

# Treatment of Alectinib in NSCLC with Brain Metastasis Patient Refractory to Radiotherapy after Resistance to Crizotinib: A Case Report and Literature Review

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## Case report

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# Abstract

**Background:** Brain metastasis is the common place of tumor recurrence after resistance to crizotinib. The therapeutic modes on brain metastasis of ALK-positive NSCLC require multidisciplinary approach, including target therapy, chemotherapy and radiotherapy. Until to nowadays, there isn't optimal therapeutic recommendations for these patients. Radiotherapy is the vital treatment for brain metastasis.

**Case presentation:** We reported one ALK-positive NSCLC patient with brain metastasis after crizotinib. ALK rearrangement wasn't found in blood sample of the patient by NGS. According to NCCN guideline, we gave the patient whole brain radiotherapy. It was unexpected that the number of brain metastasis increased after whole brain radiotherapy. After that, the patient was empirically used alectinib after radiotherapy failure. It achieved unexpected success in our patient.

**Conclusions:** We got some enlightenment from the patient. Firstly, liquid biopsy is complementary to tissue biopsy in NSCLC, mainly in EGFR mutation. However, ALK detection should use tissue biopsy as much as possible. Secondly, we suggest the brain metastasis patient of NSCLC use the second generation TKI, such as alectinib, ceritinib, after resistance to crizotinib whether ALK is positive or negative in liquid biopsy. Lastly, we believe that combined radiotherapy with TKIs is an optimal mode in the BM patient of NSCLC after resistance to crizotinib.

## Background

As a drive gene, anaplastic lymphoma kinase (ALK) gene rearrangement (ALKr) accounted for 2–7% of non-small-cell lung cancer (NSCLC) patients (Dagogojack et al., 2020). Therefore, targeting ALKr may precisely treat this subtype patients of NSCLC. As the first-generation drug of targeting ALKr, crizotinib have proved to efficaciously treat NSCLC patients harboring ALKr [2]. However, most patients go through tumor recurrence within 1 year after using crizotinib. Moreover, brain metastasis (BM), which remains a substantial cause of morbidity and mortality, is the common place of tumor recurrence [3]. The therapeutic modes on BM of ALK-positive NSCLC require multidisciplinary approach, including target therapy, chemotherapy and radiotherapy. Until to nowadays, there aren't defined recommendations for these patients yet. Haihong et al reported that BM of ALK-positive lung adenocarcinoma patients had better overall survival by tyrosine-kinase inhibitors (TKIs) or cranial radiotherapy. Moreover, cranial radiotherapy still plays an important role in these patients [4]. Ineffective for radiotherapy hasn't been previously reported in BM of ALK-positive lung adenocarcinoma patients. Herein, we reported that alectinib successfully treated one BM patient refractory to radiotherapy, which is ALK-negative in blood sample after resistance to crizotinib. In addition, we discuss the effect of different therapeutic modes in BM of ALK-positive lung adenocarcinoma by reviewing the relevant literature.

## Case Presentation

A 67-year old man had smoked for more than 20 years, 20 cigarettes/day. He had quit smoking for 10 years. In July 2015, he was in Tianjin Medical University Cancer Institute and Hospital due to right supraclavicular lymph node enlargement. Physical examination found one right supraclavicular lymph node enlargement, which wasn't pain. Laboratory data revealed all normal except that carcinoembryonic antigen (CEA) is 8.7. PET revealed that one occupying lesion is in left lung. There is one right supraclavicular lymph node enlargement and multiple mediastinal lymphadenopathy. Moreover, there were multiple bone metastases, including the fourth cervical vertebra, the left first rib and the left pubis(Fig. 1a). According to the 8th edition of the classification of lung cancer, the stage of this patient is IV(T1cN3M1b). Transcutaneous needle biopsy was performed at the right supraclavicular lymph node enlargement. According to the immunohistochemical analysis, a diagnosis of poorly differentiated adenocarcinoma was made(Fig. 1b). By next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH), ALK was found in biopsy samples. So, the patient was started with crizotinib, and had a shrinkage in all lesions in three months after crizotinib. Laboratory data revealed CEA is 6.7. During the follow-up period, all lesions were further shrinkage except lesion of the left lung which was stable disease. Laboratory data revealed CEA is normal, that is under 5.0.

