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

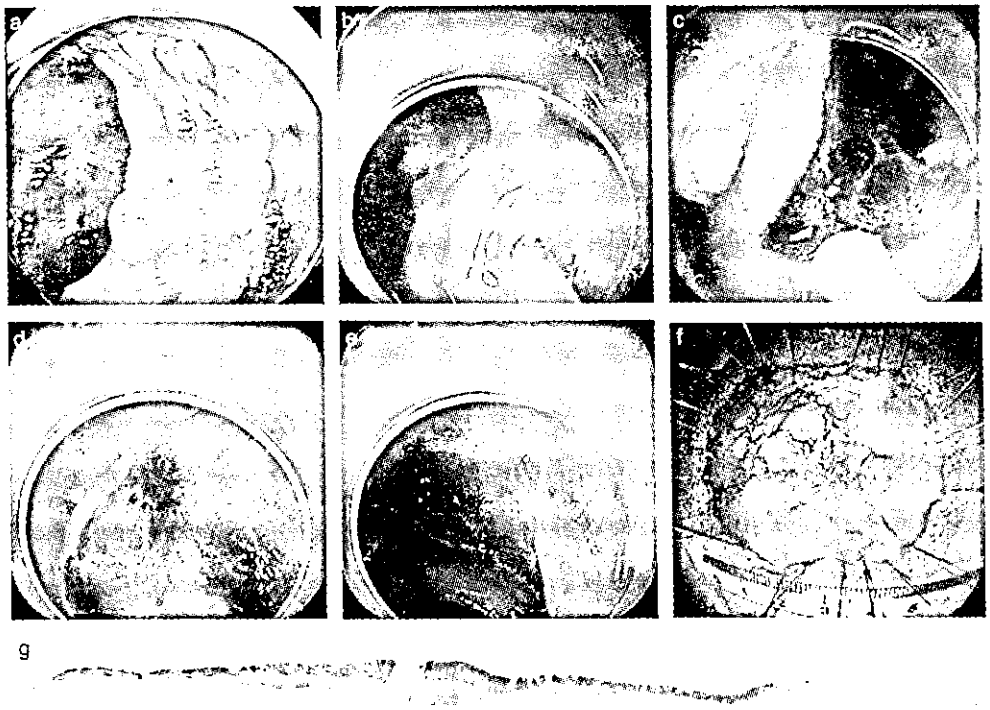

Fig. 2. A case of LST in the ascending colon. (a) After spraying indigocarmine dye, a laterally spreading tumor, granular type (LST-G) is clearly recognaized. (b) Submucosal injection of sodium hyaluronate and glyceol® with a small amount of indigocarmine and epinephrine is made. (c) Submucosa is dissected 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.

