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S- Editor Wang J **L- Editor** Wang XL **E- Editor** Bai SH

Digestive Endoscopy (2005) **17** (Suppl.), S94–S96

SPECIAL REPORT

CLINICAL EVALUATION OF THE MULTI-BENDING SCOPE IN VARIOUS ENDOSCOPIC PROCEDURES OF THE UPPER GI TRACT

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The multi-bending scope is one of the technological innovations that is making possible new techniques in endoscopic diagnosis and treatment. The multi-bending function makes it easier to approach sites that would be hard to reach with conventional scopes. Not only is this useful for observation and biopsies of difficult-to-approach sites, it is also expected to be very useful in various endoscopic treatments such as endoscopic submucosal dissection, endoscopic mucosal resection, and endoscopic hemostasis. Unfortunately, despite these obvious advantages, the incorporation of multifunctionality and high image quality results in a heavier and wider scope with reduced maneuverability. For practical clinical use, a balance between functionality and maneuverability is essential. We believe that making further improvements in this area is crucial to the successful development of this technology.

Key words: endoscopic mucosal resection, endoscopic submucosal dissection, jet irrigation function, multi-bending function, multi-bending scope.

INTRODUCTION

The development of new endoscopes and treatment devices has made possible novel methods of endoscopic diagnosis and treatment that would have been inconceivable in the past. Among these technological innovations, one in particular, the multi-bending scope (M-Scope), has been attracting a lot of attention as it not only enables observation and biopsies of sites that are difficult to approach with conventional scopes, but is also expected to be useful for endoscopic treatments such as endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) of early gastric cancer and endoscopic hemostasis of gastric bleeding.[1,2] However, because the M-Scope is still in the prototype stage, various aspects of the design need to be improved and problems remain to be solved. To clarify the advantages and disadvantages of the M-Scope, we have compiled opinions from endoscopists based on their responses to a questionnaire circulated prior to Endoscopic Forum Japan (EFJ) 2004, as well as from discussions held at the forum.

SPECIFICATIONS OF THE M-SCOPE

The biggest feature of the M-Scope is that it has a second bending section at the proximal side of the regular bending section (Fig. 1). The first bending section can be angulated in four directions in the same manner as regular scopes, while the second bending section (located approximately 11 cm from the distal end) can be angulated 70 degrees up and down. In addition to regular instrument channel(s), an auxiliary water channel is provided to enable jet irrigation using a flushing pump. With the single-channel M-Scope, a 3.2-mm diameter instrument channel is laid out at a 6 o'clock position, and the scope outer diameter is 9.8 mm. With the double-channel M-Scope, two 3.2-mm diameter instrument channels are laid out at 5 o'clock and 7 o'clock positions, respectively, and the scope outer diameter is 11.7 mm (Fig. 2). As for the image quality, the same high-resolution CCD chip used in other Q260 models is incorporated.

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EVALUATION OF THE MULTI-BENDING FUNCTION

Useful situations

There are two basic reasons why the multi-bending function (M function) is useful. First, it lets the approaching angle to the target be changed. Second, it allows the scope tip to get close to the target—even one that is in a location that is inaccessible with conventional scopes. To be more specific, the following situations are likely.

Frontal observation is likely to be achieved by using the M function in cases where observation is difficult with conventional scopes because the lesion is located tangentially to the scope or it is too far from the scope (Figs 3,4). This makes it easier for beginners to perform observation and biopsies. Successful treatment can also be ensured in EMR or hemostatic procedures because frontal observation of the lesion or the exposed blood vessel makes it easier to manipulate the device. In contrast, in EUS or ESD, imaging or device manipulation is easier in cases where the scope is located tangentially to the lesion. The M function makes it possible to adjust the scope angle to obtain an easier-to-operate position even in cases where only a perpendicular approach is possible with conventional scopes. Also, in situations where treatment is conventionally difficult because the target is too distant for

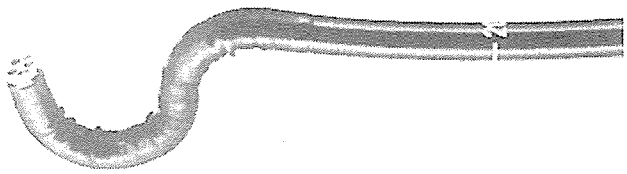

Fig. 1. Multi-bending scope has two bending section.

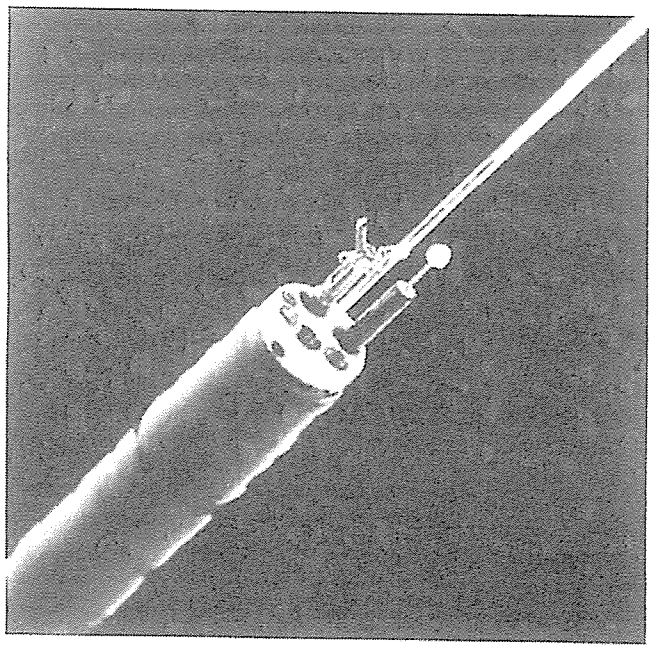

Fig. 2. Double channel M-scope has two 3.2 mm diameter instrument channels and also a jet irrigation auxiliary channel.

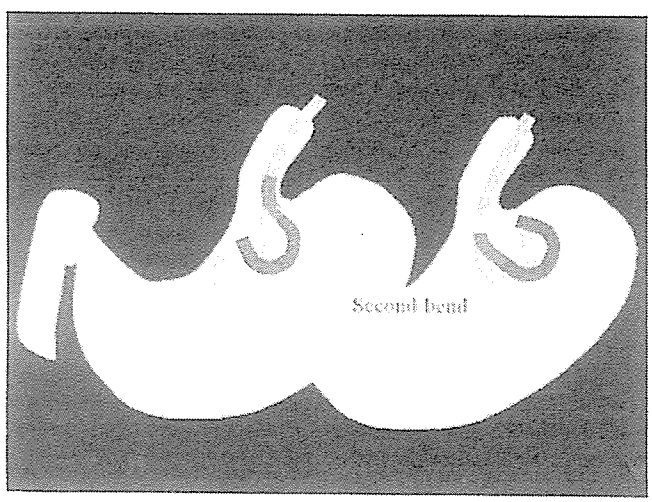

Fig. 3. M-scope facilitates easier approach to cardia and fornix.

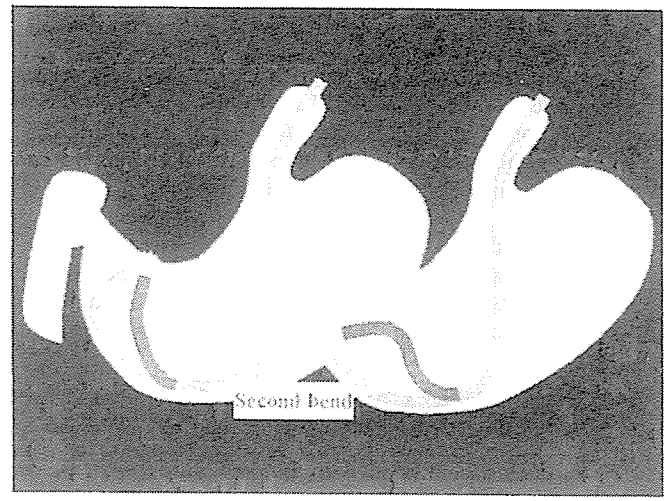

Fig. 4. M-scope also facilitates easier approach to widely opened angulus or tangent line.

a device to reach—such as in the fornix, widely opened angulus or lesser curvature of the lower body, the M function is expected to get closer to the target much easily.

Nevertheless, despite all these advantages, the current M-Scope is considered too heavy and too difficult to maneuver. Moreover, observation of a lesion at very close range is difficult because the rigid section at the distal end of the current M-Scope is slightly longer than that of conventional models.

Passing properties of treatment devices

Because the shape and bending angles of the scope tip are unprecedented when the M function is used, the passing properties of various devices need to be considered. Although the channel diameter is a generous 3.2 mm, there was concern that device manipulation might be awkward when the bending angles are great. In fact, even when the two bending sections are both angulated, all the forceps and other devices currently in use can be passed through the channel(s) with no problem. Even devices with rotation functions such as rotary clipping devices and hook knives can be used without any practical problems. It has also been reported that there is no problem with narrow-diameter ultrasound probes, although caution is required when handling the probe due to its fragility (unpubl. Igarashi Y. Toho University, Tokyo, Japan).

EVALUATION OF THE JET IRRIGATION FUNCTION

Everyone agrees on the usefulness of the jet irrigation function for cleaning. In regular observation, it removes mucus, residue, and air bubbles to ensure clearer observation of the lesion. In treatment, it removes blood to enable accurate confirmation of the exposed blood vessel; consequently, it is considered very useful for intraoperative hemostasis during ESD and hemostasis of the peptic ulcer. For example, in treatment using hemostatic forceps, reliable hemostasis is not possible without accurately grasping the exposed blood ves-

sel, so securing the visual field with continuous jet irrigation is of vital importance.

In addition to cleaning, it has been pointed out that the jet irrigation function is also useful as a substitute for submucosal injection by directly feeding water into the submucosal layer when the submucosal layer is dissected during ESD procedure (unpubl. Oyama T. Saku General Hospital, Saku, Japan).

On the negative side, it has been pointed out the incorporation of the jet irrigation function makes flares much more likely occur, resulting in poorer image quality (unpubl. Doi T. National Cancer Center East Hospital, Kashiwa, Japan).

EVALUATION OF THE INSTRUMENT CHANNEL(S)

Location(s) of the instrument channel(s)

As for the location(s) of the instrument channel(s), evaluations varied depending on the application and the treatment device used. This was especially noticeable with ESD. For example, most respondents said that, when the IT Knife[3] is used, it is easier to apply torque to cut the tissue if the knife is projected in an 8 o'clock direction like the Q240 and Q260.

