

Lian-Sheng Ma

Editor-in-Chief

World Journal of Clinical Cases

September 1, 2020

Dear Dr. Lian-Sheng Ma:

We appreciate the comments and suggestions of the reviewers regarding our manuscript titled, “Endoscopic submucosal dissection as alternative to surgery for complicated gastric heterotopic pancreas.” We thank you for the opportunity to revise and resubmit our manuscript.

We have carefully reviewed the reviewers’ comments and revised the manuscript accordingly. Our point-by-point responses are provided below, and changes to the manuscript are highlighted in blue.

We would be happy to make further corrections, if necessary, and look forward to hearing from you.

Sincerely,

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Point-by-point response to the reviewers' comments

Thank you for reviewing our manuscript. Our responses to the reviewers' queries are as follows:

Responses to Reviewer 1

Comment 1: As there were only 5 cases, the authors should use range instead of IQR for the continuous variables (age, size, procedure time, etc.).

Response: Thank you for your valuable comments. We have corrected the values presented as IQR to ranges for the continuous variables. However, in cases with a lesion size change according to conservative management, median values with their IQR would be better to understand. Table 1 shows the lesion size change and follow-up period of each patient. We have revised this content in the Abstract (P2) and Results (P4 and P5) sections as follows:

“The age of the 5 patients ranged from 28 to 43 years. Two of the patients were males. All lesions were located in the greater curvature of the antrum. On endoscopic ultrasonography during the pain episode, all lesions were located across the muscularis mucosa, submucosa, and proper muscle layers. The median lesion size was 20 (IQR, 18–35) during the pain episode at the time of the diagnosis of complicated GHP, and 15 mm (IQR, 9–33) at the time of ESD. The procedure time ranged from 15 to 120 minutes. There were no procedure-related adverse events such as perforation or bleeding. The length of hospital stay after the procedure ranged from 2 to 4 days. All patients were symptom free during the median follow-up period of 46.0 months (IQR, 39–60).”

“Five patients were diagnosed with complicated GHP and underwent ESD during the study period. The characteristics of each patient and lesion and procedure-related outcomes are shown in Table 1 and Figure 3. The age of the 5 patients ranged from 28 to 43 years. Two of the patients were males. All lesions were located in the greater curvature of the antrum and appeared to be subepithelial. Three lesions showed a typical central indentation, while 2 lesions were accompanied by surface ulcerations. All lesions involved the muscularis mucosa, submucosa, and muscularis propria layer on EUS. The median lesion size was 20 mm (IQR, 18–35) at the time of the diagnosis of complicated GHP and decreased after conservative treatment (median, 15 mm, [IQR, 9–33]).

The procedure time ranged from 15 to 120 minutes. There were no procedure-related adverse events such as perforation or bleeding. The length of hospital stay after the procedure ranged from 2 to 4 days. During the median follow-up period of 46.0 months (IQR, 39–60), no

patients experienced symptom recurrence.”

Comment 2: The EUS findings showed that all of the lesions were involved the muscular propria. The ESD technique is a method to dissect the submucosal layer, so why did the authors decided to select ESD for the lesion deeper than the submucosal layer?

Response: Thank you for your comments. GHP is a tumor with transmural growth, but most cases are limited to the second and third layers. In our cases, the GHP had acute pancreatitis and the size of the tumor increased owing to acute inflammation and complication such as pseudocyst. The tumor increased in size not only into the gastric lumen but also toward the proper muscle layer. In this situation, the entire tumor is impossible to remove with ESD, which dissects the submucosal layer. However, we believed that the inflammatory condition would improve after conservative treatment as in the acute phase treatment of acute pancreatitis, and indeed, the tumor size was decreased. Therefore, we could remove the GHP using ESD.

Comment 3: The pathological findings of case 1 and 2 showed that the mucosal muscular propria was included in the ESD resected specimen. Didn't they have a complication of perforation?

Response: Cases 1 and 2 were resected up to a part of the proper muscle layer, but no procedure-related complications such as perforation or bleeding occurred. As the stomach is wrapped by layers of subserosa and serosa outside the proper muscle layer, no risk of perforation due to damage of the proper muscle layer occurred.

Comment 4: In case 1 and 2, the margins of the resected lesions were positive. Thus, it is likely that the tissue of heterotopic pancreas remained. Did the symptoms improve or remain after ESD?

Response: In cases 1 and 2, the deep resection margin was positive for tumor involvement. After the procedure, the abdominal pain improved, and no symptom recurrence was observed during the follow-up period. As we mentioned in the Discussion section, these results suggest that the significant cauterization effect at the deep resection margin of the lesion during ESD

generally ablates any remnant cells.

Comment 5: In case 3 and 4, the tissue of the heterotopic pancreas itself was not included in the resected tissue. Thus, the causative lesion of the symptoms was not removed. Why can it be considered as an effective treatment?

Response: Thank you for your comments. In cases 3 and 4, the patients had no confirmed pancreatic tissue in the histopathological report. In cases 3 and 4, the GHP size significantly increased with the development of pancreatitis, and the ulceration on the mucosal surface occurred due to the sudden increase in size. After conservative treatment, GHPs were significantly reduced in size. However, there are no confirmed pancreatic tissues in the histopathologic report after ESD for remnant lesions. We suggested the reasons for this situation as follows. First, the pancreas tissue was eliminated because of the ulcer. Second, the severe inflammation resulted in the necrosis of normal pancreatic tissue, and there are no normal pancreatic tissues after conservative treatment. Third, significant cauterization effect at the deep resection margin of the lesion during ESD generally ablates any remnant cells. In cases 3 and 4, the symptoms were improved after the procedure, and no symptom recurrence was observed during the long-term follow-up.

We revised this content in “Discussion” section (P7) as follows:

“And other two cases were confirmed only foreign body reactions and calcification on histopathologic report. We suggested the reasons for this situation as follows. First, the pancreas tissue was eliminated because of the ulcer. Second, the severe inflammation resulted in the necrosis of normal pancreatic tissue, and eventually, there are no normal pancreatic tissues after conservative treatment. Third, significant cauterization effect at the deep resection margin of the lesion during ESD generally ablates any remnant cells.”

Comment 6: What were the main pathological diagnosis of case 1, 2 and 5? There were only descriptions about the margins.

Response: All the pathological results indicated heterotopic pancreas. We have added the following contents in the “Results” section and “Table 1” as follows:

Case 1: “According to the histopathological report, the pancreatic tissue was within the proper muscle layer, and the peripheral resection margin was negative and the deep resection

margin was positive for tumor involvement.”

Case 2: “According to the histopathological report, the pancreatic tissue was extended to the proper muscle layer, and the peripheral resection margin, but not the deep resection margin, showed tumor involvement.”

