Gastric Cancer (2009) 12: 142–147
DOI 10.1007/s10120-009-0514-y

Original article

Pilot study to assess the safety of local lidocaine injections during endoscopic submucosal dissection for early gastric cancer

Shinsuke Kiriyama[1,2], Ichiro Oda[1], Fumiya Nishimoto[1], Yumi Mashimo[1], Hisatomo Ikehara[1], and Takuji Gotoda[1]

[1]Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
[2]Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Japan

Abstract

Background. **In Japan, endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is performed by endoscopists on patients under sedation. There is an increased risk of anesthesia-related complications due to the higher sedative doses required during lengthier ESDs, so we sought to determine whether a local pain control method could safely reduce such doses.**

Methods. **Twenty EGC patients enrolled in this study received local lidocaine injections during ESDs at our hospital (lidocaine group; LG). Electrocardiography, heart rate, oxygen saturation, and blood pressure were monitored during and after the ESDs, along with the doses of midazolam and pentazocine. Pain assessments were recorded for LG patients on the day of their ESDs and the following day.**

Results. **The mean volume of lidocaine injection solution was 55.4 ml and the mean dose of lidocaine was 236 mg (range, 100–300 mg). The mean size of the resected specimens was 39.3 mm and mean procedure time was 66.0 min. There were no lidocaine-related complications, and electrocardiography, heart rate, oxygen saturation and blood pressure measurements were normal. In comparison to 157 consecutive patients (control group; CG), who had similar characteristics and had undergone ESDs previously with submucosal injections of conventional normal saline solution, the mean ± SD pentazocine dose of 15.8 ± 10.3 mg in the LG was significantly lower ($P < 0.01$) than the dose of 23.1 ± 9.5 mg in the CG, and none of the LG patients complained of abdominal pain on the day of their ESDs, whereas such pain was reported by 17% (27/157) of the CG.**

Conclusion. **Local lidocaine injections into the submucosal layer were safe when administered during ESDs performed on EGC patients under sedation.**

Key words Lidocaine · Endoscopic submucosal dissection (ESD) · Early gastric cancer · Local anesthesia · Submucosal injection

Offprint requests to: S. Kiriyama
Received: November 4, 2008 / Accepted: May 28, 2009

Introduction

Although endoscopic submucosal dissection (ESD) is less invasive for early gastric cancer (EGC) than gastrectomy, the classical open surgical procedure, some ESD patients suffer considerable postoperative pain. Localized pain both during and after ESD for large EGCs is probably caused by ulcer defects and/or electrical thermal burns extending from the submucosal (sm) layer to the serosa.

There is a problem not only with pain management but also with sedation management during the ESD procedure. In a previous report, 41% of ESDs took longer than 1 h [1]. As a result of such increased procedure times, therefore, higher doses of sedative drugs such as midazolam have become necessary, and endoscopists performing ESDs must be even more careful about the depth of patient sedation, because deep sedation can occur during endoscopic procedures [2]. Because there is an increased risk of anesthesia-related complications with the higher sedative drug doses required during lengthier ESDs, we decided to determine whether a local pain control method could safely reduce such doses.

By controlling localized pain during ESD, we thought that it might be possible to reduce the dose of the sedative drug administered during the actual procedure. In addition, administering local analgesia for pain during ESD would amount to providing preemptive analgesia for patient pain that might otherwise be experienced the day after the procedure [3].

Local anesthesia is commonly used in surgery, including laparoscopic surgery [4, 5], but there have been no previous reports on the use of lidocaine for local pain control either during or after ESD. This study intended to assess the safety of local lidocaine injections into the sm layer of EGC lesions in controlling localized pain both during and subsequent to ESD procedures performed on patients under sedation.

Patients and methods

Patients

A total of 20 EGC patients were enrolled in this study (lidocaine group; LG) between September 2005 and April 2007 at the National Cancer Center Hospital in Tokyo, Japan. These subjects were scheduled for gastric ESDs based on endoscopic mucosal resection (EMR) guideline criteria [6, 7] and had their given informed consent before undergoing the procedures. Patients with: (1) an allergy to lidocaine or other amide-type local anesthesia; (2) severe liver disease, heart disease, or renal dysfunction; (3) a gastric or duodenal ulcer; (4) atherosclerotic disease; (5) hyperthyroidism; or (6) an American Society of Anesthesiologists (ASA) physical status higher than class 2 were excluded from the study. This study was performed in accordance with the Helsinki Declaration as revised in 1989.

ESD procedures

ESDs were performed following a standard protocol, and procedure times were recorded for all LG patients. Lesion margins were delineated beforehand by using 0.2% indigo-carmine dye spraying. After the marking dots were made with a needle knife (KD-1L-1; Olympus Medical Systems, Tokyo, Japan), 0.5% lidocaine solution was injected into the sm layer to lift the lesion. A circumferential incision in the mucosa was then completed using the needle knife, an insulation-tipped knife (IT knife; KD-610L, Olympus) [7–10], and a high-frequency current electrical generator (ICC 200; ERBE, Tubingen, Germany) and, finally, the thickened sm layer was dissected using the same two endoscopic knives.

Injection solutions

As previously noted, we used 0.5% lidocaine solution consisting of 10 ml of Xylocaine Polyamp 1%, containing 100 mg of lidocaine hydrochloride (HCl; AstraZeneca, Osaka, Japan), 9.7 ml of normal saline, 0.2 ml of 0.4% indigo-carmine dye, and 0.1 ml of 0.1% epinephrine (Table 1) for the LG in this study. The maximum volume of 0.5% lidocaine solution per LG patient was 60 ml, which contained 300 mg of lidocaine HCl [11–13].

For the purpose of lifting an EGC lesion, the lidocaine injection solution was injected into the sm layer under and around the lesion, as determined by the endoscopist, using a 23-gauge needle injection catheter (NM-200L-0423; Olympus). Once the needle was inserted into the sm layer, the endoscopist's assistant would aspirate the syringe, particularly for those patients suffering from hypertension or diabetes mellitus, thereby creating negative pressure. If no blood reflex appeared, the assistant would begin injecting the solution and would stop when the lesion was sufficiently lifted and became slightly blue in color, with the total volume of the injection solution being recorded at that time.

Patient monitoring during and following ESD procedures

Electrocardiography, heart rate, oxygen saturation, and blood pressure were automatically monitored during and after each ESD; lidocaine-related complications were recorded, as were any complications resulting from the ESD itself, such as a perforation. In addition, the patient's white blood cell count and C-reactive protein level were checked on the first day following the ESD.

Sedation during ESDs

All ESDs on LG patients were performed following standard sedation procedures. Sedation was induced with 0.06 mg/kg of midazolam. Incremental 2-mg doses of midazolam were given if a patient demonstrated signs of discomfort, restlessness, or agitation, or responded to verbal commands. When additional midazolam was ineffective, 15 mg of pentazocine was infused as an analgesic agent. Each patient received oxygen by nasal cannula from the start of the ESD for a maximum period of 3 h after the procedure.

Table 1. Composition of injection solutions

	Lidocaine solution	Conventional solution
1% Lidocaine (ml) (Lidocaine 100 mg/10 ml)	10	0
Normal saline (ml)	9.7	19.7
0.4% Indigo-Carmine (ml)	0.2	0.2
0.1% Epinephrine (ml)	0.1	0.1
Lidocaine concentration (%)	0.5	0
Maximum lidocaine injection	300 mg/60 ml	

Table 2. Results

	Lidocaine group (LG)
Number	20
Sex	
Male	16
Female	4
Injection solution	
Mean injection volume (ml)	55.4
Lidocaine, mg	236
(range)	(100–300)
Laboratory data (day 1)	
Mean +/– SD white blood cell count	8700 ± 2100
C-Reactive protein (g/dl)	0.8 ± 0.7
Abnormality in monitoring	
Electrocardiography	0
Heart rate	0
Oxygen saturation	0
Blood pressure	0
Complications	
Lidocaine-related	
Intoxication	0
Convulsion	0
Arrhythmia	0
Respiratory	0
Perforation	0

In assessing the necessity for sedative drugs, we retrospectively compared the doses of midazolam and pentazocine during ESDs performed on the 20 LG patients with the doses used in 157 other consecutive EGC patients who had previously received conventional sm injections during ESDs, as a historical control group (control group; CG). The ESDs in the CG patients, whose clinical characteristics matched those of the LG patients, had been performed between January and August 2005, with the patients under sedation, as these CG patients also met the EMR guideline criteria. Their conventional sm injections consisted of a solution of 19.7 ml of normal saline, 0.2 ml of 0.4% indigo-carmine dye, and 0.1 ml of 0.1% epinephrine (Table 1).

Evaluation of abdominal pain after ESD

In evaluating the efficacy of pain control, a written questionnaire about the absence or presence of abdominal pain (no pain, mild pain without painkiller, or severe pain with painkiller) was distributed to each patient in the LG, to be completed on the day of the ESD after the procedure, and on the next day. We then proceeded to retrospectively determine the absence or presence of abdominal pain for each CG patient at the same two points in time as those in the LG, based on complete medical records. Finally we also identified those patients in each group who either received a painkiller (pain [+]) or did not receive a painkiller (pain [–]) after their procedures.

Statistical analysis

Values for all variables in this study are expressed as means ± SD. In comparing baseline characteristics between the two groups, we used a *t*-test for continuous variables, with the χ^2 or Fisher test for dichotomous variables. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program (SPSS, version 8.0 for Windows; Tokyo, Japan). The *P* values were two-sided, and $P < 0.05$ determined statistical significance.

Results

The mean volume of lidocaine injection solution was 55.4 ml and the mean dose of lidocaine was 236 mg (range, 100–300 mg; Table 2). There were no electrocardiography, heart rate, oxygen saturation, or blood pressure abnormalities recorded, nor were there any episodes of lidocaine intoxication, including respiratory depression or hypotension, convulsion, or arrhythmia, such as cardiovascular collapse or bradycardia. The mean ± SD white blood cell counts and C-reactive protein values on the first post-procedure day were 8700 ± 2100 cells/mm^3 and 0.8 ± 0.7 g/dl, respectively.

