When a video endoscope equipped with the newer technical facilities has detected an abnormal area, the next step is the analysis of the microcirculation at low magnification, with NBI and without chromoscopy. Slight vascular alterations suggest either a non-neoplastic lesion or low-grade neoplasia; the gross morphology is then assessed in standard vision with the help of chromoscopy. Severe vascular alterations suggest high-grade noninvasive or invasive neoplasia, and the surface microarchitecture (depressions and ridges) is explored under magnification with an optical zoom and chromoscopy (indigo carmine or cresyl violet). Magnification with NBI has been proposed as an alternative to magnification with chromoscopy [44]. When using a standard video endoscope that is not equipped with NBI and magnification, the analysis of the microcirculation in transparency is less accurate. The diagnosis relies on the assessment of the gross morphology of the lesion after staining with indigo carmine dye. In summary, there is still room for chromoscopy in the assessment of morphology; the major contribution of the NBI technique is in the analysis of the subepithelial vessels; and the optical zoom can be used to explore the pit pattern.

Step 4 – Classification of the lesion and treatment decisions

Classification after detection avoids the unnecessary resection of lesions with a very low malignant potential, or inappropriate endoscopic treatment of a lesion which should be treated by surgery. For lesions characterized as benign, non-neoplastic, and with no potential for malignancy, the clinician decides whether or not a biopsy is needed, and no endoscopic treatment is proposed. For lesions that are classified as benign, with a low potential for malignancy (low-grade dysplasia), the decision lies between endoscopic resection and surveillance. For lesions that are benign but with a high potential for intramucosal malignancy, endoscopic resection is proposed, with en-bloc resection preferred to piecemeal resection for lesions larger than 2 cm, though the location of the neoplastic lesion (i.e. esophagus, stomach, or colon) may play a determining role in the choice of technique. For carcinoma with invasion of the submucosa, the decision lies between endoscopic resection or surgery if deep invasion into the submucosa is suspected.

Competing interests: None

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Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video)

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Background: Endoscopic submucosal dissection (ESD) is accepted as a minimally invasive treatment for early gastric cancer; however, it is not widely used in the colorectum because of its technical difficulty.

Objective: To determine the feasibility of using ESD for treating large superficial colorectal tumors and to evaluate the clinical outcome.

Design and Setting: Case series conducted at the National Cancer Center Hospital in Tokyo.

Patients: A total of 198 consecutive patients were treated for 200 lesions.

Interventions: Procedures were performed, before July 2004, by using a monopolar needle knife or an insulation-tipped knife (IT knife). After July 2004, the procedures were performed by using a bipolar needle knife or an IT knife. After injection of glycerol and sodium hyaluronate acid into the submucosal (sm) layer, a circumferential incision was made and sm dissection was performed endoscopically.

Main Outcome Measurements: The en bloc resection rate was 84% and the curative resection rate was 83%.

Results: Among the 200 ESDs, 51 involved tubular adenomas, 99 intramucosal cancers, 22 minute sm cancers, and 28 sm deep cancers. The median operation time was 90 minutes, and the mean size of resected specimens was 38 mm (range, 20-150 mm). Perforations occurred in 10 cases (5%) and postoperative bleeding in 4 cases (2%), but only 1 perforation case needed emergency surgery, because endoscopic clipping was ineffective.

Limitations: No long-term outcome data yet.

Conclusions: ESD is a feasible technique for treating large superficial colorectal tumors, because it provides a higher en bloc resection rate and is less invasive than surgical resection. (Gastrointest Endosc 2007;66:966-73.)

T1 early colorectal cancer is defined as cancer invasion limited to the submucosal (sm) layer. Surgery, laparoscopic-assisted colectomy (LAC), and transanal endoscopic mucosectomy (TEM) have been accepted as the standard treatments for these lesions outside of Japan.

In Japan, however, EMR is indicated for the treatment of superficial, early stage colorectal cancer because of its minimal invasiveness and excellent results in terms of clinical outcomes.[1-3] Conventional EMR techniques,[4-6] eg, strip biopsy, currently used for the resection of laterally spreading tumors (LST),[7-10] however, are inadequate for the en bloc resection of flat lesions >20 mm, because both incomplete removal and local recurrence have been frequently observed and reported on occasion.[11]

To completely remove large gastric lesions en bloc, an insulation-tipped electrosurgical knife (IT knife) was developed and has produced good results,[12-16] although this procedure is not widely accepted in the colorectum because of its technical difficulty and the risk of complications, such as perforation and bleeding.

The aim of this study was to determine the feasibility of using colorectal endoscopic submucosal dissection (ESD) for the treatment of large superficial colorectal tumors and to evaluate the clinical outcome.

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TABLE 1. Indication criteria for colorectal ESD

1. Noninvasive pattern* based on magnification colonoscopy
2. LST-NG >20 mm or LST-G >30 mm

*"Invasive pattern" is characterized by irregular and distorted epithelial crests observed in a demarcated area, suggesting that sm invasion is more than 1000 μm. When high-magnification observation with indigo carmine dye was not sufficient to determine the surface structure, staining with 0.05% crystal violet also was performed.

Capsule Summary

What is already known on this topic

- Endoscopic submucosal dissection (ESD) is a minimally invasive treatment for early gastric cancer, but, because of its technical difficulty, it is not widely used for colorectal lesions.

What this study adds to our knowledge

- In 200 ESD procedures performed for large superficial colorectal tumors when using a needle knife or an insulation-tipped knife, the en bloc resection rate was 84% and the curative resection rate was 83%, providing a higher en bloc resection rate and a less invasive treatment than surgical resection.

TABLE 2. Histologic curative criteria for ESD

1. Differentiated adenocarcinoma
2. No lymphatic and/or venous invasion
3. Intramucosal cancer, regardless of tumor size
4. Minute sm cancer (sm1: <1000 μm from the muscularis mucosae)
5. Tumor-free lateral and vertical margins

PATIENTS AND METHODS

Diagnosis of colorectal lesions

When a lesion was detected by conventional endoscopic examination, surface mucous was washed away with lukewarm water that contained pronase (Pronase MS; Kaken Pharmaceutical Co, Ltd, Tokyo, Japan) and then 0.4% indigo carmine dye was sprayed over the lesion to enhance its surface detail.

High-magnification colonoscopes (CF-240ZI and PCF-240ZI; Olympus Optical Co, Ltd, Tokyo, Japan) were used to evaluate the surface character for pit patterns to differentiate an invasive pattern from a noninvasive pattern. The invasive pattern is characterized by irregular and distorted epithelial crests observed in a demarcated area, which suggests that sm invasion is more than 1000 μm, whereas a noninvasive pattern does not have this finding, which suggests intramucosal neoplasia or sm invasion less than 1000 μm.[7-9,16] When high-magnification observation with indigo carmine dye was not sufficient to determine the surface structure, staining with 0.05% crystal violet was performed.[17-21]

Patients

Between October 2003 and July 2006, 198 consecutive patients were treated for 200 lesions at the National Cancer Center Hospital (NCCH) in Tokyo, Japan.

Indication criteria for colorectal ESD

ESDs for colorectal LSTs were generally performed based on the indication for endoscopic treatment established at NCCH (Table 1).[10,22,23] Invasive findings were determined by high-magnification observation, because it has shown greater diagnostic accuracy in our experience; therefore, EUS was not used for depth diagnosis in this study. Recurrent tumors with ulcer scarring and intramucosal tumors showing nonlifting sign are usually contraindications for endoscopic treatment, but ESD enables us to resect these lesions successfully, so such lesions were considered for ESD.

Curability was determined histopathologically based on the histologic curative criteria (Table 2) and tumor margins. The location of the tumors was divided into the right colon (cecum, ascending colon, and transverse colon), the left colon (descending colon and sigmoid colon), and the rectum, based on the Japanese Classification of Colorectal Carcinoma.[24] The tumor size was determined histopathologically for en bloc resection specimens and endoscopically for piecemeal resection specimens.

An en bloc resection was defined as a 1-piece resection. Resections were considered tumor free when both vertical and horizontal margins of a specimen were negative of tumor cells, independent of the histologic features.

