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ORIGINAL ARTICLE

Analysis of clinical characteristics and prognosis of patients with anaplastic lymphoma kinase-positive and surgically resected lung adenocarcinoma

Hong Tao[1†], Yiran Cai[2†], Liang Shi[1], Junfang Tang[1], Zhidong Liu[3], Zitong Wang[3], Lianqi Bai[3] & Zhe Liu[1]

1 Department of Oncology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China
2 Department of Pathology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China
3 Department of Thoracic Surgery, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China

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Correspondence
Zhe Liu, Department of Oncology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, No. 97, Machang, Tongzhou District, 101149 Beijing, China.
Tel: +86 10 8950 9303
Fax: +86 10 8950 0153
Email: lza@vip.163.com

†Hong Tao and Yiran Cai contributed equally to this paper and are the co-first authors.

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Abstract

Background: Recent research into lung cancer-related driver genes has identified a distinctive molecular subtype of non-small cell lung cancer (NSCLC) – anaplastic lymphoma kinase (ALK)-positive NSCLC. We evaluated the clinical features and survival rates of ALK-positive lung adenocarcinoma patients who had undergone surgery but had not received ALK inhibitor therapy, along with the characteristics of patients with distant metastases.

Methods: Clinical data of 40 patients with ALK-positive, postsurgical lung adenocarcinoma were retrospectively analyzed. Relationships between the patients' clinical characteristics, distant metastases, and their disease-free survival (DFS) and overall survival (OS) rates were assessed.

Results: Most patients were relatively young, never-smokers, had peripheral tumors, and the tumors were either moderately or poorly differentiated. The most common organ of distant metastases was the brain. The median time from surgery to brain metastasis was 17.2 months. The median OS following brain metastasis was 9.4 months. DFS in patients with early stage disease, peripheral tumors, no lymph node metastases, and treated with adjuvant therapy was significantly longer than for those with late stage disease ($P = 0.015$), central tumors ($P = 0.000$), lymph node metastases ($P = 0.026$), and not treated with adjuvant therapy ($P = 0.000$). Patients with early stage disease, peripheral tumors, and treated with adjuvant therapy obtained markedly longer OS than those with late stage disease ($P = 0.021$), central tumors ($P = 0.003$), and not treated with adjuvant therapy ($P = 0.006$).

Conclusion: Patients with ALK-positive surgically resected lung adenocarcinoma have distinctive clinical characteristics. The brain is the most common site of extrapulmonary metastasis. Survival is associated with stage, tumor location, and the administration of adjuvant therapy.

Introduction

Lung cancer is the most common malignant tumor and cause of cancer mortality. In recent years, many oncogenic drivers of lung cancer, such as epidermal growth factor receptor (*EGFR*), vascular endothelial growth factor (*VEGF*), and anaplastic lymphoma kinase (*ALK*) genes have been discovered, and have led to the development of various types of targeted drugs. As a result, the efficacy of lung cancer treatment has improved among patients harboring driver genes.[1,2]

With these developments, the diagnosis and treatment of lung cancer has entered a molecular era. The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) fusion gene, generally known as the *ALK* fusion gene, was first discovered in 2007. This gene is generated by fusion of the *EML4* gene to the *ALK* gene in the form of chromosomal invertion.[3] The N-terminal of the fusion gene dimerizes and then activates protein kinase domains and downstream signaling pathways, which are important in the process of

tumorigenicity.[3,4] ALK-positivity is a specific molecular subtype of non-small cell lung cancer (NSCLC) that has distinctive clinical characteristics. The overall incidence of the *ALK* fusion gene in NSCLC is about 2–7%, and in patients with lung adenocarcinoma, incidence is as high as 5.2–11.2%.[5–9] Consequently, the *ALK* fusion gene is an important target in the treatment of NSCLC.

Studies of ALK-positive NSCLC have generally focused on advanced NSCLC patients rather than the postsurgical NSCLC population, and most studies have involved treatment with ALK inhibitors. In this study, 40 patients with lung adenocarcinoma harboring the *ALK* fusion gene and who had undergone surgical treatment were recruited, and their clinical characteristics, distant metastasis features, and survival were retrospectively analyzed. All of the patients in this retrospective study underwent pulmonary surgery between 2004 and 2013. At the time they underwent surgery, techniques to detect the *ALK* fusion gene were not widely available in China, and crizotinib, the first generation of ALK inhibitors, was not approved in China until 2013. Therefore, most patients did not have the opportunity to receive ALK inhibitor therapy when they relapsed or developed a metastasis. Consequently, the patient data we obtained did not reflect intervention with ALK inhibitors.

