

June 17<sup>th</sup> 2018

Dear Editor: Fang-Fang Ji

**Manuscript NO:** 38827

**Title:** Endoscopic diagnosis and treatment of superficial non-ampullary duodenal tumors

We would like to thank you and reviewers for your careful appraisal of our manuscript. We have carefully revised the manuscript in response to the reviewer's comments. All changes are indicated in red. We hope that this revised version of the manuscript is now suitable for publication in the World Journal of Gastroenterology Endoscopy. Thank you again for your efforts in reviewing our manuscript.

Sincerely yours,

Sho Suzuki

Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine

1-6 Kanda-Surugadai, Chiyoda-ku, Tokyo 1018309, Japan

Telephone: +81-3-3293-1711

Fax: +81-3-3293-1711

Email address: s.sho.salubriter.mail@gmail.com

Reviewer #1:

Comments:

1. Abstract: The authors described that a high-grade adenoma (HGA) should be treated because of its high malignant potential. What do you mean by “high malignant potential”? We think that SNADETs with histologically HGA should be also treated.

Thank you for your comment. Some patients with biopsy-based diagnoses of HGA before resection were subsequently diagnosed with an adenocarcinoma after resection; we described HGA as a lesion having “high malignant potential”. However, we agree that this description is ambiguous, and have therefore changed this description as below.

Original Manuscript

(page 3, line 34-37)

Previous reports suggested that a superficial adenocarcinoma (SAC) should be treated via local resection because of its low risk of lymph node metastasis. In addition, a high-grade adenoma (HGA) should be treated because of its high malignant potential.

Revised Manuscript

(page 3, line 35-39)

Previous reports suggested that a superficial adenocarcinoma (SAC) should be treated via local resection because of its low risk of lymph node metastasis, **whereas a high-grade adenoma (HGA) should be resected because of its high risk of progression to adenocarcinoma.**

2. Page 6: The authors mentioned that FAP, smoking, colorectal neoplasm, or H. pylori infection was associated with the risk of SNADET. However, they described that the reported odds ratio for advanced colorectal neoplasm among patients with sporadic duodenal adenoma was 2.3-7.8. I cannot follow this meaning. Opposite meaning? For example, is it correct that odds ratio for SNADET among patients with advanced colorectal neoplasm was 2.3-7.8?

Thank you for your comment. As you pointed out, odds ratio for SNADET among patients with advanced colorectal neoplasms should be described. However, our initial manuscript described the odds ratio for advanced colorectal neoplasm among patients with sporadic duodenal adenomas, which may confuse readers. Therefore, we updated the manuscript accordingly.

Original Manuscript

(page 6, line 94-96)

Colorectal neoplasm was reported as a risk factor of SBA and sporadic duodenal adenoma<sup>[22, 25-28]</sup>; the reported odds ratio for advanced colorectal neoplasm among patients with sporadic duodenal adenoma was 2.3-7.8.

Revised Manuscript

(page 6, line 98-101)

Colorectal neoplasm was reported as a risk factor of SBA and sporadic duodenal adenoma<sup>[22, 25-28]</sup>; **the reported odds ratio for sporadic duodenal carcinoma among patients with a history of colorectal cancer was 3.74.**

3. Pages 8-9: Diagnostic discrepancy among endoscopy, biopsy, and histology in the resected specimen by endoscopic treatment was described. So, what should we do for the diagnosis when we found SNADET during the daily procedure? I think that it is better to comment on this point.

There is no definite consensus about diagnosis and biopsy before treatment. When we find SNADETs, we should distinguish between LGA and HGA/SCA or between C3 and C4 lesions. Kakushima et al proposed a useful scoring system with a high diagnostic accuracy to determine C3 and C4 lesions. Therefore, a lesion that scored  $\geq 3$  points may be appropriate for endoscopic resection without biopsy diagnosis. However, our description on this point was ambiguous. Therefore, we changed this description as described below.

Original Manuscript

(page 6, line 116-171)

