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To the Editors
World Journal of Gastroenterology

Manuscript NO: 40578
Title: The Dimensions of Hepatocellular Carcinoma Phenotypic Diversity
Manuscript Type: Minireview

Dear Editors,

We are very grateful to you and to the reviewers for critical appraisal and constructive comments on the manuscript. We are therefore submitting a revised version which takes into account the comments of the reviewers and complies with the Editor's requests. Changes introduced to the manuscript are highlighted in red. What follows is a point-by-point response. Each response is introduced by an *arrow* (→) after citation of the respective question or comment.

Reviewer's # 1 comments: Accept

Reviewer's # 2 comments: Minor Revision

1. *"Aim was not clear. Merits of classification were not clear. It would be better to discuss the rationale of presented classifications, such as useful to predict prognosis, determine treatment strategy"* → We thank the reviewer for these comments. We have accordingly introduced the following phrases, to clarify aims, merits of classifying HCCs (prognosis and choice among therapeutic options) :

   Abstract: *… patient management is currently based upon tumor number, size, vascular invasion, performance status and functional liver reserve. Nonetheless, an impressive body of molecular evidence emerged within the last 20 years and is becoming increasingly available to medical practitioners and researchers in the form of repositories. Therefore, the aim this work is to review molecular data underlying HCC classifications and to organize this corpus into the major dimensions explaining HCC phenotypic diversity.*

   Introduction: To the paragraph addressing systemic therapies, we added locoregional therapies, which are indicated in specific subgroups of HCC patients and in whom more refined classifications will help in the future to make a more precise choice : "Importantly, HCC patients presenting beyond transplant or resection eligibility may benefit from locoregional therapies [(tumor ablation,

transarterial chemoembolization (TACE) and radioembolization with yttrium-90 microspheres (Y90)], according to recent Clinical Practice Guidelines.[1] Whereas tumor ablation is recommended as a first-line therapy for early-stage HCC;[1] TACE has been recommended for intermediate-stage HCC.[1] Y90 has been investigated as an alternative to TACE, with a good safety profile in delaying tumor progression[2] and has been proposed as a treatment of choice for down-staging HCC patients as a bridging strategy toward liver transplantation.[3] However, Y90 has not shown overall survival benefit over sorafenib in intermediate and locally advanced HCC patients after unsuccessful TACE.[1, 4]".

Conclusions and Future Perspectives: we added a discussion on how HCC classifications will probably evolve, taking into account the clinical aspects of the natural history of HCC and the particular anatomy of the liver. Therefore, we outlined the expected progress resulting from the integration of molecular data with MRI texture analysis. "It is however important to bear in mind three major features in the natural history of HCCs. First, these tumors arise in more than 80% of the cases in severely fibrotic livers, with impaired liver function. Second, HCCs show high intra-tumor heterogeneity[5, 6] despite a limited number of trunk mutational events.[7] Third, despite their metastatic capacity, HCC may develop locally advanced disease given the vascular anatomy of the liver. The natural history of HCC explains why tumor diagnosis, staging and treatment allocation is based upon tumor size and number, vascular invasion, location with respect to main vascular structures, underlying functional liver reserve and patient's performance status. As a consequence, liver and HCC imaging are thriving fields of research and development. They will benefit from statistical refinements in HCC texture analyses by MRI,[8-10] in the light of molecular tumor profiles. This body of cognitive data will spur translational efforts toward evidence-based patient management. "

Edition Comments and Recommendations: The submitted manuscript includes the Edition changes made to the Edited manuscript. PMIDs and DOIs were inserted in each reference. Please note, however, that PMIDs were unavailable for references #95; 101 and 102; DOIs were unavailable for references #38; 62; 63; 64; 94; 95.

We hope that the changes made to the revised version of this Minireview provide clearer outlines about the significance of de Dimensions of Hepatocellular Carcinoma Phenotypic diversity.

Sincerely,

Orlando Musso, MD, PhD

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