ANSWERS TO REVIEWERS

The authors appreciate the comments and suggestions about the manuscript. The specific answers are listed below.

Sincerely yours,

Aloisio Felipe-Silva, MD, PhD (corresponding author)

First Reviewer's code: 02841861

Reviewer: "This manuscript is mainly about assessing the immunohistochemical expression of some protein products of genes related to the pathogenesis of HCC. The paper was well written, I just have one question to the authors, Why they chosen these makers? are they enough to classify the different grade of HCC? I suggest the authors add this in the manuscript, so our readers could get the idea."

Answer: The twelve immunohistochemical markers used in this study are highly representative of the major molecular pathways described in HCC elsewhere. Our data in a large autopsy series of mainly advanced cases support the principle that histological grade and cellular proliferation index are related to these pathways. Further studies are necessary to test whether a panel of immunohistochemical markers could be used to subclassify HCC samples of the same histological grade, as discussed in the revised manuscript.

Second Reviewer's code: 02438768

Reviewer: "This is a well conducted study; and the experiments are described in detail. There are no major and few minor concerns. Regarding the latter, immunohistochemical markers were divided into two groups in this paper, I wonder what the basis of the author's grouping is. In addition, the format of this manuscript should be revised according to WJG's requirement."

Answer: The markers were divided according to their positive or negative association with histological grade and cell proliferation as described in the text. Interestingly, these groups were enriched in markers reported to be related with different molecular profiles in the literature, especially the "progenitor cell" feature in group 1, which was characterized by higher expression of K19, p53, ERK1, ERK2, vimentin and nuclear B-catenin. The format of the manuscript was also revised.