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Assessment of Likelihood of Submucosal Invasion in Non-Polypoid Colorectal Neoplasms

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KEYWORDS

- Non-polypoid colorectal neoplasm • Submucosal cancer
- Lymph node metastasis • Endoscopic diagnosis
- Magnifying chromoendoscopy

Endoscopic mucosal resection (EMR) is indicated to treat intramucosal colorectal carcinoma because the risk of lymph node metastasis is nil.[1,2] Surgery is indicated to treat submucosal invasive cancers (cancer cells invading through the muscularis mucosa into the submucosal layer but not extending into the muscularis propria) because of the 6% to 12% risk of lymph node metastasis.[3–7] However, there is increasing evidence to suggest that lesions with submucosal invasion lower than 1000 μm, without lymphovascular invasion and without poor differentiation, also have a minimal risk of lymph node metastasis[8] and can be cured by EMR alone. It is therefore important to be able to distinguish neoplasms that are candidates for EMR from those that will require surgery, because EMR of lesions containing massive submucosal invasive cancer is associated with the risk of bleeding and perforation and is unlikely to be curative.

Current endoscopes have high-resolution imaging that provides clear, vivid, and detailed features of the detected lesions. When combined with image enhancement, high-magnification endoscopy can provide a detailed analysis of the morphologic architecture of mucosal crypt orifices (ie, pit pattern) in a simple and quick manner.[9,10] As such, magnifying chromoendoscopy has been shown to be effective for the differential

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diagnosis between colorectal neoplastic and non-neoplastic lesions and determination of the depth invasion of colorectal cancers. The authors highlight methods to assess depth of invasion of non-polypoid colorectal cancers based on a review of the literature and our experience at National Cancer Center Hospital in Japan.

IMPORTANCE OF ESTIMATION OF SUBMUCOSAL INVASION

In Japan, findings of deep submucosal invasion ($\geq$1000 μm), and/or lymphovascular invasion, and/or poorly differentiated adenocarcinoma in the histopathology of an EMR specimen would lead to consideration for surgery. Though lymphovascular invasion and poorly differentiated adenocarcinoma components are impossible to predict before resection, the vertical depth of invasion of submucosal cancers can be estimated based on the morphologic appearance at the time of endoscopy.

However, estimation of submucosal invasion requires more than the measurement of the lesion size. Small colorectal neoplasms are historically believed to have a lower malignancy potential than large ones, and several authors have reported that the malignant potential of early colorectal cancer increases with size.[11–13] Although this observation may be true for adenomatous lesions, the data for submucosally invasive carcinomas are conflicting. In the authors' own large study involving 583 lesions, they found that that small submucosal cancers ($\leq$10 mm, n = 120) had a similarly aggressive behavior and malignant potential as the larger ones (>10mm, n = 463); the risks of lymph node metastasis were similar (small: 11.2%, large: 12.1%, $P = .85$), lymphovascular invasion (small: 21.7%, large: 27%, $P = .23$), and poorly differentiated adenocarcinoma components (small: 10%, large: 17.1%, $P = .06$).[7] They also described that small submucosal cancers were more likely to have non-polypoid growth (NPG) type[14] than the larger lesions (68.3% vs 46.0%, $P<.0001$). In this retrospective study, the rate of EMR used as an initial treatment was 33.4% (195/583). EMR was more often used to resect the small lesion rather than the large lesion group (51.6% vs 28.7%, $P<.0001$). However, they were surprised to find that there were no differences in the positive rate of cut margins in both groups (17.7% vs 19.5%, $P = .81$). This result implies that EMR should not be easily applied to small colorectal lesions when they appear to be submucosally invasive because of its risk of complication and the concept of no-touch isolation.[15]

ESTIMATION OF SUBMUCOSAL INVASION USING BARIUM ENEMA, ENDOSCOPIC ULTRASONOGRAPHY, AND NONLIFTING SIGN

Barium Enema

The superiority of barium enema over colonoscopy is summarized by Tsuji and colleagues[16] as follows: (1) Barium enema is able to describe the shape of the lesion that is difficult for colonoscopy to observe because of its location. (2) In the case of a large lesion in which it is difficult to endoscopically observe the whole lesion, barium enema can describe the entire shape of the lesion and obtain information on the oral side more easily. (3) The size and location of lesions can be assessed more objectively. (4) The degree of deformity of the lateral view enables the clinician to diagnose the depth of invasion more easily.

The authors retrospectively compared the diagnostic accuracy of colonoscopy and barium enema for submucosal colorectal cancers at 2 National Cancer Centers (Tokyo, Kashiwa) in 2001.[17] One hundred eighty-six (polypoid [Ip, Is]: 117, non-polypoid [IIa, IIa+IIc, IIc, laterally spreading tumor (LST)]: 69) lesions were examined in this study, and the authors investigated the accuracy rate of the lesion's depth by 2 modalities (**Fig. 1**). The colonoscopic accuracy rate was superior to that of the barium enema study

