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Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC

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Abstract

Purpose: The purpose of our study was to determine the incidence of various types of postoperative pulmonary complications and to evaluate the impact of chronic obstructive pulmonary disease (COPD) on the long-term survival of patients with non-small cell lung cancer (NSCLC) undergoing pulmonary resection. *Methods:* We performed a retrospective chart review of 244 patients who had undergone lung resection for NSCLC at Indiana University. COPD, defined as predicted forced expiratory volume in 1 s (FEV1) $\leqslant 70\%$ and FEV1/FVC $\leqslant 70\%$, was determined based on preoperative pulmonary function testing in 78 of 244 patients (COPD group). The remaining 166 patients were classified as non-COPD. The incidence of postoperative complications, which included air leak of $\geqslant 10$ days, atelectasis, pneumothorax, pneumonia, bronchopleural fistula, empyema, acute respiratory distress syndrome, mechanical ventilation of $\geqslant 7$ days, and outpatient oxygen supplementation were compared between the two groups. Long-term survival and mortality due to respiratory failure were analyzed between the two groups using the Kaplan–Meier method and log rank test. *Results:* All of the above-stated postoperative pulmonary complications occurred more frequently in the COPD than in the non-COPD patients (all $P < 0.01$). The overall 5-year survival rate was 36.2% in the COPD and 41.2% in the non-COPD patients ($P = 0.1023$). Five-year cancer related survival was 43.2% in the COPD and 47.7% in the non-COPD patients ($P = 0.357$). There was no significant difference in survival among patients with different stages of lung cancer. However, the intercurrent survival, which is associated with non-cancer related death, was 60.1% in patients with COPD and 86.2% in patients without COPD at 5 years ($P < 0.0001$). The major cause of non-cancer related death in the COPD group was respiratory failure ($P = 0.0008$). *Conclusion:* The presence of COPD is an acceptable predictor of postoperative pulmonary complications in patients with NSCLC. COPD is also a significant risk factor for development of respiratory-related complications, which may explain the poor long-term survival in these patients.

Keywords: Pulmonary resection; COPD; Non-small cell lung cancer; Postoperative complication; Long-term survival; Multivariate analysis

1. Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are common fatal diseases. Patients with lung cancer who also have COPD are frequently deemed inoperable due to low cardiopulmonary reserve. Preoperative evaluation and risk stratification of patients undergoing lung resection includes such tests as pulmonary function test [1], arterial blood gas analysis [2], exercise testing [3,4], and split perfusion-ventilation radionuclide scanning [5].

Pulmonary complications after lung cancer surgery are the major causes of morbidity for patients with COPD [5,6]. Studies using multivariate statistical analysis evaluating risk factors for postoperative complications in patients with COPD have previously been published [1,7,8]. However, the incidence of each type of complication and its relationship to long-term survival of lung cancer patients with COPD has not been well defined. It is well known that postoperative pathologic staging of lung cancer has a significant

Abbreviations: NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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impact on overall and disease free survival curves. However, the impact of lung disease per-se on the long-term survival has yet to be investigated. In particular in patients with postoperative pulmonary complications, whom their compromised lung function affects their survivals as well as their quality of life.

The purpose of this study was to, (a) determine the incidence of various types of postoperative complications in non-small cell lung cancer (NSCLC) patients undergoing curative surgery in the presence and absence of COPD, (b) to assess the impact of COPD on the long-term survival of these patients, and (c) to enumerate the causes of death in our patient population.

2. Patients and methods

We performed a retrospective chart review of 315 consecutive patients with NSCLC who had undergone lung resection at Indiana University Hospital between January of 1992 and August of 1997. Preoperative evaluation for each patient included documentation of patient's medical history, blood gas analysis, spirometry and 12-lead electrocardiogram (ECG). Of the above, only 244 patients, who had a complete set of pulmonary function test and arterial blood gas analysis were into the study and the rest were excluded.

