⑥ 大腸

Case 57　70歳代 女性　○○○　大腸 LST-NG②

- 既往検査：下部消化管内視鏡，腹部 CT（造影）
- 合併症：高血圧症
- 内服薬：ディオバン®（バルサルタン）
- 使用機器：PillCam® COLON
- カプセル内視鏡診断（Colon MST）：Tumor
- カプセル内視鏡後の精密検査・治療：ESD

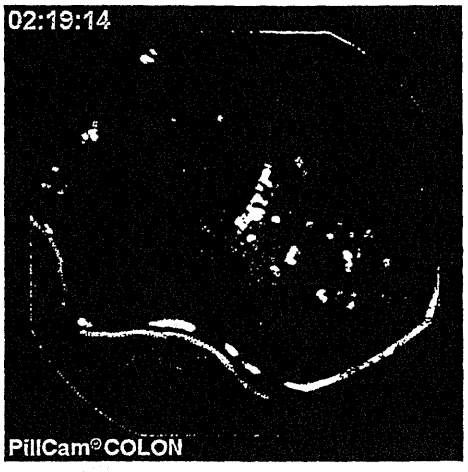

図1　(02:19:14)
ある程度丈のある扁平隆起を認める．

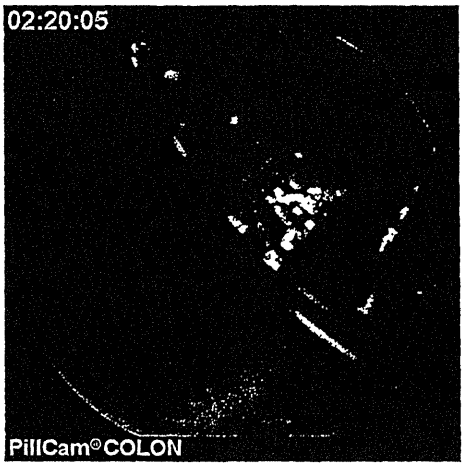

図2　(02:20:05)
ある程度丈のある扁平隆起を認める．

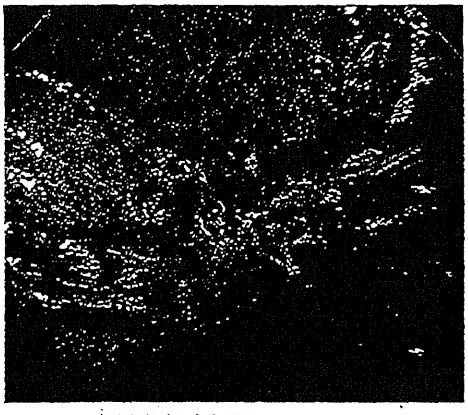

図3　下部消化管内視鏡
25 mm 大の 0-Ⅱc（LST-NG）を認める．

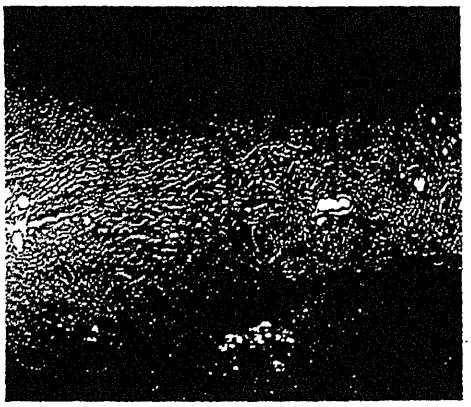

図4　下部消化管内視鏡
クリスタルバイオレット（ピオクタニン）染色下の拡大観察
V_I（non-invasive）pit pattern

解　説

横行結腸にある程度丈のある扁平隆起を認める．いずれも近接像でかつ画面の端に部分的に観察されるだけであり，病変の全貌を捉えることはできなかった．ただし，通常内視鏡で観察されるよりもむしろ丈の高さは目立っており，存在診断は比較的容易である．数多い画像による動画から，このような病変をみつけるための読影トレーニングは必要であろう．また，良好な腸管洗浄も病変発見を容易にするひとつの重要なポイントである．

この病変は下部消化管内視鏡にて 25 mm 大の 0-Ⅱc（LST-NG），sm1 までのものと判断された．通常 EMR では治療が困難であり，ESD が施行された．

なお，本症例は高分化腺癌，軽度異型，深達度 m（well differentiated adenocarcinoma, low grade atypia, depth: pM）と診断された．

A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video) CME

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Tokyo, Okayama, Shizuoka, Nagano, Chiba, Tochigi, Matsuyama, Osaka, Aomori, Japan

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

Objective: To examine the current status of colorectal ESDs at specialized endoscopic treatment centers.

Design and Setting: Multicenter cohort study using a prospectively completed database at 10 specialized institutions.

Patients and Interventions: From June 1998 to February 2008, 1111 colorectal tumors in 1090 patients were treated by ESD.

Main Outcome Measurements: Tumor size, macroscopic type, histology, procedure time, en bloc and curative resection rates and complications.

Results: Included in the 1111 tumors were 356 tubular adenomas, 519 intramucosal cancers, 112 superficial submucosal (SM) cancers, 101 SM deep cancers, 18 carcinoid tumors, 1 mucosa-associated lymphoid tissue lymphoma, and 4 serrated lesions. Macroscopic types included 956 laterally spreading tumors, 30 depressed, 62 protruded, 44 recurrent, and 19 SM tumors. The en bloc and curative resection rates were 88% and 89%, respectively. The mean procedure time ± standard deviation was 116 ± 88 minutes with a mean tumor size of 35 ± 18 mm. Perforations occurred in 54 cases (4.9%) with 4 cases of delayed perforation (0.4%) and 17 cases of postoperative bleeding (1.5%). Two immediate perforations with ineffective endoscopic clipping and 3 delayed perforations required emergency surgery. Tumor size of 50 mm or larger was an independent risk factor for complications, whereas a large number of ESDs performed at an institution decreased the risk of complications.

Limitations: No long-term outcome data.

Conclusions: ESD performed by experienced endoscopists is an effective alternative treatment to surgery, providing high en bloc and curative resection rates for large superficial colorectal tumors. (Gastrointest Endosc 2010;72:1217-25.)

Abbreviations: ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; SM, submucosal; SM1, submucosal invasion less than 1000 μm from the muscularis mucosae; SM2, submucosal invasion 1000 μm or more from the muscularis mucosae.

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For many years, conventional EMR[1-5] and surgery were the only available treatments for large colorectal tumors, even those detected at an early stage.

Conventional EMR techniques, however, are inadequate for en bloc resection of laterally spreading tumors (LSTs) larger than 20 mm because there can be incomplete removal and local recurrence occasionally after a piecemeal EMR.[6] As a result, open surgeries, laparoscopic surgeries, and lymph node dissections have been performed in the past on large LSTs limited to mucosal or submucosal (SM) invasion less than 1000 μm from the muscularis mucosae (SM1) despite the negligible risk of lymph node metastasis,[7] thus resulting in a considerably lower patient quality of life after surgery compared with EMR.[8]

The endoscopic SM dissection (ESD) procedure that was initially developed for early gastric cancer facilitates the resection of large superficial tumors en bloc[9-11] but is not widely accepted for colorectal cancer despite its minimal invasiveness because of the greater technical difficulty involved and the risk of perforation and resultant peritonitis.[12] Because of the widespread use of gastric ESDs, however, the number of medical facilities at which colorectal ESDs are performed has been increasing recently, and the effectiveness of colorectal ESD has been reported not only in Japan,[13-20] but also in a number of Western countries.[21,22] In 2 earlier series,[8,17] we found that the introduction of ESD enabled us to effectively treat large colorectal tumors that would previously have been treated by surgery because of the procedure's technical difficulty, but those studies were limited to single centers, single operators, and small numbers of patients.

