Lung Cancer Resection*

The Prediction of Postsurgical Outcomes Should Include Long-term Functional Results

Massimiliano Beccaria, MD; Angelo Corsico, MD; Paola Fulgoni, MD; Maria Cristina Zoia, MD; Lucio Casali, MD; Giulio Orlandoni, MD; and Isa Cerveri, MD

Study objectives: To assess (1) the possibility of predicting long-term postoperative lung function, and (2) the usefulness of maximal oxygen consumption (\(\dot{V}O_2\text{max}\)) as a criterion for operability and as a predictor of long-term disability.

Design: Prospective study.

Setting: Outpatients and inpatients of a university hospital.

Participants: Sixty-two consecutive patients (mean ± SD age, 62 ± 8 years; 51 male and 11 female patients) were preoperatively evaluated for lung cancer resection (pneumonectomy or bilobectomy [n = 14] and lobectomy [n = 48]).

Measurements: Clinical examination and recorded respiratory symptoms and spirometry results before surgery and 6 months after surgery. If predicted postoperative FEV1 (ppoFEV1) was < 40%, patients underwent exercise testing; if \(\dot{V}O_2\text{max}\) was between 10 mL/kg/min and 20 mL/kg/min, patients underwent a split-function study.

Results: All the patients with ppoFEV1 ≥ 40%—even those patients (26%) with FEV1 < 80%—underwent thoracotomy without further tests. Seven patients with ppoFEV1 < 40% underwent exercise testing, and three of them underwent a split-function study. Nine patients (15%; including six patients with COPD and one patient with asthma) had immediate postoperative complications (pneumonia [n = 5] and respiratory failure [n = 4]); seven of these patients had ppoFEV1 ≥ 40%. ppoFEV1 significantly underestimated the actual postoperative FEV1 (ppoFEV1; p < 0.001) 6 months after pneumonectomy or bilobectomy but was reliable for actual \(\dot{V}O_2\text{max}\) after lobectomy. Two patients with predicted postoperative \(\dot{V}O_2\text{max}\) > 10 mL/kg/min became oxygen dependent and had marked limitation of daily living.

Conclusions: ppoFEV1 ≥ 40% reliably identifies patients not requiring further tests and not at long-term risk of respiratory disability. \(\dot{V}O_2\text{max}\), effective for defining the immediate surgical risk, is not useful in predicting long-term disability.

Key words: lung neoplasms; postoperative complications; respiratory function tests; thoracotomy

Abbreviations: DLco = diffusion capacity of the lung for carbon monoxide; poFEV1 = postoperative FEV1; ppoFEV1 = predicted postoperative FEV1; ppo\(\dot{V}O_2\text{max}\) = predicted postoperative maximal oxygen consumption; TLC = total lung capacity; \(\dot{V}O_2\text{max}\) = maximal oxygen consumption

Because of common etiologic factors, patients with lung cancer frequently suffer from chronic airway obstruction and/or cardiovascular diseases.1 This puts them at increased postoperative risk of permanent respiratory disability and death. More advanced surgical and perioperative care techniques have reduced immediate postoperative risks and have extended the possibility of surgical resection to even more compromised patients who, although they survive the operation, are perhaps at risk of long-term physical debility and permanent ventilator and/or oxygen dependence.2–4 Many patients with lung cancer are old, and pulmonary resection affects quality of life substantially.5 Chronic respiratory insufficiency as a sequel of surgery is a dramatic event that patients and their relatives can find hard to accept, and can also be a heavy socioeconomic burden. A recent editorial published in CHEST6 emphasized the need for more comprehensive pre-
operative evaluation and follow-up studies addressed not only to determine raw survival figures but also to assessing interim postsurgical quality of life. An important aspect has been highlighted: patients do not regard immediate postoperative complications as sufficient cause to forego important surgery, while they do consider physical debility as extremely undesirable. Thus, long-term functional results after resection should be considered with particular care before deciding on surgery, and the final decision should not be made without also informing patients fully about their long-term postsurgical quality of life. However, the majority of the most recent studies have tried to identify preoperative variables that can identify high-risk patients in whom surgery should not be attempted and that predict immediate postoperative morbidity for patients undergoing lung resection, and have not considered long-term outcomes.

