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Computed tomography and clinical features associated with epidermal growth factor receptor mutation status in stage I/II lung adenocarcinoma

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Abstract

Background: The relationship between epidermal growth factor receptor (EGFR) gene mutation status, preoperative computed tomography (CT), and clinical features in patients with small peripheral lung adenocarcinoma (<3 cm) was investigated.

Methods: We included 209 patients who underwent surgical resection for stage I or II lung adenocarcinoma at Nanjing General Hospital between December 2010 and May 2016. 171 cases of patients underwent a pretreatment chest CT. Eleven different CT descriptors were assessed. Multiple logistic regression analyses were performed to identify independent risk factors for the prediction of EGFR mutation. Receiver operating characteristic analysis was used to evaluate the performance of the logistic regression model.

Results: EGFR mutation was determined in 126 patients (60.3%) and appeared more frequently in women ($P = 0.025$), never-smokers ($P < 0.001$), and patients with a carcinoembryonic antigen level <2.6 ng/ml ($P = 0.045$). Papillary predominant adenocarcinomas ($P = 0.014$), intermediate/low pathologic grade tumors ($P = 0.003$), tumors in the upper lobe ($P = 0.028$), and showing ground-glass opacity (GGO) or mixed GGO on CT ($P = 0.039$) also more frequently harbored EGFR mutations. GGO on CT, acinar or papillary predominant adenocarcinoma, and non-smoker were identified in multivariable analyses as significantly independent risk factors. The multiple logistic regression model showed high predictive power for identifying EGFR mutations. The CT features were similar between the L858R and 19 deletion mutations.

Conclusions: Combined CT and clinical features may be helpful for determining the presence of EGFR mutations in patients with small peripheral lung adenocarcinoma, particularly in patients where mutational profiling is not available or possible.

Introduction

Lung cancer is one of the leading causes of death in the world. About 85% of all lung cancers are non-small cell lung carcinoma (NSCLC), and adenocarcinoma is the most common histologic subtype.[1] Epidermal growth factor receptor (EGFR) mutations are associated with high sensitivity to EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib.[2] Targeted therapies have significantly improved the survival rates of lung cancer patients harboring EGFR mutations. Determining the EGFR mutation status of patients is therefore crucial for the prediction of response to EGFR-TKIs and, thereby, choice of treatment regime. However, not all patients can undergo analysis for EGFR mutation status.

Although stage I NSCLC patients have a better prognosis, with five-year survival rates ranging from 40% to 90%, nearly 30–35% will relapse.[3,4] The American Society of Pathology (CAP), the International Society for Lung Cancer Research (IASLC), and the American Society for Molecular Pathology (AMP) released a guideline for lung cancer gene testing, which recommends that patients with advanced lung cancer or those with disease recurrence or progression should be assessed for EGFR mutation status.[5] Most early stage NSCLC patients only undergo surgical resection, and while the guidelines encourage EGFR status testing in such patients, they do not directly recommend testing. Computed tomography (CT) imaging is routinely used in lung cancer. Finding specific CT features that are associated with EGFR mutation might improve treatment and care for early stage NSCLC patients who for various reasons cannot undergo genetic mutation analysis.

Previous studies that have evaluated the relationship between some CT features and EGFR genetic mutations in NSCLC[6–10] have mainly focused on patients with advanced adenocarcinomas (stages IIIB and IV), and only a few have investigated the correlation between CT features and EGFR mutation status in stage I or II adenocarcinoma patients.[6,11]

This might be because EGFR mutation status is not routinely analyzed in early stage lung adenocarcinoma. In this study, we retrospectively surveyed the EGFR mutation status of stage I/II lung adenocarcinoma patients with tumor lesions <3 cm. The aim of the present study was to identify the relationship between EGFR mutation status, clinical features, and CT characteristics in surgically resected lung adenocarcinomas in a cohort of Chinese patients.

Methods

Patient selection

The study population was retrospectively selected from patients who underwent surgical resection of their lung adenocarcinoma at Nanjing General Hospital between December 2010 and May 2016. All medical records were reviewed to extract the patients' clinical characteristics. Their EGFR mutation status was recorded. A total of 827 patients were identified. Patients who did not undergo EGFR mutation testing ($n = 465$); were pathologically diagnosed with stage III/IV lung cancer ($n = 52$); with a tumor >3 cm ($n = 41$); and who received preoperative treatment, such as radiation therapy or chemotherapy ($n = 60$), were excluded. Finally, the data of 209 patients was analyzed for any association between clinical characteristics and EGFR mutation status. Of the 209 patients, 171 underwent chest CT and were analyzed for an association between CT characteristics and EGFR mutation status. The study design was approved by the ethics committee of

Nanjing General Hospital, who waived the need for informed consent because of the non-invasive nature of the study and patient anonymity.

