Early and long-term results of lung resection for non-small-cell lung cancer in patients with severe ventilatory impairment

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Abstract

Objective: To study clinical characteristics, surgical treatment modalities, early and long-term outcome of patients with severe ventilatory impairment undergoing lung resection for NSCLC. Methods: We performed a retrospective review of clinical records of all patients with severe chronic ventilatory impairment (FEV1 and/or FVC ≤ 50% of predicted values) operated on for NSCLC in a 21-year period (1983-2003). Results: One hundred and six patients were operated on. Mean FEV1 and FVC were 40% (range 23-50%) and 69% (17-117%), respectively. Twenty-two patients needed prolonged (> 48 h) mechanical ventilation. Overall mean ppoFEV1 loss was 9.1% (0–34%). If ppoFEV1 loss was lower than 30%, Sixteen pneumonectomies, 73 lobectomies and 17 sublobar resections were carried out. Pathologic stages were I, II, IIIA and IIIB in 58, 26, 18 and 4 cases, respectively. Resection was complete in 104 patients. Operative mortality and morbidity were 8.5% (39%), respiratory function was considered subjectively improved, stable and worsened in 6 (7%), 62 (73%) and 17 (20%) cases, respectively. Twenty-two patients needed prolonged (>48 h) mechanical ventilation. Overall mean ppoFEV1 loss was 9.1% (0–34%). If ppoFEV1 loss was > 15%, the morbidity rate was 100%. Mean PaCO2 and ppoFEV1 loss were higher among patients who died (41 mmHg versus 37 mmHg, \( P < 0.02 \)) and 39 mmHg and ppoFEV1 loss > 15% (\( n = 9 \)), mortality rate was 33%. Overall 1-year and 5-year survival rates were 82 and 33%, respectively. Respiratory failure was the cause of late death in 2 patients. Among patients available at follow-up (\( n = 85 \)), respiratory function was considered subjectively improved, stable and worsened in 6 (7%), 62 (73%) and 17 (20%) cases, respectively. Eleven patients needed continuous oxygen therapy. Conclusions: Lung resection should not be denied a priori in patients with severe ventilatory impairment. Evaluation of predicted post-operative function often allows major resections, which are functionally economic, at the price of a high operative morbidity. Operative mortality, long-term survival and respiratory function are acceptable in the absence of a valid therapeutic alternative.

Keywords: Lung cancer; Lung resection; Ventilatory impairment; Spirometry; FEV1; FVC

1. Introduction

Surgery remains the best treatment option of non-small cell lung cancer (NSCLC). It is generally believed that the existence of chronic ventilatory impairment (CVI) may limit possibilities of exeresis and increase operative morbidity and mortality. As a general rule in NSCLC surgery, intervention may be planned only if a complete exeresis is anticipated, with an acceptable operative risk and a satisfactory long-term quality of life.

The choice of methods for functional assessment as well as the determination of cut-off values indicating inoperability in patients with CVI remain uncertain. On the other hand few studies have specifically evaluated results of exeresis for NSCLC in patients with severe CVI. The aim of the present study was to report our experience in surgical treatment of NSCLC in patients with severe CVI, in order to evaluate operative morbidity and mortality as well as long-term survival and functional status.

2. Methods

We retrospectively reviewed the clinical records of all patients who underwent surgery in a curative intent for NSCLC in a 21-year period (January 1983–December 2003). The same surgical team operated on all the patients, at the Marie Lannelongue Surgical Center (Le Plessis Robinson, France) up to August 2000 and at the Hôtel-Dieu Hôpital (Paris, France) thereafter. All the patients with CVI defined according to the European Respiratory Society criteria (Forced Vital Capacity [FVC] and/or Forced Expiratory Volume in 1 s [FEV1] ≤ 50% of predicted value) [1] constituted the population of the present study. In all the cases repeated lung function tests were carried out in our Institution before the operation, as recommended [2], after
a short course (2-3 weeks) of chest physiotherapy and optimal medical treatment. On the same occasion, reversibility test with inhaled beta-2 agonist agents was carried out and possible increase in FVC and FEV1 calculated. Patients were excluded from the study if the post-bronchodilator FEV1 was ≥ 55% of predicted value.