Pain evaluation in comparison with historical control group

In our comparison of LG patients with the CG as a historical control, there were no significant differences

Table 3. Comparison with historical control

	Lidocaine group	Control group	*P* value
Number	20	157	
Age, years (mean ± SD)	69.4 ± 7.2	66.7 ± 9.4	NS
Resection size, mm (mean ± SD)	39.3 ± 11.6	36.3 ± 8.3	NS
Sedating agents			
Midazolam, mg (mean ± SD)	9.7 ± 3.2	10.3 ± 4.6	NS
Pentazocine, mg	15.8 ± 10.3	23.1 ± 9.5	<0.01
Procedure time (min)	66.0 ± 36.9	61.0 ± 30.7	NS
Post-ESD pain			
Day 0			
Pain (–)	20 (100%)	130 (83%)	
Pain (+)	0	27 (17%)	<0.05
Day 1			
Pain (–)	18 (90%)	95 (61%)	
Pain (+)	2 (10%)	62 (39%)	<0.05

NS, not significant

in clinicopathological characteristics between the two groups. The mean ± SD size of the resected specimens was 39.3 ± 11.6 mm in the LG and 36.3 ± 8.3 mm in the CG, while the mean ± SD ages were 69.4 ± 7.2 years and 66.7 ± 9.4 years, respectively (Table 3). The mean ± SD doses of midazolam were 9.7 ± 3.2 mg and 10.3 ± 4.6 mg in the LG and CG, respectively (difference not significant [NS]), but the mean ± SD dose of pentazocine in the LG was significantly lower than that in the CG, at 15.8 ± 10.3 mg and 23.1 ± 9.5 mg, respectively ($P < 0.01$).

All of the LG patients completed the questionnaires regarding the absence or presence of abdominal pain on the day of the ESD following the procedure, as well as the next day. None of the LG patients complained of abdominal pain immediately following their ESDs, whereas abdominal pain that required a painkiller occurred in 17% (27/157) of the CG patients ($P < 0.05$). On the day after their ESDs, 2 (10%) of the LG patients complained of abdominal pain requiring a painkiller, whereas abdominal pain that necessitated a painkiller occurred in 39% (62/157) of the CG patients ($P < 0.05$).

Discussion

Based on the results of this pilot study, local lidocaine injection into the sm layer was demonstrated to be safe during ESDs for EGC patients under sedation. The safety and efficacy of lidocaine as preemptive analgesia has already been assessed and proven in the surgical field, particularly with respect to laparoscopic surgery, and it is now commonly accepted that local anesthesia is effective during certain surgical procedures, and it is used accordingly [14–17]. Although lidocaine has generally been associated with a number of adverse reactions, such as respiratory depression, hypotension, convulsion, and arrhythmia, including cardiovascular collapse and bradycardia [18], there were no such complications observed in the present study. All the results related to complications, as well as the laboratory data, indicated that local lidocaine injection into the sm layer could be used safely during ESDs for EGCs performed under sedation.

ESD produces higher rates of en-bloc resections and tumor-free margins compared to conventional EMR. As a result, it has been proposed as the gold standard treatment for EGC, because it facilitates more accurate histological assessment and reduces the risk of tumor recurrence [19–21]. At the present time, the indications for ESD are in the process of being expanded; this will make it possible for even more EGC patients to be successfully treated without having to undergo open surgery.

ESD for large tumors is usually a prolonged procedure requiring higher doses of sedative and pain-control drugs such as midazolam and pentazocine, but there have been no published reports as yet addressing the problem of epigastric pain associated with ESDs. In our study, patient abdominal discomfort was considerably lower in the LG, most likely because of the immediate local anesthesic effect of lidocaine, as evidenced by the significantly lower mean total dose of pentazocine.

Preemptive analgesia is defined as preventing or reducing the memory of nociceptive stimuli in the central nervous system, utilizing analgesic methods performed prior to such nociceptive stimuli, with a resultant decrease in the need for postoperative analgesics. Recent research on postoperative pain control has led to the development of the concept of preemptive analgesia, in which pain management begins at the preoperative stage so as to decrease the severity of pain in the postoperative period, by applying analgesic methods

before the onset of nociceptive stimuli [13, 22–24]. Based on this conceptual approach, local anesthesia can also have a preemptive analgesic effect, so it is likely that in the LG patients in our study the lidocaine injections had elevated their pain thresholds after completion of their ESDs. This, in turn, resulted in these patients not complaining of abdominal pain on the day of their procedures, and having fewer pain-related comments and milder pain on the day after the procedure.

The mean dose of midazolam required in the LG was lower than that in the CG, although the difference was not statistically significant, but the mean dose of pentazocine in the LG was significantly lower than that in the CG. This suggests that local lidocaine injection could reduce the amount of pentazocine required by locally controlling a patient's pain perception, thus resulting in less patient movement and fewer delays in the ESD caused by such movement. Fewer delays and less time spent administering sedative and pain-control drugs during a lengthier ESD procedure, combined with an actual reduction in the doses of such drugs, could reduce the risk of respiratory and other drug-related complications caused by oversedation.

In our study, none of the LG patients reported any abdominal pain on the day of their ESDs, indicating the probable effectiveness of local lidocaine injections for pain control during and immediately after ESD. Given lidocaine's characteristic feature of controlling pain for a only a short period, its local injection into the sm layer appears to be an effective method for pain management during and immediately following ESD, but further investigation of other longer-acting local analgesics is recommended.

Our investigation was a small pilot study of a lidocaine-treated group that was retrospectively compared to a considerably larger historical control group. A randomized control study will be necessary in the future to reliably assess the effectiveness of the particular technique that we have described. While the assessment and measurement of pain are very important considerations for both patients and physicians, pain tolerance varies greatly among patients, so further investigation will be required in accordance with the basic philosophy of preemptive analgesia.

In conclusion, local lidocaine injections into the sm layer during ESDs in EGC patients under sedation are safe. This study indicated that such lidocaine injections have a beneficial effect on local pain control during ESDs and in the immediate post-procedure period.

References

1. Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005;17:54–8.
2. Patel S, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. Am J Gastroenterol 2005;100: 2689–95.
3. Karaaslan D, Sivaci RG, Akbulut G, Dilek ON. Preemptive analgesia in laparoscopic cholecystectomy: a randomized controlled study. Pain Pract 2006;6:237–41.
4. Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. Anesth Analg 2000;91: 403–7.
5. Einarsson JI, Sun J, Orav J, Young AE. Local analgesia in laparoscopy: a randomized trial. Obstet Gynecol 2004;104:1335–9.
6. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma — 2nd English edition. Gastric Cancer 1998;1: 10–24.
7. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006;41:929–42.
8. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, et al. A new endoscopic mucosal resection (EMR) procedure using an insulation-tipped diathermic (IT) knife for rectal flat lesions. Gastrointest Endosc 1999;50:560–3.
9. Gotoda T. Endoscopic diagnosis and treatment for early gastric cancer. Cancer Review: Asia-Pacific 2004;2:17–37.
10. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–9.
11. Polk JW, Bailey AH. Topical anesthesia for endoscopy; evaluation of prilocaine (Citanest), a new local anesthetic. Dis. Chest 1967;51:293–7.
12. Mather LE, Tucker GT, Murphy TM, Stanton-Hicks MD, Bonica JJ. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia. II: Pharmacokinetics. Br J Anaesth 1976;48:989–94.
13. Garwood S, Reeder M, Mackenzie IZ, Guillebaud J. Tubal surface lidocaine mediates pre-emptive analgesia in awake laparoscopic sterilization: a prospective, randomized clinical trial. Am J Obstet Gynecol 2002;186:383–8.
14. Smith G. Intraperitoneal administration of analgesia: is this practice of any utility? Br J Anaesth 2002;89:535–7.
15. Elhakim M, Elkott M, Ali NM, Tahoun HM. Intraperitoneal lidocaine for postoperative pain after laparoscopy. Acta Anaesthesiol Scand 2000;44:280–4.
16. Carbonell AM, Harold KL, Mahmutovic AJ, Hassan R, Matthews BD, Kercher KW, et al. Local injection for the treatment of suture site pain after laparoscopic ventral hernia repair. Am Surg 2003;69:688–91.
17. Zullo F, Pellicano M, Cappiello F, Zupi E, Marconi D, Nappi C. Pain control after microlaparoscopy. J Am Assoc Gynecol Laparosc 1998;5:161–3.
18. Sweetman SC, Blake PS, McGlashan JM, Neathercoat GC, Parsons AV. Lidocaine. In: Martindale: the complete drug reference. 35th ed. London/Chicago: Pharmaceutical Press; 2006. p. 1702–6.
19. Rembacken BJ, Gotoda T, Fujii T, Axon ATR. Endoscopic mucosal resection. Endoscopy 2001;33:709–18.
20. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. Gastrointest Endosc 2003;57:567–79.
21. Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? Dig Endosc 2003;15:113–6.
22. Kedek A, Derbent A, Uyar M, Bilgen C, Uyar M, Kirazli, et al. Pre-emptive effect of ibuprofen syrup and lidocaine infiltration on post-operative analgesia in children undergoing adenotonsillectomy. J Int Med Res 2005;33:188–95.

23. Homer JJ, Swallow J, Semple P. Audit of pain management at home following tonsillectomy in children. J Laryngol Otol 2001;115:205–8.
24. Wu CT, Yett CC, Yu JC, Lee MMS, Tao PL, Ho ST, et al. Preincisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anasthesiol Scand 2000;44:63–8.

