Original Article

TNM stages inversely correlate with the age at diagnosis in *ALK*-positive lung cancer

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Background: To clearly reveal the correlations between age at diagnosis, tumor-nodes-metastasis (TNM) stages and frequency of *ALK*-positive lung cancer.

Methods: We reviewed patients who presented with *ALK* rearrangements (n=411) or *KRAS*-mutations (n=122) between September 2010 and January 2018. The clinical characteristics and overall survival were analyzed for the two genotype cohorts and stratified by different age categories (<40, 40–49, 50–59, ≥60 years).

Results: In the *ALK*-positive cohort, the younger group showed more frequent disease in the T3/4 stage (P=0.014), lymph node metastasis (P=0.011) and distant metastasis (P=0.015) than the older groups. Meanwhile, the mean age at diagnosis for the *ALK*-positive patients showed a significant inverse correlation with the clinical stages (stage I/II *vs.* III *vs.* IV, 54.7 *vs.* 52.0 *vs.* 49.7 years; P<0.001), as well as with the T, N, and M categories. However, *KRAS*-mutant patients did not exhibit similar relationships to those observed in *ALK*-positive patients. Importantly, for *ALK*-positive patients, the frequency of stage IIIb–IV disease was almost twice that of stage I–IIIa disease (6.1% *vs.* 3.4%, P<0.001); there was a similar incidence of the different disease stages in *KRAS*-mutant lung cancer (P=0.924). Lastly, in *ALK*-positive patients, the ≥60 years group was associated with a trend toward better survival than the other younger groups.

Conclusions: The TNM stages exhibited a significant inverse correlation with age at diagnosis for *ALK*-positive lung cancer patients. More unique therapeutic strategies should be required in these young patients.

Keywords: TNM stages; inverse correlation; age at diagnosis; *ALK*-positive lung cancer

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Introduction

Non-small cell lung cancer (NSCLC) is increasingly understood to be a heterogeneous disease (1,2). Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are present in 3–7% of NSCLC patients (3). *ALK* rearrangements define a distinct subgroup of NSCLC that typically occurs in young patients who have never smoked and who have adenocarcinoma histological characteristics (4-6). Several studies have demonstrated that the *ALK* gene has a high incidence in advanced NSCLC (7,8). However, there was no consensus on the frequency of surgical patients

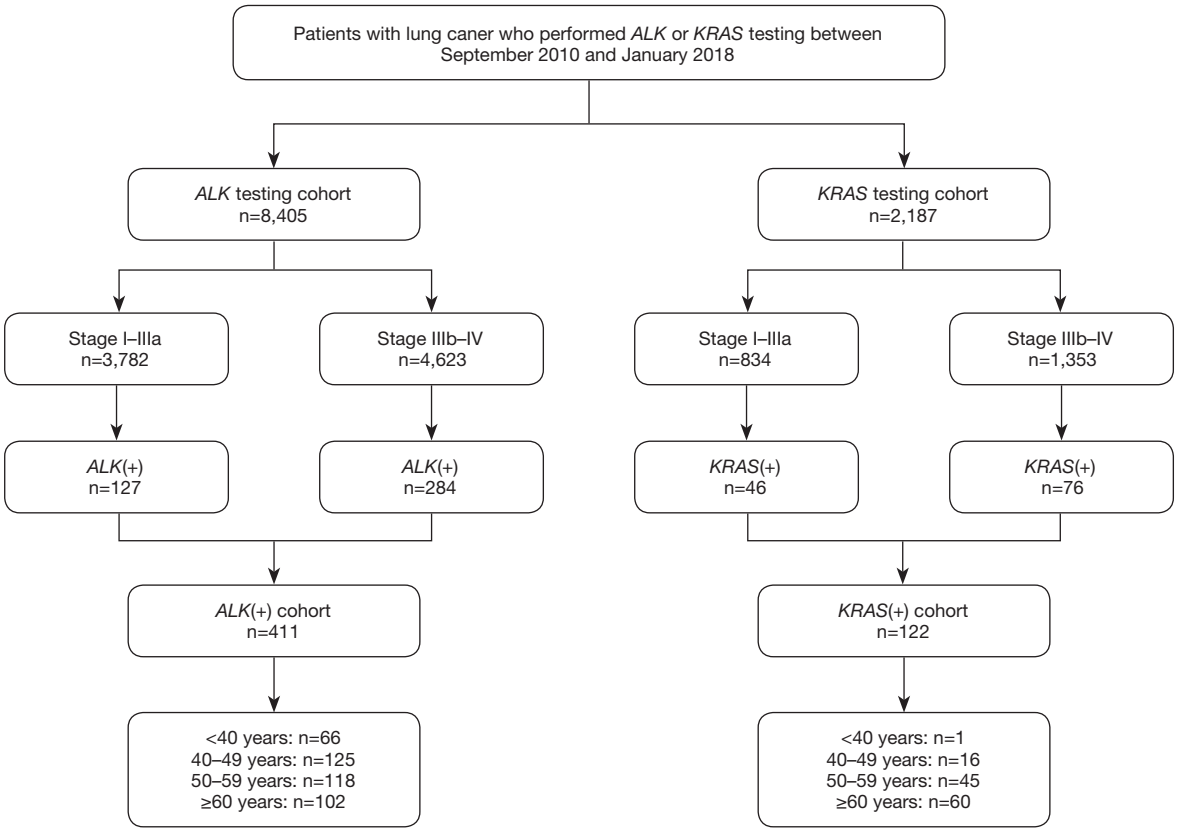

Figure 1 Study flow chart. ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog.

with *ALK*-positive lung cancer (9-11). Among NSCLC patients with a targetable genomic alteration, it suggested that younger patients were associated with an increased likelihood of initially presenting with stage IV disease (11,12) and exhibiting a poorer survival than older patients (12).