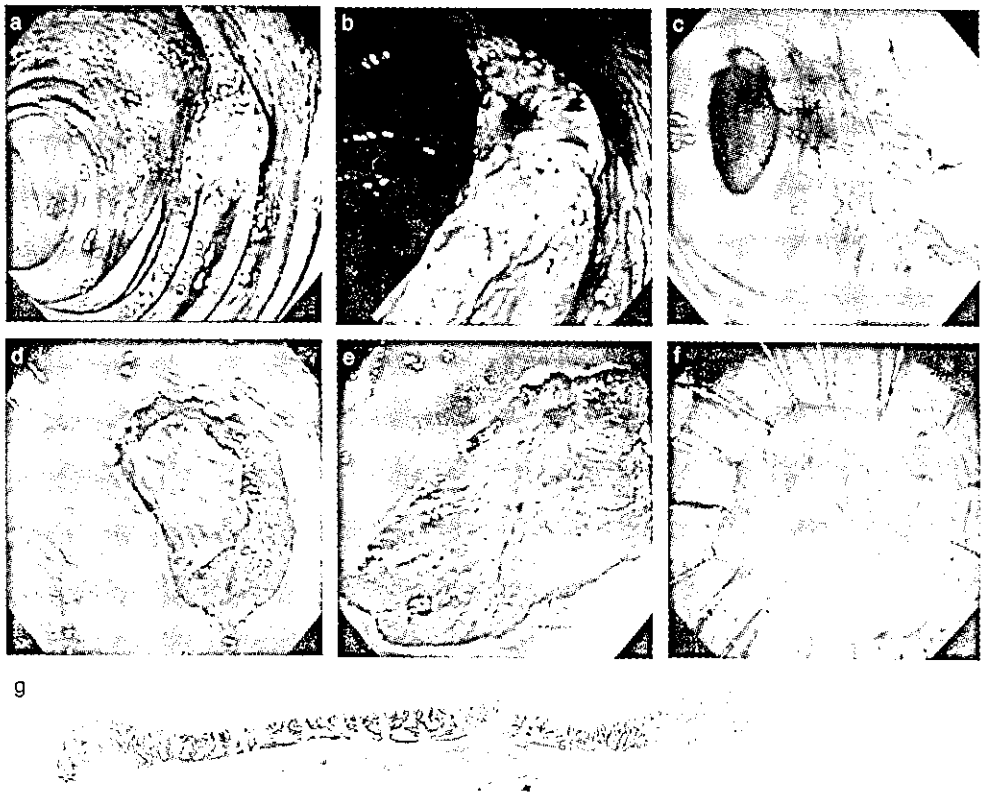

Fig. 3. A case of small IIc lesion in the sigmoid colon. (a) After spraying indigocarmine dye, small IIc lesion is clearly recognized. (b) Close view of the lesion. (c) After submucosal injection, precipitous elevation is not obtained. (d) Marginal incision and submucosal dissection is made by Flex knife®. (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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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).

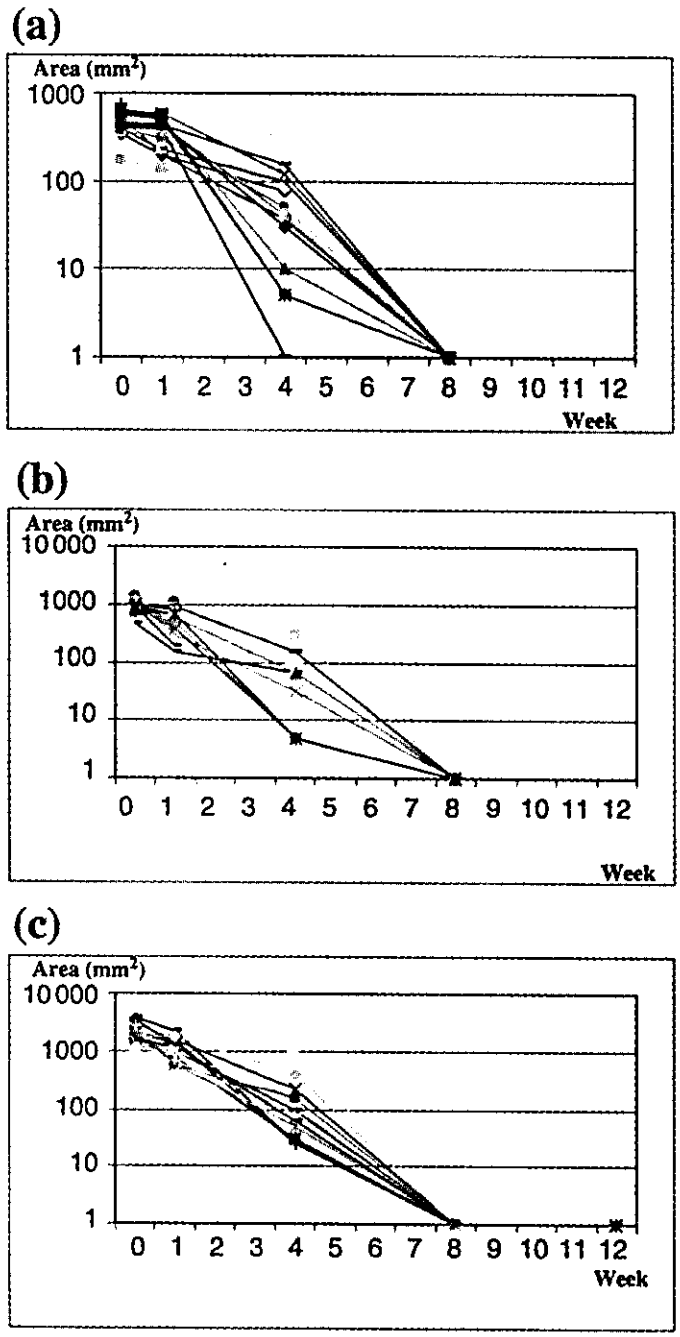

Fig. 1. Change of ulcer size after endoscopic submucosal dissection (ESD). Patients were divided into three groups by the primary ulcer diameter (d). (a) $20 \leq d < 30$, $n = 29$; (b) $30 \leq d < 40$, $n = 23$; (c) $d \geq 40$, $n = 18$.

