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ORIGINAL ARTICLE

Impact of coexistent chronic obstructive pulmonary disease on the survival of patients with small cell lung cancer receiving chemotherapy

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Chronic obstructive pulmonary disease; mortality; small cell lung cancer; spirometry.

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Abstract

Background: While there is growing interest in the correlation between chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer, very few studies have examined the interaction between COPD and small cell lung cancer (SCLC). Therefore, the aim of this study was to examine the impact of COPD on the survival of patients with SCLC.

Methods: The medical records of 110 patients with SCLC who received chemotherapy from July 2006 until April 2014 were retrospectively examined. The overall survival (OS) and progression-free survival (PFS) rates of spirometry-diagnosed COPD and non-COPD groups were compared. Predictors for poorer survival were analyzed using Cox proportional hazards regression.

Results: Of the 110 SCLC patients, 57 (51.8%) had coexistent COPD. The median OS for the COPD group was 11.6 months and for the non-COPD group was 11.2 months (log-rank test, $P = 0.581$), whereas the median PFS rates were 6.65 and 6.57 months, respectively (log-rank test, $P = 0.559$). Multivariate analysis identified Eastern Cooperative Oncology Group performance status ≥ 2 and extensive-stage SCLC as independent risk factors for shorter OS; however, coexisting COPD was not a predictor of survival.

Conclusions: Although over half of the SCLC patients receiving chemotherapy had COPD, coexisting COPD had no impact on the survival of patients with SCLC.

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are forecast to be the fourth and sixth leading causes of death by 2030, respectively. The mortality associated with these two diseases is already greater than that reported in 2002.[1]

Chronic obstructive pulmonary disease and lung cancer have a common causative factor: smoking.[2] Smoking is the most common cause of COPD worldwide, and smokers with COPD show a high number of respiratory symptoms and a rapid decline in lung function.[3] Smoking is also the main cause of lung cancer, with high mortality rates in smokers with lung cancer.[4] These two diseases are strongly linked to each other. COPD is a significant risk factor for lung cancer and a comorbidity in approximately 50% of lung cancer patients.[5,6] In addition, COPD influences the choice of treatment for patients with lung cancer[7,8] for example, patients with advanced COPD are administered radiotherapy rather than chemotherapy or surgery.[9] However, it is unclear whether COPD affects the survival of patients with lung cancer.

Previous studies have assessed the association between non-small cell lung cancer (NSCLC) and COPD.[10,11] Coexisting COPD is a poor prognostic factor for NSCLC, especially in men with squamous cell carcinoma[11] even in never-smokers.[10] By contrast, other studies have reported that coexisting COPD does not affect the survival of NSCLC patients.[9,12,13] However, there are limited data regarding the interaction between small cell lung cancer (SCLC) and COPD, mainly because the prevalence of SCLC is lower than that of other histological lung cancers, such as squamous cell carcinoma and adenocarcinoma.[14] To the best of our knowledge, this is the first study to examine the impact of COPD on the survival of patients with SCLC by comparing the mortality and clinical characteristics of SCLC patients with/without COPD.

Methods

Study population and procedures

A total of 248 patients were newly diagnosed histologically with SCLC from July 2006 to October 2013 at Gyeongsang National University Hospital, Jinju, Korea. One hundred and sixteen patients were excluded because they did not receive first-line chemotherapy, as listed in Figure 1. A further 22 patients were excluded because a pulmonary function test was not performed prior to systemic chemotherapy. The medical records of the remaining 110 patients were retrospectively reviewed.

Pulmonary function tests were conducted in accordance with criteria published by the American Thoracic Society and the European Respiratory Society.[15] Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were calculated from the flow-volume curve, which was generated using a spirometer (Jaeger, Würzburg, Germany). The highest value from at least three measurements was used. COPD was defined as a post-bronchodilator FEV_1/FVC ratio < 0.70. The Institutional Review Board of Gyeongsang National University Hospital approved the study. The retrospective nature of the study meant that the requirement for informed consent was waived.

