was 25% (15/60), whereas Kudo[4] reported that the proportion of sm1 cancers was 45.5% (147/323). As we commented in our previous study, discrepancies in the incidence of nonlifting sign in SICCs between our study and others may be due to a history of biopsy and/or the number of post-biopsy days.[1] Unfortunately, we cannot determine these factors in any of the studies cited above.

Differences in measurements of invasion depth are also important. Kobayashi et al commented that invasion depth should be measured from the surface of the lesion when the muscularis mucosa has been destroyed. However, this is true only in cases of flat or depressed-type tumors that have been resected endoscopically. In our previous study,[1] surgically resected tumors were evaluated by Kudo's classification, which considered the relative depth of the submucosal layer, and the depth of invasion of endoscopically resected subpedunculated or pedunculated tumors was measured from the level of the neck.[5] As recently described, surgically resected SICCs limited to the most superficial third and SICCs ≤ 1000 μm in depth in EMR specimens should be classified as sm1 cancers because these tumors correspond to SICCs with limited invasiveness and no risk of lymph node metastasis.[4] The proportion of flat lesions was 67.2% in the study by Kobayashi et al, [2] compared with 17.1% in our study.[1] Further studies are needed to determine the safe level of submucosal invasion for SICCs while also considering tumor configuration.

The condition of the muscularis mucosa must also be considered when measuring the depth of invasion of SICCs. When the muscularis mucosa cannot be readily identified by hematoxylin-eosin staining, we perform immunohistochemical staining for desmin, a smooth muscle marker, to identify the muscularis mucosa, allowing the depth of invasion to be measured from the residual muscularis mucosal layer. If the muscularis mucosa is completely destroyed, the depth of invasion is measured from the surface of flat tumors.

In our previous study,[1] intramucosal lesions were excluded because they are noninvasive tumors, which can be treated endoscopically except under specific conditions, and are therefore not of clinical interest in a study of endoscopic resectability. Of course, a history of biopsy may influence nonlifting signs in intramucosal lesions as well as in SICCs. Indeed, at a recent meeting of the Congress of the Korean Society of Coloproctology, we described 12 patients with noninvasive lesions showing nonlifting signs (unpublished data). Of these 12 tumors, 6 were adenomas (5 tubular adenomas and 1 tubulovillous adenoma) and 6 were intramucosal carcinomas. All 12 patients had a history of mechanical stimulation, including biopsy (8 patients), submucosal injection (2 patients), incomplete polypectomy (1 patient), and total prostatectomy (1 patient with rectal villous adenoma).

Our previous study[1] showed that both a history of biopsy and an increase in the number of post-biopsy days can increase the occurrence of nonlifting signs in endoscopically resectable SICCs. Although Kobayashi et al[2] suggested that nonlifting signs cannot predict deeper tumor invasiveness more reliably than endoscopic diagnosis, our results indicate that nonlifting signs can provide more objective information than endoscopic diagnosis does about endoscopic resectability. Furthermore, our results indicate that accurate endoscopic assessment requires minimizing unnecessary biopsies before EMR, and that EMR should be performed as soon as possible after biopsy.

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A superficial early colitic cancer that resembled a laterally spreading tumor on chromoendoscopy

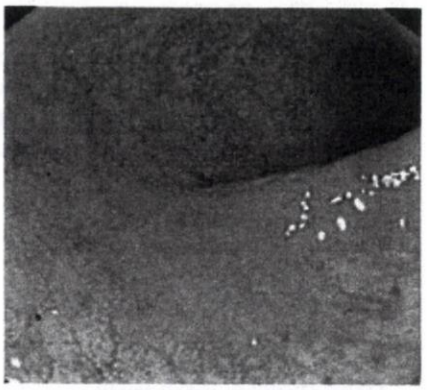

Figure **1** Colonoscopic view of the flat, reddish lesion that was observed in the sigmoid colon. The margin of the lesion could not be clearly visualized.

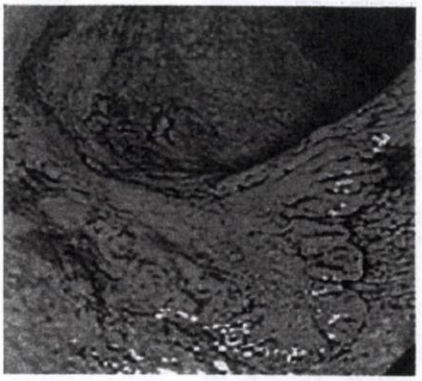

Figure **2** The margin of the lesion became much clearer after the application of indigo carmine dye.

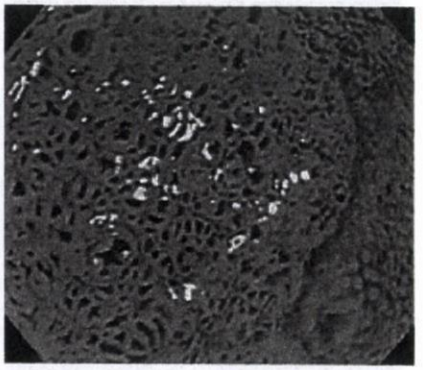

Figure **3** Magnifying chromoendoscopy revealed a noninvasive pit pattern, similar to a type IIIL pit pattern. The lesion was treated by endoscopic submucosal dissection (ESD).

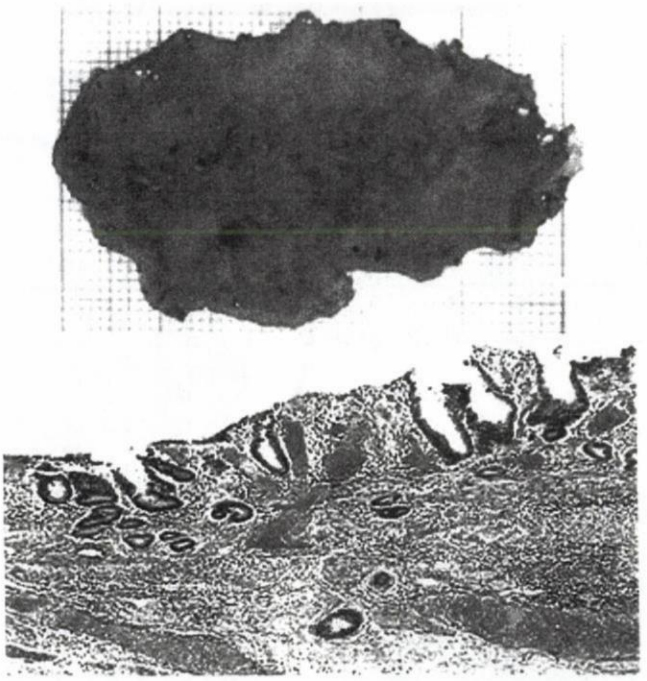

Figure **4** Histopathological examination of the resected specimen confirmed the lesion to be a well-differentiated adenocarcinoma with submucosal and lymphatic invasion. The depth of invasion was 500 µm from the muscularis mucosa (hematoxylin & eosin stain).

Patients with longstanding and extensive ulcerative colitis may be entered into a surveillance program [1], but the detection of ulcerative colitis-related colorectal neoplasia ("colitic cancer") during conventional colonoscopy is difficult. Because of this, chromoendoscopy [2] and magnifying chromoendoscopy [3] have recently been proposed as adjuvant techniques for the detection of this type of colorectal neoplasia.

A 35-year-old man with a 21-year history of extensive ulcerative colitis underwent a surveillance colonoscopy. A flat, reddish lesion was detected in the sigmoid colon (Figure **1**). After the application of indigo carmine dye, the margin of the lesion could be clearly visualized and the lesion appeared to be a flat adenoma with a broad base, resembling a laterally spreading tumor (Figure **2**). Magnifying chromoendoscopy showed a "noninvasive" pit pattern [4], suggesting that this was an intramucosal neoplastic lesion (Figure **3**). It was therefore decided to treat this lesion and the surrounding normal-looking mucosa (which had a type I pit pattern) by endoscopic submucosal dissection [5]. Histopathological examination of the resected specimen showed a well-differentiated adenocarcinoma with submucosal and lymphatic invasion; the depth of invasion was 500 µm from the muscularis mucosa (Figure **4**). Immunostaining for p53 was diffusely positive in most of the lesion and the adjacent mucosa also showed high-grade dysplasia. On the basis of these histopathological findings, this lesion was diagnosed as a colitic cancer, and a total colectomy was performed. Histopathological examination of the mucosa surrounding the scar after endoscopic submucosal dissection revealed high-grade dysplasia (Figure **5**, **6**).

