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ORIGINAL ARTICLE

The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial

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ABSTRACT

Objective To evaluate the influence of low-dose, enteric-coated aspirin tablets (100 mg/day for 2 years) on colorectal tumour recurrence in Asian patients with single/multiple colorectal tumours excised by endoscopy.

Design A double-blinded, randomised, placebo-controlled multicentre clinical trial was conducted.

Participants 311 subjects with single/multiple colorectal adenomas and adenocarcinomas excised by endoscopy were enrolled in the study (152 patients in the aspirin group and 159 patients in the placebo group). Enrolment began at the hospitals (n=19) in 2007 and was completed in 2009.

Results The subjects treated with aspirin displayed reduced colorectal tumourigenesis and primary endpoints with an adjusted OR of 0.60 (95% CI 0.36 to 0.98) compared with the subjects in the placebo group. Subgroup analysis revealed that subjects who were non-smokers, defined as those who had smoked in the past or who had never smoked, had a marked reduction in the number of recurrent tumours in the aspirin-treated group. The adjusted OR for aspirin treatment in non-smokers was 0.37 (CI 0.21 to 0.68, $p<0.05$). Interestingly, the use of aspirin in smokers resulted in an increased risk, with an OR of 3.44. In addition, no severe adverse effects were observed in either group.

Conclusions Low-dose, enteric-coated aspirin tablets reduced colorectal tumour recurrence in an Asian population. The results are consistent with those obtained from other randomised controlled trials in Western countries.

The clinical trial registry website and the clinical trial number http://www.umin.ac.jp (number UMIN000000697).

Significance of this study

What is already known on this subject?

- A considerable amount of evidence regarding the utility of aspirin as a cancer chemopreventive agent has been generated in Western populations.
- The evidence regarding aspirin as a cancer chemopreventive agent in Asian populations is limited. Moreover, no cancer chemopreventive drugs have been approved in Japan.
- The advantages of aspirin as a cancer chemopreventive agent are well recognised, as it has been in clinical use for a long period of time. In addition, aspirin's adverse effects and cost-effectiveness are well known.

What are the new findings?

- We are the first to report the efficacy of low-dose, enteric-coated aspirin tablets in the suppression of colorectal tumour recurrence in Asian patients; these findings are consistent with the observations of other aspirin adenoma trials in Western populations.
- We report the safety of low-dose, enteric-coated aspirin tablets administered to patients as a cancer chemopreventive agent for 2 years.

How might it impact on clinical practice in the foreseeable future?

- The evidence that aspirin is effective in the reduction of colorectal tumour recurrence in Asian patients may impact cancer preventive strategies in Japan and other Asian countries, including Korea and China.

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INTRODUCTION

Among chemopreventive interventions, aspirin (acetylsalicylic acid) has been examined in numerous trials that support its suppressive effect on colorectal cancer (CRC) development. Aspirin is a synthetic medicine based on the structure of salicylates, which are commonly found in fruits and vegetables. Aspirin's antineoplastic effects have been mechanistically explained by its cyclooxygenase (COX) inhibitory activity. The use of aspirin as a cancer chemopreventive agent is advantageous because it has a long history of clinical use

and its adverse effects are well known. Moreover, the cost-effectiveness of aspirin administration to prevent other diseases, such as cardiovascular disease, has also been demonstrated.[1]

An early prospective cohort study of 662 424 adults (the Cancer Prevention Study II cohort) demonstrated that the CRC death rate decreased with frequent aspirin use. The decreased relative risk (RR) of CRC among frequent aspirin users (≥16 times/month for at least 1 year with doses greater than 160 mg) was 0.60 (95% CI 0.4 to 0.89) in men and 0.58 (95% CI 0.37 to 0.9) in women.[2] An updated analysis of this cohort (the Cancer Prevention Study II Nutrition cohort) demonstrated that long-term daily aspirin use (≥325 mg/day for ≥5 years) is associated with reduced incidence of CRC compared with non-users (RR=0.68, 95% CI 0.52 to 0.90 among men and women collectively).[3 4] The factors that may affect the impact of aspirin include the population, dose of aspirin and duration of intervention.[4] In the general population, trials of 75–325 mg/day aspirin for 3 years reduced the risk of recurrent of colorectal adenoma by 17%.[5] Moreover, the use of aspirin for 5 years or longer reduced the incidence and mortality of CRC by 30%–40% after 20-year follow-up.[6]

A considerable amount of evidence on the utility of aspirin has been generated in Western populations; however, the evidence for aspirin as a cancer chemopreventive agent in Asian populations is limited. Thus, it is important to present evidence that aspirin is also effective as a cancer chemopreventive agent in Asian populations.

We recently reported a double-blinded, randomised, placebo-controlled clinical trial of a high-risk CRC group, familial adenomatous polyposis, to evaluate the effect of low-dose, enteric-coated aspirin tablets. Secondary endpoint data from the trial revealed that subjects with a mean baseline polyp diameter of <2 mm administered aspirin displayed a significant reduction in mean polyp size.[7]

We investigated the effects of low-dose, enteric-coated aspirin tablets administered for 2 years in a double-blinded, randomised, placebo-controlled clinical trial in patients with a single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa and excision by endoscopy. This population was considered to be a high-risk colorectal tumour group. Low-dose, enteric-coated aspirin tablets (100 mg/day) were chosen for the study because low-dose aspirin may circumvent the risk of upper GI toxicity.[8] In addition, the enteric coating may decrease gastric mucosal damage, as demonstrated in the MAJIC study targeting high-risk cardiovascular Japanese patients[9] as well as other short-term endoscopic studies.[10]

Here, we report the efficacy and safety of low-dose, enteric-coated aspirin tablets in the suppression of colorectal tumour recurrence in Asian patients with colorectal adenomas and/or adenocarcinomas with confined mucosal invasions that were excised by endoscopy.

METHODS

Trial methodology

In this double-blinded (both subjects and investigators), randomised, placebo-controlled trial using low-dose, enteric-coated aspirin tablets, the subjects received either 100 mg/day aspirin or placebo for 2 years. Each case was randomised by investigators using a computer-aided system from the Medical Research Support website. Using a minimisation algorithm, the primary examination selection was balanced with respect to three stratification variables: institution, age (≤60 and >60 years) and sex (male or female). The website was only available to the trial investigators. Subject enrollment and intervention assignment began at each hospital in January 2007, and the trial ended in July 2009. To further evaluate the effects of aspirin, follow-up for more than 2 years after the randomised trial was also planned. An Ethics Monitoring Committee was established for this multicentre trial (n=19) that was primarily based at Osaka Central Hospital. A system to ensure continuous follow-up of adverse events was also established. All hospitals participating in this trial obtained approval from their own ethics committees. This trial is registered and details are available at http://www.umin.ac.jp (number UMIN000000697), where the full trial protocol can be accessed.

Trial population

The trial population (n=389) consisted of patients with single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa. The colorectal tumours of all subjects participating in the trial were excised by endoscopy before the trial start. An endoscopic examination was performed twice before the start of the trial; the examinations occurred at an average of 488.4 ±472 (mean±SD) days apart to confirm that all colorectal tumours were excised. All of the subjects were Asian men or women 40–70-years-old living in Japan. The following are exclusion criteria for the trial: (1) patients with familial adenomatous polyposis, Lynch syndrome or colorectal resection; (2) patients currently taking an antithrombotic or anticoagulant, including aspirin; (3) individuals with a history of stroke or gastric/duodenal ulcers (with the exception of patients with confirmed scars resulting from the successful eradication of *Helicobacter pylori*); (4) patients with IBD, haemorrhagic diverticulitis or haemorrhagic tendency; (5) patients with a platelet count of ≤100 000/mm^3 or abnormal prothrombin time; (6) patients with a known aspirin allergy; (7) patients currently taking an anticancer drug; (8) pregnant patients or those who planned to become pregnant during the trial period; and (9) patients taking non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief more than thrice weekly. We calculated that 266 randomised patients would achieve an 80% power (with a 5% type I error) to detect a 40% difference in the recurrence rate of adenoma given a 40% risk of recurrence in the placebo group.[11] However, data were unavailable to calculate an appropriate number of individuals to recruit from the Asian population; therefore, we set our recruitment goal in the initial aspirin protocol to 700 randomised patients.

Consent interviews were performed individually, and written informed consent was obtained from all patients.

