Efficacy of Full-Spectrum Endoscopy to Visualize the Major Duodenal Papilla in Patients with Familial Adenomatous Polyposis

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Efficacy of Full-Spectrum Endoscopy to Visualize the Major Duodenal Papilla in Patients with Familial Adenomatous Polyposis

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Keywords

Esophagogastroduodenoscopy · Full-spectrum endoscopy · Major duodenal papilla · Familial adenomatous polyposis · Duodenum

Abstract

Background and Aims: Duodenal cancer is one of the extracolonic malignancies with known mortality in familial adenomatous polyposis (FAP) patients. Visualization of the major duodenal papilla (MDP) with a standard esophagogastroduodenoscopy (EGD) is currently insufficient because of the limited field of view. Full-spectrum endoscopy (FUSE), utilizing double imagers located on the front and side of the endoscopic tip, provides a wider field of view up to 245 degrees. The aim of this study was to evaluate the efficacy of FUSE in visualizing MDP in patients with FAP. ***Methods:*** This study was a single-center retrospective study including 49 FAP patients undergoing surveillance at our institution. EGD was performed by qualified endoscopists using FUSE, and visibility of the MDP was evaluated. All examinations were video-recorded, and the clips for individual patient were edited to forward view images alone (conventional group) and 2-view images of the duodenum (forward and side-view [FUSE group]). Three other qualified external endoscopists independently reviewed the videos and compared the visibility of MDP between the conventional and the FUSE groups. Primary endpoint was the rate of Type 1 visibility (whole area of the papilla) in off-site video reviews. We also assessed MDP visibility on-site as secondary endpoint. ***Results:*** The rate of type 1 MDP visibility was significantly higher in the FUSE group than conventional group in both on-site (32.6/100%, $p < 0.001$) and off-site reviews (8.2, 16.3, 14.3/100, 98, and 100%, $p < 0.001$). ***Conclusions:*** FUSE is recommended in screening and surveillance EGD to better visualize MDP in FAP patients.

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disease, characterized by the presence of large number of colorectal adenomatous polyps caused by mutations in the adenomatous polyposis coli gene. The most frequent cause of death in FAP was colorectal cancer, as hundreds to thousands of adenomatous polyps invariably progress to cancer if left untreated. Since the introduction of guidelines to better define the indications and timing of prophylactic colectomy, colorectal cancer-related mortality has reduced [1–4]. Despite this, FAP patients have a lower life expectancy. This has been attributed to extracolonic manifestations, of which upper gastrointestinal malignancies are the most common. Gastric and duodenal cancers, among other extracolonic lesions in FAP patients, have been studied. The risk of periampullary cancer is estimated to be 3–8.5%, which is 200–300 times greater than that in the general population [5–12]. It is crucial, therefore, to inspect major duodenal papilla (MDP) carefully during screening and surveillance endoscopy to ensure detection of periampullary disease.

Current visualization of the duodenum, especially MDP, is inadequate with a standard forward-viewing gastroscope because of the limited field of view [13]. For patients with FAP, observation with a side-viewing duodenoscope is recommended in addition to conventional esophagogastroduodenoscopy (EGD), when sufficient visualization of the duodenal papilla cannot be achieved [14–18]. However, additional examination with side-viewing duodenoscope is time-consuming, incurs cost, and burdensome for the patients. Full-spectrum endoscopy (FUSE; Endochoice, Inc., Alpharetta, GA, USA) EGD is a newly developed video-endoscope that provides a 245-degree field of view utilizing double imagers located at the front and left lateral aspect of the endoscopic tip. FUSE EGD designed with a standard 9.6 mm insertion tube diameter and 10.5 mm distal end diameter and with water jet function. It does not involve magnification function with image enhanced function such as narrow band imaging, blue laser imaging, and linked color imaging.

Little is known about the visibility of MDP using FUSE EGD. The aim of this study was to evaluate the efficacy of FUSE EGD in visualizing MDP in FAP patients.

Methods

Ethics

This study was conducted in accordance with Declaration of Helsinki. This study was approved by the internal review board in our institution on October 26, 2016, and written informed consent was obtained from all patients. This study was registered to University Hospital Medical Information Network Clinical Trails Registry (www.umin.ac.jp/ctr/; identification No. UMIN000033326).

Patients

This retrospective observational study was conducted at a single referral cancer center and included FAP patients under surveillance at the hospital. Patients recruited met at least one of the following criteria: (a) presence of >100 colorectal adenomas, (b) presence of <100 colorectal adenomas with family history of FAP, (c) presence of adenomatous polyposis coli gene mutation(s) detected through DNA analysis [14]. Patients were excluded if they had history of upper gastrointestinal surgery or duodenal papillectomy. Figure 1 demonstrates the study flow.

Endoscopic Procedure

Patients were instructed to overnight fast and given water with pronase (Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) as well as simethicone 10 min prior to the examination. After oral sprays of 8% topical lidocaine, patients underwent EGD in the left lateral decubitus position. The type of sedative drugs (propofol, midazolam, pethidine hydrochloride), and whether spasmolytics (butylscopolamine) administered, was determined by the individual endoscopist. Most of the study subjects previously underwent EGD at our institution and preferred the same sedative agent as used before. The order of observation follows routine EGD, starting from the esophagus, stomach, before proceeding into the duodenum. Biopsy was taken only in the cases of newly detected papillary lesions, and not performed for previously detected lesions. All tissue samples were examined by expert pathologists and graded according to the Vienna classification of gastrointestinal epithelial neoplasia [19].

On-Site Diagnosis

FUSE EGDs were performed by a total of 8 qualified endoscopists of the Japanese Gastroenterological Endoscopy Society between July 2016 and December 2017. Observation of the duodenum began with visualizing the duodenal bulb before proceeding. Following identification of MDP, the scope was advanced to the descending duodenum to observe the caudal aspect of the papilla. Upon withdrawal, the field of view was expanded and MDP was inspected again. The endoscope was manoeuvred as much as possible to optimize visibility in the forward view alone, even in cases when the MDP was observed in the side view.

