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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 muscularis 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

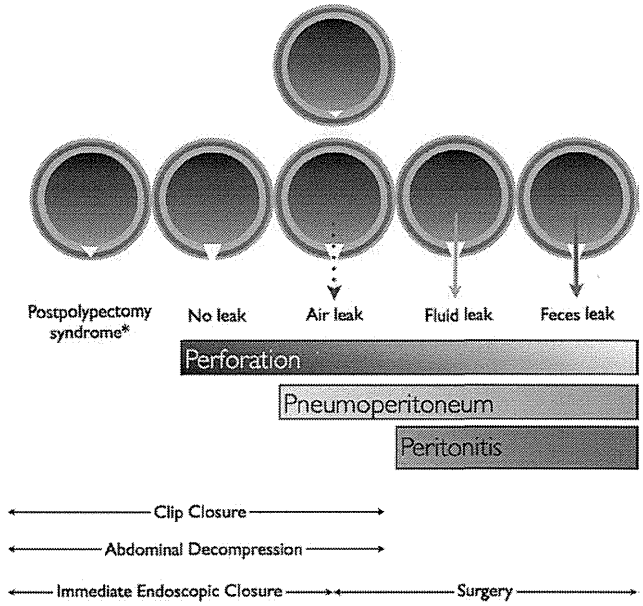


**Figure 1.** Perforation after colonoscopic resection can begin as postpolypectomy syndrome (serositis from transmural burn) that could evolve into a perforation or as a free perforation with air and fluid leakage, resulting in pneumoperitoneum and peritonitis. Immediate endoscopic closure could be useful before peritonitis develops. Prevention of postpolypectomy syndrome and its potential sequalae is most important.

*Abbreviations:: ESD, endoscopic submucosal dissection.*

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*


0016-5107/$36.00
doi:10.1016/j.gie.2011.08.007

**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]

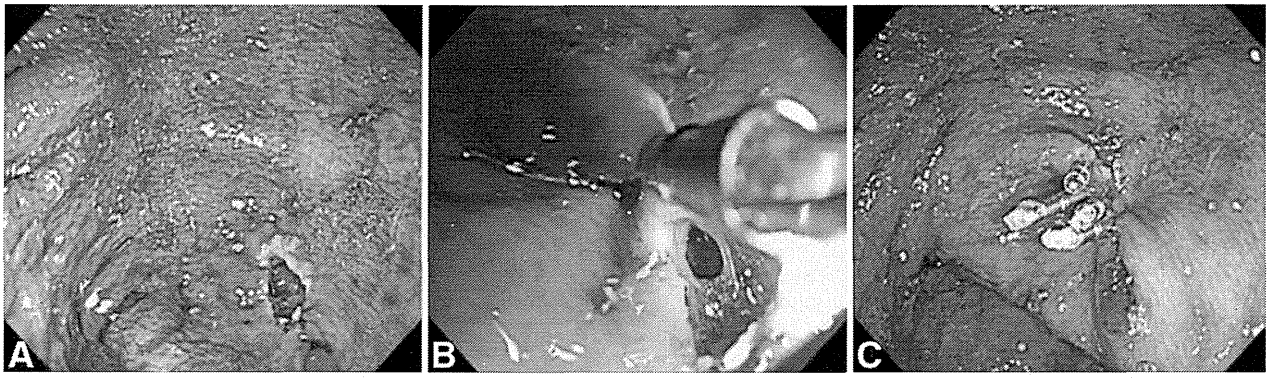


**Figure 2.** Colonoscopic clip closure of a small, linear perforation. **A,** A small, linear perforation is recognized after en bloc EMR of a cecal adenoma in a patient with ulcerative colitis being treated with steroids. **B,** The first clip is deployed, partially closing the tear. **C,** Completed 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.

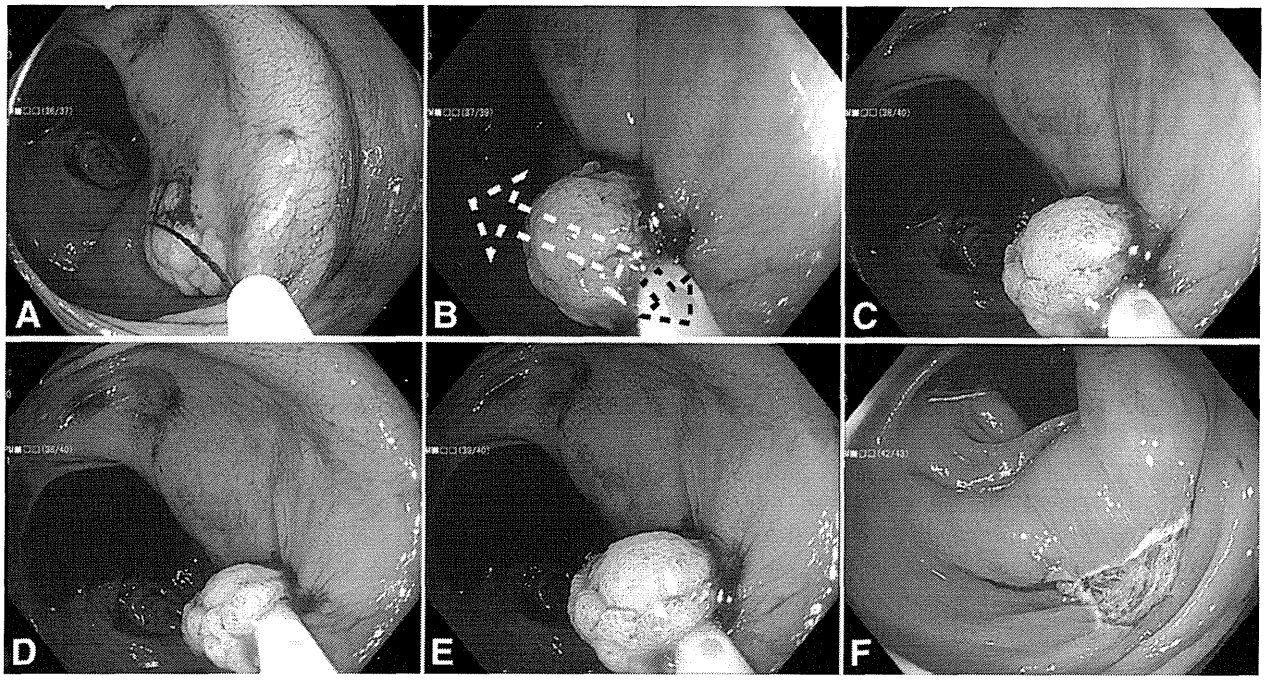


**Figure 3.** Prevention of perforation during EMR. **A,** A flat lesion after a submucosal injection of saline solution with a few drops of indigo carmine being captured with a stiff snare. **B,** After the snare was closed, the tip of the endoscope was moved to the left and upward (*white arrow*) while 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