#### **PRETREATMENT ENDOSCOPIC AND BIOPSY DIAGNOSES OF SNADETS**

Endoscopic diagnoses were made by endoscopists using endoscopic findings, which were observed via routine endoscopy, magnifying endoscopy (ME), and chromoendoscopy with indigo carmine (Figure 1). Unfortunately, there are no standard criteria for the endoscopic diagnosis of SNADETs. The associations between endoscopic diagnoses and final pathological diagnoses of resected specimens were reported in duodenal lesions. With regard to lesion size, mean tumor diameter of high-grade adenoma (HGA) lesions or superficial adenocarcinoma (SAC) lesions was significantly larger than that of low-grade adenoma (LGA) lesions<sup>[20]</sup>. The rate of lesions  $>5$  mm in diameter in HGA or SAC lesions was significantly higher than that in LGA lesions. Further, all submucosal adenocarcinoma lesions are  $\geq 10$  mm in diameter<sup>[20]</sup>. According to pathological diagnosis based on the Vienna classification, category 4 (C4) tumors had significantly larger diameters than category 3 (C3) tumors<sup>[37]</sup>. With regard to the color of lesions, a solitary or predominantly red color was significantly more frequent in HGA or SAC lesions than those in LGA lesions<sup>[20]</sup>. A solely red colored lesion was reported as an indicator of carcinoma<sup>[31]</sup>. Furthermore, all submucosal cancers were reported to be red<sup>[20]</sup>. With regard to the macroscopic characteristics of SNADETs, depression and mixed-type morphology are reported to be associated with carcinoma<sup>[31, 38]</sup>. Furthermore, submucosal cancers exhibited 0-I or 0-IIa+IIc types<sup>[20]</sup>. The features of endoscopic findings using ME with narrow band imaging (NBI) was also reported, which consists of microsurface pattern and microvascular pattern and assists endoscopic diagnosis<sup>[37, 39, 40]</sup>. In addition, Kikuchi et

al<sup>[41]</sup> proposed a diagnostic algorithm using ME with NBI for SNADETs. Recently, Kakushima *et al*<sup>[42]</sup> suggested a useful scoring system to determine C3 and C4 lesions. This system was based on lesion diameter, color, macroscopic type, and nodularity that were easily observed via endoscopy. A lesion that scored  $\geq 3$  points was judged as C4 or higher. The scoring system's diagnostic accuracy rate was 86%, and the scores of C4 or higher lesions were significantly higher than those of C3 lesions ( $P < 0.001$ ). This system assists to select treatment strategy of SNADETs without biopsy diagnosis.

Biopsy specimens were obtained after endoscopic diagnoses. However, the importance of pretreatment biopsy diagnoses of SNADETs remains controversial. Biopsy from the lesion was considered as the gold standard of diagnosis<sup>[43]</sup>. C4.1 or HGA lesions diagnosed by biopsy were reported to have their potential of progression to malignant lesions<sup>[9, 10, 44]</sup>, especially for lesions  $\geq 20$  mm in size<sup>[13, 45]</sup>. Another study stated that C4.1 tumors diagnosed by biopsy using the Vienna classification with nodular or rough surfaces with a red color were more likely to progress to adenocarcinoma during the follow-up period<sup>[13]</sup>. Malignant potential is quite different between C3 and C4.1 Vienna classified tumors and between LGA and HGA lesions diagnosed by biopsy. C3 or LGA lesion diagnosed by biopsy showed a low risk of progression to adenocarcinoma<sup>[13, 46]</sup>, for which follow-up without ER may be acceptable due to a high risk of complication. However, discordance between pretreatment biopsy diagnoses and final pathological diagnoses was reported in duodenal lesions<sup>[13, 19, 40, 47, 48]</sup>, as well as gastric epithelial lesions<sup>[49]</sup>. Some patients with biopsy diagnoses of HGA before resection were reported to have their diagnoses upgraded from HGA to adenocarcinoma after resection<sup>[46]</sup>. Pretreatment biopsy diagnoses had greater specificity and similar accuracy, but lower sensitivity compared with pretreatment endoscopic diagnoses<sup>[20, 31]</sup>. Furthermore, Kakushima *et al*<sup>[31]</sup> reported that pretreatment diagnoses of carcinomas via endoscopy or biopsy were limited to 88% (57/65) of carcinoma lesions. All lesions of carcinomas cannot be diagnosed before treatment, even if biopsy was conducted. Unintended fibrosis may be induced by the biopsy because the duodenal wall is thin, which may make ER more difficult<sup>[38, 50, 51]</sup>. In some previous study, SNADETs was categorized as LGA, HGA, or SAC in histological diagnosis. On the other hand, the revised Vienna classification was also used as the diagnostic classification for SNADETs in other reports<sup>[13, 37, 39, 41]</sup>. These two classification were inconsistent, and there remains difficulty in creating a unified classification.

Revised Manuscript

(page 7-9, line 121-177)

## PRETREATMENT DIAGNOSES OF SNADETS

Endoscopic diagnoses were made by qualified endoscopists at the time of routine endoscopy, magnifying endoscopy (ME), and chromoendoscopy with indigo carmine (Figure 1). At present, there are no standard criteria for the endoscopic diagnosis of SNADETs and current practice includes obtaining biopsy specimens after endoscopic diagnoses. C4.1 or HGA lesions diagnosed by biopsy were reported to have the potential to progress to malignant lesions<sup>[9, 10, 37]</sup>, especially for lesions  $\geq 20$  mm in size<sup>[13, 38]</sup>. Another study stated that C4.1 tumors diagnosed by biopsy using the Vienna classification with nodular or rough surfaces with a red color were more likely to progress to adenocarcinoma during the follow-up period<sup>[13]</sup>. Malignant potential is quite different between C3 and C4.1 Vienna classified tumors and between LGA and HGA lesions diagnosed by biopsy. C3 or LGA lesion diagnosed by biopsy showed a low risk of progression to adenocarcinoma<sup>[13, 39]</sup>, for which follow-up without ER may be acceptable due to a high risk of adverse events.