Seventy-eight of the 244 patients carried a diagnosis of COPD, defined as follows [9]: (1) percent predicted forced expiratory volume in 1 s (% predicted FEV1) $\leqslant$ 70%, and (2) FEV1/forced vital capacity (FVC) $\leqslant$ 70%. The patients who fulfilled these criteria constituted the COPD group; the rest constituted the non-COPD group. Calculation of the predicted postoperative FEV1 (PP op FEV1) was estimated by the following formula [10]: PP op FEV1 = preoperative FEV1 $\times$ [1 $-$ ($S \times 5.26$)/100], (S = number of resected bronchopulmonary segments). None of the participants were involved in a pulmonary rehabilitation program prior to surgery.

Postoperative complications occurring during the patient's hospitalization were reviewed from the attending physician progress notes. These included air leak $\geqslant$ 10 days, pneumothorax, atelectasis (segmental or lobar) without bronchial stenosis, protracted supplemental oxygen ($\geqslant$ 14 days) including home oxygen supplementation, pneumonia, bronchopleural fistula or empyema, acute respiratory distress syndrome (ARDS), and prolonged mechanical ventilation ($\geqslant$ 7 days). The incidence of the above complications were analyzed and compared between the COPD and non-COPD groups. Early ambulation through assistance of a physical therapist, bronchodilator treatment, and incentive spirometry were routinely done in the immediate postoperative period. The incidence of the above complications were analyzed and compared between the COPD and the non-COPD groups.

The overall survival, cancer related survival, intercurrent survival, and intercurrent death were analyzed for the patients in the either group. Intercurrent death was defined as death due to causes other than recurrence of lung cancer. Examples included death due to pulmonary or cardiac causes, organ failure, new primary malignancy, and stroke [11]. The survival data were collected from our institutional cancer registry database and from patient's follow-up visit in physician's office. Patients were followed up every month, then every 3 months from 2 to 5 years after surgery and every 6 months thereafter. Either contacting the patient or the treating physician confirmed date and cause of death. In regard to the overall survival curves, an observation was censored if the patient was alive at the last follow-up; for disease-specific curves, data were censored if the patient was alive or had died from a cause other than NSCLC; for intercurrent survival curves, an observation was censored if the patient was alive or had died due to causes other than recurrence of primary lung cancer. To identify the relationship between preoperative pulmonary function and alterations of respiratory condition after surgery, mortality rate due to respiratory failure was calculated and compared between the two groups.

3. Statistical analysis

Data were analyzed with the SAS software package Ver. 6.10 (Statistical Analysis Systems, Cary, NC). To test the differences between the patients in the COPD and non-COPD groups, we used Student's t-test for continuous variables, Wilcoxon rank sum test and the χ^2 test or Fisher's Exact Test for categorical variables. The survival curves and mortality rate due to respiratory failure were estimated with the Kaplan–Meier method, and the difference between theirs of the COPD and the non-COPD groups was analyzed using the log-rank test. A P value less than 0.05 was considered significant.

4. Results

4.1. Preoperative patient characteristics

Male patients with COPD (74.4%) were more frequent than those without COPD (57.2%) ($P = 0.01$). This might be because COPD is more prevalent in males than females [12,11]. The two groups were similar in terms of age, body mass index (BMI), frequency of hypertension, preoperative abnormal ECG, cardiac disease, and preoperative adjuvant therapy. The COPD group had a higher number of smokers than the non-COPD group ($P = 0.004$). The distribution of

lung cancer stage, operating methods, operating time, blood loss, and the length of hospital stay were otherwise similar between the two groups (Table 1).

Patients with COPD had a diminished pulmonary reserve (all $P < 0.001$), a lower arterial PO_2 ($P < 0.0001$), and a higher arterial PCO_2 ($P = 0.031$) compared to those without COPD. However, none of the COPD patients were on supplemental oxygen preoperatively. Predicted postoperative FEV1 was also lower in these patients than those without COPD ($P < 0.001$) (Table 2).

