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ORIGINAL RESEARCH

Higher frequency of occult lymph node metastasis in clinical N0 pulmonary adenocarcinoma with *ALK* rearrangement

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Objectives: There have been few studies that have fully elucidated the relationship between genomic mutations in pulmonary adenocarcinomas and occult lymph node (LN) metastases (pN1-2) despite a preoperative clinical N0 stage (cN0). It is well known that anaplastic lymphoma kinase (*ALK*) rearrangements are more likely to occur in younger patients with high grade tumors. The aim of this study was to investigate the genomic status, examine the clinicopathologic features, and evaluate whether *ALK* mutations are associated with occult LN metastases.

Materials and methods: We retrospectively evaluated 459 Japanese patients who underwent pulmonary resection of cN0 adenocarcinomas between January 2012 and December 2015. The clinicopathologic characteristics, including age, sex, smoking index, tumor maximum diameter and consolidation/tumor ratio on computed tomography (CT), maximum standardized uptake value on positron emission tomography (PET) and gene mutations (epidermal growth factor receptor [*EGFR*], *ALK*, and kirsten ras genes (*KRAS*), were evaluated.

Results: *ALK* and *EGFR* and *KRAS* mutations were all mutually exclusive. Among 324 patients found to have mutations, *ALK* was involved in 19 (5.9%), *EGFR* in 266 (82.1%), and *KRAS* in 39 (12.0%). The incidence of occult LN metastases did not differ significantly between those with or without mutations (p=0.27). On univariate and multivariate analyses, tumors with *ALK* were more likely to have occult LN metastases (p=0.03). In cN0 tumors with *ALK*, pN1 was diagnosed in 26.3% and pN2 in 10.5%, whereas pN1 or pN2 stage was found in <10.0% in those with *EGFR* or *KRAS* mutations or with no mutations at all. No significant difference was found in the 2-year disease-free survival among those with gene mutations (p=0.08).

Conclusion: This study highlights the frequency of PET- and CT-negative occult LN metastases in resected adenocarcinomas with *ALK* rearrangement. Our multivariate analysis showed that *ALK* rearrangements were associated with a significantly higher incidence of occult LN metastasis compared with *ALK*-negative adenocarcinomas.

Keywords: occult lymph node, adenocarcinoma, lung cancer, *ALK*, PET

Introduction

Lobectomy with systemic lymph node (LN) dissection is a standard procedure for non-small-cell lung cancer (NSCLC). Preoperative diagnosis of patients with LN-negative (cN0) disease poses a clinical dilemma, as approximately 10% of patients with cN0 cancer in our institution are found to have hilar or mediastinal LN involvement on the pathology of the resected specimens. There is evidence that patients with advanced NSCLC benefit from adjuvant chemotherapy after complete pulmonary resection.[1–3] Although the value of radical LN dissection remains undetermined,

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precise LN staging is a clinical essential, as the actual stage can affect the long-term outcome. Computed tomography (CT) is routinely accepted as the standard method for preoperative LN staging. Although the commonly used criterion for a clinical diagnosis of LN metastasis on CT is a short-axis diameter >10 mm, several authors have reported its low sensitivity and specificity.[4–6] Currently, positron emission tomography (PET) with 18F-fluorodeoxyglucose is considered clinically superior to CT for LN staging, but even this method carries a false-negative rate for the identification of LN metastasis.[7]

Genomic mutations as well as histologic features are recognized as critically important predictors of the biological behavior of lung adenocarcinomas. Anaplastic lymphoma kinase (*ALK*) gene rearrangements are found in approximately 2%–7% of NSCLCs.[8] It is well known that *ALK* rearrangement is more likely to be found in NSCLC with adenocarcinoma histology, younger age, light or never smoking history, and advanced stage.[9,10] Choi et al[11] reported that adenocarcinoma with *ALK* rearrangements appeared as solid masses with lobulated margins on CT and were more likely to be associated with lymphangitic metastasis, advanced LN metastasis, and pleural or pericardial metastasis than were tumors with epidermal growth factor receptor (*EGFR*) mutations. Most of these clinical discoveries highlight the importance of genetic evaluation of tumors that might enable the targeted treatment. However, the frequency of such changes, especially *ALK* rearrangements, is comparatively low.

