.6
Large cell	190	6.3
Non-small cell (nonspecific)	138	4.6
Type of surgery		
Pneumonectomy	884	29.5
Right	374	42.30
Left	510	57.70
Lobectomy	1455	48.6
Bilobectomy	152	5.1
Sublobular resections	212	7.0
Exploratory thoracotomy	291	9.7
Extended surgery	296	9.8

complications accounted for 9.9% of the total number. Overall, 21.8% of the patients had a single complication whereas 13.4% had more than 1 (Table 3).

According to Table 4, 14.2% of the patients had a single major complication and 21% had a single minor complication. The multivariate analysis of the complications confirmed the importance of the impact of major complications on mortality, with cardiovascular complications being associated with highest risk (Table 5).

The mortality rate was 6.8% (n=203; 7 patients died during surgery and 196 in the first 30 days), with marked variation among the hospitals of the GCCB-S (from 0% to 11.6%). Mortality was higher among patients with multiple complications than among those with a single complication (Table 6). Of the patients with a major complication, 40.8% died, compared to 4.5% of those with a minor complication. Overall mortality was 12.3% for pneumonectomy, 4.3% for lobectomy, and 2.5% for minor resection. However, in patients undergoing pneumonectomy who presented with major complications, the mortality was 59.2% compared to just 5.8% for those with minor complications. Among patients undergoing lobectomies, mortality was 25.4% for major complications and 4.2% for minor complications. Mortality among patients who underwent blood transfusion was 15% (n=122).

Discussion

Surgical resection is still the treatment of choice for bronchogenic carcinoma in its initial stages. This procedure

TABLE 3
Morbidity

Complication	No. of Complications	Percentage of Total Morbidity	Percentage of All Patients
Complications associated with the intervention			
Air leakage	184	9.7	6.1
Residual pleural cavity	117	5.3	5.2
Empyema	97	5.1	3.2
Bronchopleural fistula	91	4.8	3
Hemothorax	69	3.6	2.3
Infection	80	4.2	2.6
Pneumothorax	49	2.5	1.6
Total	687	36.3	22.9
Respiratory			
Pneumonia	173	9.1	5.8
Respiratory insufficiency	168	8.8	5.6
Atelectasis	158	8.3	5.2
Mechanical ventilation >72 h	84	4.4	2.8
Total	583	30.8	19.5
Cardiovascular			
Arrhythmias	233	12.3	7.7
Pulmonary embolism	15	0.8	0.5
Acute myocardial infarction	13	0.6	0.4
Congestive heart failure	23	1.2	0.7
Acute edema	22	1.1	0.7
Acute cerebrovascular accident	15	0.8	0.5
Total	321	16.9	10.7
Extrathoracic complications			
Sepsis	47	2.4	1.5
Multiorgan failure	49	2.6	1.6
Others	203	10.7	6.7
Total	299	15.8	9.9
No. of complications	1890		
No. of patients with complications	1057		
Single complications	654 (21.8%)		
Several complications	403 (13.4%)		

TABLE 4
**Mortality According to the Type of Complication
(for Single Complications Only)**

Complications	No. of Patientss	Mortality, (%)	P
Related to the intervention			
Air leakage	84	0.0	0
Residual pleural cavity	42	0.0	.015
Empyema*	15	6.7	0.5
Bronchopleural fistula*	12	25.0	.8
Hemothorax	35	5.6	.3
Infection	32	3.1	.1
Pneumothorax	19	0.0	.1
Respiratory			
Pneumonia	57	10.3	.40
Respiratory insufficiency*	26	34.6	.00
Atelectasis	71	2.8	.03
Mechanical ventilation >72 h*	1	100.0	.09
Cardiovascular			
Arrhythmias	105	3.8	.02
Pulmonary embolism*	9	66.7	.00
Acute myocardial infarction*	5	60.0	.06
Congestive heart failure	3	0.0	.70
Acute edema*	8	50.0	.08
Cerebrovascular accident*	7	14.3	.40
Extrathoracic complications			
Others*	120	13.3	.06

*Major complications, mortality greater than 6.6%.