ESD procedures

All ESDs were performed by using the same endoscopes used during the high-magnification colonoscopies. Before July 2004, ESD procedures were performed by using air insufflation and a monopolar needle knife,[25,26] an IT knife,[27] or a flex knife[28] (Olympus). After July 2004, procedures were primarily performed by using a bipolar needle knife (B-knife) (XEMEX Co, Tokyo, Japan)[29] or an IT knife, with CO_2 insufflation instead of air insufflation to reduce patient discomfort.[30] After injection of glycerol and sodium hyaluronate acid into the sm layer,[31-33] a circumferential incision was made by using a B-knife, and ESD was then carried out by using both a B-knife and

an IT knife (Figs. 1A to D, Video 1, available online at www.giejournal.org).

We recorded the incidence of perforations noted both during and after ESD. Procedure-related mortality was defined as any death within 30 days of ESD. Delayed bleeding was defined as clinical evidence of bleeding manifested by melena or hematochezia within 0 to 14 days after the procedure. Specimens were retrieved by using either a net or a sliding tube, with suction for specimens >40 mm.

Post-ESD follow-up care

Patients were examined by endoscopy 6 months after they had an ESD. Indigo carmine dye (0.4%) was sprayed on the previously resected sites, and high-magnification views were obtained. Recurrent neoplastic disease was identified as a type III_S, III_L, IV, or V crypt pattern, and was defined according to the criteria established by several investiagtors.[10,17-23]

Based on these surveillance criteria, local recurrent or residual neoplastic disease was diagnosed and subjected to a further extended endoscopic resection. Patients with histology that showed invasive disease that did not meet the curative criteria in Table 2 were referred for a direct surgical resection.

Histopathology

Resected specimens were fixed in a 10% buffered formalin solution. Paraffin-embedded samples were then sliced into 3-μm sections and were stained by hematoxylin and eosin. Histopathologic diagnoses were based on the Vienna classification.[34]

Ethics

Full ethical approval for the study was granted by the NCCH Ethics Committee, with written informed consent given by each patient before the ESD procedure.

Statistical analysis

Data obtained were evaluated with the χ^2 and t tests by using the SAS Statistical Package (SAS Institute, Tokyo, Japan). The Fisher exact test was used when necessary, and $P < .05$ was considered significant.

RESULTS

Clinicopathologic features

During the study period, we identified a total of 200 colorectal tumors in 198 consecutive patients. Lesions in which the invasive pattern was observed were excluded from this study, and those patients underwent surgery, except when a patient refused such surgery or was deemed a nonsurgical candidate because of advanced age. The mean (± standard deviation [SD]) age of the patients was 64 ± 10 years (range, 32-81 years), and the male/female ratio was 1.4 (115/83). The mean (±SD) size of the tumors was 35 ± 19 mm (range, 15-140 mm), and the mean (±SD) resected specimen size was 38 ± 19 mm (range, 20-150 mm). Among the 200 tumors, 91% (181) were ≥20 mm, and 5% had ulcer scars because of previous EMRs. Complete data on tumor location, tumor size, macroscopic type, ulcer scar, and tumor depth are described in Table 3. There were 9 cases of recurrent tumors, including 1 case of sm deep cancer (sm2), which required subsequent surgery; 5 cases of intramucosal cancers; and 3 cases of tubular adenomas.

En bloc resection rate

En bloc resections were achieved for 168 of the 200 consecutive tumors (84%). The overall en bloc resection rate with tumor-free margins was 70% (140/200).

Curability

Our assessment of histologic curability is shown in Table 2. Among 167 curative resections, 51 were tubular adenomas, 98 were intramucosal cancers, and 18 were minute sm cancers (sm1). Among the other 33 noncurative resections, 28 were identified as sm2; 4 lesions were sm1 with lymphatic or vessel invasion or a poorly differentiated component; and 1 lesion was an intramucosal cancer, which resulted in an incomplete resection because of unsuccessful clipping of the perforation.

Five cases of sm2 cancer were resected, even though they showed invasive patterns and were diagnosed as sm2 cancer before ESD because of the older ages of 4 of the patients and at the patient's specific request in the other case. Two cases were diagnosed as an invasive pattern when we retrospectively reviewed the pit patterns. The other 21 cases were diagnosed as noninvasive pattern by magnification colonoscopy; however, they revealed sm2 invasion by histology. Four of these lesions were macroscopically depressed, 10 were LST nongranular-type (LST-NG) lesions, and 7 were LST granular type (LST-G) lesions. The mean (±SD) size of these 21 noninvasive pattern lesions was 37 ± 26 mm in diameter. Finally, the specificity of a noninvasive pattern was 89% (172/193) in this series.

Twenty of the patients who were noncurative underwent surgery for lymph-node dissection, whereas 1 patient with rectal cancer received chemoradiotherapy. The remaining 7 patients who were noncurative were followed without surgery or chemoradiotherapy because of age-related or other reasons.

Operation time

Our median operation time was 90 minutes, with a mean time of 110 minutes (range, 15-480 minutes). The median procedure time for earlier procedures was longer compared with later procedures, but there was no statistical difference.

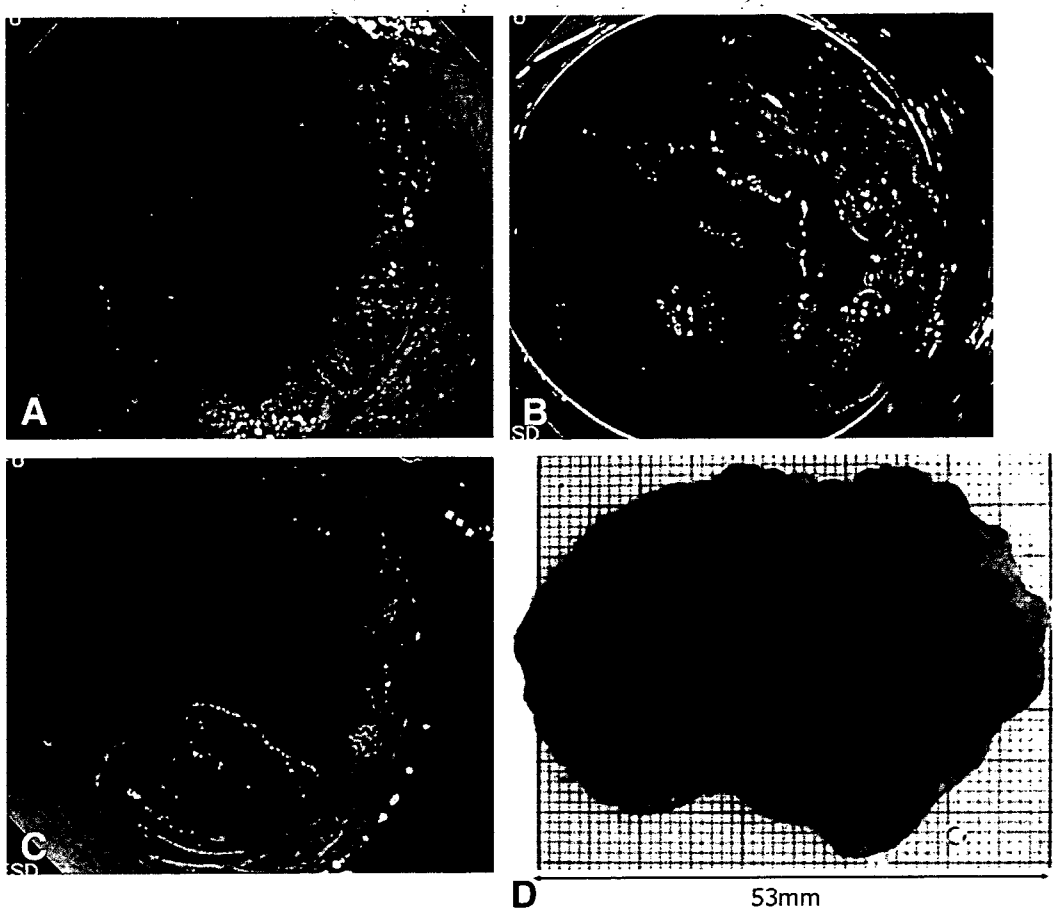

Figure 1. ESD procedure technique. **A,** The margins of the lesion were delineated before ESD by using 0.4% indigo carmine dye spraying. **B,** After the injection of glycerol, a circumferential incision in the mucosa was made by using a B-knife. Sodium hyaluronate acid solution was then injected into the sm layer to lift the lesion, and the thickened sm layer was cut by using an IT knife. **C,** The ulcer bed after the en-bloc resection. **D,** This resected specimen, which was 53 mm in diameter, revealed a high-grade dysplasia, whereas the resected margin was histopathologically free of tumor.