In contrast, when using a treatment device that cuts the tissue with its tip, such as needle knife,[4] Hook Knife,[5] or Flex Knife,[6] the majority said that operation is easier when the device is projected in the 6 o'clock direction which is right below the field of view. One respondent also felt that if the endoscopist is not sufficiently skilled to take advantage of torque, applying the 6 o'clock projection direction to the IT Knife is not a bad idea because it allows the endoscopist to cut a short stroke under direct viewing. However, it was also argued that if the projection position is in the 6 o'clock direction, the dead angle until the treatment device can be seen is larger; therefore, it would be better to use a position around 7: 30 o'clock since the dead angle would be smaller.

Number of instrument channels

Originally, the M-Scope was developed to make strip biopsy[7] easier and more reliable. While ESD is now widely used, there are still many facilities that perform EMR using conventional strip biopsy, so demand for the double-channel M-Scope is likely to be substantial. Also, some respondents felt that even in ESD the double-channel model is easier to use when the IT Knife is used because one of the channels is close to the 8 o'clock position. Other opinions favorable to the double-channel model were saying that if there are two instrument channels, either can be selected according to the position of the lesion, suction is available at anytime during the procedure, treatment is possible while a hemostatic device is inserted in the other channel, and so forth.

In contrast, when ESD is performed with a treatment device that cuts the tissue with its tip such as a needle knife, Hook Knife, or Flex Knife, it is essential that the scope be as narrow as possible and has good maneuverability as it has to enter the submucosal layer and dissect it under direct viewing. Also, when the instrument channel is located at the 6 o'clock position, the device can be manipulated both leftwards and rightwards, so there is no need to incorporate two channels. Consequently, many respondents believed that for procedures using such devices, the single-channel model is preferable since it can be made narrower.

CONCLUSION

Incorporating the two-step angulation function and jet irrigation function, the M-Scope makes possible reliable approach to sites where device manipulation is conventionally difficult, and it is considered useful for regular observation and endoscopic treatment. However, the attempt to achieve multifunctionality and high image quality made the scope heavier and wider, decreasing maneuverability. For practical clinical use, a balance between functionality and maneuverability is essential, making further improvements in this area crucial to the successful development of this technology.

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Digestive Endoscopy (2004) **16** (Suppl.), S89–S92

LOWER DIGESTIVE TRACT EMR

ENDOSCOPIC SUBMUCOSAL DISSECTION FOR THE RELIABLE EN BLOC RESECTION OF COLORECTAL MUCOSAL TUMORS

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ABSTRACT

Scheduled piecemeal resection has been actively conducted for granular type laterally spreading tumor (LST-G) in Japan, as long as a definite preoperative diagnosis is made. However, en bloc resection is desirable for depressed lesions (e.g. IIc lesion) as well as non-granular type laterally spreading tumor (LST-NG) since they have considerable high risk for submucoasl invasion and require precise histopathological evaluation. Endoscopic submucosal dissection (ESD) has been developed for the en bloc resection of mucosal tumors of gastrointestinal tract and widely applied especially in gastric lesions. Although the large intestine involves structural and technical difficulties, we conducted en bloc resection by ESD while exercising sorts of ingenuity for preparation; endoscopes, instruments, local injections, and others. ESD is a reliable technique that allows en bloc resection of gastrointestinal mucosal lesions, and even has a splendid possibility for the treatment of early stage colorectal cancer.

Key words: endoscopic submucosal dissection (ESD), colorectal mucosal tumor, LST-NG, en bloc resection, Flex knife.

INTRODUCTION

Progress has been made in determining the malignancy and extent of local invasion of colorectal tumor through a magnifying endoscope[1] and other instruments, allowing a considerably definite preoperative evaluation of the lesion. Considering granular type laterally spreading tumor (LST-G), scheduled piecemeal resection has been actively conducted even for considerably large-sized tumors,[2] as long as a definite preoperative diagnosis is made, since its malignant potential is not so high. Alternatively, depressed lesions (e.g. IIc lesion) as well as non-granular type laterally spreading tumor (LST-NG) frequently involve submucoasl invasion. Therefore, a precise histopathological evaluation is essential with respect to tumor depth and vascular infiltration with resected specimen in an en bloc fashion. Endoscopic submucosal dissection (ESD) has been developed for the en bloc resection of mucosal tumors of the gastrointestinal tract and widely applied, especially to gastric lesions.[3,4] However, the large intestine involves the following issues that are not seen in the upper gastrointestinal tract:

1. Very thin walls present a high risk of perforation;
2. Enterobacterium-induced, serious peritonitis may develop in the event of perforation; and
3. Lumen is narrow and angulated, causing poor operability of an endoscope and generating higher difficulty in endoscopic procedure.

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To overcome these issues, we exercise sorts of ingenuity for preparation, endoscopes, instruments, local injections, and others and conduct en bloc resection by ESD while ensuring operational safety.

INGENUITIES TO ENSURE SAFETY

(1) Preparation

The patient is instructed to avoid fiber-rich meals on the day before endoscopy and to take a 10-mL bottle of picosulfate after dinner. A mixture of Niflec® 2 L and 10 mL of dimeticon is used as the intestinal lavage on the day of endoscopy. Mixing of dimeticon markedly reduces adhesive residues, which makes it easier to wash the lumen in case a few residues remained.

(2) Endoscopic system

For incision and dissection, an endoscope with a diameter as small as possible is recommended to obtain good maneuverability in the narrow lumen. We use a water-jet system-furnished, ultra-slim endoscope (outer diameter: 9.8 mm). Retroflex manipuration is neccesary, especially at the oral end of large-sized lesions, and for lesions overstride a fold. Therefore, it is essential to use an endoscope where the diameter is as small as possible and provides good operability. Furthermore, use of a transparent disposable attachment (Olympus, Japan) facilitates good visual field and allows stable dissection.

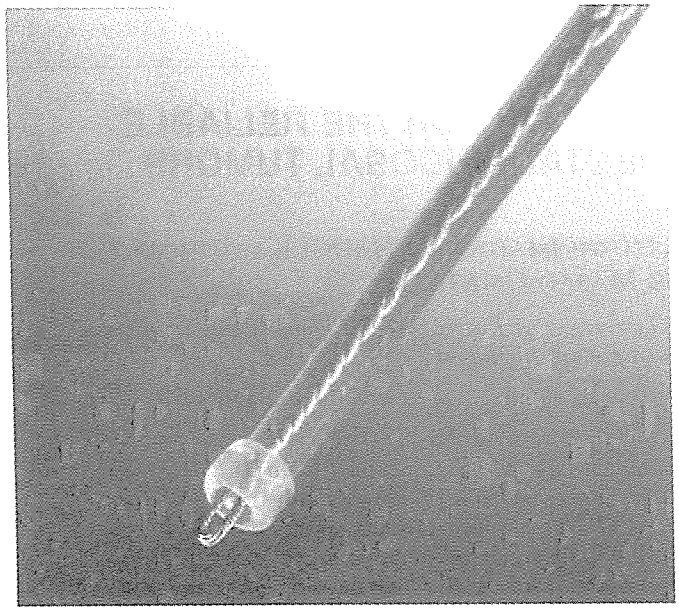

Fig. 1. Flex knife is easy to control, since it is soft and flexible. The length of the knife tip is adjustable according to circumstances.

(3) Operative instruments

A Flex knife (Fig. 1), which is soft and flexible, is the best device for incision since it provides good operability.[5] The knife has a low risk of piercing the intestinal wall because it has a blunt tip, and is easy to handle because its length is adjustable according to circumstances. In cases when it is hard to transmit the operator's force to the knife tip, or when the dessection site is very close to the muscle layer, combined use of Hook knife[6] is very useful. Also, it is necessary to prepare hemostatic forceps (Pentax, Japan) and rotatable clip fixing devices (Olympus, Japan) ready to use anytime for bleeding and perforation, respectively.

(4) High-frequency generator

ICC 200 or ICC 350 (Erbe, Germany), which is furnished not only with the endocut mode for incision, but also with mutiple coagulation modes, is very useful. We use the generator according to the following rough standards: (1) endocut mode, effect 2,60 W for mucosal incision; (2) forced mode, 40 W for submucosal dissection; and (3) soft mode, 50 W for hemostasis.

(5) Local injection solutions

It is essential to prevent perforation by forming a sufficient elevation when conducting mucosal incision and submucosal dissection. Among currently commercialized drugs, the solution of sodium hyalironate[7,8] is considered most effective from the aspect of elevation-retaining profile. Artz® (M.W. 800 kDa) and Suvenyl® (M.W. 1900 kDa), which differ in molecular weight, are commercialized in Japan. These drugs are diluted with Glyceol® (conc.glycerin solution) to two-fold and four-fold, respectively,[9] and a small volume of epinephrine and Indigocarmin are added before use.

EXPERTISE OF THE PROCEDURE

(1) Insertion of the scope

Insertion of Ultra-slim endoscope must be careful, keeping as straight as possible, not to form a loop, since it is thin and soft. Once the scope reaches the ileocecum, lavage the intestine with water-jet system and aspirate the contents. Basically, no serious peritonitis will develop unless intestinal contents outflow after perforation. Therefore, it is essential to sufficiently lavage and remove the contents of the entire intestinal tract, including the site of lesion.

(2) Chromoendoscopy and submucosal injection

Indigocarmin is sprayed to clarify the margin of the lesion. Then, conduct submucosal local injection without marking, since the border between the tumor and normal tissue is quite clear in colorectal tumors. Local injection (1–2 mL per site) provides a precipitous elevation of sufficient height. Since the elevation decreases as time passes, apply local injection only to the site to be incised, and conduct mucosal incision and submucosal dissection immediately.

(3) Marginal incision and submucosal dissection

Positioning in such a manner that the dissected tumor evaginates due to gravity frequently facilitates subsequent dissection. Therefore, it is desirable to initiate incision from the upper portion of the tumor while changing posture in consideration of gravity. The knife tip 1–2 mm long is sufficient and is gently applied to the elevated mucosa to conduct incision using the endocut mode. Try not to make a circumferential incision at once, but proceed to submucosal dissection once a certain extent of incision is made. Submucosal fibers will be easily dissected by gently applying the knife using the forced mode without changing the knife length. It is important to be aware of the direction of lumen, and to manipulate the device as parallel as possible with the intestinal wall for the prevention of perforation.