This colitic cancer was diagnosed at an early stage by chromoendoscopy and magnifying chromoendoscopy, but the extent of tumor invasion was misdiagnosed. Histopathologically, the structure of the glands, especially the density of the glands of the neoplastic mucosa adjacent to the main lesion, resembled that of

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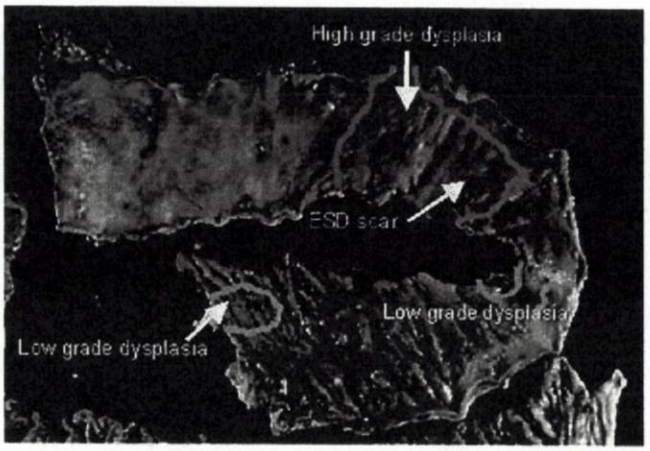

Figure **5** Macroscopic examination of the resected specimen revealed inactive ulcerative colitis with mucosal atrophy, with no evidence of a neoplastic lesion. However, histopathological examination revealed high-grade dysplasia in the mucosa surrounding the post-ESD scar. Histopathological examination of the ascending colon also revealed two areas of low-grade dysplasia.

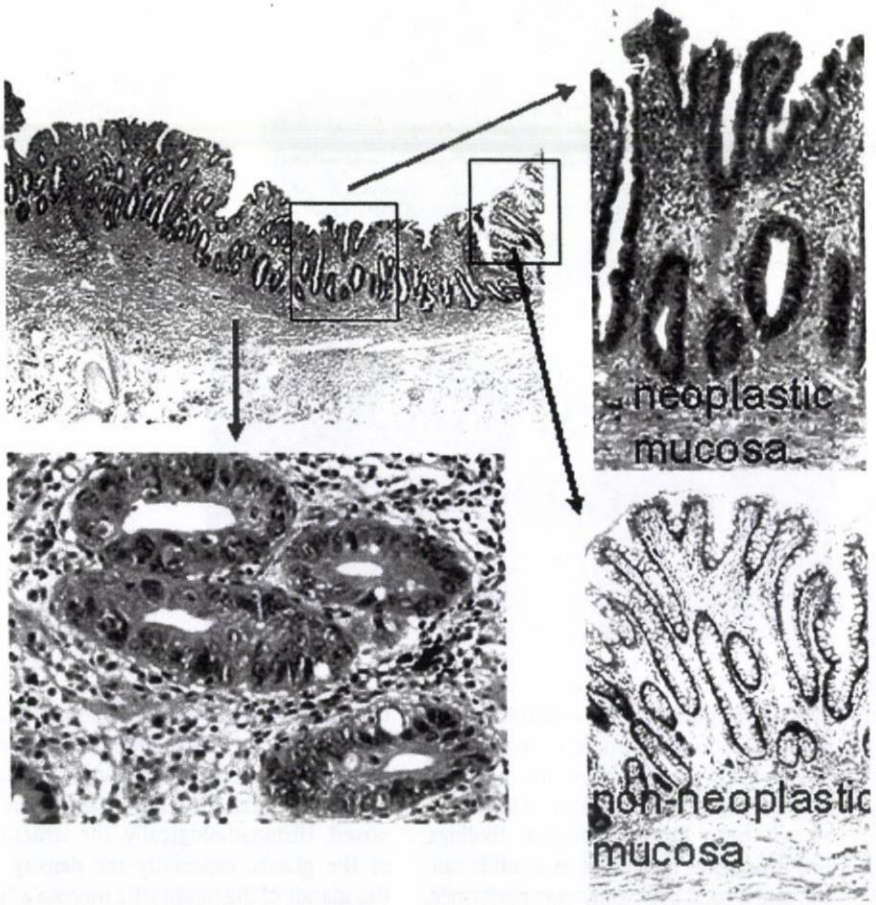

Figure **6** Histopathological examination revealed high-grade dysplasia in the mucosa surrounding the scar after ESD. The structure of the glands, especially the density of the glands of the neoplastic mucosa, resembled that of non-neoplastic colonic mucosa (hematoxylin & eosin stain).

non-neoplastic mucosa (Figure **6**). These results suggest that chromoendoscopy, even with pit pattern analysis, has its limitations when used in the diagnosis of intramucosal neoplastic lesions associated with ulcerative colitis.

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ORIGINAL CONTRIBUTIONS

Endoscopy

Efficacy of the Invasive/Non-invasive Pattern by Magnifying Chromoendoscopy to Estimate the Depth of Invasion of Early Colorectal Neoplasms

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OBJECTIVE: **During colonoscopy, estimation of the depth of invasion in early colorectal lesions is crucial for an adequate therapeutic management and for such task, magnifying chromoendoscopy (MCE) has been proposed as the best *in vivo* method. However, validation in large-scale studies is lacking. The aim of this prospective study was to clarify the effectiveness of MCE in the diagnosis of the depth of invasion of early colorectal neoplasms in a large series.**

METHODS: **A total of 4,215 neoplastic lesions were evaluated using MCE from October 1998 to September 2005 at the National Cancer Center Hospital, Tokyo, Japan. Lesions were prospectively classified according to the clinical classification of the pit pattern: invasive pattern or non-invasive pattern. All lesions were histopathologically evaluated.**

RESULTS: **There were 3,371 adenomas, 612 intramucosal cancers (m-ca), 232 submucosal cancers (sm-ca): 52 sm superficial (sm1) and 180 sm deep cancers (sm 2–3). Among lesions diagnosed as invasive pattern, 154 out of 178 (86.5%) were sm2–3, while among lesions diagnosed as non-invasive pattern, 4,011 out of 4,037 (99.4%) were adenomas, m-ca, or sm1. Sensitivity, specificity and diagnostic accuracy of the invasive pattern to differentiate m-ca or sm1 (<1000 μm) from sm2–3 (≥1000 μm) were 85.6%, 99.4%, and 98.8%, respectively.**

CONCLUSION: **The determination of invasive or non-invasive pattern by MCE is a highly effective *in vivo* method to predict the depth of invasion of colorectal neoplasms.**

(Am J Gastroenterol 2008;103:2700–2706)

INTRODUCTION

It has been reported that intramucosal colorectal cancers (m-ca) show no lymph node (LN) metastasis (LNM) and are good candidates for endoscopic resection (1, 2). In contrast, submucosal cancers (sm-ca) have approximately 6–12% of LNM, which require surgical resection including LN dissection for curative treatment (3–6). Recently, there is growing evidence supporting the theory that lesions with sm invasion limited to less than 1000 μm (sm1) without lymphovascular invasion and/or poorly differentiated component do not involve LNM (7). Therefore, it is crucial to estimate the depth of invasion of early colorectal neoplasms accurately prior to therapeutic decisions.

Magnifying chromoendoscopy (MCE) has widely demonstrated its effectiveness to differentiate between colorectal neoplastic and non-neoplastic polyps (8–15). In relation to the depth of invasion of colorectal neoplastic lesions, Kudo's classification of colonic crypts suggests that type III and IV pit patterns are found on adenomatous polyps, while type VN is strongly suggestive of sm deep cancers (16–18). In practice, however, there are limitations using only the morphological classification of the pit pattern to discriminate between m-sm1 and sm2 or beyond. MCE with detailed analysis of the pit

pattern has been proposed as the best *in vivo* method to evaluate the depth of invasion, however, validation in large-scale studies is lacking. Herein, we report a clinical classification of the colonic pit pattern, which is useful to determine the proper treatment of colorectal lesions during colonoscopy.

METHODS

Patients

A total of 3,029 consecutive patients diagnosed with a neoplastic colorectal lesion at the National Cancer Center Hospital, Tokyo from October 1998 to September 2005 were enrolled. This study was conducted prospectively, and the study protocol was approved by our institutional review board. Written informed consents for diagnosis and treatment were obtained from all patients prior to the procedures. Exclusion criteria were advanced colorectal cancer, familial adenomatous polyposis (FAP), inflammatory bowel disease (IBD), and hereditary non-polyposis colorectal cancer (HNPCC).

Magnifying Colonoscope

All examinations were performed using magnifying colonoscopes (CF-Q240ZI, PCF-Q240ZI, and CF-200Z, Olympus Optical Co., Tokyo, Japan), which enhance the image up to 80–100 times using a one-touch operation power system. These scopes have equal upward and downward bending range as well as sideways range and biopsy channel diameter but differ minimally in observation range diameters and view angles.

Definition of Terms

1. *Regular pit:* visible crypt orifice independently of shape (Fig. 1A).
2. *Irregular pit*: the orifice of each crypt is indented or jagged (Fig. 1B).
3. *Distorted pit*: the orifice of each crypt cannot be clearly traced, usually seen in desmoplastic areas (Fig. 1C).
4. *Demarcated area*: clearly visualized zone between two morphologically different types of pits, e.g., depression, large nodule, or reddened area (Fig. 1D).

Clinical Classification

1. *Non-neoplastic pattern*: normal mucosa and star-shaped crypts as observed in Kudo's type I or II, respectively (e.g., hyperplastic, juvenile and inflammatory polyps).