Computed tomography (CT) scanning protocol and image interpretation

All evaluations were performed using a multi-slice CT scanner (Somatom Sensation 64, Siemens, Erlangen, Germany). Scanning parameters were: tube voltage 120 kVp, tube current 150–200 mA, rotation time 0.5 seconds, and 2 mm reconstruction thickness with a 1 mm reconstruction interval. Two radiologists with 15 and 20 years' experience in chest image interpretation assessed CT images using both mediastinal (width, 360 HU; level, 60 HU) and lung window settings (width, 1600 HU; level, −600 HU). The radiologists were blinded to the pathological findings. When their interpretations of the CT images differed, discussion was conducted to reach a final consensus. Each CT corresponded to a single patient, and data were recorded on an Excel spreadsheet (Microsoft Office Excel 2007, Richmond, VA, USA).

The CT descriptors that were assessed are shown in Table S1.

Histologic evaluation and epidermal growth factor receptor (EGFR) mutation analysis

Adenocarcinoma was classified according to the 2011 IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification system. DNA was extracted from five pieces of formalin-fixed, paraffin-embedded tumor tissue using the QIAamp FFPE Tissue Kit (Qiagen, Valencia, CA, USA). Molecular analysis of the mutation status of EGFR exons 18, 19, 20, and 21 was examined using the Human EGFR Gene Mutations Detection Kit (AmoyDx, Xiamen, China), which is a PCR-based amplification-refractory mutation system.

Statistical analysis

Unpaired *t*-tests were used to compare two continuous variables. Categorical variables were analyzed by chi-square tests, except where a small sample size (<5) required the use of Fisher's exact test. Before performing multiple logistic regression analysis, variables were selected by a stepwise method. Receiver operating characteristic (ROC) analysis was performed to determine cut-off values and to evaluate the performance of the logistic regression model. All reported *P* values were two-tailed, and *P* values <0.05 were considered statistically significant. Statistical analyses of the

data was performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Results

Patient demographics and EGFR mutation status

The demographic and pathological data of the study population are presented in Table 1. All 209 of the enrolled patients were surgically treated: lobectomy in 181 (86.6%) patients, wedge resection in 22 (10.5%), and segmentectomy in six (2.9%) patients. There were 96 (45.9%) men and 113 (54.1%) women, with a median age of 60.1 years (range 27–81). Tumor node metastasis stage distribution was: IA in 163 patients (77.9%), IB in eight (3.8%), IIA in 30 (14.4%), and IIB in eight patients (3.8%). Most of the tumors were stage I (171, 81.8%). All cases were invasive lung adenocarcinomas and the most common histologic subtype was acinar predominant (113, 54.1%), followed by lepidic predominant (38, 18.2%), which included five cases of minimally invasive adenocarcinoma (MIA) and two adenocarcinoma in situ (AIS). In the tumors with an EGFR mutation, 67 (53.2%) had an L858R mutation and 50 (39.6%) had a 19 deletion mutation.

Correlation of EGFR mutation status with clinical features

There were significant differences in gender, smoking status, pathologic grade, serum carcinoembryonic antigen (CEA) level, and histologic subtype between the EGFR wild type and EGFR mutant groups (Table 2). EGFR mutation rates were significantly higher in women than in men (76/113, 67.2% vs. 50/113, 52.1%, odds ratio [OR] 1.890, 95% confidence interval [CI] 1.078, 3.312; $P = 0.025$). Significantly more non-smokers (110/160, 68.7%) harbored EGFR mutations than smokers (16/49, 32.6%, OR 4.537, 95% CI 2.289, 8.995; $P < 0.001$). EGFR mutations were also significantly more frequent in patients with intermediate (97/149, 65.1%) or low (23/38, 60.5%) pathologic grade (OR 4.974, 95% CI 1.836, 13.480; and OR 4.089, 95% CI 1.305, 12.807, respectively; $P = 0.003$). Patients with EGFR mutations were more likely to have lower serum CEA levels (3.75 ± 5.34 ng/ml) than patients with wild-type EGFR (7.39 ± 15.59 ng/ml) ($P = 0.021$). The cut-off value of 2.6 ng/ml for CEA level was determined by ROC analysis (Fig 1). The group of patients with a CEA level <2.6 ng/ml had a higher rate of EGFR mutation (OR 1.769, 95% CI 1.011, 3.096; $P = 0.045$). Considering tumor histology, EGFR mutations were most commonly found in papillary predominant subtypes (25/36, 69.4%, OR 5.682, 95% CI 1.741, 18.544; $P = 0.014$), followed by acinar (72/113,