In all the patients pre-operative evaluation included their history, physical examination, routine blood tests, electrocardiography, spirometry, and perfusion lung scan. Cardiac echography was carried out in case of history of cardiac disorders or if a pneumonectomy was anticipated. Myocardial isotopic scan was performed in patients with known or suspected coronary artery disease and coronarography was prescribed in the case of abnormality of the latter. Doppler of supraaortic vessels was carried out in patients aged more than 65 years or in the case of previous cerebrovascular accident. Diffusion capacity of the lung for carbon monoxide (DLCO) determination as well as exercise tests were performed on the care of referring chest physicians, so no uniform protocol was adopted. Right heart catheterisation with temporary occlusion of pulmonary artery of the affected side was carried out in patients with predicted post-operative FEV1 (ppoFEV1) between 30 and 35%, and/or PaO2 < 65 mmHg, if a pneumonectomy was anticipated.

Staging protocol included in all the cases chest X-ray, fiberoptic bronchoscopy, thoracic and upper abdominal CT scan. Cerebral CT scan was performed in the presence of cancer-related symptoms or if N2 disease was suspected. Isotopic bone scan was performed in the presence of bone pain and/or abnormalities in serum calcium or alkaline phosphatase.

The extent of maximal possible exeresis was based on the assessment of ppoFEV1. This value was calculated on the basis of best post-bronchodilator FEV1. ppoFEV1 loss was thus obtained by taking into account the function of the affected lung determined by perfusion lung scan (3): in case of anticipated pneumonectomy, the following equation was applied:

\[ \text{ppoFEV1} = \frac{\text{ppoFEV1 loss}}{\text{ppoFEV1}} \times \text{perfusion of affected lung as \% of total lung perfusion} \]

If a lobectomy was anticipated, the following equation was applied:

\[ \text{ppoFEV1 loss} = \frac{\text{ppoFEV1 loss}}{\text{ppoFEV1}} \times \frac{\text{number of functional segments of the resected lobe}}{\text{total number of segments of the affected lung}} \]

Subsequently, ppoFEV1 was calculated:

\[ \text{ppoFEV1} = \frac{\text{ppoFEV1 loss}}{\text{ppoFEV1}} \times \text{ppoFEV1} \]

If a pneumonectomy was anticipated on the basis of pre-operative work-up, it was contraindicated (‘mandatory’ lobectomy) if ppoFEV1 was lower than 30% or if right heart catheterisation with pulmonary artery occlusion showed pulmonary artery hypertension (mean pressure higher than 25 mmHg, pre- post-occlusion gradient higher than 6 mmHg, arterial desaturation during occlusion). Lobectomy was contraindicated (‘mandatory’ segmentectomy or wedge resection) if ppoFEV1 was lower than 30%. Possible predominance of affected lung, existence of associated extra-pulmonary co-morbidities, and performance status were taken into account to determine the maximal exeresis possible, regardless of ppoFEV1.

In case of incomplete fissures, their opening was achieved by automatic stapler devices. In the last 5 years, staple lines were reinforced with expanded polytetrafluorethylene in case of emphysematous changes of the lung.

In the first part of the study, part of patients underwent nodal mediastinal picking, part full nodal dissection, whereas in the second part of the study, all underwent complete dissection. Radiotherapy or chemotherapy was performed under the care of referring physicians, so no uniform protocol was employed.

Operative mortality was calculated by taking into account all the deaths occurring within 30 days from the operation or during the hospitalisation. All complications occurring during this period were collected. Patients were divided in two groups according to the occurrence or not of post-operative complications, in order to identify factors predicting a complicated post-operative course. The following parameters were evaluated by univariate and multivariate analysis: age, sex, obesity, FEV1, FVC, FEV1/FVC, total lung capacity (TLC) (all expressed both in liters and percentage of predicted values), arterial gas analysis, function of the affected lung evaluated by perfusion lung scan, consumption of O2 at peak of effort (VO2 max, when performed and expressed as both ml/kg/min and % of predicted), history of heart disease, ppoFEV1 loss, ppoFEV1, ppoVO2max, and type of operation.

