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Severity of Chronic Obstructive Pulmonary Disease and the Prognosis of Non-Small Cell Lung Cancer Patients

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Abstract

Objectives: We retrospectively analyzed whether the severity of Chronic Obstructive Pulmonary Disease (COPD) affected disease-specific survival in Non-Small-Cell Lung Cancer (NSCLC) patients after surgical resection. Methods: We enrolled 210 NSCLC patients who underwent curative surgery between 2009 and 2011. Classification of COPD severity was based on guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Results: A total of 55 patients were diagnosed with COPD. The 5-year disease-specific survival of patients with COPD was not different compared with that of patients without COPD. Among the COPD patients, 40 were classified as GOLD 1, 13 as GOLD 2, and 2 as GOLD 3. Although the number of patients with GOLD 2 - 3 was small, the 5-year disease-specific survival of patients with GOLD 2 - 3 was significantly poorer. We found the prognostic significance of GOLD 2 - 3 in univariate analysis, but failed to find this in multivariate analysis. Conclusions: There is a possibility that the severity of COPD might be useful to predict the prognosis of NSCLC patients. Further studies with large study population are needed.

Keywords

Non-Small Cell Lung Cancer, COPD, GOLD, Prognosis

1. Introduction

Lung cancer and Chronic Obstructive Pulmonary Disease (COPD) are both common diseases. Epidemiological data showed that the presence of COPD increased the risk of

lung cancer by 4.5 folds [1] [2]. Moreover, in recent years, several studies have focused on the relationship between COPD and its comorbidities. Previous analyses have shown that COPD is correlated with prolonged length of hospital stay [3], major morbidity [4], and in-hospital mortality [5] after Non-Small Cell Lung Cancer (NSCLC) surgery. It is easy to understand that COPD patients receiving pulmonary resection for NSCLC are thought to be at increased risk of short-term morbidities and surgery-related mortalities.

Furthermore, several previous studies reported that NSCLC patients with COPD had increased risk of worse disease-specific survival [6]-[9]. On the other hand, other studies did not find differences in survival [10]-[13].

With respect to COPD, its role in the prognosis of NSCLC is not yet clear. A recently reported meta-analysis of observational studies concluded that the presence of COPD was robust predictors of poor survival in patients with lung cancer [14]. However, the effect of COPD on the survival after resection of NSCLC is still uncertain. The purpose of this study is to investigate the impact of COPD severity on postoperative recurrence in patients with resectable NSCLC.

2. Patients and Methods

This retrospective study had institutional review board approval (2016-113), and the need to obtain patient consent was waived. Consecutive NSCLC patients who underwent surgery from 2009 to 2011 in our hospital were enrolled into the present retrospective study. The following patients were excluded: 1) patients who had not received complete resection, 2) patients who died of other diseases after surgery, and 3) patients who lost to follow-up. One hundred and seventy-five consecutive resected NSCLC patients were enrolled into the present retrospective study. The clinicopathologcal factors of patients were shown in **Table 1**.

Spirometric measurements were evaluated in all patients preoperatively. COPD was defined as forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) < 0.7 [15]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grades [16] were used to classify the severity of airflow limitation: GOLD 1 (mild), FEV1 ≥ 80% predicted; GOLD 2 (moderate), 50% ≤ FEV1 < 80% predicted; GOLD 3 (severe), 30% ≤ FEV1 < 50% predicted; and GOLD 4 (very severe), FEV1 < 30% predicted.

All patients with preoperative smoking had stopped smoking cigarettes for more than 1 month before surgery, even if they were current smokers. All patients with COPD received inhaled tiotropium bromide (18 μg once daily) (Spiriva®, Handi Haler; Boehringer Ingelheim, Berkshire, UK) for at least 1 week before surgery until at least 4 weeks after surgery.

Pathological (p) tumor-node-metastasis (TNM) staging was recorded in all patients based on the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) classification. Follow-up information, including cause of death, was ascertained through a review of clinic notes and direct or

Table 1. Clinical characteristics.

