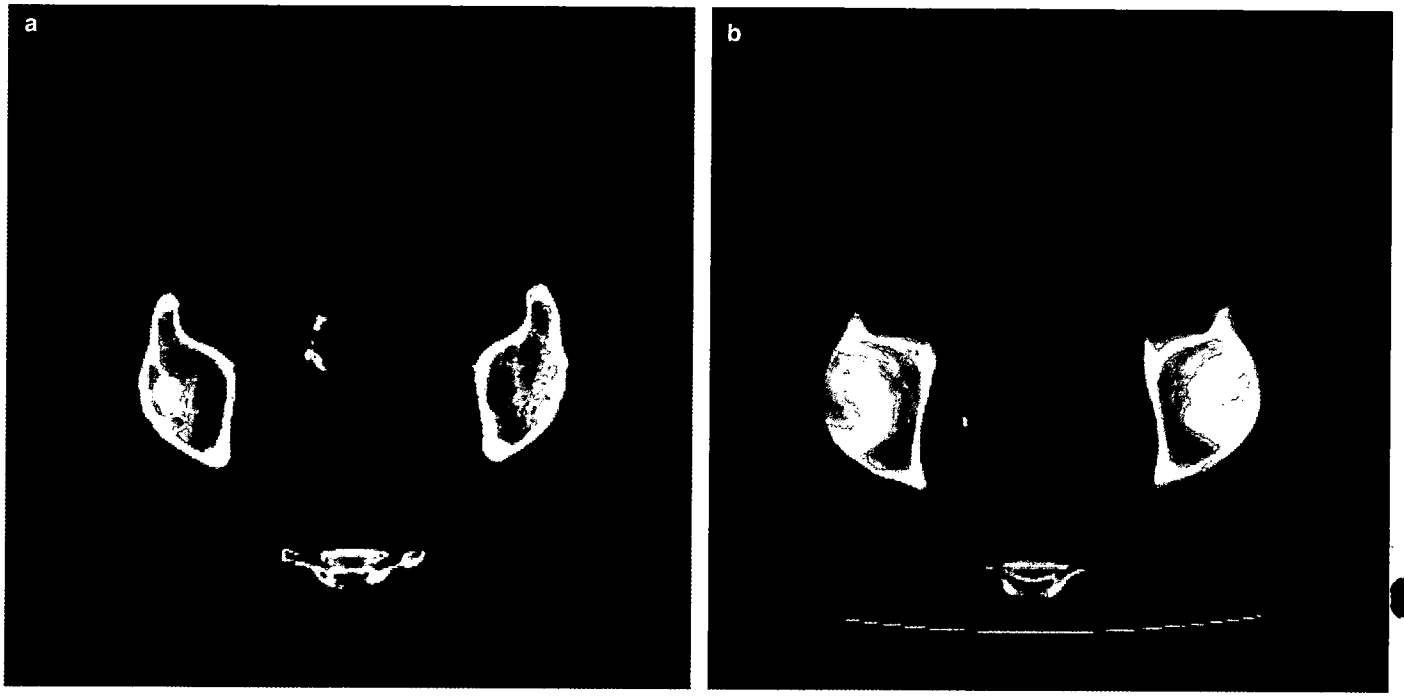

Fig. 3. (a) Computed tomography (CT) 1 day after endoscopic mucosal resection showed fluid collection close to the perforation site and an abscess was suspected. (b) CT before surgery (approx. 1 month after the previous CT examination) showed no fluid collection.

We have been using CO_2 insufflation for colonic ESD recently in order to decrease patient discomfort.[14] Although we have encountered small colonic perforations in some cases, there has been no patient abdominal distension or free air observed on abdominal X-ray, probably due to the rapid absorption of CO_2 compared to conventional air. As a result, we have been able to close colonic perforations without the need to either hurry or perform abdominal decompression.

We believe therefore that CO_2 insufflation is recommended for endoscopic therapeutic procedures such as ESD and EMR in order to decrease the risk of pneumoperitoneum caused by colonic perforation.

ESD versus EMR

ESD for early gastric cancer is widely accepted as a useful endoscopic treatment,[19–21] but ESD for colorectal cancer is not widely accepted because of its technical difficulty and the greater risk of perforation.[8,9] The en bloc resection rate using ESD has been reported to be as high as 87%, which was considerably higher compared to that of conventional EMR,[14] but the perforation rate for ESD also was considerably higher than that for conventional EMR.[21] Because ESD has been substituted in difficult cases for conventional EMR, it is hard to compare the perforation rates, but further improvements in ESD are necessary for the effective removal of large colorectal neoplasms more easily and safely.

As indicated in the present case reports, perforations during ESD usually are smaller compared to those resulting from EMR and therefore they are easier to close endoscopically.[20]

Preventing perforations

Complications resulting from ESD sometimes occur primarily due to inaccurate identification of the cutting line because the ablated mucosa cannot be stabilized and pulled away. The resultant cutting of sm vessels causes bleeding, and overestimation of the depth of the sm layer can result in perforations. In order to prevent such occurrences, we also have developed a sinker-assisted ESD[16] procedure that has been performed successfully in six cases.

CONCLUSIONS

In conclusion, conservative medical management may be possible in patients who have undergone successful colonic perforation closures using endoscopic clipping. In order to perform immediate endoscopic closure, abdominal decompression has been useful in reducing patient discomfort and preventing colonic lumen collapse. Now, CO_2 insufflation is being used effectively for the prevention of pneumoperitoneum.

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Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth?

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Background and study aims: Assessment of the invasion depth of colorectal neoplasia is important in deciding between endoscopic and surgical resection treatment methods. Prior to attempting endoscopic resection, the lesion is lifted by submucosal injection, and a positive "non-lifting sign" is usually considered to indicate deeper submucosal infiltration. The purpose of this prospective multicenter study was to assess the predictive value of the non-lifting sign for differentiating between adenoma and early cancer (up to discrete submucosal infiltration [sm1]) and cancer with deeper infiltration (sm2).

Patients and methods: During an 11-month period, a total of 271 colorectal neoplastic lesions in 239 patients were included in the study. Apart from the location, size, and macroscopic type of the lesion, the presence or absence of the non-lifting sign was recorded and compared with the endoscopic assessment of invasion depth.

Results: The non-lifting sign had a sensitivity of 61.5%, a specificity of 98.4%, a positive predictive value of 80.0%, a negative predictive value of 96.0%, and an accuracy of 94.8%. Endoscopic diagnosis of deeper infiltration had a sensitivity of 84.6%, a specificity of 98.8%, a positive predictive value of 88.0%, a negative predictive value of 98.4%, and an accuracy of 97.4%. Statistically significant differences were found in terms of sensitivity and accuracy.

Conclusion: Because of its lower sensitivity and accuracy, the non-lifting sign will not replace endoscopic assessment. If a lesion does not lift, this can make resection technically difficult, but does not reliably predict deeper cancerous invasion.

Introduction

In Japan submucosal cancers are subclassified into "sm1" cancers (where the distance from the muscularis mucosae to the deepest point of invasion is < 1 mm) and "sm2" cancers (where the distance from the muscularis mucosae to the deepest point of invasion is ≥ 1 mm). Because it is believed that sm1 lesions without lymphovascular involvement or a poorly differentiated component are rarely associated with lymph node metastasis, they are thought to be resectable endoscopically, in a similar manner to adenomas and intramucosal cancers [1,2]. In order to determine the appropriate treatment for colorectal neoplastic lesions, therefore, it is necessary to estimate whether or not the depth of invasion from the muscularis mucosae is less than 1 mm. Magnifying colonoscopy [3–9] and endoscopic ultrasound [9–13] have been reported to be helpful for this type of endoscopic assessment, although only experts are able to use these techniques adequately, and learning them requires considerable time and experience [14,15].