Long-term follow-up was obtained by referring pneumologists, who filled a questionnaire collecting data on the evolution of lung cancer, patient’s functional status (evaluated subjectively: improved, stable or worsened after the operation), smoke stopping, lung function test (performed at least 3 months post-operatively). In the absence of a clinical follow-up, information on possible death was obtained by the municipality.

Factors negatively affecting survival and post-operative functional status were also evaluated: together with the above-mentioned variables, pathologic TNM was assessed. Percentage and mean comparisons, multivariate analysis (by logistic regression method and Cox’s model), correlation tests and survival plots (according to the Kaplan-Meyer method, including operative mortality) were carried out with the SEM statistical package [4]. Results were considered significant if the P-value was less than 0.05.

3. Results

One hundred and six patients with potentially resectable NSCLC and severe CVI were operated on during the study period (86 in the first part, and 20 in the second one). They corresponded to 1.4% of patients with NSCLC treated by surgery in the same period by our team. There were 99 men and 7 women; mean age was 62 years (range 36-79). Ten patients had a marked obesity, defined as more than 20% of
ideal body weight defined according to the Broca index (ideal body weight = size in cm – 100). All the patients had a history of tobacco smoking (mean 52 pack/year), two/third of them had stopped tobacco consumption more than 1 month previously. Six patients had a history of controlateral lung resection (4 lobectomies, 1 bilobectomy, 1 segmentectomy), whereas 66 patients (62%) had associated comorbidities (Table 1).

4. Pre-operative functional assessment

Obstructive, restrictive, and combined CVI was present in 87 (82%), 1, and 18 (17%) cases, respectively. Results of initial spirometry are summarized in Table 2. Two patients had long-term domiciliary oxygen therapy.

Ninety-six (90%) patients had an improvement in FEV1 after beta-2 agonist stimulation (mean FEV1 increase = 14%). At perfusion lung scan, the affected lung was responsible, on the average, for 42% (range 0-82%) of total lung perfusion. The affected lung was predominant (more than 50% of total lung perfusion) in 37 patients (35%).

Mean DLCO (performed in 10 cases) was 49% (25-97%). In 29 patients (27%) an exercise test with VO2max determination was performed: mean value was 17.4 ml/kg/min (range 10-26), corresponding to 64% of predicted value (40-80%).

5. Treatment

All the patients underwent lung resection; a tracheotomy was performed in 26 cases (24%) within the second post-operative day.

In 16 patients (15%) a pneumonectomy (left-sided, n = 10; right-sided, n = 6) was carried out: it was extended to left atrium, main carina, chest wall, and muscular layer of oesophagus in 3, 2, 1, and 1 case, respectively. Seven patients had a non-functioning lung; in the remaining nine cases mean contribution of the resected lung to total lung perfusion was 25% (range 12-42%). Three patients had undergone right heart catheterisation with pulmonary artery blockage: in all the cases mean pulmonary artery pressure was lower than 25 mmHg and no change in oxygen saturation was observed.

Seventy-three patients (69%) underwent lobectomy (superior, inferior, middle, and bilobectomy in 51, 15, 2, and 5 cases, respectively). Eighteen of them had bronchial or broncho-vascular sleeve resections, whereas extended resections were performed in five cases (chest wall, n = 3; pericardium, n = 1; adjacent lobe, n = 1). In 67 patients (93%), lobectomy was considered 'mandatory' (pneumonectomy was contraindicated): 63 of them had a ppoFEV1 (post-pneumonectomy) lower than 30%, three had a baseline hypoxemia, and one had severe comorbidities.

Seventeen patients (16%) had a sub-lobar resection (segmentectomy, n = 7; wedge resection, n = 10). In two/third of them the operated lung was dominant. Lobectomy was contraindicated for ppoFEV1 (post-lobectomy) lower than 30% (n = 8), associated co-morbidities (n = 4), markedly dominant lung (n = 4), and baseline hypoxemia (n = 1).

If all the patients are considered together, mean ppoFEV1 loss was 9% (0-34%). ppoFEV1 loss was similar in patients undergoing lobectomy and in those undergoing pneumonectomy. The groups of different surgical treatment (pneumonectomy, lobectomy, sublobar resections) did not differ with respect to ppoFEV1 (Table 3).

Two patients underwent induction chemotherapy. Adjuvant treatments were administered in 10 patients (radiotherapy, n = 7, chemotherapy, n = 2; radio-chemotherapy, n = 1). No uniform protocol was adopted.

