Original Article

Prognostic significance of anaplastic lymphoma kinase rearrangement in patients with completely resected lung adenocarcinoma

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Background: Reports of the prognostic significance of anaplastic lymphoma kinase (ALK) rearrangement in early stage lung adenocarcinoma have been contradictory. This study aimed to identify the associations of ALK rearrangement with clinicopathologic features and prognosis in patients with surgically resected stage I–IIIA lung adenocarcinoma.

Methods: Analysis of *ALK* status was performed by a fully-automated immunochemistry assay (with rabbit monoclonal Ventana D5F3 antibody) in tissue sections of 2,103 patients with surgically-resected stage I–IIIA lung adenocarcinoma. *ALK* positive patients were matched with negative patients in a 1:1 ratio using propensity score matching (PSM). Clinical outcomes were assessed by disease-free survival (DFS) and overall survival (OS) after surgery. Initial recurrence pattern was also investigated according to *ALK* status.

Results: Among 2,103 stage I–IIIA lung adenocarcinoma cases, 81 (3.9%) were *ALK* positive. *ALK* positivity was significantly associated with younger age (P<0.001), solid predominant adenocarcinoma (P<0.001), variants of invasive adenocarcinoma (P<0.001), higher frequency of pleura invasion (P=0.040), smaller tumor size (P=0.014), mediastinal lymph node involvement (N2; P<0.001) and later pathologic stage (IIIA; P=0.001). In the match cohort, *ALK* positivity was not associated with DFS [hazard ratio (HR), 0.58; 95% confidence interval (CI): 0.33–1.03, P=0.063] or OS (HR, 0.61; 95% CI: 0.22–1.67, P=0.334). Lymph node involvement (HR: 5.36, 95% CI, 3.01–9.65, P<0.001) and solid predominant adenocarcinoma subtype (HR, 2.02; 95% CI: 1.07–3.79; P=0.029) were the independent prognostic factors of inferior DFS, and lymph node involvement was the independent prognostic factors of worse OS (HR, 6.61; 95% CI: 2.43–17.94; P<0.001). *ALK* positive patients had a higher risk of developing tumor recurrence in liver (P=0.043).

Conclusions: *ALK* rearrangement was not an independent prognostic factor in stage I–IIIA lung adenocarcinoma patients but leaded to a higher risk of developing recurrence in liver.

Keywords: Anaplastic lymphoma kinase rearrangement (*ALK* rearrangement); lung adenocarcinoma; postoperative recurrence; prognosis

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Introduction

Lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths) (1). Two main types of lung cancer are small cell lung cancer (SCLC) (10–15%) and non-small cell lung cancer (NSCLC)

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(80–85%) (2). NSCLC is subdivided into adenocarcinoma, squamous cell carcinoma (SQCC) and large cell carcinoma. Adenocarcinomas include adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma and variants of invasive adenocarcinoma. Both AIS and MIA are associated with good prognosis.

The patient with anaplastic lymphoma kinase (ALK) gene rearrangement, which is caused by the translocation or inversion of chromosome 2p, is an important patient subset of lung cancer. The prevalence of *ALK* positive patients has been reported to range from 3% to 7% in advanced NSCLC (3-6), and 2.3% to 8.6% in early stage NSCLC (7-14). *ALK* positivity is correlated with adenocarcinoma histology, particularly the solid and signet ring pattern; never or light/former smoking status; younger age; and wild type for *EGFR* or *KRAS* gene mutation (5,15-19).

ALK was first discovered in 1994 as a fusion oncogene with nucleophosmin (*NPM*) in a subset of anaplastic large-cell lymphomas (ALCLs) (20). However, it was not until 12 years ago that interest in *ALK* surged after the discovery of a novel *ALK* fusion—echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK*, a somatic gene rearrangement found in a small portion of Japanese lung cancers (21). *EML4-ALK* is formed by an inversion occurring on the short arm of chromosome 2 involving the genes encoding *ALK* (2p23) and *EML4* (2p21) with variants 1, 2, and 3a/3b (22,23). The three major variants (v1: E13; A20, v2: E20; A20, and v3; E6; A20) account for more than 90% of lung cancers associated with *EML4-ALK*. In addition to *EML4-ALK*, several other *ALK* fusions have been reported, including *TRK*-fused gene (*TFG*)-*ALK* , kinesin family member 5B (*KIF5B*)-*ALK* and kinesin light chain 1 (*KLC1*)-*ALK* (15,24,25). At the cellular level, *ALK* regulates canonical signaling pathways that are shared with other receptor tyrosine kinases (RTK) including RAS-mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)-AKT, and JAK-STAT pathways (26). In *ALK* rearrangements, 5' end partners such as *EML4* and *NPM* are fused to the intracellular tyrosine kinase domain of *ALK*. The domains in the partner proteins promote dimerization and oligomerization of the fusion proteins, inducing constitutive activation of the *ALK* kinase and its downstream signaling pathways. This leads to uncontrolled cellular proliferation and survival. The *EML4-ALK* fusion gene possesses powerful oncogenic activity, both *in vivo* and *in vitro* (21,27), which might result in poor prognosis of NSCLC. However, several published studies show the conflicting results about the prognostic value of *ALK* rearrangement in NSCLC (7-14,28-31). Tantraworasin (10), Paik (8), Fukui (29), and Ohba (12), demonstrated that *ALK* positivity was not correlated with prognosis. Conversely, five reports revealed that patients with *ALK* rearrangement NSCLC had a shorter DFS (7,9,13,14,28). In contrast, Blackhall *et al.* reported superior RFS and OS in patients with *ALK* positive early-stage NSCLC (11). Preclinical studies demonstrate that *ALK*-driven lung cancers are addicted to *ALK* and highly sensitive to *ALK* inhibition (27,32), indicating that *ALK* rearrangement is a predictive factor for the therapeutic effect of *ALK* inhibitors. Additionally, several *ALK* inhibitors are already approved for the first line treatment of advanced stage *ALK*-positive NSCLC due to their encouraging therapeutic effect (33-36). The prognostic value of ALK rearrangement will help guide management and formulate statistical assumptions in the design of future ALK inhibitor– based adjuvant clinical trials. However, the prognostic significance of *ALK* rearrangement remains unclear and further investigation is needed.