Our purpose in this study, therefore, was to examine the current status of colorectal ESDs performed at specialized institutions for endoscopic treatment in Japan. In addition, we investigated the safety and effectiveness of colorectal ESD and examined the possibility of standardizing this procedure.

PATIENTS AND METHODS

A prospective, multicenter cohort study was conducted at 10 institutions involving clinical colorectal ESD results including tumor size, macroscopic type, histology, procedure time, en bloc and curative resection rates, and complications (**Table 1**).

Consecutive patients who underwent ESD at the 10 institutions from June 1998 to February 2008 were analyzed using a prospectively completed database. The institutions were divided into 3 separate groups according to the total number of ESDs performed at each (group A, <50 ESDs; group B, ≥50 and <100 ESDs; and group C, ≥100 ESDs) (**Table 2**). This study was conducted with the approval of each institution's ethical review board, and informed written consent was obtained from all patients for each specific colonoscopic treatment.

Take-home Message

- Based on the authors' large multicenter study, endoscopic submucosal dissection (ESD) performed by experienced endoscopists is a very effective alternative treatment to surgery for large superficial colorectal tumors.
- Large tumor size (≥50 mm) was shown to be an independent risk factor for complications, whereas the large number of ESDs performed by an institution decreased the risk of complications.

Inclusion criteria for ESD

Depth of invasion was limited to mucosal or SM1, as estimated endoscopically as well as by magnification chromoendoscopy in most cases.[23] The existence of a noninvasive pattern[24-26] as determined by magnification chromoendoscopy was helpful in the diagnosis of tumor depth of invasion.

Based on extensive clinicopathological analyses,[27-29] we defined the indications for ESD[17] as nongranular type LSTs larger than 20 mm and granular type LSTs larger than 30 mm because both have a higher SM invasion rate and are difficult to treat even by piecemeal EMR.[27-29] Large villous tumors as well as intramucosal lesions, recurrent lesions, and residual mucosal lesions that showed a nonlifting sign[30,31] after EMR were also potential candidates for ESD, with the final decision made by each individual colonoscopist (**Tables 1** and **2**).

Exclusion criteria for ESD

Exclusion criteria included the existence of an invasive pattern,[24-26] as determined by magnification chromoendoscopy, and patients with other invasive cancers and circumferential tumors treated by surgery, although they may have been diagnosed as mucosal lesions because of the increased technical difficulty involved and the anticipated risk of stenosis.

Clinicopathological characteristics

The location of tumors was based on the Japanese classification of cancer of the colon and rectum[32] and included the cecum, the right side of the colon (ascending and transverse colon), the left side of the colon (descending and sigmoid colon), and the rectum. Macroscopic types included nongranular and granular types of LSTs and depressed, protruded, recurrent, and SM tumors.

ESD methods

Bowel preparation. The patient drank 2 to 3 L of polyethylene glycol solution in the hospital the morning of the procedure. In an effort to further ensure excellent bowel preparation, stool color was assessed before each procedure by a trained nurse, and additional polyethylene glycol solution was administered as necessary.

Table 1. Clinical characteristics of 1111 colorectal ESDs performed in 1090 patients at 10 institutions

	Institutions										
	1	2	3	4	5	6	7	8	9	10	Total
No. of ESDs	405	161	130	128	89	78	52	32	25	11	1111
No. of ESD patients	393	161	130	124	87	76	52	32	24	11	1090
Sex, male/female	232/161	95/66	91/39	74/50	57/30	52/24	31/21	21/11	17/7	7/4	677/413
Age, y, mean ± SD	65 ± 10	66 ± 11	69 ± 10	69 ± 10	64 ± 11	64 ± 10	66 ± 10	67 ± 11	60 ± 11	67 ± 9	66 ± 10
Range	32-86	34-86	38-89	36-90	34-87	40-87	35-85	38-83	35-84	48-81	32-90
Tumor size, mm, mean ± SD	37 ± 19	34 ± 16	41 ± 22	34 ± 17	34 ± 15	33 ± 12	36 ± 18	28 ± 19	14 ± 10	41 ± 21	35 ± 18
Range	10-140	6-86	10-110	3-100	10-81	15-70	10-100	7-90	3-38	10-75	3-140
Tumor location											
Cecum	39	7	12	25	2	9	8	0	1	0	103
Right colon	153	50	40	48	47	31	19	13	1	6	408
Left colon	102	46	31	33	14	15	13	5	3	1	263
Rectum	111	58	47	22	26	23	12	14	20	4	337
Macroscopic type											
LST-NG	168	51	40	46	35	40	19	19	0	1	419
LST-G	173	79	76	79	49	34	26	8	5	8	537
Depressed	15	4	3	0	0	1	2	3	2	0	30
Protruded	21	21	3	1	3	0	4	0	9	0	62
Recurrent	25	5	8	0	0	2	0	2	0	2	44
Submucosal tumor	3	1	0	2	2	1	1	0	9	0	19
Devices/ instruments	B + IT	Flex + IT	B + IT + M	Hook	Flush + hook	B + IT	B + IT	Flush + M	Flush	IT + Flush	
CO_2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	

B, Bipolar needle-knife; *ESD*, endoscopic submucosal dissection; *Flex*, Flex knife; *Flush*, Flush knife; *Hook*, Hook knife; *IT*, insulation-tipped knife; *LST-G*, granular type laterally spreading tumor; *LST-NG*, nongranular type laterally spreading tumor; *M*, mucosectom.

ESD procedures. The procedures were primarily performed using 1 or 2 ESD knives including a bipolar needle-knife (Xeon Medical Co, Tokyo, Japan),[14,17,35] Flex knife,[19] Hook knife (Olympus Co, Tokyo, Japan),[20] Flush knife (Fujinon Co, Tokyo, Japan),[16] Mucosectom (Pentax Co, Tokyo, Japan),[18] and insulation-tipped knife (Olympus).[9-11,13] Midazolam (2 mg intravenously) and pentazocine (15 mg intravenously) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. Hemostatic forceps (Coagrasper; Olympus) were used for hemostasis of bleeding. At 8 institutions (80%), CO_2 insufflation was used instead of air insufflation to reduce patient discomfort.[14] Lesion margins were delineated before ESD using 0.4% indigo-carmine spray dye (**Fig. 1**A-D; Video 1, available online at **www.giejournal.org**). After injection of 10% glycerol and 5% fructose in normal saline solution (Glyceol; Chugai Pharmaceutical Co, Tokyo, Japan)[34] and sodium hyaluronate acid into the SM layer,[15] a circumferential incision was made using a single ESD knife, and ESD was then performed using 1 or 2 ESD knives (**Fig. 2**A-D).