Case 5: “The histopathological report indicated that the pancreatic tissue was located in the submucosa and there was no involvement of the peripheral or deep resection margins.”

Table 1:

CT findings at the time of diagnosis	Pathological diagnosis	Procedure time (min)
Ovoid-shaped lesion with a lobulating contour in the gastric antrum	Heterotopic pancreas	15
Enhancing mass-like and cystic lesions in the gastric antrum	Heterotopic pancreas	120
Subepithelial mass with an internal low-density portion in the gastric antrum	Calcification and foreign body reaction	27
Soft tissue lesion containing a cystic portion and tiny calcification in the gastric antrum	Calcification and foreign body reaction	17
Enhancing mass-like lesion in the gastric antrum	Heterotopic pancreas	26

Comment 7: The symptoms improved after ESD in case 3, 4, and 5, but they should consider the length of the follow-up period after the ESD. The median of it was described in the Discussion section, but the results should be described in the Results section.

Response: Thank you for your comments. Patient follow-up is summarized in Table 1. The follow-up period was 59 months for case 3, 45 months for case 4, and 46 months for case 5. We have also described the median follow-up period (46 months; IQR, 39–60 months) in the Results section (P5) as follows:

“During the median follow-up period of 46.0 months (IQR, 39–60), no patients experienced symptom recurrence.”

Comment 8: According to the suspicions described above, I suppose that it is difficult to conclude ESD as an effective and feasible treatment option for heterotopic pancreas. Rather, surgery can be considered as better as it can remove the lesion completely and reliably.

Therefore, the descriptions in the Discussion are too strong.

Response: Thank you for your comments. We agree with your point that the descriptions in the Discussion section are too strong. Surgery is more efficient for complete resection of GHP. However, more advanced ESD techniques have been developed, and the indication of the procedure is currently expanding. Our study suggests that endoscopic resection can be considered an alternative therapy to gastrectomy for the treatment of complicated GHP. Our experience is limited to only 5 cases, and further study with more patients will be needed to prove the effectiveness and feasibility of ESD. We have revised the conclusion in the Discussion section as follows:

“In conclusion, when patients with GHP experience recurrent severe acute abdominal pain, complicated GHP should be considered as a differential diagnosis. [Conservative treatment followed by ESD can be a feasible minimally invasive alternative to surgical resection.](#)”

Comment 9: In the method section, the authors diagnosed all of the involved lesions as “complicated GHP” before ESD procedure, but they also defined one of the criteria of “complicated GHP” as symptom resolution after ESD. Here’s a contradiction.

Response: Thank you for your valuable comments. We agree with your point about criteria (3) and that complicated GHP is the result of the procedure rather than the diagnosis before the procedure. We have corrected this in the Materials and Methods and Discussion sections as follows:

“[The diagnosis of complicated GHP was made when the patient with GHP had a recurrent severe abdominal pain and met at least one of the following criteria: \(1\) morphological change of the GHP on endoscopy, abdominal computed tomography \(CT\), or magnetic resonance imaging \(MRI\) during the pain episode and \(2\) elevated serum pancreatic enzyme level with normal pancreas on imaging.](#)”

Comment 10: The effect of the ablation of ESD may have some effect for small remnant tissue, but some of the remnant tissues were suspected as 10 mm or larger. Isn’t the description of Page 7 Line 24 an overstatement?

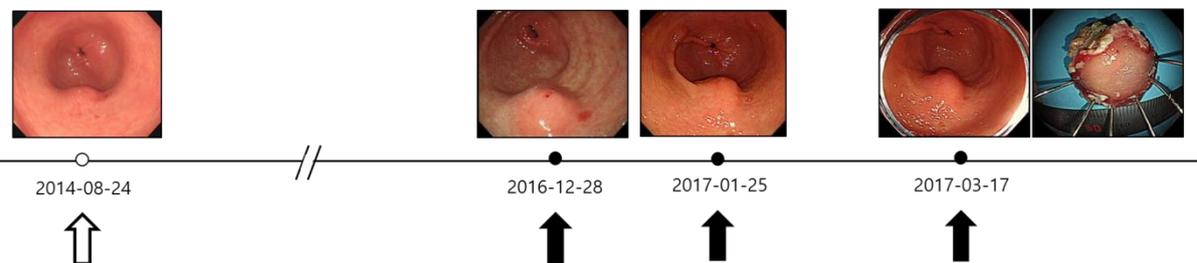
Response: Thank you for your comments. We agree with you that it is difficult to discuss the cauterization effect when the remnant tissue is suspected to be ≥ 10 mm. However, we dissected enough to expose the proper muscle layer and ablated the exposed muscle layer. The 5 cases we experienced had improved symptoms after the procedure and had no symptom recurrence during long-term follow-up. If deep dissection is performed within the range that does not cause perforation and ablation is performed sufficiently on the exposed lower layer, the cauterization effect on remnant tissues can be expected.

Comment 11: Figure 2B was drawn in Figure 2A. Please replace it to the correct figure.

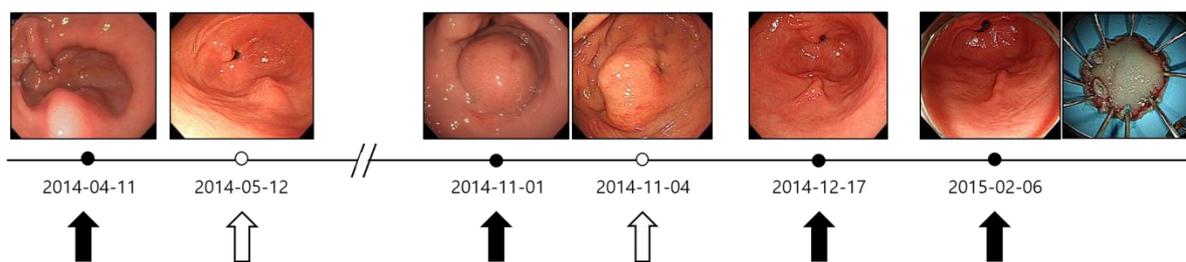
Response: Thank you for your comments. We have corrected “Patient 3” and added “Patient 5” in Figure 2 as follows:

“**Figure 2.** The clinical course of lesion size according to abdominal pain are summarized. (A) Patient 1, (B) Patient 3, (C) Patient 4, (D) Patient 5.”

