Original Article

Patient and procedural features predicting early and mid-term outcome after radical surgery for non-small cell lung cancer

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Background: Postoperative cardiovascular and pulmonary complications (PCVCs and PPCs) are frequent and result in prolonged hospital stay. The aim of this study was to update the risk factors associated with major complications and survival after lung cancer surgery.

Methods: This is a post-hoc analysis of a randomized controlled trial that was designed to assess the benefits of preoperative physical training. After enrollment, clinical, biological and functional data as well as intraoperative details were collected. In-hospital PCVCs and PPCs were recorded and survival data were adjudicated up to 4 years after surgery.

Results: Data from 151 patients were analyzed. Thirty-day mortality rate was 2.6% and the incidence of PCVCs and PPCs was 15% and 33%, respectively. Stepwise logistic regression analysis showed that, PCVCs were mainly related to elevated plasma levels of brain natriuretic peptides [odds ratios (ORs) =6.0; 95% confidence interval (CI), 1.3–27.3] and performance of a pneumonectomy (OR =9.6; 95% CI, 2.9–31.5) whereas PPCs were associated with the presence of COPD (OR =5.9; 95% CI, 2.4–14.8), current smoking (OR =2.6; 95% CI, 1.1–6.5) and the need for blood transfusion (OR =5.2; 95% CI, 1.2–23.3). Preoperative physical training was a protective factor regarding PPCs (OR =0.13; 95% CI, 0.05–0.34). Cox proportional hazards regression analysis showed that ventilatory inefficiency during exercise (expressed by a ratio >40 of ventilation to carbon dioxide elimination), coronary artery disease, elevated plasma levels of brain natriuretic peptides and the occurrence of PPCs were all predictive of poor survival after surgery.

Conclusions: Besides smoking and the extent of lung resection, preexisting cardiopulmonary disease as evidence by elevated levels of brain natriuretic peptides and inefficient ventilation are associated with poor clinical outcome after lung cancer surgery.

Keywords: Postoperative pulmonary complications; lung cancer surgery; postoperative cardiovascular complications; mid-term survival

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and surgical resection remains the standard treatment for the early disease stages (1). Tobacco smoking is not only the key driver of lung cancer but also of chronic obstructive pulmonary disease (COPD) as well as cardiovascular and cerebrovascular diseases (2). Therefore, patients scheduled for lung cancer resection often present a combination of these chronic diseases whose presence and severity increase the risk of major postoperative complications (3). Procedural factors such as excessive fluids infusion and overstretching bronchoalveolar tissues with elevated inspiratory pressure and/or tidal volume may generate edema and inflammation that contribute to postoperative cardiovascular and pulmonary complications (PCVCs and PPCs) (4).

Several indices of aerobic fitness have been shown useful to predict early complications but also later survival and quality of life after major surgery (5). By providing breath-by-breath measurements of oxygen uptake (VO_2), carbon dioxide output (VCO_2) and ventilation (VE), cardiopulmonary exercise testing (CPET) has emerged the gold standard method for assessing the severity of cardiovascular and pulmonary diseases and for selecting suitable candidates for lung cancer resection (6). A peakVO_2 less than 15–16 mL/kg/min has been shown predictive of a higher occurrence of cardiovascular and pulmonary complications (7,8). Importantly, reliance on peakVO_2 as a predictor of major complications has recently been questioned in patients with COPD undergoing lung cancer resection (9). Another CPET-derived parameter, the slope (or ratio) of ventilation to carbon dioxide [V_E/VCO_2]), has been shown effective in predicting early mortality, cardio-pulmonary complications and survival at one-year after lung cancer surgery (10). Likewise, high V_E/VCO_2 slope is a well-known predictor of survival in patients with heart failure, pulmonary hypertension and idiopathic pulmonary fibrosis (11).

