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ORIGINAL ARTICLE

Relationship between *EGFR* mutation and computed tomography characteristics of the lung in patients with lung adenocarcinoma

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Keywords
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Abstract

Background: The aim of this study was to investigate the relationship between *EGFR* mutation and computed tomography (CT) features in patients with adenocarcinoma of the lung.

Methods: One hundred and ninety two lung adenocarcinoma patients who underwent surgery were retrospectively included in this study. Examination of *EGFR* gene mutation was performed on all resected tumor samples. The 192 recruited lung adenocarcinoma patients were divided into groups according to *EGFR* mutation status: patients with mutations in exons 18–21 (effective mutated, $n = 61$) and non-mutated ($n = 131$). The clinical characteristics and lung CT imaging features of the two groups were recorded and compared. Univariate and logistic regression analysis were performed to identify the independent risk factors relevant to effective *EGFR* gene mutation.

Results: The independent risk factors relevant to effective *EGFR* mutation were evaluated by logistic regression test. The results indicated that female gender (odds ratio [OR] 3.23), lung CT features of lymphangitis carcinomatosa (OR 2.66), semi-solid lesion density (OR 3.56), and spicule sign (OR 1.61) were independent risk factors relevant to *EGFR* mutation.

Conclusion: Female patients with lung CT features of lymphangitis carcinomatosa, semi-solid lesion density, and spicule sign are more prone to harbor *EGFR* gene mutations and are more likely to benefit from targeted therapy.

Introduction

Epidemiology studies have shown that lung cancer is the most commonly diagnosed malignant carcinoma and the leading cause of cancer-related death in men and second in women.[1,2] Generally, lung cancer prognosis is poor with low long-term survival rates. It is reported that approximately 75–80% of non-small cell lung cancer (NSCLC) patients have advanced or locally advanced disease.[3] Patients with advanced disease have lost the opportunity of surgery and thus are treated by chemoradiation or targeted therapy. At present, the most commonly used target drugs for NSCLC treatment are EGFR-tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib.[4–6] However, not all NSCLC patients can benefit from EGFR-TKI treatment. Prognosis can only be improved in patients with effective *EGFR* mutations, which frequently occur in exons 18–21 and are part of the gene coding for the tyrosine kinase domain of the EGFR protein. In patients diagnosed with advanced NSCLC, the most common activating mutations observed are exon 19 deletions and an L858R point mutation in exon 21.[7,8] Treatment with EGFR-TKIs can significantly improve overall and disease-free survival in NSCLC patients with effective *EGFR* gene mutations. Therefore, evaluation of *EGFR* mutation status is recommended in patients with NSCLC before administering target drugs.[9–11] However, it is difficult to obtain adequate cancer tissue for *EGFR* mutation detection in some NSCLC patients. Thus, predicting effective *EGFR* mutation by clinical and demographic characteristics and imaging features is important.

In our present study, we investigate the relationship between effective *EGFR* mutation and computed tomography (CT) features in patients with adenocarcinoma of the lung in order to determine the CT features relevant to effective *EGFR* mutation.

Methods

Patients

One hundred and ninety two lung adenocarcinoma patients who underwent surgery were retrospectively included in the study. Examination of *EGFR* gene mutation was performed on all resected tumor samples. The 192 recruited lung adenocarcinoma patients were divided into groups according to *EGFR* mutation status: effective mutated (n = 61) and non-mutated (n = 131). The study design was reviewed and approved by the ethics committee of the Hangzhou Red Cross Hospital, Hospital of Integrated Traditional Chinese and Western Medicine affiliated to Zhejiang Chinese Medical University Review Board. Written informed consent was obtained from all subjects included in the study.

Lung computed tomography (CT) features: Collection and analysis

All patients underwent 16 multislice spiral CT or enhanced scans. Scanning parameters were: tube voltage 120 kV, tube current 200 mA, scanning field of vision (SFOV) 300 mm or 350 mm, reconstruction image layer thickness 1.5 mm, layer interval 1.25 mm, reconstruction matrix 512 *512. For the enhanced scan, 80 mL of contrast agent was injected into the anterior elbow vein. Scanning was performed in all patients while they held their breath after inhalation. The scan ranged from the apex of the lung to the diaphragm.

