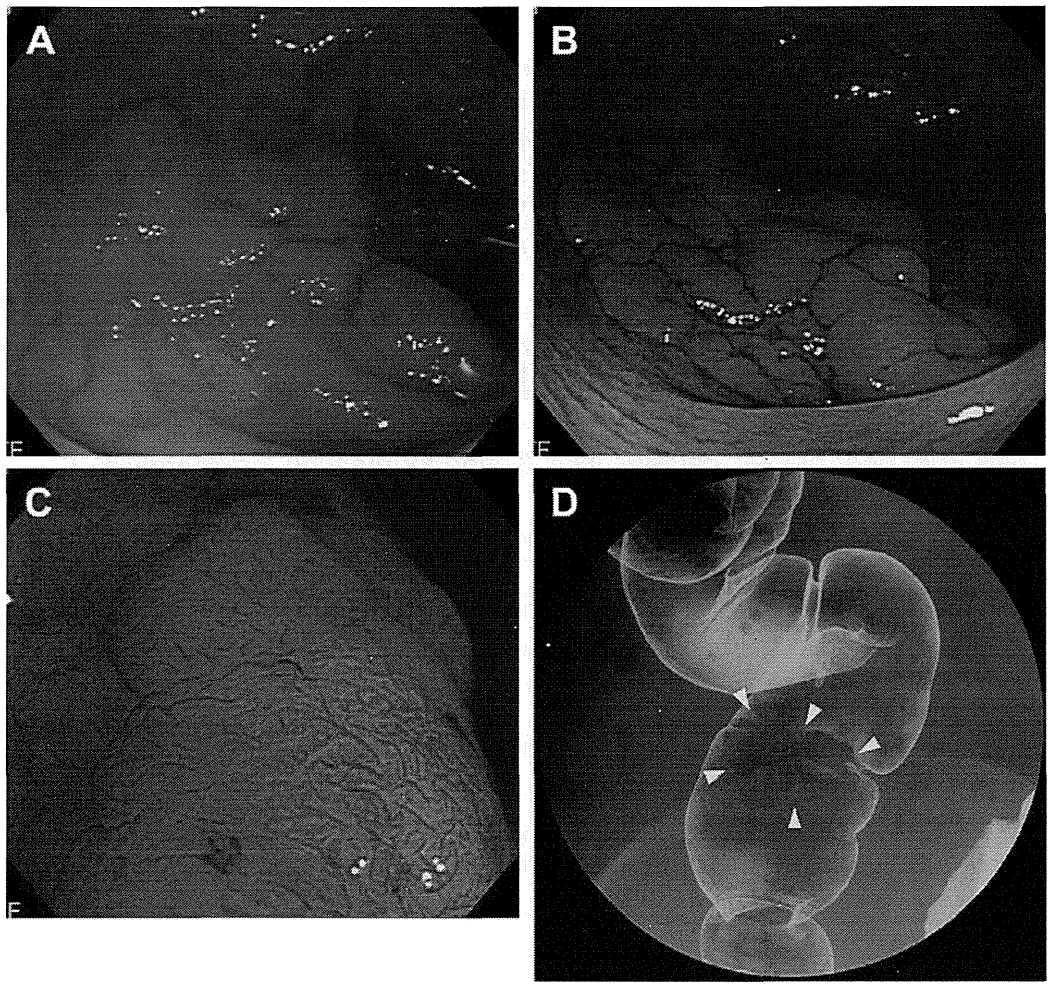

Fig. 1. (*A*) Conventional view, (*B*) Conventional view with indigo carmine dye, (*C*) Magnifying view with crystal violet staining, (*D*) Barium enema image.

(80.1% vs 69.7%, $P = .04$). This result is obtained not only in polypoid lesions (71.8% vs 60.3%, $P = .09$) but also in non-polypoid colorectal lesions (94.2% vs 83.7%, $P = .07$). As a result, the authors concluded that it is sufficient to diagnose the depth of endoscopic resectable early colorectal cancer by colonoscopy alone. However, when selecting surgical management, barium enema or computed tomographic colonography should also be performed to precisely delineate the location of the lesion.

Endoscopic Ultrasonography

Data on the utility of high-frequency endoscopic ultrasonography (EUS) in the management of the malignant colorectal polyp are conflicting. Some authors have reported the usefulness of EUS, particularly the advantages of high-frequency ultrasound (HFUS) to diagnose the invasion depth of early colorectal cancer.[18–21] Hurlstone and colleagues[20] conducted a prospective study to compare the 2 modalities (HFUS vs magnifying chromoendoscopy). They found that HFUS was superior to magnifying chromoendoscopy for determination of depth invasion (93% vs 59% accuracy, respectively [$P<.0001$]). Matsumoto and colleagues[21] also concluded that the negative predictive value of probe-EUS for deep invasion was higher than that of magnifying chromoendoscopy (90.9% vs 54.1%, respectively [$P<.01$]) in the population studied (prevalence deep submucosal invasion 56%).

In contrast, Fu and colleagues[22] have recently reported that magnifying chromoendoscopy is as accurate as EUS for preoperative staging of early colorectal cancer (87% vs 75%, $P = .0985$). Subgroup analysis was also done for polypoid and nonpolypoid lesions. For polypoid lesions, the respective overall diagnostic accuracies of magnifying colonoscopy and EUS were 88% and 72% ($P = .0785$), and for nonpolypoid lesions, 85% and 79% ($P = .7169$). HFUS requires additional training and equipment and can be time-consuming to use.

Nonlifting Sign

Observation of the lesion during and after submucosal saline injection is a simple but important method to assess the potential for deeply invasive cancer. Lesions may not lift because of desmoplastic reaction, invasion from the lesion itself, or submucosal fibrosis from prior biopsy, cautery, ink injection for marking, or ulceration.

Several studies have reported the diagnostic operating characteristics of the nonlifting sign: the positive predictive value of the nonlifting sign is approximately 80%. Originally, Uno and colleagues[23] described this terminology in 1994. Kobayashi and colleagues[24] also reported the verification of the nonlifting sign as one modality of depth diagnosis for colorectal cancers. The nonlifting sign had a sensitivity of 61.5%, a specificity of 98.4%, a positive predictive value of 80%, a negative predictive value of 96%, and an accuracy of 94.8%. In contrast, endoscopic diagnosis using magnifying chromoendoscopy of deeper infiltration had a sensitivity of 84.6%, a specificity of 98.8%, a positive predictive value of 88%, a negative predictive value of 98.4%, and an accuracy of 97.4%. Statistically significant differences were found in terms of sensitivity ($P = .031$) and accuracy ($P = .039$). In spite of the simplicity of such a technique, nonlifting sign could not reliably predict deeper cancerous invasion when compared with endoscopic diagnosis.

