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Original Article

Worse Prognosis for Stage IA Lung Cancer Patients with Smoking History and More Severe Chronic Obstructive Pulmonary Disease

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Purpose: This retrospective study examined whether the severity of chronic obstructive lung disease (COPD) affects surgical outcomes.
Methods: The subjects were 243 consecutive patients who underwent lobectomy for clinical stage IA lung cancer from 1999 to 2008 in our hospital. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) grading system was used to classify the severity of COPD in smokers.
Results: Among the 149 smokers, 62 were diagnosed with COPD (25 as GOLD 1, 33 as GOLD 2, and 4 as GOLD 3). In univariate analysis, postoperative pulmonary complications were associated with male sex and more severe COPD. The frequencies were 17.1% in non-COPD, 24.0% in GOLD 1-COPD, and 46.0% in GOLD 2/3-COPD smokers (p = 0.0006). In univariate analysis, older age, smoking history, higher smoking pack-years and more severe COPD were associated with poor relapse-free survival. Relapse-free survival at five years was 80.7%, 66.9%, and 61.3% in non-COPD, GOLD 1-COPD, and GOLD 2/3-COPD smokers, respectively (p = 0.0005). Multivariate analyses showed that only GOLD 2/3-COPD was associated with postoperative pulmonary complications and relapse-free survival. Inhaled bronchodilators were prescribed preoperatively to 24.3% of the GOLD 2/3-COPD group.
Conclusion: Smokers with GOLD 2/3-COPD are at high risk for pulmonary complications and have an unfavorable long-term prognosis.

Keywords: pulmonary disease chronic obstructive, postoperative complications, carcinoma bronchogenic, spirometry, treatment outcome

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Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in males worldwide.[1)] Tobacco smoking is the best established risk factor for lung cancer and the most common risk factor for chronic obstructive lung disease (COPD).[2)] COPD is the fourth leading cause of death worldwide and occurs in 30% of patients with lung cancer.[2)] Spirometry is used to assess the risk for perioperative death and cardiopulmonary complications after resection of the lung, with a predicted postoperative forced expiratory volume in one second (FEV_1) value of 30% indicating a high risk.[3,4)] Several analyses of large national databases have shown that

% predicted FEV_1 (%FEV_1) is correlated with prolonged length of hospital stay,[5] major morbidity,[6] and in-hospital mortality,[7] after surgical resection of lung cancer. Postoperative complications and survival were not directly evaluated in these studies.

Sekine, et al. showed that survival after pulmonary resection of stage IA lung cancer in patients with COPD was inferior to that in patients without COPD due to a higher incidence of recurrence,[8] but the severity of COPD was not addressed. More recently, the same group found that COPD severity generally correlated with the incidence of postoperative pulmonary complications and overall survival in patients undergoing surgery for lung cancer of all stages.[9] However, age, smoking history, and lung cancer stage remained as confounding factors after multivariate analysis. In this study, we examined if the severity of COPD influences the frequency of postoperative pulmonary complications and long-term prognosis after lobectomy in patients with stage IA lung cancer.

Materials and Methods

Patient population

This study was approved by the Institutional Review Board in our hospital. Written informed consent from each patient was waived for the study. We surveyed the thoracic surgery database in our hospital to select all patients with clinical stage IA lung cancer who underwent single lobectomy between January 1999 and December 2008, and reviewed the medical charts.

Definitions

Postoperative pulmonary complications were classified as prolonged air leak, atelectasis requiring bronchoscopy, pneumonia, tracheostomy or mini-tracheostomy, empyema, and other pulmonary complications. Prolonged air leak was defined as a persistent air leak for >10 days, reinsertion of a chest tube due to pneumothorax, or reoperation for prolonged air leak.

