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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Neoplastic lesions with ''superficial'' morphology in pedunculated type early invasive colorectal cancer.

Fig. S2. Haggitt's classification of pedunculated type early invasive colorectal cancer.

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Learning Curve Associated With Colorectal Endoscopic Submucosal Dissection for Endoscopists Experienced in Gastric Endoscopic Submucosal Dissection

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BACKGROUND: Colorectal endoscopic submucosal dissection requires a high level of skill and experience in therapeutic endoscopy because of the high risk of complications such as perforation and bleeding. Greater understanding of the procedural learning curve is required to standardize training and to achieve wider acceptance of this procedure.

OBJECTIVE: The aims of this study were to evaluate the clinical outcomes of colorectal endoscopic submucosal dissection and to clarify its learning curve for endoscopists.

DESIGN: We retrospectively reviewed the clinical outcomes for consecutive patients with colorectal neoplasms who underwent endoscopic submucosal dissection by 2 trainees under the guidance of experienced specialists.

SETTING: The study was performed at the National Cancer Center Hospital, Tokyo, Japan.

PATIENTS: Colorectal endoscopic submucosal dissections were performed for 101 consecutive patients with 102 colorectal neoplasms between April 2008 and December 2010.

MAIN OUTCOME MEASURES: Procedure time, en bloc resection rate, completion rate, and complications were retrospectively compared between 4 training periods in which each trainee performed 10 endoscopic submucosal dissections per period and a final training period in which the trainees performed 10 to 12 endoscopic submucosal dissections to analyze the skill improvement with time.

RESULTS: The procedure time and en bloc resection rate were not significantly different among the training periods. However, the completion rates in the fourth (100%) and fifth (95.5%) training periods ($\geq$31 cases/trainee) were significantly higher ($P < .001$) than those in the first (45%), second (70%), and third (80%) training periods (1–30 cases/trainee). Two cases of perforation occurred during the study.

LIMITATIONS: Limitations include the single-center design. Training programs and instruments vary with institution, which could affect the learning curve.

CONCLUSIONS: Trainee endoscopists are able to perform colorectal endoscopic submucosal dissection without serious complications under the guidance of experienced specialists. They can perform it safely and independently after preparatory training and experience with $\geq$30 cases.

KEY WORDS: Endoscopic gastrointestinal surgery; Colorectal cancer; Experiential learning; Treatment outcome; Intraoperative complications.

One of the most important aims of colonoscopy is prevention of the development of advanced colorectal cancer by finding and removing its precursors, adenomatous polyps.[1-6] A flat or depressed neoplasm typified as a laterally spreading tumor (LST) is considered

a risk factor for the development of advanced cancer.[7-10] Endoscopic mucosal resection (EMR) is the standard endoscopic procedure for removing such lesions; however, one indication for this procedure is the lesion size, and endoscopic piecemeal EMR is often applied for lesions larger than 20 mm.[11] Although this procedure is simple and time-saving, issues such as the high incidence of persistent or recurrent tumors and a low rate of histologically curative resections have been reported.[12,13]

Endoscopic submucosal dissection (ESD) facilitates en bloc resection of large colorectal neoplasms that are difficult to resect by EMR, allows the precise histologic evaluation of resected specimens, and reduces the risk of recurrence in comparison with piecemeal EMR.[14-16] This procedure, however, requires a high level of endoscopic skill and experience in therapeutic endoscopy because of the high risk of complications arising from the anatomical characteristics of the colon. Therefore, greater understanding of the learning curve for ESD is required to standardize training and to achieve wider acceptance of this technique. The aims of this study were to evaluate the clinical outcomes of ESD when conducted by trainees and to clarify the learning curve for this procedure.

PATIENTS AND METHODS

Patients

We retrospectively reviewed clinical outcomes for 101 consecutive patients with 102 colorectal neoplasms who underwent ESD by 2 trainees (S.F. and T.S.) under the guidance of experienced specialists at the National Cancer Center, Tokyo, Japan, between April 2008 and December 2010. T.S. performed 50 procedures, and S.F. performed 52 procedures. We conducted this study in accordance with the guidelines of our institutional review board, which approved this retrospective study without the need for informed consent. All of the patients provided written informed consent for the colonoscopy and ESD.

Prerequisites for Performing Colorectal ESD

At our institution, trainees must meet the following prerequisites to perform colorectal ESD: a high level of skill in the nonloop insertion colonoscopy technique (more than 10 cases of total colonoscopy completed within 5 min without any abdominal discomfort), skill in conventional EMR or piecemeal EMR techniques, experience with >20 gastric ESD cases, and assistance during >20 colorectal ESDs conducted by experienced endoscopists.

Indications for Colorectal ESD

All lesions to be treated endoscopically were required to have a noninvasive pattern on magnifying chromoendoscopy. An invasive pattern is characterized by irregular and distorted pits in a demarcated area, suggesting deep sub-

mucosal invasion (≥ 1000 μm), which has a high risk of lymph node metastasis; a noninvasive pattern does not have these characteristics, suggesting intramucosal neoplasia or superficial submucosal invasion (< 1000 μm).[17,18] We defined the indications for ESD as (1) an LST nongranular (LST-NG) type lesion of >20 mm or (2) an LST granular (LST-G) nodular mixed-type lesion of >30 mm. These lesions have a high submucosal invasion rate and require accurate histologic evaluation by en bloc resection. Large villous tumors, recurrent lesions, and residual intramucosal lesions showing the nonlifting sign after EMR were also considered potential candidates for ESD.

ESD Procedure

The trainees performed the procedure using a ball-tip–type bipolar needle knife (B-B knife), in which the electrical current localizes to the needle tip with carbon dioxide insufflation rather than air insufflation.[19] Bipolar coagulation forceps were also routinely applied to stop active bleeding and to decrease the risk of perforation. The lesion margins were clearly delineated before circumferential incision by the use of 0.4% indigo carmine dye spray. After injecting 10% glycerol and 5% fructose in a normal saline solution (Glyceol; Chugai Pharmaceutical Co., Tokyo, Japan) and sodium hyaluronate into the submucosal layer under the tumor, the trainees incised the mucosa with the B-B knife approximately 2 to 3 mm outside the lesion edge, on the elevation caused by the submucosal injection. An additional submucosal injection of the same solution was then applied before ESD to prevent perforation. An insulated-tip (IT) knife or B-B knife was used to dissect the submucosal layer. The electric current used for the circumferential incision and submucosal dissection was set to endocut mode (ERBE ICC-200, effect 3, output 50 W; ERBE Elektromedizin GmbH, Tübingen, Germany).

ESD was performed under conscious sedation in an endoscopy room with continued monitoring of electrocardiography and oxygen saturation. Conscious sedation allows a change in a patient's position in any direction, making it possible to apply countertraction to the lesions with the use of gravity. Moreover, under conscious sedation, we can accurately evaluate abdominal discomfort when perforation is suspected. Intravenous midazolam (2–3 mg) and intravenous pentazocine (15 mg) were administered to all patients to initiate sedation; an additional midazolam injection (2 mg) was administered if deemed necessary by the endoscopist.

Histopathological Assessment

All resected specimens were fixed in 10% buffered formalin. En bloc specimens and, where possible, larger piecemeal specimens were cut into 2-mm-thick slices. The fragments or slices were embedded in paraffin, cut into 3-μm

TABLE 1. Endoscopic characteristics of the lesions by treatment period and number of cases

| Characteristic | Treatment period/cases per trainee | | | | | P |
	First 1–10 (n = 20)	Second 11–20 (n = 20)	Third 21–30 (n = 20)	Fourth 31–40 (n = 20)	Fifth ≥41 (n = 22)	
Size (mm), median (IQR)	26 (20–31.5)	31 (25.3–36.5)	31 (25–40)	30 (24.3–41.5)	31 (25–44)	.343
Location, n (%)						.667
Rectum	7 (35.0)	8 (40.0)	3 (15.0)	5 (25.0)	6 (27)	
Colon	13 (65.0)	12 (60.0)	17 (85.0)	15 (75.0)	16 (73)	
Macroscopic, n (%)						.970
Protruded (0-I, LST-G) or SMT	12 (60.0)	12 (60.0)	11 (55.0)	10 (50.0)	12 (55)	
LST-NG or recurrent	8 (40.0)	8 (40.0)	9 (45.0)	10 (50.0)	10 (45)	

IQR = interquartile range; LST-G = laterally spreading tumor granular type; LST-NG = laterally spreading tumor nongranular type; SMT = submucosal tumor.

sections, stained with hematoxylin and eosin, and microscopically examined for histopathological type by pathologists specializing in gastrointestinal pathology.

