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# Resected stage I anaplastic lymphoma kinase-positive lung adenocarcinoma has a negative impact on recurrence-free survival

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**Abstract**

**Background:** The clinical and prognostic implications of anaplastic lymphoma kinase (ALK) status in resected lung cancers remain unclear. In this study we analyzed the prognostic and predictive significance of ALK-positive among patients with completely resected lung adenocarcinoma.

**Methods:** We retrospectively reviewed 197 patients with lung adenocarcinoma who underwent complete surgical resection and had been tested for their ALK status. We investigated the impact of an ALK-positive status on the recurrence-free survival (RFS) and overall survival (OS) and examined the predictive factors for an ALK-positive status.

**Results:** ALK positivity was noted in 36 (18%) out of 197 patients, and when limited to stage I patients, in 24 (19%) out of 124. In the pathological-stage I population, while the OS exhibited no significant difference between ALK-positive and ALK-negative patients (5-year OS rate, 81.2% vs. 89.8%, $p = 0.226$), the RFS of ALK-positive patients was significantly worse than that of ALK-negative patients (5-year RFS rate, 55.9% vs. 78.8%, $p = 0.018$). A multivariate analysis showed that ALK-positive status (hazard ratio [HR] 3.431, $p = 0.009$) was an independent prognostic factor for the RFS. Regarding the relationship between clinicopathological factors and an ALK-positive status, a high-grade histological subtype, including solid and micropapillary subtypes (odds ratio [OR] 5.464, $p < 0.001$), and never-smokers (OR 4.292, $p = 0.018$) were associated with ALK-positive.

**Conclusion:** A high-grade histological subtype and never-smokers were associated with ALK positivity, and the RFS of ALK-positive patients was worse than that of ALK-negative patients among patients with completely resected stage I lung adenocarcinoma.

KEYWORDS
anaplastic lymphoma kinase, lung adenocarcinoma, predictive factors, prognostic factors, surgical resection

## INTRODUCTION

Echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) gene rearrangement was discovered by Soda et al. in 2007.[1] ALK is a tyrosine kinase involved in cell proliferation and activates the oncogenic signaling pathway by fusing EML4 in lung cancer. Previous studies have reported that the rates of EML4-ALK gene rearrangement (ALK-positive patients) were 2%–7% in non-small cell lung cancer (NSCLC) and have a high prevalence in lung adenocarcinoma.[2–5] In addition, several factors, including never-smokers, a young age and solid-predominant lung adenocarcinoma, have been reported to be predictive factors for ALK-positive patients.[2,3]

Whether or not the ALK status can influence the prognosis of patients with surgical resection remains controversial. A previous study found that the recurrence-free survival (RFS) of ALK-positive patients was worse than that of ALK-negative

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patients only among never-smokers with surgically-resected lung adenocarcinoma.[6,7] In contrast, other studies have found that the ALK rearrangement status did not have a significant impact on the RFS in patients with resected lung adenocarcinoma.[8,9] These conflicting results based on differences in study cohorts further complicate the prognostic significance of the ALK status. Thus, despite the findings of recent analyses, the clinical and prognostic implications of ALK status in surgically resected lung cancers remain unclear.

Given these complications, in the present study, we revisited the predictive factors for ALK positivity with resected lung adenocarcinoma and assessed the impact of the ALK mutation status on the prognosis according to each pathological stage.

## METHODS

### Patients and study design

Using a prospectively maintained database, we retrospectively reviewed 277 patients with resected primary lung cancer who underwent ALK rearrangement examinations between January 2003 and December 2017 at Hyogo Cancer Center. We excluded 53 patients without adenocarcinoma, 23 who received incomplete resection and four without any follow-up data available. Consequently, 197 patients were included and analyzed (Figure 1).