We therefore designed a prospective study in a sample of patients undergoing lung surgery for cancer, reassessing lung function and clinical respiratory evaluation 6 months after thoracotomy. The aims of the study were to assess: (1) the possibility of a simple calculation of predicted postoperative FEV1 (ppoFEV1), based on the number of the bronchopulmonary segments removed, predicting long-term postoperative lung function loss; and (2) to evaluate the usefulness of maximal oxygen consumption (V02max) proposed as the final criterion for operability in predicting long-term disability.

**Materials and Methods**

**Patient Selection and Study Protocol**

We prospectively studied 93 consecutive patients with normal ECG findings and without any history of heart disease, who were sent from our surgery department to undergo a preoperative evaluation for resection of lung cancer. We chose to exclude patients with cardiovascular disease from our study because they undoubtedly had to undergo further specific clinical and functional evaluations. Thirty-one of the original 93 patients were unavailable for the follow-up study: 1 patient was considered inoperable on the basis of exercise testing and the split-function study; with his predicted postoperative VO2max (ppoVO2max) being < 10 mL/kg/min; 9 patients died (8 patients died at home within 6 months after surgery because of relapse, and 1 patient died immediately after surgery because of hemorrhage); 4 patients were withdrawn because they received radiotherapy or chemotherapy after the surgery; 2 patients were withdrawn because of bulllectomy concomitant with lung cancer resection; and 15 patients were living too far away or refused to undergo further follow-up studies.

The mean ± SD age of the sample was 62 ± 8 years; 51 patients were male and 11 were female, 6 were nonsmokers, 30 were smokers, and 26 were ex-smokers. Clinically, the stage of lung cancer was IA/B in 25 patients, IIA/B in 25 patients, and IIIA in 9 patients, according to international stage grouping. Of the 51 male patients, 2 patients underwent right pneumonectomy, 9 underwent left pneumonectomy, 3 underwent right bilobectomy, 10 underwent upper right lobectomy, 2 underwent medial lobectomy, 4 underwent lower right lobectomy, 12 underwent upper left lobectomy, and 9 underwent lower left lobectomy. Out of the 11 female patients, 5 underwent upper right lobectomy, 4 underwent upper left lobectomy, and 2 underwent lower left lobectomy.

All of the 62 patients included in the study analysis underwent preoperative clinical and functional assessments in the week prior to their operation, and again 6 months later. The preoperative workup included a complete clinical examination, detailed recording of respiratory symptoms, spirometry, and a carbon monoxide diffusion test. If the ppoFEV1 was < 40% of the predicted normal value, the patients underwent exercise testing; and, as suggested by Wyser et al, when VO2max was between 10 mL/kg/min and 20 mL/kg/min, they also underwent a split-function study to determine their ppoVO2max. This criterion is commonly reported in the recent literature as identifying high-risk patients. All patients were followed up prospectively after surgery, and respiratory complications occurring during the patient’s hospitalization were recorded. For the purposes of this study, we considered pneumonia, atelectasis, and respiratory failure as respiratory complications. Six months after surgery, the patients again underwent a complete clinical examination, and respiratory symptoms and results of spirometry were recorded.

**Pulmonary Function Tests**

Lung volumes were measured by a water-sealed spirometer (Pulmonet III; Sensor Medics; Anaheim, CA). Measurements were performed according to the European Community for Coal and Steel statements and to the American Thoracic Society recommendations. The best FVC measurement was recorded, as was the FEV1 and the FEV1/FVC ratio. Obstruction was defined as FEV1/FVC < 85% predicted.

