Original Article

Comparison of clinical and radiological characteristics between anaplastic lymphoma kinase rearrangement and epidermal growth factor receptor mutation in treatment naïve advanced lung adenocarcinoma

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Background: Gene analysis could not be performed in all patients, especially in advanced non-small cell lung cancer (NSCLC). We aimed to find some clinical futures and CT or FDG-PET characteristics, which could be combined to help distinguish anaplastic lymphoma kinase (*ALK*) rearrangement form epidermal growth factor receptor (*EGFR*) mutations in treatment naïve advanced lung adenocarcinoma of Chinese patients.

Methods: We retrospectively reviewed clinical and radiological characteristics of 145 patients with treatment naïve advanced lung adenocarcinoma. The one-way ANOVA, the Mann-Whitney test, chi-square test and logistic regression were used for comparison between patients with *ALK* rearrangement and those with *EGFR* mutation.

Results: Among 145 patients with advanced lung adenocarcinoma, only six patients had both *ALK* rearrangement and *EGFR* mutation, the sample size was too small to analysis. Univariate analysis revealed that patients with *ALK* rearrangement were younger (P=0.001) and with lower serum carcinoembryonic antigen (CEA) level (P=0.008) than those with *EGFR* mutation. More of tumors with *ALK* rearrangement were well defined (P=0.023) and have bubble lucency (P=0.026) compared with those with *EGFR* mutation (P=0.026). Lymphadenopathy was seen more frequently in patients with *ALK* rearrangement (P=0.167). Twenty-six patients received FDG-PET/CT, among this population, lesion standardized uptake values (SUV) >6.95 and lymph nodes SUV_{max} >6.25 were more often seen in *ALK* rearrangement group (P=0.011, both). In multivariate analysis, patients younger than 50 years (RR =9.878, 95% CI: 2.318–42.090, P=0.002), with lower CEA level than 4.95 μg/L (RR =8.166, 95% CI: 1.085–31.983, P=0.003) and without brain metastasis (RR =7.304, 95% CI: 1.099–48.558, P=0.040) were more likely to be *ALK* rearrangement than *EGFR* mutation. Tumor diameter less than 36 mm were prone to be *EGFR* mutation (RR =0.078, 95% CI: 0.017–0.356, P=0.001).

Conclusions: Treatment naïve advanced lung adenocarcinomas with *ALK* rearrangement were more likely to have younger age, lower serum CEA level, larger tumor volume, well defined tumor border, and non-brain metastasis than those with *EGFR* mutation. Bubble lucency and higher FDG uptake of lesion and lymph nodes may help distinguish *ALK* rearrangement from *EGFR* mutation in the absence of genetic analysis.

Keywords: High-resolution computed tomography (HRCT); anaplastic lymphoma kinase (ALK); epidermal growth factor receptor (EGFR), advanced non-small cell lung cancer (NSCLC)

Submitted Feb 14, 2017. Accepted for publication Aug 17, 2017.
doi: 10.21037/jtd.2017.08.134
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.134

Introduction

Non-small cell lung cancer (NSCLC) accounts for a large proportion of lung carcinoma, which is one of the major causes of cancer death worldwide (1). During the past decade, adenocarcinoma has been the most common pathological type and the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) published a new classification for lung adenocarcinoma in 2011 Feb (2,3). In this classification, guidance for small biopsies in advanced stage patients was also provided (2). It recommends gene test for epidermal growth factor receptor (*EGFR*) mutation in adenocarcinoma, because these mutations are related to high response to EGFR tyrosine kinase inhibitors (EGFR-TKI) (4,5). While Soda *et al.* identified anaplastic lymphoma kinase (*ALK*) gene rearrangement as another diagnostic marker and therapeutic target in 2007 (6). The fusion gene comprised the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and *ALK* gene is occurring in 2–7% of NSCLC and 8–22% of light or never smokers suffered from lung cancer (7,8). *ALK* rearrangement targeting therapies have been investigated recent years. In a phase 3 study, crizotinib is found to be superior to standard chemotherapy in advanced NSCLC with *ALK* rearrangement (9). However, due to old age, serious diseases or other reasons, not every patient could undergo *EGFR* and *ALK* gene analysis. Although liquid biopsy has developed rapidly recent years, it is expensive and has not been popularized in clinic. It is important to find some specific clinical and radiologic characteristics to distinguish adenocarcinoma with *ALK* rearrangement from those with *EGFR* mutation.

