dominates in other developed countries. Although when studying esophageal cancer, SCC and adenocarcinoma should be considered separately; only a few published studies have focused only on SCC. Therefore the present report provides very valuable data obtained from a large number of esophageal SCCs treated at a single institution in a short period.

Conclusions

The present study has demonstrated that EUS is a more accurate technique than contrast-enhanced CT for detecting abnormal lymph nodes. Sensitivity of CT was lower than that of EUS alone and CT + EUS. But some metastatic lymph nodes in the neck and abdominal fields are only detectable by CT. Therefore, both EUS and CT should be undertaken for routine examination prior to treatment of esophageal cancer.

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LETTERS

Narrow-band imaging for improving colorectal adenoma detection: appropriate system function settings are required

We read with considerable interest the report by Alder *et al* (*Gut* 2008;**57**:59–64) concerning their prospective randomised study on narrow-band imaging (NBI) versus conventional high-resolution imaging for colorectal adenoma detection. The study indicated an increased adenoma detection rate for NBI colonoscopy, but the results were not statistically significant. Wide-angle colonoscopes (Olympus, Hamburg, Germany) were used during instrument withdrawal for both the NBI and conventional groups, but details on the Olympus systems and their actual function settings were not described by the authors.

Recently, we conducted a prospective pilot study to assess the feasibility of using NBI for detecting colorectal adenomatous lesions.[1] The total number of adenomatous lesions detected by NBI was significantly higher than high definition colonoscopy ($p = 0.02$). Based on macroscopic type, flat lesions were identified more often by NBI ($p = 0.04$). We used an EVIS LUCERA SPECTRUM video endoscopic system and a CF-H260AZI conventional high definition colonoscope (Olympus, Tokyo, Japan) with all examinations performed with the enhanced image functions. In another recent study, NBI using the same EVIS LUCERA SPECTRUM system and a similar colonoscope resulted in improved adenoma detection in the proximal colon for patients undergoing hereditary non-polyposis colorectal cancer surveillance.[2]

Standard endoscope system video processors include a number of enhanced image features that perform vital functions including surface structure and adaptive index of haemoglobin (IHb) colour enhancement.[3] The surface structure enhancement function includes six different image settings that provide increased definition of the mucosal and microcirculatory structure. The adaptive index IHb colour enhancement function with three separate level settings calculates the average haemoglobin concentration for the surrounding tissue and adjusts those areas with lower-than-average IHb values by increasing the amount of white in the affected portions of the image.

By pressing a single button on the endoscope or endoscopic system control handle, an endoscopist can switch from one setting to another in less than a second with either of these two enhanced functions. It then becomes possible for the endoscopist to observe a variety of image enhanced endoscopic (IEE) views by simply and quickly adjusting the settings. Similarly, an NBI view can be improved by using these same functions to adjust the contrast of an image (fig 1). It would be very useful, therefore, if the authors of this and any similar reports in the future would provide detailed information on the specific IEE function settings used in their studies on NBI detection and diagnosis of colorectal adenomatous lesions.

There are two different Olympus endoscope video systems currently in use, the sequential LUCERA series and the simultaneous Excera series also known as the "colour chip system." Both the NBI sequential and simultaneous systems provide similar high-resolution images and the concept and basic design are the same for both types. The two imaging methods are different, however, as are their respective colour images primarily due to differences in the colour spectral characteristics of the red, green and blue (RGB) rotary filters in the LUCERA series and the colour charge coupled device (CCD) in the EXCERA series as well as in the white light source used in each system.[4] Although both systems are now being used in different parts of the world, no comparative study has yet been conducted on the detailed NBI images produced respectively by the LUCERA and EXCERA series.

In conclusion, we believe that NBI colonoscopy has the potential of becoming a highly valuable means for performing colorectal screening and surveillance examinations. A prospective study is needed, however, to comparatively assess the effectiveness of the two existing NBI systems and their various IEE function settings in the detection and diagnosis of colorectal adenomatous lesions.

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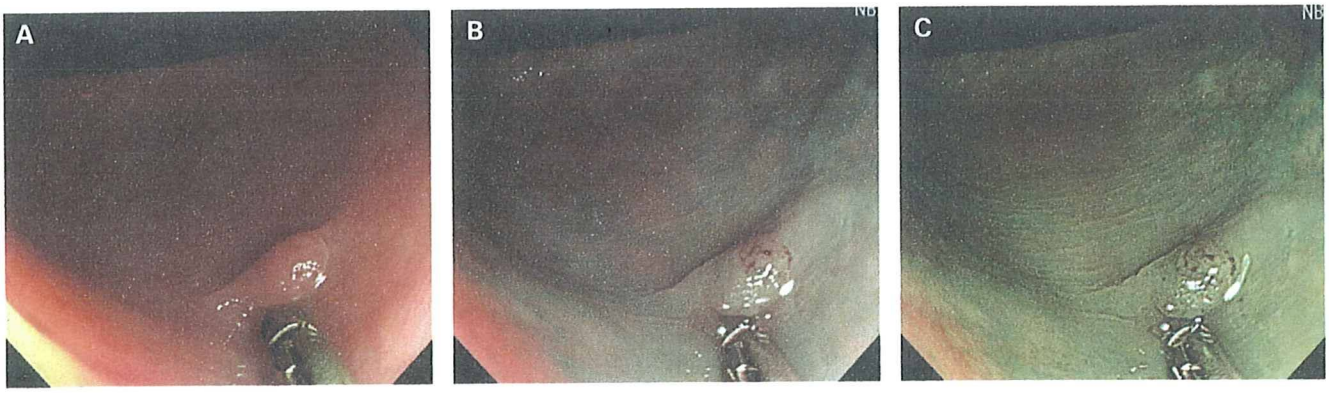

Figure 1 Narrow-band imaging (NBI) differentiation of an adenoma using the surface structure and adaptive index of haemoglobin (IHb) colour enhancement function settings. Endoscopic images provided by an EVIS LUCERA SPECTRUM video endoscopic system with a conventional high definition colonoscope. (A) Conventional view of a small adenoma. (B) NBI view without the enhanced image features; surface structure enhancement function level A-1 setting and adaptive IHb colour enhancement function level 1 setting. (C) NBI view in combination with the enhanced image features; surface structure enhancement function level A-5 setting and adaptive IHb colour enhancement function level 3 setting. Using both enhancement functions markedly improved the contrast of the image shown by the NBI system.