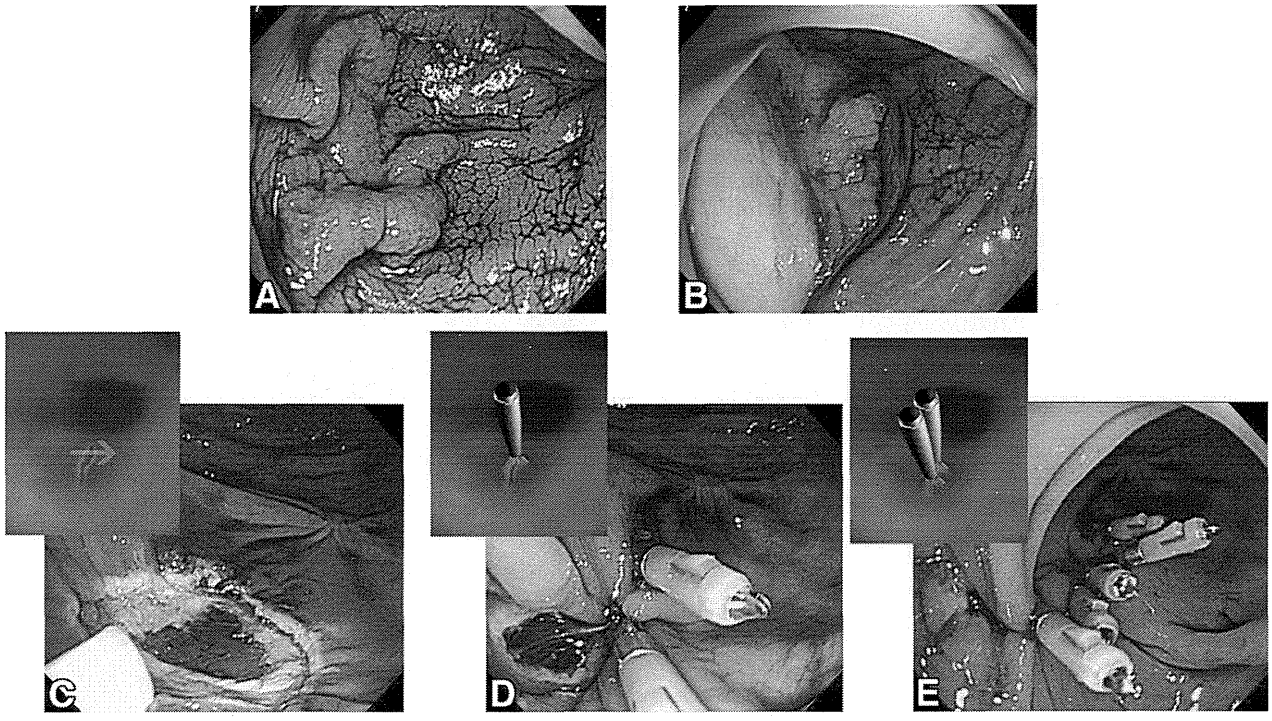


**Figure 4.** Colonoscopic clip closure of a perforation after EMR. **A, B, C,** EMR of a 2-cm, flat lesion with high-grade dysplasia resulted in a large linear perforation. **C, D, E,** This perforation was closed with clips starting at the top of the perforation and working downward. (Reproduced with 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) nongaping 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

