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Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection

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Abstract
Background and Aims Endoscopic submucosal dissection (ESD) has recently been applied to the treatment of superficial colorectal cancer. Clinical outcomes compared with conventional endoscopic mucosal resection (EMR) have not been determined so our aim was to compare the effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm.
Methods This was a retrospective case-controlled study performed at the National Cancer Center Hospital in Tokyo, Japan involving 373 colorectal tumors ≥20 mm determined histologically to be curative resections. Data acquisition was from a prospectively completed database. We evaluated histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications for both the ESD and EMR groups.
Results A total of 145 colorectal tumors were treated by ESD and another 228 were treated by EMR. ESD was associated with a longer procedure time (108 ± 71 min/29 ± 25 min; $p < 0.0001$), higher en bloc resection rate (84%/33%; $p < 0.0001$) and larger resected specimens (37 ± 14 mm/28 ± 8 mm; $p = 0.0006$), but involved a similar percentage of cancers (69%/66%; p = NS). There were three (2%) recurrences in the ESD group and 33 (14%) in the EMR group requiring additional EMR ($p < 0.0001$). The perforation rate was 6.2% (9) in the ESD group and 1.3% (3) in the EMR group (p = NS) with delayed bleeding occurring in 1.4% (2) and 3.1% (7) of the procedures (p = NS), respectively, as all complications were effectively treated endoscopically.
Conclusions Despite its longer procedure time and higher perforation rate, ESD resulted in higher en bloc resection and curative rates compared with EMR and all ESD perforations were successfully managed by conservative endoscopic treatment.

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Keywords Endoscopic submucosal dissection (ESD) · Endoscopic mucosal resection (EMR) · Recurrence · Colon · Colorectal · Short-term clinical outcome

Abbreviations

B-knife	Bipolar needle knife
CO_2	Carbon dioxide
EMR	Endoscopic mucosal resection
EPMR	Endoscopic piecemeal mucosal resection
ESD	Endoscopic submucosal dissection
IT knife	Insulation-tipped knife
LN	Lymph node
sm	Submucosal
LST	Laterally spreading tumor
LST-G	Laterally spreading tumor granular type
LST-NG	Laterally spreading tumor nongranular type
NS	Not significant
SD	Standard deviation
sm1	Minute submucosal cancer
sm2	Submucosal deep cancer

Endoscopic mucosal resection (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 [1–6]. However, conventional EMR techniques [6–8] currently used for the resection of laterally spreading tumors (LSTs) [7–10] are inadequate for the en bloc resection of flat lesions ≥20 mm because of both incomplete removal [11] and problems with local recurrence [12]. The endoscopic submucosal dissection (ESD) technique, which facilitates en bloc resection of early gastric cancer [11, 13–17], has recently been reported to be useful in the treatment of superficial colorectal tumors [18–28]. Previously, we reported on the effectiveness and safety of ESD for colorectal tumors using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan) and an insulation-tipped knife (IT knife) (Olympus Optical Co., Ltd., Tokyo, Japan), neither of which produces any coagulation effect at the needle tip [20, 21, 24]. The effectiveness and long-term clinical outcome of ESD compared with conventional EMR is unclear, however, so the purpose of this study was to demonstrate the comparative effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm

Materials and methods

Originally, 553 large (≥20 mm) colorectal tumors were resected endoscopically between January 2003 and December 2006 at the National Cancer Center Hospital (NCCH) in Tokyo with data acquisition from a prospectively completed database. Twenty-nine lesions that required surgery after endoscopic treatment because of noncurative resections and 151 lesions treated by conventional EMR for which follow-up colonoscopy examinations could not be carried out or ascertained at NCCH were excluded, leaving a final total of 373 large colorectal tumors that were included in this retrospective case-controlled study (Fig. 1). All ESD and EMR procedures were conducted by experienced colonoscopists (three staff doctors and two senior residents), each of whom had performed more than 1,000 colonoscopies annually.

The histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications were evaluated for both an ESD group and a conventional EMR group. We defined an en bloc resection as a one-piece resection of the entire lesion as observed endoscopically. In assessing for a local recurrence or the presence of a residual tumor, we repeated colonoscopy

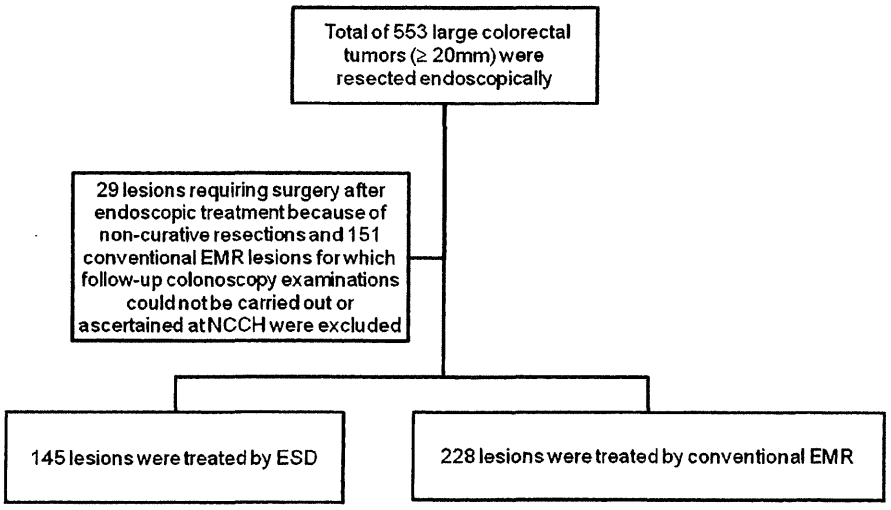

Fig. 1 Flow chart showing the patients in this study

examinations at intervals of 6 months. The procedure time was measured from the injection of a submucosal (sm) injection solution into the sm layer to removal of the colonoscope after the resection of a tumor.

Indication criteria for EMR and ESD

The existence of a noninvasive pattern [10, 24, 29–31] as determined by magnification chromoendoscopy was the minimum requirement for all lesions that were candidates for ESD and EMR. 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, PCF-240ZI and H260AZI; Olympus Optical Co., Ltd.) were used to evaluate the surface character 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 suggesting that sm invasion is $\geq$1,000 μm while a noninvasive pattern does not have this finding which suggests intramucosal neoplasia or sm invasion <1,000 μm. When high-magnification observation with indigo-carmine dye was insufficient to determine the surface structure, we performed staining with 0.05% crystal violet. Based on extensive clinicopathological analyses [10], we defined the indications for ESD [24] as an LST nongranular (LST-NG)-type lesion >20 mm and an LST granular (LST-G)-type lesion >40 mm because they both had a higher sm invasion rate and were difficult to treat even by endoscopic piecemeal mucosal resection (EPMR) [7]. Some colonoscopists chose to perform EPMR [7] to treat LST-G lesions measuring between 20 and 40 mm with the final decision based on each individual colonoscopist's judgment. Large villous tumors as well as intramucosal lesions, recurrent lesions, and residual intramucosal lesions showing nonlifting sign after EMR were also potential candidates for ESD with the final decision once again made by each colonoscopist (Table 1).

Endoscopic operating systems

ESD and EMR procedures were performed using Olympus PCF-Q240ZI, CF-Q240ZI, and CF-H260AZI video endoscopes.

Bowel preparation

Bowel preparation consisted of a patient drinking 2–3 L of polyethylene glycol (PEG) solution in the morning before the procedure. In an effort to further ensure excellent bowel preparation, stool color was assessed before each colonoscopy by a trained nurse and additional PEG solution was used when necessary.

ESD procedures

The procedures were primarily performed using a B-knife [20] or an IT knife with carbon dioxide (CO_2) insufflation instead of air insufflation to reduce patient discomfort [21]. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying (Fig. 2A, B). Following injection of Glyceol® (Chugai Pharmaceutical Co., Tokyo, Japan) (10% glycerol and 5% fructose in normal saline solution) [32] and sodium hyaluronate acid into the sm layer [33], a circumferential incision was made using the B-knife and an ESD was then carried out using both the B-knife and IT knife (Fig. 2C–F).