Consistent with the principles of fast-track surgery, risk-minimizing strategies including preoperative patient optimization as well as intraoperative goal-directed hemodynamic control, protective lung ventilation and smaller thoracic incisions or video-assisted thoracic surgery (VATS), have been implemented in the management of thoracic surgical patients (12). Given these recent improvements, there is a need to reevaluate all potential risk factors that may influence postoperative clinical outcome. Therefore, we performed a post-hoc analysis of data collected in the Lung Cancer Rehabilitation Study (LCRS) (13) and we questioned whether preoperative CPET parameters, in addition to preoperative clinical and biological factors, as well as intraoperative features, were associated with early cardio-pulmonary complications and later survival.

Methods

Study design and patient selection

The LCRS was an open blinded randomized controlled trial, registered at the ClinicalTrials.gov website (NCT01258478), and conducted at the University Hospital of Geneva and the Hospital of Valais between October 2011 and October 2014. The study was approved by the institutional ethics committee of the University Hospital of Geneva (protocol number: 06–225).

All adult patients with non-small cell lung carcinoma (NSCLC), stage IIIA or less (eligible for surgical cure), documented by CT-scan or Positron Emission Tomography CT scan, were screened for eligibility. Exclusion criteria consisted in any contraindication to perform CPET (e.g., clinically limiting or untreated heart disease, severe pulmonary hypertension) or inability to adhere to a rehabilitation program (e.g., limiting comorbidities, psychiatric condition, osteoarthritis impeding cycling). Consenting eligible patients were allocated to usual care or a rehabilitation intervention (2–3 weekly sessions of high-intensity interval training) that was performed over 2–3 weeks preceding surgery.

Perioperative management, measurements and study endpoints

Preoperative pulmonary function tests included lung volumes and carbon monoxide diffusion capacity.

Lung resections were performed by muscle-sparing thoracotomy or VATS. Standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia or wound infiltration and protective lung ventilation (12). All patients were extubated in the operating room, admitted in the postanesthesia care unit and transferred 3 to 6 hours later into the surgical ward. Postoperative physiotherapy consisted in deep breathing, coughing exercise and early ambulation.

A six minute walk test (6MWT) was conducted by physiotherapists and was followed by a symptom-limited CPET on an upright electronically braked cycle ergometer (SensorMedics Model 2200 SP; Yorba Linda, CA). Peak heart rate, peak work rate and peakVO_2 were determined as the highest averaged value over 30 s. Derived measurements included the ratio of V_E/VCO_2 calculated at the respiratory compensation point, the peak oxygen pulse and the anaerobic threshold.

Measurements and study endpoints

Preoperative clinical, functional and biological data, as well as intraoperative surgical, hemodynamic and ventilatory data, were extracted from the electronic medical files. In addition to standard blood tests, N terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured preoperatively. The 6MWT and CPET were performed twice (at enrollment and 1–2 days before surgery), the last results were included for analysis and a positive response to rehabilitation was defined by meaningful changes in VO_{2peak} (≥10%) or in 6MWT (≥30 m) between the first and the second preoperative measurements.

Study endpoints were the early mortality rate (in-hospital and/or 30-day), the incidence of major PCVCs and PPCs and survival after surgery. The modified version of the Thoracic Mortality and Morbidity (TMM) classification system was used to report any serious adverse events that occurred during the postoperative hospital stay (14). Survival was reported by directly contacting the patient or his physician (up to 4 years after surgery).

Statistical analysis

Perioperative clinical, functional and surgical characteristics of patients with and without PCVCs or PPCs were compared with the Chi-square test for categorical variables (expressed in percentage) and the Student's *t*-test (normal distribution) or Wilcoxon rank test (non-Gaussian distribution) for continuous variables (expressed as mean ± standard deviation). Variables with a univariate $P<0.15$ and those judged clinically important were selected for inclusion in a logistic regression model by stepwise forward selection. Only one variable in a set of variables with a correlation coefficient >0.5 was retained to avoid multicollinearity. Independent predictors of PCVC and PPCs as well as factor-adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. Discrimination of the model was assessed with the area under receiver operating characteristic (ROC) and calibration of the model was evaluated with the Hosmer-Lemeshow goodness-of-fit test. For survival analysis, we used a Cox proportional hazards regression model including all risk factors and computed hazard ratios (HR) and 95% CI. Survival curves were computed according to the Kaplan–Meier method, and differences in survival were compared with the log-rank test. All analyses were performed using STATA 14 software (Stata Corp., College Station, TX, USA) and statistical significance was specified as a two-tailed Type I error (P value) set below 0.05.

