


ORIGINAL ARTICLE

Survival significance of coexisting chronic obstructive pulmonary disease in patients with early lung cancer after curative surgery

Hisashi Saji^{1,2} , Tomoyuki Miyazawa¹, Hiroki Sakai¹, Yusuke Kimura¹, Masataka Tsuda¹, Yoichi Wakiyama¹, Hideki Marushima¹, Koji Kojima¹ & Haruhiko Nakamura¹

¹ Department of Chest Surgery, St. Marianna University School of Medicine, Kawasaki, Japan

² Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan

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Correspondence

Hisashi Saji, Department of Chest Surgery, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan and Department of Thoracic Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Tel: +81 44 977 8111

Fax: +81 44 976 5792

Email: saji-q@ya2.so-net.ne.jp

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Abstract

Background: The impact of chronic obstructive pulmonary disease (COPD) severity on survival after curative resection of early-stage lung cancer (NSCLC) has not been sufficiently elucidated.

Methods: We retrospectively reviewed 250 consecutive patients who underwent lobectomy with lymph nodal dissection for pathological stage I–II NSCLC.

Results: Among the COPD patients, 28 were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1, 21 as GOLD 2, and one as GOLD 3. The cumulative overall survival (OS) of the non-COPD, GOLD 1, and GOLD 2–3 groups at five years was 90.7%, 85.7%, and 55.3%, respectively, ($P < 0.0001$), while recurrence-free survival (RFS) between the groups at five years was 84.7%, 80.7%, and 72.9%, respectively. Although RFS in the GOLD 2–3 group tended to indicate a poor prognosis, there was no statistical difference between the groups ($P = 0.385$). In multivariate analysis, age ≥ 75 years, pN1, and GOLD 2–3 COPD were independent factors for a poor prognosis ($P = 0.034$, $P = 0.010$, and $P = 0.030$, respectively).

Conclusions: Our results indicate that early stage NSCLC patients with COPD had a significantly increased risk of poorer OS and potentially an increased risk of poor RFS.

Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer related death in men worldwide.¹ Cigarette smoking is the primary risk factor for developing lung cancer and the most common risk factor for developing chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death globally, occurring in 30% of patients with lung cancer.^{2,3} COPD and emphysema are comorbid conditions often found in lung cancer patients. COPD is also a significant risk factor for lung cancer.^{4,5} Epidemiological surveys reveal that patients with COPD have an approximately fivefold higher risk of developing lung cancer than that of smokers without COPD, regardless of age and smoking status.^{6–8}

Although the association of COPD with lung cancer risk is well established, the impact of COPD on survival in early lung cancer patients is relatively less well known. Recently,

a number of studies have found that early stage non-small cell lung cancer (NSCLC) patients with COPD who underwent surgical resection had increased risks of poor overall survival (OS) and recurrence-free survival (RFS).^{9,10} However, the effect of COPD severity on survival after resection of early lung cancer has not been sufficiently elucidated. The aim of this study was to investigate the impact of COPD severity on survival outcomes of patients who underwent lobectomy with lymph nodal dissection for early stage NSCLC.

Methods

Patient selection

We retrospectively reviewed 294 consecutive patients with pathological stage I–II NSCLC who underwent lobectomy with systematic lymph node dissection at our hospital from

January 2010 to December 2014. We excluded 13 patients who had received preoperative chemotherapy, radiotherapy, or both; 15 patients who had undergone non-curative resection and had macroscopic or microscopic evidence of residual cancer; and 16 patients without a smoking history or spirometry data. Consequently, we enrolled the remaining 250 patients in this study.