Resections were evaluated according to the presence of tumor cells at the margins of the resected specimen, independent of its histopathological features, as follows: R0 resection, all margins were negative for tumor cells; R1 resection, tumor cells extended to the lateral or basal margins; and Rx resection, the margins could not be evaluated. Curative resection was achieved when an R0 resection was performed and submucosal invasion >1000 μm from the muscularis mucosae, lymphatic invasion, vascular involvement, budding, and poorly differentiated components were absent. Clinical curative resection was considered achieved when the lateral margins of a resected specimen could not be evaluated histopathologically because of artifacts caused by coagulation necrosis during the ESD procedure or a lesion resected in a piecemeal manner had any of the factors absent in a curative resection. Curative resection of an adenoma with an unclear lateral margin was considered achieved if the adenoma met all of the other criteria. The histopathological diagnoses were based on the Japanese classification criteria for cancer of the colon and rectum and the Vienna classification system.[20,21]

Statistical Analysis

The endoscopic characteristics of the lesions, procedure time, en bloc resection rate, completion rate, and complications were compared between 4 training periods in which each trainee performed 10 ESDs per period, as well

as a final training period in which the trainees performed 10 to 12 ESDs to allow analysis of skill improvement with time. A complete case was considered to be one in which the procedure was completely performed by the trainee without any technical assistance. The endoscopic characteristics of the lesions and clinical outcomes of ESD were analyzed by the use of the Kruskal-Wallis test for data showing nonnormality and the χ^2 test for nominal scale data. All statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX). All tests were 2-sided, and $P < .05$ was considered statistically significant by the Fisher exact probability test.

RESULTS

Endoscopic Characteristics and Clinical Outcomes

There were no significant differences in the lesion size, macroscopic type, or location between the 5 training periods (Table 1). Further, there were no significant differences in any of the clinical outcomes except for the completion rates (Table 2): the completion rates in the fourth (100%) and fifth (95.5%) training periods (≥31 cases/trainee) were significantly higher ($P < .001$) than those in the preceding periods (1–30 cases/trainee). When the numbers of complete and incomplete cases were compared according to their endoscopic characteristics (Table 3), the completion rate for the LST-NG type and recurrent lesions (16.3%) was significantly lower than that for the other macroscopic types (83.8%; $P < .001$).

TABLE 2. Clinical outcomes by treatment period and number of cases

| Outcome | Treatment period/cases per trainee | | | | | P |
	First 1–10 (n = 20)	Second 11–20 (n = 20)	Third 21–30 (n = 20)	Fourth 31–40 (n = 20)	Fifth ≥41 (n = 22)	
Procedure time (min), median (IQR)	95 (70–120)	70 (52.5–120)	67.5 (40–117.5)	70 (47.5–100)	70 (48–112.5)	.636
Perforation, n (%)	1 (5.0)	0 (0)	0 (0)	1 (5.0)	0 (0)	.658
Completion, n (%)	9 (45.0)	14 (70.0)	16 (80.0)	20 (100)	21 (95.5)	<.001
En bloc resection, n (%)	19 (95.0)	19 (95.0)	17 (85.0)	19 (95.0)	22 (100)	.151

IQR = interquartile range.

TABLE 3. Comparison of complete and incomplete cases by endoscopic characteristics

Characteristic	Complete (n = 80)	Incomplete (n = 22)	P
Size (mm), median (IQR)	28 (25–40)	30 (25–37)	.760
Location, n (%)			.192
Rectum	26 (32.5)	4 (18.2)	
Colon	54 (67.5)	18 (81.8)	
Macroscopic type, n (%)			<.001
Protruded (0-I, LST-G) or SMT	67 (83.8)	9 (40.9)	
LST-NG or recurrent	13 (16.3)	13 (59.1)	

IQR = interquartile range; LST-G = laterally spreading tumor granular type; LST-NG = laterally spreading tumor nongranular type; SMT = submucosal tumor.

TABLE 4. Histopathological findings for the lesions

Finding	No. of lesions (%)
Histopathological type	
Tubular or tubulovillous adenoma	23 (22.5)
Well-differentiated adenocarcinoma	78 (76.5)
Carcinoid tumor	1 (1.0)
Depth of invasion	
Intramucosa	84 (82.4)
Submucosa	
Shallow (<1000 μm)	10 (9.8)
Deep (≥1000 μm)	8 (7.8)
Resection type	
Curative	
R0	30 (29.4)
Rx	64 (62.7)
Noncurative	
R0	3 (2.9)
R1	4 (3.9)
Rx	1 (1.0)

R0 = all margins of the resected specimen were negative for tumor cells; R1 = tumor cells extended to the lateral or basal margins of the resected specimen; Rx = the margins could not be evaluated.

Complications

Two cases of perforations occurred during the study (in the first and fourth periods); the first one occurred because of mechanical contact when the upper part of the scope was reversed after complete resection, resulting in a tiny tear in the muscular layer. The tear and ESD defect were easily repaired by using endoclips and were managed conservatively. The second case of perforation occurred during the initial submucosal dissection after circumferential incision. However, the aperture was very small (1 mm); the patient's vital signs (blood pressure, pulse rate, and arterial oxygen concentration) were stable, and the patient did not experience abdominal symptoms. We then continued submucosal dissection up to the point at which the endoclip would not obstruct the subsequent procedure after closure by endoclip.

These 2 patients did not exhibit any clinical symptoms such as abdominal pain, fever, or late bleeding, and resumption of the patients' normal diet and discharge were delayed by only 1 day. Delayed bleeding requiring emergency colonoscopy or prolonged hospitalization did not occur in any of the patients.

Histopathological Findings

Table 4 summarizes the histopathological findings for the resected lesions. Histologically, there were 23 (22.5%) cases of tubular or tubulovillous adenoma, 70 (68.6%) cases of intramucosal or superficial submucosal adenocarcinoma, 8 (7.8%) cases of deep submucosal cancer, and one (1.0%) case of carcinoid tumor. R0 and Rx resections were achieved in 29.4% and 69.7% of the cases. Although 7.8% of the resections were noncurative, 4 of these 8 cases were histopathologically considered R0 or Rx.

DISCUSSION

Clinical outcomes of colorectal ESD have not been reported for trainees. In this study, we evaluated the clinical outcomes of colorectal ESD performed by trainees and clarified the learning curve for this procedure.

Because colorectal ESD requires a high level of skill, we defined the prerequisites for this procedure to ensure that the operator had a certain degree of skill. The nonloop insertion technique for colonoscopy is essential for ESD for colonic lesions because inadequate control during the resection increases the risk of perforation from paradoxical scope movement. In learning the ESD technique, experience with gastric lesions should be obtained before working with colorectal lesions. ESD for gastric lesions located in the antrum is relatively easy to perform because there is sufficient working space to control the endoscope and a good visual field; moreover, the gastric wall of the antrum is thicker than the colonic wall, lowering the risk of perforation. However, in Western countries, gastric cancer is less common than colorectal cancer, and it may be difficult to introduce trainees to the resection of this lesion as the first step of ESD. If required, trainees should begin clinical training for colorectal ESD with lower rectal lesions, which have a lower risk of perforation and have a setting similar to that of gastric lesions.

Given the differences between the complete and incomplete cases in our study, we believe that the macroscopic type of lesion, rather than its location, is more important in the first stage of training for ESD. The commonly held view is that endoscopic treatment is difficult for submucosal fibrosis. LST-NG type and recurrent lesions have a higher likelihood of fibrosis in the submucosal layer. In particular, the former lesion type is more likely to be affected by a prior biopsy because of its thinness, which increases its susceptibility to submucosal fibrosis because of mechanical stimulation during biopsy.[22] On the other hand, LST-G-type lesions are relatively easy to resect by ESD, because most of them show

good elevation after adequate submucosal injection. Naturally, the risk of perforation of such lesions is lower than that of other lesions such as the LST-NG type or recurrent lesions.[22]

The lesion size is also an important factor in determining the difficulty of colorectal ESD. Saito et al[23] reported that a tumor size of >50 mm increases the risk of complications. Given this result and the indications for colorectal ESD, we recommend that 30- to 40-mm LST-G-type lesions are the most suitable for the early stage of ESD training.