TABLE 5
Multivariate Analysis (Binary Logistic Regression)*

	P	OR
Age	.022	1.574
Air leakage	.029	0.226
Residual pleural cavity	.023	0.174
Bronchopleural fistula	.000	16.376
Hemothorax	.040	2.511
Pneumonia	.000	3.057
Respiratory insufficiency	.000	8.346
Pulmonary embolism	.000	23.773
Acute myocardial infarction	.000	59.716
Acute edema	.000	35.353
Cerebrovascular accident	.008	7.047
Sepsis	.001	5.834
Multiorgan failure	.000	10.194
Others	.000	3.741

*OR indicates odds ratio.

TABLE 6
Mortality Related to the Number of Complications

Morbidity	Mortality, %
No morbidity	1.0
Single complication	9.2
2 complications	14.8
≥3 complications	48.2

offers the best chance of survival when resection is complete, regardless of whether the procedure is associated with other treatments. However, this type of surgery is also associated with a certain risk that has to be determined and evaluated.

In 1997, our group carried out a preliminary study of the morbidity and mortality in a population of 605 patients.[3] In the present study, the morbidity (35.2%) is similar to that pilot study and is still greater than the rates reported in some series.[2,9,10] The prospective design of the present study may partly explain this difference, given that Delauriers et al[11] and Ginsberg[12] have reported clear differences in mortality according to the study design. Nevertheless, certain other studies have reported similar morbidity rates to those we found.[5,6,11]

Normally, complications are classified as major or minor according to clinical criteria,[12,13] although some authors[10] prefer a classification according to whether the patient is admitted to an intensive care unit (major complications) or to a thoracic surgery department (minor complications). Therefore, the classification of complications as major or minor is subject to a certain degree of subjectivity and variability. We also used clinical criteria to classify the complications. Major complications were those which, when reported as a single complication, were associated with a higher mortality than the overall mortality in our series (6.8%). This approach for classifying major complications is in line with that normally used by other investigators.[10,11,13] Respiratory insufficiency, pneumonia, bronchial fistula, cardiovascular disease, sepsis, and multiorgan failure were the most common major complications. Only hemothorax, classified as a

major complication in some series,[13] was associated with a slightly lower mortality rate than the predefined limit, and so we defined this complication as minor. The multivariate analysis confirmed the seriousness of the complications classified as major. Of the major complications, cardiovascular disease was associated with the highest risk of death, followed by bronchial fistula. We should not forget the extrathoracic complications, which represent a relatively high risk of death when taken together.

Another aspect to consider is the frequency of appearance of multiple complications (reported in more than a third of our series) and the clear influence they have on mortality, although the task of unraveling the contribution of each complication to the outcome is an arduous one. We believe that our analysis can be more relevant to everyday clinical practice if we concentrate on single complications, despite their lower relative importance.

According to the analysis of type of morbidity, cardiovascular events were less common. Arrhythmia, however, is the most common complication, even though its incidence in our study (7.8%) lies at the lower limit of the rates normally reported (3.8%-40%).[14] This event occurs more often in pneumonectomized patients[14,15] (in our study, 28.7% vs 5% overall) than in other types of resection, and more often in patients over 70 years old (11.8% vs 6.3%), perhaps due to the decreased number of nodal cells, which disappear with age. As a result, arrhythmias seem to be more closely associated with the type of surgical technique used and the age of the patient than with comorbidity and functional status although, as some investigators point out,[16-19] none of the pathogenic

factors normally considered seem to be solely responsible for this complication. On the other hand, arrhythmias seem to respond well to standard treatments with digitalis, calcium channel blockers, amiodarone, etc.[14,16,20] Nevertheless, in some studies, both atrial fibrillation and atrial flutter have been associated with higher mortality.[17,21] In our study, the mortality was close to the rate of 22.7% reported in the literature for patients who also had other complications, and so the true contribution of these complications to mortality is difficult to assess. In our series, mortality associated with arrhythmia as a single complication was 3.8%.

