

PET-CT evaluation of the curative effect of crizotinib on malignant myofibroblastoma with rare mutation of ALK R40I: a case report and literature review

Li Yang^{1,*}
Yufeng Wu^{1,*}
Hong Tang¹
Jiuzhou Zhao²
Dongdong Zhao¹
Sen Yang¹
Qiming Wang¹

¹Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China;

²Department of Molecular Pathology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

*These authors contributed equally to this work

Objective: The purpose of this article is to explore the targeted treatment of malignant myofibroblastoma and evaluate the role of neoplasm metabolite markers in the evaluation of efficacy after targeted therapy.

Method: This report described a case of myofibroblastic sarcoma with rare mutation of *ALK R40I* in a 58-year-old man prescribed with crizotinib, to evaluate its curative effect by positron emission tomography coupled with computed tomography (PET-CT). After the progressive disease in the brain, bevacizumab combined with crizotinib was administered. The Response Evaluation Criteria in Solid Tumors (RECIST), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were used to assess the efficacy. The efficacy was assessed by comparing changes in MTV and TLG.

Result: After the treatment of crizotinib, the tumor volume was decreased. However, bevacizumab combined with crizotinib had not improved the prognosis. The change of MTV and TLG was consistent with the efficacy. The increase of MTV and TLG is an early indicator of the poor prognosis of patients.

Conclusion: The treatment of the crizotinib patient with the mutation of *ALK R40I* was effective. The values of MTV and TLG reflected the prognosis earlier than RECIST.

Keywords: malignant myofibroblastoma, PET-CT, *ALK R40I*, volume-dependent parameter

Introduction

Malignant myofibroblastoma is a rare tumor in adults and pediatric patients,¹⁻⁴ the classification of which belongs to myofibroblastic tumors. The classification of the myofibroblastic tumors is myofibroblastic sarcoma (MS), inflammatory myofibroblastic, myofibromatosis, myofibroblastoma, myopericytoma, and angio-myofibroblastoma. This report is based on low-grade fibrous myofibroblasts, which are infrequently accompanied by metastasis, and surgical treatment is common. It has been known to arise mainly in the head and neck regions and the soft tissues of the extremities,^{5,6} although it could be rarely found at the bone and breast; only a small number of cases have been reported in the literature worldwide.⁷ Inflammatory myofibroblastic tumor (IMT) and MS belong to soft tissue tumors, but the malignant level was different. The expression of anaplastic lymphoma kinase (ALK) protein occurs in 50%–70% of IMTs,^{8,9} while the ALK of MS are mostly immunonegative.^{10,11} ALK-R40I is a nonsense mutation, and its function is unknown.¹² In this case, the immunohistochemistry (IHC) of our patient did not reveal *ALK* gene mutation, but

Correspondence: Qiming Wang
Department of Internal Medicine,
Affiliated Cancer Hospital of Zhengzhou
University, Henan Cancer Hospital,
No 127 Dongming Road, Zhengzhou
450008, China
Fax +86 371 6558 8134
Email qimingwang1006@gmail.com

next-generation sequencing (NGS) supported *ALK R401* mutation in exon five. Treatment with an ALK inhibitor was found to be effective in reducing tumor size and tumor metabolism.

Tumor-response assessments are still using Response Evaluation Criteria in Solid Tumors (RECIST), which evaluate the effectiveness using the maximum and rear diameters.^{13–15} Although tumor size changes often take time (up to several months), it is necessary in the clinical treatment process to be able to predict early clinical response and to adjust treatment plans accordingly. Furthermore, metabolic changes in the tumor may reflect changes in the condition earlier. Positron emission tomography coupled with computed tomography (PET-CT) has long been a reference imaging tool for the diagnosis and staging of tumors,¹⁶ particularly in cases where the metastatic tumors of the primary lesion were unknown.¹⁷ There are some studies confirming that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as a tumor metabolic index can be used to assess the prognosis of patients.¹⁸ Herein, we reviewed the use of PET-CT to assess treatment response and found that the MTV can reflect the metabolic and volume changes, which are more conducive to predict the prognosis of patients.

Case report

A 58-year-old male presented to the hospital with paroxysmal pain in the chest and discomfort in the head on August 10, 2015. The Karnofsky performance status (KPS) score was 60. PET-CT revealed a right upper chest mass was 51×41 mm, with a maximum standardized uptake value (SUV) of 5.6, accompanied with brain, bone, liver, and right subscapularis muscle metastases with high SUV. We recorded the tumor

size of the primary tumor and metastases. The specimens showed malignant spindle cells, which displayed immunohistochemical positive staining for CK, SMA, CD34, CD99, and Bcl-2, and negative for Des, S-100, and B-Catenin. *ALK* was not supported (Ventana IHC) (Figure 1). The patient was then diagnosed with malignant myofibroblastoma with brain, bone, and liver metastases.