Demographic and clinical characteristics were obtained from medical records. Age, gender, body mass index (BMI), smoking status, smoking pack-years, pulmonary function, Eastern Cooperative Oncology Group (ECOG) performance status (PS), stage of SCLC, presenting symptoms, comorbidities, progression-free survival (PFS), and overall survival (OS) were obtained. BMI was calculated as weight divided by height^2 (kg/m^2). Never smoking was classified as a lifetime history of < 100 cigarettes. Ex-smokers were defined as patients who stopped smoking one month prior to a diagnosis of SCLC. The ECOG PS was divided into two classes according to patients' general well being and activities of daily living: < 2 or ≥ 2.[16] The

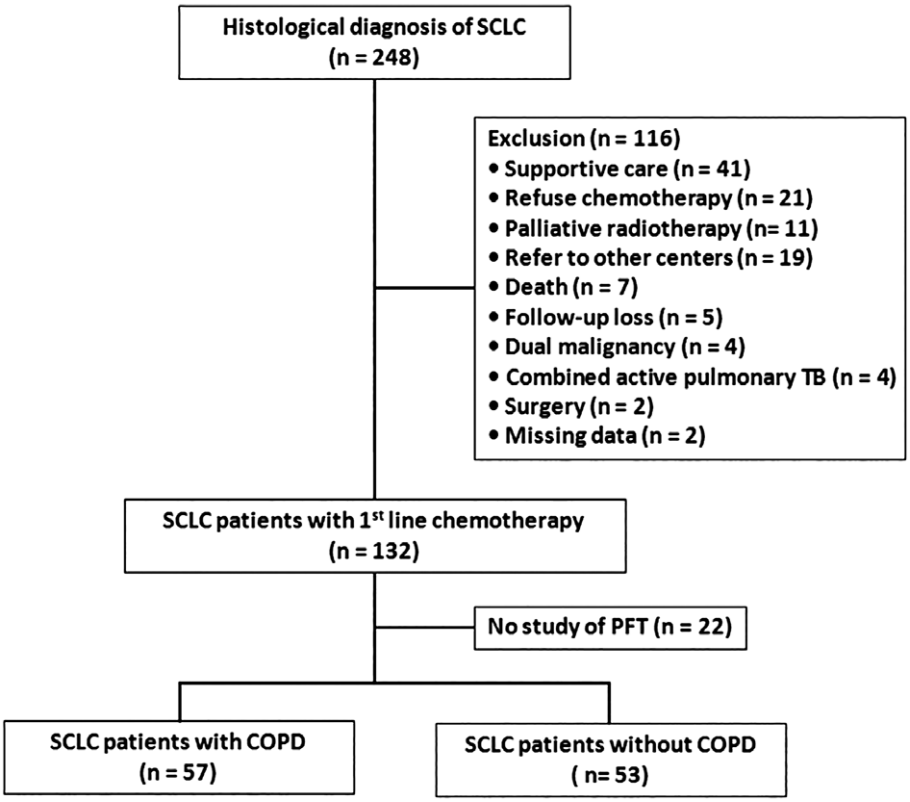

Figure 1 Study scheme. COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; SCLC, small cell lung cancer; TB, tuberculosis.

stage of SCLC was dichotomized into "limited" or "extensive" according to standard staging protocols.[17]

Overall survival was defined as the duration from diagnosis to death, or until 1 January 2016 for patients who were still alive. PFS was defined as the duration from the first chemotherapy session until clinical or radiographic progression or death from any cause. Response Evaluation Criteria in Solid Tumors version 1.1 was used to evaluate the response of measurable lesions. Death or progression of lung cancer after chemotherapy was verified from medical records documenting regular follow-up.

The clinical characteristics and the OS and PFS rates of SCLC patients with/without COPD were compared. Significant prognostic factors in patients with SCLC were then analyzed.

Statistical analysis

Data are presented as the mean ± standard deviation or as number (%). The unpaired *t*-test and Pearson's χ^2 test were used to compare continuous and categorical variables, respectively. Kaplan–Meier survival curves were used to evaluate OS and PFS between COPD and non-COPD groups, and differences were assessed using the log-rank test. Cox proportional hazards regression analysis was performed to identify prognostic factors for survival. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Only variables showing statistical significance in univariate analysis were included in the multivariate model. *P* values < 0.05 were considered significant for all tests.

Results

Clinical characteristics

A total of 110 patients were enrolled and categorized into COPD (n = 57) or non-COPD (n = 53) groups according to the results of pulmonary function testing. The basic demographic and clinical characteristics of the patients are shown in Table 1. The age, gender, BMI, smoking status, ECOG PS, stage of SCLC, and presence of pulmonary fibrosis on chest computed tomography were comparable between the groups. Most patients with SCLC were male and had a smoking history. The mean FEV_1 and predicted value of FEV_1 were 1.8 L and 68.4% in the COPD group and 2.3 L and 87.0% in the non-COPD group, respectively.