Spirometric measurements were evaluated based on reference values of the Japanese Respiratory Society in 2001.[10] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that spirometry should be performed after administration of a short-acting inhaled bronchodilator to minimize variability,[2] but medical records reflected the clinical practice of performing spirometry without an inhaled bronchodilator. COPD was defined as FEV_1/FVC <0.7 (FVC, forced vital capacity) with a smoking history.[2,11] GOLD spirometric grades were used to classify the severity of airflow limitation: GOLD 1 (mild), FEV_1 ≥80% predicted; GOLD 2 (moderate), 50% ≤FEV_1 <80% predicted; GOLD 3 (severe), 30% ≤FEV_1 <50% predicted; and GOLD 4 (very severe), FEV_1 <30% predicted [2]. Patients who had never smoked and smokers without COPD were designated as non-COPD group. We identified eight patients with asthma: three patients who had never smoked and five patientswho had a smoking history. Because discrimination of asthma from COPD is difficult in older patients, 2, 1 and 2 of the patients with asthma and a smoking history were assigned to the non-COPD, GOLD 1-COPD, and GOLD 2-COPD groups, respectively, based on spirometric measurements. Smoking status was examined based on questionnaires completed by patients. Patients who quit smoking more than one year before the operation were defined as former smokers and those who were smoking at the time of the operation or quit within one year before the operation were defined as current smokers.

Preoperative examination prior to pulmonary resection included chest X-ray, contrast-enhanced chest computed tomography (CT), and brain CT or magnetic resonance imaging, if clinically indicated. No patient underwent a mediastinoscopy. Positron emission tomography (PET) scans became available in 2002. Staging and pathological findings for lung cancer were based on the 7th TNM staging and 2004 WHO classification.[12,13] Pathological diagnosis was determined as a consensus of at least two board-certified pathologists. Postoperative administration of uracil–tegafur were indicated for selected patients with pathological stage IB adenocarcinoma and platinum-based chemotherapy for patients with pathological stage IIA-III non-small cell lung cancer. The interval between follow-up visits was every 3 months for the first two years, and then every 6 months for up to 5 years. Physical examination and chest X-ray were performed at each visit. Unless contraindicated, a contrast-enhanced chest computed tomography scan was performed every 6 months postoperatively for 2 years and annually thereafter based on the National Comprehensive Cancer Network guidelines.[14] Metachronous second primary lung cancer was discriminated from a solitary pulmonary metastasis using the proposed criteria in the American College of Chest Physicians (ACCP) Lung Cancer Guidelines.[15] Relapse-free survival was defined as the duration between the day of surgery and the day of recurrence of lung cancer or death from all causes. Patients who were alive without evidence of recurrence at the end of the follow-up period were regarded as censored cases. Overall survival was

Table 1 Baseline characteristics of the patients

		Non-COPD	GOLD 1 COPD	GOLD 2/3 COPD	p value*
		n = 181	n = 25	n = 37	
Sex	Male	85 (47.0%)	22 (88.0%)	33 (89.2%)	<0.0001[a]
	Female	96 (53.0%)	3 (12.0%)	4 (10.8%)	
Age, years	Mean	64.1	69.5	70.8	<0.0001[b]
	SD	10.2	10.1	7.7	
Smoking status	Current	33 (18.2%)	11 (44.0%)	18 (48.6%)	<0.0001[a]
	Former	54 (29.8%)	14 (56.0%)	19 (51.4%)	
	Never	94 (51.9%)	0 (0.0%)	0 (0.0%)	
Pack-years		19.6	60.0	70.2	<0.0001[b]
VATS-lobectomy		42 (23.2%)	8 (32.0%)	10 (27.0%)	0.5939[c]
Tumor size, cm	Mean	1.8	1.8	1.9	0.7720[b]
Pathology	Adenocarcinoma	160 (88.4%)	20 (80.0%)	23 (62.2%)	0.0006[a]
	Adenocarcinoma with mixed subtypes	147	17	22	
	Bronchioloalveolar carcinoma	13	3	1	
	Squamous	12 (6.6%)	3 (12.0%)	12 (32.4%)	
	Others	9 (5.0%)	2 (8.0%)	2 (5.4%)	
Pathological N	pN0	159 (87.9%)	23 (92.0%)	33 (89.2%)	0.9674[a]
	pN1	8 (4.4%)	0 (0.0%)	1 (2.7%)	
	pN2	14 (7.7%)	2 (8.0%)	3 (8.1%)	
Pathological stage	IB-IV	49 (27.1%)	5 (20.0%)	10 (27.0%)	0.7494[c]
	IB	24	2	4	
	IIA	4	0	1	
	IIB	1	0	1	
	IIIA	14	2	3	
	IIIB	6	0	0	
	IV	0	1	1	
Adjuvant chemotherapy		23 (12.7%)	4 (16.0%)	5 (13.5%)	0.9004[a]
Inhalant use	Short-acting β2-agonist	0 (0.0%)	0 (0.0%)	2 (5.4%)	
	Long-acting β2-agonist	1 (0.6%)	1 (4.0%)	6 (16.2%)	
	Inhaled corticosteroid	5 (2.8%)	0 (0.0%)	4 (10.8%)	
	Any inhalants	5 (2.8%)	1 (4.0%)	9 (24.3%)	<0.0001[a]