4.2. Postoperative pulmonary complications

Postoperative pulmonary complications are summarized in Table 3. Thirty-two of 166 patients (19.3%) without COPD had one or more postoperative pulmonary complications. On the other hand, 41 of 78 patients

Table 1
Preoperative patient characteristics

Parameters	Non-COPD ($n = 166$)	COPD ($n = 78$)	P value
Male patients	95 (57.2%)	58 (74.4%)	0.01*
Age (year) [a]	63.6±9.7	65.3±7.9	0.145
BMI (kg/m^2) [a]	26.4±5.4	27.0±5.2	0.477
Smoking history (current or ex-smoker)	141 (85.5)	75 (97.4)	0.004**
Past medical history			
Hypertension	40 (24.2)	23 (29.5)	0.384
Cardiac disease	36 (21.7)	15 (19.2)	0.654
Cancer Stage			0.949
I	100 (60.3)	46 (59.0)	
II	13 (7.8)	9 (11.5)	
III	52 (31.3)	21 (26.9)	
IV	1 (0.6)	2 (2.6)	
Pulmonary resection			0.568
Pneumonectomy	23 (13.9%)	14 (18%)	
Bilobectomy	23 (13.9)	15 (19.2)	
Lobectomy	114 (68.7)	45 (57.7)	
Segmentectomy/Wedge	4 (2.4)	3 (3.9)	
Multiple organ resection	2 (1.2)	1 (1.3)	
Length of surgery (min) [a]	184.3±74.7	204.9±87.1	0.058
Blood loss (ml) [a]	433.0±574.3	438.1±382.3	0.934
Hospital stay (days) [a]	11.0±10.2	13.9±16.1	0.151

BMI, body mass index; Chem., chemotherapy; Rad, radiation.
[a] Data are presented as mean±SD.
* $P < 0.05$.
** $P < 0.01$.

Table 2
Pulmonary function and arterial blood gas values

	Non-COPD ($n = 166$)	COPD ($n = 78$)	P value
Arterial blood gas analysis (room air)			
PH	7.43±0.03	7.42±0.03	0.143
PaO_2 (mm Hg)	77.6±9.8	70.2±8.1	<0.001**
$PaCO_2$ (mm Hg)	36.9±3.6	38.5±4.6	0.031*
Spirometry			
FVC (l)	3.3±0.9	2.9±0.8	<0.001**
Predicted FVC (%)	88.0±14.0	71.6±15	<0.001**
FEV1 (l)	2.3±0.7	1.5±0.4	<0.001**
Predicted FEV1 (%)	79.6±16.3	48.7±10.9	<0.001**
FEV1/FVC (%)	71.4±9.5	54.4±11.7	<0.001**
Predicted postoperative FEV1 (l)	1.72±0.55	1.12±0.35	<0.001**

All data are presented as mean±SD.
* $P < 0.05$.
** $P < 0.01$.

Table 3
Outcomes following lung cancer operations

Pulmonary complications	Non-COPD ($n = 166$)	COPD ($n = 78$)	P value
Prolonged air leak, pneumothorax	6 (3.6%)	12 (15.4%)	0.001**
Atelectasis	9 (5.4)	12 (15.4)	0.01*
Prolonged O_2 supplement (including home O_2 supplement)	14 (8.4)	22 (28.2)	< 0.001**
Pneumonia	5 (3)	9 (11.5)	0.008**
Bronchopleural fistura, empyema	2 (1.2)	3 (3.8)	0.174
ARDS	3 (1.8)	4 (5.1)	0.147
Prolonged mechanical ventilation	7 (4.2)	13 (16.7)	< 0.001**

Data are presented as mean ± SD, ARDS, adult respiratory distress syndrome.
* $P < 0.05$.
** $P < 0.01$.

(52.6%) with COPD experienced pulmonary complications ($P < 0.001$). Patients with COPD were more likely to experience prolonged air leak ($\geqslant 10$ days) or pneumothorax ($P = 0.001$), atelectasis ($P = 0.01$), lengthened oxygen supplement ($\geqslant 14$ days) ($P < 0.001$), pneumonia ($P = 0.008$), and protracted mechanical ventilation ($\geqslant 7$ days) ($P < 0.001$).