Table 1 Patient demographics and tumor characteristics

Characteristics	Number (%)
Age (years)	60.11 ± 9.62
Gender	
Male	96/209 (45.9%)
Female	113/209 (54.1%)
Family tumor history	
None	194/209 (92.8%)
Lung cancer	9/209 (4.3%)
Gastrointestinal cancer	3/209 (1.4%)
Other†	3/209 (1.4%)
Clinical symptoms	
Asymptomatic	75/209 (35.9%)
Symptomatic	134/209 (64.1%)
Lobe	
RUL	73/209 (34.9%)
ML	19/209 (9.1%)
RLL	38/209 (18.2%)
LUL	45/209 (21.5%)
LLL	34/209 (16.3%)
TNM stage	
IA	163/209 (77.9%)
IB	8/209 (3.8%)
IIA	30/209 (14.4%)
IIB	8/209 (3.8%)
Surgical method	
VATS	140/209 (67.0%)
Conventional thoracotomy	45/209 (21.5%)
Da Vinci surgical robotic system	24/209 (11.5%)
Operation selection	
Lobectomy	181/209 (86.6%)
Segmentectomy	6/209 (2.9%)
Wedge resection	22/209 (10.5%)
Histologic subtype	
Lepidic	38/209 (18.2%)
Acinar	113/209 (54.1%)
Papillary	36/209 (17.2%)
Micropapillary	1/209 (0.5%)
Solid	21/209 (10.0%)
EGFR status	
EGFR+	126/209 (60.3%)
L858R	67/126 (53.2%)
19 deletion	50/126 (39.6%)
L858R/T790M	1/126 (0.8%)
L858R /19 deletion	1/126 (0.8%)
Exon21 L861Q	2/126 (1.6%)
Exon18 G719X	3/126 (2.4%)
Exon20 S768I	2/126 (1.6%)
EGFR−	83/209 (39.7%)

†Other includes bladder cancer, gynecological oncology. EGFR, epidermal growth factor receptor; LLL, left lower lobe; LUL, left upper lobe; ML, middle lobe; RLL, right lower lobe; RUL, right upper lobe; TNM, tumor node metastasis; VATS, video-assisted thoracoscopic surgery.

63.7%, OR 4.390, 95% CI 1.581, 12.193) and lepidic (23/38, 60.5%, OR 3.833, 95% CI 1.215, 12.090). EGFR mutations were less frequently found in the solid predominant subtype (6/21, 28.6%). There were also no differences in stage

Table 2 Association between clinical characteristics with EGFR mutation status

Variable	All patients	EGFR mutation status		P	Univariate OR
		Positive	Negative		
Number of patients	209	126 (60.3%)	83 (39.7%)	NA	NA
Median age	60.11 ± 9.62	60.22 ± 9.42	60.02 ± 9.79	0.901	NA
Gender					
Female	113	76	37	0.025	Reference
Male	96	50	46		1.890 (1.078, 3.312)
Smoking history					
Yes	49	16	33	<0.001	Reference
No	160	110	50		4.537 (2.289, 8.995)
Histologic subtype†					
Lepidic‡	38	23	15	0.014	3.833 (1.215, 12.090)
Acinar	113	72	41		4.390 (1.581, 12.193)
Papillary	36	25	11		5.682 (1.741, 18.544)
Solid	21	6	15		NA
Differentiation					
High	50	30	20	0.324	2.250 (0.563, 8.996)
Intermediate	100	64	36		2.667 (0.706, 10.077)
Low	10	4	6		Reference
Stage					
I	171	107	64	0.152	Reference
II	38	19	19		0.598 (0. 295, 1.213)
Pathologic grade					
High	22	6	16	0.003	Reference
Intermediate	149	97	52		4.974 (1.836, 13.480)
Low	38	23	15		4.089 (1.305, 12.807)
Clinical symptoms					
+	75	48	27		Reference
−	134	78	56	0.412	1.276 (0.712, 2.287)
Family tumor history					
Yes	15	9	6	0.981	Reference
No	194	117	77		1.013 (0.347, 2.960)
CEA level (ng/ml)	5.15 ± 10.64	3.75 ± 5.34	7.39 ± 15.59	0.021	NA
CEA (ng/ml)					
≤2.6	111	74	37	0.045	1.769 (1.011, 3.096)
>2.6	98	52	46		Reference

†Histologic subtype was categorized according to the 2011 International Society for Lung Cancer Research/American Thoracic Society/European Respiratory Society classification system. ‡Histologic subtype was categorized as lepidic predominant adenocarcinoma (adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant invasive adenocarcinoma) and other subtypes of dominant histologic findings (acinar, papillary, micropapillary, and solid predominant). CEA, carcinoembryonic antigen; CI, confidence interval; EGFR, epidermal growth factor receptor; OR, odds ratio.

distribution, differentiation, family tumor history, clinical symptoms or median age between EGFR mutant and wild-type groups.

