

## Peer Review File

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### Reviewer A

Using 1470 patient's real-world data, the authors retrospectively analyzed the clinical outcome of NSCLC patients with liver metastasis according to 1st line treatment; cytotoxic chemotherapies, targeted therapies, and immune checkpoint inhibitors (ICIs). The result showed that clinical benefits of ICIs for patients with liver metastasis, because there was no difference in overall survival in the immunotherapy group in patients with or without liver metastasis (11.7 vs. 13.0 months,  $p = 0.968$ ); however, this study does not have meaningful impact.

1. The authors mainly focused on clinical effectiveness of ICIs for NSCLC patients with liver metastasis, and concluded liver metastasis did not affect prognosis in patients who treated by immunotherapy, although only 69 (4.7%) in this dataset received immunotherapy. A lot of studies including meta-analysis have been already reported that the association between tumor metastatic sites and clinical effectiveness of immune checkpoint inhibitors. Therefore, the dataset would be inadequate to analysis the clinical effectiveness of ICIs for NSCLC patients with liver metastasis.

Reply: Thank you for your valuable comment. This study did not aim to compare the prognosis or effectiveness of various systemic treatments, but compare the effect of liver metastasis on prognosis in each treatment group. To date, it has been well known that liver metastasis is associated with poor prognosis in NSCLC; however, there has been a debate on the effects of liver metastasis in patients who have undergone immunotherapy. We found that the effect of liver metastasis in the immunotherapy group was different from that in the other treatment groups. Although there is no doubt regarding the use of TKI or immunotherapy with/without chemotherapy as first-line treatment depending on the presence of a driver mutation, we emphasized the need for certain mechanisms to be revealed wherein liver metastasis does not affect prognosis in patients who have undergone immunotherapy, which could serve as another basis for developing treatment strategies for patients with liver metastasis.

However, this study did not focus on the effectiveness of immunotherapy; therefore, the title was revised to "Different prognostic implications of hepatic metastasis according to front-line treatment in non-small cell lung cancer: a real-world retrospective study" according to the reviewer's comment. In addition, the DISCUSSION and CONCLUSION have been revised.

Changes in the text: Title, Line 218-228 P1 discussion, Line 298-302 P1 conclusions

2. Currently, personalized therapies using molecular target agents based on driver mutations have been established as a standard treatment strategy for NSCLC patients. In addition, ICIs in combination with platinum-based cytotoxic regimens were mainly used as 1st line treatment for patients with no targeted driver mutations. Therefore, comparison of cytotoxic, targeted, and immunotherapy regimens in first-line setting would be meaningless.

Reply: We appreciate your valuable comment. Recent results from various RCTs and NCCN guidelines demonstrate that TKI or immunotherapy with/without chemotherapy is commonly used as first-line treatment depending on the presence of a driver mutation or PD-L1 expression. We investigated the effects of liver metastasis on each treatment group, rather than revealing the superiority of the presence of a driver mutation or the treatment type. The reason for analyzing intertreatment prognosis was to verify from a different perspective whether the same results, which could be taken for granted, are observed in patients with liver metastasis. Although, we agree that arguing about the effectiveness of immunotherapy through this study is an overstatement because of different regimens and PD-L1 statuses in the immunotherapy group, the obtained result that liver metastasis has different effects on prognosis in each treatment group was particularly interesting. We have revised the manuscript with further details to convey our opinions more clearly.

Changes in the text: Line 218-228 P1 discussion

## **Reviewer B**

The trial is interesting as upfront treatment with immune checkpoint inhibitors has become standard nowadays. Besides, the impact of the therapy used in the IMPower150 trial (atezolizumab, besides chemotherapy plus bevacizumab) on liver metastasis has increasing the interest on this issue.

This is a retrospective, single institution trial. Both limitations are well recognized, but there is a point, quite relevant here in my opinion, that needs some consideration.