Sixteen patients died 30 days after operation. The patients with COPD had a higher death rate compared to those without COPD (3 and 14.1%, respectively, $P = 0.003$). Three patients (60%) in the non-COPD and 6 patients (54.5%) in the COPD group had respiratory failure as their cause of death. Causes of respiratory failure included pneumonia in the non-COPD group (3 patients), and pneumonia (3 patients), empyema (1 patient), and ARDS (2 patients) in the COPD group.

4.3. Survival analyses

Fig. 1 shows overall survival following the surgery. The cumulative survivals at 2 and 5 years were 70.6 and 41.2% in the non-COPD, and 54.0 and 36.2% in the COPD group, respectively. Median survival was 41.8 months for the non-COPD group and 27.3 months for the COPD group ($P = 0.1023$, log rank test; hazard ratio 0.74; 95% CI, 0.83–2.23).

The cancer related survivals at 2 and 5 years were 77.1 and 47.7% in the non-COPD group, and 72.4 and 43.2% in the COPD group, respectively (Fig. 2). Median survival of cancer related survival was 51.3 months in the non-COPD group and 79.4 months in the COPD group ($P = 0.357$, log rank test; hazard ratio 1.25; 95% CI, 0.77–1.95). There was no significant difference between the two groups regarding survival at any stage of lung cancer (data not shown).

The intercurrent survivals revealed significantly reduced survival in the COPD group (Fig. 3). Although the non-COPD group kept 92.4 and 86.2% of intercurrent survival rate at 2 and 5 years, respectively, the COPD group had a gradual decrease with 74.6 and 60.1% of survival rate at 2 and 5 years. This trend was significantly lower than that in the non-COPD group ($P < 0.0001$, log rank test; hazard ratio 3.78; 95% CI, 2.31–9.15).

Causes of deaths including short and late mortalities were summarized in Table 4. Eighty-four patients (50.6%) in the non-COPD group and 53 patients (67.9%) in the COPD group died postoperatively ($P = 0.013$). The primary cause of death was recurrence of the primary lung cancer in both groups (69 patients in the non-COPD and 29 in the COPD). The second most frequent cause of deaths was respiratory failure in the COPD group (14 patients: 26.4%), while non-respiratory

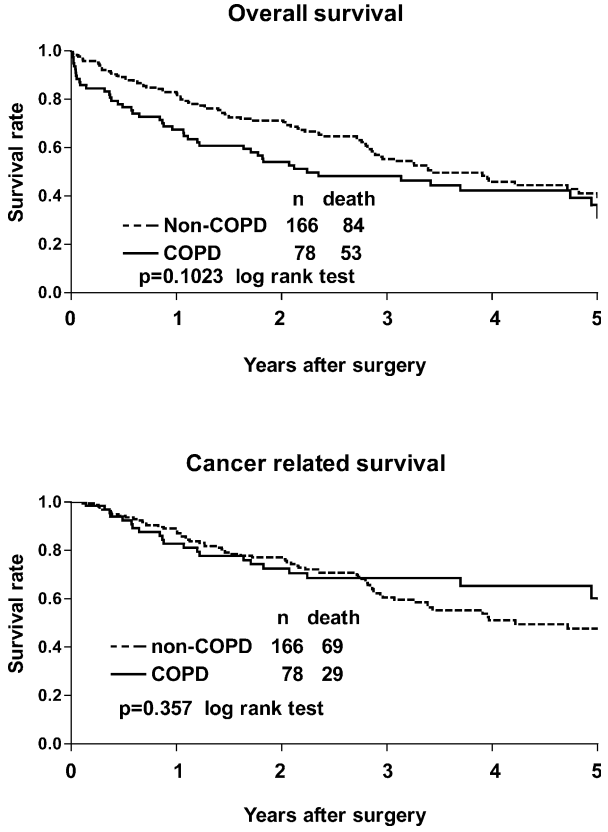

Fig. 2. Cancer related survival after pulmonary resection in COPD patients.