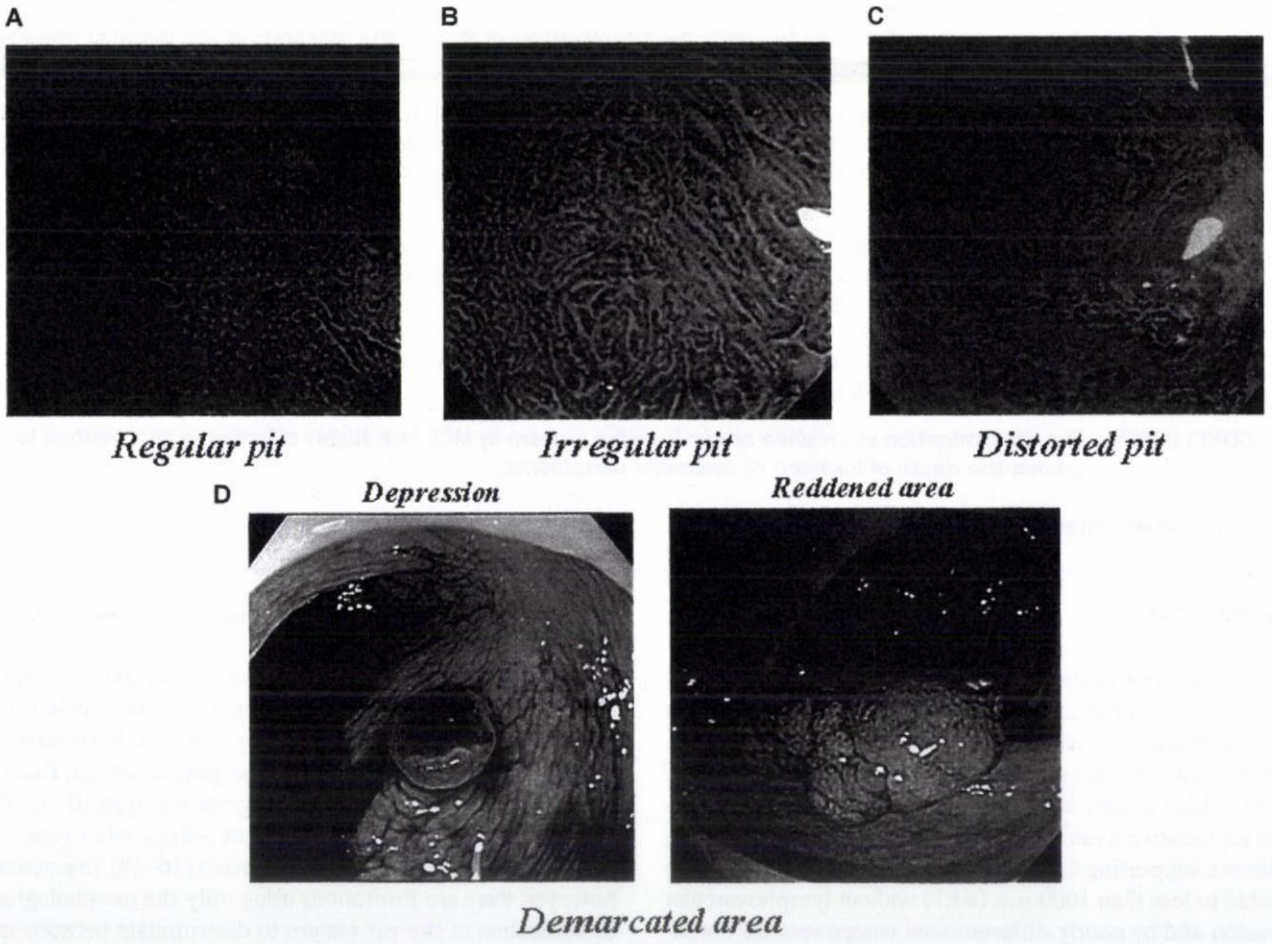

Figure 1. Definition of terms: (A) Regular pit. (B) Irregular pit. (C) Distorted pit. (D) Demarcated area: Depression/Reddened area.

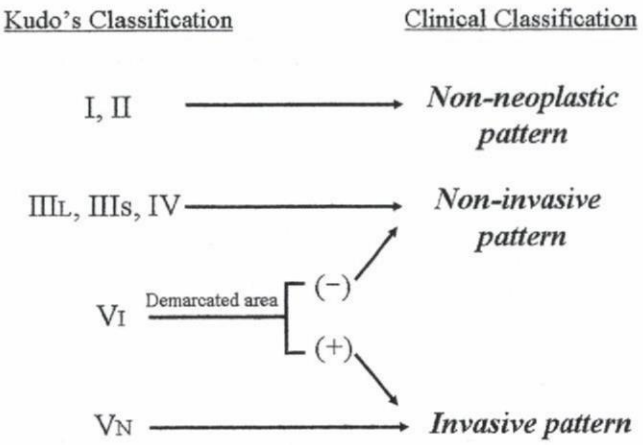

Figure 2. Relationship between Kudo's classification and clinical classification.

2. *Non-invasive pattern*: regular crypts with or without demarcated area or irregular pits without a demarcated area. Usually observed in Kudo's type IIIs, IIIL, IV, and selected cases of VI (e.g., adenomatous polyps, intramucosal, and submucosal superficial cancers), where endoscopic resection is appropriate.
3. *Invasive pattern*: irregular and distorted crypts in a demarcated area as observed in Kudo's type VN and selected cases of VI (e.g., deep submucosal invasive cancers), where surgical resection is the appropriate treatment. Kudo's type VI is observed in both non-invasive and invasive patterns (Fig. 2, 3).

Endoscopic Examination

All patients were prepared for colonoscopy with 2–3 L of polyethylene glycol-electrolyte solution administered on the morning of examination day. Scopolamine butylbromide (10 mg) or Glucagon (0.5 mg) was administered intravenously in patients with no contraindication prior to examination to avoid bowel movement.

All procedures were carried out by experienced examiners who had performed more than 500 colonoscopies per year. When a lesion was detected by conventional view, its surface was washed out with proteinase to remove overlying mucous, after which 0.4% indigo carmine (IC) dye was sprayed to accentuate the contours of the lesions. When a colonoscopist intended to perform chromoendoscopy, a volume of 3 to 5 mL IC dye was flushed through the biopsy channel with 15 mL of air using a 20cc syringe and sprayed directly over the targeted lesion. The pit pattern was evaluated by magnifying view. When high magnification observation with IC dye was not enough for determining the surface structure (pit pattern analysis), 0.05% crystal violet (CV) was applied as a staining method (19). Lesions were evaluated under MCE in real time and categorized as non-neoplastic, neoplastic non-invasive and neoplastic invasive patterns. Those diagnosed as

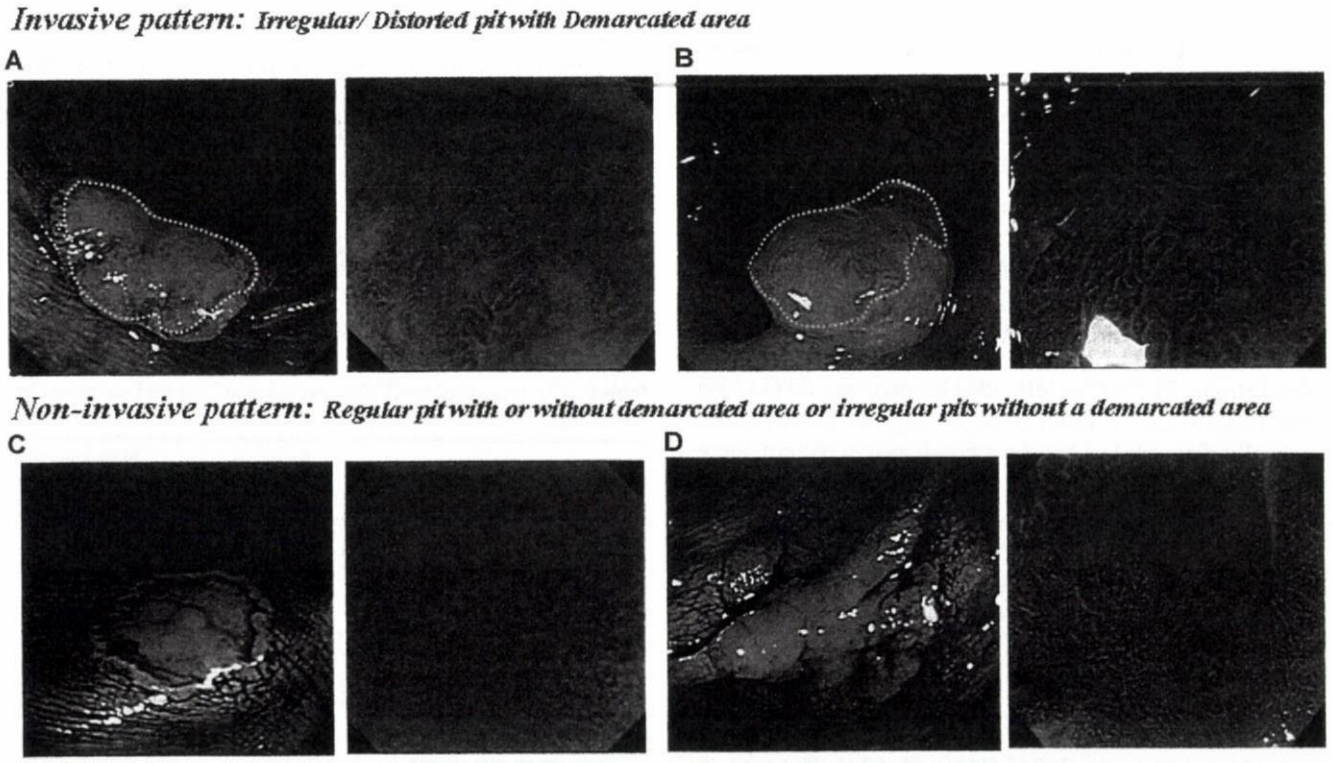

Figure 3. Definition of invasive/non-invasive pattern. Invasive pattern (*A*) Demarcated area (+): Depression, Irregular/distorted pit (*B*) Demarcated area (+): Reddened area, Irregular/distorted pit. Non-invasive pattern (*C*) Demarcated area (+): Depression, Regular pit (*D*) Demarcated area (±), Regular pit.