Considering the patient's poor KPS score (60 at diagnosis) and metastases all over the body, chemotherapy, radiochemotherapy, or surgery was excluded. Methylprednisolone was given at 800 mg/d, day (d)1-5 started from August 20, 2015. The patient then developed an aggravating headache. Fifteen days later, PET-CT imaging showed tumor volume enlargement. The MTV and TLG values are also increased. Subsequently, genetic tests revealed the fifth exon *R401* mutation of the *ALK* gene. Considering the tumor histological and biological features, crizotinib was given at 250 mg daily from September 10, 2015. After 1 month of crizotinib at 250 mg daily, the headache was eased, and PET-CT (October 9, 2015) showed a dramatic reduction in tumor size and metabolism, resulting in stable disease (SD), based on criteria in RECIST 1.1 with KPS score of 70. Conversely, the MTV and TLG values were also significantly reduced.

Two months later, the patient had headaches again, so we reviewed his PET-CT on December 7, 2015. The brain imaging showed that the primary tumor was enlarged with edema, and new metastases could be found in the lung (Figure 2). The tumor size of the right upper chest wall, liver, and right subscapularis muscle metastases were stable, while the MTV and TLG values of them were almost doubled, representing progressive disease. The patient's family rejected the second-generation ALK inhibitors. Thus, bevacizumab (500 mg/d, d1, every 21 days), combined with crizotinib at

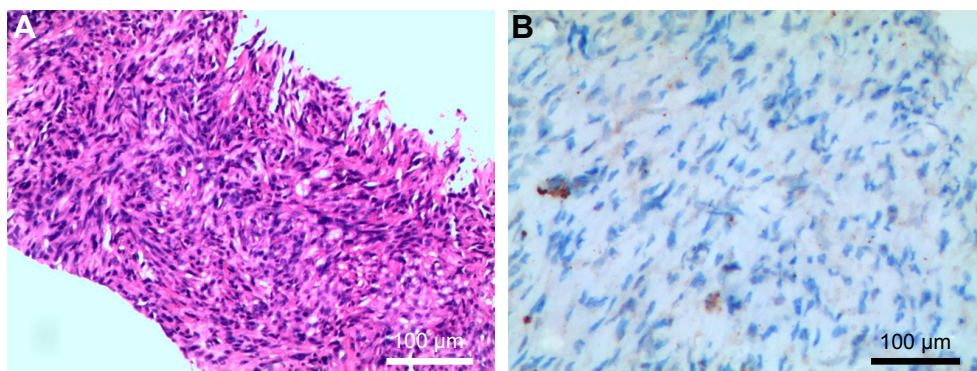


Figure 1 Histopathological and immunohistological findings of the lymph nodes tissues samples. (A) Hematoxylin and eosin staining showed malignant spindle cells (200×), which displayed immunohistochemical positive staining for CK, SMA, CD34, CD99, and Bcl-2, and negative for Des, S-100, and B-Catenin. (B) IHC of our patient did not reveal supported *ALK* gene mutation (200×).

Abbreviations: IHC, immunohistochemistry; ALK, anaplastic lymphoma kinase.