Methods

Patients

Surgical specimens from 392 lung adenocarcinoma patients who received surgical treatment between January 2004 and December 2013 at Beijing Chest Hospital were collected. Ventana assay was used to detect the *ALK* fusion gene. Forty ALK-positive patients were recruited. We retrospectively analyzed the patients' clinical data, their disease progression conditions, and their survival information.

Study methods

Patients were grouped according to gender, age, tumor node metastasis (TNM) stage, tumor location, tumor diameter, smoking history, degree of differentiation, lymph node metastasis status, and adjuvant treatment history. The location and features of distant metastases during the disease course were observed, and the patients' disease-free survival (DFS) and overall survival (OS) were analyzed. Tumors were staged according to the seventh edition of the American Joint Committee on Cancer staging manual, while treatment efficacy was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1. DFS was defined as the time from surgery to relapse, metastasis, or death from disease progression, while OS was defined as the time from surgery to death or loss to follow-up. Subsequent examinations or telephone interviews were performed every three months. The final follow-up date was 14 August 2015.

Statistical analysis

Data analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). We assessed the association of brain metastases with patient demographic and clinicopathological characteristics by Fisher's exact test. The survival time of patients who were still alive at the time of the data update were censored at the date of the last follow-up. Survival curves were estimated by the Kaplan–Meier method to generate median DFS and OS times with 95% confidence intervals, and the log-rank test was used to compare differences between groups with respect to

Table 1 Clinical characteristics of patients with ALK-positive and surgically resected lung adenocarcinoma

Characteristics	Number of patients†	(%†)
Gender		
Male	21	52.5
Female	19	47.5
Age (years)		
≤55	24	60.0
>55	16	40.0
Median	53	
Smoking history		
Current/former smoker	11	27.5
Light smoker (≤10 pack-years)	0	0
Never (<100 cigarettes)	29	72.5
Mean/median/range (pack-years)	28.5/30/20–40	
TNM stage		
Stage I	10	25.0
Stage II	3	7.5
Stage III	23	57.5
Stage IV	4	10.0
Tumor location		
Central	12	30.0
Peripheral	28	70.0
Type of resection		
Pulmonary lobectomy	29	72.5
Pneumonectomy	9	22.5
Pulmonary wedge resection	2	5.0
Adjuvant therapy (n = 30‡)		
Chemotherapy	20	66.7
Chemoradiation	5	16.7
Not given	4	13.3
Unknown	1	3.3
Differentiation		
Well-differentiated	0	0
Moderately differentiated	25	62.5
Poorly differentiated	15	37.5

†Unless otherwise specified. ‡Number of patients with stage II–IV disease who required adjuvant therapy. ALK, anaplastic lymphoma kinase; TNM, tumor node metastasis.

different demographic and clinicopathological characteristics and treatment history. $P < 0.05$ was considered statistically significant, and all P values were two-sided.

Results

Clinical features and treatments

The median age of the patients was 53 years. Non-smokers accounted for 72.5% of the total cohort. Peripheral lung tumors existed in 70.0% of patients (Table 1). In four stage IV patients (10%), two had isolated distant metastatic nodules, while two were found to have pleural nodules during surgery that were subsequently pathologically verified as metastatic. Mediastinum lymphadenectomy had been performed in all but one of the patients, who suffered from aplastic anemia. Seventeen of the 40 patients were pathologically diagnosed before surgery. Among those 17 patients, one was diagnosed with adenoid cystic carcinoma prior to surgery and the presence of adenocarcinoma was confirmed after surgery, while the other 16 patients had consistent pathological diagnostic results both before and after surgery.

Thirty patients required adjuvant therapy. The chemotherapy regimens were platinum-based doublet protocols including: vinorelbine (5 patients), paclitaxel (4), docetaxel (5), gemcitabine (6), and pemetrexed (5).

Factors influencing disease progression and disease-free survival

At the last follow-up, 28 patients had experienced disease progression while nine patients had not, and data for three patients was not available for analysis. The median DFS for all 40 patients was 17.4 months.

