

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. Kiriya 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–carmin 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<sub>2</sub> insufflation was used instead of air insufflation to reduce patient discomfort. Lesion margins were delineated before ESD using 0.4 % indigo–carmin 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 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  $\mu\text{m}$  was diagnosed as pT1a (SM-s), while one which was more than 1,000  $\mu\text{m}$  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  $\mu\text{m}$  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  $\geq 2$  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 specimens 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  $\chi^2$  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 <sup>a</sup>	273 (91.0)	–	

<sup>a</sup> 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 ( <i>n</i> = 300)	No. (%) LACs ( <i>n</i> = 190)	<i>P</i> value
Postoperative pyrexia ( $\geq 38$ °C)	13 (4.3)	103 (54.2)	<0.001
Requiring analgesic drugs <sup>a</sup>	13 (4.3)	115 (60.5)	<0.001
Mean variable value of WBC (Pre-op stage/POD1), $\mu$ l	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 ( $\geq 2$ 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

<sup>a</sup> 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 ( $\geq 38$  °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/ $\mu$ l in the ESDs and +3,100/ $\mu$ l 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  $\geq 2$  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 intra-venous 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 ( <i>n</i> = 300)	No. (%) LACs ( <i>n</i> = 190)	<i>P</i> 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)	
Paroxysmal 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 convert 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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# Randomized controlled trial comparing gastric cancer screening by gastrointestinal X-ray with serology for *Helicobacter pylori* and pepsinogens followed by gastrointestinal endoscopy

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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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**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.

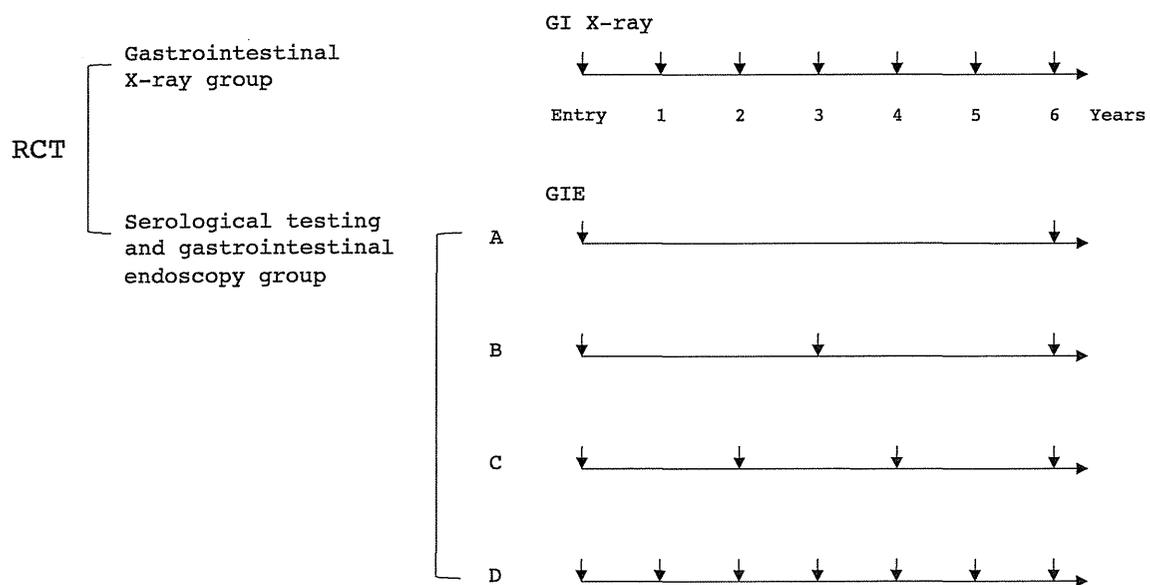
GI X-ray, which is the currently employed intervention for gastric cancer in Japan, was annually scheduled for the subjects assigned to the GI X-ray group. GI X-ray was performed according to the standard methods proposed by the Japanese Society of Gastroenterology Cancer Screening [22] and double checks 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  $\alpha$  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.

