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Clinicoradiological features associated with epidermal growth factor receptor exon 19 and 21 mutation in lung adenocarcinoma

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AIM: To retrospectively identify clinicopathological and radiological characteristics that could be independent predictors of epidermal growth factor receptor (EGFR) exon 19 and 21 mutation in surgically resected lung adenocarcinomas in a cohort of Asian patients.

MATERIALS AND METHODS: Demographics, histopathology data, and preoperative chest computed tomography (CT) images were evaluated retrospectively in 471 surgically resected lung adenocarcinomas. A total of 24 CT descriptors were assessed. Univariate analyses and multivariate logistic regression analyses were performed to identify independent predicted factors of harbouring EGFR mutations.

RESULTS: EGFR mutations were existed in 252 (53.5%) of 471 patients, and associated with 11 clinicoradiological features. For the model with both clinical and radiological features, the independent predictors of harbouring EGFR mutation were small maximum diameter ($\leq$3.9 cm), non-smokers, micropapillary pattern, pleural retraction, vascular convergence, and absence of solid pattern. The area under the receiver operating characteristic (ROC) curve (AUC) was 0.784. Multivariable logistic regression analysis indicated that non-smokers, vascular convergence, and absence of solid pattern were important independent predictors of EGFR exon 19 mutation, while non-smokers and vascular convergence were independent predictors of EGFR exon 21 mutation. The AUCs were 0.807 and 0.794, respectively. A lepidic growth pattern appeared more frequently in exon 21 mutant tumours than in exon 19 mutant group ($p<0.001$).

CONCLUSION: CT imaging features of lung adenocarcinomas in combination with clinical variables could be used to prognosticate EGFR mutation status. The separate analysis of EGFR exon 19 or 21 mutation could further improve diagnostic performance.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, accounting for 13% of newly diagnostic cancers in the world.[1] About 85% of lung cancers are non-small cell lung cancer (NSCLC), of which lung adenocarcinoma is

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histologically the most common subtype.[2] The epidermal growth factor receptor (EGFR) gene is a driving factor demonstrated in NSCLC and the discovery of activating mutations in EGFR has led to a paradigm shift in the care of NSCLC patients. The corresponding targeted drug, tyrosine kinase inhibitor (TKI), has good clinical efficacy.[3] Six randomised studies have confirmed that first-line EGFR TKI treatment presented higher tumour response rates, prolonged progression-free survival (PFS), and improved health-related quality of life compared with the standard platinum-based chemotherapy[4]; however, patients might experience shorter PFS when administered gefitinib in EGFR wild-type lung cancer,[5] emphasising the importance of identifying patients with this unique inherited subset of disease. Currently, all guidelines recommend EGFR testing before treatment to select the most effective therapy for patients.

According to the research,[6] EGFR mutation includes three types identified in exons 18 to 21 (point mutation, multinucleotide in-frame deletion, and in-frame insertion). Deletion mutation in exon 19 and point mutation in exon 21 are the most common mutations,[7] which are responsive to targeted therapies. Therefore, identifying EGFR mutation subtype, especially those responsive to TKI treatment, seems to be more critically important than just predicting EGFR mutation status. In addition, NSCLC patients with EGFR exon 19 deletion presented a higher response rate as well as a longer PFS and overall survival compared with exon 21 L858R mutation after EGFR TKI treatment.[8,9] Thus, EGFR mutation subtypes should be considered when making treatment decisions for EGFR mutation-positive NSCLC patients.

At the current stage, tumour tissue specimens for gene detection are mainly obtained through surgical resection or needle biopsy, while some patients diagnosed with lung cancer are of advanced stage or pre-existing conditions prohibit surgery. For these patients, biopsy samples may be the only tumour tissue specimens available to determine EGFR mutation status; however, aspiration biopsy is an invasive examination, and the probability of false-negative results caused by the low number and proportion of tumour cells in aspiration biopsy specimens[10] as well as intratumoural heterogeneity cannot be ignored. With logistical and financial barriers, it is almost impossible to implement continuous or multiple biopsies for subcloning in routine clinical care. Therefore, searching for clinical and radiological features associated with EFGR mutation status has attracted increasing attention.

Many studies have reported several patient characteristics associated with high mutation rates of EGFR, such as females, non-smokers, adenocarcinoma histology and Asian ethnicity.[11] EGFR mutations exist in approximately 20% of lung adenocarcinomas and the EGFR mutation rate is as high as 60% in non-smokers and Asian populations.[12] Conventional computed tomography (CT) imaging provides non-invasive and comprehensive observation of the entire tumour, which can be used to monitor tumour progression and response to treatment, or possibly identify biopsy locations to provide the most feasible data. Previous studies[13,14] identified that clinical variables combined with radiological features could prognosticate EGFR mutation status. Unfortunately, the inconsistent results and a small portion of resistance mutation in exon 20 limit the clinical practice. If the clinicoradiological predictors of EGFR exon 19 or 21 mutation are determined, TKI treatment can be provided for patients with non-resectable lung cancer. Therefore, in this retrospective study, clinicopathological and radiological characteristics analysis was performed to determine the independent predictors of EGFR exon 19 and 21 mutation of lung adenocarcinomas in a Chinese cohort.