Hospitalization

The mean hospitalization stay was 5 days (range, 1-9 days), which consisted of 1 day before the actual procedure and 3 days after the procedure, which is in line with the recognized standard in Japan. In ESD procedures without any complication, the mean patient stay was 5 days. However, in cases where perforation or postoperative bleeding occurred, the mean patient stay was 8 days.

Local recurrence or residual tumor after ESD

Follow-up colonoscopies were performed for 180 lesions (180/200 [90%]) over a median period of 220 days. There was only 1 case of local recurrence in a lesion that was previously treated by piecemeal resection, and an additional endoscopic resection completely removed it. There were no instances of distant or lymph-node metastasis in this case series.

Complications

Mortality. There were no deaths in this series of patients (mortality rate, 0%).

Perforation. Colonic-wall perforations, including rectal penetrations, were found in 10 of 200 patients (5%). The relations between the risk of perforation and tumor location, tumor size, macroscopic type, ulceration, and tumor depth are shown in Table 4. All perforations were detected endoscopically during the initial ESD procedures, and none of the patients experienced a delayed or missed perforation. Only 1 perforation case needed emergency surgery, because endoscopic clipping was ineffective. The other 9 perforations were treated endoscopically, without surgical treatment. These 9 patients were subsequently treated by withholding oral intake and by administering antibiotics for approximately 5 days. We managed 1 case of pneumoperitoneum by means of abdominal decompression by using an 18-gauge Medicut needle (Nippon Sherwood Medical Industries Ltd, Tokyo, Japan) to decrease patient pain and discomfort. More recently, we have been using CO_2 insufflation for colorectal ESDs, so there has been no need for abdominal decompression, even when a microperforation occurs.

Immediate and delayed bleeding. Immediate bleeding during ESD occurred in most cases, but it was effectively controlled by using the coagulation mode of the

TABLE 3. Clinicopathologic features

Male/female, no.	115/83
Mean ± SD age (range), y	64 ± 10 (32-81)
Macroscopic types, no.	
LST-NG	95
LST-G	75
Depressed	12
Sessile	9
Recurrence (with ulcer scar)	9
Tumor location, no.	
Right colon	97
Left colon	42
Rectum	61
Mean ± SD tumor size (range), mm	35 ± 19 (15-140)
Mean ± SD resected specimen size (range), mm	38 ± 19 (20-150)
En bloc resection rate, %	84
Histopathology, no.	
Adenoma	51
Intramucosal cancer	99
sm1 (<1000 μm)	22
sm2 or deeper (≥1000 μm)	28
Operation time, median (range), min	90 (15-480)
Hospitalization, mean (range), d	5 (1-10)
Complications, no. (%)	
Perforation/penetration	10 (5)
Postoperative bleeding	4 (2)

sm1, Minute submucosal cancer; *sm2*, submucosal deep cancer.

B-knife or the IT knife. Coagrasper forceps (FD-410LR; Olympus) were used only for active arterial bleeding, but the incidence of this was extremely low. Delayed bleeding after ESD was observed in 4 of 200 patients (2%). One patient experienced bleeding within 24 hours, and the other 3 patients had bleeding within 2 to 3 days of the procedure. Three cases of bleeding were successfully controlled by endoscopic treatment involving hemoclipping and/or electrocoagulation; 1 case needed only observation for a day; none required surgical intervention or blood transfusions.

DISCUSSION

To our knowledge, this is the largest reported case series of ESDs for LSTs in the colorectum. Based on the results, ESD in the colorectum is a feasible procedure. When performed by a qualified endoscopist, ESD has a low complication rate and, therefore, constitutes a less invasive alternative for the treatment of large superficial colorectal tumors. Without this procedure, many of the patients probably would have had surgical resections, with an increased risk of morbidity.

LSTs >20 mm are usually treated by endoscopic piecemeal mucosal resection (EPMR), and local recurrence is frequently observed after EPMR.[35-37] In contrast, no local recurrences were observed in tumors treated by en bloc endoscopic resection in earlier studies,[35,36] and our series resulted in an en bloc resection rate of 84%. This is a significant improvement compared with the recurrence rate of 20% obtained with conventional EMR techniques.[35-37] This high rate of en bloc resections resulted in a very low rate of local recurrence.

The development of the ESD technique revolutionized the management of early gastric cancer, because en bloc resection facilitates accurate histologic assessment and reduces the risk of tumor recurrence.[12-16] This procedure is not widely accepted for use in the colorectum, however, because of its technical difficulty and the risk of complications, such as perforation and bleeding in the colorectum.

ESD improvements for colorectum

The newly developed B-knife results in a safer ESD, because the electric current is localized to the needle tip.[29] The IT knife[27] also decreases the risk of colonic perforation because of the insulated tip attached to the end of the needle. The combined use of these 2 instruments enabled us to perform colorectal ESDs safely and easily. In fact, the rate of colonic perforation actually decreased during the course of this series, from 7.5% (6/80) to 4.2% (5/120) (not significant; $P = .35$), as a result of using the B-knife and the IT knife. The difference in the rate of perforation may have been because of a "learning-curve" factor involving the endoscopists rather than simply the difference in using a B-knife alone versus a B-knife and an IT knife in combination.

Even when using the B-knife and the IT knife, however, the ESD procedure takes longer compared with conventional EMR and is associated with severe patient intraoperative and postoperative abdominal discomfort because of a considerable amount of air entering the colonic lumen. In an effort to overcome this problem, CO_2 insufflation, which has been proven safe and effective during colorectal ESD,[30] was used in the second part of this study. In addition, ESD for large colorectal lesions is more difficult to perform because of difficulty in visualizing the cutting line. For such cases, therefore, we also developed a sinker-assisted ESD[38] procedure that was performed successfully in 6 cases as part of this study.

Operation time and complications

The median operation time in our series was 90 minutes, but there also may have been a learning curve factor

TABLE 4. Tumor location and characteristics in 10 patients with perforation complications resulting from ESD

Case no.	Tumor location	Tumor size (mm)	Macroscopic type	Ulcer scar	Tumor depth	Treatment
1	Rectum	22	LST-NG	+	sm1	Clipping
2	Right colon	20	LST-NG	-	sm1	Clipping
3	Rectum	50	LST-G	-	m	Clipping
4	Right colon	27	LST-NG	-	sm1	Clipping
5	Rectum	40	LST-G	-	m	Clipping
6	Rectum	30	LST-G	-	m	Clipping
7	Left colon	25	LST-G	+	Adenoma	Clipping
8	Right colon	70	LST-G	+	sm2	Clipping
9	Left colon	60	LST-G	+	m	Clipping
10	Right colon	100	LST-G	+	m	Surgery

m, Intramucosal cancer; *sm1*, minute submucosal cancer; *sm2*, submucosal deep cancer.

involved because of the relatively new ESD technique. However, there was no statistical difference between earlier procedure times and later procedure times; procedure times depended mainly on lesion size. The median procedure time was 70 minutes (mean time 85 minutes) in lesions <40 mm, and 120 minutes (mean time 160 minutes) in lesions ≥ 40 mm ($P < .0001$).

It should be noted that there were almost as many cases of perforation occurring in rectal lesions (4/10) as in lesions located in the colon (6/10) (Table 4), which has a thinner wall. This was probably because our medical facility is a training center where endoscopists, who subsequently become highly qualified in performing gastric ESDs, start with colorectal ESDs of rectal lesions, which are thought to be relatively easy and safe. In addition, lesions with a severe ulcer scar are difficult even when using the ESD technique and have a higher risk of perforation (4/10), so we should pay particularly close attention when resecting such lesions.