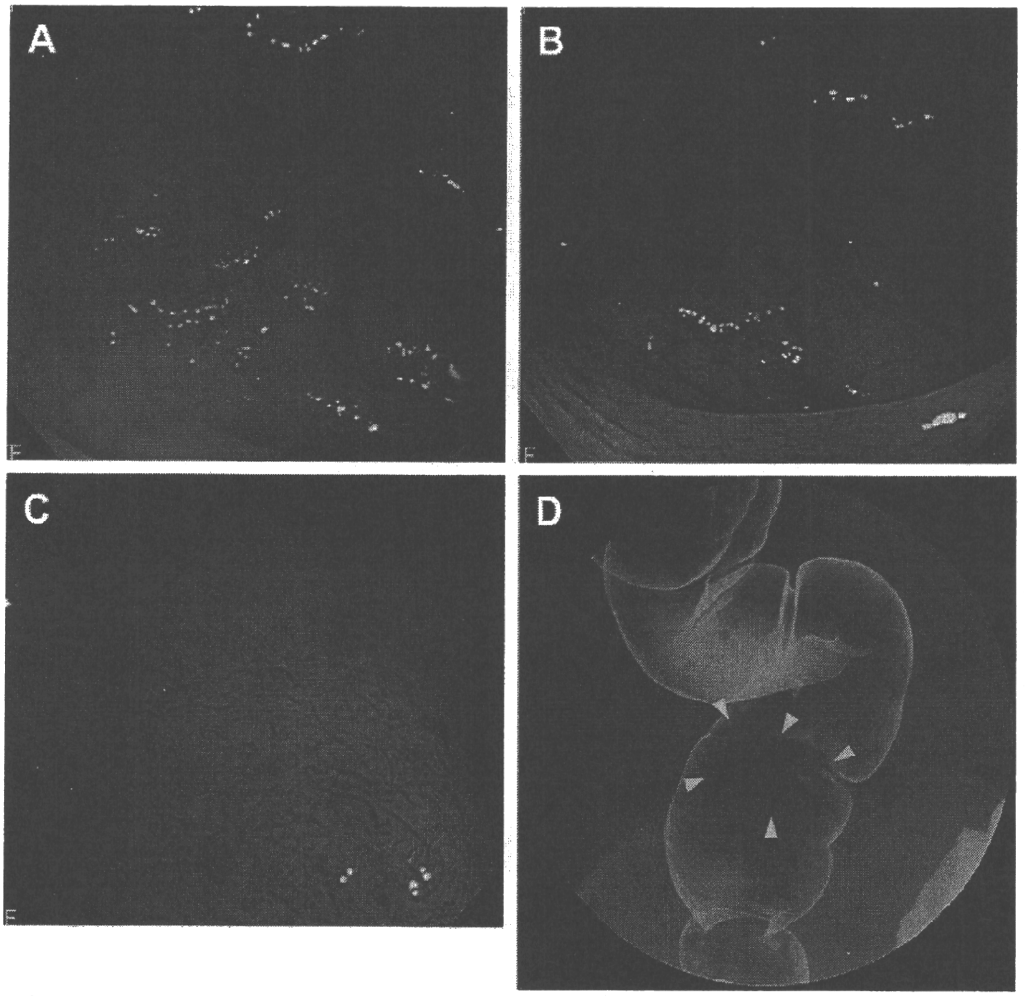

Fig. 1. (*A*) Conventional view, (*B*) Conventional view with indigo carmine dye, (*C*) Magnifying view with crystal violet staining, (*D*) Barium enema image.

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

Endoscopic Ultrasonography

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

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

Nonlifting Sign

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

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

ESTIMATION OF SUBMUCOSAL INVASION USING CONVENTIONAL AND MAGNIFYING CHROMOENDOSCOPY

Conventional Colonoscopy

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

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

Data from National Cancer Center Hospital, Tokyo

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

Table 1
Clinicopathologic characteristics of non-polypoid submucosal cancers

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

Abbreviation: SM, submucosal.

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

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

Magnifying Chromoendoscopy

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

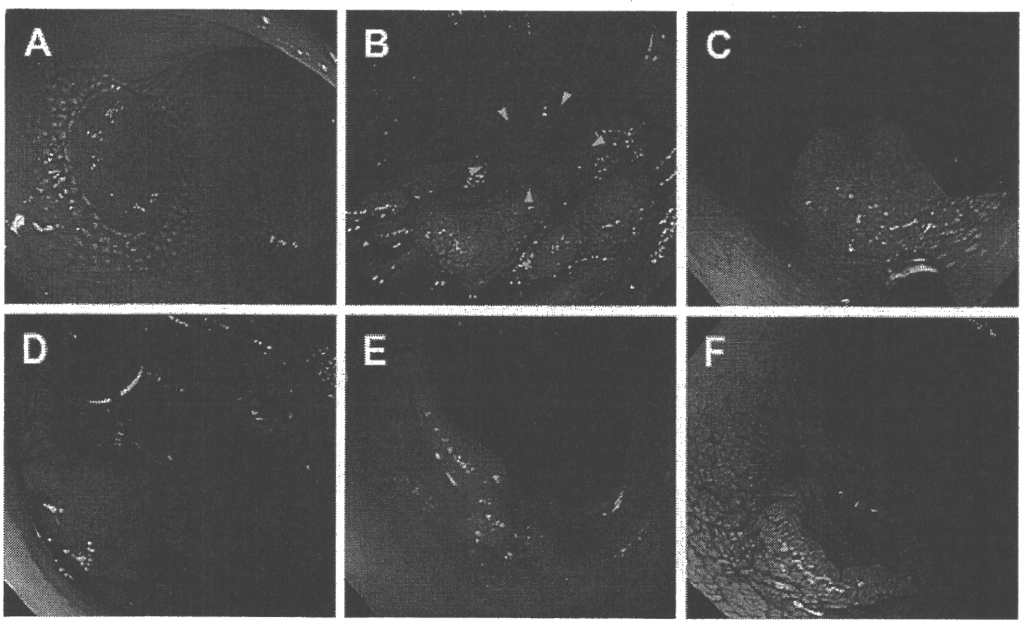

Fig. 2. Six characteristic colonoscopic findings: (*A*) white spots (chicken-skin appearance), (*B*) redness, (*C*) firm consistency, (*D*) expansion, (*E*) fold convergence, and (*F*) deep depressed area.