To clearly investigate the associations between age, tumor-nodes-metastasis (TNM) staging and frequency of *ALK*-positive lung cancer, we performed an analysis of *ALK*-positive lung cancer cases in a large-scale cohort and compared to the results to those of another clinically relevant cohort: Kirsten rat sarcoma viral oncogene homolog (*KRAS*)-mutant lung cancer cases.

Methods

Patients

The clinical records of 8,405 consecutive patients with lung cancer who had *ALK* detection and 2,187 consecutive patients with lung cancer who underwent *KRAS* testing at Guangdong Provincial People's Hospital (GDPH) between September 2010 and January 2018 were retrospectively reviewed. This study was approved by the Ethics and Scientific Committees of Guangdong Provincial People's Hospital [No. GDREC2016175H(R2)]. In our center, patients with lung cancer were routinely tested for *ALK* gene rearrangements. Of the 8,405 *ALK* screening patients, 3,782 patients had stage I–IIIa and 4,623 had stage IIIb–IV disease. Among the patients who underwent *KRAS* testing, 834 patients and 1,353 patients had stage I–IIIa and stage IIIb–IV disease, respectively (*Figure 1*). *ALK* was assayed by immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH) or next-generation gene sequencing (NGS). The age at initial diagnosis was extracted. In the resected patients, the T and N staging were from the results of surgical resection, and TNM staging in unresectable patients was based on the comprehensive imaging results. The T, N, and M stages were classified according to the International Association for the Study of Lung Cancer (IASLC) 7th TNM staging project. The mean age was compared between the *ALK*-positive and *KRAS*-mutant patients at various TNM stages. The patients were divided

into the following four groups stratified by age: <40, 40–49, 50–59 and ≥60 years; the clinical features and survival of the different age groups were analyzed. Stage I–IIIa was usually defined as resectable or potentially resectable and stage IIIb–IV was considered to have no curative treatment. For each included patient, we collected the following data: age; sex; smoking history; pathology; Eastern Cooperative Oncology Group (ECOG) score; TNM stage; presence of brain metastasis at initial diagnosis; major treatments including surgery; targeted therapy; chemotherapy or/and radiotherapy; and overall survival (OS).

Statistical analysis

Statistical analyses were performed using SPSS (version 20.0; SPSS Inc., Chicago, IL, USA). The Chi-square test or Fisher's exact test was used to compare categorical variables, and the Wilcoxon rank sum test was used for continuous variables. The Spearman correlation test was applied to assess the relations between age and clinical stages or various TNM categories. Furthermore, a linear regression test was used to estimate the trend between the percentage of stage IIIb–IV disease in various age groups. Univariate and multivariable Cox proportional hazards models were used to identify prognostic factors for survival. OS was defined as the time from the initial diagnosis until death from any cause. Survival curves were constructed using the Kaplan-Meier approach and compared using the log-rank test. A two-sided P value of <0.05 was considered statistically significant.

Results

Patient characteristics

In the *ALK*-positive cohort, 411 (4.9%) eligible patients were identified, including 127 patients with stage I–IIIa disease and 284 patients with stage IIIb–IV disease (*Figure 1*). Overall, 383 (93.2%) patients had histologically confirmed adenocarcinoma. Of the 411 eligible patients, there was almost an equal proportion of females [n=204 (49.6%)] and males [n=207 (50.4%)] in our study, and 321 (78.1%) patients in our cohort had never smoked. The ECOG scores of the patients were primarily low (score =0–1) [n=380 (92.5%)]. Moreover, the majority of *ALK*-positive patients had an absence of brain metastasis at the initial diagnosis [n=349 (84.9%)]. Of the treatment strategies, 129 (31.4%) patients underwent surgery, 180 (43.8%) patients received targeted therapy, and 150 (36.5%) patients were treated with chemotherapy or/and radiotherapy (*Table 1*).

The median age at diagnosis of the patients included in *ALK*-positive cohort was 51 years (range, 24–82 years). As shown in *Table 1*, young patients with *ALK*-positive lung cancer were associated with a high likelihood of being female (P=0.048), having histological adenocarcinoma characteristics (P=0.004), and exhibiting low ECOG scores (P=0.006). In addition, young patients more frequently had diseases in the T3/4 stage (P=0.014), lymph node metastases (P=0.011) and distant metastasis (P=0.015) (*Table 1*) than old patients.

There were 122 (5.6%) patients in the *KRAS*-mutant cohort who had a median age at diagnosis of 59 years (range, 40–88 years), including 46 patients with stage I–IIIa disease and 76 patients with stage IIIb–IV disease (*Figure 1*). As shown in *Table 1*, there were no significant differences in the clinical characteristics between the various age groups.