In October 2019, the patient was dizzy and pain in the right hip. PET revealed multiple bone metastases in the right ilium and the right ischium(Fig. 2a). Moreover, there were multiple metastatic focuses in the brain(Fig. 2a). Then, the contrasted MR showed that the number of BM is nine(Fig. 2b). Laboratory data revealed CEA is 3.6. We recommend a biopsy of the right iliac bone. Because the patient had symptoms of high intracranial pressure and deterioration of dizziness, the patient and his family members refused biopsy. ALK was not found in the biopsy of the patient by NGS. As reported [5], the patient was given the whole brain radiation therapy (WBRT) combined with simultaneous integrated boost (SIB) which aimed at metastatic focuses. WBRT was delivered in a course of 39.6 Gy in 22 fractions. SIB was delivered in a course of 55 Gy in 22 fractions(Fig. 2c). The patient was given radiotherapy in the lesion of the right iliac bone as well. Radiotherapy was delivered in a course of 60 Gy in 24 fractions(Fig. 2d). With radiotherapy, the pain of the right hip was ebbing. However, the symptoms of high intracranial pressure took a turn for the worse. The patient underwent MR after finishing 10 fractions cranial radiotherapy. The MR showed that the number of brain metastasis increased to about 50(Fig. 3a). After careful consideration, we made decision to finish WBRT. After finishing WBRT, the patient developed into coma. MR showed that the number of BM increased to about 80(Fig. 3b). Some BM were in the brain stem. Faced with such a situation, we are desperate. WBRT is ineffective for this patient. What was the next therapy for this patient? Satoh Y et al reported that the overall concordance rate of ALK status was 100% according to immunostains between histologic and paired liquid-based cytology specimens[6]. However, Aldea M et al reported that the detection rate of genomic alterations is lower in the subset of isolated central nervous system progression patients[7]. The result of blood sample was doubtful. So, the patient received alectinib 600mg twice daily. After a week of oral alectinib, the consciousness of this patient gradually improved. After a month of oral alectinib, the patient's physical symptoms gradually improved. MR showed that the number of brain metastasis decreased to about 60 and the total metastatic tumor volume decreased as well(Fig. 4a). Some metastatic focuses vanished,

especially in brain stem. It was pity that the right thalamus hemorrhaged and ruptured into ventricle in this patient because of stopping antihypertensive drugs autonomously. It was given to treat cerebral hemorrhage. Moreover, the patient continued to take alectinib. After a month of treatment in hemorrhage, the patient's condition gradually stabilized. MR showed that most of the hematoma was absorbed and the number of brain metastasis further decreased to about 20(Fig. 4b). Furthermore, the total metastatic tumor volume further decreased as well.

## Discussion And Conclusion

BM, which are a frequent complication in patients with NSCLC, is associated with poor survival outcomes and poses clinical challenges for oncologists[8]. At initial diagnosis, 10% of NSCLC patients have BM, and the brain is the only site of tumor relapse in 50% NSCLC patients[9]. However, in NSCLC patients harboring ALK<sub>r</sub>, the risk of BM is higher. The rate of BM is approximately 20% in NSCLC patients harboring ALK<sub>r</sub> at initial diagnosis and up to 75% in these patients by using crizotinib[10]. So, the therapeutic effect of BM plays an important role in prolonging overall survival and improving the quality of life. However, there isn't a standard therapeutic mode in BM of NSCLC. A large number of studies have taken different strategies to treat BM of NSCLC, including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and combination of different modes[11–15].