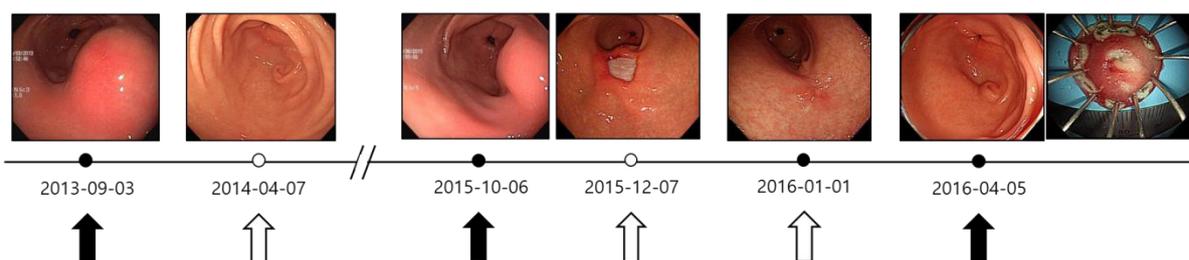
(A) Patient #1



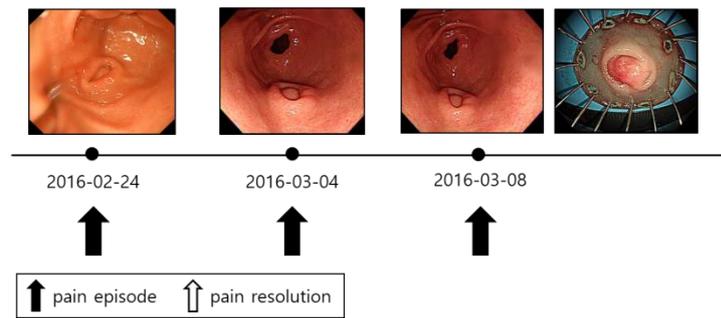
(B) Patient #3



(C) Patient #4



(D) Patient #5



Comment 12: In Table 1, “Procedure time” is supposed to be “ESD procedure time”. As for “Hospitalization”, is it for ESD? Then, “ESD hospitalization” is better.

Response: Thank you for your valuable comments. The hospitalization was for ESD as you supposed. We have revised the reason for hospitalization in Table 1 as follows:

“**Table 1.** Patient and lesion characteristics and procedure-related outcomes.”

CT findings at the time of diagnosis	Procedure time (min)	ESD hospitalization (days)	Follow-up (months)
Ovoid-shaped lesion with a lobulating contour in the gastric antrum	15	3	33
Enhancing mass-like and cystic lesions in the gastric antrum	120	4	60
Subepithelial mass with an internal low-density portion in the gastric antrum	27	3	59
Soft tissue lesion containing a cystic portion and tiny calcification in the gastric antrum	17	2	45
Enhancing mass-like lesion in the gastric antrum	26	2	46

Comment 13: In Table 1, description of CT findings are not findings, but diagnosis. Findings should be like high/low density, contrast effect, edematous change, etc.

Response: Thank you for your kind comments. We have revised the CT findings in Table 1 as follows:

“**Table 1.** Patient and lesion characteristics and procedure-related outcomes.”

CT findings at the time of diagnosis	Procedure time (min)	ESD hospitalization (days)	Follow-up (months)
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Ovoid-shaped lesion with a lobulating contour in the gastric antrum	15	3	33
Enhancing mass-like and cystic lesions in the gastric antrum	120	4	60
Subepithelial mass with an internal low- density portion in the gastric antrum	27	3	59
Soft tissue lesion containing a cystic portion and tiny calcification in the gastric antrum	17	2	45
Enhancing mass-like lesion in the gastric antrum	26	2	46

Responses to Reviewer #2

Comment 1: Several previous reports already described the clinical outcomes of the ESD for GHP: • Zhong YS, Shi Q, Yao LQ, Zhou PH, Xu MD, Wang P. Endoscopic mucosal resection/endoscopic submucosal dissection for gastric heterotopic pancreas. *Turk J Gastroenterol.* 2013;24(4):322-329. • Makarewicz W, Bobowicz M, Dubowik M, Kosinski A, Jastrzebski T, Jaskiewicz J. Endoscopic submucosal dissection of gastric ectopic pancreas. *Wideochir Inne Tech Maloinwazyjne.* 2013;8(3):249-252. doi:10.5114/wiitm.2011.33709 • Liu X, Wang G, Ge N, et al. Endoscopic removal of symptomatic gastric heterotopic pancreas: a report of nine cases. *Surg Innov.* 2013;20(6):NP40-NP46. doi:10.1177/1553350613499453 Therefore, I do not think the results or conclusions made in this manuscript adds anything novel to the current knowledge.

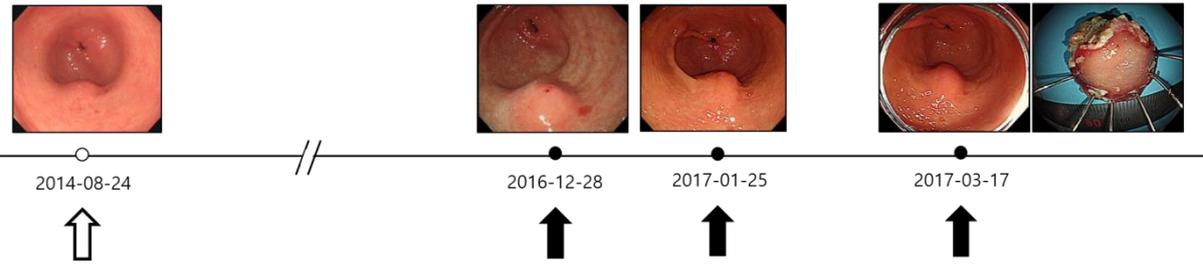
Response: Thank you for your comments. As you mentioned above, several studies on endoscopic resection of asymptomatic GHP or symptomatic GHP with abdominal pain have been reported. However, the 5 cases we experienced were not just asymptomatic or symptomatic GHPs but were GHPs complicated with pancreatitis or pseudocyst. To our knowledge, endoscopic resection of complicated GHP has not been reported, other than the video case we reported in *Gastrointestinal Endoscopy* (Gong EJ, Kim DH, Cho CJ, et al. Endoscopic submucosal dissection of ectopic pancreas with pancreatitis and pseudocyst formation. *Gastrointestinal endoscopy* 2015; 82: 1126. 2015/07/29. DOI: 10.1016/j.gie.2015.06.029.). Surgery is a general treatment for complicated GHP. However, our patients experienced symptom improvement after endoscopic resection of the complicated GHP, which suggests that ESD may be an alternative treatment to surgery. Further studies are needed with a large number of patients.

Comment 2: In figure 2 the part – A (Patient 1) is missing, instead of it, part B (patient 3) is replicated.

