

Thank you for your review. We made a point-to-point response.

Reviewer #1:

The study followed up patients with *H. pylori* eradication. Gastric cancer is a multi-factor-induced disease. Have the researchers considered factors such as dietary habits and family genetic history of different included populations?

Thank you for your insightful comments. As the reviewer wisely pointed out, these confounding factors are not included in our examination. We added these points as study limitation in discussion section.

***Fourth, several possible confounding factors including dietary habits, family genetic history, and H. pylori virulent factors are not included in this examination.***

The sample size of this study is small, and if no matching been done, the results are hardly convinced.

As the reviewer pointed out, the small sample size is major weakness of our study, but our study has the advantage of the first study. We added these points as study limitation in discussion section.

***First, the study was conducted at a single institute and included a small number of patients. Future large scale and matched study is needed.***

Have you identified *Helicobacter pylori* typing?

*H. pylori* virulence factors such as *cagA* and *cagE* were not included in our study. We added these points as study limitation in discussion section.

***Fourth, several possible confounding factors including dietary habits, family genetic history, and H. pylori virulent factors are not included in this examination.***

Is there a distinction between the pathological types of gastric cancer?

In our analysis, most of the post *H. pylori* eradication gastric cancers were the intestinal type (93.3 %, 42/45), was consistent with the findings in past report. We have not conducted the analysis limited to diffuse type gastric cancer because the sample size is too small.

The content of the discussion part of the study is inadequate, the body part does not provide conclusions, and the reference format does not meet the submission requirements.

We added the conclusion in discussion part, and revised the reference format to meet the requirements.

*In conclusion, patients diagnosed with gastric cancer after H. pylori eradication tended to have advanced gastritis. In particular, in cases of multiple gastric cancers after eradication, the endoscopic Kyoto classification score tended to be at least 5 or higher with an open type atrophic gastritis and the intestinal metaplasia extended to the corpus.*

In line with the opinion of the reviewer, we have enhanced the description of the discussion.

*In the Kyoto classification, positive findings on the items such as enlarged folds, nodularity, and diffuse redness are tended to disappear via H. pylori eradication therapy. On the other hand, both advanced intestinal metaplasia and atrophic gastritis, which have been established as risk factors for gastric cancer, did not improve in a short period of time<sup>[34]</sup>. We believe that multiple gastric carcinomas could occur in the situation of so called “point of no return”, in which gastric carcinogenesis cascade had progressed to the advanced stage due to the H. pylori infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes(35, 36).*

Reviewer #2:

In this case control study the authors studied patients who developed primary gastric cancer after 6 months from confirming H pylori eradication. They concluded that all patients with primary gastric cancer after HP eradication had high Kyoto score with more elevations noticed in patients with multiple (Synchronous or metachronous) gastric cancer. I think to be clinically relevant this work would have some improvements: A) In the study design - Why not biopsies were taken for H pylori testing at time of scoring for Kyoto i.e. Is the eradication was confirmed at time of gastric cancer diagnosis.

After the eradication therapy was completed, cure status was confirmed by  $^{13}\text{C}$  urea breath test. Additionally, at the first endoscopic examination after eradication, a biopsy of the gastric mucosa is performed to confirm the success of eradication. It is known that *H. pylori* re-infection after successful eradication is rare. Though It is also known that *H. pylori* is difficult to detect from cancerous parts, all the gastric cancers after eradication therapy were diagnosed by biopsy and *H. pylori* was not detected in any of the biopsy specimens.

- What about Kyoto scores at time of H pylori diagnosis or eradication, if available

Since there were some missing values in the Kyoto score data at the time of eradication and all of the Kyoto score data at the time of cancer detection were available, the latter was used as the reference this time.

- Patients did EDS for different indications (if possible give numbers)

All the gastric cancer patients after eradication did EDS for follow-up indications, not for symptoms.

- Supplementary video may be of benefit, if available, would be of interest

Thank you for your insightful comment. So many Kyoto score pictures are published but the video of Kyoto score is rare. It would be our future plan.

- Study flow chart may be valuable –

Our study design is really simple. To divide 45 gastric cancer patients into single gastric cancer group and multiple gastric cancer group. This time, I decided that the text information was better than the cartoons.

Scoring Kyoto score in a table may be easier to follow - Seven cases of multiple gastric cancer were found (Table 1). Three of these were metachronous gastric carcinomas and all of these patients had synchronous gastric== Except patient number 4 as shown in Table 2 had 1 lesion.

Almost all the multiple gastric cancer patients (6/7) had 5 points as Kyoto score except patient number 3 (6 points). The space of the table is too small to add the Kyoto score. So we added the text information.

***In the multiple gastric cancers group, almost all the patients (6/7) had 5 Kyoto score and one patient had 6 Kyoto score.***

B) In the manuscript writing - Some minor spelling errors e. "ingle" to be " single"

We thoroughly checked the typos and revised.

C) Some conclusions can be inferred: - Gastric cancer may be found even after the eradication treatment: This means that there were another risk factors or H pylori induced pathology that is not reversible with or even increase after treatment - .

As the reviewer pointed out, irreversible change even after eradication would be important for gastric carcinogenesis. We added the discussion.

*We believe that multiple gastric carcinomas could occur in the situation of so called “point of no return”, in which gastric carcinogenesis cascade had progressed to the advanced stage due to the H. pylori infection; therefore, even the eradication therapy could not repair the molecularly irreversible gastric mucosal changes(35, 36).*

The score was 3.8 points in the Single group, and 5.1 points in the multiple groups: how this affect the clinical practice - Would, according to the results of the current study, all H pylori eradicated patients should do follow-up endoscopy with Kyoto reporting at regular intervals

As the reviewer pointed out, both single and multiple group had high Kyoto score and needs regular surveillance endoscopy at 1 to 2 year intervals. But super high score group of 5 or higher Kyoto score might need more strict intervals such as 0.5 to 1 year. We need further study to reveal right intervals according to Kyoto score.

Science editor

(1) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

We revised the reference.

(2) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text; and

We added the “article highlight” section.

(3) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

We revised the reference.