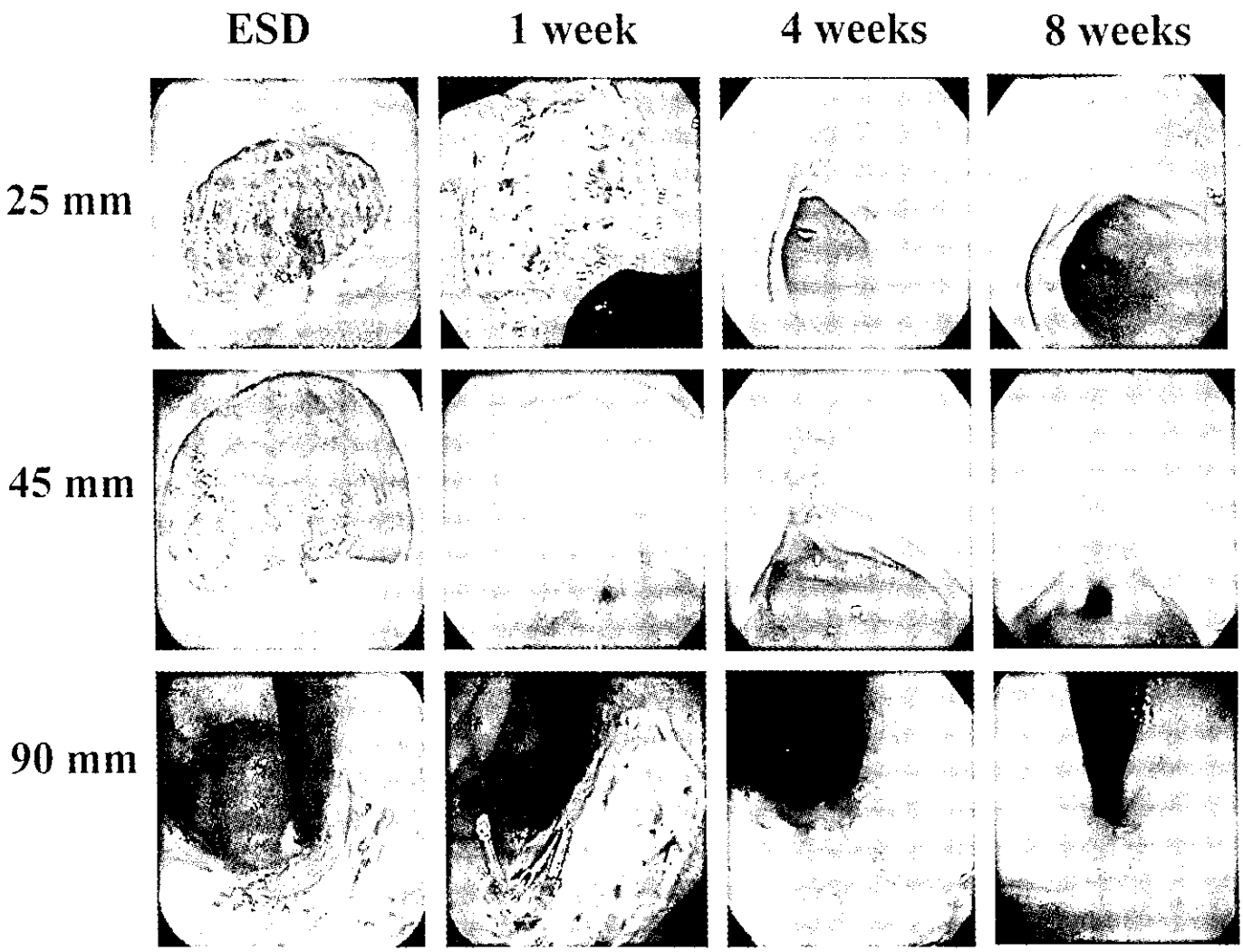

Fig. 2. Chronological endoscopic observation of three sizes of post-endoscopic submucosal dissection (ESD) ulcers (25, 45 and 90 mm). At 4 weeks, the ulcer size is remarkably reduced, and regenerative mucosa has appeared only to connect the surrounding mucosa like a zipper.