Endoscopic mucosal resection (EMR) is a safe technique for resecting large or flat colorectal neoplastic lesions after submucosal injection of liquid [16–18], and this submucosal injection is also thought to be useful for the diagnostic assessment of invasion depth [19–21]. Adenomas and intramucosal cancers are readily lifted by submucosal injection, in contrast to invasive cancer, which cannot be lifted because of submucosal fibrosis or desmoplastic change. Uno et al. [19] described this phenomenon as the "non-lifting sign", although their data were obtained at a single institution, about half of the cases they studied were small adenomas measuring less than 10 mm, and only 10 invasive cancers were evaluated. The usefulness of the non-lifting sign therefore still needs to be clarified.

The purpose of this prospective multicenter trial was to assess the accuracy of the non-lifting sign, in comparison with endoscopic diagnosis, as a diagnostic tool to determine whether or not the depth of invasion from the muscularis mucosae is less than 1 mm.

Patients and methods

This study was a prospective trial conducted at five medical centers in Japan between January 2004 and November 2004. Institutional review board approval was obtained at each participating institution, and informed written consent was obtained from all patients before the diagnostic and therapeutic procedures were carried out.

Eligibility and exclusion criteria

We included all colorectal neoplastic lesions except (a) lesions larger than 30 mm, (b) polypoid lesions smaller than 10 mm, (c) pedunculated polyps, (d) residual or recurrent lesions after endoscopic resection, and (e) colitis-associated lesions. Lesions diagnosed pathologically as colorectal cancer that had invaded beyond the submucosa (i. e. T2 or more) and non-neoplastic lesions were also excluded.

Endoscopic procedure

For colonic preparation all the centers used 2–3 liters of polyethylene glycol-electrolyte solution on the day of the procedure. All the patients received scopolamine butylbromide 20 mg intravenously unless this was contraindicated and sedation (for example with midazolam or diazepam) if required. All the investigators in this study had performed more than 500 colonoscopic procedures. When the eligible lesion was identified, its surface was washed with water before spraying 5 mL of 0.4% indigo carmine directly through the accessory channel of the scope. Each investigator diagnosed the depth of invasion after chromoscopic enhancement. Findings such as fold convergence, an expansive appearance, an irregular surface contour, a demarcated depressed area, or a large nodule (≥ 1 cm) in the flat lesion were regarded as signs of deep invasion [22–24]. Depending on the estimated depth of invasion, lesions were finally classified endoscopically as either "type A(e)" (sm2 cancers) or "type B(e)" (adenomas, intramucosal cancers, and sm1 cancers). On the basis of this endoscopic assessment, therefore, type A(e) lesions were considered to be candidates for surgical treatment and type B(e) lesions to be suitable for EMR. The location, size, and macroscopic type of the lesions were also recorded for analysis.

Submucosal injection

Submucosal injection was performed at a point approximately 2 mm from the edge of the lesion with a 23-gauge needle, and the frequency of injections was adjusted according to the size of the lesion. Normal saline or glycerol (Glyceol [10% glycerol and 5% fructose in normal saline solution]; Chugai Pharmaceutical Co., Tokyo, Japan) was used for the submucosal injection [25]. The non-lifting sign was defined (according to the criteria used by Uno et al. [19]) as positive when the surrounding mucosa, but not the lesion, was elevated, and negative when the lesion itself was elevated (**Fig. 1**, **Fig. 2**). The presence or absence of the non-lifting sign after submucosal injection was recorded for comparison with the endoscopic assessment of invasion depth.

Fig. 1 Positive non-lifting sign: the submucosal injection has resulted in elevation of the mucosa surrounding the lesion, but not of the lesion itself.

Fig. 2 Negative non-lifting sign: both the lesion and the surrounding mucosa were well elevated by the submucosal injection in this case.

Histopathological evaluation

Either EMR or surgical resection was performed for all lesions. All the specimens were fixed in 10% buffered formalin solution and stained with hematoxylin and eosin. All tissues were examined by the pathologists at each institution with reference to the Japanese classification of cancer of the colon and rectum [26]. The pathologists were all blinded to the endoscopic findings. The depth of invasion was classified histopathologically as either type A(h) (sm2 cancer) or type B(h) (adenoma, intramucosal cancer, or sm1 cancer).

Statistical analysis

The aim of this study was to assess the sensitivity and specificity of the non-lifting sign for distinguishing sm2 cancer from adenoma, intramucosal cancer, and sm1 cancer. A high specificity was considered to be necessary because it is important that patients avoid unnecessary surgery. We therefore assumed a specificity of 95%, with a 95% confidence interval (CI) of ± 3%, to decide on the sample size required for this study, and it was calculated that a total enrollment of 200 lesions would be needed.

All values are reported as means ± standard deviation when applicable. The accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were evaluated by comparing the results for the non-lifting sign or endoscopic diagnosis with the histopathological diagnosis. Comparisons were made using McNemar's test or Fisher's exact test. Probability values of less than 0.05 were considered to signify statistical significance. All calculations were performed using the SPSS statistical software package (SPSS, Chicago, Illinois, USA).

Results

At the time of the endoscopic procedures, 252 patients with 284 lesions were initially enrolled in this study. After histological evaluation, eight deep invasive colorectal cancers (T2) and five

Total number of lesions	271
Location, n (%)	
Rectum	55 (20.3%)
Distal colon	108 (39.9%)
Proximal colon	108 (39.9%)
Size, n (%)	
≤10 mm	135 (49.8%)
11–20 mm	122 (47.2%)
21–30 mm	14 (5.2%)
Mean size ± standard deviation, mm	12.3 ± 5.4
Macroscopic type, n (%)	
Polypoid	89 (32.8%)
Flat and depressed	182 (67.2%)
Histopathological type, n (%)	
Type A(h) lesions (sm2 cancer)	26 (9.6%)
Type B(h) lesions	245 (90.4%)
Adenoma	161 (59.4%)
Intramucosal cancer	72 (26.6%)
sm1 cancer	12 (4.4%)

Table 1 The clinicopathological characteristics of the lesions included in the study

non-neoplastic lesions were excluded from the analysis, and so 271 lesions in 239 patients were finally included in the study. The clinicopathological characteristics of these lesions are summarized in ● **Table 1**.

The non-lifting sign as a diagnostic tool

The overall accuracy of the non-lifting sign as a tool for determining the depth of invasion was 94.8% (257/271), and its sensitivity, specificity, PPV, and NPV were 61.5% (16/26), 98.4% (241/245), 80.0% (16/20), and 96.0% (241/251) respectively (● **Table 2**). On the basis of the macroscopic type, the accuracy, sensitivity, specificity, PPV, and NPV of the non-lifting sign were 95.5% (85/89), 55.6% (5/9), 100% (80/80), 100% (5/5), and 95.2% (80/84) respectively for polypoid lesions (● **Table 3**), and 94.5% (172/182), 64.7% (11/17), 97.6% (161/165), 73.3% (11/15), and 96.4% (161/167) respectively for flat and depressed lesions (● **Table 4**).