In contrast, in our study, acute myocardial infarction and pulmonary thromboembolism were associated with high mortality, close to the upper limit normally reported. However, control of risk factors for these complications has reduced their frequency (0.43% of the patients suffered an infarction in our series). Clinically documented pulmonary thromboembolism was reported in 0.5% of the patients our series, a rate similar to the those reported by other authors,[5,22] with rates ranging from 0.3% to 2.5%. However, it is impossible to definitively rule out the possibility that some patients with cardiorespiratory failure reported as the cause of death might have actually died of pulmonary thromboembolism. When the presence of pulmonary thromboembolism was studied with specific diagnostic tests within the first 30 days of the operation, the reported incidence was 5%, but higher in patients with large tumors, advanced stage disease, and large resections.[23] The incidence of acute pulmonary edema, which is strongly associated with mortality, was also similar in our series compared to previous studies, in which the incidence varied from 0.4% to 3%.[24,25]

The most common complications were purely surgical ones. Of these, the most common were air leakage and complications associated with the pleural cavity. Pleural empyema and bronchial fistula were less common but the repercussions were more serious. The frequency of these events—3.2% for pleural empyema and 3% for bronchial fistula—correspond to the frequencies normally reported.[17,26] As in other series consulted,[22] these complications are of great clinical importance and occur above all in patients who undergo pneumonectomy. They are associated with high mortality (in our series, 37.4% of the patients with bronchopleural fistula died). Hemothorax, classified as a major complication in some series,[13] was associated with a slightly lower mortality rate than the predefined limit, and so we classed this complication as minor. The incidence of this event usually ranges from 1% to 4%[22,26]; in our series, it was reported in 2.3% and required further surgery in most cases (82.6%).

Respiratory complications can interact with one another to form a vicious circle. Thus, complications such as atelectasis, pneumonia, and respiratory insufficiency may arise in conditions of increased respiratory load, decreased lung compliance, and/or decreased surfactant function. The patient may also present with pain, unproductive coughing, and hypoventilation. In our study, the frequency of such complications was close to that usually reported,[11,22] although pneumonia incidence rates reported

in the literature for patients who underwent thoracotomy are very variable (between 2% and 22%[5,11,22] depending largely on the diagnostic methods used). Respiratory insufficiency is due mainly to pulmonary complications such as pneumonia, atelectasis, pulmonary embolism, and respiratory distress, and to others that are not specifically pulmonary such as acute pulmonary edema and bronchopleural fistula.

The surgical mortality associated with lung resection has decreased over recent years due largely to better patient selection and better perioperative care. Even so, the mean mortality is still 3.5%, and ranges from 1% to 8.1%.[5,9,27-29] This wide range of mortality seems to be related to 2 very different factors: first, the risk factors themselves such as functional status of the patient, concurrent disease, and treatment, and, second, sampling, which includes factors such as study design, surgical experience, and hospital turnover, as discussed by some investigators.[26,30,31] The mortality in our study was 6.8%, which is at the upper limit of the rate normally reported, although similar to that of other large series.[6,31] The high mortality observed may have arisen because of the presence of adverse risk factors (such as extensive comorbidity and a high number of pneumonectomies) and because this was a series with participants from different centers. On the other hand, although mortality ranged from 0% to 11.6% in the different hospitals of the group, this difference could not be accounted for by specific factors that have occasionally been cited to explain such variation[6,31] (such as different case loads, number of surgeons/number of procedures, or differences in indications[32]). We were unable to assess other factors which might be described as "quality of health care" for each center.

In summary, we can conclude that surgical treatment of bronchogenic carcinoma in Spain is associated with high morbidity and mortality, the morbidity rate being close to rates normally reported in the literature and the mortality rate lying at the upper limit. Mortality varies widely among the published series, perhaps suggesting that it is subject to risk factors not normally taken into account. We should also bear in mind the increased risk associated with major complications and multiple complications. In any case, the data presented here may serve as a reference for assessing surgical risk for lung cancer operations in Spain.

