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 anesthetic 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. Pre-incisional 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.

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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

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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 esophago-gastro-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.

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-

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

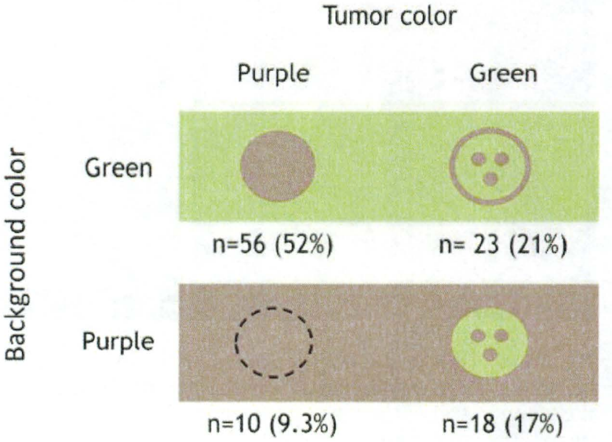

Fig. 1. Color patterns and prevalence of early gastric cancers in autofluorescence imaging videoendoscopy (AFI)

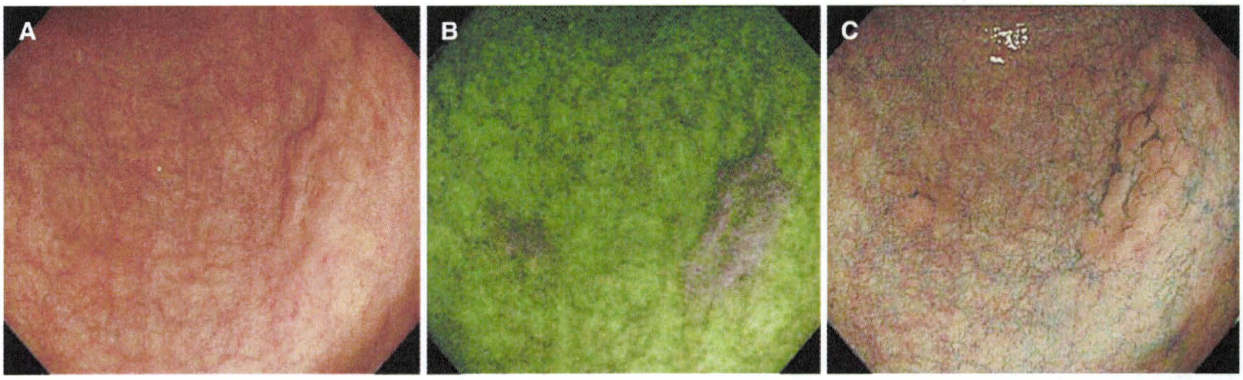

Fig. 2A–C. Endoscopic images of a purple tumor on a green background (P/G)-type tumors. **A** Conventional white-light image showing a slightly elevated tumor. However, its extent is unclear. **B** AFI image depicting the tumor as purple areas in a green background. **C** Image of two elevated tumors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

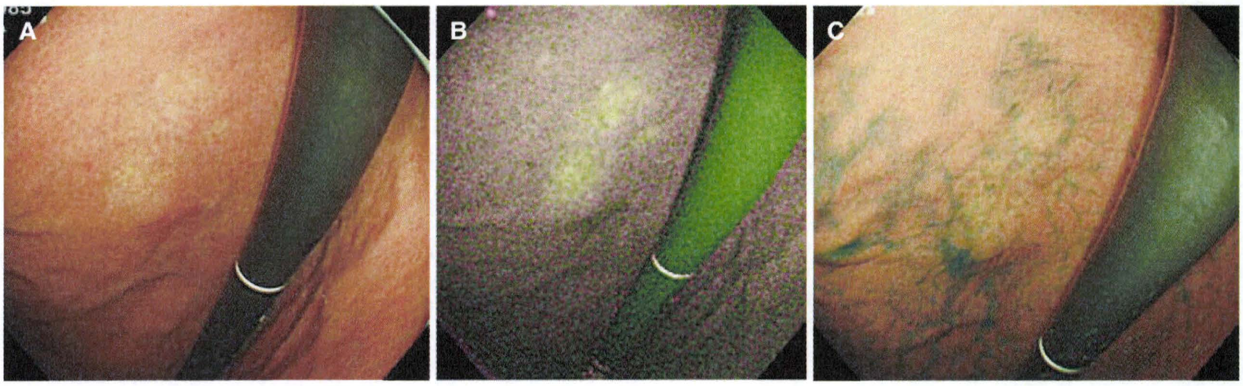

Fig. 3A–C. Endoscopic images of a green tumor on a purple background (G/P)-type tumor. **A** Image obtained using white-light endoscopy. Tumors appear as vague whitish areas. **B** AFI image showing the tumors as green areas in a purple background. **C** Image obtained using chromoendoscopy and showing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