The visibility of MDP was evaluated during the procedures and rated by the performing endoscopists after each FUSE EGD. Comparisons were made between the visibility of MDP in the forward-view alone (conventional group) and combined forward and left-side view (FUSE group). The visibility of MDP was categorized into 5 types according to Hew et al. [13] Type 1, whole area of the papilla; Type 2, upper part of the papilla, including the orifice; Type 3, upper part of the papilla without orifice; Type 4, lower part of the papilla, including the orifice; and Type 5, no part of the pa-

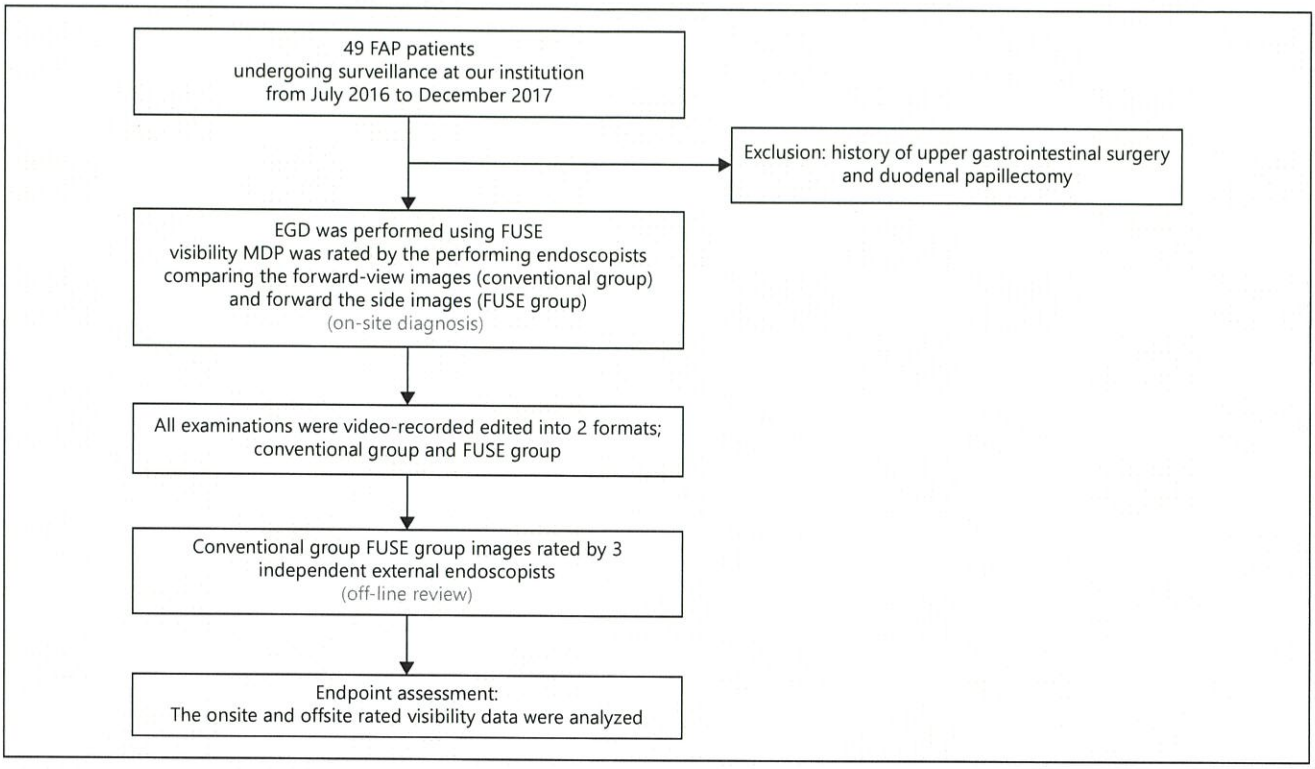

Fig. 1. Study flow. Flowchart of patient's enrollment summary of this study. FAP, familial adenomatous polyposis; EGD, esophagogastroduodenoscopy; FUSE, full-spectrum endoscopy; MDP, major duodenal papilla.

pilla was found (Fig. 2) [12]. The rated types of visibility for each patient were documented via the electronic medical records, and the data retrospectively collected.

Off-Site Review

All examinations were video-recorded. The videos were edited into 2 formats: one-screen video with the forward view visible only and the left-view obscured (conventional group), or dual-screen videos with both the forward and left-view visible (FUSE group). The video clips were presented to the reviewers in random order. Three qualified external endoscopists, blinded to patients' clinical information, independently reviewed the videos, and scored the visibility of the duodenal papilla in the same manner as the on-site diagnosis. Given no prior experience with FUSE EGD, the endoscopists were allowed to watch the videos as many times as required (Fig. 1).

Assessment

Primary endpoint was the rate of Type 1 visibility in the off-site video reviews. In addition, the rate of Type 1 visibility during on-site diagnosis, detection of MDP neoplasm and their visibility, total and duodenum inspection time, and adverse events were assessed as secondary endpoints. The total inspection time was defined as: the time from the endoscope was inserted into the patient's mouth to the time it was withdrawn. The inspection time in the duodenum was defined as: the time from insertion of scope past the pyloric ring and withdrawal from it.

Statistical Analysis

Continuous variables were expressed as medians and ranges, and categorical variables were expressed as numbers and frequencies. The between group differences of type 1 ratio was tested using Mann-Whitney U test. p values of <0.05 were considered to be statistically significant. All statistical analyses were calculated using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Forty-nine FAP patients meeting the inclusion criteria underwent FUSE EGD. Thirty-eight patients were male and 11 were female, with a median age of 37 (19–61). Mean total inspection time was 11.0 ± 2.3 min, and duodenal inspection time was 1.9 ± 0.8 min. Butylscopolamine was used as spasmolytic in 28 (57.1%) patients. Midazolam, propofol, and pethidine hydrochloride were used in 17 (34.7%), 44 (89.9%), and 7 (14.3%) of patients, respectively. All FUSE EGDs were completed without any adverse events (Table 1).

Visibility of the MDP on-site was able to be assessed and scored in all patients. The rates of Type 1, 2–4, and