Previous studies have attempted to investigate the clinicopathologic and radiogenomic features which could predict *ALK* rearrangement NSCLCs. Although a lot of studies found *ALK* rearrangement was highly occurred in younger, female and never smoked adenocarcinomas, it was overlapped with *EGFR* mutated patients on clinical profiles (10-12). Fortunately, some radiologic characteristics of *ALK* rearrangement were detected (13-16). Nakada *et al.* (14) reported that *ALK* rearrangement lesions were smaller and had a low tumor disappearance rate than *EGFR* mutated lesions on high-resolution computed tomography (HRCT). However, another study discovered *ALK* rearrangement positive lung adenocarcinomas were more likely to be large and with thoracic lymphadenopathy (15). A nearly research suggests that patents with *ALK* rearrangement is younger, and characterized by lobulated margin and solid lesion compared with *EGFR* mutant and wide type cohorts in surgically resected NSCLCs (16). These conclusions were mostly studied in early stage NSCLCs, and may remain some uncertainties.

However, a meta-analysis pooled 27 retrospective studies revealed that *EML4-ALK* was more common in adenocarcinoma lacking *EGFR* and *KRAS* mutation, never smoked and advanced NSCLC (17). Recently a retrospective study found that adenocarcinomas with *ALK* rearrangement were more likely to be solid masses and with lymph node metastasis or pleural metastasis compared with those with *EGFR* mutations (18). Nevertheless few investigations of *ALK* rearrangement and *EGFR* mutation have been conducted in advanced NSCLCs. Furthermore most of the patients who could not undergo *EGFR* and *ALK* gene analysis are first diagnosed as advanced lung cancer. We conducted this retrospective study attempted to investigate some clinical and radiologic differences between advanced NSCLCs with *ALK* rearrangement and those with *EGFR* mutations. The aim of our study was to find a few clinical futures and CT or FDG-PET characteristics, which could be combined to help distinguish *ALK* rearrangement form *EGFR* mutations in treatment naïve advanced lung adenocarcinoma of Chinese patients.

Methods

Patients

This retrospective study reviewed the clinical profiles, HRCT images, and FDG-PET features in patients with treatment naïve advanced lung adenocarcinoma (clinical stage IIIB or IV). These patients underwent small biopsies, both *ALK* rearrangement and *EGFR* mutation analysis

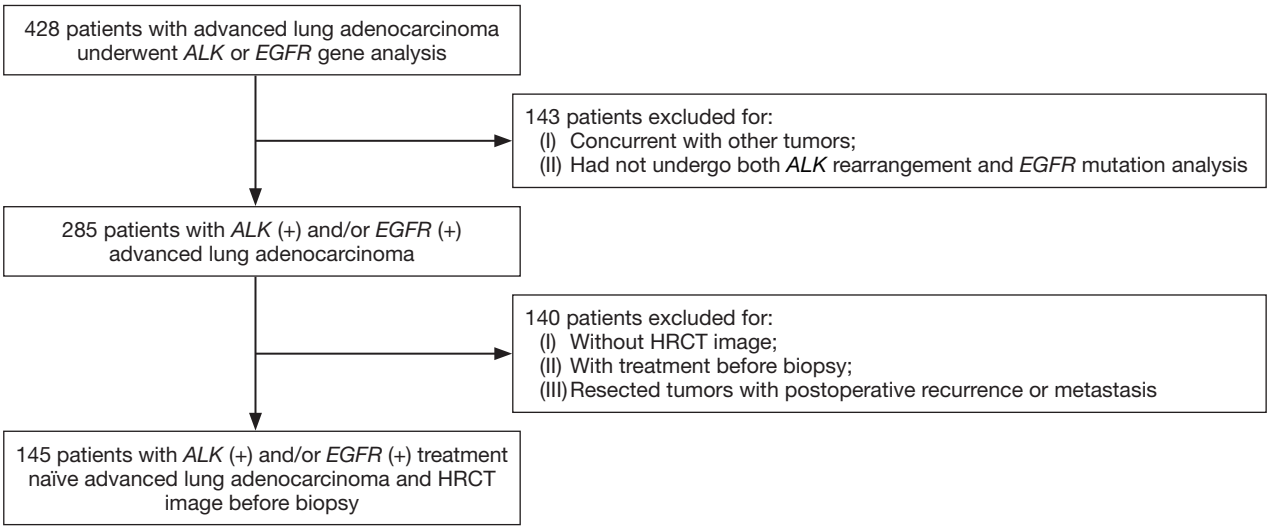

Figure 1 Selection process for untreated advanced lung adenocarcinoma with *ALK* rearrangement and/or *EGFR* mutation and HRCT image. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HRVT, high-resolution computed tomography.

