

November 8, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5129-review.doc).



Title: The efficacy of *Helicobacter pylori* eradication for the prevention of metachronous gastric cancer after endoscopic resection for early gastric cancer

Author: Jae Young Jang & Hoon Jae Chun

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5129

I am really appreciative of Editor's and reviewers' thoughtful and constructive comments. We have revised the manuscript that includes additional explanations as recommended by Editor and the reviewers. I hope that my endeavor to address these issues is satisfactory to both Editor and the reviewers. Again, on behalf of our authors, thank you.

Reviewer Comments:

Reviewer #2: "Helicobacter pylori infection after endoscopic submucosal dissection for early gastric cancer" is describing interesting findings and suggests a potential strategy for treatment of early gastric cancer. The authors conclude H. pylori eradication from the residual gastric mucosa after endoscopic resection of early gastric cancer inhibits the development of metachronous gastric cancer; thus, H. pylori eradication is recommended before the progression of gastric mucosal atrophy. But the REFERENCES provided by the authors are isolated, static and one-sided, and it appears that this manuscript have been rushed through in a careless design. There are some suggestions for improving this manuscript.

Q: 1. The manuscript is a Topic Review, as we know, the Topic Review must contain latest study of Helicobacter pylori and gastric cancer, but the viewpoint and study in this topic review are old.

Q: 2. the Topic Review must contain comprehensive view, but the paper are selective REFERENCES, the author chose the studies which supported the view of H. pylori eradication from the residual gastric mucosa after endoscopic resection of early gastric cancer inhibits the development of metachronous gastric cancer. I can see some studies object to this view, but the studies can't see in this Topic Review.

Answers (Q: 1&2) Thank you for your important suggestion. We had focused on the importance of H. pylori eradication excessively. To avoid overemphasizing, we additionally have cited a recent study on the contrary. We have added some sentences as follows.

“According to one recent multicenter retrospective study^[1], the mean annual incidence rate of metachronous cancers was 3.5% in 1258 patients with early gastric cancer who were followed after endoscopic resection. The incidence rate did not differ between patients with and without H. pylori eradication^[1].”

1. Kato M, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut 2013; 62: 1425-1432 PMID: 22914298 DOI: 10.1136/gutjnl-2011-301647

Q: 3. The author reported that H. pylori eradication from the residual gastric mucosa after endoscopic resection of early gastric cancer inhibits the development of metachronous gastric cancer, but such data were not sufficient; it can't get the conclusion; authors had to show more Study on molecular mechanism, and then it can get a whole conclusion.

Answers: We agree with your comments. As you know, there is a lack of studies on this issue, especially on molecular mechanism. So, we have so far been unable to conclude definitely. We tried to revise the manuscript a more balanced approach. We generally revised and highlighted significant changes to the manuscript.

Q: 4. Page 4, The author reported that gastric cancer can result in field carcinogenesis, as the gastric environment is likely to promote the occurrence of secondary cancer. But most readers warn against drawing absolute conclusions from a small-scale study.

Answers: Thank you for your comment. We have made a categorical statement about the evidence of field carcinogenesis. So, we slightly revised the sentence as follows.

“Therefore, field carcinogenesis may result in gastric cancer, as the gastric environment is likely to promote the occurrence of secondary cancer.”

Q: 5. Authors should do careful language editing before submission. Just a few examples, Page 7 ‘In summary, in patients who’ Obviously such statements should not be appeared in scientific papers, here, have to change to ‘In summary, patients who’. A native English speaker is needed to rewrite the whole manuscript.

Answers: I’m very sorry about that, this was our mistake. The English in this manuscript has been checked again by at least two professional editors, both native speakers of English. We corrected last paragraph as follows.

“Until now, the efficacy of *H. pylori* eradication for the prevention of metachronous gastric cancer has been controversial. Despite incongruities, as suggested by the existence of several guidelines, *H. pylori* eradication has been recommended to suppress or delay metachronous gastric cancer in patients who have undergone endoscopic resection of early gastric cancer. At the very least, we suspect that such benefits will be greater in patients without atrophy or intestinal metaplasia. However, eradication does not completely eliminate the risk of developing gastric cancer. Therefore, endoscopists using newly developed imaging techniques, such as magnifying endoscopy and narrow band imaging, should inspect the entire stomach for minute or occult metachronous gastric cancer. In addition, regular surveillance endoscopy should be performed every 6–12 months for 5 years after initial endoscopic resection.”