We consider the clinical outcomes of ESD in this study to be satisfactory, given the low incidence of complications and short procedure time. An ESD should be completed within 2 hours to reduce the burden on the patient, because this procedure is commonly performed under conscious sedation. In this study, most procedures were completed within 2 hours without serious complications, and the clinical outcomes were acceptable. There was no correlation between procedure time and experience with the ESD procedure. If trainees began by operating on only rectal lesions of a certain size, the procedure time might decrease with an increase in the number of ESD procedures. However, the lesion size, location, and configuration had nearly the same distributions between the training periods. Nearly all the lesions with similar clinical characteristics were treated within a certain time frame without serious incident. This result is sufficient to evaluate the learning curve for colorectal ESD at our institution.

Based on the results for completion rates, we believe that trainees require experience with >30 cases to perform colorectal ESD without guidance from an experienced specialist. The completion rates in the first to third training periods may seem insufficient; however, most trainees subsequently acquire troubleshooting skills such as endoscopic closure of perforations by using endoclips and understanding their technical limitations.

The R0 resection rate was lower than that previously reported.[22] This clinical outcome mainly depends on the circumferential incision during the ESD procedure; we place the circumferential incisions very close to the lesion margin at our institution. Colorectal neoplasms commonly develop via the adenoma–carcinoma sequence, and most lesions arise from the epithelium without chronic inflammation, as in ulcerative colitis. Thus, in contrast to early gastric cancer, the margins of colorectal cancer can be recognized clearly after indigo carmine dye spraying, and marking during the endoscopic procedure is not required. Moreover, Saito et al[13] reported that the local recurrence rate after ESD is only 2.1% in piecemeal resection cases. Therefore, we believe that Rx is not a determinant of curability. In fact, of the 72 patients in this study who underwent 1-year follow-up colonoscopy after curative en bloc resection, none showed recurrence or residual tumor. Of the 6 patients with fractional resection who underwent follow-up colonoscopy, one showed a local residual tumor. However, it was a small intramucosal neoplasm; additional endoscopic coagulation treatment resulted in complete remission.

The main limitation of our study is its single-center design. Recently, new instruments for ESD have been developed and applied, and their availability depends on the institution. For the ESDs in this study, the trainees mainly used B-B and IT knives. The former instrument is particularly safe because of its bipolar system. A B-B knife is designed to reduce the high-frequency current sent to the muscular layer, enabling better control and greater safety for the endoscopist; the returning current toward the sheath tip ensures greater patient safety. Furthermore, the small tip at the end of the needle enables hooking of the mucosal or submucosal tissue, similar to that achieved with an IT knife. In addition, the colorectal ESD procedure is not yet covered by insurance and can be performed at only a few institutions that fulfill certain conditions. Such institutions are high-volume centers, and trainees may gain more experience in a shorter time than at other institutions. This intensive experience may also affect the overall learning curve. Another limitation is the variation in training systems for colorectal ESD among institutions; further evaluation of these differences is warranted.

CONCLUSION

Colorectal ESD can be performed without serious complications by trainee endoscopists under the guidance of experienced specialists. Trainees in colorectal ESD can perform this procedure safely and independently after a certain degree of preparatory training and experience with >30 cases.

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Endoscopic management of colonoscopic perforations (with videos)

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INTRODUCTION

Colonoscopic perforation is a potentially life-threatening complication. Visual recognition of perforation or sites that are high risk to perforate at the time of the colonoscopy and its immediate closure offer the best potential for preventing any sequelae and for reducing its morbidity and mortality. Significant progress in endoscopic closure has been made since its first report by Yoshikane et al[1] over a decade ago. Herein, we summarize the literature on the prevalence, mechanisms, and diagnosis of perforations; review the results of experimental and clinical studies; and offer practical tips on the endoscopic closure of colonoscopic perforations (Fig. 1).

INCIDENCE

The incidence rates of colonoscopic perforations range from 0.07% to 0.1% in diagnostic and therapeutic colonoscopies, respectively (Table 1).[2-10] Most perforations occur in the rectosigmoid colon (53%), followed by the cecum (24%), the ascending and transverse colon (9% each), and the descending colon (5%).[9]

Risk factors for colonoscopic perforations include older age, female sex, increased comorbidity, diverticulosis, bowel obstruction, and biopsy or polypectomy.[7,8,10] The risk of colonoscopic perforation is lower for gastroenterologists as compared with surgeons and family physicians and further reduced for gastroenterologists with high procedure volumes.[10-12]

MECHANISMS

Colonoscopic perforation can result from a number of mechanisms including blunt trauma from the endoscope, unintended resection or dissection of the muscularis propria and serosa, and coagulation necrosis of the muscu-
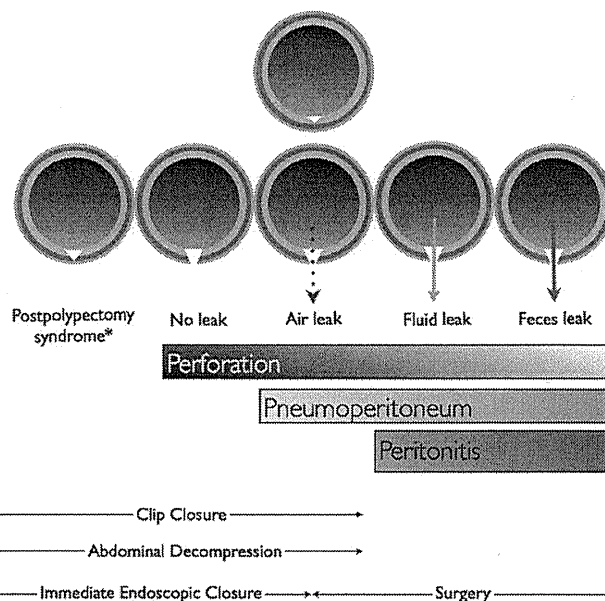
Figure 1. Perforation after colonoscopic resection can begin as postpolypectomy syndrome (serositis from transmural burn) that could evolve into a perforation or as a free perforation with air and fluid leakage, resulting in pneumoperitoneum and peritonitis. Immediate endoscopic closure could be useful before peritonitis develops. Prevention of postpolypectomy syndrome and its potential sequalae is most important.

laris propria (Fig. 1) and serosa. Characteristics of perforations include:

(1) Blunt trauma (direct trauma, torque from the colonoscope, or retroflexion injury) accounts for the majority of colonoscopic perforations. Most are large (mean diameter 2 cm) and are located in the rectosigmoid colon.

(2) Unintended endoscopic resection or dissection (electrocoagulation biopsy, snare resection, EMR, or endoscopic submucosal dissection [ESD]) are the second most common reported cause of perforations. Most are small (mean diameter 1.4 cm) and are located in the cecum and right side of the colon.

- Electrocoagulation biopsy: The degree and duration of electrocautery used determine the risk of colon perforation.[13]
- Snare polypectomy: In a prospective study of 3976 snare polypectomies among 2257 patients from 13 German institutions, perforations occurred in 26 patients (1.2%). Polyps larger than 1 cm in the right side of the

TABLE 1. Summary of perforation rate in studies reporting over 10,000 colonoscopies

Study	Study period, (no. of colonoscopies)	Origin	Perforation rate (mortality)
1	1989-1999 (n= 23,508)	Australia[2] (Teaching hospitals)	1/1000 (0.04/1000)
2	1987-1996 (n= 10,486)	United States[3] (Mayo Clinic, Scottsdale)	0.019/1000 (0.0019/1000)
3	2002-2004 (n= 12,407)	United States[4] (Community GI group practice)	0.002/1000 (no deaths)
4	2000-2004 (n= 50,138)	Poland[5] (40 centers)	0.1/1000 (no deaths)
5	1991-1998 (n= 39,286)	United States[6] (Medicare beneficiaries ≥65 y)	2/1000
6	1994-2002 (n= 16,318)	United States[7] (Kaiser Permanente ≥40 y)	0.9/1000 (0.06/1000)
7	2002-2003 (n= 97,091)	Canada[8] (British Columbia, Alberta, Ontario, and Nova Scotia)	0.85/1000 (0.074/1000)
8	1980-2006 (n=258,248)	United States[9] (Mayo Clinic, Rochester)	0.7/1000
9	2004-2006 (n= 24,509)	Canada[10] (Winnipeg hospitals)	1.0/1000, colonoscopy alone 0.8/1000, sigmoidoscopy alone 0.5/1000, colonoscopy + biopsy 1.8/1000, colonoscopy + polypectomy 59.8/1000, colonoscopy + dilation (0.04/1000)

colon or 2 cm in the left side of the colon and multiple polyps carry an increased complication risk.[14]

- EMR: The risk of perforation after EMR is about 1 in 500 from pooled analysis of 17 reports.[15-31] The low perforation rate (0.7%) may be related to submucosal injection before snaring and electrocautery and routine use of clips to approximate the mucosal defect.[32]
- ESD: The risk of perforation after ESD can be as high as 1 in 20 (5%), although most were small and successfully treated by clips.[33-40] Thus, perforation during ESD rarely requires surgical closure. Inaccurate identification of the cutting line and underestimation of the depth of the submucosal layer may result in perforation. Endoscopist's experience of less than 50 ESDs, tumors larger than 5 cm, and underlying submucosal fibrosis (recurrent tumors and lateral spreading tumors of the nongranular type with converging folds) increase the risk of perforation.[41,42] Tumor location and morphology and the type of resection knives have no effect on the risk of ESD perforation.[40]

(3) Thermal injury (argon beam coagulation or electrocautery to ablate tissue or control bleeding) accounts for 18% of cases. Most of these perforations are small (0.9 cm) and are located in the cecum.