		Non-COPD	COPD	*p* Value
Age	<65	49	11	0.093
	≥65	106	44	
Gender	Male	60	44	<0.001
	Female	95	11	
Smoking	Current/Former	65	45	<0.001
	Never	90	10	
Histology	Adeno	128	33	<0.001
	Others	17	6	
	Squamous	10	16	
pStage	I	123	42	0.645
	II-III	32	13	
pT status	pT1	115	38	0.469
	pT2 - 3	40	17	
pN status	pN0	136	47	0.667
	pN1 - 2	19	8	
CEA	Norm	118	40	0.618
	High	37	15	

CEA: carcinoembryonic antigen.

family contact. Patients who were alive without evidence of recurrence at the end of the follow-up period were regarded as censored cases. Overall survival was 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. The disease-specific survival curves of the patients were plotted by using the Kaplan-Meier method and analyzed using the log-rank test. The Cox regression hazard model was used for univariate and multivariate analyses to assess the prognostic value of COPD. The software package JMP version 12.2.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Statistical significance was considered at p less than 0.05.

3. Results

The characteristics of the 210 patients in the study are shown in Table 1. Of these patients, 100 had never smoked, 110 were current/former smokers. A total of 55/210 (26.2%) patients were diagnosed with COPD, including 40 mild cases (GOLD 1), 13 moderate cases (GOLD 2), and 2 severe cases (GOLD 3). As shown in Table 1, the presence of COPD was significantly related to gender, smoking status and histology, while age, pStage, pT status, pN status and serum carcinoembryonic antigen (CEA) level was not.

A comparison of survival curves based on COPD is shown in Figure 1. The 5-year disease-specific survival of patients with COPD was similar to those without COPD (69.1% vs. 72.4%, p = 0.492).

COPD patients were subdivided into 2 groups: GOLD 1 and GOLD 2 - 3. The 5-year disease-specific survival was 70.4% for GOLD 1 group, which was comparable with that of non-COPD group (p = 0.667). However, the disease-specific survival of GOLD 2 - 3 group was 46.7%, significantly lower than that of non-COPD group (p = 0.012) and GOLD 1group (p = 0.022) (Figure 2).

Univariate analysis revealed that the gender, smoking history, histological type, pT status, pN status, serum CEA level and GOLD classification (GOLD 2 - 3 vs. others) were significant predictors of disease-specific survival (Table 2). These variables identified by univariate analysis were included in Cox proportional hazards model to verify independent prognostic factors. Multivariate analysis demonstrated that histology, pN status and serum CEA level were independent prognostic factors for disease-specific survival (Table 3). However, we failed to find the prognostic significance of GOLD classification.

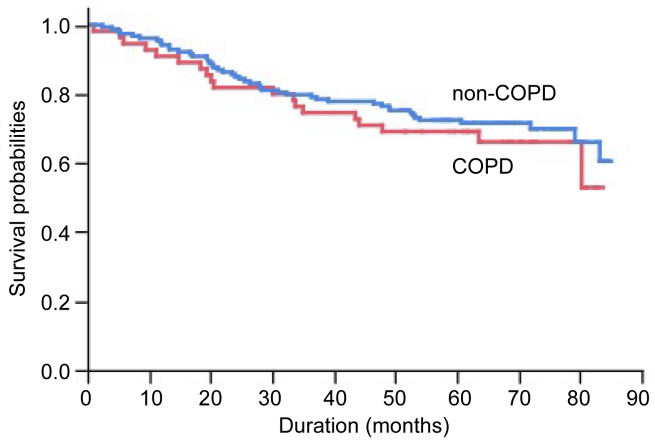

Figure 1. Survival of patients based on COPD.

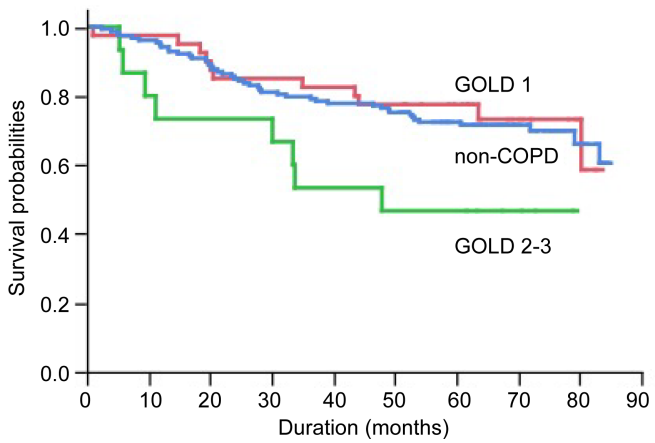

Figure 2. Survival of patients based on GOLD classification.