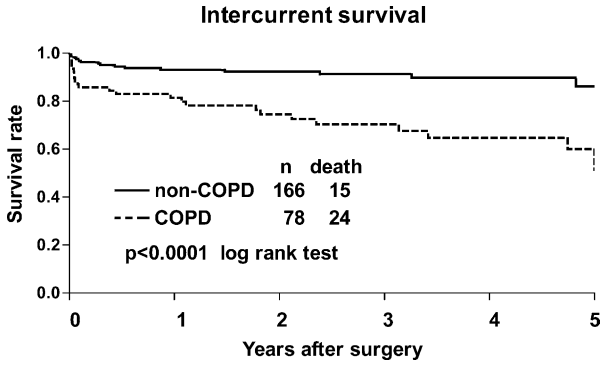

Fig. 3. Intercurrent survival after pulmonary resection.

causes were more frequent in the non-COPD group. Therefore, respiratory failure was a more significant cause of death in the COPD group ($P = 0.0008$).

Fig. 4 shows the mortality rate due to respiratory failure. Respiratory failure was less observed in the non-COPD group. In contrast, the incidence of respiratory failure leading to death constantly increased to approximately 20% in the COPD group, which was a significant difference ($P < 0.0001$).

5. Discussion

In this study we demonstrated several important clinical findings. First, the criteria of COPD (% pred. FEV1 $\leqslant$ 70% and FEV1/FVC $\leqslant$ 70%) were the critical predictor for any type of pulmonary complication in lung cancer patients undergoing pulmonary resection. Furthermore, although there was no difference in overall long-term and cancer related survivals, intercurrent survival in the COPD group was significantly shorter than that in the non-COPD group. Finally, the main cause of non cancer-related deaths in the COPD group was pulmonary insufficiency early on and in the later stages of the disease.

Lung cancer and COPD share the same common risk factors, which include cigarette smoking, genetic predisposition and environmental exposure. Lung cancer is far more common in patients with COPD than in those with normal airflow obstruction [12–14]. Recent advances in operative techniques and postoperative management has allowed a more aggressive surgical approach to lung cancer, particularly in patients with COPD. Olsen et al reported that prophylactic chest physiotherapy reduced the incidence of pulmonary complications after major abdominal surgery from 27 to 6% [15]. Pulmonary rehabilitation also improves exercise tolerance and quality of life in COPD patients [16]. Although postoperative early mobilization and physiotherapy were encouraged in our hospital, preoperative routine chest physiotherapy is not routinely performed due to lack of symptoms in most of our patients. However, we believe that preoperative physiotherapy should become standard in order to reduce risk of pulmonary complications.

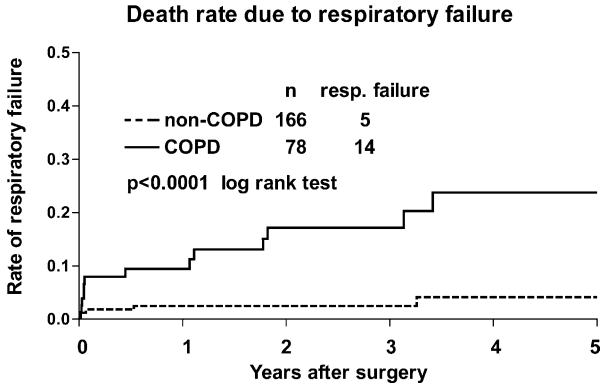

Fig. 4. Mortality due to respiratory failure after lung resection.

Table 4
Causes of death after pulmonary resection

Causes of death	Non-COPD ($n = 166$)	COPD ($n = 78$)	P value
Total (%)	84 (50.6)	53 (67.9)	0.013*
Cancer-related (%)	69 (82.1)	29 (54.7)	0.0008**
Respiratory failure	5 (6.0)	14 (26.4)	0.0008**
Other causes	10 (11.9)	10 (18.9)	0.0008**
Cardiac insufficiency	3	5	
Other malignancy	2	2	
Other organ failure	3	2	
Unknown causes	2	1	

* $P < 0.05$.
** $P < 0.01$.