Results

Between October 1, 2011 and October 31, 2014, 189 patients were screened, 164 provided consent, and 151 were analyzed and followed over a median time of 29 months (range, 2–48 months) after surgery. Thirteen patients were excluded from the study due to patient's withdrawal (N=8) and cancellation of the planned surgery (N=5). Thirty-day mortality rate was 2.6% and was related to early massive postoperative bleeding (N=1), multi-organ failure in the context of sepsis (N=1) and acute mesenteric ischemia (N=1), and delayed unexplained cardio-respiratory arrest occurring after patient discharge (N=1). The incidence of PCVCs and PPCs was 15% and 33%, respectively. Supra-ventricular arrhythmias were the most common PCVCs (12.6%) whereas atelectasis (24.5%) and pneumonia (15.2%) were the most frequent PPCs followed by prolonged mechanical ventilation (8.6%).

Patients with PCVCs had a higher prevalence of hypertension and alcohol habits, they were more likely to undergo a pneumonectomy and to receive blood transfusion, vasopressors and larger intravenous volumes of crystalloids, compared with patients without PCVCs (*Tables 1-3*). Patients with PPCs presented a greater prevalence of COPD, hypertension, diabetes mellitus and current smoking; they also presented lower physical performances during CPET and 6MWT than patients without PPCs. In addition, intraoperative vasopressors and blood transfusion were more frequently given in patients with PPCs (*Tables 1-3*).

Multivariate stepwise logistic regression analysis revealed that, elevated plasma levels of NT-pro-BNP (>100 pg/mL) and performance of a pneumonectomy were independent predictors of PCVCs (OR =6.0; 95% CI, 1.3–27.3; OR =9.6; 95% CI, 2.9–31.5, respectively). Likewise, independent risk factors for PPCs included COPD (OR

Table 1 Preoperative characteristics of patients undergoing lung cancer resection according to the presence or absence of postoperative pulmonary or cardiovascular complications

Characteristic	Pulmonary complications			Cardio-vascular complications		
	Yes (n=50)	No (n=101)	P value	Yes (n=23)	No (n=128)	P value
Age, years	66.6±8.9	63.3±11.5	0.081	66.7±11.2	64.0±10.7	0.277
Male, n (%)	33 (66.0)	58 (57.4)	0.311	16 (69.6)	75 (58.6)	0.322
Body mass index	25.2±4.4	24.4±4.3	0.260	25.1±4.4	24.6±4.3	0.569
ASA classes 3 & 4	22 (44.0)	28 (27.7)	0.045	10 (43.5)	40 (31.3)	0.251
COPD	31 (62.0)	26 (26.3)	<0.001	9 (39.1)	48 (37.5)	0.781
Hypertension	29 (58.0)	36 (36.4)	0.012	14 (60.9)	51 (39.8)	0.040
Diabetes mellitus	12 (24.0)	10 (9.9)	0.021	5 (21.7)	17 (13.3)	0.290
Coronary artery disease	7 (14.0)	12 (11.9)	0.712	4 (17.4)	15 (11.7)	0.494
Heart failure	6 (12.0)	10 (9.9)	0.693	3 (13.0)	13 (10.2)	0.713
Cardiac arrhythmias	4 (8.0)	4 (4.0)	0.311	2 (8.7)	6 (4.7)	0.336
Peripheral vascular disease	13 (26.0)	16 (15.8)	0.136	4 (17.4)	25 (19.5)	1.000
Cerebrovascular disease	4 (8.0)	7 (6.9)	0.812	2 (8.7)	9 (7.0)	0.675
Renal dysfunction*	9 (18.0)	15 (14.9)	0.618	3 (13.0)	21 (16.4)	1.000
Alcohol	16 (32.0)	25 (24.8)	0.384	2 (8.7)	39 (30.5)	0.040
Current smoking§	28 (56.0)	39 (38.6)	0.043	8 (34.8)	59 (46.1)	0.315
Smoking, pack year	51.0±30.1	42.5±26.2	0.092	48.2±33.4	45.1±26.9	0.636
Medications						
Beta-blockers	10 (20.0)	14 (13.9)	0.332	4 (17.4)	20 (15.6)	0.765
ACEIs	12 (24.0)	17 (16.8)	0.293	7 (30.4)	22 (17.2)	0.138
Statins	8 (16.0)	13 (12.9)	0.601	3 (13.0)	18 (14.1)	1.000
Calcium channel blockers	6 (12.0)	5 (5.0)	0.117	2 (8.7)	9 (7.0)	0.675
Antiplatelets	14 (28.0)	18 (17.8)	0.150	8 (34.8)	24 (18.8)	0.083
Steroids	9 (18.0)	8 (7.9)	0.065	3 (13.0)	14 (10.9)	0.725
Neoadjuvant chemotherapy	6 (12.0)	8 (7.9)	0.416	4 (17.4)	10 (7.8)	0.231