Few reports have focused on LN metastases associated with *ALK* rearrangements, especially in early-stage NSCLC. To the best of our knowledge, there have been few studies of adenocarcinomas with occult LN metastases (pN1–2) despite preoperative cN0 staging. Therefore, the aim of this current study was to investigate the relationship between genomic status, clinicopathology, and pN1–2 adenocarcinoma.

Materials and methods

Patients and clinical evaluation

Between January 2012 and December 2015, 459 Japanese patients who underwent surgical resection for a preoperative diagnosis of cN0 lung adenocarcinoma at the Aichi Cancer Center Hospital were selected for this retrospective study. Patients were included who had had surgery alone as first treatment without neoadjuvant chemotherapy or radiotherapy and no other malignant tumors in the 5 years prior to lung resection. All patients had undergone pulmonary segmentectomy or more with conventional LN dissection. All clinical data were anonymized before analyses of this study. This study was approved by the institutional review board (2017-1-297) at Aichi Cancer Center Hospital. The board waived the need for informed consent because of the retrospective nature of this study.

Clinical staging was based on CT scans of the chest and abdomen, magnetic resonance imaging of the head, abdominal ultrasound, bone scintigraphy, and/or PET. Tumors were staged according to the TNM classification system (seventh edition).[12] The pathology diagnosis was classified according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma.[13]

On preoperative on thin sliced CT (1–2 mm), we evaluated the tumor maximum diameter (TMD) and the consolidation diameter on the lung window setting (level = −550 HU; width =1,500 HU) and hilar and mediastinal LNs on the mediastinal window setting (level =40 HU; width =360 HU).[14,15] The C/T ratio was calculated by dividing the consolidation diameter by the TMD. A C/T ratio of >0.5 has previously been reported to suggest a high frequency of LN metastases in NSCLC.[14–16] LN metastasis was diagnosed on imaging when the short axis of a node was at least 10 mm in diameter or if there was evident accumulation of 18F-fluorodeoxyglucose on PET.

The following data were extracted from patient records: age, sex, smoking index, TMD and C/T ratio on CT, maximum standardized uptake value (SUV max) on PET, and gene mutations (*EGFR*, *ALK*, and kirsten ras genes (*KRAS*).

Pathology diagnosis and genetic analysis

Mutation analyzes were carried out for *EGFR*, *KRAS*, and *ALK* as previously reported.[17,18] Reverse transcriptase-polymerase chain reaction direct sequencing of *EGFR*, *KRAS*, and *ALK* was used to assess the mutational status. In addition, tissue was screened for immunohistochemistry if the ALK RNA could be assessed or with break-apart fluorescence in situ hybridization for confirmation.

Statistical analysis

We analyzed the relationships between each gene mutation and clinicopathologic factors using JMP software version 10.0 (SAS Institute, Inc., Cary, NC, USA). Significant risk factors for LN metastasis determined by univariate analysis were used for multivariate analysis. Continuous variables were expressed using the median (interquartile range).

Categorical variables, given as percentages, were compared using Fischer's exact test. Comparison among more than 3 groups was calculated by the Kruskal–Wallis test. Multivariate logistic regression analysis was used to calculate odds ratios with 95% confidence intervals and estimated probabilities for pathologic LN metastasis. A $p<0.05$ was considered significant.

Results

Patient characteristics and gene mutations

The clinicopathologic characteristics are summarized in Table 1. Of the 459 patients with adenocarcinomas, 135 (29.4%) were triple negative for the genes evaluated and 324 had a mutation. Significantly lower male-to-female ratio, smoking index, and serum carcinoembryonic antigen (CEA) levels were found in those with genomic mutations than in those with triple-negative NSCLC. The pathological LN metastasis status did not differ significantly between those with and without mutations ($p=0.27$).

Genomic mutations and clinicopathologic findings

ALK rearrangement and *EGFR* and *KRAS* mutations were all mutually exclusive. Of the 324 cases of genomic abnormalities, mutations of *ALK* were present in 19 (5.9%), *EGFR* in 266 (82.1%), and *KRAS* in 39 (12.0%) There were significant differences among the three groups in age, smoking index, TMD, C/T ratio, maximum tumor size on pathology, and pathological LN metastases (Table 2).