Accuracy of endoscopic diagnosis vs. the non-lifting sign

The results for the overall accuracy, sensitivity, specificity, PPV value, and NPV of endoscopic diagnosis were 97.4% (264/271), 84.6% (22/26), 98.8% (242/245), 88.0% (22/25), and 98.4% (242/246) respectively (● **Table 2**). The specificity of endoscopic diagnosis was similar to that of the non-lifting sign, but the sensitivity and accuracy of endoscopic diagnosis were significantly higher than the sensitivity and accuracy of the non-lifting sign ($P = 0.031$ for the difference in sensitivity and $P = 0.039$ for the difference in accuracy). On the basis of the macroscopic type, the results for the accuracy, sensitivity, specificity, PPV, and NPV of endoscopic diagnosis of polypoid lesions were 96.6% (86/89), 66.7% (6/9), 100% (80/80), 100% (6/6), and 96.4% (80/83), respectively (● **Table 3**). For flat and depressed-type lesions, endoscopic diagnosis showed an accuracy of 97.8% (178/182), a sensitivity of 94.1% (16/17), a specificity of 98.2% (162/165), a PPV of 84.2% (16/19), and an NPV of 99.4% (162/163) (● **Table 4**). The sensitivity and accuracy of endoscopic diagnosis for flat and depressed lesions were also higher than the sensitivity and accuracy of the non-lifting sign, although not to a significant degree ($P = 0.063$ for the difference in sensitivity and $P = 0.07$ for the difference in accuracy) (● **Table 5**).

Glycerol vs. normal saline for assessment of the non-lifting sign

Glycerol was used as the injection agent for 219 lesions (80.8%), and normal saline for 52 lesions (19.2%). Of the 26 sm2 cancers, 19 were included in the glycerol-injection group, and 10 of these showed the non-lifting sign. The remaining seven sm2 cancers were included in the normal saline-injection group, and six of these showed the non-lifting sign. The accuracy, sensitivity, and specificity of the non-lifting sign in the glycerol-injection lesions were 95.0% (208/219), 52.6% (10/19), and 99.0% (198/200) respectively; the accuracy, sensitivity, and specificity of the non-lifting sign in the normal saline-injection lesions were

	Non-lifting sign		Endoscopic diagnosis	
	Positive	Negative	Type A(e)	Type B(e)
Histopathology				
Type A(h) lesions	16	10	22	4
Type B(h) lesions	4	241	3	242
Sensitivity	61.5% (16/26)		84.6% (22/26)	
Specificity	98.4% (241/245)		98.8% (242/245)	
Positive predictive value	80.0% (16/20)		88.0% (22/25)	
Negative predictive value	96.0% (241/251)		98.4% (242/246)	
Accuracy	94.8% (257/271)		97.4% (264/271)	

Table 2 The non-lifting sign vs. endoscopic assessment in the diagnosis of all 271 lesions, where type A lesions were sm2 cancers and type B lesions were adenomas, intramucosal cancers, or sm1 cancers

	Non-lifting sign		Endoscopic diagnosis	
	Positive	Negative	Type A(e)	Type B(e)
Histopathology				
Type A(h) lesions	5	4	6	3
Type B(h) lesions	0	80	0	80
Sensitivity	55.6% (5/9)		66.7 (6/9)	
Specificity	100% (80/80)		100% (80/80)	
Positive predictive value	100% (5/5)		100% (6/6)	
Negative predictive value	95.2% (80/84)		96.4% (80/83)	
Accuracy	95.5% (85/89)		96.6% (86/89)	

Table 3 The non-lifting sign vs. endoscopic assessment in the diagnosis of the 89 polypoid lesions, where type A lesions were sm2 cancers and type B lesions were adenomas, intramucosal cancers, or sm1 cancers

	Non-lifting sign		Endoscopic diagnosis	
	Positive	Negative	Type A(e)	Type B(e)
Histopathology				
Type A(h) lesions	11	6	16	1
Type B(h) lesions	4	161	3	162
Sensitivity	64.7% (11/17)		94.1% (16/17)	
Specificity	97.6% (161/165)		98.2% (162/165)	
Positive predictive value	73.3% (11/15)		84.2% (16/19)	
Negative predictive value	96.4% (161/167)		99.4% (162/163)	
Accuracy	94.5% (172/182)		97.8% (178/182)	

Table 4 The non-lifting sign vs. endoscopic assessment in the diagnosis of the 182 flat and depressed-type lesions, where type A lesions were sm2 cancers and type B lesions were adenomas, intramucosal cancers, or sm1 cancers

	Non-lifting sign	Endoscopic diagnosis	*P*
All lesions (n = 271)			
Sensitivity	61.5%	84.6%	0.031
Specificity	98.4%	98.8%	1.0
Positive predictive value	80.0%	88.0%	0.682
Negative predictive value	96.0%	98.4%	0.174
Accuracy	94.8%	97.4%	0.039
Polypoid lesions (n = 89)			
Sensitivity	55.6%	66.7%	1.0
Specificity	100%	100%	
Positive predictive value	100%	100%	–
Negative predictive value	95.2%	96.4%	1.0
Accuracy	95.5%	96.6%	1.0
Flat and depressed lesions (n = 182)			
Sensitivity	64.7%	94.1%	0.063
Specificity	97.6%	98.2%	1.0
Positive predictive value	73.3%	84.2%	0.672
Negative predictive value	96.4%	99.4%	0.121
Accuracy	94.5%	97.8%	0.07

Table 5 The non-lifting sign vs. endoscopic diagnosis: summary

94.2% (49/52), 85.7% (6/7), and 95.6% (43/45) respectively. Although the sensitivity of the non-lifting sign tended to be higher in the lesions that had been injected with normal saline than it was in the lesions injected with glycerol, there was no significant difference between normal saline injection and glycerol injection in terms of the accuracy, sensitivity, or specificity of the non-lifting sign.

Outcome of EMR

No complication associated with either submucosal injection or the EMR occurred during or immediately after the procedure. Of the 10 sm2 cancers that were negative for the non-lifting sign, four were resected by EMR. One of these four lesions was found to have a positive vertical margin pathologically, but additional surgery revealed no local recurrence and no lymph-node or distant metastasis.

Discussion

This study is the first prospective multicenter investigation of the non-lifting sign as a tool for determining the depth of invasion of colorectal neoplastic lesions. Our findings revealed that the non-lifting sign alone was not enough for making an accurate diagnosis of sm2 cancer. It resulted in an increased frequency of unnecessary EMR for sm2 cancer, which had to be followed by additional surgery. On the basis of the morphology, the accuracy of the non-lifting sign and the accuracy of endoscopic diagnosis were almost the same for polypoid lesions, but the sensitivity of the non-lifting sign was inferior to that of endoscopic diagnosis for flat and depressed lesions. This suggests that endoscopic diagnosis is more reliable, especially for flat and depressed lesions. On the other hand, the accuracies of both methods were insufficient for determining the depth of invasion of polypoid lesions. Currently, to prevent unnecessary surgery, it appears that polypoid lesions that are negative for the non-lifting sign should be resected by EMR.

Uno et al. [19] defined the non-lifting sign as an indicator of invasive cancer. They evaluated 193 neoplastic lesions, and reported that the sensitivity and specificity of the non-lifting sign were as high as 100% and 99%, respectively. In our opinion, the higher sensitivity and specificity results obtained in their study might have resulted from the limited number of invasive cancers they included (only 10, including four submucosal cancers). In contrast, because we included 38 submucosal cancers and excluded advanced cancers (e.g. tumors that were T2 or more), our sensitivity result was lower than theirs. Nevertheless, we consider that our results reflect the clinical situation more precisely because we prospectively evaluated all colorectal neoplastic lesions detected by colonoscopy. In addition, the solutions used for the submucosal injection were different in the two studies. We used mainly glycerol because this makes EMR technically easier [25]. In our study there were no significant differences in the accuracy, sensitivity, and specificity of the non-lifting sign between lesions lifted by glycerol and lesions lifted using normal saline, although the sensitivity in the glycerol group tended to be inferior to that in the normal saline group. In order to clarify whether or not the use of glycerol or normal saline influences

the frequency of non-lifting-sign positivity, an additional comparative study using a prospective design is mandatory.