As well as this patient, radiotherapy plays an important role in treating BM of NSCLC harbouring driver-gene mutation, such as WBRT[13, 16, 17], stereotactic radiosurgery (SRS)[16–18], and so on. According to National Comprehensive Cancer Network (NCCN) recommendation, the patient was given the WBRT. In order to increase the local control, we used SIB to increase the dose of metastatic focuses. However, during the course of radiotherapy, it was unexpected that the number of the brain metastasis inexplicably increased in our case. The phenomenon has not been reported. The current studies mainly focus on that WBRT impairs cognitive function and quality of life and SRS is an alternative therapy for BM. Some studies showed that SRS obtained good local control and less cognitive deterioration in treating 1 to 3 brain metastases[19, 20]. Hughes RT et al reported that SRS alone adapted to treat these patients with 5 to 15 BM[21]. Recently, Robin TP et al found that BM patients with ALK<sub>r</sub> may be uniquely suited to benefit from SRS[20]. So, SRS alone may become a preferred strategy in treating brain metastases.

ALK<sub>r</sub> wasntfound  $\in$   $bl\infty dsamp \leq ofthepatientbyNGS$ . Thepatientsdt continued in using ALK inhibitor. If the patient was an ALK-positive in blood sample, the patient had combined radiotherapy with alectinib. Because of poor accumulation of crizotinib in CNS, many NSCLC patients with ALK<sub>r</sub> frequently experience BM after treatment with crizotinib. The second generation ALK inhibitor, that is alectinib, can retain a higher concentration in the CNS and enhance the efficacy in treating BM in NSCLC patients with ALK<sub>r</sub>[22]. After crizotinib failure for ALK-positive NSCLC patients, Novello S et al reported that alectinib significantly improved the efficacy of BM compared with chemotherapy[3]. Whether radiotherapy or TKIs or combined radiotherapy with TKIs can improved the efficacy of BM? By meta-analysis, Singh R et al reported that there was no significant difference between combined radiotherapy with TKIs compared with radiotherapy alone. Similarly, there was no significant difference in median overall survival among

TKIs alone, radiotherapy alone, and a combination of TKIs and radiotherapy[13]. So, the choice of three modes should be determined according to the specific situation of the patient. In our case, the patient was empirically used alectinib after radiotherapy failure. It achieved unexpected success in our patient.

In summary, we got some enlightenment from the patient. Firstly, liquid biopsy is complementary to tissue biopsy in NSCLC, mainly in EGFR mutation. However, ALK detection should use tissue biopsy as much as possible. Secondly, we suggest the BM patient of NSCLC use the second generation TKI, such as alectinib, ceritinib, after resistance to crizotinib whether ALK<sub>r</sub> is positive or negative in liquid biopsy. Lastly, we believe that combined radiotherapy with TKIs is an optimal mode in the BM patient of NSCLC after resistance to crizotinib.

## Abbreviations

NSCLC: non-small-cell lung cancer; ALK: anaplastic lymphoma kinase; ALK<sub>r</sub>: anaplastic lymphoma kinase gene rearrangement; BM: brain metastasis; TKIs: tyrosine-kinase inhibitors; CEA: carcinoembryonic antigen; NGS: next-generation sequencing; FISH: fluorescence in situ hybridization; WBRT: whole brain radiation therapy; SIB: simultaneous integrated boost

## Declarations

- **Ethics approval and consent to participate**

Not applicable; see the next item.

- **Consent for publication**

The consent form has been signed by the patient.

- **Availability of data and materials**

All the Patient's data and medical images can be found on the database of our Hospital.

- **Competing interests**

The author declare that they have no competing interest.

- **Funding**

None.

- **Authors' contributions**

Yuan Zhou carried out the literature search and drafted the article. Xianliang Zeng and Songwei Sun carried out image and data collection. Xiuli Chen and Shuang Huang collected important background information and performed image processing. Chunzhi Zhang made substantial contributions to the manuscript, including revising it critically for intellectual content. All authors read and approved the final manuscript.

