ORIGINAL ARTICLE

Identification of lung adenocarcinoma mutation status based on histologic subtype: Retrospective analysis of 269 patients

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Abstract

Background: To evaluate differences in the clinical characteristics and molecular pathology of lung adenocarcinoma subtypes as defined by the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international histological classification.

Methods: We retrospectively reviewed 269 patients with initial primary lung adenocarcinoma who had undergone complete resection at our department from August 2013 to December 2014, focusing on the new histologic subtype classification, clinical characteristics, and molecular pathology.

Results: All specimens were invasive adenocarcinoma, and were lepidic (13.0%), papillary (19.7%), acinar (51.7%), solid (8.6%), micropapillary (1.1%) or mucinous predominant (5.9%). Epidermal growth factor receptor (*EGFR*) mutations were detected in 132 cases (60.3%). Female patients and non-smokers had higher *EGFR* mutation rates ($P = 0.022$ and 0.026, respectively). The lepidic, papillary, acinar, solid, micropapillary, and mucinous predominant patterns had *EGFR* mutation rates of 70.6%, 64.8%, 72.5%, 33.3%, 100%, and 5.9%, respectively. The exon mutation distribution differed according to serum carcinoembryonic antigen (CEA) levels ($P = 0.018$). v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations were detected in 20 cases (9.2%), and were frequently found in the mucinous and solid predominant subtypes. The serum CEA levels differed among the subtypes.

Conclusions: In China, there are significant differences between lung adenocarcinoma histologic subtypes. The presence of well-differentiated components in lung adenocarcinoma indicates higher *EGFR* mutation rates; the presence of solid or mucinous components indicates higher *KRAS* mutation rates. Serum CEA levels are associated with histologic subtype and *EGFR* exon mutations.

Introduction

Currently, lung cancer is the most common cancer and the leading cause of cancer death both in China and worldwide.[1,2] Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers; lung adenocarcinoma, which accounts for more than 50% of lung cancers, is one of the most common histologic types.[3] In 2011, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a new international multidisciplinary classification of lung adenocarcinoma.[4] Recently, the Chinese government published a new guideline for primary lung cancer suggesting that the new IASLC/ATS/ERS classification be used as the histologic standard.

According to the IASLC/ATS/ERS classification, the new concepts for adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) are defined. Following comprehensive histologic subtyping, invasive adenocarcinomas are now classified according to the predominant pattern, that is, lepidic (LPA), acinar (APA), papillary (PPA) or solid (SPA); the micropapillary predominant pattern (MPA) has been

included as a new histologic subtype with a poor prognosis. The previously termed mucinous bronchioloalveolar carcinomas are now referred to as invasive mucinous adenocarcinoma (IMA).[5]

As the field of lung cancer research is rapidly evolving, particularly in the molecular arena, the importance of molecular pathology is increasing. However, the molecular correlations in lung adenocarcinoma continue to remain unclear. Currently, the only strong molecular correlation for the predominant histologic subtypes of lung adenocarcinoma is v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation for IMA.[6]

Information on the prevalence of the clinical characteristics and molecular pathology of the lung adenocarcinoma subtypes as defined by the new IASLC/ATS/ERS classification is still limited. Therefore, we retrospectively analyzed resected specimens of lung adenocarcinoma in Chinese patients in terms of the newly defined histologic subtypes and prevalence of clinical characteristics and molecular pathology.

Materials and methods

Specimens

All 285 resected specimens of primary lung adenocarcinoma (from August 2013 to December 2014) were utilized from the Department of Thoracic Surgery II of the Peking University Cancer Hospital and were confirmed by pathological examination. Sixteen patients who received preoperative chemotherapy or tyrosine kinase inhibitor (TKI) therapy were excluded; therefore, 269 initial patients' data were analyzed. Epidermal growth factor receptor (EGFR) mutation status in 219 patients and KRAS in 217 patients were examined (others were unknown).