Conventional EMR procedures

Conventional EMR procedures were performed using the inject and cut technique with a single-channel colonoscope (PCF-Q240ZI, CF-Q240ZI or CF-H260AZI; Olympus) and

Table 1 Indication criteria for endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR)

Minimum requirement
A noninvasive pattern as determined by magnification chromoendoscopy was required for all lesions that were candidates for ESD and EMR
Definite indication for ESD
LST-NG lesion ≥20 mm
Relative indication for ESD
LST-G lesion ≥40 mm
Large villous tumor, intramucosal lesion, recurrent lesion or residual intramucosal lesion showing nonlifting sign after EMR
Definite indication for EMR/EPMR
Any lesion <20 mm
LST-G lesion ≥20 mm and <40 mm

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type

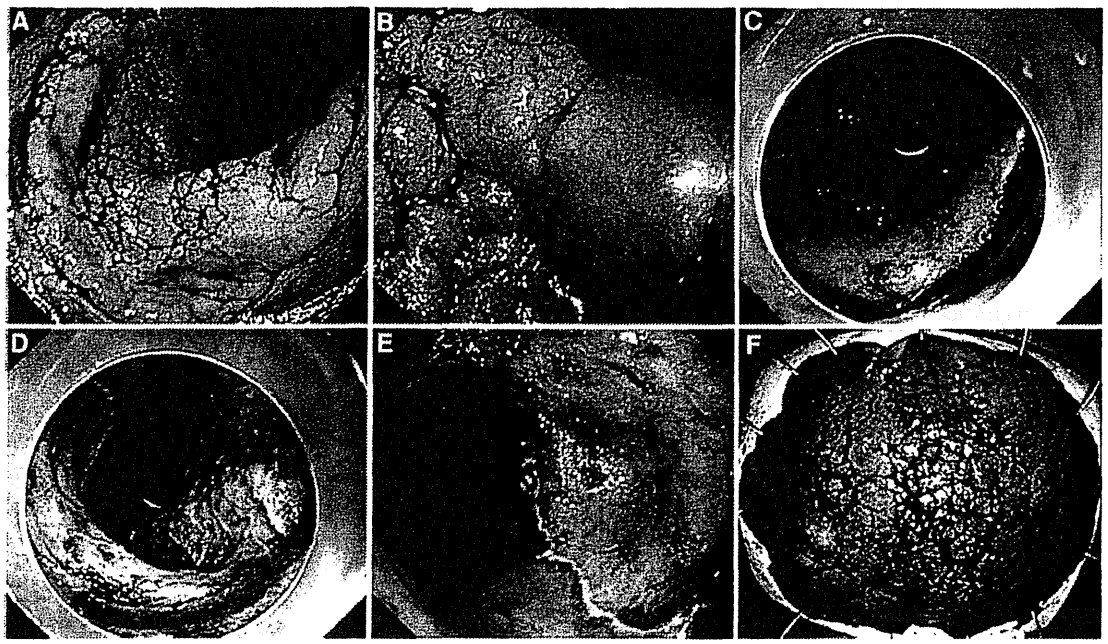

Fig. 2 Endoscopic submucosal dissection (ESD) procedures, primarily performed using a bipolar needle knife (B-knife) and an insulation-tipped knife (IT knife) with carbon dioxide (CO_2) insufflation. **A** Fifty-millimeter laterally spreading tumor nongranular (LST-NG)-type lesion located in the transverse colon. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying. **B** Magnified colonoscopy revealed a noninvasive pattern so the estimated depth of this LST-NG lesion was intramucosal despite its large size. **C** Following injection of Glycerol® (10% glycerol and 5% fructose in normal saline solution) and sodium hyaluronate acid solution into the submucosal layer, a circumferential incision was made using the B-knife. **D** An ESD was then carried out using both the B-knife and IT knife. **E** The ulcer bed is shown here after the successful en bloc resection. **F** The resected specimen was 65 × 50 mm in diameter and histology revealed an intramucosal cancer with a tumor-free margin

snare (10-mm or 25-mm snare master or 20-mm spiral snare; Olympus) as described in previous reports [1–3, 6, 7]. Glyceol® [32] was injected into the sm layer of the lesion with a 23-gauge needle and the lifted lesion was then resected using the snare.

In this study, we distinguished an EMR from an EPMR according to the number of resected pieces as either single or multiple, respectively. An LST-G ≥20 mm and <40 mm can usually be treated by EPMR rather than ESD with the area including the large nodule resected first followed by the remaining tumor (Fig. 3A–C). After EMR and EPMR, we confirmed whether or not there was any residual tumor using chromomagnification colonoscopy and performed a hot biopsy as necessary for ablative purposes.

Tumor size was estimated by measuring the resected specimen after retrieval for en bloc resected specimens and by comparing the endoscopic observation with the snare size for piecemeal resected specimens.

Sedation

Midazolam (2 mg/iv) and pentazocin (15 mg/iv) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. In conventional EMR procedures, midazolam (2 mg iv) was administered to selected patients as determined by the colonoscopist, but only when a patient complained of pain or abdominal distension.

Histological assessment

All specimens were evaluated after being cut into 2-mm slices and examined microscopically for histological type, depth of invasion, lateral resection margin, and vertical resection margin. 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 was achieved when both the lateral and vertical margins of the specimen were free of cancer and there was no sm invasion deeper than 1,000 μm from the muscularis mucosae (sm1), lymphatic invasion, vascular involvement or poorly differentiated component [34]. 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

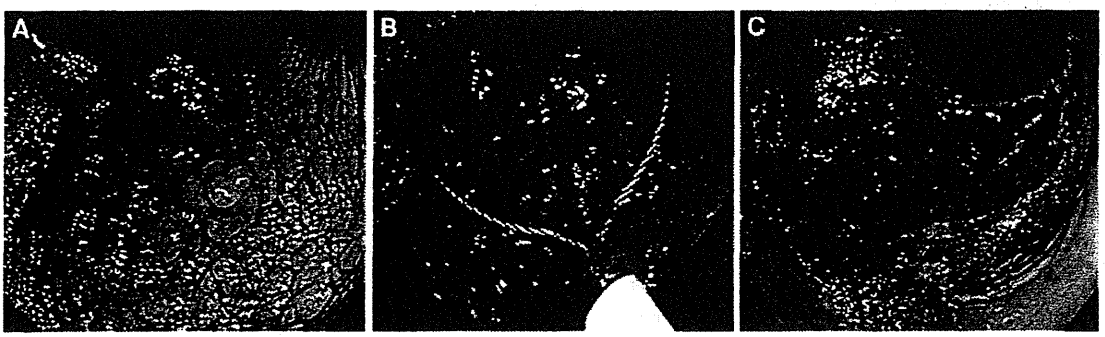

Fig. 3 Conventional endoscopic mucosal resection (EMR) procedures. Conventional EMRs were usually performed using an inject and cut technique with a single-channel colonoscope and snare. Glycerol® was injected into the submucosa of the lesion with a 23-gauge needle and then the lifted lesion was resected using a round snare. **A** A 35-mm laterally spreading tumor granular (LST-G)-type lesion located in the rectum. **B** An LST-G between 20 and 40 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than ESD with the area including the large nodule resected first followed by the remaining tumor. **C** The ulcer bed after a three-piece resection

were based on the Japanese classification of cancer of the colon and rectum [35] and the Vienna classification [36].

Follow-up endoscopic care

In assessing for local recurrence or the presence of a residual tumor, we usually repeated colonoscopic examinations at intervals of 6 months for ESD patients because the technique was still relatively new and indicated for large colorectal lesions that had previously been treated surgically. In most cases, we repeated colonoscopic examinations at intervals of 6 months for EPMRs and at 12-month intervals for EMRs with en bloc resections because of an expected lower risk of recurrence [37] with such examinations performed either by the endoscopy staff at NCCH or the patient's previous hospital.

All ESD and EMR patients with sm1 invasion were followed up regularly with annual computed tomography and endoscopic ultrasonography examinations for the detection of lymph-node metastasis. Complete endoscopic follow-up care was available for all 145 lesions in the ESD group and all 228 lesions in the EMR group. Indigo-carmine dye was sprayed on previously resected areas and high-magnification views were obtained in all cases. Recurrent neoplastic disease was identified as type IIIs, IIIL, IV or V pit pattern according to the criteria established by Kudo and Fujii [6, 9, 10, 30–32, 38–41].

Statistical analysis

All variables in this study are described as mean ± standard deviation (SD). In comparing baseline characteristics between the two groups, we used a *t*-test for continuous variables and a chi-square test for dichotomous variables. All statistical analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC). The p values are two-sided and $p < 0.05$ was used to determine statistical significance.

Ethics

The ethics committee at NCCH approved the study protocol and informed written consent was obtained from all patients in the ESD and EMR groups for each specific colonoscopic treatment and all scheduled follow-up colonoscopy examinations.

Results

During the study period, 145 lesions were treated with ESD and 228 were treated with conventional EMR (Fig. 1). All 373 lesions were eligible for outcome analysis. Clinical characteristics of the patients in the two groups are presented in Table 2. There were no differences between the two groups in terms of age, gender, endoscopic follow-up frequency or follow-up periods (Tables 2 and 3).

En-bloc resection rates

In the ESD group, 122 out of 145 lesions (84%) were completely resected en bloc compared with only 74 of 228 lesions (33%) in the EMR group ($p < 0.0001$), although tumor size was significantly larger in the ESD group ($p < 0.0001$) (Table 3).

