

Aim of the study: Pulmonary pleomorphic carcinoma (PPC) of the lung is a subset of poorly differentiated non-small cell lung cancers (NSCLCs). Because of its rarity, information on epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene (KRAS) mutations is controversial and sparse. The aim was to investigate the two key oncogenes' characteristics and their correlation with clinical variables.

Material and methods: We retrospectively screened 110 paraffin-embedded surgically resected specimens from patients with PPC. Of these, follow-up information was available for 48 patients. We then successfully analyzed 70 PPC samples and examined EGFR and KRAS mutation status by direct sequencing. The findings were correlated with a control group of patients with other NSCLCs.

Results: In our department, PPC comprised about 1.57% of surgical resected cases (110/6990). 37.4% of patients smoked. EGFR mutations were detected in 11 cases (15.7%), with a significantly higher frequency in women than men ($p = 0.011$). KRAS mutations were detected in 10 cases (14.3%) and were more often found at age 65 or older ($p = 0.02$). Of interest, in PPC, all KRAS mutations occurred in never smokers. Also, most never smokers have transversion mutations (G→T) in PPCs and other NSCLCs.

Conclusions: Our results demonstrated a similar EGFR and KRAS mutation rate in Chinese PPC patients. EGFR tyrosine kinase inhibitors may be a treatment option for PPCs with EGFR mutations. Of note, EGFR mutations in PPC were commonly identified in women; therefore women should be high-priority candidates for mutation screening.

Key words: pulmonary pleomorphic carcinoma, EGFR mutation, KRAS mutation.

Contemp Oncol (Pozn) 2015; 19 (1): 22–27
DOI: 10.5114/wo.2014.43491

EGFR and KRAS mutations in pulmonary pleomorphic carcinoma and their correlation with clinicopathologic features

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Introduction

Pulmonary pleomorphic carcinoma (PPC) is an uncommon heterogeneous tumor of non-small cell lung carcinomas (NSCLCs). The reported incidence of PPC in the literature has ranged from 0.1% to 1.6% of all lung cancer [1–3]. According to the WHO classification of lung tumors, PPC is defined as a carcinoma consisting of spindle and giant cells alone or NSCLC combined with a sarcomatoid tumor component of at least 10% [4–6]. Several studies have reported that many lung adenocarcinomas (ADs) are highly sensitive to tyrosine kinase inhibitors (TKIs), and most of these patients are from the Asian, female, nonsmoker population [7–10]. However, the information on the epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene (KRAS) mutation status of PPC is sparse and controversial because of its rarity. And whether EGFR inhibitor therapy might be effective in patients with PPC is not yet clear. Italiano *et al.* reported the lack of EGFR mutation and high rate of KRAS mutation. Most patients with PPC were not likely to benefit from EGFR-targeted therapies [11, 12]. Nonetheless, a number of other studies show the existence of EGFR mutation, and a low KRAS mutation incidence rate [13–15]. Factors such as the small series of patients, and geographical or racial variation, might explain these differences. Moreover, the incidence of EGFR mutations in Chinese PPC patients has not been defined.

In the current study, therefore, we examine the EGFR and KRAS mutation status in a relatively large series of surgically treated PPC specimens, and investigate the association of several clinical variables with the EGFR and KRAS mutation, in order to identify useful information on patient selection for targeted therapy.