Because our study was conducted at five medical centers that specialize in endoscopy, the accuracy of endoscopic diagnosis in this study could be considered to be representative of that of experienced Japanese colonoscopists. In general, endoscopic diagnosis is comparatively subjective, and probably depends to a great extent on the ability of the individual examiner. However, this issue has received little attention in clinical studies. Because both of these diagnostic modalities might depend on the ability of the investigator, it is still uncertain to what extent inexperience affects the results. For inexperienced colonoscopists, the non-lifting sign may be easier to learn than precise endoscopic diagnosis. The learning curves of endoscopic diagnosis and submucosal injection should be investigated to clarify this issue. However, the present results suggest that the non-lifting sign cannot replace endoscopic diagnosis by experienced colonoscopists.

In conclusion, although the non-lifting sign showed high specificity, its sensitivity and accuracy are insufficient in comparison with endoscopic diagnosis for diagnosing invasion depth. If colonoscopists are experienced, the non-lifting sign is not as efficient as endoscopic diagnosis for determining the appropriate treatment for colorectal neoplastic lesions. Further studies of interexaminer variation and the learning curves for each method are necessary so that these results can be adjusted to reflect the experience of all colonoscopists.

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GASTROENTEROLOGY

Further validation of magnifying chromocolonoscopy for differentiating colorectal neoplastic polyps in a health screening center

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Key words
chromoendoscopy, health screening center, magnifying colonoscopy, neoplastic lesion, non-neoplastic lesion, screening colonoscopy.

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Abstract

Background and Aim: The accuracy of conventional colonoscopy to differentiate neoplastic and non-neoplastic polyps is limited, justifying a biopsy for histologic analysis. Magnifying chromocolonoscopy has emerged as the best tool available for differentiating adenomatous and hyperplastic polyps during colonoscopy; however, magnifying endoscopes are rarely used in endoscopy units. This study aimed to further validate the effectiveness of magnifying chromocolonoscopy in the diagnosis of neoplastic colorectal polyps in a screening center.

Method: Five hundred average-risk subjects were randomly divided into two groups: a magnifying chromocolonoscopy group and a conventional chromocolonoscopy group, each of 250 subjects. Lesions were analyzed according to Kudo's classification of pit pattern (types I–V) and additionally subdivided into non-neoplastic (types I–II) and neoplastic (types III–V). Lesions judged as neoplastic were resected and those judged as non-neoplastic were left *in situ*. Only lesions ≤10 mm were included in the study. Resected lesions were analyzed with histopathological examination.

Results: The overall accuracy of magnifying chromocolonoscopy for differentiating neoplastic lesions (95%, 135 of 142), was significantly higher than that of conventional chromocolonoscopy (84%, 102 of 122; $P < 0.01$). The accuracy of magnifying chromocolonoscopy for differentiating neoplastic lesions ≤5 mm was 94% (135 of 142), whereas that of conventional chromocolonoscopy was only 78% (69 of 89; $P < 0.001$). Results were not affected by the macroscopic types.

Conclusion: Magnifying chromocolonoscopy is superior to conventional chromocolonoscopy for the diagnosis of colorectal neoplastic lesions in the setting of a health testing center.

Introduction

Hyperplastic polyps (HP) and other non-neoplastic colorectal lesions do not require endoscopic treatment because they are benign and do not have malignant potential.[1,2] In contrast, adenomatous polyps (AP) should be removed to prevent the progression of the adenoma–carcinoma sequence.[3] At present, colonoscopy is the only available procedure that allows both the diagnosis and treatment of colorectal polyps and early cancers. Because colonoscopy in the absence of magnification has a limited ability to determine the nature of colorectal polyps, biopsy is justified before treatment for histologic confirmation.[4,5] Although not comparable to biopsy, magnifying chromocolonoscopy (MCC) is the best available tool for identifying dysplastic lesions in the setting of bowel inflammatory disease[6] and is the best means for an *in vivo* selective management of colorectal polyps.[7,8]

Despite prospective randomized studies in large reference centers demonstrating the superiority of MCC over conventional colonoscopy,[9,10] magnifying endoscopes are still rarely used in endoscopy units. Technical difficulty, unrecognized necessity and lack of randomized studies validating the effectiveness of MCC in general hospitals or screening centers, are possible reasons for this.[6,11] Furthermore, to our knowledge, chromoendoscopy is seldom used by primary-care physicians in screening colonoscopy. This prospective randomized study aimed to further validate the effectiveness of MCC for the diagnosis of neoplastic colorectal polyps in the setting of a health testing center.

Methods

Patients

Five hundred asymptomatic average-risk subjects were enrolled in the study from June 2001 through March 2002 at the Center for Multiphasic Health Testing and Services, the health check-up medical center of Mitsui Memorial Hospital, Tokyo. Subjects were randomly assigned either to undergo magnifying chromocolonoscopy (Olympus CF-Q240ZI; Olympus Optical, Tokyo, Japan) or conventional chromocolonoscopy (Olympus CF-Q240I). Both colonoscopes have equal view angles (140°) and angulation ranges (up and down 180°; right and left 160°) but differ slightly in their inner channel (CF-Q240ZI, 3.2 mm; CF-Q240I 3.7 mm) and distal tip diameters (CF-Q240ZI, 14.8 mm; CF-Q240I, 13.2 mm). Endoscopic examinations were performed by an expert colonoscopist with extensive experience in MCC (YS). The study was approved by the center's ethics committee, and informed consent was obtained from all subjects. Exclusion criteria were history of colorectal cancer or colonic surgery, familial adenomatous polyposis, acute inflammatory bowel disease and anticoagulation therapy.

Endoscopic examination

Bowel preparation consisted of 2–3 L of polyethylene-glycol (PEG) solution in the morning before the procedure as previously reported.[9] To ensure quality of examination, stool color was assessed before colonoscopy by a trained nurse and additional PEG solution was used when necessary. Hyoscine methobromide (10–20 mg IV) was administered if there were no contraindications and light sedation with diazepam (3–5 mg IV) was used in selected subjects. All colonoscopies were performed with the 'one person, one hand' technique.[12] Identified lesions were rinsed with water to remove any overlying mucous on the surface, then 2–4 mL of 0.3% indigo carmine dye was flushed through the biopsy channel to accentuate the contours of the lesions. Size was estimated using the open width of standard, fully opened (7 mm) hot biopsy forceps as a reference. Locations of lesions were divided into right colon (from the cecum to the splenic flexure), left colon (from to the splenic flexure to the recto-sigmoid junction) and rectum (from the recto-sigmoid junction to the anal verge). Lesions were classified macroscopically based on the criteria of the Japanese Research Society for Cancer of Colon and Rectum.[13]

Magnification and pit pattern

In the MCC group, magnification was performed up to 100× by moving the zoom bottom of the endoscope backward; this maneuver requires about 5 s. The pit pattern was analyzed in real time, according to Kudo's classification into type I (round and regular pit), type II (star-shaped or onion-like pit), type IIIs (small pit), type III_L(large, elongated pit), type IV (branched or gyrus-like pit) and type V (non-structured pit). Lesions were additionally grouped into non-neoplastic (types I and II) and neoplastic (types III, IV and V) according to Fujii's clinical classification of the pit pattern[14,15] (Figs 1,2).

