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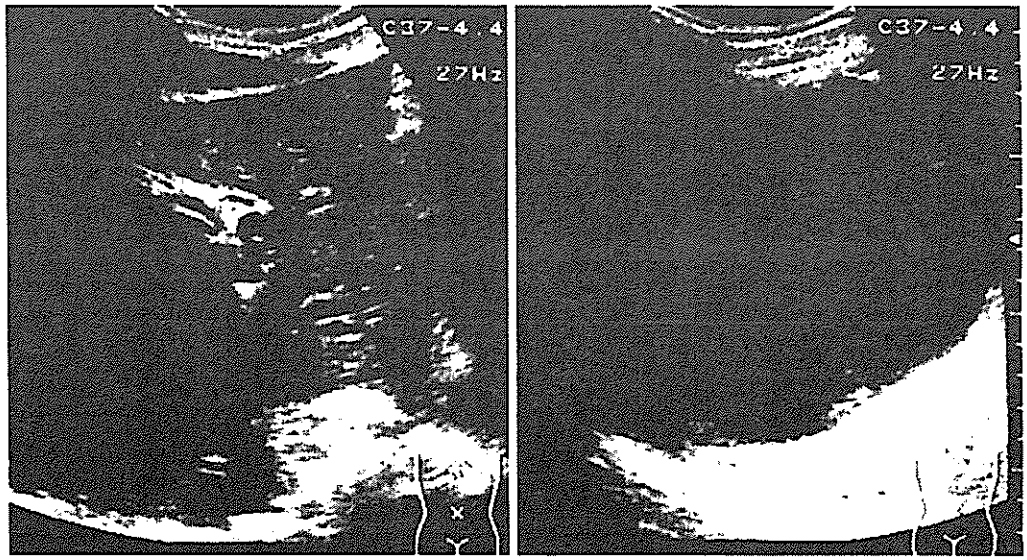

Figure 1. Abdominal ultrasound. A large cystic lesion is located in the right hepatic lobe. The content is homogeneous, without a septum or calcifications, and the intrahepatic bile ducts are dilated.

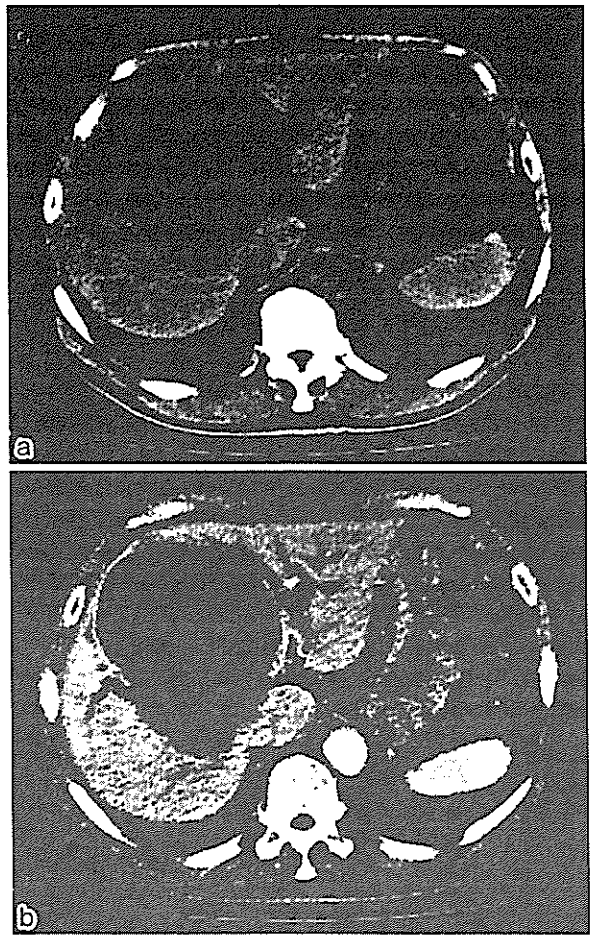

Figure 2. Upper abdominal computed tomography. a: Plain computed tomography shows a large 12 cm cystic lesion. b: Contrast computed tomography shows no internal enhancement and no enhancement of the cyst wall.

patients for whom detailed medical records of surgery were available, 11 underwent cystectomy, 9 cyst fenestration, and 5 hepatic resection. Of those who were treated non-surgically, 6 received only drainage and 16 received drainage followed by drug injection (sclerotherapy), using absolute ethanol and minocycline for 7 patients each, and monoethanolamine oleate for 2 patients.

The prognosis of solitary nonparasitic cysts of the liver with obstructive jaundice is relatively good. Irrespective of whether treatment is surgical or non-surgical, the patient should have a good clinical course. In the present case, we selected non-surgical treatment for the initial management in consideration of the patient's quality of life.

Selection of the appropriate sclerotherapy type after cyst drainage is also important. Ethanol can cause abdominal pain (15), and in some cases overdosage may lead to alcoholic intoxication (16), while adverse reactions including eosinophilia have been reported for minocycline (17). Great care must thus be taken when using these drugs. Monoethanolamine oleate is commonly used for sclerotherapy of esophageal varices. Iwasaki et al (6) have treated at least 20 patients with symptomatic hepatic cysts using monoethanolamine oleate as "cyst sclerotherapy" and reported resolution or reduced size of the cyst in all cases without any adverse reactions or recurrence. As the cyst showed regrowth following initial treatment with monoethanolamine oleate, a second drainage was needed. This regrowth was thought to be caused by insufficiency of monoethanolamine oleate injection. However, thereafter, treatment with monoethanolamine oleate was effective for our patient. As monoethanolamine oleate sclerotherapy for hepatic cysts has been reported in only relatively few cases, further studies with a larger number of patients are necessary.

In the present case, the dose of injected monoethanola-

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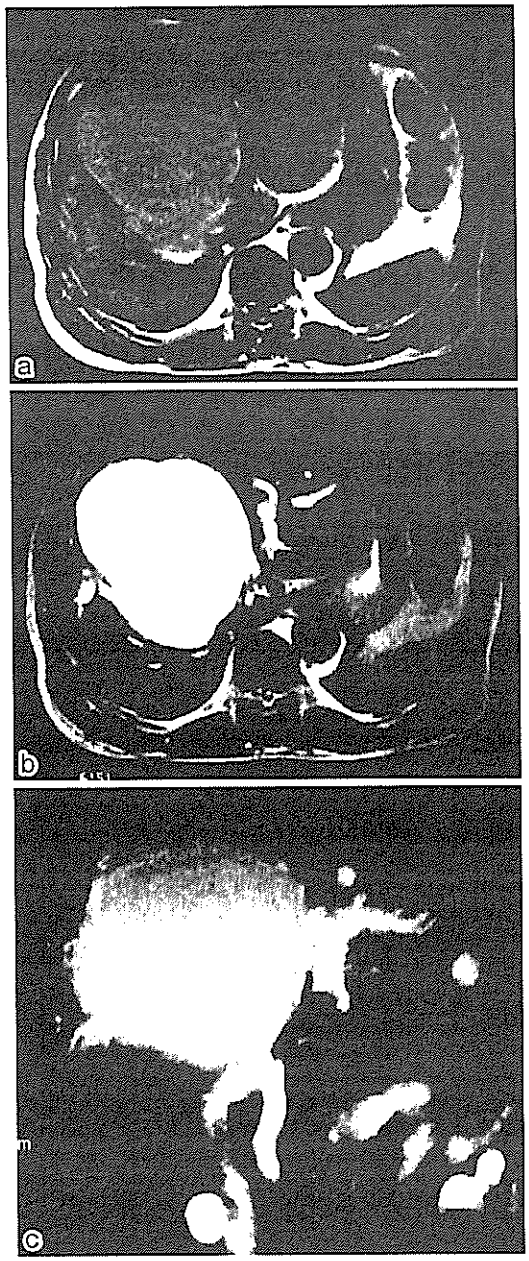

Figure 3. Abdominal magnetic resonance imaging. a: T1-weighted imaging shows a cystic lesion with homogeneous high signal intensity. b: T2-weighted imaging also shows homogeneous high signal intensity. c: Magnetic resonance cholangio-pancreatography indicates the presence of a large spherical lesion near the confluence of the right and left hepatic ducts that is compressing the intrahepatic bile ducts and keeping them separate from the common bile duct.

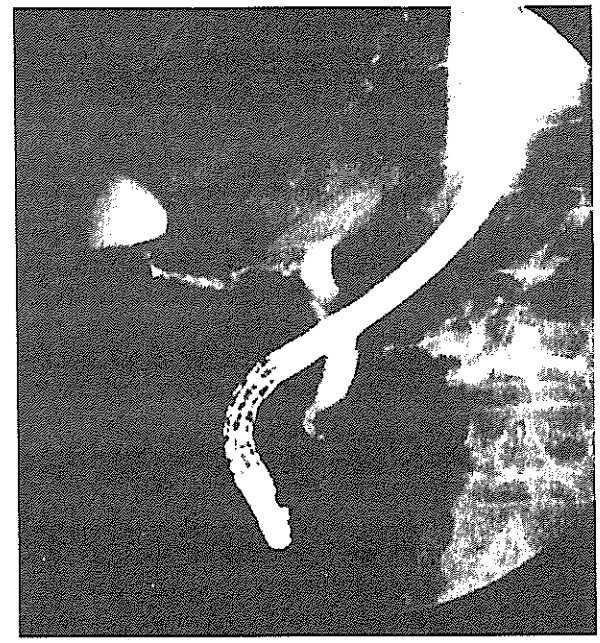

Figure 4. Endoscopic retrograde pancreatocholangiography. Downward compression of the common bile duct, gall bladder, and cystic duct. No contrast medium is seen in the intrahepatic bile ducts.

