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Different clinical features between patients with *ROS1*-positive and *ALK*-positive advanced non-small cell lung cancer

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Abstract

Objective: To compare the baseline clinical characteristics between patients with *ROS1*-positive and *ALK*-positive advanced non-small cell lung cancer (NSCLC), and the correlations of these subtypes with the distribution of metastases.

Methods: We compared the clinical characteristics and imaging features of patients with *ROS1*-positive and *ALK*-positive NSCLC using statistical methods.

Results: Data for 232 patients were analyzed. Compared with *ALK*-positive NSCLC, *ROS1*-positive NSCLC was more likely to occur in women (71% vs 53%), and primary lesions $\leq$3 cm were more common in patients with *ROS1*-positive compared with *ALK*-positive NSCLC (58% vs 37%). There was no significant difference in the distribution of metastases between the two groups. Subgroup analysis within the *ROS1*-positive group showed that, compared with primary lesions $>$3 cm, primary lesions $\leq$3 cm were more likely to present as peripheral tumors (72% vs 43%) and more likely to exhibit non-solid density (44% vs 4%).

Conclusions: Although *ROS1*-positive and *ALK*-positive NSCLCs show similar clinical features, the differences may help clinicians to identify patients requiring further genotyping at initial diagnosis.

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Introduction

Primary lung cancer is one of the most common malignant tumors in China. Treatment of non-small cell lung cancer (NSCLC) has progressed over the past decade from chemotherapy to personalized targeted precision therapy, in line with advancements in molecular medicine and the continuous emergence of targeted drugs. Gene mutations in c-ros proto-oncogene 1 (*ROS1*) and anaplastic lymphoma kinase (*ALK*) are popular therapeutic targets for NSCLC. The amino acid sequences of *ROS1* and *ALK* show nearly 49% similarity, and the homology of ATP-binding sites in the kinase catalytic domain is as high as 77%.[1–3] A recent multicenter study in China showed incidence rates of *ALK* and *ROS1* rearrangements of 12.2% and 4.4%, respectively.[4] NSCLCs haboring either of these mutations show similar clinical features, and many ALK-tyrosine kinase inhibitors, such as crizotinib, ceritinib, lorlatinib, and brigatinib, have therapeutic effects in patients with either *ROS1*- or *ALK*-positive NSCLC.

Common sites of lung cancer metastasis include the brain, bone, liver, adrenal gland, and lungs.[5] Although *ROS1* and *ALK* share a high degree of homology, the metastatic characteristics of tumors with these different mutations remain unknown, and evidence on this topic is currently lacking. In this study, we therefore compared the clinical characteristics and imaging features of *ROS1*-positive and *ALK*-positive NSCLCs and investigated the correlations of these mutations with their metastatic distribution. This study aimed to provide a basis for the clinical screening and treatment of patients with *ROS1*-positive and *ALK*-positive NSCLC.

Patients and Methods

Study population

Patients admitted to Shanghai Pulmonary Hospital with NSCLC between March 2018 and March 2020 were included in this retrospective study. All patients met the following inclusion criteria: 1) histologically or cytologically confirmed locally advanced or metastatic NSCLC (including patients with stage IIIB to IV at initial diagnosis); (2) *ROS1* or *ALK* rearrangement detected by amplification-refractory mutation system (ARMS) or positivity for ROS1 or ALK fusion protein detected by immunohistochemistry; and (3) complete imaging data at the initial diagnosis. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital. All patients provided written informed consent for inclusion in this study.

Imaging analysis

The clinical characteristics and baseline imaging features of patients with *ROS1*-positive and *ALK*-positive NSCLC were collected. Imaging examination items included chest computed tomography (CT), whole-body positron-emission tomography/CT, abdominal ultrasound,

color Doppler ultrasonography for supraclavicular or cervical lymph nodes, whole-body bone imaging, and contrast-enhanced cranial magnetic resonance imaging. All the above imaging examinations were performed in all the patients. The size (maximal diameter $\leq$3 cm or >3 cm), axial location (central or peripheral), density (solid or non-solid), cavitation, and air bronchograms of the primary tumor were analyzed. Tumor-node-metastasis (TNM) staging was annotated according to The Eighth Edition Lung Cancer Stage Classification (AJCC/UICC, 2017).[6] The presence of metastases was recorded by site. Images were also assessed for pleural effusion and lymphangitic carcinomatosis.