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

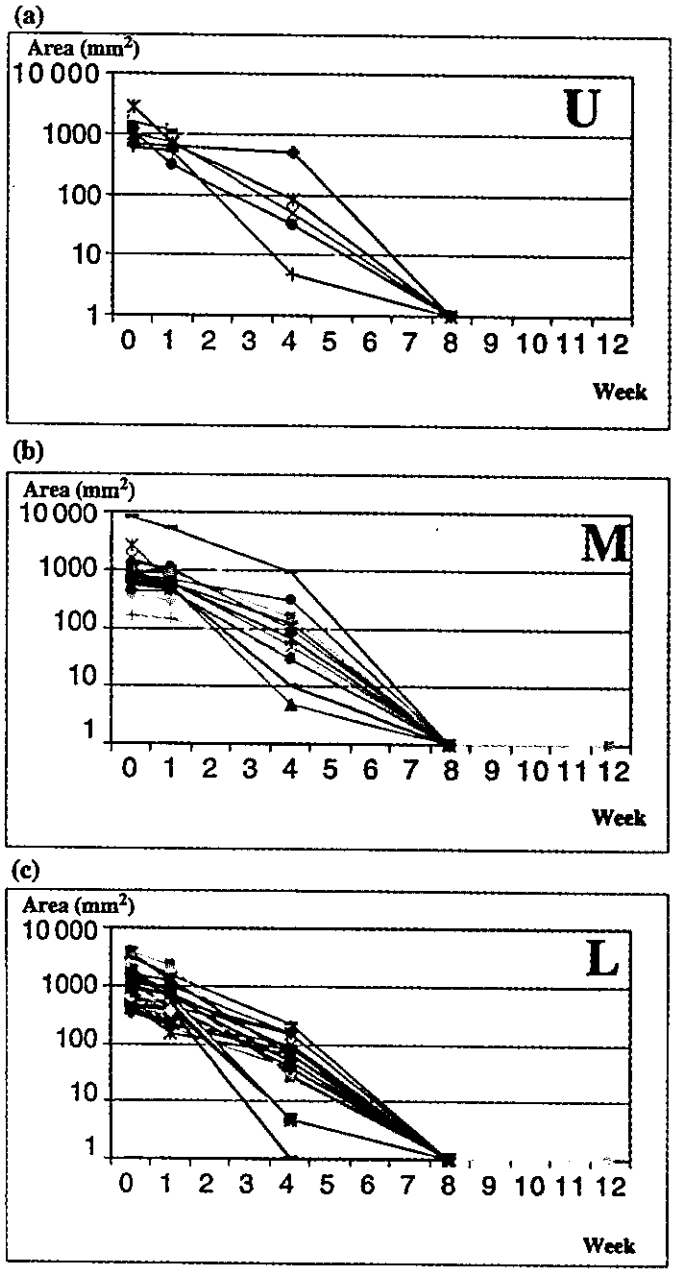

Fig. 3. Change of ulcer size after endoscopic submucosal dissection (ESD) according to location. (a) Upper (U), $n = 8$; (b) Middle (M), $n = 24$; (c) Lower part of the stomach (L) $n = 38$.

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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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

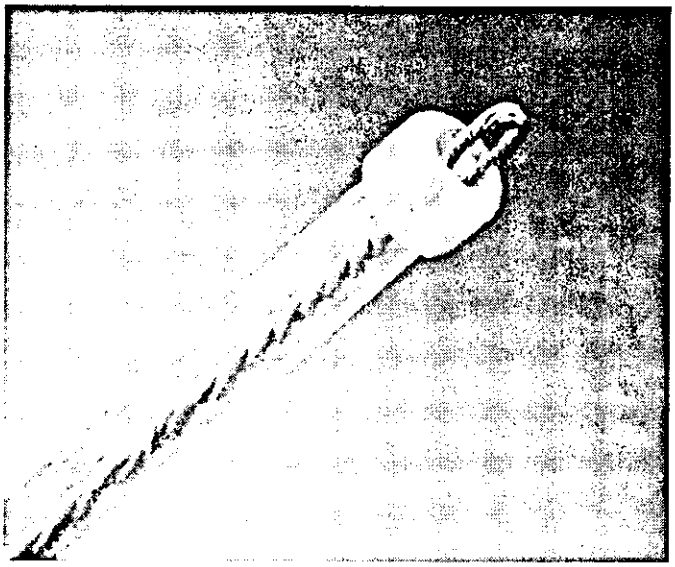

Fig. 1. Flex knife is the most suitable device for ESD of colorectal lesions.

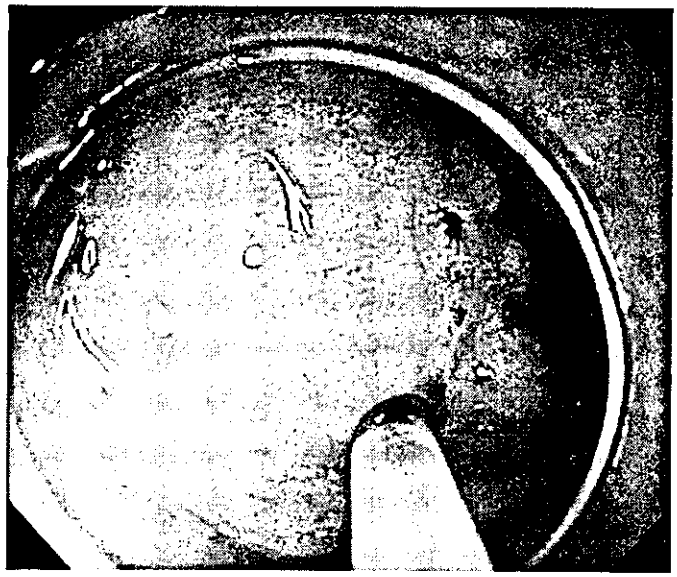

Fig. 2. Sufficient protrusion is necessary for mucosal incision and submucosal dissection.