Data given as mean ± standard deviation or number (percentage). *Glomerular filtration rate <60 mL/kg; alcohol >20 g/day. Student *t* tests or Chi-squared tests were used for statistical tests. §, smoking more than 100 cigarettes or equivalent in lifetime and continue over the last 28 days. ACEI, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease.

=5.9; 95% CI, 2.4–4.8), current smoking (OR =2.6; 95% CI, 1.1–6.5) and the need for blood transfusion (OR =5.2; 95% CI, 1.2–23.3). In contrast, preoperative rehabilitation was considered a protective factor regarding PPCs (OR =0.13; 95% CI, 0.05–0.34). The area under the curve of the receiver operating curves were 0.85 for PCVCs and PPCs with P values for the Hosmer-Lemeshow goodness of fit (0.814 and 0.685) indicating good discrimination and calibration.

Cox proportional hazards regression analysis and Kaplan-Meyer curves showed that VE/VCO_2 slope >40, coronary artery disease, elevated plasma levels of NT-pro-BNP and PPCs were associated with poor survival after surgery (*Table 4* and *Figure 1*).

Table 2 Preoperative tests of patients undergoing lung cancer according to the presence or absence of postoperative pulmonary or cardiovascular complications

Test	Pulmonary complications			Cardio-vascular complications		
	Yes (n=50)	No (n=101)	P value	Yes (n=23)	No (n=128)	P value
Laboratory values						
Hematocrit, %	41.9±5.7	43.2±6.8	0.267	42.4±5.2	42.8±6.7	0.798
Creatinine, mM/L	83.3±56.2	74.7±17.9	0.213	77.1±22.2	77.8±38.2	0.940
NT pro BNP, pg/mL	45 [19–82]	30 [18–71]	0.424	59 [29–116]	30 [12–52]	0.081
NT pro BNP >100 pg/mL	5 (10.0)	11 (10.9)	0.867	5 (21.7)	11 (8.6)	0.059
Lung function						
FVC, % pred	101.7±21.8	103.3±18.5	0.636	99.9±21.2	103.2±19.3	0.455
FEV_1, % pred	82.2±21.4	88.7±20.2	0.069	83.3±20.0	87.2±20.9	0.408
FEV_1/ FVC, %	64.7±12.4	69.1±11.0	0.027	66.7±11.5	67.8±11.7	0.695
DLCO, % pred	72.5±20.3	77.1±19.2	0.183	72.3±19.7	76.2±19.6	0.389
Cardio-pulmonary cardiopulmonary exercise test						
Peak WR, watts	89.2±42.5	103.8±37.0	0.032	99.3±35.8	98.9±40.1	0.966
VO_2peak, mL/kg/min	17.6±5.2	21.3±5.9	<0.001	20.3±5.5	20.0±6.0	0.840
Anaerobic threshold, %	46.9±12.8	50.4±16.2	0.191	53.5±18.4	48.5±14.6	0.152
Peak HR, beats/min	124.9±17.9	134.1±21.7	0.011	136.4±21.5	130.1±20.7	0.188
MET	4.4±1.4	5.0±1.9	0.038	4.8±1.9	4.8±1.7	0.917
VE/VO_2 slope	36.8±5.7	34.7±5.4	0.026	37.2±6.0	35.0±5.4	0.081
VE/VCO_2 slope	37.2±5.5	35.6±4.4	0.052	36.9±4.7	36.0±4.9	0.403
VE/VCO_2 >40	13 (26.0)	17 (16.8)	0.184	5 (21.7)	25 (19.5)	0.807
6-Min Walk test, m	360.0±100.0	448.0±97.0	<0.001	418.5±79.6	419.2±110.6	0.975
Rehabilitation group	16 (32.0)	58 (57.4)	0.004	13 (56.5)	61 (47.7)	0.435

