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ORIGINAL ARTICLE

Clinicopathologic characteristics of non-small cell lung cancer in patients with smoking-related chronic obstructive pulmonary disease

Ryo Maeda[1] · Masaki Tomita[1] · Katsuo Usuda[2] · Hidetaka Uramoto[2]

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Abstract

Background The purpose of this study was to clarify the clinicopathologic characteristics of non-small cell lung cancer (NSCLC) patients with smoking-related chronic obstructive pulmonary disease (COPD) and to evaluate the biological behavior of this disease. We investigated the association between smoking-related COPD, the recurrence-free proportion (RFP) and the clinicopathological features of clinical stage I NSCLC patients.

Methods Between 2005 and 2014, 218 consecutive patients with clinical stage I NSCLC underwent complete resection with lobectomy or greater and systematic lymph node dissection. Differences in categorical outcomes were evaluated by the χ^2 test. RFPs were estimated using the Kaplan–Meier method, and differences were evaluated using the log-rank test.

Results The 5-year RFP of clinical stage I NSCLC patients with smoking-related COPD was 55%, which was significantly lower than in those without smoking-related COPD (85%; $p<0.001$). Postoperative pathological factors, including moderate or poor histological differentiation, intratumoral vascular invasion and lymph node metastasis, were detected more often in patients with smoking-related COPD. In adenocarcinoma patients, the 5-year RFP of patients with smoking-related COPD was 47%, which was significantly lower than in those without smoking-related COPD (87%; $p<0.001$). The presence of a solid component was more frequently found in patients with smoking-related COPD ($p=0.007$).

Conclusion Clinical stage I NSCLC patients with smoking-related COPD have histologically more invasive tumors than those without smoking-related COPD.

Keywords Chronic obstructive pulmonary disease · Non-small cell lung cancer · Thoracic surgery · Clinical stage I · Adenocarcinoma

Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are two major lung diseases. Lung cancer is the leading cause of cancer-related death [1], and COPD is the fourth-leading cause of death globally [2]. Epidemiological surveys have shown that the presence of COPD increases the risk of lung cancer by 4.5-fold [3], and the prevalence of COPD is estimated to be 40–70% among patients with lung cancer [4]. Cigarette smoking is a well-established cause of both COPD and lung cancer. Even though not all smokers develop COPD or lung cancer, cigarette smoking is a main contributor to the development of both diseases. Chronic airway inflammation by cigarette smoking is reported to be a key feature in the pathogenesis of both COPD and lung cancer, and patients who are unable to cope with chronic inflammation and subsequent DNA damage may develop COPD and/or lung cancer [5].

Thus far, the correlation of COPD severity with the incidence of complications after surgery of lung cancer has been well established [6]. However, the effect of smoking-related COPD on the survival after resection of lung cancer is not fully elucidated. The purpose of this study was to investigate the clinicopathologic characteristics of non-small cell lung cancer (NSCLC) patients with smoking-related COPD. To

✉ Ryo Maeda
ryo_maeda@med.miyazaki-u.ac.jp

[1] Department of Thoracic and Breast Surgery, Faculty of Medicine, University of Miyazaki, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan

[2] Department of Thoracic Surgery, Kanazawa Medical University, Kanazawa, Japan

offset the prognostic impact of smoking-related comorbidities on the surgical outcomes, we investigated the recurrence-free proportion (RFP) as emphasized by recurrence alone. The present study focused on evaluating the biological behavior of tumors in patients with smoking-related COPD.

Materials and methods

Patients

There were 218 consecutive patients with clinical stage I NSCLC who underwent complete resection with lobectomy or greater and systematic lymph node dissection from January 2005 through December 2014 at Kanazawa Medical University. Complete resection was defined as cancer-free surgical margins both macroscopically and microscopically. Smoking-related COPD was diagnosed according to the following criteria: (1) the presence of a history of cigarette smoking and (2) a predicted forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) value ≤ 70% in accordance with the current Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines [2]. Spirometric values were presented as the postbronchodilator results. The severity of airflow obstruction in COPD was determined using the GOLD grading system [2]: grade 1 (%FEV1 > 80%), grade 2 (%FEV1 50–80%), grade 3 (%FEV1 30–50%) and grade 4 (%FEV1 < 30%). Data collection and analyses were approved and the need to obtain written informed consent from each patient was waived by the institutional review board (IRB) in September 2017 (IRB number I*205*).