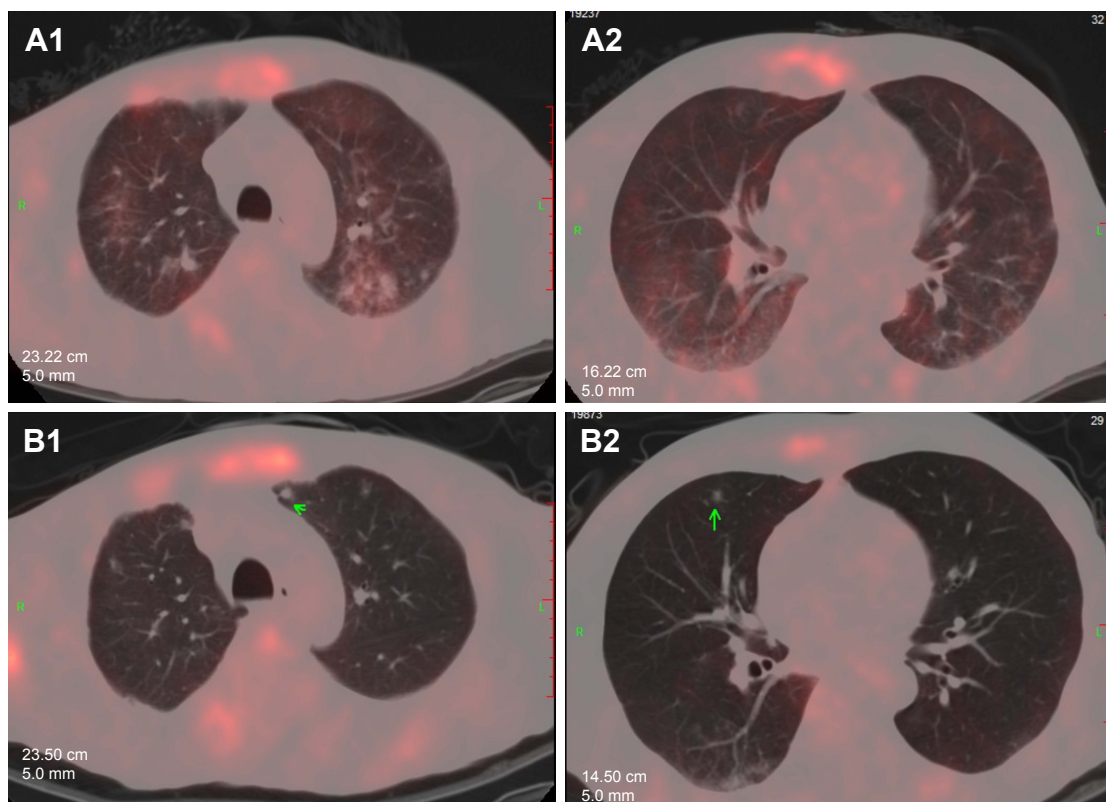


Figure 2 The progression in the lung. (A1 and A2) were taken on October 9, 2015. (B1 and B2) were taken on December 10, 2015, and the green arrows refer to the new lesions.

250 mg daily, was administered. Twenty days later, the headache was eased, and the KPS score was 80. Two months after treatment with bevacizumab (500 mg/d, d1, every 21 days) combined with crizotinib 250 mg daily, the headache was aggravated, and the patient developed a poor diet, nausea, and vomiting. The KPS score was 50, PET-CT imaging showed right pleural effusion, all body metastases were enlarged, and the MTV and TLG values were significantly increased, indicating progressive disease (Figure 3). The patient was administered nutritional supportive treatment. Unfortunately, the patient died 1 month later in March 2016 (Figure 4).

Written informed consent was obtained from the patient's wife (the patient's next of kin) for publication of this case report and accompanying images.

Discussion

Crizotinib is an ATP competitor that inhibits the multitarget protein kinase inhibitor of *Met/ALK/ROS*. Crizotinib has been used in *ALK* positive non-small cell lung cancer (NSCLC) to lengthen the period without progression. *ALK* inhibitors have been reported as effective treatments for *ALK*-rearranged IMT.^{19,20} It was reported that a patient who was diagnosed

ALK-1-rearranged IMT with brain metastases was initially treated with crizotinib, and the disease progressed after 3 months.²¹ After that, alectinib, the second-generation *ALK* inhibitor, was taken as the second-line therapy with 8-month progression-free survival. Our patient had malignant myofibroblastoma with the mutation of *ALK-R401*. There is no report about the function and treatment effect of the *ALK-R401*, but it was considered implicated in tumorigenesis. In this case, after the treatment of crizotinib, the progression-free survival was 3 months. It has been known that crizotinib has poor central nervous system (CNS) penetration, as evidenced by low concentrations detected in CNS samples during the treatment course,²² which was likely the cause of treatment failure in our patient. Also, alectinib, which is a selective *ALK* inhibitor with high CNS penetration, is active against several secondary mutations that confer acquired resistance to crizotinib.²³ It may be effective to administer the second generation *ALK* inhibitor after drug resistance.