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APPENDIX 1
Definition of Postoperative Complications, Case Report Form of the Bronchogenic Carcinoma Registry of the Bronchogenic Carcinoma Cooperative Group (GCCB-S) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)

1. *Arrhythmias.* Any electrocardiographically documented arrhythmia not present before surgery that appears during the postoperative period and that requires specific treatment.

2. *Acute myocardial infarction.* Diagnosed by electrocardiography and presence of biochemical markers.

3. *Congestive heart failure.* Clinical signs and symptoms (dyspnea, orthopnea, nocturnal paroxysmal dyspnea, tachycardia, jugular venous distension, ventricular gallop, crackling sounds at rest, peripheral edema) and radiological signs (cardiomegalia, pulmonary venous congestion) indicative of congestive heart failure.

4. *Thromboembolism.* Diagnosed by perfusion or ventilation–perfusion scintigraphy or angiography.

5. *Acute postpneumonectomy edema.* Noncardiogenic edema that presents with pulmonary artery hypertension and normal occlusion pressure of the pulmonary artery. There should be at least one x-ray showing acute pulmonary edema and hemodynamic data obtained by Swan–Ganz catheterization.

6. *Cerebrovascular accident.* Clinical signs and symptoms should be present, and if possible a computed tomography scan of the brain should have been done. It should be possible to determine whether the stroke was hemorrhagic (intracranial or subarachnoid) or occlusive (transient ischemic attack, developing infarction, established infarction, or lacunar infarction).

7. *Atelectasis.* At least one bronchoscopic intervention is needed for resolution.

8. *Pneumonia.* Appearance of new persistent infiltrate with fever, once other causes have been ruled out.

9. *Bronchial fistula.* Presence of partial or complete dehiscence of the suture of the bronchial stump after pneumonectomy, lobectomy, bilobectomy, or routine segmentectomy, confirmed by bronchoscopy, regardless of treatment applied.

10. *Air leakage for more than 7 days.* Leakage of air through pleural drainage tubes for more than 7 days, not due to bronchial fistula.

11. *Pleural cavity.* Air, fluid, or both in the pleural cavity (except for pneumonectomies), regardless of the treatment required, for 7 days or more, whether or not associated with persistent air leakage.

12. *Postoperative pneumothorax.* After less extensive resections than pneumonectomy, air trapping in the pleural cavity after the pleural drainage tube has been removed. Treatment is required (usually deployment of a new drainage catheter). Small residual pneumothoraces should not be included here if they do not compromise the patient's functional status and if they resolve spontaneously.

13. *Empyema.* Presence of pus in the pleural cavity or positive pleural fluid culture.

14. *Sepsis.* Infectious state, requiring at least 2 of the following criteria for diagnosis:

    – Temperature >39ºC or <36ºC.
    – Leukocyte count <3000 or >12 000.
    – Blood culture positive for pathogen.
    – Documented or probable focus of infection in which a pathogen has been cultivated, associated with a harmful systemic effect such as:

      a) metabolic acidosis of unknown cause
      b) base excess > –5 mEq/L
      c) systemic vascular resistance<0} <800 dynes/s/cm^5
      d) unexplained hypotension; and
      e) systolic blood pressure <90 mm Hg for more than 2 hours

15. *Hemothorax requiring treatment.* Accumulation of blood in the operated hemothorax, needing treatment (pleural drainage, thoracoscopy, or rethoracotomy).

16. *Severe respiratory insufficiency.* PaO_2 less than 50 mm Hg or $PaCO_2$ more than 46 mm Hg at an inspiratory oxygen fraction of 0.21 (values not reported prior to surgery).

17. *Prolonged respiratory insufficiency.* More than 7 days with PaO_2 less than 60 mm Hg at an inspired oxygen fraction of 0.21.

18. *Multiorgan failure.* Sequential pathological state with progressive involvement of different organs and systems (failure of 2 or more organ systems needed, with no prior disease, and not related to the current process) that appears after chemical aggression or trauma.