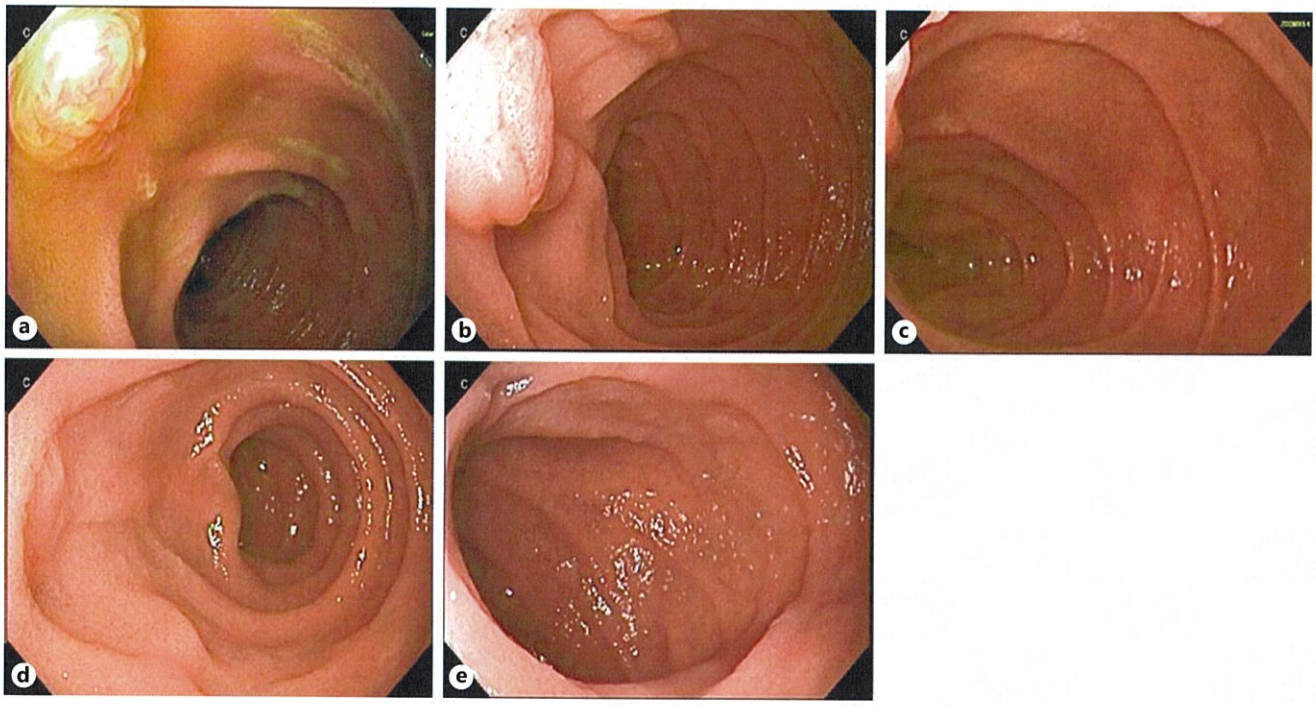

Fig. 2. The 5 classification of visualization of MDP. **a** Type 1, whole area of the papilla. **b** Type 2, upper part of the papilla, including the orifice. **c** Type 3, upper part of the papilla without orifice. **d** Type 4, lower part of the papilla, including the orifice. **e** Type 5, no part of the papilla was found.

Table 1. Patient and endoscopic characteristics

Patients characteristics, total (n = 49)	
Age, years, median (range)	37 (19–46)
Gender, % (n)	
Male	77.7 (38)
Female	22.4 (11)
Sedation	
Propofol, % (n)	89.9 (44)
Midazolam, % (n)	34.7 (17)
Pethidine hydrochloride, % (n)	57.1 (28)
Butylscopolamine, % (n)	14.3 (7)
Endoscopic procedure	
Inspection time (total), min, mean ± SD	11.0±2.3
Inspection time (duodenum), min, mean ± SD	1.9±0.8
Adenoma of MDP, % (n)	24.5 (12)
Newly detected adenoma of MDP, % (n)	8.2 (4)
Adverse events, % (n)	0 (0)

MDP, major duodenal papilla.

5 were 32.6, 38.8, and 28.6%, respectively, in the conventional group. In the FUSE group, Type 1 was scored for all 49 patients. The rate of Type 1 was significantly higher in the FUSE group than the conventional group ($p < 0.001$). During off-site reviews, the visibility scores (Type 1/2–4/5) rated by Reviewers A, B, C were 8.2, 16.3, 14.3/63.2, 53.1, 55.1/28.6, 30.6, and 30.6% in the conventional group and 100, 98, 100/0, 2, 0/0, 0, and 0% in the FUSE group. The number of Type 1 rated by all 3 reviewers was significantly higher in the FUSE group than conventional group in ($p < 0.001$; Table 2).

Neoplastic lesions of the MDP were detected in 12 patients (24.5%). Of these, 8 lesions were observed during previous EGD before study entry, and the remaining 4 were newly diagnosed. Based on the targeted biopsy results, 3 out of the 4 patients were referred for papillectomy. One patient had a small adenoma not requiring further intervention, and is undergoing regular surveillance.

In terms of the visibility of the papillary neoplasms in the 12 patients, the rates of Type 1, 2–4 and 5 were 50.0, 41.7, and 8.3% in the conventional group while the proportion of type 1 was 100% in the FUSE group. During

Table 2. MDP visibility in the conventional and FUSE groups

$n = 49$	Conventional group Type 1/2–4/5	FUSE group Type 1/2–4/5	p value
Reviewer A, % (n)	8.2 (4)/63.2 (31)/28.6 (14)	100 (49)/0 (0)/0 (0)	<0.001
Reviewer B, % (n)	16.3 (8)/53.1 (26)/30.6 (15)	98.0 (48)/2.0 (1)/0 (0)	<0.001
Reviewer C, % (n)	14.3 (7)/55.1 (27)/30.6 (15)	100 (49)/0 (0)/0 (0)	<0.001
Onsite diagnosis, % (n)	32.6 (16)/38.8 (19)/28.6 (14)	100 (49)/0 (0)/0 (0)	<0.001

FUSE, full-spectrum endoscopyMDP, major duodenal papilla.

Table 3. MDP visibility of the detected papillary lesions

$n = 12$	Conventional group Type 1/2–4/5	FUSE group Type 1/2–4/5	p value
Reviewer A, % (n)	0 (0)/100 (12)/0 (0)	100 (12)/0 (0)/0 (0)	<0.001
Reviewer B, % (n)	12.7 (2)/75.0 (9)/8.3 (1)	100 (12)/0 (0)/0 (0)	<0.001
Reviewer C, % (n)	12.7 (2)/87.3 (10)/0 (0)	100 (12)/0 (0)/0 (0)	<0.001
Onsite diagnosis, % (n)	50.0 (6)/41.7 (5)/8.3 (1)	100 (12)/0 (0)/0 (0)	<0.001

FUSE, full-spectrum endoscopy; MDP, major duodenal papilla.