[a] Fisher's exact test, [b] Kruskal-Wallis test, [c] Chi-square test; COPD: chronic obstructive lung disease; GOLD: The Global Initiative for Chronic Obstructive Lung Disease; SD: standard deviation; N/A: not applicable; VATS: video-assisted thoracic surgery

determined as the duration from the day of surgery until the day of death from all causes, with patients alive at the end of follow-up treated as censored cases.

Statistical analysis

Summary statistics were constructed using frequencies and proportions for categorical data, and means and standard deviations (SD) for continuous variables. Patient characteristics were compared by chi-square test or Fisher's exact test for categorical outcomes and by Kruskal-Wallis test for continuous variables, as appropriate. Age and smoking index were divided into groups using mean values from GOLD 2/3-COPD cases as thresholds (70 years and 70 pack-years, respectively).

The Kaplan-Meier method was used to draw survival curves for each group and survival distributions were compared by log-rank test. Multivariate analysis was performed with a logistic regression model using a stepwise selection procedure. A p-value <0.05 was considered to be significant. All statistical analyses were performed using JMP 10 and SAS 9.3 statistical software (both SAS Institute Inc., Cary, North Carolina, USA).

Results

The characteristics of the 243 patients in the study are shown in **Table 1**. Of these patients, 94 had never smoked, 87 were former smokers, and 62 were current smokers. Among the 149 smokers, 62 were diagnosed with COPD. Among the COPD patients, 25 were classified as GOLD 1, 33 as GOLD 2, and 4 as GOLD 3. Inhalants were prescribed before pulmonary resection in 24.3% of the patients

Table 2 Pulmonary complications according to severity of COPD

	Non-COPD	GOLD 1 COPD	GOLD 2/3 COPD	p value
	n = 181	n = 25	n = 37	
Prolonged air leak	20 (11.1%)	3 (12.0%)	6 (16.2%)	
Atelectasis	6 (3.3%)	1 (4.0%)	4 (10.8%)	
Pneumonia	7 (3.9%)	0 (0.0%)	6 (16.2%)	
Tracheostomy*	4 (2.2%)	3 (12.0%)	7 (18.9%)	
Empyema	2 (1.1%)	2 (8.0%)	1 (2.7%)	
Others	7 (3.9%)	1 (4.0%)	1 (2.7%)	
Any pulmonary complications	31 (17.1%)	6 (24.0%)	17 (46.0%)	0.0006[a]

* Including mini-tracheostomy; [a] Chi-square test; COPD: chronic obstructive lung disease

Table 3 Multivariate analysis of postoperative pulmonary complications

Parameter		Odds ratio	95% CI	p value
Grade of COPD	GOLD-2/3 vs. non-COPD and GOLD-1	3.88	1.85–8.14	0.0004
Sex	Male vs. Female	N/A	N/A	0.1101

COPD: chronic obstructive lung disease; GOLD: The Global Initiative for Chronic Obstructive Lung Disease; CI: confidence interval; N/A: not applicable

in the GOLD 2/3-COPD group. Mediastinal lymph node dissection or sampling were performed in 93.8% of 243 patients, with the lowest frequency of 86.5% in 37 GOLD 2/3-COPD smokers.