Materials and methods

Patients

The study population was selected retrospectively from patients who underwent surgical resection and had histologically confirmed lung adenocarcinoma in (Tianjin Medical University Cancer Institute and Hospital) between October 2015 and January 2017. A total of 524 patients initially were included according to the following inclusion criteria: (a) available preoperative thin-section CT images from the picture archiving and communication system; (b) available test results for EGFR mutation status; (c) available clinical and pathological data (age, gender, smoking status, and stage and histology subtype of lung adenocarcinoma). Smoking status was categorised into two groups: non-smokers and smokers, which included former and current smokers. The tumour stage was classified according to the new 8th lung cancer TNM classification and staging system.[15] Exclusion criteria included: (a) difficulty in defining the contour of the tumour margin on the CT images (n=8); (b) patients who received preoperative treatment, such as radiation therapy or chemotherapy (n=15); (c) the interval between CT and subsequent surgery exceeded 1 month (n=26); (d) dual mutations of the EGFR gene (n=4). Finally, a total of 471 patients were identified and subsequently used to analyse for any associations between clinicoradiological characteristics and EGFR mutation status. The institutional review board approved this retrospective study and waived the informed consent requirement.

Histopathology evaluation and EGFR mutation analysis

Tumours were diagnosed as adenocarcinoma and categorised according to the 2015 World Health Organization (WHO) classification system,[16] each component was documented with the form of frequency when patterns presented >5%. EGFR mutation status was examined with polymerase chain reaction-based amplification refractory mutation system (ARMS) by using the Human EGFR Gene Mutations Detection Kit (Beijing ACCB Biotech, Beijing, China). All medical records were reviewed to extract the patients' demographics and histopathology information as well as EGFR mutation status, which are listed in Table 1.

CT protocol

Chest CT examinations were performed using three multidetector CT systems (Somatom Sensation 64, Siemens,

Table 1
Clinical characteristics of all patients.

Variable	All (n=471)	Percentage
Age (years)	58.9 (±8.44)	
Sex		
Male	213	45.2%
Female	258	54.8%
Smoking history		
Yes	206	43.7%
No	265	56.3%
Histological subtype		
Acinar	344	73%
Lepidic	196	41.6%
Papillary	130	27.6%
Micropapillary	233	49.5%
Solid	142	30.1%
Variants of invasive	31	6.6%
MIA	7	1.5%
Other	2	0.4%
Stage		
I	276	58.6%
II	37	7.9%
III	127	27%
IV	31	6.6%
EGFR mutation status		
EGFR-	219	46.5%
EGFR+	252	53.5%
Exon 18	7	2.8%
Exon 19	115	45.6%
Exon 20	7	2.8%
Exon 21	123	48.8%

Data for age is mean±standard deviation.
Other histological subtype included one case of enteric adenocarcinoma and one case of adenocarcinoma in situ.
MIA, minimally invasive adenocarcinoma; EGFR, epidermal growth factor receptor.

Erlangen, Germany; Lightspeed16, GE Healthcare, Milwaukee, WI, USA; Discovery CT750 HD, GE Healthcare) with the following parameters: (a) 120 kVp with tube current adjusted automatically and 1.5 mm reconstruction thickness with a 1.5 mm reconstruction interval for the 64-detector scanner and (b) 120 kVp, 150–200 mA, and 1.25 mm reconstruction thickness with a 1.25 mm reconstruction interval for the other two scanners. Four hundred and thirty-three of the 471 patients underwent contrast-enhanced CT. Non-ionic iodinated contrast material (300 mg of iodine per millilitre, Ul-travist; Bayer Pharma, Berlin, Germany) was injected at a dose of 1.3–1.5 ml/kg body weight at a rate of 2.5 ml/s using an automated injector. CT-enhanced scanning was performed with a 70-second delay.

CT image interpretation

A clinical radiologist with 5 years of experience (F.Z.) in chest CT diagnosis and another radiologist with 3 years of experience (Y.Z.) independently interpreted the CT images retrospectively after training. Both radiologists were blinded to the clinical and histological findings. When their interpretations of the CT images differed, discussion was conducted in a group of three (a senior radiologist [Y.L.] was involved) to reach a final consensus. The CT descriptors were shown in Table 2. All of the CT images were read with both lung (width, 1,500 HU; level, −600 HU) and mediastinal (width, 350 HU; level, 40 HU) window settings. All the CT descriptors were evaluated on the multiplanar reconstructed images and reported with a standardised scoring sheet. Four hundred and thirty-three patients underwent contrast-enhanced CT, of which 51 patients were excluded because of pure ground-glass opacity lesions or difficulty in CT attenuation value measurement when evaluating the three enhanced descriptors. CT attenuation was measured by placing a region of interest as large as possible and avoiding the air-containing space within the confines of the tumour.

