

## Exercise capacity and extent of resection as predictors of surgical risk in lung cancer

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*Exercise capacity and extent of resection as predictors of surgical risk in lung cancer. M.H. Brutsche, A. Spiliopoulos, C.T. Bolliger, M. Licker, J-G. Frey, J-M. Tschopp. ©ERS Journals Ltd 2000.*

**ABSTRACT:** Lung resection remains the most effective treatment for non-small cell lung cancer (NSCLC). However, there is no consensus about reliable operative risk assessment in these patients. The aim of this study was to identify predictors of postoperative complications and death after lung resection for NSCLC.

In this prospective trial, 125 of 142 (88%) consecutive NSCLC patients from 1990 to August 1997 had complete data sets. All underwent functional assessment including spirometry and cardiopulmonary exercise tests and lung resection *via* thoracotomy.

Complications occurred in 31 of 125 (25%) patients including 2 (1.6%) deaths. On logistic regression analysis, only maximal oxygen uptake ( $V'O_{2,max}$ ·kg body weight<sup>-1</sup> expressed as a percentage of the predicted value ( $p < 0.0001$ ) and the estimated extent of lung tissue resection ( $p = 0.02$ ) were independent predictors of postoperative complications. Six of seven patients with a  $V'O_{2,max}$ ·kg body weight<sup>-1</sup> of  $< 60\%$  pred, but only eight of 65 with values  $> 90\%$  pred, exhibited postoperative complications.

Maximal oxygen uptake and the estimated extent of lung tissue resection are independent predictors of postoperative complications. These simple parameters should be integrated into the preoperative decision analysis for operability in patients undergoing lung resection for lung cancer.

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Lung cancer continues to have a dismal prognosis, with a 5-yr survival rate of only 13.4% [1]. Lung resection remains the most effective treatment for non-small cell lung cancer (NSCLC) with a 5-yr survival rate after resection that ranges from 60 (stage IA) to 26% (stage IIIA) [2]. Nevertheless, resection rates are quite low and vary significantly between different countries. Cancer registry-based studies show resection rates of only 10–20% in Europe [3, 4]. It is possible, that overly restrictive preoperative selection and preselection by nonspecialists, for example for patients  $> 70$  yrs of age, preclude a potentially curative therapy for some patients. Efforts must focus on establishing proper criteria for inoperability. To date, there is no consensus concerning reliable risk assessment in these patients. The decision to operate is usually based on standard spirometric criteria including radio-nuclide-calculated estimates of postoperative forced expiratory volume in one second (FEV1), known to be associated with postoperative morbidity and probably mortality [5].

Since 1982, cardiopulmonary exercise tests (CPETs) have been reported to be useful in the functional evaluation of lung resection candidates [6]. However, in different studies, different exercise parameters and different recommendations are given. EUGENE *et al.* [6] underlined the importance of the absolute value of maximal oxygen uptake ( $V'O_{2,max}$ ); SMITH *et al.* [7] and BECHARD and WETSTEIN [8] found  $V'O_{2,max}$ ·kg body weight<sup>-1</sup> to be the best parameter; BOLLIGER *et al.* [9, 10] underlined the

importance of poor exercise performance and especially  $V'O_{2,max}$ ·kg body weight<sup>-1</sup> expressed as a percentage of the predicted value as the best predictor of postoperative complications. In other studies [11–13],  $V'O_{2,max}$  was not a definite predictor of postoperative complications. In the existing literature, neither guidelines, nor precise cut-off values for CPET parameters are clearly established.

The aim of this study was to establish predictors of postoperative complications based on easily accessible lung functions and cardiorespiratory exercise testing in order to establish objective operability criteria in lung cancer patients scheduled for pulmonary resection.

### Material and methods

#### Study subjects and design

The study was designed as a prospective study looking at the value of different preoperative variables in predicting postoperative complications including death.