Investigational drug

Low-dose, enteric-coated aspirin tablets (100 mg per tablet) and the placebo tablets were kindly provided by Bayer Pharma AG (Leverkusen, Germany) and imported into Japan. The trial was financed by research funding from the Ministry of Health, Labor and Welfare, not by Bayer Pharma AG. We signed an agreement to certify that no conflicts of interest with Bayer Pharma AG existed. The investigational drugs were placed in blister packages (calendar sheets of 31 tablets), and both sides of the package were aluminium-laminated.

Trial questionnaire

At the time of trial enrolment, the height, body weight, medical history, smoking history, alcohol ingestion and use of NSAIDs were investigated for each patient using a questionnaire. In addition, data regarding everyday meals were collected using a self-administered food-frequency questionnaire developed by the Department of Health Promotion and Preventive Medicine,

Nagoya-City University Graduate School of Medical Science, Aichi, Japan.[12] Non-smokers were defined as people who had smoked in the past or never smoked. Occasional drinkers were defined as people who drank less than twice a week.

To ensure the accurate characterisation of adverse effects and evaluation of tolerability, the subjects were asked to keep a treatment diary that documented their conditions during treatment, such as drug compliance and medical conditions, and a blister sheet was sent to the data centre every month.

Trial endpoints

Colonoscopy was performed at least three times, twice before the start of the trial and once at the end of the trial. All the patients were given an oral lavage solution for colonic cleansing at the time of the colonoscopy for clear imaging, and a medical colonoscopy specialist carefully examined the patients from the rectum to the cecum. The final endoscopy examination was performed 2 years after the start of the trial. Recurrent tumours were further diagnosed by histology after tumour excision. The primary endpoint was the incidence of adenoma or adenocarcinoma recurrence. The data were analysed using logistic regression and ORs, and general factors, such as sex, age and the tumour number before the trial, were used to adjust occasional deviation during the randomised allocation. Each tumour was removed and examined histologically by a pathologist. Tumours were classified as adenomas or adenocarcinomas according to the 'Japanese Classification of Colorectal Carcinoma' criteria. The secondary endpoints included recurring tumour number, size and histology as well as the effects of lifestyle, such as smoking and alcohol drinking, and the frequency of adverse effects.

Statistical analysis

The baseline characteristics of the two arms were compared using the χ^2 test or the t test. The adverse effect rates of both arms were compared using the χ^2 test. If needed, Fisher's exact probability was applied due to sparse data in a table. To adjust for potential confounding effects at baseline, logistic regression was performed.

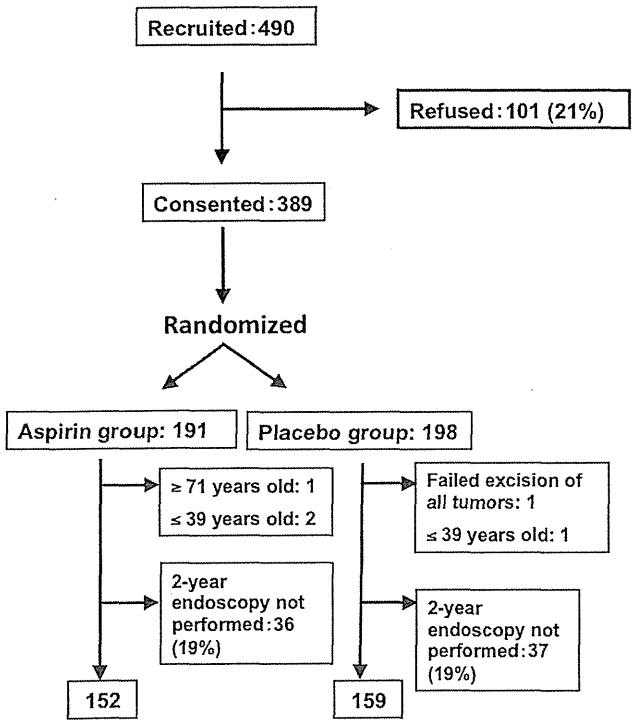

Figure 1 Flowchart of subject recruitment.

We also examined the effect modification (interaction) of several factors, such as (1) sex, (2) age, (3) smoking and (4) alcohol drinking, on the main effect of aspirin by adding an interaction term to the logistic regression. In this analysis, we determined the ORs of the subgroups of the above factors and the difference in the ORs of the subgroups.

All statistical analyses were based on the intention-to-treat and performed using PC-SAS (V.9.3; SAS Inc., Cary, North Carolina, USA), with $p<0.05$ considered statistically significant.

RESULTS

Characteristics of the trial subjects

A total of 490 patients were screened, and 389 patients provided informed consent. Subject enrolment began in January 2007, and the trial ended in July 2009. Subject recruitment ended according to the planned time schedule. After randomisation, the aspirin and placebo group consisted of 191 and 198 subjects, respectively. At the end of the trial, 152 subjects from the aspirin group and 159 subjects from the placebo group underwent a 2-year follow-up endoscopy examination (figure 1). The characteristics of the subjects in the aspirin and placebo groups after randomisation are displayed in table 1. No significant differences between the two groups were observed with regard to the following characteristics: age, sex, smoking status, alcohol drinking status, height, weight, body mass index, tumour number upon entry into the trial, past history of CRC with invasion confined to the mucosa, treatment period, compliance (ie, whether patients correctly take medicine and follow the doctors' instructions (data not shown)), surgical history (data not shown) and family history of CRC (data not shown). The serum concentrations of alanine transaminase, aspartate amino transferase, γ-glutamyl transpeptidase and triglycerides were almost identical between the groups (data not shown).

Colorectal tumour recurrence as the primary endpoint

In total, 96 patients did not experience colorectal tumour recurrence in the aspirin group (total 152), and 86 patients in the placebo group (total 159) did not recur. In crude analyses, the subjects in the aspirin group tended to demonstrate a reduced number of colorectal tumours, which was the primary endpoint, compared with subjects in the placebo group. The OR was 0.69 (95% CI

Table 1 Characteristics of the two groups

	Aspirin		Placebo	
Number	152		159	
Age	60.0	±7.3*	60.5	±6.6
Sex				
Male	121	(79.6%)	125	(78.6%)
Smoking				
Current smokers	45	(29.6%)	34	(21.4%)
Alcohol				
Drinker†	83	(54.6%)	92	(57.9%)
Height	164.7	±6.8	165.5	±7.3
Weight	64.3	±9.7	65.6	±10.1
BMI‡	23.6	±2.7	23.9	±2.8
Number of tumours upon trial entry	5.3	±5.7	5.1	±7.0
Past CRC history	40	(26.3%)	39	(24.5%)
Treatment period	751	±67 days	764	±90 days

*SD.
†Alcohol drinker: drinks more than three times a week.
‡Body mass index (BMI)=Weight (kg)/height (m) squared.
CRC, colorectal cancer.

Table 2 The effects of aspirin on colorectal tumour development in smokers

Subanalysis	No. of subjects with (+) or without (−) colorectal tumour			Adjusted OR (95% CI)
	−	+	Total	
Current smoker				
Placebo group	26	19	45	1
Aspirin group	14	20	34	3.45 (1.12 to 10.64), p=0.03
Non-smoker*				
Placebo group	60	54	114	1
Aspirin group	82	36	118	0.37 (0.21 to 0.68), p=0.01

Adjusted OR, OR is adjusted by sex, age and the number of tumours prior to the trial.
*Non-smoker: never smoked and former smokers.

0.44 to 1.08); despite a marginal difference, the value was not statistically significant. To adjust for potential confounders, such as sex, age and the number of recurrent tumours, we performed logistic regression and obtained a significant OR value of 0.60 (95% CI 0.36 to 0.98). The OR for the number of recurrent tumours <4 in the aspirin group was 0.34 (0.09 to 1.26), and the OR for a tumour >3 mm in longitudinal diameter was 0.86 (0.63 to 1.16), but the value was not statistically significant.

The effects of smoking and drinking on colorectal tumour recurrence

Using a logistic regression with smoking as the interaction term and aspirin as the effect, we observed that smoking displays strong effect modification on the main effect of aspirin (p for interaction=0.004). Namely, the OR for non-smokers was 0.37 (95% CI 0.21 to 0.68), and this value was significantly different from the OR for smokers (OR 3.44, 95% CI 1.12 to 10.64) after adjustment for age, sex and the number of tumours (table 2). In contrast, no significant effect modification for sex (p=0.68), age (p=0.53) or alcohol consumption (p=0.32) was observed. With regard to sex, the OR was 0.48 (95% CI 0.15 to 1.55) and 0.63 (95% CI 0.36 to 1.08) among men and women, respectively. For age, the OR was 0.68 (95% CI 0.36 to 1.28) and 0.49 (95% CI 0.22 to 1.08) for subjects aged <60 and ≥60 years, respectively. For alcohol consumption, the OR was 0.72 (95% CI 0.37 to 1.40) and 0.44 (95% CI 0.21 to 0.95; p<0.05) for drinkers and occasional drinkers, respectively.

