Preoperative Maximum Oxygen Consumption Is Associated With Prognosis After Pulmonary Resection in Stage I Non-Small Cell Lung Cancer

Alessandro Brunelli, MD, Cecilia Pompili, MD, Michele Salati, MD, Majed Refai, MD, Rossana Berardi, MD, Paola Mazzanti, MD, and Michela Tiberi, MD

Department of Thoracic Surgery, St. James’s University Hospital, Leeds, United Kingdom, and Division of Thoracic Surgery and Department of Medical Oncology, Ospedali Riuniti, Ancona, Italy

Background. The objective of this investigation was to evaluate whether maximum oxygen consumption (VO₂max) is a reliable prognostic factor after lung resection for pathologic stage I non-small cell lung cancer (NSCLC).

Methods. Observational analysis of 157 patients undergoing pulmonary lobectomy or segmentectomy for pathologic stage I (T1 or T2-N0 only) NSCLC, with preoperative measurement of VO₂max and complete follow-up (2006–2011). Survival was calculated by the Kaplan-Meier method. The log-rank test was used to assess differences in survival between groups. The relationships between survival and several baseline and clinical variables were determined by Cox multivariate analyses.

Results. The median follow-up time was 40 months. The average preoperative VO₂max was 16.1 mL/kg · min and 69% of predicted value. Sixty-two (40%) patients had a VO₂max below 60%. The median and 5-year overall survivals of patients with preoperative VO₂max above 60% were significantly longer than in those with VO₂max below 60% (median not reached vs 48 months: 73% vs 40%, p = 0.0004). Cox regression model showed that an age older than 70 years (p = 0.005, hazard ratio 2.3) and VO₂max below 60% (p = 0.001, hazard ratio 2.4) were independent prognostic factors significantly associated with overall survival. Cancer-specific survival was also longer in patients with VO₂max above 60% (81% vs 61%, p = 0.01).

Conclusions. Exercise tolerance may influence the physiologic outcomes associated with cancer that can potentially affect survival. Physical rehabilitation aimed at improving exercise tolerance can possibly improve the long-term prognosis after operations for lung cancer.

Patients and Methods

This was a single-center observational analysis performed on a prospective database. The local institutional review board approved the study, and all patients gave their informed consent to participate in the institutional prospective database and have their data used for research and clinical purposes.

All patients undergoing pulmonary lobectomy or segmentectomy for pathologic stage I (pT1 or pT2-N0 only) NSCLC and who performed a preoperative cardiopulmonary exercise test as part of their functional evaluation were included in the analysis. A total of 157 consecutive patients with complete follow-up were analyzed (2006–2011). No patients in this series underwent adjuvant chemotherapy or radiotherapy. Exclusion criteria were as follows: more advanced pathologic stage, incomplete resection, induction chemotherapy, inability or no indication to perform preoperative CPET.

The CPET was performed in all patients with forced expiratory volume in 1 second (FEV₁%) or carbon monoxide lung diffusion capacity (DLCO%) below 80%, those with cardiac comorbidities, and those who were older than 70 years of age according to recent guidelines [1]. Patients were staged according to the guidelines of the American Joint Committee on Cancer, Seventh Edition [7].
Board-certified general thoracic surgeons performed the operations through a muscle-sparing nerve-sparing [8] lateral thoracotomy or through a biportal video-assisted thoracoscopic approach.

As a rule, all patients were extubated in the operating room and treated in a dedicated thoracic surgery unit. Operability exclusion criteria were predicted postoperative FEV1% below 30% and predicted postoperative DLCO% below 30% in association with a VO2max below 10 mL/kg · min [1, 2].

Postoperative treatment was standardized and focused on chest physiotherapy, early mobilization, physical rehabilitation, and adequate systemic analgesic therapy, which was titrated to keep the pain visual analog score below 4 (on a scale ranging from 0 to 10) during the first 48 to 72 hours.

All patients performed a preoperative symptom-limited CPET as part of their routine preoperative functional evaluation [1, 2].

Symptom-limited CPET was performed on an electronically braked cycle ergometer by use of a ramp pattern increase in work rate to reach a test duration of 8 to 12 minutes. The exercise test was stopped when one or more of the following criteria were present: fatigue, dyspnea, excessive systemic blood pressure increase (ie, >230/130 mm Hg), a greater than 2 mm ST depression in at least two adjacent leads, angina, or a combination of these conditions. The VO2max was the average VO2 during the last 15 seconds of exercise.