Clinicopathological evaluations

Chest computed tomography (CT) was used to classify the stage of all patients. Regional lymph node metastasis was clinically defined when the shorter diameter of a given lesion was ≥ 1.0 cm. The histological type was determined according to the World Health Organization classification [7]. The histopathological stage of each tumor was determined according to the TNM classifications from the International Union Against Cancer, eighth edition [8]. The extent of smoking was quantified in pack-years (PY), with 1 PY equivalent to 20 cigarettes, on average, per day for 1 year. We reviewed the medical records of each patient for clinicopathological information, including age, sex, side of tumor (right or left), distribution within the lobe (upper, middle, or lower), smoking-related COPD (absent or present), preoperative serum carcinoembryonic antigen (CEA) level (cut-off at the normal upper limit of 5 ng/mL), tumor diameter measured by preoperative chest CT (dichotomized at 3.0 cm), tumor histology (adenocarcinoma, squamous cell carcinoma, or others), histological differentiation (well or moderately/poorly differentiated), lymphatic permeation (present or absent), vascular invasion (present or absent), visceral pleural invasion (present or absent) and lymph node metastasis (N0 or N1–3).

Statistical analyses

The analyses were performed using the statistical software program SPSS 11.0 (Dr. SPSS II for Windows, standard version 11.0; SPSS Inc., Chicago, IL, USA). Differences in the categorical outcomes were evaluated by the χ^2 test. Continuous variables were compared using the *t* test. The length of RFP was defined as the interval in months from the date of resection to the date of the first recurrence or last follow-up. To calculate RFP, patients who died without recurrence or who were known to be recurrence free at the date of last contact were censored. For the univariate analyses, all cumulative RFPs were estimated using the Kaplan–Meier method and differences in variables were evaluated using the log-rank test. Statistical significance was assumed at $p < 0.05$.

Results

Correlation between smoking-related COPD and clinicopathological characteristics

Among the 218 investigated patients, 53 (25%) were diagnosed as smoking-related COPD. According to GOLD staging for COPD patients, we reported 24 patients as GOLD stage I, 25 as GOLD stage II and 4 as GOLD stage III. The median follow-up period after surgical resection was 52 months (range 1–146 months). The 5-year RFP of the 218 patients was 77.9%. The 5-year RFP for patients with smoking-related COPD was significantly lower than for patients without COPD (55.0% and 84.9%, respectively; $p < 0.001$, Fig. 1).

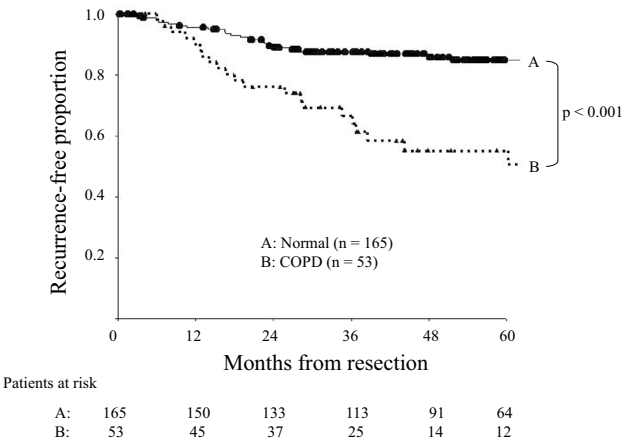

Fig. 1 Recurrence-free proportion curves of clinical stage I NSCLC patients with and without smoking-related COPD

Table 1 Correlation between smoking-related COPD and clinicopathological characteristics in entire cohort