Diffusion capacity of the lung for carbon monoxide (DLCO) was determined using the single-breath method (Transfercreen II; Jaeger, Wuerzburg, Germany) and corrected for hemoglobin content. Since the correction of DLCO for alveolar volume did not influence the results of our analysis, only uncorrected DLCO values are reported. Measurements were performed according to the European Community for Coal and Steel and American Thoracic Society guidelines.

ppoFEV1

ppoFEV1 was obtained using preoperative pulmonary function testing data and information on the number of bronchopulmonary segments removed (which can usually be predicted on the basis of preoperative radiologic studies). ppoFEV1 was calculated using the following formula: ppoFEV1 = ppoFEV1 × (1 − [S × 5.26]/100), where S is number of bronchopulmonary segments removed, and ppoFEV1 = postoperative FEV1. The right and left lower lobes were considered to have five bronchopulmonary segments, the right middle lobe had two bronchopulmonary segments, the right upper lobe had three bronchopulmonary segments, and the left upper lobe had four bronchopulmonary segments.

**Exercise Testing**

Exercise capacity was determined by an incremental exercise test on a cycle ergometer with breath-by-breath analysis of gas exchange (Vmax 29C; Sensor Medics). Baseline measurements were recorded after a resting period of at least 3 min on the
bicycle. The exercise protocol consisted of a 1-min warm-up period and a 10-W/min workload increase until the patient was unable to continue because of the severity of dyspnea or leg discomfort. Heart rate, ECG, and hemoglobin oxygen saturation were monitored during the exercise study. Continuous measurements of ventilation, \( \dot{V}_O_2 \), carbon dioxide production, and pulse rate were averaged every 10 s. \( \dot{V}O_2 \)max was defined as the highest oxygen consumption achieved during the exercise test.

Split-function Studies

Split-function studies of regional pulmonary function were performed using \(^{99m}\)Tc lung perfusion scans. The studies were performed with the patient in a seated upright position and breathing normally at rest. The postoperative exercise capacity was calculated by the fractional contribution of the lung tissue to be resected to overall lung function using the following formula: 

\[
ppoV_{2max} = \text{preoperative } V_{2max} \times (1 - \text{fractional contribution of tissue to be resected}).
\]

Data Analysis

All values are presented as mean ± SD. Differences between actual poFEV\(_1\) and ppoFEV\(_1\) were tested by the paired Student’s t test. Values of \( p < 0.05 \) were considered statistically significant. Differences between actual poFEV\(_1\) and ppoFEV\(_1\) were also compared using linear correlation analysis. Pneumonectomy and bilobectomy were considered together in the analyses.

Results

Table 1 reports the baseline mean values and SDs of total lung capacity (TLC), FVC, FEV\(_1\), FEV\(_1\)/FVC, and DLco for all the patients included in the study. Twenty-six patients (42%) had a history of chronic bronchitis and showed an obstructive pattern with a mean FEV\(_1\)/FVC of 81 ± 13% of predicted; 23% of them also had hyperinflation (TLC, 123 ± 7% of predicted). One patient had bronchial asthma with normal lung function. Eight patients (13%) reported dyspnea on exertion. Eighteen patients (29%) showed the presence of atelectasis or hilar disease or endobronchial involvement with radiologic signs of dysventilation; 8 of these patients had COPD. None of our patients had radiographic evidence of interstitial disease, and the impairment of DLco—when found—could be explained by the presence of COPD and/or atelectasis.

Table 2 shows the mean values and SDs of ppoFEV\(_1\) and ppoFEV\(_1\) percentage of the predicted normal value for the whole sample, and separately for patients who underwent pneumonectomy or bilobectomy and for those who underwent lobectomy. Seven patients (11%) had ppoFEV\(_1\) < 40% of the predicted normal value, the threshold considered to identify high-risk patients. All of these patients then carried out an exercise test: four patients had a \( V_{2max} > 20 \text{ mL/kg/min} \), and they were scheduled for surgery; three patients had a \( V_{2max} \) between 10 and 20 mL/kg/min and underwent a split-function study to determine their predicted postoperative lung function. Since their ppo\( V_{2max} \) was > 10 mL/kg/min, they were accepted for thoracotomy. Of these seven patients, two patients with peripheral lung cancer and COPD underwent lobectomy, and five patients with atelectasis underwent pneumonectomy (three of these patients also had COPD).