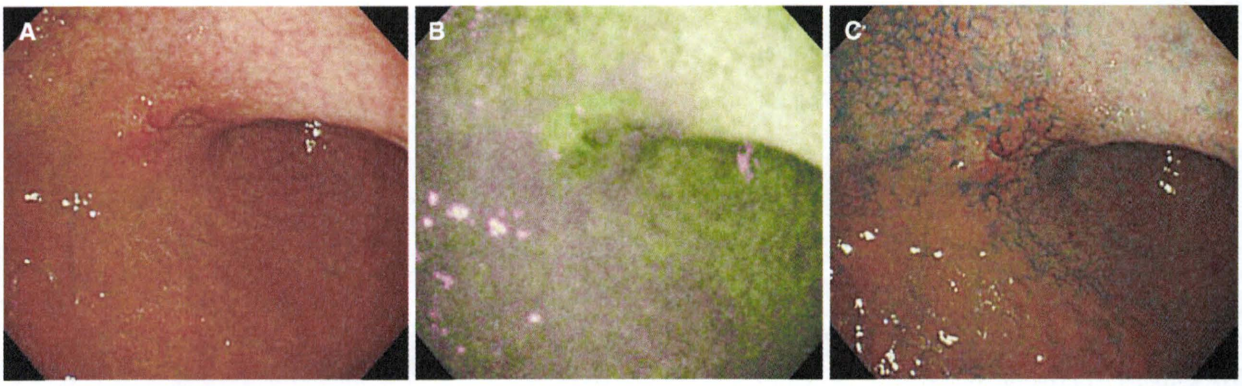

Fig. 4A–C. Endoscopic images of a green tumor on a green background (G/G)-type tumor. **A** Irregular reddish mucosa in the anterior wall of the lower gastric body. **B** AFI image. The tumor appears as a green area with a purple margin. A purple nodule is located in the center of the lesion. The tumor 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.

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

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Bibliography
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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.

Endoscopist	A	B	C
Years since graduation	7	10	5
Number of EGDs performed	2000	3200	1500
Number of EMRs performed for EGC	22	18	10
Number of colonoscopies performed	800	800	250
Number of ERCPs performed	20	65	10

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EGC, early gastric cancer; ERCP, endoscopic retrograde cholangiopancreatography.

Table 1 Profiles of three operating endoscopists.

Endoscopists	A	B	C	Total
Number of lesions	n = 30	n = 30	n = 30	n = 90
Median tumor size, mm (IQR)	15 (8.5)	15 (10.25)	13.5 (5.75)	15 (10)
Location of gastric lesions, n (%)				
Upper third	1 (3.3)	5 (17)	1 (3.3)	7 (7.8)
Middle third	13 (43)	11 (37)	14 (47)	38 (42)
Lower third	16 (53)	14 (47)	15 (50)	45 (90)
Type of tumors, n (%)				
Elevated	14 (47)	11 (37)	14 (47)	39 (43)
Depressed	16 (53)	19 (63)	16 (53)	51 (57)

IQR: interquartile range

Table 2 Characteristics of the lesions treated by ESD.

Table 3 Devices and settings of electrical surgical unit for each procedure.

Procedure	Device	ICC200	PSD60
Marking	Needle knife	Forced 20 W	Forced 30 W, effect 1
Mucosal incision	IT knife	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Submucosal dissection	IT knife	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	IT knife (fibrous submucosal tissue)	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Hemostasis	IT knife (small vessel)	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	Hemostatic forceps (large vessel)	Soft coagulation 80 W	Soft coagulation 80 W, effect 6

Patients and methods

This case series was performed in the endoscopic training and learning center of a tertiary cancer referral center.

Participants

A total of three endoscopists were involved in this study. They had experience of at least 1500 regular esophagogastroduodenoscopy procedures and more than 10 endoscopic mucosal resections by the strip biopsy or cap methods (**Table 1**). Before starting ESD, the operators participated in pre- and postoperative conferences with surgeons, gastroenterologists, radiologists, and pathologists to learn about the diagnosis and management of gastric cancer. They attended ESD procedures performed by senior doctors, as assistants, for at least 1 year, and then attended a lecture about ESD techniques, using a manual and videos, by an experienced endoscopist.

We investigated the records of 30 consecutive ESD procedures performed by each of the three endoscopists, between June 2003 and February 2005, in 87 patients (68 men, 19 women, mean age 67 years). The lesions were allocated to the three endoscopists irrespective of tumor location and size. Lesion characteristics are shown in **Table 2**. The indication for ESD in this study was differentiated-type mucosal EGC, without ulcers or scars, smaller than 2 cm, as described in the gastric cancer treatment guidelines issued by the Japanese Gastric Cancer Association [8]. Before treatment, anticipated results, possible risks and complications, and alternative treatments including surgery and no treatment, were explained by the operator to all the patients, who gave their written informed consent. Patients who had severe organ failure or coagulopathy were excluded. The study protocol was approved by the institutional review board at our center.

ESD procedure

All procedures were performed with a videoendoscope (GIF-Q240; Olympus Medical Systems Co., Ltd., Tokyo, Japan) that was fitted with a disposable attachment (D-201 – 11 804; Olympus) on its tip. A needle knife (KD-1L-1; Olympus), an insulated-tip (IT) knife (KD-610L; Olympus), and hemostatic forceps (Coagrasper, FD-410LR; Olympus) were used in the procedure. The Intelligent Cut and Coagulation 200 (ICC-200; Erbe Elektromedizin GmbH, Tübingen, Germany) or Power Supply Diathermy 60 (PSD-60; Olympus) was used as an electrical surgical unit; the output settings are summarized in **Table 3**. A solution of 2% epinephrine (Bosmin; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) with 20% concentrated glycerin–fructose (Glyceol; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was used for submucosal injection.