The associations between endoscopic diagnoses and final pathological diagnoses of resected specimens were reported in duodenal lesions. With regard to lesion size, mean tumor diameter of high-grade adenoma (HGA) lesions or superficial adenocarcinoma (SAC) lesions was significantly larger than that of low-grade adenoma (LGA) lesions<sup>[20]</sup>. The rate of lesions  $>5$  mm in diameter in HGA or SAC lesions was significantly higher than that in LGA lesions. Further, all submucosal adenocarcinoma lesions are  $\geq 10$  mm in diameter<sup>[20]</sup>. According to pathological diagnosis based on the Vienna classification, category 4 (C4) tumors had significantly larger diameters than category 3 (C3) tumors<sup>[40]</sup>. With regard to the color of lesions, a solitary or predominantly red color was significantly more frequent in HGA or SAC lesions than those in LGA lesions<sup>[20]</sup>. A solely red colored lesion was reported as an indicator of carcinoma<sup>[31]</sup>. Furthermore, all submucosal cancers were reported to be red<sup>[20]</sup>. With regard to the macroscopic characteristics of SNADETs, depression and mixed-type morphology are reported to be associated with carcinoma<sup>[31, 41]</sup>. Furthermore, submucosal cancers exhibited 0-I or 0-IIa+IIc types<sup>[20]</sup>. The features of these lesions on ME with narrow band imaging (NBI) was also reported, and have been described as consisting of a microsurface pattern and microvascular pattern, which assists endoscopic diagnosis<sup>[40, 42, 43]</sup>. In addition, Kikuchi et al<sup>[44]</sup> proposed a diagnostic algorithm using ME with NBI for SNADETs.

However, the importance of pretreatment biopsy diagnoses of SNADETs remains controversial. Discordance between pretreatment biopsy diagnoses and final pathological diagnoses was reported in duodenal lesions<sup>[13, 19, 43, 45, 46]</sup>, as well as gastric epithelial lesions<sup>[47]</sup>. Some patients with biopsy diagnoses of HGA before resection

were reported to have their diagnoses upgraded from HGA to adenocarcinoma after resection<sup>[39]</sup>. Pretreatment biopsy diagnoses had greater specificity and similar accuracy, but lower sensitivity compared with pretreatment endoscopic diagnoses<sup>[20, 31]</sup>. Furthermore, Kakushima *et al*<sup>[31]</sup> reported that pretreatment diagnoses of carcinomas via endoscopy or biopsy were limited to 88% (57/65) of carcinoma lesions. All lesions of carcinomas cannot be diagnosed before treatment, even if biopsy was conducted. Unintended fibrosis may be induced by the biopsy because the duodenal wall is thin, which may make ER more difficult<sup>[41, 48, 49]</sup>. Recently, Kakushima *et al*<sup>[50]</sup> suggested a useful scoring system to determine C3 and C4 lesions. This system was based on lesion diameter, color, macroscopic type, and nodularity that were easily observed via endoscopy. A lesion that scored  $\geq 3$  points was judged as C4 or higher. The scoring system's diagnostic accuracy rate was 86%, and the scores of C4 or higher lesions were significantly higher than those of C3 lesions ( $P < 0.001$ ). This system **helps clinicians decide upon a suitable** treatment strategy **for** SNADETs without biopsy diagnosis.

**One study categorized** SNADETs as LGA, HGA, or SAC **based on** histological diagnosis<sup>[20, 39]</sup>. On the other hand, the revised Vienna classification was also used as the diagnostic classification for SNADETs in other reports <sup>[13, 40, 42, 44]</sup>. These two **classifications** were inconsistent, and there remains difficulty in creating a unified classification.

4. Treatment for SNADET: Since ESD and LECS for the treatment of SNADET are not covered by national insurance in Japan, the authors should discuss on the high cost of those treatments.

Thank you for your important comment. I agree with your comment. We should mention the comparison of each procedure. ESD and LECS are more expensive than EMR, and furthermore, these LECS for SNADET is not covered by national insurance in Japan. Therefore, we have to take into consideration the cost in the selection of treatment method. Thus, the following additions were made to the revised manuscript.

Revised Manuscript

(page 15, line 329-332)

However, ESD and LECS are most expensive than EMR, and LECS is not covered by the national insurance system. Although ESD and LECS may be more cost-effective in the long-term because of their associated low recurrence rates, we have to take into consideration the high cost of ESD and LECS.