Nine patients (15%; six patients with COPD) developed immediate bronchopulmonary postoperative complications. Five of the nine patients had pneumonia, and the other four patients (including one patient with asthma and two patients with COPD) had acute respiratory failure requiring mechanical ventilation. Seven of these patients who suffered immediate postoperative complications had ppoFEV\(_1\) ≥ 40% of the predicted normal value; the two COPD patients with acute respiratory failure had ppoFEV\(_1\) < 40%. The mean hospital stay of all patients was 17 ± 11 days, and that of the patients with respiratory complications was 52 ± 3 days.

The mean values and SDs of ppoFEV\(_1\) and actual poFEV\(_1\) measured 6 months after surgery, for the whole sample and separately for patients who underwent lobectomy and for those who underwent pneumonectomy or bilobectomy, are given in Table 2. Figures 1, 2 show the linear correlation between ppoFEV\(_1\) and actual poFEV\(_1\), respectively; in patients who underwent lobectomy and in those who underwent pneumonectomy or bilobectomy. ppoFEV\(_1\) was reliable for all the patients who underwent lobectomy, while it differed significantly from the actual poFEV\(_1\) (\( p < 0.001 \)) in all the patients who underwent pneumonectomy or bilobectomy. Likewise, ppoFEV\(_1\) was significantly different from the actual poFEV\(_1\) (\( p < 0.01 \)) in the subgroup of patients with atelectasis or hilar disease or endobronchial involvement. Half of these subjects had undergone pneumonectomy or bilobectomy. Considering separately subjects with atelectasis who underwent pneumonectomy or bilobectomy and those who underwent lobectomy, ppoFEV\(_1\) significantly underestimated the actual poFEV\(_1\) only in the former group (Table 3).

Table 1—Baseline Pulmonary Function Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Absolute Value</th>
<th>% of Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, L</td>
<td>6.73 ± 1.73</td>
<td>98 ± 14</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.55 ± 0.89</td>
<td>97 ± 15</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>2.52 ± 0.63</td>
<td>89 ± 18</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>70.59 ± 12.08</td>
<td>92 ± 15</td>
</tr>
<tr>
<td>DLco, mL/min/mm Hg</td>
<td>7.16 ± 1.97</td>
<td>85 ± 23</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
Generally, our patients did not experience appreciable worsening of respiratory symptoms 6 months after thoracotomy. Four of seven patients with ppoFEV1, 40% of the predicted normal value and V˙\textsubscript{O}\textsubscript{2}\textsubscript{max}, 20 mL/kg/min, who underwent pneumonectomy, had a much higher actual poFEV\textsubscript{1} than that predicted and did not have appreciable worsening of their respiratory symptoms. Two of the three other patients with ppoFEV1, <40% of the predicted normal value and ppoV˙\textsubscript{O}\textsubscript{2}\textsubscript{max} > 10 mL/kg/min, who reported dyspnea on exertion during the preoperative clinical evaluation, at the assessment 6 months after surgery complained of severe dyspnea, were oxygen dependent, and had marked limitation in performing activities of daily living. One of them underwent pneumonectomy and the other a lobectomy; in both patients, the actual value was almost identical to the ppoFEV\textsubscript{1}, below 1 L. The third subject, who underwent lobectomy, again had an actual value very accurately predicted by ppoFEV\textsubscript{1}—just > 1 L—but did not report relevant worsening of dyspnea.

Because a large number of patients (31 of 93 patients) in this study were unavailable for follow-up, we report baseline pulmonary function data and ppoFEV\textsubscript{1} for this group (Table 4). Four of these patients (13%) had ppoFEV\textsubscript{1} < 40% of the predicted normal value and underwent an exercise test: two patients had a V˙\textsubscript{O}\textsubscript{2}\textsubscript{max} > 20 mL/kg/min and they were scheduled for surgery, and two patients had a V˙\textsubscript{O}\textsubscript{2}\textsubscript{max} between 10 mL/kg/min and 20 mL/kg/min and underwent a split-function study. One of them was considered inoperable on the basis of exercise testing results and the split-function study. Six patients (19%) developed immediate broncho-pulmonary postoperative complications (pneumonia and/or acute respiratory failure), and one of them died immediately after surgery because of hemor-

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**Figure 1.** Relationship between ppoFEV\textsubscript{1} and FEV\textsubscript{1} 6 months after surgery (actual poFEV\textsubscript{1}) in the patients who underwent lobectomy. Open triangles represent subjects with atelectasis or hilar disease or endobronchial involvement with radiologic signs of dysventilation. The regression line (slope = 0.75) for pooled patients is shown. The dotted line represents the identity.