EGFR mutation and CT features

Computed tomography features of the lung adenocarcinomas according to EGFR mutation status are summarized in Table 3. No significant differences were observed in any of the studied CT features except the proportion of ground-glass opacity (GGO), which was significantly higher in tumors with EGFR mutations than in EGFR wild type. When tumors were classified according to GGO proportion, EGFR mutations were significantly more frequent in tumors with GGO categorized as 0% < GGO ≤ 50% (OR 2.346, 95% CI 1.040, 5.292; P = 0.039). EGFR mutations were significantly more frequent in tumors with any GGO (0% < GGO ≤ 50% and 50% < GGO ≤ 100%) than in solid tumors (OR 2.607, 95% CI 0.888, 7.652; P < 0.039). There was a higher frequency of EGFR mutations in upper lobes compared with lower lobes (OR 1.670, 95% CI 1.008, 2.766; P < 0.046). In multivariate logistic regression analysis, tumors with any GGO were identified as an independent predictor of EGFR mutation (OR 2.746, 95% CI 1.101, 6.849; P = 0.030) (Table 4). CT images of GGOs and EGFR mutations are shown in Figure 2.
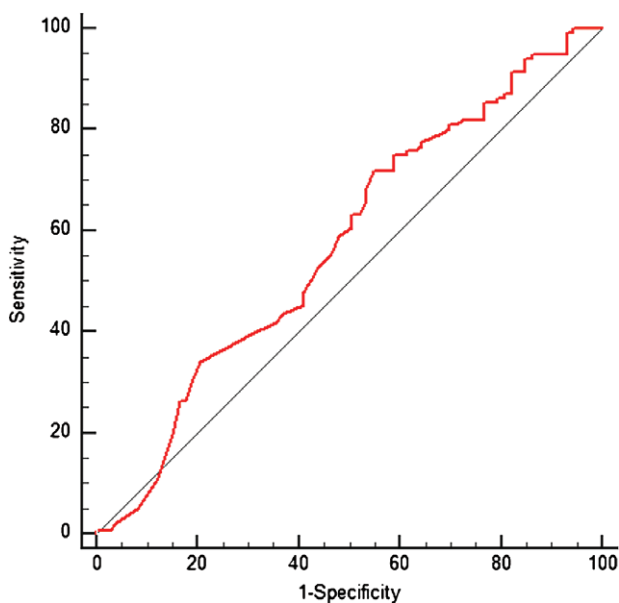
Figure 1 Receiver operating characteristic curve used to predict epidermal growth factor receptor mutation status (area under the curve 0.575; 95% confidence interval 0.501, 0.646; cut-off value of 2.6 ng/ml for carcinoembryonic antigen level; sensitivity 63.25; specificity 49.32).

Multivariable analyses of prognostic factors for EGFR mutation and receiver operating characteristic curve analysis

To construct a model with both clinical variables and CT features, four clinical features (gender, smoking history, histologic subtype, and CEA) found to be statistically significant in univariate analysis were kept in the model (Table 5). The most significant independent prognostic factors in the multivariable logistic regression analysis for harboring an EGFR mutation were: never-smokers (OR 4.039, 95% CI, 1.572, 10.377; $P = 0.004$), tumors with GGO (OR 2.731, 95% CI 1.147, 6.503; $P = 0.023$), and acinar (OR 5.110, 95% CI 1.430, 18.256; $P = 0.012$) or papillary (OR 5.227, 95% CI 1.223, 22.333; $P = 0.026$) predominant adenocarcinomas. The multiple logistic regression model produced from both clinical and radiological features showed a predictive power of 0.737 (95% CI 0.661, 0.814) for identifying EGFR mutant status by ROC analysis (Fig 3).

Differences in CT features between 19 deletion and L858R EGFR mutations

Patients with 19 deletion and L858R EGFR mutations had statistically similar tumor size, shape, border, thickening of the adjacent pleura, pleural retraction, vascular convergence, lymphadenopathy, degree of enhancement, presence or absence of air-bronchogram, speculated/lobulated, and cavitation/bubble-like lucency on CT scan (Table 6). The GGO proportion in tumors with L858R mutation was also similar to tumors with 19 deletion mutation ($P = 0.866$).