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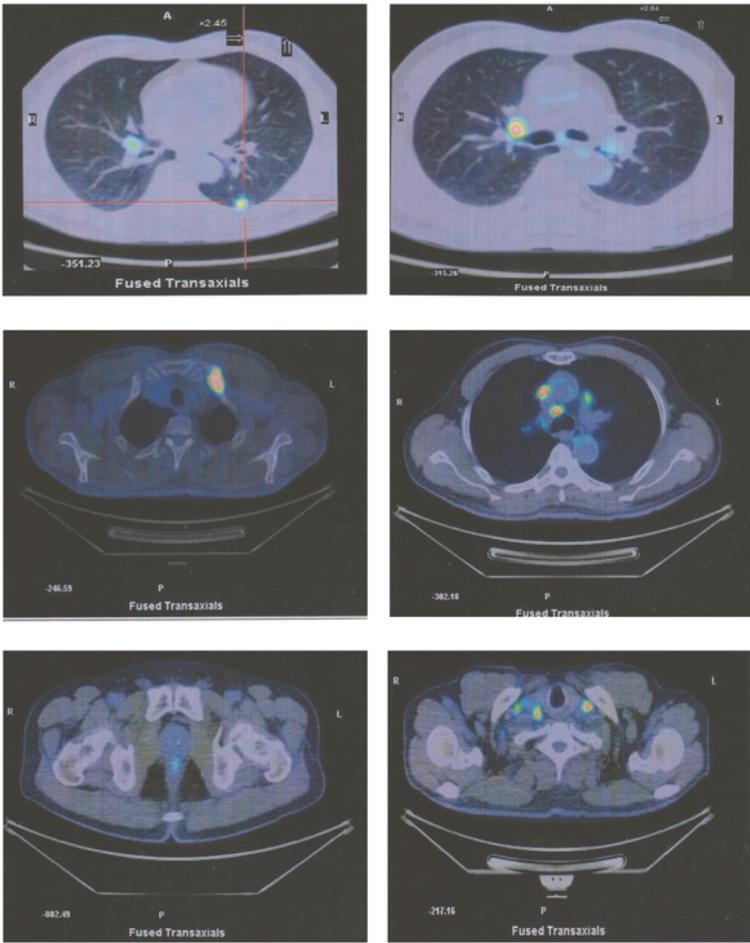
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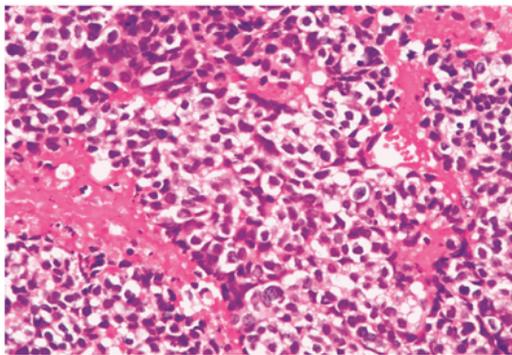
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## Figures



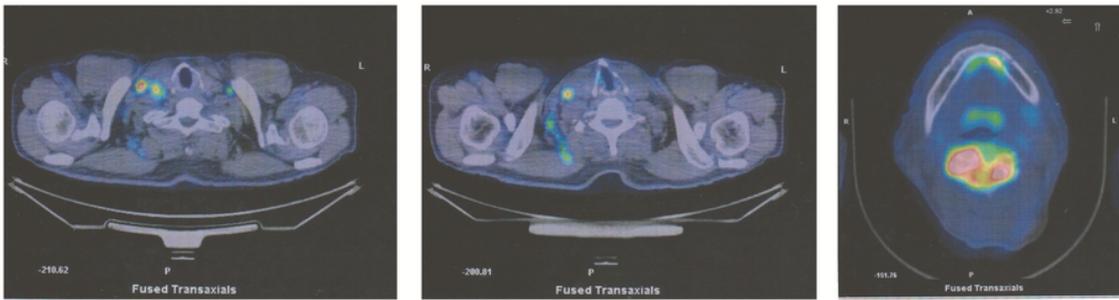
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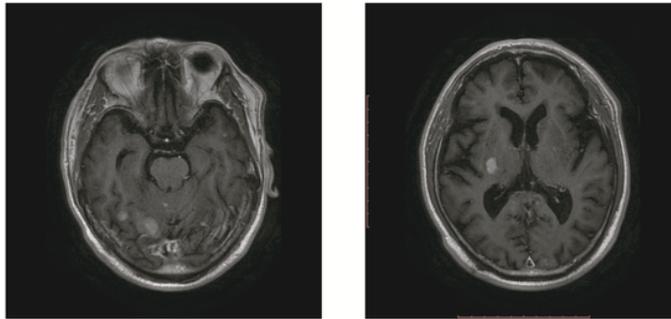
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## Figure 1

