

Response to Reviewers' Comments

I would like to thank the reviewers for their time and diligence, as well as for their instructive comments. Please find the answers to these comments below, as well as discussion of the changes made.

Reviewer No 1(02811953)

Reviewer Comments: This manuscript (Manuscript NO: 48664) entitled "Hepatocellular Carcinoma and Metabolic Syndrome: the times are changing and so should we!" is an editorial by Georgios Tsoulfas. The author explored the interconnection of metabolic diseases and how they are linked to hepatocellular carcinoma (HCC). Main comments: 2. Some additional editing is needed. For example, the last sentence on page 7, it should be "The main explanation Is...", not "... are...".

Response to Reviewer No 1 Comments:

1. A general impression that this manuscript has a many long paragraphs with multiple points discussed. For example, the second sentence (the one after CHANGING LANDSCAPE OF HCC) is too long. It may be better to separate it into defining the terms and epidemiology of NAFLD.

Response: Sentences were made shorter and the paragraphs were separated into "Defining NAFLD and NASH" and "Epidemiology of NAFLD and NASH" as suggested by the reviewer.

2. Some additional editing is needed. For example, the last sentence on page 7, it should be "The main explanation Is...", not "... are...".

Response: This sentence was changed according to the reviewer's comment.

Reviewer No 2 (00543238)

Reviewer Comments: This interesting and well-written review addresses the use of immunotherapy in HCC patients and, in particular, describes mechanisms and clinical features of NASH and Metabolic Syndrome. I have a few of suggestions for the authors:

Response to Reviewer No 2 comments:

1. The review is focused more on NASH and Metabolic Syndrome than HCC, I would suggest a change in the title

Response: I would like to thank the reviewer for the comment. I would suggest leaving the title as is, as NASH and NAFLD are considered part of Metabolic Syndrome and the

Editorial would like to stress how the changes in our understanding and the prevalence of Metabolic Syndrome are changing the landscape and how we should manage HCC. Specifically, by placing priority on prevention and management of Metabolic Syndrome and its components (NASH and NAFLD) we can make a significant difference in what has become the main cause of HCC.

2. External beam radiotherapy is under investigation. So far there is no robust evidence to support this therapeutic approach in the management of HCC. I would suggest to avoid mention it or at least clarify (Page 4) - a figure would help

Response: I agree that external beam radiotherapy is under investigation and for that reason, in following the reviewer's suggestion, I have chosen to avoid mentioning it.

Reviewer No 3 (00188507)

Reviewer Comments: The author described the importance of changing the mindset of approaching to the NASH/NAFLD in the hepatologist. The contents are clearly and well-described and should be considered for the publication as its current form.

Response to Reviewer No 3 comments:

I would like to thank the reviewer for the kind and encouraging comments.

Reviewer No 4 (00039368)

Reviewer Comments: This is a very well written Editorial paper concerning the up to date overview about interconnection of hepatocellular carcinoma (HCC), metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The author underlines the importance of changing the mindset of how to approach cirrhosis and HCC in point of view of their predominant causes and earlier prevention and changing the treatment focus of intervention for cirrhosis and HCC. The author plays special attention to recognizing the importance of obesity, metabolic syndrome, NAFLD and NASH and their combined role in progression of fibrosis, cirrhosis and HCC.

Response to Reviewer No 4 comments:

I would like to thank the reviewer for the kind and encouraging comments stressing the importance of the topic.