All patients undergoing consecutive lung resections for lung cancer and attending the Centre Valaisan de Pneumologie (Montana, Switzerland), a non-university chest hospital were included in the study from 1990 to August 1997. The functional assessment was carried out after optimization of the patient's treatment and consisted of general parameters (age, sex, body mass index), disease parameters (oncological stage, histological type), pulmonary function

tests (forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC) and symptom-limited CPET. Generally, the decision to operate was based on clinical grounds, taking into account clinical parameters and results of investigations such as laboratory findings, lung function tests and radiological staging including computed tomography. Patients with a FEV<sub>1</sub> of <35%, a New York Heart Association dyspnoea grade of ≥III, hypercapnia (arterial carbon dioxide tension (*P*<sub>a,CO<sub>2</sub></sub>) >6.0 kPa (45 mmHg) breathing ambient air) or intractable cardiac failure were excluded from operation.

Demographic, spirometric and exercise test data, together with the oncological postoperative staging and histological types of lung cancer are shown in table 1.

*Pulmonary function tests*

Spirometry before and after bronchodilator therapy was performed by two experienced technicians and according to American Thoracic Society criteria [14, 15] using a Sensormedics 9000 IV Spirometer (Sensormedics, Bilt-hoven, the Netherlands).

*Cardiopulmonary exercise tests*

All patients underwent symptom-limited CPETs on a cycle ergometer (Sensormedics 2200 SP; Sensormedics). After a 2-min warm-up period at 20 W, a ramp protocol

with 20-W·min<sup>-1</sup> workload increases was started. The exercise test was stopped when the patients were exhausted, or at any electrocardiographic signs or clinical symptoms of myocardial ischaemia, including a fall in systolic blood pressure.

As generally accepted and tested in a comparable population [9, 12, 16], the equation proposed by Charniak [15, 17], derived in nonsmoking Caucasians, was used to calculate the predicted normal values for FEV<sub>1</sub>. For *V*'O<sub>2,max</sub> and *V*'O<sub>2,max</sub>·kg body weight<sup>-1</sup> the equations of JONES and CAMPBELL [18] with correction for cycle ergometry were applied.

*Surgical procedures and postoperative care*

All patients underwent open thoracic surgery by the same team of specialized thoracic surgeons, anaesthetists and pulmonologists, who were involved in a programme of total quality management including a study on cost effectiveness (the results of which have been published elsewhere [19, 20]). The patients were extubated within 0.5–4 h after the intervention, mainly in the operating theatre at the end of the operation. Thereafter, they were transferred to a specialized intermediate care unit for 2–4 days. No patient required transfer to the intensive care unit. Thromboembolic prophylaxis was administered in the form of low-molecular-weight heparin (depending on body weight, 2,500 or 5,000 U of Low Liquemin®; Roche, Basle, Switzerland). The operations performed in the 125 patients were pneumonectomy (33), bilobectomy

Table 1. – Demographic, spirometric and cardiopulmonary exercise test (CPET) data of the total study population in comparison to patients with and without postoperative complications