In addition, no severe adverse effects, such as cardiovascular events, were reported in either group. GI bleeding was not observed. Of note, colorectal adenocarcinomas were observed in four subjects: two cases from the aspirin group (one adenocarcinoma with invasion confined to the mucosa, and one adenocarcinoma with muscularis propria invasion) and two in the placebo group (two adenocarcinomas with invasion confined to the mucosa). The remaining tumours were tubular adenomas; villous adenomas were not identified. In addition, three high-grade dysplasias were detected; one case was observed in the aspirin group, and two cases were noted in the placebo group. The adenocarcinomas were 10–20 mm in diameter. The lesions were localised to the transverse colon (n=2), the descending colon (n=1) and the sigmoid colon (n=1).

DISCUSSION

In the present trial, we enrolled subjects with single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa that were excised by endoscopy. Patients treated with low-dose, enteric-coated aspirin tablets for 2 years were shown to have a low risk of incidental colorectal tumour development, and this appeared to be reduced after adjustment for sex, age and the number of baseline tumours. Moreover, smoking significantly modified the preventive effect of aspirin.

In a meta-analysis of subjects with a history of colorectal adenoma or cancer in four randomised adenoma prevention trials (nearly 3000 patients), aspirin reduced the occurrence of advanced lesions (ie, tubulovillous adenomas, villous adenomas, adenomas ≥1 cm in diameter, adenomas with high-grade dysplasia or invasive cancer) by 28% (adenoma 17%; RR=0.83; 95% CI 0.72 to 0.96).[3] Our trial also demonstrated reduced adenoma occurrence (OR=0.69), and similar effects were obtained compared with the meta-analysis by Cole *et al*.[5] However, the ORs we used have a predictable effect on the comparison of the two sets of analyses. Regarding the limitations of our trial, the number of subjects enrolled is rather small, but the tumour recurrence results are consistent with previous studies. Thus, our data demonstrate that aspirin is also useful as a CRC chemopreventive agent in an Asian population. Of note, the first Asian adjuvant study (ASCOLT, NCT00565708) is ongoing, wherein patients with Dukes C or high risk Dukes B CRC are treated with aspirin (200 mg/day for 3 years).

Although the daily aspirin doses administered for vascular disease prevention are as effective as high-dose (1200 mg/day) aspirin,[11] analyses comparing moderate (300–325 mg/day) and lower (81–160 mg/day) aspirin doses trials (AFPPS[11] and APACC[13]) revealed that the reduced risk of all adenoma recurrence was only observed with lower doses.[5] Our trial using low-dose, enteric-coated aspirin tablets (100 mg/day) was designed in light of these trials, thereby confirming that low-dose, enteric-coated aspirin tablets effectively reduce recurrence. In addition, low-dose regimens may have an advantage in that the lower doses potentially reduce adverse effects. Aspirin has been reported to induce GI bleeding at a rate of 1–2 GI bleeds per 1000 person-years.[14] In our trial, no severe adverse effects due to aspirin treatment were observed.

Aspirin's antineoplastic effects are explained by COX-dependent and -independent mechanisms. In humans, aspirin inhibits COX-1 and COX-2 at high doses[15] and appears to effectively inhibit prostaglandin synthesis in the colon.[16] COX-independent mechanisms underlying aspirin's antineoplastic effects are attributed to the modulation of nuclear factor κ B: the induction of spermidine/spermine N1-acetyltransferase, caspase-8 and -9; and the activation of 5′ adenosine monophosphate-activated protein kinase, Erk and β-catenin.[17–23]

Despite copious information regarding aspirin's functions, the mechanism by which smoking negates aspirin's CRC chemopreventive effects remains unclear. A strong association between antiplatelet therapy resistance (aspirin resistance) and smoking has been reported. Specifically, a statistically significant interaction exists based on the multivariate analysis (risk ratio 11.47, CI 6.69 to 18.63, p<0.0001),[24] which is likely due to smoking-induced platelet hyperactivity and chronic inflammation.[25] In addition, smoking-induced decreased basal GI blood flow may also be involved.[26] Thus, it is suggested that smoking negated aspirin's chemopreventive effects in CRC. However, the evidence is limited. It is important to review and generate additional aspirin trial data to examine the association between NSAIDs use and smoking history and to determine whether the benefits of aspirin are limited to non-smokers.

In conclusion, although the size of this trial is small, the results are consistent with the observations of other aspirin adenoma trials; thus, aspirin may be useful for chemoprevention in Asian

patients with single/multiple colorectal tumours and no antecedent risk of GI bleeding. Several years of follow-up after a randomised trial are necessary to evaluate the effects of aspirin as proposed by the CAPP2 randomised trial.[27] Moreover, it would be informative to test aspirin in combination with other chemopreventive agents that have demonstrated effectiveness and agents that prevent GI bleeding (eg, proton-pump inhibitors).[28]

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Patient consent Obtained.

Ethics approval All hospitals participating in this trial obtained approval from their own ethics committees to conduct the trial.

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GUT

The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial

Hideki Ishikawa, Michihiro Mutoh, Sadao Suzuki, Shinkan Tokudome, Yoshihisa Saida, Takashi Abe, Shozo Okamura, Masahiro Tajika, Takashi Joh, Shinji Tanaka, Shin-ei Kudo, Takahisa Matsuda, Masaki Iimuro, Tomomi Yukawa, Tetsuji Takayama, Yasushi Sato, Kyowon Lee, Shinji Kitamura, Motowo Mizuno, Yasushi Sano, Nobuhisa Gondo, Kenji Sugimoto, Masato Kusunoki, Chiho Goto, Nariaki Matsuura, Toshiyuki Sakai and Keiji Wakabayashi

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ORIGINAL ARTICLE

Factors associated with technical difficulties and adverse events of colorectal endoscopic submucosal dissection: retrospective exploratory factor analysis of a multicenter prospective cohort

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Abstract
Background Colorectal endoscopic submucosal dissection (C-ESD) is a promising but challenging procedure. We aimed to evaluate the factors associated with technical difficulties (failure of *en bloc* resection and procedure time, ≥2 h) and adverse events (perforation and bleeding) of C-ESD.

Methods We conducted a retrospective exploratory factor analysis of a prospectively collected cohort in 15 institutions. Eight-hundred sixteen colorectal neoplasms larger than 20 mm from patients who underwent C-ESD were included. We assessed the outcomes of C-ESD and risk factors for technical difficulties and adverse events.

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Results Of the 816 lesions, 767 (94 %) were resected *en bloc*, with a median procedure time of 78 min. Perforation occurred in 2.1 % and bleeding in 2.2 %. Independent factors associated with failure of *en bloc* resection were low-volume center (<30 neoplasms), snare use, and poor lifting after submucosal injection. Factors significantly associated with long procedure time (≥2 h) were large tumor size (≥4 cm), low-volume center, less-experienced endoscopist, CO_2 insufflation, and use of two or more endoknives. Poor lifting was the only factor significantly associated with perforation, whereas rectal lesion and lack of a thin-type endoscope were factors significantly associated with bleeding. Poor lifting after submucosal injection occurred more frequently for nongranular-type laterally spreading tumors (LST) and for protruding and recurrent lesions than for granular-type LST (LST-G).
Conclusions Poor lifting after submucosal injection was the risk factor most frequently associated with technical difficulties and adverse events on C-ESD. Less experienced endoscopists should start by performing C-ESDs on LST-G lesions.

Keywords Colonoscopy · Colorectal neoplasm · Endoscopic gastrointestinal surgery · Endoscopic submucosal dissection

Introduction

Endoscopic resection is a noninvasive, standard treatment for patients with superficial colorectal neoplasms (adenoma/early cancer) without risk of lymph node metastasis [1–3]. Small colorectal neoplasms can be removed easily with conventional polypectomy or endoscopic mucosal resection (EMR). However, conventional EMR may result in piecemeal resection (i.e., tumor resection in multiple fragments) of large-sized tumors [4–6]. Limitations of piecemeal resection include incomplete histological assessment of the specimen and a greater risk of tumor recurrence [7]. Indeed *en bloc* resection (i.e., resecting the entire tumor in one piece) is preferred for precise histological assessment of the resected specimen and to ensure elimination of any residual tumor [4].