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

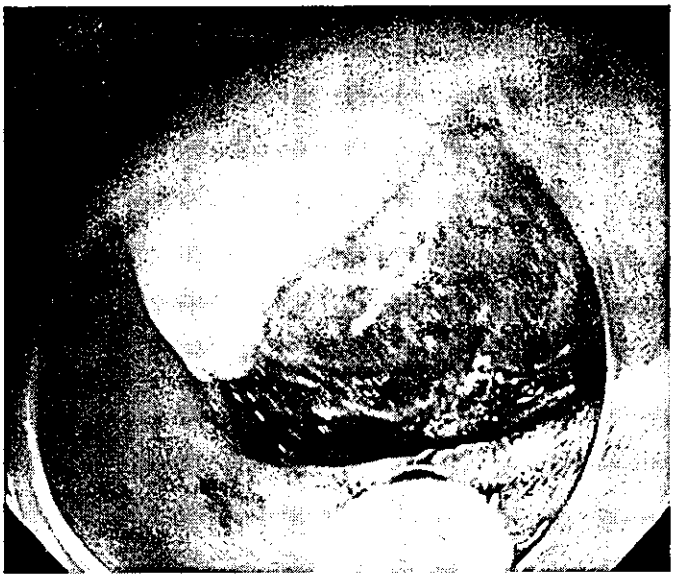

Fig. 3. The length of the knife tip is adjusted to 1–2 mm long.

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

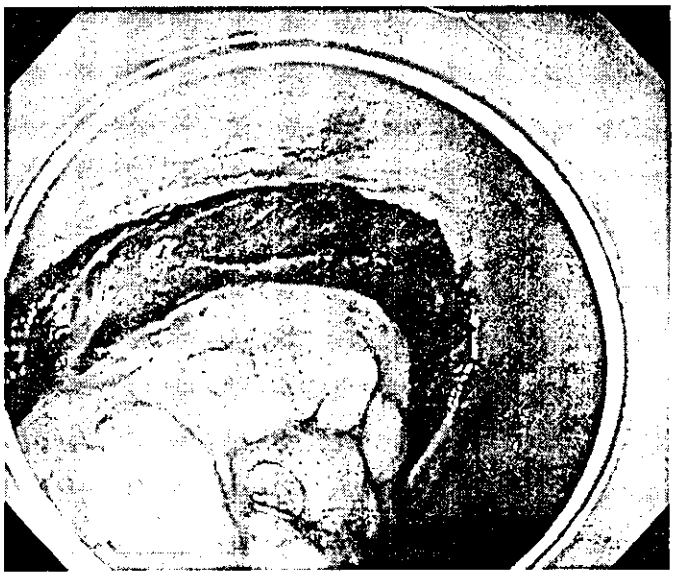

Fig. 4. Submucosa is exposed, after mucosal incision and submucosal dissection.

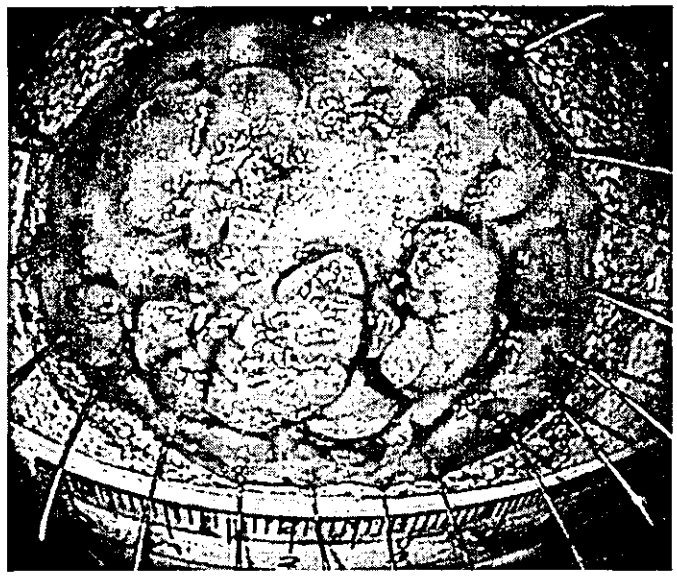

Fig. 6. Resected specimen, more than 4 cm.