ESTIMATION OF SUBMUCOSAL INVASION USING CONVENTIONAL AND MAGNIFYING CHROMOENDOSCOPY

Conventional Colonoscopy

New diagnostic modalities such as endoscopic ultrasonography using miniprobe and magnifying chromoendoscopy are reported to be useful for the depth diagnosis of early colorectal cancers. However, these modalities are relatively expensive and time-consuming. Therefore, if invasion depth could be diagnosed with only conventional colonoscopy, it would be more cost-effective and convenient.

Saitoh and colleagues[25] reported that characteristic colonoscopic findings obtained by a combination of videocolonoscopy and chromoendoscopy are clinically useful for determination of the invasion depth of depressed-type colorectal cancers. In this report, characteristic colonoscopic findings, (ie, [1] expansion appearance, [2] deep depression surface, [3] irregular bottom of depression surface, and [4] folds converging toward the tumor) are needed for surgical operation. According to their results, the invasion depth of depressed-type early colorectal cancers could be correctly determined in 58 of 64 lesions (91%) by using these findings.

Data from National Cancer Center Hospital, Tokyo

To clarify the clinically important characteristic colonoscopic findings, the authors reviewed all conventional colonoscopic images of non-polypoid submucosal colorectal cancers treated endoscopically or surgically between 1999 and 2003. There were 123 non-polypoid submucosal colorectal cancers (IIa, LST: 34; IIc, IIa+IIc, Is+IIc [NPG type]: 89) as shown in **Table 1**. In this retrospective review, 7 characteristic colonoscopic findings, (1) tumor size, (2) white spots (chicken-skin appearance), (3)

Table 1
Clinicopathologic characteristics of non-polypoid submucosal cancers

	IIa, LST	IIc, IIa+IIc, Is+IIc
Number of lesions	34	89
Tumor size (mean±SD, mm)	25.4±18.2	15.3±6.8
Histopathologic diagnosis		
SM-superficial (<1000 μm)	19 (56%)	16 (18%)
SM-deep (≥1000 μm)	15 (44%)	73 (82%)
Location		
Right colon	14 (41%)	31 (35%)
Left colon	9 (27%)	23 (26%)
Rectum	11 (32%)	35 (39%)

Abbreviation: SM, submucosal.

redness, (4) firm consistency, (5) expansion, (6) fold convergence, and (7) deep depressed area (**Fig. 2**), were evaluated for association with submucosal deep invasion and then compared with histopathologic results.

Among all the non-polypoid submucosal colorectal cancers, white spots (chicken-skin appearance), redness, firm consistency, and deep depressed area were significantly associated with an increased risk of submucosal deep invasion according to univariate analysis (**Table 2**).

Magnifying Chromoendoscopy

Magnifying chromoendoscopy is a standardized validated method that facilitates detailed analysis of the morphologic architecture of colonic mucosal crypt orifices (pit pattern) in a simple and efficient manner. However, magnifying colonoscopes are still rarely used in endoscopy units. Unrecognized necessity and lack of

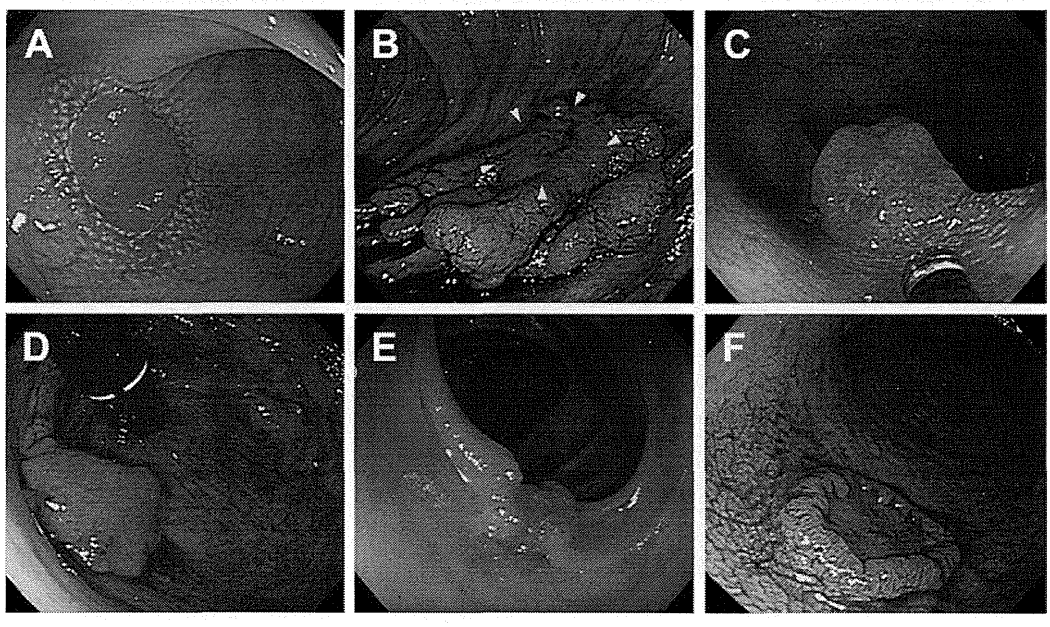

Fig. 2. Six characteristic colonoscopic findings: (*A*) white spots (chicken-skin appearance), (*B*) redness, (*C*) firm consistency, (*D*) expansion, (*E*) fold convergence, and (*F*) deep depressed area.

Table 2
Relationship between endoscopic findings and submucosal deep invasion

	SM-Superficial (n = 35)	SM-Deep (n = 88)	Univariate Analysis (P value)	Diagnostic Sensitivity and Specificity
Size (≥ 20 mm)	16/35 (45.7%)	30/88 (34.1%)	0.23	Sens. 34.1% Spec. 54.3%
White spots (chicken skin) (+)	2/35 (5.7%)	29/88 (32.9%)	0.002	Sens. 32.9% Spec. 94.3%
Redness (+)	14/35 (40.0%)	62/88 (70.4%)	0.002	Sens. 70.4% Spec. 60.0%
Firm consistency (+)	11/35 (31.4%)	69/88 (78.4%)	<0.0001	Sens. 78.4% Spec. 68.6%
Expansion (+)	2/35 (5.7%)	18/88 (20.4%)	0.07	Sens. 20.4% Spec. 94.3%
Fold convergence (+)	4/35 (11.4%)	20/88 (22.7%)	0.24	Sens. 22.7% Spec. 88.6%
Deep depression (+)	15/35 (42.9%)	70/88 (79.5%)	<0.0001	Sens. 79.5% Spec. 57.1%