The incidence of perforation associated with ESD (5%) was higher than with conventional techniques,[39,40] but all of the perforations, except 1 case that required emergency surgery, were diagnosed at the time of the ESD procedures and were successfully treated by using endoclips, without the need for surgery. However, in the event of increased abdominal pain and/or a patient experiencing a fever, surgical intervention may be necessary in the future.

This beneficial management result confirmed our previous report on a series of patients with colonic perforations who were able to be treated conservatively because of the successful endoscopic closure of their perforations.[39,40]

During colorectal ESDs, intraoperative bleeding was easily controlled by using coagulation forceps, without the need for surgical intervention or blood transfusions. Delayed bleeding occurred in 2% of the ESDs, which is comparable with other reports that used EPMR.[1,40] Thus, endoscopists performing this procedure also need to be skilled in the endoscopic treatment of iatrogenic perforations and bleeding that may occur during ESDs.

The 5-day mean length of stay for patients with no complications could have been shortened because of our low complication rate, but we followed the patients in this study very carefully because we only recently started using this new ESD technique for large colorectal tumors.

ESD versus EPMR

EPMR can be used to treat many LSTs >20 mm, with only a few cases requiring surgery after such piecemeal resections.[35] It is important, therefore, to determine which lesions should be resected en bloc and which lesions can be resected piecemeal. Based upon clinicopathologic analyses of LSTs, we previously defined the indications for ESD as an LST-NG >20 mm.[10] An LST-G >20 mm can be treated by EPMR rather than ESD with the area, including the large nodule resected first followed by the remaining tumor. LST-Gs >30 mm also are good candidates for ESD, because they have a higher sm invasion rate and are difficult to treat even by EPMR.

Laparoscopic surgery or surgical local excision

Surgical resections, including LAC,[41] TEM,[42,43] and local excisions are still the standard treatments for large T1 colorectal cancers, even when a lesion is limited to the mucosal layer because of the technical difficulty in performing an EMR. However, all of these procedures require general or lumbar anesthesia and result in a longer patient hospitalization. Major complications also were reported as being associated with surgery.[43] In addition, a higher recurrence rate (ranging from 9% to 10%) was reported for TEM or surgical local excisions.[42] Compared with such surgical treatments, ESD provides a higher en bloc resection rate, lower recurrence rate, and shorter

hospitalization stays combined with an acceptable rate of complications.

Based on the results of this study, we, therefore, concluded that the ESD technique with a B-knife and an IT knife with CO_2 insufflation is a feasible method for treating large superficial colorectal tumors. It offers the advantage of obtaining an en bloc resection that, in turn, results in more accurate histologic analysis and less frequent recurrence. In an effort to further support our position, we are currently collecting long-term outcome data from this large series of cases.

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DISCLOSURE

The authors have no commercial associations (eg, equity ownership or interest, consultancy, patent and licensing agreement, or institutional and corporate associations) that might be a conflict of interest in relation to the article.

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A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation

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Background: Endoscopic submucosal dissection (ESD) is accepted as one of the treatments for en bloc resection of large superficial colorectal lesions. This procedure is performed by using air insufflation, is time consuming, and is associated with severe abdominal discomfort. The safety and efficacy of carbon dioxide (CO_2) insufflation during colonoscopy already has been assessed in some trials.

Objective: To assess the safety and efficacy of CO_2 insufflation instead of air insufflation during colorectal ESD with the patient under conscious sedation.

Design: A case-control series with a historical control.

Patients: A total of 35 consecutive patients were enrolled in this study. Another 35 consecutive patients who previously received colorectal ESDs by using air insufflation were included as a historical control.

Interventions: Arterial partial pressure of CO_2 (pCO_2) was measured before and after each procedure with the total dose of midazolam used as an index of abdominal discomfort.

Main Outcome Measurements and Results: The mean (standard deviation [SD]) operation time was 90 ± 57 minutes in the CO_2 group and 100 ± 80 minutes in the control group (not significant). In the CO_2 group, the mean (SD) dose of midazolam was significantly lower than that of the control group; 5.6 ± 4.9 mg and 9.7 ± 5.9 mg, respectively ($P = .005$). Blood analysis revealed a slight pCO_2 elevation in the CO_2 group; however, only 2 patients complained of mild abdominal discomfort.

Limitations: Abdominal discomfort and pCO_2 were not evaluated in the control group.

Conclusions: This study strongly suggests that CO_2 insufflation is safe and effective during lengthy colonic endoscopic procedures, eg, ESD, with the patient under conscious sedation.

It has been claimed that carbon dioxide (CO_2) insufflation reduces patient pain and abdominal discomfort during and after colonoscopy. The safety and efficacy of CO_2 insufflation during colonoscopy was already assessed in some earlier trials.[1-7] Air insufflation is still the standard method, however, because of a lack of suitable equipment and continued technical improvement in colonoscopy.

Endoscopic submucosal dissection (ESD) with conventional air insufflation is accepted as one of the treatments for en bloc resection of selected large superficial colorectal lesions,[8-14] but this procedure is a lengthy one, where a considerable amount of air enters the colonic lumen and causes severe intraoperative and postoperative abdominal discomfort. CO_2 insufflation, therefore, may be preferable for longer colonoscopic procedures, eg, ESD.

In laparoscopic surgery, CO_2 insufflation is safely used with the patient under general anesthesia,[15-18] but there are no reports about its use in longer endoscopic procedures, such as colorectal ESD with the patient under conscious sedation. The aim of this study was to assess the safety and efficacy of CO_2 insufflation during colorectal ESD with the patient under conscious sedation.

PATIENTS AND METHODS

Patients

Between November 2004 and May 2005, a total of 35 consecutive patients were enrolled in this study at the National Cancer Center Hospital (NCCH) in Tokyo. All ESD

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procedures were performed by one or the other of 2 highly experienced colonoscopists (Y.S., T.U.).

Colorectal ESDs with air insufflation performed in 35 other consecutive patients by the same 2 colonoscopists between September 2003 and November 2004 were compared as a historical control group. Patients with severe chronic occlusive pulmonary disease and known CO_2 retention were excluded from the study.

Endoscopic operating system

Procedures were performed with Olympus video colonoscopes (Olympus Optical Co, Ltd, Tokyo, Japan). CO_2 was administered by using a commercially available CO_2 regulator (Gas Regulator, Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan), which was connected to a CO_2 bottle.

ESD procedures

The margins of the lesion were delineated before ESD by using 0.4% indigo carmine dye spraying (Fig. 1A). After the submucosal injection of glyceol (Chugai Pharmaceutical Co, Ltd, Tokyo, Japan),[19] a circumferential incision in the mucosa was made with a needle knife[9-12] (Fig. 1B). A sodium hyaluronate solution[9-14] was then injected into the submucosal layer to lift the lesion, and the thickened submucosal layer was cut with a needle knife or an insulation-tipped knife[8] (Fig. 1C to E). The operation time was recorded for all patients.

Arterial partial pressure of CO_2 measurements

Arterial partial pressure of CO_2 (pCO_2) was measured before and after the procedure in all patients enrolled in the CO_2 group. Arterial pCO_2 was not measured in the historical control group.

Sedation

In all cases, midazolam (2 mg, intravenous) was used before insertion of the colonoscope. In addition, 2 mg was given repeatedly when indicated, based on the individual endoscopist's judgment.

Evaluation of abdominal discomfort

A questionnaire about the presence of abdominal discomfort (none, mild, moderate, and severe) was completed immediately after the ESD procedure for all patients in the CO_2 group.

Statistical analysis

All the variables in this study are described as mean and standard deviation (SD). To compare the baseline characteristics between the 2 groups, we used the t test for continuous variables and the χ^2 test for dichotomous variables. All statistical analyses were performed by using SAS version 8.0 (SAS Institute Inc, Cary, NC). The P values were 2 sided; $P < .05$ was used to determine statistical significance.

Ethics

The ethics committee of the NCCH approved the study protocol. Informed consent was obtained from all patients in the CO_2 group before entering the study.