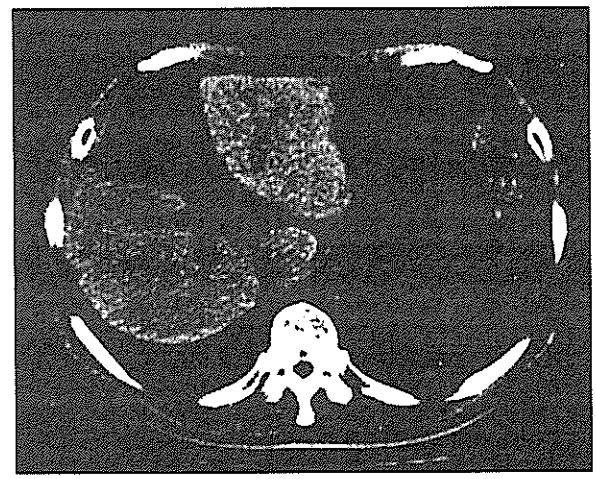

Figure 5. Upper abdominal computed tomography. The cystic lesion disappeared after drainage and monoethanolamine oleate treatment.

mine oleate was about 0.9 ml/kg (60 ml/67 kg; body weight). Kobashi et al (18) injected monoethanolamine oleate into rat liver via the portal vein to evaluate liver damage by serum transaminase and histological examination. At a dose of 0.8 ml/kg, transaminase markedly increased and the liver demonstrated extensive necrosis histologically. Seven days postinjection, transaminase levels fell within normal limits and the necrotic area had almost disappeared. Koide (19) injected monoethanolamine oleate into dog liver via the portal vein and evaluated the damage to the liver, lung and kidney by blood chemistry and histological examination. Repeated administration of monoethanolamine oleate of a total amount of 6 ml/kg injected on 12, 6 or 3 occasions over a 3-week period produced liver damage. In contrast, there was little damage to the lung or kidney. In the present case, if most of the injected monoethanolamine oleate volume (0.9 ml/kg) had been absorbed into blood

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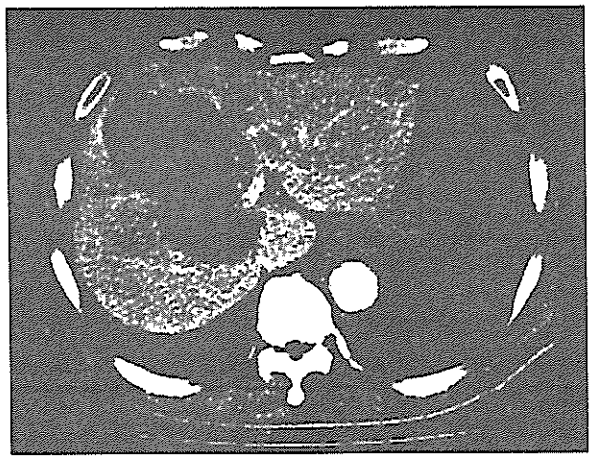

Figure 6. Upper abdominal contrast computed tomography. Regrowth of the cyst was noted 28 days after the initial drainage, for which a second drainage was performed.

vessels, liver damage would likely have continued for several days. As there was no serious liver damage in the present patient, most of the monoethanolamine oleate must have been aspirated. Watanabe et al (20) reported that retrograde infusion of monoethanolamine oleate into the common bile duct of the guinea pig resulted in extensive hepatic necrosis and hyperammonemia. In the present case, no contrast medium was detected in the cystic lesion on endoscopic retrograde pancreatocholangiography, indicating that there was no communication between the cyst and the common bile duct. This negative finding is very important, because monoethanolamine oleate injection into the liver cyst would present serious risk if it did in fact communicate with the bile duct.

Our patient was diagnosed with a simple cyst based on the basis of imaging and cytology findings. Since neoplastic changes of hepatic cysts have occasionally been reported (21, 22), careful follow-up will be necessary.

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Endoscopic Submucosal Dissection for Rectal Epithelial Neoplasia

Background and Study Aims: The technique of endoscopic submucosal dissection (ESD) has recently been developed for en-bloc resection of gastric tumors. For oncological reasons and in order to improve the patients' quality of life, it may be desirable to use the same technique for rectal neoplasia.

Patients and Methods: Thirty-five consecutive patients with rectal neoplasia who had a preoperative diagnosis of large intraepithelial neoplasias with submucosal fibrosis or located on the rectal folds were enrolled. ESD was carried out with the same technique previously described for the stomach, with some modifications. The efficacy, complications, and follow-up results of the treatment were assessed.

Results: The rates of en-bloc resection and en-bloc plus R0 resection were 88.6% (31 of 35) and 62.9% (22 of 35), respectively. Hemoglobin levels did not drop by more than 2 g/dl in any of the patients after ESD. None of the patients had to receive blood transfusions or undergo emergency colonoscopy due to bleeding during ESD or hematochezia after ESD. Perforation during ESD occurred in two patients (5.7%), who were managed with conservative medical treatment after endoscopic closure of the perforation. Excluding three patients in whom additional surgery was carried out, all but one of 32 patients were free of recurrence during a mean follow-up period of 36 months (range 12–60 months). The exception was a patient in whom a multiple-piece resection was required; the recurrent (residual) tumor, found 2 months after ESD, was a small adenoma that was again treated endoscopically.

Conclusions: ESD is applicable in the rectum with promising results, but the technique is still at a developmental stage and patients should be informed of the potential risks.

Introduction

The standard techniques for endoscopic resection of tumors in the lower gastrointestinal tract involve injection and cutting; these methods of endoscopic mucosal resection (EMR) are used not only in Japan [1] but also in Western countries [2]. However, the specimens obtained with this technique have size limitations. En-bloc resection is particularly desirable in larger and complicated lesions such as laterally spreading tumors, as it allows histological evaluation to be carried out easily and accurately. In addition, higher recurrence rates have been reported after multiple-piece resection in comparison with en-bloc resection [3,4]. To overcome these problems, the tumors are sometimes resected surgically even if they are limited to the mucosa.

The method of endoscopic submucosal dissection (ESD) was developed for en-bloc resection of large or ulcerative tumors in the stomach. Recent case reports have also described the use of this technique in the colorectum, with an insulated-tip diathermic knife (IT knife) [5] or a needle-knife with sodium hyaluronate [6,7]. However, there have been no reports to date evaluating outcomes with ESD treatment for rectal neoplasia. The present study assessed the outcomes of ESD with a specially developed technique for rectal neoplasias.

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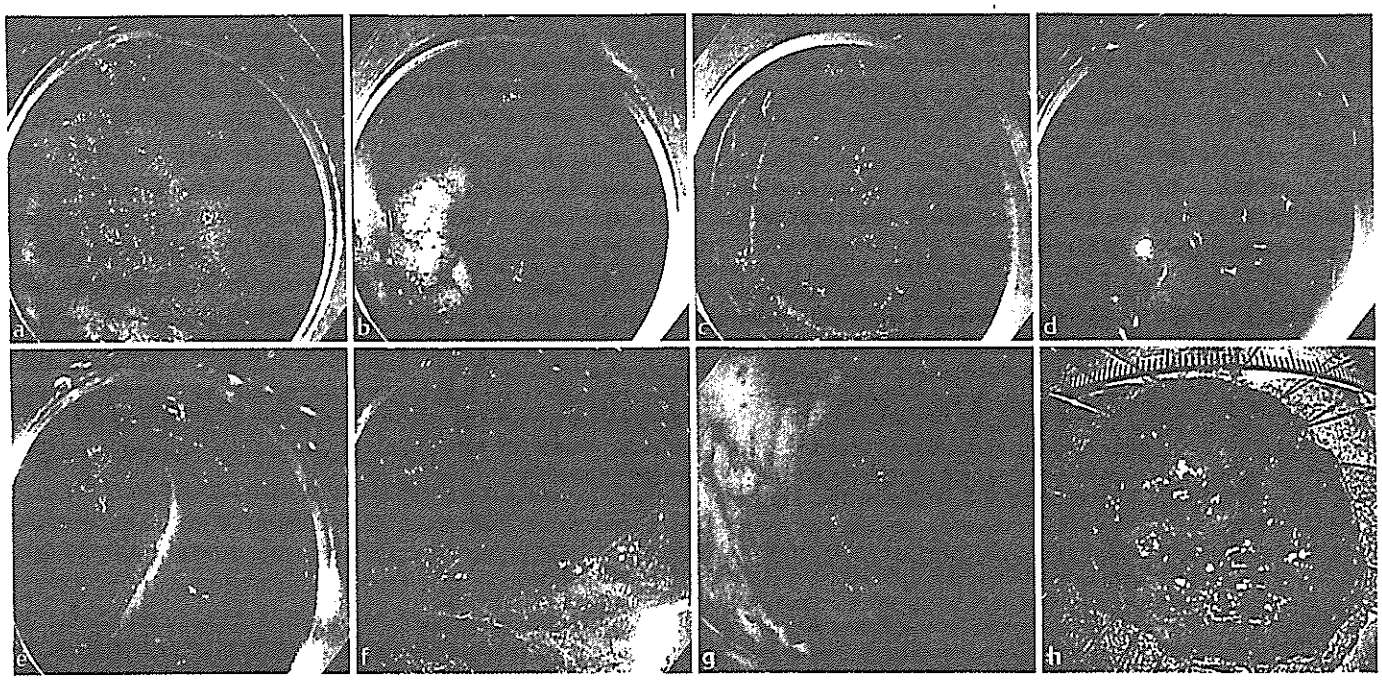

Figure 1 Endoscopic submucosal dissection for rectal neoplasia. **a** Chromoendoscopic view with indigo carmine dye, showing demarcation of the margin of the lesion, which is a type 0-IIa, laterally spreading, intramucosal adenocarcinoma in adenoma, 5 cm in size, located in the middle rectum. **b** Submucosal injection at the oral margin of the lesion, with the endoscope in a retroflexed position. **c** Initial mucosal incision at the oral margin of the lesion, with the endoscope in a retroflexed position. **d** Submucosal injection at the anal margin, with the endoscope in a straight position. **e** Mucosal incision at the anal margin and extension of the incision in a circumferential manner around the lesion, with the endoscope in a straight position. **f** Repetition of submucosal injections from the exposed submucosal layer and dissection of the submucosal connective tissue until the lesion detaches. **g** The artificial ulcer after removal. The vessels on the ulcer base are treated with hemostatic forceps to prevent delayed bleeding, and the ulcer base is sprayed with liquid sucralfate. **h** Complete resection of the lesion in one piece.