Endoscopic characteristics of resected specimens

Regarding macroscopic type, 50% of the EMR group lesions were LST-Gs and 49% of the ESD group lesions were LST-NGs. There were no differences between the two groups in terms of tumor location. The percentage of

Table 2 Clinical characteristics of patients

	EMR/EPMR	ESD	*p*-Value
Number of lesions	228 (74/154)	145	
Pathology	77/151	45/100	NS
(Adenoma/M-SM1; %)	(34%/66%)	(31%/69%)	NS
Macroscopic type	80/114/34/0	5/63/71/6	
(Is/LST-G/LST-NG/recurrence[a])	(35%/50%/15%/0)	(3%/43%/49%/4%)	<0.0001
Location (Rt/Lt/rectum)	89/52/110	44/28/73	
Tumor size (mean ± SD)	28 ± 8 mm	37 ± 14 mm	0.0006
(range)	(20–95 mm)	(20–140 mm)	
Age (mean ± SD; years)	64 ± 4	64 ± 11	NS

[a] Recurrence included local recurrence after EMR and residual tumor after incomplete en bloc resection

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *M* intramucosal; *SM* submucosal; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type; *Rt* right colon; *Lt* left colon; *SD* standard deviation; *NS* not significant

Table 3 Clinical outcomes

	EMR/EPMR	ESD	*p*-Value
Number of lesions	228 (74/154)	145	
Endoscopic follow-up times (mean ± SD; number)	2.4 ± 1.6	2.0 ± 1.1	NS
(range)	(1–8)	(1–5)	
Endoscopic follow-up periods (mean ± SD; months)	26 ± 17	20 ± 13	NS
(range)	(6–68)	(6–61)	
En bloc resection (%)	74 (33%)	122 (84%)	<0.0001
Recurrence rate (%)	33 (14%)	3 (2%)	<0.0001
En bloc/piecemeal recurrences	2/31	0/3	
Complications			
Perforation	3 (1.3%)	9 (6.2%)	NS
Delayed bleeding	7 (3.1%)	2 (1.4%)	NS
Procedure time (mean ± SD; min)	29 ± 25	108 ± 7	<0.0001
(range)	(3–120)	(15–360)	

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *SD* standard deviation; *NS* not significant

carcinomas was 69% in the ESD group and 66% in the EMR group (p = NS) (Tables 2 and 3).

Local recurrences rates

There were only three cases (2.1%) of local recurrence in the ESD group during a mean endoscopic follow-up period of 20.0 ± 12.9 months (range 6–61 months). In comparison, local recurrence occurred in 14.5% (33/228) of the lesions in the EMR group during a mean endoscopic follow-up period of 25.9 ± 17.0 months (6–68 months). All three recurrences in the ESD group had previously been resected on a piecemeal basis and each recurrence required one additional EMR. Each of these recurrences was diagnosed histologically as a tubular adenoma and curative resections were achieved for all three. The 33 recurrences in the EMR group involved 2/74 (2.7%) en bloc resections and 31/174 (17.8%) piecemeal resections (Table 3). Twenty-six of the 33 EMR recurrent cases were successfully treated by one additional EMR with the other seven cases needing two sessions of repeat EMR. Two EPMRs required surgery because of invasive recurrence (Fig. 4A–F) while a third piecemeal resection also required surgery because of technical difficulty in performing another EMR despite the intramucosal nature of that particular recurrence.

Duration of recurrence detection

Mean duration of recurrence detection was 6 months (2–18 months) in the EMR group and 6 months (4–6 months) in the ESD group (Table 3).

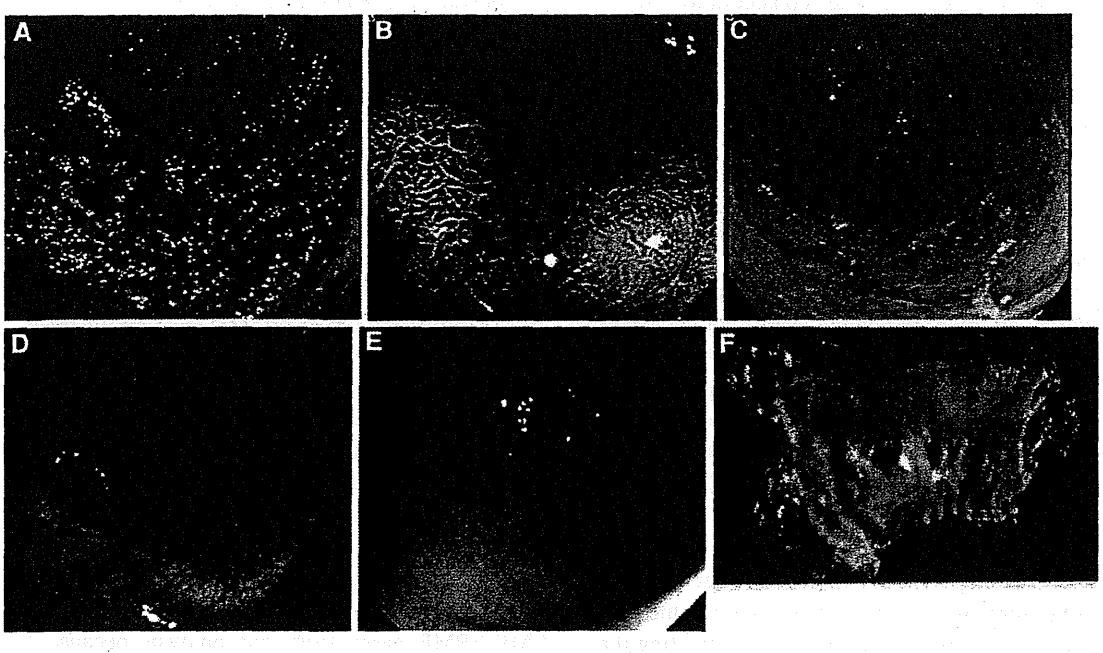

Fig. 4 **A** This case originally involved a large LST-G lesion >3/4 in circumference. **B** Magnified colonoscopy using 0.05% crystal violet staining revealed a noninvasive pattern on the large nodule. **C** An EPMR consisting of more than ten pieces finally resected the entire lesion. Histology revealed an intramucosal carcinoma without any evidence of lymphovascular invasion or a poorly differentiated component so we followed this patient closely without surgery. **D** The third follow-up colonoscopy after 18 months revealed no recurrence. **E** A fourth follow-up was performed 1 year later, at which time a submucosal tumor-like recurrence was found 1 cm from the original EPMR scar. **F** Surgery was performed on this lesion and histology revealed the recurrence of an invasive cancer

Early and late complications

Perforations occurred in 9 out of 145 patients (6.2%) in the ESD group, which was higher compared with the perforation rate of 1.3% (3/228) in the EMR group (p = NS). None of the 12 perforations was delayed and all of them were successfully treated endoscopically using endoclips and managed conservatively.

Minor delayed bleeding occurred in two patients (1.4%) in the ESD group and seven (3.1%) patients in the EMR group (p = NS), but all nine cases were successfully managed conservatively using endoclips with no blood transfusions or additional procedures necessary (Table 3).

Procedure times

The procedure time for ESDs was 108 ± 71 min (15–360 min) compared with 29 ± 25 min (3–120 min) for EMRs, resulting in a significantly shorter procedure time for the EMR group ($p < 0.0001$) (Table 3).

Discussion

This study is, to the best of our knowledge, the first to compare clinical outcomes for colorectal ESD with EMR/EPMR including mid-term follow-up.

For many years, conventional EMR and surgery were the only available treatments for large colorectal tumors, even those detected at an early stage. Conventional EMRs usually resulted in EPMRs particularly for large LSTs ≥20 mm with reports of local recurrence rates ranging from 7.4% to 17% [8, 12, 32]. Most of those recurrences, however, received repeated endoscopic treatment with excellent results regarding preservation of the colorectum [32].

In our series, the introduction of ESD enabled us to effectively treat large colorectal tumors that were LST-NGs and carcinomas, resulting in higher en bloc resection and curability rates compared with conventional EMR. EPMR also was effective in treating many LST-Gs ≥20 mm, with only three cases requiring surgery after such piecemeal resections, including two invasive recurrences cases. Those two cases were originally diagnosed histologically as intramucosal carcinomas without lymphatic or vascular invasion, but both recurrences consisted of invasive carcinomas. We suspect that each case may have originally involved either sm invasion or lymphatic invasion that was not diagnosed histologically because of the increased difficulty in assessing a piecemeal resection. Based on our results, therefore, EPMRs must be performed carefully and close follow-up is required in the event that additional treatment becomes necessary because accurate histological evaluation can be difficult or impossible in

such cases. As an alternative, greater consideration should be given to either ESD or laparoscopic surgery rather than EPMR.

Conventional EMRs in this study had an overall local recurrence rate that was similar to in previous reports [12, 33], as en bloc resection cases resulted in a low recurrence rate of 3%, but piecemeal resections had a considerably higher recurrence rate of 20%. In contrast, ESDs resulted in a significantly higher en bloc resection rate and, consequently, a significantly lower recurrence rate. In those ESDs in which en bloc resections were not achieved, however, the local recurrence rate was approximately 13%, which was much closer to the local recurrence rate for EPMRs. According to our findings, EPMR resulted in a higher recurrence rate compared with ESD, although EPMR produced results similar to those of ESD in relation to preservation of the colorectum.