Association between age at diagnosis, frequency and TNM stages

Among all patients with *ALK*-positive lung cancer, the mean age at diagnosis decreased steadily with more advanced clinical stages [I/II *vs.* III *vs.* IV, mean age ± standard deviation (SD): 54.7±11.4 *vs.* 52.0±10.5 *vs.* 49.7±11.6 years]. There was a significant difference in age at diagnosis between the various clinical stages (P=0.002), and the age at diagnosis inversely correlated with the clinical stages (P<0.001) (*Figure 2A*). Moreover, these associations also existed for T stages (T1 *vs.* T2 *vs.* T3/4, mean age ± SD: 53.2±10.7 *vs.* 52.7±11.0 *vs.* 49.4±12.1 years), N stages (N0/1 *vs.* N2 *vs.* N3, mean age ± SD: 53.6±11.8 *vs.* 51.7±11.0 *vs.* 49.2±11.4 years), and M stages (M0 *vs.* M1, mean age ± SD: 53.4±11.0 *vs.* 49.7±11.6 years). Significant differences were also observed in age between various T, N, and M stages (T stages: P=0.003; N stages: P=0.004; M stages: P=0.001) and the age at diagnosis inversely correlated with the T, N, and M categories (T stages: P=0.001; N stages: P=0.001; M stages: P=0.001) (*Figure 2B,C,D*). However, the *KRAS*-mutant patients did not demonstrate similar characteristics to those of *ALK*-positive patients. The mean age at diagnosis of *KRAS*-mutant patients was 63.0±8.9, 58.1±9.6, 59.4±10.5 years for stage I/II, III, IV disease, respectively. There was no significant difference in age at diagnosis between various clinical stages (P=0.064) and there was no significant inverse correlation between age at diagnosis and clinical stages (P=0.084) (*Figure 2A*). Although the age at

Table 1 Clinical characteristics of patients with *ALK*-positive and *KRAS*-mutant lung cancer

Characteristics	*ALK*-positive cohort						*KRAS*-mutant cohort				
	Total, No. (%)	Age, years, No. (%)				P value	Total, No. (%)	Age, years, No. (%)			P value
		<40	40–49	50–59	≥60			40–49	50–59	≥60	
Patients	411 (100.0)	66 (16.1)	125 (30.4)	118 (28.7)	102 (24.8)	NA	121[a] (100.0)	16 (13.2)	45 (37.2)	60 (49.6)	NA
Median age at diagnosis [range], years	51 [24–82]	35.5 [24–39]	45 [40–49]	54 [50–59]	64.5 [60–82]	<0.001	59 [40–88]	48.5 [40–49]	54 [50–59]	65 [60–88]	<0.001
Sex						0.048					0.092
Male	207 (50.4)	26 (39.4)	70 (56.0)	53 (44.9)	58 (56.9)		108 (89.3)	16 (100.0)	42 (93.3)	50 (83.3)	
Female	204 (49.6)	40 (60.6)	55 (44.0)	65 (55.1)	44 (43.1)		13 (10.7)	0 (0)	3 (6.7)	10 (16.7)	
Smoking history						0.100					0.846
No	321 (78.1)	58 (87.9)	98 (78.4)	92 (78.0)	73 (71.6)		32 (26.4)	5 (31.3)	11 (24.4)	16 (26.7)	
Yes	90 (21.9)	8 (12.1)	27 (21.6)	26 (22.0)	29 (28.4)		89 (73.6)	11 (68.8)	34 (75.6)	44 (73.3)	
Histology						0.004					0.411
Adenocarcinoma	383 (93.2)	63 (95.5)	116 (92.8)	116 (98.3)	88 (86.3)		115 (95.0)	16 (100.0)	41 (91.1)	58 (96.7)	
Other	28 (6.8)	3 (4.5)	9 (7.2)	2 (1.7)	14 (13.7)		6 (5.0)	0 (0)	4 (8.9)	2 (3.3)	
ECOG performance status						0.006					0.070
0–1	380 (92.5)	62 (93.9)	122 (97.6)	109 (92.4)	87 (85.3)		95 (78.5)	15 (93.8)	38 (84.4)	42 (70.0)	
2–4	31 (7.5)	4 (6.1)	3 (2.4)	9 (7.6)	15 (14.7)		26 (21.5)	1 (6.3)	7 (15.6)	18 (30.0)	
Tumor status						0.014					0.090
T1	113 (27.5)	12 (18.2)	29 (23.2)	37 (31.3)	35 (34.3)		29 (24.0)	5 (31.3)	9 (20.0)	15 (25.0)	
T2	109 (26.5)	13 (19.7)	31 (24.8)	33 (28.0)	32 (31.4)		52 (43.0)	7 (43.8)	23 (51.1)	22 (36.7)	
T3/4	164 (39.9)	32 (48.5)	58 (46.4)	42 (35.6)	32 (31.4)		36 (29.8)	4 (25.0)	9 (20.0)	23 (38.3)	
Unknown	25 (6.1)	9 (13.6)	7 (5.6)	6 (5.1)	3 (2.9)		4 (3.3)	0 (0)	4 (8.9)	0 (0)	
Nodal status						0.011					0.059
N0/1	122 (29.7)	15 (22.7)	32 (25.6)	31 (26.3)	44 (43.1)		45 (37.2)	3 (18.8)	14 (31.1)	28 (46.7)	
N2	118 (28.7)	15 (22.7)	36 (28.8)	35 (29.7)	32 (31.4)		42 (34.7)	8 (50.0)	13 (28.9)	21 (35.0)	
N3	156 (38.0)	31 (47.0)	52 (41.6)	48 (40.7)	25 (24.5)		31 (25.6)	5 (31.3)	15 (33.3)	11 (18.3)	
Unknown	15 (3.6)	5 (7.6)	5 (4.0)	4 (3.4)	1 (1.0)		3 (2.5)	0 (0)	3 (6.7)	0 (0)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	*ALK*-positive cohort						*KRAS*-mutant cohort				
	Total, No. (%)	Age, years, No. (%)				P value	Total, No. (%)	Age, years, No. (%)			P value
		<40	40–49	50–59	≥60			40–49	50–59	≥60	
Metastasis status						0.015					0.480
M0	158 (38.4)	17 (25.8)	43 (34.4)	48 (40.7)	50 (49.0)		55 (45.5)	5 (31.3)	22 (48.9)	28 (46.7)	
M1	253 (61.6)	49 (74.2)	82 (65.6)	70 (59.3)	52 (51.0)		66 (54.5)	11 (68.8)	23 (51.1)	32 (53.3)	
Clinical stages						0.025					0.184
I/II	82 (20.0)	8 (12.2)	22 (17.6)	21 (17.8)	31 (30.4)		33 (27.3)	1 (6.3)	12 (26.7)	20 (33.4)	
III	76 (18.5)	9 (13.6)	21 (16.8)	27 (22.9)	19 (18.6)		22 (18.2)	4 (25.0)	10 (22.2)	8 (13.3)	
IV	253 (61.6)	49 (74.2)	82 (65.6)	70 (59.3)	52 (51.0)		66 (54.5)	11 (68.8)	23 (51.1)	32 (53.3)	
Brain metastasis at diagnosis						0.527					0.796
Present	62 (15.1)	13 (19.7)	15 (12.0)	17 (14.4)	17 (16.7)		21 (17.4)	2 (12.5)	7 (15.6)	12 (20.0)	
Absent	349 (84.9)	53 (80.3)	110 (88.0)	101 (85.6)	85 (83.3)		100 (82.6)	14 (87.5)	38 (84.4)	48 (80.0)	
Treatment											
Surgery	129 (31.4)	14 (21.2)	34 (27.2)	40 (33.9)	41 (40.2)	0.042	37 (30.6)	4 (25.0)	13 (28.9)	20 (33.3)	0.825
Targeted therapy	180 (43.8)	42 (63.6)	61 (48.8)	45 (38.1)	32 (31.4)	<0.001	9 (7.4)	3 (18.8)	3 (6.7)	3 (5.0)	0.202
CT or/and RT	150 (36.5)	32 (48.5)	55 (44.0)	36 (30.5)	27 (26.5)	0.004	74 (61.2)	13 (81.3)	30 (66.7)	31 (51.7)	0.063