Patients and Methods

Between February 2001 and February 2005, 35 consecutive patients with rectal neoplasia were treated with ESD at the University of Tokyo Hospital. The patients provided written informed consent to the ESD treatment. The indication for ESD was established on the basis of the endoscopic features of the lesions, assessed using chromoendoscopy with or without magnifying endoscopy. For an ESD procedure to be indicated, the lesions had to meet one of the following criteria:

- Intraepithelial neoplasias > 2 cm in size or on the rectal folds that might have required a multiple-piece resection with the inject-and-cut technique.
- Intraepithelial neoplasias with scarring due to previous endoscopic treatment or biopsies, showing the nonlifting sign.

The endoscopic characteristics of the tumors were classified in accordance with the Paris endoscopic classification [8], and the tumor locations were grouped into the lower rectum (from the anal verge to the middle fold of Houston) and upper rectum (from the middle fold of Houston to the rectosigmoid junction).

The ESD Procedure

ESD was carried out using a single-channel upper gastrointestinal endoscope with a water-jet system (Olympus XGIF-Q240M, Olympus Corporation, Tokyo, Japan or Pentax EG-2931, Pentax Corporation, Tokyo, Japan) and a high-frequency generator with an automatically controlled system (Endocut mode; Erbotom ICC 200, Erbe Elektromedizin Ltd., Tübingen, Germany). A transparent cap was attached to the tip of the endoscope to provide a constant endoscopic view and to apply tension to the connective tissue for submucosal dissection. An example of the procedure is shown in Figure 1.

1. Creating a submucosal fluid cushion. A mixture of a 1% 1900 kDa hyaluronic acid preparation (Suvenyl, Chugai Pharmaceutical Co., Tokyo, Japan) plus normal saline (from January 2001 to October 2003) or 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol, Chugai Pharmaceutical Co., Tokyo, Japan; from November 2003 to February 2005) was used as a submucosal injection solution. The hyaluronic acid preparation was replaced due to new information obtained about submucosal injection solutions [9,10]. The mixing ratio of the earlier and later solutions was also changed from 1:3 (from January 2001 to March 2004) to 1:7 (from April 2004 to February 2005) due to technical advances. To clarify the area for submucosal injection and to distinguish clearly between the muscle layer and the submucosal layer and allow better hemostasis, indigo carmine and epinephrine were added to produce concentrations of 0.005% and 0.0005%, respectively. About 2 ml of the solution was injected into the submucosal layer just outside the tumor in each injection, and the injection was repeated a few times until the target mucosa was sufficiently raised.

2. Incising the mucosa outside the tumor. After lifting of the tumor, a mucosal incision was made with a tip of an electrosurgical snare (thin type) (Olympus SD-7P-1, Olympus, Tokyo, Japan; from January 2001 to October 2002) or FlexKnife (Olympus KD-

630L; from November 2002 to February 2005), as previously reported [11,12]. The knife was fixed at a length of 1–2 mm and gently pressed onto the mucosa to produce a cutting effect, using the endocutting mode with effect 2 (output 60 W). The distal (oral) half of the mucosal incision was completed first, followed by the proximal (anal) half. A retroflexed scope position was used to make the distal incision, if possible, and a straight scope position was used for the proximal incision.

3. Dissecting the submucosal layer beneath the tumor. Before the incision was made all round the tumor, dissection of the submucosa was started from the area in which the mucosal incision was completed, to prevent the lifted area from flattening over time. The principal knife used for submucosal dissection was the same knife with the same length as for the mucosal incision, using forced coagulation mode (output 40 W). In situations in which dissection was difficult, a hook knife (Olympus KD-620LR) [13] was also used. The exfoliated fragment tended to hang down due to gravity, and the patient's position was therefore changed – e.g., from supine to prone – to facilitate visualization of the tissue plane until the tumor was detached from the rectal wall. To control bleeding, hemostatic forceps (Pentax SDB2422 or an Olympus FD-410LR Coagrasper) were used in soft coagulation mode (output 50 W).

4. Treatment of the artificial ulcer after ESD. After resection of the tumor, visible vessels in the artificial ulcer were treated with hemostatic devices in soft coagulation mode (output 50 W) to prevent delayed bleeding. Finally, sucralfate was sprayed onto the ulcer base both to confirm hemostasis and to coat the surface of the ulcer [14].

Immediately after the ESD procedure, the patients were allowed to take a small amount of water. On the next day, if the patients' symptoms, laboratory findings, and abdominal radiography were unremarkable, a light meal was permitted and the patients were discharged within 1 week. If complications occurred, the schedules were changed in accordance with the patient's condition.

Histological classification was carried out microscopically in accordance with the revised Vienna classification of gastrointestinal epithelial neoplasias [15,16]. If there was massive submucosal invasion (sm2 or deeper, > 1000 µm below the muscularis mucosae), poorly differentiated adenocarcinoma, and/or vascular infiltration – regarded as indicating a high risk of positive lymph nodes – surgical intervention was recommended [8,17]. The extension of tumor cells into the resection margin was evaluated as previously reported [18]:

- Complete resection (R0): the lateral and basal resection margins are free of tumor (en-bloc resection essential).
- Incomplete resection (R1): the tumor extends into the lateral or basal margin.
- Resection not evaluable (Rx): the margins are not evaluable due to the artificial effects of coagulation necrosis or multiple-piece resection.

Resectability in the lower and upper rectum was compared using the chi-squared test, with a P value < 0.05 being regarded as significant.

All of the patients were followed up with colonoscopic examinations 2 months after ESD, to confirm healing of the artificial ulcer and assess any residual tumor; 1 year after ESD; and then annually to check for recurrence or other tumors throughout the colorectum. In cases of R1 or Rx resection, at least one biopsy was necessary to confirm that there was no residual tumor at the colonoscopy 2 months after ESD, even if the artificial scar did not appear to show any residual tumor. At the subsequent follow-up colonoscopies, it was left to the colonoscopist's discretion whether or not to take a biopsy. Abdominal and pelvic computed tomography (CT) examinations were also carried out annually for assessment of malignant neoplasias and in patients in whom there was submucosal invasion without additional surgery. In addition, CT findings and tumor markers were assessed every 6 months.

Results

Table **1** summarizes the clinicopathological features of the rectal neoplasias treated with ESD. Histological assessment showed that five of the tumors had invasion into the submucosa. Three were sm2 tumors with or without vessel infiltration. An additional rectal resection with lymphadenectomy was carried out in these three patients in whom no residual tumor or nodal metastases were found. The other two tumors with minute invasion into the submucosa (sm1, < 1000 µm below the muscularis mucosae) were closely followed up without additional surgery, as a recent study showed that the rate of lymph-node metastases in such tumors is almost zero [17].

The rate of en-bloc resection and details of the histological margins of the resected specimens are shown in Table **2**. Among 35 tumors, 31 (88.6%) were resected in an en-bloc fashion, but histological evaluation showed that the resections were Rx (lateral) in four tumors (11.4%) and R1 (lateral) in nine tumors (25.7%). All of the tumors were resected with tumor-free basal margins. The R0 resection rate was lower in the lower rectum than in the upper rectum, with a significant difference ($P < 0.05$).

Minor bleeding occurred in all of the tumors, but hemostasis was achieved during the procedures. The mean change in hemoglobin levels before and after the ESD procedures was –0.5 g/dl (range –1.4 to +1.4 g/dl). The hemoglobin level dropped by more than 1 g/dl in 10 patients (28.6%). None of the patients had massive hemorrhage requiring blood transfusion or emergency colonoscopy due to hematochezia after ESD.

Perforations occurred with two tumors (5.7%). One was a 0-IIa+I lesion of the laterally spreading type, a submucosal adenocarcinoma (sm1) in high-grade adenoma, 5 cm in size, located in the upper rectum. During dissection of the submucosal layer under the tumor, tearing of the muscle layer occurred, and this developed into a perforation. The perforation was small, less than 2 mm, and immediate suturing of the perforation by endoscopic clipping was carried out. Abdominal and chest radiography after completion of the en-bloc resection revealed pneumoperitoneum, pneumoretroperitoneum, and pneumomediastinum. The patient did not report abdominal pain except for abdominal distention, and conservative treatment with fasting and antibiotics

Table 1 Clinicopathological features of rectal neoplasias (for terminology, see refs. [8, 16])

Mean size (range)	*32.8 mm (9–91)*
Location	
Lower	14
Upper	21
Macroscopic type	
Is	7
IIa + I, LST*	14
IIa, LST	13
IIa + IIc	1
Histological depth	
Low-grade adenoma	7
High-grade adenoma	10
Noninvasive carcinoma	13
sm1	2
sm2 or deeper	3
Vascular infiltration	
Present	1
Absent	34

LST, laterally spreading tumor.