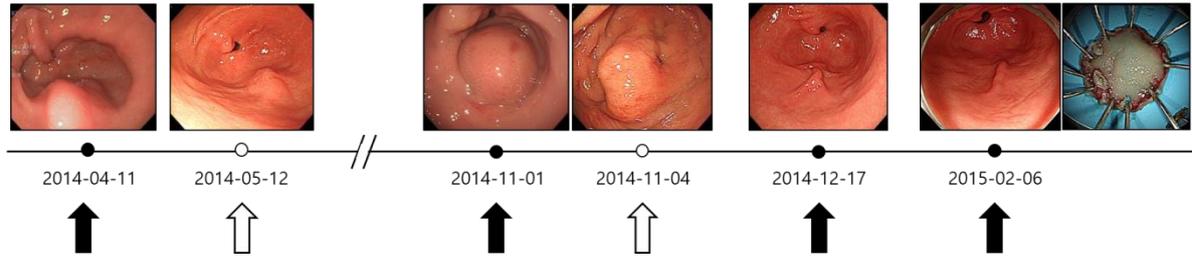
Response: Thank you for your comments. We have corrected “Patient 3” and added “Patient 5” in Figure 2 as follows:

“**Figure 2.** The clinical course of lesion size according to abdominal pain are summarized. (A) Patient 1, (B) Patient 3, (C) Patient 4, (D) Patient 5.”

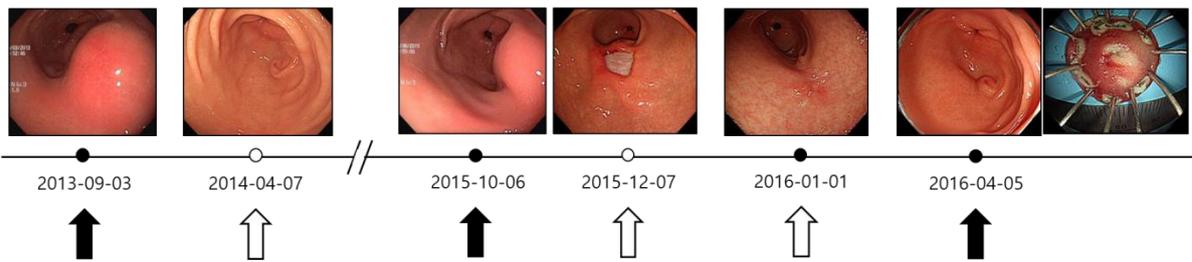
(A) Patient #1



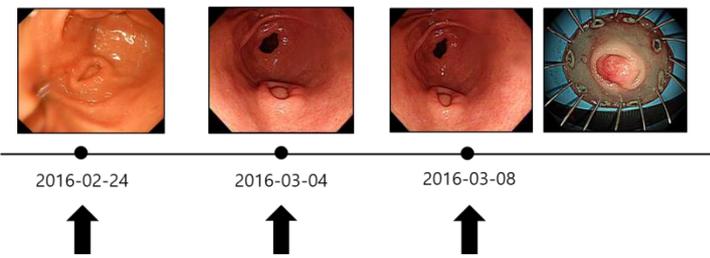
(B) Patient #3



(C) Patient #4



(D) Patient #5



↑ pain episode ↑ pain resolution

Responses to Reviewer #3

Comment 1: Is EUS-FNA indicated for ectopic pancreas to ensure prior diagnosis? Did patients 3 and patient 4 need to undergo ESD?

Response: Thank you for your comments. The FNAB (fine needle aspiration and biopsy) indications for subepithelial tumors, although slightly vary by report, are commonly known as hypoechoic tumors of 2 cm or more. Four out of five patients in our reports were adapted for tissue biopsy because they were over 2 cm in size during acute pancreatitis, but FNAB was not performed for the following reasons: 1) The characteristic of the tumor observed in the EGD and EUS strongly suggested the GHP. 2) EUS findings also did not only show hypoechoic tumors. 3) The pain was very severe due to the acute inflammation, and 4) After the improvement of symptoms, the size of the tumor was significantly reduced and FANB was not adapted.

Patients 3 and 4 wanted observation without endoscopic resection after conservative management and were followed up in the outpatient clinic. However, as shown in the clinical progress presented in Figure 2, they complained of repeated abdominal pain with complicated GHP. Eventually, they were treated with endoscopic resection. The symptoms improved after ESD, and the abdominal pain did not recur during the follow-up period.

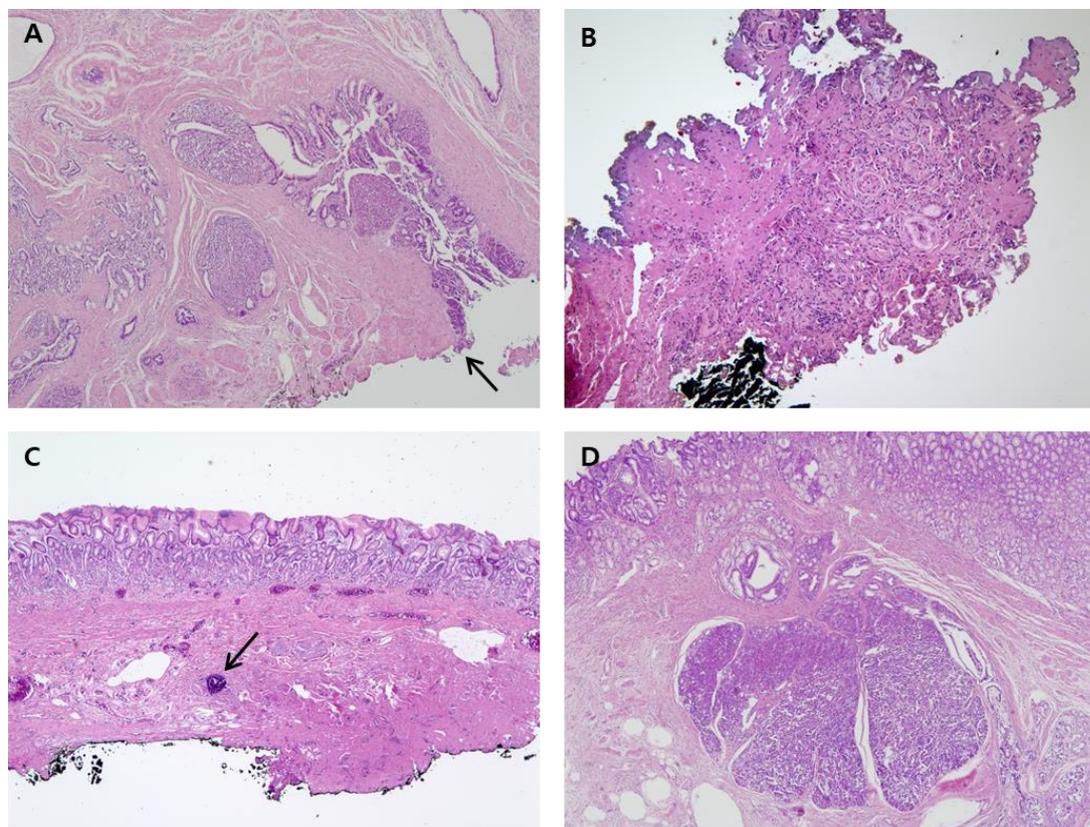
Comment 2: There is too much discrepancy between EUS findings and pathological findings in the case of Figure 1. Did you intend to perform full-thickness excision according to the EUS findings? How do you identify the resection line of the proper muscle layer?