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Progressive multifocal leukoencephalopathy in autoimmune disorders

We read with interest the recent article by Verbeeck *et al* (*Gut* 2008;**57**:1393–7) on JC viral loads as a predictor of progressive multifocal leukoencephalopathy (PML) in patients with Crohn's disease, but we have found some misconceptions.

The authors wrongly state that "Although PML has been associated with immunosuppression as a consequence of organ transplantation and haematological malignancies, it has not been associated with immune-mediated disorders such as MS, Crohn's disease or rheumatoid arthritis despite the immunosuppressive therapy used to treat their illnesses". Many case reports exist for PML in such cohorts[1–7] and PML is likely to arise in any setting implying chronic immunosuppression, ranging in potency from long-term systemic corticosteroids to the newer monoclonal antibodies.[8]

The authors also interpret JC viruria in a seronegative gastrointestinal control as evidence of "primo-infection". We think that seronegativity can only be interpreted if the immunoglobulin g (IgG) level is also reported since IgG levels are often low in chronically immunosuppressed patients and could cause false negative serology testing. Can the authors comment on the IgG level in their patients? On the other hand, the fact that the authors "could not find a significant difference in age between seropositive and seronegative patients" is in line with the fact that primo-infection occurs early in childhood.

More details would be appreciated on the two patients with Crohn's disease and positive JC viraemia, such as $CD4^+$ and $CD8^+$ T lymphocyte counts, total IgG levels, type and duration of immunosuppression. Also, the authors do not provide information on the eventual association between changes in viraemia levels and changes in treatment. Similarly, the authors conclude that "the type of immunomodulator or lymphopenia were not predictive for JC virus shedding" in urine. Could the authors provide data on eventual correlations with the load of JC virus in urine?

The authors also conclude that "the presence of JC virus DNA in body fluids such as urine, different blood compartments and cerebrospinal fluid (CSF), is thought to represent active viral shedding or replication and may be more reliable as a "screening tool" for PML than serology. Although this sentence remains true, it should be noted that the prevalence of JC viruria increases with age, reaching 50% at age 70 years[9] and that large studies have shown that the prevalence of JC virus in CSF from HIV-negative PML patients is only 50%,[10] making both tests largely useless. Could the authors explain if they have different data sources?

In our opinion the only result that retains value and could eventually increase the predictive value of suggestive magnetic resononace imaging (MRI) findings is JC virus DNA in peripheral blood: in the haematological case series occurring at our institute, the only PML patient who was tested had positive JC viraemia at the time of diagnosis of PML, even though JC virus was absent in the CSF,[11] and the same was true in patients with Crohn's disease who were treated with natalizumab (P. Duda, personal communication). Could the authors provide long-term follow-up data for their patients with positive JC viraemia?

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The utility of using bispectral index monitoring as an early intraoperative indicator of initial poor graft function after orthotopic or split-graft liver transplantation

We refer to our recent publication (*Gut* 2008;**57**:77–83) showing that bispectral index (BIS) monitoring, an electroencephalographic (EEG)-derived parameter, is a useful measure for grading and monitoring the degree of central nervous system involvement in patients with chronic liver disease. We further assessed its utility as an early intraoperative indicator of living-donor or cadaveric graft function. Initial poor graft function (IPGF) is a serious complication following liver transplantation, whereas primary non-function (PNF), the most serious type of IPGF, is a life threatening condition that occurs in about 5.8% of cases[1] and requires emergency re-transplantation. Hence there is growing need for early identification of IPGF and PNF as this may help to determine further therapeutic interventions, changes in therapeutic protocols or additional diagnostic procedures aiming at preventing IPGF/PNF.

We investigated 29 patients undergoing living-donor liver transplantations (LDLTs) and 24 patients undergoing locally procured orthotopic liver transplantation (OLT) without venovenous bypass for end-stage liver disease as a result of autoimmune hepatitis, hepatocarcinoma, or alcohol/virus related liver cirrhosis (table 1). Anaesthesia was maintained with propofol, an intravenous anaesthetic mainly excreted via hepatic metabolism, by using a Diprifusor target-controlled infusion (TCI) pump (AstraZeneca, Macclesfield, UK). Anaesthesia was first adjusted with ± 2 μg/ml propofol TCI rate adjustments to maintain a stable anaesthesia of around BIS 40 for 15 min, after which propofol TCI was recorded and kept constant throughout the whole surgical procedure. IPGF was defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1500 IU/l within 72 h after liver transplantation. Using Pearson's correlation analysis we correlated BIS gradient (cross-clamp nadir–reperfusion zenith) to postoperative ALT, AST, international normalised ratio (INR) and serum bilirubin.

Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps (CME)

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Background: Although microvascular vessels on the surface of colorectal polyps are observed by narrow-band imaging (NBI) with magnification, its clinical usefulness is still uncertain.

Objective: Our purpose was to evaluate the usefulness of meshed capillary (MC) vessels observed by NBI magnification for differentiating between nonneoplastic and neoplastic colorectal lesions.

Design: Prospective polyp study.

Setting: National Cancer Center Hospital East, Chiba, Japan.

Patients: A total of 702 consecutive patients who underwent total colonoscopy between September and December 2004 were prospectively evaluated. Patients with polyps >10 mm and those with polyps previously evaluated by histologic examination or colonoscopy were excluded.

Intervention: Lesions were classified into 2 groups: polyps with invisible or faintly visible MC vessels as nonneoplastic and polyps with clearly visible MC vessels as neoplastic. Lesions judged as nonneoplastic were subjected to biopsy and those as neoplastic were removed endoscopically. Histologic analysis was performed in all lesions.

Main Outcome Measurement: Visible or invisible surface MC vessels, prediction of histologic diagnosis.