Gastric Cancer (2009) 12: 219–224
DOI 10.1007/s10120-009-0529-4

Original article

Analysis of the color patterns of early gastric cancer using an autofluorescence imaging video endoscopy system

Motohiko Kato[1,2], Noriya Uedo[2,3], Ryu Ishihara[2], Takashi Kizu[1], Rika Chatani[2], Takuya Inoue[2], Eriko Masuda[5], Koichi Tatsumi[6], Yoji Takeuchi[2], Koji Higashino[2], Hiroyasu Iishi[2], Yasuhiko Tomita[4], and Masaharu Tatsuta[3]

[1]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan
[2]Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
[3]Department of Endoscopic Training and Learning Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[4]Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[5]Department of Internal Medicine, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan
[6]Department of Internal Medicine, Dongo Hospital, Yamatotakada, Nara, Japan

Abstract

Background. **Using a novel autofluorescence imaging video endoscopy system (AFI), tumors in the esophagus and the colon appeared purple in a green background, but the color patterns of early gastric cancer (EGC) were found to vary. Factors associated with these patterns remain unknown. The aims of the present study were to classify the color patterns of EGCs and to investigate the correlation between the patterns and clinicopathological features.**

Methods. **A total of 107 EGCs that had been evaluated by AFI endoscopy, prior to endoscopic or surgical resection, were included. The color patterns of EGCs in AFI images and the association between tumor color and clinicopathological factors were evaluated. These factors included tumor morphology, location, size, background color, histological type, depth of invasion, lymphatic or vessel permeation, and ulceration.**

Results. **The color patterns of EGCs were classified into the following four groups: purple tumors in a green background (52%); green tumors with a purple margin in a green background (21%); green tumors in a purple background (17%); and purple tumors in a purple background (10%). Univariate analysis showed that macroscopic type, histological type, ulceration, and background AFI color were significantly associated with tumor color, whereas multivariate analysis revealed that macroscopic type was the only independent contributor to tumor color.**

Conclusion. **The present study has enabled a clearer understanding of the significance of tumor color in relation to the AFI imaging of EGCs. Recognition of the color patterns in AFI images should help in the diagnosis of EGCs.**

Key words Autofluorescence endoscopy · Early gastric cancer · Atrophic gastritis · Tumor color patterns

Offprint requests to: N. Uedo
Received: September 27, 2009 / Accepted: October 27, 2009

Introduction

Early diagnosis and treatment can improve the prognosis of gastric cancers. Despite the progressive development of endoscopic modalities [1], the early detection of superficial neoplasms during routine esophagogastro-duodenoscopy (EGD) remains difficult because there are few morphological changes that differentiate malignant from nonmalignant lesions. Moreover, although treatments such as endoscopic mucosal resection [2] or endoscopic submucosal dissection (ESD) [3] are widely performed for the local resection of EGCs in Japan, accurate diagnosis of tumor extent is sometimes difficult because EGCs occasionally have flat or isochromatic tumor extensions. Chromoendoscopy can increase diagnostic yields in relation to the detection and delineation of flat tumors, by the enhancement of morphological features [4]. However, this modality is not widely used in clinical practice because its deployment can result in substantial prolongation of routine endoscopic examinations. Consequently, easier and more efficacious endoscopic modalities for diagnosing EGC are needed.

An autofluorescence imaging videoendoscopy (AFI) system produces real-time pseudocolor images from the computed detection of autofluorescence emitted by endogenous fluorophores (collagen, nicotinamide, adenine dinucleotide, flavin, and porphyrins) due to excitation by light. The system can identify lesions, including malignancies, by detecting differences in tissue fluorescence properties, and can thus reveal early-stage cancers that are not detectable by conventional white-light endoscopy [2].

In a previous study, when we investigated the diagnostic ability of an AFI system for early-stage cancers in the digestive tract, we discovered that tumors in the

esophagus and the colon appeared purple in a green background [5]. However, the color pattern of EGCs in the AFI images varied among tumors. The factors associated with these color variations were not investigated at that time [5]. The aims of the present study were to evaluate the endoscopic appearance of EGCs in AFI images and to investigate the clinicopathological factors associated with different tumor colors.

Patients and methods

Study sample

Since September 2003, the data of patients who have visited our endoscopy unit at Osaka Medical Center for Cancer and Cardiovascular Diseases, and who have undergone AFI, have been recorded consecutively in a database that is maintained prospectively and regularly updated. The input clinicopathological data were compiled according to the *Japanese classification of gastric carcinoma* protocol [6]. From this database, patients with EGC who presented between June 2004 and January 2006 were retrieved and their main tumors were included in the study. Patients with a history of gastrectomy were excluded. If a patient had multiple lesions, the largest one was selected for analysis. Approval from the Institutional Review Board at our medical center was obtained for this study.

A total of 127 consecutive patients with EGC who underwent AFI for pretherapeutic evaluation were identified from the database. Seven patients with a history of gastrectomy and one patient who transferred to another hospital were excluded. Among the 119 EGC lesions in the 119 patients involved in the study, AFI images were insufficient for evaluation in 10 lesions, and 2 lesions could not be classified. Therefore, a final total of 107 lesions were analyzed in this study.

Endoscopic procedure

The AFI system used in this study consisted of a light source (CLV-260SL; Olympus Medical Systems, Tokyo, Japan), a processor (CV-260SL; Olympus), a video monitor, and a video endoscope (EVIS-FQ260Z; Olympus) that was equipped with two charged-coupled devices (CCDs) that were available with autofluorescence and white-light modes. In the autofluorescence mode, blue excitation light (395–475 nm) to induce autofluorescence and green light (540–560 nm) to capture green reflection images were sequentially emitted from the light source through a rotation filter. A cut filter that was placed with the lens was used to permit only light with wavelengths between 490 and 625 nm to intensify the CCD for the AFI mode [7]. All examinations were performed by a single endoscopist (N.U.) who had 4 years' experience with autofluorescence endoscopy and 14 years' experience with conventional endoscopy.

Five minutes before the examination, patients ingested a mixture of a mucolytic agent, 20000 U pronase (Pronase MS; Kaken Pharmaceutical, Tokyo, Japan), a defoaming agent, 80 mg dimethylpolysiloxane syrup (Gascon Drops; Kissei Pharmaceutical, Matsumoto, Japan), and 1 g sodium bicarbonate diluted in 100 ml of tap water. After the application of topical anesthesia, the endoscope was gently inserted into the stomach. First, the color of the background mucosa and tumors were evaluated under AFI observation, and at least four AFI images of each tumor were taken from various viewing angles. After that, the tumors were thoroughly investigated by conventional white-light endoscopy. This was followed by 0.04% indigo carmine chromoendoscopy. Images obtained from the white-light endoscopy and chromoendoscopy were recorded. All images were digitally stored on an image server (Solemio Endo; Olympus).

Analysis of color patterns of EGC

Two endoscopists (M.K. and N.U.) reviewed the recorded AFI images, and the color patterns were classified into the following four types on the basis of tumor and background color: (1) a purple tumor on a green background (P/G type); (2) a green tumor on a green background (G/G type); (3) a green tumor on a purple background (G/P type); and (4) a purple tumor on a purple background (P/P type). When a tumor was located on a background color border, the color which surrounded more than half of the circumference of the tumor was designated as a background color.

The association between tumor color in the AFI images and a range of clinicopathological factors was investigated. These factors included: tumor size (≤2 cm or >2 cm), location (upper, middle, or lower third), macroscopic type (elevated or depressed), histological type (differentiated or undifferentiated), and depth of invasion (mucosal or submucosal); the presence or absence of vessel invasion; and background AFI color. For the factors that had a significant association on univariate analysis, multivariate analysis was performed to assess the strength and independence of the association. The macroscopic type of the tumor was determined under chromoendoscopic observation. Types 0I, 0IIa, and 0IIa+IIc were classified as elevated type. Types 0IIc and 0IIc+IIa were classified as depressed type. Type 0IIb (flat) and type 0III (excavated) were not found in the present study sample.

Statistical analysis

Stat View version 5.0 (SAS Institute, Cary, NC, USA) was used for data analysis. The χ^2 test and Fisher's exact probability test, when appropriate, were used for univariate analysis of the association between tumor AFI color and clinicopathological factors. Logistic regression analysis was performed for multivariate analysis. A P value of less than 0.05 was considered to be statistically significant.

Results

AFI color patterns of early gastric cancers

The characteristics of the EGCs are detailed in Table 1. The distribution of the color patterns of the EGCs observed in AFI images is shown in Fig. 1. The P/G- and G/P-type tumors could be easily identified due to clear differences in color (Figs. 2 and 3). For G/G type tumors, both the tumor and the background mucosa color were green. However, the tumors usually had a purple margin and could therefore be differentiated from the background mucosa (Fig. 4). For both G/P- and G/G-type tumors, purple nodules were sometimes seen inside the green tumors. P/P-type tumors exhibited a color similar to that of the background mucosa and could only be recognized by their shape.

Table 1. Clinical characteristics of the study subjects

Number of patients	119
Mean age (years)	70 (9)[a]
Sex (%)	Men: 77
	Women: 23
Treatment (%)	Endoscopy: 86
	Surgery: 14
Location (%)	U: 29
	M: 44
	L: 27
Mean tumor size (mm)	21.4 (15.0)
Macroscopic type (%)	0I: 3
	0IIa: 42
	0IIa+IIc: 3
	0IIc+IIa: 3
	0IIc: 49
Histological type (%)	Pap: 3
	Tub1: 73
	Tub2: 16
	Por: 4
	Sig: 4
Depth of invasion (%)	Mucosal: 79
	Submucosal: 21
Vessel invasion (%)	Absent: 91
	Present: 9
Ulceration (%)	Absent: 87
	Present: 13
Tumor AFI color (%)	Purple: 56
	Green: 34
	Not evaluable: 10
Background AFI color (%)	Purple: 28
	Green: 72

AFI, autofluorescence imaging videoendoscopy; U, upper third; M, middle third; L, lower third; Pap, papillary adenocarcinoma; Tub1, well-differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma; Por, poorly differentiated adenocarcinoma; Sig, signet-ring cell carcinoma

[a] Numbers in parentheses are SDs

Factors associated with AFI tumor color

Univariate analysis showed that macroscopic type, histological type, the presence of ulceration, and background AFI color were significantly associated with tumor color (Table 2). However, when multivariate analysis was used to further assess these factors, only macroscopic type was independently associated with tumor color (Table 3).