Statistical analysis

All statistical analyses were performed using Medcalc 15.6.1 and SPSS 19.0. The mean values and standard deviations were expressed for continuous variables (age, maximum diameter, and enhancement degree), and frequency or percentage for categorical variables. Inter-reader agreement for CT features was assessed by percent of concordant cases and kappa of agreement, with 95% confidence intervals (CI). Univariate analysis was used to assess the association between clinicoradiological features with EGFR mutation status. The non-parametric two-sample Wilcoxon test was used for the order variables and continuous variables, and chi-square test or Fisher's test for categorical variables. Subsequently, multivariate analysis was performed to calculate the odds ratios (OR) with 95% CI through a logistic regression model with backward stepwise selection of variables. Receiver operating characteristic (ROC) curves were drawn for EGFR mutation according to their significant characteristics, and the corresponding AUC value was calculated. Two areas under the ROC curve (AUCs) were compared with the non-parametric approach of DeLong, DeLong, and Clarke–Pearson. A p-value of <0.05 was considered statistically significant.

Results

Reader reproducibility

Agreement among the two readers was good. The intraclass correlation coefficient for maximum diameter, degree of enhancement, and relative enhancement was 0.92 (range, 0.90–0.94), 0.81 (range, 0.78–0.84) and 0.75 (range, 0.71–0.80), respectively.

Patient demographics and EGFR mutation status

All of the study populations were ethnically Asian, and 213 (45.2%) men and 258 (54.8%) women were included, with an average age of 58.9 years (±9.69). Most of the tumours were in stage I (276, 58.6%). The most common histology subtype was the acinar pattern (344 of 471 [73%]), followed by micropapillary and lepidic patterns (233 of 471 [49.5%] and 196 of 471 [41.6%], respectively). In tumours with EGFR mutations (252 of 471 [53.5%]), exon 19 and 21 mutations were the most common mutation subtypes,

Table 2
CT characteristics for lung adenocarcinoma.

Characteristic	Definition	Scoring and definition
Distribution	Central or peripheral location	1, central; 2, peripheral
Lobe location	Lobe location	1, right upper lobe; 2, right middle lobe; 3, right lower lobe; 4, left upper lobe; 5, left lower lobe; 6, mixed lobe
Maximum diameter	The greatest dimension on the multiplanar reconstructed images with a lung window	cm
Contour	The overall shape of roundness	1, round; 2, oval; 3, somewhat irregular; 4, irregular
Lobulation	A wavy or scalloped configuration of tumour's surface	0, none; 1, slight lobulation; 2, obvious lobulation
Spiculation	Lines radiating from the margins of the tumour	0, absence; 1, presence
Texture	Solid or GGO	0, pure GGO; 1, mixed GGO with solid part <50%; 2, mixed GGO with solid part >50%; 3, solid
Calcification	Any patterns of calcification in the tumour	0, absence; 1, presence
Air bronchogram	Tube-like or branched air structure within the tumour	0, absence; 1, presence
Bubble-like lucency	Air space in the tumour with diameter ≤5 mm at the time of diagnosis prior to biopsy or treatment	0, absence; 1, presence
Cavity	Air space in the tumour with diameter >5 mm at the time of diagnosis prior to biopsy or treatment	0, absence; 1, presence
Enhancement degree	Enhancement degree= A_{post} - A_{pre}, where A_{pre} and A_{post} is unenhanced and contrast-enhanced CT attenuation of tumour, respectively	Hu
Enhancement heterogeneity	Heterogeneity of tumour on contrast-enhanced images	1, homogeneous; 2, slight or moderate heterogeneous; 3, marked heterogeneous
Relative enhancement	Relative enhancement $E_{rel} = (A_{post} - A_{pre})/E_{art}$, where E_{art} is enhancement attenuation of the artery on the same section	%
Pleural attachment	Tumour attaches to the fissure/Pleura	0, absence; 1, presence
Pleural retraction	Retraction of the pleura toward the tumour	0, absence; 1, presence
Vascular convergence	Convergence of vessels to the tumour	0, no significant convergence; 1, obvious convergence
Peripheral emphysema	Peripheral emphysema caused by the tumour or pre-existing emphysema	0, absence; 1, slight or moderate; 2, severe
Peripheral fibrosis	Peripheral fibrosis caused by the tumour or pre-existing fibrosis	0, absence; 1, slight or moderate; 2, severe
Nodules in primary tumour lobe	Any non-calcified nodules suspected to be malignant or indeterminate	0, absence; 1, presence
Nodules in non-tumour lobes	Any non-calcified nodules suspected to be malignant or indeterminate	0, absence; 1, presence
Lymphadenopathy	Thoracic lymph nodes (hilar or mediastinal) with short-axis diameter greater than 1 cm	0, absence; 1, presence
Pleural effusion of tumour side	Pleural effusion seen in the tumour side of the thoracic cavity	0, absence; 1, presence
Pleural effusion of non-tumour side	Pleural effusion seen in the non-tumour side of the thoracic cavity	0, absence; 1, presence

CT, computed tomography; GGO, ground-glass opacity.

accounting for 45.6% (115 of 252) and 48.8% (123 of 252), respectively.