Table 2
Relationship between endoscopic findings and submucosal deep invasion

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

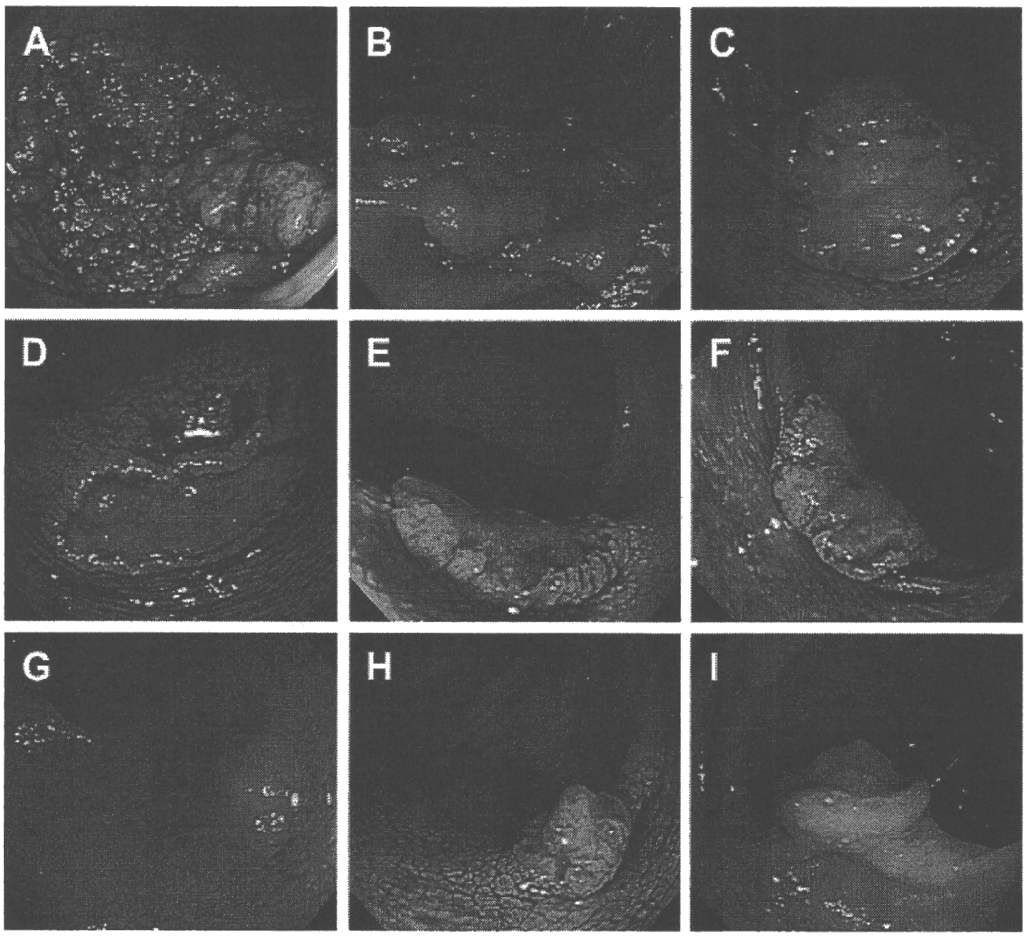

Fig. 3. Representative conventional colonoscopic images of submucosal cancers. (*A*) Is+IIa (LST-granular), (*B*) IIa (LST-nongranular [NG]), (*C*) IIa+IIc (LST-NG), (*D*) IIc, (*E-G*) IIa+IIc, (*H, I*) Is+IIc.

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

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

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

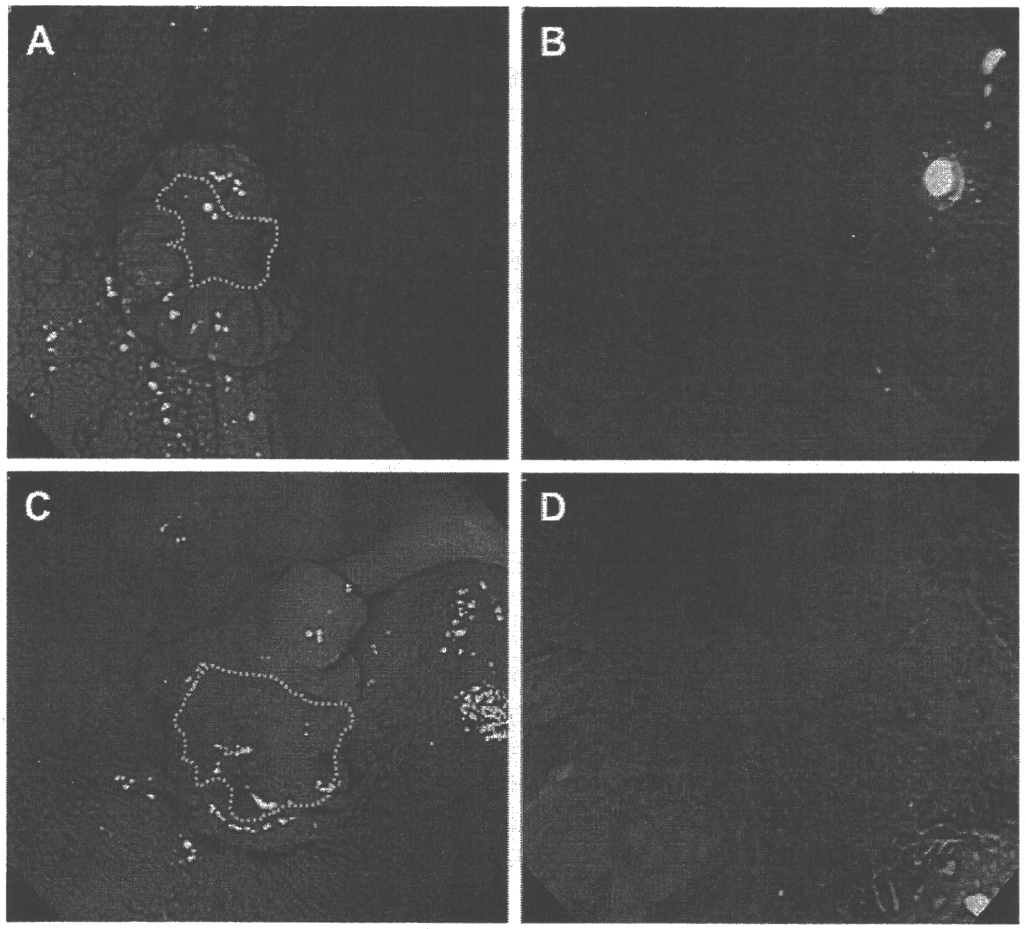

Fig. 4. Definition of invasive pattern: irregular/distorted pit with demarcated area.