Discussion

In the present study, we found that EGCs in AFI images could be classified according to the tumor and background color, and that the factor most strongly associated with tumor color was the macroscopic type. In AFI images, almost all tumors with an elevated appearance (elevated type) were purple, while most of the tumors with a depressed appearance (depressed type) were green. Although endogenous fluorophores exist in both the mucosa and the submucosa, collagen in the submucosa discharges a strong green autofluorescence [8]. AFI images differ according to the autofluorescence properties of the tissue, and the intensity of light, in particular, affects the AFI color. Areas with strong autofluorescence appear bright green and areas with weak autofluorescence appear purple or greenish-

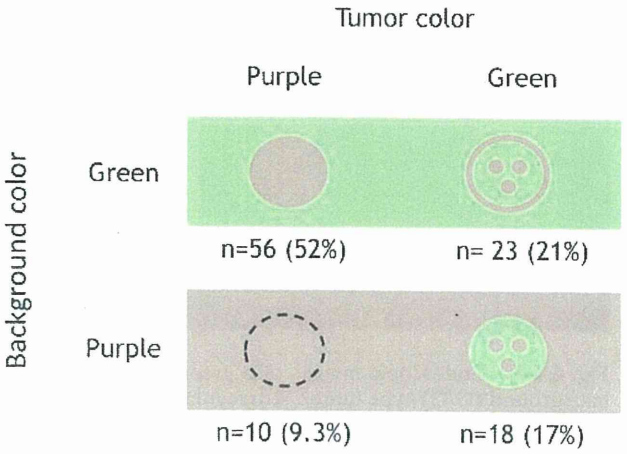

Fig. 1. Color patterns and prevalence of early gastric cancers in autofluorescence imaging videoendoscopy (AFI)

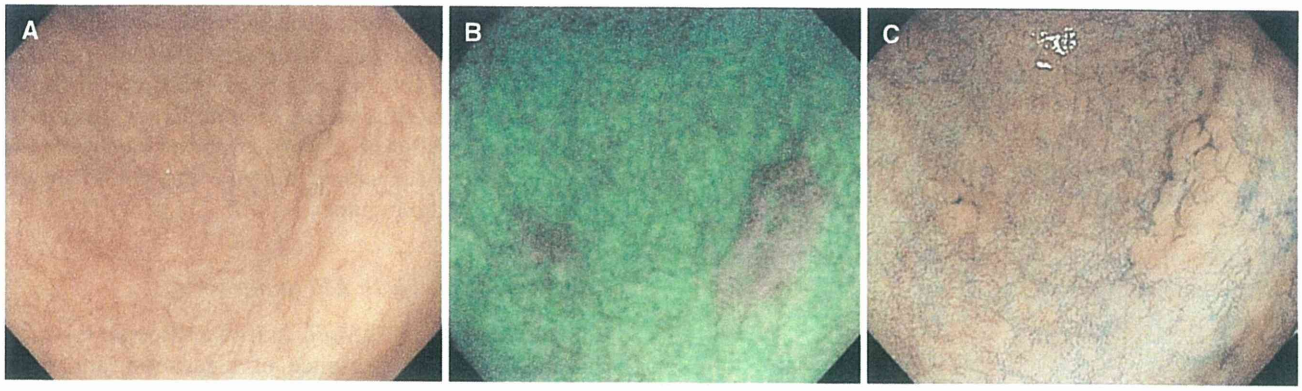

Fig. 2A–C. Endoscopic images of a purple tumor on a green background (P/G)-type tumors. **A** Conventional white-light image showing a slightly elevated tumor. However, its extent is unclear. **B** AFI image depicting the tumor as purple areas in a green background. **C** Image of two elevated tumors with contrasting topography visualized using chromoendoscopy with indigo carmine. The tumor was identified as a differentiated adenocarcinoma and removed endoscopically

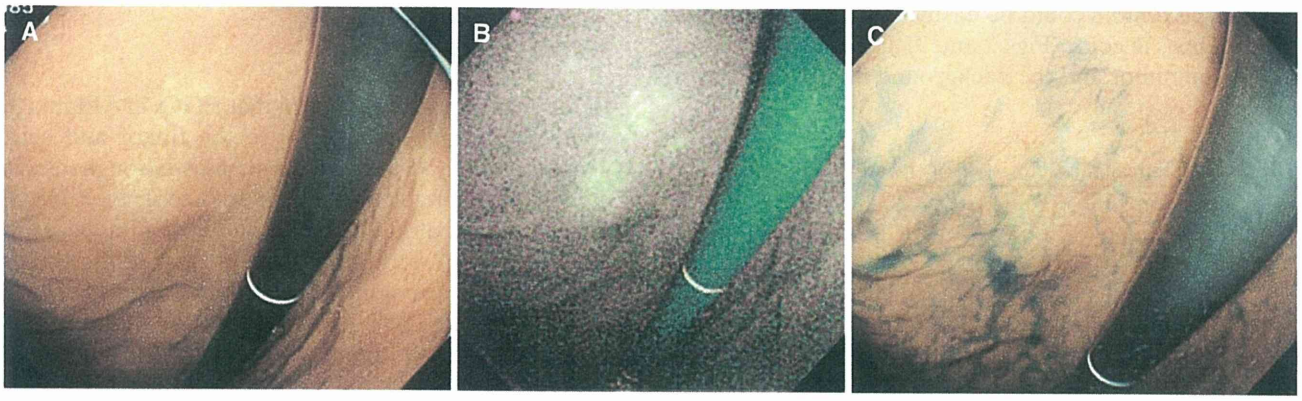

Fig. 3A–C. Endoscopic images of a green tumor on a purple background (G/P)-type tumor. **A** Image obtained using white-light endoscopy. Tumors appear as vague whitish areas. **B** AFI image showing the tumors as green areas in a purple background. **C** Image obtained using chromoendoscopy and showing a shallow depressed tumor located in the lower gastric body. An endoscopically resected specimen revealed undifferentiated adenocarcinoma confined to the mucosa

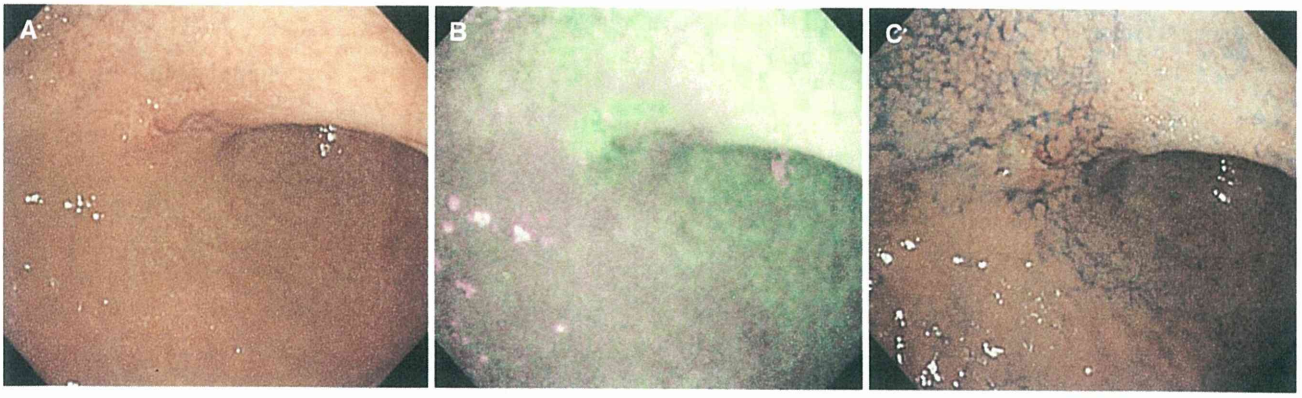

Fig. 4A–C. Endoscopic images of a green tumor on a green background (G/G)-type tumor. **A** Irregular reddish mucosa in the anterior wall of the lower gastric body. **B** AFI image. The tumor appears as a green area with a purple margin. A purple nodule is located in the center of the lesion. The tumor was located in an area adjacent to the purple-colored background mucosa, but was mostly surrounded by green background that indicated areas with chronic atrophic fundal gastritis. **C** Chromoendoscopic image revealing a depressed-type tumor with a central nodule. This tumor was identified histologically as a well-differentiated tubular adenocarcinoma

Table 2. Univariate analysis of factors associated with the color of lesions in AFI images

	No. of green tumors	No. of purple tumors	*P* value
Location			
Upper third	10	17	0.088
Middle third	24	26	
Lower third	7	23	
Size			
<20 mm	19	37	0.328
≥20 mm	22	29	
Macroscopic type			
Elevated	4	51	0.000
Depressed	37	15	
Histological type			
Differentiated	33	65	0.001
Undifferentiated	8	1	
Depth of invasion			
Mucosal	36	48	0.065
Submucosal	5	18	
Vessel invasion			
Absent	32	57	0.147
Present	9	9	
Ulceration			
Absent	32	62	0.018
Present	9	4	
Background color in AFI image			
Green	23	56	0.001
Purple	18	10	

Table 3. Multivariate analysis of factors associated with green tumor color in AFI images

	Odds ratio (95% CI)	*P* value
Macroscopic type		
Elevated	1	
Depressed	24.9 (7.12–87.3)	0.000
Background color		
Green	1	
Purple	2.56 (0.62–9.09)	0.144
Histological type		
Differentiated	1	
Undifferentiated	2.54 (0.26–2.43)	0.419
Ulceration		
Absent	1	
Present	1.00 (0.22–4.55)	0.999

CI, confidence interval

purple. Therefore, we speculate that the elevated-type tumor reduces autofluorescence from the submucosa and thus appears purple in AFI images, and that most of the depressed-type tumors do not affect autofluorescence intensity because they are thin and therefore appear green. In contrast to colon or esophageal tumors, most EGCs have been found to be of a depressed macroscopic type [9]. Therefore, their color would be green, which is uncommon in other regions of the digestive tract.