Results: Of 92 eligible patients enrolled in this study, 150 lesions, including 39 (26%) hyperplastic polyps and 111 (74%) adenomatous polyps, were detected. Observation of MC vessels detected 107 of 111 neoplastic polyps and 36 of 39 nonneoplastic polyps. The overall diagnostic accuracy, sensitivity, and specificity were 95.3%, 96.4%, and 92.3%, respectively.

Limitations: MC vessel judgment performed by a single colonoscopist with extensive experience in magnifying NBI.

Conclusion: Observation of surface MC vessels by magnifying NBI is a useful and simple method for differentiating colorectal nonneoplastic and neoplastic polyps. (Gastrointest Endosc 2009;69:278-83.)

Hyperplastic polyps and other nonneoplastic colorectal lesions do not require endoscopic treatment because they are benign and do not have malignant potential.[1,2] In contrast, the adenoma-carcinoma sequence suggests that colorectal cancers develop from adenomatous polyps and, therefore, their removal could prevent colorectal cancers.[3,4] Thus, in vivo distinction of nonneoplastic and neoplastic lesions would greatly increase the efficiency of colonoscopic procedures.[5]

In a hyperproliferative state, angiogenesis is critical to the transition of premalignant lesions to the malignant phenotype.[6,7] Narrow-band imaging (NBI) is an innovative optical technology that provides a unique image that

Abbreviations: FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; IV, intravenously; MC, meshed capillary; NBI, narrow-band imaging.

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See CME section; p. 303.

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emphasizes the morphologic and structural character of lesions as well as the surface capillary pattern.

Previously, we described how the presence of "meshed capillary (MC) vessels" by magnifying NBI are arranged in a honeycomb pattern around the mucosal glands constitutes a useful method for differential diagnosis of colorectal lesions without the need for any dye application.[8] Recently, we have proposed the capillary pattern classification (I-III) for distinction of colorectal lesions.[9-11]

The aim of the current study was to prospectively evaluate the usefulness of observing the surface MC vessels to differentiate between nonneoplastic and neoplastic polyps.

Capsule Summary

What is already known on this topic

- Narrow band imaging (NBI) emphasizes the morphologic and structural character of lesions, as well as the surface capillary pattern.

What this study adds to our knowledge

- NBI detected meshed capillary vessels in 107 of 111 neoplastic and 36 of 39 nonneoplastic polyps, for overall diagnostic accuracy, sensitivity, and specificity of: 95.3%, 96.4%, and 92.3%, respectively.

METHODS

Patients

A total of 702 consecutive patients who underwent screening colonoscopy at National Cancer Center East Hospital, Chiba, Japan, between September and December 2004 were analyzed. The study protocol was approved by the institutional review board, and informed consent was obtained from all patients before the examination. Patients with polyps larger than 10 mm, with lesions previously evaluated by histologic examination or colonoscopy, and those with invasive carcinoma were excluded from the study. Patients with inflammatory bowel disease, hereditary nonpolyposis colorectal cancer (HNPCC), and familial adenomatous polyposis (FAP) were also excluded.

Principle of NBI

NBI is based on modification of the spectral features with an optical color separation filter narrowing the bandwidth of spectral transmittance. In this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm.[12,13] By use of this narrow spectrum, the contrast of the capillary pattern in the superficial layer is markedly improved, and thus clear visualization of vascular structures is achieved during endoscopy. The electronic button on the control section of the colonoscope allowed switching between the conventional and the NBI views instantly.[14]

Colonoscopy procedure

Bowel preparation consisted of 2 to 3 L of polyethylene glycol solution in the morning before the procedure, as previously reported.[15] Hyoscine methobromide (10-20 mg given intravenously [IV]) was administered if there were no contraindications, and light sedation with diazepam (3-5 mg IV) was used in selected subjects. The location of lesions was categorized into 2 groups, according to which side of the splenic flexure they were encountered: proximal colon (including the cecum, ascending colon, and transverse colon) and distal colon (including descending colon, sigmoid colon, and rectum). Lesions were classified macroscopically on the basis of the criteria of the Paris classification of superficial GI lesions.[16]

Evaluation of MC vessels

Colonoscopies were carried out by using a magnifying video colonoscope (CF-H260ZI; Olympus, Optical, Tokyo, Japan) with a standard video processor system (EVIS 260, Lucera Spectrum Olympus Optical). Endoscope withdrawal was performed under conventional white light. All lesions detected by conventional colonoscopy were rinsed with water to remove any overlying mucus on the surface and then were examined by magnifying NBI without the use of any dye solution. Once the NBI system was activated through an easy-to-handle, 1-touch electronic bottom, MC vessels were seen as green-brown in color, and the surrounding normal colon mucosa was seen as a yellowish color. The hue of nonneoplastic lesions is very similar to that of normal epithelial layer, whereas the majority of neoplastic lesions appeared brownish. Lesions with invisible or faintly visible MC vessels were categorized as nonneoplastic, and lesions with clearly visible MC vessels were categorized as neoplastic (Fig. 1).[9-11,14] Size was estimated by using the open width of standard, fully opened biopsy forceps as a reference[5] or after removal (hot biopsy or snare polypectomy). Procedures and endoscopic evaluation were performed by an expert colonoscopist with extensive experience in magnification and NBI (Y. S,). Lesions diagnosed as nonneoplastic were subjected to biopsy, and those diagnosed as neoplastic were removed endoscopically without exception.

Endoscopic treatment

Lesions diagnosed as nonneoplastic and advanced carcinomas underwent biopsy. In lesions identified as adenomatous polyps or intramucosal carcinomas (visible MC vessels), hot biopsy, polypectomy, or 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.[17,18]