Definition of en bloc resection

We defined an en bloc resection as the 1-piece resection of an entire lesion as observed endoscopically.[17] A resection was defined as being complete when histopathological examination revealed tumor-free lateral

TABLE 2. Clinical characteristics of 1111 colorectal ESDs performed in 1090 patients at 10 institutions divided into 3 separate groups

	Group (no. of ESDs per institution)				
	A (<50)	B (≥50 and <100)	C (≥100)	Total	*P* value
Total ESDs	68	219	824	1111	
Sex, male/female	45/22	140/75	492/316	677/413	.415
Age, y, mean ± SD	64.5 ± 11.3	64.8 ± 10.3	66.6 ± 10.3	66.0 ± 10.0	.039
Tumor size, mm, mean ± SD	24.7 ± 18.3	33.9 ± 14.8	36.0 ± 19.0	34.9 ± 18.4	<.0001
Tumor location					
Cecum	1	19	83	103	
Right colon	20	97	291	408	
Left colon	9	42	212	263	
Rectum	38	61	238	337	<.0001
Macroscopic type					
LST-NG	20	94	305	419	
LST-G	21	109	407	537	
Depressed	5	3	22	30	
Protruded	9	7	46	62	
Recurrent lesion	4	2	38	44	
Submucosal tumor	9	4	6	19	<.0001
Histology					
Non-neoplastic	0	1	3	4	
Adenoma	16	77	263	356	
Mucosal cancer	28	94	397	519	
SM1 cancer	10	24	78	112	
SM2 cancer	4	19	78	101	
Other	10	4	5	19	<.0001
En bloc resection rate, %	85.0	84.0	89.0	88.0	.170
Curative resection rate, %	85.9	86.5	89.7	89.0	.309
Procedure time, min, mean ± SD	128 ± 91	108 ± 69	117 ± 91	116 ± 88	.226
Complications, no. (%)	12 (17.6)	18 (8.2)	42 (5.1)	72 (6.5)	.0011
Perforation	8 (11.8)	12 (5.5)	34 (4.1)	54 (4.9)	.043
Delayed perforation	0 (0.0)	2 (0.9)	2 (0.2)	4 (0.4)	.34
Postoperative bleeding	4 (5.9)	4 (1.8)	9 (1.1)	17 (1.5)	.043
Emergency surgery cases, no. (%)	0 (0.0)	2 (0.9)	2 (0.2)	4 (0.4)	.34

ESDs, Endoscopic submucosal dissections; *LST-NG*, nongranular type laterally spreading tumor; *LST-G*, granular type laterally spreading tumor; *SD*, standard deviation; *SM1*, submucosal invasion less than 1000 μm from the muscularis mucosae; *SM2*, submucosal invasion 1000 μm or more from the muscularis mucosae.

margins. An incomplete resection occurred whenever the lateral margins indicated tumor infiltration, and the existence of such tumor infiltration could not be determined or was unknown.

Definition of complications

Perforation during an ESD procedure was defined as immediate, and delayed perforation was defined as occurring after completion of the ESD procedure. Postoperative

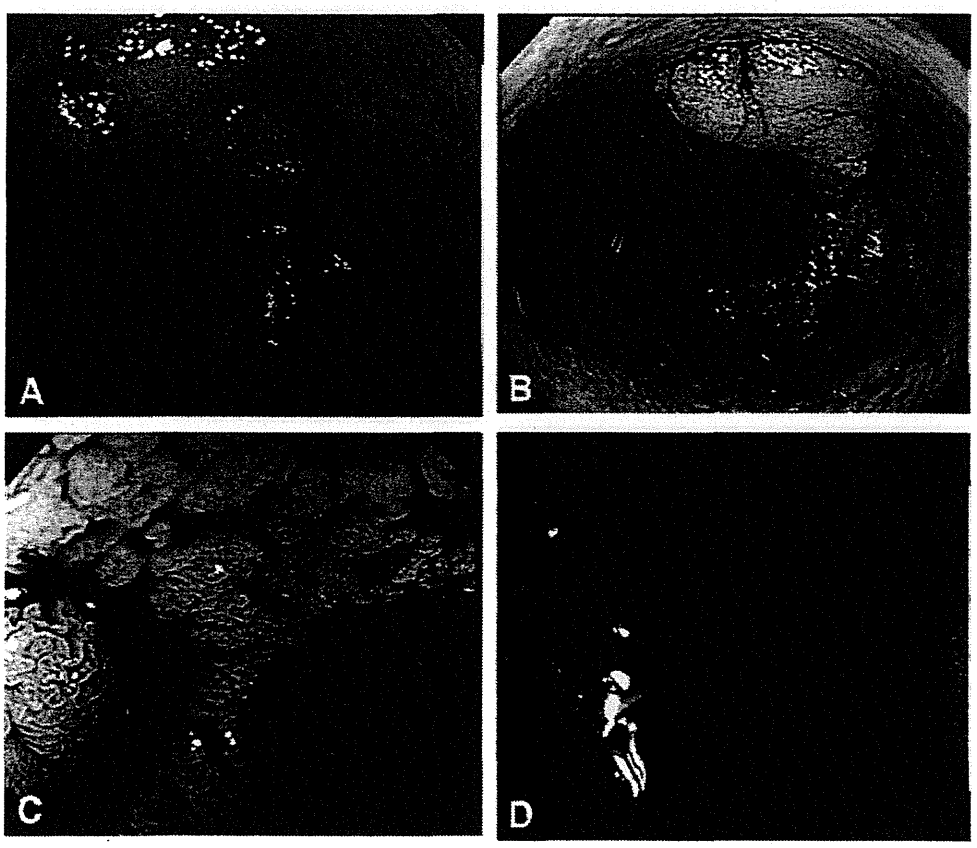

Figure 1. (with video). Endoscopic diagnosis before ESD. ESDs were primarily performed by using a bipolar needle knife and insulation-tipped knife with CO_2 insufflation at the National Cancer Center Hospital. **A**, Nongranular type LST 50 mm in size located in the descending colon. **B**, Lesion margins delineated before ESD using 0.4% indigo-carmine spray dye. **C**, Magnification colonoscopy with indigo-carmine dye revealed noninvasive III and VI pit patterns in the depressed area of this lesion. **D**, Crystal violet (0.05%) staining clearly revealed a VI (slightly irregular) noninvasive pattern suggesting intramucosal cancer and indicating a good candidate for endoscopic treatment.

bleeding was defined as clinical evidence of bleeding manifested by melena or hematochezia from 0 to 14 days after the procedure that required endoscopic hemostasis.

Histological assessment

All specimens were evaluated after being cut into 2-mm slices and examined microscopically for histological type, depth of invasion, and lateral and vertical resection margins. Resections were considered tumor free when the lateral and vertical margins of a specimen were both negative for tumor cells independent of its histological features. A curative resection[17] was achieved when both the lateral and vertical margins of the specimen were free of cancer, and there was no SM invasion deeper than SM1, lymphatic invasion, vascular involvement, or poorly differentiated component.[7] An adenoma with an unknown lateral margin was also considered to be a curative resection provided that such adenoma met all the other criteria. Histological diagnoses were based on the Japanese classification of cancer of the colon and rectum[32] and the Vienna classification.[35]

Statistical analysis

All data analysis was conducted using statistical JMP software version 7.0 (SAS Institute, Cary, NC). Data were presented as means ± standard deviation, medians, ranges, and percentages. For analysis of clinicopathological characteristics, short-term outcomes and screening of risk factors for complications, we used the Student t, χ^2, and Fisher exact tests as appropriate. Univariate and multivariate logistic regression analyses were constructed for the determination of complication predictors. All baseline characteristics were evaluated as possible predictors, and those with $P < .1$ were included in the univariate and multivariate logistic regression models. All tests were 2 tailed, and $P < .05$ was considered significant.

RESULTS

During the study period, colorectal ESDs were performed on a total of 1111 tumors in 1090 consecutive patients at 10 specialized institutions.