Table 2. Univariate analysis.

	Favorable	Unfavorable	Hazard ratio	95% CI	*p* Value
Age	<65	≥65	0.711	0.385 - 1.236	0.234
Gender	Female	Male	0.394	0.230 - 0.655	<0.001
Smoking	Never	Current/Former	0.409	0.237 - 0.684	0.001
Histology	Adenocarcinoma	Others	0.223	0.136 - 0.367	<0.001
pT status	pT1	pT2 - 3	0.385	0.236 - 0.633	<0.001
pN status	pN0	pN1 - 2	0.284	0.168 - 0.503	<0.001
Serum CEA	Normal	High	0.310	0.188 - 0.518	<0.001
COPD	non-COPD	COPD	0.825	0.491 - 1.443	0.488
GOLD	non-COPD + GOLD 1	GOLD 2 - 3	0.425	0.215 - 0.967	0.042

CI: Confidence interval.

Table 3. Multivariate analysis.

	Favorable	Unfavorable	Hazard ratio	95% CI	*p* Value
Gender	Female	Male	0.611	0.258 - 1.371	0.240
Smoking	Never	Current/Former	1.037	0.452 - 2.358	0.932
Histology	Adenocarcinoma	Others	0.274	0.152 - 0.488	<0.001
pT status	pT1	pT2 - 3	0.844	0.477 - 1.528	0.570
pN status	pN0	pN1 - 2	0.305	0.158 - 0.598	0.001
serum CEA	Normal	High	0.414	0.244 - 0.709	0.002
GOLD	non-COPD + GOLD 1	GOLD 2 - 3	0.737	0.360 - 1.713	0.452

CI: Confidence interval.

4. Discussion

In our study patients, the ratio of COPD patients was only 26.2%. Gao *et al.* [14] conducted a meta-analysis using 21 studies. Among these 21 studies published between 2001 and 2015, the sample size ranged from 114 to 18,077 and the ratio of COPD patients ranged from 6.97% to 82.46%. There is a high heterogeneity across the studies.

In the present study, we failed to find the relationship between the presence of COPD and patients' prognosis after NSCLC surgery. Similar results have been previously reported [10]-[13], while others showed that NSCLC patients with COPD had increased risk of worse disease-specific survival [6]-[9]. Furthermore, a recent meta-analysis showed the presence of COPD is a predictor of poor survival in patients with lung cancer [14]. Therefore, it remains unclear whether the presence of COPD is associated with poorer prognosis. There are several limitations in the present study. The number of overall patients and COPD patients were small. Moreover, majority of our patients with COPD was GOLD 1. In other words, the pulmonary function of majority of COPD patients in our series was not significantly different from that of non-COPD patients.

Taken together, we cannot reject the possibility of the prognostic significance of the presence of COPD. Some possible reasons for the prognostic significance of the presence of COPD are as follows: First, tobacco smoking is the best established risk factor for lung cancer and the most common risk factor for COPD [15] [16]. Our result also showed the correlation between smoking status and the presence of COPD. Therefore, it is easy to consider that majority of NSCLC in COPD patients was smoking related cancer. To date, it has been reported that NSCLC in smokers and never-smokers were quite different [17] [18]. There is a possibility that NSCLC in smokers might have more aggressive tumor growth, invasion or metastasis than those in non-smokers. Thus one of the reasons for poorer prognosis in COPD patients might be due to malignant potential of smokers NSCLC but not the effect of COPD itself. Second, previous studies [14] and our result showed that the ratio of squamous cell carcinoma in COPD patient was larger than those in overall patents. This result also showed that NSCLC in COPD patients is a smoking related cancer. Recently, the incidence of lung adenocarcinoma has increased gradually in most countries [19]. Adenocarcinoma is the predominant type of lung cancer among lifelong non-smokers and among females [19]. Our result of multivariate analysis showed that the histological subtype was an independent prognostic factor. Therefore, the difference in histologic subtype between COPD and non-COPD patients might be also one of reason for a prognostic significance of COPD at least in part.

