Original Article

Clinical characteristics and progression of pre-/minimally invasive lung adenocarcinoma harboring *ALK* or *RET* rearrangements: a retrospective cohort study

Chaoqiang Deng[1,2,3#], Zongwei Chen[4#], Jinsong Bai[5#], Fangqiu Fu[1,2,3], Shengping Wang[2,3,6], Yuan Li[2,3,7], Yang Zhang[1,2,3*], Haiquan Chen[1,2,3*]

[1]Department of Thoracic Surgery and State Key Laboratory of Genetic Engineering, Fudan University Shanghai Cancer Center, Shanghai, China; [2]Institute of Thoracic Oncology, Fudan University, Shanghai, China; [3]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [4]Department of Thoracic Surgery, Fudan University Zhongshan Hospital, Shanghai, China; [5]Department of Thoracic Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, China; [6]Department of Radiology, Fudan University Shanghai Cancer Center, Shanghai, China; [7]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China

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[#]These authors contributed equally to this work.

[*]These authors contributed equally to this work as co-senior authors.

Correspondence to: Haiquan Chen, MD, PhD; Yang Zhang, MD. Department of Thoracic Surgery and State Key Laboratory of Genetic Engineering, Fudan University Shanghai Cancer Center, 270 Dong'an Road, Shanghai 200032, China; Institute of Thoracic Oncology, Fudan University, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China. Email: hqchen1@yahoo.com; fduzhangyang1987@hotmail.com.

Background: Patients harboring anaplastic lymphoma kinase (*ALK*) or rearranged during transfection (*RET*) rearrangements are usually diagnosed at a relatively late stage with nodal and distant metastasis, and rapid progression course of *ALK/RET* fusion-positive lung cancer were well-known. However, clinical characteristics and course of pre-/minimally invasive lung adenocarcinoma harboring *ALK* or *RET* fusions are poorly described. Identifying patients with gene fusions at early stage may offer surgical options that could cure those patients.

Methods: We retrospectively included patients with surgically resected pre-/minimally invasive lung adenocarcinomas harboring epidermal growth factor receptor (*EGFR*) mutations or *ALK/RET* rearrangements, and further compared the patient clinical characteristics, nodule natural course, and survival outcomes. Radiological characteristics including ground-glass component, cystic airspace, pleural attachment, etc. were specially assessed for this study. *EGFR* (exons 18–22) was detected by Sanger sequencing and quantitative real-time polymerase chain reaction (qRT-PCR) was used to analyze the *ALK/RET* rearrangements. Lung cancer-specific survival (LCSS), relapse-free survival (RFS), and overall survival (OS) were all evaluated.

Results: Of 238 patients with pre-/minimally invasive lung adenocarcinomas, 226 patients had *EGFR* mutations, 7 patients had *ALK* fusions, and 5 patients had *RET* fusions. Average age at surgery was 45.3 years for *ALK/RET*-positive group and 52.6 years for *EGFR*-positive group (P=0.049). Radiologically, among the 12 patients with *ALK/RET* fusions, the majority of lesions (10/12) manifested as mixed ground-glass opacities (mGGOs), which was significantly more prevalent when compared with patients with *EGFR* mutations (83.4% *vs.* 24.3%, P<0.001). Moreover, a substantial proportion of cystic airspace was found in *ALK/RET*-positive group but not in *EGFR*-positive group (66.7% *vs.* 14.2%, P<0.001). Among four patients with *ALK/RET* fusions undergoing surveillance over 1 year before surgery, two of them developed rapid radiologic progression. The 5-year LCSS and RFS were 100%, 100% for *ALK/RET*-positive group, and 100%, 100%

for *EGFR*-positive group, respectively.

Conclusions: *ALK/RET*-positive pre-/minimally invasive lung adenocarcinomas were mostly characterized as mGGOs with cystic airspace developing rapid nodule progression, and no recurrence occurred during long-term follow-up after resection. This provides insights into proper curative surgery timing in the management of patients with gene fusions. However, these findings must be treated with caution and validated in future multi-center studies with larger sample size.