Characteristics	Number of patients (%)	COPD		p value[†]
		Absent	Present	
Total	218 (100)	165 (76)	53 (24)	
Age (years)				
Value (mean ± SD)		66 ± 9.2	69 + 7.9	0.017*
Sex				
Female	89 (41)	84	5	< 0.001*
Male	129 (59)	81	48	
Tumor laterality				
Right	128 (59)	97	31	0.969
Left	90 (41)	68	22	
Primary lobe				
Upper or middle lobe	141 (65)	105	36	0.570
Lower lobe	77 (35)	60	17	
Smoking extent				
PY (mean ± SD)		20 ± 39	55 ± 28	< 0.001*
CEA				
Within the normal range	137 (63)	113 (68)	24 (45)	0.002*
Elevated	81 (37)	52 (32)	29 (55)	
Tumor size (cm)				
≤ 3.0	149 (68)	117	32	0.152
> 3.0	69 (32)	48	21	
Histological type				
Adenocarcinoma	165 (76)	139 (84)	26 (49)	< 0.001*
Squamous cell carcinoma	43 (21)	21 (13)	22 (42)	
Others	10	5	5	
Histological differentiation				
Well differentiated	103 (47)	92 (56)	11 (21)	< 0.001*
Moderately/poorly differentiated	115 (53)	73 (44)	42 (79)	
Lymphatic permeation				
Absent	134 (61)	106 (64)	28 (53)	0.147
Present	84 (39)	59 (36)	25 (47)	
Vascular invasion				
Absent	130 (60)	108 (65)	22 (42)	0.004*
Present	88 (40)	57 (35)	31 (58)	
Visceral pleural invasion				
Absent	171 (78)	130 (79)	41 (77)	0.849
Present	47 (22)	35 (21)	12 (23)	
N status				
N0	186 (85)	148 (90)	38 (72)	0.003*
N1–3	32 (15)	17 (10)	15 (28)	

Numbers in parentheses indicate percentages

COPD chronic obstructive pulmonary disease, *SD* standard deviation, *PY* pack-years, *CEA* preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL

*Significance level

[†]Chi-square test or Student's *t* test

Correlations between tumors in patients with smoking-related COPD and clinicopathological characteristics are displayed in Table 1. Patients with smoking-related COPD were significantly more likely to have nonadenocarcinoma ($p < 0.001$), moderately or poorly differentiated carcinomas ($p < 0.001$), tumors with intratumoral vascular invasion ($p = 0.004$) and lymph node metastases ($p = 0.003$) than those without smoking-related COPD.

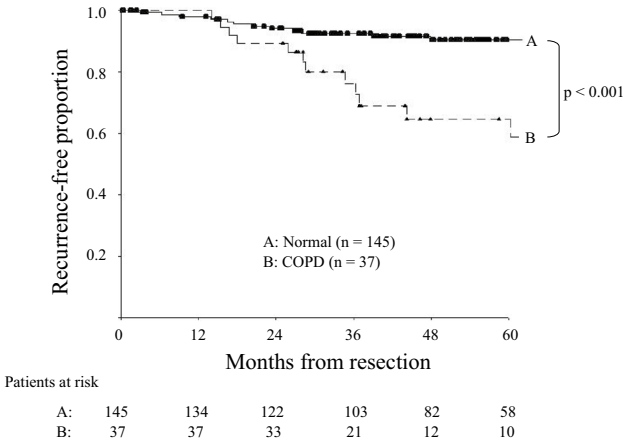

Fig. 2 Recurrence-free proportion curves of pathological stage I NSCLC patients with and without smoking-related COPD

Clinicopathological predictive factors for recurrence in pathological stage I non-small cell lung cancer patients

Of the 218 patients with clinical stage I NSCLC, 182 (83%) were also diagnosed with pathological stage I NSCLC. The 5-year RFP of the 182 patients with pathological stage I NSCLC was 85.2%. The 5-year RFP for patients with smoking-related COPD was significantly lower than for patients without COPD (64.8% and 90.5%, respectively; $p < 0.001$, Fig. 2).

A univariate analysis identified the following 8 statistically significant risk factors for recurrence: sex ($p = 0.010$), COPD ($p < 0.001$), preoperative serum CEA level ($p = 0.011$), maximum dimension of resected specimen ($p = 0.005$), histological differentiation ($p < 0.001$), lymphatic permeation ($p < 0.001$), vascular invasion ($p < 0.001$), and visceral pleural invasion ($p < 0.001$). In a multivariate analysis, histological differentiation ($p = 0.017$) and the presence of visceral pleural invasion ($p = 0.015$) were found to be statistically significant independent risk factors for recurrence for patients with pathological stage I NSCLC (Table 2).

