

Manuscript NO: 28705

**Two cases of adenocarcinoma occurring in sporadic fundic gland polyp
observed by magnifying endoscopy with narrow band imaging**

Dear Editors and Reviewers

Thank you for your letter and reviewers' comments concerning our manuscript entitled "Two cases of adenocarcinoma occurring in sporadic fundic gland polyp observed by magnifying endoscopy with narrow band imaging" (EPSS Manuscript No: 28705).

Those comments are valuable and very helpful for revising and improving our paper. According to your advice, we have revised our manuscript quite intensively. Revised portion are marked in red in the paper.

We hope that this revised version of our manuscript will be deemed suitable for publication in the *World Journal of Gastroenterology*.

Yours faithfully,

Correspondence author; Tetsuya Ueo, M.D., Ph.D.

Department of Gastoroentelogy,Oita Red Cross Hospital,

E-mail: ueo14@athena.ocn.ne.jp

Point-by-point response to Reviewers' comments

Reviewer 02954019

Comment 1) Minor point 1. Based on the findings of this case report, we must encounter more frequently a large size of early gastric cancer originated from fundic gland polyps in daily clinical practice. However, such endoscopic findings have not been known, to date. What is the fate of this well differentiated adenocarcinoma from fundic gland polyps? Is there a possibility that such cancer does not increase in size or even diminish spontaneously? Authors should refer to this point in Discussion.

Response to comment 1) Authors appreciate insightful comments regarding our manuscript. As reviewer indicated, there is no report of advanced adenocarcinoma from fundic gland polyp (FGP), especially in sporadic type. Therefore, we speculate that well differentiated adenocarcinoma from sporadic FGP may not have such malignant potential. We also speculate that there is a possibility that such cancer does not increase in size or even diminish spontaneously.

We have added the following sentences in Discussion section:

Considering the fate of this well-differentiated adenocarcinoma from sporadic FGP, there is no report of advanced adenocarcinoma from sporadic FGP. Therefore, we speculate that such cancer has less malignant potential, and may not increase in size or even diminish spontaneously.

Comment 2) The Reference concerning the background mucosa of fundic gland polyps (no H. pylori infection without atrophy) should be added. Kishikawa et al referred to the background mucosa of fundic gland polyps in Clin Res Hepatol Gastroenterol 2014, 38: 505-12.

Response to comment 2) According to reviewer's advice, we have revised the following sentences in Discussion and added the reviewer's recommended reference as follows:

However, FGPs have important clinical significance in that they basically occur in gastric mucosa without atrophic gastritis or H. pylori infection [10, 11].
Reference [11], Kishikawa H, Kaida S, Takarabe S, Miyoshi J, Matsukubo T, Miyauchi J, Tanaka Y, Miura S, Nishida J. Fundic gland polyps accurately predict a low risk of future gastric carcinogenesis. Clin Res Hepatol Gastroenterol 2014; 38: 505-512 [PMID: 24637176, DOI: 10. 1016/j. clinre. 2014. 01. 008]

Reviewer 01430832

Comment 1) The incidence of low grade dysplasia in systemic or sporadic FGP of 25% is only seen in FAP, never in patients under proton pump inhibitors.

Response to comment 1) As reviewer indicated, there is no report of dysplasia from FGP in patients under proton pump inhibitors to our best knowledge. We have added the following sentences in Discussion along with appropriate reference as follows:

Although it is unclear whether dysplasia occurs in such PPIs associated FGPs

[15], PPIs have been widely used in clinical practice.

Reference [15], **Tran-Duy A**, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD.

Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric

Cancer: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016;

doi: 10.1016/j.cgh.2016.05.018. [Epub ahead of print] [PMID: 27211501, DOI: 10.

1016/j. cgh. 2016. 05. 018]

Comment 2) The differentiation made using NBI is the first time reported and is indeed very accurate. However, this differentiation can be also easily noted by using conventional endoscopy.

Response to comment 2) As reviewer indicated, these lesions can be detected using conventional endoscopy by their reddish coloration. However, it is very difficult to distinguish from other reddish gastric polyps such as hyperplastic polyp without findings of magnifying endoscopy of NBI.

Comment 3) I am very concerned with the finding of dysplasia or adenocarcinoma in systemic FGPs. This polyps are every day more common in adults undergoing upper endoscopy examinations and in patients under proton pump inhibitors (sometimes having more than 20 polyps). Both cases reported here didn't take the proton pump inhibitors nor had FAP. It would have been appreciated if they had speculated something more in the discussion about this

finding.

Response to comment 3) According to reviewer's comments, we have revised the following sentences in Discussion along with a reference as follows:

Furthermore, a recent report from systematic review and meta-analysis revealed that long-term use of PPIs therapy increase the risk of FGPs [15]. Although it is unclear whether dysplasia occurs in such PPIs associated FGPs [15], PPIs have been widely used in clinical practice. It is expected that we encounter FGPs more frequently in future, and may encounter FGPs with cancer in such cases.

Reference [15], **Tran-Duy A**, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; doi: 10.1016/j.cgh.2016.05.018. [Epub ahead of print] [PMID: 27211501, DOI: 10.1016/j.cgh.2016.05.018]