[a], Only one patient aged 39 years was in <40 years group in *KRAS*(+) cohort, so <40 years group in *KRAS*(+) cohort was excluded in the analysis. ALK, anaplastic lymphoma kinase; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene homolog; NA, not applicable; RT, radiotherapy.

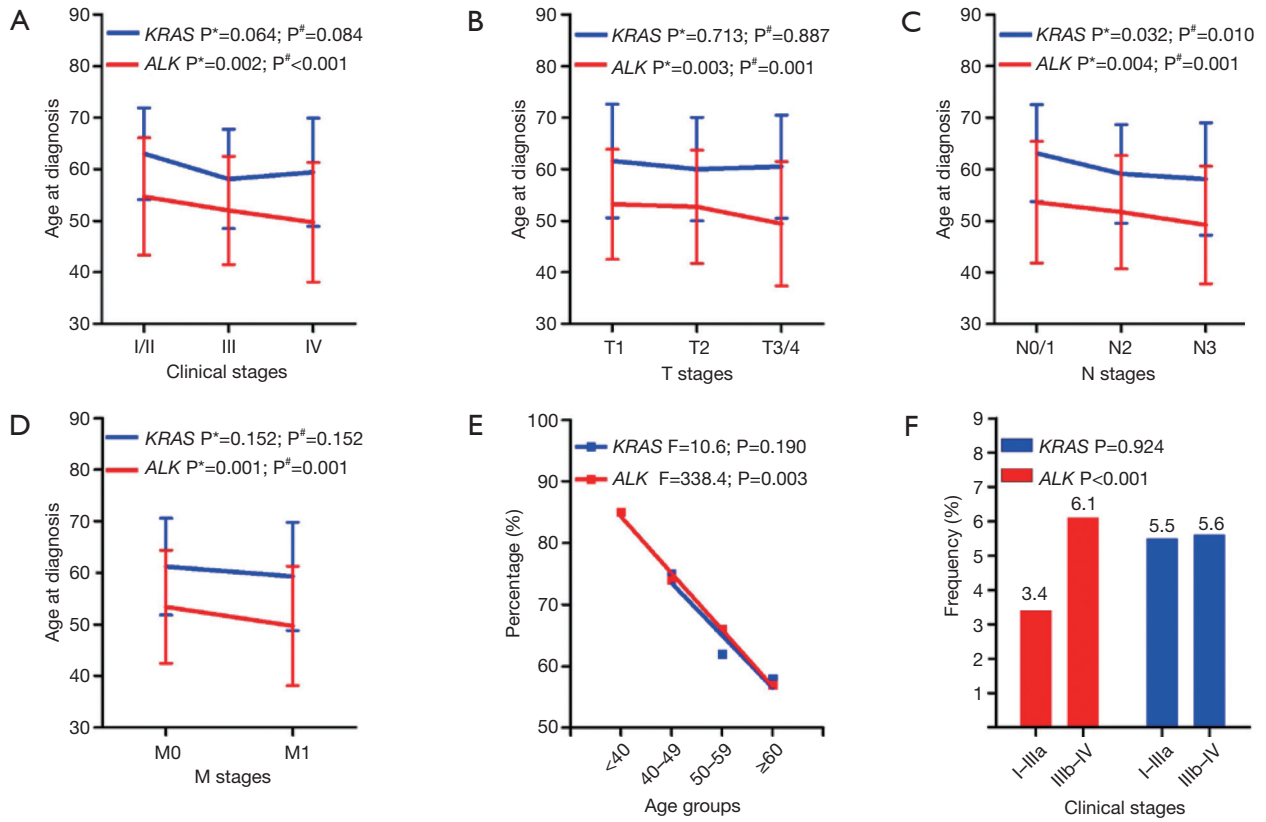

Figure 2 The correlations between age at diagnosis, frequency, and TNM stages for *ALK*-positive and *KRAS*-mutant lung cancer. (A,B,C,D) Mean ages at different TNM stages; P*, as determined by Wilcoxon rank sum tests, which demonstrated the differences in age between various TNM stages; P#, as determined by Spearman correlation tests, which demonstrated the correlation between age at diagnosis and the TNM stages; (E) percentage of *ALK*-positive and *KRAS*-mutant lung cancer being stage IIIb–IV disease in the relative age groups; P, as determined by linear regression tests, which demonstrated the trend of percentage of stage IIIb–IV disease between the various age groups; (F) frequency of *ALK*-positive and *KRAS*-mutant lung cancer being stage I–IIIa and IIIb–IV diseases in the total population. ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog.

diagnosis showed a significant inverse correlation with the N categories (P=0.010), the correlation was not significant in the T (P=0.887) or M categories (P=0.152) (*Figure 2B,C,D*).

Furthermore, the proportion of *ALK*-positive lung cancer that was stage IIIb–IV disease decreased steadily as the age groups became older (84.8% *vs.* 73.6% *vs.* 66.1% *vs.* 56.9%) (F=338.4; P=0.003). However, the *KRAS* cohort did not show this significant linear relation (F=10.6; P=0.190) (*Figure 2E*). In this study, the total frequency of *ALK* rearrangements was approximately 4.9%. We found that the frequency of *ALK* rearrangements in patients with stage IIIb–IV disease was much higher than that of the patients at stage I–IIIa disease (6.1% *vs.* 3.4%, P<0.001). However, the frequency of the *KRAS* mutation in patients with stage I–IIIa and IIIB–IV disease were similar at 5.5% and 5.6%, respectively (P=0.924) (*Figure 2F*).