The frequency of postoperative pulmonary complications showed a significant increase as %FEV1 decreased (p = 0.0006, chi-square test): 17.1% in non-COPD, 24.0% in GOLD 1-COPD, and 46.0% in GOLD 2/3-COPD smokers (**Table 2**). There were no in-hospital deaths. In univariate analysis, male sex and more severe COPD were associated with postoperative pulmonary complications (p = 0.0187 and 0.0006, respectively, Fisher's exact test and chi-square test). Age (≥70 years old vs. <70 years old), smoking status (current and former vs. never), smoking index (≥70 pack-years vs. <70 pack-years), and surgical approach (video-assisted thoracic surgery [VATS] vs. thoracotomy) did not show this association. In multivariate analysis, a GOLD 2/3-COPD status was the only predictive factor for postoperative pulmonary complications (**Table 3**).

Thirty-eight patients died during the follow-up period. The median follow-up period was 5.7 years for the 205 patients who were alive at the end of follow-up. The frequency of recurrence correlated with COPD stage (p = 0.0301, chi-square test): 28 cases (15.5%) in the non-COPD group, 7 (28.0%) in the GOLD 1-COPD group, and 12 (32.4%) in the GOLD 2/3-COPD group.

Relapse-free survival at 5 years significantly decreased as COPD stage increased (p = 0.0005, log-rank test,

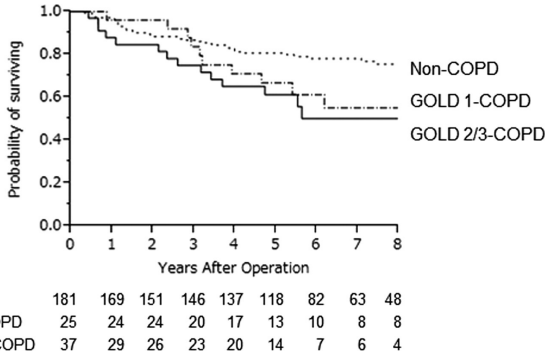

Fig. 1 Kaplan-Meier plots of relapse-free survival. COPD: chronic obstructive lung disease; GOLD: The Global Initiative for Chronic Obstructive Lung Disease.

Fig.1): 80.7% (95% CI: 74.1%–86.0%) for non-COPD, 66.9% (95% CI: 46.4%–82.5%) for GOLD 1-COPD and 61.3% (95% CI: 43.3%–76.7%) for GOLD 2/3-COPD. In univariate analysis, older age, smoking status, smoking index and more severe COPD were associated with poor relapse-free survival (p = 0.0390, 0.0387, 0.0444 and 0.0005, respectively, log-rank test). Sex, histology (adenocarcinoma vs. non-adenocarcinoma) did not show this association. In multivariate analysis, a GOLD 2/3-COPD status was the only prognostic factor predicting relapse (**Table 4**). There was also a significant difference in overall survival among the non-COPD, GOLD 1-COPD, and GOLD 2/3-COPD groups (log-rank test p = 0.0223).

Table 4 Multivariate analysis of prognostic factors for relapse-free survival

Parameter		Hazard ratio	95% CI	p value
	non-COPD	Reference		
Grade of COPD	GOLD-1	1.69	0.79–3.45	0.1693
	GOLD-2/3	2.20	1.07–4.48	0.0333
Age	≥70 vs. <70	1.39	0.84–2.28	0.1976
Smoking status	Current and Former vs. Never	1.20	0.64–2.23	0.5712
Smoking index, pack-years	≥70 vs. <70	1.14	0.60–2.10	0.6763

COPD: chronic obstructive lung disease; GOLD: The Global Initiative for Chronic Obstructive Lung Disease; CI: confidence interval

Discussion

COPD is a negative predictive factor for survival after resection of stage IA lung cancer because of recurrence.[8] Severity of COPD correlates with poor survival in all stages of lung cancer, although age, smoking history, and lung cancer stage may be confounding factors.[9] The results of this study show that GOLD 2/3-COPD is a risk for recurrence even in stage IA lung cancer patients, regardless of age, but that a GOLD 1 status does not carry a similar risk.