Keywords: Lung adenocarcinoma; gene fusion; early stage; ground-glass opacity (GGO)

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Introduction

Background

Anaplastic lymphoma kinase (*ALK*) and oncogenic rearranged during transfection (*RET*) fusions are two of the targetable driver events in non-small cell lung cancer (NSCLC), which are found in approximately 3–8% and 1–2% of non-squamous NSCLC (NS-NSCLC) populations (1-3), respectively. *ALK* fusions are reported to be very rare in lung squamous cancers with the rate of 0–1.5% (4-6), while *RET* rearrangements could also occur occasionally in about 3% of adenosquamous, large-cell carcinomas, and squamous-cell NSCLC (5), despite that none of this two gene alterations were reported to be prognostic factors for non-adenocarcinoma NSCLC (7). Clinically, the characteristics of non-adenocarcinoma NSCLC patients with *ALK/RET* rearrangements were similar with those with lung adenocarcinomas (7). *ALK* fusions are correlated with never-smokers and younger age patients (1,8), and scarcely are they detected in early-staged lung cancer (9). Next-generation tyrosine kinase inhibitors (TKIs) such as alectinib and lorlatinib result in significantly longer survival and provide impressive "brain-control" compared to the first-generation inhibitor crizotinib or chemotherapy (10,11). *RET* rearrangements are usually mutually exclusive with epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene (*KRAS*), *ALK*, or ROS proto-oncogene 1 (*ROS1*) alterations (3,5,12). Our previous study also revealed that *RET* fusions were more prevalent in never-smokers, younger age patients with more poorly differentiated tumors and distant metastatic disease (2), implicating a potential of rapid progression. Despite the superior efficacy and tolerability of TKIs, delayed diagnosis and treatment of such diseases may still lead to poorer prognosis and inability to receive radical surgical treatment for patients. Meanwhile, complex genetic heterogeneity could still lead to drug resistance and therefore rapid progression of tumor even after next-generation TKI treatments (13). On the contrast, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) are reported to carry excellent prognosis and possess an indolent natural course, for which surgical time window is relatively wide.

Highlight box

Key findings

- Anaplastic lymphoma kinase (*ALK*)/rearranged during transfection (*RET*)-positive pre-/minimally invasive lung adenocarcinoma has distinct radiologic features with rapid progression.

What is known and what is new?

- Patients harboring *ALK* or *RET* rearrangements are usually diagnosed at a relatively late stage with nodal and distant metastasis.
- *ALK/RET*-positive pre-/minimally invasive lung adenocarcinomas were mostly characterized as mixed ground-glass opacities with cystic airspace developing rapid nodule progression, and no recurrence occurred during long-term follow-up after resection.

What is the implication, and what should change now?

- This provides insights into proper curative surgery timing in the management of patients with gene fusions.

Rationale and knowledge gap

Clinical characteristics and course of pre-/minimally invasive lung adenocarcinoma harboring *ALK* or *RET* fusions are poorly described. Identifying patients with gene fusions at early stage may offer surgical options that could cure those patients.

Objective

In this study, therefore, we summarized radiologic features, natural courses and survival outcomes of pre-/minimally invasive lung adenocarcinoma with *ALK/RET* rearrangements in an attempt to identify those nodules with potential of rapid progression at an early stage. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-517/rc).

Methods

Patients

This study was approved by the institutional review board [Fudan University Shanghai Cancer Center (FUSCC) IRB 2008223-9, date: 2020/07/14]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived due to the retrospective nature of this study.

Medical records of patients with surgically resected AIS/MIA harboring *EGFR* mutations, *ALK* fusions or *RET* fusions at FUSCC from April 2008 to June 2021 were reviewed. Considering the relative low frequency and similar clinical characteristics, we combined patients with *ALK* fusions and *RET* fusions as a group, and compared it with *EGFR*-positive patients, the latter of which stands for the most common targetable driver mutation even in early-stage lung adenocarcinoma (14). Figure S1 showed the flowchart of patient recruitment. Patients with invasive adenocarcinoma or without *EGFR* or *ALK/RET* alternations were excluded. The sample size was determined by the actual cohort selection. Clinical characteristics such as age, gender, smoking history, and radiological and pathological features were prospectively evaluated for this study. The relapse-free survival (RFS) was defined as the interval from the date of surgery to the date of first recurrence or last follow-up. The overall survival (OS) was defined as the time between the date of surgery and the date of death or last follow-up. The lung cancer-specific survival (LCSS) was defined as the time from surgery to lung cancer-specific death or last follow-up.