	Total study population	Without complications	With complications	p-value*
Patients n (%)	125 (100)	94 (75)	31 (25)	
<b>Demography</b>				
Age yrs	63±11 (20–80)	63±11 (20–80)	64±9 (43–75)	0.60
Age >70 yrs n (%)	42 (34)	31 (33)	11 (35)	0.87
Male sex n (%)	101 (81)	75 (80)	26 (84)	0.62
BMI kg·m <sup>-2</sup>	25±4 (17–37)	25±4 (17–35)	26±4 (19–37)	0.59
Smoking: Current/Ex/Non n	101/24/20	84/12/16	17/12/4	0.20
Histology: AC/SCC n	61/84	48/64	13/20	0.41
Stage: I/II/IIIa/IIIb/IV n	64/23/23/0/2	46/20/16/0/2	18/3/7/0/0	0.43 <sup>+</sup>
<b>Spirometric data</b>				
FEV <sub>1</sub> L	2.49±0.69 (0.82–4.41)	2.54±0.69 (0.82–4.41)	2.32±0.65 (0.92–3.55)	0.12
FEV <sub>1</sub> % pred	87±19 (36–117)	88±19 (45–117)	81±19 (36–114)	0.09
FVC L	3.63±0.87 (1.29–6.14)	3.68±0.86 (1.57–6.14)	3.47±0.90 (1.29–5.24)	0.26
FVC % pred	98±19 (39–145)	100±19 (54–145)	94±19 (39–134)	0.14
<b>Extent of resection</b>				
SE/LE/BLE/PE n (%)	18/81/10/36 (12/52/6/23)	16/63/10/23 (14/56/9/20)	2/18/0/13 (6/55/0/39)	0.01 <sup>+</sup>
<b>CPET</b>				
Maximal workload (W)	131±33 (60–240)	133±34 (60–240)	122±30 (77–180)	0.10
<i>V</i> 'O <sub>2,max</sub> mL·min <sup>-1</sup>	1522±433 (548–2750)	1590±420 (632–2750)	1315±411 (548–2185)	0.002
% pred	75±20 (33–156)	78±20 (36–156)	66±20 (33–115)	0.004
mL·min <sup>-1</sup> ·kg body weight <sup>-1</sup>	21.1±5.7 (9.4–37.8)	22.1±5.4 (13.2–37.8)	17.9±5.4 (9.4–34.0)	0.0003
% pred body weight <sup>-1</sup>	94±21 (46–168)	99±21 (60–168)	80±17 (46–108)	<0.0001
<i>V</i> 'E <sub>max</sub> % pred	88±25 (29–167)	89±25 (29–154)	82±27 (32±167)	0.18
<i>P</i> <sub>a,O<sub>2</sub>ex</sub> kPa	9.5±1.5 (4.1–13.2)	9.5±1.5 (4.1–13.2)	9.1±1.5 (5.3–11.9)	0.22
	9.5±1.5 (4.1–13.2)	9.5±1.5 (4.1–13.2)	9.1±1.5 (5.3–11.9)	0.22

Data are presented as mean±SD (range) or absolute value. BMI: body mass index; AC: adenocarcinoma; SCC: squamous cell carcinoma; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; SE: segmentectomy; LE: lobectomy; BLE: bilobectomy; PE: pneumonectomy; *V*'O<sub>2,max</sub>: maximal oxygen uptake; *V*'E<sub>max</sub>: maximal exercise minute ventilation; *P*<sub>a,O<sub>2</sub>ex</sub>: arterial oxygen tension after exercise; % pred: percentage of the predicted value. \*: significance test, with *versus* without complications; <sup>+</sup>: Chi-squared test for linear trend.

(nine), lobectomy (68) and segmentectomy/wedge resection (15).

### Postoperative complications

As generally accepted, complications and deaths were recorded during a 30-day postoperative period. For the sake of comparison, the same definition for postoperative complications as used by SMITH *et al.* [7], BECHARD and WETSTEIN [8], MARKOS *et al.* [12] and BOLLIGER *et al.* [9] was applied (table 2).

### Extent of lung tissue resection

Similar to the formulas for the estimation of postoperative lung function [21], the percentage of lung tissue lost was calculated as the percentage of segments removed, assuming a total number of segments of 19. For example, a patient undergoing right upper lobectomy, thus, had 3 of 19 segments removed, *i.e.* 15.8% of lung tissue. These estimates were used in the multiple logistic regression analysis to "quantify" the intervention.

### Data analysis

Besides methods of descriptive statistics, patients with or without complications were compared by means of the t-test, Mann-Whitney U-test, Chi-squared test or Fisher exact test and Chi-squared test for linear trend as appropriate. For  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (absolute values and % pred), the sensitivity, specificity and positive predictive values for the identification of patients with postoperative complications were calculated at cut-off values recommended in the literature, *i.e.* 15 mL·min<sup>-1</sup>kg body weight<sup>-1</sup> [7] and 60% pred [9], respectively.

