Original Article

Distinct metastatic spread and progression patterns in patients treated with crizotinib for *ROS1*- and *ALK*-rearranged non-small cell lung cancer: a single-center retrospective study

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Background: Crizotinib has been approved for C-ros oncogene 1 (*ROS1)*- and anaplastic lymphoma kinase *(ALK)*-rearranged non-small cell lung cancer (NSCLC) patients. Few studies have examined the differences in crizotinib treatment outcomes between these patients and the progression sites during treatment. We investigated the metastatic spread, crizotinib efficacy, and progression patterns during crizotinib treatment in *ROS1*- and *ALK*-rearranged NSCLC patients.

Methods: We retrospectively reviewed crizotinib-treated *ROS1*- and *ALK*-rearranged NSCLC patients between January 2011 and March 2021. Patient characteristics, clinical outcomes, and progression patterns during treatment were collected from medical records. The metastasis extent, crizotinib response, and progression patterns between the groups were compared.

Results: We identified 26 patients with *ROS1*- and 42 with *ALK*-positive NSCLC. The baseline proportion of central nervous system (CNS) metastases did not differ between the groups (12% *vs.* 29%, P=0.10), but the proportion of extrathoracic metastases, including CNS metastases, was significantly higher in *ALK*-positive than in *ROS1*-positive NSCLC patients (35% *vs.* 71%, P=0.003). Regarding the response to crizotinib, the objective response rate (ORR), progression-free survival (PFS), or overall survival (OS) did not significantly differ between the groups (*ROS1 vs. ALK*, ORR: 69% *vs.* 69%, P=0.987; PFS: median 10.9 *vs.* 10.7 months, P=0.232; median OS: not reached *vs.* 67.7 months, P=0.495). The CNS was the most common metastasis site in both groups [*ROS1 vs. ALK*, 69% (11/16) *vs.* 46% (17/37), P=0.127], and the cumulative incidence of CNS metastasis did not differ between the groups (P=0.914).

Conclusions: Crizotinib treatment outcomes, including progression patterns, were similar between *ROS1*- and *ALK*-positive NSCLC patients.

Keywords: *ROS1*-rearrangement; non-small cell lung cancer (NSCLC); crizotinib; progression pattern; CNS metastasis

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Introduction

Oncogenic rearrangement in C-ros oncogene 1 *(ROS1)*, which is structurally homologous to the tyrosine kinase region of anaplastic lymphoma kinase *(ALK)*, occur in approximately 2% to 3% of NSCLC patients (1,2). Crizotinib, which was first approved for patients with advanced NSCLC with *ALK* rearrangements, binds with high affinity to *ROS1*, and potently inhibits *ROS1* signaling and cell viability (3-5). In clinical setting, crizotinib produced median PFS duration of 15.8 to 22.8 month in patients with advanced *ROS1*-positive NSCLC, while the median PFS of 7.7 to 10.9 months in patients with advanced *ALK*-positive NSCLC, based on the results of several clinical trials (2,6-11). Crizotinib received approval for *ROS1*-positive NSCLC. Subsequently, entrectinib, a *ROS1* tyrosine kinase inhibitor (TKI), was approved for the treatment of *ROS1*-rearranged NSCLC.

ROS1 rearrangements have been associated with a lower incidence of extrathoracic metastases, including CNS metastases at initial diagnosis and during treatment, compared to *ALK* rearrangements (12). In contrast, similar frequencies of CNS metastases have been reported in patients with *ALK* and *ROS1* rearrangements (13). *ALK* rearrangements were associated with pericardial, pleural, and liver metastases compared to *EGFR/KRAS/ALK* wild-type alterations (14). Additionally, in *ALK*-positive NSCLC patients, the CNS was the most common metastatic site during crizotinib treatment (15). In *ALK*-positive NSCLC patients, next-generation *ALK* inhibitors have been designed to more strongly inhibit the *ALK* native kinase, be active on crizotinib-induced resistance mutations, and have better blood-brain barrier (BBB) penetration to control or prevent CNS involvement. The second-generation inhibitors, alectinib and brigatinib, have become the standard first-line treatment. In contrast, crizotinib and entrectinib are still the standard of care in *ROS1* positive NSCLC patients, but due to the resistance of these TKIs, the development of next-generation *ROS1* TKIs is underway.