Reviewer #3: This is a topic highlight article that discusses the value of *H. pylori* eradication for the prevention of metachronous gastric cancer after endoscopic resection of early gastric cancer. The article addresses a relevant point, but no novel or innovative data are presented. Presentation and readability of the manuscript are overall satisfactory. I found some expressions rather unconventional ("the *H. pylori* bacterium" for *H. pylori*, "the prophylactic prevention" for primary prevention). Also please note that "non-cardiac gastric cancers" should be "non-cardia -or noncardia- gastric cancers". As to the title ("*Helicobacter pylori* infection after endoscopic submucosal dissection for early gastric cancer"), it does not accurately reflect the major topic, i.e., the role of *H. pylori* eradication for cancer prevention. Something like "The role of *H. pylori* eradication for the prevention of metachronous gastric cancer after endoscopic submucosal dissection for early gastric cancer" would be more representative. I suggest edition of the sentence "...gastric cancer can result in field carcinogenesis". It is not cancer that results in carcinogenesis, but carcinogenesis that results in cancer. Because this is a review article, authors should provide a description about how the literature search was performed and which databases (i.e., Pubmed, Medline, Embase, etc) and key-words were used. Without this, we cannot address the completeness and thoroughness of the literature review. It should be declared whether or not any article

selection criteria (e.g., based on quality or type) was used.

Answers: Thank your careful comments. We carefully revised the text as you recommended as follows.

1. From “H. pylori bacterium” to “*H. pylori*”
2. From “the prophylactic prevention” to “*the primary prevention*”
3. From “non-cardiac gastric cancers” to “*non-cardia gastric cancers*”
4. We changed the title from “Helicobacter pylori infection after endoscopic submucosal dissection for early gastric cancer” to “*The efficacy of Helicobacter pylori eradication for the prevention of metachronous gastric cancer after endoscopic resection for early gastric cancer*”
5. From “Therefore, gastric cancer can result in field carcinogenesis, as the gastric environment is likely to promote the occurrence of secondary cancer” to “*Therefore, field carcinogenesis may result in gastric cancer, as the gastric environment is likely to promote the occurrence of secondary cancer.*”
6. We have added some sentences as you recommended as follows; “*We reviewed large-scale epidemiological studies, meta-analyses, and animal model-based investigations linking gastric cancer to H. pylori infection. Literature searches using the Medline and PubMed databases were performed as part of the preparation for the implementation of this guideline. Our search was performed using index words related to H. pylori (“Helicobacter pylori” OR “Helicobacter” OR “pylori” OR “eradication”), gastric cancer (“gastric cancer” OR “stomach cancer” OR “metachronous”), and treatment (“endoscopic resection” OR “endoscopic submucosal dissection”).*”

Reviewer #4:

Q: 1. Helicobacter pylori infection is not the main cause but a possible one of gastric cancer development. About 50% of the world population is infected by this bacterium, but only a small portion of the population develops gastric cancer. Multiple factors cause this cancer. The accepted leading etiological factors are N-nitroso-compound and sterigmatocystin in unhealthy food and beverage.

Answers: We completely agree with your comments. Gastric cancer carcinogenesis is a multifactorial process related to an interaction of host factors. So, we have added this issue as follows.

“Gastric carcinogenesis is a multifactorial process influenced by an interaction of host

factors, including *Helicobacter pylori* infection and environmental factors, such as diets rich in salt and nitrates/nitrites^[1]”

1. Houghton J, Wang TC. *Helicobacter pylori* and gastric cancer: a new paradigm for inflammation-associated epithelial cancers. *Gastroenterology* 2005; 128: 1567-1578
PMID: 15887152 DOI: 10.1053/j.gastro.2005.03.037

Q: 2. In the process of gastric cancer carcinogenesis, we should also treat chronic atrophic gastritis, intestinal metaplasia, even dysplasia, besides gastritis caused by *Helicobacter pylori*.

Answers: We absolutely agree with your opinion. However, there is a dearth of evidence concerning many of these issues. Therefore, we could not suggest or recommend the treatment of chronic atrophic gastritis and intestinal metaplasia at present.

Q: 3. Page 4 last line, “secondary cancer” is inappropriate but “recurrence” should be used.

Answers: In this sentence, “secondary cancer” was used to mean “metachronous cancer”, not recurrence of cancer. We apologize for having caused misconception of you. So, we have changed this word as follow.

From “secondary cancer” to “**metachronous cancer**”

Q: 4. That recurrence rate of 3-14% after endoscopic resection suggests that current guideline the authors used for endoscopic treatment of early gastric cancer is problematic and needs revision, compared to the recurrent rate after partial gastrectomy, 1.13-1.9%.

Answers: Thank you for your comments. We compared the incidence rate of metachronous gastric cancer after endoscopic resection or surgery, not the recurrence rate. We have revised this statement after reviewing previous studies as follows.

“An increased risk of metachronous gastric cancers is expected in patients treated by endoscopic resection, in proportion to the larger area of gastric mucosa remaining in these patients. The length of follow-up has varied in previous studies, but the annual incidence rate of metachronous gastric cancer after endoscopic resection ranged from 3.3–3.5%”

Reviewer #5: It is a good topic which the relationship between *Helicobacter pylori* eradication and prevention of gastric cancer after endoscopic treatment for early gastric cancer. the manuscript requires some modifications before it can be considered for publication in World Journal of gastroenterology.

Q: 1. Author mainly talked about the relationship between *H. pylori* eradication and prevention of metachronous gastric cancer, the title should be changed.

