**ANSWERING REVIEWERS**

April 25th, 2021

Monjur Ahmed, Florin Burada, Rosa M Jimenez Rodriguez, and Pashtoon Kasi
Editors-in-Chief
World Journal of Gastrointestinal Oncology

**RE: Response to Decision Letter**

Dear Editors,

Thank you for revising and providing constructive comments on our manuscript ID 61028 titled "**Sporadic fundic gland polyps with dysplasia or carcinoma: Clinical and endoscopic characteristics**." We have revised our manuscript on the basis of your comments and suggestions and have provided point-by-point responses to your comments, where applicable.

We hope that our revised manuscript is now suitable for publication in your journal.

We look forward to hearing from you at your earliest convenience.

Sincerely,

Wataru Sano
Gastrointestinal Center, Sano Hospital
2-5-1 Shimizugaoka, Tarumi, Kobe, Hyogo 655-0031, Japan
Tel: (+81) 78-785-1000
Fax: (+81) 78-785-0077

E-mail: watasano@yahoo.co.jp

**Response to reviewers' comments**

**Reviewer 1:**

1. ***I read with interest this manuscript on FGPD/CAs. FGPs are a common finding in endoscopy, with little emphasis in the literature on the risk of FGPD/CAs and a management strategy when identified. The authors should be commended for an excellent review of the literature. My only suggestion is that they elaborate on the potential management algorithm: 1) For FGP without D/CA, do the authors recommend surveillance and if so how frequent? 2) If a FGP with dysplasia is identified, do the authors recommend endoscopic resection? 3) If a FGP with dysplasia is identified, for how long do the authors recommend q3-5y surveillance? Does surveillance vary depending on whether the lesion was resected? 4) If abnormal surface features during optical evaluation are identified, do the authors feel that biopsy is sufficient or should endoscopic resection be undertaken?***

**Response:** Thank you for your pertinent comments.

Please find below our point-by-point responses to your questions.

*1) For FGP without D/CA, do the authors recommend surveillance and if so how frequent?*

Although a longer follow-up period might be acceptable, we recommend following it up every 3–5 years, since some FGPDs may be

difficult to distinguish from ordinary FGPs.

*2) If a FGP with dysplasia is identified, do the authors recommend endoscopic resection?*

Yes, we recommend removing it endoscopically.

*3) If a FGP with dysplasia is identified, for how long do the authors recommend q3-5y surveillance? Does surveillance vary depending on whether the lesion was resected?*

If dysplasia within FGP is identified through biopsy, we recommend not following it up, but removing it endoscopically. After removal, we recommend performing surveillance every 3–5 years.

*4) If abnormal surface features during optical evaluation are identified, do the authors feel that biopsy is sufficient or should endoscopic resection be undertaken?*

We recommend performing histological evaluation with biopsy. If no findings of dysplasia or carcinoma are identified, a follow-up is acceptable; however, if either of them is identified, we recommend removing it endoscopically.

As suggested, we have revised the following text in the section of PROPOSAL OF A MANAGEMENT ALGORITHM FOR SPORADIC FGPs (Page 13 of 38):

The procedure is as follows: (1) when sporadic FGP is detected, regardless of its size, perform white light observation and, if possible, additional magnifying NBI; (2) during white light observation, pay attention to the presence of redness, irregular surface structure, depression, or erosion in the lesions; (3) during magnifying NBI observation, pay attention to the presence of irregular microvessels on the lesion surface; (4) if none of the above findings are present,