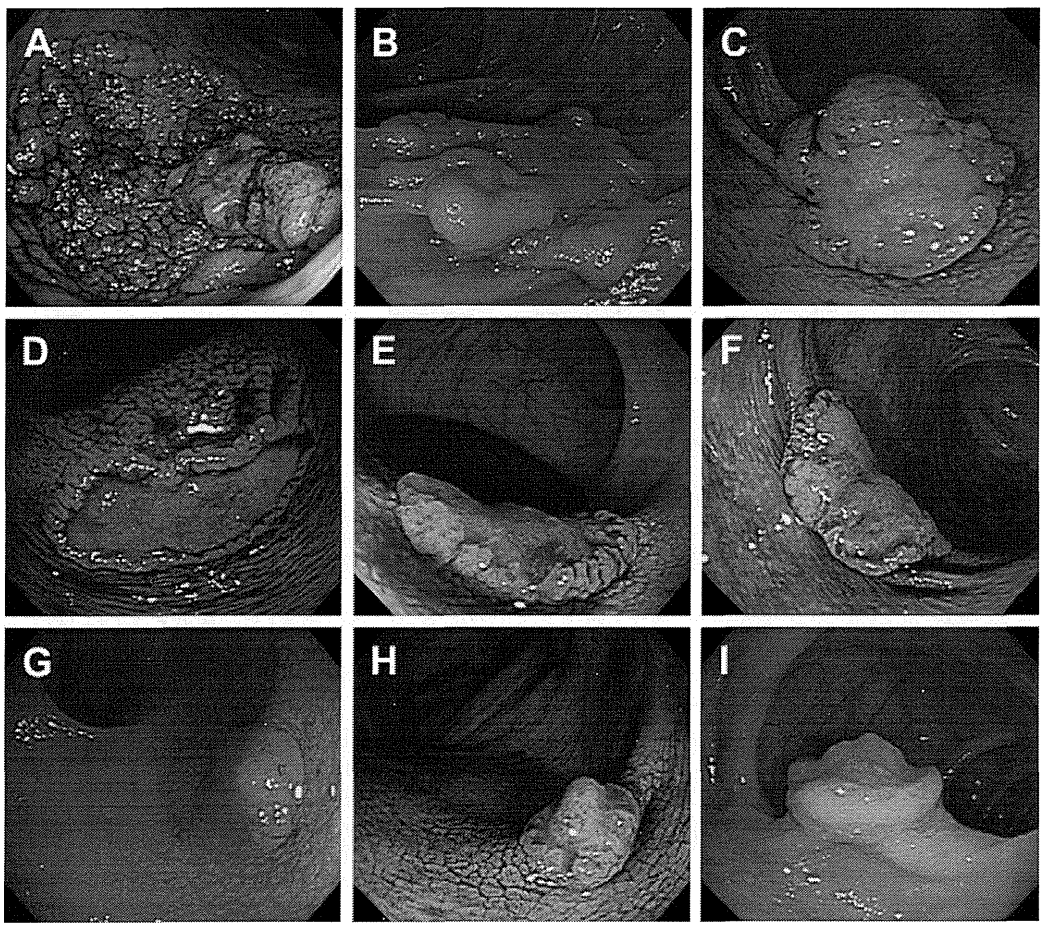

Fig. 3. Representative conventional colonoscopic images of submucosal cancers. (*A*) Is+IIa (LST-granular), (*B*) IIa (LST-nongranular [NG]), (*C*) IIa+IIc (LST-NG), (*D*) IIc, (*E-G*) IIa+IIc, (*H, I*) Is+IIc.

randomized studies validating the effectiveness of magnifying chromoendoscopy are possible reasons for this. The authors believe that magnifying chromoendoscopy is essential armamentarium in gastrointestinal endoscopy units and that its main clinical significance is the in vivo diagnosis of the nature of colorectal lesions to determine the appropriate treatment modality.

The clinical classification of the colonic pit pattern (invasive and noninvasive) using magnifying chromoendoscopy was originally described by Fujii in 1998 with the aim to discriminate between intramucosal-submucosal superficial invasion and submucosal deep invasion.[26] Contrary to the anatomic classification by Kudo and colleagues, the rationale for the clinical classification is based on the identification of irregular or distorted crypts in a demarcated area (**Fig. 3**), which strongly suggests that the cancerous lesion is already invading deeply into the submucosal layer.

Some studies have already reported the clinical usefulness of detailed determination of the V pit pattern using magnifying chromoendoscopy for predicting the depth of invasion of submucosal cancers. Kudo and colleagues[10] reported that 11 of 22 (50%) lesions having a type V pit pattern with a bounded surface were found to be invasive cancers with involvement of the submucosal layer. Other studies have reported a diagnostic accuracy of type V pit for the diagnosis of submucosally invasive cancer of 85% (81/95) and 79% (11/14), respectively.[27,28] The authors recently performed a large prospective study of 4215 lesions in 3029 consecutive patients between 1998 and 2005. All lesions were detected by conventional endoscopic view and assessed using magnifying chromoendoscopy for evidence of invasive

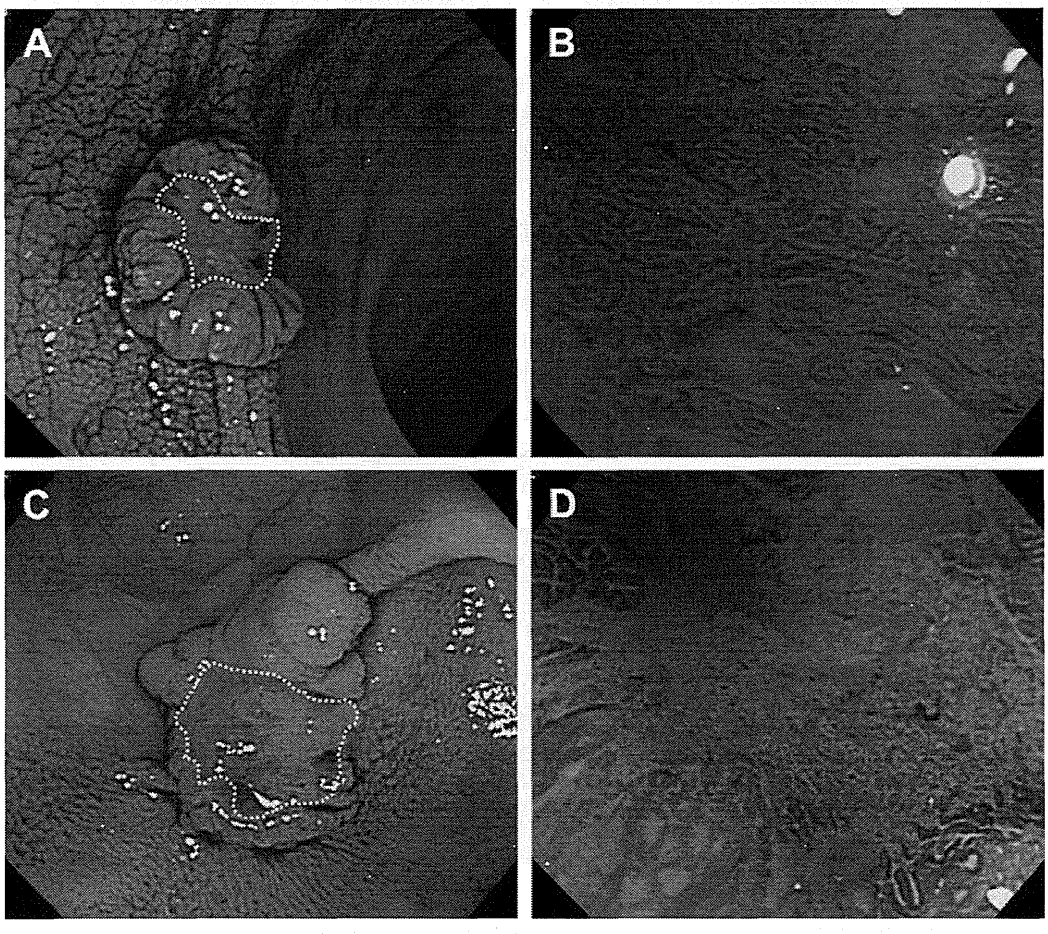

Fig. 4. Definition of invasive pattern: irregular/distorted pit with demarcated area.

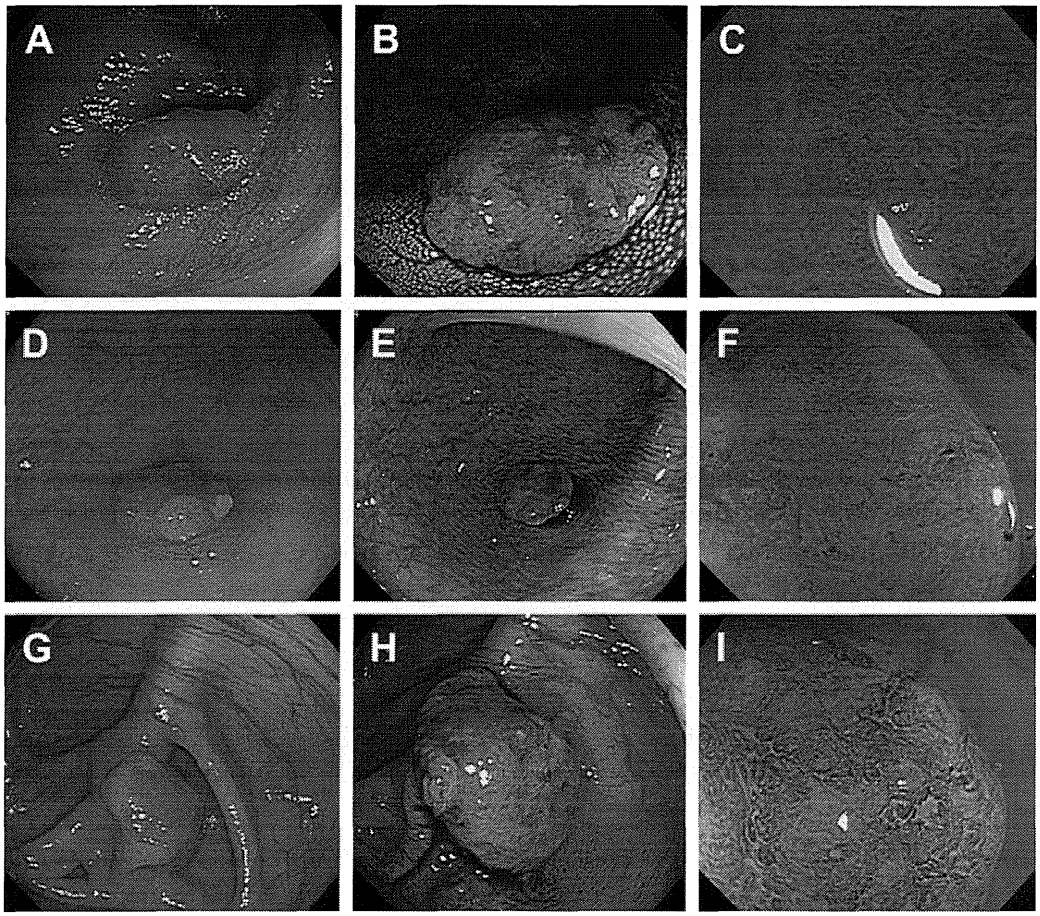

Fig. 5. Submucosal deep cancers. (*A-B*) Is-type submucosal cancer, conventional view. (*C*) Magnifying view (invasive pattern). (*D, E*) IIa+IIc-type submucosal cancer, conventional view. (*F*) Magnifying view (invasive pattern). (*G, H*) Is+IIc-type submucosal cancer, conventional view. (*I*) Magnifying view (invasive pattern).

features according to pit-pattern evaluation. Their data showed that 99.4% of lesions diagnosed as noninvasive pattern were adenoma, intramucosal cancer, or submucosal invasion less than 1000 μm. Among lesions diagnosed with invasive pattern, 87% were cancers with submucosal deep invasion (**Figs. 4** and **5**). Based on the macroscopic appearance, the diagnostic sensitivity of the clinical pit pattern to determine the depth of invasion of polypoid, flat, and depressed lesions was 75.8%, 85.7%, and 98.6%, respectively. This is the first large-scale prospective study to validate the use of magnifying chromoendoscopy as a highly effective method in the prediction of invasion depth of colorectal neoplasms.[29]

SUMMARY

Although of lower prevalence compared with polypoid neoplasms, the non-polypoid neoplasms, especially the depressed type, are important to diagnose because they belong to a distinct biologically aggressive subset, given the high rate of intramucosal or submucosal cancers. The detection and diagnosis of the non-polypoid colorectal neoplasm presents a challenge and an opportunity. Above all, characteristic colonoscopic findings obtained by a combination of conventional colonoscopy and magnifying chromoendoscopy are useful for determination of the invasion depth of non-polypoid colorectal cancers, an essential factor in selecting a treatment modality.

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Adipocytokines as new promising markers of colorectal tumors: Adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer

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Adipocytokines are adipocyte-secreted hormones associated with some malignancies such as colorectal, breast, and prostate cancer. We hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma, and investigated the association of the blood levels of several adipocytokines through a case-control study. Blood levels of adiponectin, leptin, resistin, visfatin, and C-peptide at diagnosis were measured in 115 colorectal cancer patients and 115 age-, sex-, and body mass index-matched controls. The same analysis was performed in 72 colorectal adenoma patients and 72 controls. Logistic regression models were used for estimating odds ratios and 95% confidence intervals, and one-way ANOVA was performed to determine the prevalence of each variable between two or more groups. Resistin and visfatin levels in cancer patients were significantly higher than those of controls on multivariate analysis ($P = 0.03$ and $P < 0.01$, respectively). Stage progression significantly correlated with resistin and visfatin levels ($P < 0.01$ for both). The adiponectin level in adenoma patients was significantly lower than that of controls on multivariate analysis ($P = 0.04$). Its level was inversely correlated with the number of adenoma ($P = 0.02$), but not correlated with the size of adenoma. Resistin and visfatin may be good biomarkers of colorectal malignant potential and stage progression. Adiponectin level may be a good biomarker of colorectal adenoma. (*Cancer Sci* 2010)

