stem cell population and thus a fraction of stem cells with increased cancer risk. It seems important to examine whether eradication of *H. pylori* leads to decrease in methylation levels.

Mechanistic analysis of how *H. pylori* infection induces aberrant DNA methylation is necessary. *H. pylori* infection almost always induces chronic inflammation and cell proliferation (8). Cell proliferation itself has been suggested as a promoting factor for *de novo* DNA methylation (21, 26). In addition, expression of many genes is repressed during the inflammatory processes and decreased gene expression is known to promote *de novo* methylation (27–29). Further, it was recently reported that stimulation of myeloma cells by interleukin-6 increased expression of DNA methyltransferase 1 (*DNMT1*) mRNA expression (30).

The methylation level of the *p16* core region was consistently much lower than methylation levels of other CGIs. No methylation was detected in 46 (47%) of 98 *H. pylori*–positive healthy volunteers, whereas it was only 3 (3%) when the *p16* noncore region was analyzed. Also, absolute levels of methylation were much higher in *LOX*, *HAND1*, *THBD*, and *p41ARC* of *H. pylori*–positive individuals and *H. pylori*–negative gastric cancer cases. This suggested that extensive methylation of multiple, and possibly preferential, CGIs precedes infrequent occurrence of methylation of a core region of a promoter CGI of critical tumor suppressor gene(s).

As for the effect of locations within the stomach, no significant difference in methylation levels was observed between the corpus and antrum, regardless of *H. pylori*

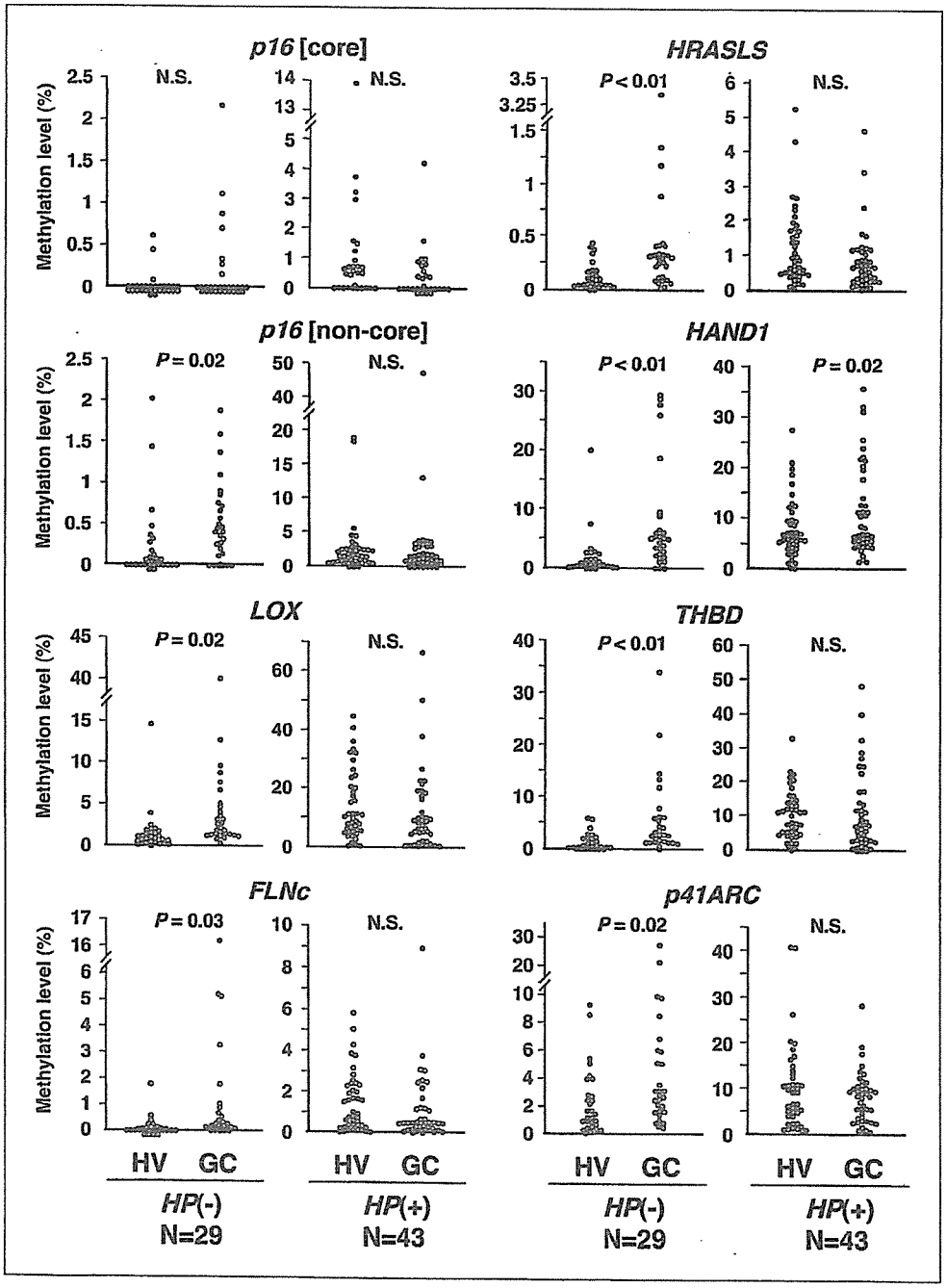

Fig. 3. Association between high methylation levels and a risk of gastric cancer development. Methylation levels of antral mucosae were measured in 29 *H. pylori*–negative and 43 *H. pylori*–positive cases with differentiated-type gastric cancers (*GC*), and the levels were compared with those in 29 *H. pylori* (*HP*)–negative and 43 *H. pylori*–positive age-matched healthy volunteers (*HV*). Among the *H. pylori*–negative individuals, methylation levels of gastric cancer cases were significantly higher (2.2- to 10-fold) than those in healthy volunteers, which showed that methylation levels in noncancerous gastric mucosae are associated with a risk of gastric cancer development. Among the *H. pylori*–positive individuals, methylation levels were highly variable within each group, and a significant increase was observed only for *HAND1* at 1.4-fold. N.S., not significant.

infection status. As for the effect of histologic changes, analysis of limited number of samples showed methylation levels of the eight CGIs were not associated with mucosal atrophy, intestinal metaplasia, or degree of inflammation (data not shown). It seems important to search for specific CGIs whose methylation levels are associated with *H. pylori* infection, with a gastric cancer risk, and with histologic changes, respectively, because various CGIs and regions within one CGI show different susceptibility to methylation (12).

In conclusion, it was indicated that *H. pylori* infection potently and temporarily induces methylation of multiple CGIs. Methylation levels of specific CGIs in noncancerous gastric mucosae may be associated with gastric cancer risk in *H. pylori*–negative individuals.

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M. Fujishiro[1]
N. Yahagi[1]
M. Nakamura[1]
N. Kakushima[1]
S. Kodashima[1]
S. Ono[1]
K. Kobayashi[1]
T. Hashimoto[1]
N. Yamamichi[1]
A. Tateishi[1]
Y. Shimizu[2]
M. Oka[2]
K. Ogura[1]
T. Kawabe[1]
M. Ichinose[2]
M. Omata[1]

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.