Discussion

Lung cancer is the leading cause of cancer death worldwide. In recent years, EGFR-TKI therapy has significantly delayed disease progression in patients with EGFR mutations and as a result, TKIs are now considered front-line therapy for patients with advanced adenocarcinoma harboring EGFR mutations.[12] Detecting EGFR mutations in lung adenocarcinomas is therefore important for determining treatment strategy. Unfortunately, EGFR mutation status cannot always be examined in patients because of inoperability, insufficient pathological material or the cost of the molecular examination. Previous studies have reported that EGFR mutations are more often observed in adenocarcinomas, particularly among female patients and in Asian populations.[13] Our study investigated the association of EGFR status with a comprehensive set of clinical characteristics and imaging features in peripheral small lung adenocarcinoma. We found a significant correlation between EGFR mutation status and papillary predominant histological subtype. Moreover, there was a significant association between never-smokers and EGFR mutation. The presence of GGO in tumors was the only significant CT feature predictive of EGFR mutation. In multivariable logistic regression analysis, the presence of GGO was closely related to EGFR mutation status.

Although EGFR mutations are frequently observed in never-smoker females with invasive adenocarcinoma with a predominant lepidic pattern, a significant percentage have also been noted in acinar and papillary variants of adenocarcinoma.[14–18] Few studies have reported correlations between the predominant subtype in lung adenocarcinomas and EGFR mutations. Liu *et al.* examined 385 surgically resected lung adenocarcinomas in Chinese patients and found that EGFR mutations occurred significantly more frequently in lepidic predominant subtypes.[10] Song *et al.* reported that EGFR mutations occurred significantly more frequently in micropapillary and lepidic predominant subtypes and were less common in the solid predominant subtype.[19] Villa *et al.* found that the lepidic predominant subtype was more common in EGFR-mutant lung cancers compared with acinar in EGFR wild-type lung cancers.[18] In a cohort of 69 surgical resection patients with stage III (N2) lung cancer, Russell *et al.* showed that EGFR mutations were associated with acinar and micropapillary predominant tumors.[20] Previous research has also reported

Table 3 Association between CT characteristics and EGFR mutation status

Variable	EGFR mutation status		P	Univariate OR
	Positive	Negative		
Diameter (mm)	19.35 ± 6.15	20.65 ± 7.33	0.215	NA
Shape				
Round/oval	78	55	0.428	Reference
Irregular	25	13		1.356 (0.638, 2.882)
Border definition				
Well defined	57	46	0.108	Reference
Poorly defined	46	22		1.687 (0.890, 3.199)
Margins				
Smooth	38	22	0.543	Reference
Lobulated/spiculated	65	46		0.818 (0.428, 1.562)
Cavitation/bubble-like lucency				
+	25	16	0.911	1.042 (0.508, 2.138)
−	78	52		Reference
Air bronchogram†				
+	37	19	0.276	1.466 (0.743, 2.812)
−	66	49		Reference
Thickening of the adjacent pleura				
+	15	15	0.207	0.602 (0.273, 1.331)
−	88	53		Reference
Pleural retraction				
+	55	29	0.169	1.541 (0.831, 2.856)
−	48	39		Reference
Vascular convergence				
+	17	11	0.955	1.024 (0.447, 2.347)
−	86	57		Reference
Lymphadenopathy				
+	15	8	0.600	1.278 (0.510, 3.204)
−	88	60		Reference
GGO proportion				
GGO negative	61	53	0.039	Reference
0% < GGO ≤ 50%	27	10	—	2.346 (1.040, 5.292)
50% < GGO ≤ 100%	15	5	—	2.607 (0.888, 7.652)
GGO presence				
GGO negative	61	53	0.011	Reference
Any GGO	42	15		2.433 (1.214, 4.875)
Lobe				
Upper lobes	90	47	0.028	1.915 (1.071, 3.424)
Lower lobes	36	36		Reference

†+ Air bronchogram present, − air bronchogram absent. CI, confidence interval; CT, computed tomography; EGFR, epidermal growth factor receptor; GGO, ground-glass opacity; NA, not applicable; OR, odds ratio.

that EGFR exon 21 mutations are commonly associated with lepidic predominant adenocarcinomas and EGFR exon 20 mutations with solid histology.[14,21] Our results indicate that EGFR mutations are associated with a higher frequency of papillary and acinar predominant subtypes, and are uncommon in the solid predominant subtype. The discrepancy in outcome between previous literature and our results regarding EGFR mutations and histologic subtypes may be related to the study sample size and the distribution of histologic type. Conflicting results may also be attributed to differences in ethnicity of the study population and the diagnostic procedures that were studied.