6. Pathologic examination

There were 64 squamous cell carcinomas, 30 adenocarcinomas, 6 large cell carcinomas, 3 mixed cellularity carcinomas (adenocarcinoma and epidermoid carcinoma, n = 2; small cell carcinoma and epidermoid carcinoma, n = 1), 2 neuroendocrine carcinomas, and 1 undifferentiated carcinoma. Pathologic stages were I, II, IIIa, and IIIIB in 58 (55%), 26 (24%), 18 (17%), and 4 (4%) cases, respectively.

Table 2

Pre-operative functional assessment (n = 106)

<table>
<thead>
<tr>
<th>FEV1 (L)</th>
<th>FEV1 (% of predicted)</th>
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<tbody>
<tr>
<td>1.17 (0.62-1.77)</td>
<td>40 (23-50)</td>
</tr>
<tr>
<td>&lt;30, n = 11</td>
<td>30-39, n = 39</td>
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<tr>
<td>40-50, n = 56</td>
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<tr>
<th>FVC (L)</th>
<th>FVC (% of predicted)</th>
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<tbody>
<tr>
<td>2.67 (1.20-4.19)</td>
<td>69 (17-117)</td>
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<tr>
<td>44 (23-77)</td>
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<tr>
<th>TLC (L)</th>
<th>TLC (% of predicted)</th>
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<tbody>
<tr>
<td>6.3 (3.07-14.3)</td>
<td>101 (54-202)</td>
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<td>72 (54-93)</td>
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<tr>
<th>PaO2 (mmHg)</th>
<th>PaCO2 (mmHg)</th>
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<tr>
<td>&lt;65, n = 18</td>
<td>37 (22-49)</td>
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<tr>
<td>&gt;42, n = 9</td>
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Values are expressed as mean and ranges (in parentheses).
Among patients treated by sublobar resections, 15 had stage I disease, and 2 stage IIIa disease. A pathological completed resection was achieved in 104 cases (98%) and only two patients had microscopical residual disease.

### 7. Post-operative outcome

Ninety-five percent of patients went to the intensive care unit (ICU) post-operatively. Post-operative course was uneventful in 32 patients (30%), with no need of prolonged mechanical ventilation (more than 24 h) and a mean hospital stay of 13 days (4 days in ICU).

Seventy-four patients (70%) experienced post-operative complications. Mean hospital stay in these patients was 20 days (range 6–90) and mean ICU stay was 12 days. Forty-five patients had respiratory complications, whereas cardiovascular, surgical and miscellaneous adverse events occurred in 23, 26, and 11 cases, respectively (Table 4). Twenty-two of them needed prolonged mechanical ventilation (more than 48 h), which lasted on the average 11 days (2–75 days).

Nine (8.5%) patients died, after lobectomy, segmentectomy, and pneumonectomy in 6, 2, and 1 case, respectively. Causes of death were pneumonia (n = 6), pulmonary embolism (n = 2), and intestinal infarction (n = 1).

Among patients treated by lobectomy (with exclusion of middle lobectomy or bilobectomy), no significant difference was observed in terms of morbidity (74% versus 66%) or mortality (7.84% versus 6.67%) after upper and lower lobectomy, respectively.

### 8. Long-term outcome

Ninety-five out of 97 operative survivors (97.9%) were available at long-term follow-up (mean 41 months, range 1–168). Eighty-five out of 97 patients (87.6%) were seen at the outpatient clinic, whereas in the remaining 10 patients (10.3%) information about possible death was obtained by the municipality.

Overall 1- and 5-year survival rates were 82 and 33%, respectively (Fig. 1). Median survival was 50 months and 25 months for stage I and stages II–III disease, respectively
(P=0.01, Fig. 2). No other factor influencing significantly the survival was identified.

Late deaths occurred in 67 out of 97 patients (69.1%): tumor recurrence (both local and metastatic), cardiovascular events, second primary cancer, pneumonia, and miscellaneous causes were responsible for deaths in 25 (37%), 6, 5, 4, and 3 cases, respectively. Two patients (treated by lobectomy) died of respiratory failure 5 and 31 months postoperatively. The cause of death was unknown in 22 out of 67 patients (32.8%).