Institution
[1] Dept. of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[2] Second Dept. of Internal Medicine, Wakayama Medical University, Wakayama, Japan

Corresponding Author
M. Fujishiro, M.D., PhD · Dept. of Gastroenterology · Graduate School of Medicine · University of Tokyo · 7-3-1, Hongo, Bunkyo-ku · Tokyo · Japan · Fax: +81-3-5800-8806 · E-mail: mtfujish-kkr@umin.ac.jp

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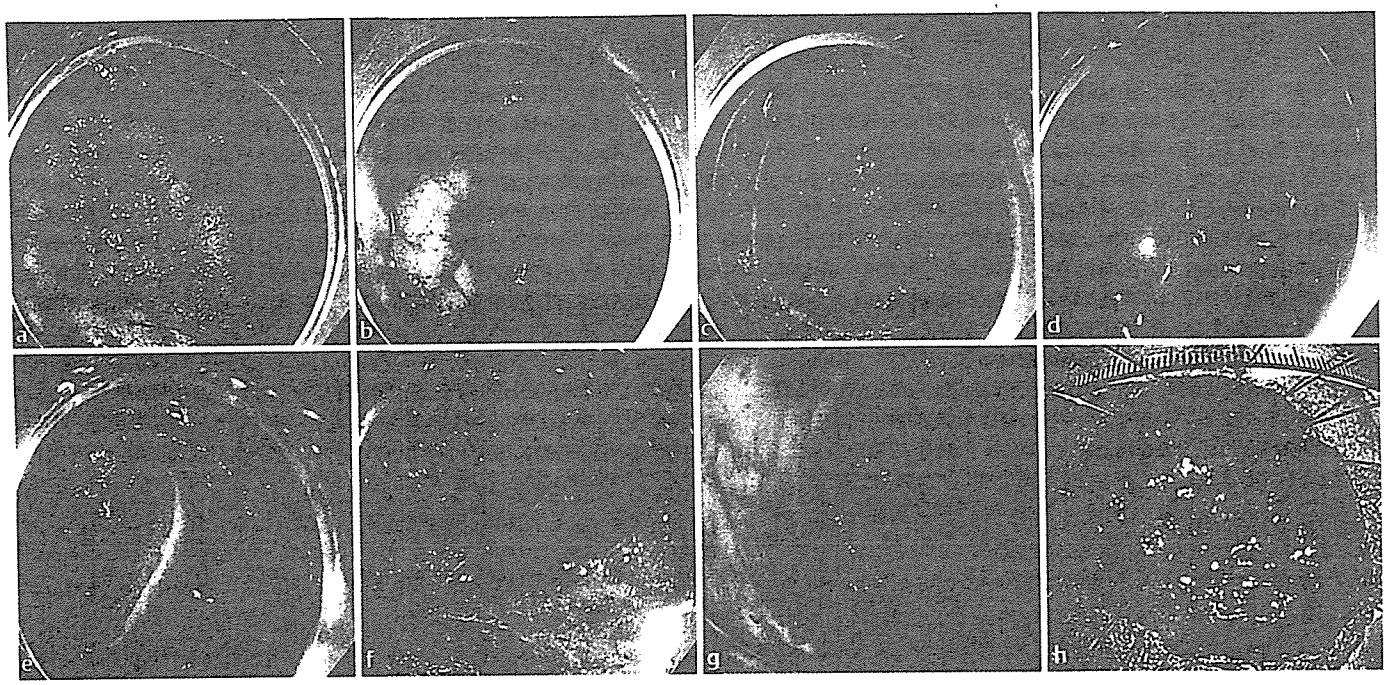

Figure **1** Endoscopic submucosal dissection for rectal neoplasia. **a** Chromoendoscopic view with indigo carmine dye, showing demarcation of the margin of the lesion, which is a type 0-IIa, laterally spreading, intramucosal adenocarcinoma in adenoma, 5 cm in size, located in the middle rectum. **b** 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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INTERNAL MEDICINE

□ CASE REPORT □

Nonparasitic Solitary Giant Hepatic Cyst Causing Obstructive Jaundice was Successfully Treated with Monoethanolamine Oleate

Masahiko Miyamoto[1], Masashi Oka[2], Takashi Izumiya[1], Tsunehiro Nagaoka[1], Yasuhito Ishihara[1], Kazuki Ueda[2], Shotaro Enomoto[2], Kimihiko Yanaoka[2], Kenji Arii[2], Hideyuki Tamai[2], Yasuhito Shimizu[2] and Masao Ichinose[2]

Abstract

A 77-year-old man hospitalized for epigastric pain showed jaundice of the skin and conjunctivae. Laboratory tests revealed elevated hepatobiliary enzymes and inflammatory markers, and imaging studies demonstrated a 12 cm hepatic cyst compressing the common bile duct. The diagnosis was a giant hepatic cyst causing obstructive jaundice. Cyst drainage and sclerotherapy with 5% monoethanolamine oleate was performed twice, resulting in almost complete disappearance of the cyst. Obstructive jaundice due to a hepatic cyst, as seen in this case, is relatively rare and this report includes a review of other similar cases in Japan.

Key words: hepatic cyst, obstructive jaundice, monoethanolamine oleate

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Introduction

Hepatic cysts are usually asymptomatic but may occasionally present as abdominal pain, nausea, vomiting, and abdominal distention (1, 2). However, even in symptomatic hepatic cysts, obstructive jaundice is rarely seen. Sanfelippo et al (3) reported obstructive jaundice in only two of 82 patients with hepatic cysts. Recent trends in the treatment of symptomatic hepatic cysts, except in cases of acute rupture, hemorrhage or where cancer is suspected, include cyst drainage followed by drug injection (sclerotherapy). Ethanol and minocycline are often used as sclerosing solutions, and more recently, monoethanolamine oleate has been used with good results (4-6). We recently encountered a patient with obstructive jaundice due to a hepatic cyst who was successfully treated with sclerotherapy using monoethanolamine oleate. This case is presented here, together with a discussion of the related medical literature.

Case Presentation

A 77-year-old man was referred to our hospital because of persistent epigastric pain. His past history was unremarkable except for appendectomy at age 18 and pulmonary tuberculosis at age 75. Physical examination on admission showed the patient to be lucid and afebrile. His blood pressure was 152/84 mmHg and pulse rate 87 bpm. The abdomen was soft and slightly distended, with mild tenderness in the upper abdomen. There was no rebound, guarding, hepatosplenomegaly, palpable masses, or lower extremity edema. Laboratory findings on admission revealed elevated hepatobiliary enzymes and inflammatory markers (Table 1), urinalysis was positive for bilirubin, and abdominal ultrasound showed a large cystic lesion in the right hepatic lobe (Fig. 1). The lesion contained no septum or calcifications, and the intrahepatic bile ducts in both hepatic lobes were dilated. Abdominal computed tomography confirmed the presence of a large cystic lesion 12 cm in diameter (Fig. 2a),

[1] Division of Internal Medicine, Nagayama Hospital, Osaka and [2] Second Department of Internal Medicine, Wakayama Medical University, Wakayama

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Correspondence to Masahiko Miyamoto, Division of Internal Medicine, Nagayama Hospital, 1-1-10 Okubohigashi, Kumatori, Sennan, Osaka 590-0406

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Table 1. Laboratory Data on Admission