Radiologic evaluation

A 64 multi-detector helical scanner was used for lung computed tomography (CT) examination. The scanning section thickness and interval were 5.0 and 5.0 mm, respectively. And the reconstruction section width and interval were 1.0 and 1.0 mm, respectively. Two radiologists evaluated the patient radiological characteristics, including the tumor size, ground-glass component, cystic airspace, pleural attachment, lobulation, spiculation, and broncho-inflation. Each CT image with vision of the lesions before surgery was reviewed. The size of the nodule was defined as the maximum diameter on the axial plane measured on the lung window [window width: 1,600 Hounsfield unit (HU); window level: 600 HU; width and interval, 1.0 and 1.0 mm, respectively]. Progression of a nodule was defined as an increase of ≥2 mm or the appearance of solid component. This was based on a series of studies on the threshold to determine true nodule growth during follow-up (15,16).

Histological evaluation

Surgical resected specimens were fixed by formalin and stained with hematoxylin-eosin (H&E). The patholigical subtype diagnosis was subclassified into AIS, MIA, and invasive adenocarcinoma according to the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification.

Mutational analysis

Mutation analysis procedure was performed as described in previous studies (17,18). Briefly, *EGFR* hot spots (exons 18–22) was amplified and detected by Sanger sequencing. *RET* rearrangements were detected by quantitative real-time polymerase chain reaction (qRT-PCR)-based fusion detection methods with validation using fluorescent in situ hybridization (FISH). *ALK* rearrangements were analyzed by qRT-PCR-based fusion detection methods or Ventana immunohistochemistry (IHC) for ALK protein expression. IHC was performed on 3.5-μm-thick formalin-fixed paraffin-embedded (FFPE) specimens using the VENTANA ALK (Clone D5F3) CDx kit according to the manufacturer's instructions.

Follow-up protocol

Routine follow-up of patients begins after surgery. Within 3 years after the operation, chest CT, ultrasonography, and brain magnetic resonance imaging or CT scans are

Table 1 Clinicopathologic details of 12 patients with pre-invasive lung adenocarcinomas harboring ALK/RET fusions

Patient no.	Age (years)	Sex	Smoking history	Radiologic tumor size (mm)	Radiologic subtype	Cystic airspace	Pleural attachment	Lobulation	Spiculation	Broncho-inflation	Operative procedure	Pathologic subtype	Lymph node status	Gene rearrangement
1	45	M	N	13	mGGO	–	–	+	–	–	SEG	MIA	N0	*ALK* fusion
2	52	M	N	6	mGGO	+	–	–	–	–	SEG	MIA	N0	*ALK* fusion
3	38	F	N	8	Solid	–	–	–	+	–	WED	MIA	N0	*ALK* fusion
4	58	M	N	7	mGGO	+	–	–	–	–	WED	MIA	N0	*ALK* fusion
5	25	F	N	12	mGGO	+	–	–	–	–	SEG	MIA	N0	*ALK* fusion
6	51	F	N	18	mGGO	–	–	–	–	–	LOB	MIA	N0	*ALK* fusion
7	34	M	N	9	mGGO	+	–	–	–	–	WED	MIA	N0	*ALK* fusion
8	65	M	Y	10	mGGO	+	–	–	–	–	SEG	MIA	N0	*RET* fusion
9	29	M	N	9	mGGO	–	–	–	–	–	WED	MIA	N0	*RET* fusion
10	28	F	N	10	mGGO	+	–	–	–	–	WED	MIA	N0	*RET* fusion
11	62	M	N	13	mGGO	+	–	–	–	+	LOB	MIA	N0	*RET* fusion
12	56	F	N	9	pGGO	+	–	–	–	–	WED	MIA	N0	*RET* fusion

ALK, anaplastic lymphoma kinase; *RET*, rearranged during transfection; M, male; N, no; mGGO, mixed ground-glass opacity; SEG, segmentation; MIA, minimal-invasive adenocarcinoma; F, female; WED, wedge resection; LOB, lobectomy; Y, yes; pGGO, pure ground-glass opacity.

performed every 4 months, and every 6 months for the next 2 years, and annually from then on. Bone scanning is performed annually.

Statistical analysis

Statistical analysis was performed using SPSS (version 24.0, Armonk, NY, USA) and R statistic language (version 3.6.2). The correlation between the two category variables was analyzed using the Pearson χ^2 test or Fisher exact test. The student *t*-test is used to compare consecutive variables between the two groups. We investigated the survival results using Kaplan-Meier method, and examined the difference between the groups using log-rank test. All tests were two-tailed.