With the patient under sedation, the ESD procedure was performed as follows [6]. *Marking for removal:* The endoscope was inserted into the stomach, and the extent of the tumor was estimated under chromoendoscopic observation to determine the resection area. Marking dots were drawn circumferentially 3 mm from the tumor boundary by a needle knife. *Mucosal incision:* The epinephrine and glycerol solution was injected into the submucosa just outside the marking dots to elevate the lesion. The procedure was performed with a downward view in the antrum and a retroflex view in the corpus. A precut hole to insert the tip of the IT knife was made outside the region to be resected with the needle knife. The hole was made at the distal side of the lesion in an endoscopic view, and it needed to be sufficiently deep to reach the submucosa. The tip of the IT knife was inserted fully into the submucosa through the precut hole, and the proximal mucosa was cut continuously outside the marking dots using an Endo Cut mode. During mucosal incision, the ceramic tip was in contact with the gastric wall and was pulled with some tension. *Submucosal dissection:* Submucosal dissection was started after completion of the circumferential mucosal cut. The epinephrine and glycerol solution was injected into the submucosa to obtain sufficient mucosal elevation. The IT knife was moved laterally, with the tip continuously touching the gastric wall. Lateral movement was achieved by torquing the scope rather than by using the scope angle. Submucosal dissection was performed with the IT knife using the coagulation mode, or the Endo Cut mode if the submucosa was fibrous. *Hemostasis:* When hemorrhage was noted from small vessels, the bleeding point was coagulated with the blade of the IT knife, using forced coagulation. When hemorrhage from larger vessels was observed, the bleeding point was stopped with the hemostatic forceps using the soft coagulation mode. *Retrieval of the specimen and prevention of delayed hemorrhage:* After removal of the mucosal area, it was retrieved by grasping forceps (FG-47L-1; Olympus). The ulcer base was washed out repeatedly and any adherent clots or suspicious protrusions were coagulated by the hemostatic forceps to avoid delayed hemorrhage. Resected specimens were sent to the department of pathology for histological assessment of completeness of resection and curability.

Assistant policy

The entire procedures were performed under the supervision of an experienced endoscopist (N.U.). The supervisor was changed under the following circumstances: (1) overtime: when time for each mucosal incision and submucosal dissection exceeded 1 hour; (2) inability to achieve hemostasis: when spurting hemorrhage could not be stopped; (3) perforation; and (4) inability to continue the procedure: when the procedure could not be continued for reasons other than inability to achieve hemostasis, or perforation. If an operator changed supervisor, the procedure was regarded as not "self-completed."

All procedures were recorded digitally on video and all events relating to the procedure were recorded on dedicated operation records.

Measured outcome parameters

Complete resection and complication rates were evaluated for assessment of feasibility. Self-completion rate, operation time, learning curve, and reasons for incompletion were analyzed to elucidate procedural difficulties. For assessment the ESD procedure was divided into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut.

Complete resection was defined as en bloc resection without cancer involvement to the lateral and vertical margin of the resected specimen, as shown by histology. Complications included delayed hemorrhage and perforation, which were classified as grade 3 or 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [9]. Operation time was measured from the start of the mucosal incision until the end of tumor removal. "Self-completion" referred to a

Endoscopist	A	B	C	Total	*P*-value*
Complete resection, n (%)	28 (93)	28 (93)	28 (93)	84 (93)	
Complication, n (%)					
Delayed hemorrhage	1 (3.3)	1 (3.3)		2 (6.7)	
Perforation	1 (3.3)	1 (3.3)		2 (6.7)	
Self-completion, n (%)					
Mucosal incision	30 (100)	20 (67)	27 (90)	77 (86)	0.000
Submucosal dissection	23 (77)	15 (50)	16 (53)	54 (60)	
Median procedure time, minutes (IQR)					
Mucosal incision	19 (13)	23 (19)	33 (26)	23 (20)	0.000
Submucosal dissection	26 (33)	34 (28)	57 (59)	39 (38)	

* *P*-value for total mean procedure time and total self-completion rate of mucosal incision vs. submucosal dissection.

Table 4 Evaluated parameters for feasibility of ESD.

Procedure	A	B	C	Total (%)
Mucosal incision				
Overtime			2	2 (2)
Inability to achieve hemostasis		1	1	2 (2)
Perforation		1		1 (1)
Inability to continue procedure		8		8 (9)
Submucosal dissection				
Overtime	2	2	6	10 (11)
Inability to achieve hemostasis	1	2	2	5 (6)
Perforation	1			1 (1)
Inability to continue procedure	3	11	6	20 (22)

Table 5 Reasons for change of supervisor.

procedure that was finished without a change of supervisor. The learning curve was assessed as the change in self-completion rate and required operation time for each 10 procedures of each operator. Reasons for a change of supervisor during each mucosal incision and submucosal dissection were analyzed with reference to the operation record and video recordings, and were categorized according to the above-mentioned assistant policy.