Endoscopic submucosal dissection (ESD), of superficial gastrointestinal neoplasms results in high *en bloc* resection rates, regardless of tumor size, location, or fibrosis in the submucosa (SM) [1]. However, colorectal ESD is associated with technical difficulties resulting in poor outcomes, such as failure of *en bloc* resection and long procedure time [8]. Additionally, the adverse events of colorectal ESD (e.g., perforation and bleeding) may be quite severe [9]. These technical difficulties and adverse events may be associated with lesion characteristics, type of endoscopic device, and operator experience. Limitations in attempting to perform colorectal ESD may be due to a lack of information on these technical difficulties and adverse events. Assessing factors associated with such technical difficulties and adverse events may help in formulating training programs for colorectal ESD and treatment strategies for large colorectal tumors. Although several large case-series have assessed the feasibility and efficacy of colorectal ESD, these were retrospective analyses in well-experienced single centers [10, 11]. Outcomes of colorectal ESD were also assessed in a prospective multicenter study, but those centers were all advanced institutions [12]. Therefore, the outcomes of colorectal ESD performed at institutions with various levels of experience have not yet been evaluated.

Considering that the rates of adverse events and tumor recurrence following EMR and ESD had never been directly compared, we performed a prospective cohort study comparing EMR and ESD for large (≥20 mm) colorectal neoplasms [13, 14]. In the prospectively collected cohort, there was a large number of ESD procedures (816 ESDs vs. 1,029 EMRs). Therefore, we retrospectively explored the factors associated with technical difficulty and adverse events on colorectal ESD in the cohort.

Patients and methods

This retrospective analysis involved the patients undergoing colorectal ESD in the prospectively selected patients undergoing colorectal endoscopic resection at 18 tertiary institutions with various levels of experience. The study was performed by the Japanese Society for Cancer of the Colon and Rectum to compare recurrence rates after EMR and ESD for colorectal neoplasms ≥20 mm [13, 14]. The study protocol was approved by the institutional review board of each center and registered in the University Hospital Medical Information Network Clinical Trials Registry as number UMIN 000001642. This manuscript followed the STROBE

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guidelines [15]. All the authors had reviewed and approved the final manuscript.

Study participants

Consecutive patients >20 years old with superficial colorectal neoplasms ≥20 mm in diameter undergoing endoscopic resection between October 2007 and December 2010 were eligible for inclusion in the original cohort trial. Lesions predicted to be noninvasive neoplasms and carcinomas with minute (<1,000 μm) SM invasion, thought to have no risk of lymph node metastasis, were removed by endoscopic resection. The subjects in that trial who underwent ESD were included in this retrospective exploratory factor analysis (Fig. 1). The choice between EMR and ESD was made by each participating colonoscopist, based on the proposed guidelines of the Colorectal ESD Standardization Implementation Working Group [16, 17]. Lesions with contraindications to endoscopic resection, as determined by the colonoscopist, including lesions involving the orifice of the appendix, those encompassing the entire circumference of the colonic wall, those showing massive invasion of the ileum, and lesions inaccessible by colonoscopy, were excluded and treated by surgical colectomy. Written informed consent was obtained from each patient.

Procedures

All procedures were performed by colonoscopists who had been physicians for at least 5 years and were either board-certified by the Japanese Gastroenterological Endoscopy Society (JGES) or had knowledge and endoscopic techniques equal to that of board-certificated colonoscopists. Therefore, no trainees were involved in any of these cases. Endoscopic devices (endoknives), endoscopes, endoscopic systems, and medications were not regulated by the study protocol, and all procedures were performed according to each institution's standard procedure. Patients were considered admitted to hospital when they underwent ESD. Although the fasting and hospitalization periods and examination after colonic ESD were determined according to each institution's protocol, in Japan the usual fasting period is 2 days, including the day on which ESD is performed, and the hospitalization period is 7 days with blood tests performed the day after ESD. The histopathology of each resected specimen was assessed at each institution, following the Japanese classification of colorectal carcinoma [2]. Lesions histopathologically diagnosed as low/high-grade adenoma, intramucosal carcinoma, or carcinoma with minute SM invasion (<1,000 μm), without high pathologic risk features (lymph-vascular involvement and/or poorly differentiated adenocarcinoma), were regarded as curable because they had no risk of lymph node metastasis. By contrast, lesions histopathologically diagnosed as carcinoma with deep SM invasion (≥1,000 μm) or with high-risk pathologic features were regarded as incurable, and these patients were referred for additional surgery, including lymph node dissection.

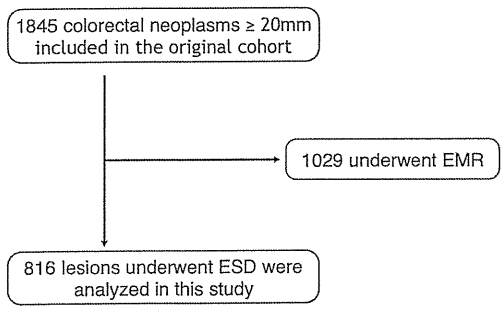

Fig. 1 Study design, showing a flow diagram of enrolled subjects

Data collection and measured outcomes

Detailed data sheets on each participating patient were completed by the investigators and faxed to the independent data center. Information about endoscopic resection (e.g., endoscopic devices, endoscopes, and medications) was collected after the procedure. Data included patient characteristics (age and sex), diagnostic modality prior to endoscopic resection (with or without magnifying endoscopy), tumor characteristics (location, estimated size, type, and history of biopsy), institution, the experience of each colonoscopist (<11 or ≥11 years), fluid injected to form a SM cushion (sodium hyaluronate or others), type of power source used for electrical cutting and its setting, type of electrosurgical endoknife, type of insufflation gas (CO_2 or air), lifting condition after SM injection (good or poor), completeness of the endoscopic resection (*en bloc*, piecemeal, or unresected), diagnostic modality for assessment of residual tumor after endoscopic resection (with or without magnifying endoscopy), procedure time (from the beginning of SM injection until lesion removal), adverse events (perforation, bleeding, and others), treatments administered for adverse events and their outcomes, histopathological diagnosis of the resected specimen (histological type, lymph-vascular involvement, and tumor involvement on the lateral and proximal margins) according to the Japanese classification of colorectal carcinoma [2], and additional therapy for incurable lesions.

Outcomes indicating technical difficulties included failure of *en bloc* resection and procedure time and adverse events included perforation and bleeding. The factors associated with each were also evaluated.

Definitions

ESD was defined as endoscopic dissection of a colorectal tumor using an electrosurgical endoknife, consisting of circumferential mucosal cutting and SM dissection or

circumferential SM incision prior to EMR (CSI-EMR) [18], as it was difficult to distinguish whether CSI-EMR was initially planned prior to the procedure or was used to rescue a procedure which was difficult to complete. As ESD is intended for *en bloc* resection, a failed procedure was defined as failure of *en bloc* resection (i.e., piecemeal resection or incomplete procedure). Tumors were classified as being located on the colon (cecum, ascending, transverse colon, descending or sigmoid colon) or the rectum. Endoknives were classified into three categories (needle knife, IT knife, and scissors types), as well as with or without water-jet function. Tumors were classified into five categories, based on the Paris classification and models of tumor growth during the development of colorectal neoplasia [3, 19]. The five types were: (1) granular-type laterally spreading tumor (LST-G), (2) nongranular-type laterally spreading tumor (LST-NG), (3) protruding tumor, (4) recurrent tumor after endoscopic resection, and (5) unclassified. Lifting conditions after SM injection were assessed as good or poor [20]. Histopathological diagnoses were based on the Japanese classification and were re-classified according to the Vienna classification [21]. Low-grade adenomas according to the Japanese classification were equivalent to noninvasive low-grade neoplasias according to the Vienna classification, whereas high-grade adenomas and intramucosal carcinomas according to the Japanese classification were equivalent to noninvasive high-grade neoplasias according to the Vienna classification. Based on the median number of ESDs performed at each institution during the study period (30 cases/3 years; i.e., 10 cases/year), institutions were classified as low (<30 lesions) and high (≥30 lesions) volume centers. Colonoscopists were classified as those who were less (<11 years) and more (≥11 years) experienced, because it takes at least 5 years to be a board-certified member of JGES and it is thought that it takes more 5 years to experience enough ESD cases. Procedure time >2 h was defined as long, because 30 % of the ESDs needs procedure time >2 h, and it can be said they are relatively difficult cases than average. Lesion size was classified as <40 and ≥40 mm. A bleeding episode was defined as bleeding resulting in (1) apparent hematochezia or melena after the procedure, (2) a ≥2-g/dL decrease in hemoglobin concentration, or (3) a blood transfusion (the decision for transfusion was left each institution's criterion and 7.0 g/dL in hemoglobin concentration is generally accepted as a criterion for transfusion). Perforation was defined as a full-thickness defect of the colonic wall with visible peritoneal fat or the presence of extra-gastrointestinal air on X-ray or abdominal computed tomography. Although observation period for delayed adverse events was not defined, the patients were generally followed up for at least one year because the follow-up period of the original cohort study was one year. Therefore, we could collect the information about late adverse events for two to four weeks [22].

