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ORIGINAL ARTICLE

Associations between epidermal growth factor receptor mutations and histological subtypes of lung adenocarcinoma according to the IASLC/ATS/ERS classification in Chinese patients

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Abstract

Background: This retrospective study was conducted to investigate the relationship between epidermal growth factor receptor (EGFR) mutation and histological subtypes of lung adenocarcinoma according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification in Chinese patients.

Methods: Three hundred and seventy six surgically resected lung adenocarcinomas from Chinese PLA General Hospital were included in the study. Patients' clinical and pathological characteristics including age, gender, smoking history, tumor size, tumor node metastasis stage, and tumor differentiation were analyzed. Histologic subtypes of adenocarcinoma were categorized according to the IASLC/ATS/ERS classification of lung adenocarcinoma. An amplification-refractory mutation system was performed to detect EGFR mutations.

Results: One hundred and fifty three lung adenocarcinomas had EGFR mutations. In univariate analysis, EGFR mutations were associated with gender ($P < 0.001$), smoking history ($P < 0.001$), tumor differentiation ($P < 0.001$), and acinar predominant ($P < 0.001$), papillary predominant ($P = 0.034$), solid predominant ($P = 0.022$), invasive mucinous ($P = 0.012$) and mucinous ($P = 0.001$) subtypes.

Conclusions: In Chinese patients with lung adenocarcinoma, smoking history, tumor differentiation, and acinar predominant and mucinous subtypes were independent predictors of EGFR mutation.

Introduction

Lung cancer is the primary cause of cancer-related mortality in men and the second in women around the world.[1] Historically, lung cancer has been divided into two categories: non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). The former primarily includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. In the past few years, the incidence of lung adenocarcinoma has increased, and has become the leading histologic subtype of lung cancer in most countries.[2]

Many advances have taken place in molecular biology, oncology, surgery, radiology, and pathology in the past decade. In 2011, a new multidisciplinary classification system of lung adenocarcinoma was recommend by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS).[3] The new classification system was intended to provide a more significant pathological classification that could provide molecular biology and prognostic information relating to clinical behavior.

Importantly, epidermal growth factor receptor (EGFR) mutations define the associations between these oncogenic drivers and histologic subtype. Activating mutations of the *EGFR* gene mean that is sensitive to EGFR tyrosine kinase

inhibitors (TKIs), such as gefitinib and erlotinib.[4] A large number of studies have focused on the pathological features of tumors harboring EGFR mutations to provide essential information for TKI treatment. In lung adenocarcinoma, many factors indicate a higher EGFR mutation rate, such as well-differentiated, lepidic, papillary, and acinar predominanthistologic subtypes, while the solid and mucinous predominant subtypes indicate a lower EGFR mutation rate.[5–12] Although EFGR mutations are associated with gender, smoking, ground glass opacity (GGO) patterns, and histologic subtypes of adenocarcinoma according to the IASLC/ATS/ERS classification, are they independent predictors of EFGR mutation in lung adenocarcinoma? In this study, we extended our comprehensive mutational analyses of EGFR with lung adenocarcinoma and incorporated these data with the clinicopathological characteristics to evaluate their mutual correlation and potential predictive value.

Methods

Patients and samples

The Chinese PLA General Hospital Institutional Review Board approved this study. All patients provided informed consent for tissue collection and gene analyses. From July 2012 to July 2015, 408 patients underwent surgical resection for lung adenocarcinoma at Chinese PLA General Hospital. Of these, 395 resected samples were available to detect EGFR mutation status. Nineteen patients who had received neoadjuvant chemotherapy were excluded. Finally, 376 resected lung adenocarcinomas were assessed for clinicopathological variables and EGFR mutation status.

Clinicopathological variables

Clinicopathological data were collected for analyses, including age at diagnosis, smoking history, tumor size, tumor node metastasis (TNM) stage, and tumor differentiation. TNM staging was applied according to the seventh edition of the Lung Cancer Staging classification system.[13] Pathological diagnoses were based on the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification system.[3] Adenocarcinomas were classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma. Invasive adenocarcinoma was further divided into lepidic predominant, solid predominant, acinar predominant, papillary predominant, micropapillary predominant, and invasive mucinous adenocarcinoma (IMA). The tumors were also divided into mucinous and non-mucinous.