Results

After exclusion, a total of 238 patients with pre-/minimally invasive lung adenocarcinoma were recruited, 226 with *EGFR* mutations, 7 with *ALK* fusions, and 5 with *RET* fusions. Detailed clinicopathologic findings of patients with *ALK/RET* fusions are demonstrated in *Table 1*. The average age at surgery was 45.3 years, which was significantly younger than patients with *EGFR* mutations (P=0.049; Table S1). Among these patients, only one patient with *ALK* fusion had smoking history. Two patients received lobectomy and the remaining ten patients received sublobar resection. All of these 12 patients presented as MIA histologically.

Radiologically, the average tumor size was 10.3±3.3 mm (*Table 1*). The majority of nodules were categorized as ground-glass opacities (GGOs) radiologically (11/12), and ten patients had mixed GGOs (mGGOs) (83.4%), which was significantly higher than that in *EGFR*-positive group (24.3%, P<0.001; Table S1). Interestingly, we found a substantial proportion of cystic airspace feature in *ALK/RET*-positive group (8/12, 66.7%; *Figure 1*) than in *EGFR*-positive group (32/226, 14.2%, P<0.001; Table S1). Other radiologic features such as pleural attachment, lobulation sign, spiculation sign and bronchoinflation sign were not specifically observed (*Table 1*).

In *ALK/RET*-positive group, four patients performed surveillance over 1 year before surgery, detailed follow-up length is demonstrated in *Figure 2*. Of note, two of them experienced significant nodule progression within approximately 12 months after the first detection, indicating rapid development of *ALK/RET*-positive adenocarcinomas

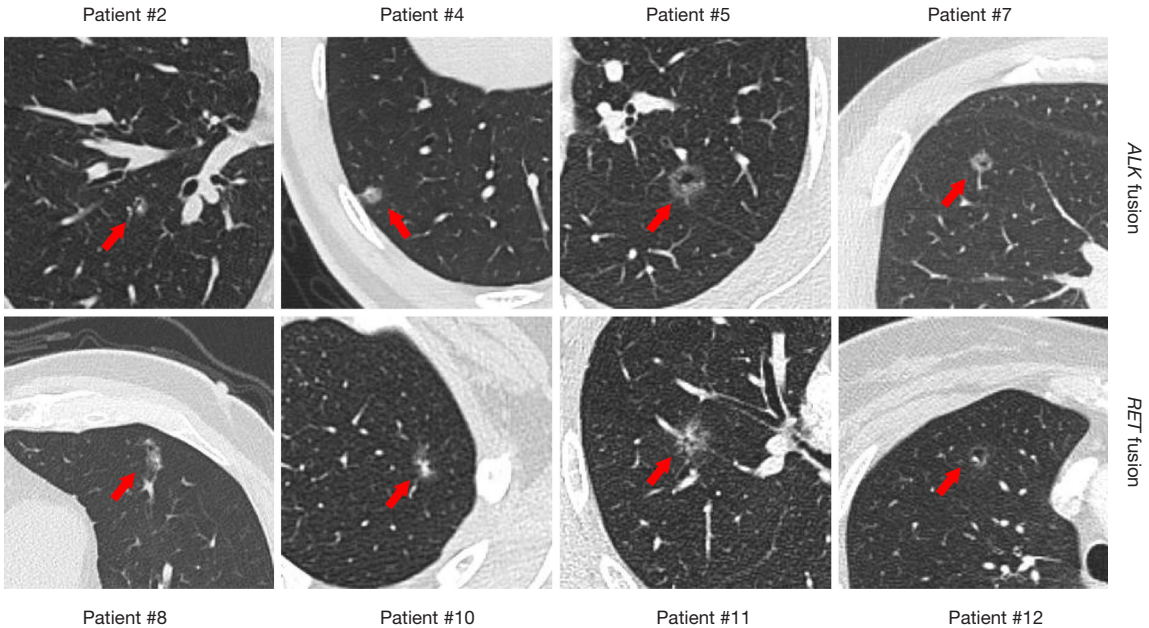

Figure 1 Representative images of patients harboring *ALK/RET* fusions with cystic airspace feature. The arrows indicate the locations of nodules. *ALK*, anaplastic lymphoma kinase; *RET*, rearranged during transfection.