Sample size estimation and statistical analysis

This study was a retrospective exploratory factor analysis of a prospective cohort study. The cohort involved 1,845 colorectal neoplasms ≥20 mm in diameter. The lesions from patients who underwent ESD were included to this exploratory analysis. Multiple lesions in the same patient were counted as independent lesions.

All data were collected and analyzed at an independent data center. Continuous, parametric variables are reported as means (standard deviation (SD)) and nonparametric data as medians (interquartile range (IQR) or range). Categorical variables were reported as incidence or rates (%) and compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate and multivariate logistic regression analyses were performed to examine the factors associated with technical difficulty (failure of *en bloc* resection and procedure time, >2 h), whereas the number of adverse events (perforation and bleeding) was too small for multivariate analysis and only univariate analysis was done to examine the factors associated with adverse events. Variables with p values for association ≤0.2 on univariate analysis were considered potential risk factors in multivariate logistic regression analysis. All statistical analyses were performed using JMP version 10 (SAS Institute Inc, Cary, NC). All analysis were exploratory and P values were two-tailed, with $p<0.05$ defined as statistically significant.

Results

Study design and baseline patient characteristics

The participants' flow is shown in Fig. 1. Between October 2007 and December 2010, 1,845 colorectal neoplasms ≥20 mm in diameter were enrolled in the prospective cohort study. Of these, 816 lesions underwent colorectal ESD and were included in this analysis, and the remainder underwent conventional EMR.

Baseline patient characteristics are shown in Table 1. ESD procedures were performed at 15 of the 18 participating institutions, with a median of 30 lesions (IQR, 11–94 lesions) treated per center. The median lesion size was 35 mm (IQR, 28–47 mm). Almost two thirds of the lesions (64 %) were located in the colon. LST-G was the most frequent type (56 %), with 55 % of the lesions biopsied prior to ESD. Approximately 90 % of the lesions were removed by colorectal ESD at a high-volume center, with 65 % of these procedures performed by more experienced colonoscopists. One fourth of the lesions (25 %) showed poor lifting after SM injection.

Table 1 Baseline demographic and clinical characteristics of the study subjects

		Number		Percent	
Number of lesions		816			
Sex (male/female)		468:348			
Mean age (year (±SD))		67 (±10)			
Median tumor size, mm (IQR)		35 (28–47)			
Tumor location					
Colon	Cecum	520	71	64 %	9 %
	Ascending colon		152		19 %
	Transverse colon		144		18 %
	Descending colon		32		4 %
	Sigmoid colon		121		15 %
Rectum		296		36 %	
Type					
LST-G		459		56 %	
LST-NG		281		34 %	
Protruding		59		7 %	
Recurrent tumor after ER		5		1 %	
Unclassified		12		2 %	
Institution					
High-volume (≥30 patients), 8 institutions		715		88 %	
Low-volume (<30 patients), 7 institutions		101		12 %	
Experience of endoscopist					
More experienced (≥11 years)		531		65 %	
Less experienced (<11 years)		285		35 %	
Lifting after submucosal injection					
Good		608		75 %	
Poor		208		25 %	

Abbreviations: *IQR* interquartile range, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection

Procedures for colorectal ESD

Almost all procedures used CO_2 gas and sodium hyaluronate (Table 2). Various types of electrosurgical endoknives were used. Of the colorectal ESDs, 68 % required one electrosurgical endoknife, with the remaining 32 % requiring two or more. Endoknives with water-jet function were used to remove 29 % of the colorectal ESDs, with only 5 % requiring an endoscopic snare. Most of the colonoscopists (86 %) preferred to use a thin endoscope (thin caliber colonoscope or gastroscope). A gastroscope was used in 25 % of the procedures, whereas endoscopes equipped with a water-jet function were utilized in 70 %.

Therapeutic outcomes

Therapeutic outcomes are shown in Table 3. The median procedure time was 78 min (IQR, 50–120 min). Procedure times were longer than 2 h for 30 % of the lesions and longer than 3 h for about 10 %. We found that 57 % of the lesions were noninvasive high-grade neoplasms, 24 % were noninvasive low-grade neoplasms, and 18 % were invasive adenocarcinomas, including 7 % that were unexpectedly deep (≥1,000 μm) invasive SM cancers. These latter tumors were regarded as incurable by endoscopic local resection and were referred for additional surgery. Almost all the tumors (94 %) were resected *en bloc*, with 6 % requiring piecemeal resection or surgical colectomy.

Perforation occurred in 17 patients (2.1 %). Although most perforations were treated endoscopically using endoclips without surgical intervention, one required emergency surgery. Bleeding occurred in 20 patients (2.2 %), with most (19 patients) being postoperative. One patient with severe uncontrolled intraoperative bleeding required emergency surgery. There were no fatal adverse events.

Factors associated with difficulty and adverse events of colorectal ESD

Tables 4, 5, 6, and 7 show the results of univariate and multivariate analyses of factors associated with technical

Table 2 Devices used for colorectal endoscopic submucosal dissection

	Number	Percent
CO_2	693	85 %
Sodium hyaluronate	788	97 %
Electrosurgical endoknife (multiple choice answers)		
Needle type[a]	806	98 %
IT type[b]	169	21 %
Scissors type[c]	32	4 %
Endoknife with water-jet function	238	29 %
Number of electrosurgical endoknives used		
1	558	68 %
≥2	258	32 %
Snare used	42	5 %
Thin-caliber endoscope (Gastroscope)	703 (205)	86 % (25 %)
Water-jet endoscope	568	70 %

[a] Includes Flushknife (DK2618JN, Fujifilm Medical, Tokyo, Japan), Flushknife BT (DK2618JB, Fujifilm Medical), Dual knife (KD-650Q, Olympus Co, Tokyo, Japan), Hook knife (KD-620QR, Olympus), Flex knife (KD-630 L, Olympus), needle-type bipolar needle knife (BSBK21S45, Xeon Medical Co, Tokyo, Japan), and ball-tipped bipolar needle knife (BSBK21B35, Xeon Medical)

[b] Includes IT knife (KD-610 L, Olympus), IT knife 2 (KD-611 L, Olympus), and IT knife nano (KD-612Q, Olympus)

[c] Includes SB knife (MD-47706, Sumitomo Bakelite, Tokyo, Japan) and SB knife Jr. (MD-47703, Sumitomo Bakelite)

difficulties (failure of *en bloc* resection and long procedure time) and adverse events (perforation and bleeding). Univariate analysis showed that protruding type tumor, low-volume center (<30 neoplasms), lack of sodium hyaluronate use, snare use, poor lifting after SM injection, noninvasive high-grade dysplasia and deeply invasive carcinoma (≥1,000SMμm)

Table 3 Clinical outcomes of colorectal endoscopic submucosal dissection

	Number	Percent
Median procedure time (min (range))	78 (50–120)	
Procedure time ≥2 h	240	30 %
Histology		
Noninvasive low-grade neoplasm	195	24 %
Noninvasive high-grade neoplasm	466	57 %
SM <1,000 μm	88	11 %
SM ≥1,000 μm	62	7 %
Unknown	5	1 %
Completeness of the procedure		
En bloc resection	771	94 %
Piecemeal resection	44	5 %
Unresected	1	1 %
R0 resection	638	78 %

Abbreviation: *SM* submucosa

were possible risk factors associated with failure of *en bloc* resection. Multivariate analysis showed that low-volume center, snare use, and poor lifting after SM injection were independent risk factors associated with failure of *en bloc* resection (Table 4). Factors associated with long procedure time (≥2 h) on univariate analysis included large tumor size (≥4 cm), colonic lesion, LST-NG, protruding-type tumor, low-volume center (<30 lesions), less-experienced endoscopist, CO_2 use, use of two or more electrosurgical endoknives, snare use, noninvasive high-grade neoplasm and deeply invasive carcinoma (≥1,000 μm). On multivariate analysis, large tumor size, low-volume center, less-experienced endoscopist, CO_2 use, and use of two or more electrosurgical endoknives were independent risk factors for long procedure time (Table 5).Univariate analysis showed that poor lifting after SM injection was the only risk factor associated with perforation (Table 6). Factors associated with bleeding on univariate analysis included rectal lesions and lack of thin-type endoscope (Table 7).