non-neoplastic were left untreated. If lesions were identified as neoplastic non-invasive lesions (adenomas or m-ca), hot biopsy, snare polypectomy, or endoscopic mucosal resection (EMR) was performed. Lesions <5 mm were resected by coagulation biopsy (hot biopsy), and flat lesions or those >5 mm were treated with loop snare polypectomy or EMR. If lesions were diagnosed as invasive pattern, biopsy specimens were taken and patients were basically referred for surgery. In cases where a polyp was not clearly diagnosed as either hyperplastic polyp (HP) or adenomatous polyp (AP), it was considered as AP and therefore removed for histopathological analysis.

Histopathology

Resected specimens were immediately fixed in 10% buffered formalin solution and subsequently stained with hematoxylin-eosin. Experienced gastrointestinal pathologists blinded to each endoscopic diagnosis evaluated all pathological specimens. Histopathological diagnosis was determined according to the Japanese Research Society for Cancer of the Colon and Rectum (JRSCCR) between 1998 and 2000. Since 2001, lesions were histopathologically evaluated according to JRSCCR and Vienna classification as well (20, 21). Non-pedunculated lesions with a vertical invasion length of less than 1000 μm in the submucosal layer, and pedunculated lesions with head invasion, were classified as submucosal superficial invasive cancer (sm1). Non-pedunculated lesions with invasion of more than 1000 μm and pedunculated lesions with stalk invasion were considered as submucosal deep invasive cancer (sm2–3) (7, 22). Regarding pedunculated lesions, level 2 according to Haggitt's classification (23) was used as the baseline to determine submucosal invasion.

RESULTS

A total of 4,215 neoplastic lesions in 3,029 patients were studied by MCE and removed endoscopically or surgically for analysis. Among lesions endoscopically diagnosed as having an invasive pattern, there were 45 (25.3%) right-sided colon lesions, 53 (29.8%) left-sided lesions, and 80 (44.9%) rectal lesions. On the other hand, among the lesions endoscopically diagnosed as having a non-invasive pattern, there were 2,032 (50.3%) right-sided, 1,475 (36.5%) left-sided and 530 (13.1%) rectal lesions. According to macroscopic type, there were 90 (50.6%) polypoid, 9 (5.1%) flat elevated, and 79 (44.4%) depressed lesions in the invasive pattern group. In contrast, there were 2,700 (66.9%) polypoid, 1,258 (31.2%) flat elevated, and 79 (2.0%) depressed lesions in the non-invasive pattern group (Table 1).

Histopathological analysis revealed adenoma: 3371 (80.0%), intramucosal cancer (m-ca): 612 (14.5%), and submucosal cancer (sm-ca): 232 (5.5%) [sm1: 52 (1.2%), sm2–3: 180 (4.3%)]. Among lesions diagnosed as invasive pattern, 154 out of 178 (86.5%) were submucosal deep invasive cancers (sm2–3), while 4,011 out of 4037 (99.4%) diagnosed as non-invasive pattern were adenomas, m-ca or sm1 (Table 2).

Table 1. Characteristics of Lesions Diagnosed by Magnifying Chromoendoscopy

	Invasive Pattern (n = 178)	Non-Invasive Pattern (n = 4037)
Location—no. (%)		
Right colon*	45 (25)	2032 (50)
Left colon**	53 (30)	1475 (37)
Rectum	80 (45)	530 (13)
Macroscopic type–no. (%)		
Polypoid	90 (51)	2700 (67)
Flat elevated	9 (5)	1258 (31)
Depressed†	79 (44)	79 (2)
Size—no. (%)		
−5 mm	2 (1)	2024 (50)
6–10 mm	30 (17)	1396 (35)
11–20 mm	101 (57)	493 (12)
21 mm−	45 (25)	124 (3)

*Cecum-transverse colon.
**Descending-sigmoid colon.
†IIc, IIa+IIc, Is+IIc.

Diagnostic Accuracy

The calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the invasive pattern to differentiate m-ca or sm1 (<1000 μm) from sm2–3 (≥1000 μm) were 85.6%, 99.4%, 86.5%, 99.4%, and 98.8%, respectively. 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% (75/99), 85.7% (6/7), and 98.6% (73/74), respectively. Meanwhile, the specificity for polypoid, flat, and depressed lesions was 99.4%, 99.8%, and 92.9%, respectively (Table 3).

Treatment Strategy

Among lesions endoscopically diagnosed as having an invasive pattern, 80.9% (144/178) were treated surgically of which sm2–3 cancer was found in 132 cases (91.7%), and

Table 2. Clinicopathologic Characteristics of Lesions Diagnosed by Magnifying Chromoendoscopy

	Invasive Pattern	Non-Invasive Pattern
No. of lesions	178	4037
Histopathology—no. (%)		
Adenoma	0 (0)	3371 (83)
m-ca	12 (7)	600 (15)
sm-ca	166 (93)	66 (2)
–sm superficial (sm1*)	12 (7)	40 (1)
–sm deep (sm2-3)	154 (86)	26 (0.6)

*sm1: sm <1000 μm.
Sensitivity: 85.6% (15/180).
Specificity: 99.4% (4011/4035).
Positive predictive value (PPV): 86.5% (154/178).
Negative predictive value (NPV): 99.4% (4011/4037).
Accuracy: 98.8% (4165/4215).

Table 3. Diagnostic Sensitivity and Specificity According to Macroscopic Type

	Polypoid	Flat	Depressed	Total
sm deep	75.8% (75/99)	85.7% (6/7)	98.6% (73/74)	85.6% (154/180)
Adenoma m-ca sm superficial	99.4% (2676/2691)	99.8% (1257/1260)	92.9% (78/84)	99.4% (4011/4035)

m-ca or sm1 in 12 cases (8.3%). Thirty-four lesions (19.1%) diagnosed as an invasive pattern were removed endoscopically. Based on lesion size, there were 31 out of 34 (91.2%) small lesions (<20 mm) and 25 out of 34 (73.5%) polypoid lesions. Among these, sm2–3 cancer was found in 22 cases (64.7%), and m-ca or sm1 in 12 cases (35.3%). Among 22 sm2–3 cancers, 15 cases underwent additional surgical treatment and in 7 cases, close follow-up was performed. In contrast, among 4,037 cases diagnosed endoscopically as having a non-invasive pattern, 4,024 (99.7%) were resected endoscopically. The remaining 13 cases (0.3%) were treated surgically. Based on size, there were 8 out of 13 (61.5%) large lesions ≥21 mm and 8 out of 13 (61.5%) polypoid lesions (Fig. 4).

DISCUSSION

This is the first large prospective study to assess the effectiveness of MCE for the endoscopic estimation of the depth of invasion of colorectal neoplasms. MCE is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern) in a simple and not time-consuming manner. Despite prospective randomized studies in large reference centers demonstrating the superiority of MCE over conventional colonoscopy, and studies that demonstrated no differences between magnifying and standard colonoscopes in the average time to reach the cecum (11), magnifying endoscopes are still rarely used in endoscopy units. Unrecognized necessity and lack of randomized studies validating the effectiveness of MCE are possible reasons for this. We believe that MCE is an essential armamentarium in gastrointestinal (GI) endoscopy units and that its main clinical significance is the *in vivo* diagnosis of the nature of colorectal lesions, which gives extremely useful information to determine the treatment modality.

The clinical classification of the colonic pit pattern (invasive and non-invasive) using MCE was originally described by Fujii in 1998 with the aim to discriminate between m-sm1 and sm2 or beyond (19). Contrary to the anatomic classification of Kudo *et al.*, the rationale for the clinical classification is based on the identification of irregular or distorted crypts in a demarcated area, (where the orifice of each crypt cannot be traced clearly) which highly suggests that the cancerous lesion is already invading deeply into the sm layer.