Grouping statistical analysis showed that DFS rates in patients with early stage disease (stage I + stage II) were significantly superior than for those with late stage disease (stage III + stage IV; 30.3 vs. 12.8 months, $P = 0.015$). Similarly, the DFS rate in patients with peripheral tumors, no lymph node metastases, and treated with adjuvant

Table 2 DFS and OS in patients with ALK-positive surgically resected lung adenocarcinoma by log-rank test

	Disease-free survival (n = 37)†			Overall survival (n = 39)‡		
Group	n	Median DFS, months (95%CI)	*P*	n	Median OS, months (95% CI)	*P*
Gender			0.108			0.588
Male	19	14.7 (1.456–27.944)		20	26.2 (15.781–36.619)	
Female	18	18.8 (14.038–23.162)		19	32.8 (25.956–39.644)	
Age (years)			0.700			0.425
≤55	22	19.1 (10.304–27.896)		23	32.8 (22.717–42.883)	
>55	15	17.4 (0.276–34.524)		16	30.0 (23.559–36.441)	
TNM stage			**0.015**			**0.021**
I + II	13	30.3 (24.454–36.146)		13	55.5 (–)	
III + IV	24	12.8 (8.913–16.687)		26	26.2 (19.176–33.224)	
Tumor location			**0.000**			**0.003**
Central	12	7.3 (0–17.824)		12	20.9 (5.978–25.822)	
Peripheral	25	27.4 (14.521–40.279)		27	39.2 (27.820–50.580)	
Smoking history			0.127			0.467
Current/former	10	7.0 (3.901–10.099)		11	22.9 (11.679–34.121)	
Light/never	27	17.4 (11.756–23.044)		28	32.8 (27.696–37.904)	
Differentiation			0.110			0.113
Moderate	23	27.0 (12.536–41.464)		24	39.2 (29.762–48.638)	
Poor	14	11.9 (10.250–13.550)		15	27.7 (19.120–36.280)	
Tumor size			0.179			0.527
>3 cm	16	12.8 (9.137–16.463)		16	32.0 (19.337–44.663)	
≤3 cm	21	27.0 (10.915–43.085)		23	30.0 (20.012–39.979)	
Lymph node metastasis			**0.026**			0.062
Yes	25	12.8 (8.955–16.645)		27	27.8 (18.322–37.278)	
No	12	30.3 (22.262–38.338)		12	45.0 (32.676–57.324)	
Adjuvant therapy§			**0.000**			**0.006**
Yes	25	17.4 (9.997–24.803)		25	33.4 (23.564–43.236)	
No	4	1.4 (0.910–1.890)		4	8.9 (0–18.014)	

P values were estimated by log-rank tests. Values in bold type indicate $P < 0.05$. †Three patients had incomplete follow-up data. ‡One patient was lost to follow-up. §One patient was lost to follow-up among the 30 who received adjuvant therapy. CI, confidence interval; DFS, disease-free survival; OS, overall survival; TNM, tumor node metastasis.

therapy were remarkably longer than those with central tumors (27.4 vs. 7.3 months, $P = 0.000$), lymph node metastases (30.3 vs. 12.8 months, $P = 0.026$), and not treated with adjuvant therapy (17.4 vs. 1.4 months, $P = 0.000$; Table 2 and Fig 1). However, gender, age, smoking history, degree of differentiation, and tumor size were not related to DFS.

Characteristics of patients with distant metastases and sites of metastases

The most frequent organ of distant metastases in the course of disease was the brain (10 patients), followed by bone (5), liver (4), adrenal gland (2), and pancreas (2). The median time from surgery to the occurrence of brain metastasis was 17.2 months. The median OS following brain metastasis was 9.4 months (Fig 2).

Brain metastasis was associated with tumor location. Patients with central tumors experienced brain metastasis events more frequently than patients with peripheral tumors (70.0% vs. 30.0%, $P = 0.004$; Table 3). However, the occurrence of brain metastasis was independent of gender, age, smoking history, disease stage, and degree of differentiation (Table S1).