The final LN status is summarized in Figure 1, with patients with *ALK* rearrangement being much more likely to have pathologically positive LNs (pN1 26.3% and pN2 10.5%) compared with those with *EGFR* or *KRAS* mutations or those who were triple negative on gene testing (pathologically positive LNs found in <10.0% in each group) ($p=0.02$, Figure 1).

Table 1 Characteristics of patients with cN0 pulmonary adenocarcinoma

Variables	Mutation (+) n=324	Triple negative n=135	*p*-value
Sex, (male/female)	127/197 (39.2%)	92/43 (68.1%)	<0.01*
Age (years)			
Mean ± SD (range)	65±10 (29–87)	66±9 (32–83)	0.36
Smoking index			
Mean ± SD (range)	269.2±438.6 (0–2500)	628.2±646.3 (0–2820)	<0.01*
CEA			
Mean ± SD (range)	3.8±5.4 (0.5–53.4)	6.1±10.1 (0.6–57.7)	<0.01*
Tumor maximum size on CT (mm)			
Mean ± SD (range)	26.5±12.8 (9–103)	28.5±15.7 (8–90)	0.46
C/T ratio (%) on CT			
Mean ± SD (range)	74.6±27.4 (0–100)	77.2±28.1 (0–100)	0.13
SUV max			
Mean ± SD (range)	3.3±4.8 (0–28)	4.8±6.3 (0–27)	0.06
Pathological maximum size (mm)			
Mean ± SD (range)	22.7±13.1 (6–132)	25.4±15.1 (7–100)	0.94
Pathological LN status			0.27
N0	270 (83.3%)	118 (87.4%)	
N1/2	54 (16.7%)	17 (12.6%)	
Pathological stage			0.44
0	2 (0.6%)	1 (0.7%)	
IA	204 (62.9%)	78 (57.8%)	
IB	58 (17.9%)	29 (21.5%)	
IIA	25 (7.8%)	14 (10.4%)	
IIB	6 (1.9%)	5 (3.7%)	
IIIA	28 (8.6%)	7 (5.2%)	
IIIB	1 (0.3%)	1 (0.7%)	
Procedure			0.59
Sublobar	60 (1.8%)	29 (21.5%)	
Lobectomy	262 (80.6%)	106 (78.5%)	
Pneumonectomy	2 (0.6%)	0 (0%)	

Note: The * symbol indicates significant difference.

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; LN, lymph node; SD, standard deviation; SUV max, maximum standardized uptake value.

Table 2 Characteristics of patients with cN0 pulmonary adenocarcinoma who had gene mutations

Variables	*EGFR* N=266	*KRAS* N=39	*ALK* N=19	*p*-value
Sex, (male/female)	98/168 (36.8%)	21/18 (53.8%)	8/11 (42.1%)	0.12
Age (years)				
Mean ± SD (range)	66±9 (29–87)	68±9 (46–83)	52±10 (33–66)	<0.01*
Smoking index				
Mean ± SD (range)	235.4±426.9 (0–2500)	517.7±492.9 (0–1680)	231.6±321.1 (0–900)	<0.01*
CEA				
Mean ± SD (range)	3.6±4.6 (0.5–53.4)	3.8±3.8 (0.6–21.7)	6.2±13.4 (0.5–52.6)	0.15
Tumor maximum size on CT (mm)				
Mean ± SD (range)	26.3±11.0 (10–67)	30.8±21.3 (10–103)	20.6±12.6 (9–54)	0.01*
C/T ratio (%) on CT				
Mean ± SD (range)	72.9±27.5 (0–100)	82.3±25.9 (26–100)	82.3±25.9 (26–100)	<0.01*
SUV max				
Mean ± SD (range)	3.3±4.9 (0–28.0)	3.0±4.4 (0–14.5)	3.2±3.8 (0–11.2)	0.83
Pathological maximum size (mm)				
Mean ± SD (range)	22.2±9.7 (7–70)	28.1±26.0 (10–132)	18.2±13.0 (6–55)	0.02*
Pathological LN status				0.02*
N0	222 (83.5%)	36 (92.3%)	12 (63.2%)	
N1/2	44 (16.5%)	3 (7.7%)	7 (36.8%)	
Pathological stage				0.84
0	1 (0.4%)	1 (2.6%)	0 (0%)	
IA	169 (63.5%)	23 (59.0%)	12 (63.1%)	
IB	50 (18.8%)	8 (20.5%)	0 (0%)	
IIA	19 (7.1%)	2 (5.1%)	4 (21.0%)	
IIB	2 (0.8%)	3 (7.7%)	1 (5.3%)	
IIIA	25 (9.4%)	2 (5.1%)	1 (5.3%)	
IIIB	0 (0%)	0 (0%)	1 (5.3%)	
Procedure				0.92
Sublobar	49 (18.4%)	8 (20.5%)	3 (15.8%)	
Lobectomy	216 (81.2%)	31 (79.5%)	15 (78.9%)	
Pneumonectomy	1 (0.4%)	0 (0%)	1 (5.3%)	