Correlation between smoking-related COPD and clinicopathological characteristics in clinical stage I adenocarcinoma

To offset the influence of histology on the correlation between smoking-related COPD and clinicopathological characteristics, we focused on the adenocarcinoma histology. Of the 218 patients with clinical stage I NSCLC, 165 (75.7%) were postoperatively diagnosed with adenocarcinoma. The 5-year RFP for patients with smoking-related COPD was significantly lower than for patients without COPD (46.6% and 87.2%, respectively; $p < 0.001$, Fig. 3).

The correlations between tumors in patients with smoking-related COPD and clinicopathological characteristics are displayed in Table 3. Adenocarcinoma patients with smoking-related COPD showed a significantly higher proportion of moderately/poorly differentiated carcinomas ($P = 0.005$) and tumors with lymphatic permeation ($P = 0.026$), vascular invasion ($P = 0.038$) and lymph-node metastases ($P = 0.009$) than those without smoking-related COPD.

Correlations between smoking-related COPD and adenocarcinoma histological subtypes

We next investigated whether or not smoking-related COPD is associated with histological subtypes of adenocarcinoma. The presence of a solid component was more frequently found in patients with smoking-related COPD than in those without smoking-related COPD ($p = 0.007$, Table 4). Lepidic predominant adenocarcinoma was more frequently found in patients without smoking-related COPD than in those with smoking-related COPD ($p = 0.002$, Table 4). In addition, epidermal growth factor receptor (EGFR) mutations were found significantly more frequently in patients without smoking-related COPD than in those with smoking-related COPD ($p = 0.004$).

Discussion

Cigarette smoking is a risk factor for various diseases of the lungs and respiratory tract. COPD is also strongly associated with cigarette smoking and has been recognized as an important risk factor for lung cancer [3]. Chronic inflammation associated with cigarette smoking may play a role in the pathogenesis of both COPD and lung cancer. Inflammation in COPD may be responsible for repeated epithelial injury, high cell-turnover rates and the propagation of DNA errors, thus causing an amplification of the carcinogenic effects [9].

The prognosis of lung cancer patients with COPD is reported to be worse than that of those without COPD [10]. However, whether or not lung cancer with smoking-related COPD behaves more aggressively or results in a poorer survival remains unclear. To clarify the characteristics of lung cancer with smoking-related COPD, we assessed the relationships between smoking-related COPD and the clinicopathological characteristics and RFP of patients with clinical stage I NSCLC. The present study showed that the RFP for patients with smoking-related COPD was significantly lower than that for patients without smoking-related COPD. Clinical stage I patients with smoking-related COPD had an increased likelihood of having tumors with poor histologic differentiation and were significantly more likely to develop

Table 2 Univariate and multivariate analyses of clinicopathological prognostic factors in pathological stage I NSCLC patients

Characteristics	No. of patients (%)	Five-year RFP (%)	Univariate *p* value†	Multivariate analysis		
				HR	95% CI	*p* value
Total	182 (100)	85.2				
Age (years)						
< 68	89 (49)	87.7	0.379	Not included in the multivariate model		
≥ 68	93 (51)	82.4				
Sex						
Female	80 (44)	92.0	0.010*	1		
Male	102 (56)	79.4		1.639	0.628–4.279	0.313
COPD						
Absent	145 (80)	90.5	< 0.001*	1		
Present	37 (20)	64.8		1.909	0.829–4.396	0.129
CEA						
Within the normal range	125 (69)	89.7	0.011*	1		
Elevated	57 (31)	75.0		1.842	0.825–4.113	0.136
Tumor laterality						
Right	110 (60)	87.7	0.892	Not included in the multivariate model		
Left	72 (40)	81.7				
Primary lobe						
Upper or middle lobe	121 (66)	87.4	0.503	Not included in the multivariate model		
Lower lobe	61 (34)	81.2				
Histological type						
Adenocarcinoma	142 (78)	88.4	0.266	Not included in the multivariate model		
Others	40 (22)	76.3				
Maximum dimension of resected specimen (mm)						
≤ 30	130 (71)	89.8	0.005*	1		
> 30	52 (29)	74.5		1.288	0.519–3.198	0.585
Histological differentiation						
Well differentiated	96 (53)	95.3	< 0.001*	1		
Moderately/poorly differentiated	86 (47)	73.1		3.202	1.226–8.360	0.017*
Lymphatic permeation						
Absent	121 (66)	91.9	< 0.001*	1		
Present	61 (34)	71.1		1.543	0.636–3.747	0.338
Vascular invasion						
Absent	118 (65)	93.1	< 0.001*	1		
Present	64 (35)	70.6		1.417	0.552–3.642	0.469
Visceral pleural invasion						
Absent	148 (81)	89.7	< 0.001*	1		
Present	34 (19)	64.7		2.983	1.232–7.222	0.015*