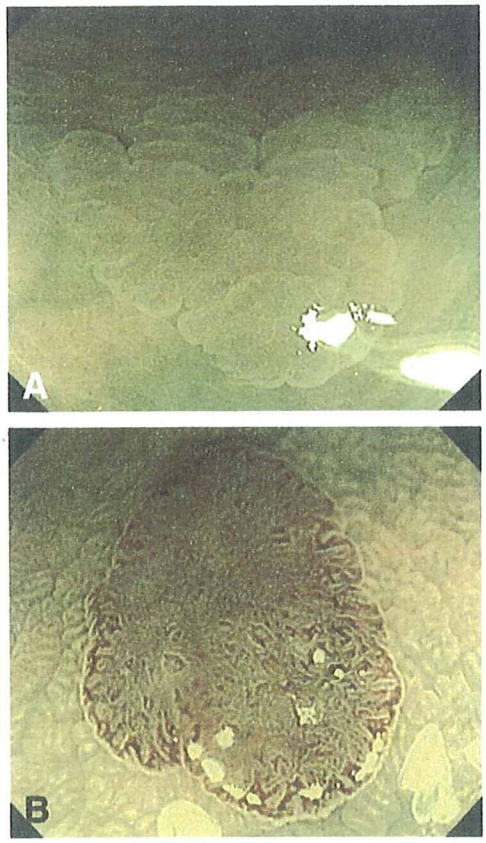

Figure 1. Magnifying endoscopic evaluation of MC vessels with NBI. **A**, Lesions with invisible or faintly visible MC vessels. This lesion was histologically diagnosed as hyperplastic polyp. **B**, Lesions with clearly visible MC vessels. This lesion was histologically diagnosed as adenomatous polyp.

Histopathologic examination

Specimens were fixed in 20% formalin and histologically examined after hematoxylin and eosin staining. Histologic diagnosis was made by a pathologist blinded to the colonoscopic diagnosis at each step. The pathologic definition of the lesions was made on the basis of the Japanese Research Society for Cancer of the Colon and Rectum.[19] Histologically, adenomatous lesions were defined as neoplastic, and other nonepithelial lesions including hyperplastic polyps were defined as nonneoplastic. The accuracy rates of the endoscopic diagnosis was evaluated on the basis of the final pathologic diagnosis.

Statistical analysis

Differences between groups were analyzed with the χ^2 test. Differences with a P value $< .05$ were considered significant.

RESULTS

Clinical data

Of 702 patients recruited for this study, 453 (64%) were found to have no polyps on colonoscopy, 152 (22%) were ineligible on the basis of the exclusion criteria, and in 5 (1%) patients, retrieving the resected specimen was not possible (Table 1). The remaining 92 (13%) patients were enrolled for prospective evaluation. The mean age was 63.6 years (range 36-80 years) with a male/female ratio of 4.7:1. In all examinations, bowel preparation was considered adequate, and colonoscopy was performed up to the cecum. There were no complications during any procedure.

TABLE 1. Patient flow chart

Patient pool (702 patients considered for the study)
Excluded: 453 patients with no polyps found on colonoscopy
Excluded: 68 patient with colorectal lesions with previous evaluation, including histologic examination or colonoscopy
Excluded: 39 patients with invasive carcinoma
Excluded: 41 patients with polyps larger than 10 mm
Excluded: 2 patients with ulcerative colitis (1 with FAP, 1 with HNPCC)
Excluded: 5 patients with polyps that were unretrievable

Clinicopathologic features of the colorectal lesions

A total of 150 lesions including 39 (26%) hyperplastic and 111 (74%) adenomatous polyps were identified, for a ratio of 1.6 lesions per participant. All adenomatous polyps had low-grade dysplasia. Macroscopically, 25 lesions were classified as type 0-Is and 125 as type 0-IIa. The overall prevalence of flat adenomas was 83%. There were no superficial depressed lesions (0-IIc). The mean diameter of the identified lesions was 3.8 mm (range 2-10 mm). On the basis of location, 63 (42%) polyps were distributed in the proximal colon and 87 (58%) in the distal colon. Clinicopathologic features of the colorectal lesions identified in this study are shown in Table 2.

Diagnostic accuracy of MC vessels

The overall diagnostic accuracy of the MC vessels for distinguishing between neoplastic and nonneoplastic lesions was 95.3% (143/150). The diagnostic accuracy for nonneoplastic lesions (negative predictive value) was 90% (36/40), and that for neoplastic lesions (positive predictive value) was 97.3% (107/110). The sensitivity and specificity of MC vessels diagnosis by NBI colonoscopy were 96.4% (107/111) and 92.3% (36/39), respectively (Table 3).

DISCUSSION

To our knowledge, this is the first prospective study on the effectiveness of observing the MC pattern by magnifying NBI for differential diagnosis of < 10 mm colorectal polyps.

TABLE 2. Patient characteristics and clinicopathologic features

No. of patients/lesions	92/150
Sex (male/female)	76/16
Mean age (y [range])	63.6 (36-30)
Macroscopic type*	
0-Is	25
0-IIa	125
Size of resected polyp (mm [range])	3.8 (10)
Location of resected polyp (proximal/distal)	63/87
Histologic findings	
TA with low- and high-grade dysplasia	111
Hyperplastic polyp	39

TA, Tubular adenoma.
*According to the Paris endoscopic classification.[16] Lesion lost after polypectomy.

TABLE 3. MC vessels by NBI and histologic examination

	Neoplastic	Nonneoplastic
MC vessels (+)	107	3
MC vessels (–)	4	36

In 1999, the first prototype of an NBI system was developed at National Cancer Center East Hospital in scientific cooperation with Olympus Corp, Japan. In 2001, we also reported for the first time its clinical usefulness for the diagnosis of lesions in the GI tract.[20] Consequently, in 2004 our first NBI clinical study reported not only equivalent results to chromoendoscopy but also a better visualization of the vascular pattern than that of conventional colonoscopy for the diagnosis of colorectal polyps.[21] After it became commercially available in December 2005, many studies have reported its advantages and effectiveness for the diagnosis of not only lesions within the GI tract[22-25] but also in other organs.[26,27]

This study included only polyps <10 mm. Although the general consensus is to remove adenomas >10 mm, there is still no consensus for polyps <10 mm. Different management strategies include resection, biopsy only, or no treatment. Recently, a rate of up to 7% of colorectal cancers <10 mm has been reported during screening colonoscopy,[28-30] which warns us to look out for small lesions and, more importantly, to treat them selectively. Herein was found that about 20% (1/5) of screened patients had polyps, most of them neoplastic (73%). This frequency is lower compared with that of other screening studies (1/3, 33%).[5] On the other hand, the frequency of invasive carcinoma (39/702, 5%) was higher than that of a similar screening study (3/500, 0.6%).[5] These results might be explained by the fact that the study was performed in a tertiary referral cancer center. The prevalence of flat neoplastic lesions in this study (125/150, 83%) was higher compared with rates reported in Japan[15] and in Western countries,[31,32] probably because of the advantage of using NBI for screening colonoscopy.