I am afraid that conclusions about the impact on immunotherapy on liver metastases were based in just 69 cases of patients with liver metastasis. I think the paper should be discussing only those 69 patients to be mentioning “immunotherapy” in the title.

Reply: We appreciate your valuable comment and agree with it. We believe that the small number of patients who received immunotherapy as first-line treatment was a limitation of this study. Since the data were collected from 2015, it is believed that the use of immunotherapy with/without cytotoxic regimen as first-line treatment according to PD-L1 expression without driver mutations was not yet

reflected in clinical practice. In addition, immunotherapy with/without chemotherapy as first-line treatment was approved in Korea at the time; however, some patients refused immunotherapy as first-line treatment due to financial burden as insurance did not cover it at the time. However, the result that liver metastasis has different effects on prognosis in the immunotherapy group was particularly interesting.

Nevertheless, this study did not focus on the effectiveness of immunotherapy, so the title has been revised to “Different prognostic implications of hepatic metastasis according to front-line treatment in non-small cell lung cancer: a real-world retrospective study” according to the reviewer’s comment.

Changes in the text: Title

Otherwise, the role of immunotherapy is diluted. Those 69 patients, if I understood properly, were treated either with chemo-immunotherapy or just immunotherapy (according to PDL1 expression I can imagine), but we do not have the figures for any of these subgroups: chemo and immunotherapy groups seem mutually exclusive as the numbers add up to 1470 exactly.

Reply: Thank you for your valuable comment. Of the 69 patients in the immunotherapy group, 30 received immunotherapy alone and 39 received combination therapy comprising immunotherapy and cytotoxic chemotherapy. Similarly, there was no difference in OS in patients with or without liver metastasis within each subgroup. We have provided this information in the revised manuscript and supplementary data.

Changes in the text: Line 146-149 P1 results, Line 167 P2 results

Same is true for the potential correlation between the presence of liver mets. and the number of metastatic sites or performance status, that are not mentioned.

Reply: Thank you for your valuable comment. An analysis of the correlation between the presence of liver metastasis and the number of metastasis sites was conducted (Figure 4). Although the effect of performance status should also be considered as per your comment, it was limited to checking the ECOG status recorded by the clinician for each patient due to the retrospective nature of this study. However, considering that patients with ECOG PS 0-1 receive chemotherapy in clinical practice, the ECOG PS in most patients in this study can be expected to be 0-1. We have discussed this concern in the revised manuscript.

Changes in the text: Line 293 P7 discussion

I don't think either that data from tumors with oncogenic drivers could be compared in terms of outcomes to patients without those drivers.

Reply: We appreciate your insightful comment. Recent results from various RCTs and NCCN guidelines demonstrate that TKI or immunotherapy with/without chemotherapy is commonly used as first-line treatment depending on the presence of a driver mutation or PD-L1 expression. We investigated the effects of liver metastasis on each treatment group, rather than revealing the superiority of the presence of a driver mutation or the treatment type. We analyzed intertreatment prognosis to verify from a different perspective whether the same results, which could be taken for granted, are observed in patients with liver metastasis. We have revised the manuscript with more details to convey our opinions clearly.

Changes in the text: [Line 218-228 P1 discussion](#), [Line 298-302 P1 conclusions](#)

Figure 2 contradicts what is written right after Point 2: "Prognosis differences according to hepatic metastasis" as in every curve (except immunotherapy of course) patients with liver mets. fared worse.

Reply: Thank you for bringing this to our attention. We have corrected the error in the revised manuscript.

Changes in the text: [Line 163 P2 results](#)

### **Reviewer C**

Myeong Guen Choi et al reported the real world data of prognostic implications of liver metastasis according to immunotherapy and other treatment in non-small cell lung cancer. Findings in this study will help the future treatment strategy of non-small cell lung cancer patients with or without liver metastasis. However, I would like to see more detail data. If detailed data is added, I believe that this study is attractive to all the oncologist as well as the readers of Translational Lung Cancer Research. My comments are listed below.