Correlation of EGFR mutation status with clinical features

Associations between clinical characteristics and EGFR mutation status are presented in Table 3. The EGFR mutation rate was significantly higher in women than in men (162/258, 62.8% versus 90/213, 42.3%; OR, 2.31, 95% CI: 1.59, 3.34; $p<0.001$). Significantly more non-smokers (175/265, 66%) harboured EGFR mutations than smokers (77/206, 37.4%; OR, 3.26, 95% CI: 2.23, 4.76; $p<0.001$). Considering tumour histology subtype, more lepidic (129/252, 49.6%) and micropapillary pattern tumours (138/252, 54.8%) were observed in EGFR mutant tumours compared with EGFR wild-type tumours (67/219, 30.6%; OR, 2.38, 95% CI: 1.63, 3.48; $p<0.001$ for lepidic pattern and 95/219, 43.4%; OR, 1.58, 95% CI: 1.10, 2.28; $p=0.014$ for micropapillary pattern), while a significantly lower frequency of the solid pattern was observed in the EGFR mutant group (48/252, 19%) compared to wild-type group (94/219, 41.9%) with an OR of 0.31 (95% CI: 0.21, 0.49; $p<0.001$). No significant association was observed between mean age and cancer stage with EGFR mutation status ($p=0.771$; $p=0.388$).

Correlation of EGFR mutation status with radiological features

Univariate analysis (Table 4) revealed that 11 CT features were associated with EGFR mutation status, including maximum diameter ($p<0.001$), pleural retraction ($p<0.001$), vascular convergence ($p<0.001$), peripheral emphysema ($p<0.001$), peripheral fibrosis ($p<0.001$), lobulation ($p=0.004$), spiculation ($p=0.037$), texture ($p<0.001$), air bronchogram ($p=0.016$), cavity ($p=0.001$), and enhancement heterogeneity ($p=0.005$). The maximum diameter of the tumour in EGFR mutant group was significantly smaller than that in wild-type group, with an OR of

Table 3
Association between clinical characteristics with EGFR mutation status.

Variable	Wild-type mutations	EGFR mutations	*p*-Value	Univariate OR (95% CI)
Number	219	252		
Age (years)	58.93 (±8.95)	58.89 (±7.97)	0.771	
Sex				
Male	123	90	<0.001	Reference
Female	96	162	…	2.31 (1.59, 3.34)
Smoking history	129	77	<0.001	Reference
Yes	90	175	…	3.26 (2.23, 4.76)
No				
Histological	153	191	0.148	
Subtype	67	129	<0.001	2.38 (1.63, 3.48)
Acinar	59	71	0.765	
Lepidic	95	138	0.014	1.58 (1.10, 2.28)
Papillary	94	48	<0.001	0.31 (0.21, 0.47)
Micropapillary	17	14	0.335	
Solid	4	3	0.851	
Variants of invasive	1	1	…	
MIA	121		0.388	
Other	22	156	…	
Stage	66	15	…	
I	10	60	…	
II		21		
III				
IV				

Data for age is mean±standard deviation.
EGFR, epidermal growth factor receptor; OR, odds ratio; CI, confidence interval; MIA, minimally invasive adenocarcinoma.

0.82 (95% CI: 0.70, 0.97). Tumours with pleural retraction (OR, 2.26; 95% CI: 1.44, 3.53), vascular convergence (OR, 4.20; 95% CI: 2.79, 6.32), spiculation (OR, 1.50; 95% CI: 1.02, 2.19), air bronchogram (OR, 1.69; 95% CI: 1.10, 2.58), ground-glass opacity (level 0: OR, 2.39, 95% CI: 0.80, 7.15; level 1: OR, 3.34, 95% CI: 1.57, 7.12; level 2: OR, 2.61, 95% CI: 1.63, 4.19), and marked heterogeneous enhancement (OR, 1.88; 95% CI: 1.21, 2.93) were more frequently in EGFR mutant group. Tumours with peripheral emphysema (level 1: OR, 0.40, 95% CI: 0.21, 0.75; level 2: OR, 0.07, 95% CI: 0.02, 0.28), peripheral fibrosis (level 1: OR, 0.11, 95% CI: 0.03, 0.36; level 2: OR, 0.20, 95% CI: 0.02, 1.76), lobulation (level 1: OR, 0.87, 95% CI: 0.55, 1.37; level 2: OR, 0.52, 95% CI: 0.34, 0.80), or cavity (OR, 0.48; 95% CI: 0.25, 0.92) were found more frequently among tumours with EGFR wild-type. No significant association was observed between EGFR mutation status and other CT features. For the model with both clinical variables and radiological features, the significantly independent predicted factors of harbouring EGFR mutation were small maximum diameter (cut-off value of 3.9 cm), non-smokers, micropapillary pattern, absence of solid pattern, pleural retraction, and vascular convergence when adjusting for lepidic pattern and peripheral emphysema via multivariable logistic regression analysis (Table 5). The AUC significantly increased to 0.784, compared with 0.706 when clinical features (independent predicted factors: non-smoking history, lepidic pattern and absence of solid pattern) were used alone ($p<0.001$; Fig 1).