Adipocytokines, such as adiponectin, leptin, resistin, visfatin, tumour necrosis factor (TNF)-α, and interleukin (IL)-6 are cytokines secreted by visceral adipose tissue, and they have recently been suggested to be associated with obesity-related diseases.[1,2] Many epidemiologic studies have shown a positive correlation between obesity and increased risk of colorectal cancer and adenoma as well as other cancers at various sites (e.g. breast, prostate gland, and endometrium).[3–5]

In obesity mouse models, severe macrophage invasion was observed in the vascular/stromal compartment of adipose tissue, suggesting that excess adiposity is associated with chronic inflammation.[6,7] Other reports have shown that prostaglandin E2 stimulates leptin secretion from cultured human adipose tissue cells and that cyclooxygenase 2 inhibitors prevent an increase in leptin production.[8] In inflammation-associated colorectal cancers, such as those associated with inflammatory bowel diseases, non-genetic stimuli such as overexpression of IL-6 also enhance the survival and proliferation of preneoplastic cells.[9] Leptin was also reported to induce IL-6 production by $Apc^{Min/+}$ colon epithelial cells which leads to autocrine/paracrine trans IL-6 receptor signaling.[10] This results in the promotion and survival proliferation of preneoplastic cells. On the other hand, adiponectin reportedly inhibits inflammation and angiogenesis while leptin induces tumor angiogenesis.[11,12]

These findings in epidemiological and basic research suggest that adipocytokines may well contribute to the induction of carcinogenesis and tumor progression. Therefore, we hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma. To evaluate whether adipocytokines are stronger biomarkers of colorectal cancer and adenoma than body mass index (BMI), we performed a BMI-matched case-control study and investigated the association between the blood levels of several adipocytokines and colorectal cancer and adenoma.

Materials and Methods

Study population. After approval of the study protocol by the Institutional Review Board of the National Cancer Center, patients who underwent upper total colonoscopy at the hospital from February 1999 to February 2007, who were considered to have no active malignancies except colorectal cancer and no inflammatory bowel diseases, and whose blood samples at diagnosis before any treatments for colorectal cancer or adenoma could be obtained, were identified and invited to participate in the study. Patients who had been newly and pathologically diagnosed with colorectal cancer by biopsy using colonoscopy and treated at our hospital were identified as colorectal cancer patients among the enrolled patients. Age-, sex-, and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. Among the enrolled patients, we identified those patients who had been newly undergone hot-biopsy, polypectomy, or endoscopic mucosal resection and were pathologically diagnosed with colorectal adenoma at our hospital as colorectal adenoma patients. Age-, sex- and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. BMI at diagnosis was calculated based on the data in medical records as follows: weight (kg)/height $(m)^2$. All subjects (patients and controls) provided informed consent prior to the collection and analysis of blood samples. Clinical and pathological information for both groups was obtained from medical records.

Adipocytokines and C-peptide measurements. All blood samples were stored at −20°C until use. None of the samples were previously thawed. Blood levels of adiponectin, resistin,

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Table 1. Clinical characteristics of patients with colorectal cancer and controls

	Patients (n = 115)	Controls (n = 115)	P-values
Age (years)	63.7 ± 10.3	63.5 ± 10.5	0.99
Sex			
Female (%)	46 (40.0)	46 (40.0)	
Male (%)	69 (60.0)	69 (60.0)	1.00
Body mass index	22.9 ± 2.9	23.1 ± 2.7	0.897
Stage*			
0	23	–	–
I	23	–	–
II	19	–	–
III	23	–	–
IV	27	–	–
Location			
Right colon	55	–	–
Left colon	7	–	–
Rectum	53	–	–
Macroscopic type*			
0 – Ip	5	–	–
0 – Isp	6	–	–
0 – Is	10	–	–
0 – IIa	17	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
1	1	–	–
2	73	–	–
3	1	–	–
4	1	–	–
5	1	–	–
Histological type*			
Well-differentiated adenocarcinoma	86	–	–
Moderately differentiated adenocarcinoma	21	–	–
Poorly differentiated adenocarcinoma	7	–	–
Mucinous adenocarcinoma	1	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

visfatin, and C-peptide at diagnosis were measured by SRL (Tokyo, Japan). Adiponectin was determined by enzyme-linked immunosorbent assay (ELISA) (Otsuka Pharmaceutical, Tokyo, Japan) with a sensitivity of 1.9 μg/mL, an intra-assay coefficient of variation of 3.5–5.1%, and an inter-assay coefficient of variation of 6.0–8.7%. Resistin was determined by ELISA (BioVender Laboratory Medicine, Brno, Czech Republic) with a sensitivity of 1.1 ng/mL, an intra-assay coefficient of variation of 2.8–3.4%, and an inter-assay coefficient of variation of 5.1–6.9%. Leptin was measured using radioimmunoassay kits (Linco Research, St. Charles, MO, USA) with a sensitivity of 0.5 ng/mL, an intra-assay coefficient of variation of 3.4–8.3%, and an inter-assay coefficient of variation of 3.0–6.2%. Visfatin was determined by ELISA (Adipo Gen, Seoul, Korea) with a sensitivity of 0.13 ng/mL, an intra-assay coefficient of variation of 4.4–10.4%, and an inter-assay coefficient of variation of 6.4–9.9%. C-peptide was determined by ELISA (Fujirebio, Tokyo, Japan) with a sensitivity of 0.04 ng/mL, an intra-assay coefficient of variation of 1.96–2.97%, and an inter-assay coefficient of variation of 1.06–2.60%. Duplicate measurements were performed in a single experiment.

Statistical analysis. The results of the comparison of clinical characteristics between patients and controls was evaluated by the χ^2-test for categorical variables and two-sample t-test for continuous variables. Conditional logistic regression models were used for estimating odds ratios and 95% confidence intervals to evaluate the association of each variable with colorectal cancer or adenoma. One-way ANOVA was performed to examine the prevalence of each variable between tumor stage groups. Log transformations were conducted on variables prior to analysis to achieve normal distribution. Differences with a P-value <0.05 were considered significant. All statistical analyses were carried out using the SAS system (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Adipocytokines and C-peptide, and colorectal cancer. The clinical characteristics and adipocytokine and C-peptide levels of the 115 colorectal cancer patients and 115 controls are shown in Tables 1 and 2. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 3. Resistin and visfatin levels were significantly higher in the colorectal cancer patients than in the controls on multivariate analysis (P = 0.03 and P < 0.01, respectively). Linear contrast analysis was conducted to evaluate the correlation between each variable and tumor stage defined by the Japanese Classification of Colorectal Carcinoma 6th edition (Table 4). Resistin and visfatin levels gradually increased with tumor stage progression (P < 0.01 and P < 0.01, respectively).