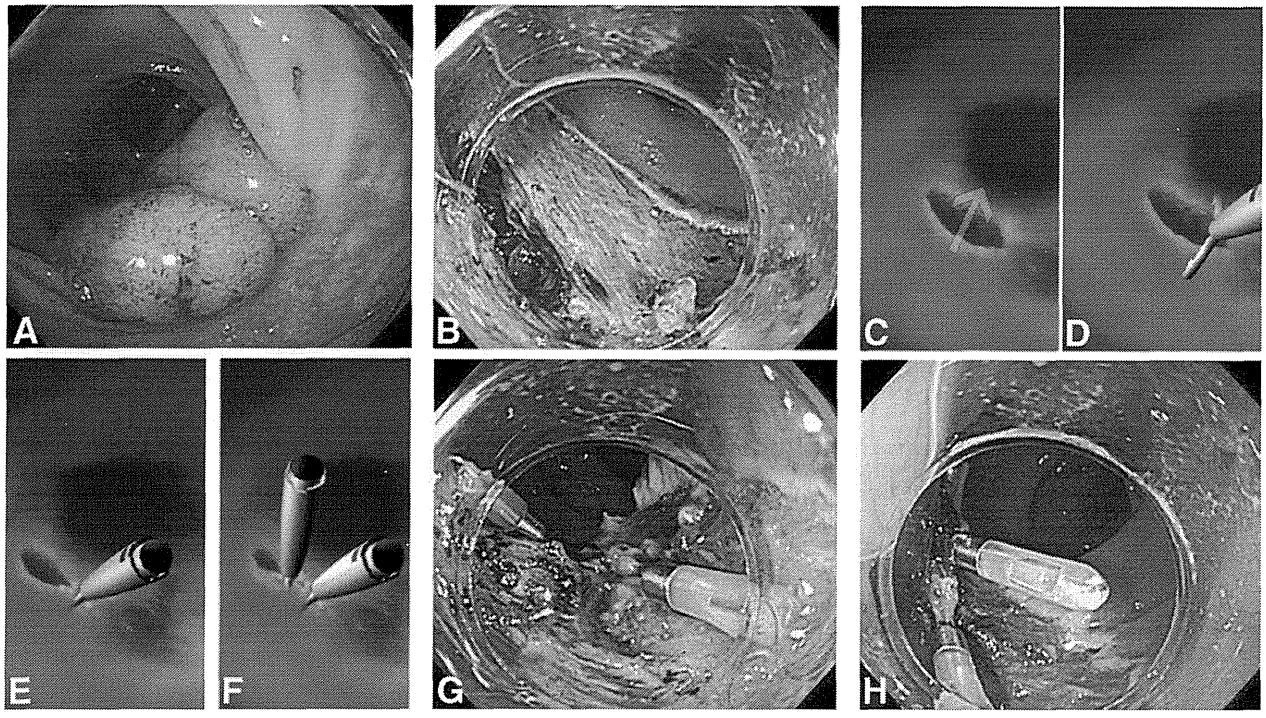


**Figure 5.** Colonoscopic clip closure of a perforation after endoscopic submucosal dissection (ESD). **A, B,** An unintended cut was made too deeply into the muscularis propria, resulting in a small linear perforation during ESD of a sessile lesion. **C-H,** The perforation as seen through a small-caliber 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)

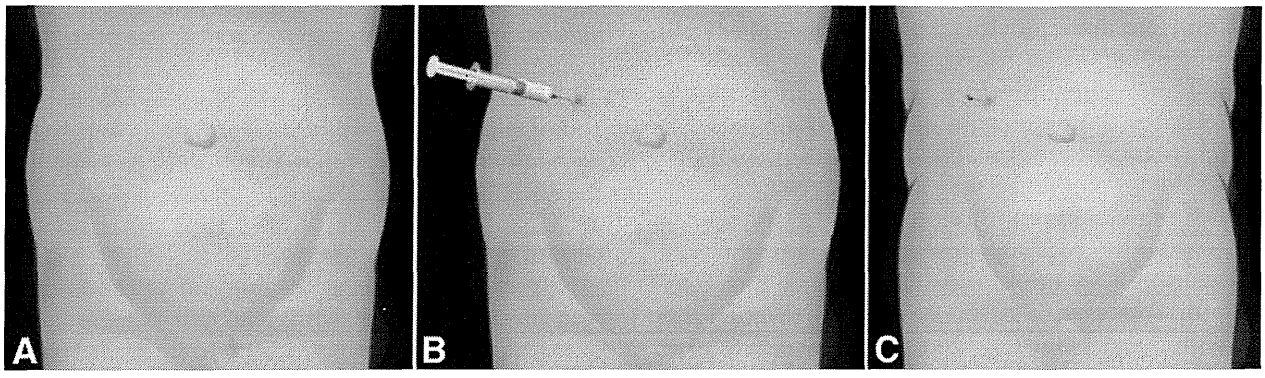


**Figure 6.** Needle decompression of tension pneumoperitoneum. (Reproduced with permission from the ASGE)

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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Received June 1, 2011. Accepted August 4, 2011.

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Techniques in Gastrointestinal Endoscopy (2011) 13, 24-32

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# Macroscopic estimation of submucosal invasion in the colon

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**KEYWORDS:**
Colorectal cancer;
Submucosal invasion;
Endoscopic diagnosis;
Magnifying colonoscopy;
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.


## 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.

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doi:10.1016/j.tgie.2011.01.004

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-

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 $\mu$m or $<$1000 $\mu$m), 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 $\mu$m) 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 (−) | Lymph node metastasis (+) | Univariate analysis ($P$ value) | Multivariate analysis $P$ value | Multivariate analysis Odds ratio | Multivariate analysis 95% Confidence interval |
|---|---|---|---|---|---|---|
| Submucosal invasion ($\geq$1000 $\mu$m/$<$1000 $\mu$m) | 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.