DIAGNOSIS

Recognition of perforation at the time of colonoscopy or high-risk sites for delayed perforation is important to prevent the dreadful complication of colonoscopy. About a third of perforations are diagnosed during the procedure and the remaining within 1 to 2 days after the procedure; a few cases present as late as 14 days.[2-4,10,14,43] Thus, the

14-day reporting period is important to capture all colonoscopic perforations.[43]

Diagnosis of perforation at the time of colonoscopy

Examination of the resection site is essential to ensure that perforation has not occurred. Routine injection of diluted indigo carmine into the submucosa can be helpful in determining the plane of resection—a blue resection base indicates intact submucosa; a white resection base indicates deeper resection into the muscularis propria. This has been described as a "target sign"—white center (muscularis propria), with surrounding blue area (indigo carmine stained submucosa).[44,45] A more subtle perforation may be recognized as shiny serosa seen through the defect (Fig. 2). Perforation also may appear as a rent in the muscularis propria during ESD or as an obvious tear in the sigmoid colon or rectum after blunt trauma.[40,46-51]

Another important physical sign is the development of tension pneumoperitoneum.[52] Thus, periodic assessment of the anterior abdominal wall tone is important.

Diagnosis of perforation after completion of the procedure

Perforation should be considered and appropriate workup performed when a patient complains of abdominal pain. A CT scan of the abdomen and pelvis are most sensitive in the detection of retroperitoneal air, even in the absence of free air under the diaphragm on plain abdominal radiographs.[53]
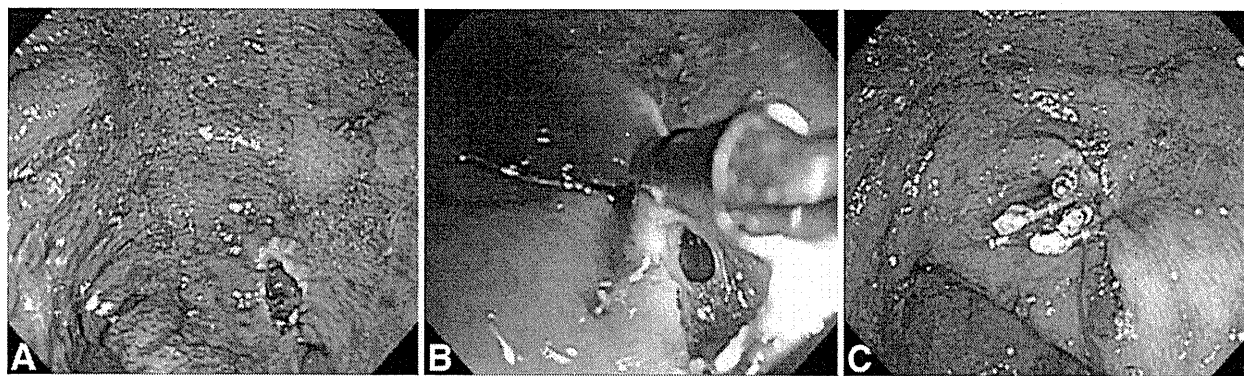
Figure 2. Colonoscopic clip closure of a small, linear perforation. **A,** A small, linear perforation is recognized after en bloc EMR of a cecal adenoma in a patient with ulcerative colitis being treated with steroids. **B,** The first clip is deployed, partially closing the tear. **C,** Completed closure is achieved with deployment of 4 clips. (Reproduced with permission from the ASGE)

MANAGEMENT

Until recently, surgery was the mainstay of treatment in the majority of patients, with nonoperative medical management in a select group (Fig. 1). Surgery is indicated in patients with large perforations, generalized peritonitis, or ongoing sepsis as well as in patients with concomitant pathology, such as a large sessile polyp, which is likely to be a carcinoma, unremitting colitis, or perforation complicating an obstructing colonic lesion. Other candidates for surgery include those whose conditions deteriorate with conservative management.[54] Surgery is associated with a significant morbidity (36%) and mortality (7%).[9] Conservative management may be undertaken in patients with asymptomatic perforations, those with localized peritonitis who improve clinically, and those with postpolypectomy coagulation syndrome.[53,55-57]

Endoscopic clips can be successful in the closure of colonoscopic perforations recognized during the colonoscopy. These clinical observations have been supported by a series of animal studies. Endoscopic closure is effective in creating a leak-proof seal of the perforation, healing of the perforation, preventing peritonitis, limiting peritoneal adhesions, and avoiding surgery.[47,58-70]

PREVENTION OF COLONOSCOPIC PERFORATION

Prevention is the most important factor in the management of colonic perforation. A number of precautions could be undertaken to avoid a perforation and complications arising from such an event.

Colon preparation

Poor bowel preparation. Defer colonoscopy in patients with poor bowel preparation to avoid the risk of fecal peritonitis.[9] In addition, deferring colonoscopy in these patients avoids the risk of colonic explosion from cautery-induced ignition of combustible gases.[71] A split-dose preparation of 4 L of polyethylene glycol solution or having the patient drink 2 to 3 liters of polyethylene glycol solution the morning of the procedure results in excellent preparation. Checking the color of the stools before each procedure and administering additional polyethylene glycol solution when necessary assures excellent preparation.[72,73]

Dry field. Suctioning of all the fluid and drying the operating field segment, along with upstream and downstream segments, prevent escape of luminal contents through a perforation. Moving the patient to the nondependent position so that the target lesion can be located may prevent fluid escape and peritonitis with perforation. Conscious sedation allows patient repositioning during the procedures.

Colonoscopy technique

A detailed review of the patient's demographics, comorbidities, and prior surgical procedures facilitates the risk assessment for colonoscopic perforation and selection of appropriate closure techniques, technologies, and precautions to prevent it (Fig. 3).

Fixed colon. Avoid excessive pushing of the colonoscope. Use of a smaller-caliber colonoscope along with careful tip deflection to negotiate the acute angles of a fixed colon in patients with adhesions from prior pelvic and abdominal surgeries is advised. Change of the patient's position, use of balloon-assisted endoscopy, use of a water immersion technique, or use of carbon dioxide insufflation also may be helpful.[74-79]

Redundant colon. Use of an enteroscope along with the application of abdominal compression at appropriate places, techniques to stiffen the endoscope further (deploying variable stiffness function, insertion of a biopsy forceps through the biopsy port, use of overtubes that lock and stiffen on demand), or holding the loops down (balloon-assisted endoscopy) may be effective.[80,81]