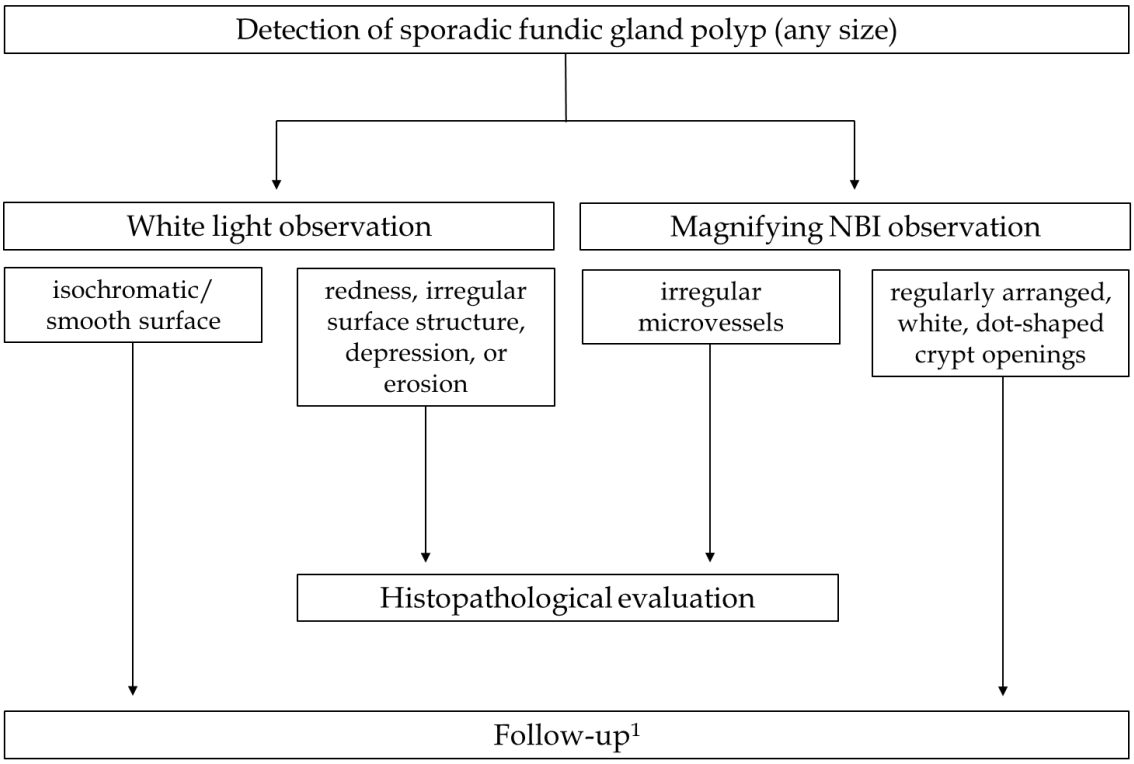
follow-up is acceptable, but if any of them are present, perform histological evaluation by biopsy or endoscopic resection; and (5) if multiple FGPs (*e.g.*, ≥20) are detected in patients receiving PPI therapy, consider reducing or discontinuing PPI or switching to H2-receptor antagonists. We believe that the above procedure can detect FGPCAs with high sensitivity. Considering that Lloyd *et al*[32] have reported that no gastric cancer occurred during the average follow-up period of 4.4 years for sporadic FGPDs, the appropriate follow-up period should be set to every 3 to 5 years.