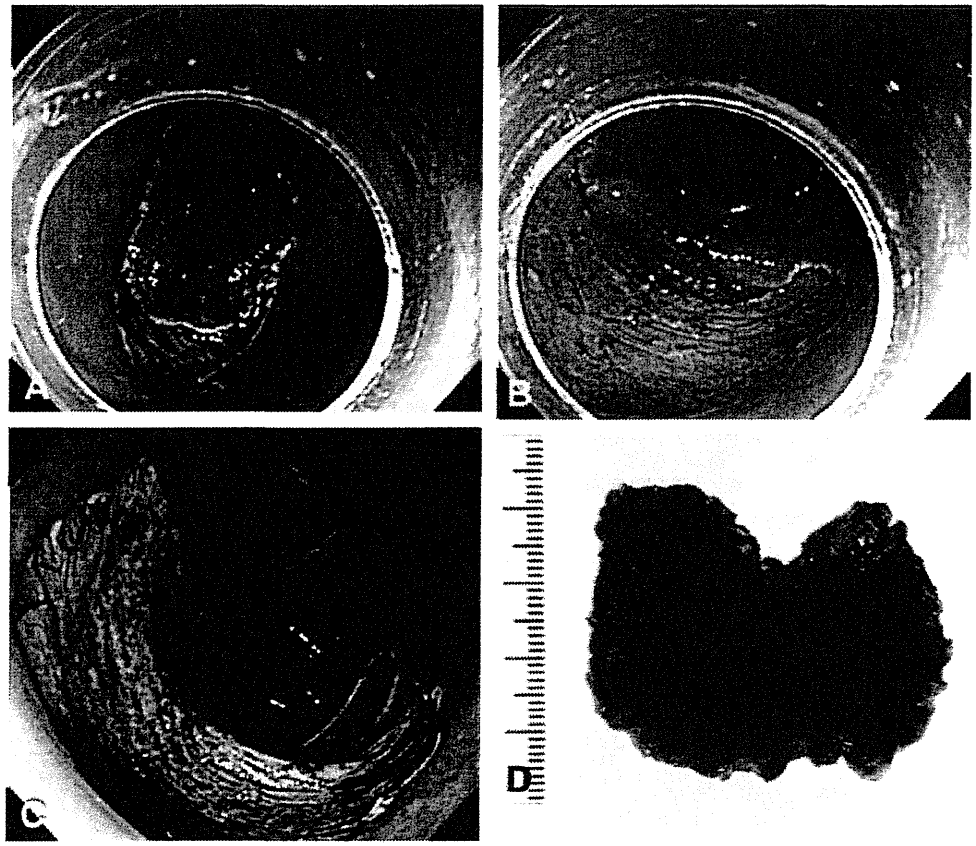

Figure 2. ESD (Video available online at www.giejournal.org). **A**, After injection of Glycerol (10% glycerol and 5% fructose in normal saline solution) and sodium hyaluronate acid solution into SM layer, partial circumferential incision performed by using bipolar needle-knife. **B**, After partial circumferential incision, SM dissection performed by using a bipolar needle-knife and insulation-tipped knife. Blue-colored SM layer clearly visualized using indigo-carmine dye and distal attachment for countertraction. **C**, Ulcer bed after successful en bloc resection completed within 2 hours. **D**, Histology of resected specimen 50 x 30 mm in diameter revealed intramucosal cancer with tumor-free margin.

Clinicopathological characteristics

The mean age was 66 ± 10 years (median 67 years, range 32-86 years), the male to female ratio was 1.6:1 and the mean tumor size was 35 ± 18 mm. Histologically, of the 1111 tumors, there were 356 tubular adenomas (32%), 519 mucosal cancers (47%), 112 SM1 cancers (10%), 101 SM invasion 1000 μm or more from the muscularis mucosae (SM2) or deeper cancers (9%), 18 carcinoid tumors, 1 mucosa-associated lymphoid tissue lymphoma, and 4 serrated or non-neoplastic lesions. Macroscopic types included 419 nongranular type LSTs (38%), 537 granular type LSTs (48%), 30 depressed (2.7%), 62 protruded (5.6%), 44 recurrent (4%), and 19 SM tumors (1.7%). Tumor location included 103 in the cecum (9.3%), 408 in the right colon (36.7%), 263 in the left colon (23.7%), and 337 in the rectum (30.3%).

There were no significant differences among the 3 groups of institutions in terms of sex or age. The mean tumor size was significantly smaller in group A ($P <$ .0001), and significant differences were also established with respect to tumor location ($P <$ .0001), macroscopic type ($P <$ .0001), and histology ($P <$ .0001).

Clinical outcomes of colorectal ESDs

The mean procedure time was 116 ± 88 minutes. The en bloc resection rate was 88% and the curative resection rate was 89%. Noncurative resections were indicated in 121 patients (11%), most of which underwent additional surgery. There were no statistically significant differences in the mean procedure time, en bloc resection rate, or curative resection rate among the 3 groups.

Complication rate

Perforations during actual ESD procedures occurred in 54 patients (4.9%), and delayed perforations occurred in another 4 patients (0.4%). In 2 patients with immediate perforation, endoscopic clipping (EZClip, HX-110QR; Olympus) was ineffective, and 2 patients with delayed perforation required emergency surgery. There were 17 patients with postoperative bleeding (1.5%), but all were successfully treated by using endoclips without the need for any blood transfusions. The overall complication rate, the number of immediate perforations, and the number of patients with delayed bleeding were significantly higher in group A institutions at which the smallest total number of

ESDs were performed. Finally, there were no procedure-related mortalities at any of the institutions (**Tables 1** and **2**).

Independent risk factors for complications assessed by univariate and multivariate analysis

In the screening analysis for complication risk factors, tumor size, tumor location, macroscopic type, and histology had no significant association with the ESD complication rate (not significant), but there was a significantly decreased risk of complications corresponding to the increased number of ESDs performed at the 3 groups of institutions (group A, <50 ESDs, 17.6%; group B, ≥50 and <100 ESDs, 8.2%; and group C, ≥100 ESDs, 5.1%) ($P <$ .0001) (**Table 3**). In the logistic regression models, the complication rate was independently higher for large tumors (≥50 mm) (multivariate analysis: odds ratio, 2.1; 95% confidence interval, 1.1-3.4; $P = .0198$), whereas the larger number of ESDs performed by groups B and C decreased the risk of complications (multivariate analyses: group B/group C: odds ratio, 0.4/0.2; 95% confidence interval, 0.2-0.9/0.1-0.5; $P = .0253/.0002$) (**Table 4**). There was no association, however, between the types of knives used during the ESDs and the complication rate (data not shown).

TABLE 3. Risk factors for ESD complications

Risk factors	Complications		
	No	Yes	*P* Value
ESDs	1039	72	
Sex, male	639	42	.595
Age, y, mean ± SD	66.2 ± 10.5	64.8 ± 9.5	.273
Tumor size, mm			
<50	851	52	
≥50	188	20	.0316
Tumor location			
Cecum	93	10	
Right colon	384	24	
Left colon	249	14	
Rectum	313	24	.451
Macroscopic type			
LST-NG	397	22	
LST-G	501	36	
Depressed (IIc)	30	0	
Protruded (Is)	54	8	
Recurrent tumor	39	5	
Submucosal tumor	18	1	.075
Histology			
Non-neoplastic	3	1	
Adenoma	328	28	
Mucosal cancer	487	32	
SM1 cancer	106	6	
SM2 cancer	96	5	
Others	19	0	.45
Institutions (no. of ESDs)			
Group A (<50)	56	12	
Group B (≥50 and <100)	201	18	
Group C (≥100)	782	42	<.0001
Trend			<.0001

ESD, Endoscopic submucosal dissection; *LST-NG*, nongranular type laterally spreading tumor; *LST-G*, granular type laterally spreading tumor; *SD*, standard deviation; *SM1*, submucosal invasion less than 1000 μm from the muscularis mucosae; *SM2*, submucosal invasion 1000 μm or more from the muscularis mucosae.