(4) Tumor resection and treatment of the postoperative ulcer

If the tumor is of size or location allowing snaring, conduct snaring when a certain extent of dissection is made and resect the tumor using the endocut mode. If the tumor is too large to be included in a snare or overstrides folds, continue to dissect the submucosa till the last in order to conduct en bloc resection. And the resected area should be carefully observed after resection. If there is an exposed blood vessel, pinch it gently with hemostatic forceps, and coagulate it using the soft cogulation mode. There is no need to suture the resected area with clips or other instruments. Even an artificial ulcer, which is as large as 10 cm in diameter, mostly becomes a scar and heals within eight weeks without causing complications.[10]

INDICATIONS AND EVALUATION CRITERIA FOR ESD

ESD is applicable to almost all lesions if it exists within the mucosa. However, ESD involves some risks due to its technical features and also takes time. Therefore, a lesion that is

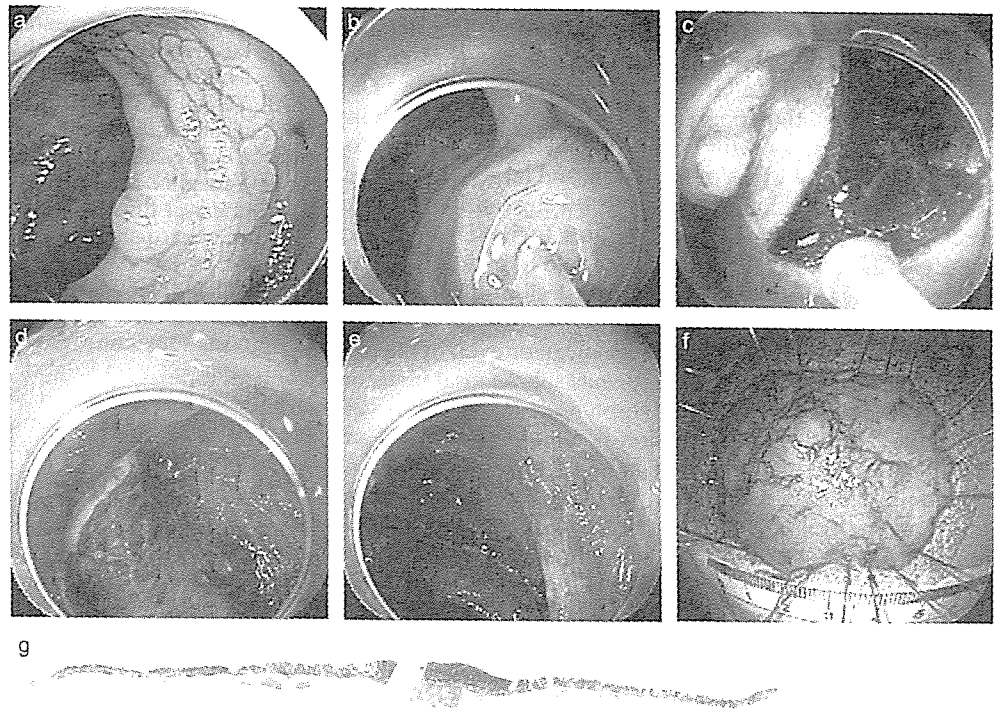

Fig. 2. A case of LST in the ascending colon. (a) After spraying indigocarmine dye, a laterally spreading tumor, granular type (LST-G) is clearly recognaized. (b) Submucosal injection of sodium hyaluronate and glyceol® with a small amount of indigocarmine and epinephrine is made. (c) Submucosa is dissected immediately after mucosal incision by Flex knife®. (d) Dissected tumor is evaginated due to gravity. (e) En bloc resection is achieved without complication. (f) The size of resected specimen was 52 × 43 mm. (g) Histopathological evaluation revealed that the tumor was well differentiated adenocarcinoma without submucosal invasion and vessel infiltration.

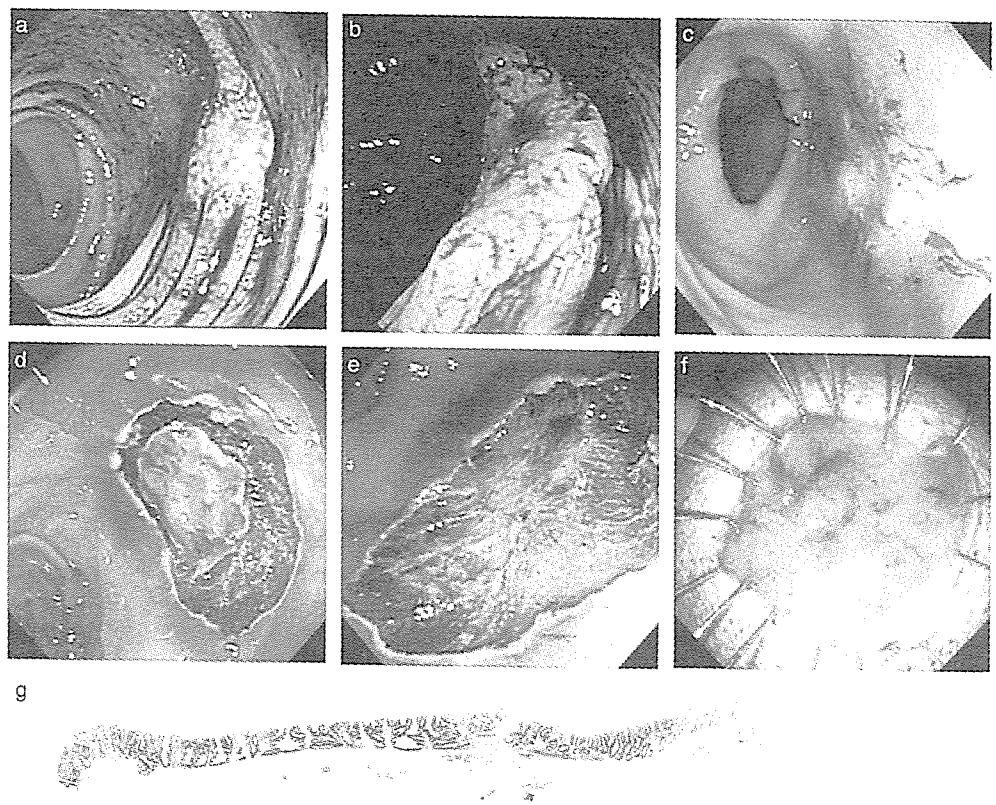

Fig. 3. A case of small IIc lesion in the sigmoid colon. (a) After spraying indigocarmine dye, small IIc lesion is clearly recognized. (b) Close view of the lesion. (c) After submucosal injection, precipitous elevation is not obtained. (d) Marginal incision and submucosal dissection is made by Flex knife®. (e) En bloc resection is achieved without complication. (f) The size of resected specimen was 22 × 18 mm. (g) Histopathological evaluation revealed that the tumor was well differentiated adenocarcinoma without submucosal invasion and vessel infiltration.

resectable en bloc by polypectomy or EMR, should be treated according to conventional procedures. The strict indications of ESD are lesions that cannot be resected en bloc by conventional procedures, but requires a precise histopathologic evaluation; depressed lesions, such as IIc legions, or LST-NG. Lesions with biopsy-induced scars, lesions on haustra or at angulations of the colon, and large-sized lesions that en bloc resection is impossible by conventional procedures are also the possible candidates for ESD. A case of slightly large-sized LST overstrides a fold of ascending colon is shown in Fig. 2. A case of small IIc lesion in the sigmoid colon is shown in Fig. 3.

After resection, an intramucosal cancer, or even in the case that histopathologic evaluation reveals submucosal invasion, it is considered that the risk of lymph node metastasis is very low if the extent of local invasion is limited up to 1000 μm, the invading part of the tumor is highly differentiated, and no budding is observed. Therefore, in such patients, we consider that the treatment was radically curative and monitor them for postoperative course with informed consent.

CONCLUSION

ESD is the procedure that allows us to conduct a reliable en bloc resection even for a depressed or large-sized lesions, and we consider that procedure has a splendid possibility also for the treatment of early stage colorectal cancer. However, the large intestine presents intrinsic risks and high procedural difficulty, so that full knowledge and training is indispensable in its treatment. The operator should address from relatively easy lesions, after that, gradually step up according to his/her skill, in order to perform a safe and reliable treatment.

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Digestive Endoscopy (2004) **16**, 327–331

ORIGINAL ARTICLE

THE HEALING PROCESS OF GASTRIC ARTIFICIAL ULCERS AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION

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Background: Due to the remarkable progress of endoscopic resection techniques, endoscopic submucosal dissection (ESD) has been widely performed for larger mucosal tumors that would result in large artificial ulcers. The healing process of peptic ulcers has been previously studied in detail; however, no precise investigation for artificial ulcers after ESD has been reported. To confirm the validity of the treatment from the aspect of wound healing, we aimed to clarify the healing process of large gastric artificial ulcers after ESD.

Methods: Seventy patients with gastric mucosal tumors treated by ESD were enrolled. The size, location and time of scar formation of the ulcers were reviewed using endoscopic pictures taken from the same view and angle. Follow-up endoscopy was performed at 1, 4, 8 and 12 weeks after ESD. For postoperative medication, all patients received normal doses of proton pump inhibitors and sucralfate for 8 weeks.

Results: The average size of the resected specimen was 34.7 mm (20–90 mm). Irrespective of ulcer size and location, all of the cases healed up to scarring stages within 8 weeks.

Conclusions: Gastric artificial ulcers after ESD healed within 8 weeks regardless of size and location using normal doses of medication as peptic ulcers. The fact that even giant ulcers after ESD heal within 8 weeks could be helpful information for candidates for ESD and for postoperative management of patients after ESD.

Key words: artificial ulcer, endoscopic resection, endoscopic submucosal dissection.

INTRODUCTION

Endoscopic mucosal resection (EMR) has been widely applied for mucosal tumors of the GI tract especially in Japan. Conventionally, the indication for EMR was considered as mucosal lesions of intestinal type no larger than 2 cm for protruded lesions, and no larger than 1 cm for depressed lesions without ulcer findings. Recently, a large study of surgically resected gastric cancers revealed particular conditions of mucosal cancers that have little risk of lymph node metastasis.[1] At the same time, remarkable progress has been made in the field of endoscopic resection, including the emergence of endoscopic submucosal dissection (ESD)[2] which enables en-bloc resection of large lesions in any part of the GI tract. Since 2000, ESD has been applied to many larger lesions, resulting in larger artificial ulcers. The validity of ESD for large mucosal tumors has been discussed from the points of lymph node metastasis and technical problems for en-bloc resection;[3] however, we should also consider the safety on the healing process of large artificial ulcers for postoperative management. Although the healing process of peptic ulcers has been previously studied in detail,[4] there has been no precise study for artificial ulcers after ESD in humans. The aim of the present study is to clarify the healing process of gastric artificial ulcers after ESD.

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Received 24 December 2003; accepted 10 May 2004.