In this study, we conducted follow-up examinations on patients 6 month after EPMRs and 1 year after EMR en bloc resections, regardless of the lateral margin findings. This was based on our preliminary data [33] indicating that EPMR recurrences were more frequent compared with EMR en bloc resection recurrences and most such EPMR recurrences occurred within 6 months. This current study once again confirmed that most EPMR recurrences were detected after the first 6 months, so such recurrences could continue to be successfully treated endoscopically, supporting the propriety of our follow-up program after EPMR.

As for complications, the perforation rate in the ESD group was 6.2%, which was considerably higher than the 1.3% perforation rate in the EMR group, although there was no statistical difference between the two groups. In other reported series, the perforation rates for colorectal ESDs [8, 27, 28] and EMRs [42] ranged from 1.4% (1/71) to 5.5% (11/200) and 0.31% to 0.93%, respectively, which were similar to our results. The target lesions for ESD in this study, however, were large LSTs that would have been treated by surgery in the past because of the technical difficulty [43]. In fact, the mean tumor size was significantly larger in the ESD group compared with the EMR group so conventional EMRs performed on such lesions undoubtedly would have resulted in a higher complication rate for the EMR group.

All perforation cases were successfully treated conservatively without surgery by endoscopic clipping. As a result, the perforation rate of 6.2% in the ESD group was considered to be acceptable, although further instrument improvements and technique refinements will both be necessary to reduce the perforation rate. The delayed bleeding rate was relatively low in both groups, but particularly in the ESD group, probably because small vessels were coagulated during the ESD procedure.

Considering the additional procedure time and increased cost of ESD devices, it would be difficult to standardize the colorectal ESD procedure on a widespread basis at the present time. We currently select lesions with more serious indications for colorectal ESD that would otherwise be treated surgically. Such ESD patients usually are discharged from the hospital sooner than if surgery had been performed, resulting in reduced medical costs.

Finally, the long-term efficacy of colorectal ESD needs to be established by evaluating an extended follow-up period, although ESD certainly appears to be a feasible alternative to conventional EMR, particularly for certain kinds of colorectal cancers. This study was not a randomized controlled trial, however, and eligibility criteria for the two endoscopy procedures were sometimes unclear for different kinds of lesions. It will be necessary, therefore, to prospectively assess the clinical outcome comparison between ESD and EMR for large colorectal tumors in the future. Another limitation of this study that may have been a source of bias was the exclusion of 40% of the total EMR/EPMR cases from our analysis because follow-up colonoscopy examinations were not carried out at NCCH or could not be ascertained by us.

In conclusion, ESD was selected more often for treating large colorectal tumors because it provided higher en bloc resection and curability rates compared with EMR despite the longer procedure time and higher perforation rate associated with ESD. All ESD perforations, however, could be successfully managed by conservative endoscopic treatment. EMR effectively treated many large colorectal tumors, and only three cases required surgery after EPMRs; such procedures should be carefully performed because it can be more difficult and occasionally impossible to make an accurate histological evaluation, meaning that close follow-up is required in the event that additional treatment is necessary in such cases.

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References

1. Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG (2002) Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc 55: 390–396
2. Yokota T, Sugihara K, Yoshida S (1994) Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum 37: 1108–1111
3. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N (2003) Endoscopic mucosal resection. Gastrointest Endosc 57:567–579
4. Tada M, Murakami A, Karita M, Yanai H, Okita K (1993) Endoscopic resection of early gastric cancer. Endoscopy 25:445–450

5. Deyle P, Largiader F, Jenny S, Fumagalli I (1973) A method for endoscopic electrosection of sessile colonic polyp. Endoscopy 5: 38–40
6. Kudo S (1993) Endoscopic mucosal resection of flat and depressed type of early colorectal cancer. Endoscopy 25:455–461
7. Saito Y, Fujii T, Kondo H, Mukai H, Yokota T, Kozu T et al (2001) Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy 33:682–686
8. Tanaka S, Haruma K, Oka S, Takahashi R, Kunihiro M, Kitadai Y et al (2001) Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc 54:62–66
9. Kudo S, Kashida H, Tamura T, Kogure E, Imai Y, Yamano H et al (2000) Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg 24:1081–1090
10. Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D et al (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut 55:1592–1597
11. Min BH, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH et al (2009) Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: Comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). Dig Liver Dis 41:201–209
12. Walsh RM, Ackroyd FW, Shellito PC (1992) Endoscopic resection of large sessile colorectal polyps. Gastrointest Endosc 38: 303–309
13. Hosokawa K, Yoshida S (1998) Recent advances in endoscopic mucosal resection for early gastric cancer. Jpn J Cancer Chemother 25:476–483 (in Japanese with English abstract)
14. Ohkuwa M, Hosokawa N, Boku N, Ohtsu H, Tajiri S, Yoshida S (2001) New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 33:221–226
15. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D et al (2001) Endoscopic mucosal resection for treatment of early gastric cancer. Gut 48:225–229
16. Kondo H, Gotoda T, Ono H, Oda I, Kozu T, Fujishiro M et al (2004) Percutaneous traction-assisted EMR by using an insulation-tipped electrosurgical knife for early stage gastric cancer. Gastrointest Endosc 59:284–288
17. Kobayashi T, Gotohda T, Tamakawa K, Ueda H, Kakizoe T (2004) Magnetic anchor for more effective endoscopic mucosal resection. Jpn J Clin Oncol 34:118–123
18. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D et al (1999) A new endoscopic resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 50:560–563
19. Kodashima S, Fujishiro M, Yahagi N, Kakushima N, Omata M (2006) Endoscopic submucosal dissection using flexknife. J Clin Gastroenterol 40:378–384
20. Sano Y, Fu KI, Saito Y, Doi T, Hanafusa M, Fujii S et al (2006) A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. Endoscopy 38(Suppl 5):E95
21. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y et al (2007) A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection under conscious sedation. Gastrointest Endosc 65: 537–542
22. Yamamoto H, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K et al (2002) Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. Gastrointest Endosc 56: 507–512
23. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T et al (2003) Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 35:690–694
24. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y et al (2007) Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc 66(5):966–973
25. Antillon MR, Bartalos CR, Miller ML, Diaz-Arias AA, Ibdah JA, Marshall JB (2008) En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). Gastrointest Endosc 67:332–337
26. Uraoka T, Kato J, Ishikawa S, Harada K, Kuriyama M, Takemoto K et al (2007) Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). Gastrointest Endosc 66:836–839
27. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S et al (2007) Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol 5(6):674–677
28. Tamegai Y, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E et al (2007) Endoscopic submucosal dissection: a safe technique for colorectal tumors. Endoscopy 39:418–422
29. Fujii T, Hasegawa RT, Saitoh Y, Fleischer D, Saito Y, Sano Y et al (2001) Chromoscopy during colonoscopy. Endoscopy 33:1036–1041
30. Saito Y, Emura F, Matsuda T, Saito D, Fujii T (2004) Invasive pattern is an indication for surgical treatment (letter to the editor). Gut online (serial online), Mar. Available at http://gut.bmjjournals.com/cgi/eletters/53/2/284
31. Matsuda T, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N et al (2008) Efficacy of the invasive/non-invasive pattern by magnifying estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 103(11):2700–2706
32. Uraoka T, Fujii T, Saito Y, Sumiyoshi T, Emura F, Bhandari P et al (2005) Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc 61:736–740
33. Yamamoto H, Sekine Y, Higashizawa T, Kihira K, Kaneko Y, Hosoya Y et al (2001) Successful en-bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps. Gastrointest Endosc 54:629–632
34. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H et al (2004) Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 39: 534–543
35. Japanese Research Society for Cancer of the Colon and Rectum (1998) General rules for clinical and pathological studies on cancer of the colon, rectum and anus: histopathological classification, 6th edn. Kanehara Syuppan, Tokyo, pp 60–90
36. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
37. Hotta K, Fujii T, Saito Y, Matsuda T (2009) Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 24(2):225–230
38. Hurlstone DP, Cross SS, Brown S, Sanders DS, Lobo AJ (2004) A prospective evaluation of high-magnification chromoscopic colonoscopy in predicting completeness of EMR. Gastrointest Endosc 59:642–650
39. Kato S, Fujii T, Koba I, Sano Y, Fu KI, Parra-Blanco A et al (2001) Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? Endoscopy 33:306–310
40. Fu KI, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T et al (2004) Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for

differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. Endoscopy 36:1089–1093
41. Emura F, Saito Y, Taniguchi M, Fujii T, Tagawa K, Yamakado M (2007) Further validation of magnifying chromocolonoscopy to differentiate colorectal neoplastic polyps in a health screening center. J Gastroenterol Hepatol 22:1722–1727
42. Taku K, Sano Y, Fu KI, Saito Y, Matsuda T, Uraoka T et al (2007) Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. J Gastroenterol Hepatol 22(9):1409–1414
43. Kobayashi N, Saito Y, Uraoka T, Matsuda T, Suzuki H, Fujii T (in press) Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of colorectal endoscopic submucosal dissection. J Gastroenterol Hepatol

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CURRENT STATUS AND FUTURE PERSPECTIVE OF ENDOSCOPIC TREATMENT FOR COLORECTAL NEOPLASIA

ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) FOR COLORECTAL TUMORS

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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.
Patients: A total of 400 consecutive patients were treated by ESD for 405 lesions at National Cancer Center Hospital, Tokyo, Japan.
Interventions: Endoscopic submucosal dissection procedures were performed using a bipolar needle knife (B-knife) or an insulation-tip knife (IT knife).
Results: The en-bloc resection rate was 87% and the curative resection rate was 86% among the 405 ESDs: 101 involved tubular adenomas, 255 intramucosal cancers and minute submucosal cancers, 46 submucosal deep cancers and 3 others (MALT and carcinoid tumors). The median operation time was 90 minutes and the mean size of resected specimens was 40 mm (range: 15 mm-150 mm). Perforations occurred in 14 (3.5%) cases and postoperative bleeding in four (1%) cases, but only one perforation case needed emergency surgery because endoscopic clipping was ineffective.
Limitations: Conducted at single center.
Conclusions: Endoscopic submucosal dissection 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.