Statistical analysis

All statistical analyses were carried out using SPSS Statistics for Windows, Version 25.0 (SPSS Inc., Armonk, NY: IBM Corp). Continuous and categorical data were compared using independent samples *t*-tests and χ^2 tests, respectively. All tests were two-sided. *P* values <0.05 were considered significant. A multivariable logistic regression model was built with candidate predictors chosen according to a value of $P < 0.20$ in univariate analysis.

Results

A total of 232 NSCLC patients were included in this study, including 55 *ROS1*-positive and 177 *ALK*-positive patients (Table 1). Among these, 209 patients were detected by ARMS (51 with *ROS1* rearrangement and 158 with *ALK* rearrangement) and 23 patients were detected by immunohistochemistry (4 ROS1 fusion protein-positive and 19 ALK fusion protein-positive). Regarding pathological type, all but three cases were adenocarcinoma, with no significant difference between the two groups in terms of TNM staging (Table 1). Two patients in the *ROS1*-positive group had other gene mutations, including one patient with a *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutation and one patient with an L858R point mutation in the epidermal growth factor receptor gene. *ROS1*-positive NSCLC was significantly more likely to occur in women than *ALK*-positive NSCLC (71% vs 53%, $P = 0.020$) (Table 1).

According to univariate analysis, significantly more patients in the *ROS1*-positive group had primary lesions $\leq$3 cm compared with the *ALK*-positive group (58% vs 37%, $P = 0.006$) (Table 2). There was no significant difference in the distribution of metastases between the two groups (Table 3). We analyzed the variables able to distinguish

Table 1. Characteristics of all patients (n = 232).

Characteristic	All (n = 232)	Rearrangement		*P* value
		ROS1 (n = 55)	*ALK* (n = 177)	
Age, years	53 (17–82)	53 (22–79)	53 (17–82)	0.883
Sex				
Female	133 (57%)	39 (71%)	94 (53%)	0.020
Male	99 (43%)	16 (29%)	83 (47%)	
TNM stage				
III	45 (19%)	15 (27%)	30 (17%)	0.091
IV	187 (81%)	40 (73%)	147 (83%)	

Values given as median (range) or n (%).

Table 2. Primary tumor imaging features in all patients (n = 232).

Primary tumor feature	All (n = 232)	Rearrangement		*P* value
		ROS1 (n = 55)	*ALK* (n = 177)	
Tumor size				
≤3 cm	98 (42%)	32 (58%)	66 (37%)	0.006
>3 cm	134 (58%)	23 (42%)	111 (63%)	
Location				
Central	85 (37%)	22 (40%)	63 (36%)	0.554
Peripheral	147 (63%)	33 (60%)	114 (64%)	
Density				
Non-solid	180 (78%)	40 (73%)	140 (79%)	0.323
Solid	52 (22%)	15 (27%)	37 (21%)	
Cavitation				
No	195 (84%)	45 (82%)	150 (85%)	0.604
Yes	37 (16%)	10 (18%)	27 (15%)	
Air bronchogram				
No	196 (84%)	47 (85%)	149 (84%)	0.820
Yes	36 (16%)	8 (15%)	28 (16%)	

Values given as n (%).

between *ROS1*-positive and *ALK*-positive NSCLC using a multivariable logistic regression model with sex, TNM stage, primary tumor size, and bone metastasis. Holding other covariates fixed, the odds of having *ROS1*-positive NSCLC were significantly higher in women than in men ($P = 0.033$; odds ratio [OR]=2.080, 95% confidence interval [CI]: 1.059–4.082) and in patients with primary lesions ≤3 cm compared with those with primary lesions >3 cm ($P = 0.005$; OR=2.476, 95%CI: 1.315–4.663). Typical imaging features of *ROS1*-positive and *ALK*-positive patients are shown in Figure 1.

We further subdivided *ROS1*-positive patients into patients with primary tumors ≤3 cm and >3 cm, respectively. Primary lesions ≤3 cm were more likely to present as peripheral tumors (72% vs 43%, $P = 0.034$), and more likely to exhibit non-solid density (44% vs 4%, $P = 0.001$) compared with larger primary lesions >3 cm (Table 4).