Factors influencing overall survival

At the last follow-up, 15 of the 40 patients were still alive, 24 had died, and one patient was lost to follow-up. The

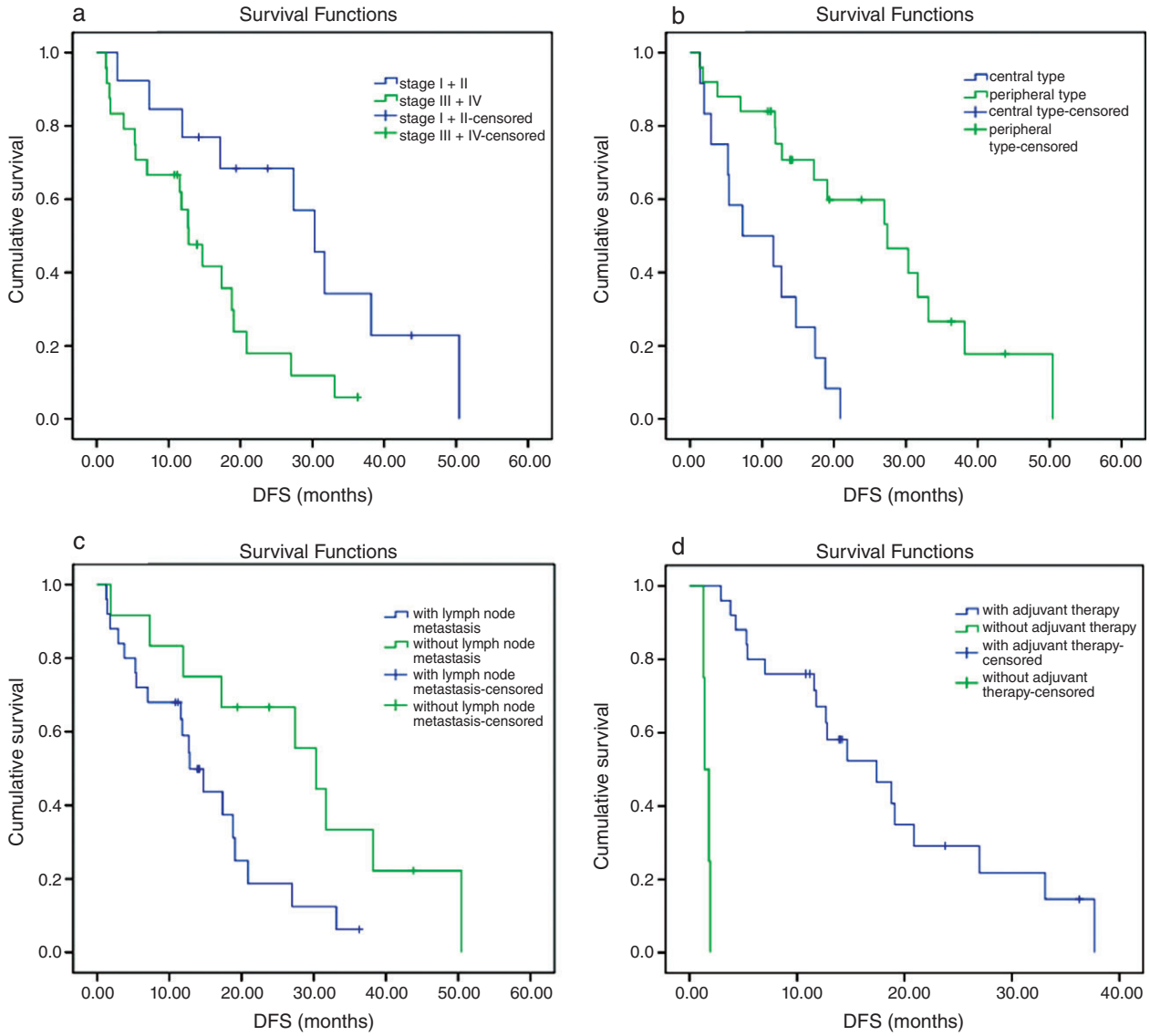


Figure 1 Disease free survival (DFS) curves for different groups of patients with anaplastic lymphoma kinase-positive and surgically resected lung adenocarcinoma: (**a**) stage, (**b**) tumor location, (**c**) lymph node metastasis, and (**d**) adjuvant therapy.

median OS was 32.0 months. OS in patients with early stage disease was significantly longer than in patients with late stage disease (55.5 vs. 26.2 months, $P = 0.021$). Similarly, patients with peripheral tumors had better OS rates than patients with central tumors (39.2 vs. 20.9 months, $P = 0.003$). Patients treated with adjuvant therapy had greater OS than patients were not treated with adjuvant therapy (33.4 vs. 8.9 months, $P = 0.006$; Fig 3). However, gender, age, smoking history, degree of differentiation, tumor size, and lymph node metastasis had no influence on OS (Table 2).