Histological evaluation

Two pathologists separately evaluated all specimens according to the new classification. Figure 1 depicts the typical histologic component of each subtype. The predominant pattern was defined as the pattern with the largest percentage of carcinoma cells, even when it was <50%. Staging was in accordance with the standards of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition.

Detection of epidermal growth factor receptor (EGFR) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations

Genomic DNA was extracted from formalin-fixed paraffin-embedded (FFPE) samples using a QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). DNA concentrations were measured by a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA). Thirty hotspot mutations

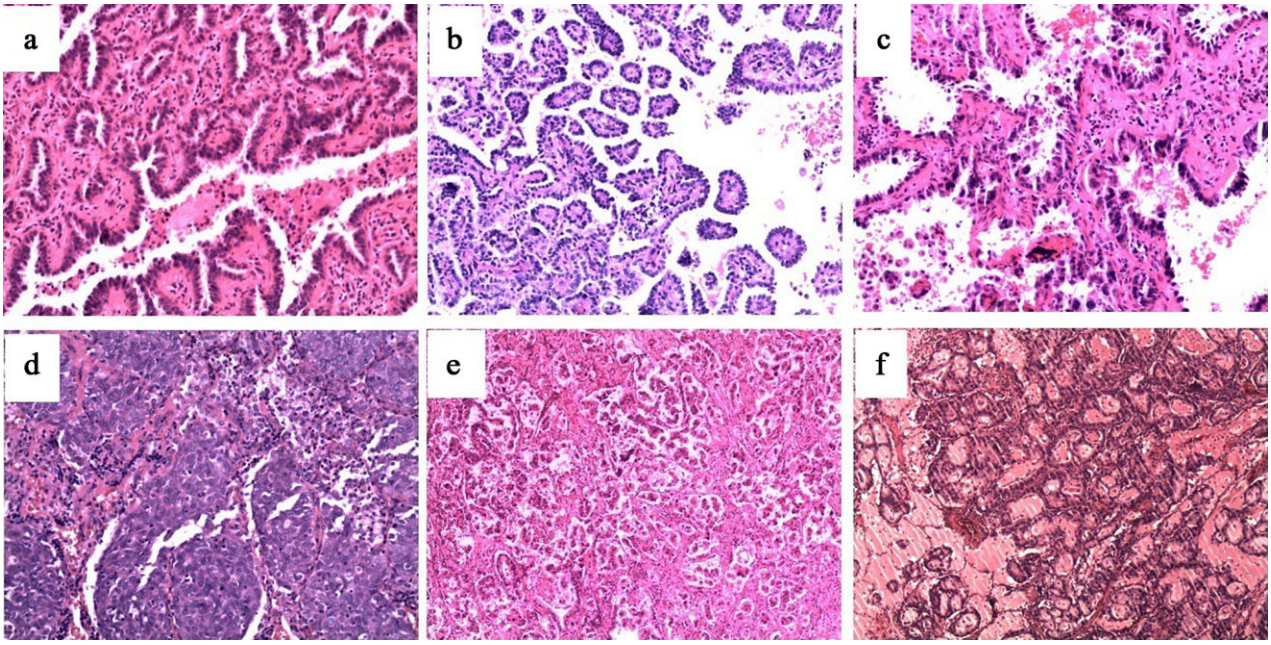

Figure 1 Lung adenocarcinoma histologic subtypes (hematoxylin and eosin stain x40): (**a**) lepidic; (**b**) papillary; (**c**) acinar; (**d**) solid; (**e**) micropapillary; (**f**) mucinous.

within exons 18–21 of the *EGFR* gene were examined using a Human EGFR Mutation Qualitative Detection Kit (Beijing ACCB Biotech Ltd, Beijing, China). Hydrolysable fluorescent probes were specifically designed to detect different mutations (point mutations, insertions, and deletions). Seven hotspot mutations in *KRAS* within codons 12 and 13 were detected using a Human KRAS Mutation Qualitative Detection Kit (Beijing ACCB Biotech Ltd). This experiment was performed using an Mx3000P PCR system (Stratagene, La Jolla, CA, USA) according to the manufacturer's protocol. The polymerase chain reaction conditions were as follows: initial denaturation at 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds, and 60°C for one minute.