Adipocytokines and C-peptide, and colorectal adenoma. The clinical characteristics and adipocytokine and C-peptide levels of the 72 colorectal adenoma patients and 72 controls are shown in Tables 5 and 6. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 7. Multivariate analysis showed that adiponectin levels were significantly lower in the colorectal adenoma patients than in the control patients (P = 0.04). Linear contrast analysis was conducted to evaluate the correlation between each variable and the number of adenomas (Table 8a). Adiponectin level inversely correlated with the number of adenomas (P = 0.02). The size of the largest adenoma among all the adenomas of a patient showed no significant correlation with any variables (Table 8b).

Table 2. Blood adipocytokine levels in patients with colorectal cancer and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	n	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	115	8.9	6.6	13	115	8.9	5.7	12.9
Resistin (ng/mL)	115	4.5	3.1	6.4	115	3.1	2.2	4.7
Leptin (ng/mL)	115	3.7	2.4	5.7	114	4.2	2.3	6
Visfatin (ng/mL)	115	3.9	2.1	7.9	115	1.4	0.8	2.6
C-peptide (ng/mL)	114	0.2	0.1	0.4	111	0.3	0.1	0.6

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Table 3. Univariate and multivariate analysis of patients with colorectal cancer and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	1.227 (0.653–2.307)	0.52	0.802 (0.321–2.003)	0.64
Resistin*	2.850 (1.700–4.777)	<0.01	2.067 (1.053–4.055)	0.03
Leptin*	0.799 (0.458–1.393)	0.43	1.057 (0.477–2.342)	0.89
Visfatin*	3.142 (2.064–4.783)	<0.01	2.985 (1.862–4.787)	<0.01
C-peptide*	0.711 (0.550–0.920)	0.01	0.983 (0.663–1.458)	0.93

*Log-transformed.

Table 4. Association between adipocytokine levels and stage progression of colorectal cancer

	Control		Stage 0		Stage 1		Stage 2		Stage 3		Stage 4		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
Adiponectin*	115	2.3 ± 0.5	23	2.3 ± 0.4	23	2.2 ± 0.6	19	2.3 ± 0.5	23	2.1 ± 0.5	27	2.3 ± 0.4	0.94
Resistin*	115	1.2 ± 0.5	23	1.3 ± 0.5	23	1.6 ± 0.5	19	1.5 ± 0.5	23	1.5 ± 0.6	27	1.7 ± 0.5	<0.01
Leptin*	114	1.4 ± 0.7	23	1.4 ± 0.7	23	1.4 ± 0.7	19	1.5 ± 0.8	23	1.3 ± 0.5	27	1.1 ± 0.6	0.11
Visfatin*	115	0.2 ± 1.1	23	0.8 ± 1.2	23	1.3 ± 1.1	19	1.0 ± 0.9	23	1.5 ± 1.0	27	1.8 ± 0.9	<0.01
C-peptide*	111	−1.4 ± 1.2	23	−1.6 ± 1.2	23	−1.6 ± 1.1	19	−1.9 ± 1.2	22	−1.8 ± 1.1	27	−1.6 ± 1.0	0.17

*Log-transformed. Data are presented as mean ± SD.

Linear contrast analysis was also conducted to evaluate the correlation between adiponectin and the adenoma-carcinoma sequence, and the result was not significant (data not shown).

Table 5. Clinical characteristics of patients with colorectal adenoma and controls

	Patients (*n* = 72)	Controls (*n* = 72)	*P*-values
Age (years)	66.8 ± 7.3	66.7 ± 7.1	0.99
Sex			
Female (%)	22 (30.6)	22 (30.6)	
Male (%)	50 (69.4)	50 (69.4)	1.00
Body mass index	23.0 ± 2.8	22.8 ± 2.8	0.74
Number of adenomas			
2>	44	–	–
≥3	28	–	–
Location			
Right colon	33	–	–
Left colon	27	–	–
Rectum	12	–	–
Macroscopic type*			
0 – Ip	4	–	–
0 – Isp	13	–	–
0 – Is	24	–	–
0 – IIa	31	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
Histological atypia			
Moderate atypia	64	–	–
Severe atypia	78	–	–
Maximum size			
−5 mm	14	–	–
6–10 mm	24	–	–
11–20 mm	17	–	–
>20 mm	17	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

Discussion

The results of this case-control study suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently from BMI, and also of stage progression of colorectal cancer. Adiponectin may be a good biomarker of colorectal adenoma independently from BMI. For gastric cancer, we have reported similar results, namely, resistin and visfatin levels in gastric cancer patients were significantly higher than those in controls, and gradually increased with tumor stage progression. Furthermore, adiponectin levels tended to be lower in early stage gastric cancer patients than in controls.[13]

Obesity is recognized as a strong risk factor for the development of several cancers.[3–5] However, many experimental and case-control studies have suggested that BMI is not the best and only marker for elucidating the physiology of obesity. Recently, adipocytokines produced by adipose tissue have been the subject of intense investigation as novel risk markers not only of metabolic syndrome but also of cancers, particularly those indicating a correlation between their risk of development and obesity such as colorectal cancer and adenoma.[14–20] To the best of our knowledge, however, the present study is the first report to evaluate a difference in visfatin level between colorectal cancer patients and controls, and the only one report has been reported for a difference in resistin level so far.[21]

Adiponectin suppresses the secretion of inflammatory cytokines such as TNF-α, and induces the secretion of anti-inflammatory cytokines such as IL-10 in the atherogenic process.[22–24] Furthermore, it has been reported to inhibit tumor growth by suppressing angiogenesis *in vitro* and *in vivo*.[25] In case-control studies, the correlation between adiponectin level and colorectal cancer remains controversial[19,26]. An inverse correlation between adiponectin level and colorectal adenoma has been also reported.[27] Our results showed an inverse correlation between adiponectin and colorectal adenoma. However, we had no information regarding body weight changes in the patients and controls before the sampling, and thus it was not possible to determine whether the decrease in adiponectin levels in the patients was caused by obesity before the sampling. It was also difficult to determine when the adiponectin level decreased, either before or after colorectal adenoma development. Instead

Table 6. Blood adipocytokine levels in patients with colorectal adenoma and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	*n*	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	72	7.5	5.4	10.3	72	8.8	6.3	13.6
Resistin (ng/mL)	72	3.1	2.4	4.8	72	2.8	1.9	3.9
Leptin (ng/mL)	71	3.3	2.4	5.4	72	3.3	1.8	5.4
Visfatin (ng/mL)	72	1	0.6	2.8	72	1.6	0.7	2.8
C-peptide (ng/mL)	71	0.3	0.1	0.7	69	0.2	0.1	0.5

Table 7. Univariate and multivariate analysis of patients with colorectal adenoma and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	0.363 (0.169–0.780)	0.01	0.422 (0.189–0.946)	0.04
Resistin*	1.293 (0.706–2.368)	0.41	1.200 (0.595–2.420)	0.61
Leptin*	1.497 (0.772–2.901)	0.23	1.331 (0.662–2.677)	0.42
Visfatin*	0.883 (0.661–1.180)	0.40	0.872 (0.604–1.260)	0.47
C-peptide*	1.208 (0.893–1.634)	0.22	1.023 (0.704–1.484)	0.91

*Log-transformed.