Prolonged procedures and failed procedures. Use of carbon dioxide, periodically venting the air out (by releasing the biopsy port cap), or intermittent suctioning may release the luminal pressure.
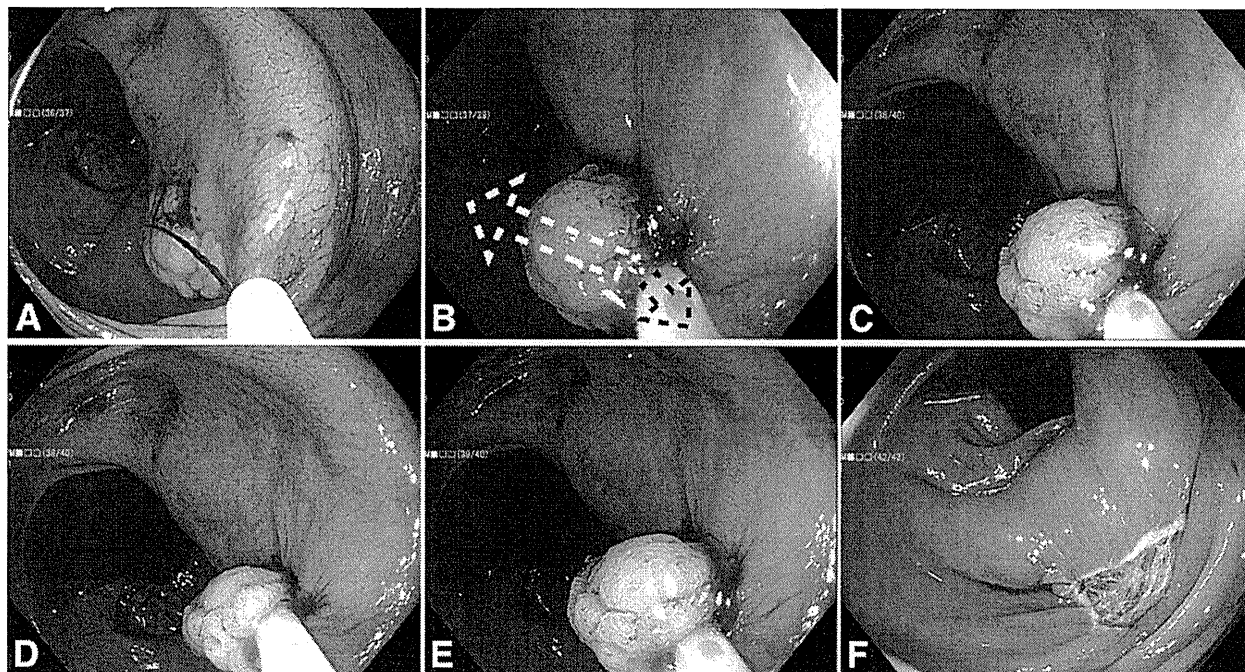
Figure 3. Prevention of perforation during EMR. **A,** A flat lesion after a submucosal injection of saline solution with a few drops of indigo carmine being captured with a stiff snare. **B,** After the snare was closed, the tip of the endoscope was moved to the left and upward (*white arrow*) while the snare was slightly pulled back (*black arrow*). **C,** The lesion after being tented away from its underlying muscularis propria. **D,** The endoscopist then asked the assistant to loosen the snare slightly, without loosening the lesion. **E,** The snare was closed snugly again. **F,** The lesion was resected.[92]

Small rectum. Avoid retroflexion in patients with small rectums.[82] Examine the rectal vault before endoscope withdrawal from the colon, because retroflexion-induced perforations could be identified and closed immediately with clips.[48,49,83-86]

Procedure note. Details of procedure duration, technical difficulties, and measures undertaken to overcome them should be noted to plan future endoscopies.

Management of lesions

Referral versus resection. It is important to decide whether it is better to refer to endoscopists with expertise in the endoscopic resection or undertake the resection if it could be done safely.[87,88]

Referral without biopsy. If a decision is made to refer, defer biopsies, because they cause submucosal fibrosis, which prevents subsequent adequate lifting and the ability to successfully resect the lesion. Avoid tattoo injection into the lesion because this leads to fibrosis in the submucosa.[89] Instead, inject it a fold away from the lesion.

Resection of diminutive polyps. Cold snare resection of diminutive polyps is safer than hot biopsy.[90,91]

Resection of pedunculated polyps. Apply a snare on the stalk of a pedunculated polyp away from the wall, and tent it up before cautery to limit transmural burn and perforation.

Resection of sessile and flat lesions. Ample injection of submucosal fluid to separate the lesion from the

muscularis propria is critical to prevent thermal injury to the muscle.[32] The dynamic submucosal injection technique creates a large, submucosal cushion.[92] Piecemeal resection of large polyps (>2 cm) may limit deeper injury to the muscle compared with large, en bloc resections. Specific routine steps to prevent perforation during EMR have been described (Fig. 3).[93]

ESD of large, flat lesions. Accurate identification of the cutting plane is critical to avoiding perforation during ESD. Starting the submucosal dissection close to the mucosal layer and after the submucosal layer has been expanded and well-visualized allows dissection to be performed at the lower third or just above the muscle layer to avoid a perforation. When fibrosis is encountered, the short-type, small-caliber-tip, transparent hood is useful for exposing the muscularis propria.

ENDOSCOPIC MANAGEMENT OF COLONOSCOPIC PERFORATION

Endoscopic closure of colonic perforation has been successful, provided that the perforation is immediately recognized and closed without delay. This could be accomplished with a variety of devices. Through-the-scope clips have been used extensively over the last decade for endoscopic closure of colon perforations.[37,40,45,46,49,63,66-68,70,94-100] Recently, over-the-scope clips have been introduced in Europe and in the United
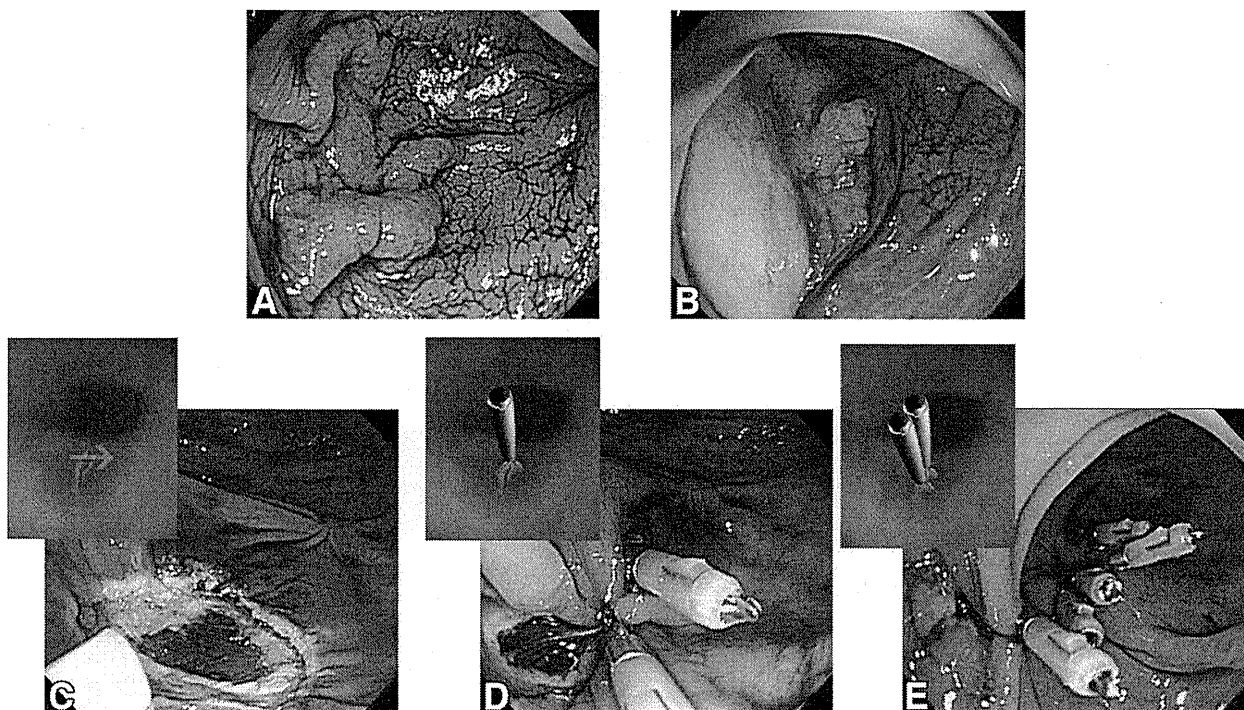
Figure 4. Colonoscopic clip closure of a perforation after EMR. A, B, C, EMR of a 2-cm, flat lesion with high-grade dysplasia resulted in a large linear perforation. C, D, E, This perforation was closed with clips starting at the top of the perforation and working downward. (Reproduced with permission from the ASGE)

States.[65,69,97,101-105] Suturing devices such as T-tags have been extensively investigated in animal models, especially in the closure of large, gaping perforations with everted edges that are not amenable to clip closure and closure of large defects after full-thickness resection of the colon, but these devices are not available in the market.[62,64,106,107] Both through-the-scope clips and over-the-scope clips produce results comparable to hand-sewn colostomy closure in terminal animal studies.[107,108] Through-the-scope clips can be deployed anywhere in the colon; hence they are ideal for immediate closure of perforations without leaving the site of perforation, thereby avoiding leakage of colon contents. Clips are useful in the closure of small (1 cm) non-gaping perforations.[40,58-61,72] However, through-the-scope clips have been reported to be unsuccessful in the closure of large, gaping perforations with everted edges and defects after full-thickness resection, which might be closed with through-the-scope suturing devices such as T-tags.[62,107,109]

Emergency decompression of accumulated air in the peritoneum with a wide-bore needle is important to reduce respiratory compromise, to prevent circulatory decompensation, and to prevent air embolism in the portal venous system. Practical tips of the endoscopic management of colonic perforations are available through the American Society for Gastrointestinal Endoscopy Learning Center and as follows:

Through-the-scope clips

Clips can be used to close perforations immediately after their recognition during the colonoscopy. Both the endoscopist and assistant must be well-versed with the use of clips before undertaking endoscopic closure of perforations. Depending on the size and shape of the perforation, the following techniques can be used for closure of colonoscopic perforations and management of pneumoperitoneum (Figs. 3-6) (Videos 1-4, available online at www.giejournal.org. Reproduced with permission from the ASGE.).