Response: Thank you for your comments. GHP is a tumor with transmural growth, but most cases are limited to the second and third layers. In our cases, the GHP had acute pancreatitis and the size of the tumor increased owing to acute inflammation and complication such as pseudocyst. The tumor increased in size not only into the gastric lumen but also toward the proper muscle layer. In this situation, the entire tumor is impossible to remove with ESD, which dissects the submucosal layer. However, we believed that the inflammatory condition would improve after conservative treatment as in the acute phase treatment of acute pancreatitis, and indeed, the tumor size was decreased. Therefore, we could remove the GHP using ESD.

Comment 3: Pathological figures of cases in which the lesion extends to the muscle layer should also be presented.

Response: Thank you for your comments. In Patients 1 and 2, the heterotopic tissue was extended to the proper muscle layer. The case of Patient 2 has already been published in *Gastrointestinal Endoscopy* as a video case (Gong EJ, Kim DH, Cho CJ, et al. Endoscopic submucosal dissection of ectopic pancreas with pancreatitis and pseudocyst formation. *Gastrointestinal endoscopy* 2015; 82: 1126. 2015/07/29. DOI: 10.1016/j.gie.2015.06.029.). We have also cited the paper in the Results section (P5). We have added the histopathological picture of each patient in Figure 4 as follows:

Figure 4. Representative histologic images of heterotopic pancreas. (A) Patient 1: Pancreatic tissue is in proper muscle with involvement of resection margin (arrow) (hematoxylin-eosin; original magnification, $\times 40$). (B) Patient 3: There is focal nest of cells and bluish material with fibrosis and severe cautery artifact ($\times 100$). (C) Patient 4: Submucosal fibrosis with foreign body reaction and dystrophic calcification (arrow) was noted ($\times 40$). (D) Patient 5: Pancreatic tissue is in submucosa overlying gastric mucosa ($\times 40$).



Comment 4: Zhou et al. World Journal of Surgical Oncology(2019)17:69 paper should be cited.

Response: Thank you for your comments. We have cited the paper in the Discussion section (P7) as follows:

“In asymptomatic GHP, close observation with serial follow-up endoscopy is sufficient because the risk of complications or malignant changes is extremely low. However, if symptoms or complications occur, complete resection should be considered.^{15, 23} In a previous study, ESD was safe and feasible for curative treatment of GHP. This procedure was performed for asymptomatic or symptomatic GHP with a nonspecific abdominal pain, and approximately 65% of lesions originated from the mucosa or the submucosa layer.²⁴ The complete resection of complicated GHP by ESD is challenging because the lesion is usually located in the deep submucosal and proper muscle layers.”

Responses to Reviewer #4

Comment 1: ESD for GHP has concerns including the risk of incomplete resection and perforation. Therefore, the vertical margin of the resected specimens is a notable point. The authors should clarify which layer they intended to dissect while performing ESD, by showing histological images of the resected specimens of each patient. Furthermore, the authors should discuss the technical difficulties associated with ESD for GHP in detail.

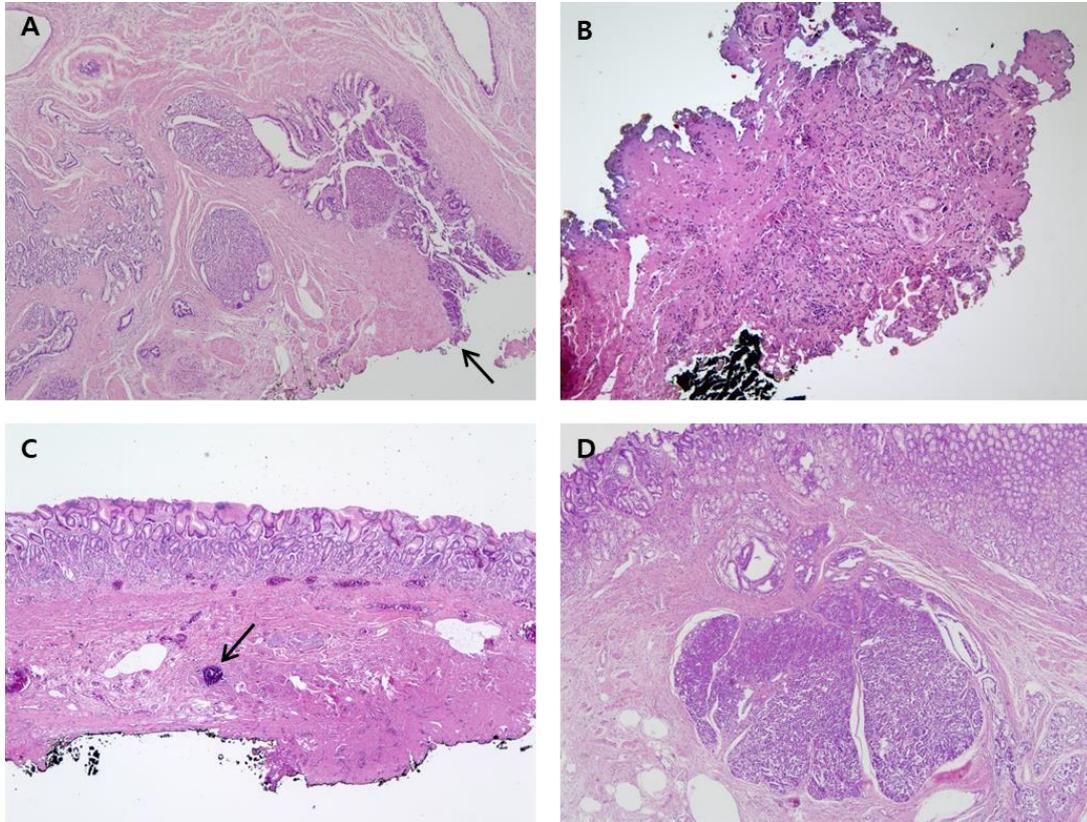
Response: Thank you for your comments. In patients 1 and 2, the resection was up to a part of the proper muscle layer. In patients 3, 4, and 5, the resection was up to the submucosal layer. The case of patient 2 has already been published in *Gastrointestinal Endoscopy* as a video case. We have also cited that paper in the Results section (P5). We have added the histopathological picture of each patient in Figure 4.