Material and methods

Tumor cases

Between February 2007 and February 2011, a total of 6990 patients with NSCLC were treated surgically in the Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Shanghai, China. A total of 110 cases of PPC (1.57%) and 225 other cases of NSCLC, i.e., 113 ADs, 40 squamous cell carcinomas (SQs), 55 adenosquamous carcinomas (ADSQs) and 17 large cell carcinomas (LCCs) of lung, were collected and diagnosed strictly using the WHO classification [4]. In every case, we used formalin-fixed and paraffin-embedded tissues from resections. All slides were reviewed blindly by 2 pathologists. In addition, in each case of PPC, the epithelial immunophenotype of the tumor was confirmed using markers of AD (TTF1, SPA and SPB) and SQ (p63, CK5/6 and 34 E12). We also performed additional immunohistochemical (IHC) stains for Vimion to demonstrate sarcoma. Clinical information, including patient sex, age at diagnosis, and smoking history was obtained for all these cases. Testing

for EGFR and KRAS mutations was successfully analyzed in 70 PPCs and 225 other cases. This study was approved by the institutional review boards, and appropriate written informed consent was obtained from all patients.

DNA extraction and sequencing analysis

For mutation detection, DNA was extracted from the formalin-fixed, paraffin-embedded tumor sections. EGFR exon 19 and 21 and KRAS codon 12 and 13 mutations were detected using direct-sequencing polymerase chain reaction as previously described [16]. To minimize necrosis and normal cell genomic DNA contamination, tumor areas were selected by manual microdissection of HE stained slides.

Statistical analysis

The data were analyzed using SPSS version 17.0 for Windows. Correlations between clinicopathologic and molecular factors were determined using the χ^2 and Fisher exact tests. The Mann-Whitney *U* test was used to detect significant differences in patient age and tumor size. Overall survival was defined as the time from surgical resection until the date of death or last follow-up for patients who remained alive. Survival curves were analyzed using the Kaplan-Meier method and compared by using the log-rank test. Univariate and multivariate relative risk were calculated using Cox proportional hazards regression. Two-sided *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Clinicopathologic characteristics of the 110 pulmonary pleomorphic carcinomas and comparison with other non-small cell lung carcinomas

Clinicopathological characteristics of all 110 PPC and other NSCLC patients are compiled in Table 1. Briefly, the case series included 92 men and 18 women (M : F ratio 5 : 1), aged from 38 to 78 years (median 62 years). There were 39 smokers, and 71 never smokers. The median diameter of the tumor was 4.5 cm (1–14 cm). The locations of the lesions were as follows: in 24 cases they were in the central, in 84 cases in the peripheral, and in 2 cases in both locations.

With respect to the comparison of clinicopathologic features, higher age (*p* = 0.027), male sex (*p* = 0.001), smoker (*p* = 0.039), and larger tumor size (*p* = 0.000) were significantly more common in the group of 110 PPCs than in the other group of 225 NSCLCs (Table 1), but the difference of tumor site was not statistically significant (*p* = 0.251).

Histologic features and mutational analysis of 70 pulmonary pleomorphic carcinomas

Sequence analysis of EGFR and KRAS genes was performed on 70 PPCs. On the basis of microscopic examination and IHC staining results, we could identify 18 tumors consisting of spindle cells and giant cells alone, and 52 contained identifiable epithelial components (36 cases showed AD, 7 had SQ, 8 had ADSQ and 1 had LCC).

We identified 11 mutations (15.7%) in EGFR and 10 mutations (14.3%) in KRAS. In particular, EGFR mutations con-

sisted of 2 frame deletions in exon 19 (E746_A750del), and 9 amino acid substitutions in exon 21 (L858R). All KRAS codon 12 and 13 mutations were missense mutations (G12C in 5 cases, G12D in 2, G12V in 1, G12A in 1, and G13C in 1), and all these patients were non-smokers. No mutations were observed simultaneously in both EGFR and KRAS genes (Table 2). Also, 10 PPCs with EGFR mutated had an identifiable epithelial component (6 ADs, 3 ADSQ and 1 SQ) and 1 was classified as pure PPC consisting only of spindle and giant cells. KRAS mutation was found in 8 cases with an epithelial component (6 ADs, 1 ADSQ and 1 SQ), and 2 showed only mesenchymal elements (Table 3).