Answers: Thank you for your important suggestion. As you recommended, we changed the title as follows.

From “Helicobacter pylori infection after endoscopic submucosal dissection for early gastric cancer” to “***The efficacy of Helicobacter pylori eradication for the prevention of metachronous gastric cancer after endoscopic resection for early gastric cancer***”

Q: 2. Author should tell us the definition of “metachronous gastric cancer”.

Answers: We have added the definition as follows.

“Metachronous gastric cancer is defined as new carcinoma that develops in areas other than the primary site at least 1 year after endoscopic resection.”

Q: 3. Author should cite more and newer studies about eradication of H. pylori in the prevention of gastric cancer after endoscopic treatment for early gastric cancer

Answers: We additionally have cited a recent study. We have added some sentences as follows.

“According to one recent multicenter retrospective study^[1], the mean annual incidence rate of metachronous cancers was 3.5% in 1258 patients with early gastric cancer who were followed after endoscopic resection. The incidence rate did not differ between patients with or without H. pylori eradication^[1].”

1. Kato M, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut 2013; 62: 1425-1432 PMID: 22914298 DOI: 10.1136/gutjnl-2011-301647

Reviewer #6: This review brings forward the relationship between Helicobacter pylori eradication and prevention of gastric cancer after endoscopic treatment for early gastric cancer. This is a hot topic in clinical treatment; however, it's a pity that the author didn't elaborate sufficiently. I feel the manuscript requires some modifications before it can be considered for publication in World Journal of gastroenterology.

Q: 1. The review was thought to discuss the H. pylori infection status after endoscopic treatment for early gastric cancer from the title, but in the text, you mainly talked about the relationship between H. pylori eradication and prevention of metachronous gastric cancer, the

title cannot convey the author's intent

Answers: Thank you for your careful comment. As you recommended, we changed the title as follows.

From “Helicobacter pylori infection after endoscopic submucosal dissection for early gastric cancer” to “*The efficacy of Helicobacter pylori eradication for the prevention of metachronous gastric cancer after endoscopic resection for early gastric cancer*”

Q: 2. The framework of the review is a bit confusing; the text should elaborate the relationship between H. pylori infection and gastric cancer recurrence after endoscopic treatment and then turn to the relationship between H. pylori and prevention of metachronous gastric cancer.

Answers: Thank you for your very appropriate comments. In this review, we have focused on the relationship between H. pylori infection and prevention of metachronous gastric cancer. So, as stated above, we have changed the title. And, we have revised some sentences to help reader's comprehension.

“An increased the risk of metachronous gastric cancers would be expected in patients treated by endoscopic resection, in proportion to the larger area of gastric mucosa remaining in these patients. The length of follow-up has varied in the literature, but an annual incidence rate of metachronous gastric cancer after endoscopic resection has ranged from 3.3–3.5%”

Q: 3. What's the definition of “metachronous gastric cancer”?

Answers: We have added the definition as follows.

“Metachronous gastric cancer is defined as new carcinoma that develops in areas other than the primary site at least 1 year after endoscopic resection.”

Q: 4. A lot of studies about eradication of H. pylori in the prevention of gastric cancer after endoscopic treatment for early gastric cancer were cited, but the results were controversial.

Answers: We absolutely agree with your opinion. So far, the efficacy of H. pylori eradication in terms of preventing metachronous gastric cancer remains controversial. However, several guidelines recommend H. pylori eradication in patients with early gastric cancer after endoscopic resection. So we have carefully revised for this issue using modest proposal.

“Until now, the efficacy of H. pylori eradication for the prevention of metachronous gastric cancer has been controversial. Despite incongruities, as suggested by the existence of several guidelines, H. pylori eradication has been recommended to suppress or delay metachronous gastric cancer in patients who have undergone endoscopic resection of early

gastric cancer. At the very least, we suspect that such benefits will be greater in patients without atrophy or intestinal metaplasia. However, eradication does not completely eliminate the risk of developing gastric cancer.”

Q: 5. The author’s comprehension and experience about the prophylactic measure should be introduced into this manuscript.

Answers: Because this issue is not conclusive, we believe that regular surveillance endoscopy is best strategy to improve prognosis of metachronous gastric cancer. Also, H. pylori eradication may help to decrease the metachronous cancer. We have added some sentences as follows.

“However, eradication does not completely eliminate the risk of developing gastric cancer. Therefore, endoscopists using newly developed imaging techniques, such as magnifying endoscopy and narrow band imaging, should inspect the entire stomach for minute or occult metachronous gastric cancer. In addition, regular surveillance endoscopy should be performed every 6–12 months for 5 years after initial endoscopic resection”

Q: 6 (minor concerns). It is noted that the manuscript needs careful editing so that the goals and results of the study are clear to the reader.

Answers: Thank you for your careful comment. We corrected and highlighted significant changes to the manuscript to clarify the meaning.

Thank you again.

Sincerely yours,

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