RESULTS

There were no differences in clinicopathologic characteristics between the groups (Table 1). The mean (SD) size of the resected specimens was 32 ± 15 mm in the CO_2 group and 30 ± 14 mm in the control group, with no statistical difference (NS). En bloc resection was achieved in 30 of 35 cases (86%) in the CO_2 group and 31 of 35 cases (89%) in the control group.

Histopathologic evaluation revealed 5 low-grade dysplasias, 24 high-grade dysplasias, and 6 submucosal (sm) carcinomas in the CO_2 group. In comparison, there were 1 low-grade dysplasia, 22 high-grade dysplasias, and 12 sm carcinomas found in the control group.

Curative resection, defined as an en bloc resection of an intramucosal or sm superficial cancer (<1000 μm), without lymph vascular invasion or poorly differentiated component, was achieved in 89% (31/35) of the patients in the CO_2 group and 80% (28/35) of the patients in the control group, respectively. All margins were free of neoplasia.

Operation time and arterial pCO_2 in the CO_2 group

The mean (SD) operation time was 90 ± 57 minutes in the CO_2 group and 100 ± 80 minutes in the control group (NS). Mean (SD) arterial pCO_2 was slightly elevated (4.5 ± 5.4 mm Hg) in the CO_2 group; however, no major adverse effects were identified. As shown in Figure 2, arterial pCO_2 had a slight tendency to increase during longer procedures, but no statistical difference was found.

Dosage of midazolam

The mean (SD) dosage of midazolam in the CO_2 group was significantly lower than that of the control group, 5.6 ± 4.9 mg and 9.7 ± 5.9 mg, respectively ($P = .005$). Even after being adjusted for the difference in operation time, the dosage of midazolam in the CO_2 group was lower than that of the control group ($P = .05$).

Abdominal discomfort and complications

Two of 35 patients in the CO_2 group (5.7%) complained of nausea and mild abdominal discomfort after the procedure, but these patients had no symptoms after 1 hour. There were no perforations in the CO_2 group, but 3 perforations and 1 case of subcutaneous emphysema were observed in the control group; however, all 4 of these cases were treated endoscopically, without surgery.

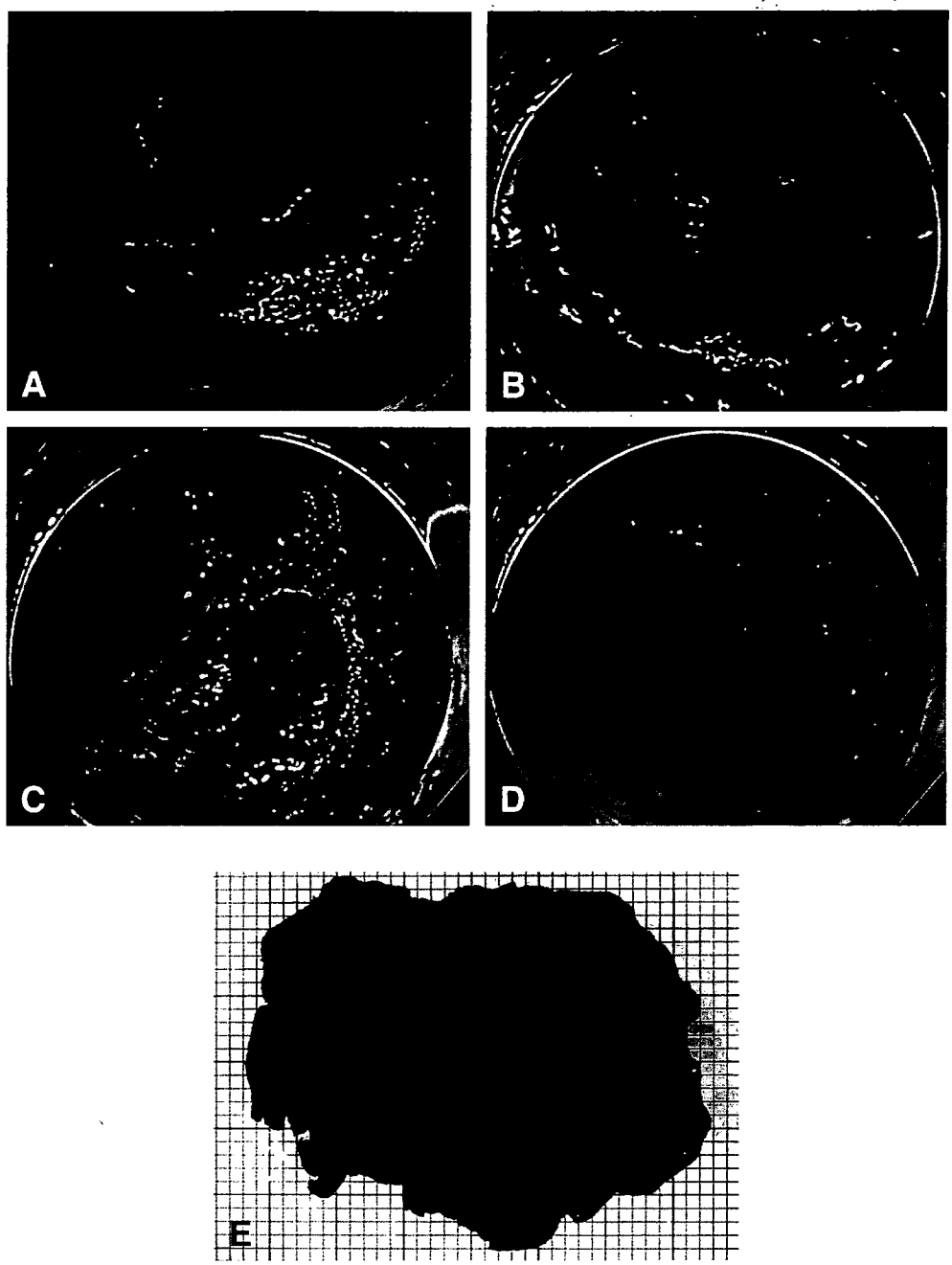

Figure 1. The ESD procedure. **A,** The margins of the lesion were delineated before ESD by using 0.4% indigo carmine dye spraying. **B,** After the injection of glyceol, a circumferential incision in the mucosa was made with a needle knife. **C,** Sodium hyaluronate solution was then injected into the submucosal layer to lift the lesion, and the thickened submucosal layer was cut with an insulation-tipped knife. **D,** The area of the colon after the en bloc resection. **E,** The resected specimen, 40 mm in diameter, revealed a high-grade dysplasia, whereas, by histologic evaluation, the resected margin was free of tumor.

DISCUSSION

Based on the results of this pilot study, CO_2 insufflation proved to be safe and effective during lengthy colonic endoscopic procedures (eg, ESD) with the patient under conscious sedation. Patient discomfort was considerably lower in the CO_2 group, probably because of a more rapid absorption of CO_2 than was caused by conventional air insufflation, as evidenced by the lower total dosage of midazolam.

In the field of conventional colonoscopy, the safety and efficacy of CO_2 insufflation has already been assessed in earlier studies, including randomized controlled trials.[1-7] Furthermore, in laparoscopic surgery, CO_2 insufflation is safely used for longer operations with the patient under general anesthesia,[15-18] but there are no reports about its

TABLE 1. Clinicopathologic characteristics between groups

	CO_2 group	Control group	*P* value
No. cases	35	35	
Tumor size (mean [SD]), mm	32 ± 15	30 ± 14	NS
Operation time, min	90 ± 57	100 ± 80	NS
Arterial pCO2 elevation, mm Hg	4.5 ± 5.4		
Dose of midazolam, mg	5.6 ± 4.9	9.7 ± 5.9	.005
Histopathology			
Low-grade dysplasia	5	1	
High-grade dysplasia	24	22	
sm1 (<1000 μm)	3	7	
sm2 (≥1000 μm)	3	5	
En bloc resection rate	30/35 (86%)	31/35 (89%)	NS
Free margin rate	25/35 (71%)	30/35 (86%)	.04
Curative resection rate	31/35 (89%)	28/35 (80%)	NS
No. complications			
Perforation	0	3	NS
Emphysema	0	1	NS

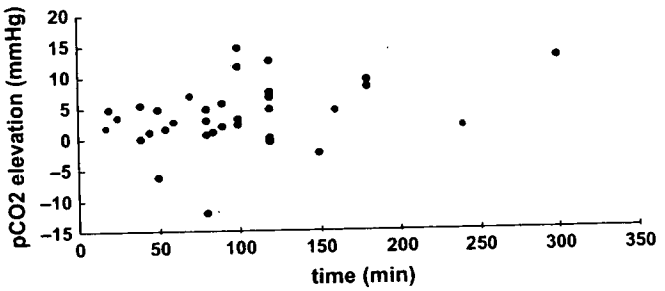

Figure 2. Arterial pCO_2 elevation (mm Hg). There was a slight tendency for arterial pCO_2 to increase when the operation time was longer, but there were no statistical differences.

extended use for more than 1 or 2 hours in colonoscopic procedures with the patient under conscious sedation.