Although the number of patients with GOLD 2 - 3 in our series was very small, we showed a trend towards an association between unfavorable survival and severity of COPD. However, we failed to find the prognostic significance of severity of COPD in multivariate analysis. We believe that there is a possibility of a relationship between patients' survival and severity of COPD when examined using large study population. It is easy to understand that the severity of COPD might be related to the smoking index. Therefore, it can be considered that NSCLC in patients with GOLD 2 - 3 has more characters of smoking-related cancer. Thus there is a possibility that NSCLC in GOLD 2 - 3 patients has more aggressive tumor. Further studies with large study population are needed.

5. Conclusion

In conclusion, there is a possibility that the severity of COPD might be useful to predict the prognosis of NSCLC patients. Further studies with large study population are needed.

Conflict of Interest

The authors have declared that no conflict of interest exists.

References

[1] Izquierdo, J.L., Resano, P., El Hachem, A., Graziani, D., Almonacid, C. and Sanchez, I.M. (2014) Impact of COPD in Patients with Lung Cancer and Advanced Disease Treated with

Chemotherapy and/or Tyrosine Kinase Inhibitors. *International Journal of Chronic Obstructive Pulmonary Disease*, **9**, 1053-1058. http://dx.doi.org/10.2147/COPD.S68766

[2] de Torres, J.P., Marin, J.M., Casanova, C., Cote, C., Carrizo, S., Cordoba-Lanus, E., Baz-Davila, R., Zulueta, J.J., Aguirre-Jaime, A., Saetta, M., Cosio, M.G. and Celli, B.R. (2011) Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease—Incidence and Predicting Factors. *American Journal of Respiratory and Critical Care Medicine*, **184**, 913-919. http://dx.doi.org/10.1164/rccm.201103-0430OC

[3] Wright, C.D., Gaissert, H.A., Grab, J.D., O'Brien, S.M., Peterson, E.D. and Allen, M.S. (2008) Predictors of Prolonged Length of Stay after Lobectomy for Lung Cancer: A Society of Thoracic Surgeons General Thoracic Surgery Database Risk-Adjustment Model. *The Annals of Thoracic Surgery*, **85**, 1857-1865. http://dx.doi.org/10.1016/j.athoracsur.2008.03.024

[4] Kozower, B.D., Sheng, S., O'Brien, S.M., Liptay, M.J., Lau, C.L., Jones, D.R., Shahian, D.M. and Wright, C.D. (2010) STS Database Risk Models: Predictors of Mortality and Major Morbidity for Lung Cancer Resection. *The Annals of Thoracic Surgery*, **90**, 875-881. http://dx.doi.org/10.1016/j.athoracsur.2010.03.115

[5] Bernard, A., Rivera, C., Pages, P.B., Falcoz, P.E., Vicaut, E. and Dahan, M. (2011) Risk Model of In-Hospital Mortality after Pulmonary Resection for Cancer: A National Database of the French Society of Thoracic and Cardiovascular Surgery (Epithor). *The Journal of Thoracic and Cardiovascular Surgery*, **141**, 449-458. http://dx.doi.org/10.1016/j.jtcvs.2010.06.044

[6] Zhai, R., Yu, X., Shafer, A., Wain, J.C. and Christiani, D.C. (2014) The Impact of Coexisting COPD on Survival of Patients with Early-Stage Non-Small Cell Lung Cancer Undergoing Surgical Resection. *Chest*, **145**, 346-353. http://dx.doi.org/10.1378/chest.13-1176

[7] Tammemagi, C.M., Neslund-Dudas, C., Simoff, M. and Kvale, P. (2003) Impact of Comorbidity on Lung Cancer Survival. *International Journal of Cancer*, **103**, 792-802. http://dx.doi.org/10.1002/ijc.10882

[8] Lopez-Encuentra, A., Astudillo, J., Cerezal, J., Gonzalez-Aragoneses, F., Novoa, N. and Sanchez-Palencia, A. (2005) Prognostic Value of Chronic Obstructive Pulmonary Disease in 2994 Cases of Lung Cancer. *European Journal of Cardiothoracic Surgery*, **27**, 8-13. http://dx.doi.org/10.1016/j.ejcts.2004.09.010

