Prevalence of underlying lung disease in smokers with epidermal growth factor receptor-mutant lung cancer

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Abstract. The prevalence of underlying lung diseases, such as emphysema and interstitial lung disease in smokers with epidermal growth factor receptor (EGFR)-mutant lung cancer remains unclear. This study aimed to clarify the correlation between the EGFR mutation status and the prevalence of underlying lung disease in smokers with lung cancer. A total of 88 consecutive smokers with non-small cell or non-squamous cell lung cancer who underwent surgical resection at our hospital from January 2007 through December 2010 were included in this study. The patients were divided into two groups on the basis of the EGFR mutation status: the mutation-positive group (n=19) and the wild-type group (n=69). The results of radiographic assessment via computed tomography (CT) and pulmonary function analysis were compared between the two groups. In the radiological evaluation, CT images at three levels were evaluated by two reviewers. Radiographic assessment revealed that the mutation-positive group tended to have milder emphysematous changes and a lower prevalence of interstitial changes compared with the wild-type group (P=0.13, 0.06). When the analysis was limited to the ipsilateral lung at the nearest CT level to the tumor, emphysematous changes were found to be less common in the mutation-positive group (P=0.02). The prevalence of the emphysematous and/or interstitial changes in the ipsilateral lung at the nearest CT level to the tumor was lower in the mutation-positive group compared to the wild-type group (P=0.005). In the pulmonary function test, the results were comparable between the two groups. In

conclusion, according to our results, EGFR-mutant lung cancer was commonly observed in the areas where emphysematous and interstitial changes were absent. EGFR-mutant lung cancer may develop in radiographically normal areas of the lungs, even in smokers. It would be of importance to evaluate the EGFR mutation status in patients with no emphysematous or interstitial changes in the ipsilateral lung near the tumor, regardless of their smoking history. These results should be confirmed in a future prospective study.

Introduction

Lung cancer, which is strongly associated with tobacco use, is a leading cause of cancer-related mortality worldwide (1). Despite the progress of therapeutic modalities, the prognosis of patients with lung cancer remains poor (2,3).

Over the past decade, epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs), which are molecular-targeted drugs, have been reported to be effective for the treatment of non-small cell lung cancer with EGFR mutation (4,5). This mutation is frequently found in never smokers and cases of adenocarcinoma (6), whereas it is uncommon in patients with a smoking history of >13-25 pack-years or in those who have not stopped smoking cigarettes <10-25 years ago (7-9).

Although smoking is a risk factor for lung cancer, pulmonary emphysema (10) and pulmonary obstructive disorders (11) are also independent risk factors. Patients with interstitial lung disease (ILD), such as combined pulmonary fibrosis and emphysema (CPFE), which is an emerging entity that is strongly associated with tobacco use (12), frequently develop lung cancer (13,14). As shown in a previous study, all lung cancer patients with ILD were reported to be smokers (15). These reports suggest that the presence of emphysema and/or ILD may negatively correlate with the development of EGFR-mutant lung cancer, which is relatively uncommon in smokers (6). However, the prevalence of these underlying diseases in smokers with EGFR-mutant lung cancer remains unclear.

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The present study was conducted to examine the correlation between the EGFR mutation status and the prevalence of underlying lung disease in smokers with lung cancer.

Patients and methods

Patients. The records for all consecutive patients with non-small cell or non-squamous cell lung cancer who underwent surgical resection at the Ibarakihigashi National Hospital (Ibaraki, Japan) from January, 2007 through December, 2010 were retrospectively investigated. According to previous studies (8,9), it was ensured that only those patients who had a smoking history of ≥15 pack-years were selected from these records. Patient characteristics such as smoking intensity and tumor site were also evaluated. This study was approved by the Institutional Human Ethics Committee of the Ibaraki-higashi National Hospital.