Follow-up was obtained through routine office visits, by telephone contact, or by data retrieved from the Regional Health Care System database. All patients were followed up through May 2013. The cause of death was recorded.

Data Analysis
The following baseline and tumor variables were tested for a possible association with survival: age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI), American Society of Anesthesiologists score, Eastern Cooperative Oncology Group (ECOG) score, FEV1%, DLCO%, FEV1/FVC ratio, history of coronary artery disease, preoperative hemoglobin level, pT stage (pT1 vs pT2), histology (adenocarcinoma vs squamous cell carcinoma vs others), VO2max. For the purpose of this study, a threshold effect was searched for the value of VO2max.

A lowess diagnostic plot graphing VO2max against hazard ratios from a Cox regression model identified a possible cutoff at 60% of predicted value. This value was then confirmed by log-rank tests for nearby multiple cutoff values (ie, 50%–55%–60%–65%–70%). The maximum statistical approach was used to select the value with the highest association with survival (VO2max 60%). Bootstrap resampling was finally used to confirm the reliability of the selected cutoff value across simulated samples and to minimize the possibility of a type I statistical error. Survival was defined as the interval between radical operation to death or last contact. Patients who were not reported as dead at the time of the analysis were censored at the date they were last known to be alive. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on survival. Predictors with $p$ values below 0.2 at univariable analysis were used in a multivariable Cox proportional hazards model.

Survival distribution was estimated by the Kaplan-Meier method. Significant differences in probability of surviving between the strata were evaluated by log-rank test. Hazard ratios and 95% confidence intervals were estimated from regression coefficients. A significant level of 0.05 was chosen to assess the statistical significance. A $p$ value below 0.05 was regarded as significant. All tests were performed on Stata 12.0 statistical software (Stata Corp., College Station, TX).

Results
Table 1 summarizes the patients’ characteristics. During the same period, 140 patients with early-stage NSCLC did not perform CPET because they did not meet the criteria or were unable to perform the test because of physical or mental limitations. They had similar 5-year survival rates compared with those who performed the exercise test (60% vs 65%, $p = 0.2$). The median follow-up time was 40 months. The average preoperative VO2max was 16.1 mL/kg · min or 69% of predicted value. Testing for a threshold effect, we found that a VO2max value of 60% predicted was the best cutoff value associated with long-term survival. Sixty-two (40%) patients had a VO2max below 60%. The median and 5-year overall survivals of patients with preoperative VO2max above 60% were significantly longer than those with VO2max below 60% (median not reached vs 48 months: 73% vs 40%, respectively; $p = 0.0004$) (Fig 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>68.4 (9.3)</td>
</tr>
<tr>
<td>Gender male, n (%)</td>
<td>129 (83)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4 (4.2)</td>
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<tr>
<td>FEV1%</td>
<td>81.7 (17)</td>
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<td>DLCO%</td>
<td>77.8 (19.6)</td>
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<td>FEV1/FVC ratio</td>
<td>0.68 (0.1)</td>
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<tr>
<td>Preoperative Hb level, g/dL</td>
<td>13.8 (1.8)</td>
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<tr>
<td>Coronary artery disease, n (%)</td>
<td>38 (24)</td>
</tr>
<tr>
<td>ASA score</td>
<td>2.3 (0.6)</td>
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<tr>
<td>ECOG score</td>
<td>0.7 (0.8)</td>
</tr>
<tr>
<td>VO2max, mL/kg · min</td>
<td>16.1 (4.1)</td>
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<td>Side of resection, right, n (%)</td>
<td>75 (48)</td>
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<tr>
<td>Site of resection, upper, n (%)</td>
<td>105 (67)</td>
</tr>
<tr>
<td>pT1 stage, n (%)</td>
<td>65 (42)</td>
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</tbody>
</table>

* $p$ values below 0.2 at univariable analysis. ASAs are expressed as means (standard deviations) unless otherwise specified. ASAs = American Society of Anesthesiology score; BMI = body mass index; DLCO% = carbon monoxide lung diffusion capacity; ECOG = Eastern Cooperative Oncology Group; FEV1% = forced expiratory volume in 1 second; FEV1/FVC ratio = ratio of forced expiratory volume in 1 second to forced vital capacity; Hb = hemoglobin; VO2max = maximum oxygen consumption.
Table 2 shows the results of the univariable analysis for overall survival. Along with the Vo2max measured at CPET, the following variables were associated with overall survival ($p < 0.2$) and were used in the multivariable analysis: age, gender, BMI, CCI, FEV1%, DLCO%, pT stage, preoperative hemoglobin level, ECOG score. Cox proportional hazards regression model showed that an age older than 70 years ($p = 0.005$, hazard ratio 2.3) and Vo2max below 60% ($p = 0.001$, hazard ratio 2.4) were independent prognostic factors significantly associated with overall survival. The 5-year cancer-specific survival was also longer in patients with Vo2max above 60% (81% vs 61%, $p = 0.01$) (Fig 2).