Several investigations had validated our previous results about the equivalency of magnifying NBI and magnifying chromoendoscopy in the evaluation of the colon pit pattern proposed by Kudo et al.[33] These studies have reported sensibilities and specificities ranging from 87% to 99% and from 72% to 94% for magnifying chromoendoscopy and magnifying NBI, respectively.[34-36] Some retrospective/pilot studies have reported the usefulness of microvessels with magnifying NBI colonoscopy.[37,38] However, prospective studies evaluating the surface visibility or invisibility of MC vessels for differential diagnosis of sessile and flat elevated colorectal polyps were absent.

Herein MC vessel evaluation demonstrated high rates of diagnostic accuracy, sensitivity, and specificity for distinction between neoplastic and nonneoplastic lesions (95.3%, 96.4%, and 92.3%, respectively). These data are similar to those of previous reports on magnifying chromocolonoscopy.[21,39,40] However, conventional chromoendoscopy is not globally used and is defined as inconvenient and difficult to reproduce in Western countries.[41] On the basis of the results of this study, we believe that MC vessel evaluation is easier to reproduce, simpler, and faster than conventional chromocolonoscopy. In addition, it seems to be more appealing to Western endoscopists because it offers a short learning curve.

When the NBI results were analyzed, it was found that 4 lesions without MC vessels were misdiagnosed as nonneoplastic lesions. These polyps were histologically diagnosed as adenoma with low-grade dysplasia. One possible explanation for this is that these lesions were diminutive polyps of 3 mm in diameter in which visualization of the MC pattern was not easy. On the other hand, 3 lesions were misdiagnosed as neoplastic (visible MC vessels). These lesions were histologically diagnosed as hyperplastic polyps. Difficulties offered by small polyps when samples are manipulated to reach a proper tissue orientation might explain these results.[42] However, the diagnostic difficulties under NBI observation encountered with small (<3 mm) polyps and atypical hyperplastic polyps, such as sessile serrated polyps, will be investigated in further studies.

Previous studies of patients undergoing colonoscopy have found that small polyps are identified during more than 50% of such examinations.[43] More than 50% of these small polyps are adenomas.[44] Therefore, a key clinical decision in patients with small polyps may depend on determination of the histologic diagnosis. According to the American Society for Gastrointestinal Endoscopy guidelines issued in 2005, every effort should be made during colonoscopy to obtain a tissue diagnosis when

encountering polyps, masses, lesions, or colon strictures.[45] However, if lesions could be accurately recognized as nonneoplastic or neoplastic at colonoscopy, then biopsies or resections would be unnecessary.[46] On the basis of these results, proper observation of MC vessels by magnifying NBI would produce a more effective procedure in terms of reducing resources, number of biopsies, total procedure time, and complications from unnecessary polypectomies.

This article is clinically valuable for several reasons. First, it has demonstrated that simple visualization of the surface mesh capillary pattern is effective to differentiate colorectal polyps. Second, the study was designed only for <10 mm polyps, which are the most common and difficult for accurate diagnosis. Finally, it constitutes an easy and reproducible study.

The primary limitation of the study is that MC vessel appearance was judged by a single endoscopist well experienced in magnifying NBI colonoscopy. Interobserver and intraobserver consistency in the endoscopic assessment of colon pit patterns has been reported to be good when the examinations are performed by experienced endoscopists. Recently, a high level of interobserver agreement was seen in both Japanese and European endoscopists evaluating a dark vascular pattern by NBI.[47] However, multicenter international research with endoscopists of different abilities and interobserver and intraobserver variability studies are necessary to validate the results of this study and to establish firm recommendations and guidelines for all endoscopists. The secondary limitation of this study is that patients with polyps larger than 10 mm, with lesions previously evaluated by histologic examination or colonoscopy, and those with invasive carcinoma were excluded from the study. Recently we have reported that the capillary patterns observed by NBI with magnification provide high accuracy for distinction between low- and high-grade dysplasia/invasive cancer and thus can be used to predict the histopathologic features of colorectal neoplasia.[11] Further prospective studies are required whether magnification NBI observation is useful for selection of therapeutic strategies of colorectal tumors and whether nonmagnification NBI truly highlights colorectal tumors efficiently.

In conclusion, we have shown that observation of the MC vessels by NBI with magnification is effective for distinguishing between nonneoplastic and neoplastic lesions without the application of any dye solution. These results suggest that NBI colonoscopy as a form of "optical-equipped–based image-enhanced endoscopy"[48] facilitates simpler and more efficient screening colonoscopy.

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ORIGINAL ARTICLE

Local recurrence after endoscopic resection of colorectal tumors

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Abstract
Background and aims Local recurrence frequently occurs after endoscopic resection of large colorectal tumors. However, appropriate intervals for surveillance colonoscopy to assess local recurrence after endoscopic resection have not been clarified. The aim of the present study was to determine local recurrence rates following en-bloc and piecemeal endoscopic resection and establish appropriate surveillance colonoscopy intervals based on retrospective analysis of local recurrences.
Materials and methods A total of 461 patients with 572≥ 10-mm lesions underwent endoscopic resection and follow-up. We retrospectively compared local recurrence rates on lesion size, macroscopic type, and histological type after en-bloc resection (440 lesions) and piecemeal resection (132 lesions). Cumulative local recurrence rates were analyzed using the Kaplan–Meier method.
Results Local recurrence occurred for 34 lesions (5.9%). Local recurrence rates for the en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132), respectively ($P<$ 0.001). The difference between the two groups was distinct in terms of lesion size, macroscopic type, and histological type. Of the 34 local recurrences, 32 were treated endoscopically and two cases required additional surgery. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. Then the 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%.
Conclusion Local recurrence occurred more frequently after piecemeal resection than en-bloc resection. However, almost all cases of local recurrences could be cured by additional endoscopic resection, so piecemeal resection can be acceptable treatment.