Furthermore, GHP is a tumor of transmural growth. In case of GHP with acute pancreatitis, each layer is difficult to distinguish because of the inflammatory changes. Even if the inflammation has improved, endoscopic dissection is difficult because the tumor boundary is not clear owing to the tissue changes caused by the inflammation. Therefore, dissection as close as possible to the proper muscle based on the easily identifiable layer, rather than on the tumor with an unclear border, would be a better tip for complete resection. We have revised this content in Discussion section (P7) as follows:

“When GHP is accompanied by complications including pancreatitis like in a normal pancreas, the lesion enlarges because of tissue inflammation and edema. In this case, each layer is difficult to distinguish because of the inflammatory changes. Even if the inflammation has improved, endoscopic dissection is difficult because the tumor boundary is not clear owing to the tissue changes caused by the inflammation. Therefore, dissection as close as possible to the proper muscle based on the easily identifiable layer, rather than on the tumor with an unclear border, would be a better tip for complete resection. In this study, there were two cases of endoscopically complete but pathologically incomplete resection of the deep resection margin. The possibility of recurrence from remnant tissues was closely followed up, but neither symptoms nor tumors recurred during the median follow-up period of 46.0 months. It might suggest that the significant cauterization effect at the deep resection margin of the lesion during ESD generally ablates any remnant cells.”

“**Figure 4.** Representative histologic images of heterotopic pancreas. (A) Patient 1: Pancreatic tissue is in proper muscle with involvement of resection margin (arrow) (hematoxylin-eosin; original magnification, $\times 40$). (B) Patient 3: There is focal nest of cells

and bluish material with fibrosis and severe cautery artifact ($\times 100$). (C) Patient 4: Submucosal fibrosis with foreign body reaction and dystrophic calcification (arrow) was noted ($\times 40$). (D) Patient 5: Pancreatic tissue is in submucosa overlying gastric mucosa ($\times 40$).”



Comment 2: (Figure 2) The clinical course of Patient 3 appears to have overlapped.

Response: Thank you for your comments. We have corrected “Patient 3” in Figure 2 and attached the revised figure in response to comment 3.

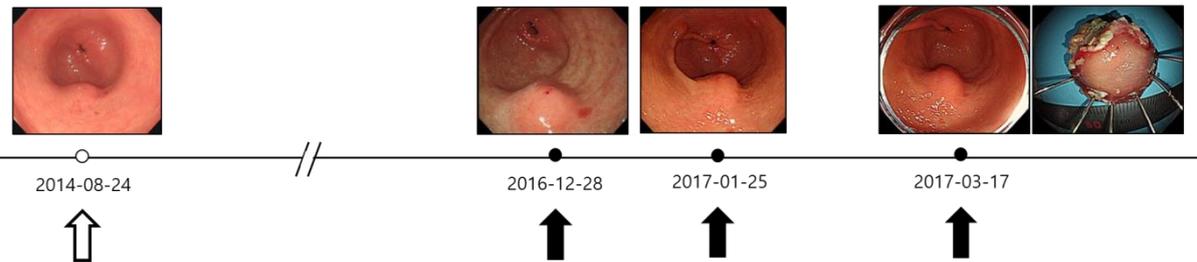
Comment 3: (Figure 2) The authors should also show the clinical course of Patients 2 and 5.

Response: Thank you for your comments. The case of Patient 2 has already been published in *Gastrointestinal Endoscopy* as a video case (Gong EJ, Kim DH, Cho CJ, et al. Endoscopic submucosal dissection of ectopic pancreas with pancreatitis and pseudocyst formation. *Gastrointestinal endoscopy* 2015; 82: 1126. 2015/07/29. DOI: 10.1016/j.gie.2015.06.029.).

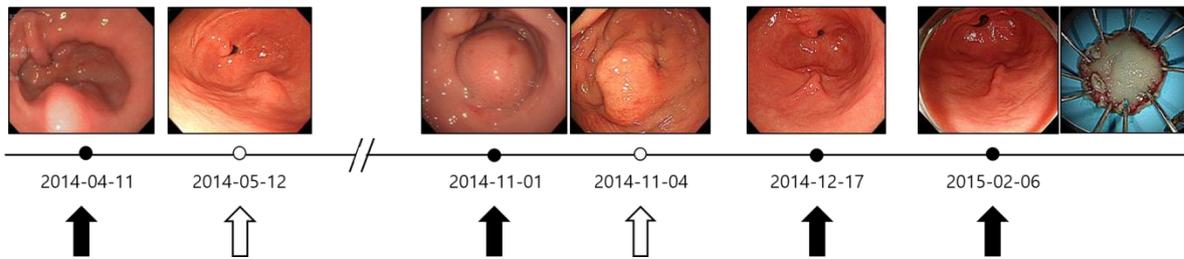
We have also cited the paper in the Results section (P5). We have added “Patient 5” in Figure 2 as follows:

Figure 2. The clinical course of lesion size according to abdominal pain are summarized. (A) Patient 1, (B) Patient 3, (C) Patient 4, (D) Patient 5.

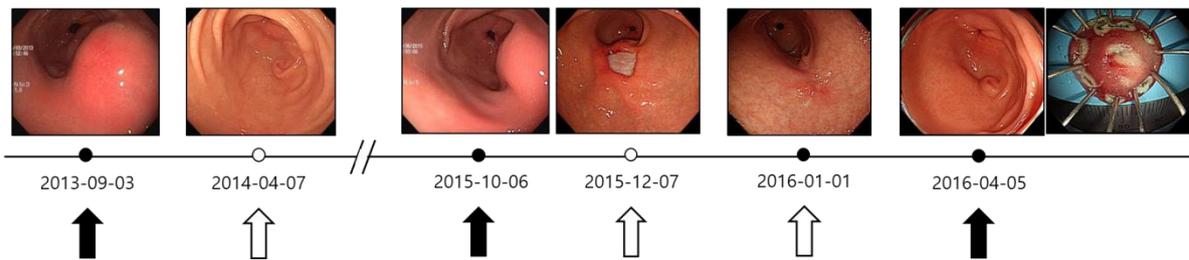
(A) Patient #1



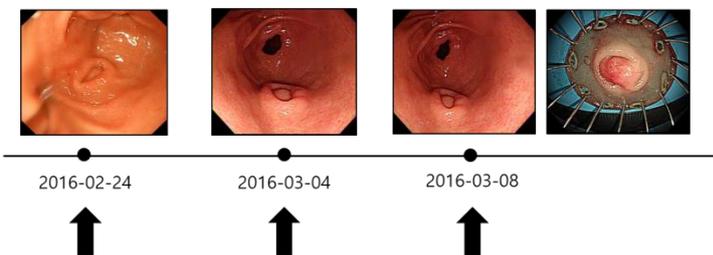
(B) Patient #3



(C) Patient #4



(D) Patient #5



↑ pain episode ↑ pain resolution

Comment 4: The pancreatic enzyme levels in Patient 5 seems to be within the normal limits.