PATIENTS AND METHODS

Seventy patients with gastric mucosal tumors treated by ESD from June 2000 to June 2003, and who were carefully followed at The University of Tokyo Hospital were enrolled. Patients with multiple gastric tumors who had been treated endoscopically and/or surgically were excluded. Patients who took anticoagulative agents daily or non-steroidal anti-inflammatory drugs daily were also excluded. For all the patients, ESD using flex-knife or thin-type snare as reported by Yahagi *et al.*[5–7] was performed. The operators were fixed to two skilled endoscopists, and each treatment was performed by either one of them. A solution of 20% dextrose with indigocarmine and minimal epinephrine was used for submucosal injection to lift the lesion. After removing the lesion, the artificial ulcer was followed without suturing. Remaining vessels in the ulcer bed were coagulated with hemostatic forceps. All patients received normal doses of proton pump inhibitors (PPI) and sucralfate for postoperative medication until 8 weeks. Patients were allowed oral intake from the next day, unless serious complications occurred, and were discharged if there was no visible vessel left in the ulcer bed at the first follow-up endoscopy performed 1 week after the resection. Further follow-up endoscopy was generally performed at 4, 8 and 12 weeks after the resection in the outpatient clinic. At least 20 endoscopic dig-

ital pictures saved as JPEG files were taken for each examination. The artificial ulcers were evaluated using the pictures taken from the same view and angle from the following two aspects. First, the healing stages at each examination were evaluated using the healing stage classification for peptic ulcers.[8] The classification is based on the degree of mucosal regeneration observed at endoscopy. The stages are: active stages 1 and 2 (A1, A2), healing stages 1 and 2 (H1, H2), scarring stages 1 and 2 (S1, S2). Second, the sizes of the artificial ulcers at each endoscopy were evaluated to find out their healing speed. The size of the primary ulcer was assumed to be identical to the resected specimen size. The virtual lengths of the major and minor axes of the ulcers at follow-up endoscopy were measured directly from the representative pictures using an image analysis software of a personal computer, WinROOF (ver. 3.51, Mitani Co., Fukui, Japan), and then the true length was calculated on comparison with the pictures of the primary ulcer. All endoscopic pictures were evaluated by two endoscopists independently, and the mean size was used for analysis. The area of ulcers (calculated from multiplication of the length of major and minor axes) was plotted in a logarithmic table according to the time after the resection.

The effect of primary ulcer size and location on healing was evaluated. Patients were divided into three groups according to the diameter of the primary ulcer as follows: (i) 20–29 mm; (ii) 30–39 mm; and (iii) 40 mm and larger. As to location, difference among upper, middle and lower areas of the stomach (UML classification), or each part of circulation (anterior, posterior, lesser and greater curvature) were evaluated.

RESULTS

Healing stage with time

Demographic characteristics of the patients are shown in Table 1. The average size of the resected specimen was 34.7 mm (20–90 mm). In all patients, ESD was performed without serious complications. At 1 week, all ulcers were at active stage 1 or 2. In 18 patients (26%), a small blood clot was observed on the ulcer bed without any exposed visible vessels. At 4 weeks, healing stage (H1, H2) was observed in all patients, with the appearance of regenerative mucosa along the rim of the remarkably reduced ulcer. At 8 weeks, the scarring stage was observed in all patients.

Table 1. Demographic characteristics of the patients

Sex	
Male	56
Female	14
Age (years)	Mean 64.6 (range 48–87)
Lesion	
Cancer	56
Adenoma	14
Location	
Upper	8
Middle	24
Lower	38
Anterior	14
Posterior	15
Lesser curvature	22
Greater curvature	19
Size of specimen (mm)	Mean 34.7 (range 20–90)

Healing speed of ulcers according to size and location

Regarding the ulcer size, the logarithmic graph showing the change in ulcer size versus weeks after the resection showed a similar pattern in each of the three groups. All cases healed within 8 weeks irrespective of the primary ulcer size (Fig. 1).

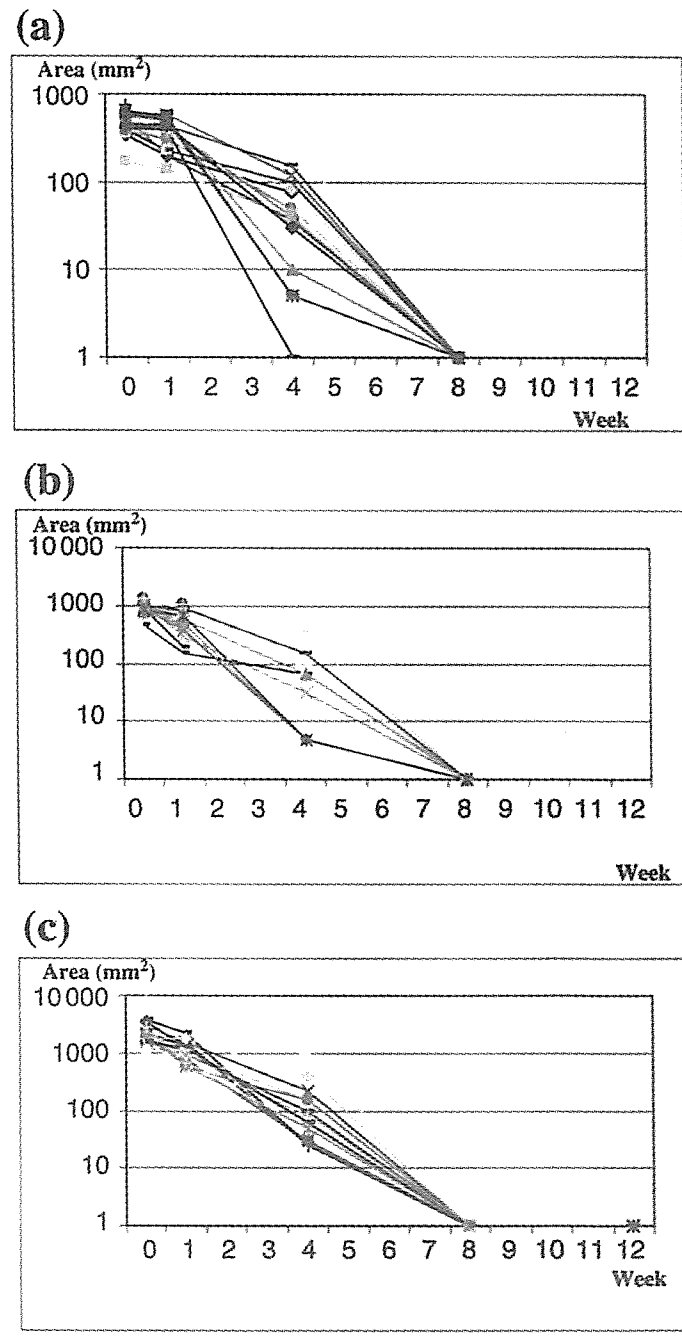

Fig. 1. Change of ulcer size after endoscopic submucosal dissection (ESD). Patients were divided into three groups by the primary ulcer diameter (d). (a) $20 \leq d < 30$, $n = 29$; (b) $30 \leq d < 40$, $n = 23$; (c) $d \geq 40$, $n = 18$.

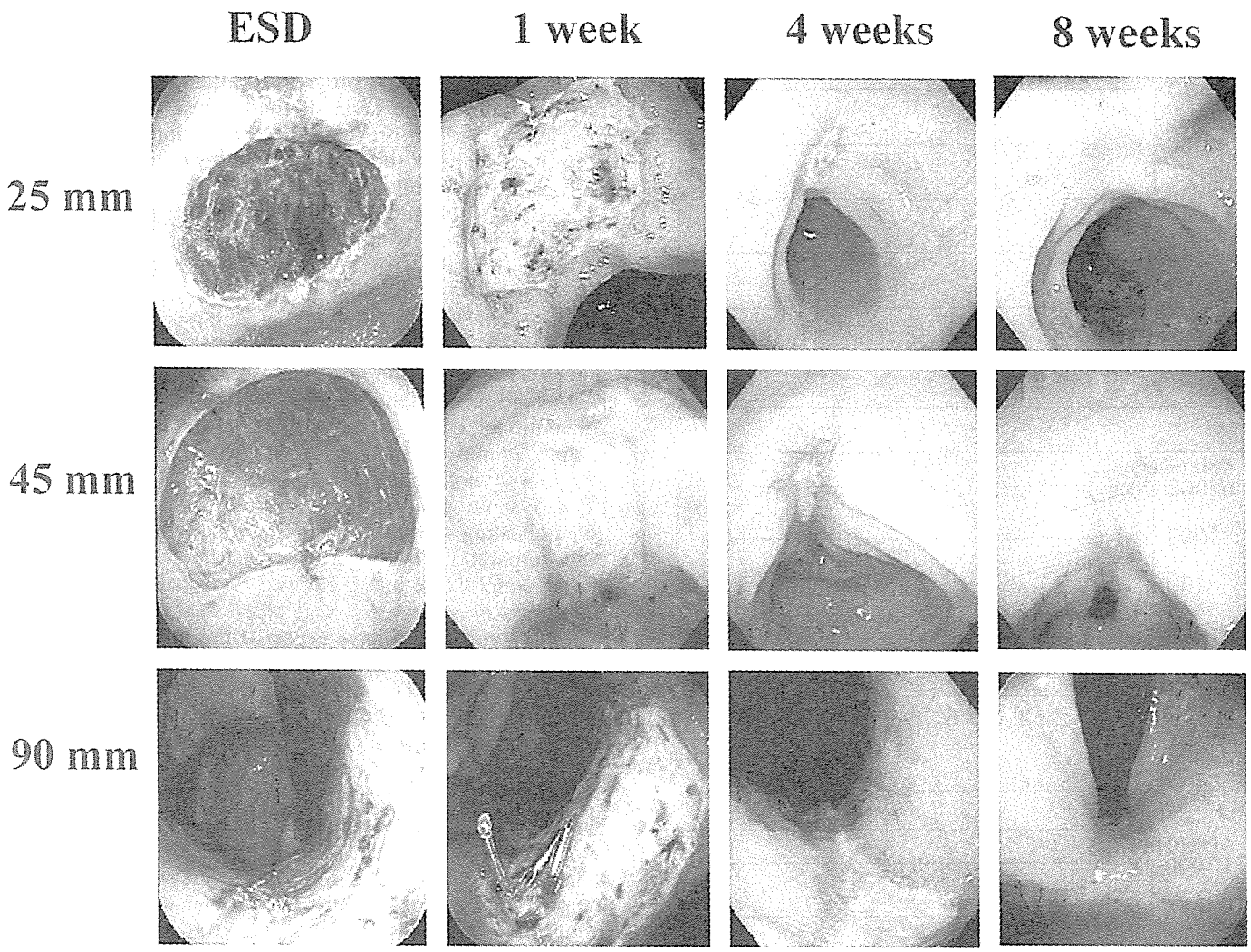

Fig. 2. Chronological endoscopic observation of three sizes of post-endoscopic submucosal dissection (ESD) ulcers (25, 45 and 90 mm). At 4 weeks, the ulcer size is remarkably reduced, and regenerative mucosa has appeared only to connect the surrounding mucosa like a zipper.