Univariate analysis of EGFR exon 19 and 21 mutation

One hundred and fifteen patients (mean age 58.79±7.95 years; M:F = 45:70) exhibited the EGFR mutation in exon 19, and 123 patients (mean age 59.07±7.99 years; M:F = 42:81) exhibited the EGFR mutation in exon 21. As shown in Tables 6 and 7, univariate analysis revealed that 13 features, including gender ($p=0.003$), smoking history ($p<0.001$), lepidic pattern ($p=0.028$), solid pattern ($p<0.001$), maximum diameter ($p<0.001$), pleural retraction ($p=0.006$), vascular convergence ($p<0.001$), peripheral emphysema ($p=0.001$), peripheral fibrosis ($p=0.001$), lobulation ($p=0.009$), texture ($p=0.001$), cavity ($p=0.039$), and enhancement heterogeneity ($p=0.002$), could be used to identify the EGFR exon 19 mutation. For patients with EGFR exon 21 mutation, gender ($p<0.001$), smoking history ($p<0.001$), lepidic pattern ($p<0.001$), micropapillary pattern ($p=0.024$), solid pattern ($p<0.001$), maximum diameter ($p<0.001$), pleural retraction ($p=0.004$), vascular convergence ($p<0.001$), peripheral emphysema ($p<0.001$), peripheral fibrosis ($p<0.001$), lobulation ($p=0.023$), spiculation ($p=0.037$), texture ($p<0.001$), and air bronchogram ($p=0.016$) exhibited significant difference compared with EGFR wild-type. The frequency of lepidic growth pattern in exon 21 mutant tumours was significantly higher ($p=0.010$) than that in exon 19 mutant tumours; however, a statistically significant difference for other radiological features was not observed.

Multivariable analyses and ROC curve analysis for EGFR exon 19 and 21 mutations

Multivariable logistic regression analysis (Table 5) indicated that non-smokers, absence of solid pattern, and vascular convergence were important independent predictors of the EGFR mutation in exon 19, when adjusting for maximum diameter and pleural retraction. The AUC significantly increased to 0.807, compared with 0.685 when clinical features (independent predicted factors: non-

Table 4
Association between CT features with EGFR mutation status.

Variable	Wild-type mutations	EGFR mutations	*p*-Value	Univariate OR (95%CI)
Number	219	252		
Maximum diameter (cm)	3.67 (±1.85)	2.94 (±1.26)	<0.001	0.82 (0.70, 0.97)
Pleural retraction				
0	64	39	<0.001	Reference
1	155	213	…	2.26 (1.44, 3.53)
Vascular convergence				
0	173	119	<0.001	Reference
1	46	133	…	4.20 (2.79, 6.32)
Peripheral emphysema				
0	168	234	<0.001	Reference
1	29	16	…	0.40 (0.21, 0.75)
2	22	2	…	0.07 (0.02, 0.28)
Peripheral fibrosis				
0	193	248	<0.001	Reference
1	22	3	…	0.11 (0.03, 0.36)
2	4	1	…	0.20 (0.02, 1.76)
Lobulation				
0	77	114	.004	Reference
1	56	72	…	0.87 (0.55, 1.37)
2	86	66	…	0.52 (0.34, 0.80)
Spiculation				
0	87	77	.037	Reference
1	132	175	…	1.50 (1.02, 2.19)
Texture				
0	5	10	<0.001	2.39 (0.80, 7.15)
1	10	28	…	3.34 (1.57, 7.12)
2	32	70	…	2.61 (1.63, 4.19)
3	172	144	…	Reference
Air bronchogram				
0	175	177	.016	Reference
1	44	75	…	1.69 (1.10, 2.58)
Cavity				
0	192	236	.025	Reference
1	27	16	…	0.48 (0.25, 0.92)
Enhancement heterogeneity[a]				
1	0	0	.005	
2	70	46	…	Reference
3	119	147	…	1.88 (1.21, 2.93)

Data for maximum diameter is mean±standard deviation.
CT, computed tomography; EGFR, epidermal growth factor receptor; OR, odds ratio; CI, confidence interval.
[a] Enhancement heterogeneity was evaluated in 382 patients.

smoking history and absence of solid pattern) were used alone ($p<0.001$). Subsequent another multivariate analysis indicated that non-smokers and vascular convergence were important independent predictors of the EGFR mutation in exon 21, when adjusting for lepidic pattern, solid pattern, and maximum diameter. The AUC value significantly increased to 0.794, compared with 0.720 when clinical features (independent predicted factors: non-smoking history, lepidic pattern, and absence of solid pattern) were used alone ($p<0.001$; Fig 2).

Discussion

The incidence of EGFR mutation in this cohort was 53.5%. As expected, EGFR mutations were more common in female patients and non-smokers; however, no correlation was observed between age and tumour stage with EGFR mutation status, which was consistent with most studies.[17–19]

Previous studies[20,21] have reported correlations between histology predominant subtypes and EGFR mutation status in patients with lung adenocarcinoma. In the 2015 WHO classification, the term “predominant" was not listed for the description of the major adenocarcinoma subtypes as it was in 2011 IASLC/ATS/ERS lung adenocarcinoma classification.[16] Therefore, any analyses based on the predominant component may not adequately determine the pathological features of the EGFR mutation. In the current study, each histology subtype was documented with the form of frequency when patterns presented >5% of the tumour. As a result, lepidic pattern and micropapillary pattern were found more commonly in adenocarcinomas with EGFR mutations, while the solid pattern was more common in those with EGFR wild-type mutations. A previous study[22] documented each component by making a semi-quantitative estimate of different histological patterns present in 5% increments and confirmed that lepidic and acinar patterns were more common in tumours with EGFR

Table 5
Multivariable logistic regression analysis of CT features combined with clinical variables predicting the presence of EGFR mutation in lung adenocarcinoma.