DISCUSSION

This is the first large prospective, multicenter cohort study of colorectal ESDs performed at specialized centers in Japan. There is increasing evidence of the effectiveness of colorectal ESD because the procedure makes it possible to treat large nongranular type LSTs (>20 mm) that had been treated by surgery in the past.[8] The longer procedure time and higher complication rate of ESD compared with conventional EMR have also been discussed previously.[3,6] In fact, a small number of analyses[11,12] conducted in an earlier Japanese multicenter study indicated a higher complication rate during colorectal ESDs and that standardization of the colorectal ESD procedure would be difficult.

This study is particularly important because more than 1000 colorectal ESD cases in 10 specialized centers were analyzed at a time when the use of colorectal ESD is spreading in Japan, and a number of trained endoscopists are starting to perform colorectal ESDs in Western countries as well.[21,22] The complication rate significantly decreased with the increased number of ESDs performed at an institution from 17.6% for group A (<50 ESDs) to 8.2% for group B (≥50 and <100 ESDs) to 5.1% for group C (≥100 ESDs), probably because of greater clinical experience in performing colorectal ESDs on a regular basis at group B institutions and even more so at group C institutions. There were no significant statistical differences for the mean procedure time, en bloc resection rate, and curative resection rate among the 3 groups, most likely because the mean tumor size was smaller and the locations differed as did the macroscopic types in group A,

TABLE 4. Risk factors for complications

	Univariate Analysis			Multivariate Analysis		
	OR	95 CI	*p* Value	OR	95 CI	*p* Value
Macroscopic Type						
LST-NG	1					
Recurrent Tumor	2.3	0.7-6.0	0.1088			
Others	1.3	0.8-2.3	0.2668			
Tumor Size						
<50 mm	1			1		
≧50 mm	1.7	1.0-2.9	0.0439	2.1	1.1-3.4	0.0198
Institutions (ESDs)						
A (<50)	1			1		
B (≧50, <100)	0.4	0.2-0.9	0.0351	0.4	0.2-0.9	0.0253
C (≧100)	0.3	0.1-0.5	0.0004	0.2	0.1-0.5	0.0002

CI, confidence interval; *OR*, odds ratio; *ESD*, endoscopic submucosal dissection.

suggesting that less-experienced endoscopists did not attempt to perform ESDs in more challenging cases.

To decrease the colorectal ESD complication rate in the future, it will be necessary to establish a learning curve based on the results of our large case series. In addition, conservative treatment of perforations should be possible in the future in those cases in which endoscopic clipping has already been shown to be effective.

The indications for ESD in this series were markedly different from those for conventional EMR,[17,36] and the overall perforation rate of 5.2% was higher compared with conventional EMR,[36] but considerably lower than the earlier Japanese multicenter analyses mentioned previously[11,12] in which delayed perforation cases were regarded as requiring emergency surgery because of the risk of peritonitis. Two of the 4 patients with delayed perforations in this series, however, were successfully treated conservatively as abdominal findings and inflammation changes based on laboratory data were slight. Taku et al[12] also reported that conservative treatment might be possible, even for cases of delayed perforation when abdominal findings and laboratory data are stable, but we must carefully follow patients with delayed perforation and continued close communication with consulting surgeons is essential because the number of such cases has been quite limited so far.

The other principal ESD complication involved postoperative bleeding, but the total postoperative bleeding rate was only 1.5%, and none of the 17 patients required a blood transfusion or emergency surgery. This relatively low rate of postoperative bleeding was probably a result of using the coagulation technique for exposed vessels during ESD procedures, and the incidence of postoperative bleeding also decreased as the total number of ESDs performed at the 3 respective groups of institutions increased.

Univariate and multivariate analysis revealed that large tumor size (≥50 mm) and less experience performing ESDs (group A, <50 cases) were independent risk factors for complications, so endoscopists should begin by performing colorectal ESDs on smaller lesions.

The mean ESD procedure time was considerably longer compared with that of conventional EMR,[36] but the indications for ESD and EMR were different, as were the tumor characteristics.[36] We should be comparing, therefore, the procedure times between ESD and surgery rather than ESD and EMR.

As for ESD devices, more than 2 knives were used in most institutions and CO_2 insufflation was used at 8 of the 10 institutions to reduce patient discomfort (Table 1). These factors also will need to be taken into account when considering costs in the future.

This was a prospective multicenter cohort study, but eligibility criteria for performing colorectal ESDs were sometimes unclear at some of the institutions. It will be necessary, therefore, to further assess the clinical outcome of using ESD for the treatment of large colorectal tumors in the future.

Another limitation of this study is that no long-term outcome data are available yet because a few of the institutions have only started performing colorectal ESDs in recent years. With more than 6 months of follow-up for cases at the National Cancer Center Hospital, there have been only 3 local recurrences (2%) in ESD cases (mean endoscopic follow-up period, 20.0 ± 12.9 months) compared with 33 recurrences (14%) in EMR cases (mean endoscopic follow-up period 25.9 ± 17.0 months).[36]

In conclusion, ESD performed by experienced endoscopists is a safe and very effective procedure for treating large superficial colorectal tumors such as nongranular type LSTs larger than 20 mm and granular type LSTs larger than 30 mm that would have previously been treated with surgery, as well as large villous tumors and intramucosal lesions, recurrent lesions, and residual mucosal lesions showing nonlifting sign after EMR.

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Endoscopic Submucosal Dissection of Non-Polypoid Colorectal Neoplasms

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KEYWORDS
- Endoscopic submucosal dissection
- Endoscopic mucosal resection
- Endoscopic piecemeal mucosal resection • Colorectum
- Laterally spreading tumor granular type
- Laterally spreading tumor nongranular type

Traditionally, endoscopic mucosal resection (EMR)[1–5] and surgery were the only available treatments for large colorectal tumors, even for those detected at an early stage. In Japan, EMR is indicated for the treatment of colorectal adenomas, intramucosal and submucosal superficial (invasion <1000 μm from the muscularis mucosae) cancers, because of its negligible risk of lymph node metastasis[6] and excellent clinical outcomes.[2–4]

The endoscopic submucosal dissection (ESD) technique, which enables en-bloc resection of large tumors, is accepted as a standard minimally invasive treatment for early gastric cancer in Japan.[7,8] However, it is not widely used to treat superficial colorectal cancer because of technical difficulty and the higher risk of complications. Conventional EMR, therefore, is used for the resection of non-polypoid colorectal neoplasms (NP-CRNs), including the large flat carpet lesions, called colorectal laterally spreading tumors (LSTs).[4,5] EMR, however, is not designed for en-bloc resection of LSTs larger than 20 mm. Piecemeal EMR is associated with the risks of incomplete removal and local recurrence[9] albeit most recurrences can be successfully treated by additional EMR and only a few cases require surgery.[9] ESD of LSTs larger than 20 mm is therefore an attractive treatment provided that it is safe to use in the colon and rectum.

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Based on the refinement of ESD instruments and progress in the development of ESD skills, the ESD technique has recently been reported to be useful in the treatment of large colorectal LSTs instead of EMR or surgery.[10–15] Herein, the authors describe their experience.

INDICATIONS FOR COLORECTAL ESD

The indication for colorectal ESD at the National Cancer Center Hospital (NCCH) in Tokyo, Japan, is a nongranular type LST (LST-NG) larger than 20 mm.[12]

Based on clinicopathologic analyses of LSTs,[4,16] LST-NGs, which are large (>1 cm) superficial elevated NP-CRNs with a smooth surface, have a higher rate of submucosal (sm) invasion, which can be difficult to predict endoscopically. About 30% of LST-NGs with sm invasions are multifocal, and such invasions are primarily superficial submucosal cancers (sm1s) and difficult to predict before endoscopic treatment.