Discussion

The study population for this investigation comprised 40 ALK-positive pulmonary adenocarcinoma patients who received surgical treatment at our hospital between 2004 and 2013. During this period, the patients did not receive ALK inhibitors because the China Food and Drug Administration did not approve the use of crizotinib until 2013. The 40 ALK-positive patients (21 men, 19 women) were selected following an analysis of 392 postoperative tissue samples from patients with lung adenocarcinoma using Ventana assay (ALK-positivity rate 10.2%). They were relatively young with a median age of 53 years, 72.5% were non-smokers, and the proportion with peripheral tumors was higher than the proportion with central tumors (70.0% vs. 30%, respectively).

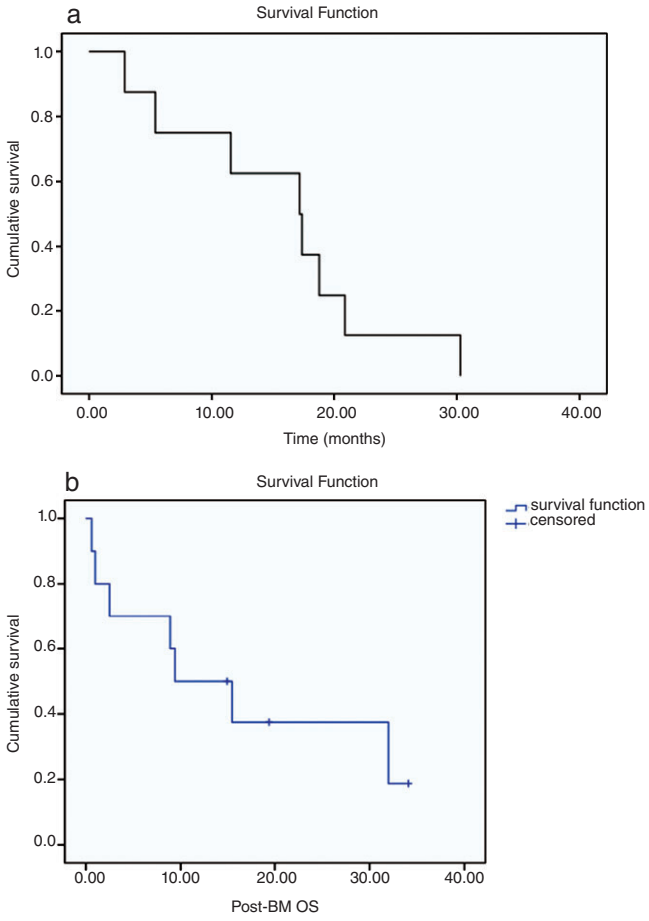


Figure 2 Survival curves for patients with brain metastasis: (**a**) time from surgery to brain metastasis (BM), and (**b**) overall survival (OS) following BM.