Key words: colorectum, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laterally spreading tumor granular type (LST-G), laterally spreading tumor non-granular type (LST-NG).

INTRODUCTION

Endoscopic mucosal resection (EMR) is indicated for the treatment of adenoma and intramucosal or submucosal superficial (sm1: less than 1000 μm from the muscularis mucosae) colorectal cancer because of its minimal invasiveness, negligible risk of lymph-node (LN) metastasis[1] and excellent results in terms of clinical outcome.[2–4] Conventional EMR techniques, such as strip biopsy, currently used for the resection of laterally spreading tumors (LSTs),[5,6] are inadequate for the en-bloc resection of flat lesions >20 mm because incomplete removal and local recurrence are occasionally observed after conventional EMR.[7,8] In order to completely remove large gastric lesions en bloc, we have developed an insulation-tip (IT) electrosurgical knife, originally reported by Hosokawa and Ono,[9] and obtained good results using it.[10]

Endoscopic submucosal dissection (ESD) for colorectal cancer[11] is not widely accepted, however, because of its technical difficulty and the risk of perforation. In addition, endoscopic piecemeal mucosal resection (EPMR) can treat many LSTs > 20 mm and only a few cases require surgery after such piecemeal resection.[8]

It is important, therefore, to investigate which lesions should be resected en bloc and which lesions can be resected piecemeal.

CLINICOPATHOLOGICAL FEATURES OF LATERALLY SPREADING TUMORS

Based upon clinicopathological analyses of LSTs,[12] LST non-granular type (LST-NG) has a higher rate of submucosal (sm) invasion and diagnosis of tumor depth is more difficult to make endoscopically compared to LST granular type (LST-G) (Tables 1,2). Histologically, 27% of sm invasions are multi-focal in LST-NGs and such invasions are difficult to predict before treatment. In contrast, LST-Gs have a lower rate of sm invasion and most such invasions are found under the largest nodule (Fig. 1).[12]

INDICATIONS FOR COLORECTAL ESD

We have defined the indications for colorectal ESD, therefore, as LST-NG > 20 mm at National Cancer Center Hospital, Tokyo, Japan (NCCH). An LST-G > 20 mm can be treated by planning EPMR rather than ESD with the area including the largest nodule resected first followed by the remaining

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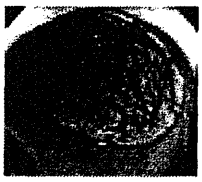
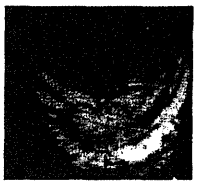
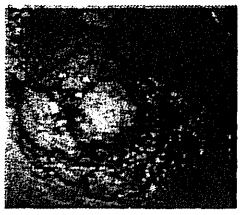
Table 1. Relationship between size of laterally spreading tumors (LSTs) and rate of submucosal (sm) invasion

	10 mm–	20 mm–	30 mm–	40 mm–	Total
 IIa (LST-G)	0/87 (0%)	0/51 (0%)	1/17 (6%)	0/6 (0%)	1/161 (0.6%)
 IS+IIa (LST-G)	3/56 (5%)	6/46 (13%)	2/34 (6%)	8/40 (20%)	19/176 (11%)
 IIa (LST-NG)	11/193 (6%)	16/56 (29%)	7/16 (44%)	3/6 (50%)	37/271 (14%)

LST-G, laterally spreading tumor-granular; LST-NG, laterally spreading tumor-non granular
1999.1–2004.3: National Cancer Center Hospital.

Table 2. Pit pattern diagnosis for laterally spreading tumors (LSTs)

LST-G		Adenoma·m·sm1*	sm2,3	
	Non-Inv. pattern	275	4	98.6% (275/279)
	Inv. pattern	3	5	62.5% (5/8)
	287	Specificity 98.9%	Sensitivity 55.6%	
LST-NG		Adenoma·m·sm1*	sm2,3	
	Non-Inv. pattern	203	2	99.0% (203/205)
	Inv. pattern	2	17	89.5% (17/19)
	224	Specificity 99.0%	Sensitivity 89.5%	

LST-G, laterally spreading tumor-granular; LST-NG, laterally spreading tumor-non granular
*sm1: <1000 μm from muscularis mucosae. 1999.1–2003.12 NCCH.

tumor (Fig. 2A,B). However, LST-G > 40 mm are also good candidates for ESD because they have higher sm invasion rates and are difficult to treat even by EPMR.

Recently, similar detailed indications for colorectal ESD have been proposed by Working Group for Standardisation of Colorectal ESD.

DEVELOPMENT OF COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSECTION

The colon mucosa is very thin and the lumen is too narrow to handle the scope freely, so some device is necessary to make the ESD in the colorectum easier and safer.

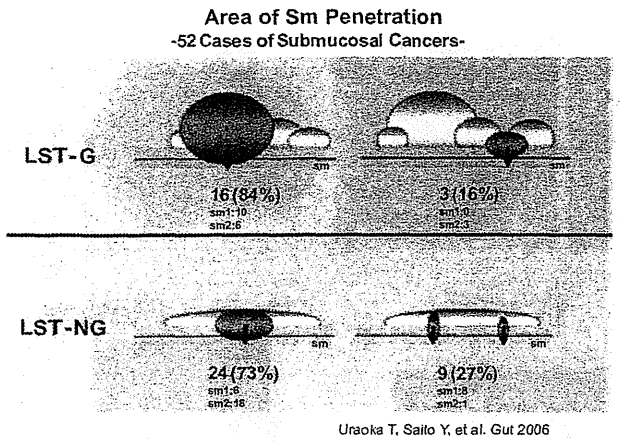


Fig. 1. Histologically, 27% of submucosal (sm) invasions are multi-focal in laterally spreading tumors (LST)-non granular (NG) and such invasions are difficult to predict before treatment. In contrast, LST-granular (G) have a lower rate of submucosal invasion and most such invasions are found under the largest nodule.

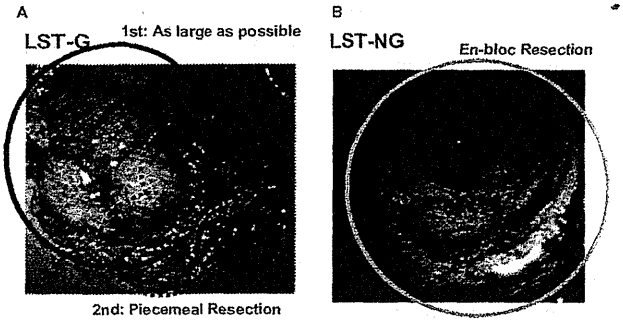


Fig. 2. (A, B) Endoscopic mucosal resection (EMR) Strategy for laterally spreading tumors (LST). An LST-granular (G) >20 mm can be treated by planning endoscopic piecemeal resection (EPMR) rather than endoscopic submucosal dissection (ESD) with the area including the largest nodule resected first followed by the remaining tumor (A). In contrast, LST-non granular (NG) >20 mm should be treated by en-bloc resection using ESD technique or laparoscopic surgery (B).

Yamamoto *et al.*[14] have reported the usefulness of sodium hyaluronate solution as a sm injecting solution in combination with a small-caliber-tip transparent hood (ST Hood) to provide a counter traction for colonic ESD. Sodium hyaluronate solution is a hypertonic solution which produces a longer lasting and higher sm elevation compared to normal saline or glycerol.[15] The ST Hood enables us to expand the narrow sm layer to visualize the cutting line.

Other traction systems that facilitate ESD procedures have been reported recently such as the percutaneous traction-assisted (PTA)-EMR[16] and the magnetic anchor system.[17] The PTA-EMR is not appropriate for colorectal ESD because of it's use of a laparoscopic device which is not suitable in the colon; and the magnetic anchor system requires a large magnetic control system that is not yet available for clinical use.

