Original Article

Prognostic factors of resectable anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) patients: a retrospective analysis based on a single center

Ao Zeng[1#], Yicheng Xiong[1#], Jing Zhang[1#], Huansha Yu[2], Lele Zhang[3], Dongliang Bian[1], Lu Han[1], Jue Wang[1], Yan Chen[1], Mohammed Saud Shaik[4], Peng Zhang[1], Jie Dai[1]

[1]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; [2]Department of Animal Experiment Center, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; [3]Central Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; [4]School of Medicine, Tongji University, Shanghai, China

Contributions: (I) Conception and design: P Zhang, J Dai; (II) Administrative support: J Dai; (III) Provision of study materials or patients: H Yu, D Bian, L Han, L Zhang; (IV) Collection and assembly of data: A Zeng, Y Xiong, J Zhang, J Wang, Y Chen; (V) Data analysis and interpretation: A Zeng, Y Xiong, J Zhang, J Dai, MS Shaik; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jie Dai, MD, PhD. Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507 Zhengmin Road, Shanghai 200433, China. Email: daijie@tongji.edu.cn.

Background: Anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) exhibited a higher propensity for lymph node metastasis (LNM). This study aimed to investigate risk factors of occult lymph node metastasis (OLNM) and recurrence in resectable ALK-rearranged NSCLC patients.

Methods: This retrospective analysis included patients with ALK-rearranged NSCLC receiving lung resections at Shanghai Pulmonary Hospital from June 2016 to August 2021. Logistic regression analysis was used to ascertain predictors of OLNM, and Cox regression analysis to identify risk factors of recurrence.

Results: A total of 603 resectable ALK-rearranged NSCLC patients were included. The mean age was 55 years old. There were 171 patients (28.4%) pathologically confirmed to have LNM, 51.5% of which were occult. Logistic regression analysis identified clinical tumor size and computed tomography (CT) density as independent factors for OLNM. Cox regression analysis showed that pleural invasion and pathological tumor size were independent prognosticators for recurrence in pathologically nodal negative patients. Among pathologically nodal positive patients, adjuvant ALK-tyrosine kinase inhibitors (TKI) showed a similar recurrence-free survival (RFS) to chemotherapy (hazard ratio, 0.454; 95% confidence interval, 0.111–1.864).

Conclusions: Assessing the potential risk of OLNM is required for ALK-rearranged NSCLC patients with large tumors characterized by high CT densities. Patients with large pathological tumor size or pleural infiltration should be closely monitored despite being pathologically nodal negative. Additionally, adjuvant ALK-TKI may present a comparable RFS to chemotherapy in pathologically nodal positive patients.

Keywords: Non-small cell lung cancer (NSCLC); anaplastic lymphoma kinase (ALK); recurrence; occult lymph node metastasis (OLNM); adjuvant treatment

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Introduction

Lung cancer remains a leading cause of cancer-related death, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases, and the 5-year survival rate of NSCLC has stagnated at around 22% (1,2). Anaplastic lymphoma kinase (ALK) rearrangement represents a distinct subtype of genetic mutation, accounting for approximately 5% of all NSCLC cases (3,4). ALK rearrangement is more frequently observed in never-smokers, adenocarcinomas, and younger patients, and those with advanced stage (5-7).

ALK rearrangement presents an aggressive tumor phenotype and a higher propensity to have lymph node metastasis (LNM) compared to wild-type in lung adenocarcinoma (8-10). Moreover, the majority of patients with LNM are occult. The survival rate was reported to be significantly worse in patients with occult lymph node metastasis (OLNM) than those without OLNM in clinically nodal negative NSCLC patients (11). Understanding the risk factors associated with OLNM is essential to improve the prognosis of patients (12).

Five-year risk of progression is higher for advanced stage lung adenocarcinoma patients with ALK mutation compared to those without ALK mutation (13). In addition, the 5-year recurrence-free survival (RFS) of ALK-rearranged patients is significantly worse compared to ALK-negative patients (55.9% *vs.* 78.8%) in stage I lung adenocarcinoma (14). ALK rearrangement is identified as an independent risk factor for recurrence (15). Advanced T stage and echinoderm microtubule-associated protein-like 4 (EML4)-ALK variant 3 are linked to worse disease-free survival (DFS) among ALK-rearranged NSCLC patients (16). However, the risk factors of recurrence and adjuvant treatment in resectable ALK-rearranged NSCLC have not been extensively studied.

Therefore, this study aimed to analyze the rate and risk factors of OLNM in ALK-rearranged NSCLC patients. Furthermore, we conducted a comprehensive analysis to identify independent risk factors for postoperative recurrence subgrouped by lymph node (LN) status. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-606/rc).

Highlight box

Key findings

- Adjuvant anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKI) may present a comparable recurrence-free survival (RFS) to chemotherapy in pathologically nodal positive ALK-rearranged non-small cell lung cancer (NSCLC) patients. Patients with occult lymph node metastasis (OLNM) exhibited a similar RFS to those with clinically evident lymph node metastasis (LNM).

What is known and what is new?

- ALK rearrangement presented an aggressive tumor phenotype and a higher propensity to have LNM in lung adenocarcinoma. ALK rearrangement was identified as a risk factor for recurrence.
- Clinical tumor size and computed tomography (CT) density were identified as predictors of OLNM in ALK-rearranged NSCLC. Pathological tumor size and pleural infiltration emerged as risk factors for recurrence in pathologically nodal negative patients. Among pathologically nodal positive patients, adjuvant ALK-TKI showed a similar RFS to chemotherapy.

What is the implication, and what should change now?