Variables with significant differences between patients with and without postoperative complications in the univariate approach were taken as potential predictors of outcome, and, thus, were used in multiple forward stepwise logistic regression analysis to identify independent predictors of postoperative complications. Only a limited number of variables can be entered into this analysis. Thus, the number of variables had to be reduced further based on previous reports and expectancy.

Computations were performed using the SPSS for Windows statistical software package (SPSS®, Inc., version 9.0, Statistical Software, Inc., Los Angeles, CA, USA).

Table 2. – Complications within 30 days after lung resection in 125 patients with lung cancer

Postoperative complications	Patients n (%)
Acute carbon dioxide retention ( $P_{a,CO_2} > 6$ kPa)	1 (0.8)
Prolonged mechanical ventilation (>48 h)	-
Treated symptomatic cardiac arrhythmia	13 (10.4)
Myocardial infarction	1 (0.8)
Pneumonia (temperature >38°C and purulent sputum and infiltrate on radiography)	9 (7.2)
Pulmonary embolism (high probability on ventilation perfusion scan or angiogram)	1 (0.8)
Lobar atelectasis (necessitating bronchoscopy)	4 (3.2)
Death	2 (1.6)
Total	31 (24.8)

$P_{a,CO_2}$ : arterial carbon dioxide tension.

Results are expressed as mean±SD with range in parentheses. All tests were two-sided and the significance level was taken at 0.05.

## Results

A total of 125 patients yielded complete data sets and were included in the study. Two patients were operated on for a single pulmonary metastasis following prior lung cancer surgery. The overall 30-day postoperative morbidity was 31/125 (25%; table 2), death occurring in 2/125 (1.6%). One patient, a 46-year-old female, with stage IIIa adenocarcinoma died suddenly 1 h after pneumonectomy due to rupture of the sutured pulmonary artery as confirmed at autopsy. The other patient, a 68-year-old male with known arterial hypertension underwent lobectomy for stage II squamous cell carcinoma, but died from a haemorrhagic stroke 13 days later.

Neither age, sex, histology, preoperative staging, smoking habits nor spirometric measurements were different in patients with and without complications (table 1). Only exercise data,  $V'O_{2,max}$  expressed in a variety of ways (mL·min<sup>-1</sup>, mL·min<sup>-1</sup>·kg body weight<sup>-1</sup> or % pred), and the extent of lung tissue resection showed significant differences between the two groups. All Chi-squared tests for linear trend for the exercise parameters were highly significant ( $V'O_{2,max}$  (absolute value): p=0.0006;  $V'O_{2,max}$  (% pred): p=0.003;  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (absolute value): p=0.0008;  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred): p=0.0001) with the most significant p-values obtained for  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred).

In order to exclude a minimum of patients from operation, a cut-off value with a high specificity for not suffering a complication is important. At the high specificity end, both  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (specificity 94% and sensitivity 35% at a cut-off of 15 mL·min<sup>-1</sup>·kg body weight<sup>-1</sup>) and  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred) (specificity 99% and sensitivity 16% at a cut-off of 60% pred) show excellent performance. However, for maximal specificity, there was a slight advantage to using  $V'O_{2,max}$ -kg body weight<sup>-1</sup> as % pred compared to absolute values (positive predictive value 86 versus 65%). Six of seven (86%) patients with a  $V'O_{2,max}$ -kg body weight<sup>-1</sup> of <60% pred, but only eight of 65 (12%) with values >90% pred, exhibited postoperative complications. In comparison, 11 of 17 (64%) patients with a  $V'O_{2,max}$ -kg body weight<sup>-1</sup> of <15 mL·min<sup>-1</sup>·body weight<sup>-1</sup> suffered complications.