There were no differences in the regimen of first-line chemotherapy and concurrent chemoradiotherapy, the response to first-line treatment, or the method of second-line treatment between the groups (Table 2). OS and PFS tended to be longer in the non-COPD than in the COPD group, but the difference was not statistically significant.

Table 1 Demographic and clinical characteristics

Characteristics	SCLC with COPD (n = 57)	SCLC without COPD (n = 53)	*P*
Age, years	67.5 ± 7.4	65.2 ± 7.8	0.106
Gender, male (%)	52 (91.2)	44 (83.0)	0.197
BMI, kg/m^2	22.2 ± 3.3	23.1 ± 2.6	0.107
Smoking status			0.215
Current smoker	31 (54.4)	37 (69.8)	
Ex-smoker	22 (38.6)	12 (22.6)	
Never	4 (7.0)	4 (7.6)	
Pack-years	49.5 ± 24.2	43.8 ± 22.2	0.216
FEV_1/FVC, %	60.0 ± 9.0	76.6 ± 4.5	< 0.001*
FEV_1, L	1.8 ± 0.6	2.3 ± 0.7	< 0.001*
FEV_1, predicted, %	68.4 ± 20.8	87.0 ± 19.4	< 0.001*
FVC, L	2.8 ± 0.7	2.8 ± 0.8	0.741
FVC, predicted, %	85.7 ± 19.8	88.4 ± 20.6	0.493
GOLD stage, n (%)			
1	19 (33.3)	NA	
2	21 (36.8)	NA	
3	16 (28.1)	NA	
4	1 (1.8)	NA	
ECOG PS			0.352
0–1	42 (73.7)	43 (81.1)	
≥ 2	15 (26.3)	10 (18.9)	
Stage			
LD	24 (42.1)	28 (52.8)	0.260
ED	33 (57.9)	25 (47.2)	
Presence of pulmonary fibrosis	6 (10.5)	7 (13.2)	0.663

*P < 0.05 was considered significant. Data are expressed as the mean ± standard deviation or as N (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, extensive disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LD, limited disease; NA, not applicable; SCLC, small cell lung cancer.

Presenting symptoms were comparable between the groups, but excess sputum tended to be more prevalent in the COPD than in the non-COPD group. Coughing and dyspnea were the most common symptoms in both groups (Table 3). Patients in the COPD group had a higher rate of comorbidities (66.7% vs. 56.6%), but the difference was not statistically significant (P = 0.278). Hypertension was the most common comorbidity in both groups, but there was no significant difference in the pattern of other comorbidities (Table 3).

Comparison of survival between groups and identification of prognostic factors

Of the 110 patients enrolled, 20 survived and 90 died. The median survival time in the COPD group was 11.6 months and in the non-COPD group was 11.2 months (log-rank test, P = 0.581) (Fig 2). Kaplan–Meier survival estimates at

Table 2 First-line chemotherapy and clinical outcomes of SCLC patients with/without COPD

Treatment/Outcome	SCLC with COPD (n = 57)	SCLC without COPD (n = 53)	P
First-line chemotherapy regimen			0.495
Etoposide + platinum	48 (84.2)	47 (88.7)	
Irinotecan + platinum	9 (15.8)	6 (11.3)	
CCRT			0.364
Yes	22 (38.6)	25 (47.2)	
No	35 (61.4)	28 (52.8)	
Response to first-line treatment†			0.554
CR or PR	53 (96.4)	46 (93.9)	
SD or PD	2 (3.6)	3 (6.1)	
OS, months	14.7 ± 12.8	17.7 ±16.6	0.289
PFS, months	8.8 ± 8.5	11.9 ±14.5	0.221
Second-line treatment			0.709
Etoposide + platinum	8 (14.0)	6 (11.3)	
Irinotecan + platinum	20 (35.1)	13 (24.5)	
Topotecan	3 (5.3)	4 (7.5)	
CAV	2 (3.5)	3 (5.7)	
Best supportive care	24 (42.1)	27 (50.9)	

*P < 0.05 was considered significant. †Six patients who experienced treatment-related mortality before the first evaluation of treatment response were excluded from the analysis of response to first-line treatment. Data are expressed as the mean ± standard deviation or as N (%). CAV, cyclophosphamide plus doxorubicin plus vincristine; COPD, chronic obstructive pulmonary disease; CCRT, concurrent chemo-radiotherapy; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; PD, progressive disease; SD, stable disease; SCLC, small cell lung cancer.

