

January 07, 2022

Peter Schemmer, FACS, MD, PhD, Chairman, Full Professor, Professor
Editors-in-Chief
World Journal of Gastrointestinal Surgery

Dear Editors-in-Chief:

We wish to re-submit the manuscript titled **“Successful treatment of hepatocellular carcinoma with laparoscopic surgery and sequential multikinase inhibitor therapy: A case report”** The manuscript ID is 72932, Case Report.

We thank you and the reviewers for your thoughtful suggestions and insights. We appreciate your kind consideration of our manuscript. We are also grateful to the reviewers for their valuable comments. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *World Journal of Gastrointestinal Surgery*.

The manuscript has been revised in line with these comments. The responses to all comments have been prepared and given below.

Our point-by-point response to all comments and suggestions is listed below:

We thank you for taking the time and effort necessary to review our manuscript and provide us with these valuable comments and suggestions. Accordingly, we revised our manuscript and made changes to it. Please note that changes to the manuscript are highlighted in red font and yellow highlights for your convenience.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The authors present a case of conversion therapy of metastatic HCC. The authors have reported all the necessary data for the case and also drawn critical medical observations from the progression of disease. I have a few minor suggestions or comments to make: 1) Stage, grade or any tumor markers (AFP, PIVKAI), grade of the original HCC diagnosis needs to be clearly mentioned, especially if known. The pathology from the first resected adrenal lesion can also be mentioned, in order to provide good data for future studies 2) The authors note through case reports that the splenic metastasis is from poor differentiation after multiple cancer treatments. However, the pathology specimen of splenic lesion shows only moderate differentiation. How do the authors explain this? 3) It was also interesting to note that regorafenib, which has anti-angiogenic properties did not prevent cavernous transformation of the portal vein/chronic portal vein thrombosis. Would the authors like to comment on this? 4) Did the patient have cirrhosis since the diagnosis or developed cirrhosis during the treatment phases (at the time of initial diagnosis, prior adrenalectomy)? The presence of/absence of/progression to cirrhosis should be explicitly mentioned in the case report.

: Thank you for your insightful comments and suggestions.

1) Response: The stage, level of tumor markers, grade of the original HCC, and pathology of adrenal lesion were as follows; T1bN0M0 Stage IB based on the 8th UICC; AFP, 25.24 ng/mL; PIVKA II, 3021 mAU/mL, moderately differentiated, and metastatic, moderately differentiated hepatocellular carcinoma. As you mentioned, we added this information to the *Chief*

complaints and *History of present illness* sections (page: 6, lines: 4-6, lines: 9-12, lines: 18-19, and line: 24 .

- 2) Response: We again assessed splenic lesions pathologically. It was found that there was some component of poorly differentiated tumor. This lesion was moderately to poorly differentiated. Therefore, we changed the figure legend of Figure 3B into: "B: Microscopic finding of viable tumor lesion shows moderately to poorly differentiated hepatocellular carcinoma. Hematoxylin-eosin stain, high-power field ($\times 200$)."
- 3) Response: As you pointed out, regorafenib is an oral multikinase inhibitor and has an anti-angiogenic potential. Although they have not been fully elucidated, the various reactions of regorafenib and LEN may originate from the different mechanisms of action between the two agents. The genes downregulated by regorafenib might be different from those controlled by lenvatinib. That would lead to their different effects. Actually, there were little cases regarding regorafenib and conversion therapy for HCC with PVTT. As per your comment, we added the following sentence to page: 10, lines: 16-21. "Although they have not been fully elucidated, the various reactions of regorafenib and LEN may originate from the different mechanisms of action between the two agents. The genes downregulated by regorafenib might be different from those manipulated by LEN. That would lead to their different effects. There have been few cases regarding regorafenib and conversion therapy for HCC with PVTT, despite REFLECT trial included patients with macrovascular invasion^[5]. "
- 4) Response: Liver fibrosis was evident at the time of initial operation (METAVIR F2-3). Then it has progressed to cirrhosis at the time of PVTT according to her FIB-4 score. As per your comment, we added several sentences to the *Chief complaints*, *Laboratory examinations*, and *Imaging examinations* sections (page: 6, lines: 20-22; page: 7, lines: 2-5 and lines: 9-10) .

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I believe the present case-report is suitable for publication in its original form. It is a very interesting case and emphasizes on the importance of a multimodal treatment.

Response: Thank you for your thoughtful comments and your encouraging words.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This manuscript presents an interest case of Successful treatment with laparoscopic surgery and sequential multikinase inhibitor therapy for hepatocellular carcinoma. The authors concluded that Conversion surgery after successful multikinase inhibitor treatment is considered an effective treatment option for advanced HCC. There are several concerns about this manuscript. Novelty is lacking. This is an accidental case and the reason of patient's favourable outcome is unknown.

Response: We appreciate your insightful comment. As you mentioned, the mechanism of this outcome remains unknown, and then this case may be an accidental case. We suggest that future research is needed to clarify the background of the patient's favorable outcome. As per your comment, we added the following sentence to page: 11, lines: 6-7): "Further studies are needed to elucidate the background of patients' favorable outcomes."

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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