Granular type LSTs (LST-Gs) have a lower rate of sm invasion, and most such invasions are found under the largest nodule or depression, which are easier to predict endoscopically.[4,16] LST-Gs larger than 20 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than by ESD, with the area that has the largest nodule resected before resection of the remaining tumor. LST-Gs larger than 30 mm or 40 mm are possible candidates for ESD because they have higher sm invasion rates and are more difficult to treat even by EPMR; so they have been treated by either EPMR or ESD, based on the individual endoscopist's judgment.

ESTIMATION OF THE DEPTH OF INVASION

A non-invasive pattern[17,18] should be verified in each lesion, indicating suitability for EMR or ESD: the estimated invasion depth should be less than that of superficial submucosal cancers (sm1s). No biopsy is performed before ESD because it can cause fibrosis and may interfere with submucosal lifting.

CESSATION PERIOD OF ANTICOAGULANT AND ANTIPLATELET BEFORE ESD

ESD is considered to be a high-risk procedure.[19] Most patients receiving aspirin or ticlopidine alone underwent ESD after a cessation period of 5 to 7 days and restarted the drugs after 7 days if possible. Patients receiving warfarin used intravenous heparin or subcutaneous low-molecular-weight heparin in the perioperative period and resumed warfarin after the ESD procedure.

ESD PROCEDURE AT NCCH

The procedures were primarily performed using a ball-tip bipolar needle knife (B-knife) (XEMEX Co, Tokyo Japan) (**Fig. 1**A)[20] and an insulation-tip (IT) electrosurgical knife (Olympus Optical Co, Tokyo, Japan) (see **Fig. 1**B) with carbon dioxide insufflations instead of air insufflation to reduce patient discomfort (see **Fig. 1**C).[11] After submucosal injection of 10% glycerin and 5% fructose (Glyceol, Chugai Pharmaceutical Co, Tokyo, Japan)[21] and 0.4% hyaluronic acid[14] (MucoUp, Seikakagu Co, Tokyo, Japan) (see **Fig. 1**D) into the sm layer, a circumferential incision was made using the B-knife and an ESD was then performed using the B-knife and IT knife (see **Fig. 1**A, B).

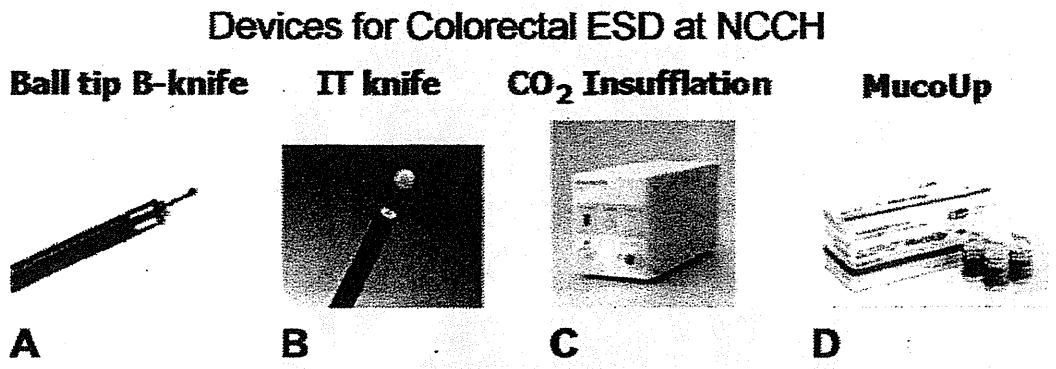

Fig. 1. The procedures were primarily performed using a B-knife (*A*) and an IT electrosurgical knife (*B*) with carbon dioxide insufflation (*C*) instead of air insufflation to reduce patient discomfort. After injection of Glyceol (Chugai Pharmaceutical Co, Tokyo, Japan) and MucoUp (Seikakagu Co, Tokyo, Japan) (*D*) into the sm layer, a circumferential incision was made using the B-knife and an ESD was performed using the B-knife and IT knife. (*From* XEMEX Co, Tokyo, Japan; with permission [*A*]; Olympus Optical Co, Tokyo, Japan; with permission [*B*]; and Seikakagu Co, Tokyo, Japan; with permission [*D*].)

SUBMUCOSAL INJECTION SOLUTION

A mixture of 2 solutions was prepared before the procedure to create a longer-lasting sm fluid cushion.

Solution 1: Indigo carmine dye (2 mL of 1% solution) and epinephrine (1 mL of 0.1% solution) were mixed with 200 mL Glyceol[21] in a container, which was then drawn into a 5-mL disposable syringe.

Solution 2: MucoUp was drawn into another 5-mL syringe with a smaller amount of indigo carmine dye and epinephrine. During the actual ESD procedure, a small amount of solution 1 was injected into the sm layer to confirm the appropriate sm layer elevation and then solution 2 was injected into the properly elevated sm layer. Finally, a small amount of solution 1 was injected again to flush out any residual solution 2.

DETAILED COLORECTAL ESD PROCEDURES

1. The margins of the lesion were delineated before ESD by spraying 0.4% indigo carmine dye (**Fig. 2**A). After creation of the submucosal fluid cushion, an initial incision was made with the B-knife at the oral side of the lesion (see **Fig. 2**B).[20] In colorectal cases, it was not necessary to actually mark around lesions because tumor margins can be visualized clearly with indigo carmine.
2. The B-knife was inserted into the initial incision, and an electrosurgical current was applied in endocut mode (50 W) using a standard electrosurgical generator (ICC 200, ERBE, Tubingen, Germany) to continue the marginal incision around the oral side of the lesion.
3. After partial resection of the margin on the oral side of the lesion to ensure adequate submucosal lifting, submucosal dissection was begun using the same B-knife in retroflex view (see **Fig. 2**B).
4. Additional resection of the margin on the anal side was performed using the B-knife in the straight view (see **Fig. 2**C).
5. After the lesion was partially dissected so that the sm layer could be visualized sufficiently, an IT knife (see **Fig. 2**D) was used to complete the dissection of the sm layer quickly and safely. The previously indicated solutions were injected