In addition, a remarkable size reduction was observed at 4 weeks, resulting in less than half of the previous ulcer size (Fig. 2).

There was also no difference in the healing speed of ulcers according to the location (Fig. 3) or circulation.

DISCUSSION

Many investigators have reported in detail the healing process of peptic ulcers in human and animal models.[4] From those studies, an ordinary peptic ulcer is first covered by a mucoid cap within several days, followed by the appearance of regenerative mucosa along the rim of the ulcer 2–3 weeks later. Regenerative mucosa appears from the edge of the existing mucosa due to the peripheral microvessels and, later, when the microvessels under the ulcer bed develop, the regenerative mucosa covers the ulcer bed, receiving blood supply from them.[9] The healing process is carried out by granulation, contraction of the ulcer itself, and by the extension of regenerative mucosa towards the center. Except for intractable ulcers, the healing process is completed within 8 weeks with administration of PPI or H2 receptor antagonists (H2-RA) in general conditions (i.e. no use of anticoagulative agents, no use of non-steroidal inflammatory drugs, no use of steroids, and the patient's compliance is good toward medication).

The present study revealed that artificial ulcers after ESD healed within 8 weeks irrespective of size and location. Even a 9-cm ulcer healed within 8 weeks under ordinary treatment in the same manner as smaller ulcers. The particular aspect of the healing process was that size reduction of these ulcers occurred rapidly before the appearance of regenerative mucosa at the ulcer rim. The surrounding mucosa of artificial ulcers came close to each other, contributing to the remarkable size reduction observed at 4 weeks. Chronological endoscopic observation revealed that the regenerative mucosa appeared only to connect the already approached surrounding mucosa like a zipper.

The contraction of the surrounding mucosa observed at 4 weeks gives us some clue of the mechanism of rapid healing of large artificial ulcers. As ESD removes the gastric mucosa with some part of the submucosa without damaging the

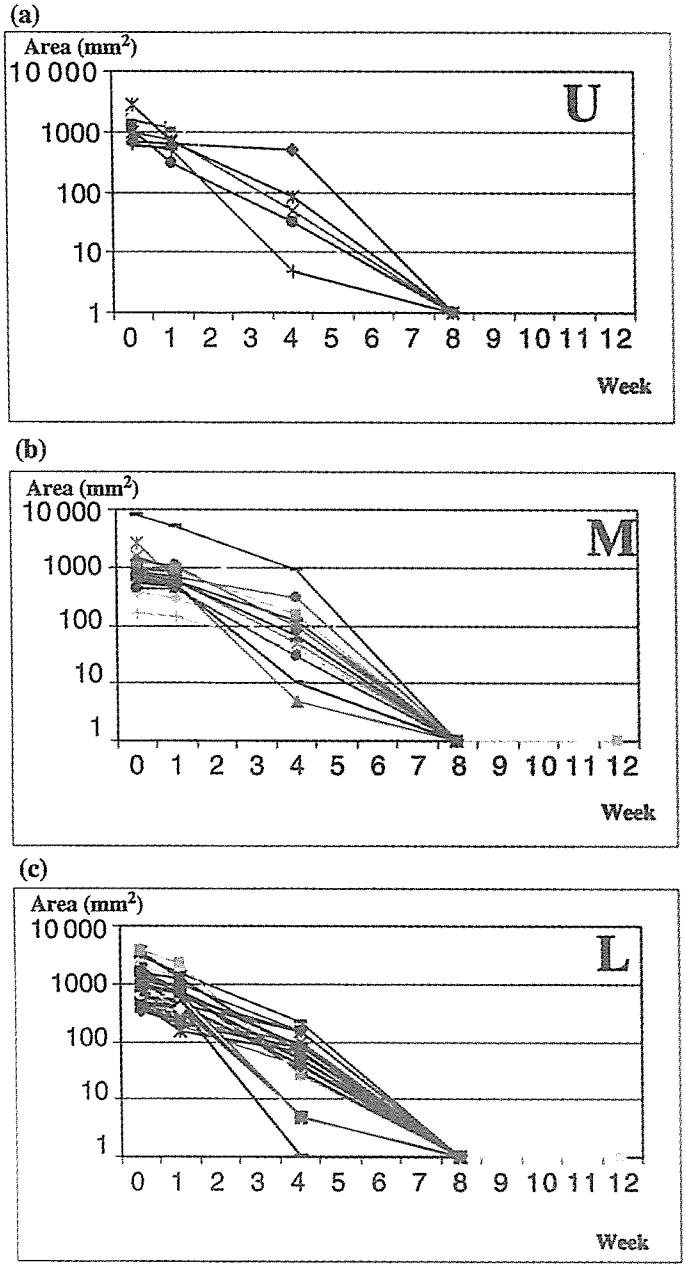

Fig. 3. Change of ulcer size after endoscopic submucosal dissection (ESD) according to location. (a) Upper (U), $n = 8$; (b) Middle (M), $n = 24$; (c) Lower part of the stomach (L) $n = 38$.

proper muscle layer, these ulcers are considered to be the same as UL-II ulcers, no matter how large they are. In addition, artificial ulcers concomitant with ESD are created very shortly, with less damage to the proper muscle layer, so that less inflammation and fibrosis of the local area occurs, preserving the contractability of the proper muscle layer under and around the ulcer. After the resection, the surrounding mucosa would come close to each other according to the contractability of that part of the stomach, together with the contraction of the resected area. In ordinary peptic ulcers, gradual formation of the ulcer induces fibrosis and granulation in the submucosa in varying degrees, or, sometimes, the proper muscle layer is damaged, which reduces the contractability of the gastric wall on which the ulcer is located. In intractable ulcers, such as deep ulcers, it has been reported that the healing process progresses rather slowly, due to the fusion of the muscle layer of the mucosa and the proper muscle layer, which prevents the contraction of the ulcer.[10] The round shape of the ulcer is preserved until regenerative mucosa appears and covers the ulcer bed. Therefore, it is assumed that the key point of rapid healing for large ESD ulcers depends on the power of contraction.

Comparing ESD to conventional EMR methods, the mechanism of development and depth of artificial ulcers are considered to be the same, as the techniques of endoscopic resection are meant to remove only lesions confined to the mucosa. Therefore, the healing process for both techniques is assumed to be identical, although the ulcer size made by conventional EMR methods would be much smaller (i.e. around 20 mm or smaller). Although ulcers smaller than 20 mm were not included in the present study, we have experienced some patients with artificial ulcers smaller than 20 mm healing at 6 weeks after ESD. So far, there is no study that compared the healing process of artificial ulcers between conventional EMR and ESD. The important finding of the present study is that even large ulcers heal within 8 weeks.

Some investigators have reported the benefit of suturing the ulcer after mucosal resection to facilitate ulcer healing and to shorten hospital stay.[11] As almost all the ulcers closed within 8 weeks without suturing, regardless of size and location, our results suggest that suturing is unnecessary even for large artificial ulcers. The mean hospital stay of the patients in our study was 6 days (4–10 days). In addition, the suturing procedure itself is sometimes not easy in large lesions and would take much time and higher cost, or it may leave a deformity in some cases. Suturing ulcers with a rotatable clipping device might be effective for smaller lesions, and it would be helpful only for day-surgery to prevent postoperative bleeding.

In the present study, the combined use of PPI and sucralfate was given for 8 weeks as anti-ulcer medication. Many studies have reported the benefit of PPI against H2-RA in patients with peptic ulcers. As to artificial ulcers after EMR, Matsumoto *et al.*[12] have compared the healing stage between PPI and H2-RA at 4 weeks after strip biopsy, a conventional EMR method. Although the size of ulcers was not mentioned, they concluded that more than twice the PPI-treated patients showed healing stage compared to those treated by H2-RA. PPI may be superior for symptomatic relief or for decreasing postoperative bleeding in the first 2 weeks. Still, it is not clear whether we need to administer PPI until scarring stage, or whether we can change over to H2-RA in the early stage.

In conclusion, artificial ulcers after ESD healed within 8 weeks regardless of size and location. The anti-ulcer treatment could be finished at 8 weeks, which is the duration permitted for ordinary peptic ulcers in the guidelines. These findings could be very helpful to backup the safety of ESD from the aspect of wound healing, and for postoperative management after ESD.

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Digestive Endoscopy (2004) **16** (Suppl.), S178–S181

EUS AND TREATMENT

ENDOSCOPIC SUBMUCOSAL DISSECTION OF COLORECTAL LESION

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Endoscopic submucosal dissection (ESD) has been developed for *en-bloc* resection of mucosal lesions of the gastrointestinal tract. It enables us to resect almost all mucosal and slightly submucosal invasive tumors, regardless of size and shape, even in the colon. Therefore, preoperative diagnosis, especially for the depth of invasion, is very important to determine the treatment strategy. The shape of the lesion, its pit pattern and also EUS findings are very useful in estimating the depth of invasion. We use an EndoEcho system with ultrasonic probe, which gives us both radial and linear image of the lesions. Remodeled three-dimensional (3D) images are also very useful in evaluating the size and the expansion of the lesion when it is located on a fold. Although the large intestine involves structural and technical difficulties, we conduct *en-bloc* resection by ESD while exercising various ingeunities in preparation, endoscopes, use of instruments and local injections. ESD is the reliable technique, which allows *en-bloc* resection of gastrointestinal mucosal lesions, and has a excellent chance of success in the treatment of early stage colorectal cancer.

Key words: endoscopic submucosal dissection (ESD), flex knife, colorectal lesion, en-bloc resection.

INTRODUCTION

Endoscopic submucosal dissection (ESD) has been developed for the *en-bloc* resection of mucosal tumors of gastrointestinal tract and widely applied especially to gastric lesions.[1,2] It enables us to resect almost all the mucosal and slightly submucosal invasive tumors, regardless of size and shape, even in the colon. However, the large intestine involves the following issues which are not seen in the upper gastrointestinal tract: (i) very thin walls present a high risk of perforation; (ii) enterobacterium-induced, serious peritonitis may develop in the event of perforation; and (iii) the lumen is narrow and angulated, causing poor operability of an endoscope and generating a higher level of difficulty in endoscopic procedure.

To overcome these issues, we use our ingeunities in preparation, endoscopes, instruments and local injections and conduct *en-bloc* resection by ESD while ensuring operational safety.