Bevacizumab, a recombinant, humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is a vascular-targeted therapy that may inhibit neovascularization,²⁴ such as slower tumor development, reduced metastasis development, and improved drug

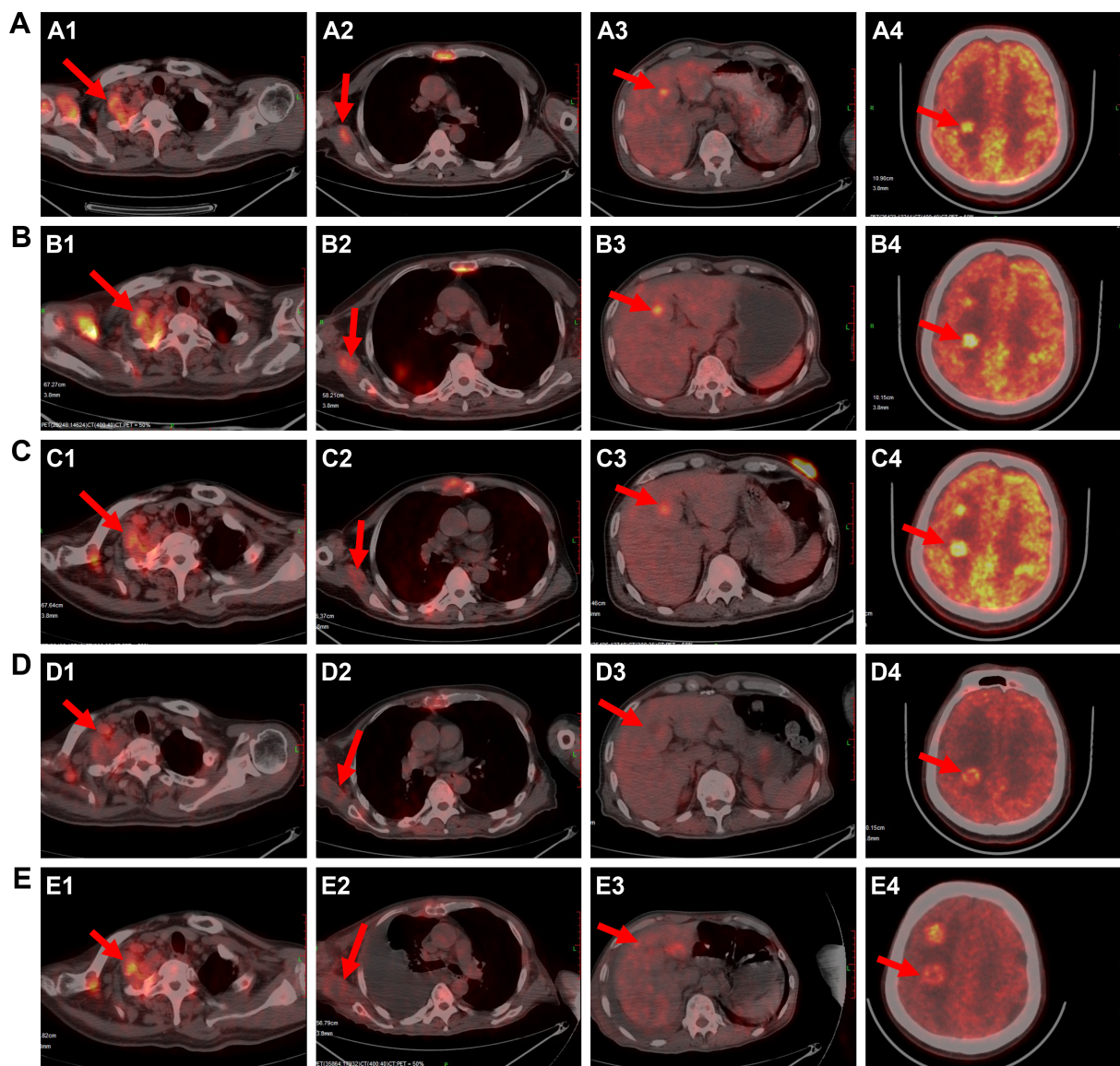


Figure 3 The dynamic evolution of the patient's primary and metastases tumors during the treatment in the PET-CT images. **(A)** Images A1–A4 were taken at the first clinic visit on August 10, 2015. The right upper chest mass was 51×41 mm, with a the maximum of standardized uptake value (SUV_{max}) of 5.6, MTV value of 28.8, and TLG value of 105 (A1). The right subscapularis muscle mass was 27×12 mm, with a SUV_{max} of 4.9, MTV value of 2.1, and TLG value of 6.4 (A2). The liver mass was 12×11 mm, with a SUV_{max} of 6.2, MTV value of 2, and TLG value of 8.2 (A3). The larger mass in the occipital lobe of the brain mass was 26×17 mm (A4). **(B)** Images B1–B4 as baseline were taken after the methylprednisolone on September 10, 2015. The right upper chest mass was 53×52 mm, with a maximum SUV value of 7.2, MTV value of 39.9, and TLG value of 174 (B1). The right subscapularis muscle mass was 27×17 mm, with a SUV_{max} value of 4.8, MTV value of 5.2, and TLG value of 15.5 (B2). The liver mass was 12×11 mm, with a SUV_{max} value of 6.7, MTV value of 4, and TLG value of 15.4 (B3). The brain mass was 27×18 mm (B4). **(C)** Images C1–C4 were taken after 1 month treatment of oral crizotinib on October 9, 2015. The size of the tumor seemed to be stable. The right upper chest mass was 44×38 mm, with a maximum SUV value of 8, MTV value of 14.2, and TLG value of 24.9 (C1). The right subscapularis muscle mass was 27×17 mm, with a SUV_{max} value of 2.9, MTV value of 4.8, and TLG value of 11.3 (C2). The liver mass was 18×14 mm, with a SUV_{max} value of 4, MTV value of 2.2, and TLG value of 6.8 (C3). The