Discussion

Rikova et al.[7] and Soda et al.[8] first reported the presence of the echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK* (*EML4–ALK*) fusion gene in lung cancer in 2007, and this fusion gene was confirmed as a driver gene for lung carcinogenesis. *ALK*-positive lung cancer was subsequently identified as a specific molecular subtype of NSCLC in 2009.[9] Rikova et al.[7] also found that *ROS1* was activated by gene rearrangements, resulting in the novel chimeric fusion proteins SLC34A2–ROS1 and CD74–ROS1. Subsequent work has identified such rearrangements in 1% to 2% of NSCLCs, representing a distinct molecular subgroup.[2,10,11]

Distant metastasis is a complex process involving the regulation of multiple gene and signaling pathways.[12] Previous studies have shown that changes in corresponding genes in different signaling pathways may be related to metastatic spread to different

Table 3. Distribution of lymphadenopathy and metastases (n = 232).

Variable	All (n = 232)	Rearrangement		*P* value
		ROS1 (n = 55)	*ALK* (n = 177)	
Pleura				
No	163 (70%)	40 (73%)	123 (69%)	0.647
Yes	69 (30%)	15 (27%)	54 (31%)	
Lung				
No	161 (69%)	41 (75%)	120 (68%)	0.343
Yes	71 (31%)	14 (25%)	57 (32%)	
Pleural effusion				
No	156 (67%)	39 (71%)	117 (66%)	0.507
Yes	76 (33%)	16 (29%)	60 (34%)	
Lymphangitic carcinomatosis				
No	186 (80%)	46 (84%)	140 (79%)	0.461
Yes	46 (20%)	9 (16%)	37 (21%)	
Node (N1+N2+N3)				
No	29 (13%)	6 (11%)	23 (13%)	0.683
Yes	203 (87%)	49 (89%)	154 (87%)	
Liver				
No	207 (89%)	47 (85%)	160 (90%)	0.302
Yes	25 (11%)	8 (15%)	17 (10%)	
Brain				
No	191 (82%)	46 (84%)	145 (82%)	0.771
Yes	41 (18%)	9 (16%)	32 (18%)	
Bone				
No	165 (71%)	44 (80%)	121 (68%)	0.096
Yes	67 (29%)	11 (20%)	56 (32%)	
Adrenal gland				
No	216 (93%)	52 (95%)	164 (93%)	0.629
Yes	16 (7%)	3 (5%)	13 (7%)	
Distant lymph nodes				
No	185 (80%)	43 (78%)	142 (80%)	0.742
Yes	47 (20%)	12 (22%)	35 (20%)	

Values given as n (%).

organs, and biological alterations in the tumor may affect its metastatic behavior and pattern.[13] Hoshino et al.[14] found molecules present on tumor-derived exosomes that 'addressed' them to specific organs, suggesting that the metastatic process is programmed. However, information on the correlation between gene mutations and organ metastasis, and the mechanism connecting them, is still lacking.

In the current study, the median age at diagnosis in both *ROS1*-positive and *ALK*-positive patients was 53 years. In contrast, Digumarthy et al.[15] found that patients with *ROS1* rearrangements were older than patients with *ALK* rearrangements (median 55 vs 50 years, $P = 0.01$). Park et al.[16] reported that the median age of 103 patients with *ROS1* rearrangements, including patients with stage I and stage II, was 56 years. Wu et al.[17] found no significant difference in age between *ROS1*-postitive and *ROS1*-negative patients, although the median age of *ROS1*-postitive patients

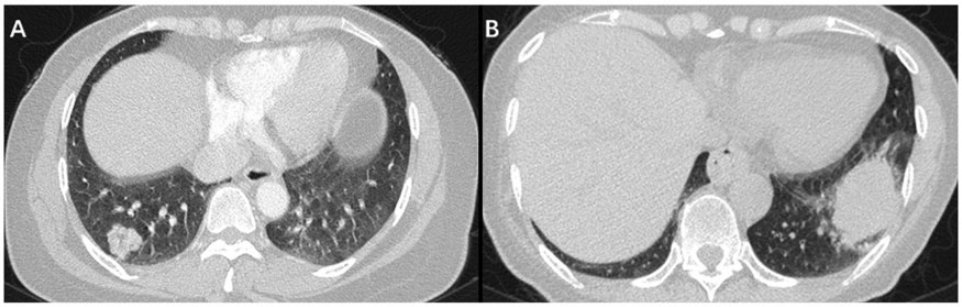

Figure 1. Typical imaging features of *ROS1*-positive and *ALK*-positive patients with non-small cell lung cancer. (a) A 49-year-old woman with adenocarcinoma. Computed tomography (CT) image showing a 2.2-cm non-solid nodule in the right lower lobe. *ROS1* rearrangement was detected by amplification-refractory mutation system (ARMS). (b) A 63-year-old woman with adenocarcinoma. CT image showing a 4.7-cm solid nodule in the left lower lobe. *ALK* rearrangement was detected by ARMS.