Table 4. Comparison of MDP visibility with or without butylscopolamine in the conventional group

$n = 49$	Conventional group Type 1/2–4/5		p value
	butylscopolamine + ($n = 28$)	butylscopolamine – ($n = 21$)	
Reviewer A, % (n)	10.7 (3)/64.3 (18)/25.0 (7)	4.8 (1)/61.9 (13)/33.3 (7)	0.625
Reviewer B, % (n)	25.0 (7)/46.4 (13)/28.6 (8)	4.8 (1)/61.9 (13)/33.3 (7)	0.115
Reviewer C, % (n)	14.3 (57.1)/57.1 (16)/8.6 (8)	14.3 (3)/52.4 (11)/33.3 (7)	1
Onsite diagnosis, % (n)	50.0 (14)/32.1 (9)/17.9 (5)	28.6 (6)/33.3 (7)/38.1 (8)	0.154

MDP, major duodenal papilla.

off-site review, the rates of Type 1, 2–4, and 5 in reviewers A, B, C were 0, 12.7, 12.7/100, 75.0, 87.3/0, 8.3, and 0%, respectively, in the conventional group, while all lesion were uniformly scored as Type 1 by the 3 reviewers in the FUSE group. The rate of Type 1 visibility was significantly higher in the FUSE group ($p < 0.001$; Table 3). Similarly, in the 4 newly diagnosed lesions, all were rated as Type 1 in the FUSE group during both on-site and off-site reviews.

Furthermore, we investigated the difference in visibility between the FUSE and conventional groups with and without butylscopolamine. There was no significant difference in the rates of Type 1 visibility between the 2 groups (Table 4, 5).

Figure 3 demonstrates a representative case of a newly detected MDP lesion viewed with FUSE EGD. In comparison, the MDP was only partially observed in forward view alone (Fig. 4).

Discussion

This study investigated the visibility of MDP using FUSE in FAP patients. FUSE EGD examination allowed observation of the entire papilla in almost all study patients, as rated by the on-site endoscopists and off-site reviewers. In this study, the order of the edited videos was presented in a random order to eliminate carryover effect,

Table 5. Comparison of MDP visibility with or without butylscopolamine in the FUSE group

$n = 49$	FUSE group Type 1/2–4/5		p value
	butylscopolamine + ($n = 28$)	butylscopolamine – ($n = 21$)	
Reviewer A, % (n)	100 (28)/0 (0)/0 (0)	100 (21)/0 (0)/0 (0)	1
Reviewer B, % (n)	100 (28)/0 (0)/0 (0)	95.2 (20)/4.8 (1)/0 (0)	0.429
Reviewer C, % (n)	100 (28)/0 (0)/0 (0)	100 (21)/0 (0)/0 (0)	1
Onsite diagnosis, % (n)	100 (28)/0 (0)/0 (0)	100 (21)/0 (0)/0 (0)	1

FUSE, full-spectrum endoscopy; MDP, major duodenal papilla.

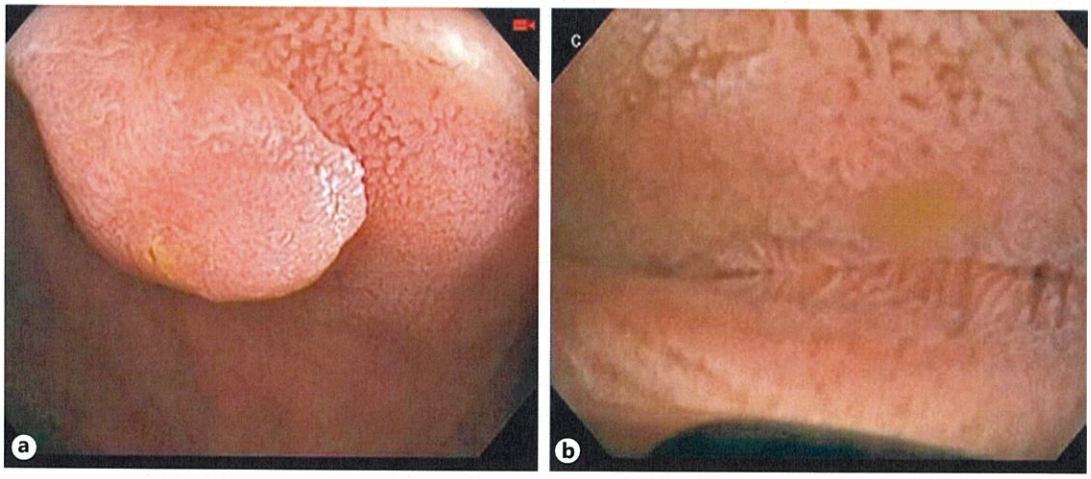

Fig. 3. FUSE images in left side (**a**) and forward (**b**) viewing (FUSE group). Whole area of the papilla was observed clearly in left side viewing. Biopsy was taken from the whitish mucosa and revealed tubular adenoma.

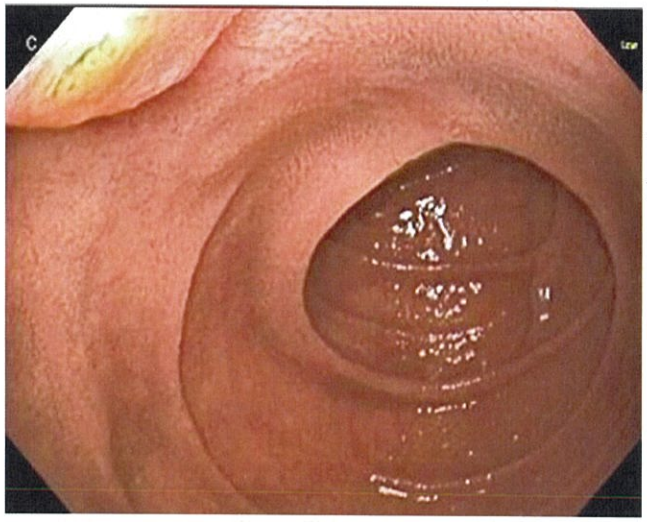

Fig. 4. Conventional image in forward view only (conventional group). Duodenal papilla was partially observed.

and the visibility was independently scored by 3 external reviewers without prior experience with FUSE EGD.

To the best of our knowledge, there are few studies of FUSE EGD [20, 21]. Kakushima et al. [20] reported that duodenal papilla was visible in 19 (90%) out of 21 cases and concluded FUSE EGD improved the visibility of MDP. However, it was a pilot study consisting of small sample of healthy volunteers. The study evaluated whether MDP was visible or not, but did not assess the level of visibility [20]. Our study included patients with FAP and demonstrated the efficacy of FUSE EGD in patients with high risk of duodenal cancer. Neoplastic lesions were found in the duodenal papilla in 12 cases in the present study. Of these, 4 lesions were missed during prior routine surveillance using standard EGD, despite using the same sedatives. The finding in our study is of paramount clinical significance. FUSE EGD increases visual field angle and prevents missing papillary neoplasm due to better visualization of MDP.

