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Original Article

Prognosis of advanced stage non-small cell lung cancer: Is it different in patients with chronic obstructive pulmonary disease?

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Abstract: Objective: To investigate the clinical features and the prognosis of patients with advanced staged non-small cell lung cancer (NSCLC) complicated by chronic obstructive pulmonary disease (COPD). Material and methods: We retrospectively analyzed the data of patients with newly diagnosed NSCLC complicated by COPD at the pulmonary clinic of an university hospital between March, 2009 and May, 2013. The clinical data included history of smoking, pulmonary function test results, initial treatments, tumor node and metastasis (TNM) stage, comorbidities and laboratory tests. The Cox proportional hazards regression model was used to explore the prognostic factors in these patients. Results: A total of 137 NSCLC patients were investigated, of which 61 (44.5%) patients had the co-morbidity of COPD as confirmed by spirometry using bronchodilator test and 76 (55.5%) patients grouped as non-COPD. Twenty (14.6%) patients had stage IIIA, 27 (19.7%) had stage IIIB, 90 (65.7%) had stage IV. The COPD group had fewer never-smokers than the non-COPD group (p=0.028). There was no significant difference in overall survival between COPD and non-COPD groups (9.8 and 10.9 months, log-rank test p=0.445). In the multivariate Cox's proportional hazard model, the hazard ratio (HR) was statistically significant for TNM stage (HR=1.7, 95% CI: 1.2-2.7; p=0.002), but not for the presence of COPD (HR=0.89, 95% CI: 0.86-1.1; p=0.543). Conclusion: In patients with advanced stage NSCLC, COPD did not have a significant deleterious impact on prognosis of patients.

Keywords: Non-small cell lung cancer, advanced stage lung cancer, COPD, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are two leading causes of death worldwide. Cigarette smoking is a well-established cause of both COPD and lung cancer. COPD is a strong risk factor for the development of lung cancer, and the prevalence of COPD is estimated at 40% to 70% of patients with lung cancer [1-7]. Chronic airway inflammation plays a major role in the pathogenesis of both COPD and lung cancer. The development of both COPD and lung cancer have been proposed as a result of the DNA damage due to chronic inflammation in the airways [8].

Smoking and other noxious particles, such as biomass exposure, which cause inflammation of the lungs, are important causes of COPD, and smoking is the most common risk factor of COPD worldwide. The clinical characteristics and survival has been thought to be different in patients with non-small cell lung cancer (NSCLC) and COPD. The results of previously published studies are controversial and most of the studies have been performed on early stage NSCLC patients. In a study by Sekine et al. [6], overall survival and disease-free survival have been found shorter in patients with COPD, while survival was found longer in Arca's study [9]. Other researchers have found no prognostic effect of COPD on the patients with NSCLC in their studies [10, 11].

The aim of the current study to evaluate the clinical characteristics of locally advanced NSCLC patients with and without COPD and the effects of COPD on survival of NSCLC patients.

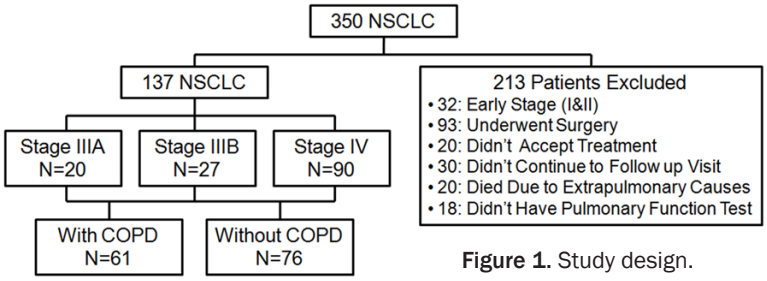

Figure 1. Study design.