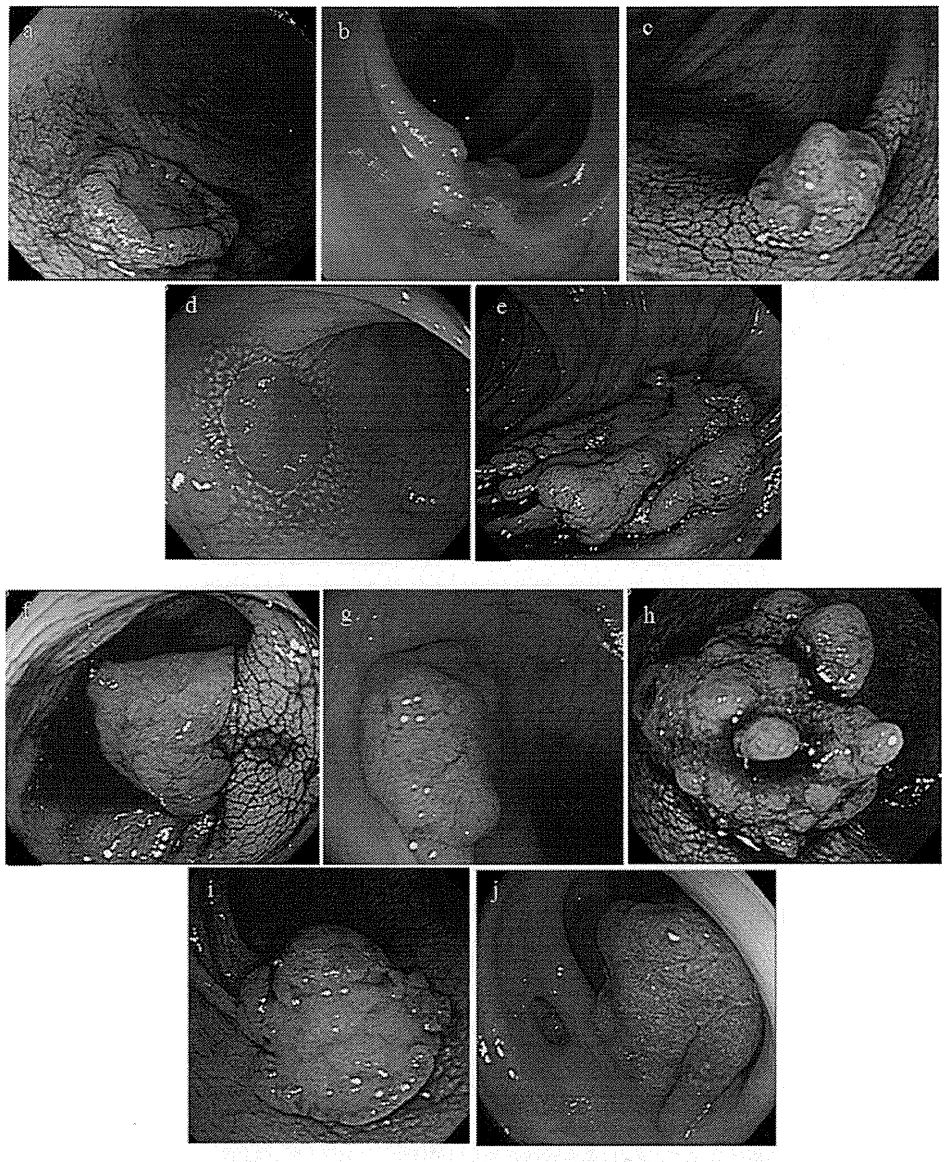


**Figure 1** Typical findings of submucosal invasive cancer. (a) Deep depression, (b) fold convergency, (c) irregular bottom of depression surface, (d) white spots (chicken skin appearance), (e) redness, (f) expansion, (g) firm consistency, (h) irregular surface, (i) loss of lobulation, and (j) thick 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 consistency, 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

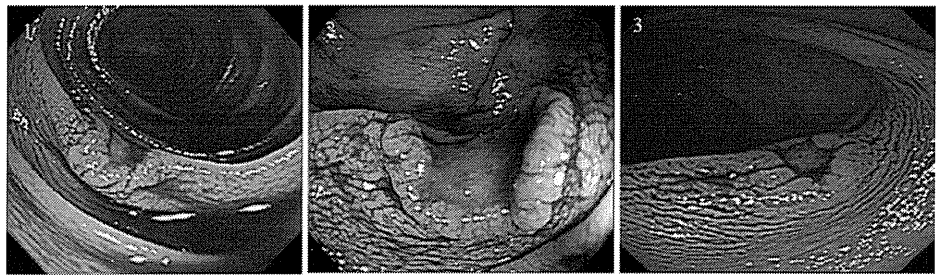

**Figure 2** Deep depression. (1 and 2) IIc, SM deep cancer; and (3) IIc, SM superficial cancer. (Color figure is available online at www.techgiendoscopy.com.)

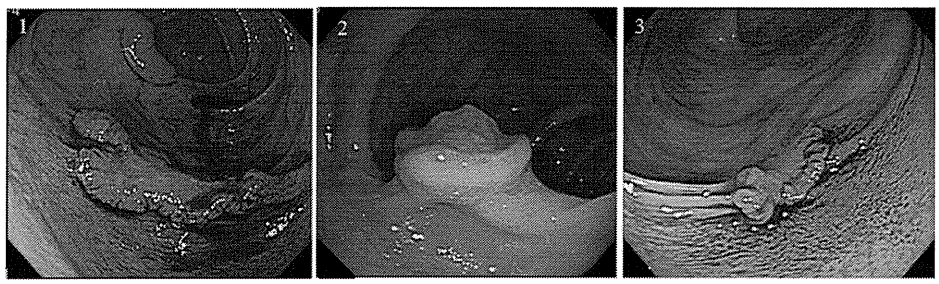

**Figure 3** Fold convergence. (1) IIa + IIc (LST-NG), SM deep cancer; (2) Is + IIc, SM deep cancer; and (3) IIa + IIc (LST-NG), SM superficial cancer. (Color figure is available online at www.techgiendoscopy.com.)

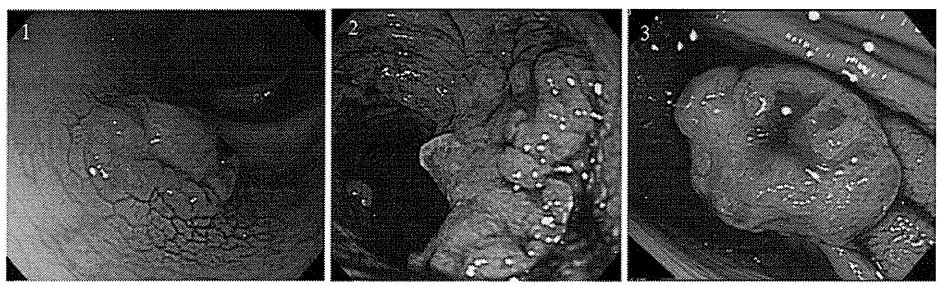

**Figure 4** Irregular bottom of depression surface. (1) Is + IIc, SM deep cancer; (2) IIa + IIc, SM deep cancer; and (3) Is + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

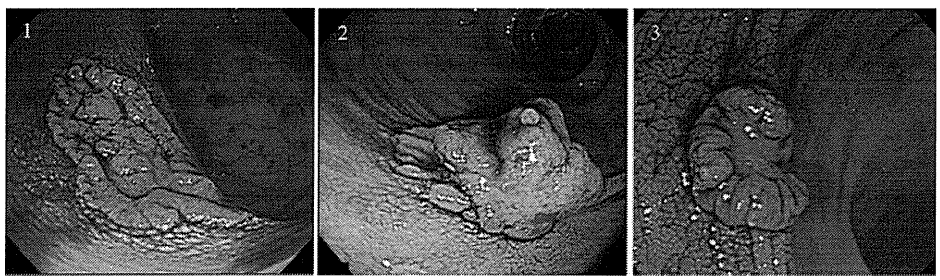

**Figure 5** White spots (chicken skin appearance). (1) IIa + IIc (LST-NG), SM deep cancer; (2) Is, SM deep cancer; and (3) IIa + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