Radiographic analysis. For each patient, a helical computed tomography (CT) scanner was utilized (slice thickness, 2.5-10 mm). In the majority of patients, the slice thickness was ≤5.0 mm (window level, -600; window width, 1,500). All measurements were independently performed by a board-certified radiologist and a board-certified pulmonologist, who were both blinded to the clinical data. CT images at three levels were evaluated: the top of the aortic arch, the tracheal carina, and 2 cm above the highest hemidiaphragm. In each slice, right and left images were assessed separately, and therefore six images in total were evaluated for each patient. The severity of emphysematous changes was scored visually according to the scoring system described by Goddard *et al* (16). Emphysematous changes were defined as the areas of low attenuation and vascular disruption (16,17). Based on the percentage of emphysematous area in the evaluated lung, each image was classified as normal (score 0), <25% affected (score 1), <50% affected (score 2), <75% affected (score 3), or ≥75% affected (score 4). Scores obtained by the two reviewers were summed for each image. The maximum possible scores were eight in one image, 16 in one slice, and 48 in the whole lung.

Interstitial changes were defined as the presence of ground-grass opacities, consolidation, reticular shadows, honeycombing and/or traction bronchiectasis or bronchiolectasis, as described in previous studies (12,15). If one or more of these findings were observed, the patients were evaluated as having ILD.

In addition, we focused on the ipsilateral image of the lung nearest to the tumor among the six images (defined as 'ipsilateral image') as shown in Fig. 1, for the purpose of assessing pulmonary status in the area surrounding the tumor.

Pulmonary function analysis. Pulmonary function testing was performed by trained technicians according to the criteria of the American Thoracic Society (18). In all patients, no bronchodilator was used since pulmonary function was examined for the purpose of evaluating tolerability to surgical resection. The diagnosis of chronic obstructive pulmonary disease (COPD) was based on the examination of forced expiratory volume (FEV) in 1 sec (FEV_1) according to the following formula: (FEV_1)/forced vital capacity (FVC) ≤70%.

Molecular analysis. All patients provided written informed consent for the comprehensive use of the results of molecular
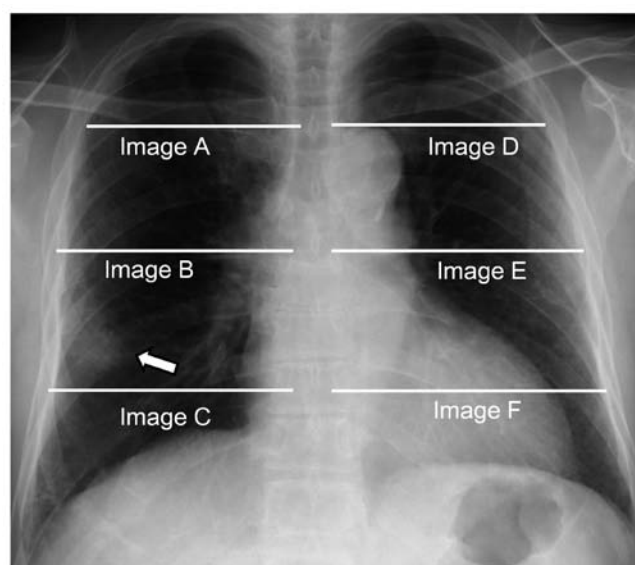

Figure 1. Bars on the chest radiograph show three CT levels: the top of the aortic arch, the tracheal carina and 2 cm above the highest hemidiaphragm in both lungs. For example, as the tumor presented in the right lower lobe in this case (arrow), the ipsilateral image of the lung nearest to the tumor was 'image C'.

analysis. Genomic DNA samples were isolated from fresh-frozen or paraffin-embedded tissues obtained mainly by surgical resection. All clinical samples were independently examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method for the detection of EGFR mutations. Testing was performed at the Saitama Medical University (Saitama) or the Mitsubishi Chemical Medience Corporation (Tokyo, Japan) (19).

Statistical analysis. Fisher's exact test were used for the comparison of categorical variables such as gender, pathology, tumor site and pathological stage. The Mann-Whitney U test was performed for continuous variables, including age, pulmonary function variables, and emphysema score. P-values <0.05 were considered to indicate statistically significant differences. All analyses were performed using GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics. The study profile is shown in Fig. 2. Of the 292 consecutive patients with non-small cell or non-squamous cell lung cancer who underwent surgical resection, 97 had a smoking history of ≥15 pack-years. Of these, nine refused to be examined for EGFR mutation status. Of the remaining 88 patients who met the inclusion criteria, 19 (21.6%) were found positive for the EGFR mutation (exon 21 L858R, n=11; exon 19 deletion, n=8).