Statistical analysis

SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The measurement data was demonstrated by $\overline{x} \pm s$ and comparison between groups was made using a Student's t-test of the sample mean. Enumeration data were expressed by a relative number and comparison between groups was made based on chi-square or Fisher's exact tests. Univariate logistic regression was performed for each candidate variable and $P < 0.05$ was considered statistically significant. $P < 0.05$ meant a statistical difference.

Results

Clinical features relevant to effective *EGFR* mutation

Single factor analysis showed that effective *EGFR* mutation was correlated with gender ($P < 0.05$) and smoking history ($P < 0.05$). Female non-smokers were more inclined to have an *EGFR* gene mutation. However, effective *EGFR* mutation was not correlated with body mass index, clinical stage, family history of tumor, or tumor differentiation (Table 1).

Lung CT imaging features relevant to *EGFR* mutation

The correlation between lung CT imaging features and effective *EGFR* mutation was evaluated by single factor analysis. Compared to non-mutated *EGFR* cases, patients with effective mutated *EGFR* had more lung lesions with a lobular sign ($P < 0.05$), spicule sign ($P < 0.05$), semi-solid lesion density ($P < 0.05$), air bronchogram ($P < 0.05$), pleural indentation sign ($P < 0.05$), and lymphangitis carcinomatosa ($P < 0.05$) (Table 2, Fig 1).

Table 1 Clinical features of the included patients with or without *EGFR* gene mutation

		EGFR status			
Characteristics	No.	Effective mutated (n = 71)	Non-mutated (n = 121)	t/χ^2	P
Gender N, (%)				9.24	0.002
Male	111	31 (27.93)	80 (72.07)		
Female	81	40 (49.38)	41 (50.62)		
Age (year)	192	62.3 ± 11.2	64.2 ± 10.6		
Smoking N, (%)	192			6.16	0.013
Positive	90	25 (27.78)	65 (72.22)		
Negative	102	46 (45.10)	56 (54.90)		
BMI ($kg \cdot m^{-1}$)	192	19.2 ± 2.1	19.6 ± 2.6		
Stage N, (%)				0.76	0.38
I–II	103	41 (39.81)	62 (60.19)		
III	89	30 (33.71)	59 (66.29)		
CEA N, (%)				0.79	0.37
Elevated	62	22 (35.48)	40 (64.52)		
Normal	130	49 (37.69)	81 (62.31)		
Family history of tumor N, (%)				0.01	0.91
Positive	29	11 (37.93)	18 (62.07)		
Negative	163	60 (36.81)	103 (63.19)		
Differentiation N, (%)				3.36	0.067
Well/moderate	77	42 (54.55)	35 (45.45)		
Poor	115	29 (30.53)	86 (69.47)		

BMI, body mass index; CEA, carcinoembryonic antigen.

Table 2 Lung CT imaging features relevant to *EGFR* mutation, N, (%)

Characteristic	No.	*EGFR* status: Effective mutated (*n* = 71)	*EGFR* status: Non-mutated (*n* = 121)	t/χ^2	*P*
Necrosis					
Positive	26	12 (46.15)	14 (53.85)	1.086	0.3
Negative	166	59 (35.54)	107 (64.46)		
Cavity				0.075	0.78
Positive	28	11 (39.29)	17 (60.71)		
Negative	164	60 (36.59)	104 (63.41)		
Calcification				0.766	0.38
Positive	22	10 (45.45)	12 (54.55)		
Negative	170	61 (35.89)	109 (64.11)		
Lobular sign				5.008	0.025
Positive	88	40 (45.45)	48 (54.55)		
Negative	104	31 (29.81)	73 (70.19)		
Spicule sign				7.646	0.0057
Positive	86	41 (47.67)	45 (52.33)		
Negative	106	30 (28.30)	76 (71.70)		
Lesion density				10.411	0.0013
Solid	166	54 (32.53)	112 (67.47)		
Semi-solid	26	17 (65.38)	9 (34.62)		
Diameter				0.635	0.426
≤ 3 cm	35	15 (42.86)	20 (57.14)		
> 3 cm	157	56 (35.67)	101 (64.33)		
Halo sign				0.165	0.685
Positive	22	9 (40.91)	13 (59.09)		
Negative	170	62 (36.47)	108 (63.53)		
Bronchus encapsulated air sign				0.715	0.398
Positive	21	6 (28.57)	15 (71.43)		
Negative	171	65 (38.01)	106 (61.99)		
Air bronchogram				4.371	0.036
Positive	84	38 (45.24)	46 (54.76)		
Negative	108	33 (30.56)	75 (69.44)		
Pleural indentation sign				4.551	0.032
Positive	58	28 (48.28)	30 (51.72)		
Negative	134	43 (32.09)	91 (67.91)		
Pleural effusion				0.329	0.566
Positive	28	9 (32.14)	19 (67.86)		
Negative	164	62 (37.80)	102 (62.20)		
Lymphangitis carcinomatosa				8.435	0.037
Positive	43	24 (55.81)	19 (44.19)		
Negative	149	47 (31.54)	102 (68.46)		
Mediastinal lymph node enlargement				2.027	0.155
Positive	94	30 (31.91)	64 (68.09)		
Negative	98	41 (41.84)	57 (58.16)		

