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

Replies to the Technical Editor’s comments

1. On the title page, please include the email addresses for all authors. The corresponding author should still be indicated. Please also ensure these email addresses match the email addresses provided in the editorial manager system.

Response: We added all of the authors’ e-mail addresses on the title page (page 1 lines 11-18)
2. In the Authors’ contributions section, the individual contributions of each author should be specified. Please use initials to refer to each author’s contribution in this section.

Response: We specified each author’s role in the Authors’ contribution section. (page 17 lines 343-347)

3. Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file. They should be placed after ‘References’ under the heading "Figures, tables additional files".

Response: Thank you. In the revised manuscript, we provided this material at the location that you requested. (page 22-23)

4. Please add a heading "Additional files" after your list of figure legends. In this section, please include your supplementary figure legends as well as a description.

Response: We added the requested heading and content. (page 22-24)

5. The reviewers have requested for English language editing for the paper to be suitable for publication. Please copyedit the paper with a native English speaker before revision is submitted. If this is not possible, you may need to use a professional language editing service. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

Response: Our revised submission has been edited by a native speaker of English who works for the Editage professional editing service (EDITAGE.co.kr).”

Thank you for your technical comments on our manuscript.

Replies to Jeanette Eckel-Passow’s comments

We thank Dr. Eckel-Passow for the valuable time that she has spent reviewing our manuscript, and for the following helpful comments.

1. It would be informative to include a supplementary figure that shows how many patients were identified and then subsequently excluded due to each of the listed exclusion criteria.

Response: Per your suggestion, we added a flow chart showing patient exclusions (Supplementary Figure 1). The revised manuscript text also provides a more detailed discussion
of the criteria used for including and excluding patients with mRCC from the prospectively recorded National Center Center RCC registry (page 6 lines 101-page 7 line 111).

A brief summary of the exclusions is given below:

- Incomplete follow-up medical records (beyond the prospectively recorded National Center Center RCC registry)
- Refused to receive systemic therapies after having the adverse events explained
  - Stopped medication because of financial expenses
  - No therapeutic effects expected
- Excluded because of missing of data (N=19)
  - Records were missing for all risk factors
  - Missing treatment method
- Excluded according to patient criteria (N=64)
  - Under 20 years of age
  - Favorable risk group, according to the Heng risk criteria
  - Patients whose progression occurred within 1 month of treatment

2. When calculating, comparing, and discussing follow-up duration, data should only be utilized for patients who have not had an event. Importantly, two endpoints are discussed in the paper: PFS and CSS. Thus, follow-up time will be endpoint specific. When discussing follow up duration throughout the manuscript, please specify whether it is respect to CSS or PFS. Additionally, while the methods have been revised, it is still not clear whether patients who died of cancer were included in the calculations. In the tables, it is similarly not clear exactly what follow up duration refers to since both PFS and CSS are described.

Response: Median follow-up was calculated in 3 different ways. In the first method, we calculated the median follow-up using all patients. This has the advantage of including data from all patients, but has the disadvantage that it is directly affected by the times of events observed. In the second method of calculating median follow-up, the analysis used censored patients or survivors. However, this method discards information because it excludes patients with events. It also provides unstable estimates when a small number of patients survive. In the third method of
calculating median follow-up, we applied the reverse Kaplan–Meier estimator (Schemper and Smith, 1996), which evaluates follow-up from a Kaplan–Meier analysis in which the events of interest are reversed such that deaths are censored and being alive is used as the event of interest. This method provides robust estimates and we view it as being better than either of the other two options. The reverse Kaplan–Meier method was used for the final results shown in our manuscript.


3. Tables 1-2: It is unclear what "survival and death due to non-cancer" means. Death due to non-cancer is not an event in CSS. The cancer specific survival status can be removed; or, simply state how many died due to cancer. The rest of the patients should be described by how much follow up information is available.

Response: We modified “survival status” to “CSS status” in Table 2. In the CSS analysis, only death due to cancer was considered as an event. Two patients for whom the cause of death was unknown were analyzed as censored records.

4. Table 3: It is interesting that metastatic type has p=0.0006 in univariate analysis but is not significant in multivariable analysis. Was this evaluated further to determine why? Is it correlated with another variable in the multivariable model?

Response: As shown in Table 2, we can confirm that there was a significant association between treatment-free interval and metastatic type. Because the two variables are related, we excluded from the regression analysis to avoid multicollinearity in the multivariable model. We added a sentence in the Discussion section that notes this (page 15 lines 303-306):

“In addition, because of multicollinearity between TFI and metastatic type (SM vs. MM), metastatic type was not a significant prognostic factor in the multivariable analysis, even though it had been significantly prognostic in the univariable analysis.”

5. The Discussion section mentions OS a couple of times; however, OS was not evaluated. Please edit.

Response: We edited OS and changed it to CSS at all locations in the manuscript. Thank you.
6. The Discussion sections makes comments regarding analyses that were not significant, please edit appropriately. For example, "...the latter showed similar or better CSS..." Equivalence analyses were not performed and thus similar cannot be concluded. Similarly, if the analysis did not show a significant difference, "better" cannot be concluded either. As another example, "One interesting finding was that IT tended to improve PFS and CSS rates in poor risk patients in both the SM and MM groups, but not significantly". What does this mean? Please edit all such remarks to reflect the observed results.

Response: We changed the ambiguous sentences to match our statistical results. We also emphasized the potential advantage of the use of IT in light of our CSS results (page 13 lines 252-257) and added some additional commentary on nonsignificant associations for poor-risk patients (page 15, lines 303-306).

7. The Discussion sections states that a limitation is short follow-up periods; however, all but 14% of the patients died. Thus, there appears to be plenty of follow up. What are the authors trying to imply?