Table 2 En-bloc resection rate and histological margin of the resected specimens

	Upper rectum (n = 21)		*Lower rectum (n = 14)*		*Whole rectum (n = 35)*	
	n	*%*	*n*	*%*	*n*	*%*
En-bloc resection	18	85.7	13	92.9	31	88.6
R0 resection	16	76.1	6	42.9	22	62.9
R1 (lateral) [1]	2	9.5	7	50.0	9	25.7
R1 (basal) [2]	0	–	0	–	0	–
Rx (lateral) [3]	3	14.3	1	7.1	4	11.4
Rx (basal) [3]	0	–	0	–	0	–

1. Tumor extending to lateral margins.
2. Tumor extending to basal margins.
3. Margins not evaluable.

resulted in an uneventful recovery. The maximum C-reactive protein (CRP) level was 4.1 mg/dl; oral intake was started 7 days after ESD and the patient was discharged from the hospital 14 days after ESD. The other perforation was with a type 0-IIa lesion of the laterally spreading type, a noninvasive carcinoma in a high-grade adenoma, 2.5 cm in size, located in the upper rectum. During treatment of a visible vessel, the hemostatic forceps passed through the muscle layer by accident. The perforation was immediately sutured with endoscopic clipping and the ESD procedure was completed in an en-bloc fashion. Abdominal radiography after ESD did not show any air accumulation. Fasting for 2 days and antibiotic treatment led to an uneventful recovery; oral intake was started 3 days after the ESD procedure, and the patient was discharged from the hospital 6 days after ESD.

The follow-up colonoscopies 2 months after ESD identified only one tumor (2.8%), in which a multiple-piece resection had been carried out – type 0-IIa, laterally spreading type, 5 cm in size, a noninvasive carcinoma in high-grade adenoma located in the lower rectum – with a persistent small adenoma on the ESD scar. This was treated by argon plasma coagulation, and no further recurrence was observed. In all 32 tumors (excluding the three cases in which additional surgery was carried out), except for the above case, the patients remained free of recurrences during a mean follow-up period of 36 months (range 12–60 months).

Discussion

Endoscopic submucosal dissection in the stomach is a new form of endoscopic treatment [11,13,19–21] that has developed from the endoscopic mucosal resection method, involving local injection of a solution of hypertonic saline and epinephrine [22]. The technique is also theoretically applicable with colorectal tumors, but the procedure is associated with a relatively high frequency of perforation [19,21,23]. In the case of the stomach, some reports have described nonsurgical treatment for perforation with endoscopic clipping, nasogastric tube placement, antibiotic treatment, and prohibiting oral intake for a few days [24]. However, considerable caution is required when ESD is carried out in the colorectum, due to the risk of bacteria and feces entering the intra-abdominal space and causing severe peritonitis if perforation occurs.

The use of ESD in the treatment of rectal neoplasia was investigated in the present study firstly because the rectum is fixed in the retroperitoneum, so that the endoscope is more easily maneuvered than in other organs in the gastrointestinal tract, and secondly because panperitonitis may be less likely even if the muscle layer tears. Two patients in the present study suffered perforation, but in both cases it was possible to manage the condition without surgical treatment. Perforation during colonoscopy can be managed non-surgically in many cases if the perforation is noticed immediately and closed during the procedure in conditions of clean bowel preparation [25,26]. When there is perforation into the retroperitoneal space, it has been reported that the pressurized air from the tip of the endoscope can cause pneumoretroperitoneum, pneumomesenterium, pneumomediastinum, pneumothorax, pneumoscrotum, and subcutaneous emphysema [27,28]. It must also be borne in mind that symptoms of perforation may not be noticed due to pneumoperitoneum or abdominal pain, but only in the form of chest pain or dyspnea after a delay.

In comparison with the high en-bloc resection rate, the R0 resection rate was quite low in the present study, particularly in the lower rectum. It is of course important to attempt complete resection and confirm it histologically as far as possible. On the other hand, however, postoperative disorders such as stenosis and the increasing complication risks that may occur after wide mucosal resection also have to be taken into account. In the case of tumors in the lower rectum, the anal margin also has to be to cut minimally in order to prevent anal pain after ESD. The mucosal incision was therefore made very close to the tumors, and this may have led to resections histologically assessed as being incomplete or not evaluable. The fragile nature of the mucosa also led to the resected specimens being partly torn in some cases during collection and stretching. The lateral margins of rectal tumors are clearly identified endoscopically, so it is rare to mistake them. With this approach, careful follow-up is necessary to de-

In Brief

This series of 35 patients with adenomas (low-grade and high-grade intraepithelial neoplasia) and also early cancers shows an 89% rate of en-bloc R0 resection; perforation occurred in 6% (managed conservatively). Three patients with cancer underwent surgery due to more than minimal submucosal infiltration, and 31 of the remaining 32 patients remained recurrence-free during a 3-year follow-up period despite a somewhat low R0 resection rate en bloc (63%).

tect any evidence of local recurrence, as complete removal may be possible in repeat procedures. Even if local recurrence should develop from positive lateral tumor margins, the recurrent lesions can usually be controlled with further endoscopic treatments, as they are likely to be intramucosal tumors, as in the present study. Positive vertical tumor margins are of course a different issue, and an additional rectal resection should be considered immediately in such cases.

In summary, this study shows that ESD is a promising technique that can be used in the resection of rectal neoplasias. However, ESD in the rectum is still in a developmental stage at present; patients need to have the risks explained to them, and further refinement of the techniques used are necessary.

Competing interests: None declared.

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Safety of Argon Plasma Coagulation for Hemostasis During Endoscopic Mucosal Resection

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Abstract: Showing the safety of argon plasma coagulation (APC) over mucosal defects during/after endoscopic mucosal resection (EMR), 2 studies using resected pig (ex vivo) and living minipig (in vivo) stomachs were performed. As an ex vivo study, APC was applied over mucosal defects in 2 groups; with prior submucosal saline injection and without injection. Only subtle tissue damage was observed in the injection group, whereas apparent damage was observed in the noninjection group. The damaged distances in depth significantly increased as the pulse duration increased and those at the pulse duration of 4 seconds, which might be maximal in clinical practice, were approximately 1 mm. As an in vivo study, APC was applied over mucosal defects immediately after EMR. Only subtle tissue damage was observed even at the pulse duration of 20 seconds as shown in the ex vivo study. APC can be performed safely over the mucosal defects during/after EMR.

Key Words: argon plasma coagulation, endoscopic mucosal resection, tissue damage, hemostasis

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Endoscopic mucosal resection (EMR) is actively performed especially in Japan for the treatment of esophageal, gastric, and colorectal tumors. One of the major EMR complications is bleeding[1] and argon plasma coagulation (APC) has been applied, as well as hemoclips, injection therapy or other thermocoagulation techniques, to prevent or cope with bleeding.[2–7] Although APC is considered to be an innovative, effective and safe endoscopic tool for devitalization of tissue and hemostasis in the gastrointestinal tract, the data showing the safety of APC were obtained from the coagulation over the mucosal surface.[8] No study was performed showing the safety over the exposed submucosal layer, which situation was clinically experienced in hemostasis during/after EMR.

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MATERIALS AND METHODS

As an ex vivo study, porcine stomachs were used within 2 hours after resection. Before application of APC, mucosal defects imitating those during or immediately after EMR were made on the stomachs as followings: (1) Five milliliters of normal saline containing 0.0005% epinephrine and 0.005% indigo carmine was injected into the submucosal layer at separate sites of the stomachs, using a disposable syringe and a 23-gauge needle. (2) The elevated mucosal layer made by injection was resected roundly using scissors to make mucosal defects containing the injected fluid with approximately 3 to 5 cm in the maximal diameter. EMR was usually performed by using a polypectomy snare and a high-frequency current, but scissors were used in this study because the size of resected area could be easily controlled and thermocoagulation for resection might influence tissue damage, which complicated the data analysis. The unit used was the standard APC equipment consisting of a high-frequency generator (Erbotom ICC 200), an automatically regulated argon source (APC 300), and a flexible APC applicator, 2.3 mm in diameter. All of them were products of ERBE Elektromedizin, Tübingen, Germany. The power setting was 40 or 60 W and argon gas flow was 1 or 2 L/min, which was usually used for hemostasis in the clinical practice. Although the pulse duration needed for hemostasis was less than 5 seconds from our clinical experiences, pulse duration of 2, 4, 8, 20 seconds was tested to check the safety of APC. As separations of 2 mm or shorter between a probe and a tissue were necessary to produce a coagulation arc,[8] a jet of ionized argon plasma was radiated on the tissue from a separation distance of 2 mm at a 90-degree angle. As the controls, mucosal defects without submucosal injection, which were made by pealing the mucosa away from the remaining muscle layer by using a knife, were also examined in the same settings. After the coagulation was performed, the specimens were cut on the points of coagulation and fixed with formalin and embedded in paraffin. A histologic section was made from each block and stained with hematoxylin

FIGURE 1. Macroscopic appearance of tissue damage by argon plasma coagulation over the mucosal defect made after saline injection into the submucosa. Only subtle superficial coagulation is observed on the surface of the mucosal defect (arrow). The setting is pulse duration of 20 seconds, power of 60 W and argon gas flow of 2 L/min.

and eosin and examined tissue damage microscopically. Each condition was tested 5 times and a mean distance of tissue damage in depth at each condition was compared. As a statistical analysis, Mann-Whitney U test was adopted and a P-value of < 0.05 was considered as a significant difference.