**Figure 2.** Relationship between ppoFEV\textsubscript{1} and FEV\textsubscript{1} 6 months after surgery (actual poFEV\textsubscript{1}) in the patients who underwent pneumonectomy or bilobectomy. Open triangles represent subjects with atelectasis or hilar disease or endobronchial involvement with radiologic signs of dysventilation. The regression line (slope = 0.29) for pooled patients is shown. The dotted line represents the identity.

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**Table 2—ppoFEV\textsubscript{1} as a Percent of the Predicted Normal Value and as an Absolute Value, and FEV\textsubscript{1} 6 Months After Surgery (Actual poFEV\textsubscript{1}) in the Whole Sample, in Patients Who Underwent Pneumonectomy or Bilobectomy, and in Those Who Underwent Lobectomy**

<table>
<thead>
<tr>
<th>Variables</th>
<th>ppoFEV\textsubscript{1}, % of Predicted</th>
<th>ppoFEV\textsubscript{1}</th>
<th>p Value†</th>
<th>Actual poFEV\textsubscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>66 ± 20</td>
<td>1.85 ± 0.60</td>
<td>&lt; 0.05</td>
<td>1.96 ± 0.60</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>73 ± 16</td>
<td>2.03 ± 0.55</td>
<td>NS</td>
<td>2.04 ± 0.62</td>
</tr>
<tr>
<td>Pneumonectomy or bilobectomy</td>
<td>42 ± 9</td>
<td>1.24 ± 0.28</td>
<td>&lt; 0.001</td>
<td>1.68 ± 0.43</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. NS = not significant.
†Differences between ppoFEV\textsubscript{1} and actual poFEV\textsubscript{1}.
Table 3—ppoFEV1 and FEV1, 6 Months After Surgery (Actual poFEV1) in Subjects With Atelectasis Who Underwent Pneumonectomy or Bilobectomy and in Those Who Underwent Lobectomy*

<table>
<thead>
<tr>
<th>Variables</th>
<th>ppoFEV1</th>
<th>p Value</th>
<th>Actual poFEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>All atelectasis</td>
<td>1.57 ± 0.54</td>
<td>&lt; 0.01</td>
<td>1.86 ± 0.59</td>
</tr>
<tr>
<td>Atelectasis and lobectomy</td>
<td>1.98 ± 0.39</td>
<td>NS</td>
<td>2.16 ± 0.58</td>
</tr>
<tr>
<td>Atelectasis and pneumonectomy</td>
<td>1.16 ± 0.30</td>
<td>&lt; 0.05</td>
<td>1.56 ± 0.45</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 2 for definition of abbreviation.

rhage. These patients that were unavailable for the follow-up study had preoperative pulmonary function data, immediate surgical risk, and immediate complications similar to the 62 patients included in the study analysis.

**Discussion**

The main result of our study is that the simple calculation of ppoFEV1 correlated well with the actual poFEV1 value 6 months after surgery in all the patients who underwent lobectomy. However, this was not the case for patients who underwent pneumonectomy; in fact, in these patients, ppoFEV1 consistently underestimated the actual poFEV1 by an average of 500 mL. This finding is consistent with data previously presented by Zeiher et al.14 Even in subjects with atelectasis or hilar disease or endobronchial involvement with radiologic signs of dysventilation, the simple calculation of ppoFEV1 is not reliable.16 However, among these patients, only in those who underwent pneumonectomy did ppoFEV1 not correlate with the actual postoperative value. The bias was always an underestimation with respect to the actual poFEV1. On the basis of these results, we can state that ppoFEV1 based on the simple calculation is reliable, when ≥ 40% of the predicted normal value, in identifying patients who can undergo lung resection without further tests and without long-term risk of respiratory disability. In the algorithm proposed by Wyser et al.,8 patients with FEV1 and DLCO < 80% predicted were considered to require further tests. In our sample, 16 patients (26%) had FEV1 < 80% but ppoFEV1 ≥ 40% of the predicted normal value; according to Wyser et al.,8 these patients should undergo further tests, whereas such a test can, in fact, be avoided on the basis of the simple calculation of ppoFEV1. This is particularly important because these studies are expensive, time-consuming, and not readily available in all hospitals, while the number of patients needing lung resection is increasing and the delay between preoperative evaluation and surgery may worsen prognosis.