Table 8. Association between adipocytokine levels and clinical features of colorectal adenoma. (a) Association between adipocytokine levels and number of colorectal adenomas. (b) Association between adipocytokine levels and maximum size of colorectal adenomas

	Control		≤2		≥3		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(a)							
Adiponectin*	72	2.2 ± 0.5	44	2.0 ± 0.6	28	2.0 ± 0.4	0.02
Resistin*	72	1.1 ± 0.6	44	1.2 ± 0.5	28	1.1 ± 0.5	0.90
Leptin*	72	1.2 ± 0.6	43	1.2 ± 0.6	28	1.4 ± 0.5	0.15
Visfatin*	72	0.3 ± 1.2	44	0.2 ± 1.5	28	0.1 ± 1.1	0.40
C-peptide*	69	−1.5 ± 1.2	43	−1.2 ± 1.2	28	−1.2 ± 1.1	0.34

	Control		−5 mm		6–10 mm		11–20 mm		>20 mm		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(b)											
Adiponectin*	72	2.2 ± 0.5	14	1.9 ± 0.4	24	1.9 ± 0.4	17	1.9 ± 0.5	17	2.3 ± 0.6	0.48
Resistin*	72	1.1 ± 0.6	14	1.2 ± 0.4	24	1.2 ± 0.6	17	1.4 ± 0.5	17	1.0 ± 0.4	0.81
Leptin*	72	1.2 ± 0.6	13	1.6 ± 0.7	24	1.2 ± 0.5	17	1.1 ± 0.6	17	1.3 ± 0.6	0.53
Visfatin*	72	0.3 ± 1.2	14	0.0 ± 1.4	24	0.3 ± 1.2	17	0.6 ± 1.5	17	−0.4 ± 1.2	0.31
C-peptide*	69	−1.5 ± 1.2	13	−0.9 ± 0.8	24	−1.1 ± 1.2	17	−1.6 ± 1.2	17	−1.3 ± 1.2	0.64

*Log-transformed. Data are presented as mean ± SD.

of these limitations, we evaluated the correlation between the number of adenomas, the size of adenomas and adenoma-carcinoma sequence, and adiponectin to speculate the possibilities as ''risk factors'' for colorectal adenoma. The results showed that adiponectin level was inversely correlated with the number of adenoma. However, we could not elucidate why the adiponectin level was not correlated with the size of adenoma. If many more patients were enrolled in this study, a significant correlation between adiponectin levels and adenoma sizes may have been detected.

We have performed the above additional investigations into the relationship between adiponectin levels and colorectal carcinoma; however, our study has a few limitations. The BMI levels of the selected target group are very important and can affect the results of the study. The mean of BMI level of the patients in this study was 22.9, which was lower than that reported previously; this low BMI level may be attributed to the fact that all the patients were Japanese. Further, it is possible that variables other than those evaluated in this study may be correlated with adiposity and may influence the levels of adipocytokines. Therefore, the implications of our findings should be carefully evaluated considering these limitations.

Leptin primarily controls body fat stores and has also roles in promoting cellular proliferation, inhibiting cellular apoptosis, and inducing angiogenesis.[28] Over the years, the association between leptin levels and the risk of colorectal cancer or adenoma has remained controversial.[20,29] The expression of the leptin receptor in normal human colon mucosa, adenomas, and cancers suggests that a direct effect of leptin may be involved in carcinogenesis.[30] In the present study, however, the level of leptin was not significantly different between controls and patients with colorectal cancer or adenoma. In our previous

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studies on the correlation between adipocytokines levels and gastric or esophageal cancer, we have shown that a strong correlation exists between leptin level and BMI. In this study, however, the BMI levels of patients and controls were similar; therefore, the value of leptin as a biomarker for colorectal could not be evaluated.[13,31]

Resistin has been demonstrated to be involved in inflammatory states corresponding to its predominant expression in mononuclear cells, particularly in atherosclerosis.[32,33] As for its correlation with cancer, three case-control studies on the risk of myelodysplastic syndrome, multiple myeloma, or colorectal cancer have been reported.[21,34,35] Dalamaga *et al.* demonstrated a decreased resistin level in myelodysplastic syndrome (MDS) patients, and speculated that it was due to a compensatory response to the up-regulation of other inflammatory factors etiologically linked to myelodysplasia. They also reported a decreased level of resistin in patients with multiple myeloma. Kumor *et al.* reported that the resistin levels in colorectal cancer patients are higher than those in controls and that the resistin levels in colorectal adenoma patients and controls were also significantly different. Our results showed that resistin levels, particularly in colorectal cancer patients, were significantly higher than those in controls independent of the BMI, and these levels gradually increased with progression in tumor stage. This may imply that resistin is a biomarker of colorectal malignant potential and stage progression.

Visfatin is a new insulinmimetic adipocytokine, which directly interacts with the insulin receptor but as the insulin-like growth factor receptor, and can subsequently promote cancer cell proliferation[36]. It is more highly expressed in primary colorectal cancer than in non-neoplastic mucosa.[37] Although the clinical correlations of visfatin with cancer have been rarely reported, we demonstrated here that it may be a novel and promising biomarker of colorectal cancer as well as resistin.

Taken together, the results suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently of BMI, and also of stage progression of colorectal cancer. Adiponectin level may be a good biomarker of colorectal adenoma independently of BMI. Further investigations as to whether the changes in adipocytokine levels are the result and/or effects of colorectal cancer or adenoma development are needed, and the elucidation of this causative association will undoubtedly clarify the correlation between obesity and cancer. Histological studies on the expression of adipocytokines in cancer tissues also should be conducted to determine whether adipocytokines derived from cancer tissues or those derived from adipose tissues are important for carcinogenesis and tumor progression.

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Disclosure Statement

The authors have no conflict of interest.

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ORIGINAL ARTICLES

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

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

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

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

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

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

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

Limitations: No long-term outcome data.

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

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

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

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

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

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

PATIENTS AND METHODS

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

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

Take-home Message

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

Inclusion criteria for ESD

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

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

Exclusion criteria for ESD

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

Clinicopathological characteristics

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

ESD methods

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

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

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

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

ESD procedures. The procedures were primarily performed using 1 or 2 ESD knives including a bipolar needle-knife (Xeon Medical Co, Tokyo, Japan),[14,17,33] Flex knife,[19] Hook knife (Olympus Co, Tokyo, Japan),[20] Flush knife (Fujinon Co, Tokyo, Japan),[16] Mucosectom (Pentax Co, Tokyo, Japan),[18] and insulation-tipped knife (Olympus).[9-11,13] Midazolam (2 mg intravenously) and pentazocine (15 mg intravenously) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. Hemostatic forceps (Coagrasper; Olympus) were used for hemostasis of bleeding. At 8 institutions (80%), CO_2 insufflation was used instead of air insufflation to reduce patient discomfort.[14] Lesion margins were delineated before ESD using 0.4% indigo-carmine spray dye (Fig. 1A-D; Video 1, available online at www.giejournal.org). After injection of 10% glycerol and 5% fructose in normal saline solution (Glyceol; Chugai Pharmaceutical Co, Tokyo, Japan)[34] and sodium hyaluronate acid into the SM layer,[15] a circumferential incision was made using a single ESD knife, and ESD was then performed using 1 or 2 ESD knives (Fig. 2A-D).