Materials and methods

Study population

A total of 137 smokers, including current and former smokers, or having biomass exposure who were newly diagnosed with NSCLC histologically and/or cytologically from March 2009 to May 2013 at Gazi University Hospital, Department of Pulmonary Medicine were recruited in this study. Only adult patients aged above 18 and diagnosed as NSCLC and staged as Stage IIIA, Stage IIIB or Stage IV according to Tumor, node and metastasis (TNM) staging system were included. TNM stages of the patients were performed radiologically with 18FDG-PET/BT, cranial magnetic resonance imaging, and clinically according to the 7th American Joint Committee on Cancer classification [9]. Tumor histology was classified as squamous cell carcinoma (SCC), adenocarcinoma, adenosquamous mixed type, bronchoalveolar dominant pattern, large cell carcinoma, and undetermined NSCLC [10]. The exclusion criteria were (1) surgery for NSCLC, (2) refusal of taking any treatment for NSCLC, (3) nonattendance to the follow-up visits (4) death unrelated to respiratory system before the cancer treatment within 14 days of diagnosis (5) the presence of a severe structural lung disease that affected lung function, such as bronchiectasis or tuberculosis-destroyed lung (6) patients without smoking history or biomass exposure.

Of these 137 patients, 61 patients were diagnosed with COPD, and 76 patients did not have COPD (non-COPD; **Figure 1**). The COPD diagnosis was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline and defined as the post-bronchodilator 1st second forced expiratory volume (FEV1)/forced vital capacity (FVC) rate less than 0.7 [12].

Data collection

The data collected for all patients included age, sex, smoking habit, pack-years index, performans scores on the Eastern Cooperative Oncology Group (ECOG) scale, TNM staging, tumor histology, treatment modality [chemotherapy (CT), consecutive CT-radiotherapy (RT) or concomitant CT-RT)], and survival.

We exempted our study from the ethics committee and informed consent requirement because we accessed an anonymized database retrospectively for this analysis.

Statistical analysis

All values are presented as mean ± standard deviation or median (range). Chi-squared statistics or Fisher's exact test was used to compare proportions. Survival curves were compared with the log-rank test, and Kaplan-Meier survival curves were plotted. Cox's proportional hazards models were used to adjust for age, sex, tumor stage, ECOG performance score, histopathological diagnosis, and the presence of COPD. All data were analyzed using a statistical software package (SPSS, version 21.0; SPSS, Inc., Chicago, IL, USA).

Results

Among all included patients with NSCLC, males accounted for 86.1%. Current smokers accounted for 50.4% of the total patients. On the other hand, 11.7% of the patients were never smokers but had the biomass exposure. SCC, adenocarcinoma, and undifferentiated NSCLC accounted for 50.4%, 31.4% and 15.3% of the total patients, respectively. Patients stage IIIA, stage IIIB and stag accounted for 14.6%, 19.7% and 65.7% respectively (**Table 1**).

In patients with COPD, the mean age was 64±10 years (range: 34-87), and 91.8% (56/61) were male. Among patients without COPD, the mean age was 62±10 years (range: 29-87), and 81.6% (62/76) were male. There was no statistical difference in age (p=0.355).

Regarding the smoking status of NSCLC patients with and without COPD, the amount of cigarettes smoked per year was higher

Table 1. Baseline characteristics of study patients

Characteristics	N=137 (%)
Age (mean ± SD)	63±10
Gender	
Male	118 (86.1)
Female	19 (13.9)
Cigarette Amount (package/year) (mean ± SD)	47.6±36.0
Status of Cigarette	
Never smoked	16 (11.7)
Active smoker	69 (50.4)
Ex-smoker	52 (38.0)
ECOG	
0	70 (51.1)
1	42 (30.7)
2	15 (10.9)
3	10 (7.3)
Histopathological Diagnosis	
Squamous Cell Carcinoma	69 (50.4)
Adenocarcinoma	43 (31.4)
Adenosquamous Mix Type	2 (1.5)
Bronchoalveolar Dominant Pattern	1 (0.7)
Large Cell Carcinoma	1 (0.7)
Unclassified NSCLC	21 (15.3)
T Stage	
T1a	2 (1.5)
T1b	8 (5.8)
T2a	17 (12.4)
T2b	15 (10.9)
T3	29 (21.2)
T4	66 (48.2)
N Stage	
N0	18 (13.1)
N1	6 (4.4)
N2	63 (46.0)
N3	50 (36.5)
M Stage	
M0	47 (34.3)
M1a	12 (8.8)
M1b	78 (56.9)
TNM Stage	
Stage IIIA	20 (14.6)
Stage IIIB	27 (19.7)
Stage IV	90 (65.7)
COPD Status	
With	61 (44.5)
Without	76 (55.5)