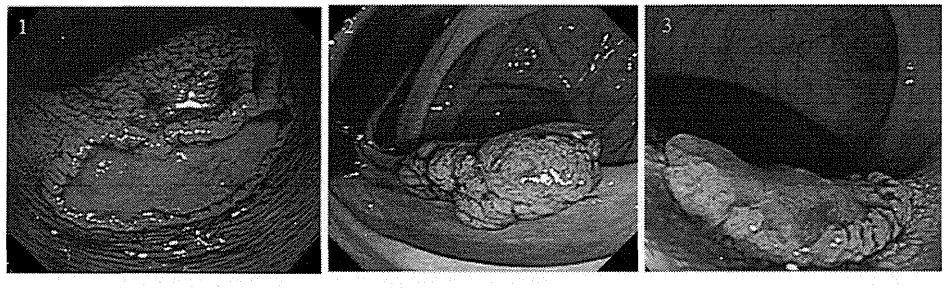

**Figure 6** Redness (reddened area). (1) IIc (LST-NG), SM superficial cancer; (2) Is, SM deep cancer; and (3) IIa + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

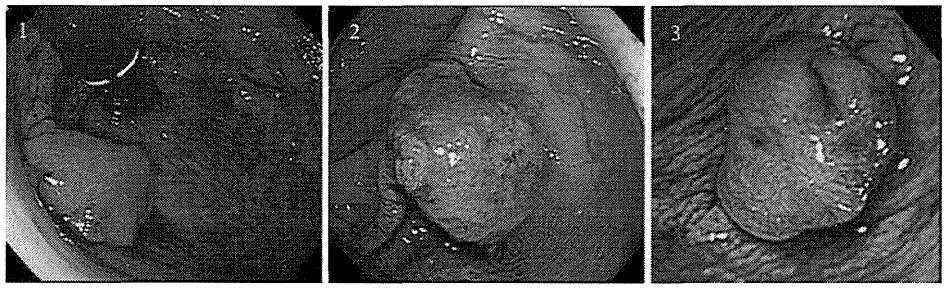

**Figure 7** Expansion. (1) Is, SM deep cancer; and (2 and 3) Is + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

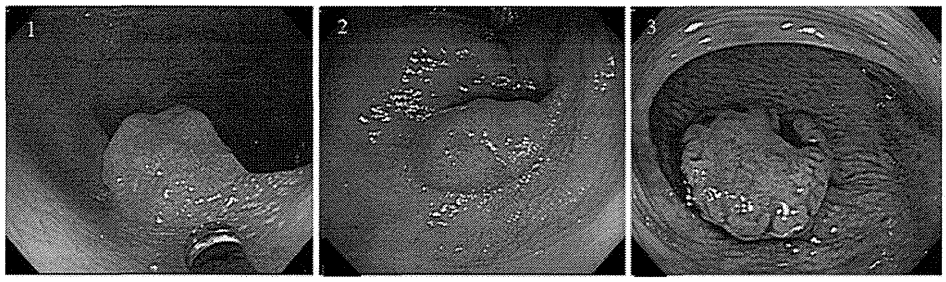

**Figure 8** Firm consistency. (1 and 2) Is, SM deep cancer; and (3) IIa + IIc, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

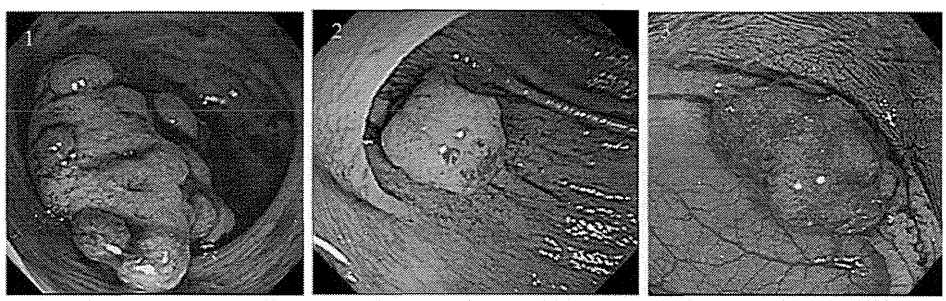

**Figure 9** Irregular surface. (1-3) Is, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

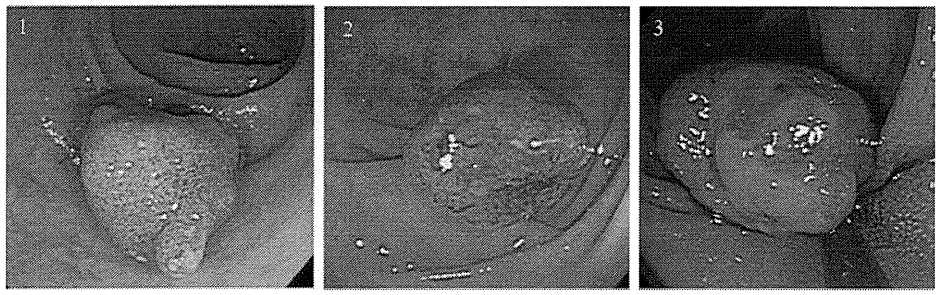

**Figure 10** Loss of lobulation. (1-3) Is, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

(LST-NG) type, which has no submucosal invasion resembles this finding because of submucosal fibrosis.

*Irregular bottom of depression surface (*Figure 4*).* Most of these lesions have cancer cells already invading deeply into the submucosal layer. Morphologically, such lesions are usually named Is + IIc type.

*White spots (chicken skin appearance;* Figure 5*).* Sometimes intramucosal lesions (adenoma or intramucosal cancer) indicate this finding.

*Redness (reddened area;* Figure 6*).* Chromoendoscopy (with indigo carmine) is helpful in recognizing this finding. Intramucosal lesions (adenoma or intramucosal cancer) sometimes resemble this finding. A combination of this finding and the other findings (eg, deep depression, irregular surface, expansion) are significant indicators of submucosal deep cancer.

*Expansion (*Figure 7*).* Most of these lesions have cancer cells already invading deeply into the submucosal layer. Morphologically, such lesions are usually named Is type. There is a strong relationship between this finding and loss of lobulation.

*Firm consistency (*Figure 8*).* It is crucial to confirm this finding under air volume control during observation. Lesions should be judged not only under deflated conditions but also under full inflation.