Table 3. – Results of stepwise logistic regression analysis

Parameter	Step	Coeff	SEM	Improvement Chi-squared	p-value
Constant factor	0	2.9883	1.2	-	-
$V'O_{2,max}$ -kg body weight <sup>-1</sup> % pred	1	-0.0573	0.014	19.7	<0.0001
Resection %	2	0.0343	0.015	5.3	0.02

For the calculation of the probability of postoperative complications ( $P_{complication}$ ) in a given patient if  $\log(\text{odds})=\mu$ :  $\mu=2.9883-0.0573V'O_{2,max}\text{-kg body weight}^{-1}\text{ \% pred}+0.0343\text{ resection (\%)}$ , and  $P_{complication}=10^{\mu}/(1+10^{\mu})$ . See table 4 for probabilities in different situations. Coeff: coefficient;  $V'O_{2,max}$ : maximal oxygen uptake percentage of the predicted value.

Table 4. – Probabilities of postoperative complications based on exercise tests and lung resection according to stepwise logistic regression analysis

$V'O_{2,max}$ -kg body weight <sup>-1</sup> % pred	SE/ wedge	LE	BLE	PE
120	0.03	0.04	0.07	0.11
110	0.04	0.07	0.12	0.17
100	0.08	0.11	0.19	0.27
90	0.13	0.19	0.29	0.39
80	0.21	0.29	0.42	0.53
70	0.31	0.42	0.56	0.67
60	0.45	0.56	0.69	0.78
50	0.59	0.69	0.80	0.86

Probabilities for postoperative complications were calculated independent of the localization assuming 50, 31, 20 and 5% tissue removed for pneumonectomy (PE), bilobectomy (BLE), lobectomy (LE) and segmentectomy/wedge resection (SE/wedge) respectively.  $V'O_{2,max}$ : maximal oxygen uptake percentage of the predicted value.

Logistic regression analysis to check the ability of preoperative variables to predict postoperative complications confirmed  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred) as an independent predictor (table 3). Entering the extent of lung tissue resection into the regression analysis did improve the fit of the model. The calculated probabilities of postoperative complications according to the present model are given in table 4.

### Discussion

Poor exercise capacity and the estimated extent of lung tissue resection were the best predictors of postoperative complications in the present study population, patients with NSCLC scheduled for lung resection. On univariate analysis,  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred) was the best independent predictor of postoperative complications. A value of <60% pred indicated postoperative complications with an excellent 99% specificity and a positive predictive value of 86%. The frequently cited absolute cut-off value of  $V'O_{2,max}$  of 15 mL·min<sup>-1</sup>·body weight<sup>-1</sup> showed had inferior test characteristics in the present study, its positive predictive value being only 65%. Absolute values do not take sex, age or body dimensions into account, and, although easier to use, might exclude certain patients from surgery, such as short elderly females.

Neither age nor spirometric results were predictive of complications in the present study. The multiple regression equation allowed calculation of the probability of postoperative complications by combining exercise performance and estimated extent of lung tissue resection (table 4). Better estimation of the patient's individual postoperative risk based on objective criteria may lead to the introduction of new cost-effective guidelines for the assessment of operability, leading to higher resection rates in such patients. Furthermore, the patient can give informed consent based on an individualized risk assessment.

The present results are in accordance with those of BOLLIGER *et al.* [9] in a completely different study population and in a non-university environment using easily accessible measures of lung function. In their study,  $V'O_{2,max}$ -kg body weight<sup>-1</sup> (% pred) proved to be the best single indicator of complications after lung resection. They concluded that patients with a  $V'O_{2,max}$ -kg body

weight<sup>-1</sup> of <60% pred should not undergo pneumonectomy, whereas a  $V'O_{2,max}$ -kg body weight<sup>-1</sup> of >75% pred was a good indicator of an uneventful postoperative course.

However, in other studies [11–13], exercise performance including  $V'O_{2,max}$  was not a definite predictor of postoperative complications. Detailed analysis of these reports reveals a variety of definitions of postoperative complications (*e.g.* including technical complications during the operation), heterogeneous exercise test protocols, retrospective design or low patient numbers.