Current FAP guidelines recommend switching to a side-viewing scope when sufficient visualization of the duodenal papilla cannot be achieved. However, use of a side-viewing duodenoscope requires 2 scope insertions, at times on a different occasion as not all endoscopists are proficient with duodenoscopes. This is time consuming and contributes to patients' discomfort and anxiety associated with the procedures with potentially more adverse events. Surveillance EGD in FAP patients without side-viewing duodenoscope is feasible when using FUSE EGD. Furthermore, FUSE colonoscopy has been shown to reduce adenoma miss rates [22–26].

Although FUSE EGD was superior to conventional endoscopy about visibility of duodenal papilla, there were some disadvantages of FUSE EGD. First, when a targeted lesion was in the side-view, biopsy needed to be performed in the forward view as done with conventional EGD because a biopsy forceps came out from the distal end of the FUSE EGD. However, if biopsy is to be performed on a lesion that can only be observed in side-view, it may be necessary to switch to side-viewing scope. All cases could be biopsied in this study. Second, FUSE EGD may be inferior to high-definition EGD in terms of neoplasm detection in esophagus and stomach because FUSE EGD does not involve image-enhanced function such as narrow band imaging, blue laser imaging, and linked color imaging, which are useful to detect esophageal squamous cell carcinoma and gastric cancer [27–33], although there is no difference in resolution between FUSE EGD and high-definition EGD. Third, FUSE EGD can be less cost-effective because another scope system is required to introduce FUSE EGD. Although the visibility of MDP was better in FUSE EGD compared with standard EGD in FAP patients, there would be little advantage in screening EGD to observe stomach and esophagus. It was one of the reasons that explained FUSE was not prevalent in Japan and other countries.

There were several limitations in this study. First, it was a single-center retrospective study. With the patients' clinical information successively stored in a FAP database, there was potential for introducing selection bias when utilizing the database for patient inclusion in our study. Second, the examinations were limited to experts. In this study, the total and duodenal observation times were longer. The mean total inspection time was 11.0 ± 2.3 min and duodenal inspection time was 1.9 ± 0.8 min, which were supposed to be longer than routine screening endoscopy. This may have contributed to the improved visibility in the FAP patients with higher risk of duodenal cancers. Third, we did not compare FUSE EGD with side-viewing duodenoscope. A side-viewing duodenoscope allows for direct visualization of the ampulla from a perpendicular view rather than tangential and allows for entire inspection of the ampulla. Although further comparative studies between FUSE EGD and a side-viewing duodenoscope are warranted, we believe that there are some merits in FUSE EGD regarding major papilla inspection compared with a side-viewing scope. First, scope access to reach major papilla in FUSE EGD is technically much easier than that in a side-viewing scope. Second, we don't need to change and reinsert the endoscope during the examination when using FUSE EGD. Finally, the performance of FUSE EGD was not compared with standard EGD, which we use in routine clinical practice. The visual field angle of the front view of FUSE EGD scope is 160°, slightly wider compared to the 140° angle of standard gastrointestinal scopes GIF-H290, GIF-Q260, and GIF-H260 (Olympus, Tokyo, Japan). The wider forward view angle of the FUSE EGD scope may produce better visibility than the normal endoscopes used in clinical practice. Further multicenter prospective studies are warranted to confirm our results.

In conclusion, FUSE is recommended in screening and or surveillance EGD in FAP patients to prevent missing periamupullary lesions through better visualization of MDP.

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Disclosure Statement

The authors declare no conflicts of interest.

Author's Contributions

R.I.: conception and design, analysis and interpretation of the data, drafting of the article. S.A.: conception and design, analysis and interpretation of the data, final approval of the article. S.K., T.M., T.T., T.N., M.Y., H.T., M.S., T.S., T.M., and Y.S.: critical revision of the article for important intellectual content. T.G.: critical revision of the article for important intellectual content, final approval of the article.

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主論文　要約

内科学系　消化器肝臓内科学専攻　市島　諒二

Efficacy of Full-Spectrum Endoscopy to Visualize the Major Duodenal Papilla in Patients with Familial Adenomatous Polyposis

FUSE（full-spectrum endoscopy）を用いた家族性大腸腺腫症患者における十二指腸乳頭視認性に関する効果

背景と目的：

十二指腸癌は、家族性大腸腺腫症（familial adenomatous polyposis: FAP）患者において大腸癌以外では死亡率の高い悪性腫瘍の一つである。通常の上部内視鏡検査における十二指腸乳頭(major duodenal papilla: MDP)の視認性は視野角と操作性の問題から不十分である。Full-spectrum endoscopy（FUSE）上部内視鏡は、内視鏡の前面と左側面の両方にカメラが設置されており、245 度まで視野角を広げることができる。本研究の目的は、FAP 患者において MDP の視認性に関する FUSE の有効性を評価した。

方法：

本研究は、当院で内視鏡にて経過観察を受けている 49 人の FAP 患者を対象とした単施設の後向き研究である。 FUSE 上部消化管内視鏡検査(FUSE-esophagogastroduodenoscopy: EGD)を用いて内視鏡専門医が施行し、MDP の視認性を評価した。すべての検査を録画し、個々の患者の動画を、前方視のみ（従来群）と前方視と左側面視（FUSE 群）に編集を行った。外部の内視鏡医が録画画像を評価し、従来群と FUSE 群で MDP の視認性を比較検討を行った。主要評価項目は、外部の評価医師(off-site)による Type1（乳頭の全領域が視認できる）と判断した割合とした。また、副次評価項目は検査を行った内視鏡医(on-site)が Type1（乳頭の全領域が視認できる）と判断した割合とした。

結果：

Type1 と診断した割合は off-site では、評価者 A,B,C でそれぞれ従来群(8.2%, 16.3%, 14.3%)FUSE 群（100%, 98%, 100%）($p < 0.001$) on-site では、従来群 32.6%, FUSE 群 100%、$p < 0.001$ であった。Off-site、On-site ともに FUSE 群では通常群よりも有意に視認性が高かった。