Data given as mean ± standard deviation, median [interquartile range], or number (percentage). Student t test, Wilcoxon rank sum test, or Chi-squared tests were used for statistical tests. *, a positive response to rehabilitation was defined by changes in VO_{2peak} (≥10%) or in 6MWT (≥30 m) between the first and the second preoperative measurements. FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; WR, work rate; VO_2, oxygen consumption; HR, heart rate; MET, metabolic equivalent task; VE, exercise ventilation, VE/VCO_2, ventilatory equivalent for carbon dioxide; VE/VO_2, ventilator equivalent for oxygen.

Discussion

The main findings of this study are summarized as follows: (I) preoperative NT-pro-BNP plasma levels and pneumonectomy were predictive of PCVCs; (II) COPD, current smoking, need for blood transfusion were independent risk factors for PPCs whereas preoperative rehabilitation afforded pulmonary protection; (III) poor mid-term survival was associated with cardiac disease, inefficient ventilation and the occurrence of PPCs.

The prognostic relevance of aerobic capacity and any frailty markers is now well established in elderly and particularly in patients with cancer and chronic diseases (5,15). Besides major clinical factors such as COPD and coronary artery disease, CPET parameters (e.g., VO_2peak, anaerobic threshold, VE/VCO_2 or end-tidal PCO_2) have been shown predictive of early cardio-pulmonary complications and poor survival after thoracic surgery (16-18). In most of these reports, the analysis was focused on a limited number of potential risk factors (e.g., cardio-pulmonary diseases, extent of resection, pathologic stages, PFT, CPET) and was focused either on

Table 3 Pathological stages, surgical characteristics and perioperative data of patients undergoing lung resection according to the presence or absence of postoperative pulmonary or cardiovascular complications

