

Reviewer 1#:

I hope you will publish the results of the study with more cases in the future.

Reply: We agree with you. The cases in this study from a single-Institution enrolled are not large and the collected follow-up data are incomplete, more and more complete cases are needed to further validate our results in multicenter studies in the future.

Reviewer 2#:

(1) Is there any regional specificity in the Gannan region?

Reply: Due to the molecular and genetic heterogeneity of lung cancer, there was a higher positive rate of 2.53%, which may be related to regional heterogeneity.

(2) If so, what is the impact on lung cancer?

Reply: If there is regional specificity in the Gannan region, obtaining the clinical profile of LUAD patients with co-mutations of EGFR and ALK genes in Gannan region could scientifically guide the selection of targeted drugs in similar patients, and ultimately realize personalized therapy.

(3) Is radiation effective? Please cite and discuss the following references Lung Adenocarcinoma Presenting as a Soft Tissue Metastasis to the Shoulder: A Case Report. *Medicina* (Kaunas). 2021;57(2):181. Published 2021 Feb 20. doi:10.3390/medicina5702018

Reply: The reference reports a rare case of soft tissue metastases (STMs) of the shoulder originating from lung cancer, which is intended to remind oncologists that STMs of lung cancer may resemble soft-tissue sarcomas at the time of initial diagnosis. As we know, radiotherapy is effective in relieving pain in advanced cancers including lung cancer, STMs and so on. Although we found that the co-mutations of EGFR and ALK genes in LUAD patients were more common in stage IV patients with bone metastasis, this study focused on the tyrosine kinase inhibitors selected (TKIs) and its therapeutic effect in the real world from a single institute experience, and aimed to explore the clinical profile of LUAD patients with co-mutations of EGFR and ALK genes, with hopes of scientifically guiding similar patients towards selected, targeted drugs.

(4) Are there any image characteristics?

Reply: Thank you for your good suggestion! We have added the CT images of case 6# (Fig. 3A-3J) to describe her clinical course, more intuitive, easy to understand.

(5) Is the treatment the same as for negative lung cancer?

Reply: According to the principle of staging treatment of NSCLC, follow-up data collected from six LUAD patients with co-mutations of EGFR and ALK genes in this study showed that four cases selected EGFR-TKIs as first-line treatment, which is the same as advanced NSCLC patients with EGFR 19del or L858R. Crizotinib is the first choice for advanced NSCLC patients with ALK fusion, and advanced NSCLC patients without specific oncogene mutations were treated systemically.

(6) How are the results of this study clinically effective or useful?

Reply: We retrospectively analyzed the clinicopathological features of patients with co-mutations of EGFR and ALK genes in lung adenocarcinoma. The results of this study are

that the positive rate of co-mutations of EGFR and ALK genes in LUAD patients, in Gannan region, is relatively high, and these patients prefer EGFR-TKIs as their preferred targeted drugs, but the therapeutic effect is not good. Obtaining the profile of LUAD patients with co-mutations of EGFR and ALK genes in Gannan region could scientifically guide the selection of targeted drugs in similar patients and ultimately realize individual precise treatment.