- Patients with large tumors characterized by high CT densities require assessing the potential risk of OLNM. Adjuvant ALK-TKI may offer comparable RFS outcomes to chemotherapy among pathologically nodal positive patients, pending further validation with substantial sample data.

Methods

Patient selection

This retrospective study included patients with ALK-rearranged NSCLC who underwent lung resections at Shanghai Pulmonary Hospital from June 2016 to August 2021. The exclusion criteria consisted of the following: (I) a history of cancer; (II) received neoadjuvant therapy; (III) incomplete information available. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the institutional board of Shanghai Pulmonary Hospital (No. K23-250). Individual consent for this retrospective analysis was waived.

ALK rearrangement confirmed by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). Tumor staging was assessed according to the 8th edition lung cancer staging system of the American Joint Committee on Cancer (AJCC), which evaluated the primary tumor (T), lymph node (N), and metastasis (M) (17). OLNM was defined as the presence of LNM confirmed through postoperative pathology in patients initially presenting with clinically negative nodes. LNs with less than or equal to 10 mm short-axis diameters on chest computed tomography (CT) images and no indication of LNM on positron emission tomography-CT (PET-CT) were characterized as clinically negative LNs. Tumor differentiation was determined according to the 2015 World

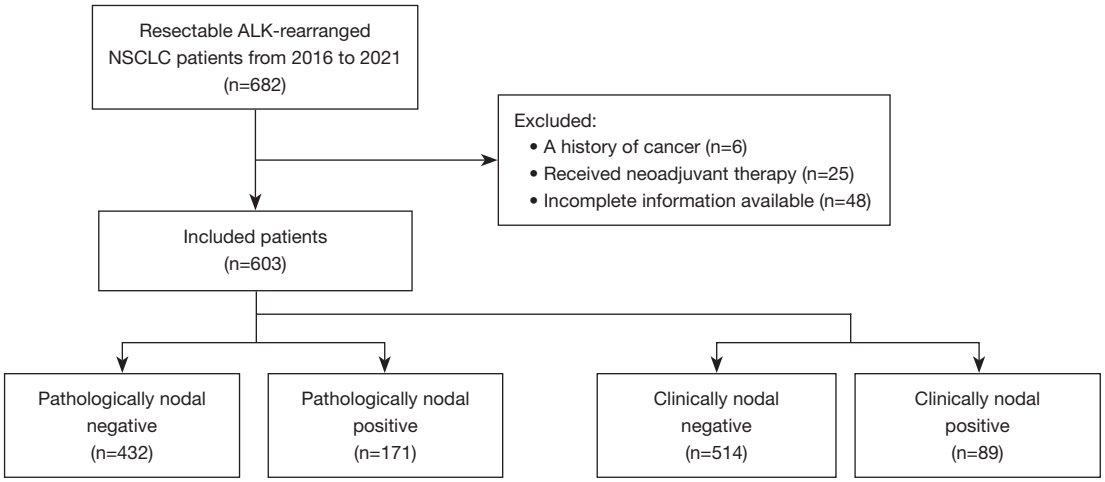

Figure 1 Study flow diagram. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

Health Organization Classification of lung tumors (18).

Follow-up and postoperative recurrence

Follow-up was conducted via regular outpatient clinic visits or telephone interviews. Patients underwent physical examinations and chest CT scans every 3 months during the first 3 years, followed by examinations every 6 months for the subsequent 3–5 years, and then annually thereafter. Brain magnetic resonance imaging (MRI), abdominal ultrasonography, and bone emission computed tomography (ECT) were performed annually or at the doctor's discretion. The last follow-up date was October 30, 2022. RFS was defined as the time interval from the date of diagnosis to recurrence or the last date known to be alive without recurrence, while overall survival (OS) was defined as the time interval from the date of diagnosis to death or the last follow-up.

Statistical analysis

Categorical variables were analyzed using the Chi-squared test or Fisher's exact test. Normally distributed continuous variables were analyzed utilizing Student's *t*-test, and non-normally distributed continuous variables were analyzed using the Mann-Whitney *U* test. Logistic regression analyses were performed to evaluate risk factors of OLNM, and Cox regression analyses were used to analyze risk factors of recurrence. Variables with P<0.05 in univariate analysis were included in multivariate analysis. RFS and OS were analyzed by the Kaplan-Meier method and compared by the log-rank test. Two-sided P<0.05 was considered statistically significant. The statistical analysis was performed using R software (version 4.2.1).

Results

Characteristics of pathologically nodal negative and positive patients

A total of 603 resectable ALK-rearranged NSCLC patients were included (*Figure 1*). The mean age was 55 years old, and the mean pathological tumor size was 20.7 mm. The majority of patients were female (n=347, 57.5%) and non-smokers (n=494, 81.9%), with nearly all cases diagnosed as adenocarcinoma (n=591, 98.0%). There were 171 patients confirmed to have LNM according to postoperative pathology. Significant differences were observed in gender (P=0.023), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (P=0.047), tumor location (P=0.007), spread through air space (STAS) (P=0.001), clinical N stage (P<0.001), and pathology (P=0.001) between pathologically nodal negative and positive patients (*Table 1*).

Video-assisted thoracoscopic surgery (VATS) was the primary surgical approach (n=569, 94.4%), with lobectomy being the most frequently performed type of resection (n=512, 84.9%). All patients underwent R0 resections. Pleural effusion was the most common postoperative complication (n=6, 1.0%), and remarkably, there were no perioperative deaths within the 90-day window (*Table 2*).