to

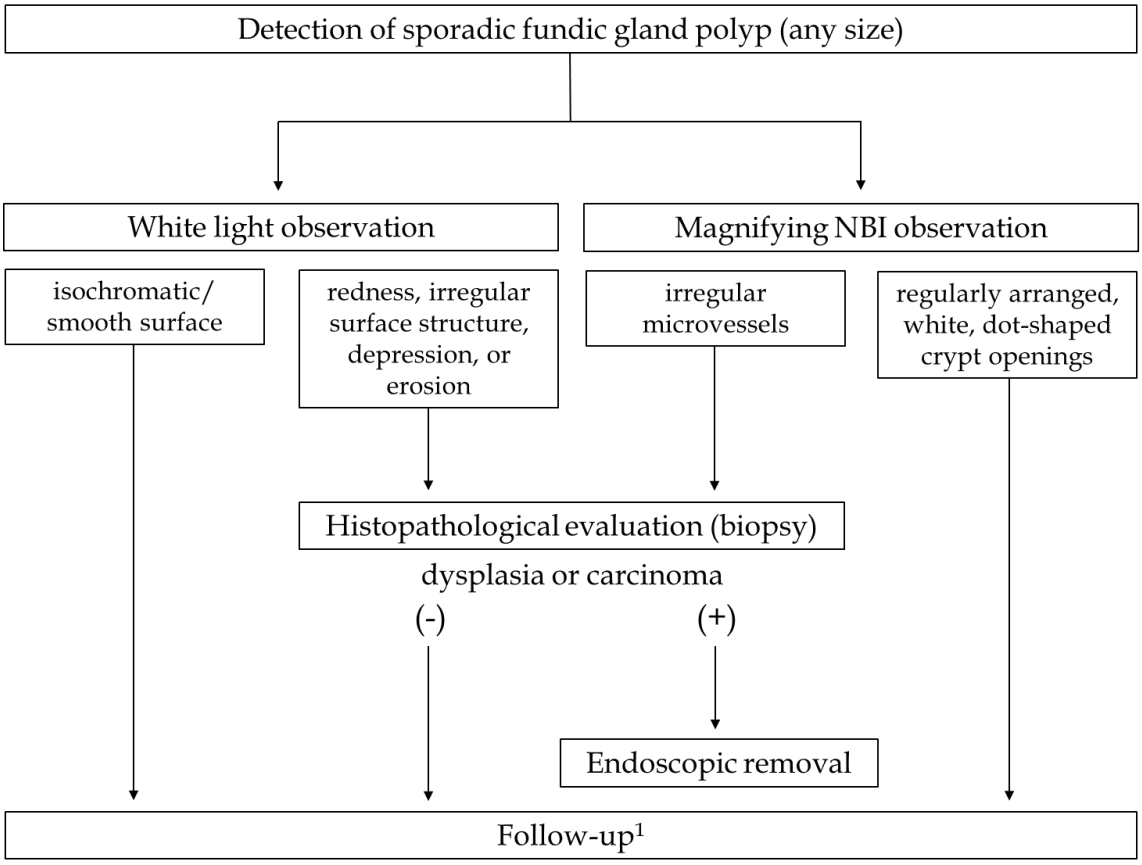
The procedure is as follows: (1) when a sporadic FGP is detected, regardless of its size, perform white light observation and, if possible, additional magnifying NBI; (2) during white light observation, pay attention to the presence of redness, irregular surface structure, depression, or erosion in the lesions; (3) during magnifying NBI observation, pay attention to the presence of irregular microvessels on the lesion surface; (4) if none of the above findings are present, a follow-up is acceptable; however, if any of them are present, perform histological evaluation with biopsy; (5) if no findings of dysplasia or carcinoma are identified through biopsy, a follow-up is acceptable; however, if either of them is identified, remove it endoscopically; and (6) if multiple FGPs (*e.g.*, ≥20) are detected in patients receiving PPI therapy, consider reducing or discontinuing PPI or switching to H2-receptor antagonists. We believe that the above procedure can detect and remove

FGPCAs with high sensitivity. Moreover, considering that some FGPDs may be difficult to distinguish from ordinary FGPs and that Lloyd *et al*[32] have reported that no gastric cancer occurred during the average follow-up period of 4.4 years for sporadic FGPDs, the appropriate endoscopy intervals should be set to every 3–5 years in both the non-removal follow-up and post-removal surveillance groups.

In addition, we have revised the Figure 3 as follows (Page 34 of 38):




to




**Reviewer 2:**

1. ***This case series explain the clinical, endoscopic and histologic characteristics of sporadic fundic gland polyps with carcinoma. The data on this topic is limited. I wonder if any reports about the association with smoking, alcohol use or socioeconomic status (factors contributing to mucosal atrophy) exists. Evaluating these possible risk factors could be proposed as future direction of studies.***

**Response:** Thank you for your pertinent comments.

In this review, majority of the patients with sporadic FGPD/CAs were

middle-aged women receiving PPI therapy and without *H. pylori* infection. However, all these characteristics were similar to those of FGPs without dysplasia, and no clinical characteristics different from those of ordinary FGPs were obtained, which implies that it is difficult to discern FGPD/CAs based on the clinical characteristics alone and that *H. pylori* infection is not likely to be involved in the malignant transformation of FGPs. In addition, Lloyd *et al*[32] and Arnason *et al*[37] have reported that the proportion of the patients with non-steroidal anti-inflammatory drug use, alcohol use, or smoking among the patients with sporadic FGPDs was low (20%–36%), suggesting that these factors are also not likely to be involved in the malignant transformation of FGPs.