The 88 patients were divided into two groups according to EGFR mutation status: the mutation-positive group (19 patients) and the wild-type group (69 patients). The characteristics of the patients in these two groups are presented in Table I. Almost all the patients in both groups were males and were diagnosed with adenocarcinoma. The lung tumor
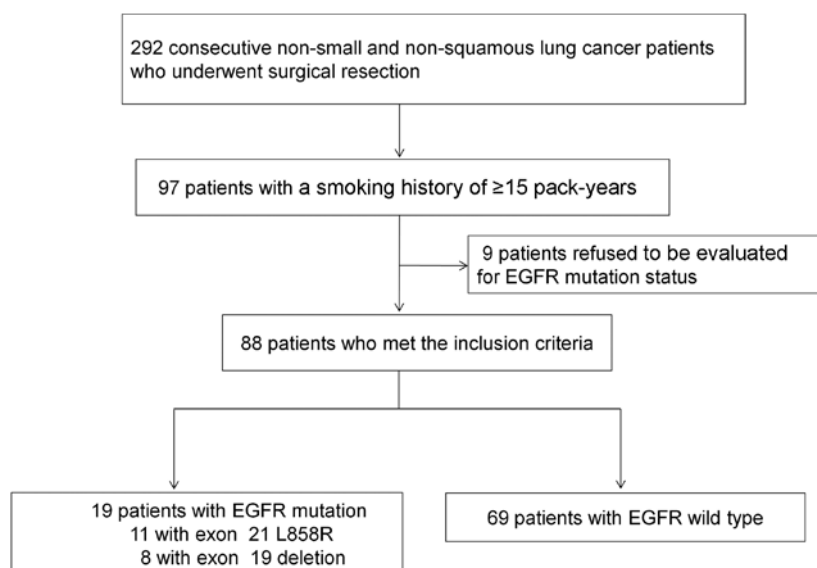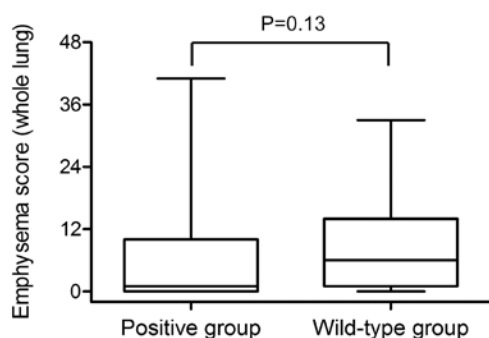
Figure 2. Study profile.

Figure 3. Box plot showing the emphysema score in the whole lung between the two groups. The horizontal bars represent the median values.

sites and smoking status in the mutation-positive group were similar to those in the wild-type group (P=0.58 and 0.80). Patients in the mutation-positive group tended to have lower smoking intensity than those in the wild-type group, although this difference was not significant (P=0.07). In terms of disease stage and tumor size, the results in the mutation-positive group were similar to those in the wild-type group (P=1.00 and 0.60).

Radiographic analysis. The median emphysema score for the whole lung was one (range, 0-41) in the mutation-positive group and six (range, 0-33) in the wild-type group (Fig. 3). Emphysema scores tended to be lower in the mutation-positive group than in the wild-type group (P=0.13). Interstitial changes were observed in 19 patients (mutation-positive group, n=1; wild-type group, n=18). Interstitial changes also tended to be less common in the mutation-positive group compared to the wild-type group (P=0.06).

When we focused on the ipsilateral image, the percentage of patients with emphysematous changes was 26.3% in the mutation-positive group and 58.0% in the wild-type group (Table II). Emphysematous changes in the ipsilateral image were less common in the mutation-positive group than in the wild-type

group (P=0.02). Interstitial changes in the ipsilateral image was observed in ten patients. All ten patients were from the wild-type group (P=0.11). Therefore, the percentage of patients who did not present with emphysematous nor interstitial changes in the ipsilateral image was 73.7% in the mutation-positive group and 36.2% in the wild-type group (P=0.005). The majority of patients in the mutation-positive group had a radiographically normal lung in the ipsilateral image.

Pulmonary function analysis. Median vital capacity (VC)/predicted VC (% VC) was 106.7% (range, 69.8-140.2%) in the mutation-positive group and 101.8% (67-152.9%) in the wild-type group. The difference between the groups for this parameter was not significant (P=0.95). In FEV_1% testing, similar results were observed for both groups (mutation-positive group: 69.9%, range, 39.1-93.7; wild-type group: 71.5%, range, 44.6-95.0; P=0.94). The percentage of patients who met the diagnostic criteria of COPD was 52.6% in the mutation-positive group and 46.3% in the wild-type group. The difference between the groups regarding this parameter was not significant (P=0.80). When the analysis was limited to patients with no interstitial changes, no significant difference was observed between the two groups in terms of % VC and FEV_1% (P=0.40 and 0.43).