結論：

FUSE-EGD での検査では、FAP 患者における MDP の視認性を向上させることができる

序論

家族性大腸腺腫症（familial adenomatous polyposis : FAP）は常染色体優性遺伝であり、大腸腺腫症遺伝子の変異によって大腸腺腫性ポリープが多数発生することが特徴である。FAPで最も多い死因は大腸癌である。何百から何千もの腺腫性ポリープは、治療せずに放置すると必ず癌に進行する。予防的に大腸全摘出術の導入以来、大腸癌関連の死亡率は減少した(1-4)。しかし、それにもかかわらず、FAP 患者の平均余命は短い。これは大腸癌以外の原因にも起因しており、その中で上部消化管悪性腫瘍が最も一般的である。FAP 患者における大腸癌以外の中では、胃癌および十二指腸癌が報告されている。十二指腸乳頭部のリスクは 3〜8.5%と推定されており、これは一般集団のリスクの 200〜300 倍である(5-12)。したがって、十二指腸乳頭部癌を確実に診断するために、内視鏡検査中に十二指腸乳頭（major duodenal papilla: MDP）を注意深く検査することが重要である。十二指腸、特に MDP の視認性に関しては、操作性や視野角の関係上、標準的なスコープでは不十分である(13)(図1)。FAP 患者の場合、十二指腸乳頭の十分な視覚化が得られない場合は、従来の上部消化管内視鏡検査（esophagogastroduodenoscopy: EGD）に加えて、側視鏡による観察が推奨されている(14-18)。しかしながら、側視鏡による追加の検査は、時間、費用がかかり、そして患者にとって身体的にも負担となる。Full-spectrum endoscopy (FUSE; Endochoice、Inc.、Alpharetta、GA、USA）は、内視鏡前面と左側面にレンズが装着されており、2 つの画面を利用して 245 度まで視野を広げることができる新規に開発された内視鏡である。FUSE-EGD は、標準の挿入チューブの直径 9.6 mm、遠位端の直径 10.5 mm で設計されており、ウォータージェット機能を備えている。狭帯域光観察、画像強調機能を備えた拡大機能はない。鉗子口は正面方向にあり、前方視野と側方視野の死角はないがわずかに重なる部分がある(図 2)。FUSE-EGD を使用した MDP の可視性についてはほとんど知られていない。この研究の目的は、FAP 患者の MDP の視認性による FUSE-EGD の有効性を評価することである。

方法

この研究はヘルシンキ宣言に従って実施した。2016 年 10 月 26 日に倫理審査委員会によって承認され、すべての患者は書面によるインフォームドコンセントを行った。本研究は、University Hospital Medical Information Network Clinical Trials Registry（www.umin.ac.jp/ctr/; 識別番号 UMIN000033326）に登録を行った。本研究は、単施設で行った後ろ向き研究である。

以下の基準の少なくとも 1 つを満たした FAP 患者を対象に行った：(a) 100 個以上腺腫性ポリープを認める、(b) FAP の家族歴有し 100 未満腺腫性ポリープを認める、(c) DNA 分析によって大腸腺腫性ポリポーシス遺伝子変異を認める(14)。上部消化管外科手術後や十二指腸乳頭切除の病歴がある患者は除外した。内視鏡検査患者は朝食をとらないように指示

され、検査の 10 分前にプロナーゼとジメチコンを含む水を摂取した。 リドカインスプレーにて咽頭局所麻酔を行った後、被検者は左側臥位で EGD を施行した。内視鏡施行医の判断により、鎮静薬（プロポフォール、ミダゾラム、塩酸ペチジン）、および鎮痙薬（ブチルスコポラミン）を使用した。内視鏡検査の観察の順序は、食道、胃を観察した後に、十二指腸を観察した。生検は、新たに十二指腸乳頭に認めた場合にのみ行い、以前から既知の病変に関しては行わなかった。すべての生検検体は消化器専門の病理医よって検査され、Vienna 分類に従って判断した(19)。

On-site diagnosis

FUSE-EGD は、2016 年 7 月から 2017 年 12 月の間に、日本消化器内視鏡学会の専門医 8 名が行った。十二指腸の観察は、十二指腸球部の観察を最初に行い、視認性の評価を行い、その後スコープを十二指腸下行脚まで進め、乳頭より肛門側の観察を行った後、スコープを短縮する操作を行い、MDP を再度観察した。MDP が側面視で十分に観察された場合でも、正面視のみでの視認性を評価した。MDP の視認性は、処置中に評価を行い、記録を残した。前方視のみ（従来群）と前方視と左側面視の組み合わせ（FUSE 群）での十二指腸乳頭の視認性を比較した。

Off-site review

すべての検査の録画をした。録画した画像を前方視のみの 1 画面のみ（左側方視がかくされている画像）（従来群）。前方視と左側面視の両方を使用した画像（FUSE 群）。ランダムな順序に並び変えたものを 3 人の外部にいる内視鏡専門医が、録画画像が並べられた順に MDP の視認性に関して評価を行った。

評価

MDP の視認性は、Hew らの既報に従って以下の 5 つのタイプに分類した(13)。 Type1、十二指腸乳頭すべてが観察できる。Type2、開口部を含む十二指腸乳頭の口側が観察できる。Type3、開口部を含まない十二指腸乳頭の口側が観察できる。Type4、開口部を含む十二指腸乳頭の肛門側が観察できる。Type5 では、十二指腸乳頭が観察できなかった（図 3）
主要評価項目は、off-site review の録画画像による Type1 と判断された視認性の割合とした。On-site diagnosis の Type1 の視認性の割合、MDP の腫瘍の認識とその視認性、総検査時間と十二指腸検査時間、および有害事象を副次的評価項目として評価した。

統計分析

連続変数は中央値と範囲として表され、カテゴリ変数は、数値と頻度として表わした。Type1 の比率のグループ間の差異は、マンホイットニーU 検定を使用した。 <0.05 の p 値は統計的に有意であるとみなした。 すべての統計分析は、SPSS バージョン 17.0（SPSS、Inc.、

Chicago、IL、USA）を使用した。

結果

適格基準を満たす49人のFAP患者がFUSE-EGDを受けた。38人が男性で11人が女性、年齢の中央値は37歳（19〜61歳）であった。平均総検査時間は11.0±2.3分、十二指腸検査時間は1.9±0.8分であった。ブチルスコポラミンは28人（57.1%）の患者で使用し、ミダゾラム、プロポフォール、および塩酸ペチジンは、それぞれ17人(34.7%)、44人(89.9%)、および7人（14.3%）の患者に使用した。すべてのFUSE-EGDで有害事象なは認めなかった。

Off-site で評価者A、B、Cによって評価されたMDPの視認性は（Type1 / 2–4 / 5）は、従来群で 評価者A (8.2% / 63.2% / 28.6%)、評価者B (16.3% / 53.1%/ 30.6%)、評価者C (14.3% / 55.1% / 30.6%)、FUSE群では評価者A（100%/ 0% / 0%)、評価者B(98%/ 2%/ 0%)、評価者C(100% / 0% / 0%) 3人の評価者によるType1の割合は、FUSE群の方が従来群よりも有意に高かった（$p < 0.001$)。

On-siteでのMDPの視認性は、すべての患者で評価を行った。タイプ1、2〜4、および5の割合は、前方視のみ（従来群）でそれぞれ32.6%、38.8%、および28.6%であった。
前方視および側面視合わせると（FUSE群）では、49人すべての患者がType1の視認性であった。Type1の割合は、FUSE群の方が従来群と比較し有意に高かった（$p < 0.001$)。