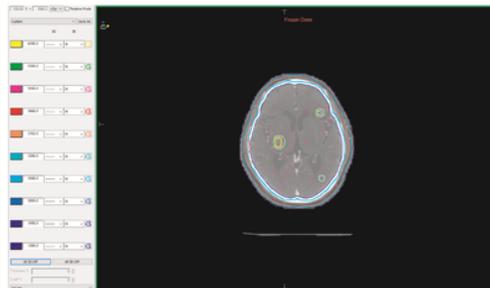
A T1cN3M1b NSCLC patient. (a). PET revealed that one occupying lesion is in left lung. There is one right supraclavicular lymph node enlargement and multiple mediastinal lymphadenopathy. Moreover, there were multiple bone metastases, including the fourth cervical vertebra, the left first rib and the left pubis. (b). According to the immunohistochemical analysis, a diagnosis of poorly differentiated adenocarcinoma was made.



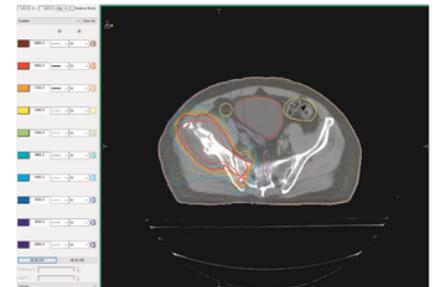
2a



2b



2c



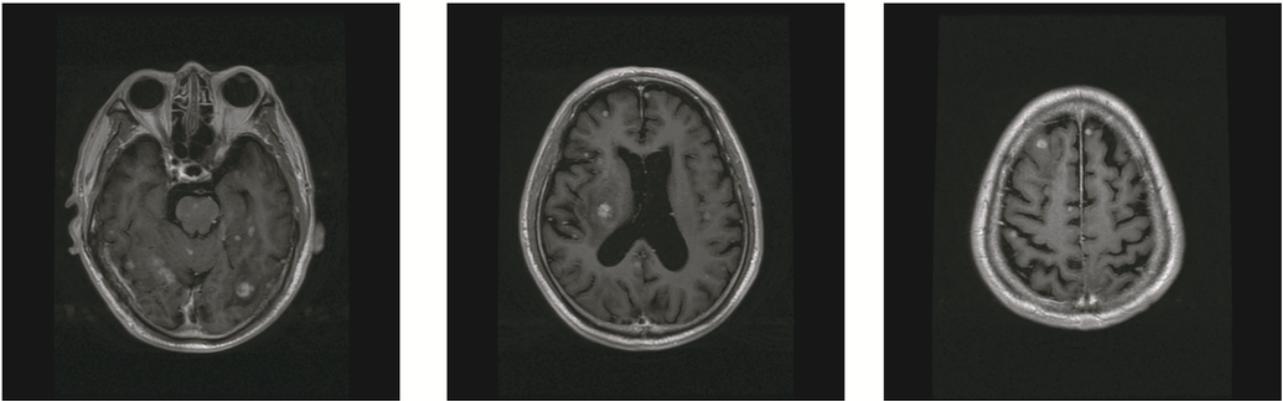
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## Figure 2

Tumor recurrence after treatment of crizotinib. (a). PET revealed multiple bone metastases in the right ilium and the right ischium. Moreover, there were multiple metastatic foci in the brain. (b). The contrasted MR showed that the patient had BM. (c). The dose distribution of radiotherapy in BM. (d). The dose distribution of radiotherapy in the lesion of the right iliac bone.