Urine		*Blood chemistry*			
Protein	(-)	AST	430 IU/l	Na	142 mEq/l
Sugar	(-)	ALT	492 IU/l	K	3.5 mEq/l
Occult blood	(-)	γ-GTP	692 IU/l	Cl	106 mEq/l
Bilirubin	(3+)	LDH	340 IU/l	BUN	26 mg/dl
Peripheral blood		ALP	1884 IU/l	Cr	0.9 mg/dl
WBC	10600 /mm³	T.Bil	7.0 mg/dl	T.Chol	214 mg/dl
Neutro	75.6%	D.Bil	6.0 mg/dl	TG	49 mg/dl
Lym 17.1%	Mo 6.2%	AMY	72 IU/l	PT/INR	1.01
Eo 0.9%	Ba 0.2%	TP	6.5 g/dl	APTT	26.1 sec.
RBC	468x10⁴ /mm³	Alb	4.1 g/dl	CEA	2.2 ng/ml
Hb	14.7 g/dl	Ch-E	274 IU/l	CA19-9	10 U/ml
Ht	44 %	CRP	2.8 mg/dl	HBs Ag	(-)
Plt	25.2x10⁴ /mm³	ESR	25 mm/hr	HCV Ab	(-)

which showed no enhancement with contrast medium (Fig. 2b). Both T1- and T2-weighted magnetic resonance images of the lesion showed homogeneously high signal intensity as compared with normal liver parenchyma (Fig. 3a and b). Magnetic resonance cholangiopancreatography indicated the presence of a large spherical lesion near the confluence of the right and left hepatic ducts that was compressing the intrahepatic bile ducts and keeping them separate from the common bile duct (Fig. 3c). Endoscopic retrograde pancreatocholangiography revealed downward compression of the common bile duct, gall bladder, and cystic duct (Fig. 4). The intrahepatic bile ducts could not be visualized on endoscopic retrograde pancreatocholangiography. No flow of contrast medium was detected in the cystic lesion, and neither gall stones, tumors, nor abnormalities of the pancreatobiliary duct could be identified. On the basis of these findings, a diagnosis was made of obstructive jaundice due to a giant hepatic cyst.

On day 15 after admission, about 600 mL of fluid was drained from the cyst by means of transcutaneous transhepatic drainage. Repeat abdominal ultrasound showed almost complete disappearance of the cyst (Fig. 5). Sixty milliliters of 5% monoethanolamine oleate was then injected, the patient was placed in different positions for 30 minutes, after which the monoethanolamine oleate was aspirated. On the following day the drainage tube was removed. The fluid drained from the cyst was reddish-brown and serous, with cell counts of less than 100 (cells could not be classified), a specific gravity of 1.019, negative Rivalta test result, and cytologically identified as class I. Bacteriologic cultures of the cyst contents were negative, but cyst fluid tumor markers were markedly elevated: CEA, 94.7 ng/mL; CA19-9, ≥ 5,000 U/mL; CA125, 1,159 U/mL. Despite the initial almost complete disappearance of the cyst, regrowth was noted 28 days after the first drainage (Fig. 6), and a second drainage was thus performed. Drainage of about 300 mL of fluid followed by injection of 60 mL of monoethanolamine oleate resulted in disappearance of the hepatic cyst and resolution of the abdominal pain. On days 33 and 41 after admission, serum transaminase and total bilirubin, respectively, were within normal limits. On day 41 after admission, the patient was discharged from hospital. He has since shown an uneventful course with no recurrence of the hepatic cyst.

Discussion

The prevalence of hepatic cysts is 0.1 to 0.5% (3) based on autopsy studies and 2.5% based on ultrasound examinations (7). Hepatic cysts have been classified by Henson et al (8) into four types: congenital, neoplastic, inflammatory, and traumatic. Congenital hepatic cysts are further categorized into solitary and polycystic cysts. The findings of the present patient are consistent with a solitary unilocular cyst.

For diagnosing a hepatic cyst, it is important to rule out hepatic cystadenoma or cystadenocarcinoma. Imaging study findings that suggest a cystadenoma or cystadenocarcinoma include the presence of solid elements with enhancement on contrast computed tomography (9). In the present patient, none of the imaging studies showed solid elements, and no enhancement was seen on contrast computed tomography. The diagnosis in this case was therefore a simple hepatic cyst. Laboratory findings on admission showed elevated hepatobiliary enzymes and inflammatory markers. In addition, serum transaminase was elevated, but normalized after cyst drainage. Since other causes of an elevated serum transaminase level were absent, this elevation was considered to be caused by obstructive jaundice.

Typical magnetic resonance imaging findings of a hepatic cyst include the same signal intensity as water (10), that is, homogeneous low signal intensity on T1-weighted imaging and homogeneous high signal intensity on T2-weighted imaging. However, our patient had homogeneous high signal intensity on both T1- and T2-weighted images, which suggests intracystic hemorrhage or a high protein concentration. This, combined with the reddish-brown color of the drained cyst fluid, indicates that the patient may have been suffering intracystic bleeding, which caused cyst enlargement prior to the development of symptoms, even though findings of abdominal ultrasound and abdominal computed tomography were not typical for intracystic hemorrhage.

Markedly elevated tumor marker levels have been reported even in histologically diagnosed simple cysts (11, 12). Iwase et al (13) reported CA19-9 levels in hepatic cyst fluid at least 100 times higher than in normal serum concentrations. The present patient also had markedly elevated cyst fluid tumor marker levels, and imaging studies indicated a simple cyst.

Solitary nonparasitic cysts of the liver causing obstructive jaundice were first reported in 1950 by Caravati et al (14). In connection with the findings for our patient, we reviewed reports of similar cases in the Japanese and English medical literature. We found a total of 51 patients with the following characteristics: mean age, 65.8±15.2 years (range, 29 to 90 years); male to female ratio, 7:6; cyst size, 12.5±5.1 cm (range, 2 to 30 cm); and total bilirubin, 10.2±7.7 mg/dL (range, 1.5 to 31.5 mg/dL). Twenty-nine patients were treated surgically and 22 were treated non-surgically. Of the

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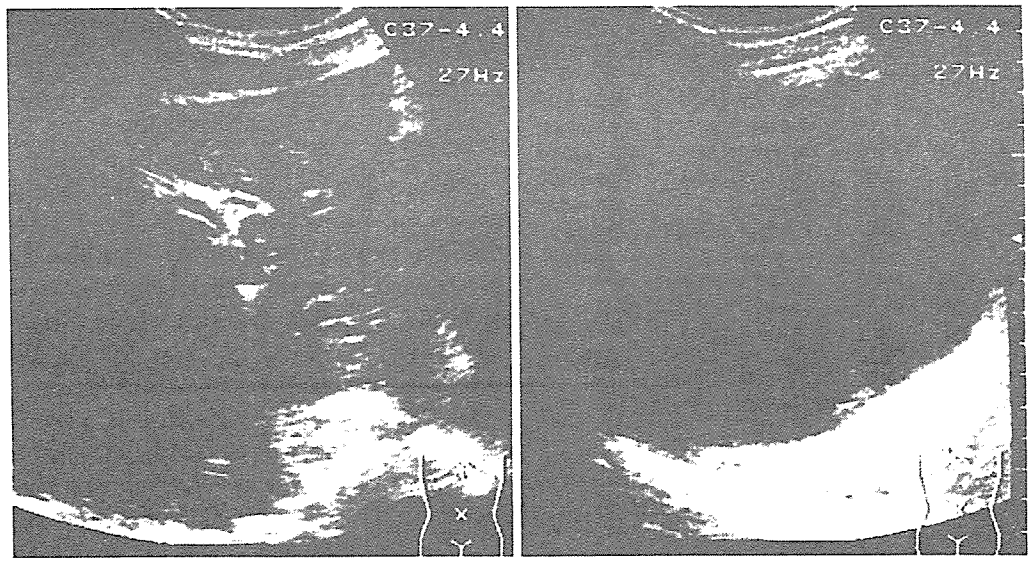

Figure 1. Abdominal ultrasound. A large cystic lesion is located in the right hepatic lobe. The content is homogeneous, without a septum or calcifications, and the intrahepatic bile ducts are dilated.