Epidermal growth factor receptor (EGFR) mutation analysis

Formalin-fixed paraffin-embedded lung cancer tissues were obtained during surgery. Tumor specimens were procured for *EGFR* gene mutational analysis using previously documented methods.[14] Briefly, DNA was extracted from the samples using a QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany). EGFR mutations at exons 18–21 were analyzed, PCR amplification was performed using a Mx3000P quantitative PCR system (Stratagene; Agilent Technologies, Inc., Santa Clara, CA, USA), and data were analyzed using MXPRO software version 4.10 (Stratagene; Agilent Technologies, Inc.).

Statistical analysis

An independent sample *t*-test was applied between categorical and continuous variables, whileχ^2 or Fisher's exact tests were used to compare categorical variables. For multivariate analyses, a logistic regression model was used. Differences were considered significant when $P < 0.05$, and all reported *P* values were two-sided. Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Patient characteristics are shown in Table 1. There were 161 women and 215 men. The mean age at diagnosis was 59 years (range 37–81). Two hundred and three (54.0%) patients were never smokers, and 173 (46.0%) were current or former smokers. The mean ± standard deviation of tumor size was 2.93 ± 0.81 cm. One hundred and eighty (47.9%) patients were in stage I, 94 (25.0%) in stage II, and 102 (27.1%) in stage III and IV. One hundred and thirty-nine (40.0%) patients had regional lymph node metastasis (N1 or N2), while 237 (60.0%) did not. Regarding degrees of tumor differentiation, 114 (30.3%) had poorly differentiated, 177 (47.1%) moderate, and 85 (22.6%) well differentiated. Of 376 lung adenocarcinoma cases, acinar predominant (39.9%) was the leading histologic subtype, followed by papillary predominant (17.8%), solid predominant (14.9%), lepidic predominant (10.1%), AIS (5.8%), micropapillary predominant (5.1%), MIA (4.0%), and IMA (2.3%) (Table 2). Mucinous subtypes included nine IMAs, seven colloid-predominant, and three MIA mucinous adenocarcinomas.

Table 1 Associations between clinical characteristics and EGFR mutation

		EFGR		
Variables	N	Mutation	Wild	*P*
Age (year)				
Mean ± SD		58.8 ± 7.4	58.9 ± 6.2	0.918
Gender				
Female	161	85	76	0.000
Male	215	68	147	—
Smoking history				
Never	210	114	96	0.000
Former/ current	166	39	127	—
Tumor size (cm)				
Mean ± SD	2.93 ± 0.81	2.89 ± 0.75	2.95 ± 0.84	0.571
TNM stage				
I	180	80	100	0.250
II	94	38	56	—
III + IV	102	35	67	—
LNM (N1, N2)				
Yes	139	56	83	0.903
No	237	97	140	—
Differentiation				
Poor	114	29	85	0.000
Moderate	177	71	106	—
Well	85	53	32	—

EGFR, epidermal growth factor receptor; LNM, lymph node metastasis; SD, standard deviation; TNM, tumor node metastasis.

EGFR mutations and clinical features

Epidermal growth factor receptor mutations were found in 153 (40.7%) of the adenocarcinoma specimens examined. The most common EGFR mutation was a missense mutation (L858R) in exon 21 (80/153, 43.8%) and the second most common was an in-frame deletion (E746_A750del) in exon 19 (43/153, 28.1%). Detailed EGFR mutation status data is listed in Table 3. EGFR mutations were observed more frequently in women (52.8% vs. men 31.6%; $P < 0.0001$) and in never smokers (54.3% vs. former or current smokers 23.5%; $P < 0.001$). There were more patients with well differentiated than poorly differentiated adenocarcinomas ($P < 0.001$). EGFR mutation was not correlated with age, tumor size, TNM stage, or lymph node metastasis. The results are shown in Table 1.

EGFR mutations and histologic subtypes

The rates of EGFR mutation in AIS, MIA, lepidic, papillary, acinar, micropapillary, and solid predominant subtypes were 45.5%, 40.0%, 55.3%, 52.0%, 52.2%, 36.8%, and 26.8%, respectively. No mutation was detected in IMA cases. Acinar and papillary predominant subtypes were correlated with EGFR mutation ($P < 0.001$, $P = 0.034$, respectively). The solid predominant subtype had a lower rate of EGFR mutation than other subtypes ($P = 0.022$). EGFR mutations occurred less frequently in mucinous compared to non-mucinous subtypes ($P = 0.001$).