The major objectives of the present study are not only to compare the clinical outcomes of *ALK*-positive versus *ALK*-negative completely resected stage I-IIIA lung adenocarcinoma patients, but also to explore the correlation of ALK rearrangement with clinical characteristics.

Methods

Study population and data collection

In our study, 2,103 patients with pathological stage I–IIIA lung adenocarcinoma who underwent complete resection in Shanghai Chest Hospital between July 2013 and December 2014, with at least 4 years of follow-up were included in the study. The patients who received neoadjuvant chemotherapy or radiotherapy were excluded. The patients did not receive *ALK*-targeted therapy before tumor recurrence in our study cohort. Histological types of lung adenocarcinoma are determined according to 2015 WHO classification of lung adenocarcinoma. The predominant pattern was defined as the pattern with the largest percentage. Lung cancer pathologic staging of the patients was based on the 8th edition of the TNM classification. All patients' clinicopathologic characteristics were collected from the medical recording system. This study was approved by Ethics Committee of Shanghai Chest Hospital Jiao Tong University.

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Detection of ALK rearrangement

Immunohistochemistry (IHC) was performed for all patients on 5-μm thick formalin-fixed paraffin-embedded surgical specimens with the fully-automated Ventana IHC system using the D5F3 anti-*ALK* rabbit monoclonal primary antibody in a Bech-mark XT staining module (Ventana Medical Systems, Illkirch Graffenstaden, France). The *ALK* status was described by a binary scoring system, either *ALK* positive or *ALK* negative. The histopathologic types and *ALK* status were evaluated independently by two experienced pathologists of Shanghai Chest Hospital.

Clinical outcomes and statistical analysis

Clinical outcomes were presented by overall survival (OS), defined as the time interval from date of surgery to death from any cause; disease-free survival (DFS), defined as the time from date of surgery to disease recurrence or death from any cause. If recurrence or death was not observed, the censoring date was the last day of follow-up. Both OS and DFS were calculated in months.

Statistical analyses were performed using SPSS®, version 24.0 (SPSS Inc., Chicago, IL, USA). Comparison of clinical characteristics according to *ALK* status was performed using Mann-Whitney U tests (continuous variables) and chi-square tests or Fisher's exact tests (categorical variables).

Association between time-to-event outcomes and *ALK* status is only explored in *ALK* matched cohort. For this cohort, survival was estimated by the Kaplan-Meier method and compared using the log-rank test. The median follow-up time was estimated using the reverse censoring method for OS. Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI). Multivariable Cox regression, with the backward elimination procedure (removal criterion of 10%), was used to choose the best model for DFS and OS, examining characteristics including sex, age at surgery, smoking status, pathologic tumor stage (pT stage), pathologic nodal stage (pN stage), adenocarcinoma subtypes and *ALK* status. In all analyses, two-tailed $P<0.05$ was considered statistically significant.

Propensity score matching (PSM)

PSM was used to control for confounding effects of known predictors for lung cancer progression or recurrence. PSM was carried out in stage IA, IB, IIA, IIB, IIIA cohort respectively to guarantee the exact balance of pathologic stage, which was considered to be the most important prognostic factor, between *ALK* positive and *ALK* negative patients in the matched cohort. Propensity scores for all patients were calculated by using a multiple logistic regression with the following covariates: age, sex, type of surgery, histological subtypes and pleura invasion status. In the *ALK* matched cohort, all 81 *ALK* positive patients were matched 1:1 with 81 *ALK* negative patients. The clinical characteristics baseline before and after PSM were shown in *Table S1*.

Follow up

The follow-up data of the matched cohort were obtained by official contact with patients or their relatives by telephone or collected from hospital records. In the matched cohort of 162 patients, seven patients lost contact after surgery in the *ALK* positive group, and 8 patients in the *ALK* negative group. The workflow of the determination of the *ALK* status and the populations identified is depicted in *Figure 1*.

Routine examinations, such as a plain chest X-ray; computed tomography scan of the thorax, head, and abdomen; and ultrasound of neck and abdomen, were generally performed every 3 months for the first 2 years after surgery and every 6 months after that for 5 years. After 5 years, the patients were assessed annually. Bone scans were performed as clinically indicated on the basis of bone pain. Positron emission tomography and bronchoscopy with biopsy were performed at the treating physician's discretion.

The follow-up period was completed in December 2018 or to the death date of patients. The median follow-up was 55.3 months (interquartile range, 51.6 to 60.2 months).