CT, computed tomography.

Independent factors related to effective *EGFR* gene mutation

The independent factors relevant to effective *EGFR* mutation were evaluated by logistic regression analysis. The results indicated that female gender (odds ratio [OR] 3.23), lung CT features of lymphangitis carcinomatosa (OR 2.66), semi-solid lesion density (OR 3.56), and spicule sign (OR 1.61) were independent factors relevant to effective *EGFR* mutation (Fig 2).

Discussion

The successful treatment of NSCLC with EGFR-TKIs marks an era of targeted cancer therapy.[12–14] Previous studies have proven that the prognosis of NSCLC patients with effective *EGFR* gene mutations can be significantly improved by EGFR-TKI treatment.[15–17] Studies have also shown that small molecule TKIs (gefitinib or erlotinib) are more effective in patients with mutations in exon 18–21 of the *EGFR* gene, especially those with mutations in exon 19, whereas these targeted drugs are almost ineffective in patients without mutations.[8] Therefore, it is important to assess *EGFR* gene status before administering target drugs. However, adequate histological specimens to assess *EGFR* gene mutation are not always available. In such patients, the effectiveness of targeted therapy is measured by clinical features, such as gender and smoking history.[18,19] Previous studies have screened clinical and demographic characteristics to determine the independent factors relevant to effective *EGFR* mutations that may be sensitive to EGFR-TKI treatment.[20] They found that female non-smoking East Asian lung cancer patients were more likely to harbor effective mutations in the *EGFR* gene.[21] Consistent with the results of previous studies, our results also showed that the mutation rate in exons 18–21 of the *EGFR* gene in female non-smokers was higher than in other patients. However, judging the effectiveness of small molecule TKI therapy by clinical characteristics alone is inadequate.

In recent years, medical radiologists have attempted to obtain gene mutation information indirectly from the imaging manifestations of lung cancer patients in order to obtain more imaging features to assist in identifying driving genes.[22,23] In our present work, we investigated the relationship between effective *EGFR* gene mutations and CT imaging characteristics and clinical features in patients with adenocarcinoma of the lung in order to provide more information for small molecule TKI therapy. Our study found that female gender, lung CT features of lymphangitis carcinomatosa, semi-solid lesion density, and spicule sign were independent factors relevant to effective *EGFR* mutation.

In conclusion, our results show that female patients with lung CT features of lymphangitis carcinomatosa, semi-solid lesion density, and spicule sign are more prone to harbor effective *EGFR* gene mutations. As a result, these patients are more likely to benefit from small molecule TKI therapy. CT imaging can be used to predict effective *EGFR* mutation in patients with inadequate tissue samples. The combination of CT features and driver gene status is