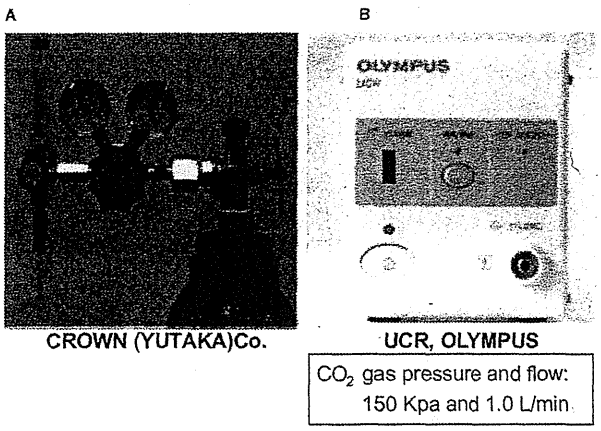


Fig. 3. (A, B) CO_2 gas regulator. (A) CO_2 was administered by using a commercially available CO_2 regulator (Gas Regulator, Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan), which was connected to a CO_2 bottle. (B) A new type CO_2 regulator (Olympus UCR, Olympus, Tokyo, Japan). CO_2 was administered by using a CO_2 regulator (Olympus UCR, Olympus), which was connected to the endoscope supply tube by means of a 'quick lock' connector, and a flow indicator provides visual confirmation that CO_2 is being delivered. CO_2 was constantly set at 1.5 liters per minutes during the procedures.

A non-invasive and simple tool that facilitates the direct visualization of the sm layer, therefore, is needed to reduce the risk of complications in colorectal ESD. As a result, we have developed a sinker system for traction-assisted ESD of colonic LST-NGs > 20 mm in size[18] and more recently a thin endoscope-assisted ESD.[19]

A. Estimation of the depth of invasion

In each lesion, a non-invasive pattern[20-22] was observed indicating that it was suitable for endoscopic resection because of an estimated depth less than sm1. No biopsies were performed before any procedure.

B. ESD procedures at NCCH

The procedures were primarily performed using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan)[23] or IT knife with CO_2 insufflation instead of air insufflation to reduce patient discomfort (Fig. 3A,B).[24-26] Following injection of Glycerol (Chugai Pharmaceutical Co, Tokyo, Japan)[15] and sodium hyaluronate acid solution into the sm layer,[14] a circumferential incision was made using a B-knife and an ESD was then carried out using both a B-knife and IT knife (Fig. 4).

CLINICAL OUTCOME OF ESD AT NCCH (Table 3)

The en-bloc resection rate was 87% and the curative resection rate was 86% among the 405 ESDs: 101 involved tubular adenomas, 255 intramucosal cancers or minute sm cancers (sm1), 46 sm2 cancers and 3 others (MALT and carcinoid tumors). The median operation time was 90 minutes and the

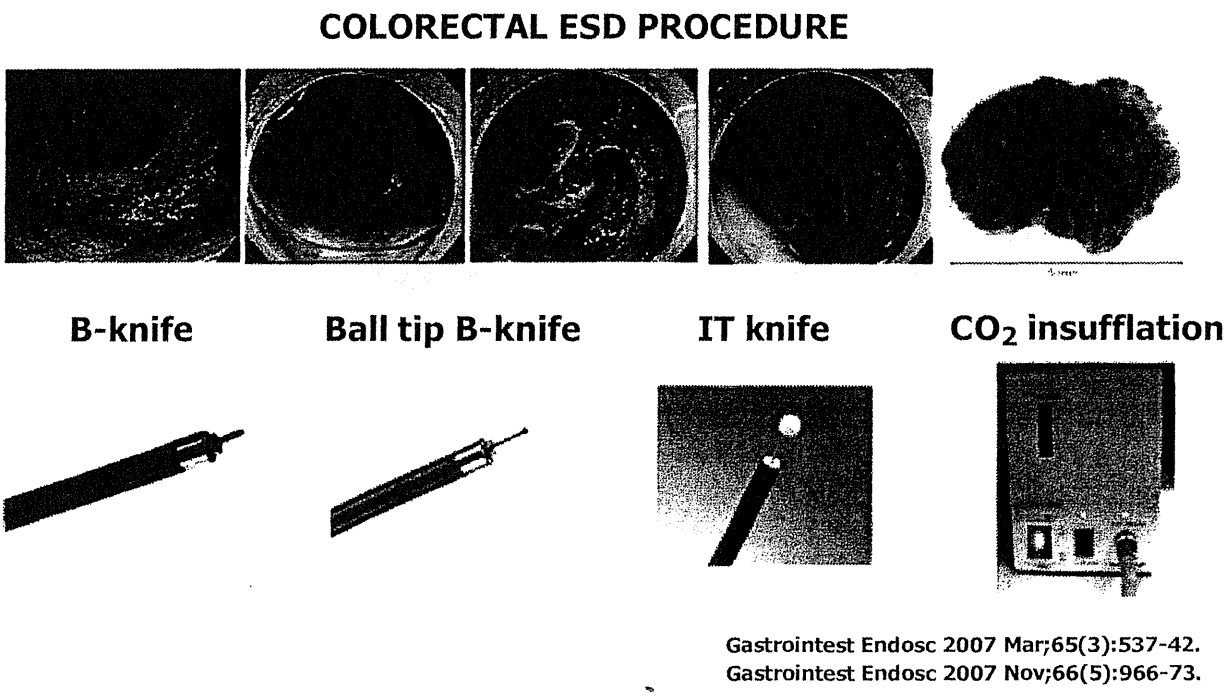


Fig. 4. (A) Colorectal endoscopic submucosal dissection (ESD) procedure. Following injection of Glycerol (Chugai Pharmaceutical Co, Tokyo, Japan) and sodium hyaluronate acid into the submucosal layer, a circumferential incision was made using a bipolar needle knife (B-knife) and an ESD was then carried out using both a B-knife and IT knife. (B) The procedures were primarily performed using a B-knife (XEMEX Co., Tokyo, Japan) or IT knife with CO_2 insufflation instead of air insufflation to reduce patient discomfort.

Table 3. Results of 405 colorectal endoscopic submucosal dissections (ESDs)

Macroscopic types	
LST-G/LST-NG	173/168
Depressed/Protruded	15/21
Recurrence	25
SMT	3
Location	C:39, Rt:153, Lt:102, R:111
Size of resected specimens Mean ± SD (range)	40 ± 20 (15–150) mm
Pathology	Adenoma:101, M-SM1:255, SM2–:46 Others:3
Procedure time	90 ± 73 (15–390) min.
En-bloc resection	352/405 (87%)
Non-curative resection	57/405 (14%)
Complications	
Perforation	14* (3.5%)
Delayed bleeding	4 (1%)

*All cases except one treated without surgery.
LST-G, laterally spreading tumor-granular; LST-NG, laterally spreading tumor-non granular; SM1, submucosal tumor.

mean size of resected specimens was 40 mm (range: 15–150 mm).

COMPLICATIONS OF ESD (Table 3)

The post-operative bleeding rate for ESD was 1.0% (4/405) which is almost the same as that for conventional EMR. In contrast, the perforation rate for ESD was 3.5% (14/405) which is considerably higher than that for conventional EMR (1.3%), but only one perforation case needed emergency surgery because endoscopic clipping was ineffective. There have been no delayed perforations observed as of now.

DISCUSSION

Until recently, colorectal ESDs have been performed mainly in Japan[25–29] because of the technical difficulty and the most frequent indication for ESD is early gastric cancer, which is a common finding in Japan but rare in Western countries. But, some trained endoscopists have started to do colorectal ESD even in Europe[30] and the USA.[31]

Complications resulting from ESD occasionally occur mainly due to inaccurate identification of the cutting line because the ablated mucosa cannot be stabilized and pulled away.[32] The resultant cutting of sm vessels causes bleeding and underestimation of the depth of the sm layer results in perforations. To reduce the perforation rate in colorectal ESD, therefore, the use of specialized knives,[9,23] distal attachment[14] and hypertonic solution which produces a longer lasting and higher sm elevation (glycerol[15] and sodium hyaluronate solution)[14] are necessary for safer ESD given the thinner colonic wall.

At NCCH, the perforation rate of 3.5% in the ESD group was considerably higher than the 1.3% perforation rate in the EMR group, however, most perforation cases were successfully treated conservatively without surgery by endoscopic

clipping and the perforation rate has been decreasing based on the increase of the endoscopists skill and recent ESD device developments.

As a result, the perforation rate of 3.5% in the ESD group was considered to be acceptable although further instrument improvements and technique refinements will both be necessary to reduce the perforation rate.

The primary advantage of ESD compared to EMR is higher en-bloc resection rate for large colonic tumors which had been treated by surgery. Consequently, ESD has a lower recurrence rate compared to EPMR and also a better quality of life for patients compared with surgery. We should compare, therefore, the clinical outcome between ESD and surgery not with EMR because the indications for ESD and EMR were different as were the tumor characteristics.