Subsequently to the ex vivo study using the resected porcine stomachs, a similar investigation was carried out in 3 living minipig (Sus scrofa; Miniature Swine; Chugai Research Institute for Medical Science, Inc, Nagano, Japan) that were fasted overnight and then placed in the left lateral decubitus position after tracheal intubation and induction with general anesthesia. The stomachs were sufficiently inflated with air after the residual food and mucus on the mucosal surface were washed out with tapped water which was splashed from the instrumental channel of an endoscope. After these preparations, EMR using endoscopic aspiration mucosectomy method[9] was carried out on the gastric body to create 3 mucosal defects per stomach. APC was applied over the mucosal defects immediately after EMR, at the setting of the power of 60 W and the argon gas flow of 2 L/min. The pulse duration was changed as 5, 10, and 20 seconds. Different pulse duration was used for different mucosal defects of each stomach. Although it was difficult to apply APC at the same condition, we tried to keep a separation distance of an applicator and tissue approximately 2 mm and the angle 10 to 30 degree. After the coagulation was completed, the minipigs were killed without delay and the resected stomachs were examined microscopically as the previous ex vivo study.

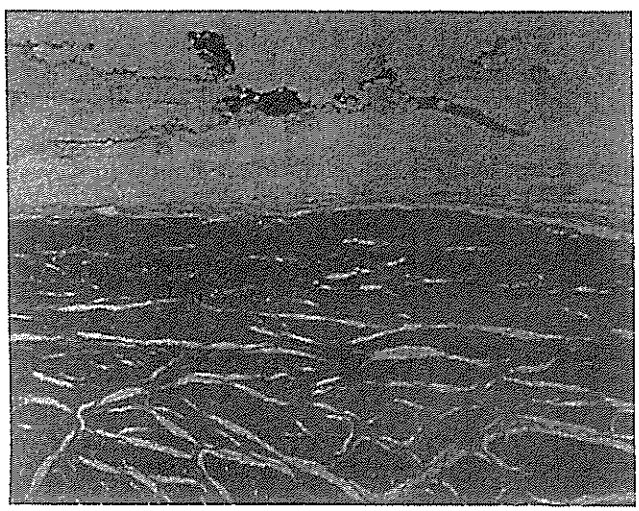

FIGURE 2. Microscopic appearance of tissue damage by argon plasma coagulation over the mucosal defect made after saline injection into the submucosa. Only a minute damage of submucosal connective tissue is observed on the surface of the mucosal defect. The setting is pulse duration of 20 seconds, power of 60 W and argon gas flow of 2 L/min (hematoxylin and eosin stain, original magnification × 20).

RESULTS

In the ex vivo study, coagulation arc was produced consistently at all the examined conditions. Only subtle superficial coagulation could be pointed out macroscopically on the mucosal defects in the injection group (Fig. 1), even though condition was set at the power of 60 W, the argon gas flow of 2 L/min and the pulse duration of 20 seconds. On the other hand, apparent coagulation necrosis was observed in the noninjection group even at the condition of the power of 40 W, the argon gas flow of 1 L/min and the pulse duration of 2 seconds. Histologic findings revealed that tissue damage from the surface of the mucosal defects was too subtle to measure the distances in depth in the injection group (Fig. 2), whereas those in the noninjection group were measured as shown in Table 1. As the pulse duration increased, the damaged distance in depth increased significantly at each setting of the power and the argon gas flow (Fig. 3). When comparing different power and argon gas flow at the same pulse duration, there was no significant difference at the pulse duration of 2 or 4 seconds. On the contrary, at the pulse durations of 8 and 20 seconds, the damaged distances in depth at the power of 60 W and the argon gas flow of 2 L/min were significantly deeper than those of the other settings.

The subsequent study using living minipigs supported the results obtained by the resected stomach. Tissue damage on the mucosal defects immediately after EMR was too subtle to measure, even though the pulse duration was 20 seconds (Figs. 4, 5).

DISCUSSION

APC has been available in flexible endoscopy since 1991 and applied for treatment of various lesions, such as

TABLE 1. Distances of Tissue Damage in Depth Over the Mucosal Defects Without Saline Injection Into the Submucosa

Settings (mean ± SD)	2 s	4 s	8 s	20 s
40 W and 1 L/min (mm)	0.32 ± 0.08	1.00 ± 0.07	1.52 ± 0.30	2.52 ± 0.19
40 W and 2 L/min (mm)	0.38 ± 0.08	1.10 ± 0.16	1.74 ± 0.23	2.42 ± 0.25
60 W and 1 L/min (mm)	0.40 ± 0.07	0.94 ± 0.11	1.90 ± 0.27	2.38 ± 0.40
60 W and 2 L/min (mm)	0.44 ± 0.11	0.98 ± 0.13	2.36 ± 0.26*	2.94 ± 0.27*

*The values are significantly different from the other values at the same pulse duration ($P < 0.05$).

hemorrhages, malignant and benign tumors, tissue ingrowth and overgrowth of stents, angiodysplasias, dysplasia, and so on.[10] One of the advantages of APC is considered to be a controllable depth of coagulation (0.5 to 3 mm),[11] and a rate of perforation is reported to be less than 0.3% in the clinical practice,[10] which is extremely low in comparison with that of laser therapy.[12] However, it is uncertain if the possibility of perforation increases or not, when APC is applied over the mucosal defect during or after EMR. This study showed that APC caused only subtle superficial damage when applied over mucosal defects during or immediately after EMR. Among available hemostatic techniques, APC is preferable especially in case of bleeding from the mucosal defect especially during EMR, because APC never disturb the next step of EMR like a hemoclip and tissue damage of injection therapy or other thermocoagulation techniques is considered to be no less than that of APC.

On the other hand, the noninjection group showed that the depth of tissue damage became significantly deeper as pulse duration increased. In the clinical practice, pulse duration for APC is usually limited to less than 5 seconds per bleeding vessel and then, another hemostatic method such as a hemoclip or injection therapy is applied, when hemorrhage cannot be controlled by APC. Although a significant difference between the settings of the power and the argon gas flow was observed at the pulse duration of over 8 seconds in the noninjection group of this ex vivo study, these longer pulse durations are unrealistic in the clinical practice. So we may consider that the difference between 40 and 60 W or 1 and 2 L/min was not major concern with respect to tissue damage. Furthermore, this ex vivo study showed that the distance of tissue damage in depth was approximately 1 mm, when APC was applied at the pulse duration of 4 seconds, which might also encourage us to use APC with little fear of perforation over the bared submucosal layer such as a peptic ulcer base or mucosal defects long time after EMR, although these findings may be confirmed in another in vivo study.

Complete different results were obtained in tissue damage between the injection group and the noninjection group. No data are available up to date, but the difference is speculated to be mainly caused by rapid cooling of

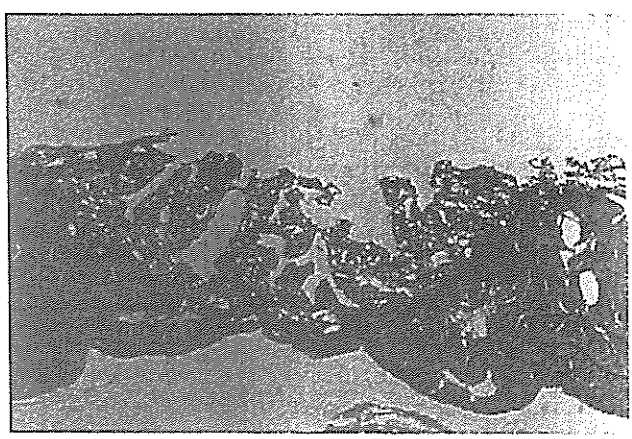

FIGURE 3. Microscopic appearance of tissue damage by argon plasma coagulation over the mucosal defect made without saline injection into the submucosa. Tissue damage is extended to the deeper layer of the proper muscle layer. The setting is pulse duration of 20 seconds, power of 60 W and argon gas flow of 2 L/min (hematoxylin and eosin stain, original magnification × 6).

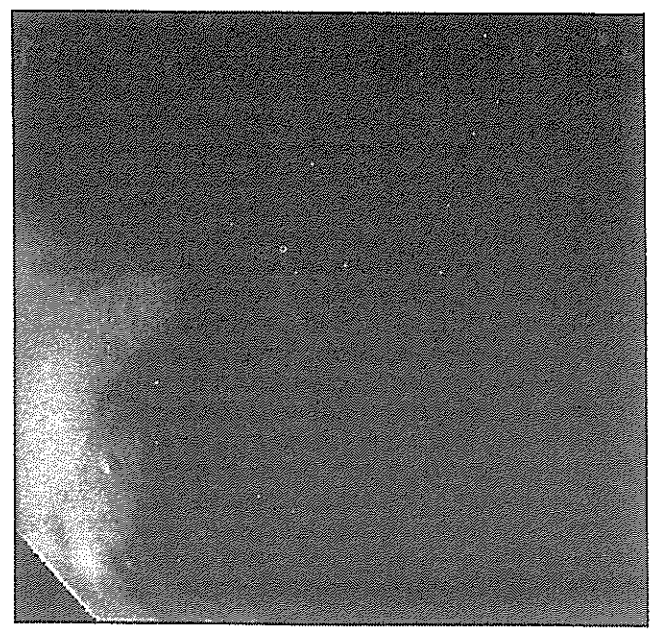

FIGURE 4. Endoscopic appearance of tissue damage by argon plasma coagulation over the mucosal defect immediately after EMR in a living minipig. Coagulation is slightly observed on the mucosal defect. The setting is pulse duration of 20 seconds, power of 60 W and argon gas flow of 2 L/min.