in Jinling Hospital (Jiangsu, China) from January 2013 to December 2015. A total of 428 patients were identified. Eligible criteria included: 18 years or older; stage IIIB/IV NSCLC with percutaneous core needle and/or bronchoscopic biopsy diagnosed as adenocarcinoma; with *ALK* rearrangement and/or *EGFR* mutation, had not underwent any treatment (chemotherapy, radiation therapy, or immunologic therapy); performed chest HRCT before lung biopsy in our institution. Finally, 145 patients (91 female and 54 male; age range, 27–78 years; average age, 57.5 years) were included. In addition, patients concurrent with other tumors were excluded (*Figure 1*). This study design was approved by the Ethics Committee of Jinling Hospital. The requirement for informed consent was waived.

HRCT and FDG-PET evaluation

All studies were performed using a multi-slice CT scanner system (Somatom Sensation 64, Siemens, Erlangen, Germany). Scanning parameters were as following: tube voltage 120 kVp, tube current 150–200 mA, rotation time 0.5 s, and 2 mm reconstruction thickness with a 1 mm reconstruction interval. Two radiologists with more than 5 years of experience retrospectively interpreted the HRCT images independently. They were blinded to the pathological findings. When there were different opinions of the CT images, these two radiologists would discuss and reach a final consensus. All of the main HRCT characteristics were shown in *Table 1*. In *Table 1*, "well-defined borders" means the boundary between the nodule and the lung tissue is clearly defined and outlined as a pencil; "poorly-defined borders" means the boundary between the nodule and the lung tissue is not clear and cannot be completely outlined with a thin nodule contour; "bubble lucency" means bronchus encapsulated air sign and cavity.

Only 26 of the included patients underwent integrated FDG-PET/CT before any clinical treatment. 18F-FDG was administered intravenously 1 hour prior to PET/CT scans. Fluorodeoxyglucose-positron emission tomography data was analyzed using standardized uptake values (SUV). We used trans-axial images for analysis. SUVs were calculated as decay-corrected activity (kBq) per milliliter of tissue volume divided by injected dose per weight (kBp/g). SUV_{max} of lymph nodes was measured after placing a region of interest over all masses.

ALK rearrangement and EGFR mutation analysis

DNA was extracted from five pieces of formalin-fixed, paraffin-embedded (FFPE) tumor tissue using the QIAamp FFPE Tissue Kit. Molecular analysis of mutation status of *EGFR* exons 18, 19, 20, and 21 was examined with Human *EGFR* Gene Mutations Detection Kit (AmoyDx, Xiamen, China), which is a polymerase chain reaction (PCR)—based amplification-refractory mutation system (ARMS). *ALK-EML4* gene rearrangements were detected by VENTANA immunological histological chemistry (IHC) kits [ALK (D5F3), VENTANA, Roche].

Table 1 Univariate analysis of HRCT characteristics and driver mutations

HRCT characteristics	Number	Genetic alteration			*ALK*+ *vs. EGFR*+	
		ALK+ and *EGFR*+	*ALK*+	*EGFR*+	χ^2/F	P value
All patients [n (%)]	145	6 [4]	27 [19]	112 [77]	–	–
Diameter (mm)*	7–120	12–75	7–120	10–102	–	0.549*
Diameter (mm)	145	–	–	–	2.129	0.198
≤36	73	4	10	59	–	–
>36	72	2	17	53	–	–
Shape	145	–	–	–	0.469	0.493
Round	72	2	12	58	–	–
Irregular	73	4	15	54	–	–
Border definition	145	–	–	–	5.143	0.023
Poorly defined	92	4	12	76	–	–
Well defined	53	2	15	36	–	–
Margin	145	–	–	–	1.250	0.262
Smooth	5	0	0	5	–	–
Spiculation or lobulation	140	6	27	107	–	–
Air bronchogram	145	–	–	–	0.469	0.493
–	72	2	12	58	–	–
+	73	4	15	54	–	–
Bubble lucency	145				4.959	0.026
–	119	6	26	87	–	–
+	26	0	1	25	–	–
Vessel convergence sign	145	–	–	–	1.789	1.818
–	47	1	6	40	–	–
+	98	5	21	72	–	–
Pleural retraction	145	–	–	–	2.734	0.098
–	32	2	9	21	–	–
+	113	4	18	91	–	–
Pleural thickening	145	–	–	–	1.426	0.232
–	89	3	14	72	–	–
+	56	3	13	40	–	–
PLC	145	–	–	–	0.150	0.699
–	132	6	25	101	–	–
+	13	0	2	11	–	–
Hydrothorax	145	–	–	–	0.163	0.687
–	91	3	18	70	–	–
+	54	3	9	42	–	–
Lymphadenopathy	145	–	–	–	1.911	0.167
–	25	3	4	31	–	–
+	120	3	23	81	–	–
Enhancement	125	–	–	–	0.204	0.652
–	2	1	0	1	–	–
+	123	5	20	98	–	–