Late functional status was evaluated in 85 patients (17 months post-operatively on the average). Nine of them continued tobacco smoking. Functional status was considered, as compared to the pre-operative conditions, improved, stable or worsened in 6 (7%), 62 (73%), and 17 (20%) cases, respectively. Among these last patients, 11 needed long-term oxygen therapy. Three of them continued tobacco smoking.

ppoFEV1 was significantly lower in patients who needed long-term oxygen therapy, as compared to the other ones (40% versus 35%, P=0.026). No patient with a ppo FEV1 higher than 43% needed late long-term oxygen therapy.

Forty-six patients had post-operative spirometry (Table 6). Post-operative FEV1 was relatively well predicted by ppoFEV1. Lung resection resulted in a moderate but significant reduction in FEV1: mean values decreased from 1.18 to 1.07 L. When patient with TLC >120% were considered alone, the reduction of FEV1 (both expressed in liters and as percent of predicted) was much less pronounced and did not reach significance. Only six patients treated by upper lobectomy with TLC >120% had post-operative spirometry. They also experienced a very low (not significant) decrease in terms of FEV1.

9. Discussion

Several studies were carried out in the attempt of defining respiratory function parameters predicting operative risk. It is generally believed that pre-operative standard spirometry allows identifying a group of patients with a high operative risk. In some authors’ opinion the value of pre-operative FEV1 would establish the maximal possible exeresis: 2 L for pneumonectomy, 1 L for lobectomy, 0.6 L for wedge resection [5]. Of note this value does not take into account the amount of resected functional parenchyma. Thus it was suggested that calculation of ppo respiratory function would be determinant in establishing limits of resectability: Olsen [6] introduced the concept that a ppoFEV1 lower than 800 ml would contraindicate a pneumonectomy or a lobectomy. On the other hand according to several authors [7-10] ppoFEV1 should be expressed as percentage of predicted value, in order to take into account variations related to sex, age, and height. According to these authors a ppoFEV1 higher than 40% would not contraindicate any resection, whereas a ppoFEV1 lower than 40% would indicate a high operative risk, and a ppoFEV1 lower than 30% a prohibitive risk. This last figure is essentially derived from knowledge of natural history of COPD: patients with a FEV1 of approximately 1 L have a yearly mortality rate of about 10% [11]. In fact 1 L corresponds to 30% of predicted FEV1 in a male subject aged 50 years and of 170 cm height [2]. On the other hand, among patients with COPD treated by long-term oxygen therapy, a FEV1 lower than 30% represents an independent risk of poor outcome [12].

Other techniques (DLCO determination, exercise tests with determination of VO2max) would allow establishing other limits indicating a prohibitive risk. A DLCO lower than 60% [13], a ppoDLCO lower than 40% [7], a VO2max lower than 15 ml/kg/min [14], a VO2max lower lower than 60% of predicted value [15], a ppoVO2max lower than 10 ml/kg/min [16] have all been identified as important indicators of high operative risk.

In our experience the most important criterion to determine the functional possibility of lung resection was the ppoFEV1, the lower limit being 30%. Anyway no value can be considered sufficient to predict accurately the possibility of surgery in a single patient, especially in case of very severe respiratory impairment [17]. The integration of several parameters including lung function tests, associated comorbidities, performance status is, in our opinion, of paramount importance in this judgment.

In our series a surgical treatment with a curative intent was possible in the great majority of cases (complete exeresis rate of 98%). To this purpose in 18 out of 73 lobectomy a sleeve resection (bronchial, arterial or...
Values are expressed as mean and ranges (in parentheses).