*Irregular surface (*Figure 9*).* Most of these lesions have cancer cells already invading deeply into the submucosal layer. There is a strong relationship between this finding and loss of lobulation.

*Loss of lobulation (*Figure 10*).* Most of these lesions have cancer cells already invading deeply into the submucosal layer. Morphologically, such lesions are usually named Is type. There is a strong relationship between this finding and expansion/irregular surface.

*Thick stalk (*Figure 11*).* The definition of this finding is "a thickened and expanded stalk." There is a strong relationship between this finding and submucosal deep invasion (ie, stalk invasion) in pedunculated lesions.

## Magnifying colonoscopy (magnifying chromoendoscopy, NBI with magnification)

Magnifying chromoendoscopy is a 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. An unrecognized need and lack of randomized studies validating the effectiveness of magnifying chromoendoscopy are possible reasons for this. We believe that magnifying chromoendoscopy is an essential tool in gastrointestinal endoscopy units, with its main clinical significance being the in vivo diagnosis of the nature of colorectal lesions to determine the appropriate treatment modality. Recently, NBI, a modified technique that provides a unique image emphasizing the CP, as well as the surface pattern, has become widely available. Its

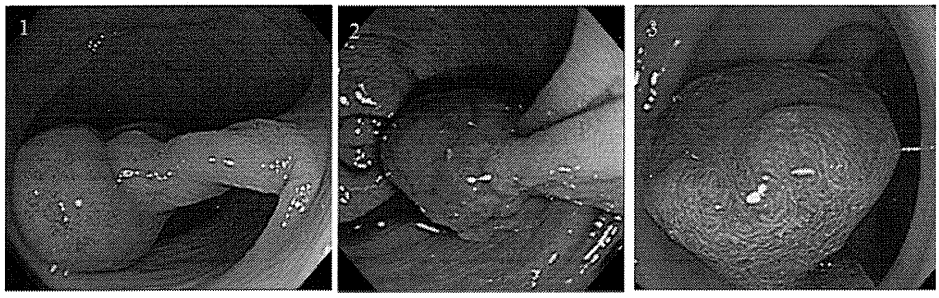

**Figure 11** Thick stalk. (1) Ip, SM deep (stalk invasion) cancer; (2) Ip, SM superficial (head invasion) cancer; and (3) Ip + IIc, SM deep (stalk invasion) cancer. (Color figure is available online at www.techgiendoscopy.com.)

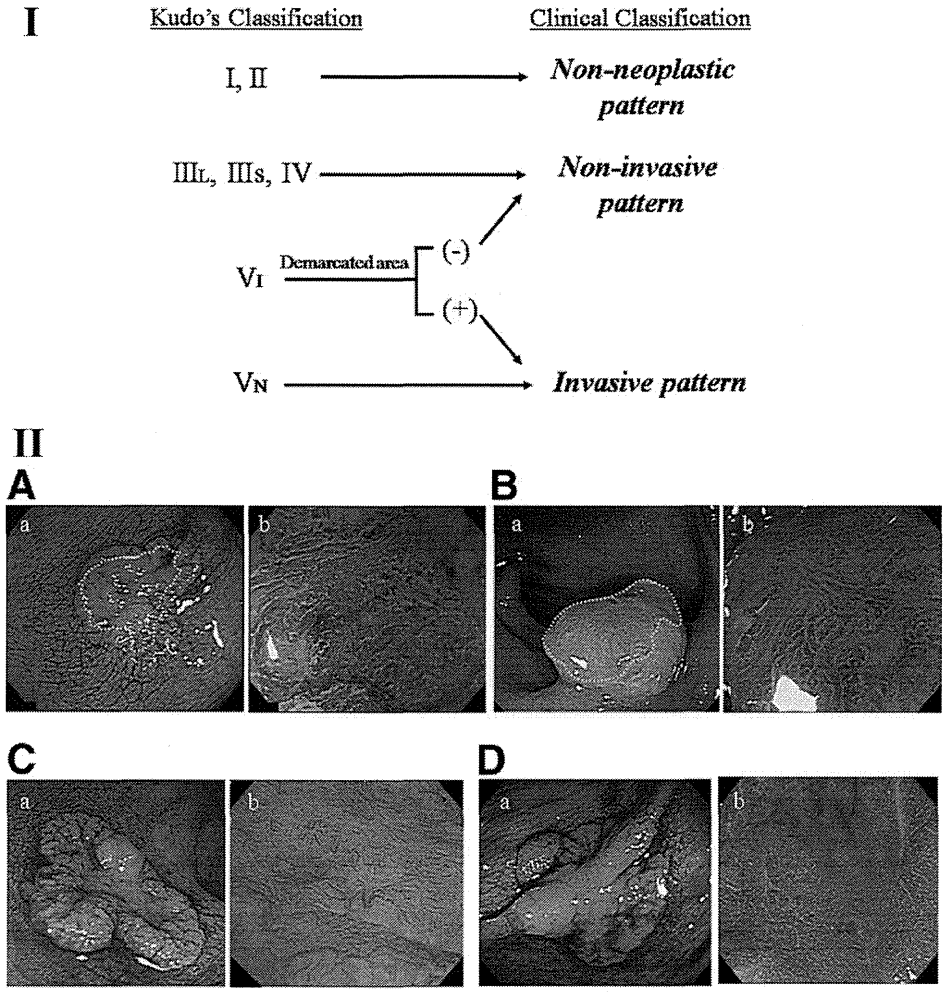


**Figure 12** Definition of invasive/noninvasive pattern. (A and B) Invasive pattern: irregular or distorted pit with demarcated area. (C and D) Noninvasive pattern: regular pit with or without demarcated area or irregular pits without a demarcated area. (Color figure is available online at www.techgiendoscopy.com.)

visual effect is similar to that of chromoendoscopy. Because of the layered nature of the gastrointestinal mucosa, assessment of the CP is critical for the diagnosis of superficial lesions. Otherwise, this system can be installed by changing the optical filters from the conventional broadband type to a narrow-band type and is available for existing endoscopes, including the magnifying endoscope.[11,22-24]

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

*Magnifying chromoendoscopy (pit pattern diagnosis).* Clinical classification of the colonic pit pattern (invasive and noninvasive) using magnifying chromoendoscopy was originally described by Fujii in 1998 with the aim of discriminating between intramucosal–submucosal superficial invasion and submucosal deep invasion.[7] Contrary to the anatomic classification of Kudo et al,[5] the rationale for the clinical classification is based on the identification of irregular or distorted crypts in a demarcated area, which highly 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.[5,9,25] We recently carried out a large prospective study of 4215 lesions in 3029 consecutive patients between 1998 and 2005. All lesions were detected by conventional endoscopic observation and assessed using magnifying chromoendoscopy for evidence of invasive features according to pit pattern evaluation.

