Reviewer’s report

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

Version: 1 Date: 20 Jun 2018

Reviewer: Jeanette Eckel-Passow

Reviewer's report:

Summary

The major concern with the paper remains the lack of utilization of appropriate statistical analysis methods for retrospective designs that compare treatment modalities. When using a retrospective design the analysis must account for factors that might have influenced a clinician's decision to treat a patient with IT versus TT. For example, were younger patients more likely to have received IT versus TT? Similarly, was KPS influential in determining which treatment a patient received? Relevant variables should be included in the survival analysis as covariates, as a propensity score or other relevant method that adequately adjusts for the probability of receiving a particular treatment.

Major Comments

* While TFI and time zero for the survival analyses (i.e., time from first treatment) are defined in the response letter, they are not defined in the manuscript. Please add these details to the manuscript.

* The response letter states that favorable-risk patients were excluded; however, this was not discussed in the methods section.

* The methods section states that patients with incomplete medical records of their survival prognoses were excluded. As stated previously, these patients should be included in analyses and censored at their last known follow-up date. Similarly, using an intent-to-treat design, patients who discontinued therapy before the first-cycle response was evaluated due to disease progression should also be analyzed. Or, at a minimum, an intent-to-treat analysis should also be conducted.

* When calculating and comparing follow-up duration, data should only be utilized for patients who have not yet had an event. It is not appropriate to include patients who have had an event when calculating and comparing follow-up.
* P-values should be provided in any sentence where the authors compare PFS or CSS across groups.

* When p-values are presented, it is not clear what comparison the p-values refer to. For example, please see the 3rd paragraph in the results section. The first sentence provides data comparing SM vs MM in parentheses; however, the p-value at the end of the sentence denotes a comparison of IT to TT. Such sentences need to be revised so that it is clear what comparison each p-values denotes.

* Instead of stating p<0.05 or p>0.05, please provide the actual p-value.

* The first paragraph of the discussion section states that the IT group included patients who benefitted from TT. More information regarding prior treatments is necessary and would be informative to include in Table 1.

* Table 1 would be more reader friendly if a row was utilized for each level of a variable. Also, for any variable that includes censoring, median (min-max) is not appropriate. These should be presented as median and 95% CI. Please see comment above regarding follow-up duration. Same comments hold for Table 2.

* Figure 2 does not appear to be labeled correctly and is confusing. Are panels A and B supposed to denote intermediate risk, and panels C and D high-risk? If so, please label similarly to panels E-H.

* If TFI is one of the variables in the Heng risk model, why is it evaluated again by itself? And if TFI is being evaluated, why not similarly evaluate the other variables that comprise the Heng model?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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