In this study, CO_2 insufflation did not lead to a clinically significant increase in pCO_2 levels. This was most likely because of the conscious sedation, even in patients undergoing a lengthy colonoscopic procedure. It is well known that sedatives may cause hypoxemia and hypoventilation. Similarly, Bretthauer et al[7] reported, in a trial that involved conventional colonoscopy examinations, that sedated patients in both CO_2- and air-insufflation groups had a slight increase in end-tidal CO_2. Sedation and not CO_2 insufflation, therefore, is the primary cause of CO_2 retention during colonoscopy.

A limitation of this pilot study was that abdominal discomfort and pCO_2 were not evaluated in the control group. According to the dose of midazolam used, however, patient discomfort was considerably lower in the CO_2 insufflation group than with usual air insufflation. In addition, abdominal radiographs were occasionally performed on a limited basis after the procedure, and our experience indicated that there was often substantially less air in the CO_2 group (Fig. 3).

As for complications, there were no perforations in the CO_2 group, but 3 perforations and 1 case of subcutaneous emphysema were observed in the control group. One reason for this lower complication rate might be related to the progressing skill of the 2 colonoscopists, because the CO_2 group procedures were performed up to 6 months after the control group procedures.

Usefulness of ESD

ESD for early gastric cancer is widely accepted as a useful endoscopic treatment[20-29]; however, ESD for colorectal cancer is not widely accepted, because of its technical difficulty and the greater risk of perforation.[8-14]

Laterally spreading tumors (LSTs) >20 mm are usually treated by piecemeal resection (EPMR), and local recurrence is frequently observed after EPMR.[30,31] In this study, most of the resected tumors were >20 mm, but the en bloc resection rate with the ESD technique was 87%,

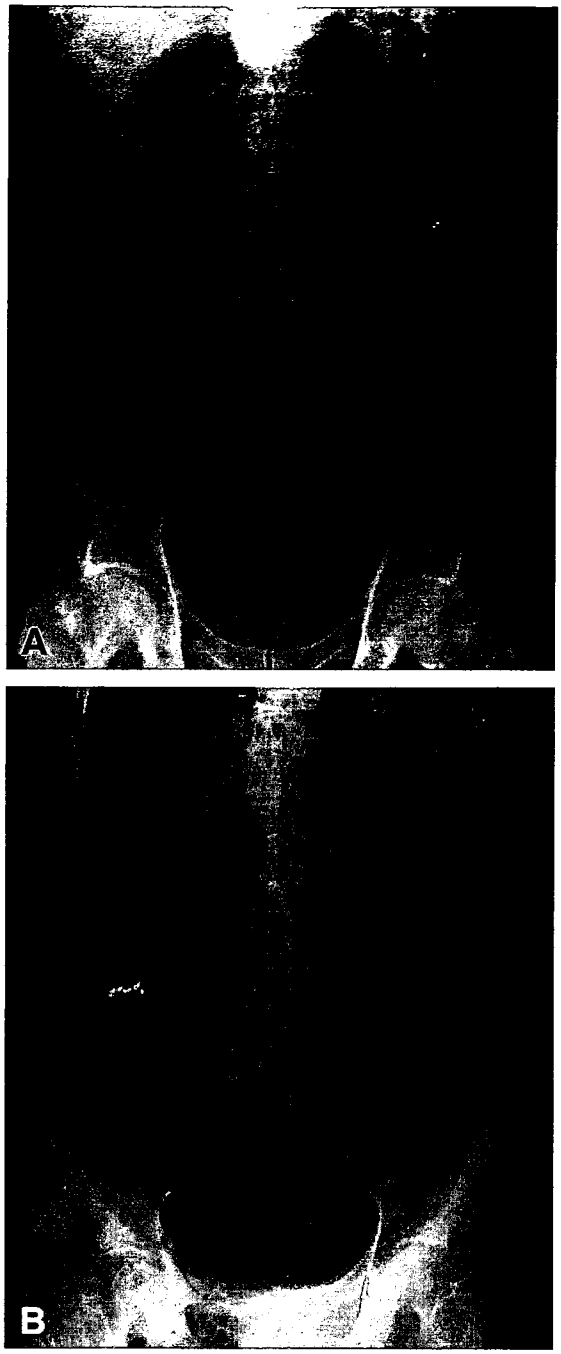

Figure 3. Abdominal radiographs after ESD. **A,** Less colonic gas in the CO_2 group than in the control group (**B**) is clearly shown. **B,** Control group.

which was considerably higher compared with that of conventional EMR techniques.[32-36]

Based on these results, we believe that colonic ESD is the preferable procedure for the en bloc resection of selected large flat neoplasia, such as nongranular type LSTs, but the operation time is much longer compared with the EPMR technique. It is important, therefore, to use CO_2 insufflation in colonic ESD procedures to reduce patient discomfort, and its safety and efficacy during long procedures was proven in this study.

CONCLUSIONS

This study strongly suggests that CO_2 insufflation is safe and effective during lengthy colonic endoscopic procedures (eg, ESD) with the patient under conscious sedation. It is possible, however, that a significant component of the reduced midazolam dosage in the CO_2 group might have been the technical improvement of the experienced endoscopists between the time of the control cases and the current series.

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DISCLOSURE

The authors have no commercial associations (eg, equity ownership or interest, consultancy, patent and licensing agreement, or institutional and corporate associations) that might be a conflict of interest.

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RISK MANAGEMENT IN ENDOSCOPIC SUBMUCOSAL DISSECTION IN COLONOSCOPY (ENDOSCOPIC MUCOSAL RESECTION AND ENDOSCOPIC SUBMUCOSAL DISSECTION)

SUCCESSFUL ENDOSCOPIC CLOSURES OF COLONIC PERFORATIONS REQUIRING ABDOMINAL DECOMPRESSION AFTER ENDOSCOPIC MUCOSAL RESECTION AND ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY COLON CANCER

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Endoscopic submucosal dissection (ESD) for colorectal cancer is not widely accepted because of its technical difficulty and the risk of perforation. In addition, the risk of peritonitis cannot be completely eliminated even if a perforation is closed successfully. Reported here are two cases of early colon cancer in which the patients sustained iatrogenic perforations of the ascending colon during conventional endoscopic mucosal resection and of the sigmoid colon during ESD, respectively, requiring abdominal decompression with an 18 G Medicut needle. Both of these perforations were successfully treated by endoscopic clipping. In conclusion, conservative medical management may be possible in patients who have undergone successful closure of colonic perforations using endoscopic clipping. In order to perform immediate endoscopic closure, abdominal decompression has been useful to decrease patient discomfort and colonic lumen collapse. Now, CO_2 insufflation is being used effectively for the prevention of pneumoperitoneum.

Key words: abdominal decompression, colonic perforation, early colorectal cancer, endoscopic closure, endoscopic mucosal resection, endoscopic submucosal dissection.

INTRODUCTION

Endoscopic mucosal resection (EMR) is indicated for the treatment of superficial, early stage colorectal cancer because it is minimally invasive and has produced excellent results in terms of clinical outcomes.[1–3] Conventional EMR techniques such as strip biopsy, currently used for the resection of laterally spreading tumors (LST),[4–6] are inadequate for the en bloc resection of flat lesions >20 mm because incomplete removal and local recurrence are often observed.[7] Endoscopic submucosal dissection (ESD)[8,9] for colorectal cancer is not widely accepted because of its technical difficulty and the risk of perforation. In addition, the risk of peritonitis cannot be completely eliminated even if a perforation is closed successfully.