tended to be younger (53 vs 62 years). Li et al.[18] found a median age of 50.8 years (range 32–78 years) among 36 patients with *ROS1* rearrangement. In summary, the median age of *ROS1*-positive NSCLC patients is approximately 50 years, and both *ROS1*-positivity and *ALK*-positivity are more likely to occur in younger patients.

The current study found a difference in sex distribution between *ROS1*-positive and *ALK*-positive patients, with a significantly higher percentage of women in the *ROS1*-positive group (71% vs 53%, $P = 0.020$). Multivariate analysis confirmed that the odds of *ROS1*-positivity were significantly higher in women than in men ($P = 0.033$; OR=2.080, 95%CI: 1.059–4.082). Digumarthy et al.[15] also found a higher proportion of women in the *ROS1*-rearrangement (72%) compared with the *ALK*-rearrangement group (45%), and Park et al.[16] found a higher proportion of women (68.9%) than men among patients with *ROS1* rearrangement. The higher frequency of *ROS1* rearrangement among women than men in the current study was thus consistent with previous studies.[19–21] However, Song et al.[4] found similar proportions of female patients in the *ALK*- and *ROS1*-rearrangement groups (52.8% and 53%, respectively). The discrepancy between these results may have been due to the low disease incidences and small sample sizes of the studies.

Analysis of the imaging features revealed significantly more primary lesions ≤ 3 cm in the *ROS1*-positive compared with the *ALK*-positive group (58% vs 37%, $P = 0.006$), but no significant differences in any other imaging features between the two groups. No previous studies have reported differences in the sizes of the primary tumors between patients with these two gene rearrangements. Further subgroup analysis of the *ROS1*-positive group also showed that primary lesions ≤ 3 cm were more likely to present as peripheral tumors (72% vs 43%, $P = 0.034$) and more likely to exhibit non-solid density (44% vs 4%, $P = 0.001$) compared with primary lesions >3 cm. Song et al.[4] found non-solid lesions in 71% and 76% of patients with *ROS1* and *ALK* rearrangements, respectively. However, Digumarthy et al.[15] found that virtually all (98%) *ROS1*-rearrangement tumors showed solid density.

The comparative metastatic features of *ROS1*-positive and *ALK*-positive tumors remain unclear. Gao et al.[13] reviewed multiple studies and found that patients with

Table 4. Characteristics and imaging features of *ROS1*-positive patients (n = 55).

Variable	*ROS1* (n = 55)	Primary tumor size		*P* value
		≤3 cm (n = 32)	>3 cm (n = 23)	
Age, years	53 (22–79)	52 (22–79)	54 (37–71)	0.456
Age, years				
≤53	28 (51%)	17 (53%)	11 (48%)	0.698
>53	27 (49%)	15 (47%)	12 (52%)	
Sex				
Female	39 (71%)	20 (63%)	19 (83%)	0.105
Male	16 (29%)	12 (37%)	11 (17%)	
TNM stage				
III	15 (27%)	7 (22%)	8 (35%)	0.289
IV	40 (73%)	25 (78%)	15 (65%)	
Primary tumor				
Location				
Central	22 (40%)	9 (28%)	13 (57%)	0.034
Peripheral	33 (60%)	23 (72%)	10 (43%)	
Density				
Non-solid	15 (27%)	14 (44%)	1 (4%)	0.001
Solid	40 (73%)	18 (56%)	22 (96%)	
Cavitation				
No	45 (82%)	27 (84%)	18 (78%)	0.726
Yes	10 (18%)	5 (16%)	5 (22%)	
Air bronchogram				
No	47 (85%)	28 (88%)	19 (83%)	0.707
Yes	8 (15%)	4 (12%)	4 (17%)	
Metastases				
Pleura				
No	40 (73%)	22 (69%)	18 (78%)	0.435
Yes	15 (27%)	10 (31%)	5 (22%)	
Lung				
No	41 (75%)	22 (69%)	19 (83%)	0.244
Yes	14 (25%)	10 (31%)	4 (17%)	
Lymphangitic carcinomatosis				
No	46 (84%)	27 (84%)	19 (83%)	0.861
Yes	9 (16%)	5 (16%)	4 (17%)	
Node (N1+N2+N3)				
No	6 (11%)	3 (9%)	3 (13%)	0.686
Yes	49 (89%)	29 (91%)	20 (87%)	
Liver				
No	47 (85%)	26 (81%)	21 (91%)	0.446
Yes	8 (15%)	6 (19%)	2 (9%)	
Brain				
No	46 (84%)	25 (78%)	21 (91%)	0.277
Yes	9 (16%)	7 (22%)	2 (9%)	
Bone				
No	44 (80%)	23 (72%)	21 (91%)	0.097
Yes	11 (20%)	9 (28%)	2 (9%)	