Some studies have already reported the clinical usefulness of detailed determination of the V pit pattern using MCE for predicting the depth of invasion of sm neoplasms. Kudo *et al.* reported that 11 of 22 (50%) lesions with a type V pit pattern with a bounded surface were found to be invasive cancers with involvement of the sm layer (16). Other studies have reported a diagnostic accuracy of type V pit for the diagnosis of sm invasive cancer of 85% (81/95) and 79% (11/14), respectively (24, 25). Recently, Ohta *et al.* reported that lesions with high-grade atypia have erosive change in the surface epithelium and histological appearance of a desmoplastic reaction. Due to these histopathological changes, lesions invading deeply into the sm layer usually show a demarcated area on its surface (26). However, protruded type lesions do not often show an invasive pattern, even if they invade deeply into sm. In such cases, it is sometimes difficult to predict the degree of invasion only evaluating the tumor surface. In this study, we found out that the clinical classification of the pit

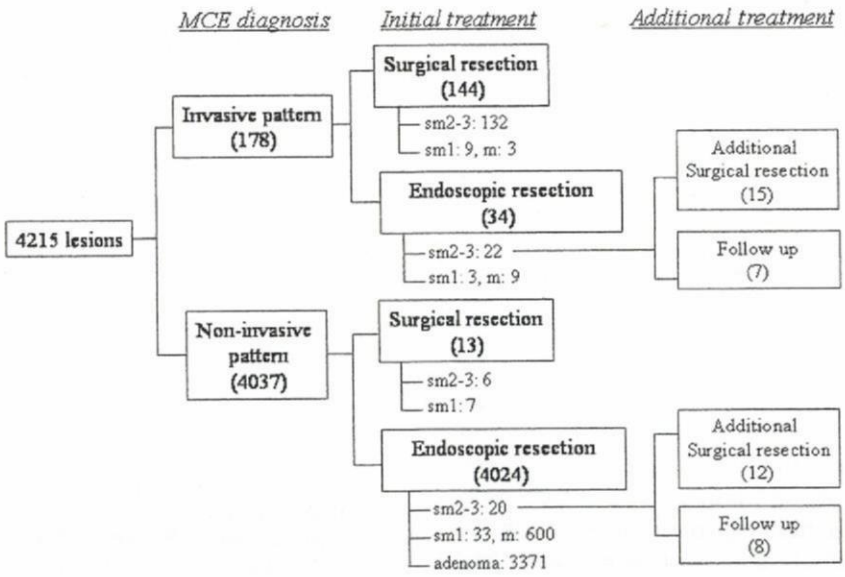

Figure 4. Treatment strategy.

pattern has an overall accuracy of 98.8% suggesting that such invasive pattern is a useful indicator to predict the invasion of sm layer especially sm deep (sm2–3) invasion. Thus, the invasive/non-invasive pit pattern might be used to determine the ideal treatment, either endoscopic resection or surgery. In addition, the diagnostic sensitivity of the clinical pit pattern classification to properly identify the depth of invasion of flat and depressed lesions was superior to that of polypoid lesions (97.5% *vs.* 75.8%). For these former cases, not only MCE but also other predictive factors or diagnostic methods should be considered for diagnosis.

Some authors have reported the usefulness of endoscopic ultrasonography (EUS) particularly the advantages of high frequency ultrasound (HFUS) to diagnose the invasion depth of early colorectal cancer (27–30). Hurlstone *et al.* conducted a study to compare the two modalities (30). According to their result, HFUS was superior to MCE for determination of depth invasion (93% *vs.* 59%, respectively). Meanwhile, Fu *et al.* have recently reported that MCE is as accurate as EUS for preoperative staging of early colorectal cancer (31). Generally, EUS colonoscopes have a rigid tip that makes it difficult to always reach the cecum when compared with conventional ones. Regarding cost-effectiveness and time-consuming issues, EUS is not as good as MCE. Furthermore, Uno *et al.* (32) and Kobayashi *et al.* (33) reported the verification of the "*Non-lifting sign*" as one modality of depth diagnosis for colorectal cancers. In spite of the simplicity of such technique, Kobayashi *et al.* concluded that the "*Non-lifting sign*" could not reliably predict deeper cancerous invasion in comparison with endoscopic diagnosis.

There are some limitations in our study. First, the endoscopic diagnosis using magnification was performed after conventional endoscopic diagnosis which means endoscopists were not blinded to diagnose only with MCE images. Therefore, we could not evaluate how much MCE diagnosis exceeded compared to conventional endoscopic diagnosis. Second, since only neoplastic lesions were included in this study, it is difficult to prove the usefulness of MCE as a differential diagnostic modality between neoplastic or non-neoplastic lesions. For such distinction, however, chromoendoscopy with magnification has already been reported to be the most reliable method to determine whether a colorectal lesion is neoplastic or not (12–14). Another point worth mentioning is that all procedures were carried out by experienced examiners. This means that the effectiveness of MCE deserves revalidation studies including ideally general endoscopists. The effort necessary for learning to identify mucosal crypt patterns is important but scarcely studied. Generally, differential diagnosis by MCE is simple and easy to learn compared with depth diagnosis (m/sm1 or sm2–3) for beginners. Togashi *et al.* investigated the efficacy of magnifying colonoscopy in the differential diagnosis of colorectal polyps and also described the learning curve in their study. They reported that a minimum experience of observing 200 lesions with high-magnification was necessary to understand pit pattern diagnosis (9). In addition, we only used the optical zoom (OZ) system, which enables a more precise magnification image than that of the electronic zoom (EZ) system. Except for a small number of institutions, the OZ system is not available in Western countries. In the near future, comparative studies between OZ and EZ should be performed to validate the usefulness of MCE.

In conclusion, the present study suggests that the diagnosis of invasive or non-invasive pit pattern observed by MCE is a highly effective *in vivo* method to predict the depth of invasion of colorectal neoplasms, and consequently a useful tool for endoscopic staging of early colorectal cancers. In the near future, multi-center trials should be performed to validate the usefulness of MCE compared to other modalities (e.g., conventional colonoscopy, EUS, non-lifting sign).

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STUDY HIGHLIGHTS

What Is Current Knowledge

- *In vivo* estimation of the depth of invasion in early colorectal lesions is crucial for an adequate therapeutic strategy.
- Magnifying chromoendoscopy (MCE) has been proposed as the best method. However, there are no large-scale validation studies concerning the clinical classification of the pit pattern.

What Is New Here

- A large prospective study of 4,215 lesions conducted at the National Cancer Center Hospital has demonstrated that the clinical pit pattern (invasive/non-invasive) evaluated by MCE is a highly effective *in vivo* method to predict the depth of invasion of colorectal neoplasms.

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CONFLICT OF INTEREST

This is not a collaborative study. Thus, this study being an absolutely independent investigation, there is neither financial support nor interest from any companies.

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LETTER TO THE EDITOR

Small intestinal CMV disease detected by capsule endoscopy after allogeneic hematopoietic SCT

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CMV disease is a serious complication after allogeneic hematopoietic SCT (Allo-HSCT) in addition to GVHD.[1] CMV disease can involve many organs and the gastrointestinal tract is a common site.[2] There are several reports on small intestinal endoscopic findings of GVHD detected by capsule endoscopy,[3–6] but only limited information has been published regarding endoscopic findings of CMV enteritis after Allo-HSCT using capsule endoscopy.[4] We report herein a case of CMV enteritis involving the small intestine after Allo-HSCT that was detected by capsule endoscopy.

A 58-year-old man with myelodysplastic syndrome underwent Allo-HSCT with HLA mismatched unrelated cord blood at the National Cancer Center Hospital in Tokyo, Japan. The conditioning regimen consisted of fludarabine (125 mg/m^2), melphalan (80 mg/m^2) and 4 Gy TBI. Tacrolimus was administered for GVHD prophylaxis.

The transplantation course was uneventful for 7 months, but the patient then started experiencing epigastric pain and watery diarrhea. Total colonoscopy revealed several erosions surrounding a single ulceration in the ascending colon (Figure 1a). Biopsy specimens obtained from the ulceration and erosions showed enlarged endothelial cells with nuclear inclusion bodies (Figure 2a) that were positive for CMV by immunohistochemical staining (Figure 2b). No definite histological feature to support GVHD was found. A simultaneous CMV antigenemia assay using the monoclonal antibody C7-HRP (Teijin, Tokyo, Japan) indicated two positive cells per 44 000 cells. A subsequent capsule endoscopy (PillCam SB, Given Imaging Inc., Israel) also revealed a single ulceration with satellite erosions in the jejunum, but we were unable to perform a biopsy because of the primary limitation of capsule endoscopy, that is, lack of any biopsy capability. The ulceration in the jejunum was very similar to the one found in the ascending colon (Figure 1b).

Antiviral therapy was started with ganciclovir (10 mg/kg/day) followed by foscarnet (60 mg/kg/day) for 6 weeks and the patient's symptoms resolved completely. A follow-up CMV antigenemia assay was negative and endoscopic findings by capsule endoscopy and total colonoscopy revealed healing scars without any active lesions.

Intestinal complications after Allo-HSCT predominantly affect the small intestine,[7] but macroscopic findings of small intestinal disorders following Allo-HSCT have not been fully investigated. Traditional small bowel examinations such as push enteroscopy are somewhat invasive in nature and most patients undergoing Allo-HSCT cannot tolerate such procedures due to the seriousness of their condition. Capsule endoscopy is now widely accepted for small intestinal investigation as being far less invasive. In the present case, this advanced technology enabled us to obtain clear endoscopic images of CMV enteritis in the small intestine after Allo-HSCT.