Note: The * symbol indicates significant difference.
Abbreviations: ALK, anaplastic lymphoma kinase; CEA, carcinoembryonic antigen; CT, computed tomography; EGFR, epidermal growth factor receptor; KRAS, kirsten ras genes; LN, lymph node; SD, standard deviation; SUV max, maximum standardized uptake value.

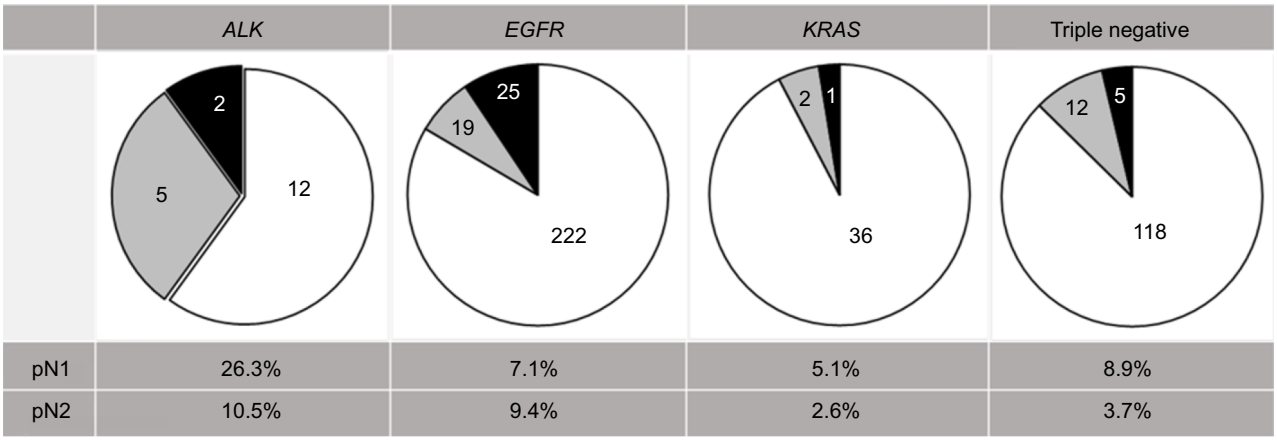

Figure 1 The proportion of patients with cN0 pulmonary adenocarcinoma found to have LN metastases on pathology (pN1, gray; pN2, black; node negative patients [cN0 → pN0], white) in each mutational classification.
Notes: Patients with *ALK* rearrangement tended to have a higher incidence of occult hilar or mediastinal LN metastases. Triple negative indicates patients with no mutation in *ALK*, *EGFR*, or *KRAS*.
Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, kirsten ras genes; LN, lymph node.

The relationship between clinicopathologic findings and pathological LN metastases

We further investigated the relationship between selected clinicopathologic findings and the risk of having occult LN metastases. When we enforced multivariate analysis using the factors in verification of the significant difference by univariate analysis, we found that patients with CEA levels >5 ng/mL, TMD >30 mm, C/T ratio >0.5, representative preoperative findings likely to be lymph node metastases, and *ALK* rearrangement, were more likely to harbor LN metastases (Table 3).