[9] Sekine, Y., Behnia, M. and Fujisawa, T. (2002) Impact of COPD on Pulmonary Complications and on Long-Term Survival of Patients Undergoing Surgery for NSCLC. *Lung Cancer*, **37**, 95-101. http://dx.doi.org/10.1016/S0169-5002(02)00014-4

[10] Ueda, K., Jinbo, M., Li, T.S., Yagi, T., Suga, K. and Hamano, K. (2006) Computed Tomography-Diagnosed Emphysema, Not Airway Obstruction, Is Associated with the Prognostic Outcome of Early-Stage Lung Cancer. *Clinical Cancer Research*, **12**, 6730-6736. http://dx.doi.org/10.1158/1078-0432.CCR-06-1196

[11] Lopez-Encuentra, A., Gomez de la Camara, A., Rami-Porta, R., Duque-Medina, J.L., de Nicolas, J.L. and Sayas, J. (2007) Previoustumour as a Prognostic Factor in Stage I Non-Small Cell Lung Cancer. *Thorax*, **62**, 386-390. http://dx.doi.org/10.1136/thx.2005.051615

[12] Lee, S.J., Lee, J., Park, Y.S., Lee, C.H., Lee, S.M., Yim, J.J., Yoo, C.G., Han, S.K. and Kim, Y.W. (2014) Impact of Chronic Obstructive Pulmonary Disease on the Mortality of Patients with Non-Small-Cell Lung Cancer. *Journal of Thoracic Oncology*, **9**, 812-817. http://dx.doi.org/10.1097/JTO.0000000000000158

[13] Gullon, J.A., Suarez, I., Medina, A., Rubinos, G., Fernandez, R. and Gonzalez, I. (2011) Role of Emphysema and Airway Obstruction in Prognosis of Lung Cancer. *Lung Cancer*, **71**, 182-185. http://dx.doi.org/10.1016/j.lungcan.2010.05.018

[14] Gao, Y.H., Guan, W.J., Liu, Q., Wang, H.Q., Zhu, Y.N., Chen, R.C. and Zhang, G.J. (2016) Impact of COPD and Emphysema on Survival of Patients with Lung Cancer: A Meta-Analysis of Observational Studies. *Respirology*, **21**, 269-279. http://dx.doi.org/10.1111/resp.12661

[15] Celli, B.R. and MacNee, W. (2004) Standards for the Diagnosis and Treatment of Patients with COPD: A Summary of the ATS/ERS Position Paper. *The European Respiratory Journal*, **23**, 932-946. http://dx.doi.org/10.1183/09031936.04.00014304

[16] Pauwels, R.A., Buist, A.S., Calverley, P.M., Jenkins, C.R. and Hurd, S.S. (2001) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *American Journal of Respiratory and Critical Care Medicine*, **163**, 1256-1276. http://dx.doi.org/10.1164/ajrccm.163.5.2101039

[17] Couraud, S., Zalcman, G., Milleron, B., Morin, F. and Souquet, P.J. (2012) Lung Cancer in Never Smokers—A Review. *European Journal of Cancer*, **48**, 1299-1311. http://dx.doi.org/10.1016/j.ejca.2012.03.007

[18] Govindan, R., Ding, L., Griffith, M., Subramanian, J., Dees, N.D., Kanchi, K.L., Maher, C.A., Fulton, R., Fulton, L., Wallis, J., Chen, K., Walker, J., McDonald, S., Bose, R., Ornitz, D., Xiong, D., You, M., Dooling, D.J., Watson, M., Mardis, E.R. and Wilson, R.K. (2012) Genomic Landscape of Non-Small Cell Lung Cancer in Smokers and Never-Smokers. *Cell*, **150**, 1121-1134. http://dx.doi.org/10.1016/j.cell.2012.08.024

[19] Nakamura, H. and Saji, H. (2014) Worldwide Trend of Increasing Primary Adenocarcinoma of the Lung. *Surgery Today*, **44**, 1004-1012. http://dx.doi.org/10.1007/s00595-013-0636-z