Answers to Reviewer (Reviewer's code: 00001114)

Reply: Thank you very much for your kind comments. We carefully studied your helpful comments and suggestions, and have revised our manuscript accordingly, including some additional sentences in the revised manuscript. We used red fonts to indicate the changes in the revised manuscript.

We would like to submit the revised version of manuscript. We hope our revised manuscript is now acceptable for "*World Journal of Gastrointestinal Oncology*".

Comments to the Author:

Thank you for giving me the opportunity to review the manuscript: "Gastric xanthoma is a predictive marker for metachronous and synchronous gastric cancer". I enjoyed this paper. I feel this article is well written and clinically important.

I have following comments.

Major comments

The authors analyzed patients with early gastric cancer comprising patients with solitary and metachronous and synchronous gastric cancer. They concluded that the prevalence of gastric xanthoma in solitary group (32.1%) was significantly higher than that in multiple group (54.2%) at the initial endoscopic evaluation and then gastric xanthoma is a useful predictive marker for multiple gastric cancer. The authors stated that this report is first report of the presence of gastric xanthoma as a useful predictive marker for metachronous and synchronous gastric cancer. This study seemed to analyze findings of with or without gastric xanthoma at one point in different cohorts, patients with solitary and metachronous or synchronous gastric cancer. Even in solitary group, about one third of patients with

gastric cancer had gastric xanthoma. Therefore, I feel a little strange to support this conclusion.

1. I am interest in how much percentage of the patients with solitary gastric cancer and xanthoma will develop a metachronous gastric cancer after endoscopic resection for a initial lesion. Sekikawa A et al. (Ref #20) reported that gastric cancer occurred in 15 (14.0%) of 107 patients with gastric xanthoma, whereas it occurred in 14 (0.8%) of 1716 patients without ($p < 0.0001$) during the endoscopic follow-up period. I feel this difference has a great impact for the risk of developing gastric cancer. Therefore, I recommend that the authors show the follow-up data of 32% patients with solitary gastric cancer.

Reply: Thank you for your kind comment. Solitary gastric cancer (GC) was defined as no past history of GC and only one GC that developed during the study period. We would like to put these contents in the chapter of "*Patients*" of "MATERIALS AND METHODS" in the revised manuscript (P8). And so, in this study, the patients of solitary GC developed no metachronous GC during our study period.

2. I recommend that the authors clarify the clinical importance from this study when a patient with solitary or metachronous and synchronous gastric cancer was detected gastric xanthoma. In other words, I am interested in if a patient with solitary gastric cancer and gastric xanthoma was in high-risk for metachronous recurrence after initial endoscopic treatment for early gastric cancer.

Reply: Thank you for your kind comment. We investigated metachronous and synchronous gastric cancer (GC) together because it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC. We think that solitary GC and gastric xanthoma (GX) is in high-risk for metachronous

recurrence after initial endoscopic treatment for early GC, as you think. However, according to our study, we don't know whether a patient with solitary GC and GX is in high-risk for metachronous recurrence after initial endoscopic treatment for early GC or not, unfortunately.

3. I am interested in if there are a relation between the number or size of gastric xanthoma and metachronous and synchronous gastric cancer. If the authors examined the detail of gastric xanthoma, please show them.

Reply: Thank you for your kind comment. The number and size of GX were not significantly different between the two groups. We would like to put these contents in the chapter of "*Endoscopic characteristics*" of "RESULTS" in the revised manuscript (P10).

4. Is there are different prevalence of gastric xanthoma between metachronous and synchronous gastric cancer?

Reply: Thank you for your kind comment. We investigated metachronous and synchronous gastric cancer (GC) together because it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC. So, according to our study, we don't know whether there are different prevalence of GX between metachronous and synchronous GC or not, unfortunately.

Minor comments

1. Please show the definition of the term, "metachronous and synchronous".

Reply: Thank you for your kind comment. We would like to revise the chapter of "*Patients*" of "MATERIALS AND METHODS" (P8).

2. Please show the diagnostic methods used to detect H. pylori infection if possible.

Reply: Thank you for your kind comment. We would like to revise the chapter of "*Patients*" of "MATERIALS AND METHODS" (P8).