In this study, to evaluate the distinct clinical features in *ROS1*- and *ALK*-positive NSCLC patients, we investigated the baseline metastatic spread, crizotinib efficacy, and progression patterns during crizotinib treatment. This article is presented in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-10/rc).

Highlight box

Key findings

- We evaluated the distinct clinical features in *ROS1*- and *ALK*-positive NSCLC patient.

What is known and what is new?

- Oncogenic rearrangement in *ROS1* is structurally homologous to the tyrosine kinase region of *ALK*.
- We demonstrated that metastatic spread at initial diagnosis differed between patients with *ROS1*- and *ALK*-positive NSCLC, but the clinical outcomes with crizotinib treatment and progression patterns, including that of CNS progression, were similar.

What is the implication, and what should change now?

- Continued efforts to develop novel TKIs that can overcome resistance to crizotinib and exhibit better intracranial activity are needed.

Methods

Patients

We retrospectively reviewed and included all advanced *ROS1*- and *ALK*-positive NSCLC patients who had been treated with crizotinib at the National Cancer Center Hospital from January 2011 to March 2021. There were no exclusion criteria. Data on patient characteristics, metastatic site at the baseline, tumor response to crizotinib, and progression patterns during crizotinib treatment were collected from medical records. *ROS1* and *ALK* rearrangements were identified by fluorescence *in situ* hybridization, targeted next-generation sequencing, immunohistochemistry, and/or real-time polymerase chain reaction (*ROS1* only), as described in previous study (12).

Statistical analysis

PFS was measured as the time from the start of crizotinib treatment to radiographic disease progression (as assessed by the investigator) or death if no disease progression was documented. Patients who survived without documented disease progression were censored at the last follow-up visit. Overall survival (OS) was measured from the initiation of crizotinib treatment to death. Patients with undocumented dates of death were censored from the data of the last visit. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (16). The objective response rate (ORR) was defined as the proportion of patients who had a complete response (CR) or partial response (PR). The disease control rate

Table 1 Patient and disease characteristics

Characteristics	ROS1, n=26	ALK, n=42	P value
Age, years, median at diagnosis of advanced disease [range]	56 [36–82]	56 [36–82]	
Sex, n [%]			
Male/female	10 [38]/16 [62]	19 [45]/23 [55]	0.583
Smoking history, n [%]			
Never/light (<10 pack years)/heavy (≥10 pack years)	15 [58]/5 [19]/6 [23]	26 [62]/5 [12]/11 [26]	0.706
Histopathology, n [%]			
Adenocarcinoma/others	23 [88]/3 [12]	42 [100]/0 [0]	0.052
Stage at diagnosis, n [%]			
III[a]–IV/recurrence	20 [77]/6 [23]	30 [71]/12 [29]	0.618
ECOG performance states, n [%]			
0–1/≥2	24 [92]/2 [8]	37 [88]/5 [12]	0.618
Brain metastasis at diagnosis, n [%]			
Present/absent	3 [12]/23 [88]	12 [29]/30 [71]	0.100
Crizotinib treatment line, n [%]			
1/2/≥3	10 [38]/6 [23]/10 [38]	23 [55]/11 [26]/8 [19]	0.199

[a], 5 patients in *ROS1*-positive NSCLC and 2 patients in *ALK*-positive NSCLC. ECOG, Eastern Cooperative Oncology Group.

(DCR) was defined as the proportion of patients who achieved CR, PR, or stable disease. Descriptive statistics were used for categorical (frequency and proportion) and continuous variables (median and range). Kaplan-Meier curves and estimates were used to assess the OS, PFS, and cumulative incidence of CNS progression during crizotinib treatment for *ROS1*- or *ALK*-positive NSCLC. Differences in OS, PFS, and CNS progression were assessed using log-rank tests. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS/Windows, Version 19.0, SPSS Inc., Chicago, USA). All tests were two-tailed, and statistical significance was set at P<0.05. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the National Cancer Center Hospital (No. 2015-355) and individual consent for this retrospective analysis was waived.