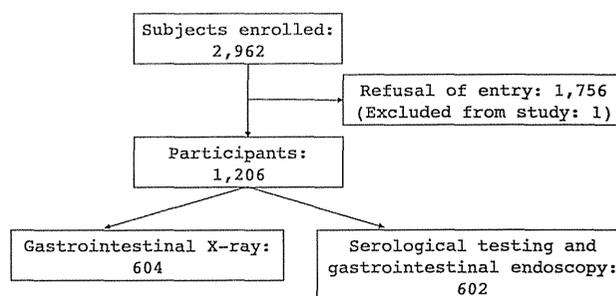


Fig. 2 Trial profile

**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	<i>p</i> value
<i>n</i>	604	602	
Sex			
Male	304	304	0.95
Female	300	298	
Age (mean $\pm$ SD)	61.5 $\pm$ 7.9	61.3 $\pm$ 7.8	0.71
Height (mean $\pm$ SD)	158.9 $\pm$ 8.2	158.6 $\pm$ 8.4	0.49
Body weight (mean $\pm$ SD)	59.6 $\pm$ 10.0	59.3 $\pm$ 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

**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	
<i>n</i>	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
<i>n</i>	604	602	
Number of gastric cancers	0	3	0.25
Number of complications	1	0	1.00

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.

**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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# Study design and patient recruitment for the Japan Polyp Study

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**Background:** The Japan Polyp Study (JPS) Workgroup was established in 2000 to evaluate colonoscopic follow-up surveillance strategies. The JPS was a multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies in patients who had undergone two complete colonoscopies for control of colorectal cancer, with removal of all detected polyps. The aim of the present analysis was to assess the patient recruitment and whether the clinical characteristics were adequate for enrollment at the participating centers.

**Materials and methods:** Among referrals for colonoscopy at the eleven participating centers, all patients who were 40–69 years old, without a family or personal history of familial polyposis, Lynch syndrome, inflammatory bowel disease, or a personal history of polypectomy with unknown histology, and had no invasive colorectal cancer or colectomy, were considered for inclusion from February 2003.

**Results:** Among 4,752 referrals, a total of 3,926 patients with a mean age of 57.3 (range 40–69) years, including 2,440 (62%) males, were included in the JPS. The participation rate was 83%. Among them, a total of 2,757 patients who had undergone two complete colonoscopies with removal of all detected polyps were eligible, giving an eligibility rate of 70% (2,757 of 3,926). Among the eligible patients, 2,166 were assigned to randomized groups, and 591 patients to a nonrandomized group. The last steps of data lock, analysis, and complete histopathological assessment based on a pathology review are ongoing.

**Conclusion:** Eligible patients recruited for the JPS were successfully assigned on the basis of the expected sample-size calculation.

**Keywords:** colonoscopy, follow-up surveillance strategies, Japan Polyp Study (JPS), study design, multicenter randomized controlled trial

## Introduction

Colorectal cancer is the third-most important cause of cancer mortality in Japan.<sup>1</sup> Identification and removal of adenomatous polyps and postpolypectomy surveillance are considered to be important for control of colorectal cancer.<sup>2,3</sup> However, there have been no established recommendations for postpolypectomy colonoscopic surveillance in Japan. In current practice, the intervals between colonoscopies after polypectomy are variable, often being up to a year, and not based on data from randomized clinical trials.

The evolution of colorectal cancer from its precursor lesion, adenoma, was first reported by Morson as the adenoma–carcinoma sequence.<sup>4</sup> The introduction of colonoscopy provided an opportunity for clarifying this sequence, because of its ability to examine the entire colon and remove polyps for pathological examination. The epidemiology and natural history of adenomas are not only important for choosing



the optimal follow-up policy after polypectomy but also for evaluating endoscopic screening for colorectal adenomas and cancer. On the other hand, depressed lesions, including some with advanced histology, have been demonstrated in a number of recent series from several Western countries and Japan.<sup>5-9</sup> However, the clinical significance of depressed lesions in the evolution of colorectal cancer, ie, the so-called *de novo* pathway, is still controversial.<sup>10</sup>

In the US, the National Polyp Study (NPS), which has been ongoing since 1980, has recommended an interval of at least 3 years between colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination.<sup>2,3,11</sup> Although long-term evaluation of colonoscopic polypectomy in the NPS demonstrated a 53% reduction in mortality due to colorectal cancer, the study was conducted prior to recent epidemiologic studies documenting the importance of non-polypoid lesions. Therefore, such techniques as chromoendoscopy, required for diagnosis of nonpolypoid lesions, were not used in the NPS, and this may at least partly explain the discrepancy between the results of the NPS and subsequent epidemiological studies.<sup>12,13</sup>