*, diameter (mm) analysis used the Mann-Whitney test, others used chi-square test. +, positive; –, negative; HRVT, high-resolution computed tomography; PLC, pulmonary lymphangitic carcinomatosis; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

Table 2 Clinical characteristics of patients with advanced lung adenocarcinoma

Characteristics	Overall (n=145), [%] or [range]
Sex	
Female	91 [63]
Male	54 [37]
Age (years)	
<50	30 [21]
≥50	115 [79]
Median	57.50±10.04 [27–78]
Smoking history	
No	110 [76]
Yes	35 [24]
Family tumor history	
No	133 [92]
Yes	12 [8]
Tumor location	
RUL	35 [24]
RML	7 [5]
RLL	37 [26]
LUL	35 [24]
LLL	31 [21]
Tumor stage	
T1 or T2	32 [22]
T3 or T4	113 [78]
Node stage	
N0 or N1	23 [16]
N2 or N3	122 [84]
Metastasis	
0	7 [5]
1a	47 [32]
1b	91 [63]
Clinical stage	
IIIB	7 [5]
IV	138 [95]
ALK-EML4	
+	33 [23]
–	112 [77]
EGFR status	
EGFR+	118 [81]
L858R	57 [39]
19-Del	52 [36]
Others#	9 [6]
EGFR–	27 [19]

#, other EGFR mutations including: Exon21 L861Q, Exon18 G719X, Exon20 S768I, L858R/T790M, L858R/19-Del, 19-Del/T790M, and 19-Del/S768I. RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; ALK, anaplastic lymphoma kinase; EML4, echinderm microtubule-associated protein-like 4; EGFR, epidermal growth factor receptor.

Statistics

Continuous variables were compared using the one-way ANOVA or the Mann-Whitney test. Categorical variables were analyzed by chi-square test or Fisher's exact test. Before compare the average diameter, serum carcinoembryonic antigen (CEA) and SUV_{max} values of tumors with *ALK* rearrangement and those with *EGFR* mutation, we calculated optimal cut-off values using a receiver operating characteristic (ROC)-based positive test with *ALK* rearrangement as categorical variables. Then the tumor diameters, serum CEA and SUV_{max} values of tumors were dichotomized as ≤ optimal cut-off value and > optimal cut-off value.

To investigate independent factors that may help distinguish tumors with *ALK* rearrangement from those with *EGFR* mutation, we performed multivariate logistic regression analysis. Variables were selected by a forward stepwise selection mode before multivariate analysis. Values of $P<0.05$ were considered statistically significant. We used Statistical Product and Service Solutions (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) to conduct statistical analysis.

Results

Patient characteristics

A total of 145 patients were enrolled in this study. Their clinical characteristics are presented in *Table 2*. All of the patients were clinically diagnosed as advanced lung adenocarcinoma: IIIB stage in 7 (5%) patients and IV in 138 (95%) patients. Most patients were female (63%) and non-smoker (76%). A majority of the patients were more than 50 years old (79%) with a median age of 57.5 years (range, 27–78 years). Family tumor history was identified rarely (8%). More of the tumor located in right lung (55%). *ALK* rearrangement was positive in 33 (23%) patients and 118 (81%) patients were *EGFR* mutated. Among tumors with *EGFR* mutation, 57 (39%) had L858R mutation, 52 (36%) had 19-Del mutation, and 9 (6%) had other mutations (including Exon21 L861Q, Exon18 G719X, Exon20 S768I, L858R/T790M, L858R/19-Del, 19-Del/T790M and 19-Del/S768I). Tumors with both *ALK* rearrangement and *EGFR* mutation were happened in only six patients. No patient received chemotherapy, radiation therapy, or immunologic therapy.