Numbers in parentheses indicate percentages

RFP recurrence-free proportion, *HR* hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *CEA* preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL

*Significance level

†Log-rank test

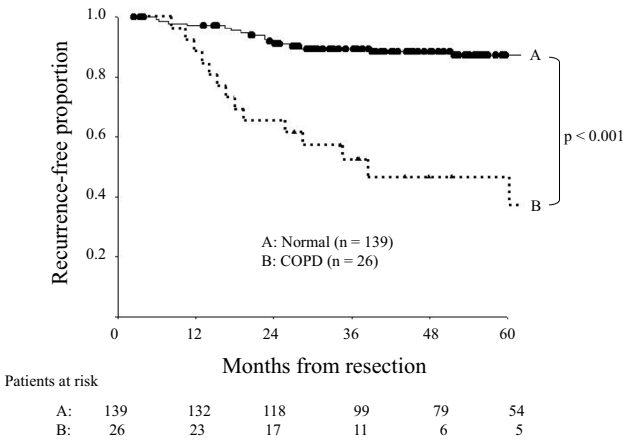

Fig. 3 Recurrence-free proportion curves of clinical stage I adenocarcinoma patients with and without smoking-related COPD

intratumoral vascular invasion and lymph node metastases than those without smoking-related COPD.

In adenocarcinoma patients, in particular, clinical stage I patients with smoking-related COPD also had highly aggressive and invasive tumors and were significantly more likely to develop lymph node metastases than those without smoking-related COPD. The histological subtypes of adenocarcinoma mainly comprise lepidic, acinar, papillary and solid components. Among these components, the solid component is the most poorly differentiated subtype. Several studies have reported that the presence of a solid component is indicative of tumor invasiveness, proliferation and dedifferentiation [11, 12]. Among adenocarcinoma patients with smoking-related COPD, significantly more cases were found to have a solid component in the present study. In addition, patients with smoking-related COPD were significantly less likely to have EGFR mutations than those without smoking-related COPD.

Sublobar resection, such as segmentectomy and wedge resection, may benefit NSCLC patients with a decreased pulmonary function caused by COPD; however, locoregional recurrence is common, even in patients with a pathologically confirmed negative surgical margin [13, 14]. This recurrence may be attributed to intratumoral vessel involvement when tumor cells spread into the surrounding parenchyma [15]. In the present study, the presence of smoking-related COPD was correlated with histologically invasive characteristics, including vascular invasion. In addition, 31% of clinical stage I adenocarcinoma patients with smoking-related COPD had lymph node metastases in the present study. Therefore, we should be careful when considering limited surgery in patients with smoking-related COPD to reduce the danger of missing nodal involvement and losing the opportunity to cure patients or administer adjuvant chemotherapy.

The mechanism by which smoking-related COPD results in more frequent NSCLC recurrence remains unclear. There may be several possible explanations for the highly aggressive and invasive biological characteristics of tumors in patients with smoking-related COPD observed in the present study. One possibility is that chronic inflammation of COPD by cigarette smoking promotes tumor proliferation, angiogenesis and metastasis through the production of inflammatory mediators, including chemokines and cytokines, such as tumor necrosis factor-α, interleukin-1 (IL-1) and IL-6 [16]. These cytokines are also reported to promote the survival of circulating tumor cells and epithelial–mesenchymal transition of cancer cells [17, 18]. Another possible explanation is that there is a direct interaction between the cancer cells and the stromal cells in the surrounding environment of smoking-related COPD, which may promote invasion and metastases of cancer cells [19]. Another possibility is that genetic mutations and abnormal gene expression by cigarette smoking may also accelerate cancer recurrence and metastasis [20]. The activation of signal transduction pathways such as nuclear-factor kappa B by cigarette smoking is reported to enhance the invasion and metastasis of tumor cells [20].