Definitions

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 such as asthma;² however most medical records documented that spirometry had been performed without an inhaled bronchodilator in a practice setting. Patients with a smoking history and a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity of less than 70% were classified as COPD patients.¹¹ GOLD spirometry grades were used to classify the severity of airflow limitation: GOLD 1 (mild), FEV1 \geq 80% predicted; GOLD 2 (moderate), $50\% \leq$ FEV1 < 80% predicted; GOLD 3 (severe), $30\% \leq$ FEV1 < 50% predicted; and GOLD 4 (very severe), FEV1 < 30% predicted.² Patients who had never smoked and smokers without COPD were designated as the non-COPD group.

Data collection

Preoperative evaluation included physical and blood examinations, chest radiography, and computed tomography (CT) of the chest and abdomen. Brain CT or magnetic resonance imaging and positron emission tomography (PET)-CT scans were performed if clinically indicated. Staging and pathological findings for lung cancer were determined according to the 7th Tumor Node Metastasis (TNM) Classification for Lung and Pleural Tumors¹² and the World Health Organization classification.²

All patients were followed-up at our hospital every six months for five years, and annually thereafter on an outpatient basis; our aim was to continue follow-up for five years or more. General follow-up procedures included physical examination, chest radiography, and blood examination (including serum tumor markers). CT scans of the chest and upper abdomen were routinely performed in every scheduled outpatient department for follow-up. Whenever any symptoms or signs of recurrence were detected, brain magnetic resonance imaging and/or PET-CT were performed. If metastasis was discovered after physical examination and diagnostic imaging, histologic or cytologic confirmation of the metastatic site was performed when clinically feasible. Metachronous second primary lung cancer was discriminated from a solitary pulmonary

metastasis using the proposed criteria of the American College of Chest Physicians Lung Cancer Guidelines.¹³

The hospital charts of all patients were reviewed to collect clinicopathological data, including age, gender, smoking history, histologic type, tumor size, OS, and RFS. OS was determined as the duration from the date of surgery until the date of death from any cause, with surviving patients at the end of follow-up treated as censored cases. RFS was defined as the duration between the date of surgery and the date of lung cancer recurrence or death from any cause. Patients living without evidence of recurrence at the end of the follow-up period were regarded as censored cases. The institutional review board of our hospital approved the protocols for data collection and analyses. The requirement for informed consent from the patients was waived because of the retrospective study design.

Statistical analysis

Summary statistics were constructed using frequencies and proportions for categorical data, and means for continuous data. Patient characteristics were compared by chi-square test or Fisher's exact test for categorical outcomes for continuous variables, as appropriate. OS and RFS were estimated using the Kaplan–Meier method, and survival differences between patient groups were determined using log-rank analysis. *P* values and hazard ratios in the multivariate analyses were calculated using the Cox regression model. *P* values of <0.05 were considered to indicate a statistically significant difference. All statistical calculations were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The characteristics of the patients enrolled in this study are listed in Table 1. Among the 139 smokers, 50 were diagnosed with COPD. Among the COPD patients, 28 were classified as GOLD 1, 21 as GOLD 2, and one as GOLD 3. Male patients, squamous cell carcinoma, and positive smoking history were more frequent in the COPD group than in the non-COPD group. The frequencies of all other pulmonary complications tended to be higher in the COPD groups, but no statistical difference was observed. No patients died postoperatively during the hospital stay.

Survival

The median follow-up for all 250 patients was 44 months (range 6.0–84.0). Sixteen patients (8.0%) in the non-COPD

Table 1 Patient characteristics ($n = 250$)

Variable	Non-COPD ($n = 200$)	GOLD 1 COPD ($n = 28$)	GOLD 2–3 COPD ($n = 22$)	<i>P</i>
Gender				
Male	84	22	20	< 0.0001
Female	116	6	2	
Age (years)				
Mean	66.6	72.75	66.6	0.922
Smoking status				
Current	28	7	11	
Former	61	21	11	
Never	111	0	0	
Pack-years				
Mean	42.0	46.3	44.9	0.413
Morbidity	8.0% ($n = 16$)	17.9% ($n = 5$)	13.6% ($n = 3$)	0.202
Mortality	0%	0%	0%	
pT factor				
T1	143	19	11	0.10
T2	51	9	6	
T3	6	0	5	
pN factor				
N0	194	26	21	0.528
N1	6	2	1	
p-Stage				
I	185	26	16	0.009
II	15	2	6	
Histology				
Adenocarcinoma	164	23	12	0.001
Squamous cell carcinoma	30	2	5	
Others	6	3	5	
Recurrence pattern				
Loco-regional	6	2	6	0.309
Distant	18	3	18	
Both	6	0	6	