Discussion

In this study, EGFR-mutant lung cancer was commonly observed in the areas where emphysematous and interstitial chnages were absent, even in smokers. This finding suggests that EGFR-mutant lung cancer develops in areas unaffected by smoking, even in smokers.

EGFR mutation is frequently detected in cases of adenocarcinoma as well as in non-smokers (4,5,20). Although the EGFR mutation has been reported to be relatively rare in non-smokers with environmental exposure to tobacco (21), the prevalence of underlying lung disease in non-smokers is low compared to that in smokers. In the present study, we examined smokers with

Table I. Patient characteristics.

Characteristics	EGFR mutation status		
	Positive (n=19)	Wild-type (n=69)	[a]P-value
Gender			
Male/female	19/0	63/6	0.34
Age			
Years (median)	72 (46-87)	73 (54-81)	0.97
Pathology			
Adenocarcinoma	18	62	
Non-small cell lung cancer (not otherwise specified or combined)	1	7	1.00
Primary site (upper lobe/middle or lingular/lower)	10/3/6	46/6/17	0.58
Smoking history			
Current/former	8/11	33/36	0.80
Smoking intensity, duration			
Pack-years, median	38 (15-68)	40 (15-144)	0.07
Pathological stage			
I and II	15	52	1.00
III and IV	4	17	
Tumor size (median, mm)	25 (15-65)	27 (10-100)	0.60

[a]Comparison between the EGFR mutation positive group and the wild-type group. EGFR, epidermal growth factor receptor.

Table II. EGFR mutation status and underlying lung disease in the ipsilateral image of the lung nearest to the tumor.

Underlying lung disease	EGFR mutation status		
	Positive 19 cases (%)	Wild-type 69 cases (%)	P-value
Emphysematous changes			
Present	5 (26.3)	40 (58.0)	0.02[a]
Absent	14 (73.7)	29 (42.0)	
Emphysema score			
0	14 (73.7)	29 (42.0)	
>0 to ≤2	1 (5.3)	22 (31.9)	
>2 to ≤4	3 (15.8)	13 (18.8)	
>4 to ≤6	0 (0.0)	3 (4.3)	
>6 to ≤8	1 (5.3)	2 (2.9)	
Interstitial changes			
Present	0 (0.0)	10 (14.5)	0.11
Absent	19 (100.0)	59 (85.5)	
Emphysematous and/or interstitial changes			
Present	5 (26.3)	44 (63.8)	0.005[a]
Absent	14 (73.7)	25 (36.2)	

[a]Indicates statistical significance. EGFR, epidermal growth factor receptor.

Table III. Prevalence of EGFR mutation in patients with underlying lung disease detected in the ipsilateral image of the lung nearest to the tumor.

Underlying lung disease	No. of patients with EGFR mutation	Total no. of patients	%
Emphysematous changes	5	45	11.1
Interstitial changes	0	10	0
None	14	39	35.9

EGFR, epidermal growth factor receptor.

a smoking history of ≥15 pack-years; this history was found to negatively correlate with the presence of EGFR mutation, and as shown by our results, EGFR-mutant lung cancer was commonly observed in areas where emphysematous and interstitial changes were absent. To the best of our knowledge, only one previous study on the correlation of the EGFR mutation status with underlying lung diseases, such as emphysema and pulmonary fibrosis has been published [Usui *et al* (22)]. In their study, the frequency of EGFR mutation was reported low in patients with emphysema and pulmonary fibrosis compared to those without. Although the results of that study seem consistent with those in the current study, their results included both never smokers and smokers (never smokers, 37.4%; smokers, 62.6%). Furthermore, lung cancer was at an advanced clinical stage in the majority of patients (stage IIIB and IV, 68.2%) and only the presence of emphysema and/or fibrosis in the whole lung was roughly evaluated in that study (22). In the present study, the detailed radiographic evaluation focused on the six images from the whole lung, and the results revealed that emphysematous changes in the image nearest to the tumor

were less common in the mutation-positive group. Therefore, EGFR-mutant lung cancer may develop in areas that appear radiographically normal, even in smokers.