Several limitations associated with this retrospective study warrant mention. First, there was a lack of diversity in the study population due to patients being selected from a single Japanese institution. Second, the study included relatively few patients with smoking-related COPD. However, despite these limitations, we have clearly shown that lung cancer with smoking-related COPD is strongly associated with tumor invasiveness and poor outcomes in patients with clinical stage I NSCLC. The treatment strategies for these patients, including operative methods, should, therefore, be evaluated in future studies.

Conclusion

Clinical stage I NSCLC patients with smoking-related COPD have histologically more invasive tumors than those without smoking-related COPD. Further studies are necessary to confirm our findings and to develop optimum strategies of surgery in NSCLC patients with smoking-related COPD.

Table 3 Correlation between smoking-related COPD and clinicopathological characteristics in clinical stage I adenocarcinoma patients

Characteristics	Number of patients (%)	COPD		*p* value†
		Absent	Present	
Total	165 (100)	139 (84)	26 (16)	
Age (years)				
Value (mean ± SD)		65 ± 9.3	68 + 8.7	0.177
Sex				
Female	89 (41)	82 (59)	3 (12)	< 0.001*
Male	129 (59)	57 (41)	23 (88)	
Tumor laterality				
Right	101 (61)	83 (60)	18 (69)	0.391
Left	64 (39)	56 (40)	8 (31)	
Primary lobe				
Upper or middle lobe	107 (65)	89 (64)	18 (69)	0.662
Lower lobe	58 (35)	50 (36)	8 (31)	
Smoking extent				
PY (mean ± SD)		12 ± 25	50 ± 36	< 0.001*
CEA				
Within the normal range	137 (63)	113 (68)	24 (45)	0.002*
Elevated	81 (37)	52 (32)	29 (55)	
Tumor size (cm)				
≤ 3.0	120 (73)	105 (76)	15 (58)	0.061
> 3.0	45 (27)	34 (24)	11 (42)	
Histological differentiation				
Well differentiated	94 (57)	86 (62)	8 (31)	0.005*
Moderately/poorly differentiated	71 (43)	53 (38)	18 (69)	
Lymphatic permeation				
Absent	104 (63)	93 (67)	11 (42)	0.026*
Present	61 (37)	46 (33)	15 (58)	
Vascular invasion				
Absent	113 (68)	100 (72)	13 (50)	0.038*
Present	52 (32)	39 (28)	13 (50)	
Visceral pleural invasion				
Absent	133 (81)	115 (83)	18 (69)	0.173
Present	32 (19)	24 (17)	8 (31)	
N status				
N0	143 (87)	125 (90)	18 (69)	0.009*
N1–3	22 (13)	14 (10)	8 (31)	

Numbers in parentheses indicate percentages

COPD chronic obstructive pulmonary disease, *SD* standard deviation, *PY* pack-years, *CEA* preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL

*Significance level

†Chi-square test or Student's *t* test

Table 4 Correlation between smoking-related COPD and adenocarcinoma histological subtypes

Characteristics	No. of patients	COPD		*P* value[†]
		Absent	Present	
Total	165	139	26	
Histological subtypes				
Lepidic component				
Absent	40 (24)	30 (22)	10 (38)	0.081
Present	125 (76)	109 (78)	16 (62)	
Papillary component				
Absent	66 (40)	54 (39)	12 (46)	0.518
Present	99 (60)	85 (61)	14 (54)	
Acinar component				
Absent	71 (43)	64 (46)	7 (27)	0.086
Present	94 (57)	75 (54)	19 (73)	
Solid component				
Absent	148 (90)	128 (92)	19 (73)	0.007*
Present	17 (10)	10 (8)	7 (27)	
Predominant subtypes				
Lepidic	59 (36)	54 (39)	5 (19)	0.002*
Papillary	48 (29)	40 (29)	8 (31)	
Acinar	44 (27)	38 (27)	6 (23)	
Solid	14 (8)	7 (5)	7 (27)	
Gene mutation status				
EGFR				
Wild type	42 (25)	29 (21)	13 (50)	0.004*
Mutated	61 (37)	56 (40)	5 (19)	
Not examined	62	54	8	

Numbers in parentheses: percentages

COPD chronic obstructive pulmonary disease, *EGFR* epidermal growth factor receptor

*Significance

[†]Chi-square test

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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