COPD, chronic obstructive lung disease; GOLD, The Global Initiative for Chronic Obstructive Lung Disease.

group, four patients (14.3%) in the GOLD 1 group, and eight patients (36.4%) in the GOLD 2–3 group died during the study period. Thirty patients (15.0%) in the non-COPD, five patients (17.9%) in the GOLD 1 group, and nine patients (41.0%) in the GOLD 2–3 group experienced primary lung cancer recurrence. Table 1 shows the recurrence patterns in each group, but no significant difference between the groups was observed ($P = 0.309$). The cumulative OS rates of the non-COPD, GOLD 1, and GOLD 2–3 groups at five years were 90.7%, 85.7%, and 55.3%, respectively, ($P < 0.0001$) (Fig 1), while RFS rates in these groups at five years were 84.7%, 80.7%, and 72.9%, respectively (Fig 2). Although RFS in the GOLD 2–3 group tended to indicate poor prognosis, there was no statistical difference between the groups ($P = 0.385$).

Prognostic factors

In univariate analysis, male gender, age ≥ 75 years, pT2–3, pN1, non-adenocarcinoma, and GOLD 2–3 COPD were

associated with poor OS ($P = 0.008$, $P = 0.032$, $P = 0.023$, $P = 0.001$, $P < 0.0001$, and $P < 0.0001$, respectively). In multivariate analysis, age ≥ 75 years, pN1, and GOLD 2–3 COPD were independent prognostic factors for poor survival ($P = 0.034$, $P = 0.010$, and $P = 0.030$, respectively) (Table 2).

Discussion

Although the biological mechanisms through which COPD may influence NSCLC prognosis are obscure, our results are biologically consistent with current theories and previous study results. The inflammatory pathways associated with COPD, emphysema, and lung cancer likely involve genetic and epigenetic modulations resulting in chronic tissue injury and remodeling, and abnormal tumor immunity in susceptible hosts.¹⁴ Increasing oxidative stress in COPD may stimulate DNA damage, which causes carcinogenesis.¹⁵ Indeed, somatic mutations in oncogenes, such as p53, *Ras*, *EGFR*, and *PTEN* abound in the bronchial epithelium