Survival analysis

The median follow-up time was 13.7 months (range, 0.1–95.8 months), and the last follow-up was recorded on August 10, 2018. In the *ALK*-positive cohort, 112 (27.3%) patients died during follow-up. The 5-year OS rates were 40.5%, 47.8%, 44.8% in the <40 years, 40–49 years and 50–59 years groups, respectively. Among the *ALK*-positive patients aged 60 years or older, the 5-year OS rate reached 65.6%. There were statistically significant differences in OS between the ≥60 years group and <40 years group (P=0.048) and between the ≥60 years group and the 50–59 years group (P=0.041). Although the OS between ≥60 years

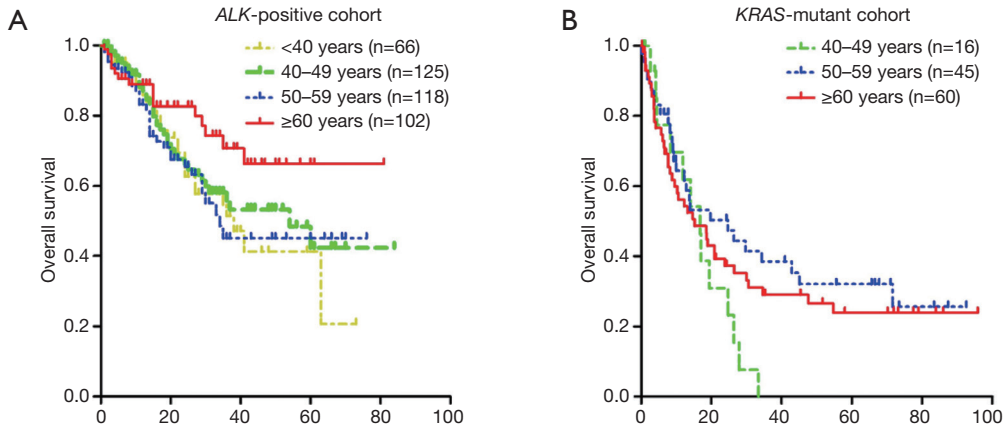

Figure 3 Survival analysis stratified by the different age groups. ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog.

Table 2 Overall survival by age groups in two genotype cohorts

Age groups (years)	Median overall survival, months (95% CI)	5-year OS (%)	P value					
			<40 *vs.* 40–49	<40 *vs.* 50–59	<40 *vs.* ≥60	40–49 *vs.* 50–59	40–49 *vs.* ≥60	50–59 *vs.* ≥60
ALK(+)			0.582	0.930	0.048	0.497	0.135	0.041
<40	38.1 (25.2–51.0)	40.5						
40–49	54.3 (30.0–78.6)	47.8						
50–59	33.5 (26.6–40.4)	44.8						
≥60	Not reached	65.6						
KRAS(+)[a]			NA	NA	NA	0.052	0.205	0.451
40–49	16.8 (10.8–22.8)	0.0						
50–59	24.7 (6.9–42.4)	32.3						
≥60	15.3 (5.8–24.7)	24.0						

[a], Only one patient aged 39 years was in <40 years group in *KRAS*(+) cohort, so <40 years group in *KRAS*(+) cohort was excluded in the analysis. ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; NA, not applicable; OS, overall survival.

group and the 40–49 years group was not significantly different (P=0.135), the patients in the ≥60 years group were associated with a trend toward better survival compared to the other age groups (*Figure 3A* and *Table 2*). However, in the *KRAS* cohort, there were no significant differences between the three age groups (40–49 *vs.* 50–59 years, P=0.052; 40–49 *vs.* ≥60 years, P=0.205; 50–59 *vs.* ≥60 years, P=0.451) (*Figure 3B* and *Table 2*).