For most mutated patients, different areas corresponding to the epithelial and sarcomatoid components were intimately admixed. Only in two EGFR and one KRAS mutated cases (patients 1, 5 and 19) were the two elements clearly distinct from each other. Therefore, we were able to easily select by manual microdissection, and analyze independently, both the epithelial and the sarcomatoid elements. The same EGFR and KRAS mutations were detected in the two different histological components in all three cases.

Comparison of EGFR and KRAS mutations with those of other non-small cell lung carcinomas

In comparison with PPCs, there was a higher EGFR mutation rate (42.5%) and lower KRAS mutation rate (4.42%) in the AD group, and the difference was significant (*p* = 0.000). When the rates of EGFR mutation between PPC and SQ groups were compared alone, near significance was achieved (*p* = 0.053). Moreover, ADSQ group had a higher mutation rate of EGFR (*p* = 0.007) than PPC group, whereas the statistical significance between the two groups in KRAS mutation rate was borderline (*p* = 0.065) (Table 2). Further, we compared the different type of KRAS mutation in these patients. The most frequent type of

Table 1. Clinicopathologic characteristics of the 110 pulmonary pleomorphic carcinomas and the comparison with other NSCLCs

Characteristic	Pleomorphic carcinoma n = 110 (%)	Other NSCLC n = 225 (%)	<i>p</i>
Age (y)			0.027
median	62	59	
range	38–78	30–79	
Sex			0.001
male	92 (83.5)	137 (60.9)	
female	18 (16.5)	88 (39.1)	
Smoking history			0.039
smoker	39 (37.4)	55 (24.4)	
never smoker	71 (62.6)	170 (75.5)	
Tumor size (cm)			0.000
median	4.5	3	
range	1–14	0.4–12	
Tumor site			0.251
central	24 (21.7)	67 (29.8)	
peridilection	84 (76.5)	156 (69.3)	
central and peridilection	2 (1.7)	2 (0.89)	

NSCLC – non-small cell lung carcinoma

base change was a G→T transversion (12 of 19 mutations). Two of the KRAS mutations were G→C transversions and 5 were G→A transitions. Still, only three of the patients were ex-smokers (2 ADs with G→A mutation and 1 ADSQ with G→T mutation) (Table 4).

Relationship between EGFR and KRAS mutations and clinicopathologic variables

We assessed the relationship between EGFR and KRAS mutations and the clinicopathologic variables listed in Table 2. No significant association was observed between mutation status and smoking history, tumor size, site, stage and histologic components. There was a statistically significant association between the frequency of EGFR mutations and sex (44.4% in females versus 11.5% in males, $p = 0.011$). KRAS mutations were more often found in old age (26.9% of cases at age 65 or older, $p = 0.02$). Additionally, all KRAS mutations occurred in non-smokers.

Prognosis and overall survival

Complete follow-up information was available for 48 cases of PPC. The 5-year survival rate and median overall survival (OS) time were 40% and 36.68 months, respectively. Of these patients, 25 (52.08%) died of disease, with a fol-

low-up ranging from 1 to 51 months; 23 patients (47.92%) were alive, with a follow-up ranging from 23 to 64 months. In univariate analysis, OS was negatively influenced by advanced stage (I–II vs. III–IVA, $p = 0.000$) and tumor size ($p = 0.012$). None of the other analyzed variables, namely gender, age, lymph node metastasis, smoking history, tumor necrosis, location and EGFR/KRAS mutation, had a significant influence on OS. The multivariate analysis confirmed age ($p = 0.019$), tumor size ($p = 0.044$) and stage ($p = 0.000$) as independent variables for OS (Table 5).

Table 3 shows clinicopathological findings and survival of 21 patients with EGFR and KRAS mutations. The survival data were available for 7 EGFR and 7 KRAS mutated patients. None of the correlations between the 2 groups in OS were statistically significant ($p = 0.88$). More significantly, patient 2 with stage IV disease, a woman who had an exon 19 deletion mutation (E746_A750del), was treated with gefitinib and achieved stable disease. This improvement has lasted for approximately 9 months, and follow-up is underway.