Keywords Colorectal tumors · Colonoscopy · Neoplasm recurrence · Follow-up studies

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Introduction

Endoscopic resection is used to treat early colorectal tumors around the world. However, the high frequency of local recurrence after piecemeal resection for large colorectal tumors is a serious problem [1–6]. Based on national polyp study [7], the appropriate interval for surveillance colonoscopy after endoscopic resection of adenomatous polyps is 3 years. However, the appropriate intervals after incomplete endoscopic resection has not yet been clarified. In the present study, we retrospectively analyzed the local recurrence frequency after en-bloc and piecemeal endoscopic resection for colorectal neoplasms ≥10 mm in size in large number of follow-up cases. We also analyzed clinicopathologic features and treatment of local recurrences. Our goal was to establish appropriate surveillance colonoscopy programs after endoscopic resection for colorectal tumors based on our retrospective analysis of local recurrence.

Table 1 The clinicopathologic characteristics

	En-bloc (n=440)	Piecemeal (n=132)
Follow-up (months)	22 (1–57)	18 (1–54)
Size (mean, mm)	13.9 (10–40)	23.3 (10–45)
Location (Rb/Ra/Rs/S/D/T/A/C)	23/23/32/140/39/73/81/29	12/4/8/20/6/25/29/28
Macroscopic type		
Protruding	324	26
Flat elevated	114	100
Depressed	2	6
Pathological type		
Adenoma	181	35
M-ca	253	88
SM-ca	5	8
Unevaluated	1	1

Rb lower rectum, *Ra* upper rectum, *Rs*: rect-sigmoid colon, *S* sigmoid colon, *D* descending colon, *T* transverse colon, *A* ascending colon, *C* cecum, *M-ca* intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma

Materials and methods

A total of 461 patients (311 men, 150 women), with 572≥10-mm lesions underwent endoscopic resection and were followed up endoscopically between January 1998 and March 2002 at the National Cancer Center Hospital (Tokyo, Japan). Patients that required additional surgical treatment immediately after endoscopic resection and in whom follow-up colonoscopy could not be performed were excluded from the study. Clinical and pathological records were retrospectively analyzed. The mean patient age was 63.8 years (range 19–89). Of 572 lesions, 440 (76.9%) were removed en-bloc and 132 (23.1%) were removed by piecemeal. The clinicopathologic characteristics of the en-bloc and piecemeal groups are shown in Table 1. There was no difference in the follow-up period for the groups. For the piecemeal group, the mean size of the lesion was 23.3 mm. For the en-bloc group, the mean size of the lesion was 13.9 mm. The rates of rectal lesions were about 20% in both groups. In the piecemeal group, the dominant macroscopic type was flat-elevated. In the en-bloc group, the dominant macroscopic was protruded. We compared the local recurrence rates in the two groups by lesion size, macroscopic type, and histological type. Furthermore, we analyzed the clinicopathologic features and treatments of cases with local recurrence. All patients provided informed consent prior to endoscopic resection.

Endoscopic technique

Good bowel preparation is essential for detection and detailed observation of lesions. We used 2 L of polyethylene glycol electrocyte solution on the day of examination. We used conventional or magnifying video colonoscopies (CF200I, CF-Q240I, CF-200Z, CF-Q240ZI, PCF-230, PCF-Q240ZI; Olympus Optical, Tokyo, Japan). Scopolamine butyl bromide was administered intravenously unless contraindicated. The initial dose was 10 mg and was increased as required. If necessary, the conscious sedation was maintained with intravenous boluses of midazolam or pethidine. We routinely used chromoendoscopy with 0.2% indigo carmine dye to accentuate the lesion contours [8]. This procedure was useful for determining the area of endoscopic resection and detecting local recurrence at the site of resection. Furthermore, we used a magnifying endoscope with 0.2% indigo carmine or 0.05% crystal violet to estimate the depth of invasion in the target lesion [8] and to detect the residual tumor immediately after

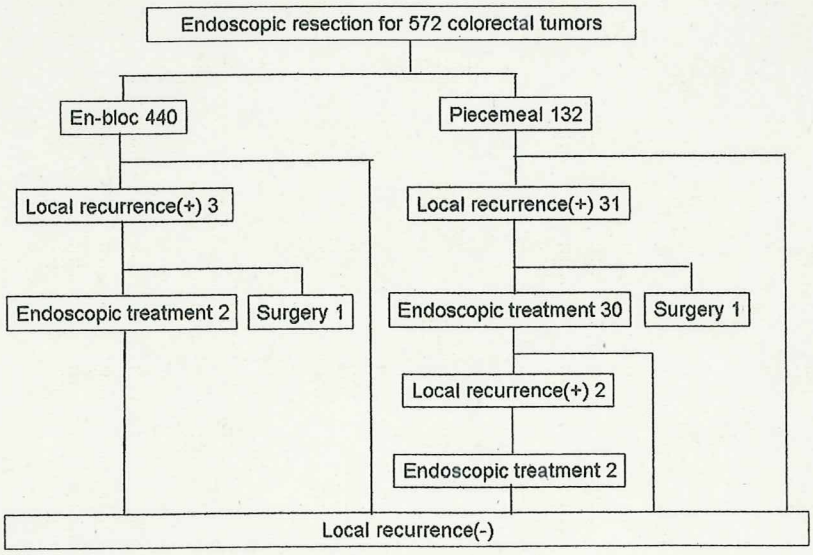

Fig. 1 A chart of 572 colorectal tumors followed up after endoscopic resection

endoscopic resection. Macroscopically, at the margins, lesions can be classified into three major groups: protruding type including sessile (Is), semi-pedunclated (Isp), pedunclated (Ip); flat-elevated type including IIa, IIa+IIc, and Is+IIa; and depressed type including IIc. The indication for endoscopic resection is lesion invasion depth limited to the mucosa and shallow submucosa. After the visible lesion was completely removed, 0.2% indigo carmine was sprayed over the area and the area was magnified. Residual tumor was removed with hot biopsy forceps. We performed all endoscopic treatments in a single session.

