**Author’s response to reviews**

**Title:** Survival of patients receiving systematic therapy for metachronous or synchronous metastatic renal cell carcinoma: a retrospective analysis

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Authors’ Reply

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Survival of patients with meta/synchronous metastatic renal cell carcinoma receiving systemic immunotherapy vs. targeted therapies: a retrospective analysis

Reply to Yona Keisari’s comments

We thank Yona Keisari for the precious time spent reviewing our manuscript, and for the following valuable comments.

1. This is a well-executed study and written report.

Response: Thank you for this comment.
2. The report claims that TT is superior to IT when PFS is the clinical outcome measured.

Response: The study showed that the difference in OS was not significant, whereas PFS was significantly different between the two treatment modalities.

3. The authors compared the effect of TT and IT on overall survival and the results are not conclusive. In most of the comparisons IT had a beneficial effect compared to TT. Thus, it can be concluded that TT is better for PFS while IT might be better for extending survival. It seems that these two effects do not match and there is no attempt in the manuscript to discuss what seems as a discrepancy.

Response: Thank you for these comments. The immune checkpoint inhibitor led to significantly better survival outcomes than did TT, whereas the cytokine in this study did not have any significant difference from TT (or it had an insignificantly shorter overall survival than that of TT). Except for some patients with long-term use of high-dose IL-2, there was a trend where most patients treated with TT had better survival than patients treated with cytokines. Some retrospective studies, including the present one, had an inherent selection bias that showed cytokine or immune therapy led to better survival than did TT because there were patients who also received second-line-after TT after first-line cytokine therapy. We have added the following sentence to the Discussion (page 9, lines 20-23):

“However, the survival benefit from IT should be considered carefully, because the IT group included patients who benefited from TT, and their follow-up periods were significantly longer than those of TT patients (data not shown)”.

Therefore, we agree with the reviewer’s comment and we have added a sentence to the Discussion section explaining that TT is better for PFS, while IT might be better for extending survival (page 9, lines 19-20).

4. The final conclusion "Dividing patients into specific subcategories helps to better predict therapeutic outcomes" is important but not sufficient without a more profound analysis and explanation of the results.

Response: Thank you for this comment. We are preparing to perform further analysis in a future study to identify additional risk factors affecting patients classified with a more detailed subgroup classification, according to the prognostic outcome. The goal is to help the current classification system to better predict the prognoses of mRCC.
Reply to Jeanette Eckel-Passow’s comments

We thank Jeanette Eckel-Passow for the precious time spent reviewing our manuscript, and for the following valuable comments.

#1. When comparing survival across treatment groups using a retrospective design, the analysis must correct for the probability of receiving a particular treatment (e.g., propensity score adjustment).

Response: This study aimed to compare survival outcomes (PFS and CSS) of IT and TT in both SM and MM. We also confirmed the PFS and CSS of subgroups divided by the TFI (≥1 year and <1 year) and Heng risk classification. As shown in Table 2, IT and TT were received by respectively 89 and 55 in the SM group and 37 and 33 in the MM group. Matching according to treatment requires the consideration of subject loss, and the reduction in sample size due to missing values for covariates used for matching (such as stage) decreases the statistical power. Accordingly, we did not use a method like propensity score matching. We have modified the text to better explain the limitations of this study, and we have added some suggestions regarding propensity-score matching to better to clarify our prognostic comparisons between the two therapeutic modalities (page 11, lines 22-25).

#2. Introduction states that TT has cancer-specific survival rates of 13-16 months; assuming this is a typo?

Response: We apologize for this error. We have corrected the value of CSS in the Introduction section (page 4, line 4) and added a new reference (line 5):

“TT produces improved prognosis, with an observed median cancer-specific survival of 29.5 months, and has markedly extended progression-free survival (PFS) intervals [Cancer Treat Rev. 2016 Nov;50:109-117].”


#3. There is no justification for using TFI<1 year. Also, what if a patient was censored prior to the 1 year threshold?

Response: The risk factor of TFI < 1 year is a well-known risk factor for mRCC from the MSKCC risk criteria. We used TFI < 1 year as a risk factor in this study because it is not only a critical decision point for choosing between the synchronous type and metachronous type of mRCC, but also a significant factor in predicting poor survival prognosis. similar to synchronous
type when the TFI < 1 year even in metachronous mRCC. We have added a sentence to the Methods section explaining the 1-year TFI duration (page 6, lines 5-7).

#4. Methods: Patients were excluded if they had incomplete medical records; incomplete with respect to what? Similarly, the methods states that patients were excluded if they had disease progression, yet progression free survival was analyzed. Additionally, were none of the patients predicted to be low risk by the Heng criteria?

Response: We have clarified the exclusion criteria in the Methods section. We excluded patients with incomplete medical records, those who stopped treatment prior to therapeutic response evaluation, or those for whom we were unable to detect PFS due to therapeutic interruption. We also clarified the meaning of disease progression. Specifically, we excluded patients who discontinued therapy due to disease progression before the end of the first cycle of therapy, before the first-line therapeutic response could be evaluated. Therefore, we changed the phrasing as follows (page 5 lines 21-24):

“…those with incomplete medical records of their survival prognoses, patients who discontinued therapy before the first-cycle therapeutic response was evaluated owing to disease progression, and those <20 years of age.”

There were no patients with favorable risk in the Heng risk criteria because of the comparative design of survival prognoses between SM and MM. Most of the MM group comprised favorable-risk patients, whereas only one favorable patient was in the SM group. The SM group mostly comprised either intermediate- or poor-risk patients, and so the favorable-risk patients in the MM group were excluded.

#5. Table 1 and Table 2: Sex is the correct term to use vs gender? Overall survival is not the same as cancer specific survival, which did the authors use? Incorrect to state how many patients "survived" as this does not account for censoring. However, appropriate to state how many events there were and likewise, follow-up duration for patients who have not experienced an event.

Response: Thank you for these remarks. We have changed “sex” to “gender” in the Tables and Results section (page 7, line 19).

Overall survival and cancer-specific survival are different terms; however, the statistical analysis showed that the overall survival outcome and cancer-specific survival outcome were the same for the patients with intermediate- and poor-risk mRCC in this study. This finding is similar to that of Heng et al., who reported that the poor- and intermediate-risk groups had less than two years of survival. We changed the term overall survival to cancer-specific survival to
clarify the results of our analysis in the revised manuscript, and we added a sentence explaining the equivalence in survival outcomes between CSS and OS obtained in this study (page 9 lines 12-13).

#6. Figures 3 and 4: Not appropriate to look ahead in time (aka, use TFI) to group patients and then go back and look at survival.

Response: We analyzed PFS and CSS in this study. The survival duration was defined as the time from the first treatment until the specified event (death due to cancer/progression). Since treatment-free interval (TFI) was defined as the period from diagnosis to treatment, there was no problem in dividing the groups by TFI and analyzing their survival accordingly.

In addition, 1-year cut-off point of TFI is a well-known risk factor for prognosis of mRCC, as described by the MSKCC and Heng risk criteria of mRCC.

Other changes:

1. We have changed “OS” to “CSS” (pages 5-12).