Statistical analysis

JMP version 6.0 (SAS Institute, Cary, North Carolina, USA) was used for data analysis. Summarized numerical data were expressed as medians (interquartile ranges). The Mann–Whitney U-test was used for comparison of procedure time between mucosal incision and submucosal dissection. The χ^2 test was used for comparison of self-completion rates between mucosal incision and submucosal dissection. Significant differences were taken to be indicated by a P-value below 0.05.

Results

Assessment of feasibility

The overall complete resection rate was 93% (84 of 90 procedures). A total of four complications were experienced (4.4%), comprising two cases of delayed hemorrhage and two perforations. The perforations were repaired successfully with endoscopic clips as soon as the operators changed. The distribution of complete resection and complication rates was similar between operators (**Table 4**).

Analysis of difficulty

The self-completion rate for submucosal dissection was significantly lower than that for mucosal incision, and operation time was significantly longer (**Table 4**).

Concerning the learning curve, the self-completion rate for mucosal incision for all operators exceeded 80% in the third group of 10 cases, whereas for submucosal dissection two of three operators stayed around 50%, even for the final 10 cases (**Fig. 1**). Median operation time for mucosal incision did not change markedly and remained around 30 minutes for all operators. Median operation time for submucosal dissection became shorter than 30 minutes for one operator whose self-completion rate increased, but did not improve for the other two operators (**Fig. 2**).

The reasons for incompletion of the procedures are listed in **Table 5**. For mucosal incision, "inability to continue the procedure" was the most frequent reason for a change of supervisor. According to the video recordings, this was mainly an inability to achieve a mucosal incision owing to unfamiliarity with use of the IT knife. For submucosal dissection, "overtime," "inability to achieve hemostasis," and "inability to continue the procedure" led to discontinuation of the procedure for about 40% of the lesions. Video recordings revealed that "overtime" was usually caused by spending too long on hemostasis, and "inability to continue the procedure" was largely the result of interference with the procedure and loss of orientation caused by hemorrhage and clotting: in other words, the main difficulty for completion of submucosal dissection was uncontrollable hemorrhage.

Discussion

In the present case series study, we found that ESD for EGC measuring less than 2 cm, performed by supervised residents, was practicable, with a complete resection rate of 93% and a complication rate of 4%, which is similar to findings in previous studies of experienced endoscopists [10]. Difficulties arose more frequently during submucosal dissection than mucosal incision, and most of these were related to uncontrollable hemorrhage.

It has been reported that closely supervised trainees can perform advanced surgery such as esophagogastrectomy, hepatectomy [11], or pancreatectomy [12] with similar outcomes to consultant surgeons. In these studies, surgeons with a large workload encouraged trainees to be accept more opportunities to participate in such complex operations, with appropriate supervision, because this improved their learning of the surgical methods and did not jeopardize patient care. We believe that this concept can be applied to endoscopic procedures, and our results support this conclusion. Needless to say, this cannot be achieved without the availability of a highly experienced supervisor, because a significant number of cases were not completed by the resident alone and complications such as perforations were generally managed by the supervisor.

The requirements and criteria for starting to perform ESD have not been clarified to date. In our center, endoscopists who intend to start ESD should attend the pre- and post-treatment conference, and take part in actual ESD procedures as an assistant for at least 1 year before beginning the procedure themselves. In addition to gastroenterologists, surgeons and pathologists participate in these conferences, and thus new endoscopists can learn how to diagnose the extent and depth of the tumor, establish the optimum treatment strategy, and manage the patients appropriately according to the histopathological findings in resected specimens. By assisting experienced endoscopists, trainees acquire the skills needed to troubleshoot various situations. Moreover, obtaining expertise in hemostasis before starting ESD is recommended since most of the difficulties surrounding the procedure were related to uncontrollable hemorrhage.

In the present study, patients with small EGCs were selected. We suspect that if a novice endoscopist performs ESD for large lesions, it could involve an extremely long operation time, and it is too difficult for them to acquire the basic techniques during their restricted time in clinical practice. For this reason, we recommend that supervision should be started with small lesions, so that trainees have the opportunity to learn the entire ESD procedure. After this, it is easier to move on to larger lesions, because the procedure for large lesions consists of repeating certain basic procedures.

Choi et al. [13] have investigated the learning curve for ESD, and reported an increase in the en bloc resection rate from 45% to 85% after experience of 40 cases. They have concluded that trainees need to perform 20–40 procedures to be able to use the technique effectively, although their method consisted of mucosal incision and snaring rather than ESD. Gotoda et al. [14] have found that experience of at least 30 cases is required for a beginner to gain early proficiency in this technique. In our study, two of the three operators could not achieve a sufficient self-completion rate for submucosal dissection after 30 cases. The fact that two of the three operators could not achieve a sufficient self-completion rate for ESD by the 30th case suggests that more extensive experience is required before endoscopists can be considered to be proficient. Our study did not include hands-on training