Results

Clinicopathologic characteristics of ALK positive patients

The clinicopathologic characteristics of 2,103 completely-resected stage I–IIIA lung adenocarcinoma patients are shown in *Table 1*. Eighty-one (3.9%) of the 2,103 patients were *ALK* positive. Eight hundred and ninety patients (42.3%) were male, and 1,213 (57.7%) were female; age (year) at surgery ranges from 24 to 83. A total of 1,840 (87.5%) were never-smokers, 252 (12.0%) were smokers, and 11 (0.5%) patients' smoking status were unknown. Tumor size (cm) ranged from 0.2 to 15.0. The pathologic stage was stage I in 1,639 patients (77.9%), stage II in

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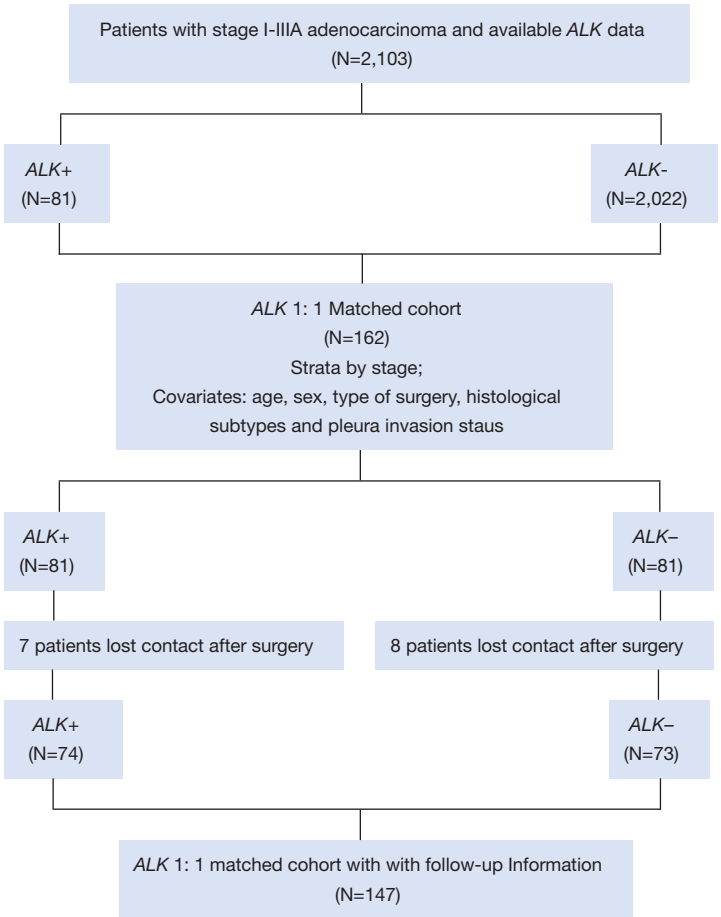

Figure 1 Patients flow diagram. *ALK*, anaplastic lymphoma kinase; *ALK*+, *ALK* positive group; *ALK*–, *ALK* negative group.

210 (10.0%), and stage IIIA in 254 (12.1%). Invasive adenocarcinoma is the only histopathologic subtypes of the whole cohort with lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, and solid predominant subtypes present in 114 (5.4%), 1,139 (54.2%), 525 (25.0%), 16 (0.8%), and 179 (8.5%) patients, respectively, and variants of invasive adenocarcinoma in 130 patients (6.2%). Pleura invasion occurred in 571 (27.2%) patients.

ALK positivity was significantly associated with younger age (median age, 53 years in the *ALK* positive group *vs.* 60 years in the *ALK* negative group; P<0.001), solid predominant adenocarcinoma (P<0.001), variants of invasive adenocarcinoma (P<0.001), higher frequency of pleura invasion (P=0.040), smaller tumor size(median size, 1.8 cm in the *ALK* positive group *vs.* 2.0 cm in the *ALK* negative group; P=0.014), mediastinal lymph node involvement (N2; P<0.001), later pathologic stage (IIIA; P=0.001) (*Table 1*).

However, there were no significant associations between *ALK* status and other factors such as sex (P=0.769), smoking status (P=0.911), and pathologic tumor stage (P=0.169) (*Table 1*).

Clinicopathologic characteristics baseline data before and after weighting

Table 1 also shows the clinicopathologic characteristics baseline of the patients after PSM with follow-up information. A total of 81 (3.9%) and 2,022 (96.1%) patients were assigned to the *ALK* positive group and *ALK* negative group, respectively. Before PSM, differences were observed in terms of age (P<0.001), adenocarcinoma subtypes (P<0.001), pleura invasion status (P=0.040), tumor size (P=0.014), pN stage (P<0.001), pTNM stage (P<0.001) (*Table 1*); after PSM, the results were similar between the two groups (P>0.05) except for tumor size (P=0.028)

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Table 1 Patients' clinicopathologic characteristics baseline before and after PSM with follow-up information