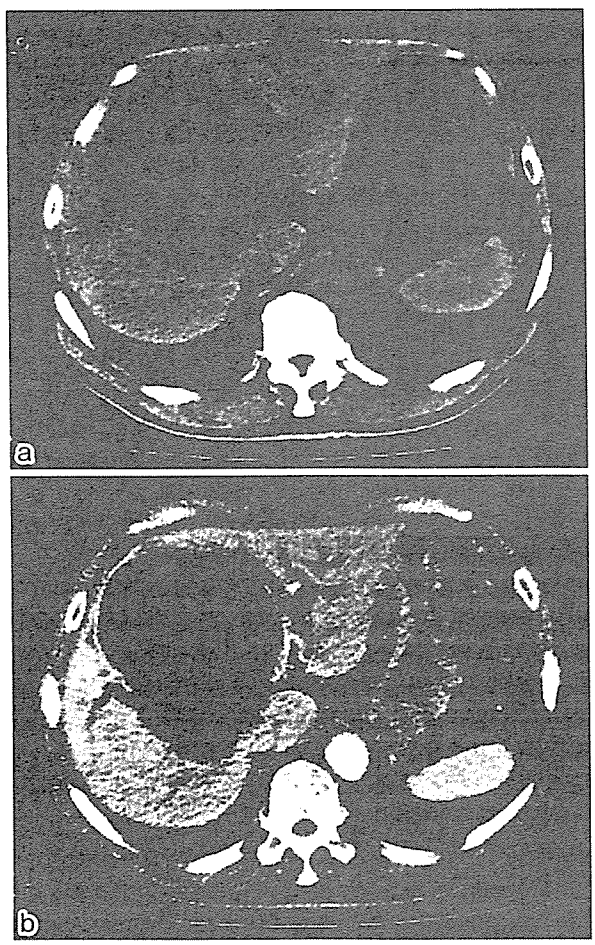

Figure 2. Upper abdominal computed tomography. a: Plain computed tomography shows a large 12 cm cystic lesion. b: Contrast computed tomography shows no internal enhancement and no enhancement of the cyst wall.

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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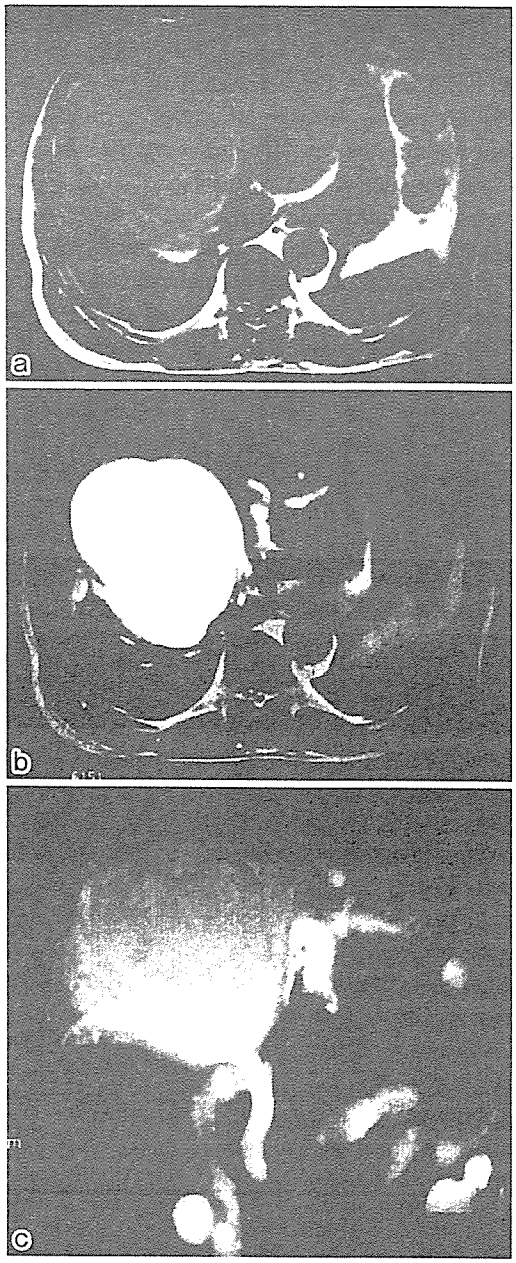

Figure 3. Abdominal magnetic resonance imaging. a: T1-weighted imaging shows a cystic lesion with homogeneous high signal intensity. b: T2-weighted imaging also shows homogeneous high signal intensity. c: Magnetic resonance cholangio-pancreatography indicates the presence of a large spherical lesion 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.

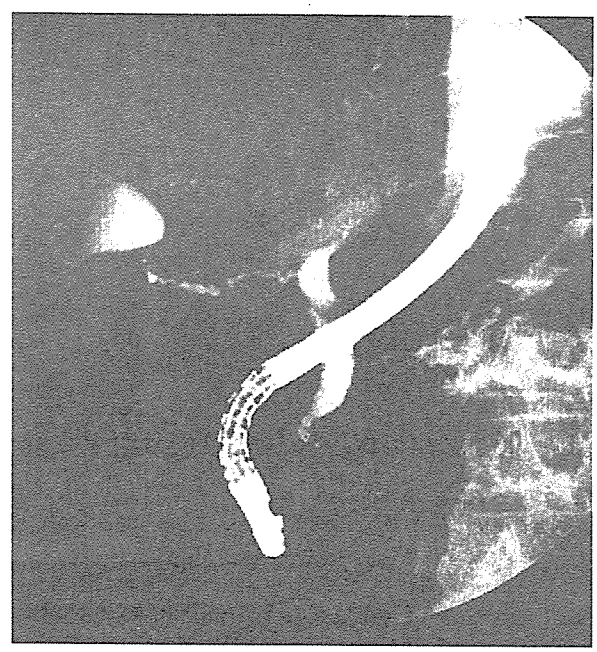

Figure 4. Endoscopic retrograde pancreatocholangiography. Downward compression of the common bile duct, gall bladder, and cystic duct. No contrast medium is seen in the intrahepatic bile ducts.

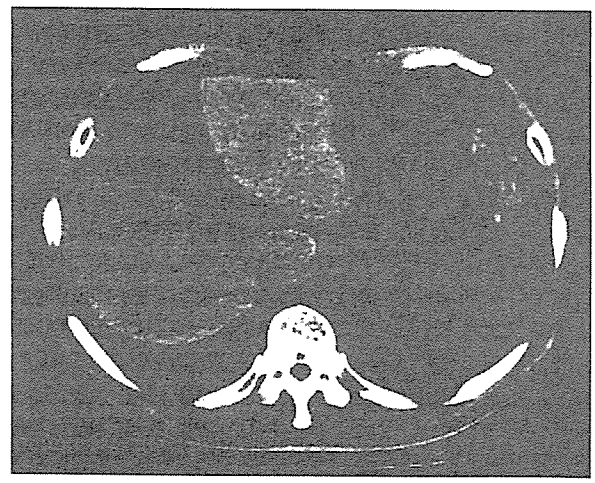

Figure 5. Upper abdominal computed tomography. The cystic lesion disappeared after drainage and monoethanolamine oleate treatment.