brain mass was 27×18 mm (C4). **(D)** Images D1–D4 were taken on December 10, 2015, after 3 months of oral crizotinib, and there was progressive disease in the brain. The right upper chest mass was 46×43 mm, with a maximum SUV value of 3.6, MTV value of 28.5, and TLG value of 72.5 (D1). The right subscapularis muscle mass was 28×16 mm, with a SUV_{max} value of 2.9, MTV value of 9, and TLG value of 15.5 (D2). The liver mass was 13×8 mm, with a SUV_{max} value of 1.7, MTV value of 11, and TLG value of 14.1 (D3). The brain mass was 28×18 mm (D4). **(E)** Images E1–E4 were taken on February 2, 2016, after two cycles of bevacizumab with oral crizotinib, and all tumors were increased in bulk. The right upper chest mass was 60×56 mm, with a maximum SUV value of 3, MTV value of 88.4, and TLG value of 168.6 (E1). The right subscapularis muscle mass was 42×34 mm, with a SUV_{max} value of 2.4, MTV value of 49.8, and TLG value of 73.4 (E2). The liver mass was 17×13 mm, with a SUV_{max} value of 3.5, MTV value of 13.1, and TLG value of 25.2 (E3). The brain mass was 30×19 mm (E4). The change of the tumor of the right chest wall (A1–E1). The change of the right upper arm muscle space (A2–E2). The change of the liver (A3–E3). The change of the brain (A4–E4).

Abbreviations: PET-CT, positron emission tomography coupled with computed tomography; SUV_{max} , the maximum of standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

delivery through vascular normalization.²⁵ Bevacizumab is more effective when combined with other conventional therapies, such as chemotherapy or radiotherapy, and may be added to treatment regimens to increase their efficacy

or to reduce developing therapeutic resistance.^{26,27} Several studies have demonstrated that bevacizumab could reduce brain edema and intracranial pressure, reducing the symptoms of headache or dizziness. Currently, the clinical trials