Major Comments:

1. Authors reported baseline characteristics as all patients, patients who had liver metastasis and who didn't have liver metastasis, respectively. However, author should show the characteristics as cytotoxic chemotherapy, target therapy and immune-check point inhibitors. Because overall survival in the

cytotoxic chemotherapy group was worse than former report. If author discuss about prognostic implication of liver metastasis, we want to know about more detail characteristics.

Reply: Thank you for your positive and valuable comment. We agree with your opinion. Even in patients without liver metastasis in the cytotoxic group, overall survival was 10.8 months, which was worse than that reported in previous studies. More patients with worse general condition or more underlying diseases might have been included in this real-world study than in previous clinical studies, resulting in shorter overall survival. In addition, there might be selection bias resulting from the higher number of critical patients visiting this largest tertiary center in Korea.

However, although there was a slight difference in overall survival between previous clinical studies and this real-world study according to the type of treatment, we investigated the effects of liver metastasis in each treatment group, rather than comparing prognosis among different treatment types.

In addition to the presence of liver metastasis, we have also provided baseline characteristics according to treatment types in supplementary data of the revised manuscript.

Changes in the text: Line 146-149 P1 results, Supplementary Table 1.

2. Authors reported according to cytotoxic therapy, target therapy and immune check point inhibitor. However author should distinguish the result for EGFR-TKI, ALK-TKI or others. Moreover, recently non-small cell lung cancer patients can receive the immune checkpoint inhibitor monotherapy or Immune check point inhibitor with cytotoxic chemotherapy. Author should report each treatment result.

Reply: We appreciate your valuable comment. There were 607 patients with EGFR-TKI, 67 patients with ALK-TKI, and 4 patients with other-TKI in the targeted therapy group. In both EGFR and ALK-TKI subgroups, OS in patients with liver metastasis was significantly worse. Meanwhile, of the 69 patients in the immunotherapy group, 30 received immunotherapy alone and 39 received combination therapy comprising immunotherapy and cytotoxic chemotherapy. Similar to the immunotherapy group, there was no difference in OS in patients with or without liver metastasis within each subgroup. We have provided this information in the revised manuscript and supplementary data.

Changes in the text: Line 146-149 P1 results, Line 167 P2 results, Supplementary Figure 1.

**Reviewer D**

In this retrospective study, overall survival was compared among metastatic sites or treatment strategies. The study showed that liver metastasis is a poor prognostic factor and that immunotherapy could ameliorate the poor prognosis. There are some unclear points in this manuscript showed below.

Majior

1) The immunotherapy group included patients who received either immunotherapy alone or the combination of immunotherapy and cytotoxic chemotherapy. The combination of immunotherapy and chemotherapy is the integrated category of the chemotherapy group and immunotherapy group. It is hard to consider this combination as immunotherapy group.

Reply: Thank you for your valuable comment. Of the 69 patients in the immunotherapy group, 30 received immunotherapy alone and 39 received combination therapy comprising immunotherapy and cytotoxic chemotherapy. Similarly, there was no difference in OS in patients with or without liver metastasis within each subgroup. We have provided this subgroup analysis of the immunotherapy group in the revised manuscript and supplementary data.

Changes in the text: Line 146-149 P1 results, Line 167 P2 results, Supplementary Figure 1.

2) Combination therapies of immunotherapy and chemotherapy are newly approved treatments. If immunotherapy group included majority of combination therapies, new therapies might affect OS results.

Reply: We agree with your comment. The patients who received combination therapy accounted for 56.5%. Although there was no significant difference between patients who had undergone immunotherapy alone and combination therapy, we believe that it is necessary to investigate the concerns you mentioned through further large-scale studies. We have discussed this concern in the revised manuscript.