ECOG: Eastern Cooperative Oncology Group performance status; NSCLC: Non-small Cell Lung Cancer; T: Tumor; N: Node; M: Metastasis; TNM: Tumor, node, metastasis; COPD: Chronic obstructive pulmonary disease.

in the COPD group (57±38 vs 40±32 packs/year, p=0.028) and the proportion of never-smoker was lower in patients with COPD than those without COPD (p=0.004).

Among lung cancer patients with COPD, SCC, adenocarcinoma, and other subtypes accounted for 55.7%, 29.5% and 14.7% of cases, respectively. The corresponding proportions among NSCLC patients without COPD were 46.1%, 32.9% and 21%, respectively. NSCLC patients with COPD had a higher rate of SCC whereas patients without COPD had a higher rate of adenocarcinoma. But these differences in the rates were not significant (p=0.511) (**Table 2**).

There were no significant differences in age, sex, ECOG performance scores, histopathological subtype, T, N and M stages and overall TNM stage between the COPD group and non-COPD group (p > 0.05). Treatment modalities did not differ between the groups (**Table 2**).

In the patient group with COPD, mean FEV1 (%), FVC (%), and FEV1/FVC (%) were 63±21, 77±22 and 63±8.0, respectively. Emphysema was detected by thoracic tomography in 23 (37.7%) patients, while it was absent in 38 (62.3%) patients. Ten (16.4%) patients did not receive any treatment for COPD at the time of the diagnosis, while 51 (83.6%) were under treatment for COPD (**Table 3**).

Prognosis analysis of patients

During follow-up period, 121 patients (88.3%) died and 16 (11.7%) were alive. Six patients (9.8%) had COPD, while 10 (13.2%) had no COPD among livings. The mean survival of COPD group was 9.8±8.4 months (median: 8.0, range: 1-38 months), while it was 10.9±8.6 (median: 9.3, range: 1-39 months) in non-COPD group. No survival difference was determined between the groups (p=0.445). The Kaplan-Meier curves for COPD and non-COPD groups are shown in **Figure 2**.

In the multivariate Cox's proportional hazard model for the most relevant variables, the hazard ratio (HR) was not statistically

Table 2. General characteristics of groups with and without chronic obstructive pulmonary disease

Characteristics	COPD Group (n=61, %)	Non-COPD Group (n=76, %)	p
Age (mean ± SD) (Range)	64±10 (34-87)	62±10 (29-87)	0.355
Gender			0.069
Male	56 (91.8)	62 (81.6)	
Female	5 (8.2)	14 (18.4)	
Cigarette Amount (package/year) (mean ± SD)	57±38	40±32	0.028
Status of Cigarette			0.004
Never smoked	1 (1.6)	15 (19.7)	
Active smoker	35 (57.4)	34 (44.7)	
Ex-smoker	25 (41.0)	27 (35.5)	
ECOG Performans Status			0.076
0	28 (45.9)	42 (55.3)	
1	22 (36.1	20 (26.3)	
2	8 (13.1)	7 (9.2)	
3	3 (4.9)	7 (9.2)	
Histopathological Diagnosis			0.511
Squamous cell carcinoma	34 (55.7)	35 (46.1)	
Adenocarcinoma	18 (29.5)	29 (32.9)	
Adenosquamous mix type	1 (1.6)	1 (1.3)	
Bronchoalveolar dominant pattern	-	1 (1.3)	
Large cell carcinoma	-	1 (1.3)	
Undifferentiated NSCLC	8 (13.1)	13 (17.1)	
N Stage			0.431
N0	7 (11.5)	11 (14.5)	
N1	1 (1.6)	5 (6.6)	
N2	30 (49.2)	33 (43.4)	
N3	23 (37.7)	27 (35.5)	
T Stage			0.183
T1a	1 (1.6)	1 (1.3)	
T1b	4 (6.6)	4 (5.3)	
T2a	6 (9.8)	11 (14.5)	
T2b	5 (8.2)	10 (13.2)	
T3	11 (18.0)	18 (23.7)	
T4	34 (55.7)	32 (42.1)	
M Stage			0.803
M0	21 (34.4)	27 (35.5)	
M1a	7 (11.5)	4 (5.3)	
M1b	33 (54.1)	45 (59.2)	
TNM Stage			0.877
Stage IIIA	10 (16.4)	10 (13.2)	
Stage IIIB	11 (18.0)	16 (21.1)	
Stage IV	40 (65.6)	50 (65.8)	
Treatment Modalities			
Concomitant CT-RT	13 (21.3)	19 (25.0)	0.125
Consecutive CT-RT	7 (11.5)	4 (5.4)	0.171
Only CT	41 (67.2)	53 (69.8)	0.313

