

Dear Ke-Qin Hu and Koo Jeong Kang,
Editors-in-Chief
World Journal of Hepatology

21st of August 2020

Dear editors,

We would like to thank you and the reviewers for the helpful and insightful comments about our manuscript. We are grateful for the opportunity to further amend our work. We have carefully revised our manuscript according to the reviewer's comments, which we believe have contributed to enriching the paper. Below you will find our point-by-point response to **all** the reviewers' suggestions, as well as the corresponding changes in the full text. In doing so, the manuscript we re-submit to you is much improved. We hope it will now be suitable for publication in *World Journal of Hepatology*.

REVIEWER COMMENTS

Reviewer 1:

This is an interesting case. It is potentially eligible for publication in this journal. A minor revision was recommended. Based on my experiences, some comments are listed.

- *Abbreviations should be used after their first time of occurrence in the abstract. For example, in the sentence "HCC with TT expansion to inferior vena cava and right atrium is ...", IVC and RA should be used.*

We are grateful for the reviewer's comments and thankful for the positive feedback on the revised version of our manuscript.

We have changed all the abbreviations accordingly.

- *Language should widely improved. For example, "A 69-years-old" should be revised as "A 69-year-old". In the sentence "... was diagnosed in 2005 of an alcoholic liver cirrhosis ...", "of" should be revised as "with".*

Both language suggestions were taken into account and the entire document has been edited by a native English speaker.

- *Figure 4 is just non-contrast, which cannot provide any accurate evaluation of vessels. Therefore, this is meaningless to evaluate the tumour in the portal vein or IVC. Accordingly, the response to sorafenib cannot be evaluated or reported.*

The kidney function of the patient did not allow us to perform a contrast enhanced CT scan. Thus, a non-contrast CT scan was performed to compare the tumour volume before and after the treatment despite not being able to assess the tumour thrombus size correctly.

The text was amended accordingly in "outcome and follow-up" section.

- *Provide the last follow-up outcome of this patient.*

Five months after receiving systemic therapy, the patient sought evaluation in the emergency department for being in a critical condition and was diagnosed with septic shock related to spontaneous bacterial peritonitis that ended fatally.

- *This patient had an extensive invasion of HCC. In such patients, the role of sorafenib has been questioned (PMID: 26516379). Please discuss them.*

The European association for the study of the Liver (EASL) recommends in patients with preserved liver function and minimally affected performance status (PS 0-2), stage C according to Barcelona Clinic Liver Cancer Group (BCLC), and in those with intermediate-stage (BCLC B) not eligible for locoregional therapies, to initiate treatment with systemic therapy. Sorafenib, a multi-kinase inhibitor (TKI), was introduced in the EASL guidelines in 2008. Sorafenib showed survival benefits, documenting prolonged median survival and a nearly 3-month extension of time to radiologic progression, which represented a breakthrough in the management of HCC.[14]

- *Indeed, some recent papers suggested the efficacy and safety of external-beam radiation therapy in advanced HCC (PMID: 30799321). Potential role of external-beam radiation therapy should be re-considered.*

Several studies have shown that EBRT alone or combined with non-surgical treatment might achieve an excellent intrahepatic tumour control and a potential survival benefit for advanced HCC. EBRT presented objective response rates ranging from 39% to 62% in patients with an associated macrovascular invasion.[20] The combination of TACE and RT has been beneficial compared with TACE alone for unresectable HCC in two metaanalysis. [21,22] Moreover, for major vessel invasion cases, combined TACE and RT had better OS and PFS than sorafenib, with a liver function not significantly worsened after treatment [23] . Further studies are needed to accurately establish the incidence of adverse events and confirm these findings.

Thanks again for all the feedback. We have thoroughly checked the entire manuscript.

We hope that our improved manuscript focusing on an interesting case of HCC is now acceptable for publication in World Journal of Hepatology and we really look forward to seeing it in print.

With best wishes.

Yours truly,

Diego Gomez and Oriol Mirallas

Reviewer's code: 02904354

This paper has undergone extensive revisions. Language should be further improved. In the sentence "a 5-year survival of 18%", a word "rate" should be added after "survival". In the sentence "HCC primarily develops in cirrhotic livers, is the major cause of deaths of this population compared with variceal haemorrhage or infections. [3] ", please delete the words "compared with variceal haemorrhage or infections", which were not accurate. In the sentence "The development of hepatocellular carcinoma is intently related to the presence of chronic liver diseases.", "hepatocellular carcinoma" should be revised as "HCC". Similar issues should be checked and revised.

Thank you for all the feedback. We have thoroughly checked and revised the entire manuscript.