12, 24, and 48 months were 53.6% versus 48.6%, 19.3% versus 30.4%, and 5.0% versus 11.0% for the COPD and non-COPD groups, respectively. The median PFS in the COPD group was 6.65 months and in the non-COPD group was 6.57 months (log-rank test, P = 0.559).

Univariate Cox proportional hazards regression analysis identified ECOG PS ≥ 2, extensive stage, and hypertension as predictors of short OS. To exclude the possible confounder, we performed correlation analyses between ECOG PS and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of COPD (r = 0.254, P = 0.057) before multivariate logistic regression analyses. Multivariate analysis identified ECOG PS ≥ 2 (HR 1.810; P = 0.024) and extensive stage (HR 1.882; P = 0.005) as independent predictors of short OS (Table 4). However, univariate and multivariate analyses did not identify COPD as a predictor of OS or PFS in SCLC patients.

Discussion

Chronic obstructive pulmonary disease was diagnosed by pulmonary function test in 51.8% of 110 patients undergoing systemic chemotherapy for SCLC. The demographic and clinical characteristics of the COPD group were comparable to those of the non-COPD group. Coexisting COPD had no significant effect on the OS and PFS of patients with SCLC. Multivariate analysis identified ECOG PS ≥ 2 and extensive-stage SCLC as independent risk factors for shorter survival.

Table 3 Presenting symptoms and comorbidities of the study patients

Symptoms/Comorbidities	SCLC with COPD (n = 57)	SCLC without COPD (n = 53)	P
Symptoms, n (%)	54 (94.7)	45 (84.9)	0.086
Cough	36 (63.2)	28 (52.8)	0.273
Sputum	24 (42.1)	14 (26.4)	0.084
Dyspnea	32 (56.1)	34 (64.2)	0.391
Hemoptysis	9 (15.8)	10 (18.9)	0.670
Weight loss	11 (19.3)	11 (20.4)	0.849
Thoracic pain	11 (19.3)	12 (22.6)	0.667
Hoarseness	7 (12.3)	4 (7.4)	0.408
Neurologic symptoms	2 (3.4)	2 (3.7)	0.941
Comorbidity, n (%)	38 (66.7)	30 (56.6)	0.278
HTN	23 (40.4)	14 (26.9)	0.139
DM	8 (14.0)	11 (21.2)	0.328
AF	3 (5.3)	1 (1.9)	0.620
Angina/MI	4 (7.0)	5 (9.6)	0.734
CVA	7 (12.3)	4 (7.7)	0.427
Pulmonary TBc	7 (12.3)	3 (5.8)	0.239
Previous malignancy	2 (3.5)	2 (3.8)	1.000
SIAD	3 (5.3)	1 (1.9)	0.620

Values are expressed as N (%). AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; SCLC, small cell lung cancer; SIAD, syndrome of inappropriate antidiuresis; TBc, tuberculosis.

Although fewer studies have examined SCLC compared to other histological lung cancers, recent reports have shown that multiple comorbidities are associated with a poor prognosis for patients with limited-stage SCLC regardless of the treatment modality,[18] and that sarcopenia is a predictor of a poor outcome.[19] However, there is no data of an association between COPD and SCLC. COPD is a common comorbidity in patients with lung cancer,[6] and many studies have examined the relationship between COPD and NSCLC.[9–13,20–23] Low FEV_1 precludes patients from undergoing curative resection or radiotherapy,[9] and patients with end-stage COPD are considered as subjects limited to palliative care.[22] Patients with both early-stage NSCLC and COPD who undergo surgical resection have a poor outcome,[11,20,21,23] particularly those at higher GOLD stages of COPD.[23] Furthermore, Turner *et al.* report that emphysema is associated with increased lung cancer mortality, even in never-smokers.[10] However, some studies have shown that coexisting COPD is not associated with prognosis in patients with NSCLC.[12] Coexisting COPD had