Several studies have explored the association between GGO on CT and EGFR-mutated lung cancer.[11,14,22–26] Glynn *et al.* investigated the association of imaging characteristics with EGFR and KRAS mutations in patients with lung adenocarcinoma with bronchoalveolar carcinoma (BAC) features.[23] The presence of GGO on CT scan was not significantly associated with EGFR mutation ($P = 0.44$). Hsu *et al.* explored EGFR mutation status with different image patterns in a cohort of 162 patients with stage I lung adenocarcinoma with tumor lesions <3 cm, and EGFR mutation was detected less frequently in pure GGO lesions than in lesions with a solid

Table 4 Multivariable logistic regression analyses of CT features predicting the presence of EGFR mutation in lung adenocarcinoma

Variable	P	Odds ratio	95% CI
Shape			
Round/oval	—	Reference	NA
Irregular	0.807	1.3	0.366, 2.187
Border definition			
Well defined	—	Reference	NA
Poorly defined	0.865	1.083	0.434, 2.700
Margins			
Smooth	—	Reference	NA
Lobulated/spiculated	0.838	1.091	0.472, 2.520
Cavitation/bubble-like lucency			
+	0.843	1.008	0.474, 2.496
−	—	Reference	NA
Air bronchogram			
+	0.260	1.584	0.711, 3.528
−	—	Reference	NA
Thickening of the adjacent pleura			
+	0.443	0.715	0.303, 1.687
−	—	Reference	NA
Pleural retraction			
+	0.176	1.607	0.809, 3.192
−	—	Reference	NA
Vascular convergence			
+	0.771	1.145	0.461, 2.841
−	—	Reference	NA
Lymphadenopathy			
+	0.298	1.696	0.627, 4.590
−	—	Reference	NA
GGO proportion			
GGO negative	—	Reference	NA
Any GGO	0.030	2.746	1.101, 6.849
Lobe			
Upper lobes	0.096	1.806	0.900, 3.624
Lower lobes	—	Reference	NA

CI, confidence interval; CT, computed tomography; EGFR, epidermal growth factor receptor; GGO, ground-glass opacity; NA, not applicable.

component, especially L858R.[11] A higher incidence of EGFR mutation occurs in invasive adenocarcinomas, such as tumors with part-solid and solid patterns. In contrast, Lee *et al.* reported that the percentage of the GGO component on CT scan was significantly higher in lepidic predominant adenocarcinoma, which contains a higher frequency of exon 21 missense mutations compared with exon 19 mutations.[14] Hong *et al.* also found that the GGO proportion in adenocarcinomas with EGFR mutation was significantly higher than in EGFR wild-type tumors, and their results showed that exon 19 deletion was the most common EGFR mutation in lepidic predominant adenocarcinomas, while no difference in GGO proportion was observed between tumors with exon 19 and 21 mutations.[24]

We found that GGO was an independent predictor of EGFR mutation and that the GGO proportion was similar in L858R and 19 deletion mutations ($P = 0.866$) (Table 6). Hsu *et al.* also focused on the correlation between image patterns and EGFR mutation in stage I lung adenocarcinoma, but reported that EGFR mutations were detected less frequently in pure GGO lesions than in lesions with a solid component, especially L858R.[11] Glynn *et al.* also reported that GGO on CT imaging was not significantly associated with the presence of EGFR mutation, and there was no characteristic CT feature that could predict EGFR mutation status.[23] An explanation for the difference between our results and previous studies may lie in the fact that small peripheral adenocarcinoma or BAC may present with a high ratio of GGO components on CT scans, and EGFR mutations are less frequently detected in atypical adenomatous hyperplasia (AAH) and BAC lesions compared with invasive adenocarcinoma.[6,27,28] In the new IASLC/ATS/ERS classification guidelines, AIS and MIA were proposed as substitutes for BAC to define non-invasive adenocarcinomas. Glynn *et al.* used a relatively small sample and we assume that the histological type was mainly BAC.[23] Hsu *et al.* did not provide detailed information of the histologic subtypes of their study population, but reported that a pure GGO pattern tended to be correlated with tumors < 2 cm with less typical EGFR mutation, while AIS/MIA tend to appear radiologically as pure GGO.[11] The histological subtypes in our study population mainly consisted of invasive adenocarcinoma rather than AIS or MIA, and EGFR mutations are less frequently observed in non-invasive lesions (AIS/MIA) compared with invasive adenocarcinoma, which may lead to the different results.