Histological type and background AFI color were two factors that were found to be significantly associated with tumor color on univariate analysis. However, this association did not prove to be the case on multivariate analysis. We believe that there are a number of reasons for this. With regard to morphology, although differentiated-type EGCs have the appearance of both elevated- and depressed-type tumors, undifferentiated-type EGCs are mostly of the depressed type [10]. As for the background color, the color of the gastric body mucosa is closely related to the grade of atrophic fundal gastritis [11]. The normal fundic mucosa looks purple, whereas abnormal mucosa with gastritis appears green. Our chromoendoscopic investigation showed that undifferentiated-type EGCs were likely to develop in the areas adjacent to, or sometimes inside, the normal fundic mucosa [12], which appears purple in AFI images. The undifferentiated EGCs are likely to be of the depressed type and, therefore, look green. By contrast, differentiated-type EGCs that are often of the elevated type frequently look purple and develop in areas with atrophic fundal gastritis or in the pyloric mucosa [12]. The pyloric mucosa appears green in AFI images.

In P/G- and G/P-type tumors, we found that the tumor profile was well delineated in the AFI images. We compared the diagnostic ability of AFI, white-light endoscopy, and chromoendoscopy for the extent of the EGC lesions. It was found that the accuracy of AFI was not as good as that of chromoendoscopy, but that it was better than white-light endoscopy [5]. Mucosal thickening or edema caused by ulceration and scarring looked purple, mimicking the tumor color. In some cases, this led to the misdiagnosis of tumor extent. Consequently, AFI may not be suitable for the evaluation of lesions with ulceration or scars. We believe, therefore, that chromoendoscopy is still necessary for pretreatment examination, although AFI would be a useful adjunct in routine EGD, because it does not require a troublesome dye spraying procedure and is less time-consuming.

Our study had several limitations. Patients with EGC who were referred for endoscopic resection accounted for more than 80% of our study subjects. Therefore, our study may not reflect the ECG profile in the actual population. In other words, the majority of the ECGs evaluated in our study were small, elevated, and differentiated types of mucosal EGCs. To correct for such bias in the analysis of factors associated with tumor color, we performed multivariate analysis. This revealed that the strongest independent correlation was between tumor color and macroscopic type.

The incidence of the P/P-type tumor was relatively low as compared with that of the other types of EGC tumor. For tumor types where the tumor color and background color differed, such as was the case with the

P/G and G/P types, the tumor was clearly delineated. However, for tumors that had a color similar to that of the background mucosa, it was sometimes difficult to identify them by their color. Although G/G-type tumors were frequently associated with a purple rim or central nodules, and were recognized by their color, P/P-type tumors were the most difficult to recognize. As a consequence, it is possible that some of these tumors were missed in the screening process using AFI.

In conclusion, the present study has enabled a clearer understanding of the significance of tumor color in relation to the AFI imaging of EGCs. The color pattern of the EGCs was classified into four types and their color appeared to be primarily associated with the macroscopic type of the tumor. Recognition of these color patterns should facilitate a clearer interpretation of endoscopic findings in relation to AFI diagnosis.

References

1. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–43.
2. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Long term outcomes after endoscopic mucosal resection for early gastric cancer. Gastric Cancer 2006;9:88–92.
3. Takeuchi Y, Uedo N, Iishi H, Yamamoto S, Yamamoto S, Yamada T, et al. Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). Gastrointest Endosc 2007;66:186–93.
4. Ohkawa A, Miwa H, Namihisa A, Kobayashi O, Nakaniwa N, Ohkusa T, et al. Diagnostic performance of light-induced fluorescence endoscopy for gastric neoplasms. Endoscopy 2004;36: 515–21.
5. Uedo N, Iishi H, Tatsuta M, Yamada T, Ogiyama H, Imanaka K, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc 2005;62:521–8.
6. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1998;1: 10–24.
7. Uedo N, Iishi H, Ishinhara R, Higashino K, Takeuchi Y. Novel autofluorescence videoendoscopy imaging system for diagnosis of cancers in the digestive tract. Dig Endosc 2006;18(Suppl 1): S131–6.
8. Izuishi K, Tajiri H, Fujii T, Boku N, Ohtsu A, Ohnishi T, et al. The histological basis of detection of adenoma and cancer in the colon by autofluorescence endoscopic imaging. Endoscopy 1999; 31:511–6.
9. Everett SM, Axon AT. Early gastric cancer in Europe. Gut 1997; 41:142–50.
10. Fujishiro M, Oka M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, et al. Correlation of serum pepsinogens and gross appearances combined with histology in early gastric cancer. J Exp Clin Cancer Res 2006;25:207–12.
11. Inoue T, Uedo N, Ishihara R, Kawaguchi T, Kawada N, Chatani R, et al. Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis. J Gastroenterol 2009. doi:10.1007/s00535-009-0150-7.
12. Tatsuta M, Okuda S, Taniguchi H, Tamura H. Gross and histological types of early gastric carcinomas in relation to the acid secreting area. Cancer 1979;43:317–21.

J Gastroenterol (2010) 45:45–51
DOI 10.1007/s00535-009-0150-7

ORIGINAL ARTICLE—ALIMENTARY TRACT

Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis

Takuya Inoue · Noriya Uedo · Ryu Ishihara · Tsukasa Kawaguchi · Natsuko Kawada · Rika Chatani · Takashi Kizu · Chie Tamai · Yoji Takeuchi · Koji Higashino · Hiroyasu Iishi · Masaharu Tatsuta · Yasuhiko Tomita · Ervin Tóth

Received: 25 July 2009 / Accepted: 18 September 2009 / Published online: 30 October 2009

Abstract
Purpose Diagnosis of chronic atrophic fundal gastritis (CAFG) is important to understand the pathogenesis of gastric diseases and assess the risk of gastric cancer. Autofluorescence imaging videoendoscopy (AFI) may enable the detection of mucosal features not apparent by conventional white-light endoscopy. The purpose of this study was to estimate the diagnostic ability of AFI in CAFG.
Methods A total of 77 patients were enrolled. Images of the gastric body in AFI and white-light mode were taken to assess the extent of gastritis, and biopsies were taken from green ($n = 119$) and purple ($n = 146$) mucosa in AFI images. The diagnostic accuracy of green mucosa for CAFG was investigated according to the Sydney system.
Results In per-patient analysis, the accuracy of green mucosa in patients with activity, inflammation, atrophy and intestinal metaplasia was 64, 93, 88 and 81%, respectively. In per-biopsy analysis, the accuracy for activity, inflammation, atrophy and intestinal metaplasia was 55, 62, 76 and 76%, respectively. Green areas in the gastric body exhibited more inflammation ($p < 0.001$), atrophy ($p < 0.001$) and intestinal metaplasia ($p < 0.001$), whereas purple areas rarely contained atrophy or intestinal metaplasia. The kappa statistics for inter- and intra-observer agreement of AFI on assessing the extent of CAFG were 0.66 and 0.47, while those for white-light endoscopy were 0.56 and 0.39.
Conclusions AFI could diagnose the extent of CAFG as a green area in the gastric body, with higher reproducibility compared with white-light endoscopy. Therefore, AFI may be a useful adjunct to endoscopy to identify patients at high risk of developing gastric cancer.

Keywords Atrophic gastritis · *Helicobacter pylori* · Autofluorescence endoscopy · Image-enhanced endoscopy

T. Inoue · N. Uedo (✉) · R. Ishihara · T. Kawaguchi · N. Kawada · R. Chatani · T. Kizu · C. Tamai · Y. Takeuchi · K. Higashino · H. Iishi · M. Tatsuta
Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
e-mail: uedou-no@mc.pref.osaka.jp

N. Uedo · M. Tatsuta
Department of Endoscopic Training and Learning Center, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

Y. Tomita
Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

E. Tóth
Department of Medicine, Malmoe University Hospital, Lund University, Malmoe, Sweden

Introduction

Chronic atrophic fundal gastritis (CAFG) is related to the development and incidence of various gastric diseases, including malignancy. Therefore, evaluating the prevalence and state of gastritis is important to understand the pathogenesis of gastric diseases and assess the risk of gastric cancer [1]. Currently, histological diagnosis of biopsy specimens from certain parts of the gastric mucosa, i.e., the updated Sydney system, is the most widely accepted method for evaluating CAFG [2]. Aside from the limitation of biopsy histology in providing only focal diagnosis, one reason why biopsy is still a standard method to assess the grade of gastritis is related to its low

accuracy and poor observer agreement in terms of conventional white-light endoscopy for the diagnosis of gastritis [3, 4]. We previously developed the endoscopic Congo red test to evaluate the development and extent of CAFG in terms of a pH-dependent color change reaction of the Congo red dye [5]. We have reported that the extent of CAFG evaluated by this test is related to the risk of gastric cancer development [6], location and healing of gastric ulcer [7], gastric emptying [8] or types of polyp [9]. However, despite recent attempts to refine the method [10, 11], it is not widely used in clinical practice because it may be associated with substantial prolongation of routine endoscopic examinations, possible adverse effects and a general underestimation of the potential benefits of this method.

Autofluorescence imaging (AFI) videoendoscopy produces real-time pseudocolor images based on natural tissue autofluorescence emitted by light excitation from endogenous fluorophores such as collagen, nicotinamide, adenine dinucleotide, flavin and porphyrins [12]. Because AFI enables the detection of mucosal features not visible with conventional endoscopy, it might improve the identification and characterization of the premalignant status in gastric mucosa. During observation of the gastric body by AFI, we noticed that the mucosa of patients who were not infected with *H. pylori* appeared purple, whereas the mucosa of patients with infection and CAFG exhibited green areas that were predominantly located in the lesser curvature [13]. Therefore, we suspected that the green areas in the gastric body in AFI images represented changes in CAFG. Based on these considerations, the aims of the present study were to estimate the diagnostic accuracy of AFI for CAFG, and to determine how colors in the AFI images relate to histological changes in gastritis.

