

Invited Review (Author ID 00188507)

Science Editor

World Journal of Gastroenterology

Ze-Mao Gong

Mar 22, 2017

Dear Editors and Reviewers,

Thank you and the reviewers for a thorough review of our manuscript entitled “**Spontaneous regression of hepatocellular carcinoma: A mini-review**” (Manuscript number 33581, **INVITED REVIEW ID 00188507**) by Akira Sakamaki, Satoshi Abe, Atsunori Tsuchiya, Masaaki Takamura, Hirokazu Kawai, Satoshi Yamagiwa, Shuji Terai and myself. The thoughtful comments from the reviewers are greatly appreciated. In preparing for revision, we have carefully studied reviewers’ comments and incorporated many of their suggestions into the revised manuscript. For your convenience, we have highlighted the changes made in blue. We hope this revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*. **The provided ID for this invited review is (00188507).**

We declare that this work is original, the manuscript is not under consideration by other journals, and the material has not been previously published. All authors approved the contents submitted. We look forward to hearing from you at your earliest convenience.

Thank you for your consideration.

Sincerely yours,

Kenya Kamimura, M.D., Ph.D.

Division of Gastroenterology and Hepatology

Graduate School of Medical and Dental Sciences

Niigata University

1-757 Asahimachi-dori, Chuo-ku, Niigata, Niigata, 9518510, JAPAN

Tel: +81 (25) 227-2207

Fax: +81 (25) 227-0776

E-mail: kenya-k@med.niigata-u.ac.jp

Dear Reviewers:

Thank you very much for your thoughtful comments and suggestions. In preparing the revision, we have carefully studied your comments and incorporated many of your suggestions into the revised manuscript. The following are our point-by-point responses to your comments/concerns. For your convenience, we have highlighted the changes made in blue.

Title: Spontaneous regression of hepatocellular carcinoma: A mini-review
(Author ID 00188507)

Author: Akira Sakamaki, Kenya Kamimura, Satoshi Abe, Atsunori Tsuchiya, Masaaki Takamura, Hirokazu Kawai, Satoshi Yamagiwa, Shuji Terai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 33581

Reviewer #1

The current mini-review is a very interesting manuscript to describe the possible mechanism on the spontaneous regression of HCC and would like to show out a new generation of immunotherapies. This manuscript is well written.

Response: We appreciate for a thorough review of our manuscript and are grateful for the positive comments.
1. Herein, only one point to be concern that because this is not an original article, the references should need to mention in the possible factors of tumor hypoxia in table 2.

Response: We agree with the reviewer's comment. We have added the reference number after the factors of spontaneous regression in Table 2.

Reviewer #2

In this study, Dr Sakamaki et al reviewed the cases of spontaneous regression of hepatocellular carcinoma and analyzed the mechanism of spontaneous regression. They provided some new information to the current therapy of hepatocellular carcinoma. Generally, this manuscript is well written and of great interests for clinical readers. Actually, the manuscript is potential acceptable for publication.

Response: We are grateful to the reviewer for the positive comments and for recognizing the significance of our work.

1. It would be better if the authors explain the definition of spontaneous regression of hepatocellular carcinoma in introduction section.

Response: Thank you for your thorough review on our manuscript. We have added the definition of spontaneous regression of HCC in the introduction section and added a reference (page 6, line 5-6, new ref. #10).

2. When discussing the mechanisms of spontaneous regression in HCC, the authors should explore more roles of hypoxia in the pathophysiology of HCC.

Response: We have significantly added description in introduction with additional references (page 5, line 2, new ref. #1-#6) and description in prognosis section (page 12, line3 from the bottom).

3. Please make a confirmation that how many patients were recruited in this review.

Response: We have stated this points in materials and method section (page 6, line 2 from the bottom).

4. *Some typos and grammar errors should be further corrected.*

Response: Thank you for your thorough review on our manuscript. We have carefully corrected several grammatical errors and professional language editing was performed.

Reviewer #3

This paper examined the mechanisms of spontaneous tumor regression by summarizing 24 case report literatures, which provide valuable insight into therapies of Hepatocellular carcinoma.

Response: We are grateful to the reviewer for the positive comments and for recognizing the significance of our work.

1. *The authors should state the similarity between the spontaneous tumor regression and therapies of HCC by explaining about each mechanisms more in detail.*

Response: We appreciate the reviewer's suggestions. To describe the points, we have significantly modified the introduction with additional references (new ref. #1-#6) and showed the similarity between regression and therapies of HCC (page 5). We have also added the description in page 6, line 7; page 10, line 2; and page 10, line 4 from the bottom.