A total of 145 lesions treated with ESD and 228 lesions with conventional EMR for which follow-up colonoscopy examinations could be carried out more than six months after treatment were further analyzed for recurrence rate. There were only three cases (2%) of local recurrence in the ESD group (mean endoscopic follow-up period, 20 ± 13 months). In comparison, local recurrence occurred in 14% (33/228) of the lesions in the EMR group (mean endoscopic follow-up period, 26 ± 17 months). Two EPMRs required surgery because of invasive recurrence while a third piecemeal resection also required surgery because of technical difficulty in performing another EMR despite the intramucosal nature of that particular recurrence. Curative EMR resections were achieved for all other recurrences.

FUTURE PROSPECTS

Currently, most sm2 cancers have been treated surgically because of the risk of LN metastasis, however, few cases of those surgical patients proved to have LN metastasis. As a result, most of those surgical patients received unnecessary surgeries without any evidence of LN or distant metastasis.

Lesions without risk of LN metastasis will be elucidated by further analysis including molecular biology in the near future. ESD for invasive cancer without risk of LN metastasis will then be appropriate.

CONCLUSIONS

The ESD technique with CO_2 insufflation is a feasible method for treating large superficial colorectal tumors safely. It offers the advantage of obtaining an en-bloc resection which, in turn, results in more accurate histological analysis and less frequent recurrence.

CONFLICT OF INTEREST

No conflict of interest has been declared by Y Saito, T Sakamoto, S Fukunaga, T Nakajima, S Kiriyama or T Matsuda.

REFERENCES

1. Kitajima K, Fujimori T, Fujii S *et al.* Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: A Japanese collaborative study. *J. Gastroenterol.* 2004; **39**: 534–43.
2. Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: A study of 101 cases. *Gastrointest. Endosc.* 2002; **55**: 390–96.
3. Yokota T, Sugihara K, Yoshida S. Endoscopic mucosal resection for colorectal neoplastic lesions. *Dis. Colon Rectum.* 1994; **37**: 1108–11.
4. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest. Endosc.* 2003; **57**: 567–79.
5. Saito Y, Fujii T, Kondo H *et al.* Endoscopic treatment for laterally spreading tumors in the colon. *Endoscopy* 2001; **33**: 682–6.
6. Kudo S, Kashida H, Tamura T *et al.* Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. *World J. Surg.* 2000; **24**: 1081–90.
7. Walsh RM, Ackroyd FW, Shellito PC. Endoscopic resection of large sessile colorectal polyps. *Gastrointest. Endosc.* 1992; **38**: 308–09.
8. Hotta K, Fujii T, Saito Y, Matsuda T. Local recurrence after endoscopic resection of colorectal tumors. *Int. J. Colorectal Dis.* 2009 Feb; **24** (2): 225–30.
9. Hosokawa K, Yoshida S. Recent advances in endoscopic mucosal resection for early gastric cancer. *Jpn J. Cancer Chemother.* 1998; **25**: 476–83. (in Japanese with English abstract.)
10. Ono H, Kondo H, Gotoda T *et al.* Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225–29.
11. Gotoda T, Kondo H, Ono H *et al.* A new endoscopic resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: Report of two cases. *Gastrointest. Endosc.* 1999; **50**: 560–63.
12. Uraoka T, Saito Y, Matsuda T *et al.* Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592–7.
13. Tanaka S, Oka S, Chayama K. Colorectal endoscopic Submucosal dissection (ESD): The present status ans future perspective including its differentiation from endoscopic mucosal resection (EMR). Review. *J. Gastroenterol.* 2008; **43** (9): 641–51.
14. Yamamoto H, Kawata H, Sunada K *et al.* Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690–94.
15. Uraoka T, Fujii T, Saito Y *et al.* Effectiveness of glycerol as a submucosal injection for EMR. *Gastrointest. Endosc.* 2005; **61**: 736–40.
16. Kondo H, Gotoda T, Ono H *et al.* Percutaneous traction-assisted EMR by using an insulation-tipped electrosurgical knife for early stage gastric cancer. *Gastrointest. Endosc.* 2004; **59**: 284–8.
17. Gotoda T, Oda I, Tamakawa K, Ueda H, Kobayashi T, Kakizoe T. Prospective clinical trial of magnetic-anchor-guided endoscopic submucosal dissection for large early gastric cancer (with videos). *Gastrointest. Endosc.* 2009; **69**: 10–15.
18. Saito Y, Emura F, Matsuda T *et al.* A new sinker-assisted endoscopic submucosal dissection for colorectal tumors. *Gastrointest. Endosc.* 2005; **62**: 297–301.
19. Uraoka T, Kato J, Ishikawa S *et al.* Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). *Gastrointest. Endosc.* 2007; **66**: 836–9.
20. Fujii T, Hasegawa RT, Saitoh Y *et al.* Chromoscopy during colonoscopy. *Endoscopy* 2001; **33**: 1036–41.

21. Saito Y, Emura F, Matsuda T, Saito D, Fujii T. Invasive pattern is an indication for surgical treatment. Gut online, Letter to the editor, March 4, 2004.
22. Matsuda T, Fujii T, Saito Y *et al.* Efficacy of the invasive/non-invasive pattern by magnifying estimate the depth of invasion of early colorectal neoplasms. *Am. J. Gastroenterol.* 2008; **103**: 2700–6.
23. Sano Y, Fu KI, Saito Y *et al.* A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. *Endoscopy* 2006; **38** (Suppl 5): E95.
24. Saito Y, Uraoka T, Matsuda T *et al.* A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection under conscious sedation. *Gastrointest. Endosc.* 2007; **65**: 537–42.
25. Saito Y, Uraoka T, Matsuda T *et al.* Endoscopic treatment of large superficial colorectal tumors: A cases series of 200 endoscopic submucosal dissections (with video). *Gastrointest. Endosc.* 2007; **66**: 966–73.
26. Yamazaki K, Saito Y, Fukuzawa M. Endoscopic submucosal dissection of a large laterally spreading tumor in the rectum is a minimally invasive treatment. *Clin. Gastroenterol. Hepatol.* 2008; **6**: e5–6.
27. Fujishiro M, Yahagi N, Kakushima N *et al.* Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin. Gastroenterol. Hepatol.* 2007; **5**: 674–7.
28. Tamegai Y, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E *et al.* Endoscopic submucosal dissection: A safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418–22.
29. Tanaka S, Oka S, Kaneko I *et al.* Endoscopic submucosal dissection for colorectal neoplasia: Possibility of standardization. *Gastrointest. Endosc.* 2007; **66**: 100–7.
30. Hurlstone DP, Atkinson R, Sanders DS, Thomson M, Cross SS, Brown S. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *Br. J. Surg.* 2007; **94**: 1536–42.
31. Antillon MR, Bartalos CR, Miller ML, Diaz-Arias AA, Ibdah JA, Marshall JB. En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: Expanding the frontiers of endoscopic surgery (with video). *Gastrointest. Endosc.* 2008; **67**: 332–7.
32. Oda I, Gotoda T, Hamanaka H *et al.* Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc.* 2005; **17**: 54–8.

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Case Report

Application of Endoscopic Submucosal Dissection for Removal of Deep Invasive Submucosal Colon Carcinoma

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Endoscopic submucosal (sm) dissection (ESD) is a recently used technique that enables *en-bloc* resection of large colorectal tumors allowing a more precise histopathological analysis of the resected specimen. However, it has not been widely adopted even in Japan mainly due to its technical difficulty and increased risk of perforation. Herein, we present an ESD-treated lesion with deep sm invasion removed without complications, such as bleeding or perforation, from a patient at high-risk for surgical intervention. A successful ESD was achieved although the sm invasion was greater than 1000 μm from the muscularis mucosae, and the nonlifting sign was positive. It is our belief that this procedure should be performed at least in patients at high-risk for surgical intervention. At present, we have removed 16 lesions with deep sm invasion by ESD without complications, demonstrating that deep sm cancer can be successfully resected by this technique as a local resection. Herein, we report on one of these cases

1. Introduction

In Japan, as shown in [1–3], EMR is the treatment of choice for superficial early colorectal cancer due to the minimal invasiveness and efficacy of the procedure. However, when dealing with flat lesions greater than 20 mm in diameter, the rate of piecemeal resection, incomplete removal, and local recurrence after EMR increases, as discussed in [4–6]. Endoscopic submucosal (sm) dissection (ESD) is a recently used technique that enables *en-bloc* resection of large colorectal tumors allowing a more precise histopathological analysis of the resected specimen, as shown in [7, 8]. However, as cited in [9, 10], colorectal ESD has not been widely adopted even in Japan mainly due to its technical difficulty and increased risk of perforation.

Herein, we report on an ESD-treated lesion with deep sm invasion removed from a patient at highrisk for surgical intervention. The role of ESD for lesions with sm invasion greater than 1000 μm from the muscularis mucosae is discussed.

2. Case Presentation

A 79-year-old male was diagnosed to have a lesion of 28 mm in diameter located in the rectosigmoid colon, with a 0-IIa + IIc macroscopic type (Figure 1). Pathological findings of biopsy specimens revealed a well-differentiated adenocarcinoma. The nonlifting sign was positive. As discussed by Matsuda [11], high magnifying observation with crystal violet staining showed an invasive pattern with irregular and distorted epithelial crypts in the demarcated area suggesting sm invasion greater than 1000 μm from the muscularis mucosae. Open surgery was the first choice offered to the patient. However, as he was considered to be at high risk for surgical intervention due to his history of two acute myocardial infarction episodes and an abdominal aorta bypass procedure, endoscopic resection of the lesion was recommended to avoid open surgery.