### Clinical classification

1. Nonneoplastic pattern: normal mucosa and star-shape crypts as observed in Kudo's type I or II, respectively (eg, hyperplastic, hamartomatous, and inflammatory polyps).
2. Noninvasive pattern: regular crypts with or without demarcated area or irregular pits without a demarcated

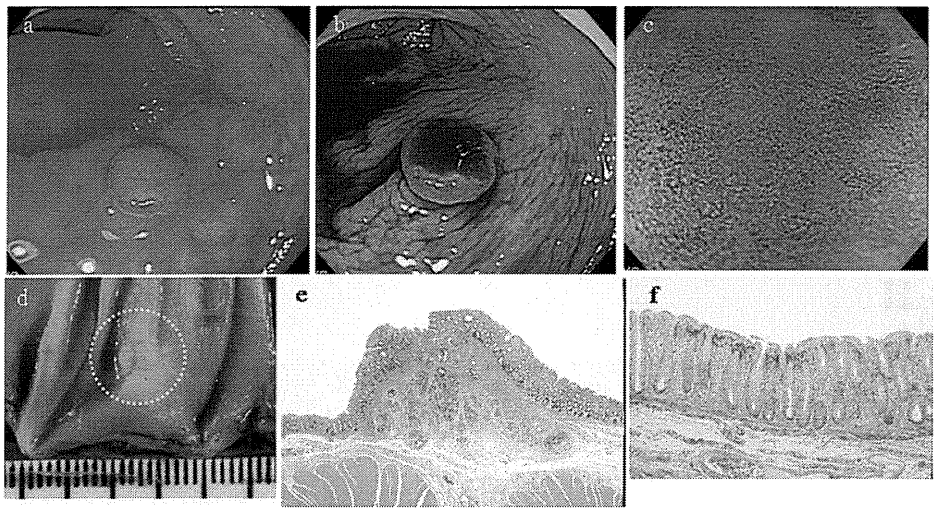

**Figure 13** SM deep sigmoid colon cancer , IIa + IIc, 5 mm. Moderately differentiated adenocarcinoma with collagenous colitis. pSM (2500 $\mu$m), ly1, v0, n0. Final treatment, surgery. (Color figure is available online at www.techgiendoscopy.com.)

area. Usually observed in Kudo's type IIIs, IIIL, and IV and in selected cases of VI (eg, adenomatous polyps, intramucosal and submucosal superficial cancers), where endoscopic resection is appropriate.

3. Invasive pattern: irregular and distorted crypts in a demarcated area as observed in Kudo's type VN and selected cases of VI (eg, deep submucosal invasive cancers), where surgical resection is the appropriate treatment. Kudo's type VI is observed in both noninvasive and invasive patterns (Figures 12 and 13).

Our data showed that 99.4% of lesions diagnosed as noninvasive pattern were adenoma, intramucosal cancer, or submucosal invasion less than 1000 $\mu$m. Among lesions diagnosed with invasive pattern, 87% were cancers with submucosal deep invasion. 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.[10]

*NBI with magnification.* Based on the surface characteristics of the meshed capillaries, CP type III were defined as demonstrating an irregular and unarranged pattern in the mesh-like microvascular architecture and exhibiting at least one of the following: irregular size, complicated branching,

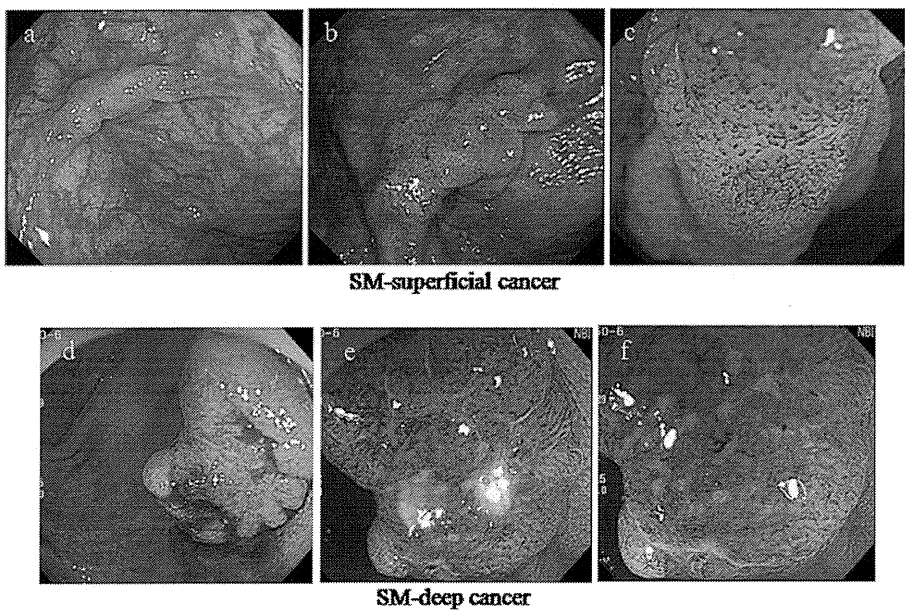


**Figure 14** (a-c) CP type IIIA, SM superficial cancer; and (d-f) CP type IIIB, SM deep cancer. (Color figure is available online at www.techgiendoscopy.com.)

and disrupted irregular winding when compared with the regular small-caliber capillaries observed in adenomatous polyps (CP type II). Moreover, CP type III lesions were further classified into 2 groups: type IIIA or IIIB.