Histological examination

All tissue was retrieved for histological evaluation. Removed specimens were fixed in 10% formalin for 24 h and embedded in paraffin wax. Serial sections (3 μm) were stained with hematoxylin and eosin. Two or more pathologists specializing in gastroenterology made histological diagnoses including histological type, invasion depth, vessel invasion, and surgical margin. In the present study, histological type was classified into three groups: adenomas, mucosal carcinomas (M-ca), and submucosal carcinomas (SM-ca).

A principle of additional surgical treatment

Patients that were (1) diagnosed with deep SM-ca >1,000 μm, (2) positive for vessel invasions, (3) positive for poorly differentiated adenocarcinoma at the sites of invasion, and (4) positive for vertical margins were judged to require additional surgical treatment with resection of regional lymph nodes. Cases that were judged to have positive or indistinct for lateral margins were followed up endoscopically.

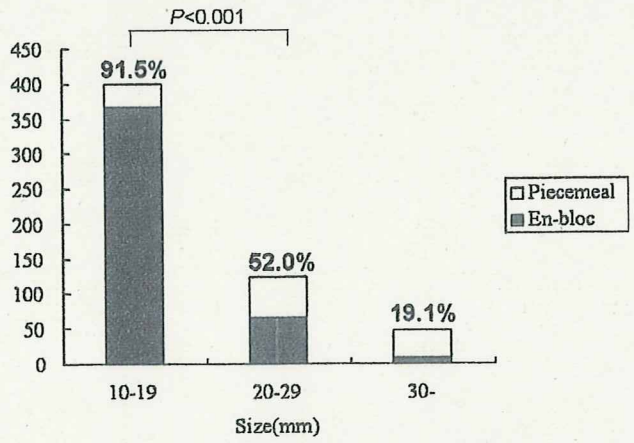

Fig. 2 En-bloc resection rates by lesion size

Table 2 Local recurrence rates by the lesion size

Size (mm)	10–19	20–29	30+	Total
En-bloc	0.8%* (3/366)	0%* (0/65)	0% (0/9)	0.7% (3/440)
Piecemeal	14.7% (5/34)	21.7% (13/60)	34.2% (13/38)	23.5% (31/132)
Total	2.0% (8/400)	10.4% (13/125)	27.7% (13/47)	5.9% (34/572)

*$P<0.001$

Statistical analysis

Local recurrence rates were compared with a chi-square test. Cumulative local recurrence rates were analyzed with the Kaplan–Meier method. Comparison of local recurrence rates were analyzed with log rank test. All statistical analysis was performed with Stat Mate Ver.3 for Windows (ATMS Tokyo, Japan). Calculated P values <0.05 were considered statistically significant.

Results

Local recurrence occurred in 34 lesions (5.9%) of 572 lesions. The local recurrence rates in en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132, chi-square, $P<0.001$; Fig. 1). The en-bloc resection rates of lesions (Fig. 2) decreased in proportion to increase in size (chi-square; $P<0.001$). The local recurrence rates by lesion size are shown in Table 2. Based on lesion size, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group (10–19 and 20–29 mm, chi-square, $P<0.001$). Based on macroscopic type, local recurrence rates of the en-bloc group were significantly lower than those in the piecemeal for protruding and flat-elevated types (chi-square, $P<0.001$; Table 3). Based on histological type, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group for adenoma and M-ca (chi-square, $P<0.001$; Table 4).

Table 3 Local recurrence rates by macroscopic type

Type	Protruding	Flat elevated	Depressed	Total
En-bloc	0%* (0/324)	2.6%* (3/114)	0% (0/2)	0.7% (3/440)
Piecemeal	19.2% (5/26)	24.0% (24/100)	33.3% (2/6)	23.5% (31/132)
Total	1.4% (5/350)	12.6% (27/214)	25.0% (2/8)	5.9% (34/572)

*$P<0.001$

Table 4 Local recurrence rates by histological type

Type	Adenoma	M-ca	SM-ca	Unevaluated	Total
En-bloc	1.1%* (2/181)	0.4%* (1/253)	0% (0/5)	0% (0/1)	0.7% (3/440)
Piecemeal	17.1% (6/35)	26.1% (23/88)	25% (2/8)	0% (0/1)	23.5% (31/132)
Total	3.7% (8/216)	7.0% (24/341)	15.4% (2/13)	0% (0/2)	5.9% (34/572)

M-ca intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma
*$P<0.001$

Twenty-eight of the 34 lesions with local recurrence were detected by the first follow-up colonoscopy that occurred at a median of 114 days (range 74–471) after resection. Local recurrence was detected in the remaining six lesions at the second or subsequent colonoscopy that occurred at a median of 726 days (range 337–910). For four of the six local recurrences that were missed by the first colonoscopy, the colonoscopy was performed within 3 months of resection.

The cumulative rate of local recurrence using the Kaplan–Meier method is shown in Fig. 3. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. The 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%. Local recurrences were significantly frequent in the piecemeal group (log rank test, $P<0.001$). Therefore, we considered the proper first follow-up interval for the piecemeal group to be 6 months. The treatment for local recurrence endoscopic resection was performed in 32 cases (94.1%), and almost all of them were performed in a single session (mean 1.1, range 1–2; Fig. 1). Neither bleeding nor perforation occurred during endoscopic treatment. Two patients required additional surgery (Fig. 1), and the finding was intramucosal carcinoma without lymph node metastasis. The rate of additional surgery after endoscopic en-bloc and piecemeal resection was 0.23% (1/440) and 0.75% (1/132).

Discussion

Endoscopic resection for an early colorectal tumor has been used throughout the world since the 1970s [9, 10]. An endoscopic mucosal resection (EMR) with submucosal saline injection technique [1, 11–14] allowed us to remove a large colorectal tumor that appeared to be not only sessile but also flat and depressed. However, local recurrences frequently occurred after endoscopic piecemeal resection for large sessile tumors, which is a serious problem. Previous studies have reported the rate of local recurrence following piecemeal resection to be 25–50% [1, 2, 6]. Consequently, a combination of snare polypectomy and argon plasma coagulator (APC) [4, 5] or YAG laser [3, 15] was attempted to reduce local recurrence. One randomized controlled study demonstrated that there were fewer local recurrences with APC than without APC (1/10 vs. 7/11) [5]. However, the randomized group consisted of the patients in whom initial polypectomy was apparently complete, and local recurrence frequently occurred despite APC in patients with incomplete polypectomies (6/13). On the other hand, Palma et al. [15] reported that YAG laser reduced remnant tumor in ≥40-mm adenomas. However, the number of treatments with the YAG laser were frequently as many as three, which is a disadvantage of the method. The effort to reduce the local recurrence of piecemeal resection has stalled.