ECOG: Eastern Cooperative Oncology Group; NSCLC: Non-small Cell Lung Cancer; T: Tumor; N: Node; M: Metastasis; TNM: Tumor, node, metastasis; CT: Chemotherapy; RT: Radiotherapy; CT-RT: Chemo-raditherapy.

Table 3. Pulmonary function test values and treatment modalities of patients with and without chronic obstructive pulmonary disease

Characteristics	COPD Group N=61/137 (44.5%)	Non-COPD Group N=76/137 (55.5%)	*p* value
PFT Values (mean ± SD)			<0.001
FEV1 (%)	63±21	100±16.8	
FEV1 (cc)	1724±640	2210±0.8	
FVC (%)	77±22	104±15.0	
FVC (cc)	3416±597	3600±840	
FEV1/FVC (%)	63±8	78±6.3	
Emphysema (%)			-
With	23 (37.7)	-	
Without	38 (62.3)	-	
Medical Treatments at the time of COPD (%)			-
LAMA + SABA	1 (1.6)	-	
LAMA + SAMA	1 (1.6)	-	
LABA + LAMA	5 (8.2)	-	
LABA + Inhaler steroids	8 (13.1)	-	
LABA + Inhaler steroids + LAMA	10 (16.4)	-	
LABA + Inhaler steroids + LAMA + SABA	12 (19.7)	-	
LABA + Inhaler steroids + LAMA + SABA + LTOT	2 (3.2)	-	
SAMA Nebulized	4 (6.6)	-	
SABA Nebulized	8 (13.1)	-	
No treatment	10 (16.4)	-	

PFT: Pulmonary Function Test; FEV1: Forced expiratory volume in 1st second; FVC: Forced vital capacity; LAMA: Long-acting anti-muscarinic agent; LABA: Long-acting beta agonist agent; SAMA: Short-acting anti-muscarinic agent; SABA: Short-acting beta agonist agent; LTOT: Long-term oxygen therapy.

significant for age (≥ 65 years) (HR: 0.84, 95% CI: 0.6-1.04; p=0.9), male sex (HR=1.07, 95% CI: 0.7-1.6-19; p=0.68), ECOG performans scores 2-3 (HR=0.69, 95% CI: 0.56-1.24; p=0.72), and presence of COPD (HR=0.89, 95% CI: 0.86-1.1; p=0.543), but significant for the TNM stage III-IV (HR=1.7, 95% CI: 1.2-2.7; p=0.002) (**Table 4**).

Discussion

In the present study, COPD was not significantly associated with survival of locally-advanced NSCLC patients. The presence of COPD might not be a concern for withholding treatment in advanced-stage NSCLC patients.

Several prognostic factors such as age, tumor stage, pathology, and ECOG performance score have been reported in NSCLC patients [12-14]. In our study, there were no significant differences in these factors between COPD and non-COPD groups. Moreover, we excluded NSCLC patients treated with trimodal therapy including surgery to minimize the impact of treatment intensity on prognosis in comparison of COPD and non-COPD patients. Consistent with our results, a previous study showed that the presence of COPD was not associated with poor prognosis of NSCLC patients who received chemotherapy or targeted therapy [14].