The pathological tumor stage was classified according to the eighth edition of the Union for International Cancer Control-Tumor, Node, Metastasis classification for malignant tumors. The ALK positivity status of the resected specimen was evaluated immunohistochemically (IHC) using ALK monoclonal antibody (clone 5A4), and specimens were diagnosed as negative or positive by experienced pathologists. Clone 5A4 yielded a strong contrast between positive and negative staining, so the positive staining could be easily noted. The representative ALK staining (5A4) is shown in Figure 2. Fluorescence in situ hybridization (FISH) and reverse transcription-polymerase chain reaction (RT-PCR) were not examined in all patients with ALK positive on IHC, only those who had relapsed and scheduled to receive ALK-tyrosine kinase inhibitor (TKI) in our institution. We defined the most predominant subtype as the histological subtype, and micropapillary and solid subtypes were defined as high-grade histological subtypes according to the 2015 World Health Organization lung tumor classification.[10] In addition, the papillary, acinar and mucinous subtypes were intermediate grade, and the lepidic subtype and other types were classified as a low-grade subtype. Adjuvant chemotherapy was performed in patients with a p-stage of II–III or tumor size of 2–4 cm (p-stage IA2-IB). In principle, patients with p-stage II–III disease were administered platinum-based chemotherapy, and those with p-stage IA2-IB were administered tegafur uracil.

### Preoperative examination and follow-up

Contrast-enhanced chest and abdominal computed tomography (CT) and brain magnetic resonance imaging (MRI) were routinely performed for preoperative staging. Positron emission tomography (PET)-CT was also performed after its introduction to our institution in 2004. Patients were evaluated postoperatively at three-month intervals for two years, at six-month intervals for the subsequent three years and annually thereafter. Follow-up examinations included chest radiography, contrast-enhanced CT, brain MRI and

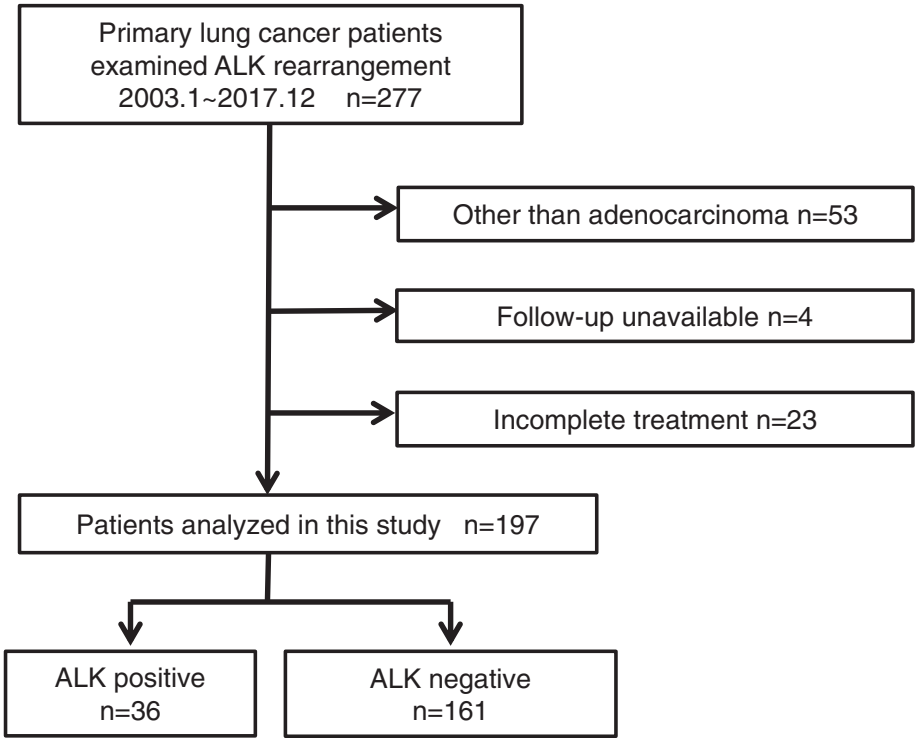


**FIGURE 1** Study profile of 277 surgically resected lung cancer patients whose ALK status was examined. A total of 197 patients were ultimately analyzed