Changes in the text: Line 281-290 P6-7 discussion

3) Treatments with bevacizumab are known to improve NSCLC with liver metastasis more than immunotherapies. Authors did not show any data of bevacizumab treatment.

Reply: We appreciate your valuable comment. There has been a debate on the effects of liver metastasis in patients who have undergone immunotherapy. We found that the effect of liver metastasis in the immunotherapy group was different from that of the other treatment groups. We have referred several studies that have reported results similar to those of our study, for example, the study of atezolizumab in combination with bevacizumab reported similar results and a potential underlying mechanism. We

emphasized the need for exact mechanisms to be revealed, wherein liver metastasis does not affect prognosis in patients who undergo immunotherapy, through these references. Of patients included in our study, only two patients received bevacizumab. We have revised the manuscript to convey our opinions more clearly.

Changes in the text: Line 254-257 P4 discussion

4) PFS is not appropriate for retrospective studies because tumor evaluations are not performed at the same intervals.

Reply: Thank you for your valuable comment. We agree with your comment, so we presented this analysis as supplementary data other than the main figure. Although the results might be inaccurate due to the difference in the intervals of disease evaluation, they were obtained from real-world data with a long-term follow-up period, which resulted in the occurrence of progression in most patients.

Minor

P7 Line1~3: 'In the cytotoxic chemotherapy group and the targeted therapy group, the OS of patients with liver metastasis was longer than that of patients without liver metastasis'  
longer than -> shorter than

Reply: Thank you for pointing this out. We have corrected the error in the revised manuscript.

Changes in the text: Line 163 P2 results

## **Reviewer E**

I read with attention the manuscript entitled " Different prognostic implications of hepatic metastasis according to immunotherapy in non-small cell lung cancer: a real-world retrospective study", authored by Choi et al., submitted to Translational Lung Cancer Research to be considered for publication as an Original Article. In this manuscript the authors aimed to verify the effects of liver metastasis on the prognosis of metastatic non-small cell lung cancer patients according to their first-line treatment. As presented, in my opinion, this manuscript needs some clarification/corrections to be accepted for publication in Translational Lung Cancer Research.

INTRODUCTION

1.Line 68-69: I suggest removing the following sentence: Bone is the most common metastatic site, followed by the pleura, lung, brain, and liver in patients with NSCLC (11,12).

Reply: We appreciate your valuable comment. We agree with your comment and accordingly deleted unnecessary sentences in the revised manuscript.

Changes in the text: [Line 75-76 P1 introduction](#)

## METHODS

2. Line 110: I suggest removing the following sentence: The exclusion criteria were stage 1, 2, or 3 NSCLC patients. The authors specified that only stage 4 was included.

Reply: Thank you for valuable comment. We agree with your comment and accordingly deleted unnecessary sentences in the revised manuscript.

Changes in the text: [Line 118 P3 methods](#)

3. Statistical analysis: Which p value was considered to perform the multiple analysis?  $P < 0.05$ ? Include in the text.

Reply: Thank you for your valuable comment. We used the t-test and Chi-square test for comparing baseline characteristics, log-rank test for comparing OS and PFS, and Cox-regression analysis for obtaining hazard ratios. We have mentioned this in paragraph 4 of the METHODS of the revised manuscript. Further,  $p\text{-value} < 0.05$  was considered statistically significant.

## Discussion

4. Limitations: Emphasize that only 11 patients with liver metastases underwent immunotherapy.

Reply: We appreciate your valuable comment. We have added further details in the revised manuscript.

Changes in the text: [Line 274-281 P6 discussion](#)

## CONCLUSIONS

5: I suggest that the conclusion only answer the objective of the study. The small number of patients with liver metastases who underwent immunotherapy does not allow further suggestions. Further studies need to be carried out.

Reply: Thank you for your valuable comment. We agree with your comment and have accordingly revised the CONCLUSION.

Changes in the text: [Line 298-302 P1 conclusions](#)