Discussion

Pulmonary pleomorphic carcinoma of the lung is rare. In the current study, we collected a relatively large number

Table 2. Mutational analysis and clinicopathologic findings of pulmonary pleomorphic carcinomas and comparison of the mutations with those of other NSCLCs

Variable	N	EGFR mutation (%)	p	KRAS mutation (%)	p
Age			0.461		0.02
< 65	44	8 (18.2)		3 (6.8)	
≥ 65	26	3 (11.5)		7 (26.9)	
Gender			0.011		0.19
male	61	7 (11.5)		10 (16.4)	
female	9	4 (44.4)		0 (0.0)	
Tumor location			0.557		0.433
central	17	4 (23.5)		4 (23.5)	
predilection	52	7 (13.5)		6 (11.5)	
central and predilection	1	0 (0.0)		0 (0.0)	
Tumor size (cm)			0.324		1.00
< 3	14	1 (7.14)		2 (14.3)	
≥ 3	56	10 (17.8)		8 (14.3)	
Smoking status			0.775		0.074
never	55	9 (16.4)		10 (18.2)	
ever	15	2 (13.3)		0 (0.0)	
Stage			0.606		0.209
I	29	4 (13.8)		6 (20.7)	
II	14	2 (14.3)		3 (21.4)	
III	17	2 (11.8)		0 (0.0)	
IV	10	3 (30)		1 (10)	
Histologic component			0.645		0.973
AD	36	10 (27.8)		6 (16.7)	
SQ	7	1 (14.3)		1 (14.3)	
ADSQ	8	2 (25)		1 (12.5)	
LCC	1	0 (0.00)		0 (0.00)	
mixed	18	1 (5.56)		2 (11.1)	
Other NSCLC vs. PPC					
AD	113	48 (42.5)	0.000	5 (4.42)	0.025
SQ	40	1 (2.5)	0.053	2 (5.0)	0.205
ADSQ	55	21 (38.2)	0.007	2 (3.6)	0.065
LCC	17	0 (0.0)	0.112	0 (0.0)	0.199

Table 3. Histologic features and survival of 21 pulmonary pleomorphic carcinomas with EGFR and KRAS mutations

Patient	Age/Sex	Size	Epithelial component	Sarcoma component	EGFR mutation	KRAS mutation	OS (months)	Outcome	Stage
1	59/F	1.8	AD	spindle	E746-A750del		12	live	T2N0M0IB
2	60/F	3	AD	mixed	E746-A750del		12	live	T2N2M1IV
3	51/M	4	AD	spindle	L858R		15	live	T2N0M1IV
4	58/M	3.5	AD	mixed	L858R		3	dead	T2N2M0IIIA
5	55/M	5	ADSQ	spindle	L858R		NA	NA	T2N1M0IIB
6	65/F	5	AD	mixed	L858R		NA	NA	T3N0M0IIB
7	64/M	4	AD	giant	L858R		7	dead	T4N1M1IV
8	63/M	5	ADSQ	giant	L858R		16	live	T2N0M0IB
9	77/F	4	ADSQ	mixed	L858R		No	no	T2N2M0IIIA
10	78/M	4.5	SQ	mixed	L858R		15	live	T2N0M0IB
11	53/M	5.5		mixed	L858R		NA	NA	T2N0M0IB
12	55/M	11	AD	mixed		G12A	NA	NA	T2N1M0IIB
13	64/M	8	AD	mixed		G12C	34	live	T2N0M0IB
14	56/M	5.5	AD	mixed		G12C	7	dead	T3N0M0IIB
15	66/M	3	SQ	mixed		G12C	NA	NA	T2N0M0IB
16	75/M	7	AD	mixed		G12C	6	live	T2N2M1IV
17	70/M	4		mixed		G12C	14	live	T2N0M0IB
18	71/M	2.5	AD	giant		G12D	24	live	T2N0M0IB
19	68/M	6.5	ADSQ	giant		G12D	NA	NA	T3N0M0IIB
20	66/M	7.5		mixed		G12V	10	dead	T2N1M0IIB
21	75/M	1	AD	spindle		G13C	10	dead	T1N0M0IA