Nearly half of the patients received adjuvant

Table 1 Basic information about resectable ALK-rearranged NSCLC patients

Characteristics	Total (n=603)	Pathologically nodal negative (n=432)	Pathologically nodal positive (n=171)	P
Age, years	55.0±11.2	55.2±11.4	54.6±10.8	0.504
Gender				0.023
Male	256 (42.5)	171 (39.6)	85 (49.7)	
Female	347 (57.5)	261 (60.4)	86 (50.3)	
Smoking history				0.624
Current or ever	109 (18.1)	76 (17.6)	33 (19.3)	
Never	494 (81.9)	356 (82.4)	138 (80.7)	
ECOG PS				0.047
0	507 (84.1)	373 (86.3)	134 (78.4)	
1	93 (15.4)	57 (13.2)	36 (21.1)	
2	3 (0.5)	2 (0.5)	1 (0.5)	
pT stage				<0.001
T1	447 (74.1)	354 (81.9)	93 (54.4)	
T2	126 (20.9)	69 (16.0)	57 (33.3)	
T3	25 (4.1)	8 (1.9)	17 (10.0)	
T4	5 (0.8)	1 (0.2)	4 (2.3)	
pN stage				<0.001
N0	432 (71.6)	432 (100.0)	0 (0.0)	
N1	63 (10.4)	0 (0.0)	63 (36.8)	
N2	108 (18.0)	0 (0.0)	108 (63.2)	
cN stage				
N0	514 (85.2)	426 (98.6)	88 (51.4)	<0.001
N1	30 (5.0)	3 (0.7)	27 (15.8)	
N2	57 (9.5)	3 (0.7)	54 (31.6)	
N3	2 (0.3)	0 (0.0)	2 (1.2)	
CT density	–91.1±197.0	–135.4±213.0	20.7±69.2	<0.001
Tumor SUV_{max}	7.5±5.1	6.3±4.3	10.3±5.8	<0.001
LN SUV_{max}	2.0±3.4	1.2±2.0	4.1±5.0	<0.001
Location				0.007
Peripheral	472 (78.3)	352 (81.5)	120 (70.2)	
Central	127 (21.1)	77 (17.8)	50 (29.2)	
Unknown	4 (0.7)	3 (0.7)	1 (0.6)	
Metastatic LN station				<0.001
Not involved	432 (71.6)	432 (100.0)	0 (0.0)	
Single	101 (16.8)	0 (0.0)	101 (59.1)	
Multiple	70 (11.6)	0 (0.0)	70 (40.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=603)	Pathologically nodal negative (n=432)	Pathologically nodal positive (n=171)	P
Pathology				0.001
Adenocarcinoma	591 (98.0)	429 (99.3)	162 (94.7)	
Squamous cell carcinoma	5 (0.8)	1 (0.2)	4 (2.3)	
Adenosquamous carcinoma	4 (0.7)	1 (0.2)	3 (1.8)	
Sarcomatoid carcinoma	2 (0.3)	0 (0.0)	2 (1.2)	
Large cell carcinoma	1 (0.2)	1 (0.2)	0 (0.0)	
Histological differentiation				<0.001
Well	22 (3.6)	21 (4.9)	1 (0.5)	
Moderate	220 (36.5)	198 (45.8)	22 (12.9)	
Poor	349 (57.9)	210 (48.6)	139 (81.3)	
Unknown	12 (1.9)	3 (0.7)	9 (5.3)	
Lateral				0.421
Left	270 (44.8)	189 (43.8)	81 (47.4)	
Right	333 (55.2)	243 (56.3)	90 (52.6)	
Pathological tumor size, mm	20.7±12.3	18.0±10.2	27.6±14.3	<0.001
STAS				0.001
Yes	313 (51.9)	206 (47.7)	107 (62.6)	
No	290 (48.1)	226 (52.3)	64 (37.4)	
Pleural invasion				<0.001
PL0	520 (86.2)	389 (90.0)	131 (76.7)	
PL1	63 (10.4)	37 (8.6)	26 (15.2)	
PL2	19 (3.2)	6 (1.4)	13 (7.6)	
PL3	1 (0.2)	0 (0.0)	1 (0.5)	
Vascular invasion				<0.001
Yes	56 (9.3)	21 (4.9)	35 (20.5)	
No	547 (90.7)	411 (95.1)	136 (79.5)	
Mutation type				0.748
ALK	587 (97.3)	421 (97.5)	166 (97.0)	
ALK + EGFR 19-DEL	8 (1.3)	6 (1.4)	2 (1.2)	
ALK + EGFR L858R	6 (1.0)	3 (0.7)	3 (1.8)	
ALK + EGFR T790M	1 (0.2)	1 (0.2)	0 (0.0)	
ALK + KRAS	1 (0.2)	1 (0.2)	0 (0.0)	

Values are mean ± SD or n (%). NSCLC, non-small cell lung cancer; ECOG PS, Eastern Corporative Oncology Group Performance Status; pT stage, pathological T stage; pN stage, pathological N stage; cN stage, clinical N stage; LN, lymph node; STAS, spread through air space; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; CT, computed tomography; SUV_{max}, maximum standardized uptake value; SD, standard deviation.