Response: We were attempting to state that additional follow-up time would provide a larger number of outcome measurements for those who were alive at the study endpoint. We replaced the word “short” with “the different follow-up periods in the compared subgroups” (page 16 lines 309-310) to emphasize that having similar durations of follow-up for the compared subgroups would have been preferable.

Replies to Sophie Gourgou’s comments

We thank Dr. Gourgou for the valuable time that she spent reviewing our manuscript, and for the following helpful comments.

1. The main bias of this paper is the comparison of 2 treatments without randomisation in 2 subgroups of treatment. So, a sub-group analysis was proposed (Table 2 and figures) due to different medical history of patients and justified by logical different median follow-up between synchronous and metachronous patients.

Response: As the reviewer has suggested, we performed multivariate analyses of PFS and of CSS, including metastasis subgroup (SM vs. MM). We reorganized the previous Table 3 into two separate tables (Table 3 and Table 4), including results for PFS and CSS.
2. In table 2: The median follow-up data (performed with the reverse KM method) are discordant with respect to the presented CSS data (50% of the patients died at 9 and 21 months in SM and MM respectively, with a median follow-up of 81 and 142 months), this data seems strange.

Response: The median follow-up times are not inconsistent in light of the prognostic characteristics of the SM and MM groups. The MM group including patients with no primary tumor originating in the kidney, and were mostly classified as either favorable or intermediate risk. Accordingly, the MM group had better survival than the SM group, which included patients with primary tumors originating in the kidney and higher tumor burdens. As compared with the MM group, the poor-risk SM group had much shorter survival times and the favorable-risk SM group had much longer or similar survival times. Therefore, the follow-up time was reasonable.

3. In the cox model presented in Table 3, univariate and multivariate cox model including subgroups with different follow-up; so the estimated effect-size of treatment if biased and the subgroups SM/MM is not identified as independent prognosis parameter which would lead to disregard for the rest of the analysis.

However, it is clear the sub-groups are justified to evaluate the impact of treatment in each of them.

This multivariate result is discordant to explain the methodology and need to be explain. I suggest a multivariate prognosis model for each sub-group of patients (SM and MM).

Response: Thank you for the comments. We changed Table 3 to provide results for each sub-group of patients (SM and MM), as you suggested.

4. In addition, comparison between TT and IT is biased in each sub-group of patients (metachronous or synchronous) because of no randomisation. To compare the trt TT vs IT, it will be appreciate to know the median follow-up of patient by treatment group to estimate the bias for comparison.

Indeed, if you observe the subjects for a shorter time, you are less likely to observe the event of interest and we can wrongly conclude that there is a difference between TT and IT. The use of the propensity score method will be appreciated as complementary analysis to conclude for the comparison of 2 treatments as discussed by the authors. These results must be presented in order to be able to interpret and measure the sensitivity between the presented biased analysis and the analyses using the propensity score.
Response: Thank you for the comments. As you have mentioned, the SM and MM groups and the IT and TT groups have different underlying characteristics, and between-group comparisons might result in different outcomes because of the different follow-up times. The propensity score matching method is one of the methods that could be used to compensate for this selection bias, and to equalize the differences. Another method to address some of the issue of selection bias would be to perform a study with a prospective design. However, because SM cases are rarer than MM cases, it would require considerable effort, monetary expenses, and time to match the groups 1:1, and the propensity score methods require a large number of samples to obtain matched pairs.

We think that the results of the present study remain important, even though they are limited by the possibility of selection bias and differences in characteristics between groups. In particular, we think that it is clinically relevant to compare groups of mRCC patients using retrospective samples, in order to obtain a general assessment of the patterns of therapeutic outcomes. In response to your remarks, we added some text at the end of the Discussion section, in which we recommend the use of a prospective study design and propensity score matching to evaluate differences between metastasis types and systematic therapies according to risk criteria and treatment-free intervals (page 16 lines 315-319).

5. L103 : TFI definition is not clear: Heng score defined as from time of diagnosis to systemic therapy. Why is it not the same definition?

Response: The TFI definition was corrected (page 7 lines 117-118). Thank you for noticing the error.

6. In the Statistical analysis section :

L132 : please clarify PFS and CSS definitions separately with each event of interest and date of point.

Response: As requested, we provided separate explanations of the PFS and CSS definitions in the Statistical analysis section (page 8, lines 143-147).

7. In the figures :

To evaluate the level of evidence of the data described, it is necessary to add in the figures the number of patients at risk in each of the subgroups.

Response: We added the numbers of patients at risk in each of the subgroup figures.
8. x-axis legend is confused with "first-line TT time" : TT for treatment ?? or for Target Therapy ???. It is expected to have "first line treatment time" in order to match the 2 compared treatments. If it is not the case, please clarify.

Response: We relabeled the x-axes with “Time (months)” to denote the follow-up time after first-line treatment was started.

9. Table 1:

Put capital letters on each title variable

Modify the modalities for cancer specific survival status:

Survival >> Alive and death due to non-cancer =32 (I don't understand survival, is it ALIVE)

Response: We modified the Survival prognoses and added capital letters for each title variable.

10. Table 2:

Age (years) (add the range)

Response: We added the range of “Age” in Table 2.

11. Table 3:

Justify the reason of sample size decrease N=214 >> 207 (PFS)

Justify the reason of sample size decrease N=214 >> 202 (CSS)

/ due to missing data for variables?

Response: We corrected Tables 3 and 4, for which the total number of patients is indeed 214. There was no missing data.

Other changes

1. We changed the title of the manuscript as follows: (page 1 line 1-2)

“Survival of patients receiving systematic therapy for metachronous or synchronous metastatic renal cell carcinoma: a retrospective analysis”
2. We corrected minor grammatical errors and typos at a variety of locations in the manuscript.