Characteristic	Entire cohort (n=2,103)			Matched cohort with follow-up information (n=147)		
	ALK-positive group (%)	*ALK*-negative group (%)	P value	*ALK*-positive group (%)	*ALK*-negative group (%)	P value
Total	81	2,022		74	73	
Sex			0.769[a]			0.924[a]
Male	33 (40.7)	857 (42.4)		32 (43.2)	31 (42.5)	
Female	48 (59.3)	1,165 (57.6)		42 (56.8)	42 (57.5)	
Age, years			<0.001[b]			0.209[b]
Mean	53.8	60.1		53.7	55.5	
95% CI	51.6–55.9	59.7–60.5		51.4–55. 9	53.5–57.5	
Median	53	60		52.5	56	
Range	34–81	24–83		34–81	37–80	
Smoking history			0.911[c]			0.457[a]
No	71 (87.7)	1,769 (87.5)		64 (86.5)	66 (90.4)	
Yes	10 (12.3)	242 (12.0)		10 (13.5)	7 (9.6)	
Unknown	0	11 (0.5)		0	0	
Type of surgery			0.967[c]			0.982[a]
Lobectomy	76 (93.8)	1,866 (92.3)		69 (93.2)	68 (93.2)	
Wedge resection	5 (6.2)	111 (5.5)		5 (6.8)	5 (6.8)	
Segmentectomy	0	19 (0.9)		0	0	
Pneumonectomy	0	3 (0.1)		0	0	
Bilobectomy	0	5 (0.2)		0	0	
Other	0	18 (0.9)		0	0	
Adenocarcinoma subtype			<0.001[c]			0.752[c]
Lepidic predominant	1 (1.2)	113 (5.6)		1 (1.4)	1 (1.4)	
Acinar predominant	36 (44.4)	1,103 (54.5)		33 (44.6)	30 (41.1)	
Papillary predominant	11 (13.6)	514 (25.4)		10 (13.5)	16 (21.9)	
Micropapillary predominant	0	16 (0.8)		0	1 (1.4)	
Solid predominant	18 (22.2)	161 (8.0)	<0.001[a]	16 (21.6)	13 (17.8)	
Variants of invasive adenocarcinoma	15 (18.5)	115 (5.7)	<0.001[a]	14 (18.9)	12 (16.4)	
Pleura invasion			0.040[c]			0.539[c]
No	47 (58.0)	1,431 (70.8)		42 (56.8)	46 (63.0)	
Yes	31 (38.3)	540 (26.7)		29 (39.2)	26 (35.6)	
Unknown	3 (3.7)	51 (2.5)		3 (4.1)	1 (1.4)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristic	Entire cohort (n=2,103)			Matched cohort with follow-up information (n=147)		
	ALK-positive group (%)	*ALK*K-negative group (%)	P value	*ALK*-positive group (%)	*ALK*-negative group (%)	P value
Tumor size			0.014[b]			0.065[b]
Mean	2.07	2.35		2.10	2.34	
95% CI	1.86–2.28	2.30–2.40		1.88–2.32	2.10–2.58	
Median	1.8	2.0		1.8	2.0	
Range	0.6–5.0	0.2–15.0		0.6–5.0	1.2–7.5	
pT stage			0.169[c]			0.869[c]
T1	44 (54.3)	1,255 (62.1)		39 (52.7)	40 (54.8)	
T2	36 (44.4)	671 (33.2)		34 (45.9)	31 (42.5)	
T3	1 (1.2)	85 (4.2)		1 (1.4)	1 (1.4)	
T4	0	11 (0.5)		0	1 (1.4)	
pN stage			<0.001[a]			0.977[a]
0	51 (63.0)	1,726 (85.4)		48 (64.9)	48 (65.8)	
1	11 (13.6)	85 (4.2)		10 (13.5)	9 (12.3)	
2	19 (23.4)	211 (10.4)	<0.001[a]	16 (21.6)	16 (21.9)	
pTNM stage			<0.001[c]			1.000[c]
I	48 (59.3)	1,591 (78.7)		45 (60.8)	44 (60.3)	
IA	28 (34.6)	1,146 (56.7)		26 (35.1)	26 (35.6)	
IB	20 (24.7)	445 (22.0)		19 (25.7)	18 (24.7)	
II	14 (17.3)	196 (9.7)		13 (17.6)	12 (16.4)	
IIA	2 (2.5)	55 (2.7)		2 (2.7)	2 (2.7)	
IIB	12 (14.8)	141 (7.0)		11 (14.9)	10 (13.7)	
IIIA	19 (23.5)	235 (11.6)	0.001[a]	16 (21.6)	17 (23.3)	

[a], chi-square tests; [b], Mann-Whitney U tests; [c], Fisher's exact tests. PSM, propensity score matching; *ALK*, anaplastic lymphoma kinase; CI, confidence interval; pN stage, pathologic nodal stage; pT stage, pathologic tumor stage.

(*Table S1*), and after the follow-up with 7 patients in the *ALK* positive group and 8 patients in the *ALK* negative group losing contact after surgery, the results were still similar between the two groups in the remaining 147 patients even for tumor size (P>0.05; *Table 1*).

Prognostic value of the ALK rearrangement in completely-resected stage I–IIIA lung adenocarcinoma

We next evaluated the associations between *ALK* rearrangement and prognosis in the 147 completely-resected stage I–IIIA lung adenocarcinoma patients. At the time of analysis, the median follow-up time was 55.3 months (interquartile range, 51.6 to 60.2 months). At last follow-up evaluation, a total of 18 (12.2%) of 147 patients died and all deaths were tumor-related, with a 4-year OS rate of 90.5%. The median OS time is not yet reached. A total of 55 (37.4%) of 147 patients experienced a DFS event, with a 4-year DFS rate of 64.0%. The median DFS time was also not yet reached.