Statistical analysis

The χ^2 test and Fisher's exact test for independence were used to compare the frequencies of the clinicopathologic variables. The Kruskal–Wallis test and logistic regression for independence were used to compare serum carcinoembryonic antigen (CEA) levels in the histologic subtypes. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 19.0 software (IBM Corp., Armonk, NY, USA).

Results

Clinicopathologic characteristics and histologic features

Table 1 lists the clinicopathologic characteristics and histologic features of the patients. All specimens were invasive adenocarcinoma: 35 cases were LPA (13.0%), 53 cases were PPA (19.7%), 139 cases were APA (51.7%), 23 cases were SPA (8.6%), three cases were MPA (1.1%), and 16 cases were IMA (5.9%).

Table 1 Characteristics of study population

Factor	Patient number (%)
Gender	
Female	171 (63.6)
Male	98 (36.4)
Age (years)	
Range	32~78
Mean	61
Pathologic stage	
IA	123 (45.7)
IB	59 (21.9)
IIA	43 (16.0)
IIB	1 (0.4)
IIIA	32 (11.9)
IIIB	5 (1.9)
IV	6 (2.2)
Smoking status	
Former/current	72 (26.8)
Never	197 (73.2)
Histologic subtype	
AIS	0
MIA	0
LPA	35 (13.0)
APA	139 (51.7)
PPA	53 (19.7)
MPA	3 (1.1)
SPA	23 (8.6)
IMA	16 (5.9)
CA	0
FA	0
EA	0
Total	269

AIS, adenocarcinoma in situ; APA, acinar predominant invasive adenocarcinoma; CA, colloid adenocarcinoma; EA, enteric adenocarcinoma; FA, fetal adenocarcinoma; IMA, invasive mucinous adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma; MPA, micropapillary predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Serum carcinoembryonic antigen levels and lung adenocarcinoma histologic subtypes

The serum CEA levels of cases were compared among the lung adenocarcinoma histologic subtypes; differences were detected using the Kruskal–Wallis test ($P = 0.004$; Fig 2). There were significant differences between LPA ($P = 0.007$) and APA ($P = 0.009$) (Table 2). In the logistic regression for histologic subtypes including factors of gender, age, CEA level, and pathologic stage, CEA level was significantly associated with LPA ($P = 0.018$, odds ratio = 7.403; 95% confidence interval: 1.414 to 38.769).

EGFR mutation and clinicopathologic characteristics

EGFR mutations were detected in 132 of 219 cases (60.3%). The *EGFR* mutation rate in women was higher than in men, as well as in never-smokers compared to patients who were smokers. There were no significant differences in the *EGFR* mutation rate in terms of age, serum CEA level, lung membrane invasion, or stage. The *EGFR* mutation rates in the LPA, PPA, APA, SPA, MPA, and IMA were 70.6%, 64.8%, 72.5%, 33.3%, 100%, and 5.9%, respectively. The difference in *EGFR* mutation rates among the subtypes was significant ($P < 0.001$). *EGFR* mutation was frequently found in the LPA, APA, PPA, and MPA subtypes (Table 3). In men and in patients who were smokers, *EGFR* mutation was seldom found in the SPA and IMA subtypes; in women and in patients who were non-smokers, *EGFR* mutation was seldom found in the IMA subtype (Table 4). Exon mutations were divided into two groups: 57 cases (43.2%) with exon 19 mutation and 75 cases (56.8%) with other exon mutations. The distribution of exon mutations differed according to serum