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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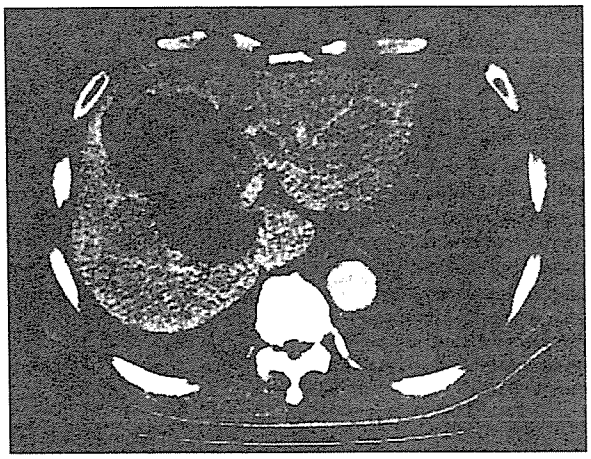

Figure 6. Upper abdominal contrast computed tomography. Regrowth of the cyst was noted 28 days after the initial drainage, for which a second drainage was performed.

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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ORIGINAL ARTICLES

Endoscopic Submucosal Dissection of Esophageal Squamous Cell Neoplasms

MITSUHIRO FUJISHIRO,* NAOHISA YAHAGI,* NAOMI KAKUSHIMA,* SHINYA KODASHIMA,* YOSUKE MURAKI,* SATOSHI ONO,* NOBUTAKE YAMAMICHI,* AYAKO TATEISHI,* YASUHITO SHIMIZU,† MASASHI OKA,† KEIJI OGURA,* TAKAO KAWABE,* MASAO ICHINOSE,† and MASAO OMATA*

*Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo; and †Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan

Background & Aims: Endoscopic submucosal dissection (ESD) has recently been developed for en bloc resection of stomach neoplasms, which results in high tumor eradication rates as well as a modality for the precise histologic assessment of the entire lesion. Application of the technique is desirable for esophageal squamous cell neoplasms (SCNs), but there have been no reports on the use of this procedure in the esophagus. *Methods:* An ESD with methods similar to those used for resections of early gastric cancer was performed on 58 consecutive esophageal SCNs with preoperative diagnoses of intraepithelial neoplasm or intramucosal invasive carcinoma occurring in 43 enrolled patients. The therapeutic efficacy, complications, and follow-up results were assessed. *Results:* The rate of en bloc resection was 100% (58/58), and en bloc resection with tumor-free lateral/basal margins (R0 resection) was 78% (45/58). There was no evidence of significant bleeding. Perforation occurred in 4 (6.9%) patients during the ESD, who were managed by conservative medical treatments after endoscopic closure of the perforation. Removal of 9 (16%) lesions resulted in esophageal stricture requiring balloon dilation after ESD. Of 40 lesions occurring in 31 patients fulfilling the criteria of node-negative tumors (mean follow-up, 17 months), 1 lesion resected by en bloc resection with nonevaluable tumor-free lateral margins (Rx [lateral] resection) recurred locally 6 months after ESD, which was treated successfully by a second ESD procedure. *Conclusions:* The ESD is applicable to the esophagus with promising results, but notification of risk is essential.

With the recent development of endoscopy and iodine staining,[1,2] the discovery of esophageal squamous cell neoplasms (SCNs) indicated for local treatment has increased markedly. Endoscopic mucosal resection (EMR) has been aggressively indicated for select localized neoplasms as an alternative to esophagectomy, especially in Japan,[3] because the rates of surgical mortality and postsurgical complications related to esophagectomy are high.[4–6] The long-term survival outcomes after EMR in the esophagus show similar efficacy when compared with esophagectomy for small, early-stage neoplasms.[7,8]

A large number of retrospective histopathologic analyses of surgically resected esophageal SCNs showed that noninvasive carcinoma (carcinoma in situ, m1) and intramucosal invasive carcinoma limited to the lamina propria mucosae (m2) without vessel infiltration have no lymph node or distant metastases[3,9,10] and might be considered targets for endoscopic resection. However, large-sized or complex-shaped lesions might be treated by esophagectomy, chemotherapy, or radiation therapy because of technical difficulties in achieving complete removal of these lesions. By contrast, conventional EMR techniques such as the "inject, lift, and cut technique" or the "inject, suck, and cut technique" are limited in resection size, and large lesions have to be resected in multiple fragments. Moreover, the resected area cannot be precisely controlled by the operators, which might lead not only to incomplete removal of even small lesions but also to excessive non-neoplastic mucosal resection. Unnecessary excessive resection should be avoided, especially in the esophagus, so as not to cause deformity and stenosis of the narrow esophageal space. A newly developed therapeutic endoscopy with cutting knives, endoscopic submucosal dissection (ESD), was originally developed for en bloc resection of large and ulcerative

Abbreviations used in this paper: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SCN, squamous cell neoplasm

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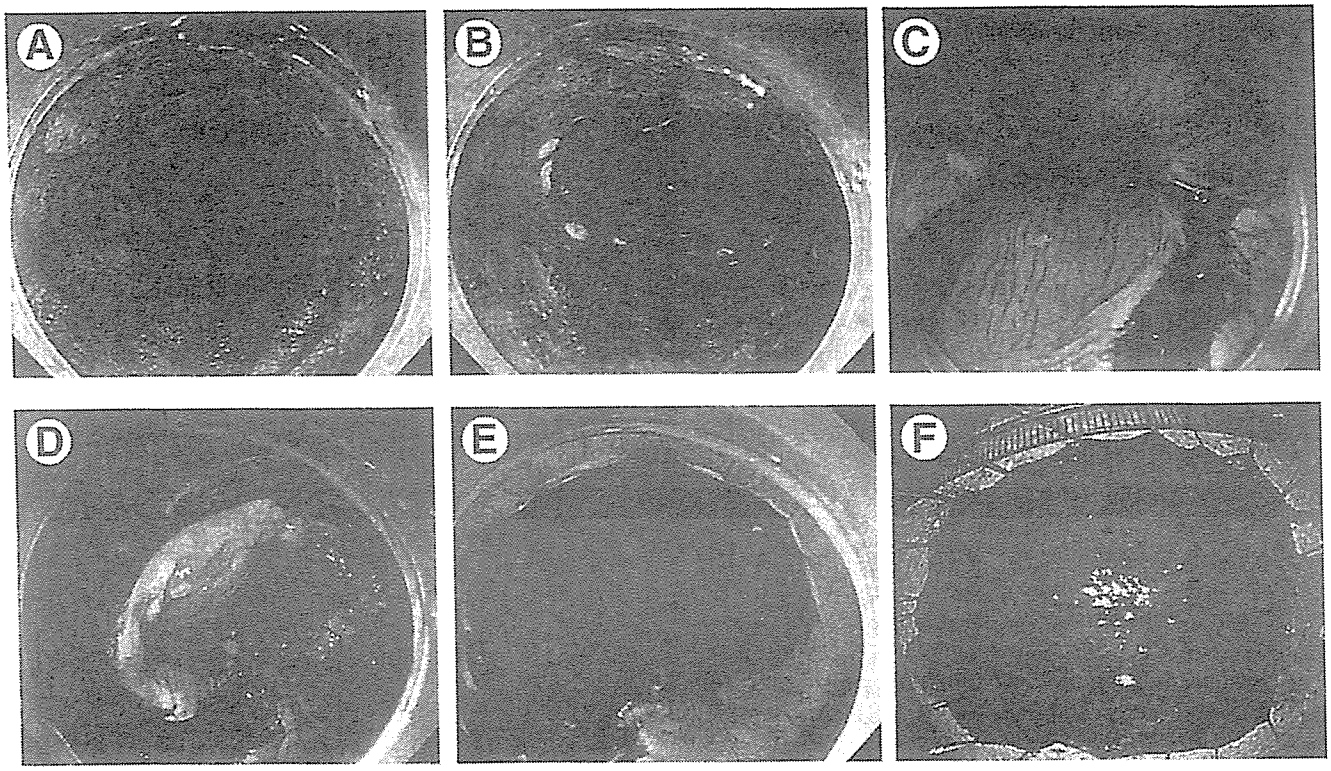