3. What is O-P in the criteria of Kimura-Takemoto? Please explain it.

Reply: Thank you for your kind comment. O-P was listed with severe atrophy and the state that gastric atrophy progressed in the whole stomach. We would like to put these contents in the chapter of "*Patients*" of "MATERIALS AND METHODS" in the revised manuscript (P8).

Answers to Reviewer (Reviewer's code: 01468173)

Thank you very much for your kind comments.

We carefully studied your helpful comments and suggestions, and have revised our manuscript accordingly, including some additional sentences in the revised manuscript. We used red fonts to indicate the changes in the revised manuscript.

We would like to submit the revised version of manuscript. We hope our revised manuscript is now acceptable for "*World Journal of Gastrointestinal Oncology*".

Thank you for submitting your manuscript. The author analyzed that gastric xanthoma has a potential to be a predictive marker for multiple gastric cancers. I have read this paper and had some queries concerning the clinical application. The following are the essential aspects that are missing which can significantly improve the value of this review.

Major comments

1. How did the author think about the difference between a single cancer and multiple synchronous cancers? Great concern for the reader is to know whether a patient with gastric xanthoma is a high-risk patient or not for developing the metachronous cancer during follow-up. Could you comment about this issue?

Reply: Thank you for your kind comment. We investigated metachronous and synchronous gastric cancer (GC) together because it is often difficult to clearly distinguish metachronous GC from synchronous GC because of missed detection of synchronous GC. We think that a patient with gastric xanthoma (GX) is a high-risk patient for developing the metachronous GC during follow-up, as you think. However, according to our study, we don't know whether a patient with GX is a high-risk patient for developing the metachronous GC during follow-up or not, unfortunately.

2. There was no description of the diagnostic criteria about the gastric atrophy, intestinal metaplasia, or endoscopic features.

Reply: Thank you for your kind comment. We would like to revise the chapter of "*Patients*" of "MATERIALS AND METHODS" (P8-9).

3. In this study, all endoscopic features were evaluated by only one endoscopist. Did he get the information of enrolled patients before judgement?

Reply: Thank you for your kind comment. He did not get the information of enrolled patients before judgement.

4. In the discussion, the author has speculated the reason why gastric cancer developed more frequently in patients with gastric xanthoma. However, in this manuscript, the author discussed the difference between the single cancer and multiple cancers. Therefore, the author should speculate why multiple cancers developed more frequently in patients with gastric xanthoma.

Reply: Thank you for your kind comment. We would like to revise the chapter of "DISCUSSION" (P13).

Answers to Reviewer (Reviewer's code: 01047575)

Thank you very much for your kind comments.

We carefully studied your helpful comments and suggestions, and have revised our manuscript accordingly, including some additional sentences in the revised manuscript. We used red fonts to indicate the changes in the revised manuscript.

We would like to submit the revised version of manuscript. We hope our revised manuscript is now acceptable for "*World Journal of Gastrointestinal Oncology*".

This retrospective study aims to investigate predictive markers for metachronous and synchronous gastric cancer (GC). I want to point out some problems of the manuscript.

1、In the part of introduction, metachronous and synchronous gastric cancer, and gastric xanthoma should be introduced well.

Reply: Thank you for your kind comment. We would like to revise the chapter of "*Introduction*" (P7).

2、How is intestinal metaplasia assessed by image-enhanced endoscopy? Please state.

Reply: Thank you for your kind comment. We assessed intestinal metaplasia by white light imaging. We would like to revise the chapter of "*Patients*" of "MATERIALS AND METHODS" (P9).

3. Why is $P < 0.2$ selected as the cut-off value in the univariate analysis?

Reply: Thank you for your kind comment. In the multivariate logistic analysis, we selected baseline variates that was significant to some extent. In that case, the candidate of cut-off

value was $P < 0.1$ or 0.2, in general. So, in our study, baseline variates with $P < 0.2$ in univariate analysis were included in the multivariate logistic analysis.

4、There are many spelling mistakes in the manuscript.

Reply: Thank you for your kind comment. We would like to revise the manuscript.