Table 2 Association between histologic subtypes and EGFR mutation

		EFGR		
Histologic subtype	N (%)	Mutation	Wild	*P*
AIS				
Yes	22 (5.8)	10	12	0.639
No	254 (94.2)	143	211	
MIA				
Yes	15 (4.0)	6	9	0.956
No	361 (96.0)	147	214	
Lepidic predominant				
Yes	38 (10.1)	21	17	0.054
No	338 (89.9)	132	206	
Acinar predominant				
Yes	150 (39.9)	78	72	0.000
No	226 (60.1)	75	151	
Papillary predominant				
Yes	67 (17.8)	35	32	0.034
No	309 (82.2)	118	191	
Micropapillary predominant				
Yes	19 (5.1)	7	12	0.726
No	357 (94.9)	146	211	
Solid predominant				
Yes	56 (14.9)	15	41	0.022
No	320 (85.1)	138	182	
IMA				
Yes	9 (2.3)	0	9	0.012
No	367 (97.7)	153	214	
Mucinous	19 (5.1)	1	18	0.001
Non-mucinous	357 (94.9)	152	223	

AIS, adenocarcinoma in situ; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; MIA, minimally invasive adenocarcinoma.

Multivariate analyses of predictors of EGFR mutation

The relationships between EGFR mutation and clinical features were further analyzed by logistic regression analysis (Table 4). Smoking history (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.18–0.55; $P < 0.001$), tumor differentiation (OR 0.45, 95% CI 0.26–0.77; $P = 0.004$), acinar predominant subtype (OR 2.03, 95% CI 1.26–3.27; $P = 0.004$) and mucinous subtypes (OR 0.07, 95% CI 0.01–0.60; $P = 0.015$) were independent predictors of EGFR mutation.

Discussion

Epidermal growth factor receptor mutation is known to be associated with specific characteristics, such as lung

Table 3 Information of gene mutation status

Gene	Exon	Amino acid change	Nucleotide change	N (%)
EGFR	18	G719A	2156G>C	1 (0.64)
		G719S	2155G>A	1 (0.64)
	19	E746_A750del	2235–2249 del 15	43 (28.1)
		E746_A750del	2236–2250 del 15	5 (3.27)
		L747_P753>S	2240–2257 del 18	17 (11.1)
		E746_T751>A	2237–2251 del 15	1 (0.64)
		E746_T751>I	2235–2252>AAT del 18	1 (0.64)
		L747_A750>P	2238–2248>GC del 11	5 (3.27)
		L747_A750>P	2239–2248>C del 10	1 (0.64)
		L747_T751del	2239–2253 del 15	2 (1.31)
		L747_T751del	2240–2254 del 15	1 (0.64)
		L747_S752del	2239–2256 del 18	1 (0.64)
		L747_T751>P	2239–2251>C del 13	1 (0.64)
		E746_S752>V	2237–2255>T del 19	2 (1.31)
		S768I	2303G>T	1 (0.64)
	20	V769_D770insASV	2307–2308 ins GACAACGTG	1 (0.64)
		T790M	2369C>T	2 (1.31)
	21	L858R	2573T>G	67 (43.8)

adenocarcinoma, non-smoking status, female gender, and East Asian ethnicity.[15,16]

The new IASLC/ATS/ERS classification system provides a morphological predictor of prognosis and potentially also of therapy response. The integration of these clinicopathological characteristics may potentially extend our understanding of lung adenocarcinoma. Our study was conducted to evaluate the relationship between EGFR mutations and clinicopathologic features, particularly histologic subtypes of adenocarcinoma according to the new IASLC/ATS/ERS classification.