The Japan Polyp Study (JPS) Workgroup was established in 2000 to evaluate follow-up colonoscopic surveillance strategies, partly supported by a Grant for Scientific Research Expenses for Health and Welfare Programs.<sup>14</sup> The JPS was a multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies in patients who have undergone two complete colonoscopies for control of colorectal cancer, with the removal of all detected polyps by high-resolution chromoendoscopy, including nonpolypoid lesions. From 2000 to 2002, we confirmed whether randomization was feasible after one complete colonoscopy as far as the cecum, with removal of all detected adenomatous polyps, as was the case in the NPS. Initially, we had investigated a retrospective cohort study to estimate the incidence of advanced neoplasia after initial colonoscopy at six institutes of the JPS Workgroup.<sup>14,15</sup> Unexpectedly, the study showed higher cumulative incidences of index lesions, which were defined as large adenomatous polyps measuring >10 mm, adenomas with high-grade dysplasia, or invasive cancer (1 year after initial colonoscopy, 3.2%, including seven invasive cancers; 3 years after initial colonoscopy, 7.5%, including 13 invasive cancers).<sup>16</sup> Based on these results, the JPS Workgroup considered it necessary to perform two complete colonoscopies before randomization in order to avoid overlooking any clinically significant lesions. All of the institutional review boards finally agreed that randomization into two groups undergoing either 1) follow-up examination

at 1 year and 3 years or 2) follow-up examination at 3 years after two complete colonoscopies as far as the cecum, with removal of all adenomatous polyps detected, was acceptable (Figure 1).<sup>16</sup>

The primary end point of the JPS was to address the hypothesis that after two complete colonoscopies with the removal of all detected polyps, the incidence of index lesions would not be different between patients undergoing two further follow-up examinations and those undergoing just one. The aim of the present analysis was to assess the patient recruitment of the JPS and to determine whether the clinical characteristics were adequate for enrollment at the participating centers.

## Materials and methods

### Organization

This multicenter prospective study was initiated by the JPS Workgroup, which was established in 2000 in Japan. Eleven participating centers accrued patients for the JPS (Table 1). All entries and follow-up examinations were the responsibility of the study investigators. Quality-assurance programs were instituted in each of the disciplines encompassed by the study. An independent pathology-review team was established at the National Cancer Center (Tokyo, Japan) to examine all resected polyps prospectively, and for each polyp a consensus among the three pathology reviewers (TS, TF, and YA) was reached. The pathologic classification adopted for the JPS was based on the World Health Organization classification.<sup>17</sup> All depressed lesions and index lesions were reviewed independently by the endoscopic review team at the National Cancer Center. The endoscopic classification was based on the Japanese Society for Cancer of the Colon and Rectum system.<sup>18</sup> All data obtained on the basis of the JPS protocol were overseen by Medical Support Research (Osaka, Japan).

### Sample-size calculation

For determining the sample size required for a noninferiority trial, we set the incidence of index lesions at 3% at 3 years after initial examination of a clean colon. We also set the noninferiority margin at 2% (considered as clinically relevant), the one-sided alpha at 2.5% (one-sided), and the statistical power at 80%. For each group, 1,142 patients were required, and a total of 2,284 patients were required for the trial. Considering the patient dropout rate (20%) and patients who did not have polyps (who were not eligible for the randomized trial: 20%), we planned to recruit at least 4,000 patients for the study.