Table 2 Therapy information about resectable ALK-rearranged NSCLC patients

Characteristics	Total (n=603)	Pathologically nodal negative (n=432)	Pathologically nodal positive (n=171)	P
Surgical approach				<0.001
VATS	569 (94.4)	421 (97.5)	148 (86.5)	
RATS	5 (0.8)	2 (0.4)	3 (1.8)	
Open	29 (4.8)	9 (2.1)	20 (11.7)	
Operative procedure				<0.001
Wedge resection	9 (1.5)	9 (2.1)	0 (0.0)	
Segmentectomy	71 (11.8)	65 (15.0)	6 (3.5)	
Lobectomy	512 (84.9)	358 (82.9)	154 (90.1)	
Sleeve resection	6 (1.0)	0 (0.0)	6 (3.5)	
Pneumectomy	5 (0.8)	0 (0.0)	5 (2.9)	
Surgical complication				0.033
Pleural effusion	6 (1.0)	5 (1.2)	1 (0.6)	
Chylothorax	2 (0.3)	0 (0.0)	2 (1.2)	
Pyothorax	2 (0.3)	1 (0.2)	1 (0.6)	
Bronchopleural fistula	1 (0.2)	1 (0.2)	0 (0.0)	
Pulmonary embolism	1 (0.2)	0 (0.0)	1 (0.6)	
Discontinuous hypertension	1 (0.2)	1 (0.2)	0 (0.0)	
Pulmonary abscess	1 (0.2)	0 (0.0)	1 (0.6)	
Hemothorax	1 (0.2)	0 (0.0)	1 (0.6)	
None	588 (97.4)	424 (98.2)	164 (95.8)	
Number of LN stations resected	5.6±1.6	5.3±1.6	6.2±1.3	<0.001
Blood loss, mL	67.9±123.0	63.3±130.0	79.4±102.0	0.110
Adjuvant treatment type				<0.001
Chemotherapy	266 (44.1)	130 (30.1)	136 (79.5)	
ALK-TKI	13 (2.2)	2 (0.4)	11 (6.4)	
Chemotherapy + ALK-TKI	2 (0.3)	0 (0.0)	2 (1.2)	
Immunotherapy	1 (0.2)	0 (0.0)	1 (0.6)	
EGFR-TKI	1 (0.2)	0 (0.0)	1 (0.6)	
None	320 (53.0)	300 (69.5)	20 (11.7)	
Radiotherapy				<0.001
Yes	40 (6.6)	0 (0.0)	40 (23.4)	
No	563 (93.4)	432 (100.0)	131 (76.6)	
Recurrence location				<0.001
Local	59 (9.8)	24 (5.6)	35 (20.5)	
Distant	37 (6.1)	7 (1.6)	30 (17.5)	
None or missing	507 (84.1)	401 (92.8)	106 (62.0)	

Values are mean ± SD or n (%). NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery; RATS, robotic-assisted thoracoscopic surgery; LN, lymph node; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor; SD, standard deviation.

chemotherapy (n=266, 44.1%), while a small number of patients received adjuvant radiotherapy (n=40, 6.6%) or ALK-tyrosine kinase inhibitors (TKI) alone (n=13, 2.2%). Alectinib and Crizotinib were commonly used ALK-TKI. None of the patients discontinued medication due to severe drug-related side effects. Pathologically nodal positive patients were more likely to experience surgical complications and receive adjuvant treatment (*Table 2*).

OLNM analysis

Among 514 clinically nodal negative ALK-rearranged NSCLC patients, 88 patients (17.1%) were confirmed to occur OLNM based on postoperative pathology, and 426 patients (82.9%) were confirmed not to occur OLNM. Patients with OLNM were observed to have a higher ratio of ECOG PS 1–2, STAS and vascular invasion than patients with no OLNM (NOLNM). In addition, patients with pathological N2 stage exhibited a higher ratio of OLNM than patients with pathological N1 stage (*Figure 1*; *Table 3*). Univariate logistic regression analysis revealed that clinical tumor size, CT density and ECOG PS were associated with OLNM. Multivariate analysis confirmed that clinical tumor size [odds ratio (OR), 1.032; 95% confidence interval (CI): 1.011–1.054] and CT density (OR, 1.007; 95% CI: 1.004-1.010) remained as independent risk factors (*Table 4*).

RFS and OS analysis

The median follow-up time was 33 months [interquartile range (IQR), 22–52 months]. The 3-year RFS were 92.5% and 59.7% in patients with pathologically nodal negative and nodal positive patients, respectively. Pathologically nodal positive patients had a worse RFS (median: 48 months) and OS compared to those with pathologically negative LNs, and pathologically nodal positive patients did not reach the median OS (*Figure 2A*,*2B*).

In pathologically nodal negative patients, univariate Cox regression analysis showed that vascular invasion, histological differentiation, pathological tumor size, and pleural invasion were associated with postoperative recurrence. Multivariate Cox regression analysis demonstrated that pathological tumor size [hazard ratio (HR), 1.061; 95% CI: 1.036–1.086] and pleural infiltration (HR, 4.009; 95% CI: 1.759–9.135) remained independent risk factors of postoperative recurrence (*Table 5*).

Adjuvant chemotherapy and ALK-TKI in pathologically nodal positive patients were further analyzed. Patients receiving ALK-TKI therapy were typically older than those undergoing chemotherapy. There were no significant differences between the two treatment groups in terms of gender, smoking history, tumor location, pathology, operative procedure, and histological differentiation. In addition, adjuvant chemotherapy and ALK-TKI had comparable side effects, with digestive symptoms being the most common adverse effect for both treatments (*Table 6*). The Kaplan-Meier analysis found that patients with adjuvant chemotherapy obtained a similar RFS (median: 46 months) and OS compared to those with adjuvant ALK-TKI, and patients with adjuvant chemotherapy did not reach the median OS (*Figure 2C*,*2D*).