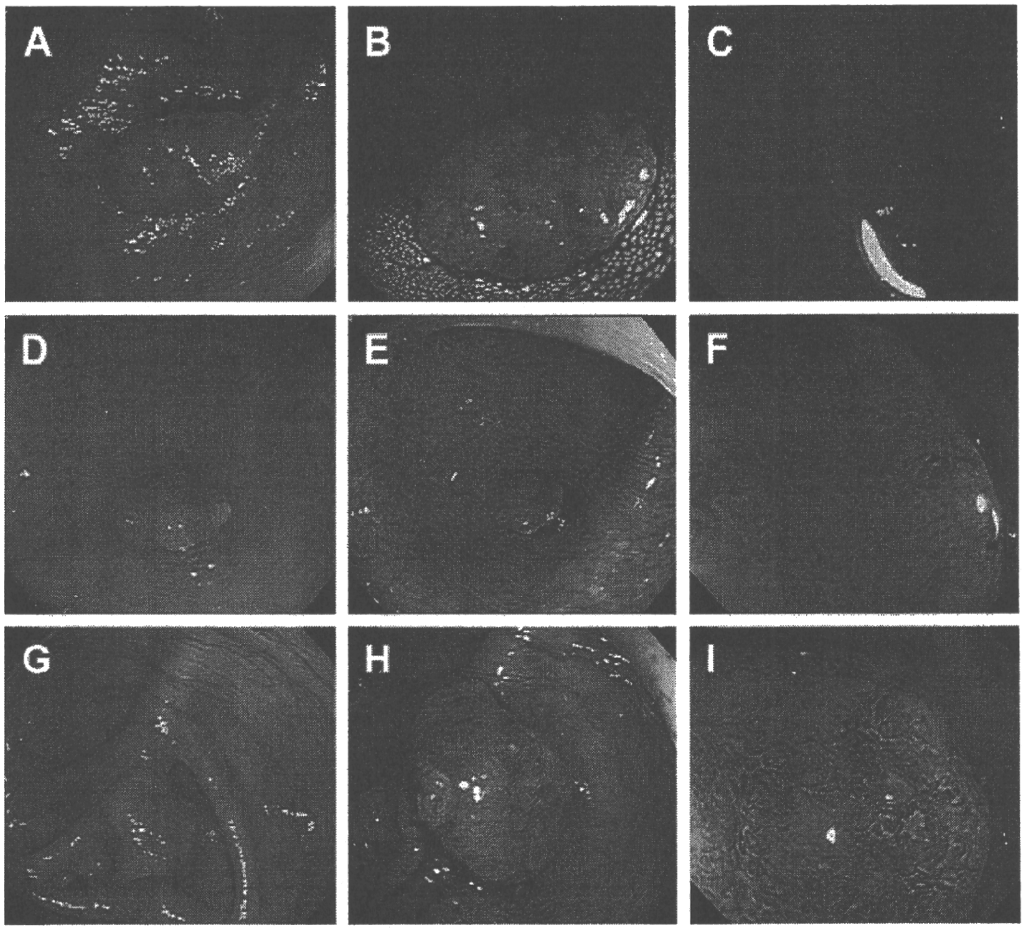

Fig. 5. Submucosal deep cancers. (*A-B*) Is-type submucosal cancer, conventional view. (*C*) Magnifying view (invasive pattern). (*D, E*) IIa+IIc-type submucosal cancer, conventional view. (*F*) Magnifying view (invasive pattern). (*G, H*) Is+IIc-type submucosal cancer, conventional view. (*I*) Magnifying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

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

SUMMARY

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

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MINI REVIEW

Our perspective on endoscopic resection for colorectal neoplasms

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Summary Endoscopic mucosal resection (EMR) is a minimally invasive technique for effective treatment of early stage colorectal lesions with no invasive potential. However, the high frequency of local recurrence after piecemeal EMR for large lesions is considered a serious problem. In contrast, endoscopic submucosal dissection (ESD) allows *en-bloc* resection, irrespective of the lesion's size. ESD has been established as a standard method for the endoscopic removal of early cancers in the upper gastrointestinal tract in Japan. Although the use of ESD for colorectal lesions has been studied clinically, ESD is not yet established as a standard therapeutic method. We define the indications for *en-bloc* resection, based on extensive clinicopathological analyses, as a laterally spreading tumor (LST) non-granular type (LST-NG) lesion greater than 20 mm and an LST granular (LST-G) type lesion greater than 40 mm. Both of these lesions had a high submucosal invasion rate. Especially, LST-NG type lesions greater than 20 mm are technically difficult to remove completely even by piecemeal EMR and are considered a "definite indication for *en-bloc* resection". The ESD procedure is undoubtedly an ideal method to achieve *en-bloc* resection, however, the prevalences of suitable lesions among all neoplastic lesions and among all early cancers were not high (1.0% and 5.0%, respectively). Therefore, it is crucial to master more fundamental therapeutic techniques and have knowledge of surveillance strategy after endoscopic treatment.

Introduction

Colorectal cancer is the third most important cause of cancer mortality in Japan [1]. The recognition and removal of early stage colorectal cancer and precancerous lesions are considered to be important for control of colorectal cancer [2]. Endoscopic mucosal resection (EMR) is now a well-established technique worldwide for the treatment of colorectal neoplasms with minimal invasiveness [3–6],

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however, the high frequency of local recurrence after piecemeal EMR for large lesions is considered a serious problem [7,8]. To avoid this problem, Japanese endoscopists developed a new technique that allows *en-bloc* resection of larger colorectal lesions. This technique, known as endoscopic submucosal dissection (ESD), starts with the submucosal injection, followed by dissection beginning at the lateral edges and working through the submucosal layer until the lesion is removed in one piece. Despite its longer procedure time and higher complication rate, ESD resulted in a higher *en-bloc* resection rate compared to that seen with conventional or piecemeal EMR [9–11]. This paper summarizes recent data of colorectal neoplasms, indications for *en-bloc* resection, and prevalence of candidate lesions among all early stage colorectal neoplasms from the database of National Cancer Center Hospital, Tokyo, Japan.

Indication criteria for endoscopic treatment

EMR is indicated to treat intramucosal colorectal cancer because the risk of lymph node metastasis is nil [12,13]. Surgery is indicated to treat submucosal invasive cancers because of the 6–12% risk of lymph node metastasis [14–18]. There is increasing evidence, however, to suggest that lesions with submucosal invasion less than 1000 μm – without lymphovascular invasion and without poor differentiation – also have a minimal risk of lymph node metastasis [19] and can be cured by EMR alone. Though lymphovascular invasion and poorly differentiated adenocarcinoma components are impossible to predict before resection, the vertical depth of invasion of submucosal cancers can be estimated based on the morphologic appearance at the time of endoscopy. It is therefore quite important to be able to distinguish neoplasms that are candidates for EMR from those that will require surgery, because EMR of lesions containing massive submucosal invasive cancer is associated with the risks of bleeding and perforation and is unlikely to be curative.

Current status of colorectal EMR and limitations

EMR is a minimally invasive technique for effective treatment of early stage colorectal lesions with no invasive potential. Several EMR techniques have been described (i.e. strip biopsy [inject, lift, and cut method], cap-assisted EMR [EMR-C], EMR with ligation [EMR-L]). The "inject and cut" method is simple and safe and is used widely for colorectal neoplasms. Lesions that do not lift during submucosal injection are generally not candidates for resections using the standard EMR technique. Due to the size of the snare, cap, and ligation device, these EMR techniques cannot be used to remove larger than 2 cm in one piece. This limitation prevents precise histopathological assessment and increases the risk of local recurrence. For such large colorectal lesions endoscopically diagnosed as intramucosal or submucosal superficial (< 1000 μm) invasion, piecemeal removal is possible, however, studies have shown that the risk of local recurrence is 2.7–23.5% [9–11]. Varying frequencies have been reported across institutions, probably related to the resection technique and varying abilities to judge for a diminutive residual tumor after piecemeal EMR. However, it has been proved that almost all local residual recurrences are not serious problems, because they are adenomatous lesions that have developed from the edge of primary lesions and can be managed by additional endoscopic treatment if vigilant follow-up is carried out [9,10,20]. The length of a suitable interval of surveillance colonoscopy after piecemeal EMR is still controversial (2–6 months) [21].

Endoscopic depth diagnosis and definite indication for "*en-bloc*" resection

Estimation of the depth of cancer invasion before treatment is crucial to decide the therapeutic plan. New diagnostic modalities such as endoscopic ultrasonography using mini-probe and magnifying chromoendoscopy are reported to be useful for the depth diagnosis of early colorectal cancers. However, these modalities are relatively expensive and time consuming. Therefore, if invasion depth could be diagnosed with only conventional colonoscopy, it would be more cost effective and convenient. Saitoh et al. reported that characteristic colonoscopic findings obtained by a combination of videocolonoscopy and chromoendoscopy are clinically useful for determination of the invasion depth of depressed type colorectal cancers [22]. In this report, characteristic colonoscopic findings (i.e. [1] expansion appearance, [2] deep depression surface, [3] irregular bottom of depression surface, and [4] folds converging toward the tumor) suggested the need for surgical treatment.

Magnifying chromoendoscopy is a standardized, validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern) in a simple and efficient manner. The clinical classification of the colonic pit pattern (invasive and noninvasive) by using magnifying chromoendoscopy was originally described by Fujii et al. with the aim to discriminate between intramucosal-submucosal superficial invasion and submucosal deep invasion [23]. The existence of a non-invasive pattern as determined by magnifying chromoendoscopy is the minimum requirement for all lesions that are candidates for endoscopic treatment [24]. An invasive pattern is characterized by irregular and distorted pits observed in a demarcated area suggesting submucosal deep invasion (> 1000 μm).

We define the indications for *en-bloc* resection, based on extensive clinicopathological analyses [25], as a laterally spreading tumor (LST) non-granular type (LST-NG) lesion greater than 20 mm and an LST granular (LST-G) type lesion greater than 40 mm. Both of these lesions had a high submucosal invasion rate (Table 1). Especially, the LST-NG type lesion greater than 20 mm is technically difficult to remove completely even by piecemeal EMR; we define these lesions as a "definite indication for *en-bloc* resection". In contrast, LST-G type lesions greater than 40 mm are considered a "relative indication for *en-bloc* resection". Moreover, large villous tumors, recurrent lesions, and residual intramucosal lesions showing non-

Table 1 Relationship between size of LSTs and rate of submucosal invasion National Cancer Center Hospital, Tokyo, 1998–2006.

	10 mm (%)	20 mm (%)	30 mm (%)	40 mm (%)	Total (%)
IIa (LST-G)	0/115 (0)	0/70 (0)	1/31 (3.2)	0/13 (0)	1/229 (0.4)
Is + IIa (LST-G)	4/72 (5.6)	6/70 (8.6)	9/65 (13.8)	25/114 (21.9)	44/321 (13.7)
IIa (LST-NG)	12/246 (4.9)	24/106 (22.6)	11/33 (33.3)	8/17 (47.0)	55/402 (13.7)

LST-G: laterally spreading tumor, granular type; LST-NG: laterally spreading tumor, non-granular type.

Table 2 Prevalence of LSTs and indicated lesions for ESD National Cancer Center Hospital, Tokyo, 2000–2006.

	All neoplastic lesions % (n = 11,488)	Early colorectal cancers % (n = 1691)
LSTs[a]	5.9 (674)	22.6 (382)
Indication for ESD	2.3 (267)	12.1 (205)
Definite indication for ESD[b]	1.0 (115)	5.0 (85)
Relative indication for ESD[c]	1.3 (152)	7.1 (120)

[a] LSTs: LST-G and LST-NG.
[b] Definite indication: LST-NG lesion ≥ 20 mm.
[c] Relative indication: LST-G mixed type (Is + IIa [LST-G]) ≥ 40 mm.

lifting sign after EMR were also potential candidates for ESD.

ESD procedures

The ESD procedure is undoubtedly one of the ideal methods to achieve *en-bloc* resection. In our center, ESD procedures are primarily performed using a bipolar knife (B-knife) [26] or an IT knife with carbon dioxide (CO_2) insufflations instead of air insufflations to reduce patient discomfort [10,27,28]. Lesion margins are delineated before ESD by using 0.4% indigo-carmine dye spraying. After injection of Glyceol® (10% glycerol and 5% fructose in normal saline solution) [29] and sodium hyaluronate acid into the submucosal layer [30], a circumferential incision is made using the B-knife and ESD is then carried out using both the B-knife and IT-knife.

Prevalence of "definite indication" for ESD-data from National Cancer Center Hospital, Tokyo

Between January 2000 and December 2006, a total of 11,488 colorectal neoplasms (except advanced cancers) in 6369 patients were treated endoscopically or surgically at the National Cancer Center Hospital, Tokyo. To clarify the prevalence of "definite indication for colorectal ESD", we reviewed and analyzed records from our database. There were 9797 adenomas and 1691 early colorectal cancers (intramucosal cancer: 1294, submucosal cancer: 397). Among all neoplastic lesions, the prevalence of LSTs (LST-G and LST-NG) and the proportion for which ESD would have been indicated were 5.9% and 2.3%, respectively (Table 2). In contrast, among all early cancers, the prevalence of LSTs was 22.6% and proportion for which ESD would have been indicated was 12.1%. Moreover, the prevalences of "definite indication for ESD" among all neoplastic lesions and all early cancers were 1.0% (115/11,488) and 5.0% (85/1691), respectively.