The 4-year DFS rates were 66.2% in the *ALK* positive group and 61.9% in the *ALK* negative group. The 4-year OS rates in *ALK* positive and negative group were 94.6% and 86.3%, respectively. The median DFS and median

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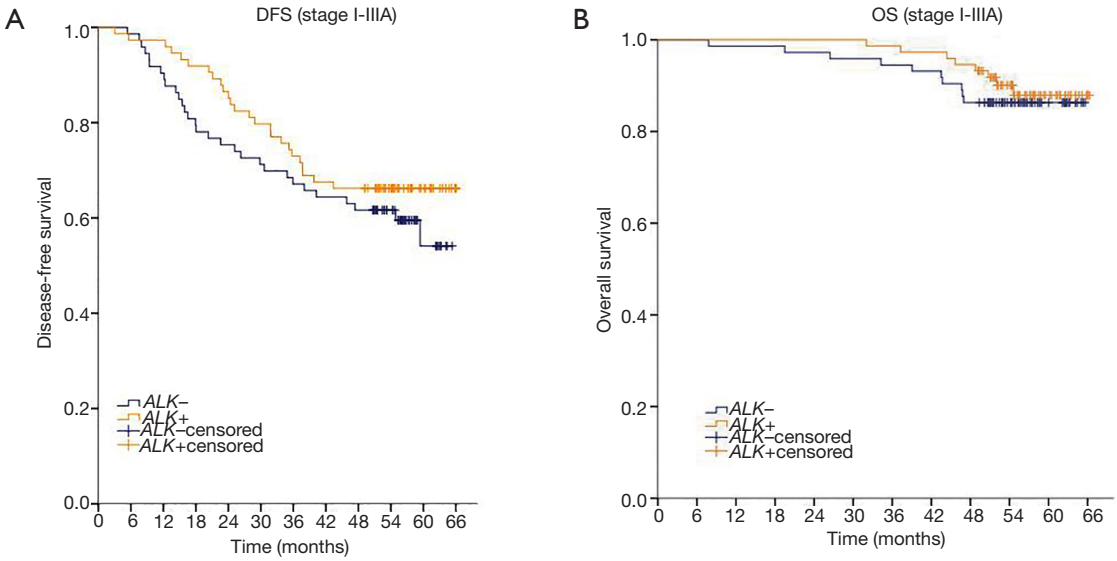

No. at risk												
ALK+	74	72	72	68	63	59	54	50	49	49	49	49
ALK–	73	72	66	57	55	52	49	47	45	45	43	43

No. at risk												
ALK+	74	74	74	74	74	74	73	72	70	67	66	66
ALK–	73	73	72	72	71	70	69	68	63	63	63	63

Figure 2 Kaplan-Meier survival curves for (A) DFS, and (B) OS by *ALK* status (n=147). The median DFS and median OS of both *ALK* positive group and *ALK* negative group were not yet reached. The log-rank test showed that *ALK* positivity was not associated with DFS or OS (DFS, P=0.289; OS, P=0.549). *ALK*, anaplastic lymphoma kinase; DFS, disease-free survival; OS, overall survival; *ALK*+, *ALK* positive group; *ALK*–, *ALK* negative group.

OS of both *ALK* positive group and *ALK* negative group were not yet reached. The log-rank test showed that *ALK* positivity was not associated with better DFS or OS (DFS, P=0.289; OS, P=0.549; *Figure 2*). We further analyzed the associations between *ALK* positivity and prognosis by pathologic stage. The median OS of both *ALK* positive group and *ALK* negative group were not yet reached in each stage. The median DFS of both two groups was not reached in stage I. The median DFS of *ALK* positive group and *ALK* negative group is not reached and 54.8 months respectively in stage II. The median DFS of *ALK* positive group and *ALK* negative group is 35.2 and 15.9 months respectively in stage IIIA. The log-rank test still showed no significantly difference of DFS and OS between *ALK* positive group and *ALK* negative group in each stage (I: DFS, P=0.535; OS, P=0.565; II: DFS, P=0.903; OS, P=0.338; IIIA: DFS, P=0.138; OS, P=0.068; respectively).

A univariate analysis showed that disease free survival was significantly shorter in patients with high lymph node status (N2) (HR: 5.07, 95% CI: 2.93–8.60, P<0.001; *Table 2*) or solid predominant adenocarcinoma subtype (HR: 2.22, 95% CI: 1.25–3.93, P=0.006; *Table 2*). And lymph node status was the only prognostic factor of OS (HR: 6.87, 95% CI: 2.66–17.74, P<0.001; *Table 2*). *ALK* positivity was not associated with better DFS or OS (HR, 0.75; 95% CI: 0.44–1.28; P=0.291; HR: 0.75, 95% CI: 0.30–1.91, P=0.551, respectively; *Table 2*). A multivariate analysis using a Cox proportional hazards model compared survival between *ALK* positive and *ALK* negative patients. After adjusting for sex, age, smoking history, adenocarcinoma subtypes, pathologic nodal staging, tumor staging and *ALK* rearrangement status, the variables that remained significantly associated with decreased DFS were mediastinal lymph node involvement (HR: 5.36, 95% CI: 3.01–9.65, P<0.001; *Table 2*) and solid predominant adenocarcinoma subtype (HR, 2.02; 95% CI: 1.07–3.79; P=0.029; *Table 2*). *ALK* positivity was not associated with DFS (HR, 0.58; 95% CI: 0.33–1.03, P=0.063; *Table 2*) or OS (HR, 0.61; 95% CI: 0.22–1.67, P=0.334; *Table 2*). These results suggested that *ALK* rearrangement may not be a prognostic factor in completely

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Table 2 Disease-free and overall survival analysis results for 147 stage I–IIIA adenocarcinoma patients