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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【原 著】

葛飾区におけるペプシノゲン2段階法による住民胃がん検診3年間の評価

Evaluation of Two-step Gastric Cancer Detecting Program Using Serum Protein Test for People in Katsushika Ward in Tokyo from 2000 to 2003

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要 旨

葛飾区では、節目年齢（40，45，50，55歳）の住民を対象に平成12年度からペプシノゲン2段階法胃がん検診を実施してきた。これまでの3年間の成績をまとめ検討する。本検診の受診者総数は13,705人で、全体の胃がん発見率は13人0.095％で、早期胃がんは11人で早期胃がん率は84.6％と高かった。このうちペプシノゲン（以下PG）陽性がんは11人、PG陰性がんは2人であった。本検診におけるPG陰性がんの発見率はX線検査受診者（6,483人）の0.031％で、陽性反応適中度は0.33％であった。地域住民の胃がん検診においてもPG2段階法は、PG法とX線法を相補って胃がん発見に寄与していると思われる。一人当たり1次検診コストはX線単独法の比して低いが、それほど大きな差はなかった。老人保健法対象人口に対する受診率は28.9％であった。

キーワード：胃がん検診 ペプシノゲン法 2段階法

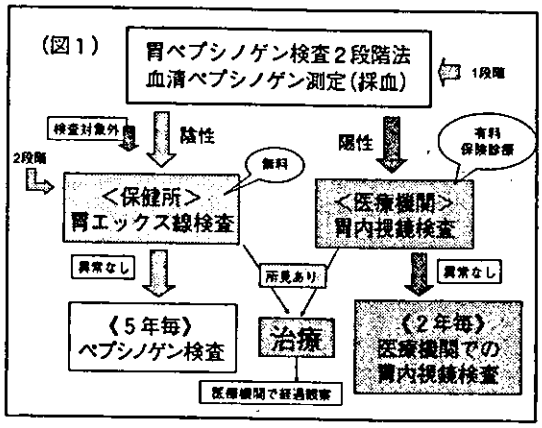
Key Words：Gastric cancer screening pepsinogen test two-step program

[目 的]

総人口約43万の葛飾区では、平成12年度から、壮年者の節目健診に併せてペプシノゲン2段階法による胃がん検診を実施してきた。平成14年度まで3年間の成績をまとめ、胃がん発見状況、現時点での本法の検診コスト、対象者に対する検診カバー率及び課題等について検討する。

[対象と方法]

検診の対象と方法は、既に詳細に述べている[1]のでその要旨を記載する。節目健診においては、40歳、45歳、50歳及び55歳の節目年令の区民全員に健診通知を発送する。健診希望者は保健所に申し込み、保健所及び保健センター(計6ヵ所)で健診を受ける。この際採取した血液サンプルは民間の検査機関に送付しエンザイムイムノアッセイ(EIA)法により血清ペプシノゲン(以下PG)の測定を行う。PG値の判定基準はPGⅠ値70ng／ml以下且つⅠ／Ⅱ比3.0以下を陽性とし、PG陽性者には医療機関で胃内視鏡検査を勧め、PG陰性者には保健所直営の胃X線間接撮影を勧める。さらにPG陽性者には、2年後に管理健診の通知を発送し、受診勧奨を行っている(図1)。検診コストについては、区職員人件費を除いた胃がん検診に要する総コスト(胃がん検診車の維持管理費、X線撮影に要するフィルム、造影剤等消耗品費、葛飾区医師会への撮影フィルム読影委託、PG検査委託料、返信料を含む諸通信費及び臨時職員の人件費)を積算し、1人当たりの経費及び1次検診での1胃がん発見費用を算出した。検診カバー率は、平成12年度に東京都が行った検診対象人口の調査[2]をもとに算出した。



[結　果]

平成12年度から3年間の胃がんの発見状況は、PG検査受診総数13,705人中発見数13人、内早期胃がん11人で発見率は0.095％(早期胃がん率84.6％)であった(表1)。これをPG陽性群とPG陰性群別に見ると、陽性群では胃がん11(内早期胃がん9)、陰性群では2(内早期胃がん2)であった(表2)。PG陽性者の精検受診率は4年齢平均67.8％(66.0～70.1％)で、胃がん発見率は0.08％、陽性反応適中率は0.53％であった。一方PG陰性者の胃X線検査実施状況は、要精検率は14.9％、受診率57.2％、医療機関での精検受診率は62.6％であった。なお、12年度受診者のフォローの管理検診を14年度に実施したが、受診率はPG陽性者の22.3%で、胃がん発見はなかった。発見された胃がんの自覚症状、手術所見、治療法、術前術後の病期比較を一覧表に示した(表3)。本検診で発見されたPG陰性胃がんは2例とも未分化型早期がんであった。胃がん検診に要する費用では、平成12,13,14年3年間の一般公募による胃X線 単独法と2段階PG法に要したそれぞれの総コストを算出し、検診受診者1人当たりの1次検診コストを見ると、X線単独法では2,680円、2