Results

Patients characteristics at baseline

We identified 26 *ROS1*-positive NSCLC and 42 *ALK*-positive NSCLC patients who had been treated with crizotinib. Patient characteristics are presented in *Table 1*. The baseline characteristics were similar between both groups. In *ROS1*-positive NSCLC, crizotinib was administered to 10 patients (38%) as a first-line treatment, 6 patients (23%) as a second-line treatment, and 10 patients (38%) as a third-line or later treatment. In *ALK*-positive NSCLC, crizotinib was administered to 23 patients (55%) as a first-line treatment, 11 patients (26%) as a second-line treatment, and 8 patients (19%) as a third-line or later treatment (*Table 1*).

At the baseline, patients with *ROS1*- and *ALK*-positive NSCLC had similar intrathoracic metastasis spread (*Figure 1A*). However, patients with *ROS1*-positive NSCLC had significantly lower rates of extrathoracic metastases, including CNS metastasis, especially that of extrathoracic lymph node metastases (*ROS1*, 35%; *ALK*, 71%; P=0.003; *Figure 1B* and *ROS1*, 0%; *ALK*, 17%; P=0.028; *Figure 1C*). Regarding CNS metastasis at baseline, three patients with *ROS1*-positive NSCLC had previously been treated with radiotherapy or surgery, and three patients had untreated brain metastases at the initiation of crizotinib. All of these patients achieved a reduction in brain metastasis with crizotinib. Among patients with *ALK*-positive NSCLC, 12 had been previously treated for brain metastases

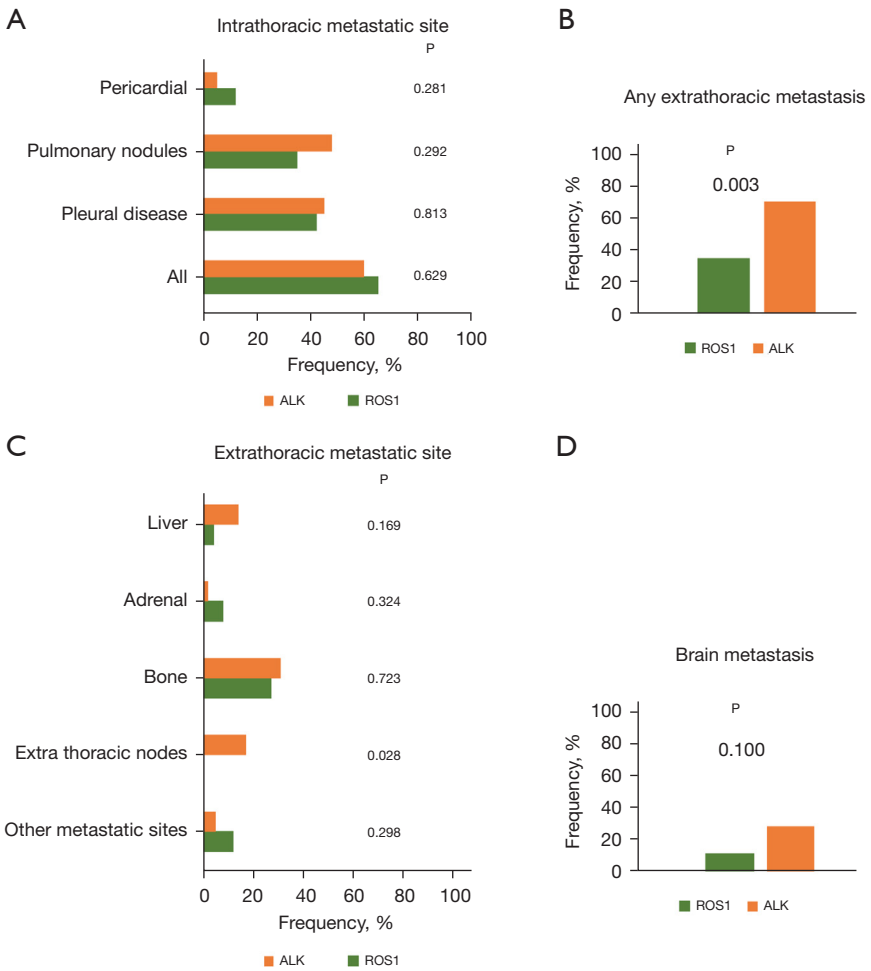

Figure 1 Frequency of metastatic sites of malignant disease at initial metastatic diagnosis. Frequency of (A) intrathoracic sites, (B) extrathoracic sites including CNS metastases, (C) extrathoracic sites, and (D) brain metastases. *ROS1*, C-ros oncogene 1; *ALK*, anaplastic lymphoma kinase; CNS, central nervous system.

before receiving crizotinib, and three had untreated brain metastases at its initiation. The percentage of brain metastases was also lower in *ROS1*-positive patients, although the difference was not statistically significant (*ROS1*, 12%; *ALK*, 29%; P=0.100; *Figure 1D*).