5. Treatment for SNADET: One of the causes of difficulty of duodenal ESD is related to abundant blood vessels in the submucosal layer and a thin muscle layer in the duodenum (Matsuda Y, et al. World J Gastrointest Surg 2017; 9: 161-6.). Please cite this article.

Thank you for your comment. As you correctly advised, it is not only the thinness of the muscle layer, but also the abundance of blood vessels in the submucosal layer of the duodenum that are associated with difficulty of duodenal ESD. Thus, the following explanation was added to the revised manuscript, quoting from the report by Matsuda, et al.

Original Manuscript

(page 12, line 237-239)

ESD was invented for en bloc resection of gastrointestinal lesions. It is frequently used in the stomach, colon and esophagus, but is not adequately used in the duodenum. ESD requires a high skill level and requires a long learning curve.

Revised Manuscript

(page 12, line 246-251)

ESD was invented for en bloc resection of gastrointestinal lesions **where it is frequently used for the treatment of gastric, colonic and esophageal lesions, but rarely used for duodenal lesions. This may be partly explained by the fact that ESD requires a high skill level and a qualified operator with thorough knowledge of duodenal anatomy, which is characterized by an abundance of blood vessels in the submucosal layer and a thin muscle layer<sup>[65]</sup>.**

6. Closure of the mucosal defect after ER: Please cite a recent report by Nishizawa et al (GIE 2018; 87: 1074-8.).

Thank you for your important comment. The string clip suturing method seems to be a useful and promising method for more reliable closure of the mucosal defect. Therefore, we cited this report.

Original Manuscript

(page 13, line 272-274)

If fact, some clips drop off, resulting in reports of delayed perforation<sup>[80]</sup>. The combination of endoclip and Endoloop was reported for closure of large mucosal defects after ER<sup>[81-83]</sup>.

Revised Manuscript

(page 14, line 292-296)

**In fact**, some clips drop off, resulting in reports of delayed perforation<sup>[81]</sup>. The combination of endoclip and Endoloop **using a double-channel endoscope** was reported for closure of large mucosal defects after ER<sup>[82-84]</sup>. **Recently, closure via the string clip suturing method was developed, which can be completed with a single-channel endoscope<sup>[85]</sup>.**

Minor comments: 1. Revision by native speaker is recommended to improve a style of English.

Thank you for your important comment. I am not native English speaker. Therefore, proofreading in English was conducted for this manuscript.

Reviewer #2:

1. Authors mention that double-balloon enteroscopy was useful for maneuverability, but this method is insufficient. Please mention the reasons.

Double-balloon enteroscopy is a useful method to solve the difficulty of securing the appropriate visual field. However, there are still difficulties of duodenal ESD other than visualization. That's why we described double-balloon enteroscopy. This description may give a misunderstanding for readers. Therefore, we delete this description from our manuscript.

Original Manuscript

(page 10, line 188-191)

It is often difficult to maintain the appropriate visual field to operate using endoscopy and endo-knife because the duodenum is deeply located with narrow and bent lumen. Double-balloon enteroscopy was rereported as useful for maneuverability<sup>[53]</sup>, but this method is insufficient.

Revised Manuscript

(page 10, line 194-197)

It is often difficult to maintain **an** appropriate visual field **during** endoscopy **while using the** endo-knife because the duodenum is **located deep within the abdomen and has a** narrow and bent lumen. Double-balloon enteroscopy was reported as useful for maneuverability<sup>[52]</sup>.

2. Duodenal ESD using a ST hood are conducted in some centers and are often conducted under general anesthesia for larger lesions. Please mention about them.

Thank you for this important comment. A ST hood was considered useful tool for ESD. Using the ST hood makes it easy to get into the submucosal layer, especially in the case of the pocket creation method.

Original Manuscript

(page 13, line 261-263)

ESD is a challenging procedure due to its complication rate; therefore, an appropriate closure technique after ESD is required.

Revised Manuscript

(page 13, line 274-282)

Where duodenal ESD was indicated, cases tended to be performed under general anesthesia, and this was especially true for larger lesions, in order to ensure safety and to facilitate transition to surgery in the case of an adverse event<sup>[58, 68]</sup>. Recently, the pocket-creation method using an ST hood was proposed as a safe and quick alternative for duodenal ESD<sup>[78]</sup>, which facilitates access into the submucosal layer via the ST hood. The evidence summarized above demonstrates that ESD is still a challenging procedure due to its high adverse events rate; and therefore, regardless of the procedure used, an appropriate closure technique after ESD is required.

Minor

1. Please change “complication” to “adverse events.”
2. Please change “H.pylori” to “Helicobacter pylori (H.pylori).”
3. P13, line 22: Please change “If fact” to “In fact.”

Thank you for these important comments. We have updated the manuscript accordingly.