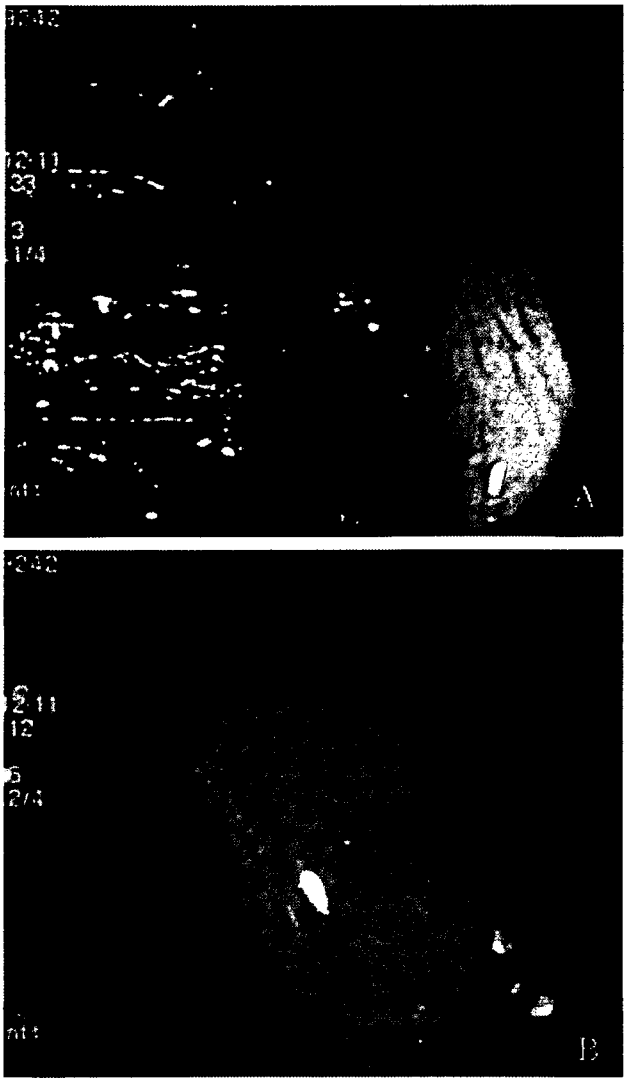


Figure 1 (a) Chromocolonoscopy revealed a Is, small, oval polyp, 4 mm in diameter. The nature of the lesion was poorly determined with conventional chromocolonoscopy. (b) Magnifying chromocolonoscopy disclosed a type II (star-like) pit pattern; the lesion was diagnosed as non-neoplastic and no treatment was performed.

Endoscopic treatment

In both groups, lesions diagnosed as non-neoplastic were left *in situ* and advanced carcinomas were biopsied. Both these lesion types were excluded from analysis. If lesions were identified as adenomas or intramucosal carcinomas (neoplastic non-invasive lesions), hot biopsy, polypectomy or endoscopic mucosal resection (EMR) were 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.[16,17] In cases where a polyp was not clearly diagnosed as HP or AP, it was considered as AP and therefore resected for histological analysis. The frequency of finding these difficult lesions was very low.

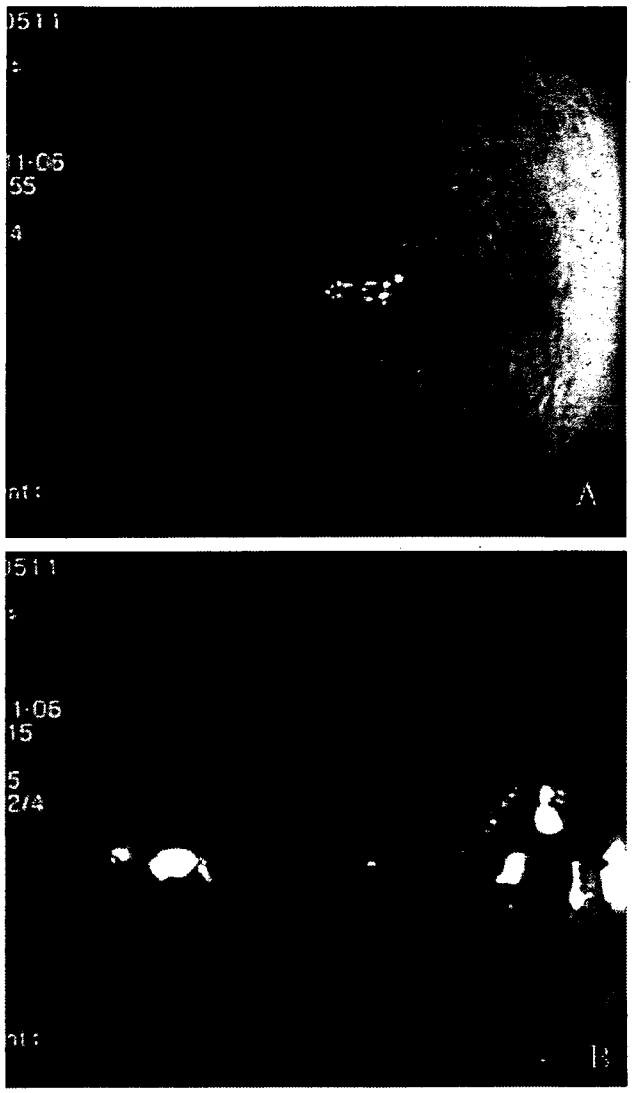
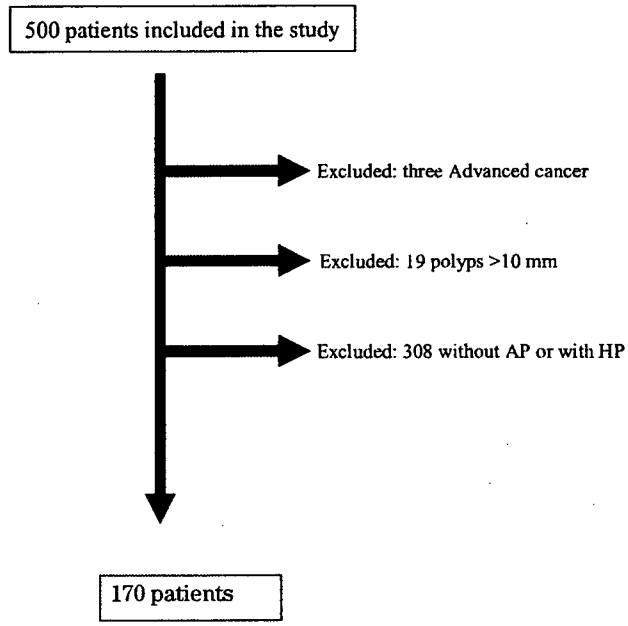


Figure 2 (a) Chromocolonoscopy revealed a Is, small round polyp, 6 mm in diameter. The nature of the lesion was poorly determined with conventional chromocolonoscopy. (b) Magnifying chromocolonoscopy disclosed a type IV (gyrus-like) pit pattern; the lesion was diagnosed as neoplastic and resected by snare polypectomy. Histologic examination revealed an adenoma with low-grade atypia.

Histopathological evaluation

Specimens were immediately fixed in 10% formalin solution and embedded in paraffin. Serial sections (3 μm) were cut and stained with hematoxylin–eosin. Two pathologists blinded to the endoscopic findings examined the retrieved tissues. Hyperplastic polyps, inflammatory polyps and juvenile polyps were categorized as non-neoplastic lesions. Adenomas were categorized as low-grade dysplasia (LGD) or high-grade dysplasia (HGD) on the basis of degree of atypia. Lesions with mild or moderate atypia were classified as LGD, and lesions with severe atypia or non-invasive carcinoma classified as HGD.[18]

Table 1 Patient flow chart



Statistical analysis

Differences between groups were analyzed using the χ^2 test. Differences with a P-value < 0.05 were considered significant.