Poor lifting after SM injection occurred more frequently in LST-NG and in protruding and recurrent lesions than in LST-G, with the incidence of poor lifting after SM injection being extremely high (80 %) for recurrent lesions, although the incidence of poor lifting was not related to history of biopsy (Table 8).

Discussion

We found that colorectal ESD yielded satisfactory outcomes in this prospective cohort treated at several participating institutions with various levels of experience. Acceptable outcomes of colorectal ESD have also been reported in western countries, but improvements are needed because of its technical difficulties [23]. Adverse events such as perforation and bleeding [13] have been reported, as have failure of *en bloc* resection and long procedure time. We therefore assessed factors independently associated with these technical difficulties and adverse events.

We found that poor lifting after SM injection was independently associated with failure of *en bloc* resection and with increased perforation. Poor lifting after SM injection is thought to be associated with fibrosis in the SM layer. In single center trials, fibrosis was reported related to failure of *en bloc* resection and perforation [20]; and tumor size and the presence of fibrosis were found to be independent risk factors for perforation [24, 25]. Although a multicenter trial showed that only large tumor size and performance of the procedure at a low-volume institution were risk factors for perforation and postoperative bleeding, that trial did not assess lifting condition or fibrosis [13]. Our finding, that poor lifting was a significant risk factor for failure of *en bloc* resection and

Table 4 Univariate ($p \leq 0.2$) and multivariate logistic analyses of factors associated with failure of *en bloc* resection during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	*En bloc* resection	Failure of *en bloc* resection	*p* value	Adjusted OR	95 % CI	*p* value
Institution (*n*; %)						
High volume (≥30 patients)	682/715 (95)	33/715 (5)				
Low volume (<30 patients)	89/101 (88)	12/101 (12)	0.0008	5.52	2.25–13.37	0.0003
Snare						
−	744 /774 (95)	30/774 (4)				
+	27/42 (64)	15/42 (36)	<0.001	25.32	10.37–63.94	<0.0001
Lifting condition after SM injection						
Good	590/608 (97)	18/608 (3)				
Poor	181/208 (87)	27/208 (13)	<0.001	10.74	4.49–25.18	<0.0001

Abbreviations: *OR* odds ratio, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

adverse events, was similar to the results of these earlier trials. The causes of fibrosis are not completely known, but we frequently observed the lesions with poor lifting in LST-NG and in protruding and recurrent lesions. These findings suggest that endoscopists in low-volume centers should start by performing colorectal ESDs on LST-G lesions.

We also found that performance of ESD at a low-volume institution was an important risk factor for failure of *en bloc* resection and long procedure time. Similarly, another study reported that the total number of ESDs performed per institution was inversely associated with the incidence of adverse events [13]. In this study, institutions performing fewer than ten colorectal ESDs per year were regarded as low-volume centers and these institutions should be selective in performing colorectal ESD. Unfortunately, we could not collect the colorectal ESD volume of each colonoscopist and we had to assess the experience of ESD by each institution, not by each colonoscopist. However, since colorectal ESD is a technically challenging and relatively rare procedure, we expect that within each institution such cases are performed by

Table 5 Univariate ($p \leq 0.2$) and multiple regression analyses of factors associated with longer procedure time (≥2 h) during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	<2 h	≥2 h	*p* value	OR	95 % CI	*p* value
Tumor size (%)						
<4 cm	396/477 (83)	81/477 (17)				
≥4 cm	180/339 (53)	159/339 (47)	<0.0001	4.97	3.35–7.47	<0.0001
Institution (*n* (%))						
High volume (≥30 patients)	516/715 (72)	199/715 (28)				
Low volume (<30 patients)	60/101 (59)	41/101 (41)	0.01	2.75	1.59–4.78	0.0003
Endoscopist						
Experienced	400/531 (75)	131/531 (25)				
Less experienced	176/285 (62)	109/285 (38)	<0.0001	2.31	1.61–3.34	<0.0001
CO_2						
−	98/123 (80)	25/123 (20)				
+	478/693 (69)	215/693 (31)	0.02	2.02	1.17–3.61	0.012
Number of electrosurgical endoknives used						
1	425/558 (76)	133/558 (24)				
≥2	151/258 (58)	107/258 (42)	<0.0001	2.48	1.70–3.62	<0.0001

Abbreviations: *OR* odds ratio, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

Table 6 Univariate analysis of factors associated with perforation during colorectal endoscopic submucosal dissection

	Univariate analysis		
Variable	Perforation (−)	Perforation (+)	*p* value
Institution (*n* (%))			
High volume (≥30 patients)	702/715 (98)	13/715 (2)	
Low volume (<30 patients)	97/101 (96)	4/101 (4)	0.15
Snare			
−	760/774 (98)	14/774 (2)	
+	39/42 (93)	3/42 (7)	0.05
Lifting condition after submucosal injection			
Good	601/608 (99)	7/608 (1)	
Poor	198/208 (95)	10/208 (5)	0.003

Abbreviations: *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

Table 8 Relationship between poor lifting after submucosal injection and lesion characteristics

	Poor lifting after SM injection		*p* value
	Incidence (%)	*n*	
Type			
LST-G	16 %	(73/459)	<0.01
LST-NG	38 %	(108/281)	
Protruding	32 %	(19/59)	
Recurrent	80 %	(4/5)	
Unclassified	33 %	(4/12)	
History of biopsy			
Positive	27 %	(119/446)	0.42
Negative	24 %	(89/370)	

Abbreviations: *SM* submucosa, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor

or with the assistance of the most experienced ESD operator whenever possible. Therefore, we believe that the institutional experience with colorectal ESD is an accurate and adequate surrogate marker for the colonoscpists' ESD experience.

The mechanisms by which rectal location and lack of use of a thin-type endoscope enhance bleeding are unclear. Lesion location in the colon has been reported to be a significant risk factor for delayed bleeding following colonic EMR for large lesions [26]. By contrast, we found that the risk of bleeding was lower for lesions in the colon than the rectum. Differences between the two studies may be due to differences in the resection method (EMR vs. ESD), the race or ethnic background of the patients, and/or lesion characteristics. However, we found that the incidence of bleeding after endoscopic resection for large superficial colorectal tumors was lower (2.2 %) than previously reported (7 %) [26]. This difference may have been due to post-ESD coagulation (PEC), which uses a coagulation forceps to prevent bleeding by visible blood vessels in the resection area [27]. As PEC is not usually performed after conventional EMR, it may explain the reduced bleeding rate after ESD and the different characteristics of bleeding after EMR and ESD. Additionally, thin-type endoscopes are flexible, making it easier for them to access any part of mucosal defects after colorectal ESD. Use of these endoscopes would better detect visible vessels on the mucosal defect after colorectal ESD, resulting in a reduction in bleeding rate due to easier coagulation. Moreover, CO_2 and multiple endoknives use were also independent risk factors for longer ESD procedure time in our study, although CO_2 was reported to reduce the procedure time of colorectal ESD and endoknives are generally used to make the procedure easier [28]. We suppose these are not causative factors but rather than the opposite, symptoms of an expected complicated clinical situation. That is, the endoscopists may tend to use CO_2 or multiple endoknives for especially difficult cases.

Although our prospectively collected large sample size was one of the strengths of this trial, our results may have been limited by selection bias. Our study subjects consisted of consecutive patients who underwent endoscopic resection in a prospective cohort trial, but more than half the subjects screened underwent EMR [16, 17]. Flat-type lesions, rectal lesions, and SM cancers were more frequently removed by ESD than by EMR. Additionally, the mean lesion size was larger in the ESD than in the EMR group (39.4 vs. 26.4 mm). Despite any possible selection bias, however, the *en bloc* resection rate was greater for ESD than for conventional EMR (94.5 vs. 56.9 %). Moreover, of the 816 lesions removed by ESD, 140 (17.2 %) showed unfavorable results (failure of

Table 7 Univariate analysis of factors associated with bleeding during colorectal endoscopic submucosal dissection

	Univariate analysis		
Variable	Bleeding (−)	Bleeding (+)	*p* value
Location (*n* (%))			
Colon	513/520 (99)	7/520 (1)	
Rectum	285/296 (96)	11/296 (4)	0.04
CO_2			
−	117/123 (95)	6/123 (5)	
+	679/693 (98)	14/693 (2)	0.1
Thin-type endoscope			
−	105/113 (93)	8/113 (7)	
+	691/703 (98)	12/703 (2)	0.003

Abbreviations: *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

en bloc resection, perforation, bleeding or operation time longer than 2 h), indicating that colorectal ESD remains difficult even after selection. Although the necessity of *en bloc* resection for colorectal neoplasm is controversial, especially in western countries, *en bloc* resection is superior to piecemeal resection in eliminating residual tumor and for accurate histopathological assessment of the resected specimen [4]. We found that 18 % of the enrolled lesions were invasive adenocarcinomas, including 7 % that were unexpectedly deep (≥1,000 μm) invasive SM cancers. Examination of a single resected specimen would be more accurate in assessing lymphovascular involvement and depth of tumor invasion. Moreover, no one knows long-term outcomes after piecemeal resection for large colorectal tumor so far. We believe that endoscopists should therefore attempt to resect these lesions *en bloc*, with the information about these technical difficulties being valuable for training endoscopists and for selecting patients at less experienced institutions for colorectal ESD. Additionally, we cannot exclude the possibility that as yet unknown associated factors may have been omitted from multivariate analysis, despite our careful selection of variables. Moreover, we could not assess the effect of lesion location on technical difficulty, although colorectal ESD is considered more technically challenging in certain locations (e.g., transverse colon and flextures). Thus, such opinion is not generally established.

In conclusion, we found that the outcomes of colorectal ESD in a large cohort of patients at participating institutions with various levels of experience were satisfactory. We found that poor lifting after SM injection was the most frequent risk factor for technical difficulty and adverse events. The lesions with poor lifting were frequently observed in LST-NG and in protruding and recurrent lesions. These findings suggest that less experienced endoscopists should start by performing colorectal ESDs on LST-G lesions.

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Potential perioperative advantage of colorectal endoscopic submucosal dissection versus laparoscopy-assisted colectomy

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Abstract
Background Endoscopic submucosal dissection (ESD) has recently provided a new treatment strategy for large colorectal neoplasms, as an alternative to laparoscopy-assisted colectomy (LAC). Prospective comparative data on the perioperative course of ESD vis-à-vis LAC are scarce.
Methods We prospectively evaluated the perioperative course of colorectal ESD in 300 patients. We evaluated *en bloc* and curative resection, procedure duration, postoperative parameters [white blood cell count (WBC), C-reactive protein (CRP), and hemoglobin], pain, recovery duration (time to achieve full mobilization, normal diet, and length of hospitalization), and complications. We also prospectively evaluated 190 patients undergoing LAC as a control group.
Results The median size of the lesions was 30 mm for ESDs (LACs: 20 mm). The median procedure time was 90 min for ESDs (LACs: 185 min). Postoperative pyrexia was reported in 4 % of ESDs (LACs: 54 %). Only 4 % of ESDs required analgesia (LACs: 61 %). Between the preoperative period and postoperative day 1, the mean difference in WBC and CRP was +1,300/μl for ESDs (LACs: +3,100/μl), and +0.91 mg/dl for ESDs (LACs: +3.96 mg/dl), respectively. A ≥2 g/dl decrease in hemoglobin was observed in 5 % of ESDs (LACs: 30.0 %). Complications were seen in 7 % of ESDs (LACs: 15 %). The rate of delayed bleeding and perforation was 5 and 1.7 % of ESDs, respectively. Although only one of them required laparotomy for peritonitis caused by delayed perforation, others could be managed endoscopically. Additional LAC was required in 16 ESDs due to redefined risk for lymph node metastases. The median hospital stay was 5 days for ESDs (LACs: 10 days). These were consecutive patients with prospective data collection.
Conclusions Colorectal ESD is effective, minimally invasive and safe in terms of periperative clinical course. Colorectal ESD provides advantages for treatment of large adenomas and early cancers with no risk of lymph node metastasis.

Keywords Colon · Early colorectal cancer · Endoscopic submucosal dissection · Laparoscopy-assisted colectomy · Quality of life

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Conventional endoscopic mucosal resection (EMR) is technically inadequate for *en bloc* resection of early

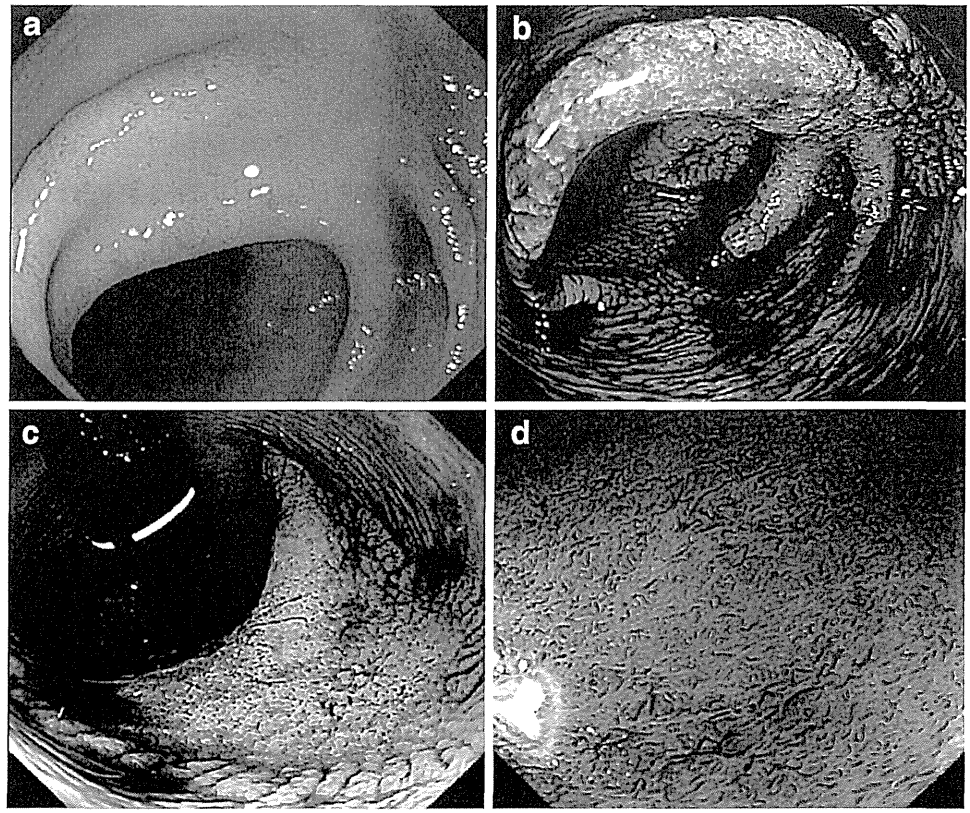

Fig. 1 Endoscopic diagnosis before ESD (Case 1). **A** A 0-IIa + IIc non-granular type laterally spreading tumor (LST-NG) 70 mm in size located in the transverse colon. **B**, **C** Lesion margins delineated before ESD using 0.4 % indigo–carmine spray dye. **D** Magnification colonoscopy with crystal violet (0.05 %) staining clearly revealed III_s and III_L pit patterns in the depressed area, suggesting a non-invasive tumor and indicating a good candidate for endoscopic treatment