The frequencies of postoperative pulmonary complications increased with the severity of COPD. Among patients with a GOLD 2 or 3 status, 6 (16.2%) had pneumonia, which is much higher than the rate of 3.9% in the Society of Thoracic Surgeons database.[16] Seven GOLD 2/3 patients (18.9%) required tracheostomy and 17 (46.0%) had at least one pulmonary complication after lobectomy (**Table 2**), a markedly high incidence. These results indicate a need for new strategies to improve perioperative outcomes in patients with poor pulmonary function. In our study, inhalants were prescribed for only 24.3% (9/37) of patients with GOLD 2/3-COPD. Inhaled bronchodilators have established efficacy for improving pulmonary function,[17] and prospective trials to evaluate the use of preoperative bronchodilators are underway.[18] Accumulation of evidence is needed to establish the role of inhalation therapy for surgical patients with lung cancer and severe COPD. Pulmonary rehabilitation, including exercise and education, is effective in candidates for lung volume reduction surgery,[19] and preoperative intensive physical therapy appears to be effective for surgical patients with lung cancer.[20] Inhalation therapy can improve exercise tolerability by decreasing hyperinflation of lungs,[21] and preoperative smoking cessation can also play a role.[22] ERS/ESTS guidelines recommend smoking cessation two to four weeks before surgery for lung cancer,[3] but 28.6% of patients continue to smoke within two weeks of surgery.[16] Thoracoscopic surgery has fewer postoperative complications than standard thoracotomy,[23] and the rates of thoracoscopic lobectomy were similar between three groups in the current study. Greater use of mini-tracheostomy is likely to reduce the incidence of pneumonia in patients with difficulty coughing up.

Despite our finding that patients with a GOLD 2 or 3 status were at high risk for pulmonary complications after lobectomy, surgery should not be withheld in this group of patients. Many studies have shown minimal loss or even improvement of pulmonary function after lobectomy by the so-called "lung volume reduction effect" in patients with airflow limitations, thus making estimations of postoperative pulmonary function difficult.[24] Quality of life after lobectomy in patients with COPD is similar to patients without COPD, despite an increased risk of postoperative cardiopulmonary complications,[25] and there were no in-hospital deaths in the current study.

Relapse-free survival deteriorated with increased severity of COPD, even though the pathological stages were similar across the groups. Poorer long-term survival in patients with COPD due to a higher incidence of tumor recurrence has been found previously.[8,9] One possible explanation is the immunological status of patients with COPD. Lung cancers that arise from the lung parenchyma with abnormal and excessive inflammatory responses in COPD are thought to have an aggressive character.[26] Also, COPD often coexists with diseases such as cachexia, cardiovascular disease, osteoporosis and diabetes, which are all associated with systemic inflammation,[27] and such comorbidities might directly or indirectly affect prognosis. Determination of the basis of the association of GOLD 2/3 COPD with a worse prognosis may lead to better treatment and outcomes.

There are several limitations in this retrospective study. Although GOLD recommends only post-bronchodilator spirometry, we included examinations before administration of an inhaled bronchodilator. Diagnosis of COPD

was made based only on smoking status and airflow limitations without taking clinical signs and symptoms into account, although we believe this definition is acceptable in a retrospective study because smoking is the primary risk factor for COPD and approximately 85 to 90% of COPD deaths are caused by smoking.[28] Guidelines recommend measurement of the diffusing capacity of the lung for carbon monoxide (DLCO), in addition to FEV_1, in preoperative assessment in all cases[3,4] because DLCO is a predictive risk factor for postoperative pulmonary complications in non-COPD patients.[29] However DLCO was examined in only 57% of patients in the STS database[29] and in only selected patients in our study.

Conclusion

In conclusion, our results show that the severity of COPD is a predictive risk factor for pulmonary complications, as well as a poor prognostic factor after lobectomy for stage IA lung cancer. Among patients with GOLD 2/3-COPD, 46.0% had pulmonary complications after lobectomy, while inhaled bronchodilators were prescribed for only 24.3% before surgery. This suggests that COPD is not recognized in patients with lung cancer and that a multidisciplinary approach is needed to improve perioperative outcomes in these patients. New strategies are also required to improve long-term outcomes of resectable lung cancer in patients with COPD.

Disclosure Statement

The authors declare that there is no conflict of interest associated with this study.

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