Figure 1. ESD for esophageal neoplasms. (*A*) Chromoendoscopy with iodine staining to demarcate the lesion from the non-neoplastic area. (*B*) Marking around the lesion. (*C*) Initial mucosal incision after submucosal injection at the distal margin of the lesion. (*D*) Mucosal incision after submucosal injection at the proximal margin of the lesion and subsequent submucosal dissection from the proximal end. (*E*) Artificial ulcer after removal. (*F*) Complete resection of the lesion in one piece.

neoplasms in the stomach,[11–14] and these techniques have been applied to other organs of the gastrointestinal tract including the esophagus and colorectum.[15–17] The outcomes of ESD have not been reported in detail, even in the stomach, because the long-term data are still being collected. Furthermore, few studies have elucidated the technical feasibility of the procedure in other gastrointestinal tract organs, including the esophagus and colorectum. In this study, we assessed ESD with our own technique for esophageal SCNs with special reference to the technical feasibility and short-term follow-up outcomes.

Patients and Methods

Fifty-eight consecutive superficial esophageal SCNs occurring in 43 patients were resected by ESD between January 2002 and September 2005 at the University of Tokyo Hospital, Tokyo, Japan. All patients with esophageal neoplasm who had a preoperative diagnosis of high-grade intraepithelial neoplasm (high-grade dysplasia and noninvasive carcinoma) or intramucosal invasive carcinoma were candidates for ESD. Diagnosis was made by using chromoendoscopy with iodine staining, endoscopic biopsy, and occasionally by endoscopic ultrasonography for suspicious lesions of submucosal invasion. All patients were informed of the risks and benefits of several treatment options including ESD, conventional EMR, ablation therapy, conventional surgery, and radiation therapy with or without concomitant chemotherapy, and written informed consent to perform ESD was obtained from all the patients preoperatively.

Endoscopic Submucosal Dissection Procedure

ESD was carried out by using a single-channel upper gastrointestinal endoscope with a water-jet system (XGIF-Q240M; Olympus Optical Co, Tokyo, Japan, or EG-2931; Pentax Co, Tokyo, Japan) and a high-frequency generator with an automatically controlled system (ENDOCUT mode) (Erbotom ICC 200; ERBE Elektromedizin GmbH, Tübingen, Germany). The transparent attachment was fitted on the tip of the endoscope mainly to obtain a constant endoscopic view and to create tension on the connective tissue for the submucosal dissection. A representative case of the procedure is shown in Figure 1.

Marking around the lesion. Lugol chromoendoscopy was necessary before marking the lateral margin of

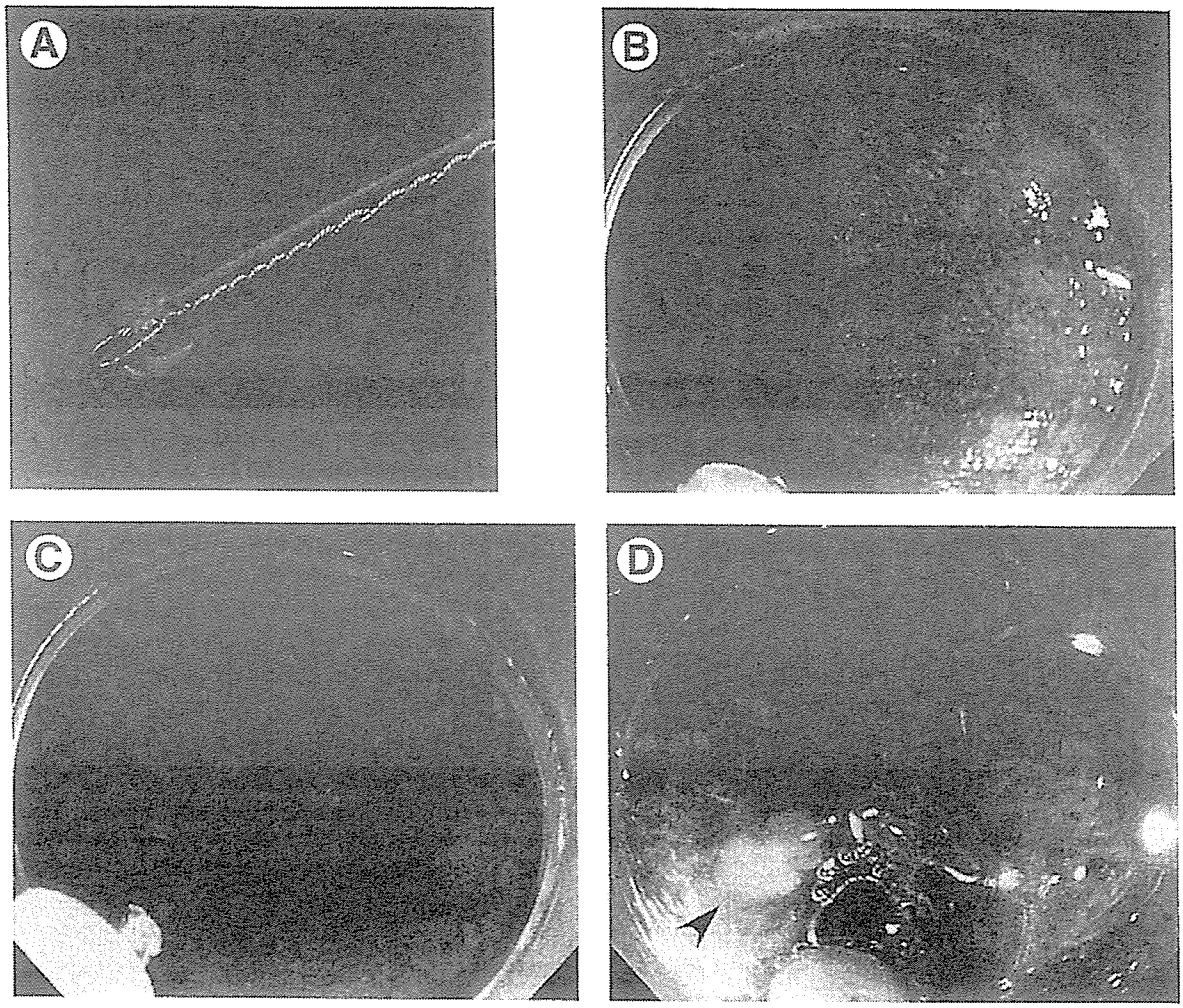

Figure 2. (*A*) Flexknife. (*B*) Tip of the Flexknife used for marking the circumference of the lesion. (*C*) Tip of the Flexknife used for the mucosal incision and submucosal dissection. (*D*) The proper esophageal glands observed in the submucosal layer (*arrowheads*).

the lesion, which could be visualized as the border between the stained and unstained areas. With the tip of an electrosurgical snare (thin type, SD-7p-1; Olympus, used from January 2002–December 2002) or Flex knife (KD-630L; Olympus, used from January 2003–September 2005) (Figure 2*A*),[14,15] dots placed about 5 mm outside of the lesion margin at 2-mm intervals were made to mark the circumference of the target lesion. The knife was fixed at a length of 1 mm (Figure 2*B*) and placed on the mucosal surface with little tension so as not to induce contact bleeding from the mucosa. Soft coagulation mode (output, 50 W) was used as the electronic current.