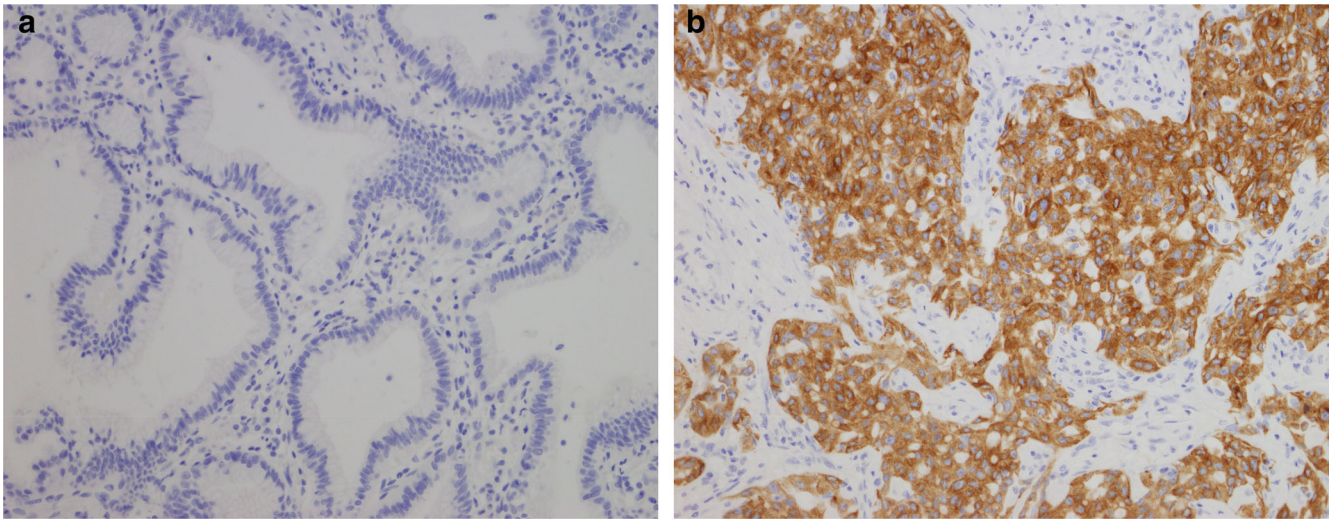


**FIGURE 2** The negative (a) and positive (b) case of immunohistochemical staining for ALK in non-small cell lung cancer (clone 5A4, ×200)

bone scintigraphy as well as hematological and biochemical analyses, including the measurement of tumor markers. The overall survival (OS) was defined as the time interval between the date of surgery and the date of death. The RFS was defined as the time interval between the date of surgery and the date of death without recurrence or the date of the first recurrence detected by a radiological examination.

## Statistical analysis

Fisher's exact test and the Mann–Whitney U test were used to compare the ALK-positive and ALK-negative groups. The OS and RFS were calculated according to the Kaplan–Meier method, and the log-rank test was used to evaluate differences in the distributions. A logistic regression analysis was used to evaluate independent predictive factors for an ALK-positive status. The Kaplan–Meier method was used to calculate the survival curves in the ALK-positive and ALK-negative groups. A Cox proportional hazard regression model was used to perform a multivariate analysis for the RFS. A $p$-value of <0.050 was considered to indicate a statistically significant difference, and all statistical tests were two-sided. $p$-values may not be interpreted as confirmatory but rather descriptive.

All statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012; version 1.40).[11]

# RESULTS

## A comparison of the clinicopathological characteristics between the ALK-positive and ALK-negative groups

The patient characteristics are shown in Table 1. ALK positivity was found in 36 patients (18.3%), while negativity was found in 161 patients (81.7%). Among them, 10 patients were examined by FISH or RT-PCR, and all 10 with FISH showed ALK-positive findings, while only one showed RT-PCR positivity. One patient underwent both FISH and RT-PCR. The detailed characteristics and subtype are shown in Table 1. The rates of ALK-positive patients were significantly higher in younger patients ($p = 0.026$), never-smokers ($p = 0.016$) and those with a high-grade histological subtype ($p < 0.001$) than in others. Other factors were not significantly different between the ALK-positive and ALK-negative groups. When limited to those with pathological (p)-stage I, ALK positivity was found in 24 patients (19.4%), and ALK negativity was found in 100 patients (80.6%). The rate of ALK-positive patients was significantly higher in patients with vascular invasion ($p = 0.022$) and a high-grade histological subtype ($p < 0.001$) than in others. In patients with p-stage II-III, ALK positivity was found in 12 patients (16.4%), and ALK negativity was found in 61 patients (83.6%). There were no significantly different factors between the ALK-positive and ALK-negative groups. In addition, recurrence occurred in 19 patients with ALK positivity, and among them, nine underwent ALK-TKI treatment. The reasons for not using ALK-TKI were refusal of treatment and a poor performance status.