Lung cancer in COPD patients is a real problem since mortality studies of patients with COPD suggest that 20%-30% of patients die from lung cancer. Cross-sectional studies show that the prevalence of COPD is around 50% of those diagnosed with lung cancer, although the prevalence might change depending on the patient's age, sex, and smoking exposure [15, 16]. The frequency of COPD in patients with NSCLC has been evaluated in a few studies. In the studies by Mina et al. [17] and Arca et al. [7], the incidence of COPD confirmed with spirometry at the time of the diagnosis was reported 32.5% and 39.8% respectively; while it was higher as 50.2% in the study by Lee et al. [18]. Out of 44.6% NSCLC cases had coexisting

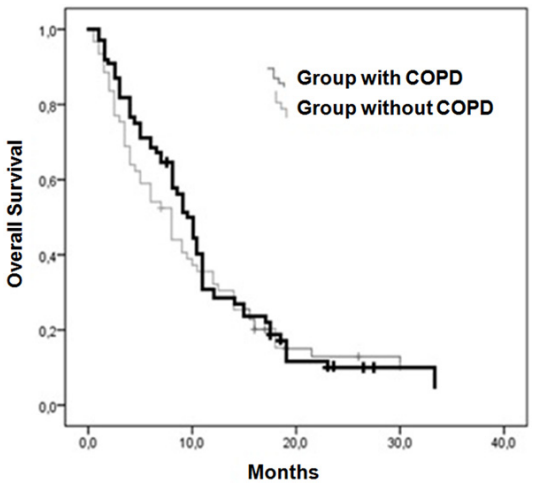

Figure 2. Kaplan-Meier survival curve for survival of patients (P=0.445).

COPD in our study. Similar to Lee et al's study, we excluded the patients who were never smokers. We also excluded the patients who had never exposed to biomass. Exclusion of these patients in our study may be the cause of the higher prevalence of COPD.

Squamous cell carcinoma (SCC) was the major histological tumor type with 50.4% frequency in our cohort. Also the proportion of SCC was higher in the NSLC patients with versus without COPD. This finding may be due to the associations of the SCC subtype of lung cancer and COPD with smoking. The smoking effect on squamous cell has been reported to be twofold: (1) an indirect effect mediated through COPD and (2) a direct effect mediated by pathways other than COPD [19]. Miao et al. [20] investigated the clinicopathological characteristics and risk factors in patients with lung cancer and COPD. Similar to our results adenocarcinoma and SCC were found more common histopatological types; these subtypes had been constituted 35.6% and 35.1% of cases, respectively. Also the proportion of adenocarcinoma was found significantly higher in lung cancer patients without COPD in their study.

It remains controversial whether the presence of COPD is associated with prognosis of advanced-stage (Stage III-IV) NSCLC patients who didn't undergo surgery. So far, most lung cancer studies regarding COPD have been focused on the early stages of the disease, trying to prevent complications and mortality related to surgery. But the results of previous studies in early stage NSCLC patients with COPD are quite diverse. Sekine et al. [6] reported two conflicting results regarding the impact of COPD on survival of patients with lung cancer. There was no significant difference in survival in a report from 2002; otherwise, the survival of the COPD group was significantly worse than that of the non-COPD group in a report from 2007 [21]. Nakajima et al. [22] reported worse survival of the COPD group, Mina et al. [17] reported similar survival between the two groups, and Arca et al. [7] reported better survival in the COPD group. Meanwhile, Ueda et al. [11] reported that the degree of airway obstruction was not associated with the prognostic outcome. There was no impact of COPD on the mortality of patients with NSCLC, and COPD was not a prognostic factor for worse survival in our study.