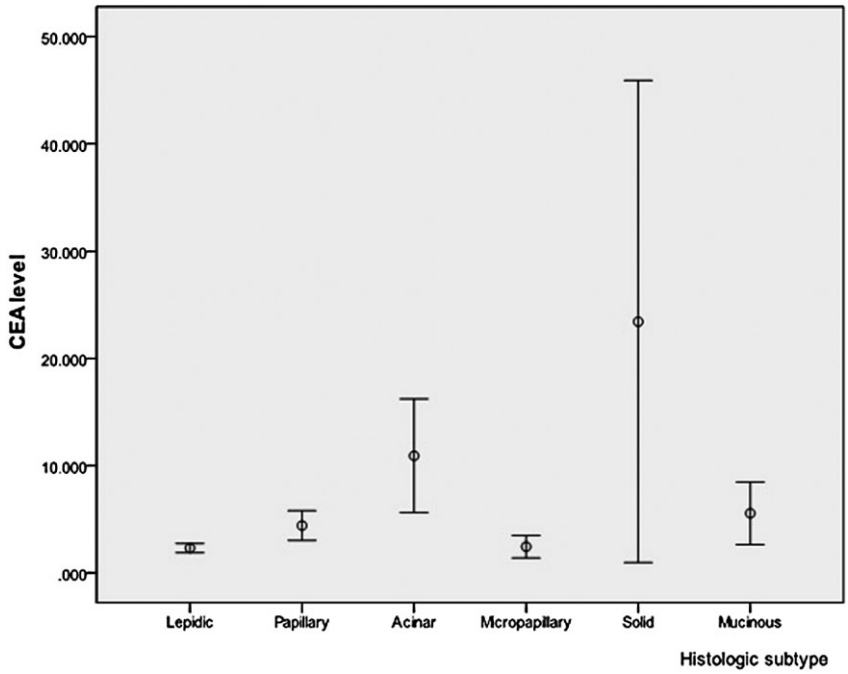

Figure 2 Serum carcinoembryonic antigen (CEA) levels according to lung adenocarcinoma histologic subtype. Lepidic, 2.23 ± 0.20 ng/mL; papillary, 3.44 ± 0.58 ng/mL; acinar, 7.80 ± 2.46 ng/mL; micropapillary predominant pattern, 2.45 ± 0.24 ng/mL; solid, 15.73 ± 9.85 ng/mL; and invasive mucinous adenocarcinoma, 4.28 ± 1.40 ng/mL. $P = 0.004$ (Kruskal–Wallis test). Error bars indicate standard error.

CEA level ($P = 0.018$). There were no significant differences in exon mutations according to gender ($P = 0.568$), smoking status ($P = 0.662$) or histologic subtype ($P = 0.831$) (Table 5).

Table 2 Correlation between serum CEA level and lung adenocarcinoma histologic subtype

IASLC/ATS/ERS adenocarcinoma subtype	CEA level (ng/mL)		*P*
	<5	≥5 (%)	
Lepidic			0.007
With	31	1 (3.1)	
Without	171	54 (24)	
Papillary			0.118
With	45	7 (13.5)	
Without	157	48 (23.4)	
Acinar			0.009
With	96	37 (27.8)	
Without	106	18 (14.5)	
Solid			0.779
With	16	5 (23.8)	
Without	186	50 (21.2)	
Mucinous			0.321
With	11	5 (31.3)	
Without	191	50 (20.7)	

ATS, American Thoracic Society; CEA, carcinoembryonic antigen; ERS European Respiratory Society; IASLC, International Association for the Study of Lung Cancer.

Relationship between KRAS mutation and lung adenocarcinoma histologic subtype

KRAS mutations were detected in 20 of 217 cases (9.2%) and were frequently found not only in the IMA subtype, but also in the SPA subtype. There were significant differences in KRAS mutations according to gender ($P = 0.027$), smoking status ($P = 0.001$), and histologic subtype ($P = 0.006$) (Table 6).

Discussion

Since the IASLC/ATS/ERS classification was published, dozens of published reports have validated various aspects of the classification in resection specimens. However, information on the prevalence of clinical characteristics of lung adenocarcinoma subtypes as defined by the new classification, molecular pathology in particular, remains limited. Thus, we retrospectively analyzed 269 resected cases of initial primary lung adenocarcinoma to identify differences between the histologic subtypes, particularly in terms of *EGFR* mutation.