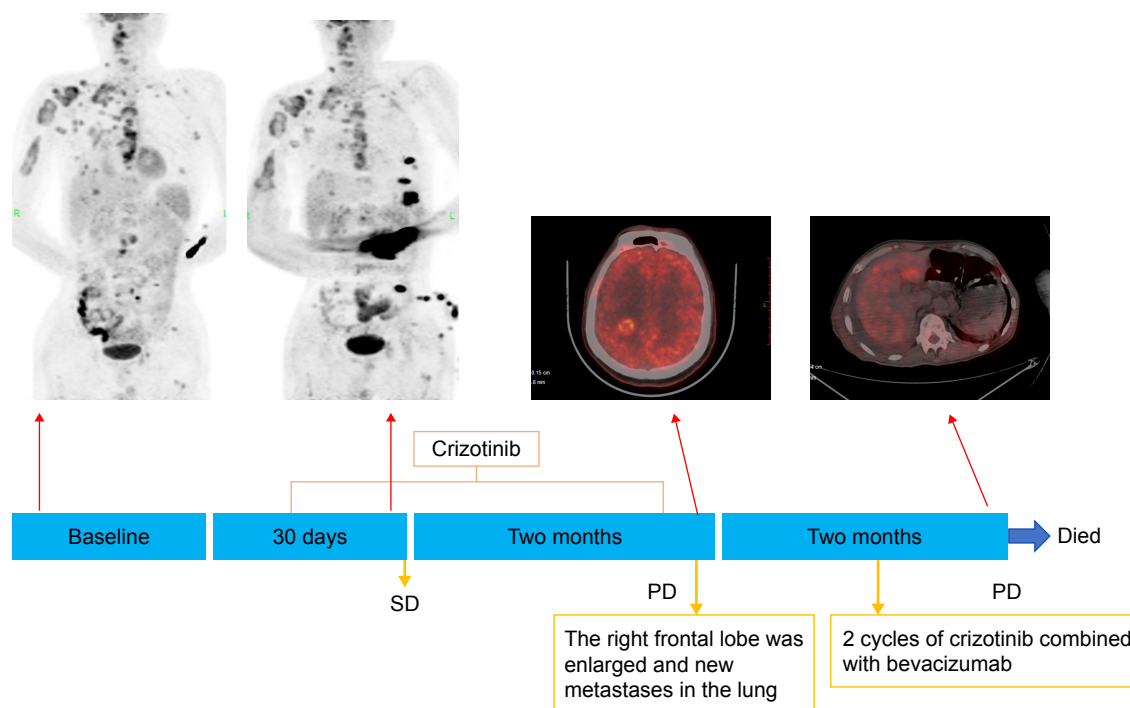


Figure 4 The clinical course of the diagnosis and treatment of the patient. On August 11, 2015, the PET-CT scan of the patient suggested right upper chest, brain, bone, liver, and right subscapularis muscle metastases. Methylprednisolone was given at 800 mg/d, d1-5, started on August 20, 2015. On September 10, 2015, PET-CT imaging showed tumor volume enlargement, and crizotinib was given at 250 mg daily. On October 9, 2015 (after one month of crizotinib treatment), PET-CT imaging showed a dramatic reduction in tumor size and metabolism, resulting in SD. (The concentrations in the left elbow and chest wall were radioccontamination.) On December 7, 2015, the brain imaging PET-CT showed that the primary tumor was enlarged, representing progressive disease in the brain, and bevacizumab (500 mg/d, d1, every 21 days), combined with crizotinib at 250 mg daily, was administered. On February 2, 2016 (after two cycles of bevacizumab with crizotinib), PET-CT imaging showed right pleural effusion, all body metastases were enlarged, and pleural cavity and peritoneal effusions could be found. Then, nutritional supportive treatment was given. The patient died in March 2016. **Abbreviations:** PET-CT, positron emission tomography coupled with computed tomography; PD, progressive disease; SD, stable disease.

of the EGFR-TKI (Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor), combined with bevacizumab, have shown good curative effects in the treatment of lung adenocarcinoma.^{28,29} So, in our treatment, when the disease progressed after oral crizotinib, bevacizumab combined with crizotinib was given. Then the headache was eased transient, but the treatment effect was unsatisfactory. Whether bevacizumab combined with an ALK inhibitor is efficacious is worth exploring.

PET-CT is not only a reference imaging tool for the diagnosis and staging of tumors, but can also reflect the metabolic status of the tumor, to be used for evaluation of efficacy and prognosis.³⁰ Currently, the prognostic information was deduced from the SUV, MTV, and TLG, which were significantly associated with an early metabolic response.³¹ Additionally, once PET-CT was used to evaluate the effects of a patient with multiple metastases, clinicians can comprehensively assess patient's condition changes. In targeted therapy, PET-CT can reflect the metabolic abilities of the cells to predict the curative effect early and adjust the treatment plan in time. At present, MTV is considered a prognostic indicator of tumor survival, being a volumetric

and metabolic biomarker of the tumor.³² Thus, unlike SUV_{max} , MTV can quantify the overall tumor burden. In some studies, higher MTV and TLG were significantly associated with shorter progression-free survival (PFS). In this case, the multiple growth of MTV may be related to the poor prognosis of the tumor.

Conclusion

Targeted therapy can be considered in the treatment of the poor KPS scores patient of advanced tumor with multiple metastases. Patients with mutated *ALK-R401* are effective in the treatment of crizotinib. However, crizotinib has low penetration into the central nervous system, patient with head metastases is responded poorly to it. Bevacizumab, combined with crizotinib, had not improved the prognosis. Bevacizumab combined with crizotinib had not achieved excellent outcome in this advanced tumor patient with head metastases. PET-CT can be used to comprehensively assess the condition of patients with advanced tumor. MTV and TLG can reflect the metabolic changes of the tumor, and the sudden increase in its value may be related to the poor prognosis of the patient.

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Disclosure

The authors report no conflicts of interest in this work.

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