Clinical features

Although there were six patients with both *ALK* rearrangement

and *EGFR* mutation, the sample size was too small to analysis. We just compared *ALK* rearrangement positive group and *EGFR* mutation positive group. Significant differences were only found in age and serum CEA level (*Table 3*). Patients with *ALK* rearrangement were younger (51.85±10.37) than those with *EGFR* mutation (58.98±9.42, P=0.001). *EGFR* mutation was more likely to be positive in patients older than 50 years old (P=0.015). *ALK* rearrangement had no preference in sex (female 48% *vs.* male 52%), while *EGFR* mutation was seen more frequently in female (65%), however there was no significant difference. Serum CEA level had significant difference in two driver mutations (P=0.005). We conducted ROC (ROC) analysis to determine the cut-off value for CEA level (*Figure 2A*). Patients were divided into two groups: CEA level less or equal than 4.95 μg/L and CEA level more than 4.95 μg/L. Patients with *ALK* rearrangement were more likely to have lower serum CEA level, while those with *EGFR* mutation were mostly with CEA level more than 4.95 μg/L (P=0.008). Although no statistically significant difference was found, tumors with *ALK* rearrangement had higher rate of pleura metastasis (52% *vs.* 35%) and pericardial metastasis (15% *vs.* 9.8%), lower rate of lung metastasis (52% *vs.* 67%), bone metastasis (44% *vs.* 55%) and brain metastasis (15% *vs.* 29%) compared with those with *EGFR* mutations. There was also no significant difference in smoking history, family tumor history, clinical stage, clinical symptom and liver metastasis between patients with *ALK* rearrangement and *EGFR* mutations (*Table 3*).

HRCT and FDG-PET features

We conducted the Mann-Whitney test or chi-square test to find some differences among *ALK* rearrangement and *EGFR* mutation groups (*Table 1*). Tumor diameter had no significant difference in these two groups (P=0.549). Then we used ROC analysis to determine the cut-off value for tumor diameter and the calculated cut-off value was 36 mm (*Figure 2B*). There was still no significant difference (P=0.198) when divided into less or equal than 36 mm group and more than 36 mm group, but tumors with *ALK* rearrangement had higher rate in diameter more than 36 mm than those with *EGFR* mutation. Most of the tumor borders with *EGFR* mutation were poorly defined, while more of those with *ALK* rearrangement were well defined (P=0.023). In addition, tumors with *ALK* rearrangement were more likely to have bubble lucency than those with *EGFR* mutation (P=0.026). Lymphadenopathy was seen more frequently in patients with *ALK* rearrangement (P=0.167). We did not find statistically significant difference in tumor shape, margin, air bronchogram, vessel convergence sign, pleural retraction, pleural thickening, pulmonary lymphangitic carcinomatosis (PLC), hydrothorax, and enhancement (*Table 1*).

Twenty-six patients also received FDG-PET/CT in our institution. Among these patients, eight were *ALK* rearrangement positive and 18 were *EGFR* mutation positive. We pooled their lesion FDG uptake and lymph nodes FDG uptake in *Table 4*. The cut-off values of lesion SUV and lymph nodes SUV_{max} were calculated using ROC analysis (*Figure 2C,D*). The median SUV of lesions with *ALK* rearrangement and *EGFR* mutation was 10.79±6.57 and 7.78±5.61, respectively, however there was no significant difference (P=0.243). The median SUV_{max} of lymph nodes with *ALK* rearrangement and *EGFR* mutation was 7.56±1.92 and 5.56±5.00, respectively, and there was also no significant difference (P=0.309). Then we dichotomized the patients with cut-off value of lesion SUV 6.95 and lymph nodes SUV_{max} 6.25. Patients with lesion SUV >6.95 and lymph nodes SUV_{max} >6.25 were more frequently seen in *ALK* rearrangement group than *EGFR* mutation group (P=0.011, both).

Multivariable analysis

We conducted the multivariate analysis referenced to *EGFR* mutation group to pool influence of both clinical variables and HRCT features. Five features were found to have significant difference in this logistic regression model (*Table 5*). These independent prognostic factors to distinguish *ALK* rearrangement from *EGFR* mutation were age, serum CEA, tumor diameter, border definition, and brain metastasis. Patients younger than 50 years (RR=9.878, 95% CI: 2.318–42.090, P=0.002), with lower CEA level than 4.95 μg/L (RR=8.166, 95CI%: 1.085–31.983, P=0.003) and without brain metastasis (RR=7.304, 95% CI: 1.099–48.558, P=0.040) were more likely to be *ALK* rearrangement than *EGFR* mutation. Tumor diameter less than 36 mm were prone to be *EGFR* mutation (RR=0.078, 95% CI: 0.017–0.356, P=0.001). The border definition of tumors with *ALK* rearrangement was preferred to be well defined (RR=4.902, 95% CI: 1.222–19.662, P=0.025).