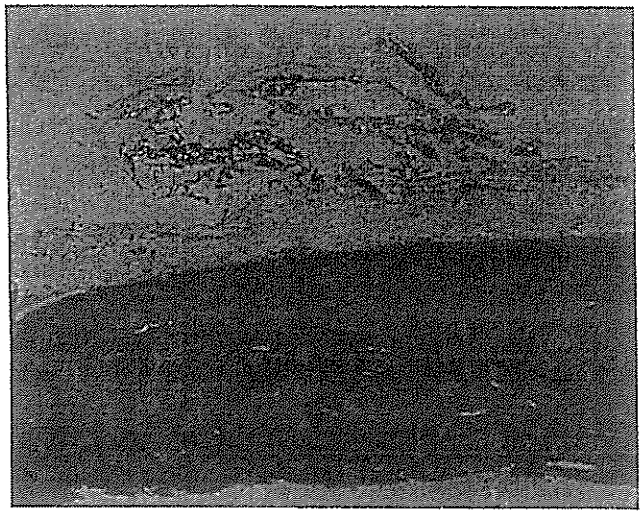

FIGURE 5. Microscopic appearance of tissue damage by argon plasma coagulation the mucosal defect immediately after EMR in a living minipig. Only subtle tissue damage of the submucosal layer is observed on the surface of the mucosal defect. The setting is pulse duration of 20 seconds, power of 60 W and argon gas flow of 2 L/min (hematoxylin and eosin stain, original magnification × 20).

coagulation arc with trapped fluid in the submucosal layer. So the volume of containing water may be one of the major dependent factors influencing the extent of tissue damage. The next promising study to confirm the above speculation may be the setting of different thickness of the exposed submucosal layer created by different volume of saline injection.

In summary, this experimental study showed that APC on the mucosal defects for hemostasis during and immediately after EMR was extremely safe even at a longer pulse duration and the shorter pulse duration generally used for hemostasis in the clinical practice might be safely performed on the bared submucosal layer such as a peptic ulcer base or mucosal defects long time after EMR.

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ORIGINAL ARTICLE

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Risk factors for knee osteoarthritis in Japanese men: a case-control study

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Abstract Risk of knee osteoarthritis (OA) was assessed in a population-based case-control study of Japanese men. The study covered three health districts in Wakayama and Osaka prefectures, Japan. Subjects were male individuals ≥45 years old diagnosed radiographically with knee OA, and who did not display any established causes of secondary OA. Controls selected randomly from the general population were individually matched to cases for age, sex, and residential district. Subjects were interviewed using structured questionnaires to determine medical history, physical activity, socio-economic factors, and occupation. Interviews were obtained from 37 cases and 37 controls. In univariate analysis, heaviest weight in the past and physical work such as factory, construction, agricultural, or fishery work as the principal occupation significantly raised the risk of male knee OA ($P < 0.05$). Odds ratios (OR) were determined using conditional logistic regression analysis mutually adjusted for potential risk factors using the results of univariate analysis. Heaviest weight in the past (OR 6.01, 95% confidence interval (CI) 1.18–30.5, $P < 0.05$), past knee injury (OR 6.25, 95% CI 1.13–34.5, $P < 0.05$), and physical work as the principal occupation (OR 6.20, 95% CI 1.40–27.5, $P < 0.05$) represented independent factors associated with knee OA after controlling for other risk factors. Physical work is associated with knee OA, demonstrating the influence of working activity on the development of OA. The present study suggests that risk factors for knee OA in men resemble those in women.

Key words Case control study · Heavy weight · Knee joint · Osteoarthritis (OA) · Physical work

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Introduction

Since osteoarthritis (OA) is a frequent cause of pain and disability in elderly individuals, the recent World Health Organization report on the global burden of disease indicated knee OA as an increasingly important cause of disability in both men and women, suggesting that strategies for preventing OA are urgently required.[1] In Japan, knee OA seems to represent a frequent cause of pain and disability, but few epidemiological studies have examined associated factors.

Several investigations regarding risk factors for hip and knee OA performed in Western populations have

suggested obesity, previous injury, polyarticular joint involvement, and occupational activities as important risk factors for the disorder.[2-8] However, few studies of risk factors for OA in Japanese populations have been performed. Our earlier case-control study of hip OA identified some variations in risk factors in Japan.[9] In the previous case-control study of hip OA, occupational lifting was identified as a risk factor and sedentary work as a protective factor for hip OA. In addition, obesity was not identified as a risk factor for Japanese hip OA. For contrast, an identical case-control study was performed for knee OA in women in a Japanese population.[10] In the female study, risk factors of obesity, previous knee injury, and period of total work were identified, and sedentary work as the initial occupation represented a preventive factor.[10] The results from these two investigations suggest various similarities and differences in risk factors between hip and knee OA in Japanese populations.

The present study sought to clarify risk factors for knee OA among men in Japan, by performing a survey identical to that used in the previous female knee OA study. Results for men were compared to those from the female study.[10] Risk factors were then compared between knee OA and hip OA to address differences in risk factors for constitutional and mechanical factors between OA at different sites. Finally, risk factors for knee and hip OA were compared to those identified in a British study[11,12] that used identical methods to the Japanese studies, to clarify differences in risk factors for OA between Japanese and Western populations.

Patients and methods

Methods of data collection in the present study were basically identical to those of the case-control studies for female knee OA and hip OA reported previously.[9,10] A brief summary is provided here. Cases were identified from the registration systems of the six hospitals participating in the study, which were located in three cities in Japan (Wakayama City and Arita City in Wakayama Prefecture, and Sennan City in Osaka Prefecture).

Cases comprised men ≥45 years old who suffered knee pain and walking difficulties, and who were first diagnosed by an orthopedic surgeon as displaying a tibiofemoral joint with radiographic grade of ≥3 on the Kellgren and Lawrence scale[13] within the year preceding the start of the study. Cases with a history of knee injury in the previous year, rheumatoid arthritis, or ankylosing spondylitis were excluded.

For each case, a single control was randomly selected from among men of the same age and district of residence on city registers of the local population, which are updated as residents move into or leave the city. Controls who had suffered knee OA were excluded from the study.

All eligible cases and controls were initially approached using a letter to determine willingness to participate in the study. After providing informed consent, cases and controls were interviewed by the same trained interviewer.

An identical questionnaire to that used in the British case-control study was used to ascertain risk factors of knee OA.[11,12] The questionnaire was translated and back-translated from Japanese to English. Subjects completed a structured questionnaire that requested details of medical history, socio-economic status and education, cigarette smoking and alcohol consumption, functional status, and lifetime history of leisure activities. Lifetime history of leisure activities included participation in sports such as soccer, swimming, tennis, cricket, and golf, in addition to frequency and duration of less physical activities, such as gardening. Information about eight types of occupational physical activity was requested, namely: standing; sitting; climbing stairs; kneeling; squatting; driving; walking; and heavy lifting. Information on these activities was obtained for the initial job, defined as the earliest job reported, and for the principal job, defined as the job at which the subject had worked longest. For each job, the questionnaire enquired whether work entailed lifting weights (≥10 kg, ≥25 kg, or ≥50 kg) more than once during an average working week. Information regarding use of transport, including frequency and duration of cycling and motorcycling was obtained. Information was also requested on the involvement of other joints, including hands, shoulders, and hips. Furthermore, questions were added about back pain and stiffness, which were not included in the British study. Once heaviest reported weight after 25 years old was obtained, height and weight of each subject was measured at the time of the interview.

After analysis to clarify risk for male knee OA, results were compared between men and published results for women.[10] Risk factors for knee OA and hip OA were also compared to address differences in constitutional and mechanical risk factors between OA at different sites. Finally, risk factors for knee and hip OA were compared to the findings of the British study, which used identical methods to the Japanese studies.

Data were calculated using McNemar's Chi-square test and conditional logistic regression tests for matched sets. Results were summarized as odds ratios (OR) with 95% confidence intervals (CI). Odds ratios were calculated for categories of exposure, and tests of trend were performed across these categories. Statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA) and the STATA statistical package (STATA, College Station, TX, USA).

Results

A total of 40 men ≥45 years old fulfilled the entry criteria for the study. Among these eligible cases, 37 men (92.5%) agreed to participate after information was provided. Unilateral knee OA ($n = 21$) was more common than bilateral disease ($n = 16$). Among the 21 men with unilateral disease, OA tended to be right-sided ($n = 13$) more often

than left-sided (n = 8), but no significant difference was identified.

For controls, we approached age-, sex-, and residence-matched candidates for each case. To recruit the 37 matched controls, we approached 70 subjects (overall response rate 52.9%).

Table 1 shows background characteristics for the 37 case-control pairs in the present study. Mean body weight was significantly greater for cases than for controls ($P < 0.05$). Furthermore, body mass index was significantly higher for cases than for controls ($P < 0.05$). No differences in personal habits such as smoking or drinking were noted between cases and controls.

The association between knee OA and heaviest reported body weight was analyzed. Under univariate analysis, mean heaviest reported body weight for cases was 72.1 kg (standard deviation (SD) = 13.0 kg), significantly higher than that for controls ($P < 0.01$) in men. Odds ratios for heaviest reported body weight were 1.07 (95% CI 1.02–1.13), suggesting that a 1-kg increase in heaviest reported body weight raised the risk of knee OA by 7%.

To more clearly address the influence of heaviest reported weight on development of knee OA, cases were categorized into the following three groups according to the distribution of heaviest reported weight: high, ≥72.0 kg; middle, 61.0–72.0 kg; and low, <61.0 kg. These categories were defined by dividing total distributions into equal thirds. Cases in the high group displayed a >4-fold elevation in risk compared with cases in the low group (OR 4.22, 95% CI 1.13–15.8 for high vs low, $P < 0.05$; OR 1.60, 95% CI 0.50–5.08 for middle vs low, $P = 0.43$) (Fig. 1).