## Comparison of the OS and RFS between the ALK-positive and ALK-negative groups for each pathological stage

The OS and RFS rates in the total patient cohort were not significantly different between the ALK-positive and ALK-negative groups (5-year OS: ALK-positive patients 77.4% vs. ALK-negative patients 80.9%, $p = 0.512$; 5-year RFS: ALK-positive patients 48.8% vs. ALK-negative patients 63.5%, $p = 0.123$; Figure 3a). This tendency was similar in patients with p-stage II-III (5-year OS: ALK-positive patients 70.7% vs. ALK-negative patients 67.2%, $p = 0.817$;

**TABLE 1** Patient characteristics in study

| Variable | ALK-positive patients $n = 36$ | ALK-negative patients $n = 161$ | $p$-value |
|---|---|---|---|
| mean age, range (years) | 64 (35–82) | 68 (37–87) | **0.026** |
| Sex | | | |
| Male | 16 (44%) | 90 (56%) | 0.268 |
| Female | 20 (56%) | 71 (44%) | |
| Smoking status | | | |
| Never-smoker | 24 (67%) | 70 (43%) | **0.016** |
| Past/current smoker | 12 (33%) | 91 (57%) | |
| Lung function | | | |
| Mean FEV1.0% | 93.1% | 97.2% | 0.227 |
| CEA, ng/ml | | | |
| ≥5.0 | 9 (25%) | 48 (30%) | 0.686 |
| <5.0 | 27 (75%) | 113 (70%) | |
| Operation procedure | | | |
| Lobectomy | 30 (89%) | 140 (93%) | 0.328 |
| Sublobectomy | 6 (11%) | 21 (7%) | |
| Histology | | | |
| High-grade | 14 (39%) | 22 (14%) | **<0.001** |
| Solid predominant | 14 (100%) | 17 (77%) | |
| Micropapillary predominant | 0 (0%) | 5 (23%) | |
| Other types | 22 (61%) | 139 (86%) | |
| Papillary predominant | 9 (41%) | 94 (68%) | |
| Acinar predominant | 10 (45%) | 18 (13%) | |
| Mucinous predominant | 3 (14%) | 11 (8%) | |
| Lepidic predominant | 0 (0%) | 11 (8%) | |
| MIA | 0 (0%) | 5 (3%) | |
| Pathological stage | | | |
| I | 24 (67%) | 100 (62%) | 0.225 |
| II | 7 (19%) | 31 (19%) | |
| III | 5 (14%) | 30 (25%) | |
| Adjuvant chemotherapy | | | |
| Not performed | 18 (50%) | 75 (47%) | 0.717 |
| Performed | 18 (50%) | 86 (53%) | |
| Lymphatic permeation | | | |
| (−) | 24 (67%) | 88 (55%) | 0.199 |
| (+) | 12 (33%) | 73 (45%) | |
| Vascular invasion | | | |
| (−) | 19 (53%) | 93 (58%) | 0.583 |
| (+) | 17 (47%) | 68 (42%) | |

*Note*: Micropapillary and solid-predominant lung adenocarcinomas were defined as high-grade histological subtypes.
Abbreviations: CEA, carcinoembryonic antigen; FEV1.0%, forced expiratory volume in 1 s; MIA, minimally invasive adenocarcinoma.

5-year RFS: ALK-positive patients 33.3% vs. ALK-negative patients 38.8%, $p = 0.965$; Figure 3b). Interestingly, when limited to those with p-stage I, there was a significant difference between the ALK-positive and ALK-negative groups in the RFS rate (5-year RFS: ALK-positive patients 55.9% vs. ALK-negative patients 78.8%, $p = 0.018$; Figure 3c), while the OS rate showed no significant difference between the ALK-positive and ALK-negative groups (5-year OS: ALK-positive patients 81.2% vs. ALK-negative patients 89.8%, $p = 0.226$; Figure 3c). In patients with p-stage I, a multivariate Cox proportional analysis showed that an ALK-positive status (hazard ratio [HR] 3.431, 95% confidence interval [CI] 1.368–8.605, $p = 0.009$) was a significant prognostic factor for RFS (Table 2).