Discussion

Our study retrospectively reviewed 145 patients with

Table 3 Univariate analysis of clinical characteristics and driver mutations

Clinical characteristics	Number	Genetic alteration			*ALK*+ *vs. EGFR*+	
		ALK+ and *EGFR*+	*ALK*+	*EGFR*+	χ^2/F	P value
All patients [n (%)]	145	6 [4]	27 [19]	112 [77]	–	–
Median age*	57.50±10.04 [27–78]	55.33±12.09	51.85±10.37	58.98±9.42	11.976	0.001*
Age (years)	145	–	–	–	5.945	0.015
<50	30	2	10	18	–	–
≥50	115	4	17	94	–	–
Sex	145	–	–	–	2.675	0.102
Female	91	5	13	73	–	–
Male	54	1	14	39	–	–
Smoking history	145	–	–	–	0.789	0.374
Yes	35	0	5	30	–	–
No	110	6	22	82	–	–
Family tumor history	145	–	–	–	0.470	0.493
Yes	12	1	3	8	–	–
No	133	5	24	104	–	–
Clinical stage	145	–	–		2.586	0.108
IIIB	7	0	3	4	–	–
IV	138	6	24	108	–	–
Clinical symptom	145	–	–	–	0.665	0.717
No	20	1	3	16	–	–
Pulmonary symptom	101	5	18	78	–	–
Extrapulmonary symptom	24	0	6	18	–	–
Serum CEA level (μg/L)	0.7–1,123	1.1–156.6	0.7–1,123	0.8–1,010	–	0.005*
Serum CEA (μg/L)	141	–	–	–	7.094	0.008
≤4.95	48	3	14	31	–	–
>4.95	93	3	11	79	–	–
Pleura metastasis	145	–	–	–	2.675	0.102
–	89	3	13	73	–	–
+	56	3	14	39	–	–
Pericardial metastasis	145	–	–	–	0.563	0.453
–	129	5	23	101	–	–
+	16	1	4	11	–	–
Lung metastasis	145	–	–	–	2.157	0.142
–	53	3	13	37	–	–
+	92	3	14	75	–	–
Bone metastasis	145	–	–	–	1.041	0.308
–	71	6	15	50	–	–
+	74	0	12	62	–	–
Brain metastasis	145	–	–	–	2.145	0.143
–	107	4	23	80	–	–
+	38	2	4	32	–	–
Liver metastasis	145	–	–	–	0.037	0.847
–	126	6	23	97	–	–
+	19	0	4	15	–	–

*, median age analysis used the one-way ANOVA analysis, serum CEA level analysis used the Mann-Whitney test, and others used chi-square test. +, positive; –, negative; CEA, carcinoembryonic antigen; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