Risk factors for recurrence in pathologically nodal positive patients were further analyzed. Univariate Cox regression analysis revealed that pathological N stage, pathological tumor size, vascular invasion, OLNM and metastatic LN station were associated with postoperative recurrence. Subsequent multivariate Cox regression analysis showed that only pathological N stage (N2 *vs.* N1, HR, 2.734; 95% CI: 1.409–5.307) remained an independent predictor, while OLNM exhibited a comparable RFS to clinically evident LNM (HR, 0.625; 95% CI: 0.378–1.034) (*Table 7*).

Discussion

Our study comprised the largest cohort of resectable ALK-rearranged NSCLC patients. Clinical tumor size and CT density resected were predictors of OLNM. Additionally, pathological tumor size and pleural infiltration emerged as risk factors for recurrence in pathologically nodal negative patients. Furthermore, among pathologically nodal positive patients, OLNM exhibited a comparable RFS to clinically evident LNM, and adjuvant ALK-TKI demonstrated a comparable RFS to chemotherapy.

OLNM is a potential risk factor for recurrence and metastasis, being of great clinical significance for prognosis (19,20). In comparison to a large cohort of 2,623 NSCLC patients who underwent surgery, wherein 29.7% had LNM (21), our study revealed a similar rate (28.4%) of LNM in ALK-rearranged NSCLC patients, with 51.5% of which being occult. In addition, ALK rearrangement was reported to be associated with a higher rate of OLNM compared to ALK-negative adenocarcinomas (22,23). We further identified clinical tumor size and CT density as independent predictors. Patients with tumors (>30 mm) exhibited a significantly higher rate of OLNM. Gallina *et al.*

Table 3 Basic information between OLNM and NOLNM groups in resectable ALK-rearranged NSCLC patients

Characteristics	NOLNM (n=426)	OLNM (n=88)	P
Age, years	55.2±11.4	54.9±11.4	0.798
Gender			0.150
Female	258 (60.6)	46 (52.3)	
Male	168 (39.4)	42 (47.7)	
Smoking history			0.941
Never	352 (82.6)	73 (83.0)	
Current or ever	74 (17.4)	15 (17.0)	
ECOG PS			0.007
ECOG PS 0	368 (86.4)	66 (75.0)	
ECOG PS 1–2	58 (13.6)	22 (25.0)	
pT stage			<0.001
T1	352 (82.6)	49 (55.6)	
T2	66 (15.5)	27 (30.7)	
T3	7 (1.7)	10 (11.4)	
T4	1 (0.2)	2 (2.3)	
pN stage			<0.001
N0	426 (100.0)	0 (0.0)	
N1	0 (0.0)	36 (40.9)	
N2	0 (0.0)	52 (59.1)	
CT density	−137.5±214.0	9.0±80.8	<0.001
Tumor SUV_{max}	6.3±4.3	9.4±5.9	0.011
LN SUV_{max}	1.1±1.8	1.3±2.6	0.676
Location			0.474
Peripheral	348 (81.7)	68 (77.3)	
Central	75 (17.6)	20 (22.7)	
Unknown	3 (0.7)	0 (0.0)	
Clinical tumor size, mm	17.7±9.3	24.5±13.4	<0.001
Pathology			0.057
Adenocarcinoma	424 (99.6)	86 (97.7)	
Adenosquamous carcinoma	1 (0.2)	0 (0.0)	
Sarcomatoid carcinoma	0 (0.0)	2 (2.3)	
Large cell carcinoma	1 (0.2)	0 (0.0)	
Histological differentiation			<0.001
Well	21 (4.9)	1 (1.2)	
Moderate	197 (46.2)	15 (17.0)	
Poor	206 (48.4)	70 (79.5)	
Unknown	2 (0.5)	2 (2.3)	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	NOLNM (n=426)	OLNM (n=88)	P
Lateral			0.394
Left	187 (43.9)	43 (48.9)	
Right	239 (56.1)	45 (51.1)	
STAS			<0.001
Yes	203 (47.7)	64 (72.7)	
No	223 (52.3)	24 (27.3)	
Vascular invasion			<0.001
Yes	21 (4.9)	19 (21.6)	
No	405 (95.1)	69 (78.4)	
Operative procedure			0.001
Wedge resection	9 (2.1)	0 (0.0)	
Segmentectomy	65 (15.3)	3 (3.4)	
Lobectomy	352 (82.6)	85 (96.6)	
Mutation type			0.511
ALK	415 (97.5)	85 (96.5)	
ALK + EGFR 19-DEL	6 (1.4)	1 (1.2)	
ALK + EGFR L858R	3 (0.7)	2 (2.3)	
ALK + EGFR T790M	1 (0.2)	0 (0.0)	
ALK + KRAS	1 (0.2)	0 (0.0)	
Recurrence location			<0.001
Local	23 (5.4)	14 (15.9)	
Distant	7 (1.6)	13 (14.8)	
None or missing	396 (93.0)	61 (69.3)	

Values are mean ± SD or n (%). NSCLC, non-small cell lung cancer; ECOG PS, Eastern Corporative Oncology Group Performance Status; pT stage, pathological T stage; pN stage, pathological N stage; CT, computed tomography; STAS, spread through air space; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; OLNM, occult lymph node metastasis; NOLNM, no occult lymph node metastasis; SUV_{max}, maximum standardized uptake value; LN, lymph node; SD, standard deviation.

also reported similar results, showing that tumor diameter significantly predicted OLNM (23). These risk factors could be further utilized to construct a model for predicting OLNM, thereby offering enhanced guidance for surgery.

