Reviewer's report

Title: RASSF1A protein expression and correlation with clinicopathological parameters in renal cell carcinoma

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Reviewer: Alex Sgambato

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Ms. Title: RASSF1A protein expression and correlation with clinicopathological parameters in renal cell carcinoma by Hossein Tezval et al.

In this study the Authors analyze the immunohistochemical expression of RASSF1A protein in a series of renal cell carcinomas (RCC) and report an association between RASSF1A expression levels and several clinicopathological parameters in clear cell RCC. Overall the Results suggest that while expression of RASSF1A tend to decrease in cancer cells compared to normal tissues, RCC tumorigenesis without depletion of RASSF1A may be associated with an adverse clinical outcome.

The study is potentially of interest. However, several flaws need to be taken care of in order to improve it.

Major Compulsory Revisions

1. It is not clear from the Abstract as well as from the Results and Table 2 in which direction is the association between RASSF1A immunopositivity and other pathological parameters (i.e., high protein expression is associated with low or high pT stage?).

2. In the MATERIAL AND METHODS section in the paragraph Patient characteristics and follow up the Authors state that: “Survival analysis was carried out for 187 selected patients with pathologically proved clear cell carcinoma of RCC…..”. It is not well clear how those cases were selected. Moreover, it is not clear whether all the 318 cases were clear cell-RCC or not.

3. In the same paragraph, the Authors also state that: “Seventeen patients demonstrated metastasis at the time of diagnosis…………….”. however, 35 patients (out of 187) are indicated as M1 in Table 1.

4. In the RESULTS section in the paragraph Expression of RASSF1A protein it is not clearly indicated whether analysis was performed on all 318 cases or only refers to the 187 clear cell-RCC. In the former case, it is extremely important to know whether all tumors were clear cell-RCC or not.

5. In the same paragraph, the Authors state that: “In tumors a mean positivity of 19% (median 11%) was detected…….” but they do not mention how much it was in normal cells.
6. Survival analysis was carried out using the cut-off value of 25% positive cells. As the Authors mention, 85% of tumors exhibited a RASSF1A labelling index of 25%. Thus, the two groups are numerically very different and this might have biased the statistical analysis.

Discretionary Revisions
1 Manuscript should be checked throughout for English.
2 The thoughts regarding VHL pathway at the end of the DISCUSSION are not well integrated with the findings of the study.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests