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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Conflict of interests None of the authors has any financial relationships to disclose relevant to this publication.

References

1. Soetikno RM, Gotoda T, Nakanishi Y et al (2003) Endoscopic mucosal resection. Gastrointest Endosc 57:567–579
2. Japanese Society for Cancer of the Colon and Rectum (2009) Japanese classification of colorectal carcinoma. Second English Edition. Tokyo: Kanehara & Co Ltd
3. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58:S3–S43
4. Iishi H, Tatsuta M, Iseki K et al (2000) Endoscopic piecemeal resection with submucosal saline injection of large sessile colorectal polyps. Gastrointest Endosc 51:697–700
5. Moss A, Bourke MJ, Williams SJ et al (2011) Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 140:1909–1918
6. Terasaki M, Tanaka S, Oka S et al (2012) Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. J Gastroenterol Hepatol 27:734–740
7. Hotta K, Fujii T, Saito Y et al (2009) Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 24:225–230
8. Saito Y, Kawano H, Takeuchi Y et al (2012) Current status of colorectal endoscopic submucosal dissection in Japan and other Asian countries: progressing towards technical standardization. Dig Endosc 24(Suppl 1):67–72
9. Uraoka T, Parra-Blanco A, Yahagi N (2012) Colorectal endoscopic submucosal dissection in Japan and Western countries. Dig Endosc 24:80–83
10. Fujishiro M, Yahagi N, Kakushima N et al (2007) Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol 5:678–683
11. Lee EJ, Lee JB, Lee SH et al (2013) Endoscopic submucosal dissection for colorectal tumors–1,000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc 27:31–39
12. Saito Y, Uraoka T, Yamaguchi Y et al (2010) A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 72:1217–1225
13. Nakajima T, Saito Y, Tanaka S et al (2013) Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc 27:3262–3270
14. Oka S, Tanaka S, Saito Y et al. Multicenter prospective study on local recurrence after endoscopic resection of large colorectal neoplasia conducted by the colorectal endoscopic resection standardization implementation working group of Japanese society for cancer of the colon and rectum. Endoscopy 2012;44:A70 [abstract]
15. von Elm E, Altman DG, Egger M et al (2007) STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457
16. Tanaka S, Oka S, Chayama K (2008) Colorectal endoscopic submucosal dissection: present status and future perspective, including its differentiation from endoscopic mucosal resection. J Gastroenterol 43:641–651
17. Tanaka S, Terasaki M, Kanao H et al (2012) Current status and future perspectives of endoscopic submucosal dissection for colorectal tumors. Dig Endosc 24(Suppl 1):73–79
18. Moss A, Bourke MJ, Tran K et al (2010) Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. Endoscopy 42:400–404
19. Kudo S, Lambert R, Allen JI et al (2008) Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 68:S3–S47
20. Matsumoto A, Tanaka S, Oba S et al (2010) Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. Scand J Gastroenterol 45:1329–1337
21. Schlemper RJ, Riddell RH, Kato Y et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
22. Cotton PB, Eisen GM, Aabakken L et al (2010) A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 71:446–454

23. Probst A, Golger D, Anthuber M et al (2012) Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy 44:660–667
24. Kim ES, Cho KB, Park KS et al (2011) Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. Endoscopy 43:573–578
25. Lee EJ, Lee JB, Choi YS et al (2012) Clinical risk factors for perforation during endoscopic submucosal dissection (ESD) for large-sized, nonpedunculated colorectal tumors. Surg Endosc 26: 1587–1594
26. Metz AJ, Bourke MJ, Moss A et al (2011) Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. Endoscopy 43:506–511
27. Takizawa K, Oda I, Gotoda T et al (2008) Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection—an analysis of risk factors. Endoscopy 40:179–183
28. Saito Y, Uraoka T, Matsuda T et al (2007) A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. Gastrointest Endosc 65:537–542

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

Fumihiko Nakamura · Yutaka Saito · Taku Sakamoto · Yosuke Otake · Takeshi Nakajima · Seiichiro Yamamoto · Yoshitaka Murakami · Hideki Ishikawa · Takahisa Matsuda

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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

F. Nakamura (✉) · Y. Saito · T. Sakamoto · Y. Otake · T. Nakajima · T. Matsuda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: jymxg256@ybb.ne.jp

Y. Saito
e-mail: ytsaito@ncc.go.jp

F. Nakamura
Digestive Disease Center, Kohseichuo General Hospital, Tokyo, Japan

S. Yamamoto
Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

S. Yamamoto
Department of Surgery, Hiratsuka City Hospital, Kanagawa, Japan

Y. Murakami
Department of Health Science, Shiga University of Medical Science, Shiga, Japan

H. Ishikawa
Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan

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

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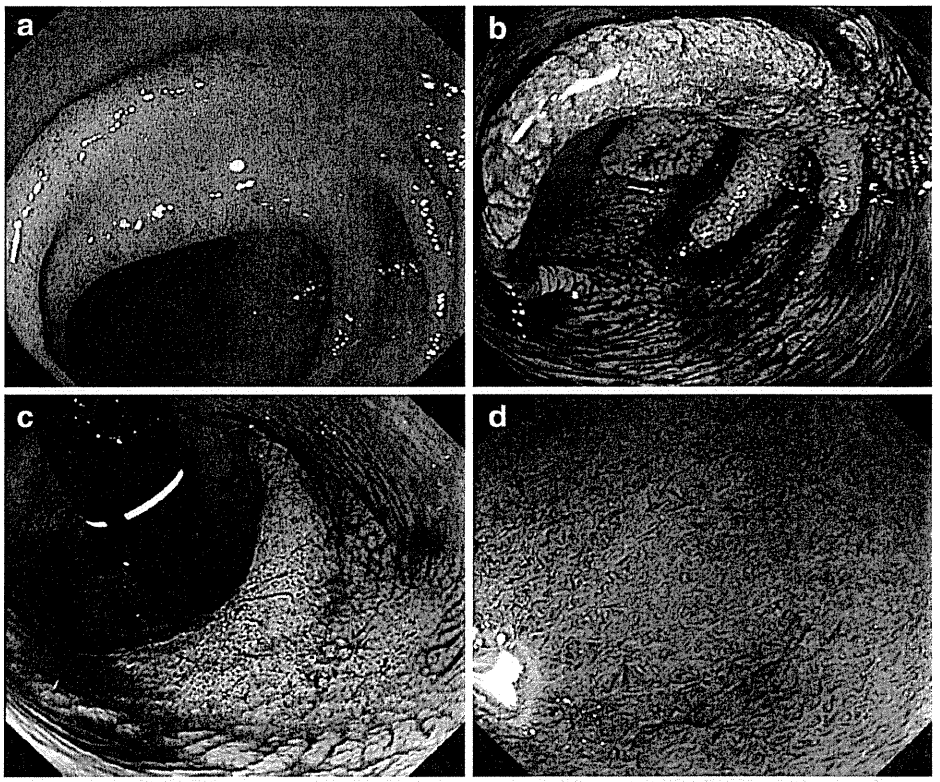

Fig. 1 Endoscopic diagnosis before ESD (Case 1). **A** A 0-IIa + IIc non-granular type laterally spreading tumor (LST-NG) 70 mm in size located in the transverse colon. **B**, **C** Lesion margins delineated before ESD using 0.4 % indigo–carmine spray dye. **D** Magnification colonoscopy with crystal 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

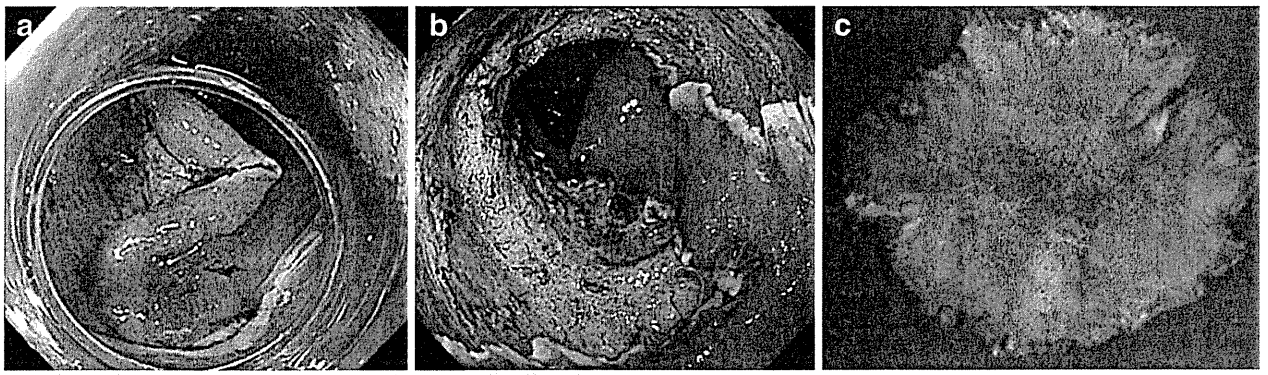

Fig. 2 Images of colonic ESD (Case 1). **A** After injection of glycerol (10 % glycerol and 5 % fructose in normal saline solution) and sodium hyaluronate acid solution into SM layer, partial circumferential incision performed by using bipolar needle knife. SM dissection performed by using a bipolar 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].

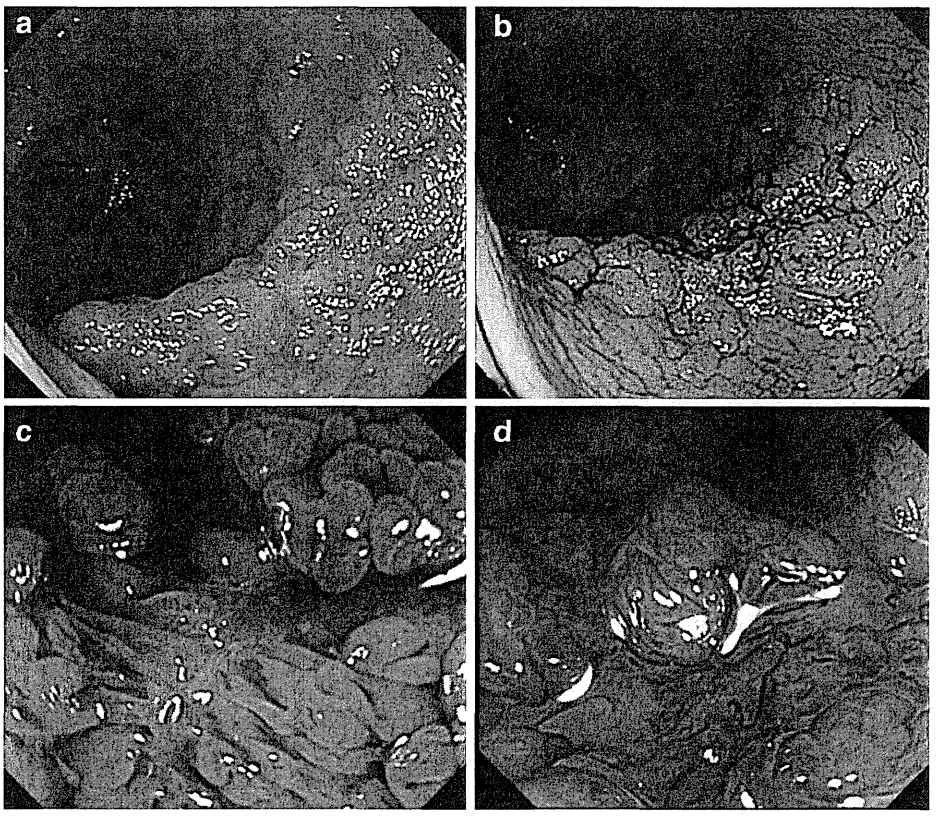

Fig. 3 Endoscopic diagnosis before ESD (Case 2). **A** A recurrent tumor was identified at the scar site of a previous endoscopic mucosal resection in the lower rectum. **B** Lesion margins delineated using 0.4 % indigo–carmine spray dye. **C** Magnification colonoscopy with indigo–carmine dye revealed 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

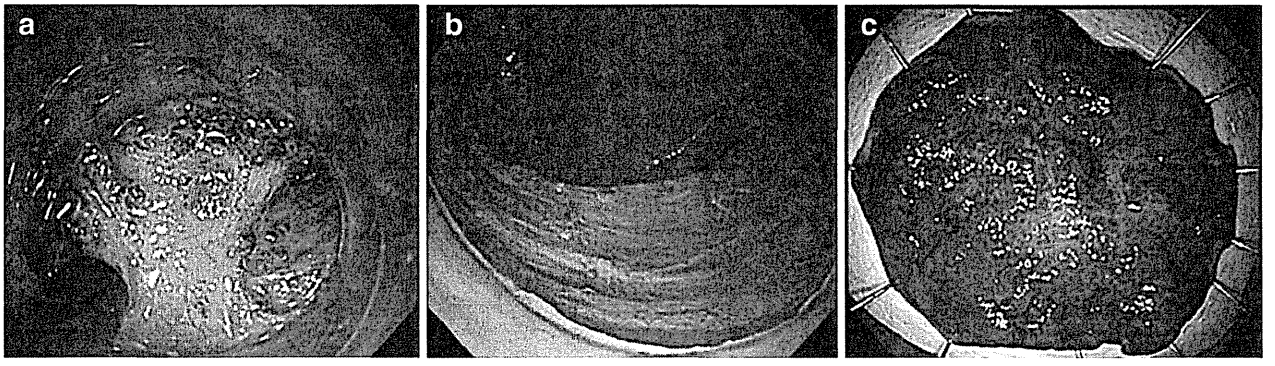

Fig. 4 Images of rectal ESD (Case 2). **A** ESD was performed. Marked fibrosis was observed during the procedure. **B** ESD was completed without any complications. **C** Histology of resected specimen (*en bloc* resection) 60 × 40 mm in diameter revealed intramucosal cancer with tumor-free margin

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

ESD. Another key factor is that anorectal function can be absolutely preserved in rectal ESD.

We have previously reported that rectal ESD significantly decreases the incidence of local recurrence and preserves postoperative QOL, compared with transanal resection [18]. In Korea, a comparison between ESD and transanal endoscopic microsurgery (TEM), the former was less invasive, although there was no significant difference in clinical outcome between the groups [19]. Rectal ESD has recently been introduced in western countries too [20].

In some industrialized institutions or hospitals, ESD is performed for rectal as well as colonic neoplasms and there are many reports of good safety and clinical outcomes for colorectal ESD.Kiriyama and Saito et al. reported good clinical outcomes for colorectal ESD compared with LAC [21]. There are, however, no data to compare the perioperative clinical course after colorectal ESD and LAC, although several prospective studies on colorectal ESD have been reported. It is important to clarify objectively the invasiveness and safety of colorectal ESD as well as its effectiveness.

The primary indication for colorectal ESD used as a local treatment without lymph node dissection is non-invasive lesions diagnosed as adenoma, mucosal, or SM-s colorectal cancer. The absolute indication for LAC with lymph node dissection is T1 colorectal cancer with deep invasion of the submucosa (SM-d). There are different indications and procedures for the two methods and simple comparison is not possible. Considering the present position, in which LAC is still performed instead of colorectal ESD for lesions with less than SM-s invasion in the world, we decided to compare colorectal ESD with LAC for T1 cancer. We prospectively evaluated the perioperative clinical course of colorectal ESD and LAC. Preoperative diagnostic accuracy was also calculated.

Materials and methods

Patients

We prospectively enrolled ESD patients diagnosed with adenoma or T1 cancer with less than SM-s invasion at the preoperative conference of the Endoscopy Division, National Cancer Center Hospital (NCCH) in Tokyo, Japan, from January 2009 to March 2012. We also prospectively enrolled a control group at the preoperative joint conference between Endoscopy Division and Colorectal Surgery Division in NCCH. This comprised patients who underwent LAC for SM-d cancer (cT1) diagnosed endoscopically or pathologically after endoscopic treatment. Patients who underwent ESD in our institute have the possibility of requiring additional LAC after histological examination of the excised sample. Since this research is observational study and the process until LAC is completed in such case is a series of clinical course on the basis of colorectal ESD, such cases were decided to be included in the ESD group in this study. All patients gave written informed consent for the endoscopic and surgical resections prior to treatment. This study was performed in accordance with the Helsinki Declaration.

Exclusion criteria

Exclusion criteria were: (1) non-neoplastic polyps; (2) familial adenomatous polyposis; or (3) submucosal tumor.

Preoperative diagnosis

Preoperative diagnosis was performed by colonoscopy with magnifying function (CF-HQ290I, CF-H260AZI, PCF-Q240ZI, or PCF-Q260AZI; Olympus Medical Systems Corp., Tokyo, Japan). All lesions were subjected to pit pattern analysis by magnifying chromoendoscopy (MCE) with indigo–carmine dye (0.4 %) and narrow-band imaging (NBI) system. If type V pit pattern was suspected, we also performed estimation by MCE using crystal violet staining (0.05 %). Invasive pattern is used as an index for SM-d cancer [25].

ESD procedure

ESD was carried out with a PCF-Q240JI, PCF-Q260AZI or GIF-Q260J endoscope (Olympus Medical Systems Corp., Tokyo, Japan) equipped with a short type small caliber-tip transparent hood (Fujifilm Corp., Tokyo, Japan) fitted to the tip of the endoscope to retract the SM layer, thereby facilitating dissection. The procedures were primarily performed using a bipolar needle knife (Xeon Medical Corp., Tokyo, Japan) and insulation-tipped knife (Olympus Medical Systems Corp., Tokyo, Japan). Midazolam (2 mg intravenously) and pentazocine hydrochloride (15 mg intravenously) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. Bipolar hemostatic forceps (Pentax Corp., Tokyo, Japan) were used for hemostasis of bleeding. CO_2 insufflation was used instead of air insufflation to reduce patient discomfort. Lesion margins were delineated before ESD using 0.4 % indigo–carmine spray dye. After injection of 10 % glycerol and 5 % fructose in normal saline solution (glycerol; Chugai Pharmaceutical Corp., Tokyo, Japan) and sodium hyaluronate acid (Muco-up; Johnson & Johnson Corp., Tokyo, Japan) into the SM layer, a circumferential incision was made using a bipolar needle knife, and ESD was the performed using one or two ESD knives.

LAC procedure

One of three expert colorectal surgeons performed LAC according to standard procedures with the patient under general anesthesia. Four trocar incisions were used, which were followed by resection of the diseased colon and rectum, a D2 lymph node dissection, and functional end-to-end anastomosis in the colon or double-stapling anastomosis in the rectum. In some patients with tumors located in the lower rectum, temporary ileostomies were performed as the surgeon judged appropriate.

Histopathological assessment

The endoscopically resected specimens, after being fixed in formalin, were sectioned serially at 2–3 mm intervals and the surgically resected specimens at 4–5 mm intervals. Histological diagnosis was based on the Japanese Research Society for Cancer of the Colon and Rectum (JSCCR) and the Vienna classification. Invasion depth of early colorectal cancer was subclassified as adenoma, pTis (M), pT1a (SM-s), pT1b (SM-d) or defined as category 5.1 (intramucosal carcinoma) or category 5.2 (SM carcinoma) according to the Vienna classification of gastrointestinal epithelial neoplasia. The depth of SM tumor invasion was measured between lower muscularis mucosae and the tumor invasive top. If the muscularis mucosae were disrupted by tumor invasion, the depth was measured from the surface of the tumor. In the SM carcinoma, the depth of SM invasion which was <1,000 μm was diagnosed as pT1a (SM-s), while one which was more than 1,000 μm was diagnosed as pT1b (SM-d) in accordance with the JSCCR guideline [22].

Postoperative analysis

We analyzed (1) operation duration, *en bloc* resection and curative resection; (2) postoperative pyrexia requiring analgesic drugs (non-steroidal anti-inflammatory drugs, pentazocine hydrochloride, or fentanyl), early laboratory investigation, hospitalization, early resumption of normal activities such as walking, drinking and eating; and (3) any complications associated with the procedure.

Curative resection was defined as free margins, SM invasion <1,000 μm from the muscularis mucosae without lymphovascular invasion, a poorly differentiated adenocarcinoma component [22]. ESD procedure time was measured from the initial incision to complete removal of the tumor. LAC procedure time was calculated from the start of the operation to its completion. Analgesic use was related to the presence of postoperative pain, and consisted of non-steroidal anti-inflammatory drugs, pentazocine hydrochloride, or fentanyl. We examined the patients on morning and evening ward rounds as well as reference of their charts to register it prospectively. We validated the results of early laboratory investigations. The mean differences in white blood cell count (WBC) and C-reactive protein (CRP) level between the preoperative period and postoperative day (POD) 1 were calculated. Decreases in hemoglobin level of ≥2 g/dl were noted. We assessed patients for resumption of normal activities such as walking, fluid and food intake, and hospital stay, at round visits and from their chart records. We analyzed complications associated with the procedures. In the ESD group, perforation, penetration, peritonitis, and delayed bleeding were assessed prospectively as major complications and anesthesia complications as minor complications. In the LAC group, major complications (anastomotic leakage, peritonitis, and delayed bleeding) and minor complications (ileus, wound infection and dehiscence, and anesthesia complications) were also analyzed prospectively. The rate of diverting stoma due to postoperative adverse event (perforation, anastomotic leakage, or delayed bleeding) was also considered as a major complication in both groups. Total cases of stoma, in addition, were analyzed.

Preoperative endoscopic diagnostic accuracy was also calculated, excluding the cases in which accurate estimation of histopathological invasion depth of resected specimen were difficult. Accordance between preoperative endoscopic estimation and histopathological invasion depth (M-SM-s or SM-d) was defined as proper diagnosis.

Statistical analysis

Statistical differences were analyzed using the Wilcoxon signed-rank test, Mann–Whitney U test, and χ^2 test. A two-tailed P value below 0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, version 10.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

We excluded three cases of non-neoplastic polyps in the ESDs; three cases of familial adenomatous polyposis in the LACs; one case of submucosal tumor in the ESDs. Moreover, two cases in the ESDs for which postoperative information, including blood analysis data, was lacking were excluded in this study term. This left a final total of 300 ESDs that were included in the study. Among these, 16 required additional LAC based on pathological assessment after ESD: one case with SM-s carcinoma with lymphovascular invasion and 15 with SM-d carcinoma.There were 190 cases enrolled in the LACs.

Table 1 Clinical characteristics of patients

	No. (%) ESDs	No. (%) LACs
Number	300 (ESD + LAC: 16)	190
Age, median (range), y	68 (36–98)	65 (20–86)
Male	157 (52.3)	101 (53.2)
Size, median (range), mm	30 (8–110)	20 (8–150)
Location (rectum/colon)	83/217 (27.7/72.3)	33/160 (17.4/82.6)

The median age was 68 years in the ESDs (range 36–98 years) and 65 years (20–86 years) in the LACs. The male to female ratio was 1.1:1 in both groups. The median tumor size was 30 mm (range 8–110 mm) in the ESDs and 20 mm (8–150 mm) in the LACs (Table 1).

In the ESDs, 232 patients (77.3 %) had laterally spreading tumors (LSTs); these comprised 140 granular LSTs (LST-G) (46.7 %) and 92 non-granular LSTs (LST-NG) (30.7 %). In the LACs, there were 106 non-LSTs (55.8 %) and 19 LSTs (11 LST-G and 8 LST-NG) (10.0 %). Sixty-five (34.2 %) of the operations in the LACs were for post-EMR lesions because of non-curative resection. Twenty (6.7 %) of all ESDs were for local recurrence after previous endoscopic resection. Three cases (1.6 %) of local recurrence required LAC. Two of these were diagnosed as SM-d carcinoma by preoperative colonoscopy at NCCH. The other had lymph vessel invasion diagnosed by histological examination of the resected specimen at the referring hospital.

For histopathological diagnosis, 276 lesions (92.3 %) were adenoma or mucosal to SM-s carcinomas, and 21 lesions (7.0 %) were SM-d carcinomas. Although seven of 21 cases of SM-d carcinomas were suspected at preoperative colonoscopy, ESD was carried out diagnostically in accordance with the age, general status, and wish of the patient. In the LACs, 154 (81.0 %) of all cases were SM-d carcinomas and 34 (17.9 %) were mucosal to SM-s carcinomas. In 34 mucosal and SM-s carcinomas further analysis revealed that 13 cases had lymphovascular infiltration or positive vertical margin (pVM) on pathological analysis after EMR in our hospital or the referring hospital. Four cases did not have an indication for ESD because of invasion to the appendix orifice, and two cases underwent LAC at the outset at the patients' request. Eight patients were selected for LAC because of large protruding lesions (Paris type 0-Is, >40 mm diameter) such as villous tumors, which were likely to be indicated for multiple piecemeal resection or perforation on preoperative endoscopic examination. Only seven cases were mucosal to SM-s carcinomas, although these were suspected of SM-d carcinomas on preoperative colonoscopy.

Table 2 Tumor features (LSTs versus non-LSTs) and pathological tumor depth

	No. (%) ESDs (n = 300)	No. (%) LACs (n = 190)
LSTs	232 (77.3)	19 (10.0)
Granular	140	11
Non-granular	92	8
Non-LSTs	68 (22.7)	106 (55.8)
Protruding	21	24
Depressed	27	79
Local recurrence	20	3
Scar from previous EMR	–	65 (34.2)
Pathological tumor depth		
M-SM-s	277 (92.3)	34 (17.9)
SM-d	21 (7.0)	154 (81.0)
Unknown	2 (0.67)	2 (1.1)

LST laterally spreading tumor, *EMR* endoscopic submucosal resection, *M* mucosa, *SM-s* submucosal invasion <1,000 μm from the muscularis mucosae, *SM-d* submucosal invasion 1,000 μm or more from the muscularis mucosae

Table 3 Clinical outcomes: effectiveness (procedure time, en bloc, and curative resection)

	No. (%) ESDs (n = 300)	No. (%) LACs (n = 190)	P value
Procedure time, median (range), min	90 (15–540)	185 (48–449)	<0.001
En bloc resection	275 (91.7)	–	
Curative resection[a]	273 (91.0)	–	

[a] Curative resection : free margin, submucosal invasion with <1,000 μm from muscularis mucosae without lymphovascular invasion, a poorly differentiated component

In two (0.67 %) of the ESDs and two (1.1 %) of the LACs, pathological evaluation was difficult even after retrospective reviews (Table 2).

Preoperative endoscopic diagnostic accuracy

In two cases in the ESDs, we were unable to obtain accurate pathological information. Sixty-five cases in the LACs (2 of which also had difficult pathological examination) had scarring from previous EMR. All these cases were excluded from the present analysis.

Preoperative endoscopic diagnostic accuracy on the depth of invasion was 95 % (282/298) in the ESDs and 93 % (116/125) in the LACs. Overall diagnostic accuracy was 94 % (398/423). In the ESDs, 11/298 (3.7 %) cases had additional surgery, because of preoperative estimation of shallow invasion depth. In the LACs, 7/125 (5.6 %)

Table 4 Clinical outcomes: less invasiveness (pyrexia, requirement for analgesic drugs, early laboratory investigations, hospitalization, and early resumption of normal activities)

	No. (%) ESDs ($n = 300$)	No. (%) LACs ($n = 190$)	*P* value
Postoperative pyrexia (≥38 °C)	13 (4.3)	103 (54.2)	<0.001
Requiring analgesic drugs[a]	13 (4.3)	115 (60.5)	<0.001
Mean variable value of WBC (Pre-op stage/POD1), μl	1,300 (5,900/7,200)	3,100 (5,400/8,500)	<0.001
Mean variable value of CRP (Pre-op stage/POD1), mg/dl	0.90 (0.13/1.04)	3.96 (0.12/4.08)	<0.001
Rate of drop (≥2 mg/dl) in Hb value	15 (5.0)	57 (30.0)	<0.001
Transfusion (RCC-LR)	0 (0)	5 (2.6)	0.005
Hospital stay, median (range), day	5 (4–17)	10 (6–41)	<0.001
Start of walk, median (range), POD	0 (0–1)	1 (0–2)	<0.001
Start of drink, median (range), POD	1 (0–4)	1 (1–20)	NS
Start of diet, median (range), POD	2 (1–6)	3 (1–21)	<0.001

POD post-operative day, *Hb* hemoglobin, *RCC-LR* red cell concentrates-leukocytes reduced, *NS* not significant

[a] Non-steroidal anti-inflammatory drugs (NSAIDs), pentazocine hydrochloride, or fentanyl

cases turned out to be over surgeries, because of preoperative estimation of deep invasion.

Procedure time and en bloc and curative resection

The median procedure duration in the ESDs was 90 min (range 15–540 min) compared with 185 min (48–499 min) in the LACs ($P < 0.001$). The *en bloc* and curative resection rates in the ESDs were 91.7 % (275/300) and 91.0 % (273/300), respectively (Table 3).

Postoperative pyrexia and early laboratory investigations

The rate of postoperative pyrexia (≥38 °C) was 4.3 % (13/300) in the ESDs, compared with 54.2 % (103/190) in the LACs ($P < 0.001$). The number of patients requiring analgesic drugs because of postoperative, abdominal or wound pain was 13/300 (4.3 %) in the ESDs and 115/190 (60.5 %) in the LACs ($P < 0.001$). In the early laboratory investigations, the mean difference in WBC and CRP between the preoperative stage and POD 1 was +1,300/μl in the ESDs and +3,100/μl in the LACs ($P < 0.001$) and +0.90 mg/dl in the ESDs and +3.96 mg/dl in the LACs ($P < 0.001$), respectively. In the ESDs, only 11/300 (3.6 %) had decrease in hemoglobin level of ≥2 g/dl, compared with 57/190 (30.0 %) in the LACs ($P < 0.001$). No transfusions were required the in ESDs, but they were required in the LACs (5/190; 2.6 %) ($P = 0.005$) (Table 4).

Hospital stay and resumption of normal activities

The median hospital stay in the ESDs was 5 days (range 4–17 days), compared with 10 days (6–41 days) in the LACs ($P < 0.001$). The median time for a patient who underwent ESD to start walking was POD 0 (range POD 0–1), compared with POD 1 (POD 0–2) in the LACs ($P < 0.001$). There was no significant difference in the median time for start of fluid intake between the two groups: POD 1 (range POD 0–4) in the ESD group and POD 1 (POD 1–20) in the LACs (P = NS). The median time for start of food intake was POD 2 (range POD 1–6) in the ESDs, and POD 3 (POD 1–21) in the LACs ($P < 0.001$) (Table 4).

Intra- and postoperative complications

Intra- and postoperative complications were seen in 21 cases (7.0 %) in the ESDs, and in 28 cases (14.7 %) in the LACs ($P = 0.005$). Delayed bleeding and perforation associated with colorectal ESD was seen in 15 (5.0 %) and five (1.7 %) cases, respectively. All of the cases of delayed bleeding in the ESDs could be cured endoscopically. None of the patients in the ESDs needed a blood transfusion. With regard to perforation, four of five cases were cured by endoscopic clipping and ESD could also be completed. The other case had delayed perforation with acute generalized peritonitis and required emergency surgery. Diverting stoma due to postoperative adverse event was none in the ESDs. There were, in addition, no complications of intravenous anesthesia during ESD.

For major complications in the LACs, three patients (1.6 %) had delayed bleeding, four (2.1 %) had anastomotic leakage, and three (1.6 %) had peritonitis. For minor complication, three each (1.6 %) had wound infection or pneumonitis, two (1.1 %) had postoperative ileus, and one each (0.5 %) had wound dehiscence, subcutaneous hematoma, cholecystitis, paroxysmal atrial fibrillation, hives, or

Table 5 Clinical outcomes: safety (intra and postoperative complications and total cases of stoma)

	No. (%) ESDs ($n = 300$)	No. (%) LACs ($n = 190$)	P value
Total	21 (7.0)	28 (14.7)	0.005
Postoperative bleeding	15 (5.0)	3 (1.6)	
Perforation	5 (1.7)	–	
Anastomotic leakage	–	4 (2.1)	
Peritonitis	1 (0.3)	3 (1.6)	
Diverting stoma	0 (0)	3 (1.6)	
Ileus	0 (0)	2 (1.1)	
Surgical wound dehiscence	–	1 (0.5)	
Surgical wound infection	–	3 (1.6)	
Subcutaneous hematoma	–	1 (0.5)	
Pneumonitis	0 (0)	3 (1.6)	
Cholecystitis	0 (0)	1 (0.5)	
Abdominal incisional hernia	–	1 (0.5)	
Hives	0 (0)	1 (0.5)	
Paroxysmall atrial fibrillation	0 (0)	1 (0.5)	
Delirium	0 (0)	1 (0.5)	
Total cases of stoma	3 (1.0)	20 (10.5)	<0.001
Temporal/permanent, No	3/0	17/3	

delirium. Three patients (1.6 %) required diverting stoma due to postoperative anastomotic leakage.

Temporal stoma was finally required in three of 16 cases in the ESDs in which additional LAC was performed because SM-d carcinoma or lymphovascular invasion in the lower rectum was confirmed by pathological investigation, while 20 cases (10.5 %) in the LACs required stoma (17 cases and three cases required temporal and permanent stoma, respectively) ($P < 0.001$) (Table 5).

These were consecutive patients with prospective data collection.

Discussion

Current status of colorectal ESD—compared with LAC

This is believed to be the first study to evaluate prospectively the clinical outcomes and perioperative clinical course in patients undergoing colorectal ESD and LAC. Simple comparison between ESD and LAC is problematic because each indication differs in Japan, as do procedures. ESD is used as a local treatment without lymph node dissection for adenoma, intramucosal or SM-s carcinomas, whereas LAC is performed for SM-d carcinomas and includes lymph node dissection. Worldwide, however, LAC is performed as the standard for lesions that are a good indication for colorectal ESD in Japan. The reasons are as follows: LAC is a low-invasive procedure compared with laparotomy and maintains QOL [23, 24]. Colorectal ESD, on the other hand, seems to be a difficult and hazardous procedure for non-expert endoscopists.

Endoscopic diagnosis of T stage in early cancer is also a hurdle and controversy, especially in western countries. High diagnostic accuracy of invasion depth of the lesion using magnifying colonoscopy, however, has been reported in Japan. ESD and LAC are selected for cT1a and cT1b, respectively, on the basis of preoperative diagnosis. Good clinical outcome and safety of colorectal ESD have been reported recently in Korea and Japan. Data on the perioperative clinical course and QOL evaluation of colorectal ESD, however, are scant at present. Postoperative QOL assessment for various diseases, in recent years, has been conducted and has become an important part of outcome assessment. The need for minimally invasive treatment to maintain patient QOL has increased. With further dissemination of colorectal ESD in the future, it will be crucial to establish its effectiveness and safety, as well as its minimal invasiveness compared with LAC. Although randomized controlled trials are ideal, their implementation is already difficult in Japan because the indications for colorectal ESD have been established and the technique has become popular.

Characteristics of objective lesions and endoscopic diagnosis—in this study

Looking at the macroscopic type of lesions in this study, LST lesions accounted for 77 % in the ESD group. These lesions are large and difficult to treat by *en bloc* EMR, but

it suggests that LSTs with the features of lateral growth type, which retain within SM-s invasion is an adaptive lesions for most of the colorectal ESD. In the LACs, on the other hand, depressed lesions accompanied with the feature of the likely SM-d invasion accounted for 42 %, even if the lesions were small in size.

Preoperative diagnosis of invasion depth based on conventional and magnifying colonoscopy is therefore important for the choice of ESD or LAC for early colorectal cancer [25]. Although endoscopic ultrasonography (EUS) is also a useful tool for evaluation of lesion depth, magnifying colonoscopy and EUS do not differ significantly for preoperative diagnosis of early colorectal cancer [26]. It is also a major advantage that magnifying colonoscopy can be used regardless of the size and location of the lesion immediately by just touching the zoom lever. In this study, there was a high rate of discrimination of lesion invasion depth by conventional and magnifying colonoscopy and treatment for early colorectal cancer could be selected adequately. If the preoperative diagnostic accuracy was poor and resulted in a high number of non-curative cases that underwent ESD, which then required additional LAC, ESD would not have been developed.

One of the two cases of ESD that had difficulty with histopathological evaluation was resected *en bloc* by ESD for local recurrence after TEM. In the other case, perforation occurred during ESD. Although endoscopic closure was achieved soon and the ESD procedure was completed, specimen collection was difficult. Adenoma was diagnosed by preoperative colonoscopy in this case and no recurrence was detected after 2.5 years.

Both of the LACs that had difficulty in histopathological evaluation had undergone EMR at another hospital. Although pathological evaluation showed that these cases had SM invasion after EMR, it was difficult to establish the precise depth of invasion according to the unknown orientation of the resected specimen and pVM. Six patients in the ESDs that were diagnosed pathologically as SM-d carcinoma did not receive additional LAC on request of the patients. One of these six patients did not visit our institution for the duration of follow-up. The remaining five cases did not experience any relapse after follow-up of 1.5–3.5 years.

Effectiveness, less invasiveness, and safety—colorectal ESD

Median procedure time of colorectal ESD in this study was half that of LAC. In addition to shorter procedure time, colorectal ESD had high *en bloc* and curative resection rates. Colorectal ESD, therefore, demonstrated a high rate of effectiveness as a short-term clinical outcome.

With regard to perioperative clinical course, incidence of pyrexia ($\geq$38 °C) and requirement for analgesic drugs were initially significantly lower for ESDs than LACs. This reflects the advantage of colorectal ESD; it can complete local resection of the intestinal, mucosal, and SM layers without laparotomy and interperitoneal procedures, including lymph node dissection.

We also investigated changes in WBC, CRP, and hemoglobin value between the preoperative period and POD 1. Variations in the inflammatory response indicators (WBC and CRP) were insignificant in the ESDs. Also, only 4 % of the ESD group had a $\geq$2 g/dl decrease in hemoglobin level. These absolute objective data indicate that ESD is less invasive than LAC. The reasons why the decrease in hemoglobin was low in the ESDs were the small amount of bleeding and immediate hemostasis during colorectal ESD.

Hospital stay in the ESDs was half that of the LACs. The time to resume fluid and food intake in the ESDs was POD 1 and POD 2, respectively. Although fluid intake in the ESDs started at almost the same time as in the LACs, food intake in the ESDs was significantly earlier. The median time to start walking was POD 0 in the ESDs. This indicated that patients could start walking soon after the procedure and this is one important factor associated with the lower level of invasiveness of colorectal ESD compared with LAC. Considering the lesser invasiveness of colorectal ESD, although hospital stay was 5 days in this study according to the clinical pathway which concerns the standardization of care process, day surgery may not be impossible [27].

The rate of major and minor complications with ESDs was 7.0 %. This was lower than with LACs, which is an established method of treatment worldwide. In four of five patients in the ESDs with perforation, complete closure was achieved utilizing an endoscopic clip (the other case required emergency ileo-cecal resection because of delayed perforation). A stable clinical course after the closure for perforation was achieved on the basis of conservative therapy such as fasting, hydration, and antibiotics. ESD has the following attributes for the management of perforation: (1) perforation occurs during the procedure, endoscopic closure using a clip can be achieved because the diameter of perforation is small compared to those by EMR; and (2) sufficient preparation can help the endoscopic management and prevent severe peritonitis.

The rate of delayed bleeding with ESD was higher than with LAC. Endoscopic hemostasis, however, could be achieved in all cases and no transfusions were required in the ESDs. In the LACs, there were three cases of delayed bleeding and two of them required blood transfusion; endoscopic and surgical hemostasis was required in one case each. The other case had a coexistent anastomotic

leakage and required diverting stoma. Physical stress caused by delayed bleeding in ESD patients is lower than for LAC patients because it is only a minor factor and transfusion is not necessary in ESD. This is probably because ESD were conducted with coagulation of all exposed vessels in SM layer during and after the procedures.

Our results indicate the safety of colorectal ESD, because procedural complications such as delayed bleeding and perforation could be managed endoscopically, and there were no anesthesia complications. We should, however, pay attention to delayed perforation because emergency surgery is not preventable even though the incidence is quite low. Excess heating of endoscopic devices against the intestinal layer, which can lead to perforation, should be avoided so we prefer to use mainly bipolar devices and we should repair any damage to the muscularis layer by careful endoscopic clipping. These procedures are essential to prevent delayed perforation.

Stoma is associated with postoperative QOL but was only required in three cases (1.0 %), with additional LAC after ESD. In contrast, it was required in 20 cases (10.5 %) in the LACs. ESD enabled patients to maintain perioperative QOL with regard to anorectal function.

Problem points and management guide of colorectal ESD

The technical difficulty and complications of ESD preclude the standardization of this novel procedure. Colorectal ESD, at present, is only practiced in Japan, Korea, and a few facilities in other countries. To overcome these obstacles, it is necessary to undergo ESD training using animal models and to accumulate experience of basic procedures such as endoscope insertion and EMR. The delay in applying ESD devices that are used exclusively in Japan is one of the hurdles in the dissemination of ESD overseas.

According to our study, rectal ESD is easier to perform than cecal ESD. The latter is likely to be difficult technically because the cecum is located in the innermost part of the large intestine and its wall is thin. The risk of perforation in the lower rectum is lower and there is better access for the endoscope and other devices. Rectal LAC is, paradoxically, more difficult because the pelvic cavity is anatomically narrow, surgical injuries tend to be more serious in lower rectal LAC. Temporary or permanent stomas are also necessary in some rectal LAC cases, despite the early stage nature of the lesions. Cecal LAC, in contrast, is easier to perform [21]. To decide on selection of treatment method (ESD or LAC), we should consider the following as well as preoperative endoscopic diagnosis: skill of the operator, reputation of the institution, and invasiveness for the patient. We should conduct diagnostic rectal ESD, to some extent aggressively, even if the lesion is all circumferential, or the differential diagnosis is difficult between SM-s and SM-d carcinoma by preoperative colonoscopy. We should, in contrast, select cecal LAC if cecal ESD is difficult to perform, in accordance with the endoscopist's skill level.

Patient safety and accurate pathological assessment are important in terms of prognosis. If completion of ESD is difficult, we should stop the procedure and covert to LAC. This would enable us to avoid the complications of ESD and multiple piecemeal resection, which is associated with a high incidence of local recurrence or residual lesions [3]. Adequate additional surgery cannot be performed if the degree of SM invasion or lymphovascular invasion is suboptimal because of multiple piecemeal resection.

Our study had the following limitation. This was a single center study and the postoperative clinical course of colorectal ESD and LAC was based on the clinical pathway of our institution. Thus, a future multicenter study is required.

In conclusion, colorectal ESD is an effective technique with a short procedure time, high rate of curative resection, and procedural safety, as well as being less invasive than LAC. It is expected that colorectal ESD will continue to spread worldwide in the future with the development of endoscopic devices and simplification of treatment. Also, we should not forget that patients always request the less invasive, safe and adequate treatment.

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References

1. Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fjii T (2010) Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 24:343–352
2. Tanaka S, Haruma K, Oka S, Takahashi R, Kunihiro M, Kitadai Y, Yoshihara M, Shimamoto F, Chayama K (2001) Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc 54:62–66

3. Sakamoto T, Matsuda T, Otake Y, Nakajima T, Saito Y (2012) Predictive factors of local recurrence after endoscopic piecemeal mucosal resection. J Gastroenterol 47:635–640
4. Hosokawa K, Yoshida S (1998) Recent advances in endoscopic mucosal resection for early gastric cancer. Jpn J Cancer Chemother 25:476–483
5. 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
6. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S (2001) Endoscopic mucosal resection for treatment of early gastric cancer. Gut 48:225–229
7. Kondo H, Gotoda T, Ono H, Oda I, Kozu T, Fujishiro M, Saito D, Yoshida S (2004) Percutaneous traction-assisted EMR by using an insulation-tipped electrosurgical knife for early stage gastric cancer. Gastrointest Endosc 59:284–288
8. 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
9. Yamamoto H (2005) Endoscopic submucosal dissection of early cancers and large flat adenomas. Clin Gastroenterol Hepatol 3(7 Suppl 1):S74–S76
10. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, Yokota T (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
11. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K (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
12. Saito Y, Emura F, Matsuda T, Uraoka T, Nakajima T, Ikematsu H, Gotoda T, Saito D, Fujii T (2005) A new sinker-assisted endoscopic submucosal dissection for colorectal cancer. Gastrointest Endosc 62:297–301
13. Sano Y, Fu KI, Saito Y, Doi T, Hanafusa M, Fujii S, Fujimori T, Ohtsu A (2006) A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. Endoscopy 38(suppl 2):E95
14. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Kozu T, Saito D (2007) A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. Gastrointest Endosc 65:537–542
15. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu kI, Sano Y, Saito D (2007) Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc 66:966–973
16. Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut 55:1592–1597
17. Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D (2010) A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissecions (with video). Gastrointest Endosc 72:1217–1225
18. Kiriyama S, Saito Y, Matsuda T, Nakajima T, Mashimo Y, Joeng HK, Moriya Y, Kuwano H (2011) Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: a retrospective study. J Gastroenterol Hepatol 26: 1028–1033
19. Park SU, Min YW, Shin JU, Choi JH, Kim YH, Kim JJ, Cho YB, Kim HC, Yun SH, Lee WY, Chun HK, Chang DK (2012) Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer. Endoscopy 44:1031–1036
20. Repici A, Hassan C, Pagano N, Rando G, Romeo F, Spaggiari P, Roncalli M, Rerrara E, Malesci A (2013) High efficacy of endoscopic submucoal dissection for rectal laterally spreading tumors larger than 3 cm. Gatrointest Endosc 77:96–101
21. Kiriyama S, Saito Y, Yamamoto S, Soetikno R, Matsuda T, Nakajima T, Kuwano H (2012) Comparison of endoscopic submucosal dissection with laparoscopic-assisted colorectal surgery for early-stage colorectal cancer: a retrospective analysis. Endoscopy 44:1024–1030
22. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K (2012) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 17:1–29
23. Velanovich V (2000) Laparoscopic vs open surgery—a preliminary comparison of quality-of-life outcomes. Surg Endosc 14:16–21
24. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G (2002) Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 287:321–327
25. Matsuda T, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T (2008) Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 103:2700–2706
26. Fu KI, Kato S, Sano Y, Onuma EK, Saito Y, Matsuda T, Koba I, Yoshida S, Fujii T (2008) Staging of early colorectal cancer: magnifying colonoscopy versus endoscopic ultrasonography for estimation of depth of invasion. Dig Dis Sci 53:1886–1892
27. Aoki T, Nakajima T, Saito Y, Matsuda T, Sakamoto T, Itoi T, Khiyar Y, Moriyasu F (2012) Assessment of the validity of the clinical pathway for colon endoscopic submucosal dissection. World J Gastroenterol 18:3721–3726

Gastric Cancer
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ORIGINAL ARTICLE

Randomized controlled trial comparing gastric cancer screening by gastrointestinal X-ray with serology for *Helicobacter pylori* and pepsinogens followed by gastrointestinal endoscopy

Takuji Gotoda · Hideki Ishikawa · Hirohide Ohnishi · Kentaro Sugano · Chika Kusano · Chizu Yokoi · Yutaka Matsuyama · Fuminori Moriyasu

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Abstract

Background Based on the results of several case–control and cohort studies gastrointestinal X-ray (GI X-ray) has been recommended for use in the nationwide screening program for gastric cancer.. Although this was the only effective screening program when almost all of the Japanese population were *Helicobacter pylori* (*H. pylori*) positive, there has been concern whether an alternative effective screening system should be established for the *future H. pylori*-negative generation. We therefore conducted the first randomized controlled trial (RCT) comparing GI X-ray and gastrointestinal endoscopy (GIE) scheduled according to results of serological testing (ST); this was done to determine the potential for an alternative screening method.

Methods Subjects who fulfilled the inclusion criteria were residents between the ages of 30 and 74 and who were able to receive gastric cancer screening in the Yurihonjo area. Participants were assigned to the GI X-ray group or the GIE-ST group by computer randomization. Subjects in each group were further subdivided into 4 categories according to their different risks for gastric cancer. The feasibility of stratified randomization was serologically assessed and detection rates of gastric cancer at entry by the different screening methods were also compared.

Results Of the 2,962 subjects invited, 1,206 individuals (41 percent) were included in the first stage of this stratified RCT, and 604 and 602 individuals were assigned to the GI X-ray group and the GIE-ST group, respectively. There were no statistically significant differences in sex, age, height, body weight, smoking, alcohol intake and family history of cancer between the 2 groups. During ST the GI X-ray group showed a distribution that was not statistically different from that of the GIE-ST group. Although 3 cases of gastric cancer were detected in the GIE-ST group, there was no statistically significant difference between the 2 groups. One complication found was barium aspiration during the examination in the X-ray group.

Conclusion We confirmed that baseline demographic features of the 2 groups were well balanced. We are now organizing the first RCT to compare the existing screening method and the alternative method (Clinical trial registration number: UMIN000005962).

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T. Gotoda (✉) · C. Kusano · F. Moriyasu
Department of Gastroenterology and Hepatology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
e-mail: takujigotoda@yahoo.co.jp

H. Ishikawa
Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Osaka, Japan

H. Ohnishi
Department of Gastroenterology, Akita University Graduate School of Medicine, Akita, Japan

K. Sugano
Division of Gastroenterology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan

C. Yokoi
Gastroenterology and Hepatology Division, National Center for Global Health and Medicine, Tokyo, Japan

Y. Matsuyama
Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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Keywords Gastric cancer · Gastrointestinal X-ray · Serological testing · Gastrointestinal endoscopy · Randomized controlled trial

Abbreviations

GI X-ray	Gastrointestinal X-ray
ST	Serological testing
GIE	Gastrointestinal endoscopy
RCT	Randomized controlled trial
H. pylori	*Helicobacter pylori*

Introduction

Gastric cancer is the second most common cause of death from cancer worldwide [1], and especially in Eastern Asia countries such as China, Japan and Korea [2]. The need for efficient, cost-effective and practical nationwide mass screening systems for gastric cancer in Eastern Asia remains controversial, although the incidence of gastric cancer remains high [3]. It is well known that early detection and treatment are essential in reducing gastric cancer death rates. In Japan, there were 50,136 deaths from gastric cancer in 2010, which accounts for 14.2 percent of all cancer deaths [4]. Japanese population screening using gastrointestinal X-ray (GI X-ray) with a double-contrast barium meal began in 1964 [5–7]. More than 6 million individuals are currently screened annually in this program.

A meta-analysis of 3 case–control studies showed that screening by GI X-ray results in reduced mortality from gastric cancer [8]. Thus, Japanese guidelines established in 2006 recommended the population undergo gastric cancer screening using GI X-ray [9, 10]. However, these guidelines did not recommend gastrointestinal endoscopy (GIE) as a population screening system instead of GI X-ray since no satisfactory evidence of decreased mortality from gastric cancer upon GIE screening was in the literature.

The pathogenic role of *Helicobacter pylori* (*H. pylori*) in gastric cancer has been reported both in epidemiological and basic research studies [11–13]. Gastric atrophy, corpus-predominant gastritis or intestinal metaplasia caused by long-time *H. pylori* infection were indicated as increased risk factors for gastric cancer [14, 15]. Infection with *H. pylori* plays an important role in gastric cancer development, even in high-risk geographical regions [16]. It is well known that gastritis is more prevalent and severe when there is more corpus-predominant atrophy and intestinal metaplasia, which may partially explain the higher incidence of gastric cancer in Japan [17].

Serum pepsinogen was recently found to be a promising biomarker for predicting the status of the gastric mucosa [18]. Thus, the use of serum pepsinogen I concentration and pepsinogen I/II ratio for the detection of gastric atrophy was proposed. Consequently, serum pepsinogen may be useful in gastric cancer screening [19]. Recently, the combination of serum pepsinogen concentration and presence of the *H. pylori* antibody has been recommended and used in some cases as a useful marker for gastric cancer screening [20, 21]. Although a change to more efficient and cost-effective population screening methods is necessary, serological risk-testing methods for population screening are still in question because satisfactory evidence showing decreased mortality rates from gastric cancer using these methods has not yet been demonstrated.

We are therefore conducting the first randomized controlled trial (RCT) to study gastric cancer screening by GI X-ray with serology for *H. pylori* and pepsinogens followed by GIE scheduled according to the results of serological testing (ST); GI X-ray is the currently employed intervention in Japan. The first stage of this RCT evaluates the feasibility of stratification of this RCT at the time of recruitment and the detection rate of gastric cancer during the first stage.

Subjects and methods

Subjects and participants of this study

This RCT has been named "gastric cancer screening labeled by serum examination" in place of aged gastric cancer organized screening system (GALAPAGOSS) and is now ongoing in the Yurihonjo area (Yurihonjo city and Nikaho city, Akita prefecture, Japan). Subjects included in the study were 30- to 74-year old residents with access to screening in the Yurihonjo area; they were recruited between June 2011 to March 2013. Candidates were excluded if they had any history of malignant disease, gastrectomy or severe co-morbidities with less than 5 years of life expectancy. Candidates whose informed consent could not be obtained and those whom the doctors considered would have difficulty participating in the study were also excluded. Participants were defined as those who provided written informed consent. All information of the subjects was anonymously processed at the data center.

The study protocol was approved by the ethics review board of the Tokyo Medical University and written informed consent was obtained from each individual according to the Declaration of Helsinki. This trial is registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, number UMIN000005962.

Study design

Participants of this study were assigned to the GI X-ray group or the GIE-ST group by computer randomization, and thus were screened according to the protocol shown in Fig. 1. Gender and age (30–59 and 60–74 years) were adopted as stratified factors for randomization.

GI X-ray, which is the currently employed intervention for gastric cancer in Japan, was annually scheduled for the subjects assigned to the GI X-ray group. GI X-ray was performed according to the standard methods proposed by the Japanese Society of Gastroenterology Cancer Screening [22] and double checks were performed in a blind manner. For the individuals of this group who showed abnormalities in their GI X-ray results a high definition video GIE was performed by experienced endoscopists with certification from the Japanese Society of Gastrointestinal Endoscopy (JSGE). The video was conducted after a pre-endoscopic drink of 100 ml of water, 2 ml of Gascon (Kissei Pharmaceutical Co., Ltd., Nagano, Japan) and 20,000 units of Pronase (Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) [23] according to the nationwide gastric cancer-screening program. A gastric biopsy was performed if necessary. Serological assessment was also carried out in both groups to assess the validity of the stratified randomization of this study at enrolment.

GIE-ST subjects were subdivided into 4 categories with different risks of gastric cancer, according to the combination of *H. pylori* status and serum pepsinogen concentration. The groups were scheduled for high definition video GIE (GIF-Q260, Olympus, Tokyo, Japan) with 25 images taken as follows (Fig. 1): no screening in A, GIE every 3 years in B, GIE every 2 years in C and annual GIE in D [24]. Biopsies that were taken from any gastric mucosal abnormality were histologically diagnosed. GIE was performed at the first stage in all individuals allocated to the GIE-ST group to confirm the absence of any abnormalities of the stomach; this was done in order to avoid disadvantaging subjects, especially those who were serologically assessed as group A. Furthermore, GIE is planned at the end of this RCT for all subjects, including those allocated to the GI X-ray group, to evaluate any lesions overlooked.

Serological examinations

H. pylori status was evaluated by the detection of a specific *H. pylori* IgG antibody using a commercial enzyme immunoassay kit (E-plate; Eiken Kagaku, Tokyo, Japan). The levels of pepsinogen I (PG I) and pepsinogen II (PG II) were also measured by radioimmunoassay (pepsinogen kit; BML Inc., Akita, Japan). The results were considered indicative of atrophic gastritis when the PG I level was <70 ng/L and the PG I/II ratio was <3.0 (atrophic pepsinogen), as proposed by Miki et al. [25]. All other cases were considered to be non-atrophic [26]. According to the results of the serological examination, subjects were subdivided into 4 groups: Group A: negative for *H. pylori* and non-atrophic pepsinogen; Group B: positive for *H. pylori* and non-atrophic pepsinogen; Group C: positive for *H. pylori* and atrophic pepsinogen; and, Group D: negative for *H. pylori* and atrophic pepsinogen.

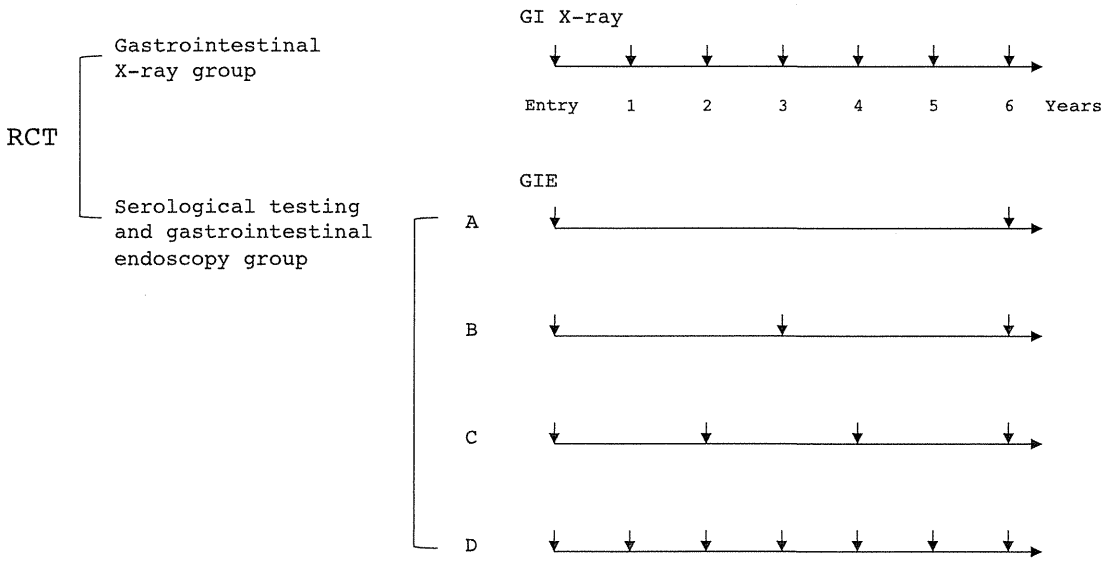

Fig. 1 RCT protocol comparing GI X-ray with GIE scheduled according to the results of serological testing, as a new detection method for gastric cancer

Endpoints

The aim of this RCT is to compare GI X-ray by barium meal, which is the nationwide screening program for gastric cancer, with the new method of screening using GIE scheduled according to the results of ST of *H. pylori* antibody and pepsinogen status. The primary endpoint of this study is to calculate the mean medical fee per examination and the mean medical expense required to detect a single gastric cancer case, enabling assessment of the total medical cost in the GI X-ray group and the GIE-ST group.

This study will assess the detection rate of gastric cancer between GI X-ray and ST with GIE at the first stage, the rate of gastric cancer and tumor stage detected during the observation period, the overlooked rate of gastric cancer and tumor stage by the final GIE at the end of the study, complications during the study and the reduction in the mortality rate from gastric cancer. This assessment will provide a means of comparing the GI X-ray group and the GIE-ST group as the secondary endpoint. This paper evaluated as the first report of the study the feasibility of stratification of this RCT at the time of recruitment and the detection rate of gastric cancer at the first stage.

Sample size and statistical analyses

We calculated the required sample size from the average medical expense of each individual under the Japanese medical insurance system, with a statistical power of 0.8 using an α error of 0.05, and the number of subjects required was determined to be 254 in each group, which we then increased to 1,000 subjects in total in expectation of a significant drop-out rate. Medical fees calculated for this sample size were the following: 4,500 Japanese yen/time/person for the GI X-ray, 11,140 yen/time/person for the GIE, 5,000 yen/time/person for endoscopic biopsy and 2,000 yen/time/person for the *H. pylori* antibody + pepsinogen ST.

Statistical significance of the differences was assessed using the Chi square test. A value of $p < 0.05$ was regarded as indicating a statistically significant difference between groups. All statistical evaluations were performed using SPSS version 20.0 J software (IBM).

Results

Feasibility of stratification

Of the 2,962 subjects enrolled, 1,206 participants were registered in this RCT (Fig. 2) and 604 and 602 participants were assigned to the GI X-ray group and the GIE-ST group by computer randomization, respectively (Table 1).

There were no statistically significant differences in sex, age, height, body weight, smoking, alcohol intake and family history of cancer between the 2 groups. Serologically, the 2 groups also showed no statistically significant differences.

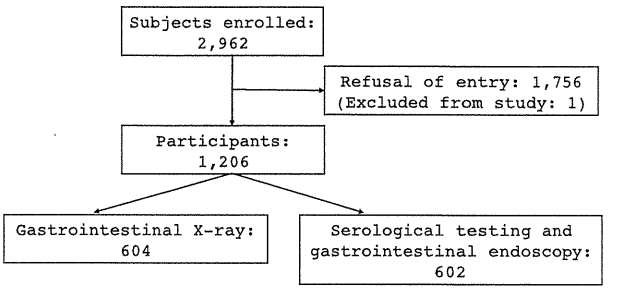

Fig. 2 Trial profile

Table 1 Characteristics of study participants and serological data on the presence of a specific *Helicobacter Pylori* IgG antibody and pepsinogen

	Gastrointestinal X-ray	Gastrointestinal endoscopy scheduled according to the results of serological testing	*p* value
n	604	602	
Sex			
Male	304	304	0.95
Female	300	298	
Age (mean ±SD)	61.5 ±7.9	61.3 ±7.8	0.71
Height (mean ±SD)	158.9 ±8.2	158.6 ±8.4	0.49
Body weight (mean ±SD)	59.6 ±10.0	59.3 ±10.3	0.64
Smoking			
Non-smoker	520	519	0.95
Smoker	84	83	
Alcohol			
Non-drinker	269	258	0.56
Drinker	335	344	
Family history of cancer			
No	416	393	0.18
Yes	188	209	
Serological testing			
Group A	197 (33.1 %)	198 (32.9 %)	0.97
Group B	147 (24.3 %)	150 (24.9 %)	
Group C	222 (36.8 %)	215 (35.7 %)	
Group D	41 (6.8 %)	39 (6.5 %)	

Refusal reasons

More than half of the eligible individuals refused to register in the study because they did not wish to be tested by GIE (Table 2). The individuals who did not wish to be tested by GIE tended to be younger in age. On the other hand, there was a higher tendency to refuse randomization in the elderly compared with the younger people.

Rate of secondary examination in the GI X-ray group

A total of 100 individuals (16.7 percent) were recommended to undergo secondary examination using a high definition video GIE. The rate of secondary examination is shown according to the serological results in Table 3. Of the 100 individuals, 21 (10.8 percent) were serologically subdivided into Group A.

Detection rate of gastric cancer and complications at entry

The rate of complications and gastric cancer detection rate was not statistically different between the 2 groups (Table 4). Three cases of gastric cancer were detected from Group C of the GIE-ST group, compared to 0 in the GI X-ray group. All gastric cancer cases were treated by endoscopic resection. One complication found was barium aspiration during examination in the GI X-ray group. However, no therapeutic procedures were required for this case.

Table 2 Reasons eligible subjects refused to register in the study

Sex	Male		Female		Total (1,755)
Age group (years)	30–59	60–75	30–59	60–75	
n	210	493	328	724	
Dislike of gastrointestinal endoscopy	127	223	219	356	925 (52.7 %)
Dislike of gastrointestinal X-ray using barium meal	4	16	9	27	56 (3.2 %)
Refusal of randomized controlled trial	63	199	69	233	564 (32.1 %)
Long restriction	13	49	24	93	179 (10.2 %)
Others	3	6	7	15	31 (1.8 %)

Table 3 Number of participants chosen for secondary examination using gastrointestinal endoscopy in the gastrointestinal X-ray group

Serological testing	Primary gastrointestinal X-ray	Secondary gastrointestinal endoscopy	%
Group A	194	21	10.8
Group B	147	26	17.7
Group C	222	42	18.9
Group D	41	11	26.8

Table 4 Number of gastric cancers detected and complications encountered upon screening by gastrointestinal X-ray, or upon gastrointestinal endoscopy scheduled according to the results of serological testing

	Gastrointestinal X-ray	Gastrointestinal endoscopy scheduled according to the results of serological testing	p value
n	604	602	
Number of gastric cancers	0	3	0.25
Number of complications	1	0	1.00

Discussion

Early detection and treatment is an important way to reduce deaths from gastric cancer. To the best of our knowledge, mass screening for gastric cancer has not been assessed in an RCT and more data should be collected to support the current screening program [27]. Thus, this paper assessed the feasibility of an RCT comparing gastric cancer screening by GI X-ray with serology for *H. pylori* and pepsinogens followed by GIE scheduled according to the results of ST, with the final aim of the study being to assess the cost-effectiveness of the 2 methods. We confirmed that the participants were randomly assigned by the following 2 stratified factors: gender and age (30–59 and 60–74 years). The risk of gastric cancer is generally higher in men; most studies have reported a 1.8–2.0 times higher risk of gastric cancer in men compared with women [28]. Of the 2,962 subjects invited, 1,206 individuals were recruited at the first stage of the study. Furthermore, the GI X-ray group showed a serological distribution equal to the GIE-ST group. Although there was no statistically significant difference in the gastric cancer detection rate between the 2 groups, all 3 gastric cancer cases were detected in the GIE-ST group.

Although comprehensive data are not available, the acceptance rate in this study (41 percent) was much higher compared to the general rate, which is known to be 10–30 percent[29]. Reasons for refusal indicated, consistent with previous data, that GIE is still a feared medical procedure, and thus should be improved for comfort. Although the rate of the population subdivided into serological Group A (around 30 percent) was higher

than recent average rates in urban areas, this is probably because this RCT is being conducted in a rural area of Japan with a large aging population. Furthermore, there were no statistical differences in refusal rate between each of the categories (data not shown). The rate of secondary examination in the GI X-ray group was slightly higher than the average rate reported by the Japanese Society of Gastroenterology Cancer Screening. However, considering the mean age of the subjects in this RCT, the rate may not be so high compared to the number of Japanese citizens in their 60's.

In Japan GI X-ray using a barium meal is the method for mass gastric cancer screening and is available to asymptomatic individuals older than 40; this is the established nationwide program [8]. Upon positive findings in the barium meal examination [30] further investigation with GIE is recommended. However, the actual participation rate among eligible individuals is only around 20 percent [31]. In Japan, an individual pays no more than 30 percent of the total medical fee associated with such an examination; government insurance covers the rest. This means that asymptomatic individuals can readily receive GIE as an opportunistic screening at an outpatient clinic or even at a hospital under the Japanese health insurance system. Consequently, many endoscopic examinations outside the mass-screening program contribute to the high detection rate of early gastric cancers in Japan [32]. A study from Niigata, Japan reported that the detection rate of gastric cancers by GIE is about 2.7 to 4.6 times higher than the detection rate using barium [33].

Whether cost-effective mass screening for gastric cancer should be performed remains controversial, especially in counties with a low or moderate incidence of gastric cancer. A study from Singapore suggested that endoscopy screening every 2 years for a moderate- to high-risk population (e.g., Chinese men aged 50–70 years) was highly cost effective in the health-care system [34]. Therefore, endoscopy screening in targeted high-risk populations might be more cost effective than mass screening in countries with intermediate to low risk of gastric cancer. Cost-effectiveness is affected by the cost of the GIE and the gastric-cancer incidence rate among the screened population [35]. The cost of GIE is therefore the major modifiable factor that affects the ultimate cost-effectiveness of such a screening program.

In Korea the National Cancer Screening Program recommends biennial stomach-cancer screening for men and women older than 40 years of age by GI X-ray and/or GIE. According to the 2005 National Cancer Screening Program report, the expected frequency of gastric-cancer detection is 0.12 percent (i.e., detection of 1,381 gastric cancers in the 1.15 million people screened) [36]. GIE seems to be the most cost-effective screening method in Korea given the relatively low cost of this technique (about the same as GI X-ray) and the high incidence of gastric cancer. However, considering the decline in the incidence of gastric cancer in the near future in Japan and Korea mass screening for gastric cancer, particularly by only GIE, may not be the most practical approach because of reasons such as acceptance, availability and cost. Multistage screening by serum-PG testing or *H. pylori* serology, or both, might help identify at-risk individuals for further invasive screening.

In multiracial countries, such as Malaysia and Singapore, gastric cancer is more common in the Chinese people than in those of Malay and Indian origin [37]. Therefore, screening of high-risk populations rather than mass population screening might be more cost effective. A study from Singapore reported that the age-standardized rate of gastric cancer is 21.4 per 100,000 per year in Chinese males and 10.8 per 100,000 per year in Chinese females [38]. There is no nationwide population-screening program. A cost-benefit analysis of screening for gastric cancer showed that screening by endoscopy was cost effective in a moderate- to high-risk population (e.g., Chinese men infected with *H. pylori)* [34].

To identify individuals at high risk in countries with moderate to low incidence rate for gastric cancer a stepwise approach starting from demographic factors and *H pylori* status seems feasible. For the younger Japanese generation the cost-effective screening of epidemiological factors, genetic or hereditary risks and status of *H. pylori* infection might be the method adopted within the next 2 decades. Thus, we conducted the first RCT with feasible stratification comparing the existing screening method and an alternative method that may be useful for the next generation.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5, version 2.0. Lyon: IARC Press, 2004.
3. International Agency for Research on Cancer. GLOBOCAN 2008. http://globocan.iarc.fr/.
4. National Cancer Center, Center for Cancer Control and Information Services. http://ganjoho.ncc.go.jp/professional/statistics/index.html.
5. Hisamichi Y, Nishino Y, Hisamichi S. Screening for gastric cancer. World J Surg. 1989;13:31–7.
6. Tsubono Y, Nishino Y, Hisamichi S. Screening for gastric cancer in Miyagi, Japan: evaluation with a population-based cancer registry. Asian Pac J Cancer Prev. 2000;1:57–60.
7. Shiratori Y, Nakagawa S, Kikuchi A, Ishii M, Ueno M, Miyashita T, et al. Significance of a gastric mass screening survey. Am J Gastroenterol. 1985;80:831–4.
8. Tsubono Y, Nishino Y, Hisamichi S. Screening for gastric cancer in Japan. Gastric Cancer. 2000;3:9–18.
9. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guideline for gastric cancer screening. Jpn J Clin Oncol. 2008;38:259–67.
10. Sobue T, Fukao A, Tsuji I, Ohnuki K, Sagawa M, Aoki D, et al. The Japanese Research Group for Development of Cancer Screening Guideline. Japanese guideline for gastric (stomach) cancer screening. (In Japanese). Tokyo: The Japanese Ministry of Health, Labour and Welfare; 2006.
11. Personnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med. 1991;325:1127–31.
12. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese American in Hawaii. N Engl J Med. 1991;325:1132–6.
13. Hirata Y, Maeda S, Mitsuno Y, Takeishi K, Yanai A, Akanuma M, et al. *Helicobacter pylori* CagA protein activates serum response element-driven transcription independently of tyrosine phosphorylation. Gastroenterology. 2002;123:1962–71.
14. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process-First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992;52:6735–40.
15. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.
16. Huang JQ, Scridhar S, Chen Y, Hung RH. Meta-analysis of the relationship between *elicobacter pylori* seropositivity and gastric cancer. Gastroenterology. 1998;114:1169–79.
17. Naylor GM, Gotoda T, Dixon M, Shimoda T, Gatta L, Owen R, et al. Why does Japan have a high incidence of gastric cancer? Comparison of gastritis between UK and Japanese patients. Gut. 2006;55:1545–52.
18. Samloff IM, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. Gastroenterology. 1982;83:204–9.
19. Yoshihara M, Hiyama T, Yoshida S, Ito M, Tanaka S, Watanabe Y, et al. Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: a case-control study. Scand J Gastroenterol. 2007;42:760–4.
20. Yamaji Y, Mitsushima T, Ikuma H, Okamoto M, Yoshida H, Kawabe T, et al. Inverse background of *Helicobacter pylori* antibody and pepsinogen in reflux oesophagitis compared with gastric cancer: analysis of 5732 Japanese subjects. Gut. 2001;49:335–40.
21. Watabe H, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, et al. Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut. 2005;54:764–8.
22. Guidelines for standard method of stomach radiography (in Japanese). J Gastroenterol Mass Surv. 2002;40:437–447.
23. Bhandari P, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, et al. Use of Gascon and Pronase either as apre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: aprospective, randomized, controlled, blinded trial. Scand J Gastroenterol. 2010;45:357–61.
24. Asaka M, Kato M, Graham DY. Strategy for eliminating gastric cancer in Japan. Helicobacter. 2010;15:486–90.
25. Miki K, Ichinose M, Kakei N, Yahagi N, Matsushima M, Tsukada S, et al. The clinical application of the serum pepsinogen I and II levels as a mass screening method for gastric cancer. Adv Exp Med Biol. 1995;362:139–43.
26. Watanabe Y, Kurata JH, Mizuno S, Mukai M, Inokuchi H, Miki K, et al. Helicobacter pylori infection and gastric cancer. A nested case-control study in a rural area of Japan. Dig Dis Sci. 1997;42:1383–7.
27. Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008;9:279–87.
28. Yang L. Incidence and mortality of gastric cancer in China. World J Gastroenterol. 2006;12:17–20.
29. Wittes RE, Friedman MA. Accrual to clinical trials. J Natl Cancer Inst. 1988;80:884–5.
30. Kunisaki C, Ishino J, Nakajima S, Motohashi H, Akiyama H, Nomura M, et al. Outcomes of mass screening for gastric carcinoma. Ann Surg Oncol. 2006;13:221–8.
31. Foundation for Promotion of Cancer Research. Cancer statistics in Japan—2012. Tokyo, Japan.
32. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. Gastric Cancer. 2006;9:315–9.
33. Tashiro A, Sano M, Kinameri K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. World J Gastroenterol. 2006;12:4874–5.
34. Dan YY, So JB, Yeoh KG. Endoscopic screening for gastric cancer. Clin Gastroenterol Hepatol. 2006;4:709–16.
35. Riecken B, Pfeiffer R, Ma JL, Jin ML, Li JY, Liu WD, et al. No impact of repeated endoscopic screening on gastric cancer mortality in a prospectively followed Chinese population at high risk. Prev Med. 2002;34:22–8.
36. Choi IJ. Screening and surveillance of gastric cancer. Korean J Gastroenterol. 2007;49(suppl):15–22.
37. Goh KL, Cheah PL, Md N, Quek KF, Parasakthi N. Ethnicity and *H. pylori* as risk factors for gastric cancer in Malaysia: a prospective case control study. Am J Gastroenterol. 2007;102:40–5.
38. National Registry of Diseases Office. Singapore Cancer Registry Interim Report. Trends in cancer incidence in Singapore 2001–2005. http://www.hpb.gov.sg/nrdo/files/Cancer%20reports/Cancer%20interim%20report%20v3%2001-05_for%20web.pdf. Accessed 5 Feb 2008.