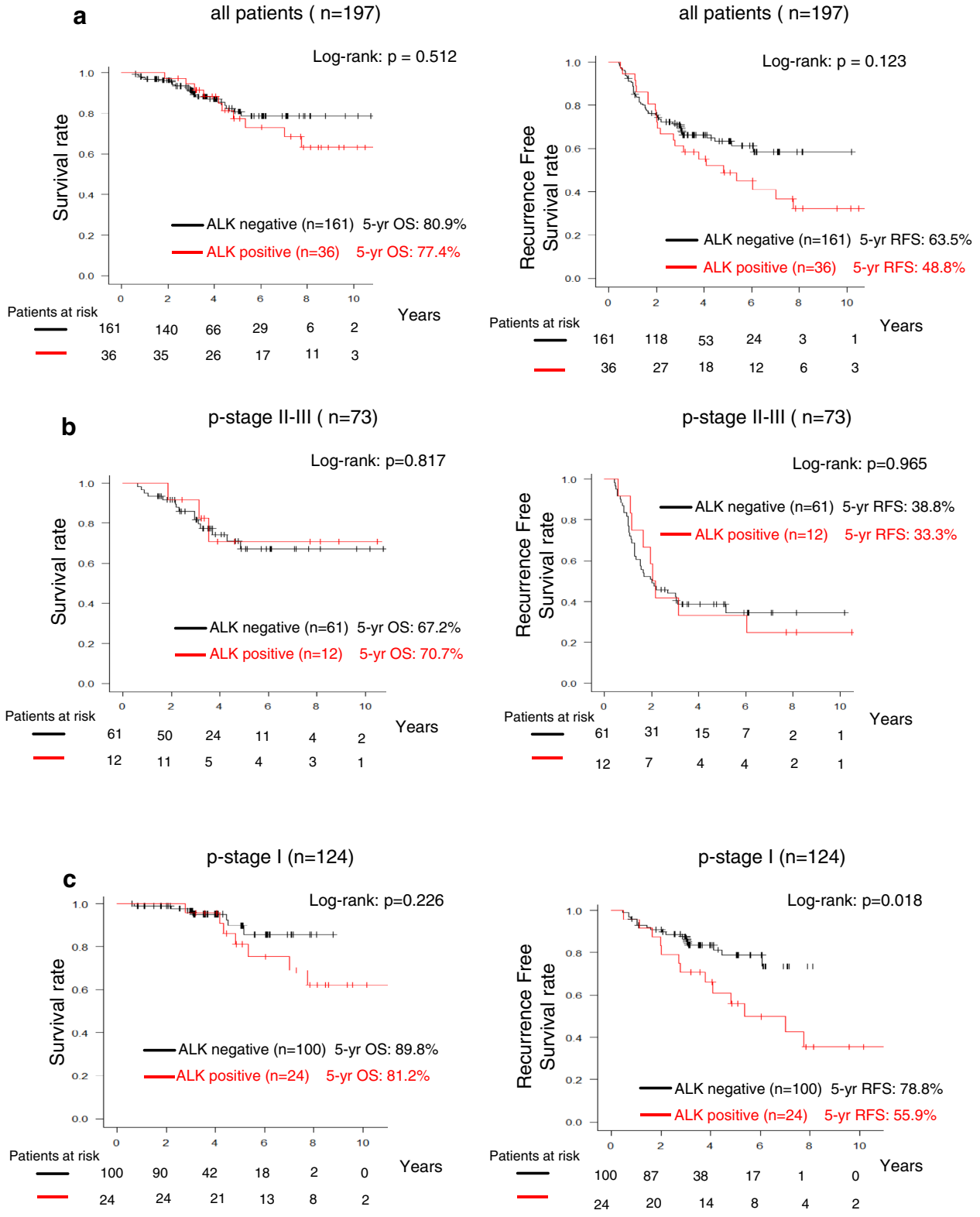


**FIGURE 3** (a) The overall survival (OS) and recurrence-free survival (RFS) rates in all patients. (b) The OS and RFS rates in p-stage II–III patients. (c) The OS and RFS rates in p-stage I patients

## Predictive factors for ALK positivity

We performed a multivariable logistic regression analysis to search for predictive factors of an ALK-positive status (Table 3). A high-grade histological subtype (odds ratio [OR] 5.988, 95% CI: 2.083–14.29, $p < 0.001$) and never-smokers (OR 4.292, 95% CI: 1.280–14.29, $p = 0.018$) were found to independently predict an ALK-positive status.