Creating a submucosal fluid cushion. One percent 1900 kd hyaluronic acid preparation (Suvenyl; Chugai Pharmaceutical Co, Tokyo, Japan) was mixed in normal saline (in use from January 2002–October 2003) or 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol; Chugai Pharmaceutical Co) (in use from November 2003–September 2005). The solvent solution used for the hyaluronic acid preparation was changed because of novel knowledge of submucosal injection solutions.[18,19] Glyceol contains sugar that interacts with hyaluronic acid to increase the viscoelasticity of the hyaluronic acid solution over that of normal saline. The ratio of Glyceol and Suvenyl was also changed from a 1:3 ratio (used from January 2002–March 2004) to a 1:7 ratio (used from April 2004–September 2005) as a result of technical advances. To clarify the area of the submucosal injection, to distinguish clearly between the muscle layer and the submucosal layer, and to produce higher hemostatic ability, indigo carmine and epinephrine were added to the solution at concentrations of 0.005% and 0.0005%, respectively. About 2 mL of the solution was injected into the submucosal layer at a time, and the injection was repeated a few times until the mucosa that was intended to be incised was lifted to an acceptable level.

Incising the mucosa outside the lesion. After lifting the lesion, a mucosal incision was made with the tip of an electrosurgical snare (thin type) or Flexknife. The knife was fixed at a length of 2 mm (Figure 2*C*) and gently pressed onto the mucosa to produce a cutting effect by using the ENDOCUT mode with effect 2 (output, 60 W). The distal half of the mucosal incision was completed first, followed by the proximal half.

Dissecting the submucosal layer beneath the lesion. Before incising the entire circumference of the lesion, dissection of the submucosa was begun from the area in which the mucosal incision was completed to keep from flattening the lifted area as the procedure progressed. When a proper esophageal gland was observed during dissection, it was important to dissect at a level deeper than the gland to prevent resection with tumor-exposed basal margins (R1 [basal] resection) (Figure 2*D*). The principal knife used for the submucosal dissection was the same length as that used for the mucosal incision with forced coagulation mode (output, 40 W), and in difficult dissections the Hookknife (KD-620LR; Olympus)[20] was also used in combination with the principal knife. To control bleeding, hemostatic forceps (SDB2422; Pentax or Coagraspers FD-410LR; Olympus) were used in soft coagulation mode (output, 50 W). These hemostatic devices have a narrow opening angle, a small cup, and a blunt edge that look similar to small-sized hot-biopsy forceps. After pinpoint holding and mechanical compression, electrocoagulation is easily performed to obtain hemostasis. The water-jet system supplies a continuous jet of water at high pressure, which easily and swiftly washes away any blood obstructing the visual field, allowing identification of the vessel that is bleeding.

Treatment of artificial ulcer after endoscopic submucosal dissection. After resection of the lesion, visible vessels of the resulting artificial ulcer were treated with the hemostatic devices in soft coagulation mode (output, 50 W) to prevent delayed bleeding. Finally, sucralfate was sprayed onto the base of the ulcer by using the outer sheath of a clipping device that was inserted into the instrument channel of an endoscope both to confirm the hemostasis and to coat the surface of the ulcer.[21]

Three hours after ESD, patients were permitted to drink a small amount of water. The next day, if the patient's symptoms, laboratory findings, and chest x-ray were unremarkable, a light meal was permitted, and the patients were discharged within 1 week. If complications occurred, the schedules were changed according to the individual patient's condition.

All evaluations of esophageal SCNs were performed according to the Paris classification and revised Vienna classification.[22–24] To aid in the orientation, thin, curled-up ESD specimens were flattened and fixed at their periphery with thin needles pinning them to an underlying cork board before the specimens were immersed overnight in 10% formalin. The fixed specimens were then sectioned serially at 2-mm intervals parallel to a line that included the closest resection margin of the specimen, so that the resected margins and invasion depth could be assessed accurately. The sectioned materials were embedded in paraffin to make histologic sections that were stained with hematoxylin-eosin and were examined microscopically. The patients who had a histopathologic diagnosis of invasive carcinoma deeper than the lamina propria mucosae (the muscularis mucosae [m3], or the submucosa [sm] and/or vessel infiltration or incomplete resection on the basal margins, resection with nonevaluable tumor-free basal margins [Rx (basal) resection], or resection with tumor-exposed basal margins [R1 (basal) resection]) were recommended for additional treatments such as esophagectomy with lymph node dissection or radiation therapy with or without chemotherapy for possible lymph node metastases. Even if the histopathologic evaluation revealed that the lesions fulfilled the criteria of node-negative tumors but were incompletely resected on the lateral margins, resection with nonevaluable tumor-free lateral margins (Rx [lateral] resection), or resection with tumor-exposed lateral margins (R1 [lateral] resection), the patients were followed without additional treatments because the burn effects on the resected tissue or artifactual problems with processing the resected tissue sometimes made a precise histopathologic evaluation of the lateral margins difficult.

Follow-up endoscopy with iodine staining was usually performed about 2 months after ESD to confirm healing of the postprocedure ulcers and to exclude the presence of residual tumors, then again at about 6 months and 12 months after ESD, followed by annual endoscopic examinations to check for local recurrence and/or a second primary lesion for cases fulfilling the criteria of node-negative tumors. The existence of distant or lymph node metastases was evaluated with computed tomography and endoscopic ultrasonography indefinitely.

Results

The clinicopathologic features of the included patients are shown in Table 1. All the lesions were resected in an en bloc fashion. En bloc resection with tumor-free lateral/basal margins (R0 resection) was ac-

Table 1. Clinicopathologic Features of the Esophageal SCNs

		No. of SCNs
Mean size, *mm* (range)	24 (2–66)	
Location	Ce/Ut/Mt/Lt/Ae	0/7/29/17/5
Circumference of the esophageal lumen	<1/2/1/2 to <3/4/>3/4	39/12/7
Macroscopic type	IIa/IIb/IIc/IIc + IIa	2/20/35/1
Histologic depth	Dysplasia/m1/m2/m3/sm1/sm2	18/24/8/11/4/3
Vessel infiltration	Presence/absence	7/51

NOTE. The terms of macroscopic type and histologic depth are derived from reference 22. Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; IIa, superficial, elevated type; IIb, flat type; IIc, superficial shallow, depressed type; m1, intraepithelial carcinoma; m2, microinvasive carcinoma (invasion through the basement membrane); m3, intramucosal carcinoma (invasion to the muscularis mucosae); sm1, superficial invasion (less than 200 μm below the muscularis mucosae) in the submucosa; sm2, middle invasion (more than 200 μm below the muscularis mucosae) in the submucosa.

complished in 45 of the 58 dissected lesions (78%) (Table 2). The mean resection size was 38 mm (range, 11–72 mm), and the mean lesion size was 24 mm (range, 2–66 mm). The small lesions for which conventional EMR seemed to be applicable in terms of lesion size were treated by ESD because of the single piece resection with coexisting lesions located nearby, or the existence of scarring caused by previous chemotherapy, radiation therapy, or endoscopic treatments. Fifty-three lesions (91%) were located in the thoracic esophagus, and 39 lesions (67%) were spread over less than half of the circumference of the esophageal lumen. Forty lesions (69%) (8 dysplasias, 24 m1, and 8 m2) were considered node-negative tumors by histopathologic evaluations of the ESD specimens.