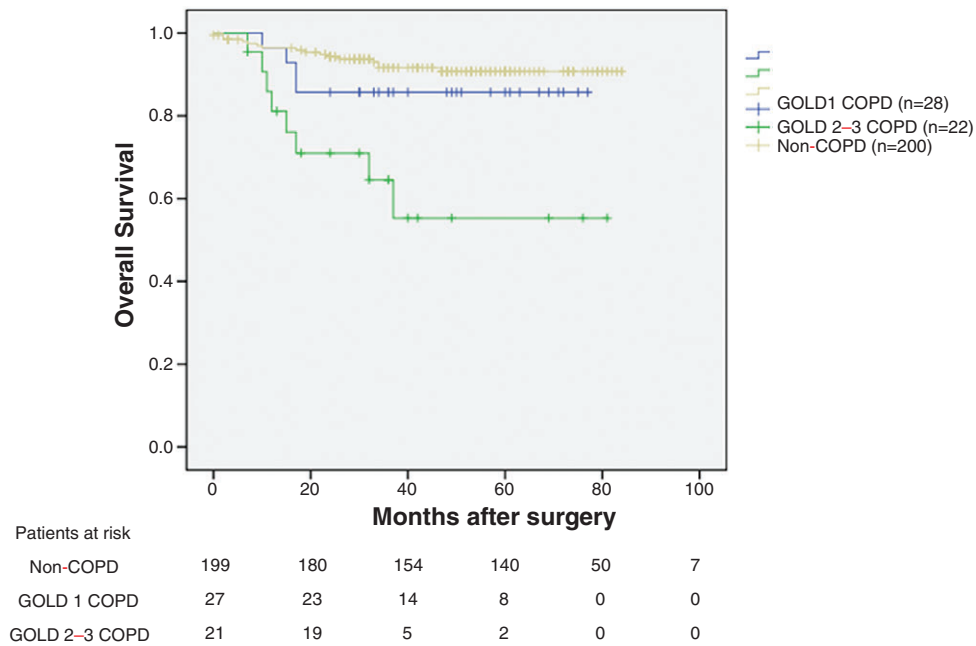


Figure 1 Kaplan–Meier plots of overall survival. COPD, chronic obstructive lung disease; GOLD, The Global Initiative for Chronic Obstructive Lung Disease.

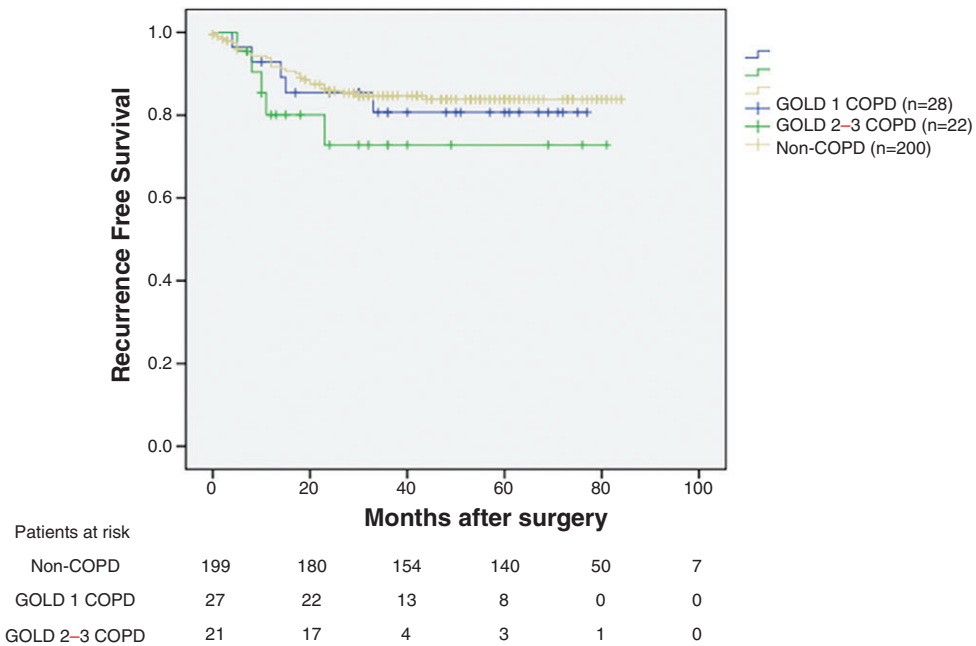


Figure 2 Kaplan–Meier plots of recurrence-free survival. COPD, chronic obstructive lung disease; GOLD, The Global Initiative for Chronic Obstructive Lung Disease.

of smokers. COPD is also associated with abnormal apoptosis and cell cycle regulation, which is a critical mechanism implicated in NSCLC prognosis.¹⁶ Consequently, COPD also plays an important role in the carcinogenesis

and progression of lung cancer. Additionally, COPD itself has been associated with clinical comorbidities, which may adversely affect the survival outcomes in patients with coexisting NSCLC.¹⁷

Table 2 Univariate and multivariate analyses for OS (*n* = 250)