MDPの腫瘍性病変は12人の患者（24.5%）で見つかった。このうち、8つの病変は本研究開始前の上部内視鏡検査ですでに見つかっており、残りの4つは新規に発見され、4人のうち3人が乳頭切除術を行う目的で他院に紹介した。残る1人の患者は小さな腺腫であり経過観察となった。病変の見つかった12人の患者におけるOff-siteでの評価は、従来群では、評価者A（Type1 / 2–4 / 5）(0% / 100% / 0%)、評価者B(12.7% / 75.0% / 8.3%)、評価者C(12.7% / 87.3% / 0%)であったが、3人の評価者ともFUSE群ではすべてType1であった。On-siteでのMDPの視認性は、従来群で（Type1 / 2–4 / 5）(50.0%、41.7%、8.3%)であったが、FUSE群ではすべてType1であった。同様に、新たに診断された4つの病変でも、on-siteとoff-siteの両方で、FUSE群ではすべてType1と評価された。
ブチルスコポラミンの使用の有無におけるType1と評価したMDPの視認性の違いをFUSE群と従来群でそれぞれ検討したが、いずれの群においても差はなかった。

考察

本研究では、FAP患者におけるFUSEを使用したMDPの視認性を検討した。FUSE- EGDでは、ほぼすべての患者でMDPの全体を観察することができた。本研究では、持ち越し効果を排除するために、編集した動画の順序をランダムに入れ替え、FUSE-EGDの経験がな

い、3 人の外部評価者が視認性を個別に評価した。FUSE-EGD の研究はこれまでにほとんど報告がなかった(20-21)。Kakushima らは、21 例中 19 例（90%）に MDP が見られたと報告し、FUSE-EGD によって視認性を改善したと報告している。しかし、その報告は基礎疾患のない小さな母集団の研究であった。また、MDP が見えるかどうかを評価したが、視認性のレベルは評価していなかった(20)。本研究には十二指腸癌のリスクが高い FAP の患者を対象とした。結果として、12 例の腫瘍性病変を認めた。これらのうち、4 例は通常の EGD では見落とされていた。このことは臨床的な意義があると考えられる。FUSE-EGD は、視野角が増加するため、十二指腸乳頭部癌の見落としを防ぐことができた。現在の FAP ガイドラインでは、MDP を十分に視認できない場合は、側視鏡に切り替えることが推奨されている。しかし、側視鏡を使用するには、2 種類の内視鏡を挿入する必要があるし、すべての内視鏡医が側視鏡に習熟しているとは限らない。そのため、時間、患者の負担を増やすことになる。FUSE- EGD を使用すると、側視鏡を使用せず、FAP 患者の定期チェックを行うことができる。FUSE 大腸内視鏡では腺腫の見逃しを防ぐと報告もされている(22－26)。本研究は、MDP 以外の視認性に関して評価は行っておらず、FAP 患者の腺腫の見逃しを防ぐ効果を検討したものではない。しかしながら、FUSE-EGD は FAP 患者の見逃されやすい MDP 病変を見つける一つの手段になりうると考えられる。

FUSE-EGD にはいくつかの欠点がある。まず、病変が側面視野にある場合でも、従来の EGD と同様に正面から、処置具（生検鉗子やスネアなど）がでてくるため、処置を行うのは困難なことがある。したがって、側面でしか観察できない病変に対して処置を行う場合は、側視鏡への切り替えが必要になる。第二に、FUSE- EGD は、画像強調機能を含まないため、食道や胃の検出率は EGD より劣る可能性がある。画像強調機能には、胃癌や食道癌の発見に効果的であると報告がある(27-33)。 第三に、FUSE -EGD を導入するには別のシステムが必要になるため、FUSE-EGD は費用効果が低い可能性がある。 MDP の視認性は従来群と比較して FUSE 群の方が優れていたが、胃と食道を観察するために EGD をスクリーニングすることには FUSE-EGD はほとんど利点がない。このことが FUSE が日本や他の国で普及しなかった理由であると考えられる。しかしながら、今回の検討で明らかになった前方・側方視野を得ることにより、人工知能の技術を応用すればより消化管腫瘍を見つけやすくすることができる可能性もあるし、スコープに改良を加え側方視から処置具を出すことができれば胆膵領域における処置をしやすくする可能性もあると考えられる。

この研究にはいくつかの制限がある。まず、単一施設の後向き研究であること。第二に、試験は内視鏡専門医に限定して行っていたこと。第三に観察時間と十二指腸観察時間が長かったことである。平均総検査時間は 11.0±2.3 分、十二指腸検査時間は 1.9±0.8 分であり、通常のスクリーニング内視鏡検査よりも長いと考えられる。このことは、視認性の向上に貢献した可能性がある。第三に、FUSE-EGD を側面鏡と比較していないことがあげられる。最後に、日常の臨床診療で使用する標準 EGD と比較されていないことである。FUSE- EGD の正面図の視野角は 160° であり、GIF-Q260、および GIF-H260 の 140° の角度と比較し

てわずかに広くなっている。 FUSE -EGD スコープの前方視角が広いと、通常の内視鏡よりも視認性が向上する可能性がある。MDP の視認性、および FAP 患者における腺腫の見逃しを防ぐ工夫に関して、今後さらなる多施設前向き研究が必要と考えられる。
結論として FUSE-EGD は、MDP の視認性の向上に寄与すると考えられた。

表 1 消化管上皮性腫瘍の Vienna 分類

Category 1	Negative for neoplasia/ dysplasia
Category 2	Indefinite for neoplasia/ dysplasia
Category 3	Non-invasive low-grade neoplasia Low-grade adenoma /dysplasia
Category 4 4.1. 4.2. 4.3.	Non-invasive high grade neoplasia High-grade adenoma/ dysplasia Non-invasive carcinoma Suspicious for invasive carcinoma
Category 5 5.1. 5.2.	Invasive neoplasia Intramucosal carcinoma Submucosal carcinoma or beyond