CMV antigenemia assay is one of the most widely used methods to detect CMV reactivation in a variety of clinical settings;[8] however, it is of little value in predicting and diagnosing gastrointestinal CMV disease.[9] The differential diagnosis of intestinal disorders following Allo-HSCT includes intestinal GVHD, thrombotic microangiopathy, treatment-related toxicities and *clostridium difficile*

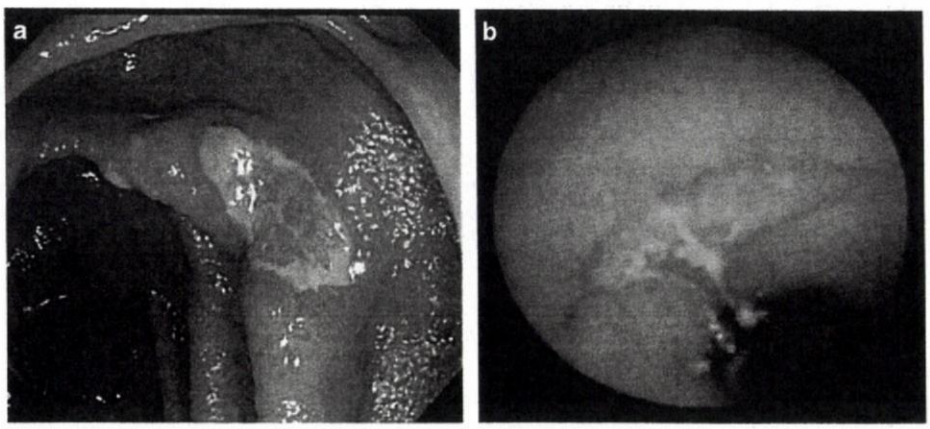

Figure 1 Total colonoscopy revealed a single ulceration (**a**) with several erosions in the ascending colon. Capsule endoscopy also revealed a single ulceration (**b**) with several erosions in the jejunum very similar to the one found in the ascending colon.

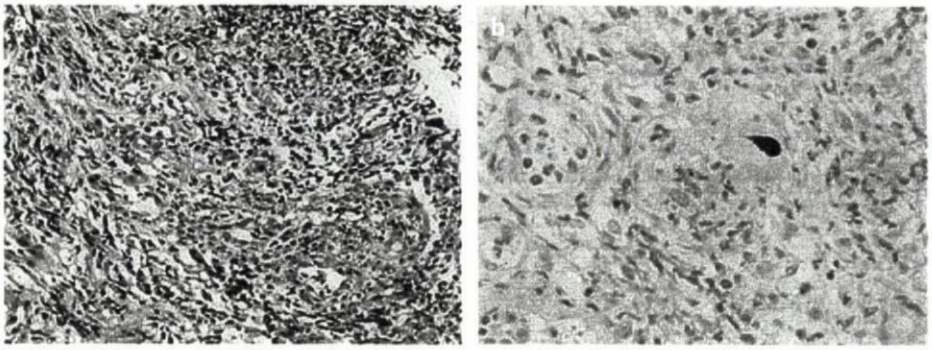

Figure 2 Biopsy specimens obtained from the ulceration and erosions showed cellular enlargement of endothelial cells with nuclear inclusion bodies (**a**) that were positive for CMV by immunohistochemical staining (**b**).

enterocolitis as well as CMV enterocolitis.[7] Actual diagnosis is usually based on pathological examinations of endoscopically obtained mucosal biopsy specimens, but this is not possible with capsule endoscopy due to its lack of biopsy capability.

In the present case, we were able to make a diagnosis of CMV enteritis in the small bowel without histological biopsy because of similar coincident findings in the ascending colon that were proven by pathological examination to be CMV colitis. This diagnosis was subsequently confirmed clinically by prompt resolution of intestinal symptoms, endoscopic findings and CMV antigenemia assay after antiviral treatment using ganciclovir and foscarnet.

Fortunately, CMV enteritis involved both the small intestine and colon in this case. CMV colitis, which was proven by biopsy, was a factor in diagnosing small intestinal CMV disease; however, CMV enteritis involving only the small intestine without colon involvement may not be rare after Allo-HSCT because the small intestine is a frequent and severe site for gastrointestinal complications following Allo-HSCT.[7] In such a situation, our picture (Figure 1a) showing ulceration detected by capsule endoscopy may be useful in diagnosing small intestinal CMV disease after Allo-HSCT.

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Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection – An analysis of risk factors*

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Background and study aim: Endoscopic submucosal dissection (ESD) has been reported to be associated with a higher complication rate than standard endoscopic mucosal resection. We aimed to clarify the risk factors for delayed bleeding after ESD for early gastric cancer (EGC).

Methods: 1083 EGCs in 968 consecutive patients undergoing ESD during a 4-year period were reviewed. Post-ESD coagulation (PEC) preventive therapy of visible vessels in the resection area, using a coagulation forceps, was introduced and mostly performed during the later 2 years. Various factors related to patients, tumors, and treatment including PEC were investigated using univariate and multivariate analysis with regard to delayed post-ESD bleeding, evidenced by hematemesis or melena, that required endoscopic treatment.

Results: Delayed bleeding occurred after ESD of 63 lesions (5.8% of all lesions and 6.5% of patients), controlled in all cases by endoscopic hemostasis; blood transfusion was required in only one case. Tumor location in the upper third of the stomach and PEC were independent factors indicating a lower rate of delayed bleeding according to both univariate and multivariate analysis.

Conclusions: This retrospective study suggested that preventive coagulation of visible vessels in the resection area after ESD may lead to a lower bleeding rate.

Introduction

Endoscopic resection for early gastric cancer (EGC) has made remarkable progress since the development of endoscopic submucosal dissection (ESD). In Japan, ESD is becoming used more widely as a treatment for EGC because it preserves the stomach and allows one-piece resection with tumor-free margins, even in cases of large and ulcerative lesions [1]. It also permits accurate histological assessment and reduces the risk of local recurrence [2–9]. Although its safety has been substantiated, complications such as perforation and bleeding are still a serious problem.

As we have reported previously [1], both perforation and immediate bleeding are easily recognized at the time of the procedure and can be treated endoscopically [10]. On the other hand, delayed bleeding manifested as hematemesis or melena may occur days after the procedure (sometimes after discharge from hospital). As any delay in recognition of such an event may result in cardiovascular complications, prevention of delayed bleeding is important, and was therefore selected as the focus of the present study.

In the initial period of the study, we had applied hemostasis, using hemoclipping and/or electrocoagulation, only for bleeding or oozing vessels after specimen resection. Previous studies have suggested that all visible vessels of peptic ulcers, irrespective of the presence of bleeding, should be treated by endoscopic hemostasis at the first endoscopy [11–13]. Based on this principle, around January 2003 we started post-ESD coagulation (PEC) therapy, regardless of the presence of bleeding at visible vessels, to prevent delayed bleeding.

To our knowledge, only one previous report [14] has mentioned the risk factors for delayed bleeding after conventional endoscopic mucosal resection (EMR), and there have been no reported case

* Presented at the 13th United European Gastroenterology Week, UEGW 2005, Copenhagen, Denmark, 15–19 October 2005.

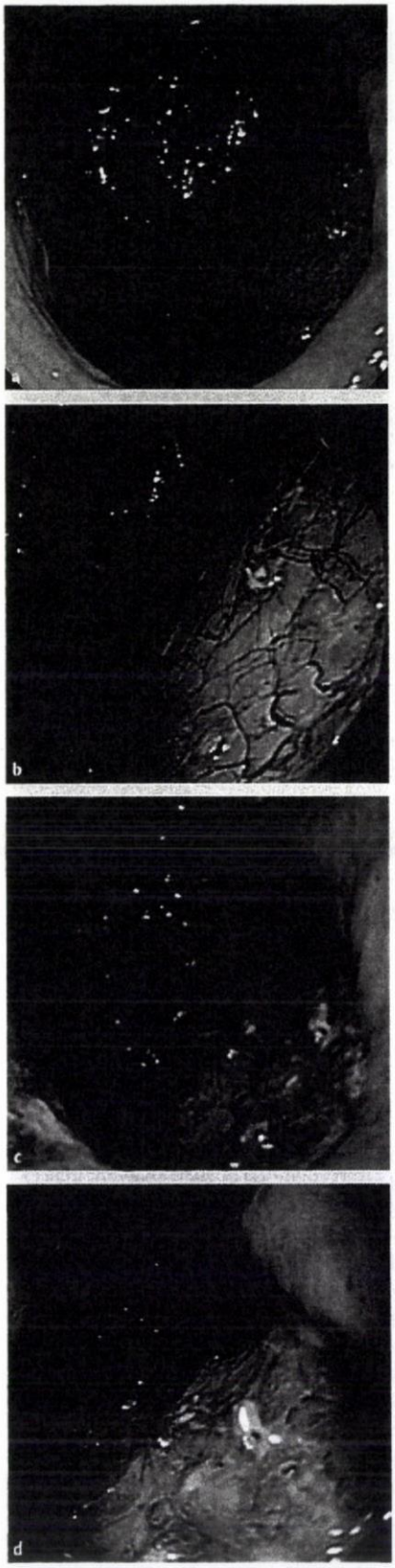

Fig. 1 Endoscopic appearance of endoscopic submucosal dissection (ESD) defect: **a, b** before post-ESD coagulation, and **c, d** after PEC.

series focusing on delayed bleeding after ESD except for our previous report [1]. Therefore the aim of this study was to clarify the risk factors for delayed bleeding after ESD for EGC.