EVALUATION OF THE LESION AND TREATMENT POLICY

Preoperative diagnosis, especially for the depth of invasion, is very important to determine treatment strategy. Lesion shape, its pit pattern and also EUS findings are very useful in estimating the depth of invasion. We usually perform chromoendoscopy using indigo carmine dye, when a lesion is detected during colonoscopy. If we suspect that a lesion may be cancerous, magnifying endoscopy is performed. And then, EUS is followed if submucossal invasion is suspected by magnification.

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We use the EndoEcho system (EU-M2000 and MAJ-935, Olympus, Japan) with ultrasonic probe (UM-DP20–25R, Olympus, Japan). It gives us both radial and linear image of the lesions at once. A three-dimensional (3D) image is obtained by computer processing making the size and expansion of the lesion easily comprehensible, even when the lesion is located on a fold.

If massive submucosal invasion is mostly suspected by endoscopic and EUS findings, we opt for laparoscopic or open surgery. On the other hand, if the lesion is obviously a mucosal lesion, therapeutic ESD is performed. Diagnostic ESD may be performed, if the lesion seems to be limited to the mucosa but the findings of endoscopy and EUS are inconsistent.

METHODS TO ENSURE SAFETY

Preparation

The patient is instructed to avoid fiber-rich meals on the day before treatment and to drink a 10 mL bottle of picosulfate after dinner. A mixture of Niflec (Ajinomoto Pharma, Saitama, Japan) 2 L and 10 mL of Dimeticon (Kissei Pharmaceutical, Matsumoto, Japan) is used as the intestinal lavage on the day of treatment. The mixing of Dimeticon markedly reduces adhesive residues, which makes it easier to remove any remaining residues in the lumen.

Endoscopic system

For incision and dissection, an endoscope with as small a diameter as possible is recommended to obtain good maneuverability in the narrow lumen. We use a water-jet system-furnished, ultra-slim endoscope (outer diameter: 9.8 mm). Retroflex manipulation is necessary, especially at the oral end of large-sized lesions, and for lesions over a fold. Therefore, it is essential to use an endoscope whose diameter is as

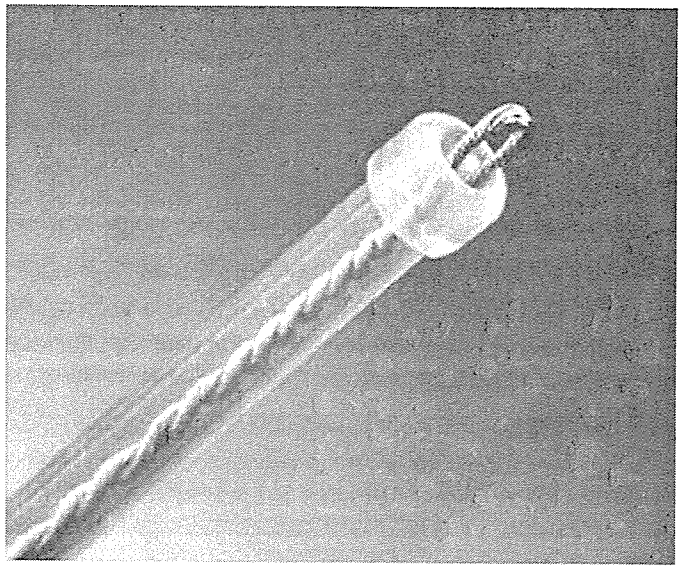

Fig. 1. Flex knife is the most suitable device for ESD of colorectal lesions.

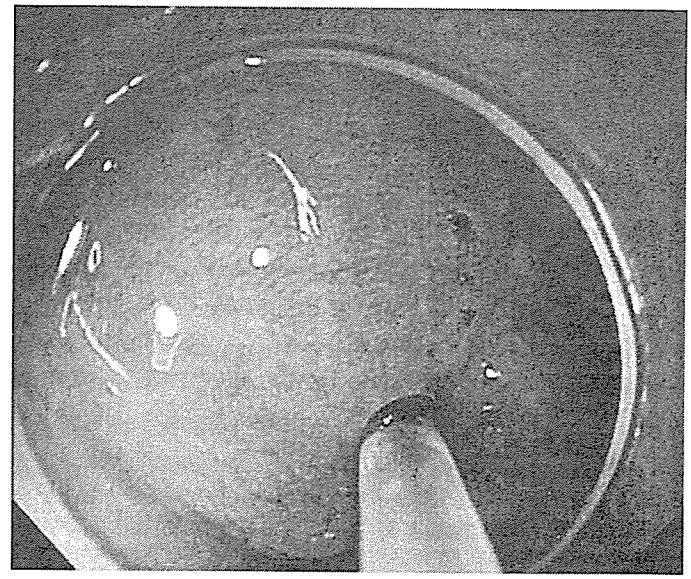

Fig. 2. Sufficient protrusion is necessary for mucosal incision and submucosal dissection.

small as possible and provides good operability. Furthermore, use of a transparent disposable attachment (Olympus, Japan) facilitates good visual field and allows stable dissection.

Operative instruments

A flex knife (Fig. 1), which is soft and flexible, is the best device for incision because it provides good operability.[3] The knife has a low risk of piercing the intestinal wall because it has a blunted tip, and is easy to handle because its length is adjustable according to circumstances. In cases when it is difficult to transmit the operator's force to the knife tip, or when the dissection site is very close to the muscle layer, the combined use of Flex knife and a hook knife[4] is very useful. Also, it is necessary to prepare hemostatic forceps (Pentax, Tokyo, Japan) and rotatable clip fixing devices (Olympus, Tokyo, Japan) ready to use at any time in case of bleeding and perforation, respectively.

High-frequency generator

ICC 200 or ICC 350 (ERBE, Tübimgen, Germany), which are furnished not only with the endocut modes for incision but also with multiple coagulation modes, are very useful. We use the generators according to the following rough standards: endocut mode, effect 2, 60 W for mucosal incision; forced mode, 40 W for submucosal dissection; and soft mode, 50 W for hemostasis.

Local injection solutions

It is essential to prevent perforation by forming a sufficient elevation when conducting mucosal incision and submucosal dissection. Among currently commercialized drugs, the solution of sodium hyaluronate[5,6] is considered most effective from the aspect of elevation-retaining profile. Artz (M.W.: 800 kDa, Kaken Pharmaceutical, Tokyo, Japan) and Suvenyl (M.W.: 1900 kDa, Chugai Pharmaceutical, Tokyo, Japan), which differ in molecular weight, are commercialized in Japan. These drugs are diluted with Glyceol (10% glycerin with 0.9% NaCl and 5% fructose, Chugai Pharmaceutical, Tokyo, Japan) to two and fourfold, respectively,[7] and a small volume of epinephrine and indigo carmine are added before use.

PROCEDURE OF ESD

Chromoendoscopy and submucosal injection

Indigo carmine is sprayed to clarify the margin of the lesion. Then, a submucosal local injection is conducted without marking, because the border between the tumor and normal tissue is quite clear in colorectal tumors. Local injection (1–2 mL per site) provides a precipitous elevation of sufficient height (Fig. 2). Because the elevation decreases when time passes, local injection is applied only at the site to be incised, and mucosal incision and submucosal dissection are conducted immediately.

Marginal incision and submucosal dissection

We usually use a Flex knife for both mucosal incision and submucosal dissection, because it is safe and easy to control. Positioning in such a manner that dissected tumor evaginates due to gravity frequently facilitates subsequent dissection. Therefore, it is desirable to initiate incision from the upper portion of the tumor while changing posture in consideration of gravity. The knife tip 1–2 mm long is sufficient (Fig. 3) and is gently applied to the elevated mucosa to conduct incision using the endocut mode, effect 2, 60 W (ICC200, ERBE). Then, submucosal dissection is performed immediately after the marginal incision (Fig. 4). We try not to make a circumferential incision at once, but proceed to submucosal dissection once a certain extent of the incision has been made. Submucosal fibers can be easily dissected by gently applying

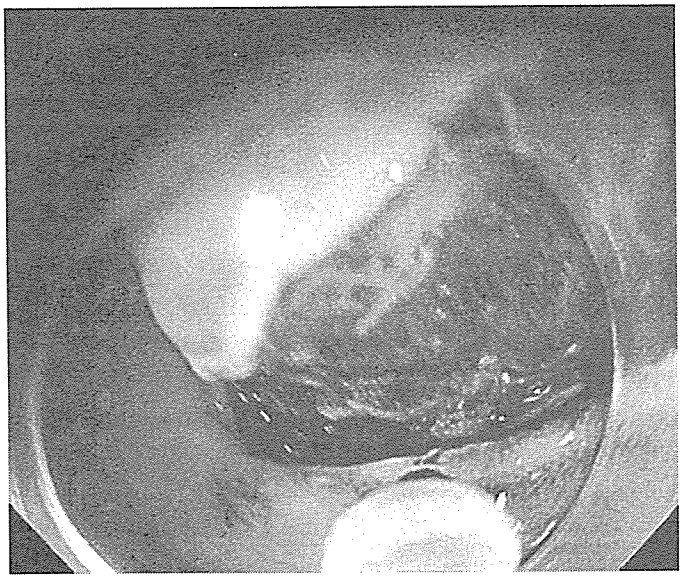

Fig. 3. The length of the knife tip is adjusted to 1–2 mm long.

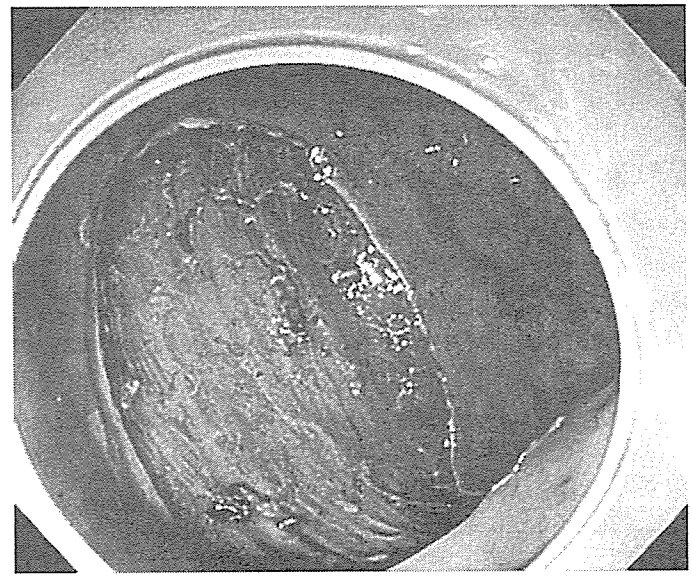

Fig. 5. En-bloc resection is completed without any complications.

