Peer Review File

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Reviewer A

Comment 1: The Authors should specify whether all the patients in the small cohort analyzed are in brain progression before ensartinib or the site of progression in a percentage of patients was different.

Reply 1: Thanks for pointing out this unclearness. The data of patients with brain metastases in this article came from a phase II single-arm multicenter clinical study in China (ClinicalTrials.gov identifier: NCT03215693)[1]. According to the inclusion criteria of the clinical trial, the progression sites of the patients in this cohort included brain metastases and lesions in other sites. In this article, patients with brain metastases were eligible if they had not undergone cranial radiation and their CNS metastases did not require steroids therapy and were asymptomatic. We are sorry to make this confusion and redescribed the inclusion criteria to make it more accurate and detailed.

References:

1. Yang Y, Zhou J, Zhou J, et al. Efficacy, safety, and biomarker analysis of ensartinib in crizotinib-resistant, ALK-positive non-small-cell lung cancer: a multicentre, phase 2 trial. Lancet Respir Med. 2020; 8(1):45-53.

Changes in the text: we have modified our text as advised (see Page 7-8, line 142-148).

Comment 2: The Authors should specify why the patients did not undergo brain radiotherapy after progression during crizotinib.

Reply 2: We thank the reviewer raising this important issue. As mentioned in the previous question, the data in this article is from a phase II single-arm multicenter clinical study. In this study, a total of 97 patients with brain metastases were enrolled, of which 34 patients had brain radiation therapy before or during crizotinib treatment

and 3 between crizotinib and ensartinib. Because radiotherapy will affect the analysis of radiomic features[1-3], we only analyzed the images of those patients who have not undergone cranial radiation in this article, which is one of the reasons for the small number of patients. We are sorry for putting this criterion in the exclusion criteria before, which caused ambiguity. Fortunately, the reviewer gave us a hint that the prognostic study of targeted therapy for brain metastases that have received radiotherapy is undoubtedly a difficult and hot spot, and we will pay attention to these patients in future research.

References:

1. Angel Moran, Megan E Daly, Stephen S F Yip, et al. Radiomics-based Assessment of Radiation-induced Lung Injury After Stereotactic Body Radiotherapy. Clin Lung Cancer. 2017;18(6):e425-31.

2. Philipp Lohmann, Martin Kocher, Garry Ceccon, et al. Combined FET PET/MRI radiomics differentiates radiation injury from recurrent brain metastasis. Neuroimage Clin. 2018 19;20:537-42.

3. Osamu Fujii, Kayoko Tsujino, Toshinori Soejima, et al. White matter changes on magnetic resonance imaging following whole-brain radiotherapy for brain metastases. Radiat Med. 2006;24(5):345-50.

Changes in the text: we have modified our text: moved the standard of " no previous cranial radiation" to the inclusion criteria (see Page 8, line 147-148).

Comment 3: The Authors should specify in the Results section clearly how many patients progressed and how many patients did not progress during the follow up period.

Reply 3: We thank the reviewer raising this unclearness. As shown in Table 1 of the results section, among the 24 patients we analyzed, 8 had intracranial progression (1 at 12 weeks after ensaratinib treatment, 1 at 18 weeks, 1 at 24 weeks, 2 at 33 weeks, 3 at 42 weeks), and 16 had no intracranial progression within one year. We have clarified this unclearness in the revised manuscript.

Table 1. Patient and tumor characteristics.

Variables	Progression group	Non-progression group	*p*
No. of Included Patients	8	16	
Mean Age (years)	51.0 (32-66)	51.4 (34-69)	0.94
Sex			0.56
female	5 (62.50%)	8 (50.00%)	
male	3 (37.50%)	8 (50.00%)	
No. of Metastases	28	59	
Mean size (cm)	1.13 (0.54-2.76)	1.19 (0.46-3.38)	0.95
Location			0.69
frontal lobes	10 (35.71%)	26 (44.07%)	
parietal lobes	2 (7.14%)	6 (10.17%)	
occipital lobes	4 (14.29%)	9 (15.25%)	
temporal lobes	3 (10.71%)	8 (13.56%)	
cerebella	4 (14.29%)	6 (10.17%)	
other parts	5 (17.86%)	4 (6.78%)	
Enhancement			0.06
whole	2 (7.14%)	14 (23.73%)	
peripheral	26 (92.86%)	45 (76.27%)	
Extent of edema			0.28
0	12 (42.86%)	34 (57.63%)	
1	8 (28.57%)	16 (27.12%)	
2	8 (28.57%)	9 (15.25%)	

Changes in the text: We added a description of this part in the results (see Page 13, line 251-254).

Comment 4: The Authors should implement the discussion with hints regarding

new approaches in radiomics analysis: the delta radiomics. This approach analyse the percentage change in two subsequent imaging, and I believe that could be really useful in this scenario, as it seems to increase the reliability of results among centers (see and cite Jeong J et al. Machine-learning based classification of glioblastoma using delta-radiomic features derived from dynamic susceptibility contrast enhanced magnetic resonance images: Introduction. Quant Imaging Med Surg. 2019 and Nardone V et al. Delta-radiomics increases multicentre reproducibility: a phantom study. Med Oncol. 2020);

Reply 4: Thanks for your constructive suggestion. As the reviewer suggested, delta radiomics could dynamically reflect tumor heterogeneity with treatment, and to some extent could lessen the impact on the scanning differences between hospitals. However, due to the small number of cases and the fact that some patients did not undergo enhanced MR scanning during follow-up, performing delta radiomics analysis would reduce the number of eligible patients, making it impossible to build an effective predictive model, we had to give up this idea temporarily and only analyzed the baseline radiomic features before treatment. We will further analyze the relationship between delta radiomic features and prognosis when more patients are included.

But we strongly agree with the reviewer's suggestion that even if the data in this article does not support delta radiomics analysis, this important new approach should be explained in the text, so we added a description about it and cited this important landmark literature (Jiwoong Jeong, Liya Wang, Bing Ji, et al. Machine-learning based classification of glioblastoma using delta-radiomic features derived from dynamic susceptibility contrast enhanced magnetic resonance images: introduction. Quant Imaging Med Surg. 2019; 9(7):1201-1213. Valerio Nardone, Alfonso Reginelli , Cesare Guida, et al. Delta-radiomics increases multicentre reproducibility: a phantom study. Med Oncol. 2020; 37(5):38.) in the revised manuscript.

Changes in the text: We added this part in the discussion of the revised manuscript (see Page 20, line 388-394 and Page 27, line 530-535).

Reviewer B

Comment 1: The small sample is a limitation as you also mention in the text, but this study is a good start. But an issue for speculation, is the 3 different imaging machines that were used in the different sites and how the results of the images of the 7 patients (GE & Siemens) are really comparable to those of the images of the 17 patients (Philips).

Reply 1: Thanks for raising this important issue. We also considered that the difference in various scanning parameters among different equipment might affect the feature values. In order to reduce this effect, we preprocessed the image with voxel resample and intensity standardization. We are sorry that the previous description was not detailed enough, and we have added explanations in the revised text. As the reviewer suggested, we will further stratified analyze the images before and after preprocessing as well as images scanned by different machines, with the increasing cases collected.

Changes in the text: we added explanations in the text (see Page 10, line 191-194).