For the *ALK*-positive cohort, multivariable analyses revealed that non-intracranial metastatic disease [hazard ratio (HR): 2.87; P<0.001] and the presence of brain metastases at diagnosis (HR: 3.72, P<0.001) were associated with poor survival, as was the presence of high ECOG scores (HR: 3.97; P<0.001). Furthermore, non-intracranial metastatic disease (HR: 4.90; P<0.001) and the presence of brain metastases at diagnosis (HR: 4.76, P<0.001) were also prognostic factors in *KRAS*-mutant patients (*Table 3*).

Discussion

The rearrangements of *ALK* defined a molecular subset of NSCLC with distinct clinical and pathological features. The included patients shared similar clinical features, including never/light smoking history, adenocarcinoma, and

Table 3 Cox-regression survival analysis in patients with *ALK*-positive and *KRAS*-positive lung cancer

Variables	*ALK*-positive cohort						*KRAS*-mutant cohort					
	Univariate analysis			Multivariable analysis			Univariate analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosis[a]	0.99	0.97–1.00	0.081	–	–	–	0.99	0.97–1.02	0.572	–	–	–
Female sex	1.02	0.71–1.48	0.909	–	–	–	1.05	0.51–2.19	0.893	–	–	–
Smoking history	1.27	0.82–1.95	0.289	–	–	–	0.73	0.45–1.18	0.195	–	–	–
ECOG =2–4	3.32	1.92–5.74	<0.001	3.97	2.26–7.00	<0.001	1.70	1.01–2.86	0.044	1.15	0.67–1.95	0.617
Adenocarcinoma histology	1.01	0.47–2.17	0.979	–	–	–	0.58	0.21–1.60	0.297	–	–	–
Non-intracranial metastatic disease at diagnosis	1.67	1.15–2.44	0.007	2.87	1.80–4.58	<0.001	3.12	1.94–5.03	<0.001	4.90	2.77–8.65	<0.001
Intracranial metastatic disease at diagnosis	2.07	1.29–3.31	0.003	3.72	2.08–6.66	<0.001	2.34	1.35–4.05	0.002	4.76	2.47–9.17	<0.001
Targeted therapy received	1.43	0.98–2.10	0.063	–	–	–	0.94	0.41–2.16	0.877	–	–	–

[a], The variable of age at diagnosis was conducted in COX regression model as continuous variable. ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR: hazard ratio; KRAS, Kirsten rat sarcoma viral oncogene homolog; NA, not applicable.

young age (4,6,13). However, few large-scale studies have clearly explored the correlations between the age, TNM stage and frequency of *ALK*-positive lung cancer.

In the most recent decade, several small-scale studies of this subgroup described the frequency of *ALK*-positive lung cancer in young patients or groups of patients stratified by age. In addition, some surgeons also explored the proportion of *ALK* rearrangements among the surgical population. These studies are summarized in *Table 4* (4,5,8-19). As shown in *Table 4*, the frequency of *ALK*-positive lung cancer in the younger group ranged from 10.1% to 40.7% and was much higher than that of the older group, which ranged from 0.9% to 4.2%. Tanaka *et al.* (11) and Sacher *et al.* (12) demonstrated that the likelihood of exhibiting *ALK* translocations steadily decreased with age. In this study, we also identified this downtrend in a large-scale population. Regarding the difference in frequencies between TNM stage groups, few studies have focused on the proportion of *ALK* mutations in advanced lung cancer. However, the *ALK* rearrangements were more frequent in stage IV disease, with a high rate that ranged from 9.7–28.0% (7,8,14), than in the unselected population (3), which had a rate that ranged from 3–7%. In contrast, the frequency of *ALK*-positive lung cancer varied from 1.0% to 9.0% in the surgical patients with relatively early-stage disease. Yip *et al.* performed genotyping profiles of resected tissues from 204 patients with stage IB primary lung adenocarcinoma and found that only 2 (1%) patients exhibited *ALK* rearrangements (9). However, Zhou *et al.* reported that the frequency of *EML4-ALK* fusions was 9.0% in 134 stage IA NSCLC cases (10); Blackhall *et al.* compared the difference between detecting for *ALK* with IHC and Fish in 1,281 European surgical patients with stage I to III adenocarcinoma, and reported two distinct frequencies of 6.2% and 2.2%, respectively (5). The various results may be attributed to multiple confounding factors, including small-scale patient samples, differing diagnosis technology, selected patients with a young age and nonsmoker. In our hospital, testing for *ALK* is a routine examination for patients treated with surgery. Our results demonstrated that the frequency of *ALK* mutation was 3.4% (127/3,782) in stage I–IIIa patients. However, in our results, the *ALK*-positive patients had a 79% increased likelihood of exhibiting stage IIIb–IV disease at the initial diagnosis, whereas, the *KRAS*-mutant patients did not demonstrate these special characteristics.