Characteristic	Pulmonary complications			Cardio-vascular complications		
	Yes (n=50)	No (n=101)	P value	Yes (n=23)	No (n=128)	P value
TNM cancer stage			0.189			0.142
Stage I	22 (44.0)	52 (51.5)		7 (30.4)	67 (52.3)	
Stage II	23 (46.0)	32 (31.7)		12 (52.2)	43 (33.6)	
Stage III & IV	5 (10.0)	17 (16.8)		4 (17.4)	18 (14.1)	
Duration of surgery, min	157.8±51.5	161.4±57.8	0.710	174.2±62.8	157.6±54.1	0.191
Lung Resection			0.804			<0.001
Wedge/segment	10 (20.0)	16 (15.8)		2 (8.7)	24 (18.8)	
Lobectomy	30 (60.0)	65 (64.4)		9 (39.1)	86 (67.2)	
Pneumonectomy	10 (20.0)	20 (19.8)		12 (52.2)	18 (14.1)	
VATS	9 (18.0)	22 (21.8)	0.588	2 (8.7)	29 (22.7)	0.166
Duration of anesthesia, min	246.7±78.2	235.9±61.8	0.324	259.2±65.0	235.8±67.7	0.128
Ventilation, TLV						
V_T, mL/kg PBW	8.3±1.8	8.1±1.9	0.580	8.4±1.7	8.1±1.9	0.490
PEEP, cmH_2O	5.3±1.0	5.1±1.0	0.466	5.0±1.0	5.2±1.0	0.461
$P_{Plateau}$, cmH_2O	19.0±5.6	18.8±5.7	0.855	20.9±6.3	18.4±5.5	0.060
Ventilation, OLV						
V_T, mL/kg PBW	6.3±1.8	6.3±1.5	0.968	6.4±1.5	6.3±1.4	0.818
PEEP, cmH_2O	5.5±1.2	5.3±1.0	0.441	5.3±0.7	5.4±1.1	0.743
$P_{Plateau}$, cmH_2O	22.0±5.2	21.3±6.4	0.485	24.1±5.2	21.0±6.2	0.029
Duration, min	111.3±47.8	107.0±50.7	0.634	125.6±50.1	105.2±49.2	0.070
Fluid management						
Intraoperative Fluids, mL	1,101.8±520.1	1,133.3±665.9	0.772	1,407.9±799.1	1,070.9±570.4	0.016
IV fluids on POD1, mL	1,282.9±636.0	1,223.3±959.4	0.709	1,351.0±827.1	1,223.3±866.5	0.535
NE infusion intra-operative	18 (36.0)	23 (22.8)	0.085	11 (47.8)	30 (23.4)	0.015
NE infusion on POD	15 (30.0)	11 (10.9)	0.003	11 (47.8)	15 (11.7)	<0.001
Patients transfused	7 (14.0)	4 (4.0)	0.042	4 (17.4)	7 (5.5)	0.065
Laboratory values						
Hematocrit, %	35.1±5.6	35.7±5.2	0.544	34.6±5.0	35.7±5.4	0.352
Creatinine, mM/L	83.7±56.3	76.4±26.7	0.316	87.1±43.7	77.2±37.9	0.286

Data given as mean ± standard deviation or number (percentage). Student t tests or Chi-squared tests were used for statistical tests. VATS, video-assisted thoracic surgery; TLW, two lung ventilation; V_T, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; OLV, one lung ventilation; POD1, first postoperative day; NE, norepinephrine.

PPCs or a composite of cardiopulmonary complications that were often poorly defined. In the current study, we collected more than 200 individual data to describe the full spectrum of preoperative patient condition, medical and surgical interventions as well as the time course of postoperative recovery using objective definition criteria

Table 4 Cox regression analysis of factors associated with poor survival after lung cancer surgery

Risk factor	Hazard ratio	95% confidence interval	Z	P
V_E/VCO_2 slope >40	8.28	3.39–20.23	4.64	<0.001
Preop coronary artery disease	3.34	1.33–8.37	2.58	0.010
Preop NT-pro- BNP >100 pg/mL	3.40	1.22–9.47	2.35	0.019
Postoperative pulmonary complications	2.72	1.16–6.35	2.31	0.021