As decribed in [12–15], under conscious sedation, with CO_2 insufflation, after indigocarmine dye spraying and injection of glycerol and sodium hyaluronate acid into

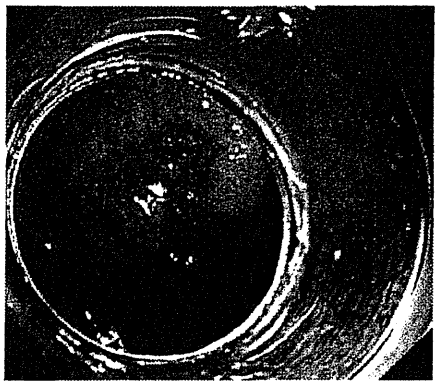

FIGURE 1: Conventional view of a 0-IIa + IIc lesion located in the rectosigmoid colon. A definite depressed margin and irregular reddened surface of depression suggested submucosal deep invasion.

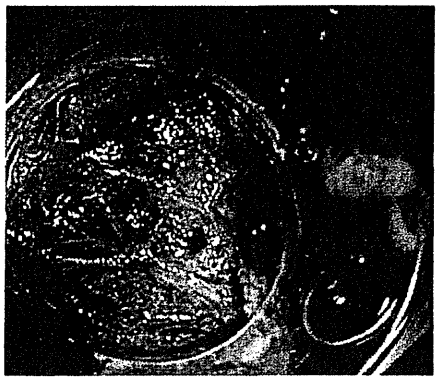

FIGURE 2: Direct observation of the submucosal and muscle layers is possible due to the utility of distal attachment.

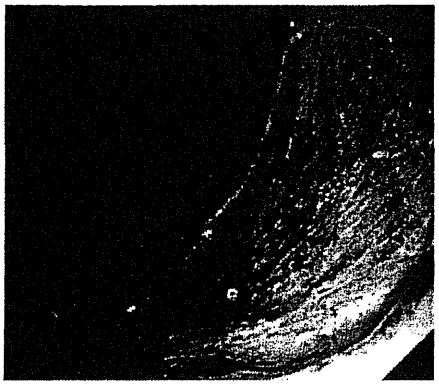

FIGURE 3: Ulcer bed after *en-bloc* resection of the lesion. There is no muscle damage or bleeding.

FIGURE 4: A view on the *en-bloc* resected specimen. The surgical margin is visible.

FIGURE 5: Histopathological analysis of the resected specimen showed a well-differentiated adenocarcinoma, and the depth of invasion was sm 2500 μm with negative lateral and vertical margins.

the sm layer, a circumferential mucosal incision was made using a bipolar current needle knife (B-knife) (XEMEX Co., Tokyo, Japan). The sm dissection was performed using a B-knife and an insulation-tipped diathermic knife (IT-knife) (Olympus Medical Systems Corp., Tokyo, Japan) providing a direct observation of the sm and muscle layers (Figure 2). The resection left an ulcer bed without muscle damage or bleeding (Figure 3). The *en-bloc* resection and removal of the specimen was completed in approximately 80 minutes without any complication (Figure 4). Histopathological analysis of the resected specimen showed a well-differentiated adenocarcinoma, and the depth of invasion was sm 2500 μm with negative lateral and vertical margins (Figure 5).

3. Discussion

According to the Paris classification of superficial neoplastic lesions [16], lesions with sm invasion of less than 1000 μm from the muscularis mucosae should be removed by ESD. In contrast, lesions with sm invasion exceeding 1000 μm are currently considered for surgical resection, as shown in [17, 18]. In this particular case, due to the patient's critical heart condition, ESD was performed although the sm invasion exceeded 1000 μm in depth, and the nonlifting sign was positive.

At the National Cancer Center Hospital a total of 16 cases with deep invasive sm lesions have been successfully removed by ESD, with negative lateral and vertical margins observed during histopathological analysis of the resected specimen.

During ESD for sm cancer, a direct observation of the sm and muscle layers possibilitates a total sm resection. If the lesion has invaded the muscularis propria though, ESD should not be performed because of the risk of colonic perforation. However, as discussed by Saito [7], the use of the B-knife in ESD has decreased the perforation rate. By using this device, a safer procedure is achieved probably because

the electric current is centered to the tip of the needle, as shown in [19].

This case has demonstrated that the removal of lesions with sm invasion greater than 1000 μm from the muscularis mucosae can be successfully resected by ESD as a local resection. It is our belief that this procedure should become the treatment of choice for deep invasive sm cancer at least in patients at high risk for surgical intervention, which would avoid the risk of a surgical procedure and would improve the patient's quality of life.

References

[1] T. Yokota, K. Sugihara, and S. Yoshida, "Endoscopic mucosal resection for colorectal neoplastic lesions," *Diseases of the Colon and Rectum*, vol. 37, no. 11, pp. 1108–1111, 1994.

[2] N. A. Ahmad, M. L. Kochman, W. B. Long, E. E. Furth, and G. G. Ginsberg, "Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases," *Gastrointestinal Endoscopy*, vol. 55, no. 3, pp. 390–396, 2002.

[3] R. M. Soetikno, T. Gotoda, Y. Nakanishi, and N. Soehendra, "Endoscopic mucosal resection," *Gastrointestinal Endoscopy*, vol. 57, no. 4, pp. 567–579, 2003.

[4] S. Tanaka, K. Haruma, S. Oka, et al., "Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm," *Gastrointestinal Endoscopy*, vol. 54, no. 1, pp. 62–66, 2001.

[5] Y. Saito, T. Fujii, H. Kondo, et al., "Endoscopic treatment for laterally spreading tumors in the colon," *Endoscopy*, vol. 33, no. 8, pp. 682–686, 2001.

[6] R. M. Walsh, F. W. Ackroyd, and P. C. Shellito, "Endoscopic resection of large sessile colorectal polyps," *Gastrointestinal Endoscopy*, vol. 38, no. 3, pp. 303–309, 1992.

[7] Y. Saito, T. Uraoka, T. Matsuda, et al., "Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections," *Gastrointestinal Endoscopy*, vol. 66, no. 5, pp. 966–973, 2007.

[8] Y. Tamegai, Y. Saito, N. Masaki, et al., "Endoscopic submucosal dissection: a safe technique for colorectal tumors," *Endoscopy*, vol. 39, no. 5, pp. 418–422, 2007.

[9] Y. Saito, F. Emura, T. Matsuda, et al., "A new sinker-assisted endoscopic submucosal dissection for colorectal cancer," *Gastrointestinal Endoscopy*, vol. 62, no. 2, pp. 297–301, 2005.

[10] M. Fujishiro, N. Yahagi, M. Nakamura, et al., "Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar," *Gastrointestinal Endoscopy*, vol. 63, no. 2, pp. 243–249, 2006.

[11] T. Matsuda, T. Fujii, Y. Saito, et al., "Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms," *American Journal of Gastroenterology*, vol. 103, no. 11, pp. 2700–2706, 2008.

[12] Y. Saito, T. Uraoka, T. Matsuda, et al., "A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation," *Gastrointestinal Endoscopy*, vol. 65, no. 3, pp. 537–542, 2007.

[13] H. Yamamoto, H. Kawata, K. Sunada, et al., "Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate," *Gastrointestinal Endoscopy*, vol. 56, no. 4, pp. 507–512, 2002.

[14] H. Yamamoto, H. Kawata, K. Sunada, et al., "Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood," *Endoscopy*, vol. 35, no. 8, pp. 690–694, 2003.

[15] T. Uraoka, T. Fujii, Y. Saito, et al., "Effectiveness of glycerol as a submucosal injection for EMR," *Gastrointestinal Endoscopy*, vol. 61, no. 6, pp. 736–740, 2005.

[16] "The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon," *Gastrointestinal Endoscopy*, vol. 58, supplement 6, pp. S3–S43, 2003.

[17] W. A. Bemelman, "Minimally invasive surgery for early lower GI cancer," *Best Practice and Research: Clinical Gastroenterology*, vol. 19, no. 6, pp. 993–1005, 2005.

[18] T. Uraoka, Y. Saito, T. Matsuda, et al., "Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum," *Gut*, vol. 55, no. 11, pp. 1592–1597, 2006.

[19] Y. Sano, K. I. Fu, Y. Saito, et al., "A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors," *Endoscopy*, vol. 83, supplement 2, p. E95, 2006.

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ORIGINAL ARTICLES

Size does not determine the grade of malignancy of early invasive colorectal cancer

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Abstract

AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤ 10 mm) and large (> 10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥ 1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

Key words: Colorectal cancer; Submucosal invasion; Lymph node metastasis; Endoscopic mucosal resection

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INTRODUCTION

Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still