**TABLE 2** Results of the multivariate analysis of prognostic factors for the recurrence-free survival in p-stage I (Cox proportional hazards model)

| Variable | HR | 95% CI | *p*-value |
|---|---|---|---|
| Age, years | | | |
| <70 | 1 | | |
| ≥70 | 1.842 | 0.822–4.125 | 0.138 |
| Sex | | | |
| Female | 1 | | |
| Male | 2.080 | 0.692–6.255 | 0.192 |
| Smoking status | | | |
| Never-smoker | 1 | | |
| Past/current smoker | 1.001 | 0.322–3.112 | 0.999 |
| CEA, ng/ml | | | |
| <5.0 | 1 | | |
| ≥5.0 | 1.611 | 0.686–3.781 | 0.274 |
| Histology | | | |
| Other types | 1 | | |
| High-grade | 0.746 | 0.256–2.179 | 0.592 |
| Pathological stage | | | |
| IA | 1 | | |
| IB | 1.366 | 0.614–3.041 | 0.445 |
| Operation procedure | | | |
| Sublobectomy | 1 | | |
| Lobectomy | 0.956 | 0.362–2.520 | 0.927 |
| Adjuvant chemotherapy | | | |
| Not performed | 1 | | |
| Performed | 2.186 | 0.946–5.049 | 0.067 |
| Lymphatic permeation | | | |
| (−) | 1 | | |
| (+) | 1.869 | 0.787–4.441 | 0.157 |
| Vascular invasion | | | |
| (−) | 1 | | |
| (+) | 1.882 | 0.783–4.522 | 0.158 |
| ALK rearrangement | | | |
| (−) | 1 | | |
| (+) | 3.431 | 1.368–8.605 | **0.009** |

*Note*: Micropapillary and solid-predominant lung adenocarcinomas were defined as high-grade histological subtypes.
Abbreviations: ALK, anaplastic lymphoma kinase; CEA, carcinoembryonic antigen.

When analyzing by p-stage I and p-stage II–III, a multivariable analysis revealed that a high-grade histological subtype remained a significant predictive factor for ALK positivity in each cohort.

## DISCUSSION

In the present study, we showed that several clinicopathological factors, including a young age, never-smoker status and high-grade histological subtype, were associated with an ALK-positive status. Notably, a high-grade histological subtype and never-smoker status were independent predictive factors for ALK positivity in a multivariable analysis. We also revealed that an ALK-positive status was a significant negative prognostic factor in patients with p-stage I, but ALK positivity did not affect the prognosis in p-stage II-III. Thus, the present findings confirmed the significance of an ALK-positive status comprehensively among patients with surgically resected p-stage I lung adenocarcinoma.

**TABLE 3** Results of the multivariable analysis of the predictive factors for ALK positivity in all patients

| Variable | OR | 95% CI | *p*-value |
|---|---|---|---|
| Age, years | | | |
| <70 | 1 | | |
| ≥70 | 0.553 | 0.245–1.250 | 0.153 |
| Sex | | | |
| Female | 1 | | |
| Male | 1.410 | 0.446–4.440 | 0.560 |
| Smoking status | | | |
| Past/current smoker | 1 | | |
| Never-smoker | 4.292 | 1.280–14.29 | **0.018** |
| CEA, ng/ml | | | |
| <5.0 | 1 | | |
| ≥5.0 | 0.875 | 0.327–2.340 | 0.789 |
| Histology | | | |
| Other types | 1 | | |
| High-grade | 5.464 | 2.083–14.29 | **<0.001** |
| Lymphatic permeation | | | |
| (−) | 1 | | |
| (+) | 0.403 | 0.162–1.000 | 0.050 |
| Vascular invasion | | | |
| (−) | 1 | | |
| (+) | 1.340 | 0.498–3.630 | 0.560 |

*Note*: Micropapillary and solid-predominant lung adenocarcinomas were defined as high-grade histological subtypes.
Abbreviations: CEA, carcinoembryonic antigen.