(表1)　胃がん発見状況

墓飾区

平成年度	PG法受診者数	胃がん（早期）人		
		PG陽性	PG陰性	計
12	4,577	6(5)	1(1)	7(6)
13	4,476	4(3)	0(0)	4(3)
14	4,652	1(1)	1(1)	2(2)
計	13,705	11(9)	2(2)	13(11)

胃がん発見率　0.095%

(表2) 胃がん検診3年間の成績

(墓飾区・平成12,13,14年度)

ペプシノゲン法(PG法)陽性者

年齢	健診対象者(人)	PG法受診者(人)	PG法陽性者(人)	PG法陽性率(%)	精検受診者(人)	精検受診率(%)	がん(早期)(人)
40	17,388	4,156	524	12.6	358	68.3	2 (2)
45	15,346	2,704	526	19.5	369	70.1	1 (0)
50	18,368	3,493	898	25.7	615	68.5	2 (2)
55	17,921	3,352	1,103	32.9	728	66.0	6 (5)
計	69,022	13,705	3,051	22.3	2,070	67.8	11 (9)

発見率：0.08%　陽性反応適中度0.53%

ペプシノゲン法(PG法)陰性者

年齢	PG法受診者(人)	X線対象者(PG陰性者)(人)	胃X線受診者(人)	X線受診率(%)	精検対象者(人)	精検受診者(人)	精検受診率(%)	がん(早期)(人)
40	4,156	3,975	2,231	56.1	303	193	63.7	0 (0)
45	2,704	2,245	1,310	58.4	197	126	64.0	0 (0)
50	3,493	2,771	1,490	53.8	240	153	63.8	0 (0)
55	3,352	2,341	1,452	62.0	216	126	58.3	2 (2)
計	13,705	11,332	6,483	57.2	956	598	62.6	2 (2)

発見率：0.03%　陽性反応適中度 0.33%

(表3)　発見胃がん一覧

平成年度	No	年齢性別	PG法判定	自覚症状	手術所見 肉眼型	組織型	深達度	占拠部位	治療法	病期 内視鏡	病期 手術後
12	1	40 F	陽性	なし	IIc+IIa	por	sm	幽門部小弯	胃切除	早期	早期
	2	45 F	陽性	あり	IIc+III	sig por	mp	体上部前壁	胃切除	早期	進行
	3	50 M	陽性	なし	IIc	tub2	m	幽門部小弯	胃切除	早期	早期
	4	55 M	陽性	なし	(A)IIc (B)I	tub1	sm	(A)幽門部前壁 (B)体上部後壁	胃切除	早期	早期
	5	55 M	陽性	なし	IIc	tub2	m	幽門部大弯	胃切除	早期	早期
	6	55 M	陽性	なし	(A)IIc (B)IIc	(A)tub1 (B)por	(A)m (B)srg	(A)体部前壁 (B)体部後壁	胃切除	早期	早期
	7	55 F	陰性	あり	IIc	sig por	m	幽門部大弯	胃切除	進行	早期
13	8	40 F	陽性	なし	IIa	tub2 tub1	m	胃角部前壁	胃切除	早期	早期
	9	50 F	陽性	なし	IIb+IIc	tub2	sm	幽門部大弯	胃切除	早期	早期
	10	55 M	陽性	あり	Borr3	por	se	体部前庭部	胃切除	進行	進行
	11	55 F	陽性	なし	IIc	tub2	m	体中部前壁	胃切除	早期	早期
14	12	55 M	陽性	なし	IIc	tub2	m	小弯前壁	胃切除	早期	早期
	13	55 M	陰性	なし	V	sig por	sm	体中部後壁	胃切除	早期	早期

段階PG法では2,070円であった。1胃がん発見コストは、PG法導入前の3年間の同節目年令のX線単独法による胃がん発見数を用いて比較すると、271万円(X線)、218万円(PG)、1早期胃がん当りそれぞれ301万円、258万円であった(表4)。当区における検診対象人口に対する胃がん検診のカバー率は、平成14年度において、PG法及び一般公募によるX線法胃がん検診受診者の合計で見ると40歳以上の老健法対象人口の5.1％で、PG法では、4区分の節目年令では対象者の28.9％を占めていた。