Variable	EGFR mutations		EGFR 19 mutations		EGFR 21 mutations	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Sex	NA	NA	NA	NA	NA	NA
Smoking history						
0	2.62 (1.65, 4.16)	<0.001	3.59 (2.05, 6.26)	<0.001	2.03 (1.15, 3.56)	0.014
1	Reference	…	Reference	…	Reference	…
Lepidic						
0	Reference	…	NA	NA	Reference	…
1	1.19 (0.74, 1.92)	0.465			1.68 (0.96, 2.95)	0.070
Micropapillary						
0	Reference	…	NA	NA	NA	NA
1	1.63 (1.04, 2.54)	0.034				
Solid						
0	1.70 (1.01, 2.86)	0.045	1.89 (1.01, 3.52)	0.046	1.73 (0.89, 3.33)	0.104
1	Reference	…	Reference	…	Reference	…
Maximum diameter	0.82 (0.70, 0.97)	0.020	0.82 (0.68, 1.00)	0.050	0.85 (0.68, 1.01)	0.142
Pleural retraction						
0	Reference	…	Reference	…	NA	NA
1	1.78 (1.02, 3.13)	0.044	1.53 (0.78, 3.01)	0.218		
Vascular convergence						
0	Reference	…	Reference	…	Reference	…
1	3.89 (2.44, 6.21)	<0.001	5.18 (2.94, 9.17)	<0.001	3.29 (1.85, 5.85)	<0.001
Peripheral emphysema						
0	Reference	…	NA	NA	NA	NA
1	0.33 (0.06, 1.76)	0.194				
2	0.53 (0.09, 3.13)	0.484				
Peripheral fibrosis	NA	NA	NA	NA	NA	NA
Lobulation	NA	NA	NA	NA	NA	NA
Spiculation	NA	NA	NA	NA	NA	NA
Texture	NA	NA	NA	NA	NA	NA
Air bronchogram	NA	NA	NA	NA	NA	NA
Cavity	NA	NA	NA	NA	NA	NA
Enhancement heterogeneity	NA	NA	NA	NA	NA	NA

CT, computed tomography; EGFR, epidermal growth factor receptor; CI, confidence interval; NA, not applicable (variables that were not included in the equation of multivariate logistic regression analysis with backward stepwise selection).

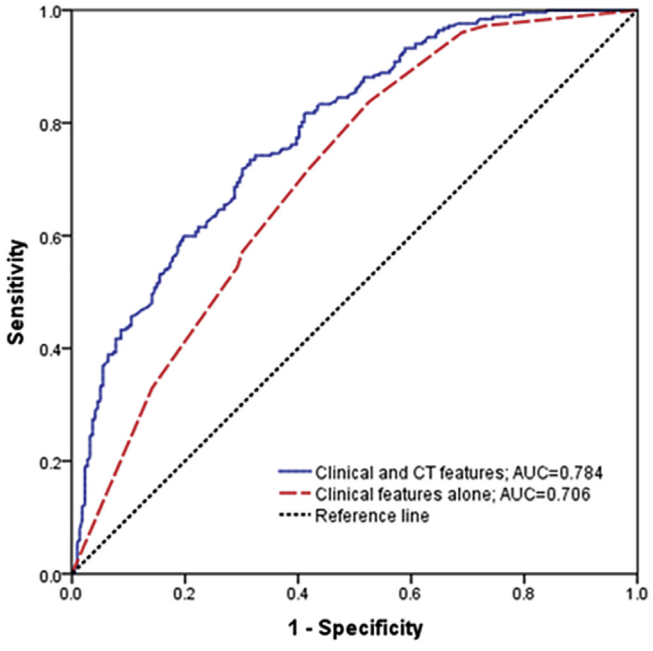

Figure 1 ROC curves were used to predict EGFR mutation status with clinical variables alone and combined with CT features.

mutations compared to those with ALK rearrangements; however, it is not enough to identify mutation status through histological features alone due to intratumoural heterogeneity.

The associations between EGFR mutation status and CT features have been reported by many articles; however, the results were not exactly the same. For example, Rizzo *et al.*[13] revealed that EGFR mutation status was associated with small lesion size, air bronchogram, pleural retraction, and absence of fibrosis. This result was consistent with another study,[23] which discovered a significant correlation between small lesion size and air bronchogram with EGFR mutation in lung adenocarcinomas; however, Zhou *et al.*[24] reported that no statistically significant difference was observed between CT features and EGFR mutation status. In the current study, 24 detailed CT descriptors were quantified and 11 of them were found to be associated with EGFR mutation status. The results were consistent with the findings of previous studies,[13,22] while contrary to the findings of Zhou *et al.*[23] The conflicting results might be caused by the differences in research design and grouping method, as well as the mixed mutation subtypes.

Classically, several mutation subtypes are described in the EGFR gene of exons 18 to 21. The most common are deletion mutation in exon 19 (45–50%) and point mutation

Table 6
Association between clinical characteristics with EGFR 19/21 mutations.