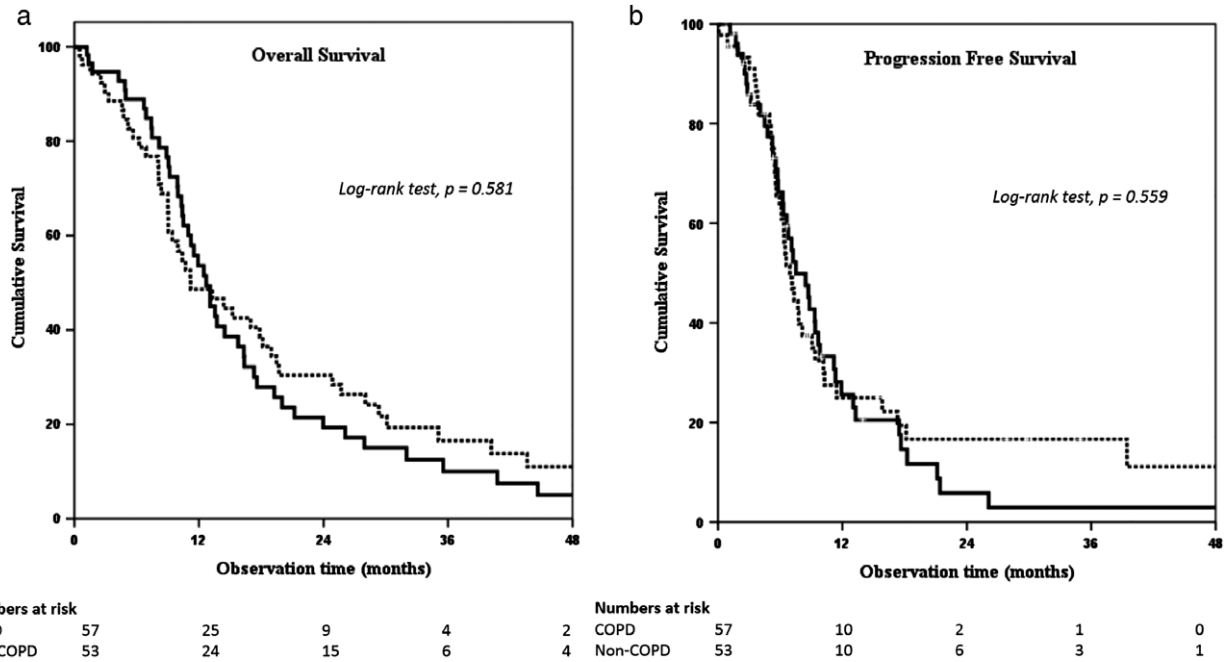

Figure 2 Kaplan–Meier curve showing (**a**) overall survival and (**b**) progression-free survival in patients with small cell lung cancer with/without chronic obstructive pulmonary disease (COPD). ····· Non-COPD, ····· COPD.

no discernable impact on the survival of patients with advanced inoperable lung cancer.[12] Lee *et al.* also reported that coexisting COPD does not show a negative correlation with prognosis in patients with NSCLC, including surgical cases, even though patients with COPD have unfavorable clinical factors.[13] The prognostic impact of COPD on patients with lung cancer may be relative. Overall, the prognosis of patients with operable early-stage lung cancer is affected by the presence of COPD, but had little influence in those with advanced lung cancer. We found that coexisting COPD did not increase mortality rates in SCLC patients. It was difficult to verify the effect of coexisting COPD in each of these groups separately because the number of patients with limited or extensive-stage SCLC was small. In subgroup analyses, the severity of COPD did not have any impact on the survival of SCLC patients.

Several prognostic factors for SCLC patients have been reported: staging, treatment, ECOG PS, and comorbidities.[18,19,24,25] The classic method of SCLC staging is based on limited or extensive-stage disease.[17] Patients with limited-stage SCLC have longer survival than those with extensive-stage SCLC. The five-year survival rate for patients with limited-stage SCLC who undergo standard chemotherapy with etoposide and cisplatin and concurrent radiotherapy is 25–34%,[24,26] whereas the five-year survival rate for patients with extended-stage SCLC treated with standard chemotherapy is 10–13%.[25,26] The median OS for the former was 19.9 months and for the latter 12.7 months in our study. The patients examined herein, particularly those with extensive-stage SCLC, survived for longer than the 8.5–9.1 months reported by other studies.[25,26] These differences in survival duration in patients with early-stage SCLC result from several factors: our study was based on a real-world setting, not a randomized study, to evaluate the efficacy of the chemotherapy agent; and we included the latest data available on SCLC patients.