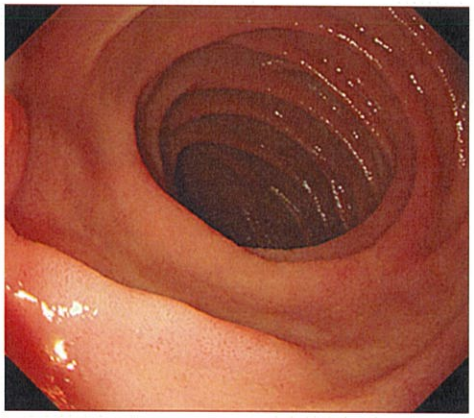


図 1 通常スコープでの十二指腸下行脚の観察画像

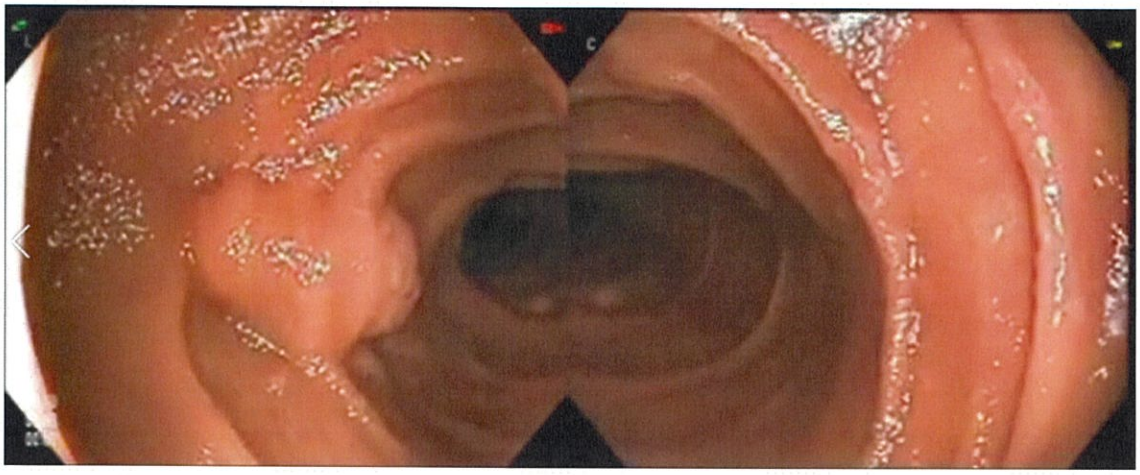
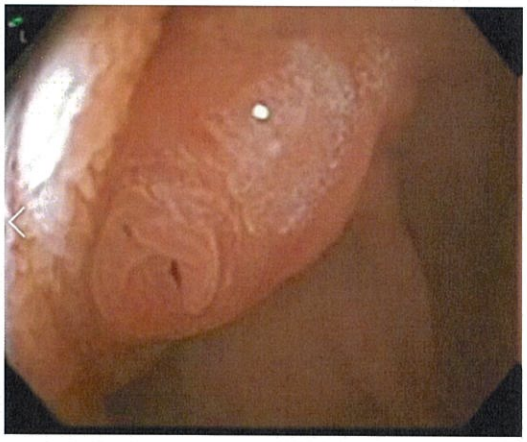
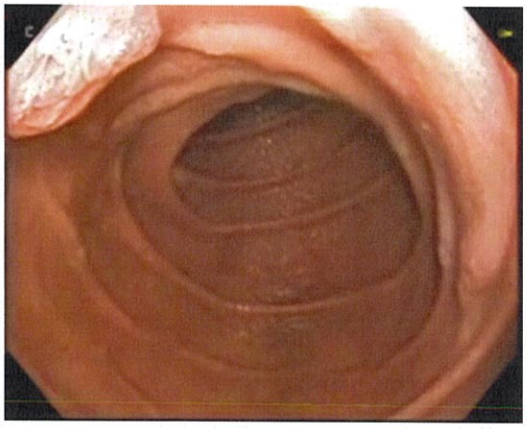


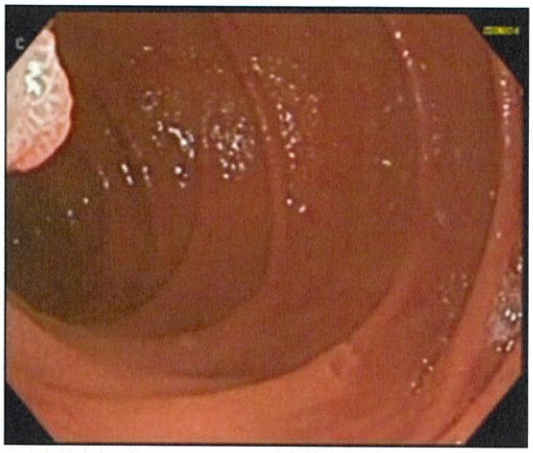
図 2　FUSE (Full-spectrum endoscopy) の画像
正面視と左側面視から構成されており、死角はないもののわずかに重なる部分がある。



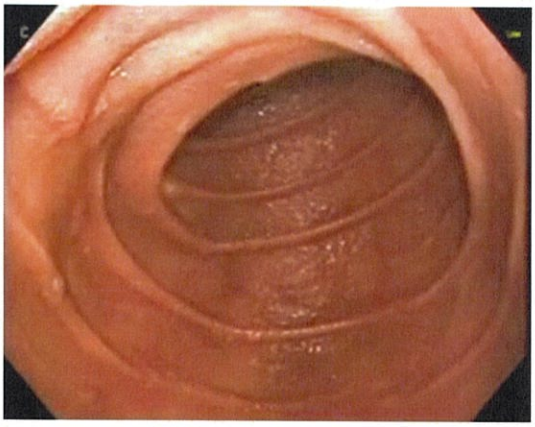
(a)



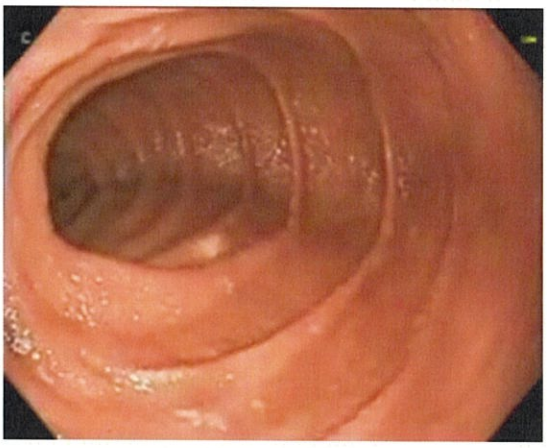
(b)



(c)



(d)



(e)

図 3 十二指腸乳頭の視認性を Hew らの既報(13)に基づき 5 つに分類した

(a) Type1 十二指腸乳頭すべてが観察できる

(b) Type2 開口部を含む十二指腸乳頭の口側が観察できる

(c) Type3 開口部を含まない十二指腸乳頭の口側が観察できる

(d) Type4 開口部を含む十二指腸乳頭の肛門側が観察できる

(e) Type5 二指腸乳頭が観察できない

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