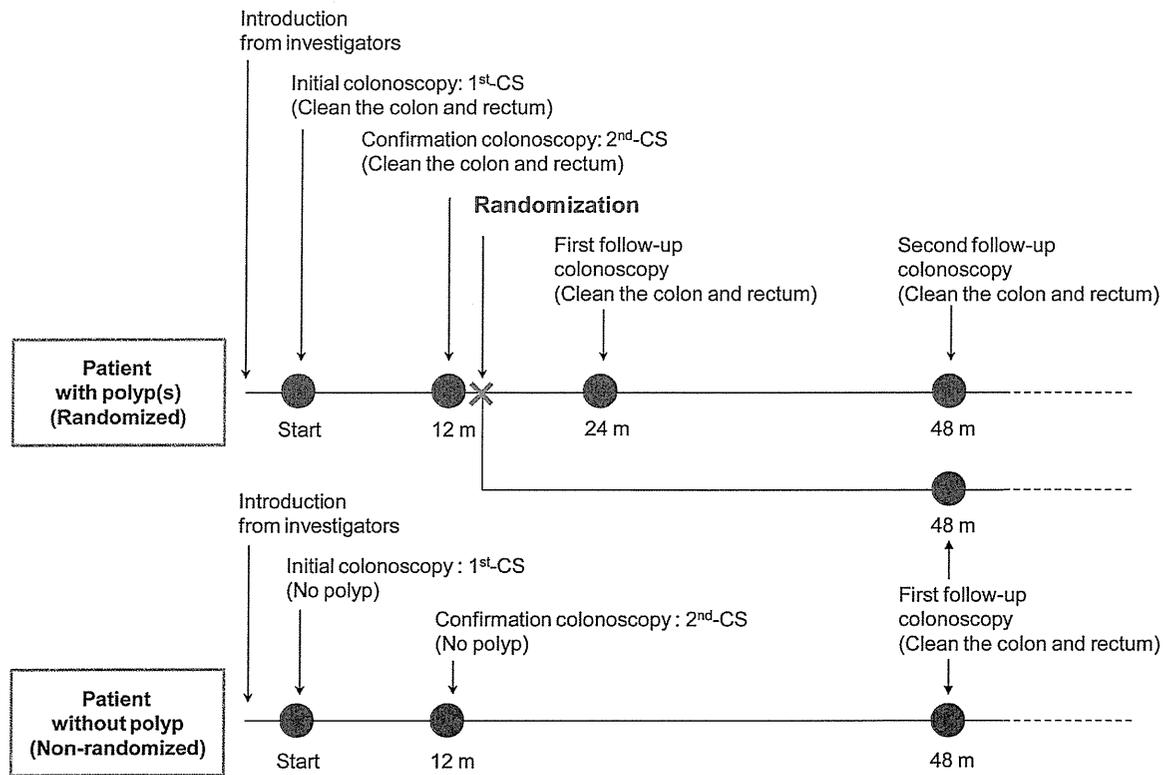


Figure 1 Design of the Japan Polyp Study. Abbreviations: CS, colonoscopy; m, months.

Table 1 Participating, review, and data centers in the Japan Polyp Study

	Location (prefecture)
<b>Participating center</b>	
1. National Cancer Center Hospital	Tokyo
2. National Cancer Center Hospital East	Chiba
3. Saku Central Hospital	Nagano
4. Showa University Hospital	Tokyo
5. Showa University Northern Yokohama Hospital	Kanagawa
6. Kitasato University East Hospital	Kanagawa
7. Shizuoka Cancer Center	Shizuoka
8. Hattori GI Endoscopy and Gastroenterology Clinic	Kumamoto
9. Osaka Medical Center for Cancer and Cardiovascular Diseases	Osaka
10. Takahiro Fujii Clinic	Tokyo
11. Tochigi Cancer Center*	Tochigi
<b>Pathology review</b>	
1. National Cancer Center Hospital	Tokyo
2. Dokkyo Medical University	Tochigi
3. Niigata Medical University	Niigata
<b>Endoscopic review</b>	
1. National Cancer Center Hospital	Tokyo
<b>Data Center</b>	
1. Medical Research Support	Osaka

Note: \*Since 2005.

### Informed consent

Information on the protocol was given to all patients, and informed consent was secured after the respective interventions. In regular checkups, there was no discrimination according to agreement/refusal to take part in the study, or any drawback resulting from withdrawal. Only patients who gave informed consent were included in the study.

### Patient accrual

All patients referred for colonoscopy at the eleven participating centers shown in Table 1, who were 40–69 years old, without a family or personal history of familial polyposis, Lynch syndrome, or inflammatory bowel disease, or a personal history of polypectomy with unknown histology, and without invasive colorectal cancer or colectomy, were considered for inclusion from February 2003.

Patients were excluded if colonoscopy revealed colorectal cancer invading beyond the muscularis mucosae, or a sessile adenoma with a base exceeding 3 cm in diameter. The data collected for these patients consisted of the reason for referral, the outcome of the examination, and certain items of

demographic information. Patients were eligible if they had undergone two complete colonoscopies (first CS and second CS) as far as the cecum, with removal of all polyps detected. The patients were assigned to two groups: 1) a nonrandomized group (patients without polyps), and 2) a randomized group (patients with polyps). Data for all patients in these two groups included detailed demographics, medical history, and information on the procedure employed and the individual polyp(s) resected. Nonrandomized patients included those who had no neoplastic lesions were enrolled at 3 years only after undergoing two complete colonoscopies (first CS and second CS).