The association between knee OA and history of injury in other joints was calculated. Under univariate analysis, although ORs exceeded a 2-fold increase, no significant difference was observed between cases and controls (OR 2.50, 95% CI 0.78–7.97 for yes vs no, $P = 0.12$).

The association between knee OA and methods of transportation was examined by comparing the frequency of regular bicycle use between cases and controls. Under univariate analysis, while OR was higher for men (OR 2.67, 95% CI 0.71–10.05), no significant differences were noted between cases and controls.

Associations between knee OA and occupational history were analyzed. The most frequent areas of employment for all subjects were factory/construction, agriculture/fishery, clerical/technical, and shop assistant/manager (Table 2). Distributions of initial and principal occupations differed

Table 1. Anthropometric and background characteristics of cases and controls for knee OA in men

	Men	
	Cases	Controls
No. of participants	37	37
Age (years)	70.0 ± 6.6	70.1 ± 7.0
Weight (kg)	64.1 ± 10.7*	59.3 ± 8.7
Height (cm)	162.5 ± 6.9	163.0 ± 6.7
Body mass index (kg/m^2)	24.2 ± 3.4*	22.4 ± 3.8
Heaviest weight in the past (kg)	72.1 ± 13.0**	64.0 ± 9.2
Age at the heaviest weight (years)	57.4 ± 15.1*	51.7 ± 17.8
Current smoking (%)	16 (43.2)	15 (40.5)
Current drinking (≥5 times/week, %)	20 (54.1)	22 (59.5)

Mean ± SD; percentage in parentheses
* $P < 0.05$, ** $P < 0.01$ cases vs controls

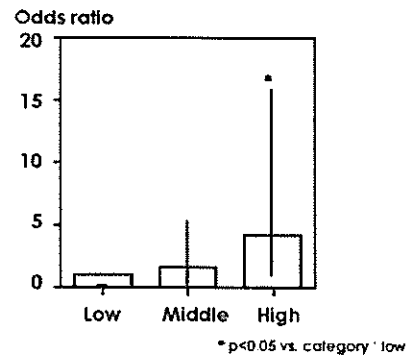

Fig. 1. Association of knee osteoarthritis with heaviest weight in the past. *Low*, lowest 3rd of the heaviest weight category, <61.0 kg; *Middle*, middle 3rd, ≥61.0 kg, <72.0 kg; *High*, highest 3rd, ≥72.0 kg. *Bar* represents 95% confidence interval

Table 2. Occupations reported as initial and principal jobs in men

	Initial occupation				Principal occupation			
	Cases	%	Controls	%	Cases	%	Controls	%
Total	37	100	37	100	37	100	37	100
Factory/construction workers	18	48.6	14	37.8	22	59.5	16	43.2
Agricultural/fishery workers	10	27.0	6	16.2	7	18.9	4	10.8
Clerical workers/technical experts	4	10.8	6	16.2	2	5.4	9	24.3
Shop assistants and managers	2	5.4	9	24.3	2	5.4	6	16.2
Clinical workers	2	5.4	0	0.0	1	2.7	0	0.0
Housekeepers	0	0.0	0	0.0	0	0.0	0	0.0
Hairdressers	0	0.0	0	0.0	0	0.0	0	0.0
Dressmakers	0	0.0	0	0.0	0	0.0	0	0.0
Teachers	0	0.0	0	0.0	2	5.4	0	0.0
Others (soldier, taxi driver, etc.)	1	2.7	2	5.4	1	2.7	2	5.4
No work, no answer	0	0.0	0	0.0	0	0.0	0	0.0

Table 3. Crude and adjusted odds ratios with risk factors for knee osteoarthritis in men

Men	Risk factors	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Heaviest reported weight[a]	Middle vs Low	1.60 (0.50–5.08)	1.25 (0.29–5.35)
	High vs Low	4.22 (1.13–15.8)*	6.01 (1.18–30.5)*
Past injury of either knee	Yes vs No	2.50 (0.78–7.97)	6.25 (1.13–34.5)*
Occupational factors	Physical work[b] as principal occupation (vs Others)	2.80 (1.01–7.77)*	6.20 (1.40–27.5)*

Adjusted odds ratio refers to values after mutual adjustment for other potential risk estimates
95% CI, 95% confidence interval
[a] Lowest 3rd, <61.0 kg; middle 3rd, ≥61.0 kg, <72.0 kg; highest 3rd, ≥72.0 kg in men
[b] Physical work meaning factory, construction, agriculture or fishery work
* $P < 0.05$

Table 4. Crude and adjusted odds ratios with risk factors for knee osteoarthritis in women (cited from ref. 10)

Women	Risk factors	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Heaviest reported weight[a]	Middle (vs Low)	1.68 (0.79–3.84)	3.33 (0.95–11.7)
	High (vs Low)	3.10 (1.26–7.98)*	3.92 (1.03–14.8)*
Past injury of either knee	Yes vs No	5.00 (2.44–10.2)*	7.51 (2.40–23.5)**
Transportation	Cycling almost every day for ≥12 months (vs Less)	1.88 (1.02–3.94)*	1.67 (0.61–4.57)
Occupational factors	Physical work[b] as initial occupation (vs Others)	2.54 (1.34–4.82)**	2.08 (0.88–5.61)
	Sitting ≥2 h/day at initial job (vs Less)	0.43 (0.23–0.78)**	0.44 (0.47–1.10)
	No. of jobs (1 job)	1.24 (1.02–1.50)*	0.91 (0.66–1.25)
	Total working period (1 year)	1.05 (1.03–1.07)***	1.05 (1.01–1.08)**

Adjusted odds ratio refers to values after mutual adjustment for other potential risk estimates
95% CI, 95% confidence interval
[a] Lowest 3rd, <55.0 kg; middle 3rd, ≥55.0 kg, <62.0 kg; highest 3rd, ≥62.0 kg in women
[b] Physical work meaning factory, construction, agriculture or fishery work
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

significantly between cases and controls. Physical work (factory/construction or agriculture/fishery) at the principal job was significantly more common among cases than controls (OR 2.80, 95% CI 1.01–7.77 for yes vs no). Mean age at commencement of the first job was 16.3 years (SD 3.8 years) compared to 16.6 years (SD 4.1 years) for controls, indicating no significant difference between cases and controls. Occupational activities including standing, climbing stairs, kneeling, squatting, driving, walking, sitting, and heavy lifting were not associated with increased risk of knee OA in men.

Table 3 shows ORs determined using conditional logistic regression analysis mutually adjusted for potential risk factors. Various risk factors were entered into the conditional logistic model, comprising: heaviest reported weight; previous knee injury; and physical work at the principal occupation in men. Heaviest reported weight in the past (OR 6.01, 95% CI 1.18–30.5, $P < 0.05$), past injury of the knee (OR 6.25, 95% CI 1.13–34.5, $P < 0.05$), and physical work at the principal occupation (OR 6.20, 95% CI 1.40–27.5, $P < 0.05$) represented independent factors associated with knee OA after controlling for other risk factors (Table 3).

Discussion

The results of the present case-control study indicate that heavy weight in the past and previous knee injury are associated with knee OA in men. Also in men, the proportion engaged in physical work (factory, construction, agriculture, or fishery work) was significantly higher among cases than controls. These risk factors for male knee OA are similar to those seen for female OA knees. Although we have already reported the results elsewhere,[10] we briefly compared results for men and women. Table 4 shows ORs in women determined using conditional logistic regression analysis mutually adjusted for potential risk factors. Various risk factors were entered into the conditional logistic model, comprising: heaviest reported weight in the past; previous knee injury; regular bicycle use; physical work in initial occupation; sedentary work in initial occupation; number of jobs; and total working period, summarizing all years of all jobs that subjects worked. Heaviest reported weight in the past, past injury of the knee, and total working period in women represented independent factors associated with knee OA after controlling for other risk factors. The results of the present case-control study indicate that heavy weight in the past and previous knee injury are associated with knee OA in both men and women.

Several limitations apply to the present study. Firstly, this investigation was based on a relatively small number of male cases and controls. Before the start of the research, we had calculated the sample size. We accumulated 155 pairs of cases and controls based on assumed values of a 0.05 level of significance, 80% statistical power, 2.0 risk ratio, and the 30% prevalence of cases. As a result, we succeeded in identifying 160 cases (40 men, 120 women) >45 years old

Table 5. Comparison of risk factors for hip and knee osteoarthritis (OA) in Britain and Japan (combined results for men and women)

	Risk factors	Britain	Japan
Hip OA	Obesity	Yes	No
	Past joint disturbance	Yes	No
	Occupational factors	Yes (lifting)	Yes (lifting)
Knee OA	Obesity	Yes	Yes
	Past joint disturbance	Yes	Yes
	Occupational factors	Yes (kneeling/squatting)	Yes (physical work, working period)

who fulfilled the entry criteria for the study. Of the eligible cases, 138 (86.3%; 37 men, 101 women) agreed to participate. However, the lack of gender balance for cases resulted in a small number of male subjects, which might reduce statistical power, and thus might not have detected other risk factors among lifestyle variables. This could be due to the use of identical case definitions for subject selection as the case-control hip OA and British studies. Cases were defined as those suffering knee pain and walking difficulties, who were first diagnosed by an orthopedic surgeon as displaying a tibiofemoral joint with a radiographic grade of ≥3 on the Kellgren and Lawrence scale. Our previous comparative study of OA in the lumbar spine indicated that OA in the general population tends to display lower prevalence and severity in Japan than in Britain.[14] In addition, the small number of male cases reflects gender differences in prevalence of knee OA in Japan. As a second limitation in the present study, the response rate for controls (52.8%) was lower than that for cases (92.0%). The present results may therefore be subject to some degree of overestimation.