Characteristics	Number of patients	Recurrence					Death				
		Number	Univariate		Multivariate		Number	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value		HR (95% CI)	P value	HR (95% CI)	P value
Sex				0.961		0.581			0.515		0.891
Male	63	24	Ref				9	Ref			
Female	84	31	0.99 (0.58–1.68)		1.20 (0.63–2.29)		9	0.74 (0.29–1.85)		0.92 (0.30–2.85)	
Age, years				0.870		0.829			0.935		0.998
≤55	76	28	Ref				9	Ref			
>55	71	27	1.04 (0.62–1.77)		1.06 (0.61–1.85)		9	1.04 (0.41–2.62)		1.00 (0.38–2.66)	
Smoking history				0.409		0.629			0.116		0.596
No	130	47	Ref				14	Ref			
Yes	17	8	1.37 (0.65–2.90)		0.80 (0.33–1.97)		4	2.44 (0.80–7.42)		1.46 (0.36–6.03)	
Adenocarcinoma subtype				0.006		0.029			0.124		0.581
Others	118	38	Ref				12	Ref			
Solid predominant	29	17	2.22 (1.25–3.93)		2.02 (1.07–3.79)		6	2.16 (0.81–5.75)		1.35 (0.47–3.88)	
pT stage				0.933		0.595			0.759		0.671
T1	79	29	Ref				9	Ref			
T2–T4	68	26	1.02 (0.60–1.74)		1.17 (0.65–2.10)		9	1.16 (0.46–2.91)		1.24 (0.46–3.36)	
pN stage				<0.001		<0.001			<0.001		<0.001
N0–N1	115	30	Ref				7	Ref			
N2	32	25	5.07 (2.93–8.60)		5.36 (3.01–9.65)		11	6.87 (2.66–17.74)		6.61 (2.43–17.94)	
ALK rearrangement				0.291		0.063			0.551		0.334
Negative	73	30	Ref				10	Ref			
Positive	74	25	0.75 (0.44–1.28)		0.58 (0.33–1.03)		8	0.75 (0.30–1.91)		0.61 (0.22–1.67)	

ALK, anaplastic lymphoma kinase; HR, hazard ratio; CI, confidence interval; pN stage, pathologic nodal stage; pT stage, pathologic tumor stage.

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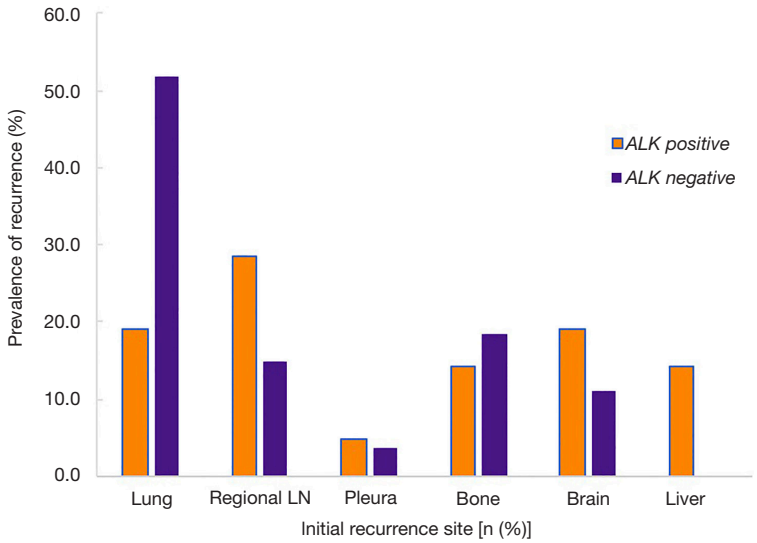

ALK positive, n=21 (%)	4 (19.0)	6 (28.5)	1 (4.8)	3 (14.3)	4 (19.0)	3 (14.3)
ALK negative, n=27 (%)	14 (51.9)	4 (14.8)	1 (3.7)	5 (18.5)	3 (11.1)	0
P value	0.020	0.244	0.856	0.696	0.440	0.043

Figure 3 Initial recurrence site according to ALK IHC status among 48 patients with tumor recurrence (7 patients with multiple recurrence sites detected at the same time were excluded). *ALK*, anaplastic lymphoma kinase; LN, lymph node; IHC, immunohistochemistry.

resected stage I–IIIA lung adenocarcinoma.

The association of ALK positivity with the initial recurrence site

There were 55 patients with recurrent tumor in the matched cohort with follow up information. And 7 patients detected multiple recurrence sites at the same time and it was hard to find out what was really the initial site of these patients. In this case, we analyzed the association of *ALK* positivity with initial recurrence site in the remaining 48 patients with mono recurrence site. As shown in *Figure 3*, we found that there was an association between *ALK* status and liver and lung recurrence, more patients experienced liver recurrence and less experienced lung recurrence in *ALK* positive group than in *ALK* negative group [14.3% (3/21) *vs.* 0% (0/27), P=0.043; 19.0% (4/21) *vs.* 51.9% (14/27), P=0.020, respectively, *Figure 3*]. There were no differences of other initial recurrence sites including regional lymph nodes, pleura, bone and brain between the two groups.

Discussion

The prevalence of *ALK* positive patients was 3.9% in our study, consistent with the previous reports looking at unselected populations with mostly advanced adenocarcinoma (3-6). Several studies showed a higher prevalence of *ALK* positivity in younger patients, light smokers or never-smokers, females (15,16,28,30,37), and solid predominant adenocarcinoma subtype (14,38,39). In this study, we also found *ALK* rearrangements were detected more frequently in younger age patients and solid predominant adenocarcinoma subtype. However, *ALK* positivity showed no association with sex or smoking status, in accord with the results reported in other two studies (10,14). Although several previous studies showed that *ALK* rearrangement was not related to pleural invasion, we found *ALK* positive patients tend to have pleural invasion more frequently compared with *ALK* negative patients. A recent meta-analysis concluded that *ALK* rearrangement was more common in higher pathologic stages (40), which is in line with our results (IIIA, P=0.001). Furthermore, a previous study found that *ALK* positive lung cancer showed earlier tumor stage (T1) (P=0.02) (8), whereas it tended to harbor lymph node metastasis in adenocarcinoma (P=0.09), which is also consistent with our results. We revealed that *ALK* positive patients were more likely to have smaller tumor size (P=0.014) and mediastinal lymph node involvement

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(P<0.001). However, no significant difference of pathologic tumor stage (P=0.169) between *ALK* positive and negative group was observed in our study.