Table 3 Univariate and multivariate analyses of clinicopathological variables associated with occult LN metastases in pulmonary adenocarcinoma

Variables	Univariate	Multivariate	
	p-value	HR (CI)	*p*-value
Patient characteristics			
Sex: male vs female	0.97	–	–
Smoking: >600 vs ≤600	0.07	–	–
Tumor marker			
CEA: >5 vs ≤5	<0.01	2.14 (1.19–3.88)	0.01
Preoperative radiological findings			
Tumor maximum diameter on CT: >30.0 vs ≤30.0	<0.01	2.41 (1.36–4.27)	<0.01
C/T ratio: >50.0 vs ≤50.0	<0.01	3.87 (1.76–8.48)	<0.01
SUV: >3 vs ≤3	<0.01	1.35 (0.76–2.41)	0.31
Procedures			
Lobectomy: vs sublobar	0.03	0.77 (0.31–1.85)	0.55
Pathological genomic mutation			
ALK: vs non-*ALK*	0.01	4.57 (1.54–3.5)	<0.01

Note: The en-dashes indicate no verification of the significant difference by univariate analysis.

Abbreviations: ALK, anaplastic lymphoma kinase; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; CT, computed tomography; LN, lymph node; SUV, standardized uptake value.

Postoperative prognosis

As shown in Figure 2A, the 2-year disease-free survival rates were 88.1% for triple negative and 84.4% for any mutation status, but no significant difference was obtained (p=0.21) (Figure 2A). The 2-year disease-free survival in patients with *KRAS* (81.7%) and *ALK* mutations (79.5%) showed a tendency to poorer prognosis as compared to those with *EGFR* mutations (89.9%), although a significant difference was not obtained (p=0.08) (Figure 2B).

Discussion

In this study of patients with cN0 adenocarcinoma, the incidence of pN2 was 7.2% and that of pN1 or 2 was 15.5%, compatible with data reported for previous studies.[19] We found that the incidence of occult LN metastases did not differ significantly between tumors with one of the three gene mutations (*ALK, EGFR,* and *KRAS*) and those which were triple negative for the mutations. However, we found that tumors with *ALK* rearrangement were significantly more likely to have occult LN metastases than those with the other two mutations (p=0.03). Finally, on multivariate analysis, *ALK* rearrangement was associated with a significantly higher risk of occult LN metastases. A few investigators have performed detailed evaluations of the occult LN metastases in cN0 lung adenocarcinomas with *ALK* rearrangement.

We evaluated preoperative LN status using CT and PET for all patients. Patients with *ALK* rearrangement were more likely to have occult LN metastases on multivariate analysis. Park et al. reported that SUV max and volume-based parameters are significant risk factors for occult LN metastasis in patients with small peripheral NSCLCs (<3 cm in diameter) who underwent surgical resection with mediastinal LN dissection based on PET findings.[20] This observation was consistent with another study.[21] On the

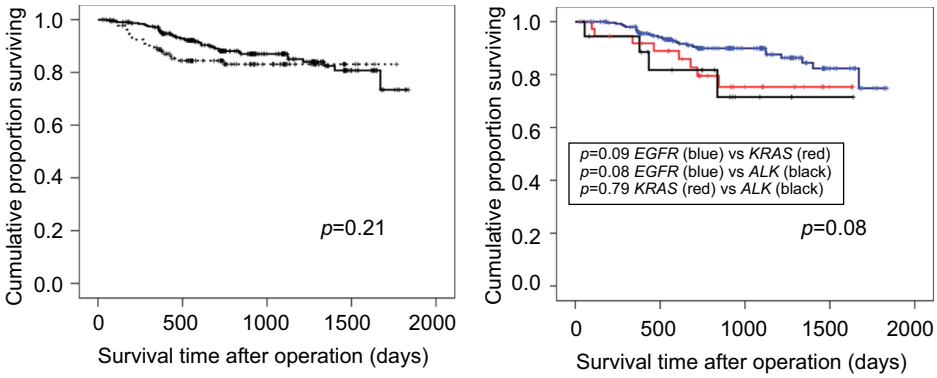

Figure 2 Kaplan-Meier curves for the disease-free survival: (**A**) comparison of triple negative (dotted line) versus any mutation status (solid line); and (**B**) comparison of each of the mutations: *EGFR*, *KRAS*, and *ALK*.