Efficacy of crizotinib in ROS1 and ALK-positive NSCLC patients

The ORR and DCR for crizotinib in *ROS1*-positive patients were 69% and 85%, respectively (*Table 2*). In *ALK*-positive patients, the ORR and DCR were 69% and 81%, respectively. There were no significant differences in tumor response and PFS with crizotinib between the two groups (ORR, P=0.987; DCR, P=0.484; median PFS: 10.9 *vs.* 10.7 months, P=0.232) (*Figure 2A*). The OS did not significantly differ between *ROS1*- and *ALK*-positive NSCLC patients [not reached (95% CI: NR–NR), and 67.7 months (95% CI: 47.6–87.8), respectively (P=0.495)] (*Figure 2B*).

Progression patterns during crizotinib treatment in ROS1 and ALK-positive NSCLC

Data on progression patterns were available for 16 patients with *ROS1*-positive and 37 with *ALK*-positive NSCLC (*Figure 3*). Progression patterns were similar between the two groups. Brain metastases, including isolated CNS

metastasis, were the most common sites of progression in both groups (*ROS1*, 69%; *ALK*, 46%; P=0.127). The cumulative incidence of CNS progression in patients with *ROS1*- and *ALK*-positive NSCLC during crizotinib treatment is presented in *Figure 4*. There were no significant differences between the two groups for all patients (P=0.914) or for patients with no CNS metastasis at baseline (P=0.437).

Table 2 Best response to crizotinib therapy

Efficacy	*ROS1*, n=26	*ALK*, n=42	P value
Response			
CR	2 (8%)	5 (12%)	
PR	16 (62%)	24 (57%)	
SD	4 (15%)	5 (12%)	
PD	2 (8%)	3 (7%)	
NE	2 (8%)	5 (12%)	
Clinical benefit			
ORR	69%	69%	0.987
DCR	85%	81%	0.484

ALK, anaplastic lymphoma kinase; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not estimable; ORR, objective response rate; DCR, disease control rate.

Discussion

In this study, we retrospectively evaluated the metastatic spread at baseline and progression patterns during crizotinib treatment in patients with advanced *ROS1*- and *ALK*-positive NSCLC. The clinical outcomes of crizotinib were similar in both groups. Additionally, CNS was the most common progression site, and progression patterns during crizotinib treatment in both patient groups were similar.

Two phase II studies evaluating the efficacy of crizotinib in *ROS1* fusion-positive NSCLC patients showed that PFS was 15.9 to 22.8 months, while phase III trials revealed that it was 11 months in patients with treatment-naive advanced *ALK* fusion-positive NSCLC (7,10). Although direct comparison between clinical trials is challenging due to the varying trial designs, the differences in the clinical outcomes with crizotinib treatment between patients with *ROS1*- and *ALK*-positive NSCLC could be related to the difference in inhibitory effects of this drug. Indeed, crizotinib had better inhibitory effect on *ROS1*-dependent cell lines than on *ALK*-dependent cell lines (1,3). Another reason could be the differences in metastatic spread at baseline. Gainor *et al.* reported that patients with *ROS1*-positive disease had significantly lower rates of extrathoracic metastases, including lower rates of brain metastases at the initial metastatic diagnosis, which was consistent with the results of our study (12). Regarding progression patterns