Conclusion

The ESD procedure is an ideal method to provide "*en-bloc* resection" even for large colorectal lesions, however, the prevalence of lesions with a "definite indication for ESD" among all colorectal neoplasms is limited. In addition, although the use of ESD for colorectal lesions has been studied clinically, ESD is not yet established as a standard therapeutic method. Therefore, it is crucial to master more fundamental techniques (e.g. hot biopsy, snare polypectomy, conventional EMR, piecemeal EMR) and have knowledge of surveillance strategy after endoscopic treatment.

Furthermore, characteristic colonoscopic findings obtained by a combination of conventional colonoscopy and magnifying chromoendoscopy are useful and clinically important for determination of the invasion depth of early stage colorectal cancers, an essential factor in selecting a treatment modality (i.e. endoscopic treatment or surgical operation). As the therapeutic techniques are developed, preoperative endoscopic diagnosis will become more and more important.

Conflict of interest

The authors have not declared any conflict of interest.

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Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection

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Abstract

Background and Aims Endoscopic submucosal dissection (ESD) has recently been applied to the treatment of superficial colorectal cancer. Clinical outcomes compared with conventional endoscopic mucosal resection (EMR) have not been determined so our aim was to compare the effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm.

Methods This was a retrospective case-controlled study performed at the National Cancer Center Hospital in Tokyo, Japan involving 373 colorectal tumors ≥20 mm determined histologically to be curative resections. Data acquisition was from a prospectively completed database. We evaluated histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications for both the ESD and EMR groups.

Results A total of 145 colorectal tumors were treated by ESD and another 228 were treated by EMR. ESD was associated with a longer procedure time (108 ± 71 min/29 ± 25 min; $p < 0.0001$), higher en bloc resection rate (84%/33%; $p < 0.0001$) and larger resected specimens (37 ± 14 mm/28 ± 8 mm; $p = 0.0006$), but involved a similar percentage of cancers (69%/66%; p = NS). There were three (2%) recurrences in the ESD group and 33 (14%) in the EMR group requiring additional EMR ($p < 0.0001$). The perforation rate was 6.2% (9) in the ESD group and 1.3% (3) in the EMR group (p = NS) with delayed bleeding occurring in 1.4% (2) and 3.1% (7) of the procedures (p = NS), respectively, as all complications were effectively treated endoscopically.

Conclusions Despite its longer procedure time and higher perforation rate, ESD resulted in higher en bloc resection and curative rates compared with EMR and all ESD perforations were successfully managed by conservative endoscopic treatment.

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Keywords Endoscopic submucosal dissection (ESD) · Endoscopic mucosal resection (EMR) · Recurrence · Colon · Colorectal · Short-term clinical outcome

Abbreviations

B-knife	Bipolar needle knife
CO_2	Carbon dioxide
EMR	Endoscopic mucosal resection
EPMR	Endoscopic piecemeal mucosal resection
ESD	Endoscopic submucosal dissection
IT knife	Insulation-tipped knife
LN	Lymph node
sm	Submucosal
LST	Laterally spreading tumor
LST-G	Laterally spreading tumor granular type
LST-NG	Laterally spreading tumor nongranular type
NS	Not significant
SD	Standard deviation
sm1	Minute submucosal cancer
sm2	Submucosal deep cancer

Endoscopic mucosal resection (EMR) is indicated for the treatment of superficial, early-stage colorectal cancer because of its minimal invasiveness and excellent results in terms of clinical outcomes [1–6]. However, conventional EMR techniques [6–8] currently used for the resection of laterally spreading tumors (LSTs) [7–10] are inadequate for the en bloc resection of flat lesions ≥20 mm because of both incomplete removal [11] and problems with local recurrence [12]. The endoscopic submucosal dissection (ESD) technique, which facilitates en bloc resection of early gastric cancer [11, 13–17], has recently been reported to be useful in the treatment of superficial colorectal tumors [18–28]. Previously, we reported on the effectiveness and safety of ESD for colorectal tumors using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan) and an insulation-tipped knife (IT knife) (Olympus Optical Co., Ltd., Tokyo, Japan), neither of which produces any coagulation effect at the needle tip [20, 21, 24]. The effectiveness and long-term clinical outcome of ESD compared with conventional EMR is unclear, however, so the purpose of this study was to demonstrate the comparative effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm

Materials and methods

Originally, 553 large (≥20 mm) colorectal tumors were resected endoscopically between January 2003 and December 2006 at the National Cancer Center Hospital (NCCH) in Tokyo with data acquisition from a prospectively completed database. Twenty-nine lesions that required surgery after endoscopic treatment because of noncurative resections and 151 lesions treated by conventional EMR for which follow-up colonoscopy examinations could not be carried out or ascertained at NCCH were excluded, leaving a final total of 373 large colorectal tumors that were included in this retrospective case-controlled study (Fig. 1). All ESD and EMR procedures were conducted by experienced colonoscopists (three staff doctors and two senior residents), each of whom had performed more than 1,000 colonoscopies annually.

The histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications were evaluated for both an ESD group and a conventional EMR group. We defined an en bloc resection as a one-piece resection of the entire lesion as observed endoscopically. In assessing for a local recurrence or the presence of a residual tumor, we repeated colonoscopy

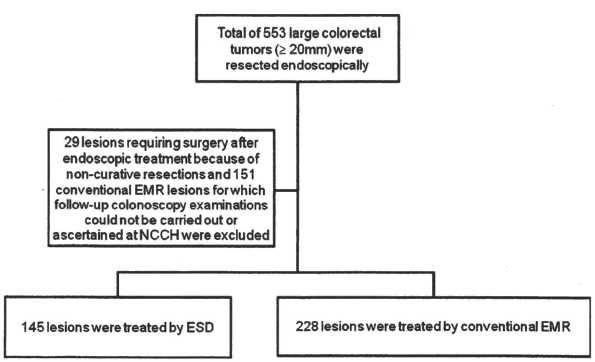

Fig. 1 Flow chart showing the patients in this study

examinations at intervals of 6 months. The procedure time was measured from the injection of a submucosal (sm) injection solution into the sm layer to removal of the colonoscope after the resection of a tumor.