Closure of a large perforation

Keeping the clip close to the end of the endoscope, with the hinge of the clip blades just outside the endoscope, allows the clip–endoscope to be maneuvered as a single unit. Open the clip and rotate the blades to align them at right angles to the defect. After engaging the lower blade to the lower edge of a transverse perforation, gently push the clip–endoscope unit while applying gentle suction to collapse the lumen so that as much tissue as possible from the opposite edge of the perforation can be grasped while the clip is slowly closed. For longitudinal perforations, apply the clip just above the upper end of a longitudinal perforation to pucker the edges below for easier application of subsequent clips, one below the other. Place additional clips from the top, down, in longitudinal perforations or left-to-right in circular perforations
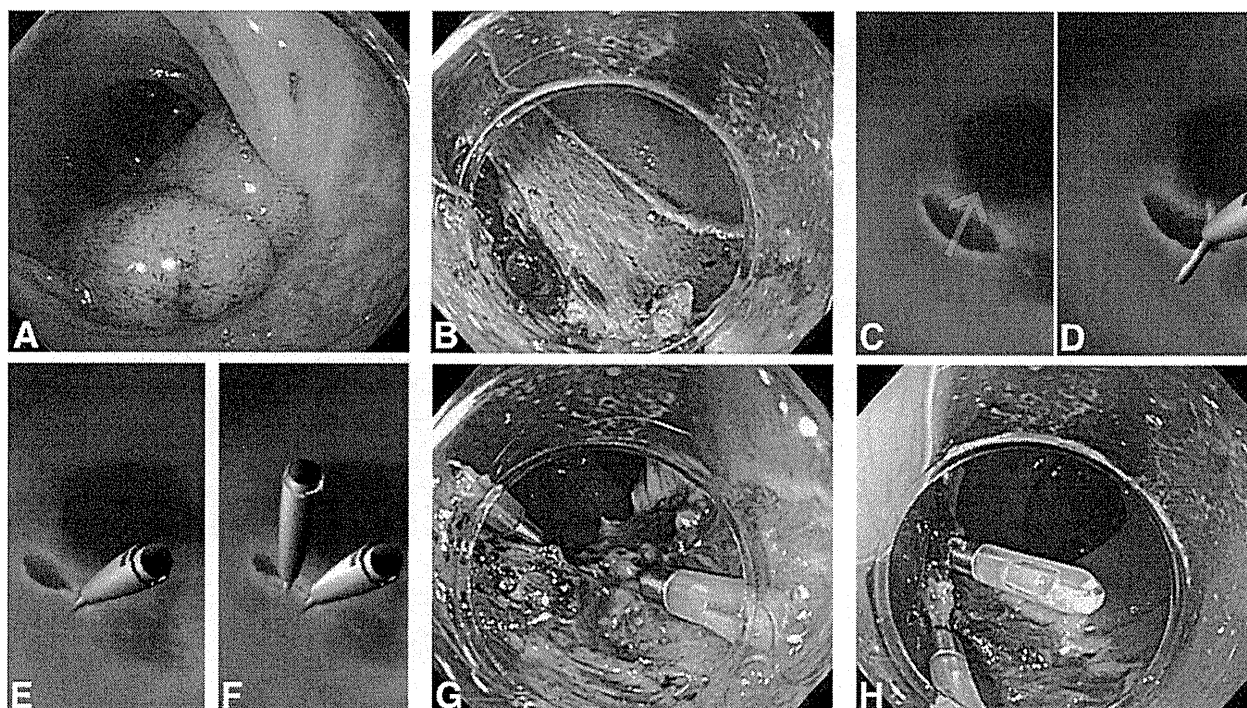
Figure 5. Colonoscopic clip closure of a perforation after endoscopic submucosal dissection (ESD). **A, B,** An unintended cut was made too deeply into the muscularis propria, resulting in a small linear perforation during ESD of a sessile lesion. **C-H,** The perforation as seen through a small-caliber tip transparent hood (ST hood). The perforation has been successfully closed by using 2 clips by approximating the lower edge to the upper edge of the perforation. (Reproduced with permission from the ASGE)
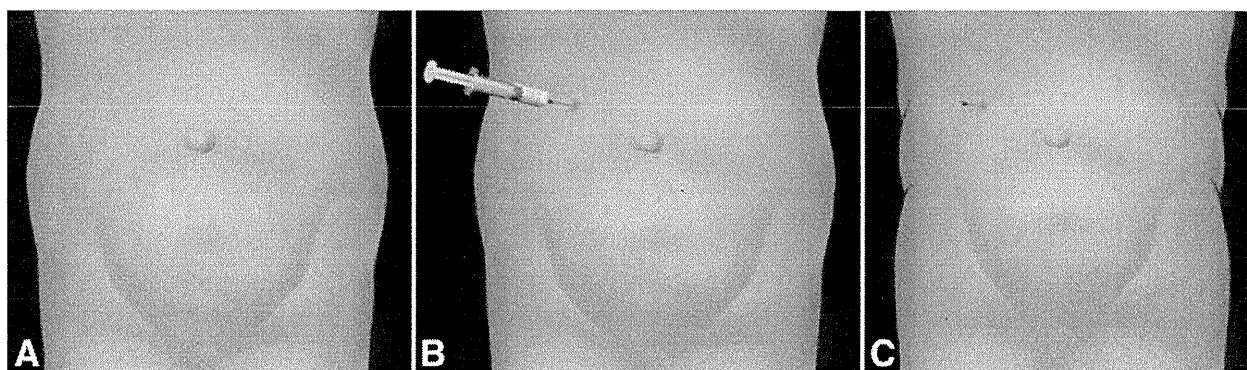

Figure 6. Needle decompression of tension pneumoperitoneum. (Reproduced with permission from the ASGE)

after satisfactory application of the first clip, which is the most critical component of closure. It is important to confirm satisfactory approximation of the edges before deployment of the clip. Perforations that are difficult to close with clips can potentially be closed with a loop-snare.[51]

Closure of small perforations during ESD

Instead of immediate closure of the perforation, it is important to continue ESD in order to make enough space to apply endoscopic clips. If endoscopic clips are hastily applied immediately after the recognition of the perforation, the clips may interfere with further ESD. After successful clip closure of the perforation, ESD can

be continued at the earliest opportunity and the lesion removed during the same session. Finally, the resection bed after en bloc resection should be checked carefully, and additional clips should be applied accordingly.

What should be avoided during clipping

Panic. Be calm and steady once you recognize a perforation. Be patient while applying a clip because a clip misplaced to one edge of the perforation could lead to difficulty in applying additional clips for satisfactory closure.

Long shots. Keep the endoscope close to the site of perforation and avoid deploying clips from a distance

away, because long shots will interfere with precise delivery of the clips.

Stretching of the colon. Too much pushing of the clip against the wall limits grasping of the tissue and approximation of the edges of the perforation. Once the blades of the clip are placed across the perforation, gentle suction, instead of pushing the clip, allows the tissue to come into the blades to allow better closure. Avoid air insufflation, because it can worsen pneumoperitoneum.