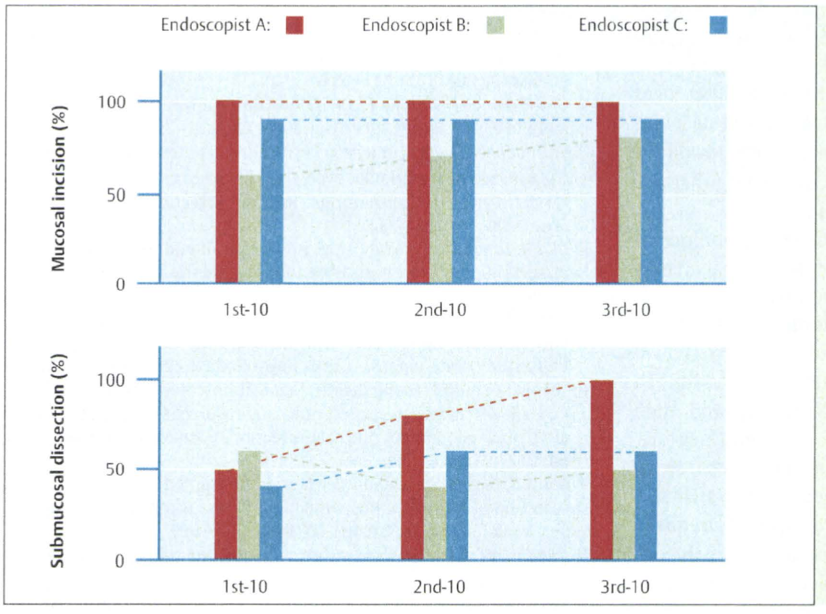

Fig. 1 Learning curves for self-completion rate for mucosal incision and endoscopic submucosal dissection.

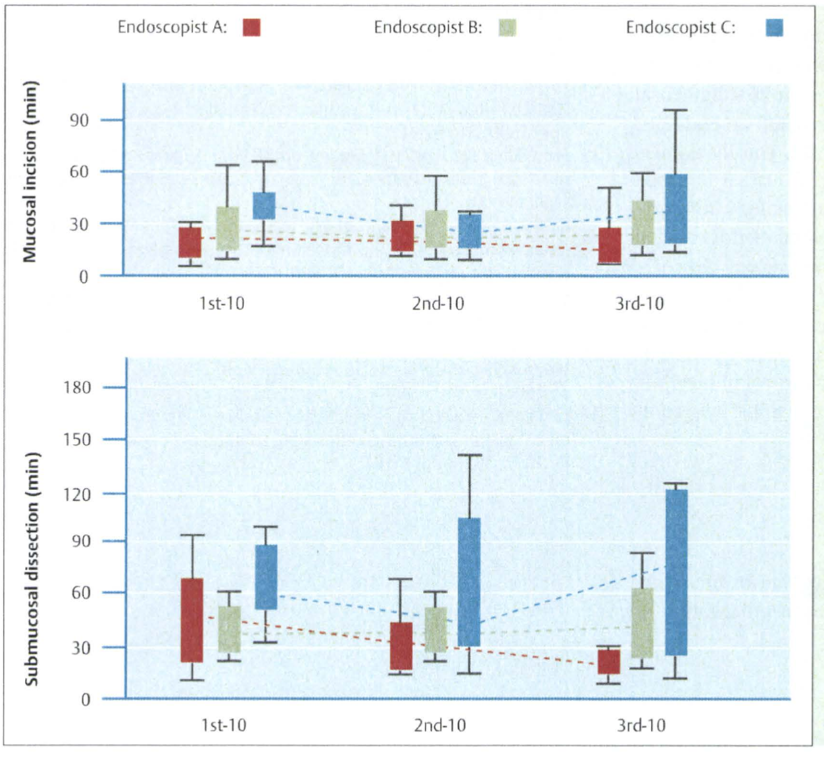

Fig. 2 Learning curves for operation time for mucosal incision and endoscopic submucosal dissection.

on ex vivo animal models such as the Erlangen Active Simulator for Interventional Endoscopy (EASIE) or living animals, which might have improved the learning curve of our three endoscopists. Nevertheless, we feel that incorporation of supervised clinical procedures is imperative.

The baseline profile of our operators, such as graduation year or number of cases experienced, was not associated with learning speed. Kakushima et al. [15] have indicated that a change in en bloc complete resection and complication rates did not represent operator proficiency with ESD under supervision, but that a decrease in operation time is a marker of proficiency. We evaluated self-completion rate as a parameter of expertise and it was associated with a decrease in procedure time, and as a result it may be a marker of proficiency. Differences in learning speed have been attributed to variations in individual talent. However, clarifying the objective parameters that reflect the actual expertise of a trainee and setting up relevant acquisition conditions are important for the establishing of a training system for advanced therapeutic procedures. Because our data are limited by the number of participating endoscopists and procedures, further investigations using common evaluation parameters are required.

The three residents in this study had different profiles in terms of their endoscopic experience. The allocation of the lesions was not randomized and we therefore cannot exclude the possibility that some lesions may have been allocated on the basis of differences in profile between the residents. We attempted to avoid such bias as much as possible and found no statistically significant differences in the size of lesions or their locations, suggesting that any bias due to residents' profiles may have been minor.

