

Peer Review File

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Reviewer A

I have thoroughly reviewed your paper titled "Negative impact of the microvascular to tumor area ratio on the response to EGFR-TKI in NSCLC with an EGFR mutation" and find your proposed insights on combining anti-angiogenic agents with EGFR-TKIs to be particularly intriguing. I concur with your suggestions because they represent a promising avenue for expanding treatment modalities.

Your work sheds light on the potential of combination therapies, offering a comprehensive approach toward enhancing treatment strategies for NSCLC patients with EGFR mutations.

Thank you for your valuable research, and I look forward to seeing its impact on future clinical approaches.

Reply: Thank you for your positive comments for our study. We will develop further research to contribute to lung cancer treatment.

Reviewer B

The reviewer is honored to review an article about the negative impact of MVR on the response to EGFR-TKI in NSCLC with EGFR mutation. This paper is unique, but there are several points to be clarified, as follows:

- 1) This paper included only 40 patients with NSCLC with EGFR mutation. The number of patients were so small that we could not draw a persuasive and definitive conclusion from this number of patients. Four types of EGFR-TKI were used in this study.

Reply: Thank you for your thoughtful comments. As you point out, the small number of patients is important limitations of this study. Additionally, this study was included 4 types of EGFR-TKIs. We investigated the use of 4 types EGFR-TKIs in low and high MVR groups and found that there were no significant differences both groups regarding type of EGFR-TKIs. However, the types of EGFR-TKIs may affect the results of this study.

Thus, we added the data in table 1 and 2, and some sentences to discussion section.

Changes in the text: Page 11, Line 222 'small number of patients were included'

Page 11, Line 226 'Third, four types of EGFR-TKIs (gefitinib, erlotinib, afatinib and osimertinib) were included in this study. In the LUX-lung 7 and FLAURA trials, afatinib and osimertinib significantly prolonged PFS compared to the first-generation EGFR-TKIs (gefitinib and erlotinib) in *EGFR*-mutant NSCLC (13, 32). Although there was no significant difference in the type of EGFR-TKI between low and high MVR groups, the type of EGFR-TKI might have affected the results of this study.'

Table1 and 2: we add data of EGFR-TKIs.

2) The title should be revised. “microvascular to tumor area” seemed a grammatical error.
Please check again.

Reply: Thank you for your comment and suggestion. As you pointed out, ‘microvascular area to tumor area’ are correct.

Changes in the text: Manuscript, Table, Figure. from “microvascular to tumor area ratio ” to “ratio of microvascular area to tumor area”

3) In table 2, The font of “II” is different. Please fix it.

Reply: Thank you for your comments. We corrected the font.

Changes in the text: Table II, Pathological stage, from ‘I-II’ to ‘I-II’

4) MVD and MVR would be known as a prognostic marker for NSCLC, which is not very new.

Reply: Thank you for your comment and suggestion. MVD and MVR were reported as a prognostic marker for NSCLC as you pointed out. Although high MVR was an independent predictive factor of PFS to EGFR-TKI in this study, the results should be interpreted with caution. This was one of the limitations of this study and we added sentences to discussion section.

Changes in the text : Page 12, Line 233 ‘Fifth, MVD and MVR were previously reported as a negative prognostic marker for NSCLC(3, 33). Although high MVR was significantly associated with shorter PFS of EGFR-TKI for *EGFR*-mutant NSCLC in this study, further study involving large cohort is needed to determine whether MVR is truly predictive factor of EGFR-TKI in patients with *EGFR* mutation-positive NSCLC.’

Reference: 33 Ge G, Zhou Q, Zhang S, Liu L, Chen J, Cheng N, et al. [Detection of micro-vascular density(MVD) and its clinical significance in lung cancer]. *Zhongguo Fei Ai Za Zhi*. 2000;3(4):284-7.

Reviewer C

Major

- Generally, EGFR mutants are more common in female non-smokers. Most of the subjects in this study were male, and a large proportion of them were smokers. Namely, this study may not represent the characteristics of common EGFR mutants. In order to resolve this issue, it is necessary to investigate a larger number of cases.

Reply: Thank you for your thoughtful comments and suggestions. As you pointed out, this study had the small number of patients, which might affect the difference of patient characteristics compared to the well-known *EGFR*-mutant NSCLC patients features such as female and non-smoker. We added following sentence to discussion section.

Changes in the text:

Page 11, Line 222 ‘this study included small number of Japanese patients and various selection biases might be existed.’

Minor

- StrataQuest used in this study is not widely popular. Please describe in more detail the benefits of using this software.

Reply: Thank you for your thoughtful comments and suggestions. As you pointed out, the evaluation of microvessels has been reportedly performed using several image analysis software. In this study, we used only Strata Quest, thus, could not clarify whether Strata Quest is better than other software. The lack of Validation with various image analysis software is a limitation in this study. We added some sentence to discussion section.

Changes in the text: Page 11, Line 231 ‘Fourth, image analysis software of MVR evaluation we employed was only StrataQuest in this study although previous studies on MVR have been used various image analysis software to evaluate MVR. It is necessary to verify the reliability and validity for MVR evaluation of each software.’

- Please add the percentage (%) of the total, following the number of cases in Table 1.

Reply: Thank you for your suggestions. We added percentages to each breakdown in Table 1.

Changes in the text: We added percentages to each breakdown in Table 1.