The status of LN could influence the recurrence, and thus, we analyzed recurrence factors subgrouped by LN status. Pathological tumor size and pleural infiltration were identified as independent predictors in pathologically nodal negative patients. These findings were consistent with the research by Schuchert *et al.*, who also found that large tumors had a significantly higher risk of recurrence (24). Additionally, Wang *et al.* ever demonstrated that visceral pleural invasion was remarkably associated with a higher rate of recurrence in patients with stage I NSCLC (25). These findings contributed to a better assessment of recurrence risks in pathologically nodal negative patients and provided guidance for monitoring strategies.

LNM can potentially change the risk factors of postoperative recurrence. Our study reported a lower 3-year RFS in pathologically nodal positive patients compared to those with pathologically negative LNs (59.7% *vs.* 92.5%). Further analysis of the risk factors for recurrence

Table 4 Logistic regression analysis of factors affecting OLNM in resectable ALK-rearranged NSCLC patients

Characteristics	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age						
≤60 years	Reference					
>60 years	0.785	0.478–1.266	0.329			
Gender						
Female	Reference					
Male	1.402	0.882–2.225	0.151			
Smoking history						
Never	Reference					
Current or ever	0.977	0.515–1.756	0.941			
ECOG PS						
0	Reference			Reference		
1–2	2.115	1.195–3.652	0.008	1.735	0.939–3.136	0.072
CT density	1.008	1.005–1.011	<0.001	1.007	1.004–1.010	<0.001
Location						
Peripheral	Reference					
Central	1.365	0.766–2.349	0.274			
Pathology						
Adenocarcinoma	Reference					
Others	4.930	0.585–41.548	0.113			
Lateral						
Left	Reference					
Right	0.819	0.517–1.299	0.394			
Clinical tumor size	1.053	1.033–1.074	<0.001	1.032	1.011–1.054	0.003
Mutation type						
ALK	Reference					
ALK + EGFR	1.465	0.323–4.906	0.568			

NSCLC, non-small cell lung cancer; OLNM, occult lymph node metastasis; OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Corporative Oncology Group Performance Status; CT, computed tomography; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

demonstrated that N2 stage patients obtained a worse RFS than N1 stage patients. Isaka *et al.* also showed that N2 with N1 stage was the primary risk factor for local recurrence compared to N1 stage (26). These emphasized the need to tailor more specific treatments for patients with different N stages. In addition, Cho *et al.* showed that multiple metastatic N2 stations exhibited a higher RFS than single N2 station in N2 stage NSCLC (27). However, multiple metastatic LN stations presented a comparable RFS to single metastatic LN station in pathologically nodal positive patients in our study. The difference may be because single and multiple LN stations could be classified as similar N stages and not restricted to specific N2 stage, as in the study of Cho *et al.* In addition, OLNM exhibited a comparable