Methods

Participants

This was a case series study performed in a cancer referral center. Patients who visited an outpatient clinic in our center to receive esophagogastroduodenoscopy (EGD) and who gave written informed consent after explanation of the study were enrolled. Patients were excluded if they had severe symptoms, including >10% weight loss within 3 months, anemia (hemoglobin < 10 g/dl), vomiting or symptoms suggestive of acute bleeding, obstruction or perforation of the gastrointestinal tract; advanced gastric cancer; history of gastric surgery; previous *H. pylori* eradication therapy; major organ failure; anticoagulation therapy or coagulopathy; use of aspirin or non-steroidal anti-inflammatory drugs within 30 days; or pregnancy. The study protocol was approved by the ethical committee of our institution.

Endoscopy system

The AFI system used in this study consisted of a light source (CLV-260SL; Olympus Medical Systems Co. Ltd., Tokyo, Japan), a processor (CV-260SL, Olympus), a video monitor and a high-resolution videoendoscope (EVIS-FQ260Z, Olympus) equipped with two charged-coupled devices (CCDs) that were available for autofluorescence and white-light modes. In the autofluorescence mode, the light source emits blue excitation light (395–475 nm) to induce autofluorescence and green light (540–560 nm) to capture green reflection images sequentially through a rotation filter [14]. A cut filter was placed with the lens to permit only light with wavelengths between 490 and 625 nm to intensify the CCD for the AFI mode. The modes were changed within 3 s by pressing a small button on the control head of the endoscope.

Endoscopic procedure

All examinations were performed by an endoscopist (N.U.) who had 4 years of experience in performing autofluorescence endoscopy in more than 2,000 cases and 14 years of conventional endoscopy in 15,000 cases. The patients ingested a mixture consisting of a mucolytic agent (20,000 U pronase, Pronase MS; Kaken Pharmaceutical Co. Ltd., Tokyo, Japan), a defoaming agent (80 mg dimethylpolysiloxane syrup, Gascony Drops; Kissei Pharmaceutical Co. Ltd., Matsumoto, Japan) and 1 g sodium bicarbonate diluted in 100 ml of tap water 5 min before the examination. After topical anesthesia, the endoscope was gently inserted into the stomach. During routine observation of the entire stomach, at least two corresponding images of downward and retroflex views of the gastric body under white light and in the AFI mode were taken to evaluate the extent of CAFG. For the evaluation, the lumen of the gastric body was adequately distended with sufficient air insufflations to obtain good images. After all of the endoscopic observations had been completed, biopsy specimens were taken from areas at 2 and 0.5 cm from the border of the green and purple area of the gastric body under AFI observation. In cases in which the entire gastric body was purple, two biopsy specimens were taken 2 cm proximal to the gastric angle, and in cases in which the entire gastric mucosa appeared green, two biopsies were taken from the greater curvature in the middle portion of the gastric body.

Histology

All biopsy specimens were placed in separate labeled small pots filled with 10% buffered formalin. Each specimen was processed, embedded in paraffin, sectioned into 4-μm-thick slices and stained with hematoxylin and eosin (H&E). These preparations were reviewed by a single pathologist (Y.T.) who was blinded to the endoscopic findings. The pathologist had more than 15 years of experience in general pathology. Based on the updated Sydney system [2], all specimens were classified as none, mild, moderate or severe for the following four features: activity (polymorphonuclear cell infiltration), inflammation (mononuclear cell infiltration), glandular atrophy and intestinal metaplasia.

Assessment of the diagnostic accuracy of AFI for CAFG

For per-biopsy analysis, each histological feature of gastritis was defined as present if the grade was greater than mild and absent if the grade was classified as none. In per-patient analysis, the individual was defined as having a particular feature of gastritis when it was present in any of the biopsy specimens, and without gastritis when none of the biopsy specimens had the particular feature of gastritis. Therefore, in per-biopsy analysis, the diagnostic accuracy of the green areas in the gastric body for histologically proven gastritis was evaluated. In per-patient analysis, the accuracy of the green mucosa in the gastric body for diagnosing patients with histological finding of gastritis was evaluated.

Inter- and intra-observer variability

Reproducibility of the diagnosis of CAFG by AFI was assessed by an experienced endoscopist (N.U.) and by a resident who was less familiar with AFI (T.I.), and was compared with the reproducibility of the diagnosis by white-light imaging. One downward and one retroflex view image of the gastric body was obtained by AFI and white-light imaging in each patient, and they were randomly arranged and reviewed by the two endoscopists twice, at an interval of at least 2 weeks. In the AFI images, the extent of CAFG was considered to be the green areas in the gastric body and was classified into six categories based on the Kimura–Takemoto classification (Fig. 1) [15]: AF-C-I, the entire gastric body looked purple to dark green; AF-C-II, a color border on the lesser curvature was observed at a lower part of the gastric body; AF-C-III, a color border on the lesser curvature was observed at an upper part of the gastric body; AF-O-I, a color border was observed between the lesser curvature and the anterior wall; AF-O-II, a color border was observed between the anterior wall and the greater curvature; and AF-O-III, a color border on the greater curvature was observed proximal to the lower gastric body. In the white-light images, the extent of CAFG corresponded to areas of whitish mucosa, increased

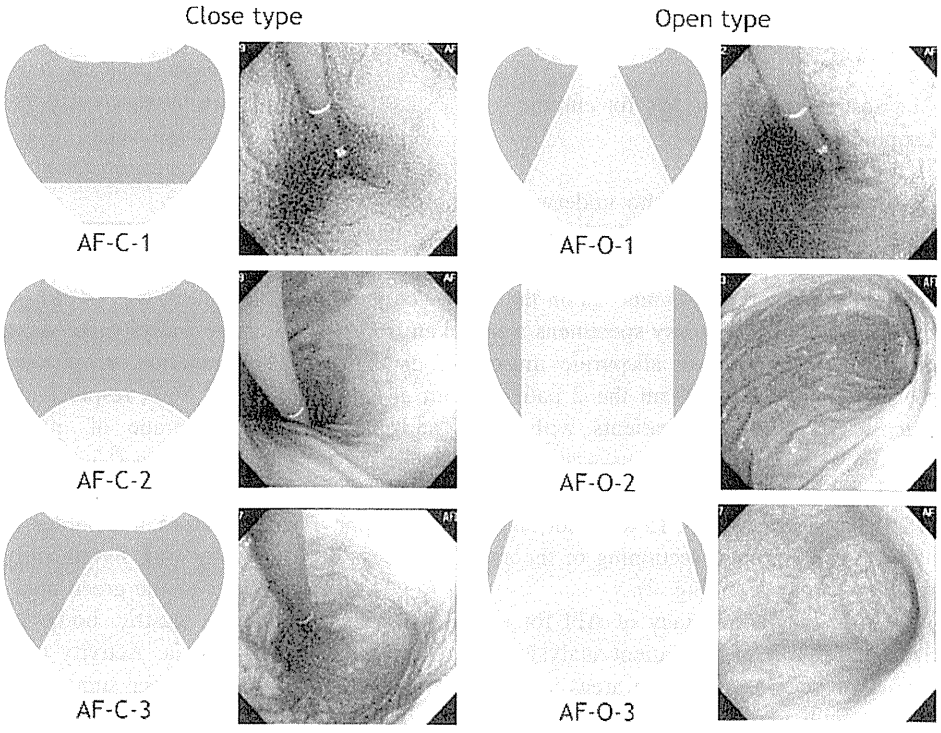

Fig. 1 Classification of the extent of atrophic fundal gastritis according to AFI color

visibility of mucosal vessels and loss of gastric rugae, and was classified into C-I to O-III according to the Kimura–Takemoto classification.

Statistical analysis

All statistical analyses were performed using JMP version 6.0 (SAS Institute Inc., Cary, NC). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AFI for diagnosis of CAFG in per-patient and per-biopsy analyses were calculated. The grade of gastritis at each biopsy site, 0.5 and 2 cm from the color border in both green and purple mucosa, was compared by Friedman's test. The kappa (κ) values for the inter- and intra-observer agreement of the extent of CAFG in each AFI and white-light image was calculated. Agreement was considered poor if $\kappa < 0.2$, fair if $\kappa < 0.4$, moderate if $\kappa < 0.6$, substantial if $\kappa < 0.8$ or good if $\kappa > 0.8$.

Results

Participants

A total of 79 patients were enrolled between November 2006 and April 2007. We excluded one patient who had previously unknown diffuse advanced gastric cancer in the gastric body and another who had a large amount of food residue because of antral deformation that resulted from a scar after endoscopic resection of early gastric cancer. Finally, a total of 77 patients underwent AFI observation. Their demographics are shown in Table 1.

Table 1 Subject characteristics

Median age (range, years)	67 (63–75)
Sex	
Male	48
Female	31
H. pylori infection	
Positive	48
Negative	27
Not examined	4
Indication for esophago-gastro-duodenoscopy	
Follow-up examination	
Post endoscopic treatment for early gastric cancer/adenoma	35
Post-chemoradiation therapy for esophageal cancer	2
Esophageal varices	2
Gastric ulcer	1
Gastric polyp	1
Post-operation for laryngeal cancer	1
Pre-treatment evaluation	
Early gastric cancer or adenoma	9
Esophageal cancer	2
Abnormality in barium study	10
Symptoms	
Bloating	7
Epigastralgia	5
Chest discomfort	2
Dysphagia	2
Localized lesions in the stomach	
Post EMR/ESD scar	37
Early gastric cancer/adenoma	10
Gastric polyp	10
Malignant lymphoma	2
Gastric ulcer/ulcer scar	2
Submucosal tumor	2
Advanced gastric cancer	1
None	15

Diagnostic accuracy of AFI for chronic atrophic fundal gastritis

Among the 77 patients who underwent AFI, for 17 the entire mucosa in the gastric body was purple, 2 had all-green mucosa, and 58 had green mucosa on the lesser curvature side and purple mucosa on the greater curvature side (Fig. 2). Thirty biopsy specimens were taken from 15 of the 17 patients with all-purple mucosa; four biopsy specimens were taken from the 2 patients with all-green mucosa. From the 58 patients with green and purple mucosa, 115 biopsy specimens were taken from the green mucosa and 116 from the purple mucosa (Fig. 2). Of a total of 265 biopsy specimens, 15 were not evaluable for atrophy because of horizontal sectioning of the surface mucosa or small specimen size (Fig. 2).