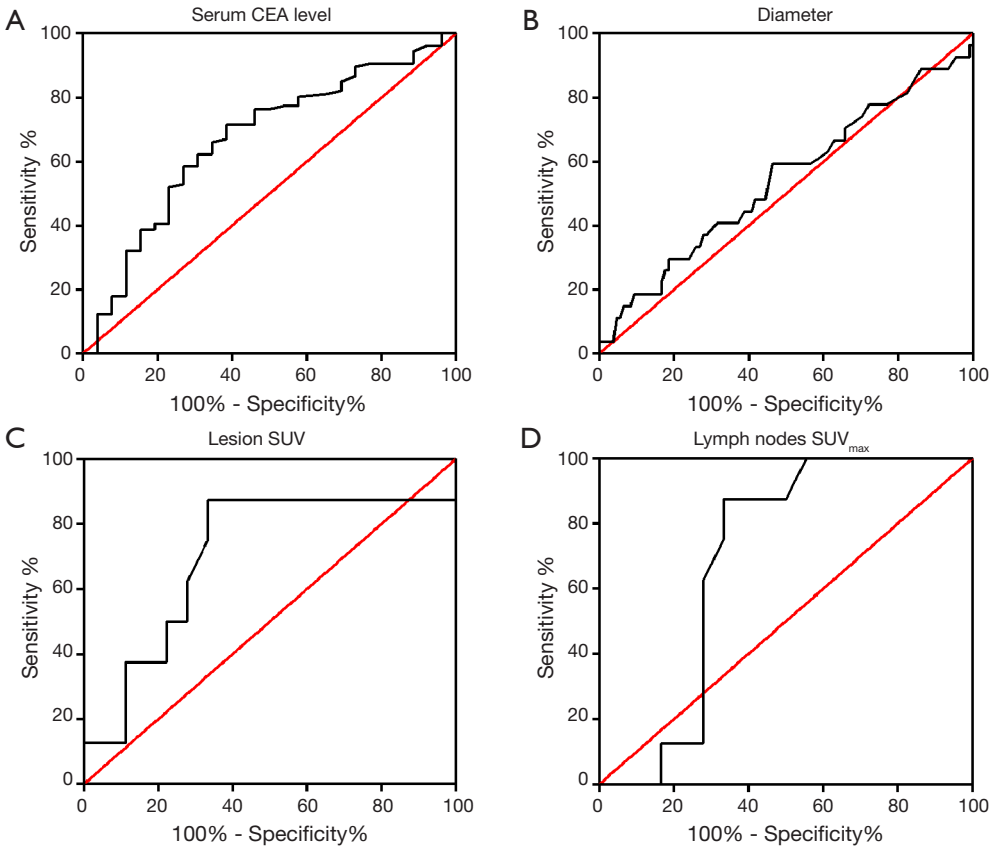

Figure 2 ROC curve for clinical and radiological features. (A) Serum CEA level; (B) tumor diameter; (C) lesion SUV; (D) lymph nodes SUV_{max}. ROC, receiver operating characteristic; CEA, carcinoembryonic antigen. SUV, standard uptake value.

Table 4 Univariate analysis of PET/CT characteristics and driver mutations

PET/CT characteristics	Number	Driver mutations			
		ALK+	*EGFR*+	χ^2/F	P value
All patients [n (%)]	26	8 [31]	18 [69]	–	–
Lesion FDG uptake	–	–	–	–	–
–	0	0	0	–	–
+	26	8	18	–	–
Lesion SUV	8.71±5.95*	10.79±6.57*	7.78±5.61*	1.434	0.243
≤6.95	13	1	12	6.500	0.011
>6.95	13	7	6	–	–
Lymph nodes FDG uptake	–	–	–	2.101	0.147
–	4	0	4	–	–
+	22	8	14	–	–
Lymph nodes SUV_{max}	6.24±4.34*	7.56±1.92*	5.65±5.00*	1.079	0.309
Lymph nodes SUV_{max}	–	–	–	6.500	0.011
≤6.25	13	1	12	–	–
>6.25	13	7	6	–	–

*, the mean and standard deviation of SUV. +, positive; –, negative. FDG, 18F-FDG; SUV, standard uptake value; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

Table 5 Multivariate analysis of differences in clinical/HRCT characteristics between patients with *ALK* rearrangement and those with *EGFR* mutation

Clinical/HRCT characteristics	P value	RR	95% CI
Age (years)			
<50	0.002	9.878	2.318–42.090
≥50	Reference*	–	–
CEA (μg/L)			
≤4.95	0.003	8.166	1.085–31.983
>4.95	Reference*	–	–
Diameter (mm)			
≤36	0.001	0.078	0.017–0.356
>36	Reference*	–	–
Border definition			
Well defined	0.025	4.902	1.222–19.662
Poorly defined	Reference*	–	–
Brain metastasis			
–	0.040	7.304	1.099–48.558
+	Reference*	–	–

*, the reference category is: EGFR+ group. +, positive; –, negative; RR, relative risk; CI, confidence interval; HRVT, high-resolution computed tomography; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

untreated advanced adenocarcinoma in East Asian Chinese population. We investigated the clinical, HRCT, and FDG-PET features between tumors with *ALK* rearrangement and *EGFR* mutations.

Patients with *ALK* rearrangement were younger than those with *EGFR* mutation. *EGFR* mutations were more likely to be positive in patients older than 50 years old. These results were consistent with previous studies in NSCLC (10,15,18). CEA is an important serum tumor marker; recent studies have found that patients with *ALK* rearrangement were seen more frequently to have normal serum CEA level in lung adenocarcinoma (19,20). However the study populations of these retrospective investigations were most with early clinical stage. In our study, we found that advanced lung adenocarcinomas with *ALK* rearrangement were more likely to have lower serum CEA level, while those with *EGFR* mutation were mostly with CEA level more than 4.95 μg/L. These clinical features may be helpful in distinguishing *ALK* rearrangement from *EGFR* mutation in the absence of genetic analysis.