The estimated extent of lung resection in the present patients also entered the regression model as statistically significant, which is consistent with reports in the literature [3, 22, 23] and clinical expectancy. Its predictive value is yet to be confirmed by further studies. To choose an anatomical estimation of the amount of lung tissue to be removed has the advantage that no further investigations need to be performed and the present probability model is directly applicable in every lung resection candidate having undergone CPET. Conversely, anatomical estimates are less accurate at predicting postoperative lung function than functional estimates based on radionuclide studies, *e.g.* ventilation/perfusion scans [24], particularly in patients of borderline operability, as they generally overestimate the functional loss. Using a functional estimate of the amount of remaining lung tissue in further studies might even improve the prediction model.

The overall very low mortality rate and the fact that the two deaths were not predicted by the functional assessments clearly limit the applicability of the present study results on mortality. Mortality rate cut-off values are needed for patients suffering from a disease that invariably leads to death if untreated. Even though there was no definite cut-off value, patients with a  $V'O_{2,max}$ -kg body weight<sup>-1</sup> of <60% pred exhibited a very high morbidity. This is in accordance with the study of BOLLIGER *et al.* [9], in which eight of nine patients with a  $V'O_{2,max}$ -kg body weight<sup>-1</sup> of <60% pred had complications, including all three patients who died. As the three patients who died had all undergone major resection (two pneumonectomy, one bilobectomy), this cut-off value clearly presents a high risk for major resection. Two other studies [25, 26], which did not account for the extent of resection, independently found 50% pred to be the lowest acceptable  $V'O_{2,max}$  for lung resection of high-risk patients. The validity of these suggested lower limits of  $V'O_{2,max}$  will have to be tested by further prospective studies.

A limitation of the present study is the lack of measurement of the diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ), which has recently gained in importance [27] and also been integrated into an algorithm for functional evaluation by BOLLIGER and coworkers [24, 28]. At the time the study was planned, the importance of measuring  $DL_{CO}$  in such patients had not been firmly established and, therefore, this lung function parameter was not used in the present patients.

Previous studies have indicated that mortality in patients of >70 yrs of age is greater than that in younger patients. In a recent representative survey [3] in 7,899 patients, a mortality rate of 8% for pneumonectomy and 3% after lesser resection was found in patients of >70 yrs of age, compared to an overall 1.4% mortality rate in patients of <60 yrs of age. Interestingly, age was not an independent

predictor for postoperative complications in the present regression analysis. The higher frequency of complications in older patients, which was also found in the present study, is probably due to a relatively poorer cardiorespiratory reserve and increased comorbidity as indirectly assessed by CPET and not due to a higher operative risk in older age *per se*. Nevertheless, in the absence of a real therapeutic alternative, informed older patients may be in favour of an operation even in the light of a higher operative risk given the reasonable life expectancy at 70 yrs of age, ~10.3 yrs for males and 14.7 yrs for females in Switzerland [29, 30]. The present 0% (0/42) mortality rate in patients of >70 yrs of age, the low mortality rate found in the literature and the fact that the 2-yr survival of such patients is reported to be independent of age [28] encourage an aggressive approach in this population subgroup. Therefore, chronological age alone should not be a reason for excluding patients from surgery.

Cardiopulmonary exercise testing is of value for the assessment of operative risk in patients undergoing resection for lung cancer. Maximal oxygen uptake per kilogram of body weight expressed as a percentage of the predicted normal value and the estimated extent of lung tissue resection are probably the best predictors of postoperative complications and should be integrated into the preoperative decision analysis for operability. With the present prediction model an individual's probability of experiencing postoperative complications can be obtained by every physician around the world with largely accessible, cheap and noninvasive measures. Patients with a maximal oxygen uptake per kilogram of body weight of  $\leq 60\%$  of the predicted value have a high risk for postoperative complications and should probably not undergo pneumonectomy. A maximal oxygen uptake per kilogram of body weight of  $\geq 90\%$  of the predicted value is a good marker of a favourable postoperative course. A larger prospective study is needed to clearly establish proper mortality-based cut-off values, the effect on resection rates and the cost-effectiveness of cardiopulmonary exercise testing.

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