Definition of en bloc resection

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

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

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

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

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

Definition of complications

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

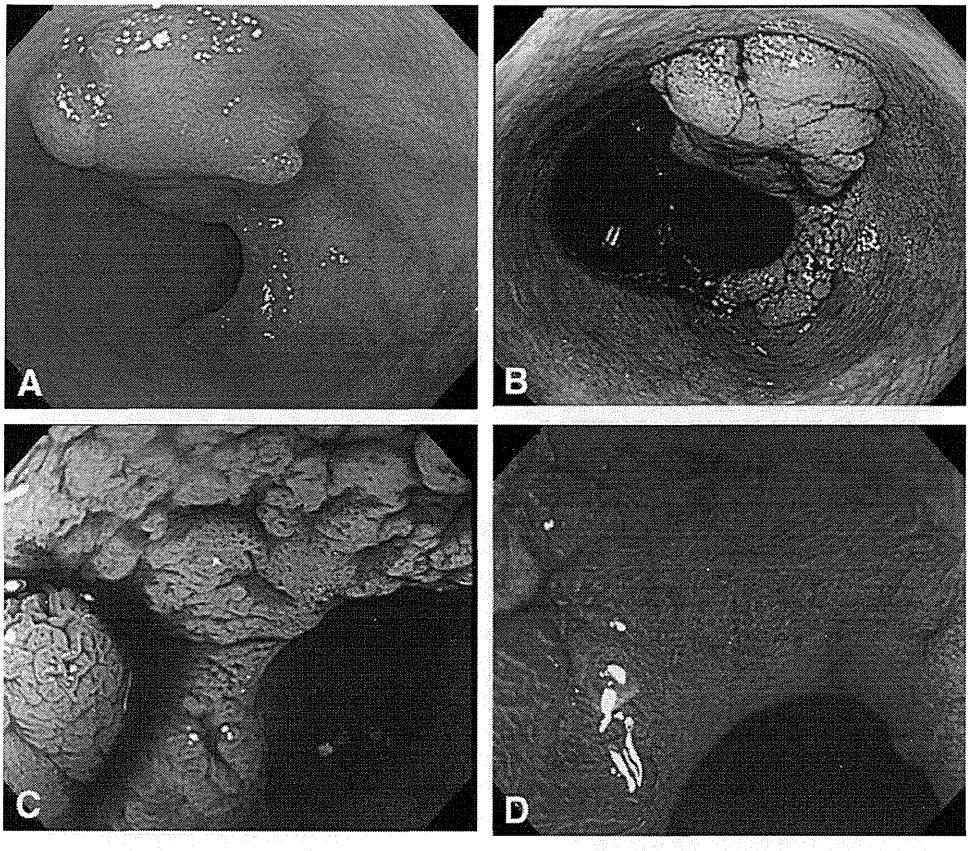

Figure 1. (with video). Endoscopic diagnosis before ESD. ESDs were primarily performed by using a bipolar needle knife and insulation-tipped knife with CO_2 insufflation at the National Cancer Center Hospital. **A**, Nongranular type LST 50 mm in size located in the descending colon. **B**, Lesion margins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

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

Histological assessment

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

Statistical analysis

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

RESULTS

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

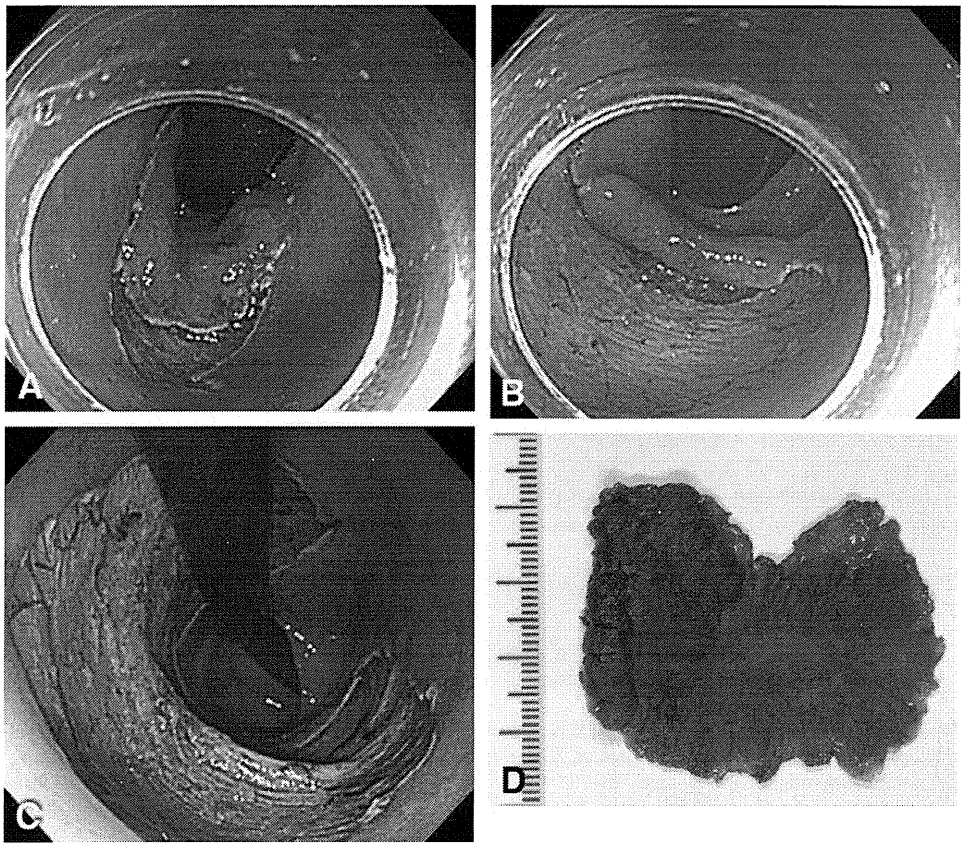

Figure 2. ESD (Video available online at www.giejournal.org). **A**, After injection of Glycerol (10% glycerol and 5% fructose in normal saline solution) and sodium hyaluronate acid solution into SM layer, partial circumferential incision performed by using bipolar needle-knife. **B**, After partial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

Clinicopathological characteristics

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

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

Clinical outcomes of colorectal ESDs

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

Complication rate

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