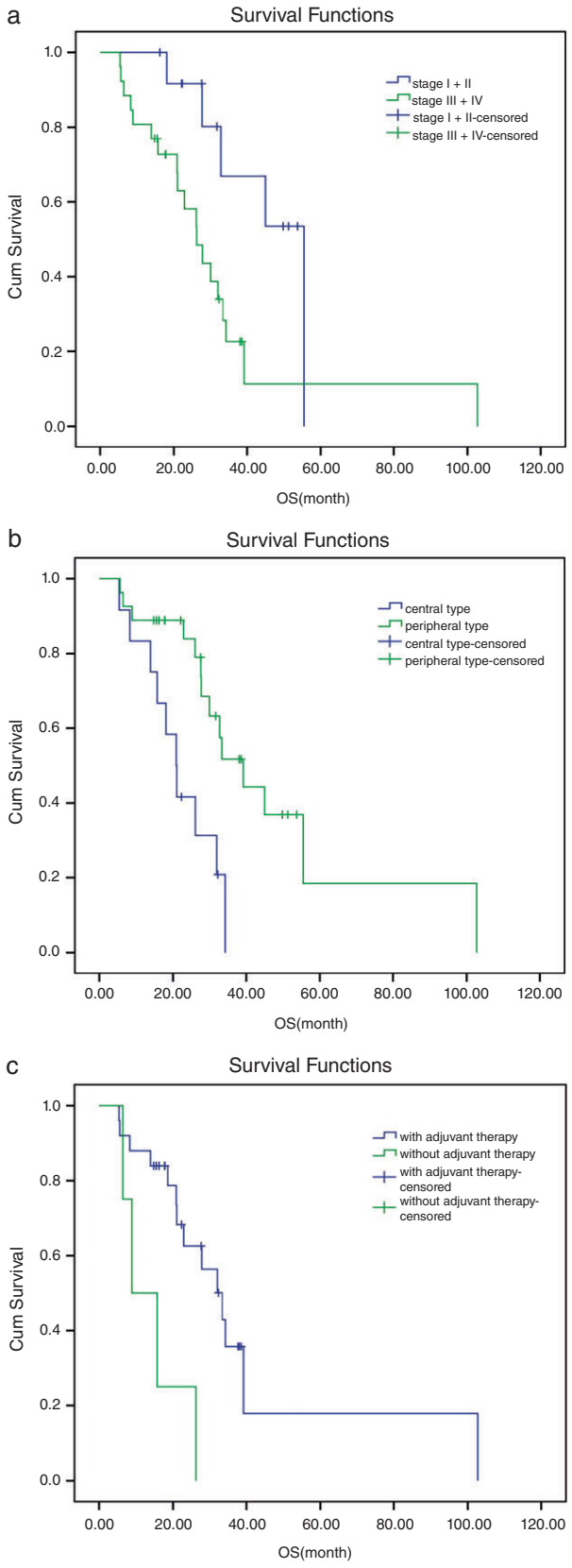
Our findings in terms of the patients' clinical features, sites of distant metastasis, and survival are consistent with those of previous reports.[1,6–8,10] Because all of the patients in our study had moderately or poorly differentiated tumors and none had well-differentiated tumors, ALK-positive adenocarcinoma of lung may be associated with high malignancy. In this regard, Zhang *et al.* reported that ALK rearrangement occurred in NSCLC patients with poor differentiation.[11] However, there are few relevant published reports on this issue.

Survival conditions were assessed in this study. We found that patients with early stage disease exhibited a longer DFS and OS than those with late stage disease. In addition, DFS was longer in patients who did not have lymph node metastasis than in those with lymph node metastasis. In other studies, pathologic stage has been found to be the major factor that affects the survival of surgically resected NSCLC patients.[12,13] Paik *et al.* concluded that the earlier the T and N stages of tumors, the longer the DFS and OS.[7] We also found that DFS and OS were related to tumor stage. Moreover, our results indicated that patients with peripheral lung tumors had longer DFS and OS than those with central tumors, which has rarely been mentioned in previous reports. Compared with central tumors, peripheral tumors usually have a lower T stage, which leads to better survival. Our results revealed that survival was not related to age, smoking status, or gender, which have not been conclusively proven by previous published reports.[12–15] However, differences between the results of our study and previous reports may be attributed to differences in sample sizes and study population characteristics.

Previous studies of patients with NSCLC have identified prognostic factors in unselected patients regardless of ALK status, and we identified virtually the same prognostic

Table 3 Relationship between brain metastasis and tumor location

	Tumor location		
Brain metastasis	Central n (%)	Peripheral n (%)	*P*
Yes ($n = 10$)	7 (70.0)	3 (30.0)	0.004
No ($n = 29$)	5 (17.2)	24 (82.8)	n/a



factors in an ALK-positive population. However, the available research on this issue is limited. Some researchers are of the view that ALK status does not influence prognosis. Paik *et al.* demonstrated no significant differences in DFS and OS between ALK-positive and ALK-negative postoperative lung adenocarcinoma patients.[7] Pan *et al.* concluded that neither relapse-free survival nor OS differed according to ALK status.[10] ALK-positive postoperative NSCLC patients may share some important prognostic factors, such as TNM stage, with NSCLC patients with unknown ALK status. ALK-positive surgically resected NSCLC patients probably have specific prognostic factors that are yet to be identified. As it is widely known that crizotinib therapy improves the survival of patients with ALK-positive advanced NSCLC, we speculate that ALK inhibitors may also be beneficial in a surgically resected population.