Indication criteria for EMR and ESD

The existence of a noninvasive pattern [10, 24, 29–31] as determined by magnification chromoendoscopy was the minimum requirement for all lesions that were candidates for ESD and EMR. When a lesion was detected by conventional endoscopic examination, surface mucous was washed away with lukewarm water that contained pronase (Pronase MS; Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion to enhance its surface detail. High-magnification colonoscopes (CF-240ZI, PCF-240ZI and H260AZI; Olympus Optical Co., Ltd.) were used to evaluate the surface character to differentiate an invasive pattern from a noninvasive pattern. The invasive pattern is characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting that sm invasion is ≥1,000 μm while a noninvasive pattern does not have this finding which suggests intramucosal neoplasia or sm invasion <1,000 μm. When high-magnification observation with indigo-carmine dye was insufficient to determine the surface structure, we performed staining with 0.05% crystal violet. Based on extensive clinicopathological analyses [10], we defined the indications for ESD [24] as an LST nongranular (LST-NG)-type lesion >20 mm and an LST granular (LST-G)-type lesion >40 mm because they both had a higher sm invasion rate and were difficult to treat even by endoscopic piecemeal mucosal resection (EPMR) [7]. Some colonoscopists chose to perform EPMR [7] to treat LST-G lesions measuring between 20 and 40 mm with the final decision based on each individual colonoscopist's judgment. Large villous tumors as well as intramucosal lesions, recurrent lesions, and residual intramucosal lesions showing nonlifting sign after EMR were also potential candidates for ESD with the final decision once again made by each colonoscopist (Table 1).

Endoscopic operating systems

ESD and EMR procedures were performed using Olympus PCF-Q240ZI, CF-Q240ZI, and CF-H260AZI video endoscopes.

Bowel preparation

Bowel preparation consisted of a patient drinking 2–3 L of polyethylene glycol (PEG) solution in the morning before the procedure. In an effort to further ensure excellent bowel preparation, stool color was assessed before each colonoscopy by a trained nurse and additional PEG solution was used when necessary.

ESD procedures

The procedures were primarily performed using a B-knife [20] or an IT knife with carbon dioxide (CO_2) insufflation instead of air insufflation to reduce patient discomfort [21]. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying (Fig. 2A, B). Following injection of Glyceol® (Chugai Pharmaceutical Co., Tokyo, Japan) (10% glycerol and 5% fructose in normal saline solution) [32] and sodium hyaluronate acid into the sm layer [33], a circumferential incision was made using the B-knife and an ESD was then carried out using both the B-knife and IT knife (Fig. 2C–F).

Conventional EMR procedures

Conventional EMR procedures were performed using the inject and cut technique with a single-channel colonoscope (PCF-Q240ZI, CF-Q240ZI or CF-H260AZI; Olympus) and

Table 1 Indication criteria for endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR)

Minimum requirement
A noninvasive pattern as determined by magnification chromoendoscopy was required for all lesions that were candidates for ESD and EMR
Definite indication for ESD
LST-NG lesion ≥20 mm
Relative indication for ESD
LST-G lesion ≥40 mm
Large villous tumor, intramucosal lesion, recurrent lesion or residual intramucosal lesion showing nonlifting sign after EMR
Definite indication for EMR/EPMR
Any lesion <20 mm
LST-G lesion ≥20 mm and <40 mm

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type

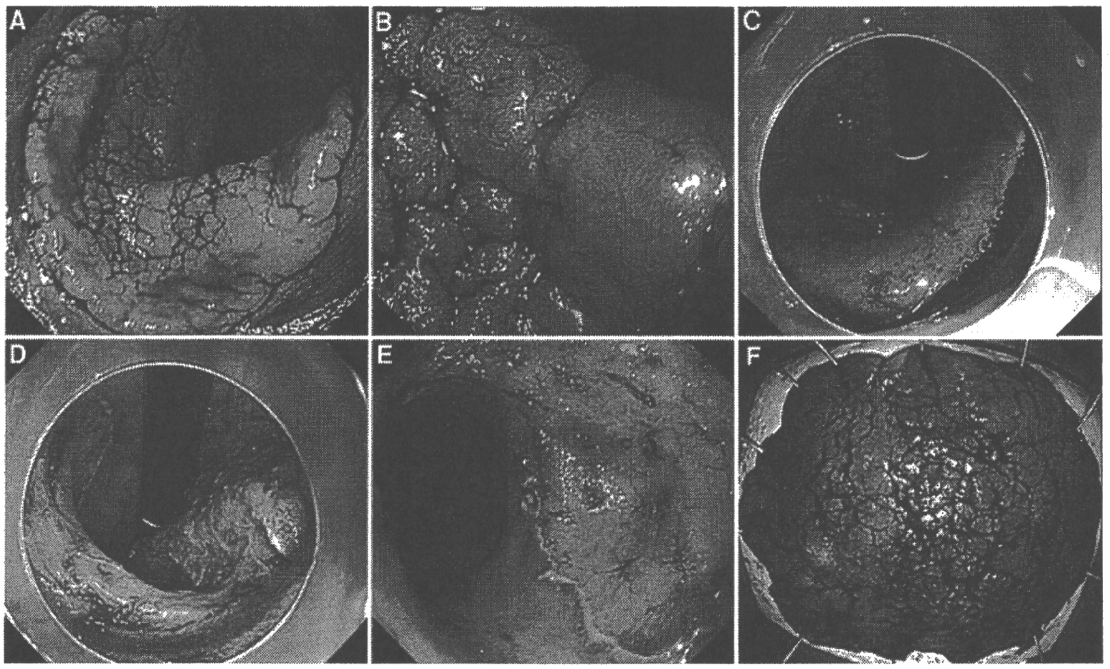

Fig. 2 Endoscopic submucosal dissection (ESD) procedures, primarily performed using a bipolar needle knife (B-knife) and an insulation-tipped knife (IT knife) with carbon dioxide (CO_2) insufflation. **A** Fifty-millimeter laterally spreading tumor nongranular (LST-NG)-type lesion located in the transverse colon. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying. **B** Magnified colonoscopy revealed a noninvasive pattern so the estimated depth of this LST-NG lesion was intramucosal despite its large size. **C** Following injection of Glycerol® (10% glycerol and 5% fructose in normal saline solution) and sodium hyaluronate acid solution into the submucosal layer, a circumferential incision was made using the B-knife. **D** An ESD was then carried out using both the B-knife and IT knife. **E** The ulcer bed is shown here after the successful en bloc resection. **F** The resected specimen was 65 × 50 mm in diameter and histology revealed an intramucosal cancer with a tumor-free margin

snare (10-mm or 25-mm snare master or 20-mm spiral snare; Olympus) as described in previous reports [1–3, 6, 7]. Glyceol® [32] was injected into the sm layer of the lesion with a 23-gauge needle and the lifted lesion was then resected using the snare.