Response: Thank you for your comments. In our hospital, the normal ranges of amylase level is up to 110 U/L and lipase levels are up to 60 U/L. In patient 5, the laboratory data confirmed the amylase level of 120 U/L, which is higher than the normal range.

Comment 5: (Table 1) The authors should add the histological findings of all resected specimens.

Response: Thank you for your comments. We have added the histological finding of all the resected specimens in Table 1 as follows:

CT findings at the time of diagnosis	Pathological diagnosis	Procedure time (min)
Ovoid-shaped lesion with a lobulating contour in the gastric antrum	Heterotopic pancreas	15
Enhancing mass-like and cystic lesions in the gastric antrum	Heterotopic pancreas	120
Subepithelial mass with an internal low-density portion in the gastric antrum	Calcification and foreign body reaction	27
Soft tissue lesion containing a cystic portion and tiny calcification in the gastric antrum	Calcification and foreign body reaction	17
Enhancing mass-like lesion in the gastric antrum	Heterotopic pancreas	26

Comment 6: Please describe the location of the patients' abdominal pain in more detail.

Response: Thank you for your comments. We have described the location of the patients' abdominal pain in accordance with your comments in the Results section as follows:

Patient 1: "In patient 1, the laboratory test was normal and there were no specific findings, except for gastric subepithelial tumor (SET), on CT at the time of the presentation of abdominal pain. The abdominal pain was localized to the epigastric and right upper quadrant areas."

Patient 2: "Patient 2 complained of epigastric and right upper quadrant pain and had elevated pancreatic enzyme levels during pain."

Patient 3: "One month later, the patient complained of recurrent epigastric pain."

Patient 4: "She complained of epigastric pain and had elevated pancreatic enzyme levels during times of abdominal pain."

Patient 5: “In patient 5, the GHP was 12 mm, and the pancreas appeared normal on MRI. He complained of epigastric pain and showed no changes in GHP size on EUS during the pain.”

Comment 7: Did the authors perform EUS after ESD to try and identify any remnant pancreatic tissues or cystic lesions at the site of the ESD scar?

Response: Thank you for your valuable comments. We did not perform EUS after ESD to identify any remnant pancreatic tissues or cystic lesions because of the difficulty to stratify the mucosal layer and differentiate the pancreatic tissue due to the scar change after ESD. Instead, the patients were continuously monitored for symptom recurrence in the outpatient clinic and underwent endoscopy periodically. Only post ESD ulcer scar with normal mucosa was observed on surveillance endoscopy. In the next follow-up of these patients, we will consider the EUS as recommended.

Comment 8: Can the histological findings of only foreign body reactions and calcification be seen after pancreatitis in GHP? The authors should refer previous reports in the pertinent literature which described the histological findings of GHP.

Response: Thank you for your comments. Cases of calcification on GHP have been reported (1. Rie Oka, et al. Heterotopic pancreas with calcification: a lesion mimicking leiomyosarcoma of the stomach, *Gastrointestinal Endoscopy* VOLUME 56, NO. 6, 2002; 2. Suzuki H, et al. A case of gastric aberrant pancreas with pancreatic stone, *The Japanese Journal of Gastro-enterology*. 1992 Oct;89(10):2634-2637).

In cases 3 and 4, the GHP size increased with the development of pancreatitis, and the ulcer on the mucosal surface was caused by the sudden increase in the GHP size. We performed ESD for GHP, which was significantly reduced in size after the conservative treatment. The histopathological report only indicated a foreign body reaction and calcification. The calcification developed in the necrotic tissue, probably because of degenerated proteins that bind phosphate ions to form a precipitate of calcium phosphate. In cases 3 and 4, the pancreas tissue also might have been necrotized by the ulcer on the GHP and severe inflammation. We revised this content in “Discussion” section (P7) as follows:

“And other two cases were confirmed only foreign body reactions and calcification on histopathologic report. We could not exclude the possibility that pancreatic tissue was confined to the proper muscle layer, or the pancreas tissue was eliminated because of the

ulcer, or the severe inflammation resulted in the necrosis of normal pancreatic tissue. The possibility of recurrence from remnant tissues was closely followed up, but neither symptoms nor tumors recurred during the median follow-up period of 46.0 months. It might suggest that the significant cauterization effect at the deep resection margin of the lesion during ESD generally ablates any remnant cells.”

Responses to Reviewer #5

Comment 1: There is no indication of ESD for lesions that extend to the muscularis propria layer.

Response: Thank you for your comments. The indications of ESD for SET have not been established yet, and many papers have been reported. It is believed that ESD indications will be established when oncological results are achieved.

Comment 2: Follow-up schedule is unclear.

Response: Since the reason for endoscopic treatment of complicated GHP is not a potential risk of malignancy, there are no regular follow-up schedules as in gastric cancer. Therefore, we monitored symptoms and performed follow-up endoscopy periodically according to the general screening schedule. We have mentioned this in the Materials and Methods section (P4):

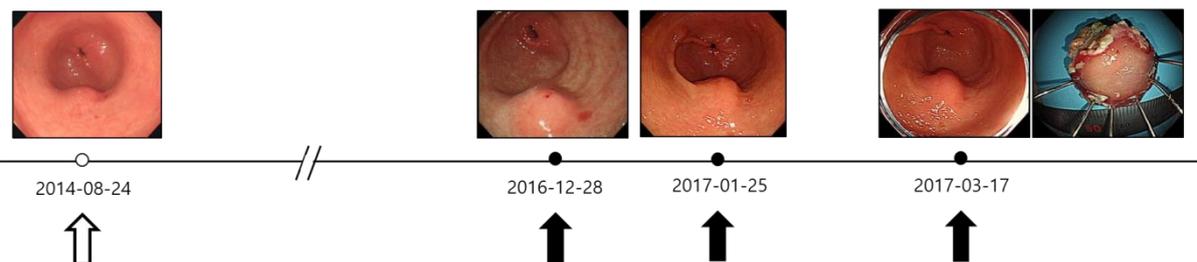
“After the procedure, patients were monitored in an outpatient clinic to assess symptom recurrence. The endoscopy was performed 6 months after the procedure, and was performed annually thereafter.”