Over-the-scope clips

Recently, the over-the-scope clip was introduced into the market, and preliminary reports are encouraging. Conceptually, the technique is similar to using a band ligation device, which has been reported as successful.[110] For this procedure, suction the perforation margins with or without the aid of a device to pull the edges into the cap, then deploy the clip, which creates a leak-proof seal.[97,111]

Management after endoscopic closure

A team approach involving surgeons in the management of the patients immediately after endoscopic closure of perforations is critical. The patient should have nothing by mouth and begin therapy with broad-spectrum intravenous antibiotics and hydration. Closely monitor all patients for signs of peritoneal irritation. Resume oral intake as soon as pain and fever resolve, appetite and bowel function return, and laboratory test signs of inflammation such as leukocytosis and elevated C-reactive peptide levels return to normal. If there is any deterioration, surgery should be undertaken.

SUMMARY

Colonoscopic perforation is a serious complication of colonoscopy. Its prevention is the best treatment strategy, although when it occurs and is immediately recognized, endoscopic clip closure can be very useful to manage select cases. It is emphasized that endoscopists need to have the necessary knowledge, ability, equipment, and team required to close the perforations safely.

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ELSEVIER

Macroscopic estimation of submucosal invasion in the colon

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Pit pattern;
Narrow-band imaging

Colorectal cancer is the third most prevalent cause of cancer-related mortality in Japan, and the incidence of submucosal colorectal cancer is increasing. To reduce colorectal cancer mortality, however, early detection of colorectal cancer is required and adequate diagnosis of depth is needed. Current endoscopes provide high-resolution imaging that result in clear, vivid features of the detected lesions. In particular, when combined with image enhancement, high-magnification endoscopy can provide a detailed analysis of the morphologic architecture of the pit pattern and the capillary pattern in a simple and quick manner. Characteristic colonoscopic findings obtained by a combination of conventional colonoscopy, magnifying chromoendoscopy, and narrow-band imaging are useful for determining the depth of invasion of early-stage colorectal cancers, an essential factor in selecting a treatment modality.
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Introduction

Colorectal cancer is the third most prevalent cause of cancer-related mortality in Japan, and the incidence of early invasive colorectal cancer (ie, submucosal cancer) is increasing. In the National Cancer Center patient population from 1962 to 1990, cancers confined to the submucosa accounted for 6.9% (162/2337) of all invasive cancers treated surgically. Between 1991 and 2009 the incidence of submucosal cancers increased to 17.5% (974/5572). The most likely reasons for this increased incidence include a greater recognition of early-stage lesions by Japanese endoscopists and the 1992 introduction of immunochemical fecal occult blood testing in Japan.

To reduce colorectal cancer mortality, not only is early detection of colorectal cancer required, but also adequate decision making (ie, depth diagnosis) is needed. Small colorectal neoplasms are believed to have a lower malignant potential than large ones, and several authors have reported that the malignant potential of early colorectal cancer increases with size.[1-3] However, evaluation for submucosal invasion requires more than just the measurement of the lesion size. Although this finding may be true for adenomatous lesions, the data for submucosal invasive cancers are conflicting.

Current endoscopes provide high-resolution imaging that results in clear, vivid, and detailed features of the detected lesions. In particular, when combined with image enhancement, high-magnification endoscopy can provide a detailed analysis of the morphologic architecture of mucosal crypt orifices (ie, pit pattern) and the microvascular architecture (capillary pattern, CP) in a simple and quick manner.[4-6] As such, magnifying chromoendoscopy and NBI with magni-

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fication have been shown to be effective for differentiating between colorectal neoplastic and nonneoplastic lesions and for determination of the depth invasion of colorectal cancers.[7-11] We highlight methods to assess the depth of invasion of early-stage colorectal cancers based on a review of the literature and endoscopic images.

Importance of estimating depth of submucosal invasion

Endoscopic mucosal resection is indicated to treat intramucosal colorectal cancers because the risk of lymph node metastasis is nil.[12,13] In contrast, surgery is indicated to treat submucosal invasive cancers because of the 6% to 12% risk of lymph node metastasis.[14-17]

Between 1998 and 2004, a total of 378 submucosal cancers (except pedunculated type lesions) were treated surgically at the National Cancer Center Hospital. We retrospectively analyzed clinicopathological features, incidence of lymph node metastasis, and risk factors for lymph node metastasis, such as depth of submucosal invasion ($\geq$1000 μm or <1000 μm), lymphovascular invasion, poorly differentiated adenocarcinoma, tumor size, and growth pattern (polypoid growth type/nonpolypoid growth type)[18] in all cases (Table 1).

The overall incidence of lymph node metastasis was 11.9% (45/378) and univariate analysis identified a strong relationship between lymph node metastasis and the following 3 factors: depth of submucosal invasion, lymphovascular invasion, and poorly differentiated adenocarcinoma. Therefore, the findings of deep submucosal invasion ($\geq$1000 μm) and/or lymphovascular invasion and/or poorly differentiated adenocarcinoma in an endoscopic mucosal resection specimen indicate the need to consider additional surgery with lymph node dissection.[19] Although 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.

Estimation of submucosal invasion using conventional and magnifying colonoscopy

Conventional colonoscopy (including chromoendoscopy)

How to differentiate between mucosal/submucosal superficial and submucosal deep cancers?

New diagnostic modalities such as endoscopic ultrasonography using miniprobe and magnifying chromoendoscopy are reported to be useful for the depth diagnosis of early-stage colorectal cancers. However, these modalities are relatively expensive and time consuming. If invasion depth could be diagnosed using 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 determining the invasion depth of depressed type colorectal cancers.[20] In this report, characteristic colonoscopic findings (ie, expansion appearance, deep depression surface, irregular bottom of depression surface, and 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%). In our own large study involving 379 lesions (179 intramucosal cancers and 200 submucosal cancers), we analyzed the endoscopic features of submucosal deep invasion using a high-definition colonoscope.[21] Lesions were divided into 3 macroscopic subtypes (pedunculated type, sessile type, and superficial type) based on endoscopic findings. Eight endoscopic factors (tumor size, loss of lobulation, excavation, demarcated depressed area, stalk swelling, fullness, fold convergence, and pit pattern) were evaluated retrospectively for association with submucosal invasion and then compared with histopathologic results. In this report, the superficial type had a significantly higher frequency of submucosal deep invasion [52.4% (77/147) vs 24.6% (14/57) and 39.4% (69/175), P value < 0.05, respectively, for pedunculated and sessile types]. Moreover, "fullness: a bursting appearance due to expansive growth of the

| Table 1 | Risk factors for lymph node metastasis in patients with submucosal cancer |

| Variable	Lymph node metastasis		Univariate analysis (P value)	Multivariate analysis		
	(−)	(+)		P value	Odds ratio	95% Confidence interval
Submucosal invasion ($\geq$1000 μm/<1000 μm)	286/47	44/1	0.03	0.35	2.8	0.3-23.4
Lymphovascular invasion (ly/v) (+/−)	87/246	33/12	<0.0001	<0.0001	6.8	3.3-13.9
Poorly differentiated adenocarcinoma (por) (+/−)	45/288	13/32	<0.01	0.09	1.9	0.9-4.2
Tumor size ($\geq$20 mm/<20 mm)	163/170	20/25	NS	—	—	—
Growth pattern (polypoid growth/nonpolypoid growth)	173/160	28/17	NS	—	—	—