(表4)　胃がん検診の費用

■検診単価（平成12,13,14年度）

2段階PG法　2,070円／人　節目年齢13,705人受診　PG検査委託
X線単独法　2,680円／人　一般公募7,774人受診　読影委託

■1胃がん発見コスト（節目年齢）

	受診数（人） 胃がん（早期）	1次検診費用（万円） 胃がん（早期）
X線単独法 (平成9,10,11)	12,571 10 (9)	271 (301)
2段階PG法 (平成12,13,14)	13,705 13 (11)	218 (258)

[考　察]

本検診では、40歳から55歳までの各節目年令において胃がんが発見されている。ペプシノゲン法による胃検診は、早期胃がんの発見を目的として行われるが、葛飾区における3年間の成績でも、PG陽性胃がんでは早期がんが81.8％と高率であった。一方、進行胃がんがPG陰性を示す場合が多いことから、PG陰性者には胃X線検査を行うことが推奨されている[3]。本区で実施した2段階の胃X線撮影では2例のPG陰性がんが発見された。これらは、肉眼的に進行がん様であったが、1例は無症状、1例は胃部痛を訴えていた。病理組織学的所見ではいずれも未分化型早期胃がんで、早期がんの拾いあげにも有効であった。このように住民検診における2段階PG法による胃がん検診は、現時点ではPG法とX線法の限界を相補い合い胃がんの発見効率を高めていると思われる。次に、PG法を導入した平成12年度から年次ごとの胃がん発見数を見ると、順に7(内PG陰性がん1名)、4名、2(内PG陰性がん1名)とPG陽性がんの発見が減少傾向にある。我が国の胃がん罹患率は減少しつつあることが示されているが[4]、地域で短期間に同様な傾向をとるとするのは無理があると思われる。しかし、検診の対象集団の質、検診方法、受診率等に変更がないので、この減少傾向は一過性のものか、あるいは胃がん罹患数の減少傾向の影響を受けているのか、内視鏡読影上の精度管理を進めつつ、今後の推移をみて検討が必要と思われる。また、X線検査における要精検率が14.9％と高く、15年度より高濃度低粘張性バリウムを使用した新撮影法を[5]導入し、要精検者の絞込みを図ることとした。次に、検診コストであるが、行政としては、先ず1人当たりの所要経費が問題となる。葛飾区においては、2段階PG胃がん検診の他に30歳以上の区民を対象とした公募方式によるX線単独法による胃がん検診を実施している。両方式の胃がん検診の一人当りの経費は2段階法が低額であるが差はそれ程大きくなかった。さらに、他地域(足立区、高崎市及び熊本県)の例にならって[6]、1胃がん当たりの1次検診コストを、PG検査導入前の平成9,10,11年に同じ節目年令対象者に実施していたX線単独法による胃がん検診の成績を用いて算出し比較すると、2段階PG法が低コストであった。この値はPG単独法を採用している他地域より2.5～4.5高い。しかし、1胃がん発見に要する経費は、検診方法あるいは発見胃がん数に大きく左右され、さらに、発見胃がん数は集団の年令構成、男女比、内視鏡の検出力等に大きく影響される。上記の3地域においては、対象者に60歳節目、あるいはより高齢者群を含んでいるので、55歳以下を対象とする葛飾区との比較は困難である。1胃がん発見コストは、当該地域で採用した検診方法が従来法のX線単独法に比してどの程度かを知る目安を意味するものであろう。とは言え、行政検診においては1人でも多くの早期がんを発見し、1人当たりのコストを下げることは重要である。葛飾区においては検診対象を胃がん罹患率がより高い60歳節目へと拡大することも必要と思われた。最後に、検診対象のカバー率であるが、東京都は区部を含めた全都の調査を昭和60年から5年ごとに実施し、平成13年2月に4回目を実施している。この調査から得られた胃がん検診の対象人口率は40歳以上人口の68.9％であった。対象人口率で補正した検診対象者を真の検診対象者とするならば、葛飾区における2段階胃がん検診受診者の真の対象者に対する受診率は28.9％であった。40歳以上の検診カバー率については、PG陽性者のフォロー検診実施者は2年間、PG陰性者で胃X線検査受診者は5年間継続受診者とみなすことが可能なので、実体的にはさらに高いものと考えられる。一般に、対象集団の30％以上が受診するとがん死亡の減少が期待できるとされているので、受診率をさらに上げることにより当該年令の胃がん死亡の減

少が期待できる。

[結 語]

1 地域住民を対象とした2段階ペプシノゲン胃がん検診においてもPG陰性がんが発見され、胃がん検診としての見逃しを最小限におさえている。
2 ペプシノゲン陰性がんの発見率は胃X線検査受診者(6,483人)の0.031％であった。
3 胃がん発見効率を高めるため、60歳節目検診への2段階法導入が必要である。
4 胃がん検診の真の対象者に対する受診率(カバー率)は28.9％であった。

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