Minor bleeding was encountered in all the dissections when incising the mucosa or dissecting in the submucosal layer, but hemostasis was achieved with thermocoagulation and without the use of clips during the procedure. A mean change in hemoglobin levels between pre-ESD and post-ESD of −0.22 g/dL (range, −1.5 to +1.3 g/dL) was observed, and the hemoglobin levels dropped by more than 1 g/dL in 7 (16%) of the 43 patients. No patient experienced massive hemorrhage requiring a blood transfusion or a postprocedure emergency endoscopy.

Perforation, which was diagnosed by endoscopic findings of tearing of the proper muscle layer, occurred in the dissection of 4 (6.9%) lesions, and all cases of perforation were accompanied by pneumomediastinum. The size of all 4 perforations was less than 5 mm, which was measured by comparison with the tip of an electrosurgical knife. After immediate closure of the perforations by endoscopic clipping and completion of ESD, conservative treatments with intravenous antibiotics and allowing no oral intake were prescribed by the primary physician who advised the patients and their family after informed consent. Leukocytosis returned to within a normal range after a few days without any evidence of mediastinitis in all the patients with perforation. Re-feeding was begun gradually with pureed foods, and antibiotics were subsequently stopped. Endoscopy or fluorography was not performed to confirm the complete sealing of the perforation before beginning oral feeding because all the perforations were treated with immediate closures with clips. Pneumomediastinum disappeared spontaneously within a week in all the patients, which was confirmed by chest x-ray. All perforations occurred before July 2003, before the techniques and experience with esophageal ESD were completely established. No patients experienced pneumomediastinum without perforation, which was confirmed by chest x-rays taken after ESD.

Nine lesions in 9 (16%) patients required several (median, 3; range, 1–16) sessions of periodic balloon dilatation after ESD for esophageal stricture, which was repeated every 1–2 weeks after dysphagia was recognized. ESD for 7 lesions that spread over more than three fourths of the circumference of the esophageal lumen, which required semicircular or complete circular resection, caused esophageal stricture requiring balloon dilatation. All the postprocedure strictures were successfully managed endoscopically.

Of 40 lesions in 31 patients that fulfilled the criteria of node-negative tumors, 22 lesions in 18 patients were successfully followed in our hospital for more than 6 months by endoscopy. The reasons for excluding the other lesions from the follow-up analysis were due to 4 with concurrent lesions that required additional treatments, 8 were followed up at another hospital, and 6 had

Table 2. En Bloc Resection Rate and Histologic Margin of the Resected Specimens

	Lesions	
	n	%
En bloc resection	58	100
R0 resection	45	78
R1 (lateral) resection (tumor extending to lateral margins)	5	8.6
R1 (basal) resection (tumor extending to basal margins)	2	3.4
Rx (lateral) resection (not evaluable for lateral margins)	6	10
Rx (basal) resection (not evaluable for basal margins)	0	0

a follow-up duration of less than 6 months. During a mean follow-up duration of 17 months (range, 6–36 months), only 1 noninvasive carcinoma with Rx (lateral) resection (4.5%) recurred locally 6 months after ESD as noninvasive carcinoma. This lesion was completely resected by a second ESD, and an additional follow-up of 12 months' duration revealed no further local recurrence. No lymph node or distant metastases were observed.

Of 18 lesions in 16 patients with concomitant risks of nodal metastases, 6 lesions in 5 patients were closely followed up without additional treatment because of the patient's decision. All of these lesions were intramucosal invasive carcinomas into the muscularis mucosae (m3), and only 1 lesion had lymphatic vessel infiltration, which increased the possibility of nodal metastasis. During a mean follow-up of 15 months' duration (range, 6–23 months), the lesion with lymphatic vessel infiltration recurred in the regional lymph nodes 18 months after ESD as a nonresectable, recurrent tumor. The patient was followed with computed tomography every 6 months and with annual endoscopic ultrasonography. The lymph node swelling was not detected by endoscopic ultrasonography and computed tomography 6 months before its detection.

Discussion

To show the efficacy of the ESD procedure for esophageal SCNs, 2 aspects, the technical feasibility of the procedure and follow-up data showing the efficacy of the procedure, have to be considered. Although the duration of follow-up is short, the present study shows that no patient with esophageal SCNs that met the criteria of node-negative tumors postoperatively treated with ESD experienced recurrence extraluminally. One noninvasive carcinoma with Rx (lateral) resection recurred locally in the epithelial layer, but it was successfully treated by a second ESD procedure. Our data suggest that ESD can be a successful treatment for esophageal SCNs fulfilling the criteria of node-negative tumors. Furthermore, considering the lack of complications, ESD could be a relatively safe procedure for most patients. The perioperative mortality rate was zero, and the most serious postoperative complication was benign stricture of the esophagus, which was successfully treated with balloon dilatation. Although 4 patients had small perforations, these were managed successfully without surgical rescue. We emphasize again that all the perforations occurred during the early period of this study before the procedure was perfected, and no further perforations have occurred for more than 2 years. The esophagus is one of the most accessible sites for any instrumentation and is fixed in the retromediastinum. Hence, the endoscopic approach is easier, and the technical difficulty is less than that for other gastrointestinal organs such as the stomach and colon. When we master the strategy for the esophagus, ESD might be safely performed in this location because the other serious complication, namely bleeding, is also considerably less than that observed in the stomach.

The major drawbacks of conventional EMR such as strip biopsy[25] and EMR with cap[26] are local recurrences, which are reported in up to 20% of EMR series.[27] The reason why esophageal SCNs treated by conventional EMR recur locally at such a considerable frequency is unknown, but we speculate that one of the reasons is multifragmental resection by EMR, which might leave tumor cells between the spaces of resected mucosa and which is impossible to evaluate through the histology of the resected specimens. Another possibility might be the incomplete resection of ductal extensions of tumor cells into the proper esophageal glands. It is known from thorough histologic analysis that ductal extension of tumor cells in the proper esophageal glands has no risk of nodal metastases, which is considered to be noninvasive carcinoma even if the tumor cells are observed in the submucosal layer.[28] Both situations are preventable by applying ESD for local treatment rather than conventional EMR, because the en bloc resection allows for a check of the tumor margin, even when the lesion has a complex shape or a large size, and ductal extension of tumor cells into the glands can removed by resecting the submucosal connective tissues beneath the proper esophageal glands with direct endoscopic views.

In summary, this study shows that ESD is a promising technique that is not limited to the stomach, but it can also be used for the resection of esophageal SCNs after refinement of the technique. However, further evaluation and assessments of case series are necessary before ESD can be widely accepted as a standard endoscopic treatment for esophageal SCNs.

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Address requests for reprints to: Mitsuhiro Fujishiro, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan. e-mail: mtfujishkkr@umin.ac.jp; fax: +81-3-5800-8806.

Safety of Argon Plasma Coagulation for Hemostasis During Endoscopic Mucosal Resection

Mitsuhiro Fujishiro, MD, Naohisa Yahagi, MD,* Masanori Nakamura, MD,* Naomi Kakushima, MD,* Shinya Kodashima, MD,* Satoshi Ono, MD,* Katsuya Kobayashi, MD,* Takuhei Hashimoto, MD,* Nobutake Yamamichi, MD,* Ayako Tateishi, MD,* Yasuhito Shimizu, MD,† Masashi Oka, MD,† Masao Ichinose, MD,† and Masao Omata, MD**

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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From the *Department of Gastroenterology, Graduate school of Medicine, University of Tokyo, Tokyo, Japan; and †Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan.

Reprints: Mitsuhiro Fujishiro, MD, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan (e-mail: mtfujish-kkr@umin.ac.jp).

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