Of note, we identified with the Spearman correlation test that the TNM stages exhibited an inverse correlation with

Table 4 Summary of reported data about age, TNM staging and frequency in *ALK*-positive lung cancer

Author	Year	Study period	Population of origin	Patients included	Number of patients with *ALK*(+)/*ALK* testing	Age, years	Frequency stratified by age groups, %	Median age of *ALK*-positive patients, years	Stage of *ALK*-positive patients (rate, %)	Frequency stratified by stage groups, %
Tian	2017	2011–2013	China	LC	71/1,387	–	–	48	I–IIIa (25.4); IIIb–IV (74.6)	I–IIIa: 3.2; IIIb–IV: 6.4
Corrales-Rodríguez	2017	2012–2017	Latin American countries	NSCLC	19/188	≤40 and stage IV	10.1	–	Stage IV and ≤40 years [100]	10.1
Tanaka	2017	2009–2015	Japanese	ADC	103/1,746	≤40/>40	40.7/4.2[a]	–	–	–
Igata	2016	2008–2015	Japanese	LC	4/26	<50	15.4	–	–	–
Sacher	2016	2002–2014	American	NSCLC	84/1,783	<40/40–49/50–59/60–69/≥70	19.1/12.8/5.1/2.7/0.9[a]	–	–	–
Wang	2015	2008–2014	Chinese	LC	6/22	≤30	27.2	–	–	–
Blackhall	2014	2003–2009	European	NSCLC	IHC: 80/1,281; FISH: 28/1,281	–	–	FISH: 58	I–III [100]	IHC: 6.2; FISH: 2.2
Liu	2014	2011–2012	Chinese	NSCLC	56/200	–	–	48	IV [100]	28.0
Kim	2014	2005–2012	Korean	Non-smokers with ADC	14/162	–	–	–	–	–
VandenBussche	2014	2010–2014	American	NSCLC	5/43	≤50	11.6	–	–	–
Yip	2013	1990–2008	American	ADC	2/204	–	–	–	Ib [100]	1.0
Zhou	2013	2007–2010	Chinese	NSCLC	28/488	–	–	–	I–IIIa [99]	I–IIIa: 5.7; Ia: 9.0; IIIa: 5.5
Fukui	2012	2001–2010	Japanese	ADC	28/720	–	–	58	I–IIIa [96]	3.9
Paik	2012	2003–2008	Korean	NSCLC	28/735	–	–	55	I–III [100]	3.8
Wang	2012	2005–2011	Chinese	NSCLC	11/113	–	–	62	IV [100]	9.7
Wong	2009	NR	Chinese	LC	13/266	–	–	59	I–III [100]	4.9

[a], Percentage was recalculated because the same accuracy was required; ALK, anaplastic lymphoma kinase; ADC, adenocarcinoma; FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry; LC, lung cancer; NR, not reported; NSCLC, non-small cell lung cancer.

age at diagnosis, which suggested that patients who were younger at the initial diagnosis had a greater likelihood of being diagnosed with a more advanced diseases than patients who were older. A retrospective study by Liu *et al.* analyzed the clinicopathological features of *ALK* fusion in 200 advanced NSCLC patients. The median age was 48 years in the *ALK*-positive group (14). Nevertheless, the *ALK*-positive patients with early-stage disease exhibited an older median age of 55–59 years than the patients with late-stage patients (5,13,17,18). In fact, previous studies have indicated that young patients have a high proportion of stage III–IV disease in unselected NSCLC that ranges from 74% to 97% (8,11,12,20-23), which suggests that younger NSCLC patients exhibit more progressive biology than older patients. The correlation between age and TNM stages could be explained by the steady downward trend of frequencies with age and the high incidence of stage IIIb–IV disease in *ALK*-positive lung cancer.

In fact, we hypothesized that *ALK* rearrangements are involved in different biological activities at the early and advanced stages in the course of the tumor evolution, which features a period of rapid growth from the early stage into the advanced stage. Therefore, most patients with *ALK* mutations were diagnosed with advanced disease at the initial diagnosis. This process could explain the low incidence of *ALK* rearrangements in patients with ground-glass opacity (GGO) (13), but patients with GGO tended to present with more lymph node metastases than patients with *ALK*-negative lung cancer (17) and have a shorter recurrence-free survival (RFS) than *EGFR*-mutant patients (24). Furthermore, it has been supported that *EML4-ALK*-positive patients were observed to have more extrathoracic metastases including brain metastases at the initial diagnosis than *EGFR*-mutant patients (25) and patients with *ROS1* gene rearrangements (26).

The realization that NSCLC in young patients is a genetically unique disease naturally (11,27) lends itself to the question of whether the natural history and underlying disease biology of NSCLC is also distinct in this subgroup. Similarly, the difference in disease biology between younger and older patients in *ALK*-positive lung cancer was previously unknown. Our study found that patients aged 60 or older were associated with a trend toward improved prognosis compared with the other younger groups. Therefore, age may be an independent factor to predict the frequency of *ALK*-positive lung cancer, disease biology and prognosis of patients with *ALK*-positive lung cancer.

In interpreting these findings, some inherent limitations in this study must be considered. The patients included our study were drawn from a single institution and the duration of follow-up was short. Additionally, the screening methods for detecting the *ALK* gene varied, and included IHC, Fish, and NGS, which led to false positives.

