

Response to Reviewers

The authors are grateful for the helpful comments and constructive suggestions of this reviewer. We have revised the manuscript according to the reviewer's suggestions.

We look forward to a publication of our manuscript in WJGO.

Sincerely,
Katsunori Iijima, Reina Ohba.

The following comments are in response to each of reviewer's points:
(Reviewer's comment are shown in blue, and our responses are written in black.)

Reviewer #1: Reviewer's code: 03488034

The infection by *H. pylori*, an important etiological factor, continues to increase subsequent gastric cancer risk even after treating the bug and making surgical/endoscopic intervention. To address this main objective of the review, the contents are confusing and disorganized. Authors shift across various things and rather squeeze the conclusions from evidences, make repetitions and inconsistencies. Given the huge published information on the topic and expertise of the author, the authors could have structured the review with great clarity and connectivity as suggested below: 1. To start with describing in a paragraph, how the *H. pylori* infection increases risk of gastric cancer with brief mechanisms also. 2. Followed by, how the infection is treated and what extent the infection eradication attenuated the gastric cancer risk. 3. What is conclusive evidence in subsequent gastric cancer risk after *H. Pylori* eradication and tumor removal (surgery or endoscopic one) will follow. a. In addition how you rule out the role of other risk factors of gastric cancer in metachronous gastric cancer formation. b. What is the argument that the subsequent metachronous cancer is not due to reinfection of the *H. pylori*. What are the studies which have assessed that *H. pylori* infection was absent in such subsequent cancers after primary cancer. 4. After establishing the risk (in post treatment and post operated) patients due to *H. pylori*, in the review, you can explain the pathology as many sections are in the article are relevant. Establish that treatment of the bug, does not help in stopping the various carcinogenic events initiated by such infection. The committed events possibly lead to metachronous cancer. (The pathology of metachronous gastric cancer in patients who had no infection needs attention seriously). 5. Eventually, you make your recommendations as stated that surveillance/follow up is important after treating against *H. pylori*. Further can we make suggestions like partial or totally gastric removal will reduce metachronous cancer development in stomach i.e. treating the infection along with the removal of the committed events of *H. pylori* related previous infections, is advisable.

Thank you for your helpful comments.

According to the Reviewer's comments (No.1), we added the sentence in the first

paragraph "H.PYLORI-INDUCED GASTRIC CANCER" after introduction. And we described mechanism of gastric cancer (p6-7).

Following this, in the next paragraph "PREVENTION OF GASTRIC CANCER BY H.PYLORI ERADICATION", we modified the sentence of helicobacter pylori eradication pointed No2 (eradiation attenuated the gastric cancer risk) and part of No4 (no infection needs attention seriously) (p10).

In the paragraph "GASTRIC CANCER DEVELOPMENT AFTER ERADICATION", we entered your opinions pointed out No3.a, b, c, (p11-12) and after this content, we explained various mechanism of gastric cancer after H.pylori eradication (No.4, p13-15). Our conclusion and view were summarized in the last section as you recommended No5 (p21).

Thank you again for your comments on our paper. We trust that the revised manuscript is suitable for publication.

Reviewer #2: Reviewer's code: 00044980

This manuscript is the topic highlight of pathogenesis and risk factors for gastric cancer after HP eradication. This manuscript is well written. I have several minor comments as follows. 1. Authors should explain full words for abbreviations "AID", "PAI", "TNF", and "ESD". 2. P9, line 18: Authors should confirm the reference numbers. 3. P15, line 9: Authors should change "CpG islands" to "CGIs".

Thank you for pointing this out. The reviewer's comment is correct. According to Reviewer's comment, we corrected these as follow.

1. We corrected all words you commented.
2. We confirmed the reference number. (p12, line7)
3. We changed "CpG islands" to "CGIs". (p18, line18)

We thank the Reviewer for valuable comments.

Reviewer #3: Reviewer's code: 02980806

The authors reviewed the role of the H. pylori in carcinogenesis and the histological and endoscopic characteristics and risk factors for metachronous gastric cancer after eradication as well as the risk predictions, the possible approaches for reducing the risk of metachronous gastric cancer after eradication. The topic is valuable, the content is informative and detailed, and the logic is clear. However, there are still some small problems as follows 1. The title was "Pathogenesis and risk factors for gastric cancer after H. pylori eradication", however, there seems to be only very tiny part focusing on the risk factors of metachronous gastric cancer (Page 15), and content of "Pathogenesis"

was also small. It makes readers wonder whether the title fits the main body of the content. 2. If possible, please provide a clear definition of “metachronous gastric cancer” and explain the difference between “metachronous gastric cancer” and “gastric cancer after H. pylori eradication”. 3. The authors should clearly illustrate the “possible approaches” was aimed to all gastric cancer, or with gastric cancer with Helicobacter pylori infection, or the development of gastric cancer after H. pylori eradication, or metachronous gastric cancer 4. In Page 1, “The endoscopic removal of early-stage gastric tumors does not affect the overall cancer.” What’s the “overall cancer”. Please provide some explanation. 5. In Page 14, 16, 19, and other positions, the paragraph was built with one sentence. It looks unfriendly and informal.

We wish to thank you for this comment. The comments have helped us improve the paper.

About No1. , We agreed with reviewer’s comment. If we focus the only risk, it seems to a tiny part. However there is a part where overlap the pathogenesis with gastric cancer induced H.pylori and even after successful eradication, as far as an inflammation continues, metachronous gastric cancer will occur. Therefore we think the part of the cause of gastric cancer after H.pylori eradication is also included in the molecular mechanism above-mentioned. For simplicity's sake, we revised the introduction part and middle part of each paragraph.

As you pointed out No2, we provide a definition the difference between “metachronous gastric cancer” and “gastric cancer after H. pylori eradication” in the paragraph “GASTRIC CANCER DEVELOPMENT AFTER ERADICATION”. (p11, line7-9.)

No3; It wasn’t everything, but we made the example figure of a part of mechanism for possible approaches added to the end of the pages.

No.4; We sincerely apologize for this incorrect sentence. True meaning is “over all cancer risk” not “over all cancer”. (p4, line 22.)

No.5; Your comments is correct. Separation of the sentence may occur at the first time correction. We corrected it along the flow of the sentence.

Thank you again for your comments on our paper. We trust that the revised manuscript is suitable for publication.