The diagnostic accuracy of AFI for CAFG is summarized in Table 2. In per-patient analysis, we found that the diagnostic accuracy of green areas in the gastric body for patients with activity, inflammation, atrophy and intestinal metaplasia was 64, 93, 88 and 81%, respectively. In per-biopsy analysis, the accuracy of AFI for areas of activity, inflammation, atrophy and intestinal metaplasia was 55, 62, 76 and 76%, respectively.

The grade of inflammation, atrophy and intestinal metaplasia at 0.5 and 2 cm from the border of the green area was significantly more severe than that at 0.5 and 2 cm from the border of the purple area. The grade of atrophy was significantly more severe at 2 cm from the border of the green area than at 0.5 cm. The purple areas in the gastric body had little atrophy and intestinal metaplasia. Activity (polymorphonuclear cell infiltration) did not differ significantly between the green and purple areas (Fig. 3).

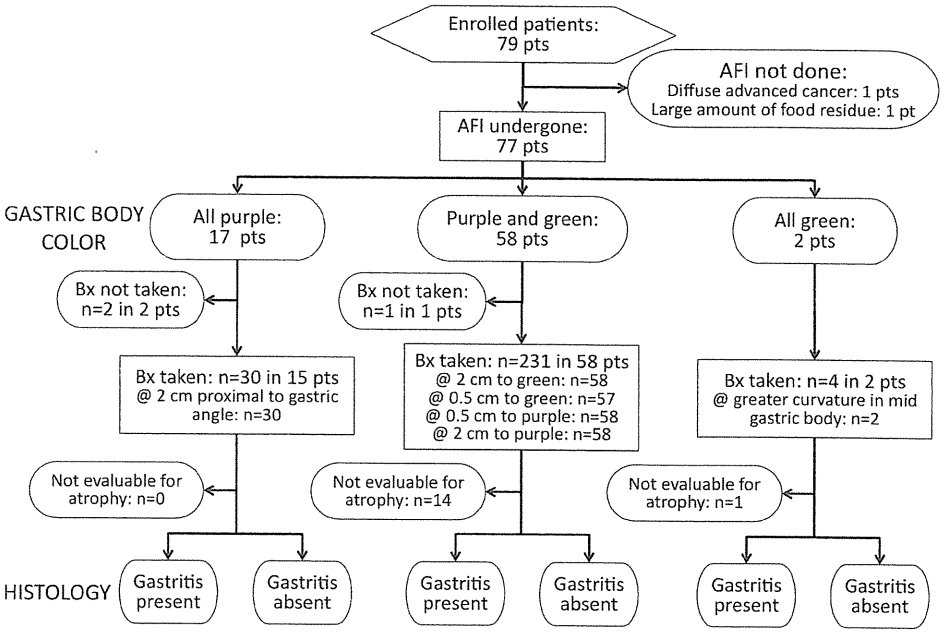

Fig. 2 Flow diagram of study samples

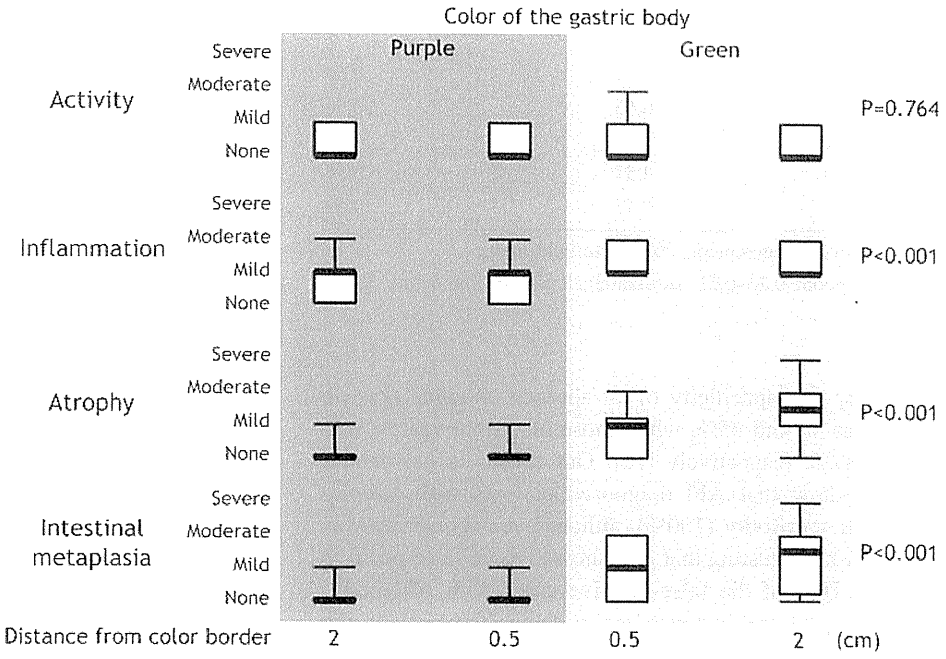

Fig. 3 Histological findings of biopsy specimens in relation to distance from AFI color border. Box plot indicates maximum, 75% percentile, median, 25% percentile and minimum. *P* values by Friedman's test

Reproducibility of AFI for the diagnosis of atrophic fundal gastritis

A total of 156 AFI images and 156 white-light images were obtained in 77 patients to evaluate reproducibility. For assessment of the extent of CAFG, the intra-observer agreement was substantial ($\kappa = 0.67$, 95% CI 0.55–0.80) for AFI, but only moderate ($\kappa = 0.56$, 95% CI 0.42–0.70) for the white-light images. The inter-observer agreement between the experienced endoscopist and the resident was moderate ($\kappa = 0.47$, 95% CI 0.37–0.57) for AFI and fair ($\kappa = 0.39$, 95% CI 0.29–0.49) for the white-light images (Table 3).

Discussion

Although gastritis is a histological entity, attempts have been made to diagnose the disease macroscopically during EGD. Redeen et al. investigated the diagnostic ability of conventional white-light endoscopy for patients with moderate-to-severe atrophy, and they demonstrated that the

Table 2 Diagnostic accuracy of green mucosa in the gastric body for gastritis

	%Sensitivity [95% CI]	%Specificity [95% CI]	%PPV [95% CI]	%NPV [95% CI]	%Accuracy [95% CI]
Per patient					
Activity	97 [92–100]	35 [20–50]	57 [44–69]	93 [81–100]	64 [53–75]
Inflammation	98 [95–100]	78 [59–97]	93 [87–100]	93 [81–100]	93 [88–99]
Atrophy	100 [100–100]	63 [43–82]	85 [76–94]	100 [100–100]	88 [81–95]
Intestinal metaplasia	100 [100–100]	52 [34–70]	77 [66–70]	100 [100–100]	81 [73–90]
Per biopsy					
Activity	50 [40–60]	57 [50–65]	38 [30–47]	68 [61–76]	55 [49–61]
Inflammation	55 [48–62]	86 [77–94]	93 [88–97]	37 [29–45]	62 [56–68]
Atrophy	72 [64–81]	78 [71–85]	70 [62–79]	80 [73–86]	76 [70–81]
Intestinal metaplasia	77 [69–85]	75 [68–82]	67 [58–75]	83 [77–89]	76 [71–81]

PPV positive predictive value, *NPV* negative predictive value

Table 3 Agreement for the diagnosis of the extent of atrophic gastritis

	Method	
	AFI	WLI
Intra-observer		
Pa	0.74	0.65
κ	0.66	0.56
Inter-observer		
Pa	0.57	0.51
κ	0.47	0.39

Pa proportion of agreement, *WLI* white-light image

κ: >0.80, good; 0.80–0.61, substantial; 0.60–0.41, moderate; 0.40–0.21, fair

sensitivity and specificity of an absence of rugae (gastric folds) was 67 and 85%, while those of visible vessels was 48 and 87%, respectively [16]. Our results in per-patient analysis show that AFI diagnosed patients with atrophy with high sensitivity (100%), although the specificity was low (63%), suggesting that AFI showed more false-positive findings. Half of the false-positive cases with AFI had a small area (<2 cm) just proximal to the gastric angle in the lesser curvature of the lower gastric body. Therefore, we suspect that a small green area in this region is unlikely to be related to CAFG and may be excluded from the diagnostic criteria. In the reminder of the false-positive cases, although atrophy was diagnosed as none in all of the biopsy specimens, moderate-to-severe inflammation or intestinal metaplasia was found in many of the biopsy specimens, so histological diagnosis in small biopsy specimens might underestimate the presence of atrophy, causing a discrepancy between endoscopic diagnosis and histology.

Kaminishi et al. assessed the accuracy of endoscopic findings for diagnosing chronic gastritis. They found that ash-colored nodular changes were specific (98–99%), but not sensitive (6–12%), for identifying histological intestinal metaplasia, and concluded that conventional endoscopy is unsuitable for diagnosing intestinal metaplastic gastritis [17]. The low specificity of white-light endoscopy for diagnosing intestinal metaplasia is because it usually appears in flat mucosa and has few morphological changes [18]. In our study, AFI recognized areas of intestinal metaplasia in the gastric body with a sensitivity of 77% and specificity of 75%. Intestinal metaplasia is commonly distributed in a scattered pattern, or regionally; however, AFI only showed homogeneous green areas in which intestinal metaplasia was prevalent. Therefore, the actual distribution of intestinal metaplasia could not be evaluated, and this might have lowered the sensitivity and PPV of AFI for the diagnosis of intestinal metaplasia. The current AFI system works tri-modally, so it can easily switch to a narrow-band imaging (NBI) mode, and the scope is equipped with a zoom function. In magnified NBI images, intestinal metaplasia can be identified by the specific finding of the light blue crest, which represents the presence of a histological brush border [19]. Thus, the system can reveal areas of intestinal metaplasia by AFI, and subsequently specify the location and evaluate the micro-morphological features by the magnifying NBI. If the findings of this endoscopic imaging technique offer an alternative to histology of biopsy specimens, it would provide a convenient indicator of the extent/grade of CAFG during endoscopic examination.