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, kirsten ras genes.

contrary, no significant difference for SUV or volume was observed on univariate analysis in our study (Table 3). The subtle differences between facilities in how PET is performed may be one reason for the discrepancy. They demonstrated that the SUV max was higher, but not significantly so, in patients with pN1–2 (6.95±3.91) compared to those with pN0 (4.12±3.85). In our study, however, the SUV max was significantly higher in patients with pN1–2 (6.99±7.41) than in those with pN0 (3.09±4.61), (p<0.01). Park et al[20] noted that accurate markers other than SUV max and solid tumor size are needed because of the results of the area under the curve for SUV max on receiver operating characteristic curve analysis in previous studies.

We previously reported on 27 surgically resected lung adenocarcinomas, analyzing the radiologic patterns. Compared with patients who were negative for *ALK* rearrangement, those who were ALK positive had significantly smaller tumors and had a lower tumor disappearance rate on CT, and spiculation was more frequent in small lesions.[17,22] Recently, Choi et al[11] demonstrated that adenocarcinomas with *ALK* rearrangement appeared as a solid mass with lobulated margins on CT and were more likely to be associated with lymphangitic metastasis, advanced LN metastasis, and pleural or pericardial metastasis than tumors with *EGFR* mutations. The numbers in most studies are <100, because the frequency of fusion genes is comparatively low. Among clinicopathologic factors in our study aside from *ALK* rearrangement, CEA levels >5ng/mL, TMD >30 mm, and C/T ratio >0.5 were more likely to be associated with LN metastases on multivariate analysis. These associations may not necessarily correspond with the radiologic features found in those with *ALK* rearrangement. Clinically, the prediction of LN metastasis on preoperative CT and PET is more difficult in patients with *ALK* rearrangement than in those with other mutations (*EGFR* and *KRAS*) or who are triple negative, although further studies with accumulation of more data may improve our understanding.

In this study, patients with cN0 adenocarcinoma with *ALK* rearrangement were significantly more likely to have hilar or mediastinal LN metastases than those with *KRAS* or *EGFR* mutations. A few studies have performed detailed evaluations of lung adenocarcinomas with *ALK* rearrangement, noting a tendency for a higher rate of LN metastases.[23] Interestingly, Xu et al[24] noted that *ALK*-positive adenocarcinomas might metastasize to LNs early, despite the small size of the primary tumor. Several authors reported a lack of association between *ALK* rearrangement and prognosis, which was compatible with our current report. Therefore, accurate staging by radical mediastinal LN dissection may be associated with the long-term outcomes for tumors with *ALK* rearrangements.[10,25] It is well known that *ALK* rearrangement in lung adenocarcinoma has a strong association with younger age, nonsmoking status, and clinically advanced stage.[26] However, it is not clear whether preoperative radiologic findings enable definitive prediction of prognosis, LN metastasis, or invasiveness for patients with clinically early-stage *ALK*-positive adenocarcinomas. Therefore, if *ALK* positivity is suspected based on clinical features, radical mediastinal LN dissection should be performed.

This current study had several limitations. First, the definition of LN metastasis by imaging is equivocal. A short axis of >10 mm is widely used for enlarged mediastinal and hilar LNs on CT.[4,5] However, size criteria provide poor specificity for LN metastases. Although the diagnostic ability of PET-CT is superior to that of CT, diagnostic criteria for LN metastasis on PET-CT are still controversial. Second, the outcome of the patients, such as disease-free survival or overall survival, is not clear in this study because of a relatively short follow-up period.[27–29] Third, this was a retrospective, single-institutional study with a small sample size. To provide meaningful data on prognostic differences and to avoid the increasing the error of this study, a prospective, multicenter study is required, which is in the planning phase. Fourth, patient bias existed regarding the procedure selection. We considered that lobectomy is higher in diagnosis precision than segmentectomy about hilum LN dissection. Therefore, we limited the indication of segmentectomy according to the CT mediastinal diameter from the previous studies because segmentectomy is not the standard therapy for invasive lung cancers.[14,16] Fifth, it was impossible to argue about the curative effect of adjuvant chemotherapy, because small numbers of patients with mutations in *ALK* (4/19, 21.1%) underwent adjuvant chemotherapy.

In conclusion, this study highlights the frequency of PET- and CT-negative occult LN metastases in resected adenocarcinomas with *ALK* rearrangement. Our multivariate analysis showed that *ALK* rearrangement in cN0 NSCLC is significantly associated with a higher risk of occult LN metastasis compared to tumors without *ALK* mutations.

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Disclosure

The authors report no conflicts of interest in this work.

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