Our study is different from previous publications studying the relationship between radiogenomics and lung adenocarcinomas with EGFR mutation.[8–11,23] Firstly, we focused mainly on peripheral small lung adenocarcinoma <3 cm, and most of our patients were stage I (171/209, 81.8%). Secondly, the histological subtype in our study population was invasive adenocarcinoma, which was further classified as low to intermediate (lepidic, acinar, and papillary) and high growth patterns, such as solid or micropapillary components. Therefore, our study population may present a more accurate example of histological subtypes of invasive adenocarcinomas and their imaging features, according to the new the IASLC/ATS/ERS guidelines. We evaluated 209 cases of consecutive patients with surgically resected lung adenocarcinomas and EGFR mutation who did not undergo preoperative chemotherapy intervention, which may give a more precise picture of the correlation between radiogenomics and EGFR mutation status in lung adenocarcinoma.
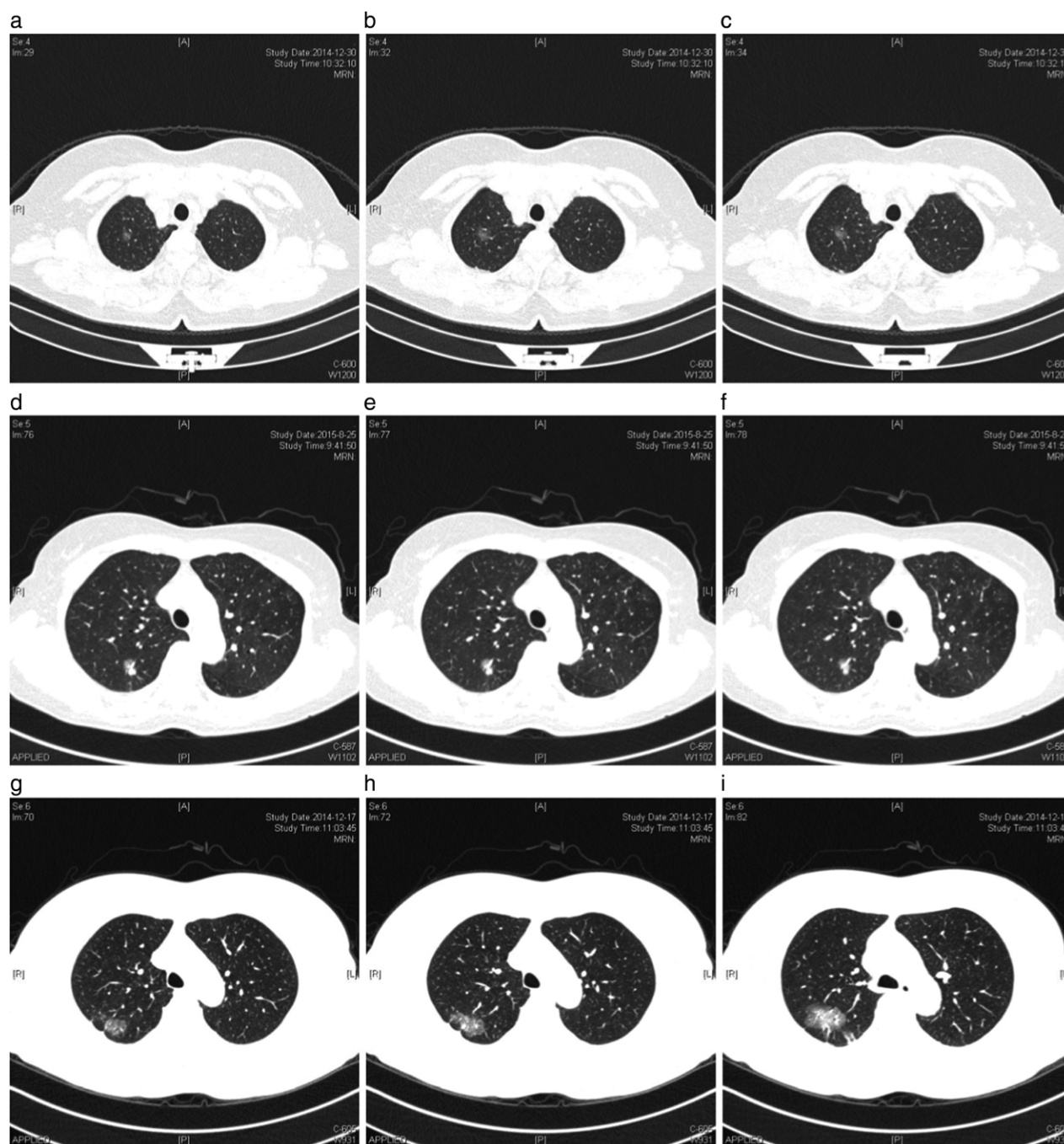
Figure 2 Chest computed tomography images of patients with ground glass opacity. (**a–c**) Patient #1 with lepidic predominant subtype and L858R mutation; (**d–f**) patient #2 with acinar predominant subtype and L858R mutation; (**g–i**) patient #3 with acinar predominant subtype and 19 deletion mutation.