The precise mechanism accounting for the results of this study remains unknown. However, it is generally accepted that the presence of emphysema is related to the development of lung cancer (10,23-25). In addition, patients with ILD such as CPFE, which is strongly associated with tobacco use, have been reported to develop lung cancer more frequently than those with emphysema alone (12-14). Recent reports indicate that patients with underlying lung diseases are susceptible to smoking-related inflammation, which may ultimately contribute to lung cancer development (13,22,23,26,27). Although the mechanisms underlying this association have not been clearly

identified, the results of the present study may indicate a clinical possibility: EGFR-mutant lung cancer may develop in areas less affected by tobacco use and the mechanism of carcinogenesis in EGFR-mutant lung cancer in smokers may resemble that in non-smokers. In the present study, EGFR-mutant lung cancer in smokers was commonly observed in the areas where emphysematous and interstitial changes were absent compared to wild-type lung cancer. Of note, although the degree of emphysematous changes in the whole lung was not significantly different between the two groups (P=0.13), the difference became clearer when the assessment of emphysematous changes focused on the ipsilateral image (P=0.02). These results suggest that the absence of emphysematous and interstitial changes in the ipsilateral image, not in the whole lung, is correlated with the development of EGFR-mutant lung cancer.

The results of this study may provide two important implications for clinical practice. First, EGFR-TKIs may be effective for EGFR-mutant lung cancer even in smokers. Previous studies have reported no differences in progression-free and overall survival rates between smokers and non-smokers with EGFR-mutant lung cancer (22,28-30). However, detailed information regarding smoking intensity was not provided in those reports. Lung cancer in smokers has been associated with more widespread chromosomal abnormalities than in non-smokers (31). Therefore, various genetic alterations in patients with lung cancer may be associated with resistance to EGFR-TKIs. For example, EGFR-mutant lung cancer other than adenocarcinoma has been reported to exhibit a poor response to EGFR-TKIs, indicating that multiple factors other than EGFR signaling may play an important role in carcinogenesis and tumor growth (32,33). Considering that EGFR-mutant lung cancer was commonly observed in the areas where emphysematous and interstitial changes were absent even in smokers, these tumors may bear a genetic resemblance to those in non-smokers. Therefore, these tumors, similar to the ones found in non-smokers, may respond well to EGFR-TKI treatment, although, the fatal adverse effects of ILD should be carefully monitored in smokers (34). Second, smokers without emphysematous and interstitial changes may have a high possibility of developing EGFR-mutant lung cancer compared to those with such changes. The present study revealed that EGFR mutation was found in 5/45 (11.1%) patients with emphysematous changes, 0/10 (0%) patients with interstitial changes and 14/39 (35.9%) patients without these underlying diseases in the ipsilateral image (Table III). Although a number of studies have revealed that the prevalence of EGFR mutation in smokers ranges from 8.4 to 15.6% (8,28,30), the prevalence of EGFR mutation in smokers without emphysematous and interstitial changes seems much higher. Therefore, our results indicate the importance of evaluating the EGFR mutation status in patients with no emphysematous nor interstitial changes in the ipsilateral lung near the tumor, regardless of smoking history.

The present study had several limitations. First, the study was carried out at a single institution and was a retrospective study with a small sample size. In addition, the slice thickness of the CT images in the majority of patients was ≤5.0 mm; therefore, the results do not reflect the evaluation of the high-resolution CT images and thus, the prevalence of underlying lung disease could be underestimated. Finally, the evaluation of emphysema was conducted visually and semiquantitatively, not automatically or densitometrically. However, a systemic review and meta-analysis by Smith *et al* (25) reported a significant association of lung cancer risk with emphysema detected by visual evaluation rather than by automated methods.

In conclusion, our results revealed that EGFR-mutant lung cancer was commonly observed in the areas where emphysematous and interstitial changes were absent, even in smokers. EGFR-mutant lung cancer definitely exists in smokers and may develop in areas that appear radiographically normal. It would be important to evaluate the EGFR mutation status in patients with no emphysematous or interstitial changes in the ipsilateral lung near the tumor, regardless of smoking history. The results of this study should be confirmed in a future prospective study.

Acknowledgements

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