In pathologic staging, it is often difficult to evaluate the surgical margins and invasion depth after piecemeal removal of lesions because specimens may be difficult to reconstruct [16]. On the other hand, surgical margins and invasion depth are easily assessed after en-bloc resection

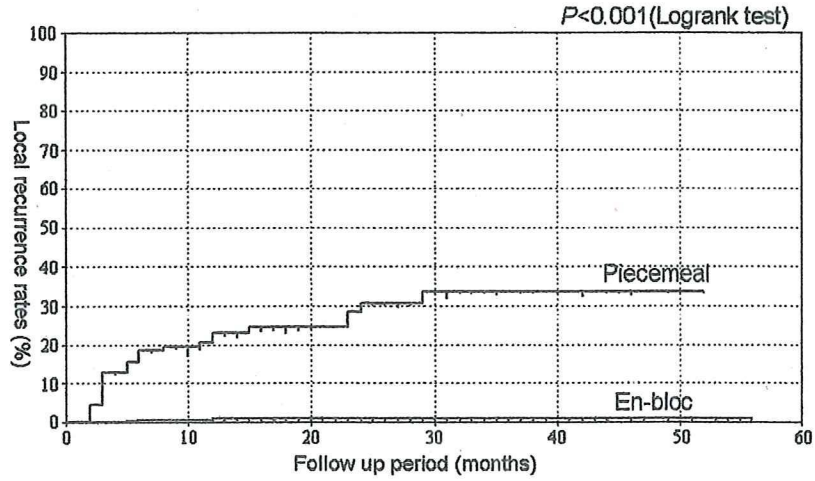

Fig. 3 Cumulative local recurrence rates after endoscopic resection (Kaplan–Meier method)

[16]. Moreover, one can easily evaluate the lateral margin after an en-bloc procedure by immediate observation of the retrieved specimen.

Could the en-bloc method reduce local recurrence after endoscopic resection? In the present study of 572 colorectal tumors that were endoscopically resected, local recurrence occurred for 34 lesions (5.9%). Furthermore, the local recurrence rate for the en-bloc group was significantly lower (0.7%) than that for the piecemeal group (23.5%; $P<$ 0.001). The difference was maintained in subgroups with different lesion sizes (i.e., 10–19 vs. 20–29 mm). We could rationalize that the 10- to 19-mm lesions in which local recurrence occurred were difficult to locate, and therefore, we could not perform en-bloc resection.

Localization of the lesion in the large bowel is an important factor for the detection of remnant tumor immediately after endoscopic resection. Moreover, neither the macroscopic nor the histological type affected the local recurrence rate. Therefore, en-bloc resection appears to be an important factor for reducing local recurrences. Iishi et al. [17]. reported that of 56 large sessile colorectal polyps, the local recurrence after an en-bloc resection was less than that after piecemeal resection (0% vs. 50%). We confirmed this result in a large number of cases in the present study, and we added a detailed analysis for each factor. Although we routinely use magnifying observation of artificial ulcer's edges after endoscopic resection, local recurrence rate of the piecemeal group was significantly higher than the en-bloc group. We speculate this reason that there were micro-residual lesions made by intra-plural snaring method in the center of artificial ulcers, which were difficult to diagnose by observation of ulcer edges. Moreover, higher local recurrence rate might be caused by detailed detection during follow-up colonoscopy using magnified observation.

For the part of large rectal lesions, transanal endoscopic microsurgery (TEM) was considered for an alternative therapy for endoscopic resection. Local recurrence rates (0–10%) of TEM were reported [18], and these were better than our data of endoscopic piecemeal resection. However, TEM required experienced techniques and special instruments, and some complications such as incontinence and urinary retention which never arose in endoscopic resection occur [18].

Recently, several Japanese endoscopists [19, 20] developed novel techniques for large en-bloc resection, endoscopic submucosal dissection (ESD). Gotoda et al. [19] reported EMR on two rectal tumors using an insulation-tipped knife with which they cut the normal mucosa surrounding the target lesions before snaring. Yamamoto et al. [20] successfully removed a 40-mm rectal laterally spreading tumor with submucosal injection of a large amount of sodium hyaluronate. They also cut normal mucosa surrounding the target lesions with a needle knife before snaring. There are several problems with these novel techniques, including technical difficulty, the inability to determine the rate of perforation, and long procedure time. For those reasons, ESD is not widely used.

Based on our result, local recurrence is rare following en-bloc resection. Therefore, the 3- to 5-year interval for surveillance colonoscopy suggested by the national polyp study [7] and the guidelines of the American Gastroenterological Association (AGA) [21] should be appropriate after en-bloc resection. Definite surveillance intervals after incomplete resection have not been proposed by the AGA [21]. In our piecemeal resection group, local recurrence increased gradually from 18.4% at 6 months to 30.8% at 24 months. Based on those findings, an earlier surveillance colonoscopy (e.g., 3 months) would have missed local recurrence. Therefore, a 6-month interval for surveillance colonoscopy after piecemeal resection seems appropriate. That interval will provide accurate diagnosis of local recurrences >50% of the time.

The limitations of our study include using retrospective analysis and being non-randomized. Prospective randomized controlled studies are necessary for determining the appropriate interval for surveillance colonoscopy after piecemeal resection.

In our study, only two instances of local recurrence required additional surgery; the remainder were treated with additional endoscopic resection. We consider piecemeal resection an acceptable treatment until the efficacy and safety of large en-bloc resection are established.

In the future, an effective injection fluid or snare should be developed for safer and larger en-bloc resection based on conventional EMR procedures. We recently injected 10% glycerin solution into the submucosa during EMR, which resulted in a better en-bloc resection rate compared to normal saline [22]. Furthermore, we should make an effort to establish an ESD technique while paying a great deal of attention to safety.

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