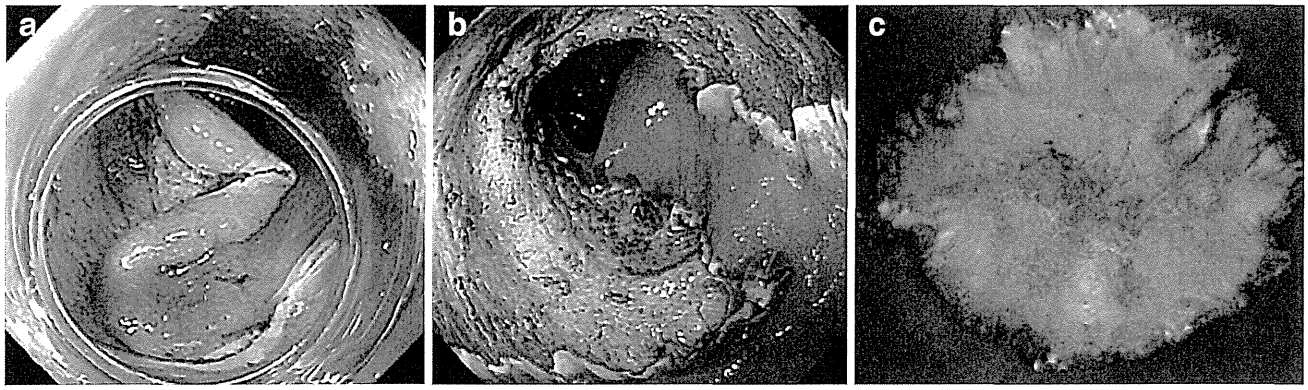

Fig. 2 Images of colonic ESD (Case 1). **A** After injection of glycerol (10 % glycerol and 5 % fructose in normal saline solution) and sodium hyaluronate acid solution into SM layer, partial circumferential incision performed by using bipolar needle knife. SM dissection performed by using a bipolar needle knife and insulation-tipped knife. **B** *En bloc* resection was completed. **C** Histology of resected specimen 70 × 55 mm in diameter revealed intramucosal cancer with tumor-free margin

colorectal cancer ≥20 mm. Endoscopic piecemeal mucosal resection is associated with a high incidence of local recurrence or suboptimal estimation of pathological invasion depth [1–3].

Endoscopic submucosal dissection (ESD) was initially developed for early gastric cancer and facilitates the resection of large superficial tumors *en bloc* despite the lesion size [4–8]. The introduction of ESD, consequently, has enabled effective treatment of large colorectal tumors and local recurrent lesion after EMR that would previously have been treated by laparoscopy-assisted colectomy (LAC), not only in Asian countries such as Japan, Korea and China, but also in several western countries [9–16] (Figs. 1, 2, 3, and 4). Colorectal ESD, however, can take longer to perform than EMR, according to the location or size of the lesions. ESD is, in addition, technical difficult and may also carry the risk of perforation or peritonitis due to the thin muscularis layer of the colon [17].

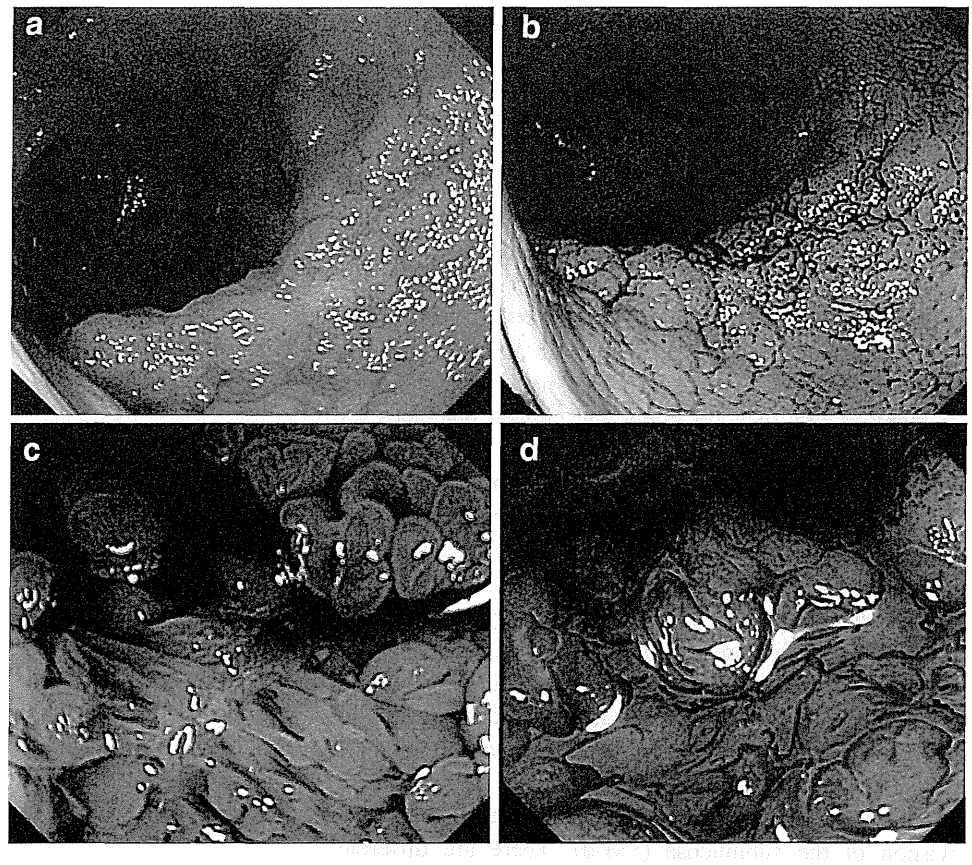

Fig. 3 Endoscopic diagnosis before ESD (Case 2). **A** A recurrent tumor was identified at the scar site of a previous endoscopic mucosal resection in the lower rectum. **B** Lesion margins delineated using 0.4 % indigo–carmine spray dye. **C** Magnification colonoscopy with indigo–carmine dye revealed scarring and non-invasive IV pit pattern in this lesion. **D** Crystal violet (0.05 %) staining revealed IV pit pattern suggesting non-invasive tumor and indication of ESD

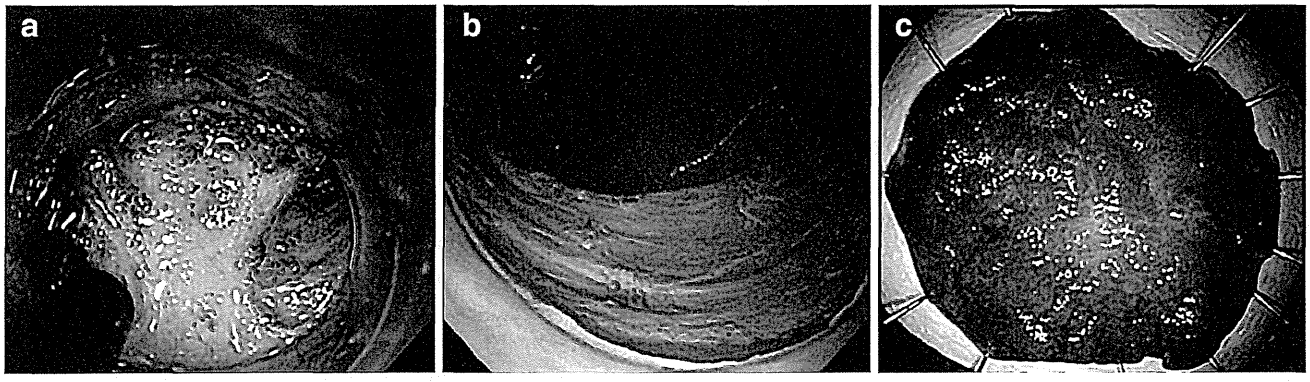

Fig. 4 Images of rectal ESD (Case 2). **A** ESD was performed. Marked fibrosis was observed during the procedure. **B** ESD was completed without any complications. **C** Histology of resected specimen (*en bloc* resection) 60 × 40 mm in diameter revealed intramucosal cancer with tumor-free margin

In many cases outside Japan, LAC, which is less invasive than open surgery, is still performed even if the lesion is a good indication for colorectal ESD. Such lesions include adenoma, with mucosal or shallow submucosal (SM) invasion <1,000 μm from the muscularis mucosae (SM-s), with negligible risk of lymph node metastasis. The standard techniques and safety of LAC have been established, and especially in the colon, it is less invasive and does not adversely affect postoperative quality of life (QOL).

Colorectal ESD, in contrast to LAC or open colectomy, allows intraoperative management by utilizing conscious sedation (midazolam or pentazocine hydrochloride), and does not require general anesthesia with intratracheal intubation. We can, therefore, avoid the risk associated with general anesthesia. Patients who undergo colorectal ESD, in addition, can start walking soon after treatment and achieve early recovery of physical ability. These patients can also resume food intake in the early stage because intestinal tract anastomosis is not required for