Conclusions

Despite the aforementioned limitations, the findings of this study expanded the understanding of the associations between age, frequency of *ALK*-positive lung cancer and TNM stages in *ALK*-positive lung cancer. Younger *ALK*-positive patients exhibited a higher frequency but tended to have more advanced disease than older patients. The combination of opportunity and risk requires the unique and precise therapeutic strategies.

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Footnote

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

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References

1. Chen Z, Fillmore CM, Hammerman PS, et al. Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer 2014;14:535-46.
2. Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the Evolution of Non-Small-Cell Lung Cancer. New Engl J Med 2017;376:2109-21.
3. Lin JJ, Riely GJ, Shaw AT. Targeting ALK: Precision Medicine Takes on Drug Resistance. Cancer Discov 2017;7:137-55.

4. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247.
5. Blackhall FH, Peters S, Bubendorf L, et al. Prevalence and Clinical Outcomes for Patients With ALK-Positive Resected Stage I to III Adenocarcinoma: Results From the European Thoracic Oncology Platform Lungscape Project. J Clin Oncol 2014;32:2780-7.
6. Tufman AL, Edelmann M, Gamarra F, et al. Preselection based on clinical characteristics in German non-small-cell lung cancer patients screened for EML4-ALK translocation. J Thorac Oncol 2014;9:109.
7. Wang Z, Zhang X, Bai H, et al. EML4-ALK rearrangement and its clinical significance in Chinese patients with advanced non-small cell lung cancer. Oncology 2012;83:248-56.
8. Corrales-Rodríguez L, Arrieta O, Mas L, et al. An international epidemiological analysis of young patients with non-small cell lung cancer (AduJov-CLICaP). Lung Cancer 2017;113:30-6.
9. Yip PY, Yu B, Cooper WA, et al. Patterns of DNA Mutations and ALK Rearrangement in Resected Node Negative Lung Adenocarcinoma. J Thorac Oncol 2013;8:408-14.
10. Zhou JX, Yang H, Deng Q, et al. Oncogenic driver mutations in patients with non-small-cell lung cancer at various clinical stages. Ann Oncol 2013;24:1319-25.
11. Tanaka K, Hida T, Oya Y, et al. Unique prevalence of oncogenic genetic alterations in young patients with lung adenocarcinoma. Cancer 2017;123:1731.
12. Sacher AG, Dahlberg SE, Heng J, et al. Association Between Younger Age and Targetable Genomic Alterations and Prognosis in Non-Small-Cell Lung Cancer. JAMA Oncol 2016;2:313-20.
13. Fukui T, Yatabe Y, Kobayashi Y, et al. Clinicoradiologic characteristics of patients with lung adenocarcinoma harboring EML4-ALK fusion oncogene. Lung Cancer 2012;77:319-25.
14. Liu YT, Shi YK, Hao XZ, et al. Analysis of clinicopathological features of the echinoderm microtubule-associated protein-like-4-anaplastic lymphoma kinase fusion gene in Chinese patients with advanced non-small-cell lung cancer. Thorac Cancer 2014;5:255.
15. Kim MH, Shim HS, Kang DR, et al. Clinical and prognostic implications of ALK and ROS1 rearrangements in never-smokers with surgically resected lung adenocarcinoma. Lung Cancer 2014;83:389-95.
16. Igata F, Uchino J, Fujita M, et al. Clinical Features of Lung Cancer in Japanese Patients Aged Under 50. Asian Pac J Cancer Prev 2016;17:3377-80.
17. Paik JH, Choi CM, Kim H, et al. Clinicopathologic implication of ALK rearrangement in surgically resected lung cancer: a proposal of diagnostic algorithm for ALK-rearranged adenocarcinoma. Lung Cancer 2012;76:403-9.
18. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-33.
19. VandenBussche CJ, Illei PB, Lin MT, et al. Molecular alterations in non-small cell lung carcinomas of the young. Hum Pathol 2014;45:2379-87.
20. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive Characteristics of Non-small Cell Lung Cancer (NSCLC) in the Young: A Surveillance, Epidemiology, and End Results (SEER) Analysis. J Thorac Oncol 2010;5:23-8.
21. Arnold BN, Thomas DC, Rosen JE, et al. Lung cancer in the very young: treatment and survival in the National Cancer DataBase. J Thorac Oncol 2016;11:1121-31.
22. Zhang J, Chen SF, Zhen Y, et al. Multicenter analysis of lung cancer patients younger than 45 years in Shanghai. Cancer 2010;116:3656.
23. Lara MS, Brunson A, Wun T, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a California Cancer Registry analysis. Lung Cancer 2014;85:264-9.
24. Chaft JE, Dagogo-Jack I, Santini FC, et al. Clinical outcomes of patients with resected, early-stage ALK-positive lung cancer. Lung Cancer 2018;122:67-71.
25. Kang HJ, Lim HJ, Park JS, et al. Comparison of clinical characteristics between patients with ALK-positive and EGFR-positive lung adenocarcinoma. Respir Med 2014;108:388.
26. Gainor JF, Tseng D, Yoda S, et al. Patterns of Metastatic Spread and Mechanisms of Resistance to Crizotinib in ROS1-Positive Non-Small-Cell Lung Cancer. JCO Precis Oncol 2017;2017. doi: 10.1200/PO.17.00063.
27. Hou H, Zhu H, Zhao H, et al. Comprehensive Molecular Characterization of Young Chinese Patients with Lung Adenocarcinoma Identified a Distinctive Genetic Profile. Oncologist 2018;23:1008-15.

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