The prognostic value of *ALK* rearrangement in early stage NSCLC is controversial. Tantraworasin (10), Paik (8), Fukui (29), and Ohba (12), demonstrated that *ALK* positivity was not correlated with prognosis, which is consistent with our results. Conversely, five reports revealed that patients with *ALK* rearrangement NSCLC had a shorter DFS after adjusting for main prognostic clinical factors (7,9,13,14,28), and two studies showed that *ALK* positivity was not associated with OS (9,13), while other two studies concluded that *ALK* positive patients had inferior OS (7,14). In contrast, Blackhall *et al.* reported superior RFS and OS in patients with *ALK* positive early-stage NSCLC (11). To our knowledge, our study is one of the largest data set to report on the outcome of *ALK* positive patients with stage I to IIIA resected lung adenocarcinoma. Since the significant discrepancies of age, adenocarcinoma subtypes, pTNM stage etc. between the *ALK* positive group and *ALK* negative group in the entire cohort, we used PSM method to control the confounding effects of these known prognostic factors for lung cancer recurrence before we compared the prognostic impact of *ALK* rearrangement. And this is the first report using PSM to reveal that *ALK* positivity is not associated with DFS or OS. It indicates that *ALK* rearrangement is not an independent prognostic factor in stage I to IIIA completely resected lung adenocarcinoma patients.

In patients with advanced NSCLC, Shaw *et al.* found that *ALK* FISH-positive patients seemed to have similar survival to that of the general population of wild-type patients lacking either *ALK* rearrangement or *EGFR* mutation (41), whereas in a report in patients free of Crizotinib with wild-type *EGFR* lung adenocarcinoma, *ALK* rearrangement was associated with longer OS (42). As to patients with early stage NSCLC, Chaft *et al.* found that adjusted for stage *ALK* rearrangement NSCLC was associated with worse RFS compared to *EGFR*-mutant, but not when compared to *KRAS*-mutant (31), In our study, among 73 *ALK* negative patients in the matched cohort, there were 19 patients with *EGFR*-mutation,13 with *EGFR* wild-type and 41 with unknown *EGFR* mutational status. Adjusted for main prognostic clinical factors, *ALK* positive patients showed better DFS compared to both EGFR-mutant and EGFR wild-type patients (HR 0.29, 95% CI: 0.14–0.61, P=0.001; HR 0.27, 95% CI: 0.12–0.63, P=0.002, respectively). However, there was no significant difference of DFS between ALK positive patients and EGFR status unknown patients (HR 1.42, 95% CI: 0.61–3.33, P=0.421). These results might attribute to that EGFR status was not regularly tested in our study cohort after surgery. In this case, ALK negative patients who had already experienced recurrence were more likely to undergo the test for EGFR mutation to find out whether they could be treated with EGFR-tyrosine kinase inhibitors (TKI). This might result in significantly higher prevalence of recurrence in patients with clear EGFR status than ALK positive or unknown EGFR status patients in our study cohort. Therefore, it is plausible that the prognostic significance of ALK will alter relative to the *EGFR* mutational status of ALK-negative patients.

Furthermore, we found that mediastinal lymph node involvement (N2) and solid predominant adenocarcinoma subtype were independent prognostic factors of DFS, while mediastinal lymph node involvement (N2) was the independent prognostic factor of OS. Previous studies have shown that patients with solid predominant adenocarcinoma have poor prognosis (43-45), which is consistent with our results. Notably, a higher prevalence of *ALK* positivity in mediastinal lymph node involvement (P<0.001) and solid predominant adenocarcinoma subtype (P<0.001) was found in our study. When the balance was achieved for these two factors in the matched cohort, there were no significant differences of DFS and OS between *ALK* positive group and *ALK* negative group. This result indicated that *ALK* rearrangement might have an indirect impact on prognosis through its unique biologic features with early nodal metastasis and solid predominant adenocarcinoma subtype. However, when these factors were adjusted using PSM, we found *ALK* rearrangement was not an independent prognostic factor.

Yang *et al.* reported that *ALK*-positive tumors might have an increased risk of brain and liver metastases compared with *ALK*-negative disease in late stage (28). In our study, we found that more patients experienced liver recurrence and less experienced lung recurrence in *ALK* positive group than in *ALK* negative group. This result indicated that there was an association between ALK status and liver and lung recurrence. But the risk of brain metastases was similar in two groups.

Nevertheless, our study has several limitations. Firstly, we did not analyze the survival of entire cohort and the method PSM has its intrinsic limitation including that there may be other prognostic factors not covered in our regression model. Secondly, fifteen patients were lost to

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follow-up, although the clinicopathologic characteristics were still balanced between the two groups in the remaining patients. Thirdly, the *EGFR* or *KRAS* status were unknown in more than half of *ALK* negative patients, which made it challenging to analyze the prognostic impact of these genomic subsets. Fourthly, post-recurrence therapy information was lacking in our study and this might affect the OS of patients who experienced recurrence. In addition, since the majority of the patients in our study cohorts were woman and non-smokers, which is not typical of a non-East Asian population with lung cancer, the applicability of this study's results may be limited in North American/European population.