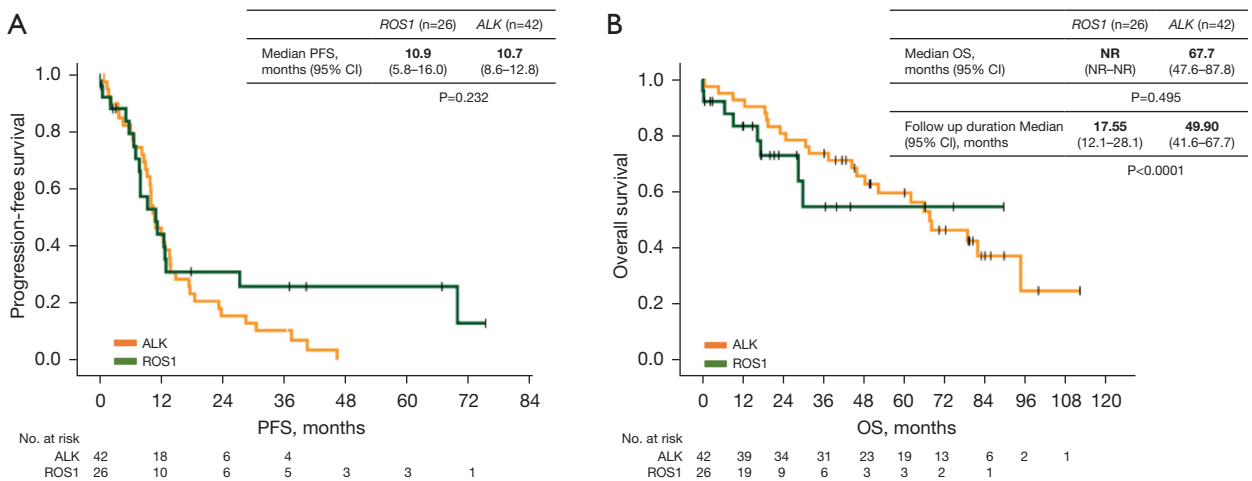

Figure 2 Kaplan-Meier curves for PFS and OS of patients with *ROS1*- and *ALK*-positive NSCLC. (A) PFS with crizotinib treatment (any line of therapy). (B) OS with crizotinib treatment (any line of therapy). PFS, progression-free survival; OS, overall survival; *ROS1*, C-ros oncogene 1; *ALK*, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

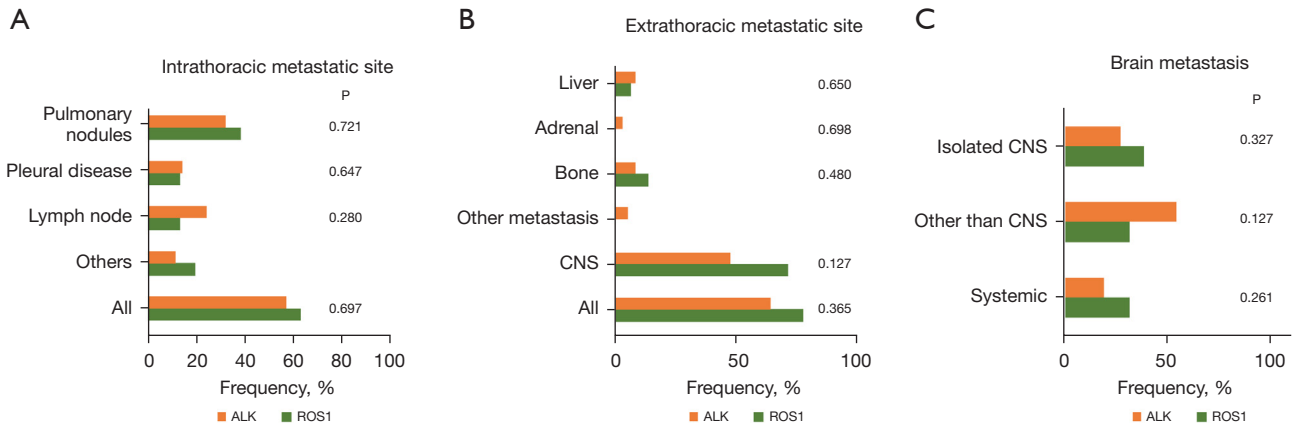

Figure 3 Progression pattern of *ROS1*- and *ALK*-positive NSCLC during crizotinib treatment. Frequency of occurrence of (A) intrathoracic and (B) extrathoracic sites, and (C) brain metastases. *ROS1*, C-ros oncogene 1; *ALK*, anaplastic lymphoma kinase; CNS, central nervous system; NSCLC, non-small cell lung cancer.