Our results demonstrated that the brain is the most frequent site of distant metastases in patients with ALK-positive surgically resected NSCLC. The median time from surgery to the occurrence of brain metastasis was 17.2 months. Other studies have also reported that brain metastases are common in patients with ALK-positive NSCLC. The PROFILE 1005 and 1007 studies, which included 888 patients with ALK-positive advanced NSCLC, found that 275 patients (31%) had brain metastasis at baseline, and another 51 patients (5.7%) developed brain metastasis after commencing crizotinib therapy.[16] Data from another retrospective study showed that 213 of 753 patients with ALK-positive NSCLC (28.3%) developed brain metastases.[17] It has been reported that the frequency of brain metastasis ranges from 45% to 70% in patients with ALK-positive NSCLC treated with ALK inhibitors, while in patients not treated with ALK inhibitors, the frequency was 40.3%.[18] In this study, the incidence of brain metastasis in patients with ALK-positive surgically resected NSCLC was somewhat lower at 25.6%. This difference in comparison with other reports may be because of differences in disease stages. The patients in this study underwent surgical resection, while those in the reports mentioned above had advanced-stage NSCLC. At the final follow-up, nine of the 40 patients had not yet experienced progressive disease. However, if the follow-up period had been longer, we probably would have been able to obtain more detailed data on brain metastases.

Interestingly, in this study, patients with central lung tumors were more likely to experience brain metastasis

Figure 3 Overall survival (OS) curves for different groups of patients with anaplastic lymphoma kinase-positive and surgically resected lung adenocarcinoma: (**a**) stage, (**b**) tumor location, and (**c**) adjuvant therapy.

than those with peripheral tumors (70.0% vs. 30.0%, $P = 0.004$). However, the reason for this finding is unclear. Further studies of brain metastasis in patients with ALK-positive NSCLC are needed to obtain more definitive information.

The emergence of brain metastasis in patients with NSCLC indicates disease progression and a poor prognosis. The median OS following brain metastasis was only 9.4 months in this study. Therefore, it is very important to determine effective treatment for patients with ALK-positive NSCLC who develop brain metastases. Brain radiotherapy, including whole brain radiotherapy and stereotactic radiotherapy, is currently advocated ahead of systemic therapy as it provides better efficacy. In a study of patients with advanced ALK-positive NSCLC with brain metastasis treated with crizotinib, 109 patients who did not receive brain radiotherapy prior to systemic therapy were compared with 166 patients who did receive brain radiotherapy. The median times to intracranial progression in the two groups were 7 and 13.2 months, respectively, and the median times to systemic progression were 12.5 and 14 months, respectively.[16]

Depending on the circumstances, patients who receive ALK inhibitor therapy prior to developing brain metastasis can continue such therapy.[18] In a study of 34 patients who suffered from brain metastases after initiating crizotinib treatment (27 of whom had also received local radiotherapy), continuation of crizotinib therapy for a median of 19.3 weeks proved to be effective.[17] In another study, Takeda *et al.* reported that seven NSCLC patients experienced central nervous system progression after crizotinib prescription, then received local radiotherapy followed by continued crizotinib therapy for a further 4.4–11.0 months.[19] Three of the seven patients had not progressed at the last follow-up.[19] Another treatment option in patients exhibiting resistance to crizotinib is the administration of second-generation ALK inhibitors, such as ceritinib and alectinib.[20]

Crizotinib, a selected tyrosine kinase inhibitor, has been reported to be effective in patients with ALK-positive advanced NSCLC, providing objective response rates of 48–74% whether it is used as initial or subsequent treatment.[2,21,22] In this study, only one patient received crizotinib as fourth-line treatment, 33.8 months after surgery. This patient had experienced brain, pleural, lung, bone, and liver metastases before crizotinib prescription. Other patients did not receive ALK inhibitor therapy; therefore, our results could objectively reflect the disease progression and survival status of ALK-positive surgically resected lung adenocarcinoma patients without intervention from an ALK inhibitor.

The limitations of this study include its retrospective nature, single-arm design, the relatively small number of patients studied, and the relatively short duration of follow-up. If the follow-up duration had been longer, more metastatic sites would have been observed, which would have provided additional information about disease progression in patients with ALK-positive surgically resected NSCLC.

In conclusion, by recording the clinical characteristics, sites of distant metastasis, and survival of patients with ALK-positive postsurgical lung adenocarcinoma not treated with ALK inhibitor therapy, this study has provided useful data for screening ALK-positive patients in clinical practice. We need to be vigilant to detect the occurrence of brain metastases, especially in patients with central lung tumors. Patients with early stage disease, peripheral tumors, and those who receive adjuvant treatment appear to achieve better survival. By providing clinical data on patients not treated with ALK inhibitors, these findings may be beneficial for future research on the efficacy of ALK inhibitor treated patients with surgically resected NSCLC.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 Relationship between brain metastasis and demographic and clinicopathological characteristics.