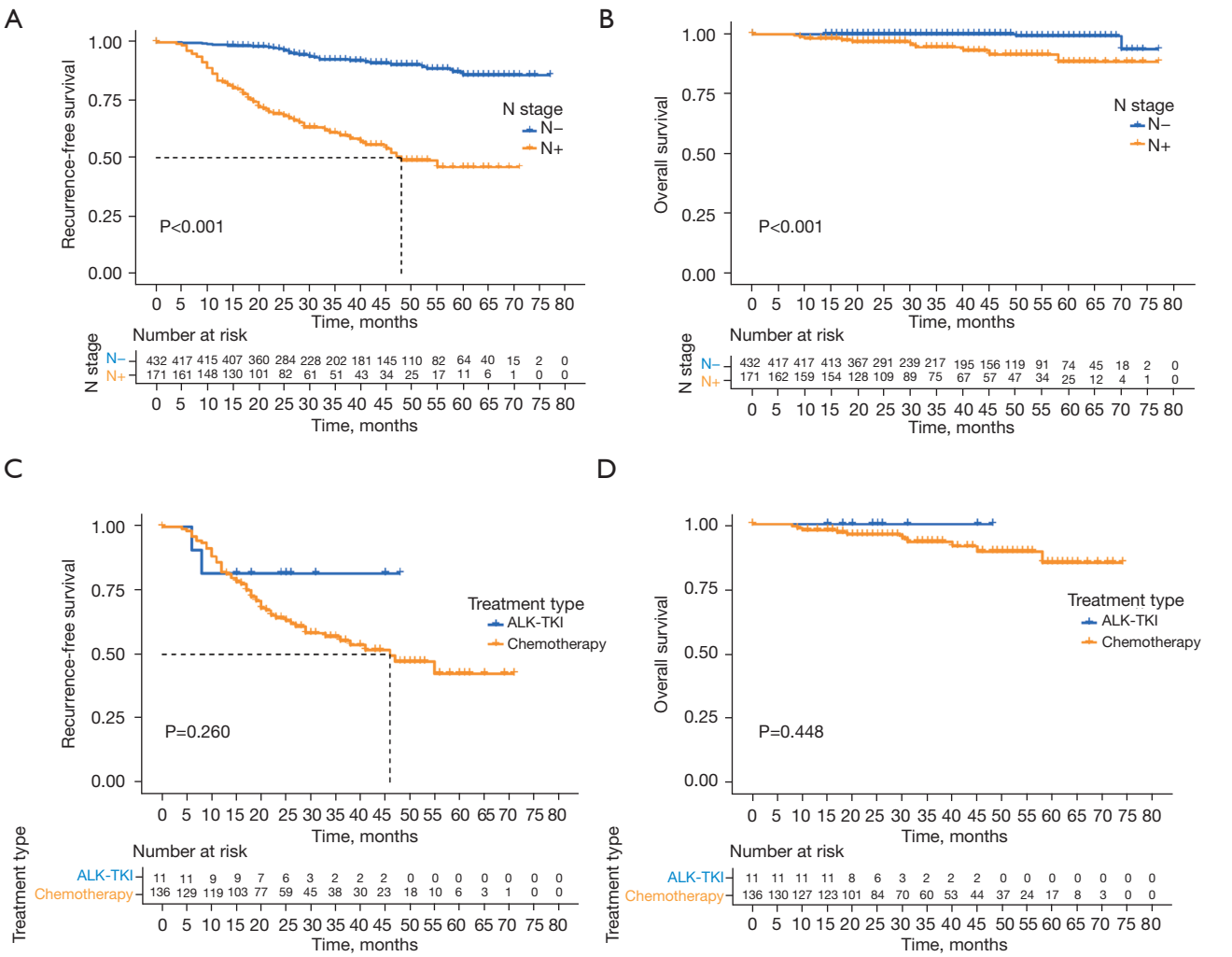

Figure 2 Survival curves of ALK-rearranged NSCLC patients. (A) Comparison of RFS between nodal negative (N–) and positive (N+) patients. (B) Comparison of OS between nodal negative (N–) and positive (N+) patients. (C) Comparison of RFS in nodal positive patients with adjuvant chemotherapy versus ALK-TKI. (D) Comparison of OS in nodal positive patients with adjuvant chemotherapy versus ALK-TKI. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; RFS, recurrence-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor.

RFS to clinically evident LNM, suggesting that the hidden nature of the LNM was not the primary factor for monitoring recurrence.

Adjuvant treatment is usually necessary for nodal positive ALK-rearranged patients; however, the most effective treatment type remains to be determined. ALK rearrangement was reported to be associated with a low response rate to immunotherapy (28). Advanced stage ALK-rearranged NSCLC patients treated with ALK-TKI reported superior progression-free survival (PFS) and objective response rates (ORRs) compared to those undergoing chemotherapy (29,30). A recent study analyzed the efficacy of adjuvant therapy in a cohort of 59 ALK-rearranged lung cancer patients and found that patients with adjuvant ALK-TKI demonstrated a better DFS and OS compared to those with chemotherapy (31). However, our study did not find a significant difference in postoperative RFS between ALK-TKI and chemotherapy in pathologically nodal positive patients, but adjuvant ALK-TKI showed a trend toward a lower risk of recurrence. The limited number of patients (n=11, 6.4%) who received ALK-TKI may reduce this statistical power. The ALINA

Table 5 Cox regression analysis in pathologically nodal negative resectable ALK-rearranged NSCLC patients

Characteristics	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age	1.003	0.972–1.035	0.849			
Gender						
Female	Reference					
Male	0.833	0.403–1.720	0.620			
Smoking history						
Never	Reference					
Current or ever	0.908	0.372–2.217	0.832			
ECOG PS						
ECOG PS 0	Reference					
ECOG PS 1–2	1.785	0.769–4.145	0.178			
Location						
Peripheral	Reference					
Central	1.556	0.696–3.48	0.281			
Histological differentiation						
Moderate-well	Reference			Reference		
Poor	4.342	1.860–10.136	0.001	2.259	0.903–5.649	0.081
Lateral						
Left	Reference					
Right	0.873	0.432–1.767	0.707			
Pathological tumor size	1.068	1.048–1.089	<0.001	1.061	1.036–1.086	<0.001
STAS						
No	Reference					
Yes	1.258	0.606–2.608	0.538			
Pleural invasion						
No	Reference			Reference		
Yes	6.984	3.236–15.072	<0.001	4.009	1.759–9.135	0.001
Vascular invasion						
No	Reference			Reference		
Yes	4.823	1.440–16.149	0.011	1.833	0.524–6.409	0.343
Operative procedure						
Lobectomy	Reference					
Sublobectomy	0.388	0.092–1.629	0.196			

NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Corporative Oncology Group Performance Status; STAS, spread through air space.

Table 6 Basic information between adjuvant chemotherapy and ALK-TKI in pathologically nodal positive resectable ALK-rearranged NSCLC patients

Characteristics	Chemotherapy (n=136)	ALK-TKI (n=11)	P
Age, years	52.9±9.9	62.3±11.5	0.023
Gender			0.808
Male	69 (50.7)	6 (54.5)	
Female	67 (49.3)	5 (45.5)	
Smoking history			0.698
Current or ever	24 (17.6)	3 (27.3)	
Never	112 (82.4)	8 (72.7)	
ECOG PS			0.747
0	111 (81.6)	8 (72.7)	
1–2	25 (18.4)	3 (27.3)	
Location			0.516
Peripheral	101 (74.3)	7 (63.6)	
Central	34 (25.0)	4 (36.4)	
Unknown	1 (0.7)	0 (0.0)	
Lateral			0.296
Left	66 (48.5)	3 (27.3)	
Right	70 (51.5)	8 (72.7)	
pT stage			0.072
T1	78 (57.4)	3 (27.3)	
T2	41 (30.1)	5 (45.5)	
T3	15 (11.0)	2 (18.2)	
T4	2 (1.5)	1 (9.0)	
pN stage			0.690
N1	52 (38.2)	3 (27.3)	
N2	84 (61.8)	8 (72.7)	
Pathology			1.000
Adenocarcinoma	128 (94.1)	11 (100.0)	
Squamous cell carcinoma	4 (3.0)	0 (0.0)	
Adenosquamous carcinoma	3 (2.2)	0 (0.0)	
Sarcomatoid carcinoma	1 (0.7)	0 (0.0)	
Histological differentiation			0.524
Moderate-well	18 (13.2)	0 (0.0)	
Poor	110 (80.9)	11 (100.0)	
Unknown	8 (5.9)	0 (0.0)	