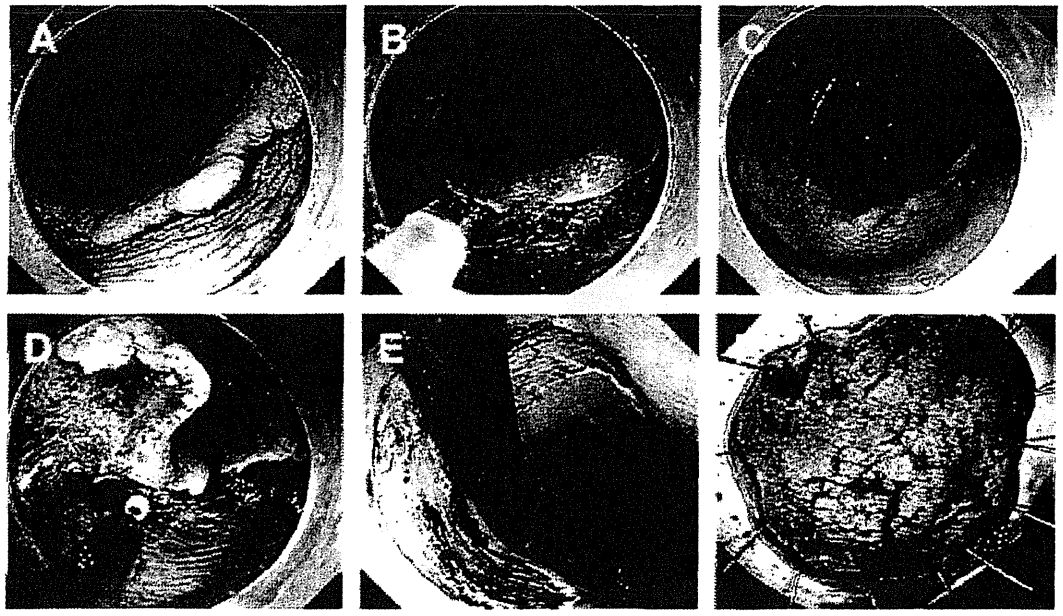

Fig. 2. ESD procedures. (*A*) An LST-NG type lesion 40 mm in size located in transverse colon (reverse view). Lesion margins delineated before ESD using 0.4% indigo carmine dye spraying. (*B*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, a half-circumferential incision (anal side) was performed using B-knife (retroflex view). After circumferential incision, sm dissection was performed using the same B-knife. (*C*) Straight view of the lesion after half-circumference marginal resection and sm dissection of the oral side. Additional resection of the margin on the anal side was performed using the B-knife in the straight view. (*D*) Dissection of the sm layer from outside to inside of the lesion is easily performed using the IT knife. (*E*) Ulcer bed after successful en-bloc resection in 1.5 hours. (*F*) Resected specimen was 40 × 30 mm in diameter and histologic findings revealed intramucosal cancer with tumor-free margin.

repeatedly into the sm layer to maintain the sm fluid cushion so as to minimize the risk of perforation.

6. Hemostatic forceps were used in soft coagulation mode (70–80 W) to control visible bleeding. The patient's position was sometimes changed to facilitate visualization of the tissue plane, and dissection continued until the lesion was completely excised.
7. After the colorectal ESD was completed, routine colonoscopic review to detect any possible perforation or exposed vessels was conducted and minimum coagulation was performed using hemostatic forceps on nonbleeding visible vessels to prevent postoperative bleeding (see **Fig. 2**E).
8. The resected specimen was stretched and fixed to the board using small pins (see **Fig. 2**F).

CLINICAL OUTCOME OF ESD AT NCCH

The en-bloc resection rate was 88% and the curative resection rate was 86% among 500 ESDs (**Table 1**). Of these, 127 were tubular adenomas, 315 were intramucosal cancers or minute sm cancers (sm1s), 55 were submucosal deep cancers (sm2s), 2 were carcinoid tumors, and 1 was mucosa-associated lymphoma tissue. The median operation time was 90 minutes, and the mean size of resected specimens was 40 mm (range, 20–150 mm).

COMPLICATIONS OF ESD AT NCCH

The postoperative bleeding rate for ESD was 1.0% (5 of 500), which is almost the same as that for conventional EMR (see **Table 1**). In contrast, the perforation rate for ESD

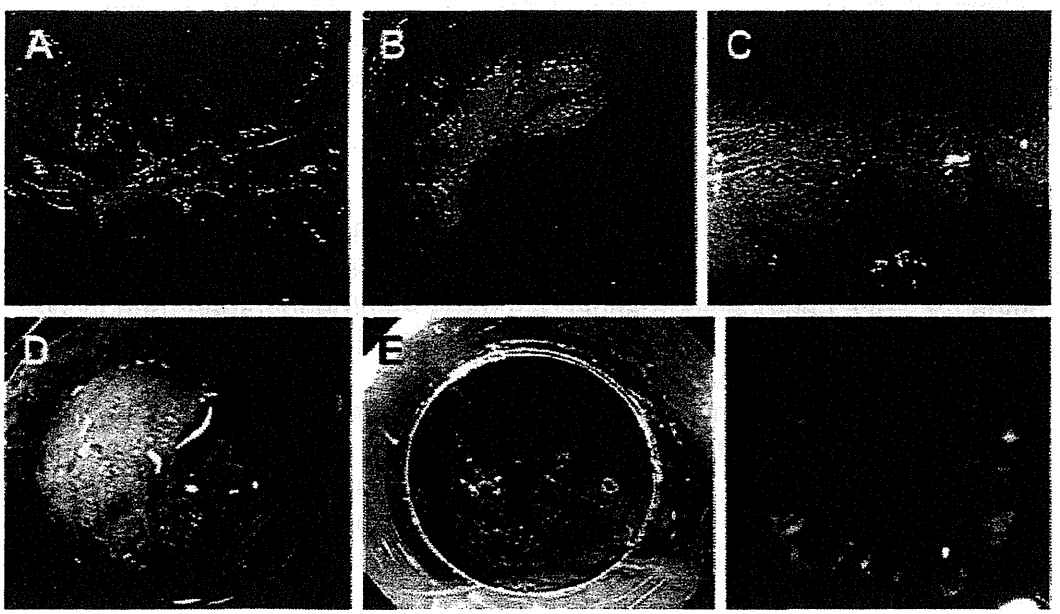

Fig. 3. ESD procedures for recurrent tumor. (*A*) A 20-mm flat-type lesion with ulcer scar was located in the transverse colon, and prominent fold convergences were noticed. (*B*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*C*) Crystal violet (0.05%) staining clearly revealed IIIL and IIIs (non-invasive) pit pattern and indicated that this lesion was a good candidate for endoscopic treatment despite severe fibrosis and nonlifting sign. (*D*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, circumferential incision was performed using B-knife. After circumferential incision, sm dissection was performed using B-knife and IT knife. Severe sm layer fibrosis was visualized clearly due to the distal attachment, and the sm layer was carefully dissected just below this fibrosis. (*E*) Ulcer bed after successful en-bloc resection in 1 hour. (*F*) Resected specimen was 20 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

Table 1
Clinical outcomes of 500 colorectal ESDs at NCCH

Macroscopic Types	
LST-G/LST-NG	220/200
Depressed/Protruded	18/30
Recurrence	28
SMT	4
Location	C:35, Rt: 195, Lt: 130, R:140
Size of Resected Specimens [Mean±SD (range)]	40 ± 20 (20–150) mm
Pathology	Adenoma, 127; m-sm1, 315; sm2, approximately 55; Others, 3
Procedure Time	90 ± 73 (15–390) min
En-bloc Resection	88%
Curative Resection	86%
Complications	
Perforation	13[a] (2.6%)
Delayed Bleeding	5 (1%)

Abbreviations: C, cecum; Lt, left; m-sm1, intramucosal-submucosal superficial (invasive <1000 mm from the muscularis mucosae) cancer; R, rectum; Rt, right; sm2, submucosal deep; SD, standard deviation; SMT, submucosal tumor.

[a] All cases except 1 treated without surgery.

was 2.6% (13 of 500), which is considerably higher than that for conventional EMR (1.3%); only 1 perforation case needed emergency surgery because of ineffective endoscopic clipping. There have been no delayed perforations observed.

TECHNICAL PROGRESS OF COLORECTAL ESD

Until recently, colorectal ESDs have been performed mainly in Japan[10–15,22,23] because of the technical difficulty involved in the procedure. Also, the most frequent indication for ESD, early gastric cancer, is more common in Japan than in Western countries.[24] Some trained endoscopists, however, have started to do colorectal ESDs in Europe[25] and the United States.[26]

Given the thinness of the colonic wall, the use of specialized knives,[7,20] distal attachments,[14] and hypertonic solutions (Glycerol[21] and MucoUp[14]) that produce a longer-lasting and higher sm elevation cushion are necessary for safe ESD and to reduce the perforation rate. The B-knife[20] is safer because the electric current is limited to the needle and the bipolar system prevents electric current from passing to the muscle layer.

A noninvasive and simple tool that facilitates the direct visualization of the sm layer was needed to reduce the risk of perforations in colorectal ESD. As a result, the authors developed a sinker system for traction-assisted ESD[10] and more recently a thin-endoscope–assisted ESD.[27] In addition, Sakamoto and colleagues[28] reported the usefulness of a new traction device (S-O clip) for ESD of superficial colorectal neoplasms.