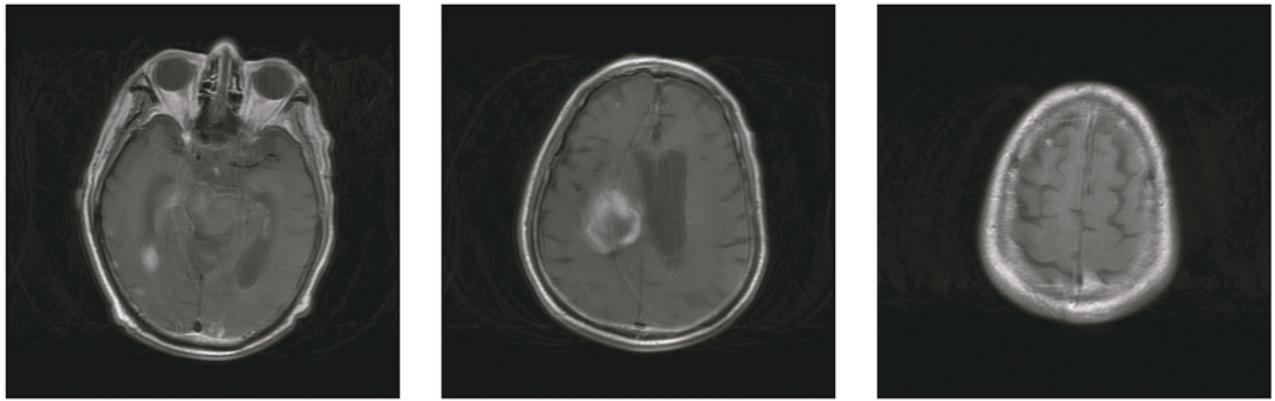
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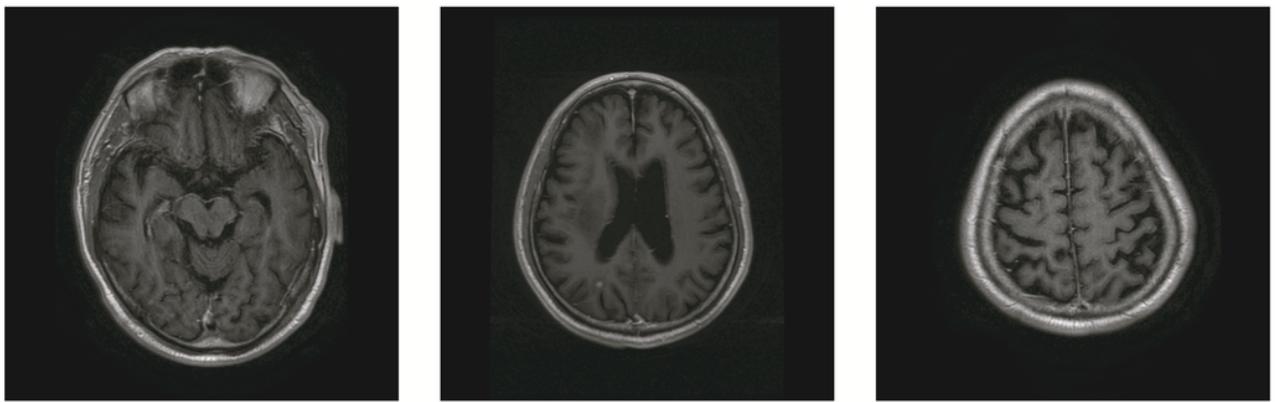
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**Figure 3**

The number of BM increased after radiotherapy. (a). The MR showed that the number of brain metastasis increased to about 50. (b). MR showed that the number of BM increased to about 80.



4a



4b

**Figure 4**

The number of BM decreased after treatment of alectinib. (a). MR showed that the number of brain metastasis decreased to about 60. (b). The number of brain metastasis further decreased to about 20.