(continued)

Table 4. Continued.

Variable	*ROS1* (n = 55)	Primary tumor size		*P* value
		≤3 cm (n = 32)	>3 cm (n = 23)	
Adrenal gland				
No	52 (95%)	31 (97%)	21 (91%)	0.565
Yes	3 (5%)	1 (3%)	2 (9%)	
Distant lymph nodes				
No	43 (78%)	24 (75%)	19 (83%)	0.500
Yes	12 (22%)	8 (25%)	4 (17%)	

Values given as median (range) or n (%).

ALK rearrangements were more prone to lymph node, pleural, and brain metastases. Digumarthy et al.[15] compared the CT features of *ROS1*- and *ALK*-rearrangement patients and found significantly lower incidences of brain and extrathoracic metastases in patients with *ROS1* compared with *ALK* rearrangement (9% vs 25%, $P = 0.03$; 49% vs 75%, $P < 0.01$). A previous retrospective study found that *ALK* rearrangement in lung adenocarcinoma was correlated with lymph node and pleural metastases, with distant lymph node metastasis mostly occurring in the abdominal cavity, few axillary lymph node metastases, and pleural metastasis manifested as pleural nodules or malignant pleural effusion.[22] The current study found no significant differences in the distributions of major metastases, such as pleural (27% vs 31%), liver (15% vs 10%), bone (20% vs 32%), and brain metastases (16% vs 18%), between the *ROS1*- and *ALK*-positive groups. This result may still be due to the small sample sizes.

According to the "seed" theory, the most common metastatic location of lung cancer is the brain, accounting for up to 50% of all metastases, followed by bone, liver, and adrenal glands.[23] In a phase II clinical study, Wu et al.[24] found an incidence of brain metastases in *ROS1*-rearrangement patients of 18.1%, which was similar to our current results. Patil et al.[25] found no difference in the incidence of brain metastases between *ROS1*- and *ALK*-rearrangement patients.

Gainor et al.[26] found that the incidences of extrathoracic and brain metastases were significantly lower in the *ROS1*-rearrangement compared with the *ALK*-rearrangement group (59.0% vs 83.2%, $P = 0.002$; 19.4% vs 39.1%, $P = 0.033$). In addition, progression-free survival (PFS) after crizotinib treatment was significantly longer in the *ROS1* than in the *ALK* group (11 vs 7.9 months, $P = 0.007$), with no difference in overall survival (OS) between the two groups (2.5 vs 3 years). Liu et al.[27] found that *ALK*-rearrangement patients with adrenal metastasis at baseline had poorer PFS, and Ock et al.[28] showed that patients with at least three metastatic organs had significantly shorter PFS and OS among patients with *ALK*-positive NSCLC. Pacheco et al.[29] also showed that more baseline metastases was associated with shorter OS.

This study had several limitations associated with the investigation of rare mutations. The sample size was small and samples were collected over a long period of time, leading to imbalance between the experimental groups. In addition, we did not analyze the correlation between

metastatic distribution and treatment efficacy, which is worthy of further investigation.

In conclusion, this study identified differences in clinical and imaging features between patients with NSCLC with *ROS1* and *ALK* rearrangements, including differences in the proportions of women and of primary lesions $\leq$3 cm. These results need to be validated in future studies with larger sample sizes. However, the presence of these features may help clinicians to determine which NSCLC patients require further genotyping at the initial diagnosis.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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