Obesity has previously been shown to display strong associations with risk of knee OA,[2–8] and epidemiological studies performed in Japan have confirmed associations between obesity and knee OA.[15,16] In the present study, a history of heavy weight was shown to exert significant influences on risk of knee OA among men, resembling the results of women,[10] and consistent with previous studies. These findings indicate that the influence of heavy weight on knee OA is consistent across gender in both Japanese and Western populations.

The involvement of other joints is believed to play a role in increased risk of OA. In the British study paralleling the present study, presence of Heberden's node and previous knee injury were both strongly and independently associated with knee OA.[11,12] Although the present study did not seek information regarding the presence of Heberden's node, information was obtained about past history of the involvement of other joints and areas, as diagnosed by a medical doctor, indicating an independent association between previous knee injury and knee OA. In particular, site of knee OA was basically in accordance with the injured site among cases with previous knee injured (right side 91.7%, left side 100%). These findings were again consistent among men and women across Japanese and Western populations.

Mechanical stress represents another factor in the pathogenesis of OA at any joint site. In the present study, although occupational activities of standing, climbing stairs, kneeling, squatting, driving, walking, and heavy lifting were not associated with increased risk of knee OA in men, physical work at the principal occupation raised the risk of knee OA. Physical work represented by factory, construction, agricultural, or fishery work for long periods involved mechanical stress on the knee joints. The previous report utilized conditional logistic regression analysis without physical work, and identified sedentary work as a preventive factor in women.[10] These occupational activities influencing the risk of knee OA suggest that excess stress at the joint raises the risk, while reduced load on the joint decreases risk.

The present case-control study of knee OA paralleled our previous study of hip OA,[9] and was identical in format to some British studies.[17,18] Table 5 summarizes the results of studies using the same methods, indicating differences in risk factors between hip OA and knee OA, and between populations in Britain and Japan. Occupational factors clearly influence the development of both of hip and knee OA in Japan, as in Britain, although differences exist in specific activities exerting influence. Moreover, previous joint injury represented a risk factor for knee OA in Japan, as in the British studies. Conversely, obesity did not represent an independent risk factor for hip OA in Japan, but was a risk factor for both hip and knee OA in the British studies. This may be because local mechanical factors such as acetabular dysplasia might exert stronger influences on hip OA in Japan than other general mechanical factors such as adiposity. However, these results suggest that the pathogenesis of knee OA is similar in Japan and Western countries. Further studies of OA in other sites are required to characterize the risk profile in Japan.

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Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms

Background and study aims: Endoscopic submucosal dissection (ESD) is a novel technique used for the treatment of gastrointestinal neoplasia. One of its major limitations, however, is the complication of perforation.

Patients and methods: We included in our study all the cases of perforation that occurred during ESD procedures for gastrointestinal epithelial neoplasia between February 2000 and February 2005. Clinical outcomes after perforation were investigated.

Results: Perforation was experienced at 27 lesions in 27 patients (four in the esophagus, fourteen in the stomach, seven in the colon, and two in the rectum). Fibrosis under the lesions was confirmed histologically in seven patients (26%). Immediate closure using endoclips was performed in all patients except for three asymptomatic patients in whom a stomach perforation was first noticed when free air was noticed on a radiograph the morning after the ESD procedure. Air accumulation was detected radiographically in 21 patients (78%). The mean duration of antibiotic treatment was 6.7 days and the patients were fasted for a mean period of 5.3 days. The mean maximum body temperature was 37.3 °C, the mean white blood cell count was 9733/mm^3, and the mean C-reactive protein level was 5.0 mg/dl. All the patients were discharged well from the ward after a mean time of 12.1 days after ESD, and no recurrence caused by tumor spread from the perforation occurred in any patient after a median follow-up period of 36 months (range 9–52 months).

Conclusion: Successful nonsurgical management after ESD complicated by perforation is a highly feasible option if intensive conservative treatments are used following immediate endoscopic closure of the perforation.

Introduction

Endoscopic submucosal dissection (ESD) has been developed for en-bloc resection of node-negative gastrointestinal epithelial neoplasms that are either large or associated with submucosal fibrosis [1–3]. However, ESD has not been widely performed, even in Japan, because of technical difficulties and the risks accompanying the procedure. Considerable efforts have been made to reduce these, resulting in the development of a number of innovative therapeutic devices [1,4–6] and submucosal injection solutions [7–12].

Although these advances have improved the experience with this technique, the ESD-related complication rate will never fall to zero, and the most serious complication is probably perforation. There have been several studies on the management of iatrogenic perforation in the gastrointestinal tract using conservative treatments [13–16], and one recent study with a large number of consecutive cases of gastric perforation caused by endoscopic resection of early gastric cancer showed that the patients who were treated by endoscopic closure using endoclips and other appropriate treatments showed recovery rates similar to those of patients who had no complications [17]. In the present study, a series of patients who developed perforation during ESD for the treatment of gastrointestinal epithelial neoplasia

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were analyzed and the possibility of successful nonsurgical management was investigated.

Patients and methods

ESD was performed for 528 gastrointestinal epithelial neoplasms between February 2000 and February 2005 at the University Hospital, University of Tokyo, Tokyo, Japan, and perforation occurred during the ESD procedure at 27 lesions in 27 patients (5.1%).

All the lesions that were considered suitable for ESD were predicted preoperatively as fulfilling the criteria of node-negative cancer [18–20] or premalignant neoplasia, and were considered to be technically unsuitable for en-bloc resection by conventional endoscopic mucosal resection techniques such as "inject, lift, and cut" or "inject, suck, and cut" techniques [21]. All the patients undergoing ESD were fully informed of the necessity of treatment, the risks and benefits of ESD, and alternative treatments, such as endoscopic mucosal resection, surgical resection, or ablation. The possibility of perforation, potentially leading to emergency surgery, subsequent inflammation, and bacteremia, was also thoroughly explained to patients. Written informed consent to perform ESD was obtained from all the patients.

The ESD procedure was performed in three steps: injection of fluid into the submucosa to elevate the lesion from the muscle layer; precutting of the mucosa surrounding the lesion; and dissection of the connective tissue in the submucosa beneath the lesion, as described previously in more detail [1–3,12].

A perforation was defined by our institution when:

Other organs, extraluminal fat, or extraluminal space were observed endoscopically through the muscle layer during ESD, irrespective of the presence of air accumulation in the abdomen, retroperitoneum, or mediastinum.

Plain chest or abdominal radiographs showed air accumulation in the abdomen, retroperitoneum, or mediastinum. (These radiographs were routine for all patients the morning after ESD, even if no muscle tears were noticed during the procedure.)

When perforation was noticed endoscopically during ESD, it was closed immediately using endoclips (HX-5QR-1, HX-600-090L; Olympus, Tokyo, Japan) to minimize deterioration in the patient's condition. If tension pneumoperitoneum occurred, percutaneous transabdominal air deflation was performed using an 18-gauge elastic needle [17]. All perforations were managed by two skillful endoscopists who had experience of clip application for emergency endoscopic hemostasis or the closure of mucosal defects after the removal of large colorectal polyps. When the perforation was closed and the patient's condition was stable, the procedure was continued and the resection completed. In cases where the procedure had to be stopped because of the patient's poor condition, the completion of the resection was delayed for a few days until their clinical condition had improved. Other patients were referred immediately to the surgeons for further management. The decision on whether to refer a patient for surgical treatment or to treat conservatively was made by the doctors in charge, the surgeons, the patient, and the patient's family.

After completion of ESD, all the patients with a perforation were intensively managed with a nil-by-mouth regime and peripheral fluid replacement, bedrest, and intravenous antibiotic therapy with a second-generation cephalosporin. In cases of stomach perforation, a nasogastric tube was placed for a few days for suction. Patients whose perforation was diagnosed by the presence of air in the plain chest or abdominal radiographs were managed similarly to the patients whose perforation was diagnosed endoscopically.

Perforations that became evident after a greater delay were diagnosed on the basis of clinical symptoms and laboratory findings. These patients were always considered for surgical repair, because a large amount of gastrointestinal tract contents could already have leaked out into the abdomen or mediastinum, which was considered likely to lead to deterioration in the patient's clinical condition. When the patient's symptoms and laboratory findings suggested only mild abnormality, however, conservative treatments were continued.

When the white cell count returned to a level within the normal range and there was no evidence of mediastinitis or peritonitis, patients were restarted on a liquid oral diet, gradually progressing to solids, and antibiotics were subsequently stopped on the basis of clinical and laboratory findings. Endoscopy or fluorography was not usually performed to confirm complete sealing of the perforation before restarting oral fluids because all the perforations treated conservatively had undergone immediate closure using endoclips. The algorithm for the management of ESD-related perforation is shown in Figure **1**.

Results

The demographic and clinicopathological features of the patients who had ESD-related perforations are summarized in Table **1**. Perforations occurred in all the organs of the gastrointestinal tract except for the small intestine; 14 lesions (52%) were located in the stomach. Nine of the resected lesions (33%) were histologically diagnosed as submucosal invasive carcinoma and seven lesions (26%) were accompanied by submucosal fibrosis.

Three patients had stomach perforations without showing any evidence of perforation during the ESD procedure itself. In these cases we did not know at which step of the procedure the perforation had occurred. Of the other 24 perforations, 21 (88%) occurred during the submucosal dissection. Perforation size was estimated using the size of the knives. The mean perforation size was 2.5 mm and the maximum perforation size was 5 mm. Successful perforation closure was achieved with a median of three endoclips (range 1–8) immediately after endoscopic observation of the perforation in all patients. ESD was completed after closure of the perforation in all cases.

The three patients with stomach perforations that were detected by the presence of a small amount of free air on the plain chest radiograph the morning after ESD were carefully followed up by