All randomized patients were randomly assigned to undergo follow-up colonoscopy at 1 and 3 years, or at 3 years only. For randomization, we used a dynamic allocation scheme to ensure balance between the two groups over time.<sup>19</sup> There were five prognostic factors: 1) institution, 2) sex (male/female), 3) age category ( $\geq 65$  years and  $< 65$  years), 4) risk stage of colon cancer – a) patients with polyps measuring  $\leq 5$  mm only on two complete colonoscopies (first CS and second CS), b) patients with polyps measuring  $\geq 6$  mm on two complete colonoscopies, independently of the presence of polyps measuring  $\leq 5$  mm, and c) patients with any intramucosal cancer, independently of the presence and size of the polyp on colonoscopy – and 5) history of colonoscopy, chosen for balance between the groups. The study design of the JPS is shown in Figure 1.

### Follow-up

All patients were contacted by post 2 months before their scheduled follow-up month, with a request to undergo the follow-up examination.

### Statistical analysis

Basic descriptive analyses of the pool of patients referred for colonoscopy and those eligible for the surveillance study are presented. The percentages were recorded in the categorical data (eg, sex and reason for referral) for each center. Means and standard deviation were used for quantitative data (eg, age).

### Ethical considerations

The protocol was reviewed a priori and approved by the institutional review boards at all of the participating hospitals in 2003. This trial is registered, and details are available at <http://www.umin.ac.jp> (UMIN C00000058), where the trial protocol can be accessed.

### Funding

The study was supported by Grants-in-Aid for Clinical Cancer Research (13S-8, 16S-33, 20S-12, and 23S-8) from the Ministry of Health, Labour and Welfare, Japan. The JPS website is <http://www.jps21.jp/index.html> (Japanese only).

### Results

A flowchart for the JPS is shown in Figure 2.

### Patient recruitment for the JPS

Patient accrual began in February 2003 and ended in December 2006. A total of 4,752 patients were referred to the eleven participating centers for colonoscopy, and none of them had a history of familial polyposis, Lynch syndrome, or inflammatory bowel disease, a personal history of polypectomy with unknown histology, or had had invasive colorectal cancer or colectomy. A total of 3,926 patients with a mean age of 57.3 (range 40–69) years, including 2,440 (62%) males, who consented to join the study were included in the JPS (Table 2). The participation rate was 83% (3,926 of 4,752).

### Reason for referral

Although most patients were referred for a number of reasons, each patient was categorized according to the main finding on which the referral was based (Table 3). The predominant reason for referral was a positive result for fecal occult blood testing (FOBT; 37.2%), followed by overt symptoms (16.9%).

### First colonoscopy

A total of 3,895 patients underwent colonoscopy, among whom 178 were excluded due to 1) invasive cancers (109 patients: 45 with advanced cancer, 66 with submucosal invasive cancer, and three with intramucosal cancer, with a certain degree of overlap), 2) lesions more than 30 mm in diameter, or for which surgery was indicated (16 patients: nine with adenoma, seven with intramucosal cancer), 3) carcinoid tumor (seven patients), and 4) other reasons (46 patients: inflammatory bowel disease/poor bowel preparation/failure to clean the colon or total colonoscopy). A total of 930 patients dropped out before receiving the second CS in spite of postal notification. The prevalence of patients with invasive colorectal cancer was 2.8% (109 of 3,895).

### Second colonoscopy

A total of 2,787 patients underwent colonoscopy at 1 year after the first CS. A total of 30 patients were excluded due to 1) invasive cancer (four patients: one with advanced cancer,