AD – adenocarcinoma; SQ – squamous cell carcinoma; ADSQ – adenosquamous carcinoma; mixed – spindle and giant cell carcinoma; OS – overall survival; NA – not available

of PPCs to better define their clinicopathologic features and explored the relationship between EGFR and KRAS mutation status and multiple variables. In agreement with a previous work on PPCs [2], it accounted for 1.57% (115/6990) of surgically resected NSCLC cases in our department, prevailing in males as a large peripheral lesion. The smokers in our series comprised 37.4% (43/115) and the incidence rate is lower than in other reports [2, 3]. Recently, Mochizuki *et al.* mentioned that PPC has distinctive clinicopathological features compared with other NSCLCs [17]. Consistent with their report, our analysis demonstrates a higher number of male smokers, older age and larger tumor size.

Since EGFR and KRAS genes were the most clinically relevant molecular biomarkers in NSCLC, we examined the two key oncogenes' characteristics in 70 resected PPCs. Activating EGFR mutations were seen in 11 patients (15.7%), whereas KRAS mutations were identified in 10 patients (14.3%). Our results revealed that the EGFR mutation rate of PPC is lower than that of AD and ADSQ, but might be higher than that of SQ. The KRAS positive rates are largely concordant with the recently evaluated value

of 9–22% in PPC patients [13–15]. Some investigators have also noted that patients with single classical mutations (del-19 or L858R) show a better response to gefitinib than those without the classical mutations [18, 19]. In our study, we identified 10 classical mutations; among these, 2 cases had exon 19 deletions and 8 had L858R point mutations. These results suggested that mutational analysis in patients with PPC should be considered before deciding on a course of treatment. In addition, although there is a male preponderance in PPC, EGFR mutations were also more frequent in females ($p = 0.011$). Consequently, women should be high-priority candidates for EGFR mutation screening. Additionally, in our cohort, 2 tumors with a non-AD component had activating EGFR mutations. Thus, the distribution of EGFR mutation was not associated with the type of malignant epithelial components. Also, KRAS mutations occurred in different subtypes of PPC. Still, we found that KRAS mutation was more frequently detected in older patients than younger patients (age ≥ 65 vs. < 65) ($p = 0.02$).

With regard to the histogenesis of PPC, two possible pathways have been proposed, divided into monoclonal and polyclonal pathways. Kyoichi Kaira *et al.* described

Table 4. Relationship between KRAS mutation type and smoking history in NSCLCs

NSCLCs	KRAS mutation type	Smoking history
PPC	G12A (GGT→GCT)	no
PPC	G12C (GGT→TGT)	no
PPC	G12C (GGT→TGT)	no
PPC	G12C (GGT→TGT)	no
PPC	G12C (GGT→TGT)	no
PPC	G12C (GGT→TGT)	no
PPC	G12D (GGT→GAT)	no
PPC	G12D (GGT→GAT)	no
PPC	G12V (GGT→GTT)	no
PPC	G13C (GGT→TGT)	no
AD	G12C (GGT→TGT)	no
AD	G12D (GGT→GAT)	yes
AD	G12D (GGT→GAT)	yes
AD	G12V (GGT→GTT)	no
AD	G12V (GGT→GTT)	no
SQ	G12R (GGT→CGT)	no
SQ	G12S (GGT→AGT)	no
ADSQ	G12C (GGT→TGT)	yes
ADSQ	G12C (GGT→TGT)	no

PPC – pulmonary pleomorphic carcinoma; AD – adenocarcinoma;
SQ – squamous cell carcinoma; ADSQ – adenosquamous carcinoma

three patients with two different histologic types exhibiting EGFR mutations. Their cases revealed that the adenocarcinomatous component had an EGFR mutation and the sarcomatoid component did not [20]. In our series, in contrast, we found that both epithelial and sarcomatoid components carried identical EGFR and KRAS mutations, favoring the contention that PPCs were monoclonal in origin [16, 21].