Results

Of the 500 screened subjects, 192 (38%) had clinically significant lesions: 170 patients with polyps ≤10 mm were included in the study, and 19 patients with polyps >10 mm and three patients with advanced cancer were excluded. The remaining 308 patients had no polyps or had clearly diagnosed HP. These 308 patients were also excluded from analysis (Table 1). In all endoscopic procedures, bowel preparation was considered adequate and colonoscopy performed up to the cecum.

The 170 eligible subjects with polyps ≤10 mm had a mean age of 60 years and a male to female ratio of 8:1. A total of 264 lesions were diagnosed, for a ratio of 1.5 lesions per participant.

Macroscopically, there were 125 protruded lesions (Ip, 7; Isp, 12; Is, 106), 136 flat or depressed lesions (IIa, 135; IIc, 1) and three residual adenomas. The overall prevalence of flat adenomas was 51% (136 of 264). In the MCC group, 144 (54%) lesions were found, and 122 (46%) lesions were found in the conventional chromocolonoscopy group. There were no differences in the distribution of macroscopic types among the groups.

According to size, 142 (54%) lesions were ≤5 mm and 122 (46%) lesions were >5 mm. In the MCC group there were 93 (65%) lesions ≤5 mm and 49 (35%) >5 mm. There were 89 (73%) lesions ≤5 mm and 33 (27%) lesions >5 mm in the conventional chromocolonoscopy group.

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Table 2 Clinicopathological features of colorectal lesions in MCC and conventional chromocolonoscopy groups

	MCC ($n = 142$)	Conventional chromocolonoscopy ($n = 122$)
Macroscopic type		
Protruded	66	59
Flat	75	61
Depressed	0	0
Residual	1	2
Size		
≤5 mm	93	89
>5 mm	49	33
Location		
Right colon	73	53
Left colon	54	58
Rectum	15	11
Histopathology		
Non-neoplastic	7	20
Neoplastic	135	102
LGD	131	99
HGD	2	3
Serrated adenoma	2	0

LGD, low-grade dysplasia; HGD, high-grade dysplasia; MCC, magnifying chromocolonoscopy.

Table 3 Diagnostic accuracy of neoplastic lesions by magnifying chromocolonoscopy and conventional chromo colonoscopy

	Histopathology		
	Non-neoplastic	Neoplastic	Accuracy rate
Magnifying chromocolonoscopy			
Neoplastic lesions ($n = 142$)	7	135	95% *
Conventional chromocolonoscopy			
Neoplastic lesions ($n = 122$)	20	102	84% *

*$P < 0.01$.

Table 4 Diagnostic accuracy of neoplastic lesions ≤5 mm with magnifying chromocolonoscopy and conventional chromocolonoscopy

	Histopathology		
	Non-neoplastic	Neoplastic	Accuracy rate
Magnifying chromocolonoscopy			
Neoplastic lesions ($n = 93$)	6	87	94% *
Conventional chromocolonoscopy			
Neoplastic lesions ($n = 89$)	20	69	78% *

*$P < 0.001$.

Based on location, lesions were distributed as follows: right colon, 126 (48%); left colon, 112 (42%); rectum, 26 (10%). No differences in the distribution of lesions according to location were found.

On histologic examination, 135 lesions were diagnosed as neoplastic and seven lesions as non-neoplastic in the MCC group. In contrast, 102 lesions were diagnosed as neoplastic and 20 lesions as non-neoplastic in the conventional chromocolonoscopy group. Of the 135 neoplastic lesions in the MCC group, 131 (97%) and two (1.5%) showed adenoma with LGD and HGD, respectively. There were two serrated adenomas. Among 102 neoplastic lesions diagnosed with conventional chromocolonoscopy, 99 (97%) and three (3%) lesions showed LGD and HGD, respectively.

Intramucosal cancer (adenoma with HGD) was identified in 3% (five of 264) of adenomas ≤10 mm; macroscopically there were three protruded and two flat lesions. Three cancers were located in the right colon and two in the left colon. After endoscopic resection, histopathological examination revealed invasion limited to the mucosal layer and no evidence of vascular or lymphatic invasion. Clinicopathological data of colorectal lesions is shown in Table 2.

In relation to the pit pattern, seven lesions diagnosed by MCC as AP (pit type III_L, 5; IIIs, 1; and IV, 1) were histologically HP.

The overall accuracy of magnifying colonoscopy for differentiating neoplastic from non-neoplastic lesions was significantly higher (95%, 135 of 142) than that of conventional chromocolonoscopy (84%, 102 of 122; $P < 0.01$; Table 3). As for lesions ≤5 mm, the accuracy of MCC was 94% (87 of 93), and that of conventional chromocolonoscopy was 78% (69 of 89; $P < 0.001$; Table 4).

Discussion

To our knowledge, this is the first prospective study conducted in a health check medical center that provides further validation of the effectiveness of MCC for differentiating neoplastic colorectal polyps ≤10 mm.

Magnifying colonoscopes have dramatically progressed since the first zoom observation of the colonic mucosa in 1978.[19] At present, magnifying colonoscopes have the same shape and functions as conventional colonoscopes with the addition of zoom magnification using an easy-to-handle, one-touch electrical power system. Studies have found that insertion, manipulation, average time to reach the cecum and total procedure time with magnifying colonoscopes do not differ from those with conventional colonoscopies.[9] Although the time to reach to cecum was not evaluated in this study, our impression is that the insertion time and manipulation of magnifying colonoscopes are identical to those of conventional colonoscopes.

Chromoendoscopy using indigo carmine, a non-absorbed, non-toxic dye, is widely used in Japan for diagnosis of early gastrointestinal malignancies. Because of its demonstrated superiority over conventional colonoscopy,[20] chromoscopy was used in both arms of this study.

We found that one out of three average-risk subjects had neoplastic lesions, most ≤10 mm (92%). Taking into account lesions ≤10 mm, the rectum harbors a lower number of AP (10%, 26 of 264) compared with the left (42%) or right colon (48%, $P < 0.05$). These results are similar to those observed in large medical centers[21,22] and suggest a different carcinogenetic pathway in distal

lesions.[23] The prevalence of flat lesions in this study (52%) was similar to rates in previous reports from Japan but was higher than those in studies conducted in the USA (30%)[24] and UK (20%).[25] Three percent of these lesions were diagnosed as adenomas with HGD (intramucosal cancer).

There were two out of 264 (0.7%) polyps diagnosed as serrated adenomas (SA); SA show morphological features of HP but also contain cytological features of conventional AP and therefore are considered precursors of colorectal cancer.[26] During colonoscopy, polypoid SA are recognized as III_L or IV pit pattern associated with serrated change (also called IV_H or IV_{SA}) and thus removed as AP.[27] In contrast, superficial SA usually shows type II-like pit and thus might be misdiagnosed as HP. In these cases, both the presence of a prominent granular or nodular surface[28] and the identification of a type II-like pit (also called III_H or III_{SA}), characterized by tubular appearance and serrated crypt orifices, favors the possibility of SA.[29] Resection is indicated in SA, particularly in >10 mm right-sided superficial lesions, because of the possibility of intraepithelial neoplasia.[27,29] Special consideration should be paid to right-sided HP since recently it has been suggested that these are molecularly more similar to SA than left-sided ones.[30,31]

Seven of 142 lesions (5%) were misdiagnosed as MCC; however, six of these seven lesions were ≤5 mm. The III_L pit pattern was identified in five lesions (71%). These results are similar to those in studies by Kudo and other experienced endoscopists where 3.1% of III_L and 2.6% of IV lesions were histologically HP.[7,14] The difficulty of handling small samples during pathological analysis might explain these results. Sometimes polyps diagnosed as HP turn out to be AP after a deeper cut dissection.