We report here two cases of early colon cancers in which the patients sustained iatrogenic perforations of the ascending colon during conventional EMR and of the sigmoid colon during ESD, respectively, requiring abdominal decompression with an 18 G Medicut needle (Nippon Sherwood Medical Industries Ltd, Tokyo, Japan). Both of these perforations were successfully treated by endoscopic clipping.

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CASE REPORTS

Case 1

A 56-year-old man was referred to National Cancer Center Hospital, Tokyo, to remove a flat type early colon cancer. The lesion was located in the sigmoid colon and was 25 mm in diameter. The macroscopic type was 0-IIa (LST non-granular type: LST-NG) and the lesion was difficult to identify without chromoendoscopy (Fig. 1a,b) so endoscopic tattooing[10,11] was performed close to the lesion in the previous hospital to help with detection. Magnification colonoscopy showed a non-invasive pattern[12,13] (Fig. 1c) so either EMR or ESD was indicated for this lesion. ESD was performed on the lesion because of its flat morphology and in accordance with the ESD criteria at the National Cancer Center Hospital in Tokyo (Table 1).[14] ESD was carried out routinely,[14–16] but the submucosal layer was difficult to identify due to the previous tattooing. A small pinhole perforation occurred during the procedure due to poor visualization of the submucosal layer (Fig. 1d). We managed pneumoperitoneum by means of abdominal decompression using an 18 G Medicut needle to decrease patient discomfort and prevent colonic lumen collapse. Endoscopic clipping was immediately performed (Fig. 1e) after the decompression procedure and ESD was subsequently completed with an en bloc resection achieved in 1 h. This patient was then treated by withholding oral intake and administering antibiotics for 5 days.

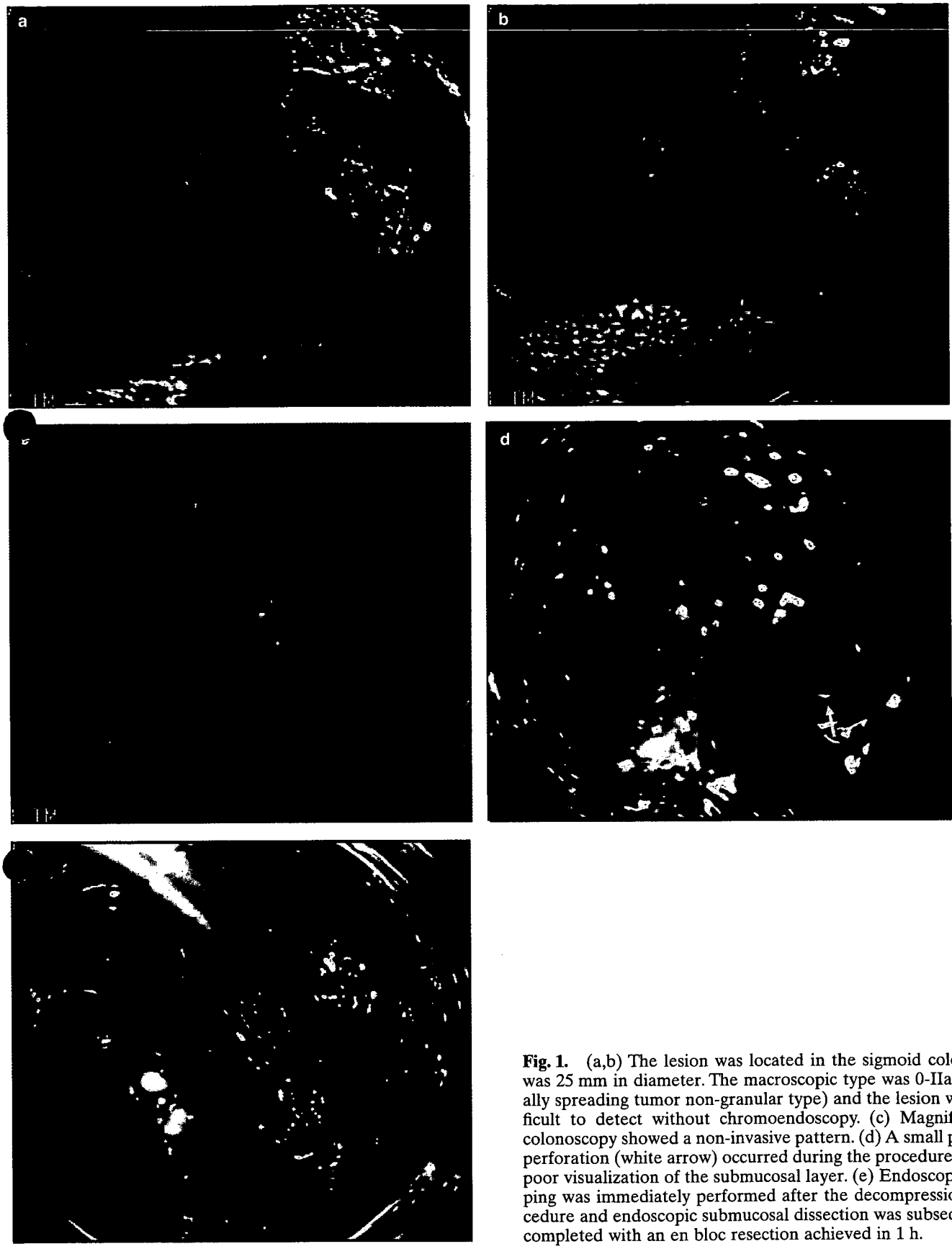

Fig. 1. (a,b) The lesion was located in the sigmoid colon and was 25 mm in diameter. The macroscopic type was 0-IIa (laterally spreading tumor non-granular type) and the lesion was difficult to detect without chromoendoscopy. (c) Magnification colonoscopy showed a non-invasive pattern. (d) A small pinhole perforation (white arrow) occurred during the procedure due to poor visualization of the submucosal layer. (e) Endoscopic clipping was immediately performed after the decompression procedure and endoscopic submucosal dissection was subsequently completed with an en bloc resection achieved in 1 h.

Table 1. Indications for colorectal ESD

1	No deep invasive findings in the submucosal layer
2	Non-invasive pattern† was identified
3	LST-NG >20 mm
4	LST-G >30 mm
5	Recurrent tumor or intramucosal tumor with non-lifting sign

ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type.

† Invasive pattern is characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting that sm invasion is >1000 μm. When high-magnification observation with indigo carmine dye was not sufficient to determine the surface structure, staining with 0.05% crystal violet also was performed.

Table 2. Histological curative criteria for EMR and ESD

1	Differentiated adenocarcinoma
2	No lymphatic and/or venous invasion
3	Intramucosal cancer regardless of tumor size
4	Minute submucosal cancer (sm1: <1000 μm from the muscularis mucosae)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

The histological diagnosis was a well-differentiated adenocarcinoma and the depth of invasion was submucosal superficial (sm1: 750 μm). The vertical and lateral cut margins were negative with no lymphatic or vessel invasion histologically and a curative resection was achieved (Table 2).[17]

The patient's post-treatment course was uneventful. An abdominal CT performed 2 days after the ESD showed a small amount of free air, but there was no fluid collection. The patient experienced no tenderness or rebound pain, his C-reactive protein (CRP) decreased from 6.7 mg/dL to 0.8 mg/dL in 3 days and the amount of free air in the abdomen decreased considerably by the end of the first week. The patient began to eat 5 days after the successful clipping procedure and was discharged after 1 week.

The patient received a follow-up colonoscopy and abdominal CT examination after 6 months and at 1 year intervals and no recurrent tumors or lymph node (LN) metastasis were identified.

Case 2

Another 56-year-old man was referred to National Cancer Center Hospital, Tokyo, to remove a large polypoid cecal polyp. The lesion was 35 mm in diameter (Fig. 2a,b), but magnification colonoscopy identified a non-invasive pattern[12,13] on the tumor surface so we decided to perform EMR on this lesion despite its large size.