Variable	UVA	MVA		
	<i>P</i>	HR	95% CI	<i>P</i>
Female (vs. male)	0.008*	0.404	0.149–1.093	0.074
Age < 75 years (vs. ≥75 years)	0.032*	0.417	0.186–0.936	0.034*
pT1 (vs. pT2–3)	0.023*	0.280	0.301–1.416	0.280
pN0 (vs. pN1)	0.001*	0.220	0.070–0.692	0.010*
Adenocarcinoma (vs. non-Adenocarcinoma)	< 0.0001*	0.460	0.197–1.071	0.072
GOLD 2–3 COPD (vs. non-COPD, GOLD 1 COPD)	< 0.0001*	2.779	1.104–6.997	0.030*

**P* < 0.05. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; MVA, multivariate analysis; OS, overall survival; UVA, univariate analysis.

Current studies report that COPD is a negative predictive factor for survival after complete resection of stage IA lung cancer because of high recurrence.^{18,19} The present study shows that GOLD 2–3 COPD is an independent poor prognostic factor for OS in stage I–II lung cancer patients. Unfortunately our result was not statistically significant for RFS. However, the poorer long-term survival in patients with GOLD 2–3 COPD because of a higher incidence of tumor recurrence demonstrated in our series was consistent with previous reports.^{9,18,19} Because of the small sample in this study, our results may not clearly demonstrate the survival impact on RFS. However, the RFS curve seemed to indicate that moderate to severe COPD correlates with poor survival, even in early stage lung cancer patients, while mild COPD does not create a similar risk.

Increased COPD severity was more frequent in men, older patients, smokers, and non-adenocarcinoma patients. These factors might be explained by the following: smoking-induced inflammatory response contributes to the development of COPD and squamous cell carcinoma, and age reflects cumulative exposures throughout life. These factors also seemed to introduce bias in our results.

Patients undergoing pulmonary resection for lung cancer with COPD are thought to be at increased risk of short-term complications and surgery-related death. The correlation of COPD severity with the incidence of cardiopulmonary complications after surgery has been demonstrated in previous studies.^{18,19} Therefore, several investigators have recommended therapeutic options to reduce the risk for COPD patients undergoing lung cancer surgery such as perioperative administration of a long-acting bronchodilator and prevention of postoperative cardiopulmonary complications.^{20,21} Although postoperative morbidity of patients with COPD was higher than those without COPD in this study, there was no difference in hospital mortality between the groups. Additionally, recent studies have shown that postoperative complications (especially pulmonary complications) were a significant predictor of cancer recurrence.²² COPD patients had an increased risk of postoperative respiratory complications in our series, but the result was not statistically

significant. There was no correlation between cancer recurrence and postoperative complications in our series, likely a result of our small sample.

This retrospective study has some limitations. The main limitation of this study, and of other studies of this type, is that we are unable to distinguish whether COPD is in the causal pathway for NSCLC prognosis or whether both COPD and NSCLC are related to an underlying exposure or molecular mechanism. Second, although GOLD recommends only post-bronchodilator spirometry, we made a diagnosis of COPD based only on smoking status and air-flow limitations without administration of an inhaled bronchodilator, taking clinical signs and symptoms into account. However, we believe this definition is acceptable in a retrospective study because smoking is the primary risk factor for COPD, accounting for approximately 85–90% of COPD deaths.^{19,23} Lastly, the current study is a retrospective, single-institute study with a small sample size. Further prospective, multi-institutional investigations and substantial clinical studies are warranted for the detailed evaluation of survival correlations between COPD and early stage operable lung cancer.

We retrospectively reviewed 250 consecutive patients who underwent lobectomy with lymph nodal dissection for early stage NSCLC to investigate the impact of COPD severity on survival outcomes. Our results suggest that patients with COPD had increased risks of poor OS and some effect was made on RFS in patients with early stage NSCLC undergoing surgical resection.

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Disclosure

No authors report any conflict of interest.