The accuracy of MCC (95%, 135/142) was significantly higher than that of conventional chromocolonoscopy (84%, 102/122; $P = 0.01$). In lesions ≤5 mm the diagnostic accuracy of MCC remained similar (94%, 87/93), but accuracy using conventional chromocolonoscopy decreased (78%, 69 of 89; $P < 0.001$). These results are similar to those of large reference centers.[9,10,32]

The recent Paris endoscopic classification of superficial neoplastic lesions recommends avoiding resection of colorectal non-neoplastic lesions by performing biopsy before resection.[5] In addition, the practical guidelines of the American College of Gastroenterology[4] recommends biopsy when a <10 mm polyp is encountered during flexible sigmoidoscopy. We believe that since HP account for up to 30% of all colorectal polyps,[33] and they do not require treatment, polypectomy of these non-neoplastic lesions increases post-polypectomy complication rates,[34] overload cost and delays diagnosis. Therefore, rather than making technical changes to decrease polypectomy complications rates, efforts to reduce the number of unnecessary biopsies or polypectomies in patients with non-neoplastic polyps would be more beneficial.

This study included only polyps ≤10 mm. Although the general consensus is to remove adenomas >10 mm,[35,36] no consensus exists for polyps ≤10 mm. Different management strategies include resection, biopsy only or no treatment. Recently, an increasing rate of colorectal cancers <10 mm has been reported,[37–39] which warns us to look out for small lesions and, more importantly, treat them selectively. In summary, a method to determine the character of the lesion during colonoscopy is greatly needed and MCC could fulfill this role.

In this series, biopsy was not performed for histopathological confirmation because the efficacy of MCC in the diagnosis of these polyps was previously reported by us[14] and also because of these polyps' lack of clinical significance.

This paper has several points that make it clinically valuable. First, it validates the superiority of MCC for differentiating AP. Second, it confirms the limitations of conventional chromocolonoscopy for determining the nature of small polyps, even in expert hands; and also demonstrates that the probability of finding intramucosal cancer in lesions ≤10 mm is not null (3%, five of 264). These results suggest that colorectal polyps should not be treated only on the basis of the polyp size, but also on the basis of the underlying histological characteristics observed during MCC. Fortunately, HP and AP are distinguishable on endoscopy and therefore only neoplastic lesions should be removed and sent for histologic confirmation. In conclusion, this study provides further validation that MCC is more effective than conventional chromocolonoscopy for diagnosing neoplastic colorectal polyps; MCC should be used routinely for screening colonoscopy even in health check-up medical centers.

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Diseases of the Colon & Rectum

Case Reports

Minute Depressed-Type Submucosal Invasive Cancer–5 mm in Diameter with Intermediate Lymph-Node Metastasis: Report of a Case

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We report a rare case of colon cancer in which a depressed-type tumor only 5 mm in diameter invaded the submucosal layer and produced intermediate lymph node metastasis. A 47-year-old male received a total colonoscopy for a depressed-type lesion with marginal elevation in the sigmoid colon. The lesion measured 5 mm in diameter. On chromoendoscopic examination, the depression was clearly demarcated and an irregular pit pattern was identified in the demarcated area by magnification suggesting invasion of the submucosal layer requiring surgery. Laparoscopic-assisted sigmoidectomy was performed and the resected specimen demonstrated well-differentiated adenocarcinoma. The depth of invasion was only 900 μm. There was no lymphovascular invasion although not only paracolic, but also intermediate lymph node metastasis was detected. There have been some reports about small depressed-type colorectal cancer invading the submucosal layer; however, intermediate LN metastasis is very rare in submucosal colorectal cancer. In this case, there were two noteworthy points: 1) despite the small size, submucosal invasion could be estimated preoperatively, therefore, a successful lymph node dissection was performed by laparoscopic surgery; and 2) although this depressed-type cancer invaded the submucosal layer only 900 μm and there was no lymphovascular invasion, intermediate lymph node metastasis was detected. [Key words: Early colorectal cancer; Chromoendoscopy; Magnifying colonoscopy]

Colorectal polypoid-type adenoma is considered the precursor in the majority of colorectal cancer (CRC) cases. The early detection and treatment of these lesions is thought to reduce CRC mortality. Morson[1] estimated that up to two-thirds of CRC develop from adenomatous polyps. Recently, improved endoscopic imaging and advancements in diagnostic technology have led to a higher rate of detection of superficial and small colorectal tumors,[2,3] It has been reported that lesions <10 mm in diameter, whether polypoid or nonpolypoid, were unlikely to be advanced cancer[4]; however, Japanese researchers have reported the existence of advanced cancer lesions <10 mm in diameter.[5,6] Several reports, mostly from Japan, have suggested that some CRC also can develop *de novo* from normal mucosa.[7–9] An alternative explanation is that some carcinomas have an especially aggressive growth pattern that quickly destroys the adjacent adenomatous tissue.

With regard to the pathology, the method of measuring the depth of submucosal (sm) invasion remains controversial. A relative classification system

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Figure 1. Conventional colonoscopic views showing a reddish lesion approximately 5 mm in diameter located in the sigmoid colon.

has been used to evaluate sm depth of invasion as follows: sm1, infiltration into the upper third of the submucosal layer; sm2, middle third; and sm3, lower third. Several studies have demonstrated the usefulness of this method for predicting lymph node metastasis[10]; however, this method has not been useful for specimens obtained endoscopically because these specimens do not include the muscularis propria. An absolute classification system, therefore, has become generally accepted to evaluate endoscopic resected specimens. This method classifies the vertical depth of sm invasion from the lowest edge of the muscularis mucosae as follows: sm superficially,<1 mm; and sm deep, >1 mm. A standardized method of measuring sm depth has not been established yet. We report a case of small Dukes C colon cancer in which a 5-mm depressed-type tumor was diagnosed endoscopically.

Figure 2. Slightly reddish and depressed lesion detected with marginal elevation (IIa+IIc).

Figure 3. Chromoendoscopy after indigo carmine dye spraying more clearly showed the demarcated depressed area with the center of the depressed area slightly elevated.

REPORT OF A CASE

A 47-year-old male was referred to our institution for further treatment of a colonic lesion in September 2004. Neither the patient nor the patient's family had a past medical history of cancer. The patient had consulted the previous hospital because of a positive fecal-occult-blood-test. At that time, a total colonoscopy identified a small, depressed lesion in the sigmoid colon. Conventional colonoscopic examination showed a slightly reddish depressed-type lesion with a marginal elevation (IIa+IIc) in the sigmoid colon (Figs. 1 and 2). This lesion measured only 5 mm in diameter and there were no other lesions in the colorectum. After 0.2-percent indigo carmine dye spraying, chromoendoscopic examination showed a clearly demarcated depression (Fig. 3) and crystal violet staining with magnified view (Olympus CF Q 240ZI; Olympus, Tokyo, Japan) identified an irregular pit pattern in the demarcated area corresponding to an invasive pattern (Fig. 4).[11,12] This tumor, therefore, was diagnosed as having invaded the sm layer, resulting in a contraindication for endoscopic mucosal resection (EMR). A biopsy sample demonstrated well-differentiated adenocarcinoma, and there was

Figure 4. Magnified view with crystal violet staining of the surface of the central depression with an irregular pit pattern identified in the demarcated area.