Table 6
Pre-operative and post-operative FEV1

<table>
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<tr>
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<th>Pre-operative</th>
<th>Post-operative</th>
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<tbody>
<tr>
<td>FEV1 (L) (n = 46)</td>
<td>1.18 (0.62–1.65)</td>
<td>1.07 (0.62–1.76)</td>
</tr>
<tr>
<td>FEV1 (% of predicted) (n = 46)</td>
<td>40.0 (23–50)</td>
<td>37 (19–54)</td>
</tr>
<tr>
<td>Predicted post-operative FEV1 (% of predicted) (n = 46)</td>
<td>38.9 (27–53)</td>
<td>37 (19–54)</td>
</tr>
<tr>
<td>FEV1 (L) (patients with pre-operative TLC &lt;120%, n = 32)</td>
<td>1.18 (0.62–1.77)</td>
<td>1.046 (0.62–1.46)</td>
</tr>
<tr>
<td>FEV1 (% of predicted) (patients with pre-operative TLC &lt;120%, n = 32)</td>
<td>40.6 (23–53)</td>
<td>37.6 (22–54)</td>
</tr>
<tr>
<td>FEV1 (L) (patients with pre-operative TLC &gt;120%, n = 15)</td>
<td>1.15 (0.7–1.73)</td>
<td>1.13 (0.65–1.76)</td>
</tr>
<tr>
<td>FEV1 (% of predicted) (patients with pre-operative TLC &gt;120%, n = 15)</td>
<td>37.9 (23–53)</td>
<td>35.7 (19–50)</td>
</tr>
<tr>
<td>FEV1 (L) (patients with pre-operative TLC &gt;120% undergoing upper lobectomy, n = 6)</td>
<td>1.208 (0.7–1.73)</td>
<td>1.17 (0.65–1.76)</td>
</tr>
<tr>
<td>FEV1 (% of predicted) (patients with pre-operative TLC &gt;120% undergoing upper lobectomy, n = 6)</td>
<td>38.8 (23–53)</td>
<td>36.8 (19–50)</td>
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</table>

In our patients the occurrence of an infectious pneumonia was a life-threatening event, responsible of eight out of nine deaths.

In our patients only the ppo functional loss influenced negatively the morbidity, whereas only the PaCO2 influenced the mortality. The other factors, which are classically believed to negatively affect the post-operative outcome (pre-operative and ppo respiratory function and VO2max as well as the extra-respiratory comorbidities) were not determinant in influencing the occurrence of complications. Similar results have been published by Cerfolio et al. [21], who did not find any predictive factor of post-operative complications in a series dealing with 85 patients with airflow limitation (FEV1 lower than 1.2 L) undergoing lung resection for NSCLC. These authors reported a low mortality rate (2.4%), but in their experience, 41% of patients underwent sublobar resections (wedge resection or segmentectomy).

Not surprisingly 5-year survival rate of our patients was relatively low (overall 5-year survival, 33%; 5-year survival in stage I disease, 44%), probably because of the poor respiratory reserve, responsible by itself for a part of mortality [11]. Our long-term results are similar to those published in the few series reporting 5-year survival rates in patients with limited respiratory reserve: in stage I disease values of 54% have been reported [21], whereas overall survival rates (regardless of the stage) ranging 29-44% have been published [21-22].

In these patients with a high operative risk, other therapeutic options can be discussed. Walsh et al. [23] enrolled 66 patients (FEV1 or ppoFEV1 lower than 40% or PaCO2 higher than 45 mmHg) which were further selected on the basis of results of the exercise test. Twenty-five patients (20 of them with a VO2max>15 ml/kg/min, and five with a VO2max<15 ml/kg/min) were operated on, whereas 41 (34 of them had a VO2max<15 ml/kg/min and seven refused the operation) underwent radiotherapy and/or chemotherapy. Mean survival in the surgical group was 48 months, versus 17 months in the medical group (P = 0.0014).

In the absence of a prospective data collection, it was not possible to objectively evaluate late quality of life. On the other hand, 80% of patients did not experience a subjective worsening of respiratory function and few changes were evident at lung function tests. As in previous
studies [3] ppoFEV1 correctly predicted post-operative FEV1. Of note in our patients, ppoFEV1 was calculated on the basis of better FEV1 obtained after administration of bronchodilators, whereas post-operative FEV1 was measured at baseline.

We conclude that a complete exeresis is possible in selected patients with severe airflow limitation. The mobilization of respiratory reserve with bronchodilator therapy and the evaluation of functioning parenchyma to be resected allow an exact planning of resection: oncologically satisfactory but functionally economic. These interventions carry a high morbidity requiring a heavy and expensive management in the intensive care unit. In the absence of valid therapeutic alternatives, long-term survival has to be considered acceptable at the price of a worsening of respiratory status in 20% of cases.

References