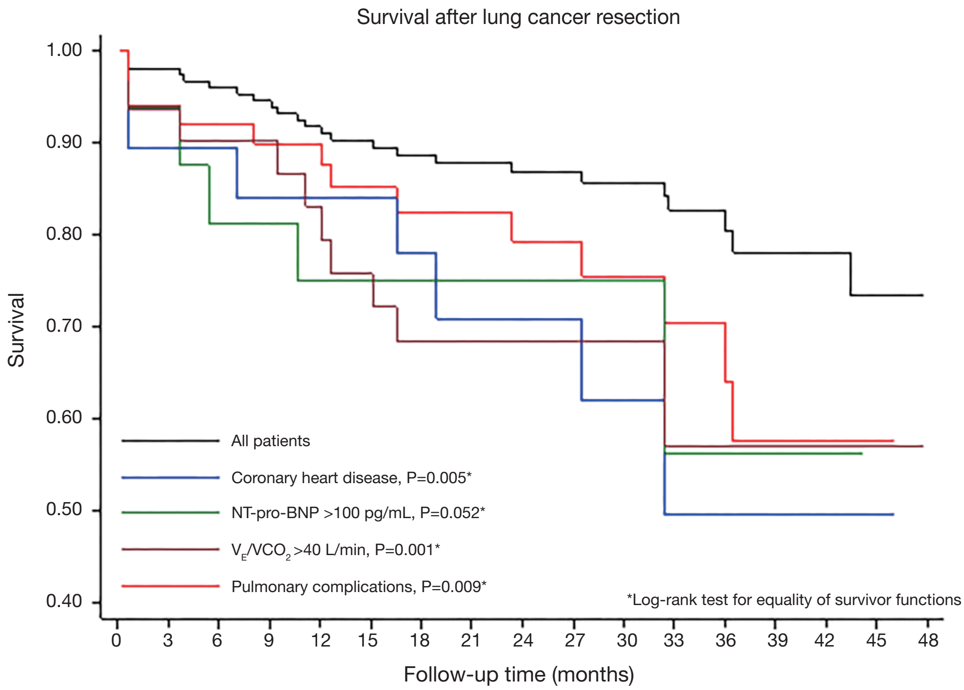

Figure 1 Kaplan-Meier survival curves after lung cancer surgery and log-rank test for differences in survival according to the presence of coronary artery disease, elevated plasma levels of cardiac biomarkers (NT-pro-BNP <100 pg/mL), ventilatory inefficiency (VE/VCO2 >40) and the occurrence of postoperative pulmonary complications.

for PPCs, PCVCs and other adverse events. Standardized perioperative processes of care entailed preoperative patient selection and optimization coupled with the implementation of fast-tracking interventions involving restrictive fluid administration, mechanical ventilation with low tidal volume and limited inspiratory driving pressure as well as multimodal analgesia and early mobilization.

Pneumonectomy and brain natriuretic peptide were identified as risk factors of PCVCs that mainly consisted in supra-ventricular arrhythmias. Performing extensive lung resections inevitably causes injuries of autonomic nerves and partial remodeling of the left atrium that have been incriminated in the development of arrhythmias (19). Interestingly, increased NT-pro-BNP was found predictive of PCVCs and poor survival. Previous studies have shown that brain natriuretic peptides were valuable predictors of cardiovascular complications, namely atrial fibrillation after thoracic surgery (20). As the release of natriuretic peptides from the cardiomyocytes correlates with the extent of ventricular dysfunction, elevated circulating BNP or NT-pro-BNP have also emerged as predictors of survival after cardiac and non-cardiac surgical procedures (21). Not surprisingly, preexisting coronary artery disease was found predictive survival since ischemic heart diseases remains the first cause of death among Western populations (22).

The occurrence of PPCs was related to known risk factors, namely preexisting COPD and current smoking (4,23). Blood transfusion that was given in a minority of patients (14%) was also predictive of PPCs as it has already been reported elsewhere (24). In the context of frequent postoperative atelectasis, bacterial growth and emergence of pneumonia are promoted by transfusion-induced immunosuppression that is related to reduced natural killer cell activity, decreased interleukin-2 production, lower CD4/CD8 ratio and decreased macrophage activity (25). In contrast with earlier reports, none of the CPET-derived parameters (e.g., VO_2peak, anaerobic threshold, V_E/VCO_2, work load) were identified as a risk factor for PPCs by multivariate analysis. The short preoperative rehabilitation program resulted in improved aerobic fitness (+15% VO_2peak) and was associated with a 40% reduction in PPCs. Besides physical training-induced enhancement in physiological reserves, minimally invasive surgical approach and intraoperative patient optimization with hemodynamic control, fluid therapy and ventilatory management likely contributed to improve perioperative outcome, particularly in the higher risk patients (26).