ESD enables us to treat recurrent lesions after incomplete endoscopic resections (see **Fig. 3; Fig. 4**) and large colorectal LSTs greater than 10 cm in diameter (**Fig. 5**). It is important, therefore, to diagnose the lesion carefully using chromomagnification colonoscopy[17,18] before treatment to reduce unnecessary noncurative resection for sm deep invasive cancers.[6]

COMPARISON BETWEEN ESD AND EMR

The primary advantage of ESD compared with EPMR is a higher en-bloc resection rate for large colonic tumors that had been treated by surgery previously. Consequently, ESD has a lower recurrence rate compared with EPMR (2% vs 14%) and also results

Fig. 4. Histologic findings revealed an intramucosal cancer with tumor-free margin. Severe fibrosis caused by previous EMR was observed at the center of this lesion.

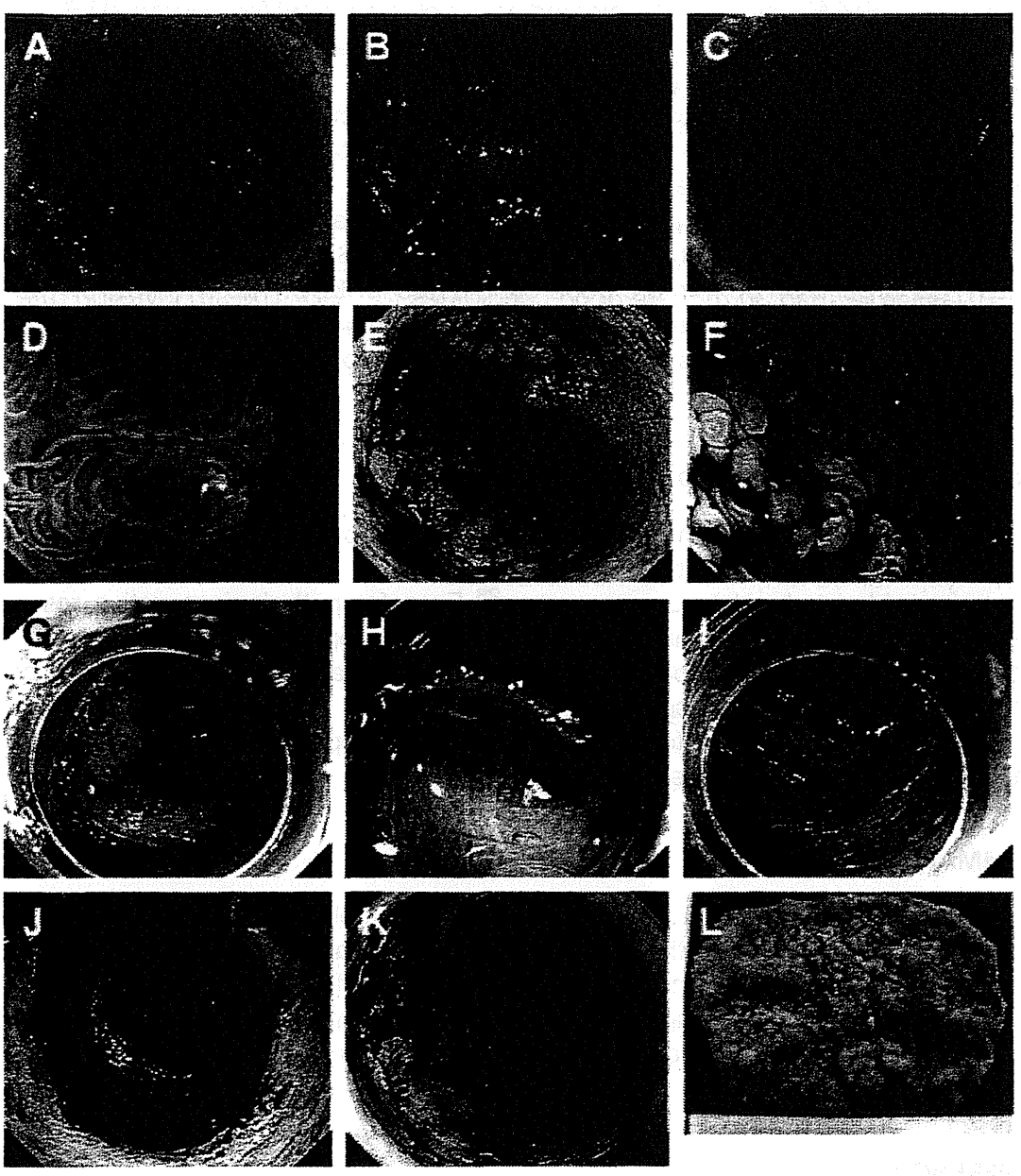

Fig. 5. ESD procedures for large LST-Gs. (*A*) An LST-G type lesion 100 mm in size located in the sigmoid colon. (*B*) A large nodule was identified in this LST-G. (*C*) Narrow-band imaging (NBI) revealed this LST-G lesion as brownish and the margin of this lesion became apparent. (*D*) NBI with magnification revealed a type II or IIIA Sano capillary pattern, suggesting intramucosal neoplastic lesion. (*E*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*F*) Magnification colonoscopy with indigo carmine dye revealed non-invasive (IV) pit pattern at the elevated area of this lesion. (*G*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, half-circumferential incision was performed using B-knife. (*H*) and (*I*) After circumferential incision, sm dissection was performed using B-knife and IT knife. Thickened sm layer was visualized as blue because of the distal attachment and indigo carmine. Sm dissection was performed carefully at this thickened sm layer above the muscle layer. (*J*) and (*K*) Ulcer bed after successful en-bloc resection in 2 hours. (*L*) Resected specimen was 100 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

in a better quality of life for patients compared with surgery. Future studies should be designed to compare the clinical outcomes of ESD and surgery but not of ESD and EMR because the indications for ESD and EMR are different as are the tumor characteristics.

Until now, EPMR had been considered a feasible treatment for colorectal LSTs. Low rates of local recurrence for such tumors and of repeat endoscopic resection were considered sufficient for most local recurrent tumors.[9]

In the authors' case series,[29] EPMR was also effective in treating many LST-Gs 20 mm or larger, but 3 cases (1.3%) required surgery after such piecemeal resections, including 2 cases of invasive recurrence.

Based on these results, cases for EPMRs in which accurate histologic evaluation would be difficult to make should be considered for ESD or laparoscopic surgery.

LST-Gs larger than 30 mm are good candidates for ESD. The sm invasion rate for such lesions was 16%, and multifocal invasion rate outside the large nodule or depression was 25%, which was more difficult to diagnose even using magnification colonoscopy.

INSTRUCTIONS ON POST-ESD CARE

From data analysis between ESD and EMR, follow-up endoscopy is recommended after 1 year for curative en-bloc ESD cases and after 6 months for piecemeal ESD cases considering local recurrence rates.[28] Even for pathologic curative resection cases, computed tomographic examination or endoscopic ultrasound imaging is recommended to examine lymph node metastasis or distant metastasis for sm1 cases and piecemeal resection cases.

Surgery is recommended for sm2s or cancers of deeper invasion or when lymphovascular invasion is diagnosed histologically.[6]

SUMMARY

ESD is a safe and effective procedure for treating colorectal LST-NGs larger than 20 mm and LST-Gs larger than 30 mm because it has a higher en-bloc resection rate and is less invasive than surgery. Establishment of a training system for technically more difficult colorectal ESD and further refinement of ESD instruments are encouraged for the increased use of colorectal ESD not only in Japan but also throughout the world.

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