References

- 1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. (Published erratum appears in *CA Cancer J Clin* 2011; 61: 134.). *CA Cancer J Clin* 2011; **61**: 69–90.
- 2 Lozano R, Naghavi M, Foreman K *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **15**: 2095–128.
- 3 Lim SS, Vos T, Flaxman AD *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **15**: 2224–60.
- 4 de Torres JP, Marin JM, Casanova C *et al.* Lung cancer in patients with chronic obstructive pulmonary disease--incidence and predicting factors. *Am J Respir Crit Care Med* 2011; **184**: 913–9.
- 5 Raviv S, Hawkins KA, DeCamp MM Jr, Kalhan R. Lung cancer in chronic obstructive pulmonary disease: Enhancing surgical options and outcomes. *Am J Respir Crit Care Med* 2011; **183**: 1138–46.
- 6 Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. *Am J Epidemiol* 1999; **149**: 13–20.
- 7 Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* 2007; **176**: 285–90.
- 8 Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J* 2009; **34**: 380–6.
- 9 Sekine Y, Suzuki H, Yamada Y, Koh E, Yoshino I. Severity of chronic obstructive pulmonary disease and its relationship to lung cancer prognosis after surgical resection. *Thorac Cardiovasc Surg* 2013; **61**: 124–30.
- 10 Zhai R, Yu X, Shafer A, Wain JC, Christiani DC. The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection. *Chest* 2014; **145**: 346–53.
- 11 Kondo R, Yoshida K, Eguchi T *et al.* Clinical features of lung cancer in smokers with light and mild chronic obstructive pulmonary disease: A retrospective analysis of Japanese surgical cases. *Eur J Cardiothorac Surg* 2011; **40**: 1439–43.
- 12 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 7th edn. Wiley-Blackwell, Hoboken NJ 2009.
- 13 Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143** (5 Suppl): e369S–99S.
- 14 Lee G, Walser TC, Dubinett SM. Chronic inflammation, chronic obstructive pulmonary disease, and lung cancer. *Curr Opin Pulm Med* 2009; **15**: 303–7.
- 15 Anderson GP, Bozinovski S. Acquired somatic mutations in the molecular pathogenesis of COPD. *Trends Pharmacol Sci* 2003; **24**: 71–6.
- 16 Singhal S, Vachani A, Antin-Ozerkis D, Kaiser LR, Albelda SM. Prognostic implications of cell cycle, apoptosis, and angiogenesis biomarkers in non-small cell lung cancer: A review. *Clin Cancer Res* 2005; **11**: 3974–86.
- 17 Corsonello A, Pedone C, Incalzi RA. Comorbidities and risk assessment in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; **186**: 804.
- 18 Sekine Y, Yamada Y, Chiyo M *et al.* Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. *Ann Thorac Surg* 2007; **84**: 946–50.
- 19 Yoshida Y, Kage H, Murakawa T *et al.* Worse prognosis for stage IA lung cancer patients with smoking history and more severe chronic obstructive pulmonary disease. *Ann Thorac Cardiovasc Surg* 2015; **21**: 194–200.
- 20 Suzuki H, Sekine Y, Yoshida S *et al.* Efficacy of perioperative administration of long-acting bronchodilator on postoperative pulmonary function and quality of life in lung cancer patients with chronic obstructive pulmonary disease. Preliminary results of a randomized control study. *Surg Today* 2010; **40**: 923–30.
- 21 Nojiri T, Inoue M, Yamamoto K *et al.* Inhaled tiotropium to prevent postoperative cardiopulmonary complications in patients with newly diagnosed chronic obstructive pulmonary disease requiring lung cancer surgery. *Surg Today* 2014; **44**: 285–90.
- 22 Nojiri T, Hamasaki T, Inoue M *et al.* Long-term impact of postoperative complications on cancer recurrence following lung cancer surgery. *Ann Surg Oncol* 2017; **24**: 1135–42.
- 23 Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002; **156**: 738–46.