In contrast with our data, Arca et al. [23] found that survival of NSCLC patients with COPD was significantly higher. They retrospectively investigated 996 lung cancer patients. Mortality risk was higher at stages 3B and 4, and in the absence of surgery and chemotherapy. But, surprisingly survival was significantly higher in COPD patients. To explain this result, the authors suggest that COPD patients might be diagnosed in earlier stages. However, in an adjusted Cox regression model using significant variables in the bivariate analysis, only stage and treatment remained significant. On the other hand, COPD, was not independent risk factor for mortality similar to our results.

In Lee et al's study [24], 221 patients were evaluated for the effects of COPD on mortality in all stages of NSCLC, of those 67% were stage III-IV, while 33% were stage I-II. Out of 41.6% of cases underwent surgery, while 58.4% received chemo-radiotherapy without surgery. When all stages were considered, COPD was not found a negative prognostic factor for NSCLC. In our study, 10% of the patients were unaware of their COPD at the time of NSCLC diagnosis and they had not received any treatment for COPD. Similar to our result, in Lee et al's study 7.2% of patients with COPD had been unaware of their disease.

Wang et al. [25] recently analysed 200 elderly patietns (> 60 years) with newly diagnosed NSCLC complicated by COPD, of which 107 (53.5%) patients had the co-morbidity of COPD as confirmed by spirometry using bronchodila-

Table 4. Multivariate analysis exploring factors associated with non-small cell lung cancer prognosis

Parameter	Hazard Ratio	95% Confidence Interval	P
Age (year) (≤ 65 vs > 65 years old)	0.84	0.6-1.04	0.9
Sex (male vs female)	1.07	0.7-1.6	0.68
ECOG (0-1 vs 2-3)	0.69	0.56-1.24	0.72
TNM Stage (Stage IIIA vs Stage IIIB, IV)	1.7	1.2-2.7	0.002
Presence of COPD	0.89	0.86-1.1	0.543

ECOG: Eastern Cooperative Oncology Group performance status, TNM: Tumor, node, metastasis, COPD: Chronic obstructive pulmonary disease.

tor test. The prevalence of COPD was found higher (32.8%) in lung cancer patients compared to controls (16.0%) in their study. After adjustment for age, sex, body-mass index, and smoking status, the presence of COPD significantly increased the risk of lung cancer (OR: 2.88, 95% CI: 2.48-3.34) and all common histological subtypes (OR: 2.04-5.26). Older age, a higher GOLD stage, advanced disease stage (stages III and IV), SCC, nonsurgical initial treatment, coughing and an elevated serum CEA level were found independent risk factors for shorter survival of the patients and in elderly patients a higher COPD GOLD stage that fails to respond to treatment within 3 months was found the independent risk factor for survival of the patients in their study.

In our study, patient population was homogeneous. We excluded the patients with Stage IIIA and Stage IIIB who received cancer surgery for NSCLC. All patients received similar medical treatment for NSCLC. The diagnosis of COPD was confirmed with pulmonary function test objectively. Very few patients were not receiving treatment for COPD. The majority of the patients were on medical therapy appropriate for the stage of their COPD. The compliance of patients to the COPD treatment was complete and all patients were receiving the specified medical therapy regularly. All stages of patients were followed from the time of diagnosis; the treatment they received and follow-up visits until death were all recorded. No patient was lost to follow-up.

The limitations of this study include the following: (1) This was a retrospective observational study based on medical records. Thus, control of many kinds of bias was impossible, even with use of statistical methods. (2) The number of enrolled patients was relatively small because a considerable number (n=213) were excluded because of an unidentifiable smoking history or lung function. (3) We could not identify co-morbidities of patients but we excluded the death unrelated to lung cancer. Instead of co-morbidity scores we evaluated the ECOG performance score and the incidence of patients with ECOG performance status of 3 was only 7.3%.

In conclusion, our study found that the proportions of active smokers and the amount of smoking per year were significantly higher among NSCLC patients with COPD than without COPD. COPD was not found to be a negative prognostic factor for the patients with advanced stage NSCLC. When the patients were effectively treated for COPD, it does not seem to be a factor affecting the prognosis of NSCLC. Future large-scale, multicentre studies are warranted to confirm and expand on our findings.

Disclosure of conflict of interest

None.

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