Variable	Wild-type mutations	EGFR 19 mutations	*p*-Value[a]	EGFR 21 mutations	*p*-Value[b]
Number	219	115		123	
Age (years)	58.93 (±8.95)	58.79 (±7.95)	0.657	59.07 (±7.99)	0.938
Sex					
Male	123	45	0.003	42	<0.001
Female	96	70	…	81	…
Smoking history					
Yes	129	35	<0.001	40	<0.001
No	90	80	…	83	…
Histological subtype					
Acinar	153	86	0.344	95	0.143
Lepidic	67	49	0.028	73	<0.001
Papillary	59	34	0.611	32	0.853
Micropapillary	95	59	0.167	69	0.024
Solid	94	24	<0.001	22	<0.001
Variants of invasive	17	10	0.766	4	0.152
MIA	4	2	1.000	0	0.301
Other	1	0	…	1	…
Stage					
I	121	67	0.961	80	0.206
II	22	10		5	
III	66	25		30	
IV	10	13		8	

Data for age are mean ± standard deviation.
EGFR, epidermal growth factor receptor; MIA, minimally invasive adenocarcinoma.
[a] Based on comparison between the EGFR exon 19 mutation group with the wild-type group.
[b] Based on comparison between the EGFR exon 21 mutation group with the wild-type group.

in exon 21 (45–50%), both of which are responsive to targeted therapies.[6] The most common resistance mutation is T790M mutation in exon 20, accounting for approximately 60% of EGFR TKI resistance mutation, which is responsive to the third-generation inhibitor[25]; however, the insertion of exon 20 is also a driver mutation, which cannot be inhibited by any available TKIs.[26] Therefore, identifying the EGFR mutation subtype, especially those responsive to TKI treatment, seems to be more critically important than just predicting EGFR mutation status. In addition, several articles[8,9] reported that NSCLC patients with exon 19 deletion appeared to have longer PFS compared with patients with the exon 21 L858R mutation after the first-line treatment of TKIs.

Therefore, EGFR mutation subtypes should be considered when making treatment decisions for EGFR mutation-positive NSCLC patients. In the current study, the differences between EGFR mutation subtypes and EGFR wild-type mutations were investigated and it was discovered that EGFR exon 19 and 21 mutations were associated with 13 and 14 clinicoradiological features, respectively. The present results were consistent with the findings of Shi *et al.*[27] Multivariate regression analysis indicated that the independent predictors of the exon 19 mutation were non-smokers, with absence of the solid pattern and vascular convergence, the area AUC was 0.807; non-smokers and vascular convergence were the independent predictors of the exon 21 mutation, the AUC value was 0.794. The prediction efficiency was improved compared with the AUC value of 0.774 for all mixed mutation subtypes. Thus, analysis of a specific EGFR mutation subtype seems to be more scientific than comparing mixed mutation subtypes with the wild type. Of course, this conclusion needs to be confirmed by a study with larger sample size. Vascular convergence was found to be a significant predictor of EGFR mutations, which was consistent with previous studies.[13,14] Vascular convergence is one of the characteristic manifestations of lung cancer, and manifests as one or several thickened pulmonary vessels pulled to the lesion and then interrupting or penetrating the lesion on CT images (Fig 3).

In addition, an attempt was made to compare the features between exon 19 and 21 mutant groups and it was discovered that only the lepidic growth pattern presented a statistically significant difference. The frequency of the lepidic growth pattern in the exon 21 mutant group was higher than that in the exon 19 mutant group. This is supported by a previous study,[28] which indicated that EGFR exon 21 mutations were significantly more common in patients with lepidic predominant adenocarcinoma. Another study[29] reported that EGFR exon 21 mutations were usually associated with the lepidic growth pattern, while EGFR exon 20 mutations were associated with the solid growth pattern. Differences in the histopathology of EGFR mutation subtypes might explain the conflicting outcomes in previous studies. No statistically significant difference in CT features between exon 19 and 21 mutations was observed in the present study, which is consistent with the findings of Zou *et al.* and Hong *et al.*,[21,30] suggesting the difficulty in discrimination EGFR exon 19 and 21 mutations via CT images. Therefore, in non-smokers and tumours with vascular convergence, the presence of lepidic and micropapillary patterns, spiculation, or air bronchogram might indicate an EGFR exon 21 mutation; while tumours with marked heterogeneous enhancement or absence of a cavity

Table 7
Association between CT features with EGFR mutation subtype.

Variable	Wild-type mutations	EGFR 19 mutations	*p*-Value[a]	EGFR 21 mutations	*p*-Value[b]
N	219	115		123	
Maximum diameter (cm)	3.67 (±1.85)	2.91 (±1.31)	<0.001	2.97 (±1.23)	<0.001
Pleural retraction					
0	64	18	0.006	19	0.004
1	155	97	…	104	…
Vascular convergence					
0	173	49	<0.001	63	<0.001
1	46	66	…	60	…
Peripheral emphysema					
0	168	104	0.001	117	<0.001
1	29	10	…	6	…
2	22	1	…	0	…
Peripheral fibrosis					
0	193	113	0.001	122	<0.001
1	22	2	…	1	…
2	4	0	…	0	…
Lobulation					
0	77	56	0.009	52	0.023
1	56	28	…	41	…
2	86	31	…	30	…
Spiculation					
0	87	37	0.175	35	0.037
1	132	78	…	88	…
Texture					
0	5	4	0.001	6	<0.001
1	10	13	…	12	…
2	32	26	…	42	…
3	172	72	…	63	…
Air bronchogram					
0	175	83	0.109	84	0.016
1	44	32	…	39	…
Cavity					
0	192	109	0.039	113	0.230
1	27	6	…	10	…
Enhancement heterogeneity					
1	0	0	0.002	0	0.184
2	70	18	…	28	…
3	119	74	…	67	…

Data for maximum diameter is mean ± standard deviation.
CT, computed tomography; EGFR, epidermal growth factor receptor.
[a] Based on comparison between the EGFR exon 19 mutation group with the wild-type group.
[b] Based on comparison between the EGFR exon 21 mutation group with the wild-type group.