Patients and methods

Patients

Between January 2000 and March 2004, ESD was performed with curative intent for 1123 EGCs in 1008 consecutive patients at the National Cancer Center Hospital, Tokyo, Japan [1]. In this study, EGCs arising from remnant stomach (21 lesions) and gastric tube after esophagectomy (19 lesions) were excluded (none of these 40 excluded lesions showed delayed bleeding), so finally, a total of 1083 lesions in 968 patients were investigated.

ESD procedure

The ESD procedure used was as follows. Marking dots were made using a precutting knife along the circumference of the target lesion to clarify the margin. Saline with epinephrine was injected into the submucosal layer around the lesion to lift it off the muscle layer. Incision of the mucosa outside the marking dots was then done. Subsequent submucosal dissection of the lesion was performed with an insulated-tip knife. The submucosal connective tissue was dissected and the raised lesion was cut off completely from the muscle layer.

Delayed bleeding

Delayed bleeding was defined as clinical evidence of bleeding after ESD, shown by hematemesis or melena, that required endoscopic treatment.

PEC therapy

Around January 2003, we started to use PEC after ESD, regardless of the presence of bleeding. PEC was performed upon completion of ESD. All visible exposed vessels on the artificial ulcer were coagulated using hemostatic forceps with the soft coagulation mode (80 W, ICC200; ERBE, Tübingen, Germany), even if there was no evidence of bleeding at the end of ESD (© **Fig. 1**).

After ESD treatment

Patients without complication started drinking water on the day after ESD and eating a soft diet 2 days after ESD, and were discharged within 5–7 days. Proton pump inhibitors (PPIs) were prescribed for up to 2 months after ESD.

Data analysis

We reviewed the clinical records, endoscopic images, endoscopic reports, and histological reports for all of these patients. A data collection sheet was designed to record the relevant demographic and clinical information. Patients who underwent ESD were divided into two groups: one with, and one without delayed bleeding. The two groups were retrospectively compared with regard to: (i) patient-related factors such as age, sex, comorbidities, and daily use of anticoagulants and/or antiplatelet drugs; (ii) tumor-related factors such as location, pathological ulceration, and depth; and (iii) treatment-related factors such as size of resected specimen, operation time, operator's experience of ESD, and use of PEC.

The presence of the following co-morbidities was examined: hypertension, other gastric/duodenal peptic ulcer, heart disease, diabetes mellitus, and hyperlipidemia. Patients who usually

Table 1 Endoscopic submucosal dissections (ESDs): patient characteristics

Patient characteristics	
Number, n	968
Age, years	
Mean ± S.D.	66 ± 10
Median (range)	67 (29–93)
Sex, n (%)	
Men	779 (80.5)
Women	189 (19.5)
Co-morbidities, n (%)	
Hypertension	310 (32.0)
Peptic ulcer	138 (14.3)
Heart disease	120 (12.4)
Diabetes mellitus	86 (8.9)
Hyperlipidemia	72 (7.4)
Anticoagulants and/or antiplatelet drugs used, n (%)	77 (8.0)
Lesion characteristics	
Number, n	1083
Location, n (%)	
Upper (U)	180 (16.6)
Middle or lower third (ML)	903 (83.4)
Pathological ulceration, n (%)	
Present	230 (21.1)
Absent	853 (78.9)
Depth, n (%)	
Intramucosal	894 (82.5)
Deeper than intramucosal	189 (17.5)
Size of resected specimen, mm	
Mean ± SD	44 ± 16
Median (range)	40 (8–140)
Duration of operation, minutes	
Mean ± SD	79 ± 64
Median (range)	60 (10–540)
Procedure characteristics	
Experience of operator (number of cases), n (%)	347 (32.0)
Beginner (50 or fewer)	736 (68.0)
Expert (50 or more)	
Post-ESD coagulation (PEC), n (%)	
Without	732 (67.6)
With	351 (32.4)

used anticoagulants and/or antiplatelet drugs were instructed to stop using them for 1 week before and 1 week after ESD.

Tumor location was categorized into two groups, based on the Japanese classification of gastric carcinoma [15]: location in the upper third of the stomach ("U"), or location in the middle or lower third ("ML"). We had previously reported [1] that the occurrence of delayed bleeding in the middle and in the lower thirds was similar, and was higher than that in the upper third. Pathological ulceration and depth were determined histopathologically after ESD. Depth was categorized into "m" (intramucosal) or greater.

The size of the resected specimen was measured as the greatest diameter after ESD. Experience of the operator (the number of cases dealt with by the operator before each procedure) was classified as beginner (50 or fewer cases) or expert (more than 50 cases). Use of PEC was categorized as with or without PEC.

Statistical analysis

Data were analyzed using the chi-squared test and Student's *t* test. Differences at $P < 0.05$ were considered statistically significant. Multivariate logistic regression analysis was performed to

Table 2 Patient-related factors and delayed bleeding

	No delayed bleeding	Delayed bleeding	*P* value
Patients, n	905	63 (6.5%)	
Age, median (range), years	66 (29–93)	67 (34–84)	n.s.*
Sex, n			
Men	724	55 (7.1%)	n.s.
Women	181	8 (4.2%)	n.s.
Co-morbidities, n			
Hypertension			
Present	289	21 (6.8%)	n.s.
Absent	616	42 (6.4%)	n.s.
Peptic ulcer			
Present	126	12 (8.7%)	n.s.
Absent	779	51 (6.1%)	n.s.
Heart disease			
Present	116	4 (3.3%)	n.s.
Absent	789	59 (7.0%)	n.s.
Diabetes mellitus			
Present	81	5 (5.8%)	n.s.
Absent	824	58 (6.6%)	n.s.
Hyperlipidemia			
Present	81	5 (5.8%)	n.s.
Absent	824	58 (6.6%)	n.s.
Anticoagulants and antiplatelet drugs, n			
Used	74	3 (3.9%)	n.s.
Not used	831	60 (6.7%)	n.s.

n.s., not significant; * *t* test.

Table 3 Tumor-related and treatment-related factors and delayed bleeding

	No delayed bleeding	Delayed bleeding	*P* value
Lesions			
Number, n	1020	63 (5.8%)	
Location, n			< 0.005
Upper	178	2 (1.1%)	
Middle or lower	842	61 (6.8%)	
Pathological ulceration, n			n.s.
Present	215	15 (6.5%)	
Absent	805	48 (5.6%)	
Depth, n			n.s.
Intramucosal	841	53 (5.9%)	
Deeper than intramucosal	179	10 (5.3%)	
Size of resected specimen, median (range), mm	40 (8–140)	45 (25–110)	n.s.*
Treatment			
Duration of operation, median (range), minutes	60 (10–540)	60 (20–260)	n.s.*
Experience (number of cases) of operator, n			n.s.
Beginner (50 or fewer)	327	20 (5.8%)	
Expert (more than 50)	693	43 (5.8%)	

Table 4 Multivariate logistic regression analysis

		Odds ratio (95%CI)	*P* value
Location	Middle and lower third	6.74 (1.64–27.95)	< 0.01
Post-ESD coagulation (PEC)	Without	2.47 (1.27–4.80)	< 0.01

CI, confidence interval; ESD endoscopic submucosal dissection.

examine the effects of independent variables adjusted for the effects of each of the others.

Results

Patient, lesion, and tumor characteristics are summarized in ○ **Table 1**. A total of 34 operators were involved in the study (seven experts and 27 beginners).

The data for delayed bleeding are shown in ○ **Table 2** and ○ **Table 3**. Delayed bleeding occurred in 63 of 1083 lesions (5.8%) in 63 of 968 patients (6.5%). Of these patients, 75% bled within 24 hours and the remaining 25% bled between 2 and 15 days after the procedure. All cases of bleeding were controlled by endoscopic treatments (hemoclipping and/or electrocoagulation) and did not require any surgical intervention. Blood transfusion was required in only one patient.

Univariate analysis showed that tumor location (upper third, U, 1.1% vs. middle or lower, ML, 7.4%; $P < 0.005$) and use of PEC (with 3.1% vs. without 7.1%; $P < 0.01$) were significantly related to delayed bleeding. Other factors (age, gender, co-morbidities, daily use of anticoagulants and/or antiplatelet drugs, pathological ulceration, tumor depth, size of resected specimen, procedure time, and operator's experience of ESD) were not related to delayed bleeding.

Multivariate logistic regression analysis showed that tumor location (ML > U; $P = 0.008$) and use of PEC (without > with; ($P = 0.008$) were independent factors related to delayed bleeding (○ **Table 4**).

Discussion

ESD is a technically difficult procedure and may cause major complications such as bleeding and perforation. All perforations were sealed endoscopically [10] except for one case where this was technically difficult due to previous Billroth I gastrectomy, and therefore surgery was required. Both perforation and immediate bleeding are diagnosed at the time of the ESD procedure and are treated simultaneously. However, delayed bleeding is usually manifested as hematemesis or melena (sometimes after discharge from hospital), and therefore there may be a delay until treatment can be initiated. Delayed recognition of delayed bleeding may result in cardiovascular complications. Therefore we think that delayed bleeding is the most serious complication related to ESD, and steps should be taken to reduce its incidence.