Unfortunately, there was no significant difference in sex, smoking history, family tumor history, clinical stage, clinical symptom and liver metastasis between patients with *ALK* rearrangement and *EGFR* mutations. Both of the groups were prone to be non-smokers, which was consistent with previous studies (20-23). No statistically significant difference was found in tumor metastasis, but the tendencies were agree with Choi *et al.* (18). Tumors with *ALK* rearrangement had higher rate of pleura metastasis and pericardial metastasis, lower rate of lung metastasis, bone metastasis and brain metastasis compared with those with *EGFR* mutations (*Table 3*).

Our study identified several HRCT characteristics, among which only border definition and bubble lucency had significant difference. Tumors with *ALK* rearrangement were more likely to have well defined border and bubble lucency. Wang *et al.* demonstrated five CT characteristics had significant difference between *ALK* rearrangement and *EGFR* mutation, including tumor size, ground-glass opacity (GGO), bubble-like lucency, lymphadenopathy, and tumor shadow disappearance rate (24). However, in this research, we did not find significant difference in tumor diameter and lymphadenopathy, and GGO was not seen in all of the *ALK* rearrangement population. When we dichotomized the patients with cut-off value of diameter, there was still no significant difference. Whereas the tendency was in agreement, tumors with *ALK* rearrangement had higher rate in diameter more than 36 mm than those with *EGFR* mutation. Lymphadenopathy was also seen more frequently in patients with *ALK* rearrangement. And among the 26 patients received FDG-PET/CT in our institution, lesion FDG uptake and lymph nodes FDG uptake were higher in those with *ALK* rearrangement than with *EGFR* mutations. Patients with lesion SUV >6.95 and lymph nodes SUV_{max} >6.25 were more frequently seen in *ALK* rearrangement group than *EGFR* mutation group. These FDG-PET evaluations were keeping with the results of previous study (25).

In the logistic regression model, we found five independent prognostic factors to distinguish tumors with *ALK* rearrangement from those with *EGFR* mutation. Patients younger than 50 years and with lower CEA level than 4.95 μg/L were more prone to be *ALK* rearrangement than *EGFR* mutation. Tumor diameters less than 36 mm were likely to be *EGFR* mutation. The border definition of tumors with *ALK* rearrangement was preferred to be well defined. Tumors with *ALK* rearrangement were less seen to have brain metastasis. Our results were consistent with

several previous studies (18,20,24,25).

There were also some limitations in our study. The present study was a retrospective study and was conducted in a single large institution. Patient number was relatively small for our strict inclusion criteria and low rate of *ALK* rearrangement. Some cases were also excluded for not available HRCT image. There should be a large sample prospective study to validate these results. It was not impossible to analyze clinical and HRCT features according to histopathologic subtypes of invasive adenocarcinoma for limited small biopsy. Most of the patients did not undergo *KRAS*, *ROS1*, or *c-MET* gene analysis; this may have some influence of the results. We could not get complete prognostic information now, because our study reviewed patients from January 2013 to December 2015. We look forward to confirm these results in advanced lung adenocarcinoma prognosis by follow-up research.

Conclusions

In summary, we demonstrated that patients with younger age, lower serum CEA level, large tumor volume, well defined tumor border, and non-brain metastasis are more likely to be *ALK* rearrangement positive than *EGFR* mutation positive in treatment naïve advanced lung adenocarcinoma. Other features such as bubble lucency and higher FDG uptake of lesion and lymph nodes may help distinguish advanced lung adenocarcinoma with *ALK* rearrangement from those with *EGFR* mutation in the absence of genetic analysis.

Acknowledgements

Funding: This work was supported by the Clinical Science and Technology Project of Jiangsu Province (No. BL2013026) and the National Natural Science Foundation of China (No. 81572273), Natural Science Foundation of Jiangsu Province (No. BK20161386).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Ethical Committee (approval number: 2017NZHX-002). The requirement for informed consent was waived.

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Cite this article as: Miao Y, Zhu S, Li H, Zou J, Zhu Q, Lv T, Song Y. Comparison of clinical and radiological characteristics between anaplastic lymphoma kinase rearrangement and epidermal growth factor receptor mutation in treatment naïve advanced lung adenocarcinoma. J Thorac Dis 2017;9(10):3927-3937. doi:10.21037/jtd.2017.08.134