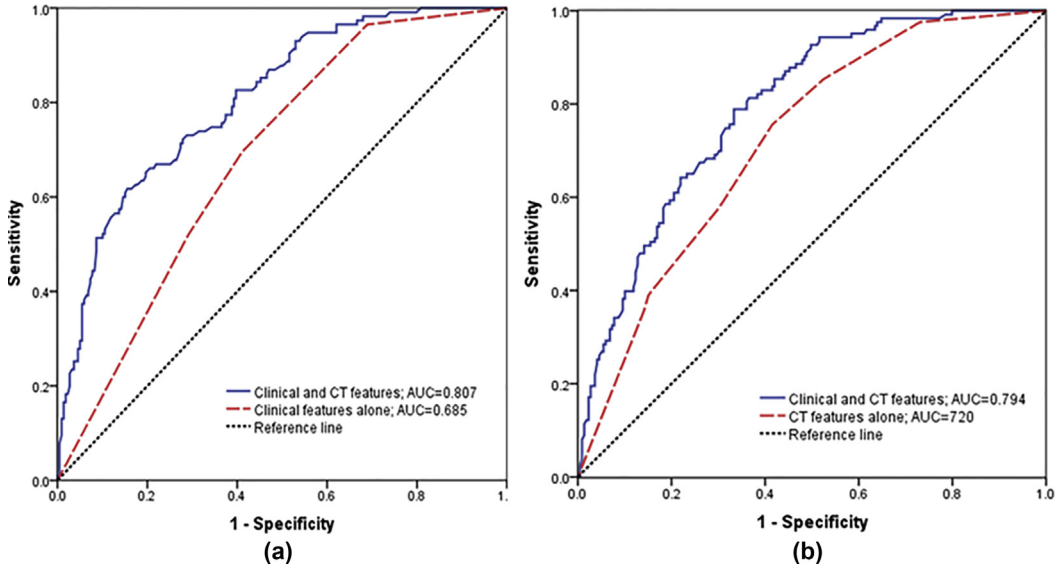

Figure 2 ROC curves were used to predict the EGFR exon 19 mutation (a) and exon 21 mutation (b) with clinical variables alone and combined with CT features.

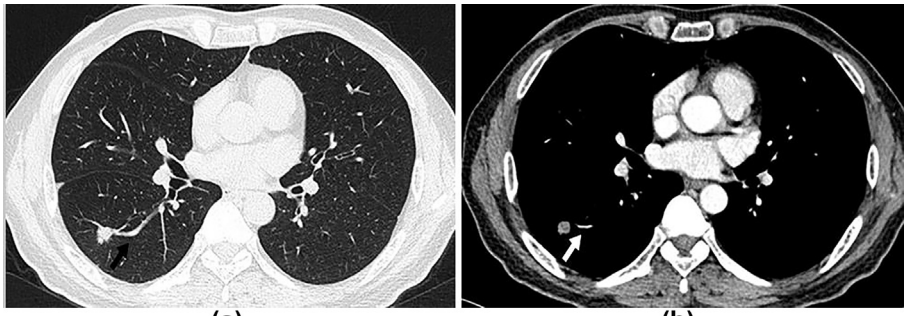

Figure 3 CT images of a 48-year-old man with EGFR exon 19 mutation lung adenocarcinoma. (a) CT lung window image shows that a thickened pulmonary vessel is pulled and then cut off by the lesion (arrow). (b) Enhanced CT image shows thickened enhanced blood vessels (arrow).

might harbour the EGFR exon 19 mutation, which could better benefit from TKI treatment.

In the current study, routine CT features were used to identify the association with EGFR mutation subtypes. If useful predictors can be determined, patients may benefit from TKI treatment especially those with unresectable lung cancer. The CT-based risk model can also provide clinicians with additional information on whether or not a re-biopsy of an EGFR mutation-negative patient is required.

Several limitations exist in the present study. First, the study was retrospective, limited to only Eastern Asian populations. Second, only adenocarcinoma confirmed by surgical resection was analysed; other histology subtypes were not included. Third, patients with EGFR exon 18 and 20 mutations were not analysed separately in the present study, which will need a larger patient cohort for confirmation. Future research will reveal the relationship between EGFR mutation subtypes with treatment options, PFS or overall survival, as well as looking for quantitative radiological features that can accurately predict EGFR mutations.

In conclusion, clinical and radiological analysis of EGFR mutation status revealed that the combination of CT imaging characteristics with clinical variables can be used to predict EGFR mutation status. The separate study of EGFR mutation subtypes, including exon 19 (independent predictors: non-smokers, absence of solid pattern, and vascular convergence) and exon 21 (non-smokers and vascular convergence) can further improve diagnostic performance.

Conflict of interest

The authors declare no conflict of interest.

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