The long-term mortality rate from causes other than cancer was higher in patients with Vo2max below 60% than in those with Vo2max above 60% (35% vs 10%, $p = 0.01$). In patients with pT1 stage disease, those with Vo2max above 60% had a longer overall survival than did those with Vo2max below 60% (82% vs 41%, $p = 0.007$) (Fig 3). In patients with pT2 stage disease, this difference was less evident (68% vs 40%, $p = 0.2$) (Fig 4).

Comment

Background and Rationale

A growing body of literature is showing an association between better physical fitness and long-term survival in lung cancer patients.

In other types of cancers, improving fitness through regular exercise has been shown to be associated with a 30% to 50% reduction in risk of cancer-specific mortality and all-cause mortality [9–12].

ASA = American Society of Anesthesiology score; BMI = body mass index; CAD = coronary artery disease; DLCO% = carbon monoxide lung diffusion capacity; ECOG = Eastern Cooperative Oncology Group; FEV1% = forced expiratory volume in 1 second; Hb level = preoperative hemoglobin level; Vo2max = maximum oxygen consumption.
In lung cancer patients, some authors have found that impaired physical condition at preoperative exercise testing [5, 6, 13] and the patient’s perception of physical functioning and well-being [14, 15] are associated with survival after an operation for lung cancer.

The objective of the present study was to verify whether preoperative VO2max value measured with a CPET was associated with long-term survival after radical operations for stage I NSCLC patients. The rationale of this investigation was to find a prognosticator that could be modified through the institution of specific rehabilitation programs [16–20].

Main Findings
We found that a VO2max value of 60% of predicted was the best cutoff value associated with survival. Patients with VO2max below 60% had poorer survival than did those with higher VO2max. This association was independent of other confounders when adjusted in a multivariable analysis and can be in part explained by increased mortality resulting from both cancer recurrence and causes other than cancer (such as cardiopulmonary adverse events). In fact, both cancer-specific and non-cancer mortality rates were two- to three-fold higher in patients with lower VO2max%.

Clinical and Scientific Implications
Patients with better performance status before operation have a lower risk of early and late postoperative cardiopulmonary adverse events, which would explain the reduction of mortality for causes other than cancer. However, the most intriguing finding of our analysis was that higher aerobic capacity was associated with longer cancer-specific survival and lower cancer-related mortality. Better physical functioning and performance status have recently been shown to positively influence physiologic outcomes associated with cancer, such as a reduction in body weight and composition, beneficial changes in metabolic and sex hormones, growth factors, adipokines, immune function, or inflammation that can potentially affect survival [21–23].

Our findings may have important clinical implications because exercise tolerance is a modifiable prognosticator. Several studies have shown that structured rehabilitation programs are effective in improving aerobic capacity in the preoperative setting [16–20, 24, 25]. They may have, therefore, the potential not only to reduce perioperative adverse events but also to influence residual quality of life and long-term survival by modifying the biology of the tumor.

Limitations
This study may have potential limitations. We included pathologic stage I NSCLC (T1-2N0) only. Further studies are warranted to confirm our findings in other stages of disease. We assessed the preoperative aerobic capacity only. Although preoperative and postoperative fitness levels may be correlated [26], their relationship across time may change, and their relative influence or interaction on prognosis need to be investigated. Given the observational nature of our findings, poor exercise tolerance may be a surrogate of other unknown prognosticators. Furthermore, a cause-and-effect relationship between fitness and prognosis cannot be definitely assumed. Only well-designed prospective randomized trials can demonstrate whether increased physical activity can reduce recurrence or deaths resulting from cancer [27].

In conclusion, we were able to find that preoperative cardiopulmonary fitness was a significant prognostic risk factor in patients operated on for early-stage lung cancer. Physical rehabilitation aimed at improving aerobic capacity can possibly improve the long-term prognosis after operations for lung cancer.

References