The most frequent subtype among the resected specimens was APA (52%). Similar results were reported in studies from France (47%), the United States (45%), Korea (41%), and China (40%).[7–10] In contrast, PPA was the most common subtype reported in Taiwan (35%) and Japan (35%).[11,12] This

Table 3 Relationship between *EGFR* mutation and clinicopathologic characteristics

	EGFR mutation		
Factor	+	–	*P*
Gender			0.022
Female	92 (66.2)	47	
Male	40 (50.0)	40	
Age (years)			0.658
<65	88 (59.1)	61	
≥65	44 (62.9)	26	
Smoking status			0.026
Former/current	26 (47.3)	29	
Never	106 (64.6)	58	
CEA (ng/mL)			1.000
<5	84 (60.4)	55	
≥5	48 (60.0)	32	
Lung membrane invasion			0.776
With	48 (58.5)	34	
Without	84 (61.3)	53	
Stage			0.270
I	78 (59.1)	54	
II	25 (54.3)	21	
III/IV	29 (70.7)	12	
Histologic subtype			0.000
LPA	12 (70.6)	5	
APA	83 (64.8)	45	
PPA	29 (72.5)	11	
MPA	2 (100)	0	
SPA	5 (33.3)	10	
IMA	1 (5.9)	16	
Total	132 (60.3)	87	

APA, acinar predominant invasive adenocarcinoma; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; MPA, micropapillary predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

suggests that the most frequent subtype varies according to geographic region or ethnicity.

In NSCLC, serum CEA levels have been widely reported as being correlated with advanced disease, *EGFR* mutation, and survival.[13–15] Our study marks the first time serum CEA levels were compared among lung adenocarcinoma histologic subtypes; differences were detected using the Kruskal–Wallis test ($P = 0.004$). We suspect that the LPA subtype with lower CEA levels might indicate better survival than the APA subtype with higher CEA levels.

Several institutions have reported the percentages of *EGFR* gene mutations in each lung adenocarcinoma histologic subtype. The *EGFR* mutation rates in lung adenocarcinoma differ between Asians and Caucasians.[16] In 138 patients undergoing lung resection in Korea, *EGFR* mutation rates were highest in the MIA subtype (82%), followed by the LPA

Table 5 Relationship between *EGFR* exon mutations and clinicopathologic characteristics

	EGFR mutation		
Factor	19 exon	Other exons (18,20,21)	*P*
Gender			0.568
Male	19	21	
Female	38	54	
Smoking status			0.662
Former/current	10	16	
Never	47	59	
Serum CEA level			0.018
<5	43	41	
≥5	14	34	
Histologic subtype			0.831
LPA	6	6	
APA	38	45	
PPA	11	18	
SPA	2	3	
MPA	0	2	
IMA	0	1	
Total	57	75	

APA, acinar predominant invasive adenocarcinoma; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; MPA, micropapillary predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Table 4 Relationship between EGFR mutation and histologic subtypes

	Male		Female		Non-Smoker		Smoker	
Histologic subtype	N	EGFR +	N	EGFR +	N	EGFR +	N	EGFR +
LPA	5	3 (60)	12	9 (75)	15	11 (73.3)	2	1 (50)
APA	50	27 (54)	78	56 (71.8)	94	64 (68.1)	6	4 (66.7)
PPA	9	7 (77.8)	31	22 (71)	34	25 (73.5)	34	19 (55.9)
MPA	1	1 (100)	1	1 (100)	1	1 (100)	1	1 (100)
SPA	9	1 (11.1)	6	4 (66.7)	6	4 (66.7)	9	1 (11.1)
IMA	6	1 (16.7)	11	0 (0)	14	1 (7.1)	3	0 (0)
Total	80	40 (50)	139	92 (66.2)†	164	106 (64.6)‡	55	26 (47.3)

†Fisher-Freeman-Halton exact test: $P = 0.018$. ‡Fisher-Freeman-Halton exact test: $P = 0.000$. APA, acinar predominant invasive adenocarcinoma; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; MPA, micropapillary predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Table 6 Relationship between *KRAS* mutation and lung adenocarcinoma histologic subtype