NS = nonsignificant.
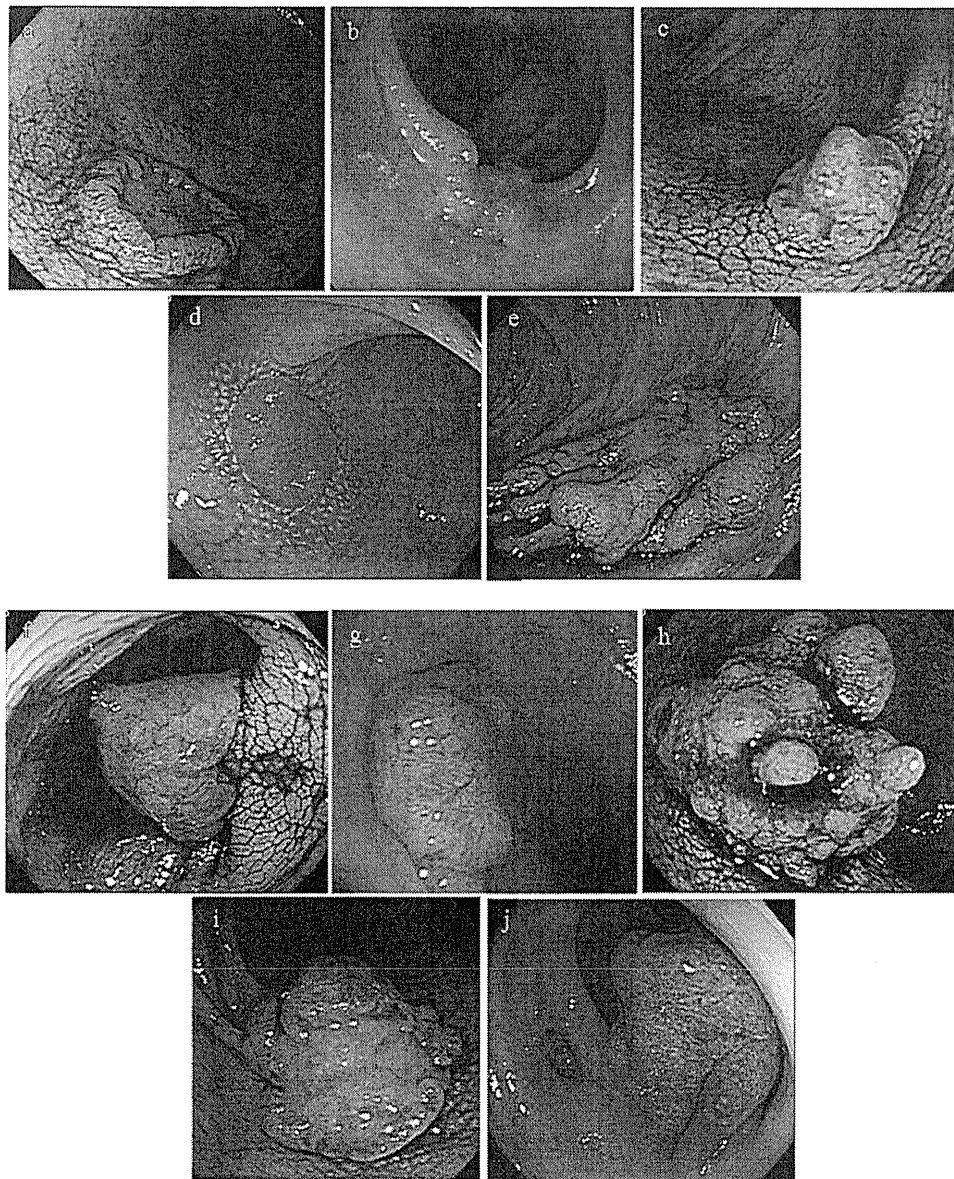
Figure 1   Typical findings of submucosal invasive cancer. (a) Deep depression, (b) fold convergency, (c) irregular bottom of depression surface, (d) white spots (chicken skin appearance), (e) redness, (f) expansion, (g) firm consistency, (h) irregular surface, (i) loss of lobulation, and (j) thick stalk. (Color figure is available online at www.techgiendoscopy.com.)

tumor" was considered an independent risk factor for submucosal deep invasion in the superficial type (odds ratio = 9.25). There were no independent risk factors for submucosal deep invasion in the pedunculated type.

Typical findings of submucosal invasive cancer

To clarify the clinically important characteristic colonoscopic findings, the authors reviewed all conventional colonoscopic images of submucosal invasive colorectal cancers treated endoscopically or surgically. In this current retrospective review, the following 10 characteristic colonoscopic findings were recognized as indicating an increased risk of submucosal invasion: deep depression, fold convergence, irregular bottom of depression surface, white spots (chicken skin appearance), redness, expansion, firm consis-

tency, irregular surface, loss of lobulation, and thick stalk (Figure 1).

Deep depression (Figure 2). The definition of this finding is "deep depression with demarcated area." Chromoendoscopy (using indigo carmine) is helpful in recognizing this finding. Nonpolypoid growth type IIa + IIc lesions are usually submucosal or deeper cancers. The size of these lesions is relatively small compared with polypoid growth type submucosal cancers.

Fold convergence (Figure 3). The definition of this finding is the "existence of 3 or more folds convergence toward the tumor." Sometimes a laterally spreading tumor, nongranular
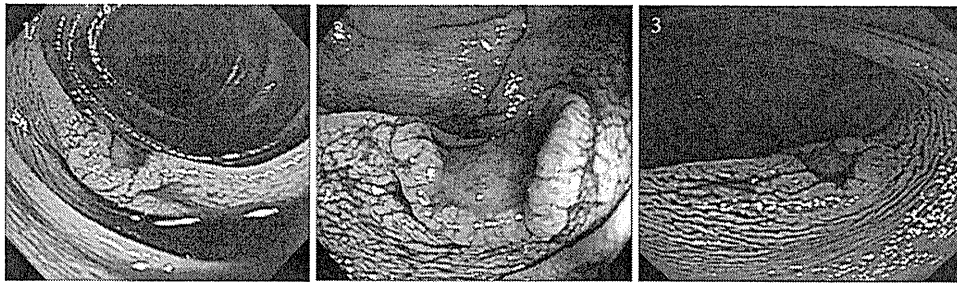
Figure 2   Deep depression. (1 and 2) IIc, SM deep cancer; and (3) IIc, SM superficial cancer. (Color figure is available online at www.techgiendoscopy.com.)
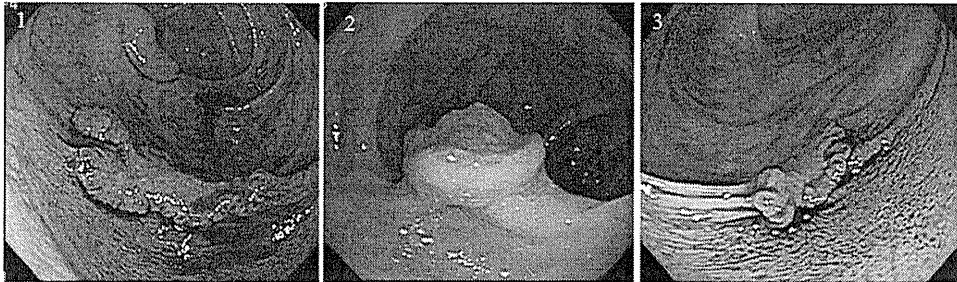

Figure 3   Fold convergence. (1) IIa + IIc (LST-NG), SM deep cancer; (2) Is + IIc, SM deep cancer; and (3) IIa + IIc (LST-NG), SM superficial cancer. (Color figure is available online at www.techgiendoscopy.com.)
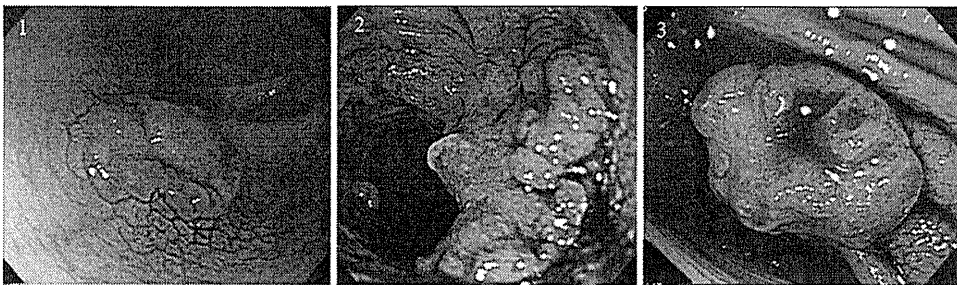

Figure 4   Irregular bottom of depression surface. (1) Is + IIc, SM deep cancer; (2) IIa + IIc, SM deep cancer; and (3) Is + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)
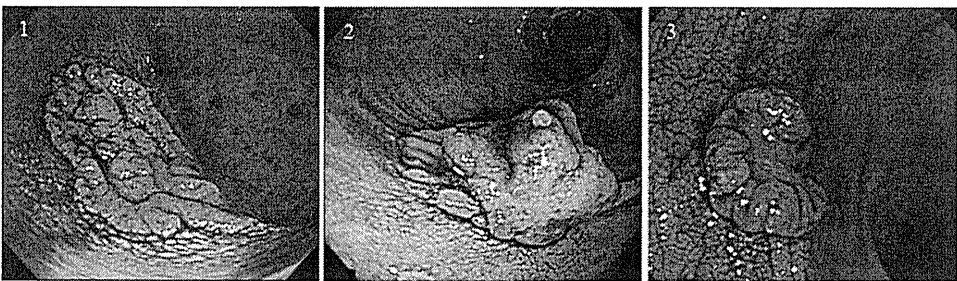

Figure 5   White spots (chicken skin appearance). (1) IIa + IIc (LST-NG), SM deep cancer; (2) Is, SM deep cancer; and (3) IIa + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)