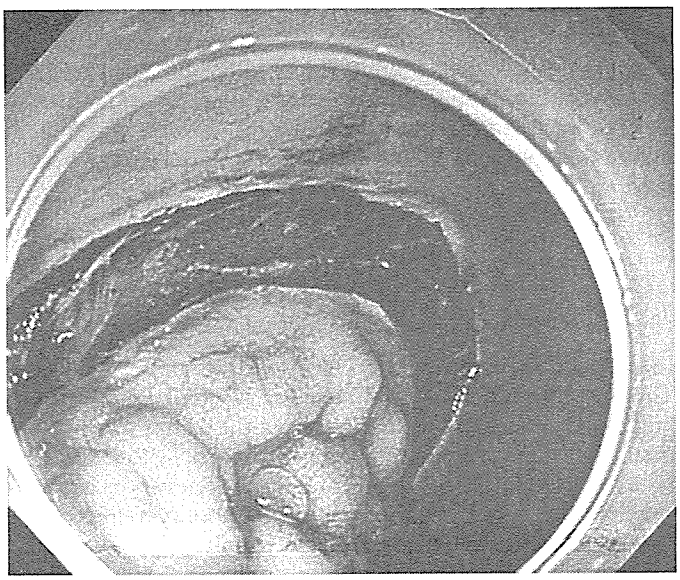

Fig. 4. Submucosa is exposed, after mucosal incision and submucosal dissection.

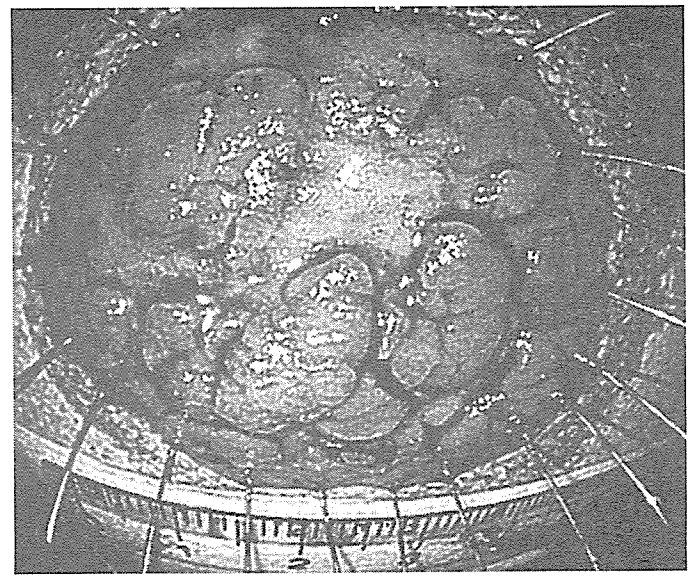

Fig. 6. Resected specimen, more than 4 cm.

the knife using the forced mode, 40 W, without changing the knife length. It is important to be aware of the direction of lumen, and to manipulate the device as parallel as possible with the intestinal wall, to prevent perforation.

Tumor resection and treatment of postoperative wound

If the tumor is of a size or in a location to allow snaring, it should be conducted once a certain amount of the dissection has been made. If the tumor is too large to be included in a snare or lies over folds, dissection of the submucosa should be continued until completion in order to conduct *en-bloc* resection (Figs 5 and 6) and the resected area should be carefully observed after resection. If there is an exposed blood vessel, it should be pinched gently with hemostatic forceps, and coagulated using the soft coagulation mode. There is no need to suture the resected area with clips or other instruments. Even an artificial ulcer, which is as large as 10 cm in diameter, mostly becomes a scar and heals within 8 weeks without causing complications.[8]

INDICATIONS AND EVALUATION CRITERIA FOR ESD

Endoscopic submucosal dissection is applicable to almost all lesions if they exist within the mucosa. However, ESD involves some risks due to its technical features and also takes time. Therefore, a lesion, which is resectable *en bloc* by

polypectomy or EMR, should be treated according to conventional procedures. The strict indications that ESD should be performed are: lesions that are difficult to resect in an *en bloc* fashion by conventional procedures, but require a precise histopathologic evaluation; depressed lesions, such as IIc legions; or LST-NG. Lesions with biopsy-inducted scars, lesions on haustra or at angulations of the colon, and large-sized lesions where *en-bloc* resection is impossible by conventional procedures, are also indications for ESD.

If resection reveals an intramucosal cancer, or even if histopathologic evaluation reveals minor submucosal invasion, the risk of lymph node metastasis is considered to be very low if the local invasion extent is under 1000 μm, the invading part of the tumor is highly differentiated, and no budding is observed. Therefore, in such patients, we consider the treatment to have been radically curative and monitor them for postoperative course with informed consent.

RESULTS

One hundred and forty-six colorectal lesions were treated by ESD between July 2000 and July 2004 at our institution. Mean tumor size was 35.8 mm (6–109 mm). 133 lesions were resected in single pieces and the *en-bloc* resection ratio was 92%. Another 13 lesions resected in a piecemeal fashion but were completely resected. Among them, 127 lesions (87%) were judged to be radically curative by histopathological evaluation. Two patients had vascular infiltration or massive submucosal invasion of more than 1000 μm and underwent operations. Because of diathermic effect, the lateral margin was unclear in four patients and they were followed endoscopically. No recurrent tumor was found in the patient treated in an *en bloc* fashion but one recurrent tumor was found in a patient treated by piecemeal resection. This recurrent lesion, sized less than 5 mm, was judged to be mucosal lesion and abraded with APC.

CONCLUSION

ESD is a procedure that allows us to conduct a reliable *en-bloc* resection even for a depressed or large-sized lesion, and we consider that this procedure is splendidly suited to the successful treatment of early stage colorectal cancer. EUS is also helpful in confirming the depth of invasion when the lesion is suspected to have submucosal invasion. 3D-EUS is also useful in getting the perspective of a lesion that is located on a fold.

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Digestive Endoscopy (2006) **18**, 79–83 doi:10.1111/j.0915-5635.2006.00588.x

REVIEW

NODULAR GASTRITIS AND GASTRIC CANCER

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Nodular gastritis is defined as antral gastritis usually characterized endoscopically by a miliary pattern resembling gooseflesh and pathologically by prominent lymphoid follicles and infiltration of mononuclear cells. This physiological phenomenon was once considered particular to young women. Recent studies have shown that nodular gastritis is strongly associated with *Helicobacter pylori* infection and may be associated with gastric cancer. Reported cases of gastric cancer with nodular gastritis showed some features in common: all gastric cancers were diagnosed histologically as the diffuse-type, and all were located in the corpus with *Helicobacter pylori* infection. Because nodular gastritis may be a risk factor for diffuse-type gastric cancer, *Helicobacter pylori* may need to be eradicated to prevent gastric cancer in patients with nodular gastritis.

Key words: eradication, gastric cancer, *Helicobacter pylori*, nodular gastritis.

INTRODUCTION

Nodular gastritis was first described as the 'gooseflesh phenomenon' and was considered a physiological phenomenon particular to young women.[1] Nodular gastritis, a particular type of gastritis, is now defined as antral gastritis and is mainly characterized endoscopically by an unusual, small granulated pattern.[2–4] The histological features of nodular gastritis are hyperplasia of lymphoid follicles with germinal centers in the proper lamina of the stomach.[2,3] Since the discovery of *Helicobacter pylori* (*H. pylori*), several studies have shown nodular gastritis to be strongly associated with *H. pylori* infection, not only in children[2–11] but also in adults.[11–15]

The death rate associated with gastric cancer has decreased throughout the world, but gastric cancer remains the most common malignancy in Japan. Before the discovery of *H. pylori*, it was generally accepted that histological gastritis including atrophic gastritis and intestinal metaplasia could be important in the pathogenesis of gastric cancer in older patients. Since the discovery of *H. pylori*, strong evidence has accumulated that *H. pylori* infection plays an important role in the pathogenesis of chronic gastritis, peptic ulcer, and gastric cancer.[16–19] Hassall and Dimmick[7] reported that nodular gastritis was closely associated with duodenal ulcer. Additionally, recent studies[13,14] showed that nodular gastritis with *H. pylori* infection might be associated with diffuse-type gastric cancer of the corpus.

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Received 9 September 2005; accepted 7 November 2005.

HISTORY OF NODULAR GASTRITIS

The first report of nodular gastritis in Japan was that of Takemoto and Mizuno in 1962.[1] They observed extensive marked granulation resembling gooseflesh on gastric camera images obtained from a 20-year-old woman who underwent gastric surgery. The patient did not show atrophic changes with insufficient gastric wall stretch during rigid endoscopy because of severe mental tension. Takemoto and Mizuno described the appearance as the 'endoscopic gooseflesh phenomenon'.[1] In 1985, Miyagawa *et al.*[20] examined 21 patients with 'gooseflesh-like gastric mucosa' and reported that this change was frequently observed in young women, upper abdominal pain was observed in 50% of patients and, histologically, hyperplasia of the crypt epithelium and formation of lymph follicles were frequently observed. Miyagawa *et al.*[20] also suggested that the phenomenon could be due to an overreaction in the local gastric mucosa because formation of lymph follicles was marked, and thus, histologically, they considered it to be follicular gastritis. In 1987, Konishi *et al.*[21] referred to the phenomenon 'gooseflesh-like gastritis', but neither Miyagawa *et al.* nor Konishi *et al.* discussed the relationship with *H. pylori* infection in their reports.

Internationally, there have been reports discussing the relationship between nodular gastritis and *H. pylori* infection since the late 1980s. In 1986, Czinn *et al.*[2] described endoscopic features of *H. pylori*-related gastritis in five young children as those of nodular antral gastritis. In 1988, Eastham *et al.*[3] described the phenomenon as antral nodular hyperplasia and confirmed histopathologically that it was due to hyperplasia of lymph follicles in the mucosa itself. They also reported alleviation of symptoms by eradication therapy. In 1990, Bujanover *et al.*[6] referred to the phenomenon as nodular gastritis, and Conti-Nibali *et al.*[10] found that 14 (88%) of 16 young children with this condition, which they called nod-

ular antritis, were *H. pylori* positive. In 1996, Sbeih *et al.*[11] called it antral nodularity and reported that it was observed not only in young children but also in adults and that in five patients who underwent successful *H. pylori* eradication, endoscopic and histological findings improved. Thus, nodular gastritis is called by a variety of names. In the updated Sydney system,[22] the international classification of gastritis, nodularity is described as an endoscopic finding, but it is currently not included as a diagnostic classification for gastritis.