	KRAS mutation		
Factor	+ (%)	–	*P*
Gender			0.027
Male	12 (15.4)	66	
Female	8 (5.8)	131	
Age (years)			0.804
<65	13 (8.8)	134	
≥65	7 (10.0)	63	
Smoking status			0.001
Former/current	12 (21.8)	43	
Never	8 (4.9)	154	
Serum CEA level			0.810
<5	12 (8.8)	125	
≥5	8 (10.0)	72	
Histologic subtype			0.006
LPA	1 (5.9)	16	
APA	9 (7.1)	117	
PPA	1 (2.5)	39	
SPA	3 (20.0)	12	
IMA	6 (35.3)	11	
Total	20 (9.2)	197	

APA, acinar predominant invasive adenocarcinoma; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LPA, lepidic predominant invasive adenocarcinoma; MPA, micropapillary predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

(74%), APA (53%), AIS (50%), PPA (50%), MPA (50%), SPA (11%), and IMA subtypes (0%).[9] In 320 surgical patients in Japan, *EGFR* mutation rates were highest in the APA subtype (48.9%), followed by the MIA (45%), PPA (43.8%), MPA (40%), LPA (33.3%), IMA (33.3%), AIS (23.8%), and SPA subtypes (17.4%), representing rather high mutation rates for lepidic-type adenocarcinomas (AIS, MIA, LPA).[12] Another Chinese study (206 cases) reported *EGFR* mutation rates of 80%, 70.7%, 68.8%, 69.5%, 22.5%, and 25% in the MPA, PPA, LPA, APA, SPA, and IMA subtypes, respectively, which were consistent with our results. In our study, the prevalence of *EGFR* gene mutations was highest in the MPA subtype (100%), followed by the PPA (72.5%), LPA (70.6%), APA (64.8%), and SPA subtypes (33.3%), and was lowest in the IMA subtype (5.9%).[10]

Epidermal growth factor receptor mutations are not usually found in the IMA subtype; however, we found an *EGFR* mutation in an IMA subtype.[17] The subtype, as confirmed by the pathologists, showed that the tumor had mixed mucinous and nonmucinous components. We suspect that the mutation was detected from the nonmucinous component.

As tumors with exon 19 deletions are more susceptible to EGFR-TKI therapy than patients with other exon mutations, such as exon 21 mutation, we divided the 132 *EGFR* mutation cases into two groups: exon 19 mutation (57 cases, 43.2%) and other exon mutations (75 cases, 56.8%).[18,19] The distribution of the exon mutations differed according to serum CEA level ($P = 0.018$) but was not related to gender, smoking status or histologic subtype.

Although there are many correlations between histological subtype and EGFR mutations, no histological subtype of lung adenocarcinoma can fully predict EGFR mutation status. Therefore, histological subtypes generally should not be used to guide treatment based on molecular testing in daily clinical practice, and the EGFR mutation test is necessary for any case of lung adenocarcinoma.[5]

When processing small biopsies, there is often not enough tissue for molecular testing or re-biopsy is difficult to achieve. For these reasons, EGFR mutation status cannot be detected for numbers of patients with advanced lung adenocarcinoma, especially in China, where EGFR mutation rates are quite high. In our study, certain predominant subtypes had quite high EGFR mutation rates. Therefore, we propose that tentative EGFR-TKI therapy may be acceptable in selected patients.

Multiple reports indicate that *KRAS* mutations are associated with IMA, while others have reported that they are associated with the SPA subtypes.[17,6] We believe that *KRAS* mutations are frequently found not only in the mucinous-predominant subtype, but also in the SPA subtype.

Conclusions

In China, there are significant differences between lung adenocarcinoma histologic subtypes. The presence of well-differentiated components in lung adenocarcinoma, such as the lepidic, papillary, and acinar components, indicates higher *EGFR* mutation rates, while the presence of solid or mucinous components indicates higher *KRAS* mutation rates. Additionally, serum CEA levels may be associated with the histologic subtype and *EGFR* exon mutation.

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Disclosure

No authors report any conflict of interest.

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