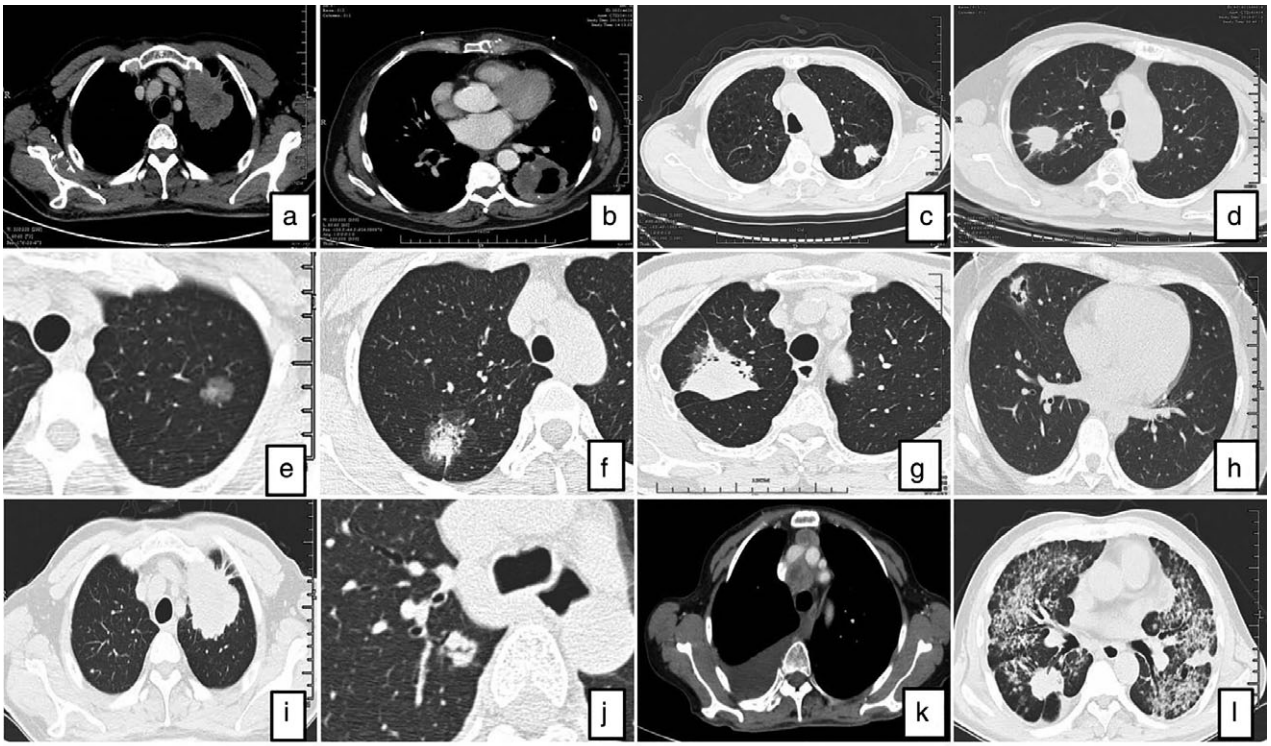

Figure 1 Computed tomography features in patients with adenocarcinoma of the lung: Mass in the left lung accompanied by (**a**) necrosis and (**b**) with carcinomatous cavity; carcinoma of the left lung with (**c**) lobulated and (**d**) spicule sign; (**e**) ground glass nodule of the left lung; (**f**) right lung mass with halo sign; right lung carcinoma (**g**) diameter > 3 cm and (**h**) with bronchus encapsulated air sign; (**i**) left lung carcinoma with pleural indentation sign; (**j**) right lung mass with air bronchogram; (**k**) right thorax pleural effusion with enlarged mediastinal lymph node; and (**l**) right lung carcinoma with lymphangitis carcinomatosa.

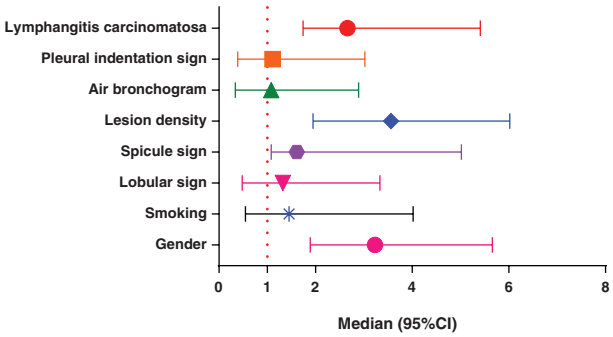

Figure 2 Multivariate odds ratios and 95% confidence intervals for the estimated risks of *EGFR* mutation in in patients with adenocarcinoma of the lung.

helpful to further understand the occurrence and development of tumors to predict prognosis and promote the development of imaging genomics.

Disclosure

No authors report any conflict of interest.

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