Previous studies have shown that postoperative pulmonary complications were closely linked to several preoperative variables. These included obesity [17], COPD [6,18–21], extent of the operation [1,20], cigarette smoking [17], diminished pulmonary function [1,5,8,22,23] and poor exercise tolerance [4,24]. Since the report by Gaensler et al. [22], many investigators have been utilizing preoperative pulmonary function tests to risk stratify patients for postoperative pulmonary complications. FEV1 $<$ 0.8 l [5] or 1.2 l [23], maximum voluntary ventilation (MVV) $<$ 60% [25], predicted postoperative FEV1 $<$ 1 l [1], % predicted postoperative FEV1 $<$ 40% [7], % predicted postoperative DLco $<$ 40% [7], and oxygen consumption during exercise ($V\mathrm{o}_{2\mathrm{Peak}}$) of $<$ 15 ml/kg/min [4] were proposed as predictors of pulmonary complications. In this study, we clarified that % predicted FEV1 $\leqslant$ 70 and % FEV1/FVC $\leqslant$ 70 (criteria for COPD) were important predictors of any type of postoperative pulmonary complications in lung cancer patients.

Patients with COPD are more prone to pneumothorax, pneumonia, and chronic hypoxemia because of impaired total distance of alveolar surface to the capillary endothelium, reduced area of gas exchange, and reduction of surface capillary area and hemoglobin concentration [26]. Atelectasis due to increased sputum and altered mucociliary clearance also occurs more frequently in these patients. Our COPD patients required more prolonged mechanical ventilation and home oxygen supplementation than the patients without COPD possibly because of lower preoperative PaO_2 and higher $PaCO_2$.

It is well established that lung cancer stage, nodal stage and performance status are significant independent prognostic variables in long-term survival of lung cancer patients [27,28]. However, pulmonary function has not been previously identified as an independent risk factor, and no report has been published in terms of long-term survival for lung cancer patients with COPD after pulmonary resection. In this study, although poor pulmonary reserve such as % predicted FEV1 $\leqslant 70$ and % FEV1/FVC $\leqslant 70$, had no impact on overall survival or cancer related survival, patients with COPD had significantly worse long-term intercurrent survival because of more frequent incidence of pulmonary insufficiency. Since pathologic staging was not different between the two groups, it made common sense that cancer related survival to be similar between the two groups. Despite lack of statistical difference between survival rates, death rate in the COPD group was lower than the non-COPD group from immediately after surgery until 3 years. Furthermore, intercurrent death in the COPD group was significantly higher than that in the non-COPD group. This phenomenon was mainly because of early and late onset of respiratory deterioration in the COPD group, which is shown in Fig. 4. We previously reported that patients with 30 or more pack-years of smoking had poor prognosis after resection of stage I NSCLC [29]. Tobacco smoking is strongly associated with chronic airway obstruction as well as lung cancer [13,30], and COPD patients have a higher mortality due to respiratory failure, cor-pulmonale and lung cancer [31]. Therefore, our results suggest that COPD has a strong impact on deterioration of pulmonary condition after surgery and in long run, is associated with worsening of pulmonary function.

Lung volume reduction surgery has been a surgical tool for correction of severe emphysema since 1990s. This operative technique improves not only the FEV1 but also the patient's quality of life. One report states that pulmonary function improves after resection in selected lung cancer patients with severe emphysema [32]. Our experience also shows that in some cases postoperative pulmonary function are better than predicted after resection in lung cancer patients with COPD. Better operative techniques, pre-and post-operative rehabilitation, and better patient care may explain this difference. One explanation for this difference could be restoration of the elastic recoil of pulmonary parenchyma and the improvement of thoracic motion. However, once pulmonary complications occur, lung function is compromised and ensuing inflammatory changes accelerate the destruction of viable lung tissue. These alterations may be precedents to formation of pneumonia and exacerbation of COPD, therefore causing higher morbidity and mortality. We recommend establishing a model of predicting postoperative pulmonary function according to preoperative respiratory status in patients with COPD undergoing lung cancer surgery.

In conclusion, the criteria of COPD in this study are acceptable predictors for the development of postoperative pulmonary complications in lung cancer patients. COPD was also a risk factor for the poor long-term intercurrent survival due to respiratory insufficiency. Even after successful surgical treatment for NSCLC, COPD patients still have a high mortality because of deteriorated pulmonary status.

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