Conclusions

ALK rearrangement was not an independent prognostic factor in stage I–IIIA lung adenocarcinoma patients, but it significantly correlated with younger age, solid predominant adenocarcinoma, higher frequency of pleura invasion, smaller tumor size, mediastinal lymph node involvement and later pathologic stage. In addition, there was an association between ALK status and liver and lung recurrence, more patients experienced liver recurrence and less experienced lung recurrence with ALK positive tumors than with ALK negative tumors.

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Footnote

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

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 Ethics Committee of Shanghai Chest Hospital. Written informed consent was obtained from all individual participants included in this study. And this study was conducted in accordance with the Declaration of Helsinki.

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Supplementary

Table S1 Patients' clinicopathologic characteristics baseline before and after PSM

Characteristic	Entire cohort (n=2,103)			Matched cohort (n=162)		
	ALK-positive group (%)	*ALK*-negative group (%)	P value	*ALK*-positive group (%)	*ALK*-negative group (%)	P value
Total	81	2,022		81	81	
Sex			0.769[a]			0.873[a]
Male	33 (40.7)	857 (42.4)		33 (40.7)	32 (39.5)	
Female	48 (59.3)	1,165 (57.6)		48 (59.3)	49 (60.5)	
Age, years			<0.001[b]			0.289[b]
Mean	53.8	60.1		53.8	55.4	
95% CI	51.6–55.9	59.7–60.5		51.6–56.0	53.5–57.3	
Median	53	60		53	56	
Range	34–81	24–83		34–81	37–80	
Smoking history			0.911[c]			0.430[c]
No	71 (87.7)	1,769 (87.5)		71 (87.7)	74 (91.4)	
Yes	10 (12.3)	242 (12.0)		10 (12.3)	6 (7.4)	
Unknown	0	11 (0.5)		0	1 (1.2)	
Type of surgery			0.967[c]			1.000[a]
Lobectomy	76 (93.8)	1,866 (92.3)		76 (93.8)	76 (93.8)	
Wedge resection	5 (6.2)	111 (5.5)		5 (6.2)	5 (6.2)	
Segmentectomy	0	19 (0.9)		0	0	
Pneumonectomy	0	3 (0.1)		0	0	
Bilobectomy	0	5 (0.2)		0	0	
Other	0	18 (0.9)		0	0	
Adenocarcinoma subtype			<0.001[c]			0.694[c]
Lepidic predominant	1 (1.2)	113 (5.6)		1 (1.2)	1 (1.2)	
Acinar predominant	36 (44.4)	1,103 (54.5)		36 (44.4)	33 (40.7)	
Papillary predominant	11 (13.6)	514 (25.4)		11 (13.6)	18 (22.2)	
Micropapillary predominant	0	16 (0.8)		0	1 (1.2)	
Solid predominant	18 (22.2)	161 (8.0)	<0.001[a]	18 (22.2)	15 (18.5)	
Variants of invasive adenocarcinoma	15 (18.5)	115 (5.7)	<0.001[a]	15 (18.5)	13 (16.0)	
Pleura invasion			0.040[c]			0.763[c]
No	47 (58.0)	1,431 (70.8)		47 (58.0)	50 (61.7)	
Yes	31 (38.3)	540 (26.7)		31 (38.2)	28 (34.6)	
Unknown	3 (3.7)	51 (2.5)		3 (3.7)	3 (3.7)	
Tumor size			0.014[b]			0.028[b]
Mean	2.07	2.35		2.08	2.34	
95% CI	1.86–2.28	2.30–2.40		1.86–2.28	2.12–2.56	
Median	1.8	2.000		1.8	2.0	
Range	0.6–5.0	0.2–15.0		0.6–5.0	1.0–7.5	
pT stage			0.169[c]			0.811[c]
T1	44 (54.3)	1,255 (62.1)		44 (54.3)	45 (55.6)	
T2	36 (44.4)	671 (33.2)		36 (44.4)	33 (40.7)	
T3	1 (1.2)	85 (4.2)		1 (1.2)	2 (2.5)	
T4	0	11 (0.5)		0	1 (1.2)	
pN stage			<0.001[a]			0.885[a]
0	51 (63.0)	1,726 (85.4)		51 (63.0)	54 (66.7)	
1	11 (13.6)	85 (4.2)		11 (13.6)	10 (12.3)	
2	19 (23.4)	211 (10.4)		19 (23.4)	17 (21.0)	
pTNM stage			<0.001[c]			1.000[c]
I	48 (59.3)	1,591 (78.7)		48 (59.3)	48 (59.3)	
IA	28 (34.6)	1,146 (56.7)		28 (34.6)	28 (34.6)	
IB	20 (24.7)	445 (22.0)		20 (24.7)	20 (24.7)	
II	14 (17.3)	196 (9.7)		14 (17.3)	14 (17.3)	
IIA	2 (2.5)	55 (2.7)		2 (2.5)	2 (2.5)	
IIB	12 (14.8)	141 (7.0)		12 (14.8)	12 (14.8)	
IIIA	19 (23.5)	235 (11.6)	0.001[a]	19 (23.5)	19 (23.5)	

[a], chi-square tests; [b], Mann-Whitney U tests; [c], Fisher's exact tests. PSM, propensity score matching; *ALK*, anaplastic lymphoma kinase; CI, confidence interval; pN stage, pathologic nodal stage; pT stage, pathologic tumor stage.