Conventional EMR was performed on the lesion because of the polypoid morphology. Glycerol was injected into the submucosal layer and appropriate submucosal lifting was achieved, but a conventional snare (25 mm Snare Master, Olympus, Tokyo, Japan) was inadequate for such a large lesion. A prototype 30 mm hard snare was then used for this lesion in order to perform an en bloc resection. The endoscopist loosened the snare slightly in order to avoid involving the muscle layer and the patient complained of no pain while snaring the lesion. After resection, we identified a large perforation (approx. 20 mm in diameter) so we suctioned air to prevent abdominal distension, but some of the intestinal fluid outflowed into the abdominal cavity because of the lumen collapse. There was no need for abdominal decompression because the patient did not complain of any abdominal pain or discomfort and complete closure of the colonic perforation was performed using endoclips (Fig. 2c). Subsequently, the EMR was completed and an en bloc resection was achieved in 30 min. Stereomicroscopic examination of the resected specimen showed a definite layer of muscle at the cut margin (Fig. 2d).

Computed tomography (CT) 1 day after the EMR showed fluid collection close to the perforation site and an abscess was suspected (Fig. 3a), but abdominal pain and rebound tenderness were slight. This patient was then treated by withholding oral intake and administering antibiotics for 5 days. He was discharged after 7 days.

This patient's post-treatment course also was uneventful. He experienced slight tenderness and rebound pain for 3 days, his CRP decreased from 6.7 mg/dL to 0.8 mg/dL in 5 days and the amount of free air in his abdomen decreased considerably by the end of the first week. The patient began to eat 5 days after the successful clipping procedure and was discharged after 1 week. The histological diagnosis was a well-differentiated adenocarcinoma and the vertical and lateral cut margins were negative histologically, but the depth of invasion was submucosal deep (sm2: 1200 μm) so a non-curative resection was achieved (Table 2).[17]

The patient underwent surgical cecal resection with LN dissection due to the risk of LN metastasis. There was no abscess or adhesion close to the perforation site (Fig. 3b). The resected specimen showed that no cancer cells remained and there was no LN metastasis histologically. Abdominal CT 1 month after EMR showed no fluid collection.

DISCUSSION

We report here two cases of early colon cancers in which the patients sustained iatrogenic perforations of the ascending colon during conventional EMR and of the sigmoid colon during ESD, respectively, both of which were successfully treated by endoscopic clipping.

The patient who sustained an ascending colon perforation required abdominal decompression to decrease abdominal distension and we successfully performed endoscopic closure after reducing the patient's discomfort and improving the endoscopic view.

Emergency surgery criteria

In the present case reports both patients experienced intestinal fluid leakage, low-grade fevers and increased serology results (white blood cells [WBC], CRP), but they were able to be treated conservatively without emergency surgery.

The perforation in the ascending colon produced fluid collection in the pelvic cavity on CT (Fig. 3a) and a pelvic abscess was highly suspected. The ascending colon lesion of this patient was diagnosed as an sm2 deep cancer

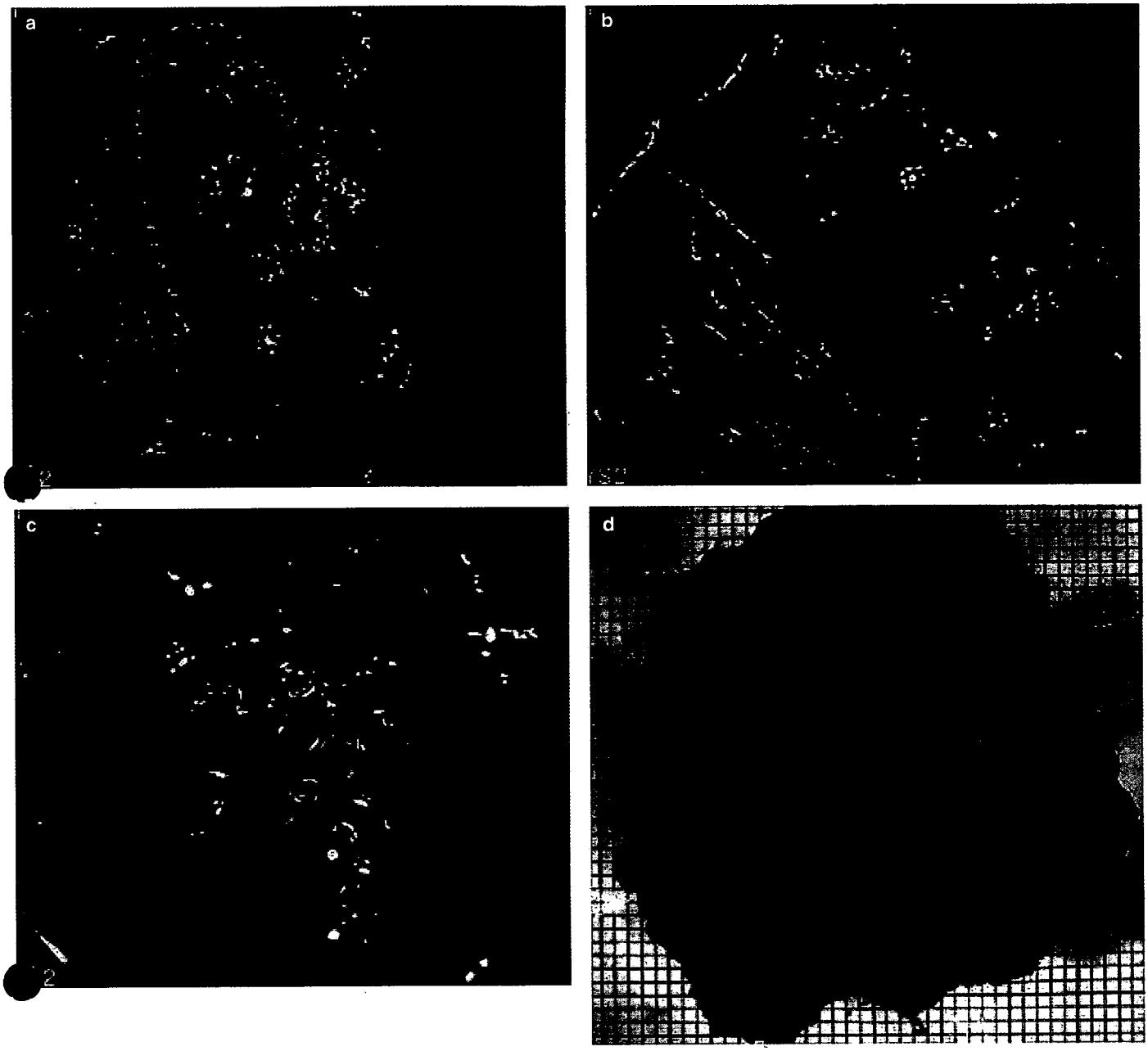

Fig. 2. (a,b) The lesion was approximately 35 mm in diameter. (c) Successful closure of the colonic perforation was performed using endoclips. (d) Stereomicroscopic examination of the resected specimen showed a definite layer of muscle at the cut margin.

histologically, requiring surgery. CT before surgery (taken approx. 1 month after the previous CT examination) showed no fluid collection (Fig. 3b) and there was no abscess or adhesion close to the EMR ulcer scar at the time of surgery.

Previous reports have suggested that both CT findings and serology results (WBC, CRP) are poor predictors of surgery.[18–20] Both of the present patients satisfied the conservative management criteria concerning abdominal pain, fever and serology results. Intestinal fluid, however, leaked into the abdominal cavity and one patient had fluid collection suggesting an abscess, which turned out to be only intestinal fluid.

Based on these limited case reports, there is a possibility that colonic perforation can be treated conservatively when abdominal distension, fever and serology results are within acceptable tolerances, even when CT shows fluid collection. Justifications for this position include adequate bowel preparation using polyethylene glycol electrolyte solution[18–20] as well as the preventive administration of antibiotics.

Abdominal decompression

The patient who sustained an ascending colon perforation required abdominal decompression to decrease abdominal distension. Endoscopic closure was difficult because the colonic lumen collapsed and the patient was experiencing discomfort, but we finally succeeded in performing endoscopic closure after abdominal decompression.