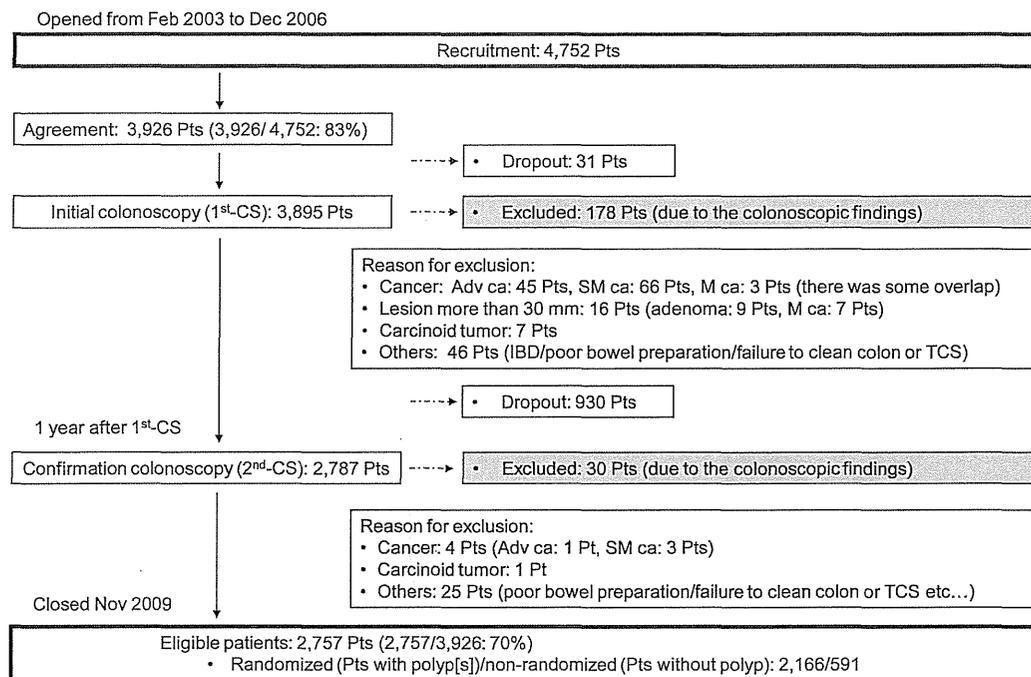


Figure 2 Japan Polyp Study flow.

Abbreviations: Pts, patients; CS, colonoscopy; Adv, advanced; ca, cancer; SM, submucosal invasive; M, intamucosal; IBD, inflammatory bowel disease; TCS, total colonoscopy.

three with submucosal invasive cancer), 2) carcinoid tumor (one patient), and 3) other reasons (25 patients: poor bowel preparation/failure to clean the colon or total colonoscopy). The prevalence of patients with interval invasive colorectal cancer was 0.14% (four of 2,787).

### Patients eligible for the JPS

A total of 2,757 patients who underwent two complete colonoscopies (first CS and second CS) as far as the cecum, with removal of all polyps detected, were eligible. The eligibility rate was 70% (2,757 of 3,926). Among the eligible patients, 2,166 were assigned to randomized patient groups (patients with polyp[s]) and 591 patients to a nonrandomized patient group (patients without polyp).

### Discussion

The NPS, which was started in the USA in 1980, showed that the removal of all polyps by colonoscopy reduces the incidence of colorectal cancer, and recommended an interval of at least 3 years between colonoscopic removal of newly diagnosed adenomatous polyps and subsequent follow-up examination.<sup>2,3</sup> In Japan, however, there are no established recommendations for postpolypectomy colonoscopic surveillance based on reliable evidence.

The JPS Workgroup was established in 2000 to evaluate colonoscopic follow-up surveillance strategies under a Grant for Scientific Research Expenses for Health and Welfare Programs. The JPS is the largest clinical study conducted in ethnic Japanese communities, documenting for the first time follow-up surveillance strategies for patients who have undergone two complete colonoscopies for control of colorectal cancer, with the removal of all detected polyps.<sup>16</sup> It will provide preexisting comorbidity data, including the prevalence of both flat and depressed colorectal lesions, the quality of colonoscopy, and the risk of colon cancer. Furthermore, these follow-up data will help to clarify the long-term impact of colonoscopic removal on mortality due to colorectal cancer. The evidence will form a basis for the surveillance and management of colorectal cancer in community-dwelling individuals who undergo colonoscopy in Japan.

Although the subjects in the JPS underwent two complete colonoscopies before randomization, the participation rate was high (83%). However, 24.5% (961 of 3,926) of the patients dropped out from the study before randomization, mostly after the first CS. One possible reason for the high dropout rate was that all examinations were performed under the national health insurance scheme. Patients had to pay expenses ranging from US\$35 to \$80 per colonoscopy, or \$100–\$300