Table 6 (*continued*)

Table 6 (*continued*)

Characteristics	Chemotherapy (n=136)	ALK-TKI (n=11)	P
Radiotherapy			0.086
Yes	39 (28.7)	0 (0.0)	
No	97 (71.3)	11 (100.0)	
STAS			0.021
Yes	82 (60.3)	11 (100.0)	
No	54 (39.7)	0 (0.0)	
Vascular invasion			0.094
Yes	26 (19.1)	5 (45.5)	
No	110 (80.9)	6 (54.5)	
Operative procedure			0.732
Segmentectomy	5 (3.7)	1 (9.1)	
Lobectomy	121 (89.0)	10 (90.9)	
Sleeve resection	6 (4.4)	0 (0.0)	
Pneumectomy	4 (2.9)	0 (0.0)	
Medication duration	4.0 [4.0–4.0]	25.0 [16.5–28.0]	–
Side effects			0.184
Myelosuppression	10 (7.4)	0 (0.0)	
Liver injury	8 (5.8)	1 (9.1)	
Digestive symptom	16 (11.8)	2 (18.2)	
Myelosuppression + liver injury	3 (2.2)	0 (0.0)	
Myelosuppression + digestive symptom	1 (0.7)	0 (0.0)	
Liver injury + digestive symptom	0 (0.0)	1 (9.1)	
None or missing	98 (72.1)	7 (63.6)	
Recurrence location			0.294
Local	30 (22.1)	2 (18.2)	
Distant	26 (19.1)	0 (0.0)	
None or missing	80 (58.8)	9 (81.8)	

Values are mean ± SD, median [IQR] or n (%). NSCLC, non-small cell lung cancer; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; ECOG PS, Eastern Corporative Oncology Group Performance Status; pT stage, pathological T stage; pN stage, pathological N stage; STAS, spread through air space; Medication duration: chemotherapy in cycles, ALK-TKI in months; SD, standard deviation; IQR, interquartile range.

trial was an ongoing phase III randomized trial targeting patients with resectable ALK-rearranged NSCLC to compare the efficacy of 2 years of adjuvant alectinib treatment with chemotherapy (5,32).

There are several limitations that should be acknowledged. First, as a retrospective study, there may be potential selection bias such as the administration of adjuvant treatment. Second, the small number of ALK-rearranged NSCLC patients who received adjuvant ALK-TKI could affect statistical power. Third, the follow-up regarding drug side effects should have been more thoroughly investigated. Fourth, the study lacks a detailed

Table 7 Cox regression analysis in pathologically nodal positive resectable ALK-rearranged NSCLC patients

Characteristics	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age	0.990	0.968–1.013	0.394			
Gender						
Female	Reference					
Male	1.064	0.653–1.732	0.803			
Smoking history						
Never	Reference					
Current or ever	1.000	0.553–1.808	1.000			
ECOG PS						
0	Reference					
1–2	0.956	0.520–1.756	0.884			
Location						
Peripheral	Reference					
Central	1.182	0.707–1.977	0.524			
pN stage						
N1	Reference			Reference		
N2	2.997	1.601–5.610	0.001	2.734	1.409–5.307	0.003
Metastatic LN station						
Single	Reference			Reference		
Multiple	1.708	1.050–2.779	0.031	1.145	0.678–1.935	0.612
Histological differentiation						
Poor	Reference					
Moderate-well	0.648	0.306–1.372	0.257			
Adjuvant treatment type						
Chemotherapy	Reference					
ALK-TKI	0.454	0.111–1.864	0.273			
Radiotherapy						
No	Reference					
Yes	1.302	0.768–2.205	0.327			
Lateral						
Left	Reference					
Right	0.998	0.614–1.625	0.995			
Pathological tumor size	1.015	1.001–1.030	0.038	1.012	0.997–1.028	0.119
STAS						
No	Reference					
Yes	0.823	0.500–1.355	0.444			

Table 7 (*continued*)

Table 7 (*continued*)

Characteristics	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Pleural invasion						
No	Reference					
Yes	0.672	0.359–1.258	0.214			
Vascular invasion						
No	Reference			Reference		
Yes	1.937	1.079–3.477	0.027	1.543	0.850–2.802	0.154
Occult						
No	Reference			Reference		
Yes	0.604	0.369–0.990	0.046	0.625	0.378–1.034	0.067
Operative procedure						
Lobectomy	Reference					
Sublobectomy	0.336	0.047–2.422	0.279			
Sleeve resection	0.427	0.059–3.080	0.398			
Pneumectomy	0.802	0.196–3.285	0.759			

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Corporative Oncology Group Performance Status; pN stage, pathological N stage; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitors; LN, lymph node; STAS, spread through air space.

analysis of ALK variants. Fifth, only 180 patients (29.9%) underwent PET-CT scans, and for the remaining patients, clinically negative LNs could not be defined using PET-CT. Sixth, this study is single-center, and its applicability to a broader population awaits further analysis.

Conclusions

ALK-rearranged NSCLC patients with large tumors characterized by high CT densities require assessing the potential risk of OLNM when crafting surgery strategies. Even with pathologically negative LNs, patients with large tumors or pleural infiltration should undergo vigilant postoperative monitoring. Moreover, adjuvant ALK-TKI may offer comparable RFS outcomes to chemotherapy among pathologically nodal positive patients, pending further validation with substantial sample data.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-606/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the institutional board of Shanghai Pulmonary Hospital (No. K23-250). Individual consent for this retrospective analysis was waived.

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