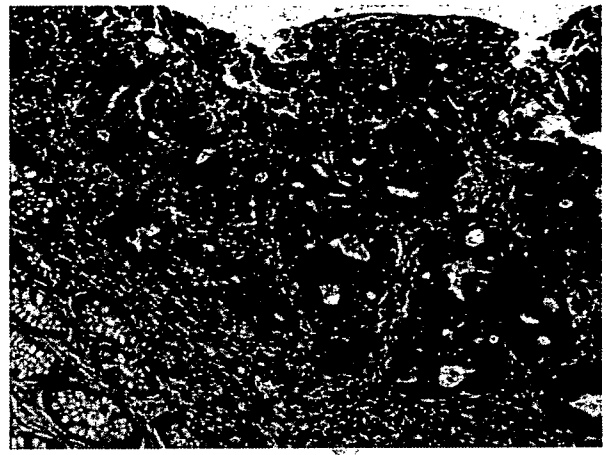

Figure 6. High-power magnification showing the surface glands of the depressed area were destroyed was consistent with the magnifying colonoscopy findings.

no evidence of metastasis found on computed tomography. A laparoscopic-assisted sigmoidectomy was performed without complication and the resected specimen also demonstrated well-differentiated adenocarcinoma. The depth of invasion was 900 μm and there was no lymphovascular invasion found (Figs. 5 and 6). A deeper cut was performed to evaluate for lymphatic invasion, but there were no findings suggesting such invasion. As for lymph-node metastasis, 14 lymph nodes were examined: two were positive and one of these was intermediate LN metastasis (Fig. 7).

DISCUSSION

There have been some reports about small, depressed-type CRC invading the sm layer; however, intermediate LN metastasis was very rare.[13] In this case, there were two noteworthy points as follows: 1) despite the small size of the lesion, endoscopic findings, including magnifying chromoendoscopy were able to diagnose sm invasion before treatment; and 2) although this depressed-type cancer invaded the sm layer only 900 μm and there was no lymphovascular invasion, intermediate LN metastasis

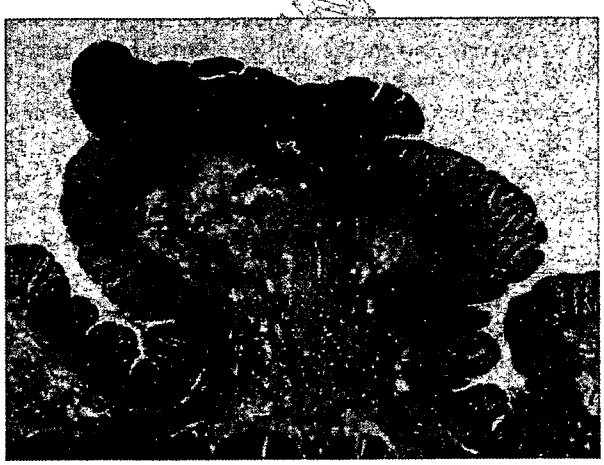

Figure 5. Histologic views showing a central depressed area with a well-differentiated adenocarcinoma invading the submucosa (900 μm). Although there was no lymphovascular invasion, the muscularis mucosa was completely destroyed.

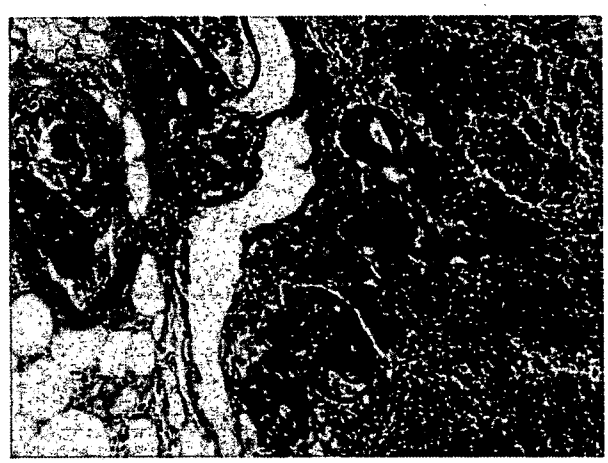

Figure 7. High-power magnification of the cut section of the intermediate lymph node showed focal well-differentiated adenocarcinoma suggesting metastasis.

was detected. After the preoperative diagnosis, successful LN dissection was performed by laparoscopic surgery and this lesion was definitively diagnosed as Dukes C colon cancer.

The adenoma-carcinoma sequence is thought to be the main pathway of CRC carcinogenesis in which carcinoma develops from adenoma.[1] Various oncogenes and tumor suppressor genes, including the APC, K-*ras*, p53, and DCC genes, have been reported to be involved in the carcinogenesis of CRC.[14] In addition, the existence of some depressed-type CRC has been reported, particularly from Japan, raising the possibility that some cancers may develop *de novo* following a different pathway from the adenoma-carcinoma sequence. In fact, a lower frequency of K-*ras* gene mutations is more likely to be found in these lesions, showing a much higher rate of sm invasion despite their small size in contrast to protruding-type lesions.[15,16] Endoscopists, therefore, should pay particular attention to depressed lesions given their higher malignancy potential.

Recently, endoscopic resection has become a generally accepted procedure for superficial or small CRC where the probability of lymph-node metastasis is low and depth of sm invasion is considered an important predictive factor for lymph-node metastasis. According to the Paris workshop guidelines, superficial-type CRC with a depth of invasion <1,000 μm has a very low risk of lymph-node metastasis.[17] The incidence of lymph node metastasis is reported to be approximately 10 percent for CRC with sm invasion, 2 to 3 percent for CRC superficially invading the sm, and 8 to 12 percent for CRC deeply invading the sm.[18] In a recent collaborative Japanese study of nonpedunculated sm invasive CRC, the rate of lymph-node metastasis was 0 percent when the sm depth of invasion was <1,000 μm.[19] In that analysis, 1) an undifferentiated-type tumor, 2) existence of lymphatic or venous infiltration, and 3) a depth of invasion ≥ 1,000 μm from the muscularis mucosae (mm) were independent risk factors for LN metastasis based on multivariate analysis, whereas univariate analysis identified the destruction of the mm as an additional risk factor. Another study conducted at our institution recently[20] used multivariate analysis to show that lymphatic invasion and high-grade focal dedifferentiation at the submucosal invasive front were independent factors predicting lymph-node metastasis.

In this case, only destruction of the mm met these criteria and there were no other risk factors for LN metastasis. The depth of invasion was only 900 μm, and there was no lymphovascular invasion or poorly differentiated component. According to our institution's recent study,[20] univariate analysis showed that the status of the remaining muscularis mucosa had a significant connection with lymph-node metastasis. Physicians should be careful when encountering this type of lesion, because the complete destruction of the mm may be one of the risk factors for LN metastasis. After the preoperative diagnosis, a lymphadectomy was successfully performed by laparoscopic surgery, and there has been no apparent recurrence detected 12 months after surgery.

CONCLUSIONS

We report a rare case of CRC invading the sm layer and showing metastasis to not only the paracolic but also intermediate LN despite the small size of the lesion. For a depressed-type cancer, it is necessary to carefully examine the lesion to establish an accurate diagnosis and perform suitable treatment.

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主題

大腸ESDに対する工夫と進歩

sinker法・CO_2送気装置

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