Previous studies reported that the ALK positivity rate in NSCLC was 2%–7%,[3–5] and the incidence was as high as 13% in patients with lung adenocarcinoma.[2] Furthermore, an ALK-positive status was extremely frequent at a young age and among never-smokers.[2,3] In the present study, the ALK positivity rate was 18.3%, which was higher than in previous studies. This was because the present study cohort was limited to those with adenocarcinoma, and there was selection bias regarding the decision to perform an examination for the ALK status. A univariate analysis showed that a young age ($p = 0.026$) and never-smoker status ($p = 0.016$) were predictive for ALK positivity, and a multivariable analysis showed that a never-smoker status (OR 4.292, $p = 0.018$) was an independent predictive factor for ALK positivity, which was compatible with the findings of previous studies.[2,3] In addition, a high-grade histological subtype was also a predictive factor in both the univariable ($p < 0.001$) and multivariable (OR 5.464, $p < 0.001$) analyses. This result was also consistent with previous studies,

which reported that high-grade histological subtypes of lung adenocarcinoma were more common among ALK-positive patients than other subtypes, while the lepidic-predominant subtype was relatively uncommon among ALK-positive patients.[12,13] In contrast, epidermal growth factor receptor (EGFR)-positive lung adenocarcinoma was reported to be predominantly of the lepidic type,[14,15] and the low frequency of EGFR-ALK double-positive lung adenocarcinoma suggests that EGFR-positive and ALK-positive tumors undergo different oncogenic processes.[16]

An ALK-positive tumor of p-stage I was a significantly negative prognostic factor for the RFS. Several reports thus far have elucidated the prognosis of ALK-positive lung cancer. Ping et al. and Kim et al. reported that ALK-positive lung adenocarcinoma exhibited a worse RFS than ALK-negative cancer in the patient cohort limited to never-smokers.[6,7] However, they concluded that the ALK status was not a significant prognostic factor for the OS, which is consistent with the findings of our present study. This finding can be explained by the higher administration rate of ALK-TKIs in ALK-positive patients than in ALK-negative ones, which might have contributed to the improved OS. However, a few reports have described conflicting results, with no significant difference in the RFS noted between ALK-positive and ALK-negative tumors.[8,9] The different conclusions concerning the prognosis in these studies may be due to differences in study cohorts. Indeed, ALK-positive tumors were not a prognostic factor for the RFS among p-stage II-III disease or the total patient cohort, with other clinicopathological factors having a greater impact on the prognosis than the ALK status in these populations.

The molecular and biological perspectives might be related to the poor prognosis of ALK-positive tumors. Various proteins, including mitogen-activated protein kinase and phosphatidylinositol3-kinase/Akt, produced by ALK rearrangement activate downstream oncogenic pathways involved in the cell proliferation and survival, which can cause aggressiveness in ALK-positive tumors.[17] In addition, it has been demonstrated that epithelial-mesenchymal transition (EMT) was overexpressed in tumor cells of ALK-positive NSCLC.[18] However, how ALK positivity is related to tumor aggressiveness has not been fully clarified. Further molecular biological research will be needed to clarify these points.

The efficacy of ALK-TKI for adjuvant therapy remains unknown. Although ALK-TKI might improve the RFS compared with platinum-based chemotherapy in advanced ALK-positive lung cancer,[19,20] only platinum-based chemotherapy is currently intended as adjuvant chemotherapy for ALK-positive lung cancer. A phase III study, in which ALK-TKI (alectinib) is compared with platinum-based chemotherapy as adjuvant therapy in patients with ALK-positive patients, is now ongoing.[21] Given the poor prognosis of ALK-positive p-stage I patients, we assumed that such adjuvant therapy would be indicated even in early-stage patients.

Several limitations were associated with the present study. First, this study was retrospective and performed at a single institute with a relatively small sample size; 36 ALK-positive patients, of whom only 24 exhibited ALK positivity in p-stage I. A further study with a larger sample size will be needed to draw a definitive conclusion. Second, we only used IHC to evaluate the ALK positivity; companion diagnostics, such as FISH or RT-PCR, should be performed to confirm the ALK status. Nonetheless, many reports have revealed that IHC has a high concordance rate with FISH and RT-PCR in terms of both sensitivity and specificity.[22–25] Third, the present study may have had selection bias as not all of the resected patients underwent an examination of ALK status. The decision to perform an examination for the ALK status was made by the tumor board, which included thoracic surgeons, pulmonologists and pathologists, depending on the degree of disease progression or patients' background.

In conclusion, the RFS was worse in ALK-positive cases of pathological stage I lung adenocarcinoma than ALK-negative ones. A high-grade histological subtype and never-smoker status in lung adenocarcinoma predicted ALK positivity. Patients with these predictive factors should be examined for their ALK status, and even in cases in an early disease stage, ALK-positive tumors should be carefully followed after resection.

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Not applicable.

## CONFLICT OF INTEREST

None declared.

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