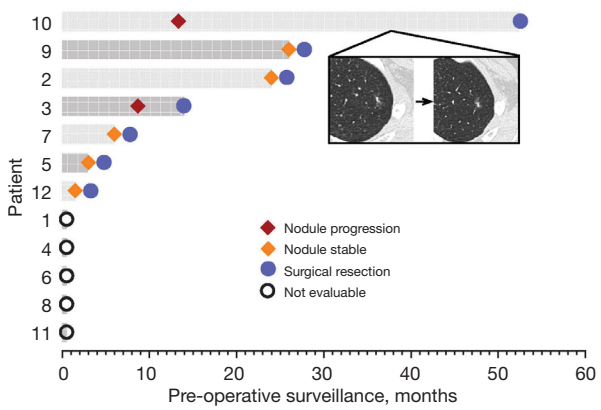

Figure 2 Swimmer plot indicating length of surveillance time and nodule courses before surgery for patients with *ALK/RET* fusions. The CT image showed the nodule progression during surveillance. *ALK*, anaplastic lymphoma kinase; *RET*, rearranged during transfection; CT, computed tomography.

even at pre-/minimally invasive stage. The 5-year OS was 98.6% and 100% for *EGFR*-positive group and for *ALK/RET*-positive group, respectively (P=0.758; Figure S2). The 5-year LCSS and RFS were all 100% for *EGFR*-positive group and for *ALK/RET*-positive group (Figure S2).

Discussion

The development of molecular detection of driver mutations has revolutionized the diagnose and treatment of advance staged lung cancer. Subsequently, molecular testing has been extensively applied clinically. Other than medication guidance, mutational profiles have also been applied in prognosis prediction and patient characterization. *ALK* and *RET* fusions have been characterized as younger aged and advanced-staged. There is noticeable difference in the incidence rate of *ALK/RET* rearrangements in advanced-staged and pre-invasive lung cancer (2,19), which indicates the rapid progression course of *ALK/RET* fusion-positive lung cancer even at early stage. Therefore, we assumed that performing radical resection for pre-/minimally invasive lung adenocarcinomas with *ALK/RET* fusions may offer a curative opportunity. In this study, we found that radiologic characteristics and natural course of AIS/MIA harboring *ALK/RET* fusions were distinct from patients with *EGFR* mutations. mGGOs with cystic airspace were significantly more prevalent in *ALK/RET*-positive AIS/MIAs than in *EGFR*-positive lesions, with relatively rapid progression during follow-up. After radical resection, however, the long-term survival was still excellent for pre-/

minimally invasive lung adenocarcinomas with *ALK/RET* fusions, which validated our hypothesis.

Radiologic features of lung adenocarcinoma with gene fusions have been reported in previous studies, solid masses and lobulated margins were summarized as key characteristics (20,21). Yet, patient cohorts in those studies were composed of advanced-staged lung cancer. Our study firstly identified mGGO with cystic airspace as specific radiologic feature in a subgroup of early-staged adenocarcinoma with *ALK/RET* fusions. The mechanism of cystic airspace formation in lung cancer is not fully understood. Some researchers believe that cystic airspace is correlated with rapid tumor growth that oversteps the blood supply of the tumor, thus creating necrosis in the middle of the tumor (22). Clinically, cystic airspace has been reported to be an independent factor for poor prognosis in patients with resected early-staged lung cancer (23). Furthermore, cystic airspace is also reported to be lower in AIS/MIA when compared with invasive adenocarcinoma (24), indicating its predictive ability of tumor invasiveness. In our study, up to 66.7% of cystic airspace was found in patients with AIS/MIA harboring *ALK/RET* fusions compared with 14.9% in *EGFR*-positive group, which was consistent with the aggressive behavior of *ALK/RET* rearrangements in lung adenocarcinoma.

GGO-featured lung adenocarcinoma is generally considered as an indolent subtype. Studies reported a rather small proportion of GGOs would progress in long-term follow-up. Kakinuma *et al.* reported a probability of 11% for GGOs to progress during 5-year follow-up (25). In our cohort, however, four patients with *ALK/RET* fusions performed surveillance over 1 year before surgery, two of them developed rapid radiologic progression of the nodules. Identifying radiologic features of those patients that may progress rapidly could give hints on the proper timing for intervention.

Our study has several limitations. First, only 12 patients with AIS/MIA with *ALK/RET* rearrangements were included in this study, and these findings must be treated with caution and validated in future multi-center studies with larger sample size. Second, this was a retrospective, single-institution study. Thus, selection bias and time-trend bias are inevitable.

Conclusions

ALK/RET-positive pre-/minimally invasive lung adenocarcinomas were mostly characterized as mGGOs with cystic airspace developing rapid nodule progression, and no recurrence occurred during long-term follow-up after resection. This provides insights into proper curative surgery timing in the management of patients with gene fusions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-517/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-517/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board [Fudan University Shanghai Cancer Center (FUSCC) IRB 2008223-9, date: 2020/07/14]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived, because this was a retrospective study.

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