Although there are many reports about bleeding related to endoscopic resection, probably associated with various definitions, only one report [14] has mentioned risk factors for "delayed bleeding" distinguished from immediate bleeding after conventional EMR, and no other reported series has addressed the issue of "delayed bleeding" after ESD except for a previous study [1] conducted at our institution. In that study the incidence was about 5% in cases treated by conventional endoscopic resection techniques, such as strip biopsy and EMR-C (EMR using a transparent plastic cap) [14]. The incidence of delayed bleeding after ESD at our center was 5.8% [1], and there was no difference in the incidence of bleeding between conventional endoscopic resection and ESD.

In this study, the parameters showing significant differences in patients with delayed bleeding were location (ML > U) and use of PEC (without > with) by multivariate logistic regression analysis.

Intraoperative bleeding has been reported to occur significantly more frequently in the upper area of the stomach than in the middle and lower areas[1,16,17]. Hirao et al. [16] examined arteries in the submucosal layer of resected gastric specimens histologically, and found that those from the upper stomach were significantly more stubby or thick than those from other gastric sites. Narimiya et al. [17] also found that the diameter of submucosal arteries was larger in the upper area than in the middle or lower stomach. Therefore, the risk of intraoperative bleeding is higher in the upper stomach and intraoperative hemostasis is needed more frequently during removal of a lesion in this area. In other words, there is a lower frequency of intraoperative hemostasis in the middle and lower gastric areas, and if vessels in these areas are not coagulated, they may bleed later. We speculate that this is one of the reasons why tumor location (ML > U) was an independent risk factor for delayed bleeding.

In a previous report about delayed bleeding after endoscopic resection [14], the only factor found to differ significantly between cases with and without delayed bleeding was the occurrence of immediate bleeding during EMR. The authors considered that the occurrence of delayed bleeding may not have been due to insufficient initial hemostasis but rather to insufficient coagulation during resection, because sites where immediate bleeding was controlled endoscopically were not those responsible for delayed bleeding. On the basis of our experience, we agree with this conclusion.

We also consider that antral peristaltic activity and bile juice reflux may be contributory to a certain extent.

The other risk factor revealed by the present multivariate logistic regression analysis was the non-use of PEC. Therefore, we believe that PEC might reduce the risk of delayed bleeding. PEC was performed upon completion of ESD and all visible exposed vessels on the artificial ulcer created by ESD were coagulated by hemostatic forceps, even if there was no evidence of bleeding at the time. In addition, there was no complication related to PEC, such as delayed perforation (data not shown).

Furthermore, multivariate logistic regression analysis showed that both tumor location and use of PEC were independent factors related to delayed bleeding after ESD. However, the incidence of delayed bleeding in the middle and lower stomach was also lower with PEC (data not shown: 3.3% compared with 8.5%). Thus PEC appears to be an important factor for prevention of delayed bleeding after ESD, even if the lesion is located in the middle or lower stomach.

It seems very likely that PEC reduced the risk of delayed bleeding in our series, although conclusive evidence of the usefulness of PEC can only be provided by a randomized prospective study comparing ESD with PEC against ESD without PEC. While this is, in principle, desirable, it would be difficult to justify such a

study in view of the clear results obtained in the present investigation.

In this study, age and gender had no relevance to delayed bleeding after ESD. No co-morbidity (hypertension, peptic ulcer, heart disease, diabetes mellitus, or hyperlipidemia) was a risk factor for delayed bleeding. Although daily use of anticoagulants and antiplatelet drugs is considered a risk factor for bleeding, our study showed that withdrawal of such drugs for 1 week before and 1 week after ESD was able to alleviate their effects.

Conclusion

The risk factors associated with delayed bleeding are tumor location (lower risk with upper compared with middle or lower stomach) and non-use of PEC. Delayed bleeding after ESD for early gastric cancers might be prevented by PEC.

Competing interests: None

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Answer to the Clinical Challenges and Images in GI Question: Image 3: Small Depressed Colon Cancer

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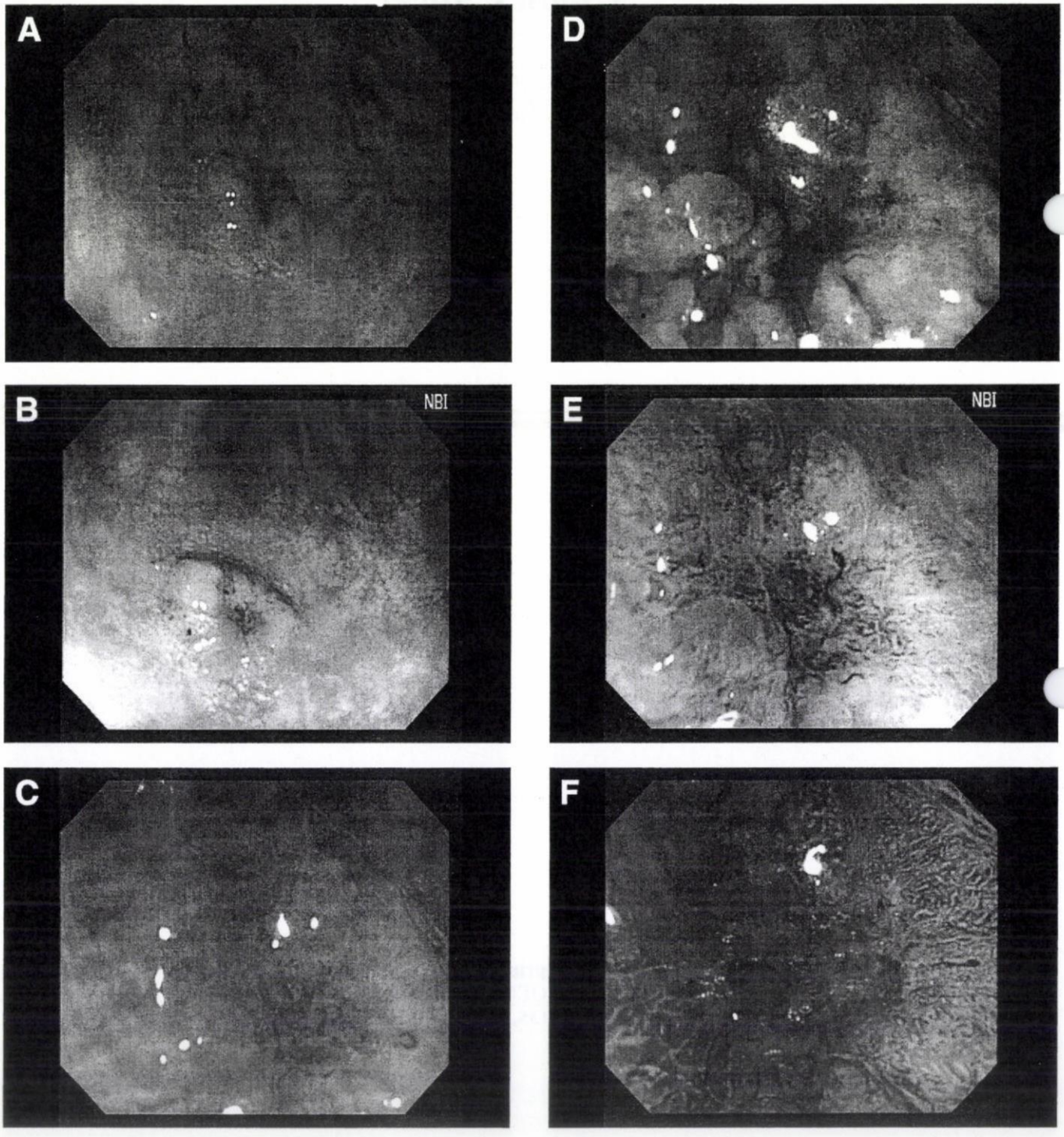
Image 3



Question: A 53-year-old man was referred to our hospital from a local clinic because of a positive fecal occult blood test. The patient had no prior history of cancer and there was no family history of colorectal cancer. Blood test results including hemoglobin and carcinoembryonic antigen were within normal limits.

We performed a colonoscopy with dye spraying and magnification using a narrow-band imaging (NBI) system. The NBI system included dedicated filters incorporated into the light source unit (CLV-260SL, Olympus, Tokyo, Japan), a video processor (CV-260SL, Olympus) and a magnified videoendoscope (CF-H260AZI, Olympus). Colonoscopy identified 1 slightly reddish flat lesion located in the sigmoid colon (Figure *A*) and NBI revealed increased vascular intensity in the depressed area of the lesion (Figure *B*). The depressed morphology of the lesion became clear after spraying with a 0.2% indigo carmine dye solution. The lesion was about 10-mm in diameter with a well-demarcated depression margin. The magnified view of the depressed area showed irregular microvessels (Figure *C*). Examination of the depression's pit pattern suggested type V, but this could not be confirmed solely by indigo carmine dye spraying (Figure *D*). What was the diagnosis based on the clearly visible central depressed area using NBI with magnification (Figure *E*) and crystal violet staining (Figure *F*)?

See the GASTROENTEROLOGY website (www.gastrojournal.org) for more information on submitting your favorite image to Clinical Challenges and Images in GI.

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