Table 5. Univariate and multivariate analyses concerning PPC ($n = 48$)

Variables	Univariate <i>p</i> value	Multivariate		
		<i>p</i> value	HR	95% CI
male vs. female	0.992	0.964	0.961	0.169–5.453
age (y) ≥ 65 vs. < 65	0.081	0.019	0.297	0.108–0.816
tumor size ≥ 3 cm vs. < 3 cm	0.012	0.004	0.255	0.068–0.962
with vs. without tumor necrosis	0.053	0.239	0.549	0.202–1.489
early stage vs. late stage	0.000	0.000	0.061	0.020–0.183
with vs. without EGFR/KRAS mutation	0.709	0.649	0.857	0.443–1.661
smoking vs. no smoking	0.516	0.919	1.066	0.310–3.672

HR – hazard ratio; CI – confidence interval

Another interesting finding is the lack of association between KRAS mutation and smoking. In our studies, even though it was not statistically significant ($p = 0.074$), non-smokers tended to exhibit KRAS mutations more commonly (10/55, 18.2%) than smokers (0/15, 0.0%). In addition, in comparison with other NSCLCs, smokers were more frequent in the PPC group ($p = 0.039$). Consequently, we speculated that although smoking is a risk factor for the development of PPC, it may be less strongly associated with KRAS mutations in Chinese patients, arguing against the notion that all KRAS mutations are confined to smokers [15].

Ahrendt *et al.* reported that in KRAS transversions (substituting a pyrimidine for a purine, or a purine for a pyrimidine) are more common than transitions (substituting a purine for a purine, or a pyrimidine for a pyrimidine), and KRAS mutations were significantly more frequent in lung ADs from smokers compared with those from nonsmokers (43% vs. 0%; $p = 0.001$) [22]. Riely *et al.* found that KRAS transversion mutations (G→T or G→C) were more common in smokers with lung AD [23]. In contrast, our studies demonstrated that KRAS mutations in AD were present in only 5 (4.42%) patients. Of the 5 mutations, 2 in smokers were transition mutations and 3 in non-smokers were transversion mutations. Also, we found that most never smokers have transversion mutations (G→T) in PPCs and other NSCLCs. The discrepancy might be attributed to geographical or racial differences in these studies. However, the distinct profile of KRAS mutations observed here in never smokers further suggests that while some mutations in KRAS are associated with cigarette smoking, KRAS tumor status cannot be easily predicted on the basis of smoking history alone.

Several researchers [24–26] have reported that gefitinib was effective in PPC patients with L858R EGFR mutation. In our series, one patient who had a deletion mutation in exon 19 of EGFR and was treated with gefitinib achieved SD. These findings may suggest that gefitinib is effective in PPC with EGFR mutation. Our study also indicated that sex, smoking history, lymph node status, mutation type, tumor size and site did not have an impact on length of survival, whereas old age and late stage may have significant value in predicting a poor prognosis.

In summary, we observed a similar EGFR and KRAS mutation rate in Chinese PC patients. Our findings fur-

ther confirmed that some patients with PPC may possess active EGFR mutations and benefit from EGFR-targeted therapies. Of note, EGFR mutations in PPC were commonly identified in women; therefore women should be high-priority candidates for EGFR mutation screening.

The authors declare no conflict of interest.

This work was supported by the Fundamental Research Funds for the Central Universities (grant No. 1511219018) and by the grant from Youth Research Project of Shanghai Municipal Health Bureau (grant No. 20124y088).

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Submitted: 17.02.2014

Accepted: 11.04.2014