### CP Type IIIA

CP type III lesions clearly show visible microvascular architecture and high microvessel density with lack of uniformity, blind ending, branching, and curtailed irregularity.

### CP Type IIIB

CP type III lesions show a clear distinction between normal/cancerous mucosa on the surface (demarcated area) and the presence of a nearly avascular or loose microvascular area (Figure 14).

The diagnostic sensitivity, specificity, and diagnostic accuracy of the CP type IIIA/IIIB for differentiating intramucosal cancer or submucosal invasion less than 1000 $\mu$m from submucosal deep invasion ($\geq$1000 $\mu$m) were 84.8%, 88.7%, and 87.7%, respectively. The accuracy of CP type IIIA (negative predictive value) was 94.5% (86/91) and that for lesions of CP type IIIB (positive predictive value) was 71.8% (29/39).[11] The identification of CP type IIIA/IIIB by magnifying NBI is useful for estimating the depth of invasion of early colorectal cancers; however, there is a greater interobserver variability compared with the pit pattern diagnosis.

## Conclusions

The detection and diagnosis of early colorectal cancer presents both a challenge and an opportunity. Above all, characteristic colonoscopic findings obtained by a combination of conventional colonoscopy and magnifying chromoendoscopy are useful for determining the depth of invasion of these lesions, an essential factor in selecting a treatment modality.

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Cancer Science
The official journal of the Japanese Cancer Association

# Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: A retrospective multicenter study

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(Received November 11, 2010/Revised February 14, 2011; May 20, 2011/Accepted May 25, 2011/Accepted manuscript online May 31, 2011/Article first published online July 21, 2011)

**Depth of invasion in early invasive colorectal cancer is considered an important predictive factor for lymph node metastasis. However, no large-scale reports have established the relationship between invasion depth of pedunculated type early invasive colorectal cancers and risk of lymph node metastasis. The aim of this retrospective cohort study was to clarify the risk of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series. Patients with pedunculated type early invasive colorectal cancer who underwent endoscopic or surgical resection at seven referral hospitals in Japan were enrolled. Haggitt's line was used as baseline and the invasion depth was classified into two groups, head invasion and stalk invasion. The incidence of lymph node metastasis was investigated between patients with head and stalk invasion. We analyzed 384 pedunculated type early invasive colorectal cancers in 384 patients. There were 154, 156, and 74 endoscopic resection cases, endoscopic resection followed by surgical operation, and surgical resection cases, respectively. There were 240 head invasion and 144 stalk invasion lesions. Among the lesions treated surgically, the overall incidence of lymph node metastasis was 3.5% (8/230). The incidence of lymph node metastasis was 0.0% (0/101) in patients with head invasion, as compared with 6.2% (8/129) in patients with stalk invasion. Pedunculated type early invasive colorectal cancers pathologically diagnosed as head invasion can be managed by endoscopic treatment alone. (*Cancer Sci* 2011; 102: 1693–1697)**

It has been reported that intramucosal colorectal cancers show no lymph node metastasis and are good candidates for endoscopic resection.[1,2] In contrast, 6–12% of early invasive colorectal cancers (i.e. cancer cells invade through the muscularis mucosae into the submucosal layer but do not extend into the muscularis propria) are associated with lymph node metastasis requiring surgical resection including lymph node dissection for curative treatment.[3–7] Recently, increasing evidence suggests that lesions with submucosal invasion limited to <1000 μm without lymphovascular invasion and/or poorly differentiated components do not metastasize to lymph nodes.[8] Endoscopic resection is an appropriate treatment for early stage colorectal cancers, however, the resected specimen must be examined to determine whether there is a clinically significant risk of lymph node metastasis that would warrant additional surgery. Colorectal lesions can be subdivided according to endoscopic appearance using the Paris classification (Fig. S1), whereas Haggitt's classification is frequently used to define the depth of invasion of pedunculated lesions.[9] Haggitt and colleagues stratified the level of cancer invasion according to the following criteria: level 0, carcinoma *in situ* (i.e. has not extended below the muscularis mucosae); level 1, carcinoma invading through the muscularis mucosae but limited to the head of the polyp (i.e. above the junction between the adenoma and its stalk); level 2, carcinoma invading the level of the neck (i.e. the junction between adenoma and its stalk); level 3, carcinoma invading any part of the stalk; and level 4, carcinoma invading into the submucosa of the bowel wall below the stalk (Fig. S2). The authors concluded a low risk of metastasis or local recurrence when the level is <4. Pedunculated lesions can easily be treated endoscopically, however, there are no large-scale reports establishing the risk of lymph node metastasis in this lesion type stratified by depth of invasion. We report the incidence of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series.

## Materials and Methods

**Patients.** Patients with pedunculated type early invasive colorectal cancers that had been treated by endoscopic resection or surgical resection at seven institutions in Japan (National Cancer Center Hospitals [Tokyo, Kashiwa], Tokyo Medical University Hospital, Okayama University Hospital, Shizuoka Cancer Center, Tochigi Cancer Center, and Okayama Saisei-kai General Hospital) between January 1992 and December 2007 were examined retrospectively. Patients eligible for this study had pathologically proven adenocarcinoma invading through the muscularis mucosae into the submucosal layer but not extending deeply into the muscularis propria. Eligibility also required the lesion to be endoscopically diagnosed as pedunculated type suitable for one-piece resection. Patients with synchronous advanced colorectal cancer, multiple early invasive colorectal cancers, inflammatory bowel disease, hereditary non-polyposis colorectal cancer, and familial adenomatous polyposis were excluded from this study. This study was carried out with the approval of each institution's ethics review board.

**Treatment strategy.** *Endoscopic resection:* All lesions diagnosed as intramucosal or superficial submucosal invasive cancers at colonoscopy were removed by polypectomy or endoscopic mucosal resection. If the histopathological result did not meet the criteria for complete endoscopic resection, additional surgery was recommended. *Surgical operation:* Patients with endoscopic features suggestive of submucosal invasion into the stalk were referred directly for surgical operation (i.e.

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doi: 10.1111/j.1349-7006.2011.01997.x