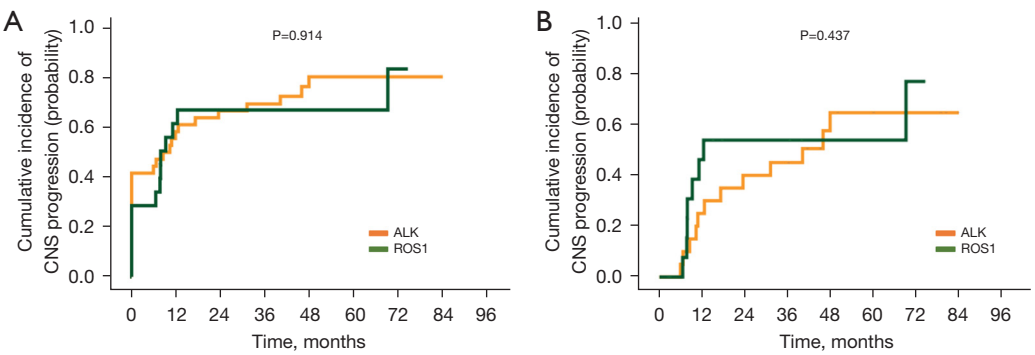

Figure 4 Cumulative incidence of CNS progression (probability) in patients with *ROS1*- and *ALK*-positive NSCLC during crizotinib treatment. (A) Cumulative incidence of CNS progression in all patients. (B) Cumulative incidence of CNS progression in patients without brain metastasis at the time of crizotinib initiation. *ROS1*, C-ros oncogene 1; *ALK*, anaplastic lymphoma kinase; CNS, central nervous system; NSCLC, non-small cell lung cancer.

during treatment, patients with *ROS1*-positive NSCLC had a significantly lower cumulative incidence of brain metastases over time. In contrast, Patil *et al.* reported that there were no statistically significant differences in CNS progression in *ROS1*- and *ALK*-positive patients, who were taking crizotinib (13). Our study showed that the progression patterns during crizotinib treatment in *ROS1*- and *ALK*-positive NSCLC were similar, and there were no significant differences in the incidence of CNS progression. The difference in the clinical outcomes with crizotinib, including the progression sites, between patients with *ROS1*- and *ALK*-positive NSCLC remains controversial.

Crizotinib poorly penetrates the cerebrospinal fluid (CSF) (17). In *ALK*-positive NSCLC patients, the CNS is the common initial progression site, including isolated progression, and brain metastasis status was significantly associated with both PFS in crizotinib-treated patients and CNS progression. In patients with *ROS1*-positive NSCLC, it remained unclear how baseline brain metastasis affects the clinical outcomes with crizotinib because two phase II trials evaluating the efficacy of crizotinib treatment in *ROS1*-positive NSCLC excluded patients with untreated CNS metastases (2,10). The METROS study showed that among six *ROS1*-positive NSCLC patients with intracranial disease, the intracranial ORR was 33%, and five patients experienced intracranial progression as a pattern of failure (8). In our study, six patients with *ROS1*-positive NSCLC with brain metastases at baseline,

regardless of prior radiotherapy for CNS metastases, and four patients developed CNS progression. Our study showed that the presence of CNS metastasis at baseline in *ROS1* fusion-positive NSCLC affected the clinical outcome with crizotinib. Although the biology of brain metastasis is poorly understood, metastases to the CNS, unlike metastases to other distal organ sites, involve the breach of the BBB. BBB effectively prevents the free exchange of substances between the blood and the interstitial fluid of the brain (18-20). The CNS is considered a sanctuary site for metastatic cancer cells because many therapeutic agents cannot cross the BBB. A better understanding of molecular biology of lung cancer metastasis to the brain and efficient drug delivery across the BBB will be essential to find the appropriate treatment strategy for prevention of brain metastasis.

The present study had several limitations. The sample size was small, and the study was conducted in a single institute, which included potential confounders, such as the number of lines of prior treatment and treatment duration. Moreover, although the prognostic impact of distinct fusion genes on clinical outcomes has been reported, details of the fusion types were unavailable (21-23).

Conclusions

We demonstrated that metastatic spread at initial diagnosis differed between patients with *ROS1*- and *ALK*-positive NSCLC, but the clinical outcomes with crizotinib treatment and progression patterns, including that of CNS progression, were similar. Continued efforts to develop novel TKIs that can overcome resistance to crizotinib and exhibit better intracranial activity are needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-10/rc

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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). The study was approved by institutional ethics board of National Cancer Center Hospital (No. 2015-355) and individual consent for this retrospective analysis was waived.

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