CLINICAL CHARACTERISTICS OF NODULAR GASTRITIS

Miyamoto *et al.*[12] reported that nodular gastritis was observed in 187 patients (0.19%) among 97 262 patients aged 16 years or older who underwent upper gastrointestinal endoscopy. Patients were usually in their twenties or thirties, the ratio of male to female patients was 1 : 2.8, and all patients were *H. pylori* positive with histological hyperplasia of lymph follicles. In addition, they reported that peptic ulcer occurred in 22 of the 187 patients, gastric cancer in two, and mucosa-associated lymphoid tissue as a complication in one. Symptoms such as abdominal pain or abdominal discomfort were observed in 151 (81%) of the 187 patients, but these symptoms and endoscopic findings were clearly improved by eradication of *H. pylori*. In their report, serum pepsinogen I and II and gastrin concentrations were significantly higher in patients with nodular gastritis than in *H. pylori*-positive control subjects, whereas the pepsinogen I/II ratio was significantly lower in patients than in control subjects (Fig. 1).[12] In addition, Shimatani *et al.*[15] showed that marked mononuclear cell and neutrophil infiltrations but no apparent glandular atrophy were observed in both the antrum and corpus of patients with nodular gastritis. They also showed that the serum pepsinogen I/II ratio was significantly lower in patients with nodular gastritis than in normal subjects or in patients with antrum-predominant gastritis, whereas the serum gastrin concentration was significantly higher in patients with nodular gastritis than in normal subjects, patients with antrum-predominant gastritis, or patients with pangastritis.

A typical endoscopic image of nodular gastritis is shown in Fig. 2a. Antral nodularity is highlighted after a dye spraying with indigo carmine solution (Fig. 2b). Histological examination of a biopsy specimen of antral nodularity shows intense inflammatory cell infiltration with a large, superficial-located lymphoid follicle (Fig. 2c).

ASSOCIATION BETWEEN NODULAR GASTRITIS AND GASTRIC CANCER

Helicobacter pylori infection plays an important role in the pathogenesis of gastric cancer. Uemura *et al.*[23] reported that during 8 years of follow up, gastric cancer developed in 36 of 1246 *H. pylori*-infected patients (2.9%) but that it did not develop in any of 280 uninfected patients. They estimated the risk of gastric cancer in *H. pylori*-positive patients to be about 5% at 10 years. Haruma *et al.*[24] showed that *H. pylori* infection was strongly associated with gastric cancer and atrophic gastritis and that it might contribute to the pathogenesis of gastric cancer in young patients.

Even though a close relationship between nodular gastritis and duodenal ulcer is reported,[7] a relationship between nodular gastritis with *H. pylori* infection and gastric cancer has been previously reported only by Miyamoto *et al.*[13] and Kamada *et al.*[14] In their reports,[13,14] six cases of gastric cancer with nodular gastritis showed the same characteristics: all gastric cancers were diagnosed histologically as the diffuse-type and were located in the corpus with *H. pylori* infection (Figs 3,4). However, the pathophysiology of nodular gastritis and the exact mechanisms of the associated gastric tumorigenesis remain unclear. Shimatani *et al.*[15] reported that gastric acidity was significantly reduced in patients with nodular gastritis in comparison to control subjects, as measured by 24-hour intragastric pH-metry. They speculated that inflammatory cytokines or *H. pylori*-infection-induced prostaglandins might strongly inhibit gastric acid secretion in patients

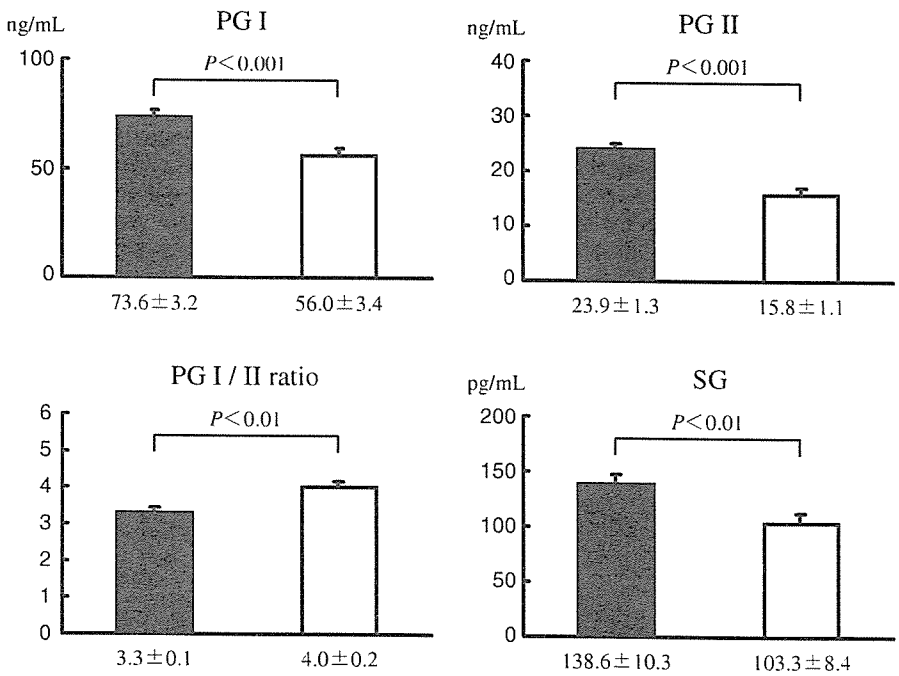

Fig. 1. Serum concentrations of pepsinogens and gastrin in patients with NG and *H. pylori*-positive controls. NG, nodular gastritis; PG, pepsinogen; SG, serum gastrin. Results are expressed as mean ± standard error. ■, Nodular gastritis; □, control.

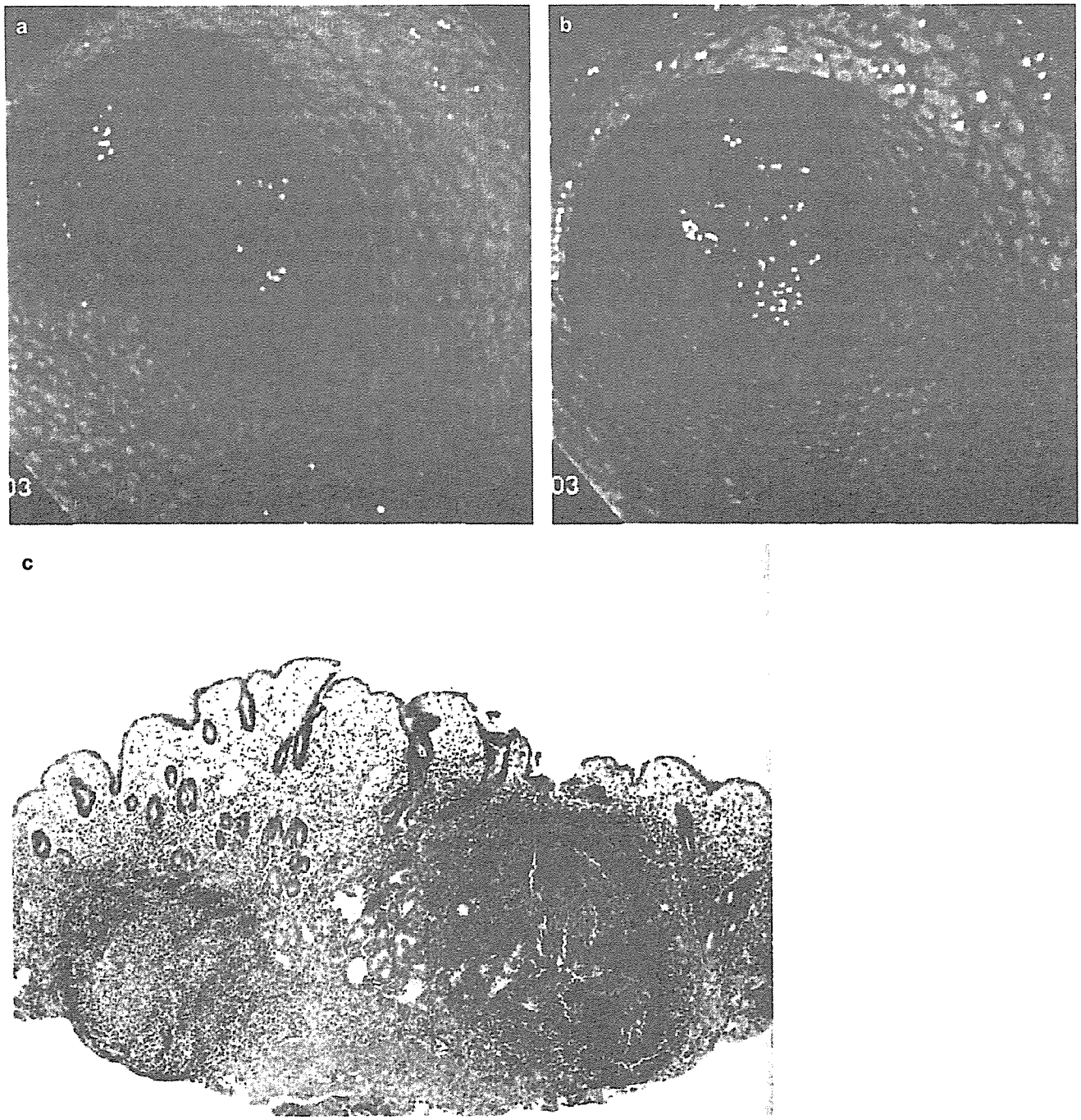

Fig. 2. (a) Endoscopic examination showed an unusual miliary pattern resembling 'gooseflesh' in the antrum. (b) Antral nodularity is highlighted after a dye spraying with indigo carmine solution. (c) Histological examination of a biopsy specimen of an antral nodularity showed intense inflammatory cell infiltration with a large and superficial-located lymphoid follicle (hematoxylin and eosin, × 100).

with nodular gastritis. In addition, they suggested that nodular gastritis should be considered a particular type of pangastritis, which itself is strongly related to diffuse-type gastric cancer. Because nodular gastritis may be associated with diffuse-type gastric cancer in the corpus, endoscopists need to examine carefully not only the antrum but also the corpus.

Recent studies have shown that *H. pylori* eradication might contribute to the chemoprevention of gastric cancer. Uemura *et al.*[25] showed that *H. pylori* eradication improved neutrophil infiltration and intestinal metaplasia in the gastric mucosa and inhibited the development of new carcinomas after endoscopic resection of gastric cancer. Correa *et al.*[26] showed in a very high-risk population that anti-*H. pylori* treatment might interfere with the precancerous process and might be an effective strategy in preventing gastric carcinoma. Wong *et al.*[27] showed that eradication of *H. pylori*