Importantly, mid-term survival after curative lung cancer resection was mostly related to baseline ventilatory efficiency (V_E/VCO_2 ratio) and the occurrence of PPCs. Calculation of V_E/VCO_2 ratio (or slope) at the ventilation threshold overcomes the challenging condition of peakVO_2 measurements during maximal exercise performance. Nowadays, there is growing scientific evidence of the utility of V_E/VCO_2 in assessing athletic performances and in providing diagnostic and prognostic information in patients with cardiovascular, pulmonary and neuromuscular diseases as well as in those with deconditioning related to immobilization, sedentarity and aging (11). The V_E/VCO_2 ratio is independent of peak VO_2 as a prognostic marker, and a subgroup of patients with a high V_E/VCO_2 and a low peak VO_2 have been identified to experience the worst outcome (27). Likewise, in a small cohort of 55 COPD patients undergoing lung cancer resection, Shafiek *et al.* reported that V_E/VCO_2 slope >35 was a predictor of one-year survival (10). Furthermore, in a larger cohort of 225 candidates for curative lung cancer surgery, Brunelli *et al.* found that V_E/VCO_2 slope was the strongest predictor of PPCs, but no data were provided regarding long term outcome (17). From a physiological standpoint, inefficient ventilation during intense exercise reflects ventilation/perfusion mismatch with inappropriate gas exchange that requires higher minute ventilation volume for a given level of CO_2 production. As seen from the modified alveolar equation [$V_E/VCO_2 = 863/(1 - V_D/V_T) \times PaCO_2$; VD, dead space volume; VT, tidal volume], a low $PaCO_2$ setpoint with impaired chemoreflex control and increasing dead space fraction characterizes a pattern of wasted ventilation that contributes to an "exhausting" ventilatory response during exercise as a result of airflow limitations, increasing pulmonary arterial pressure and/or impaired cardiovascular responses (11).

In agreement with recent studies, we found that patients who experienced PPCs were more likely to die after being discharged from the hospital (28-30). We included PPCs based on TNM classification (grade 2 and higher) that ranged from atelectasis requiring supplementary oxygen to respiratory failure requiring ventilatory mechanical support (13). The fact that these minor-to-moderate PPCs were associated with a 2.6-fold increase in mortality is an important message. From a prospective database including 675 patients, Nojiri *et al.* demonstrated that the occurrence of major PPCs after NSCLC resection was predictive of cancer recurrence (28). Both surgical trauma and bacterial local proliferation in the lungs have been associated with immunosuppression and upregulation of vascular adhesion molecules and that could promote the attachment of residual cancer cells to the endothelium and later tumor recurrence (31). In contrast to PPCs, the occurrence of CVCs did not affect survival in our study owing to their predominantly benign nature (supra-ventricular arrhythmias).

This study had several limitations. First, the study population included patients with early cancer disease stages considered operable according to previously validated criteria. Different risk factors could influence the outcome of patients with more advanced cancer stages and those with greater impairment in physical fitness. Second, the V_E/VCO_2 ratio was calculated at the respiratory compensation point. Measurements of end-expiratory PCO_2 and other methods of the ventilatory equivalent for CO_2 (ratio or slope of V_E/VCO_2) could have provided further prognostic information. In patients with heart failure, determination of V_E/VCO_2 slope at peak exercise was shown the best predictor of later survival (32). Third, the cause of mortality and information on the progression (or cure) of the cancer was not reported after hospital discharge and we could not assess the effect of PPCs on cancer disease-free survival nor the importance of cardiovascular disease.

In conclusion, this study emphasizes the importance of preexisting cardiopulmonary disease, smoking and the extent of lung resection as risk factors of major complications and poor survival after thoracic surgery. Further studies should be focused on modifiable risk factors to reduce the incidence of PPCs and improve long term outcome. Besides individualized perioperative patient care and fast tracking pathways, patient's physiological reserves could potentially be enhanced by tobacco withdrawal and adhesion to rehabilitation programs promoting a shift from sedentary to a physically active phenotype.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the institutional ethics committee of the University Hospital of Geneva (protocol number: 06–225). Written informed consent was obtained from all participating patients.

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