Comment 3: Figure2 is wrong.

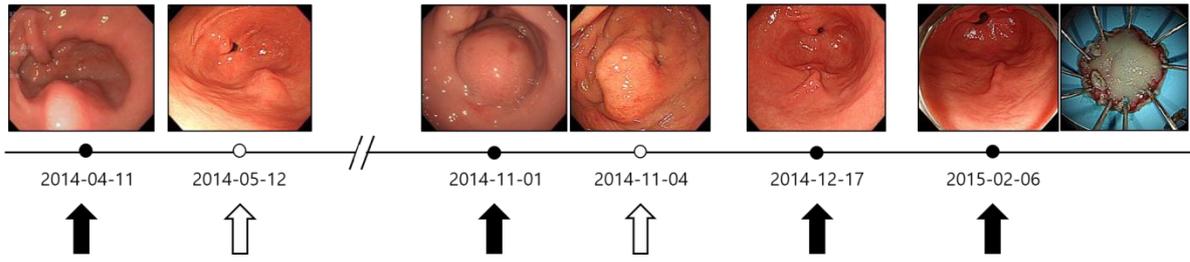
Response: Thank you for your comments. We have corrected “Patient 3” and added “Patient 5” in Figure 2 as follows:

“**Figure 2.** The clinical course of lesion size according to abdominal pain are summarized. (A) Patient 1, (B) Patient 3, (C) Patient 4, (D) Patient 5.”

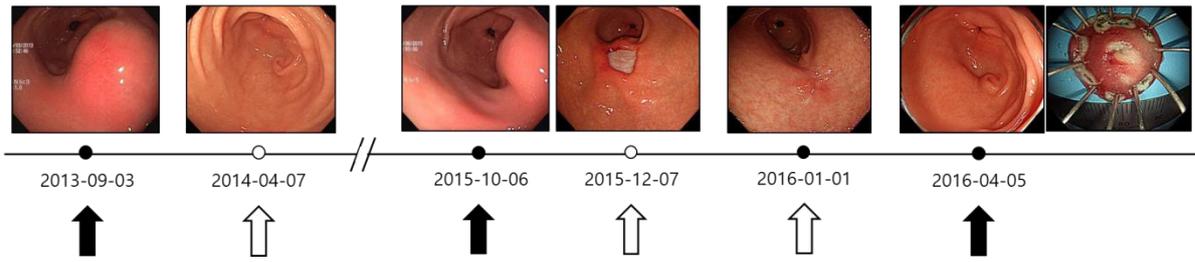
(A) Patient #1



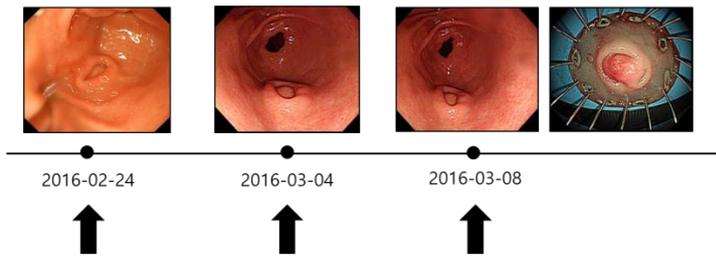
(B) Patient #3



(C) Patient #4



(D) Patient #5



↑ pain episode ↑ pain resolution

Responses to Reviewer #6

Comment 1: This study included only five cases. Therefore, this study is appropriate not for retrospective study but for case series. Please change appropriate article style.

Response: Thank you for your comments. We will submit this article to the *World Journal of Clinical Cases* based on your and the editor-in-chief's recommendations.

Comment 2: The efficacy and safety of ESD for gastric submucosal tumors have been already reported. Are there any reason to focus on gastric heterotopic pancreas? Please clarify the difference of ESD between gastric heterotopic pancreas and other gastric submucosal tumors.

Response: Thank you for your comments. As you mentioned above, several studies on endoscopic resection of SET, including GHP, have been reported. Regarding GHP, almost all the studies were about the endoscopic procedure for asymptomatic or symptomatic GHP with nonspecific abdominal pain. However, the 5 cases we experienced were not just asymptomatic or symptomatic GHPs but were GHPs complicated with pancreatitis or pseudocyst. To our knowledge, endoscopic resection of complicated GHP has not been reported, other than the video case we reported in *Gastrointestinal Endoscopy* (Gong EJ, Kim DH, Cho CJ, et al. Endoscopic submucosal dissection of ectopic pancreas with pancreatitis and pseudocyst formation. *Gastrointestinal endoscopy* 2015; 82: 1126. 2015/07/29. DOI: 10.1016/j.gie.2015.06.029.). Surgical resection is a general treatment for complicated GHP. However, our patients experienced symptom improvement after endoscopic resection of the complicated GHP, which suggests that ESD may be an alternative treatment to surgery. Further studies are needed with a large number of patients.

Comment 3: Was gastric heterotopic pancreas diagnosed by biopsy or EUS-FNAB?

Response: The EUS-FNAB indications for subepithelial tumors, although slightly vary by report, are commonly known as hypoechoic tumors of 2 cm or more. Four out of five patients in our reports were adapted for tissue biopsy because they were over 2 cm in size during acute pancreatitis, but FNAB was not performed for the following reasons: 1) The characteristic of the tumor observed in the EGD and EUS strongly suggested the GHP. 2)

EUS findings also did not only show hypoechoic tumors. 3) The pain was very severe due to the acute inflammation, and 4) After the improvement of symptoms, the size of the tumor was significantly reduced and FANB was not adapted.

Comment 4: Please show the number of patients who achieved successful conservative management without ESD during study period.

Response: Thank you for your comments. Complicated GHP is rare and difficult to define as a general characteristic. In our experience, in patients with complicated GHP, pancreatitis recurred repeatedly without debulking therapy. Eventually, all the patients underwent endoscopic resection, without symptom recurrence after the procedure. This means that conservative treatment is one of the pre-stage treatments in endoscopic resection and is not considered a radical therapy for complicated GHP.

Comment 5: Please mention the reason for selecting not EMR but ESD. EMR seems to be appropriate for the local treatment of gastric heterotopic pancreas because lower complication rate in EMR than that in ESD was reported.

Response: Thank you for your comments. EMR is an endoscopic treatment that removes small lesions localized within the mucosa layer. As the complicated GHP was involved with the deep submucosa or proper muscle layer on EUS, we selected ESD for removing the lesion.