None of our subjects with ppoFEV1 ≥ 40% of the predicted normal values had long-term complications. ppoFEV1, besides being easy, simple, and cost saving and time saving, also offers a useful measurement for evaluating residual lung function. There was only a 15% short-term incidence of pulmonary complications after thoracotomy in our sample; this is consistent with results from other studies.8,9 Four of our five patients with pneumonia had COPD; one of the two patients with acute respiratory failure requiring mechanical ventilation was asthmatic with normal preoperative lung function. Many factors may contribute to the risk of postoperative complications, including smoking, poor general health status, older age, obesity, COPD, and asthma.17 A variety of indexes have been tested in attempts to predict pulmonary complications, but without definitive results having been reached.3,8,9,18 One of the difficulties encountered in analyzing the literature on preoperative pulmonary testing arises from a lack of consensus about what constitutes a postoperative pulmonary complication.4 Our sample was a selected one, being composed of subjects without cardiac comorbidity in whom resection was planned after evaluation of operative factors. Unfortunately, because of the small number of our subjects with complications, we could not perform a multivariate analysis. From our results, we can only argue that, independently of lung function, concomitant respiratory diseases—very common in these patients—play an important role in determining the onset of perioperative pulmonary complications.

All seven patients with ppoFEV1 < 40% of the predicted normal value were operated on, their surgical risk having been defined as acceptable on the basis of the further tests proposed by Wyser et al.8 What is an acceptable surgical risk in a disease with high mortality is, however, still an open problem,19 even if some functional cut-off values are now available.2 Olsen4 concludes an editorial by stating, “do what you and your center do best... but treat
the patient.” There is consensus in literature that resections not exceeding one lobe lead to very little permanent functional deficit, whereas pneumonectomies cause a permanent deficit that is greater for pulmonary function than for exercise capacity. However long-term problems are possible even following lobectomy if the functional situation is already critical before surgery.

As far as long-term respiratory disability is concerned, our results document that two of seven patients with ppoFEV1 < 40% of the predicted normal value and ppoVO2max > 10 mL/kg/min, thus with acceptable surgical risk, developed chronic respiratory failure, were oxygen dependent with severe dyspnea, and had a very poor quality of life. The cut-off values we used according to Wyser et al., effective for defining the immediate surgical risk, were not able to predict long-term disability in our two patients. One of these patients had only lobectomy, and even the low permanent loss in pulmonary function caused by lobectomy can be sufficient to cause severe worsening of symptoms. Indeed, it is well-known that dyspnea ratings and lung function are separate factors that independently characterize the condition of patients with COPD, even if there is a significant correlation between them. Although there are studies that describe quality-of-life issues, predictors of debility, and other poor outcomes, they have gained little attention, especially as applied to pulmonary patients with severe impairment. In any case, their results are mixed and, moreover, they did not test the more recently proposed lung function indexes as predictors. Therefore, we emphasize the need for selective studies on severely ill patients, using appropriate tools, such as a dyspnea scale and questionnaires on quality of life, to evaluate long-term results.

In conclusion, we suggest that the ppoFEV1 can be used as a first-line test to define patients as having a low risk for surgery and for long-term complications. While awaiting validation studies of new cut-off points to predict long-term risks, patients defined as having a short-term, high—but acceptable—risk for surgery should be informed on the possible long-term consequences of thoracotomy. The final decision should be made only after discussing their transient state and the intermediate and long-term scenario after surgery with the patients.

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