However, there are still a number of limitations to our study. Firstly, the final study population was considerably smaller than the initial identified group because preoperative imaging for many patients was not available at our institution. Secondly, CT images were interpreted by consensus, and inter-observer variability was not assessed. Thirdly, the maximum one-dimensional diameter on CT images was used to estimate the GGO proportion rather than using a two-dimensional measurement or dedicated software for volumetric estimation of the GGO component.

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

Variable	*P*	Odds ratio	95% CI
Gender			
Female	—	Reference	NA
Male	0.648	1.207	0.538, 2.710
Smoking			
Yes	—	Reference	NA
No	0.004	4.039	1.572, 10.377
Histologic subtype			
Lepidic	0.266	2.279	0.533, 9.744
Acinar	0.012	5.110	1.430, 18.256
Papillary	0.026	5.227	1.223, 22.333
Solid	—	Reference	NA
CEA			
≤2.6	0.318	1.434	0.706, 2.913
>2.6	—	Reference	NA
GGO proportion			
GGO negative	—	Reference	NA
Any GGO	0.023	2.731	1.147, 6.503

CI, confidence interval; CEA, carcinoembryonic antigen; CT, computed tomography; EGFR, epidermal growth factor receptor; GGO, ground-glass opacity; NA, not applicable.

This measurement strategy was chosen because it is faster and easier to implement in daily clinical practice. Fourthly, we did not check for KRAS mutations, and it has been reported that EGFR-TKI therapy is unsuitable for such
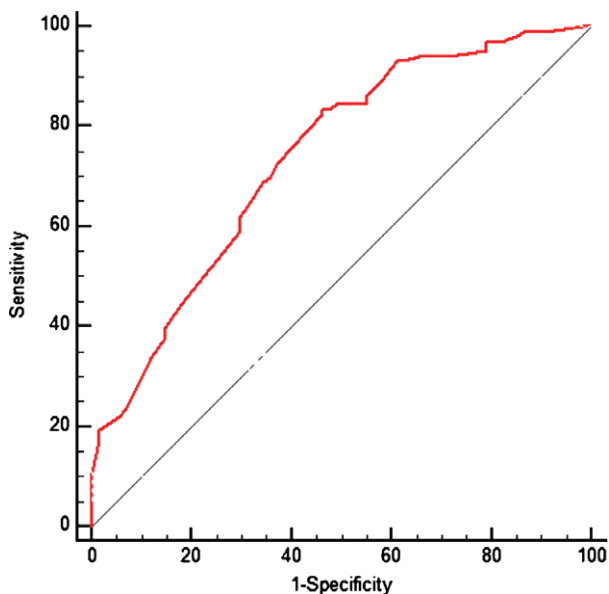

Figure 3 Predicting epidermal growth factor receptor mutation status with clinical variables and computed tomography features by receiver operating characteristic curve (area under the curve 0.737; 95% confidence interval 0.661, 0.814).

mutations.[29,30] Further studies are necessary to elucidate this issue. Finally, the correlation between CT imaging and progression-free and overall survival was not addressed.

In conclusion, in stage I/II lung adenocarcinoma with tumor size <3 cm, the GGO proportion in adenocarcinomas with EGFR mutation was significantly higher than in adenocarcinomas without EGFR mutation. GGO proportion was identified as an independent predictor of positive EGFR mutation, and papillary predominant subtype has the highest EGFR mutation rate. Combined CT findings and clinical features, which include never-smoking, may be helpful for determining the presence of EGFR mutations in

Table 6 Comparison of EGFR exon mutations based on CT findings

	EGFR mutation status		
Variable	19 deletion (*n* = 41)	L858R (*n* = 54)	*P*
Diameter (mm)	19.46 ± 5.61	19.51 ± 6.43	0.965
Shape			
Round/oval	8	16	0.261
Irregular	33	38	
Border definition			
Well defined	23	29	0.816
Poorly defined	18	25	
Margins			
Smooth	12	25	0.092
Lobulated/ spiculated	29	29	
Cavitation/bubble-like lucency			
+	10	13	0.972
−	31	41	
Air bronchogram			
+	12	21	0.329
−	29	33	
Thickening of the adjacent pleura			
+	5	8	0.713
−	36	46	
Pleural retraction			
+	25	26	0.214
−	16	28	
Vascular convergence			
+	8	7	0.386
−	33	47	
Lymphadenopathy			
+	8	6	0.253
−	33	48	
GGO proportion			
GGO negative	25	32	0.866
Any GGO	16	22	
Lobe			
Upper lobes	33	51	0.229
Lower lobes	17	16	

CT, computed tomography; EGFR, epidermal growth factor receptor; GGO, ground-glass opacity.

patients with peripheral small lung adenocarcinoma, particularly in patients whose mutational profiling is not available or not possible.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 Definition of computed tomography descriptors.