Attard *et al*[3] have reported that dysplasia within FGPs was more common in familial adenomatous polyposis patients on long-term PPI therapy than in those without PPI therapy. Fukuda *et al*[33] have stated that PPI therapy may affect the progression of dysplasia within FGPs through their research on the PPI-treated patient harboring FGPD/CA with long-term follow-up. Currently, it remains unclear whether PPI therapy is involved in the malignant transformation of FGPs. However, considering that the development of FGPs in association with PPI therapy is reversible, we recommend reducing or discontinuing PPIs or switching to H2-receptor antagonists for carcinogenesis prevention, at least in cases with multiple FGPs.

As suggested, we have revised the following text in the section of CLINICAL CHARACTERISTICS OF SPORADIC FGP WITH OR WITHOUT DYSPLASIA/CARCINOMA (Page 7 of 38):

> All these characteristics were similar to those of FGPs without dysplasia,

and no clinical characteristics different from those of ordinary FGPs were obtained, which implies that it is difficult to discern FGPD/CAs from clinical characteristics alone.

to

All these characteristics were similar to those of FGPs without dysplasia, and no clinical characteristics different from those of ordinary FGPs were obtained, which implies that it is difficult to discern FGPD/CAs based on the clinical characteristics alone and that *H. pylori* infection is not likely to be involved in the malignant transformation of FGPs. In addition, Lloyd *et al*[32] and Arnason *et al*[37] have reported that the proportion of the patients with non-steroidal anti-inflammatory drug use, alcohol use, or smoking among the patients with sporadic FGPDs was low (20%–36%), suggesting that these factors are also not likely to be involved in the malignant transformation of FGPs.

***2. Another important issue is defining the background of mucosal atrophy when finding a sporadic fundic gland polyp. The authors have proposed that some polyps could be followed up without excision (table one). This suggestion does not seem to be a reasonable approach especially in patients with diffuse mucosal atrophy in high incidence area with gastric cancer. Please clarify this issue and express more data to classify high risk patients for developing fundic gland polyps with carcinoma.***

**Response:** Thank you for your pertinent comments.

In this review, majority of the FGPD/CAs occurred in the *H. pylori*-uninfected

stomachs without mucosal atrophy, as with ordinary FGPs without dysplasia. Some FGPs occur also in the *H. pylori*-eradicated stomachs and very rarely in the *H. pylori*-positive stomachs, and Kawase *et al*[27] have reported a case of FGPCA in the patient with *H. pylori* infection. However, considering the small number of the *H. pylori*-positive patients among the patients with FGPD/CAs (Table 1), it seems unlikely that *H. pylori* infection and atrophic gastric mucosa are involved in the malignant transformation of FGPs. In addition, considering the increasing prevalence of FGPs, rarity of FGPD/CAs, and slow progression of FGPDs to cancer, we believe that FGPs can be left *in situ* and be followed up every 3–5 years, except for FGPs with endoscopic findings suspected of FGPD/CAs. However, as described in the section of Management, when an FGP is detected in the *H. pylori*-eradicated stomach, a shorter endoscopy interval is necessary because of the higher risk of developing conventional gastric cancer, which does not originate from an FGP, in the atrophic mucosa. Nonetheless, even in the *H. pylori*-eradicated stomachs, we believe that it is not necessary to remove FGPs because of the low possibility of *H. pylori* infection and atrophic gastric mucosa involving the malignant transformation of FGPs.

As suggested, we have revised the following texts in the sections of Endoscopic Characteristics and Management to clarify the association among FGPs, *H. pylori* infection, mucosal atrophy, and conventional gastric cancer:

1) Sporadic FGPs without dysplasia ordinarily occur in the body or fundus of the non-atrophic stomachs. (Page 9 of 38)

   to

   Sporadic FGPs without dysplasia ordinarily occur in the body

or fundus of the *H. pylori*-uninfected stomachs without mucosal atrophy.

2) However, a shorter follow-up period is necessary for patients after *H. pylori* eradication because of the higher risk of developing conventional gastric cancer that does not originate from FGP[46]. (Page 13 of 38)

to

However, a shorter endoscopy interval is necessary for the *H. pylori*-eradicated patients with sporadic FGP because of the higher risk of developing conventional gastric cancer, which does not originate from an FGP, in the atrophic mucosa[46].