Our results suggest that improving the process of submucosal dissection, especially the controllability of hemorrhage, may have contributed to the decrease in completion rate and shortening of operation time. To facilitate hemostasis during submucosal dissection, we attempted to improve the following. Firstly, we tried to dissect a deeper layer of the submucosa. The vessels in the gastric wall penetrate the muscularis propria and then branch in the submucosa toward the superficial layer. Therefore, when we dissect the superficial layer of the submucosa, small branched vessels are disrupted and more bleeding occurs. Dissection of deeper layers causes spurting hemorrhage but its frequency becomes less, and it can be stopped more easily because bleeding from the stump of the vessel trunk can be observed at a single point. Secondly, during submucosal dissection, we prefer to use the coagulation mode of the electrosurgical unit, e.g., a forced coagulation mode of 50 W for the ICC200 (Erbe) or swift coagulation of 100 W, for the VIO300D (Erbe). Dissection in the coagulation mode can cut and prevent bleeding, especially in loose submucosal tissue, but sometimes it cannot cut fibrous submucosal tissue in the gastric body; therefore, we alternated an Endo Cut mode with the coagulation mode in such cases. Thirdly, we use an endoscope with waterjet function for ESD [16]. The scope was developed originally to clean out mucus or food residues, but it can be used for washing out of shed blood or clots during ESD without withdrawing the device from the working channel.

In conclusion, with appropriate supervision, gastric ESD by residents is practicable, with equivalent clinical outcomes to those of experienced endoscopists, although there is a difficulty with self-completion of submucosal dissection. Better control of bleeding during submucosal dissection may be the key to improving completion rates and procedure times.

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Competing interests: None

References

1 *Ohkuwa M, Hosokawa K, Boku N et al.* New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001; 33: 221 – 226
2 *Ono H, Kondo H, Gotoda T et al.* Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225 – 229
3 *Watanabe K, Ogata S, Kawazoe S et al.* Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. Gastrointest Endosc 2006; 63: 776 – 782
4 *Oka S, Tanaka S, Kaneko I et al.* Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointest Endosc 2006; 64: 877 – 883
5 *Takeuchi Y, Uedo N, Iishi H 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 – 193
6 *Yokoi C, Gotoda T, Hamanaka H, Oda I.* Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. Gastrointest Endosc 2006; 64: 212 – 218
7 *Rosch T, Sarbia M, Schumacher B et al.* Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy 2004; 36: 788 – 801
8 *Nakajima T.* Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002; 5: 1 – 5
9 *National Cancer Institute.* Common terminology criteria for adverse events v. 3.0. Cited 7 Jan 2007. Available from: https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm
10 *Oda I, Saito D, Tada M et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 2006; 9: 262 – 270
11 *Paisley AM, Madhavan KK, Paterson-Brown S et al.* Role of the surgical trainee in upper gastrointestinal resectional surgery. Ann R Coll Surg Engl 1999; 81: 40 – 45
12 *Praseedom RK, Paisley A, Madhavan KK et al.* Supervised surgical trainees can perform pancreatic resections safely. J R Coll Surg Edinb 1999; 44: 16 – 18
13 *Choi IJ, Kim CG, Chang HJ et al.* The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. Gastrointest Endosc 2005; 62: 860 – 865
14 *Gotoda T, Friedland S, Hamanaa H, Soetikno R.* A learning curve for advanced endoscopic resection. Gastrointest Endosc 2005; 62: 866 – 867
15 *Kakushima N, Fujishiro M, Kodashima S et al.* A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991 – 995
16 *Enomoto S, Yahagi N, Fujishiro M et al.* Novel endoscopic hemostasis technique for use during endoscopic submucosal dissection. Endoscopy 2007; 39 (Suppl 1): E156

S. Abe, H. Kondo, T. Sumiyoshi,
T. Mizushima, M. Sugawara, Y. Shimizu,
S. Okushiba:

Treatment strategy for early gastric cancer with the risk of pyloric stenosis after endoscopic resection

We read with great interest the study by Dr. Coda and his colleagues, "Risk factors for cardiac or pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment," regarding early gastric cancer (EGC) [1].

At our center, endoscopic submucosal dissection (ESD) was performed for 433 EGCs (185 located in the lower third of the stomach, 146 in the middle third, and 102 in the upper third) from July 2000 to October 2008, and post-ESD stenosis occurred in five of the 185 pyloric resections. Four of the five had risk factors for post-ESD stenosis, that is a circumferential extent of the mucosal defect of more than ¾ or longitudinal extent of more than 5 cm, as described in the paper of Coda et al. [1].

The authors concluded that endoscopic balloon dilation was useful for pyloric stenosis after ESD. However, we think that balloon dilation is not always appropriate, considering the frequency of procedures needed, and risk of adverse events to the patient. In our series, four patients suffered from nausea and vomiting for a mean of 38 days (range 31 – 70), although the stenoses finally resolved with frequent balloon dilations. Furthermore, one patient sustained a perforation during her first balloon dilation, requiring an emergency operation (**Fig. 1**).

We believe, therefore, that balloon dilation is not always a safe treatment for post-ESD pyloric stenosis.