2. *Are there any necessary literatures of references except for that of published in recent 5-years?*

Response: We would like to thank you for your thorough reviewing. We have included the references #7 and #8 summarized in before and to make the advances in imaging modalities in recent 5-years clearer, descriptions are added (page 8, line 5 from the bottom).

3. *The authors should refer literatures which state about spontaneous regression tumor histopathologically diagnosed not only by diagnostic imaging.*

Response: We agree with the reviewer's comment. We have added the histopathological findings in the prognosis section (page 12, line 16-18).

4. *The authors should state that the written informed consent was obtained from the patient/the patient's family.*

Response: We have added the statement in Materials and method section. (page 7, line 4).

5. *Abstract P3, line 15 In the manuscript, the authors state that "immunotherapies". What are the immunotherapies? Please provide examples about that.*

Response: Thank you again for your thorough review on our manuscript. We have expressed the immunotherapies about PD-1 and PD-L1 antibody in the conclusion section and added these contents in the abstract section (page 3, line 16-17).

6. *Introductions Please expand the introduction so that it is longer than the abstract. For example, further information on the incidence and prognosis of hepatocellular carcinoma, and background on what is currently known about the pathogenic mechanism of hepatocellular carcinoma necrosis could be included. Abstract P3, line 15 In the manuscript, the authors state that "immunotherapies". What are the immunotherapies? Please provide examples about that.*

Response: We have significantly modified the introduction and made it longer including the detail information regarding HCC and added additional references (page 5, line 2, new ref. #1-6). According to this modification the number of the reference list has been modified.

7. *Materials and methods P5, line12 In the manuscript, the authors state that "PubMed". Please confirm all company detail in the*

materials and methods. These should include Company name, City, State and Country.

Response: We have added the information (page 6, line 5 from the bottom).

8. Epidemiology P6, line10-11 In the manuscript, the authors state that “regional difference in the world and the higher frequency of spontaneous regression in the Asian countries”. If it is possible, please state the cause of that result.

Response: We are also interested in this result, however, we are unable to find the clear reason about this difference. We have added the description (page 7, line 3 from the bottom).

9. Clinical Course P8 In the manuscript Authors’ case is stated. Please show more examination such as blood test, abdominal ultrasound, Magnetic Resonance Imaging.

Response: Thank you again for your thorough review on our manuscript. We have added the information regarding the laboratory test including tumor markers and clinical data regarding tumor sizes (page 9, line 7). We have no data of abdominal ultrasound and magnetic resonance imaging for spontaneously regressed tumor.

10. Hypoxia page9 Is it appropriate if thromboses and rapid growth, hepatic arteriportal shunts are categorized in Hypoxia? They are causes of ischemic change, so do they mean not only hypoxia but also poor nutrition and dehydration, etc.?

Response: We agree with the reviewer’s comment and modified the description (page 11, line 3).

11. Immunological Reaction P10, line3-4 Immunological mechanism was stated in the latter half of this paragraph, are “Abstinence of alcohol and smoking, herbal medicines, prolonged fever, antidiabetics, and vitamin K administration” the same mechanism?

Response: Thank you again for your thorough review on our manuscript. The mechanism of spontaneous regression of tumor following the various types of immunological reaction is still unclear and therefore, we have no clear-cut answer for this question. We have modified description (page 12, line 1).

12. Prognosis P11, line13-17 The author should additionally state about relapse of HCC and viable persistence of tumor cell for the reason of “additional therapies” after the last sentence.

Response: Thank you again for your thorough review on our manuscript. We have significantly modified the section of “Prognosis” and added the description (page 13, line 4; page 13, line 7 from the bottom)

13. Figure Legends Figure1. There are images of lymph node metastasis before and after the tumor regression, are they mean spontaneous regression happened in the lymph node too? If so, what is the mechanism? Does it happen caused by Hypoxia or Immunological reaction?

Response: Thank you again for your thorough review on our manuscript. Yes, as the reviewer kindly pointed out, since the hypoxia and immunological reaction might be the reason of the spontaneous regression of the tumor, we believe that it is understandable to see the regression of metastatic lesion in the lymphnodes, although further analyses are necessary. We have added the description (page 10, line 7 from the bottom).

Reviewer #4

The theme of this review is interesting and useful for scientist and practitioners. 1. Unfortunately the authors studied a single database and only in the last 5 years. So they could find and analyze a small number of cases. Spontaneous regressions had also been in the past. They can also be found in other places. The authors could not provide physiological explanations additional to those contained in the analyzed articles. Thus, the topic remains open for future studies.

Response: We appreciate for a thorough review of our manuscript and are grateful for the positive comments. We agree with the reviewer that this topic remains open and further studies are necessary.

1. There are several grammatical errors that must be corrected.

Response: Thank you for your thorough review on our manuscript. We have carefully corrected several grammatical errors and professional language editing was performed.