ECOG or Karnofsky scores are used to assess functional status in cancer patients. These scores are associated with clinical outcomes for lung cancer,[27] because the patient's condition has immediate and direct effects on decision-making of the appropriate treatment strategy. Although a poor functional condition is a relative contraindication to receive chemotherapy, some patients are administered systemic chemotherapy as they are expected to be in a better condition after treatment.[28] Fifteen of the 57 COPD patients (26.3%) that received systemic chemotherapy in our study had an ECOG PS ≥ 2. Nevertheless, the ratio of patients who had poor functional status (ECOG PS ≥ 2) was comparable in the COPD versus the non-COPD group (26.3% vs. 18.9%, respectively; $P = 0.352$). There was no correlation between ECOG PS and GOLD stages of COPD ($r = 0.254$, $P = 0.057$). Multivariate analysis identified ECOG PS ≥ 2 as an independent predictor for shorter OS (HR 1.810; $P = 0.024$). This is consistent with results reported in other studies of patients with NSCLC.[12,13] Patients with COPD are ineligible for systemic chemotherapy, even in cases of colon cancer, because of their poor health and late stage of disease.[29]

Table 4 Hazard ratios for overall survival of patients with SCLC according to univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Characteristics	HR	95% CI	*P*	HR	95% CI	*P*
COPD						
No	1			1		
Yes	1.124	0.742–0.704	0.581	0.877	0.561–1.371	0.566
Age, years						
≥ 65	1					
< 65	0.919	0.600–1.409	0.700			
Gender						
Female	1					
Male	0.893	0.485–1.646	0.717			
BMI, kg/m^2						
< 25	1					
≥ 25	1.299	0.753–2.240	0.347			
Smoking						
Never	1					
Ex-smoker	1.036	0.469–2.288	0.930			
Current smoker	0.558	0.263–1.182	0.128			
Pack-years	0.996	0.987–1.005	0.356			
ECOG PS						
0–1	1			1		
≥ 2	2.107	1.288–3.446	0.003*	1.810	1.080–3.032	0.024*
Stage						
LD	1			1		
ED	1.931	1.258–2.965	0.003*	1.882	1.213–2.920	0.005*
Pulmonary fibrosis						
Absent	1					
Present	1.442	0.721–2.883	0.301			
Symptom						
None	1					
Any	1.206	0.583–2.495	0.614			
Weight loss	1.446	0.884–2.365	0.142			
Hoarseness	1.201	0.578–2.496	0.623			
Dyspnea						
mMRC 0–1	1					
mMRC ≥ 2	1.667	0.902–3.082	0.103			
Comorbidity						
None	1			1		
Any	1.381	0.902–2.114	0.138			
HTN	1.639	1.046–2.569	0.031*	1.543	0.952–2.500	0.078
DM	1.194	0.671–2.126	0.546			
Other cancer	1.179	0.371–3.746	0.780			

Values are expressed as N (%). BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, extensive disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HR, hazard ratio; HTN, hypertension; LD, limited disease; mMRC, modified Medical Research Council; SCLC, small cell lung cancer.

This study has several limitations. First, it was a retrospective observational study that examined a small number of patients; in particular, only four female patients were included. The incidence of lung cancer in women is escalating as the number of female smokers increases.[30] Thus, female patients are under-represented in the present study. Because this was a retrospective study, an effective sample size could not be calculated. Assuming the HR for death in the non-COPD group compared to the COPD group was 0.8, 859 patients with SCLC were required to achieve 80% power for detecting a 15% difference in OS between the groups using a two-sided log-rank test with a type 1 error rate of 5%.

Second, a considerable number of patients (n = 22) were excluded because they had not undergone a pulmonary function test, which might cause selection bias. Third, we only included patients who were healthy enough to undergo systemic chemotherapy. COPD patients with

severe airflow obstruction or frequent exacerbations leading to difficulties in carrying out activities of daily living cannot undergo radical therapy. Finally, we could not identify the cause of death, as this was not documented in the medical records. Therefore, the results of this study are preliminary and we cannot confirm that there are no associations between SCLC and COPD.

In conclusion, COPD was present in approximately half of the patients who underwent systemic chemotherapy to treat SCLC in this study. However, the coexistence of COPD had no impact on clinical characteristics (including presenting symptoms), ECOG PS, response to first-line treatment, OS, or PFS. ECOG PS ≥ 2 and extensive-stage SCLC were independent prognostic factors for poor survival. Further studies with larger cohorts are required to more accurately determine an association between COPD and SCLC.

Disclosure

No authors report any conflict of interest.

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