Coda and colleagues also reported that one of eight patients with pyloric stenosis had to undergo an additional distal gastrectomy with lymph node dissection following balloon dilation. Since the risk of lymph node metastasis is pathologically evaluated from the resected ESD specimens, the indication for ESD with high risk factors for pyloric stenosis should be decided carefully from the viewpoint of minimizing invasiveness.

Considering the above, we have started to recommend laparoscopic distal gastrectomy (LDG) including lymph node dissection for EGC with high risk of post-ESD pyloric stenosis. LDG for EGC is considered less invasive than open distal gastrectomy and is widely accepted in Korea and Japan. Long-term clinical outcome and survival have not been found to be different for the two surgical methods [2 – 4]. Our recent cases of EGC with high risk of pyloric stenosis have been successfully resected by LDG without complication, and with a median hospitalization of 20 days (**Fig. 2 a, b**).

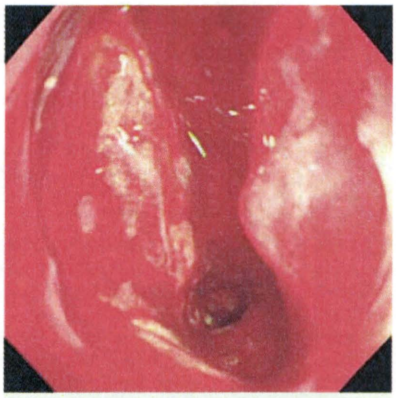

Fig. 1 Endoscopic image of perforation caused by balloon dilation for pyloric stenosis after endoscopic submucosal dissection (ESD). Omental fat tissue was seen in the anterior side of the pyloric ring.

We agree that EGC near the cardia should be treated by ESD although this has high risk factors for cardiac stenosis. The standard operation for EGC near the cardia is total gastrectomy, which often makes the quality of life of patients worse because of weight loss, anorexia, dysphagia, and so forth [5 – 7]. ESD for cardiac lesions could avoid total gastrectomy if resection is curative, and consequently could preserve gastric function, although balloon dilation is required for cardiac stenosis [8].

ESD for EGC with a negligible risk of lymph node metastasis has been recognized as less invasive and more economical than conventional surgery. However, we should take into consideration the benefits and risks of ESD and LDG when deciding upon treatment strategies for EGC, especially in patients with lesions at high risk of post-ESD stenosis.

Competing interests: None

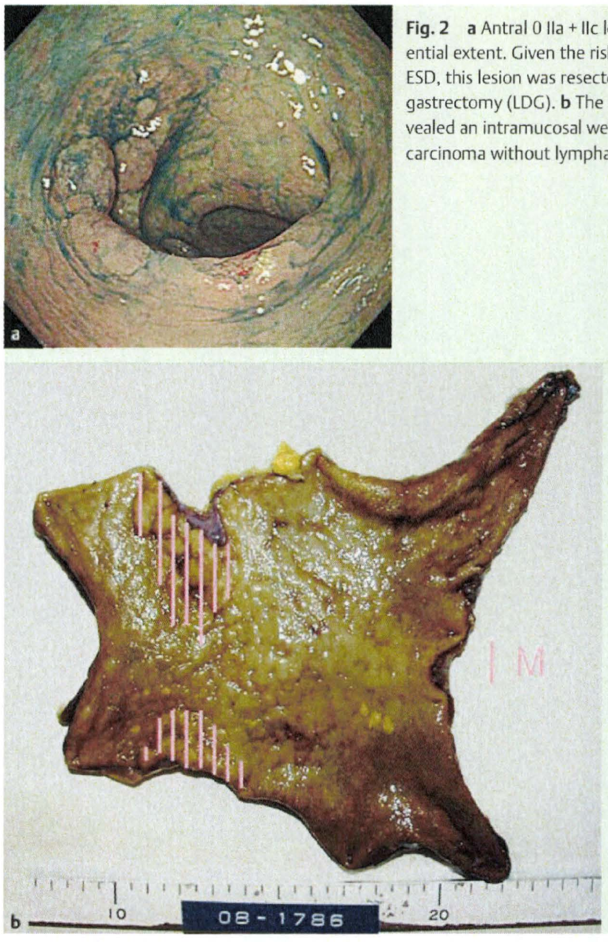

Fig. 2 **a** Antral 0 IIa + IIc lesion with ⅔ circumferential extent. Given the risk of pyloric stenosis after ESD, this lesion was resected by laparoscopic distal gastrectomy (LDG). **b** The resected specimen revealed an intramucosal well-differentiated adenocarcinoma without lymphatic or venous invasion.