In this study, we distinguished an EMR from an EPMR according to the number of resected pieces as either single or multiple, respectively. An LST-G ≥20 mm and <40 mm can usually be treated by EPMR rather than ESD with the area including the large nodule resected first followed by the remaining tumor (Fig. 3A–C). After EMR and EPMR, we confirmed whether or not there was any residual tumor using chromomagnification colonoscopy and performed a hot biopsy as necessary for ablative purposes.

Tumor size was estimated by measuring the resected specimen after retrieval for en bloc resected specimens and by comparing the endoscopic observation with the snare size for piecemeal resected specimens.

Sedation

Midazolam (2 mg/iv) and pentazocin (15 mg/iv) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. In conventional EMR procedures, midazolam (2 mg iv) was administered to selected patients as determined by the colonoscopist, but only when a patient complained of pain or abdominal distension.

Histological assessment

All specimens were evaluated after being cut into 2-mm slices and examined microscopically for histological type, depth of invasion, lateral resection margin, and vertical resection margin. Resections were considered tumor free when the lateral and vertical margins of a specimen were both negative for tumor cells independent of its histological features.

A curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer and there was no sm invasion deeper than 1,000 μm from the muscularis mucosae (sm1), lymphatic invasion, vascular involvement or poorly differentiated component [34]. An adenoma with an unknown lateral margin was also considered to be a curative resection provided that such adenoma met all the other criteria. Histological diagnoses

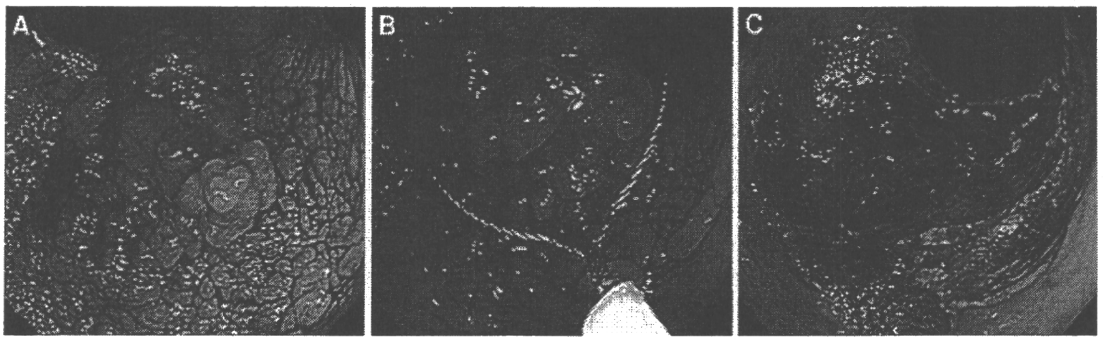

Fig. 3 Conventional endoscopic mucosal resection (EMR) procedures. Conventional EMRs were usually performed using an inject and cut technique with a single-channel colonoscope and snare. Glycerol® was injected into the submucosa of the lesion with a 23-gauge needle and then the lifted lesion was resected using a round snare. **A** A 35-mm laterally spreading tumor granular (LST-G)-type lesion located in the rectum. **B** An LST-G between 20 and 40 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than ESD with the area including the large nodule resected first followed by the remaining tumor. **C** The ulcer bed after a three-piece resection

were based on the Japanese classification of cancer of the colon and rectum [35] and the Vienna classification [36].

Follow-up endoscopic care

In assessing for local recurrence or the presence of a residual tumor, we usually repeated colonoscopic examinations at intervals of 6 months for ESD patients because the technique was still relatively new and indicated for large colorectal lesions that had previously been treated surgically. In most cases, we repeated colonoscopic examinations at intervals of 6 months for EPMRs and at 12-month intervals for EMRs with en bloc resections because of an expected lower risk of recurrence [37] with such examinations performed either by the endoscopy staff at NCCH or the patient's previous hospital.

All ESD and EMR patients with sm1 invasion were followed up regularly with annual computed tomography and endoscopic ultrasonography examinations for the detection of lymph-node metastasis. Complete endoscopic follow-up care was available for all 145 lesions in the ESD group and all 228 lesions in the EMR group. Indigo-carmine dye was sprayed on previously resected areas and high-magnification views were obtained in all cases. Recurrent neoplastic disease was identified as type IIIs, IIIL, IV or V pit pattern according to the criteria established by Kudo and Fujii [6, 9, 10, 30–32, 38–41].

Statistical analysis

All variables in this study are described as mean ± standard deviation (SD). In comparing baseline characteristics between the two groups, we used a *t*-test for continuous variables and a chi-square test for dichotomous variables. All statistical analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC). The p values are two-sided and $p < 0.05$ was used to determine statistical significance.

Ethics

The ethics committee at NCCH approved the study protocol and informed written consent was obtained from all patients in the ESD and EMR groups for each specific colonoscopic treatment and all scheduled follow-up colonoscopy examinations.

Results

During the study period, 145 lesions were treated with ESD and 228 were treated with conventional EMR (Fig. 1). All 373 lesions were eligible for outcome analysis. Clinical characteristics of the patients in the two groups are presented in Table 2. There were no differences between the two groups in terms of age, gender, endoscopic follow-up frequency or follow-up periods (Tables 2 and 3).

En-bloc resection rates

In the ESD group, 122 out of 145 lesions (84%) were completely resected en bloc compared with only 74 of 228 lesions (33%) in the EMR group ($p < 0.0001$), although tumor size was significantly larger in the ESD group ($p < 0.0001$) (Table 3).

Endoscopic characteristics of resected specimens

Regarding macroscopic type, 50% of the EMR group lesions were LST-Gs and 49% of the ESD group lesions were LST-NGs. There were no differences between the two groups in terms of tumor location. The percentage of