According to the histology of the biopsy specimens, the green areas in the gastric body were associated with a higher grade of inflammation, atrophy and intestinal metaplasia. Because these histological features usually coexist with each other, the main cause of the green color could not be determined in this study. In AFI images, areas with strong autofluorescence appear bright green, and those with weak autofluorescence are purple or dark green. Although the

fluorophores exist in both the mucosa and submucosa, collagen in the submucosa discharges strong green autofluorescence [14]. When we investigated the color patterns of early gastric cancer in AFI images, the tumor color was strongly associated with morphology, irrespective of whether it was elevated or depressed, rather than histologic type [20]. In other words, elevated tumors appeared purple because of their thickness, which reduced autofluorescence from the submucosa, while most depressed tumors did not affect autofluorescence intensity because they were thin and appeared green. Likewise, we speculate that the presence of thick fundic mucosa reduces autofluorescence and appears purple in AFI images, and the decreased height of the fundic mucosa, caused by glandular atrophy, permits autofluorescence from the submucosa to penetrate the thin mucosa, which results in a green color similar to the intestinal mucosa. Accordingly, we suspect that the green mucosal color in the gastric body is mainly due to atrophy of the fundic mucosa.

This study has several limitations to be considered. In this study, we found that the inter- and intra-observer agreement in AFI for diagnosis of the extent of CAFG was higher than that of white-light images. However, the diagnostic accuracy of AFI was not compared with that of white-light images in relation to the histology. Therefore, whether the accuracy of AFI was superior to that of white-light images is unknown. Moreover, because our study included many patients with gastric cancer or a history of endoscopic resection of early gastric cancer, which is associated with a high prevalence of atrophy or intestinal metaplasia, we may have overestimated the accuracy of this test. In fact, we experienced a few patients whose gastric body appeared greenish, even though they were not infected with *H. pylori* and had no atrophy in the gastric fundus. Consequently, a good indication for this method is the identification of patients with extensive CAFG or intestinal metaplasia who have a higher risk for developing gastric cancer among those with *H. pylori* infection.

In conclusion, AFI diagnosed the extent of CAFG as a green area in the gastric body more precisely compared with white-light endoscopy. Because this method is easier and associated with fewer adverse effects than chromoendoscopy, it may facilitate its application in clinical practice or studies that assess CAFG. Thus, AFI may be a useful adjunct to identify patients at high risk for developing gastric cancer.

Conflict of interest statement There are no conflicts of interest to disclose.

References

1. Correa P. Chronic gastritis as a cancer precursor. Scand J Gastroenterol. 1984;104(Suppl.):131–6.
2. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996;20:1161–81.
3. Bah A, Saraga E, Armstrong D, Vouillamoz D, Dorta G, Duroux P, et al. Endoscopic features of *Helicobacter pylori*-related gastritis. Endoscopy. 1995;27:593–6.
4. Laine L, Cohen H, Sloane R, Marin-Sorensen M, Weinstein WM. Interobserver agreement and predictive value of endoscopic findings for *H. pylori* and gastritis in normal volunteers. Gastrointest Endosc. 1995;42:420–3.
5. Tatsuta M, Saegusa T, Okuda S. Extension of fundal gastritis studied by endoscopic Congo-red test. Endoscopy. 1974;6:20–6.
6. Tatsuta M, Iishi H, Nakaizumi A, Okuda S, Taniguchi H, Hiyama T, et al. Fundal atrophic gastritis as a risk factor for gastric cancer. Int J Cancer. 1993;53:70–4.
7. Tatsuta M, Okuda S. Location, healing, and recurrence of gastric ulcers in relation to fundal gastritis. Gastroenterology. 1975;69:897–902.
8. Tatsuta M, Iishi H, Okuda S. Gastric emptying in patients with fundal gastritis and gastric cancer. Gut. 1990;31:767–9.
9. Tatsuta M, Okuda S, Tamura H, Taniguchi H. Polyps in the acid-secreting area of the stomach. Gastrointest Endosc. 1981;27:145–9.
10. Tóth E, Sjölund K, Fork FT, Lindstrom C. Chronic atrophic fundic gastritis diagnosed by a modified Congo red test. Endoscopy. 1995;27:654–8.
11. Tóth E, Sjölund K, Thorsson O, Thorlacius H. Evaluation of gastric acid secretion at endoscopy with a modified Congo red test. Gastrointest Endosc. 2002;56:254–9.
12. Haringsma J, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, et al. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc. 2001;53:642–50.
13. Uedo N, Iishi H, Tatsuta M, Yamada T, Ogiyama H, Imanaka K, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc. 2005;62:521–8.
14. Uedo N, Iishi H, Ishihara R, Higashino K, Takeuchi Y. Novel autofluorescence videoendoscopy imaging system for diagnosis of cancers in the digestive tract. Dig Endosc. 2006;18(Suppl. 1):S131–6.
15. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy. 1969;3:87–97.
16. Redeen S, Petersson F, Jonsson KA, Borch K. Relationship of gastroscopic feature to histological findings in gastritis and *Helicobacter pylori* infection in a general population sample. Endoscopy. 2003;35:946–50.
17. Kaminishi M, Yamaguchi H, Nomura S, et al. Endoscopic classification of chronic gastritis based on a pilot study by the research society for gastritis. Dig Endosc. 2002;14:138–51.
18. Rugge M, Farinati F, Baffa R, Sonego F, Di Mario F, Leandro G, et al. Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. Gastroenterology. 1994;107:1288–96.
19. Uedo N, Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T, et al. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. Endoscopy. 2006;38:819–24.
20. Kato M, Uedo N, Iishi H. Analysis of color pattern of early gastric cancer by autofluorescence imaging videoendoscopy system. Gastrointest Endosc. 2007;65:AB356.

Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve*

Authors Shunsuke Yamamoto[1,3], N. Uedo[1,2], R. Ishihara[1], N. Kajimoto[1], H. Ogiyama[1,3], Y. Fukushima[1], Sachiko Yamamoto[1], Y. Takeuchi[1], K. Higashino[1], H. Iishi[1], M. Tatsuta[1,2]

Institutions
[1] Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[2] Endoscopic Training and Learning Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[3] Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan

submitted 10 July 2009
accepted after revision 22 July 2009

Bibliography
DOI 10.1055/s-0029-1215129
Published online 2 October 2009
Endoscopy 2009; 41: 923–928 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
N. Uedo, MD
Endoscopic Training and Learning Center
Department of Gastrointestinal Oncology
Osaka Medical Center for Cancer and Cardiovascular Diseases
1-3-3 Nakamichi
Higashinari-ku
Osaka 537-8511
Japan
Fax: +81-6-69814067
uedou-no@mc.pref.osaka.jp

Please see the accompanying editorial by J. J. G. H. M. Bergman on page 988.

Background and aim: Endoscopic submucosal dissection (ESD) is feasible as a treatment for early gastric cancer (EGC) when it is performed by an experienced endoscopist. We investigated whether it was feasible for novice endoscopists to perform ESD for EGC, and how difficult it was to learn the procedure.

Methods: This case series study was performed in a cancer referral center. Three resident endoscopists, who had already learned basic procedures, performed ESD under supervision for 30 consecutive lesions, and their procedures were analyzed. The procedure was divided for assessment into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut. An insulated-tip knife was used for mucosal incision and submucosal dissection. A total of 90 mucosal EGCs (≤ 2 cm) without ulcers or scars in 87 patients were included. Outcomes were: rates of complete resection, complications, and self-completion; operation time; learning curve; and reasons for change of supervisor as an indicator of difficulty.

Results: Among the 90 procedures, there was a good overall complete resection rate of 93 %, with an acceptable complication rate of 4.4 %; the complications were delayed hemorrhage in two patients, and perforations in another two patients that were repaired successfully by endoscopic clipping. The self-completion rate and operation time were significantly worse for submucosal dissection than for mucosal incision. Two of the three operators showed a flat learning curve for submucosal dissection. Difficulty with the procedure was related mainly to uncontrollable hemorrhage.

Conclusions: With appropriate supervision, gastric ESD by residents is feasible, with equivalent complete resection rates and acceptable complication rates compared with those of experienced endoscopists, although there was difficulty in achieving sufficient self-completion rates in submucosal dissection. Better control of bleeding during submucosal dissection may be a key to improving the procedure.

Introduction

Endoscopic submucosal dissection (ESD) was developed as an advanced technique of endoscopic resection for early gastric cancer (EGC) [1,2]. It yields a higher complete resection rate than do conventional methods of endoscopic mucosal resection [3,4], and enables en bloc removal of previously unresectable lesions, such as large mucosal tumors [5] or tumors with scars [6]. Although effective, the technique of ESD is complicated and requires considerable expertise and a prolonged operation time [7].

Previous studies have indicated that ESD for EGC is technically feasible when performed by experienced endoscopists [5]; however, its practicability for novice endoscopists and the difficulty of learning this advanced endoscopic procedure are still unclear. If we can identify the difficulties involved, we can establish a way to overcome these and reduce the time required to learn the ESD procedure.

The present study investigated the practicability of supervised residents performing ESD for EGC, and the difficulty of learning the procedure.

* Note: The article's guarantor is N. U. The authors contributed to the study as follows: S. Y., analysis of the data, and drafting of the article; N. U., conception and design, analysis and interpretation of the data, drafting and final approval of the article; R. I., final approval of the article; N. K., H. O. and Y. F., provision of study materials and patients, and collection and collation of data; S. Y., Y. T. and K. H., provision of study materials and patients; H. I. and M. T., final approval of the article.