In this study, the incidence of EGFR mutations in Chinese patients with lung adenocarcinoma was 40.7% (153/376). EGFR mutations were not associated with age. In contrast, Eberhard *et al.* reported a correlation between EGFR mutation and younger age, which may be attributed to their sample of mainly Caucasian and non-adenocarcinoma patients.[17]

Epidermal growth factor receptor mutations occurred more frequently in women and never smokers (both $P < 0.0001$). However, multivariate analyses of logistic regression revealed no significant differences between genders. Correlations of EGFR mutations with gender were further evaluated. EGFR mutation status was analyzed by gender and stratified by smoking history. In the subgroups of never smokers and former/current smokers,

Table 4 Multivariate analyses of factors that might affect the presence of EGFR mutation

Variable	Category	OR (95% CI)	*P*
Age	—	0.99 (0.96–1.03)	0.800
Smoking	Former & current/never	0.32 (0.18–0.55)	0.000
Gender	Female/male	1.54 (0.91–2.60)	0.110
Tumor size	—	1.05 (0.78–1.42)	0.759
TNM stage	I + II/III + IV	1.52 (0.88–2.62)	0.134
Differentiation	Poor/moderate/well	0.45 (0.26–0.77)	0.004
LNM (N1, N2)	Yes/no	1.03 (0.64–1.69)	0.892
AIS	Yes/no	1.33 (0.50–3.56)	0.572
MIA	Yes/no	0.86 (0.25–3.04)	0.818
Lepidic predominant	Yes/no	1.79 (0.83–3.88)	0.140
Acinar predominant	Yes/no	2.03 (1.26–3.27)	0.004
Papillary predominant	Yes/no	1.69 (0.91–3.13)	0.096
Micropapillary predominant	Yes/no	0.95 (0.32–2.81)	0.928
Solid predominant	Yes/no	0.51 (0.25–1.05)	0.066
IMA	Yes/no	0.000	0.999
Mucinous	Yes/no	0.07 (0.01–0.60)	0.015

AIS, adenocarcinoma in situ; CI, confidence interval; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; LNM, lymph node metastasis; MIA, minimally invasive adenocarcinoma; OR, odds ratio; TNM, tumor node metastasis.

there was no correlation between gender and EGFR mutation ($P = 0.421$, $P = 0.094$, respectively; see supplementary material). The most likely reason for this result was that 62.2% of men were former/current smokers compared to 17.4% of women in our study. Gender may be a confounding factor, as reported by Tam *et al.*[18]

Our results show that EGFR mutations occurred in 40% (6/15) of MIA patients, lower than the 80% (16/20) rate reported in a previous study.[19]A possible reason for this result was that there were three mucinous MIA adenocarcinomas in our study, and none of these displayed EGFR mutations. The most frequent subtype of invasive adenocarcinoma in our resected tumor specimens was papillary predominant adenocarcinoma, followed by acinar predominant adenocarcinoma. Similar results have been reported in studies from China, Japan, and Taiwan.[20–23] In contrast, acinar predominant adenocarcinoma was reported as the most common subtype in Australia, France, Germany, and the United States.[24–27] This suggests that subtypes vary according to geographic region or ethnicity, because EGFR mutation rates differ between Asians and Caucasians in lung adenocarcinoma.

Univariate analysis identified that the following histologic features were significantly associated with EGFR mutation: tumor differentiation, and acinar predominant, papillary predominant, solid predominant, IMA, and mucinous subtypes. Chen *et al.* reported that tumor differentiation was correlated with EGFR mutation, consistent with our results.[9] Several studies have demonstrated that EGFR mutation status is significantly associated with histologic subtype, including AIS, lepidic predominant, papillary predominant, micropapillary predominant, and mucinous, according to the IASLC/ATS/ERS classification.[22,23,28–30] In our study, multivariate analysis revealed tumor differentiation ($P = 0.004$), acinar predominant ($P = 0.004$), and mucinous ($P = 0.015$) subtypes were independent predictors of EGFR mutation, after adjusting for potential confounding factors. No EGFR mutations occurred in IMA samples, thus IMA was not correlated with EGFR mutation in logistic regression analysis.

In summary, an analysis of resected lung adenocarcinoma samples in 376 Chinese patients revealed that EGFR mutation status was associated with gender, smoking history, tumor differentiation, and acinar predominant, papillary predominant, solid predominant, and mucinous subtypes. Logistic regression analysis indicated that smoking history, tumor differentiation, and acinar predominant and mucinous subtypes were independent predictors of EGFR mutation. Given the potential effectiveness of TKIs, our findings contribute to the determination of a therapeutic strategy for patients with lung adenocarcinoma.

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Disclosure

No authors report any conflict of interest.

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