References

1 *Coda S, Oda I, Gotoda T et al.* Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment. Endoscopy 2009; 41: 421 – 426
2 *Kitano S, Shiraishi N, Uyama I et al.* A multicenter study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg 2007; 245: 68 – 72
3 *Lee JH, Yom CK, Han HS.* Comparison of long-term outcomes of laparoscopy-assisted and open distal gastrectomy for early gastric cancer. Surg Endosc 2009; 8: 1759 – 1763 [Epub ahead of print Dec 5 2008]
4 *Kim YW, Baik YH, Yun YH et al.* Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg 2008; 248: 721 – 727
5 *Wu CW, Chiou JM, Ko FS et al.* Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial. Br J Cancer 2008; 98: 54 – 59
6 *Davies J, Johnston D, Sue-Ling H et al.* Total or subtotal gastrectomy for gastric carcinoma? A study of quality of life. World J Surg 1998; 22: 1048 – 1055
7 *Wu CW, Hsieh MC, Lo SS et al.* Quality of life of patients with gastric adenocarcinoma after curative gastrectomy. World J Surg 1997; 21: 777 – 782
8 *Yoshinaga S, Gotoda T, Kusano C et al.* Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008; 67: 202 – 209

H. Kondo, MD, PhD
Tonan Hospital
North-1, West-6
Chuo-ku
Sapporo 060-0001
Japan
Fax: +81-11-2618692
hkondo@tonan.gr.jp

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潰瘍合併早期胃癌は，『胃癌治療ガイドライン』では内視鏡治療の適応条件とはされていない．しかし，内視鏡的粘膜下層剝離術（ESD）の開発ならびに技術の進歩に伴い，潰瘍合併早期胃癌に対しても一括切除と詳細な病理学的検索が可能となり，分化型，M，3cm以下の病変は適応拡大病変としてESDが行われるようになってきている．この病変に対するESDはガイドライン病変と比較して技術的難易度は高いものの，潰瘍瘢痕部を確実に処理することにより一括切除が可能である．

阿部清一郎[1,2]，Seiichiro ABE
金城　徹[1]，Tetsu KINJO
草野　央[1]，Chika KUSANO
小田一郎[1]，Ichiro ODA
科長 住吉徹哉[2]，Tetsuya SUMIYOSHI
診療部長 近藤　仁[2]，Hitoshi KONDO
上部消化管医長 後藤田卓志[1]，Takuji GOTODA

1）国立がんセンター中央病院内視鏡部
2）KKR札幌医療センター斗南病院消化器内科

潰瘍合併早期胃癌に対するESD

Key words

早期胃癌／内視鏡治療／内視鏡的粘膜下層剝離術／潰瘍

はじめに

早期胃癌に対する内視鏡的粘膜下層剝離術（endoscopic submucosal dissection；ESD）は，2006年4月から保険収載されて以降急速に普及しているが，一方で切除困難病変や合併症等の課題も残されている．本稿では潰瘍合併早期胃癌（以下UL（+）病変）に対するESDについて，適応，技術的治療成績，問題点ならびにITナイフ2を用いた治療手技について概説する．

1 早期胃癌に対する内視鏡治療の原則

内視鏡治療はリンパ節郭清を伴わない局所切除であるため，治療法を選択するうえでリンパ節転移の有無は重要なポイントとなる．『胃癌治療ガイドライン（第2版）』では，内視鏡治療の適応原則を「リンパ節転移の可能性がほとんどなく，腫瘍が一括切除できる大きさと部位にあること」とし，具体的には「2cm以下の肉眼的粘膜癌（cM）で，組織型が分化型（pap, tub1, tub2），陥凹型ではUL（−）に限る」と記載されている．この適応は内視鏡的粘膜切除術（endoscopic mucosal resection；EMR）による治療を前提としているため，局注による粘膜下層の挙上が不可能なUL（+）病変は内視鏡治療の適応外とされている[1)]．

一方，内視鏡治療の適応病変を検討するために，国立がんセンター中央病院と癌研究会附属病院における早期胃癌5,265例の，過去の外科手術症例の病理組織学的検討からリンパ節転移のリスクの推測を行った．その結果，脈管侵襲陰性の分化型腺癌で，①潰瘍の有無にかかわらず腫瘍径3cm以下のM癌，②M癌，潰瘍（−）で腫瘍径に制限なし，また③潰瘍の有無にかかわらず腫瘍径3cm以下のSM1癌（粘膜下浸潤500μm以内）ではリンパ節転移がほとんどないことが明らかになった（表1）[2)]．これらの条件を満たす早期胃癌は，内視鏡治療で外科手術と同等の根治性（5年生存率：M癌99%，SM癌96%）が得られる可能性が高いと考えられた[3)]．この検討結果をもとに，術前に分化型，M，3cm以下と診断したUL（+）病変は，適応拡大病変として内視鏡治療が行われるようになってきている（表2）[2)]．

従来は早期胃癌に対してstrip biopsy法，透明プラ

表1　病理組織所見に基づく早期胃癌のリンパ節転移のリスク（国立がんセンター中央病院・癌研究会附属病院）

条件			リンパ節転移	95%信頼区間
分化型腺癌 脈管侵襲（−）	M癌	潰瘍の所見にかかわらず，腫瘍径≦3cm	0/1,230（0%）	0〜0.3%
		潰瘍（−）で，腫瘍径に制限なし	0/929（0%）	0〜0.4%
	SM1（500μm）以内の粘膜下浸潤癌	潰瘍の所見にかかわらず，腫瘍径≦3cm	0/145（0%）	0〜2.5%
未分化型腺癌 脈管侵襲（−）	M癌	潰瘍（−）で，腫瘍径≦2cm	0/141（0%）	0〜2.6%

（文献2より引用）