Chapter 7

The Diagnosis and Treatment of Early-Stage Colorectal Cancer

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Abstract

The introduction of colorectal endoscopic submucosal dissection (ESD) has expanded the applications for endoscopic treatment; as a result, lesions with low metastatic potential can be treated endoscopically regardless of the lesion size. The most attractive feature of ESD is the achievement of en bloc resection with a lower local recurrence rate in comparison to that of endoscopic piecemeal mucosal resection. However, in case of gastric cancers, ESD is not as widely applied to the treatment of colorectal neoplasms because of its technical difficulty, longer procedural time, and increased perforation risk. In the movement toward diversified endoscopic treatment strategies for superficial colorectal neoplasms, endoscopists who begin to perform ESD need to recognize the indications of ESD, as well as the technical issues and associated complications of this procedure.

Keywords: Superficial colorectal neoplasm, pit pattern, endoscopic submucosal dissection

1. Introduction

Endoscopic therapy is a major step forward in the management of early-stage gastrointestinal cancers. In the colorectum, lymph node metastasis always occurs only with deep invasion of

the submucosa (≥1000 μm), and lesions that are diagnosed as well-differentiated adenocarcinomas that are limited to the mucosa (intramucosal) or that superficially invade the submucosa (<1,000 μm from the muscularis mucosa) without lymphovascular invasion or a component with poor differentiation component (or both) are usually considered to not involve lymph node metastasis [1-3]. Among these factors, however, only the depth of invasion can be estimated by endoscopy prior to treatment. Thus, the depth of invasion must be accurately estimated before any therapeutic decision is made. Endoscopic resection plays two important roles in gastrointestinal surgery: achieving curative resection and allowing an accurate histological evaluation of lesions. As lesions measuring more than (or equal to) 10 mm have the potential for malignancy, they should be resected en bloc to avoid either residual or recurrent lesions (or both) [4].

Endoscopic submucosal dissection (ESD) is a state-of-the art technique for the treatment of large colorectal neoplasms that enables en bloc resection regardless of lesion size [5-8]. This chapter describes in detail the method for estimating depth invasion and ESD for colorectal neoplasms.

2. Diagnosis

Magnifying observation techniques, including chromoendoscopy and narrow-band imaging (NBI), have been recognized as high-precision methods for the diagnosis of depth invasion. With NBI, avascular or loose vascular findings are considered a key indicator of a submucosal and deep invasive cancer [9, 10]. However, NBI is a relatively new method with an unknown learning curve and different classifications, even within a single country like Japan. In contrast, pit pattern analysis using crystal violet staining has now become standardized due to its longer availability and one-to-one comparisons of endoscopic and pathological findings. In our view, pit pattern analysis is the most reliable predictor of depth invasion. During this analysis, each lesion should be confirmed to include a non-invasive pattern and Type V pit(s) with clearly demarcated areas, as this indicates that the lesion is suitable for endoscopic mucosal resection (EMR) or ESD with an estimated depth of invasion less than that of a submucosal invasive cancer [11].

In this section of the chapter, we will describe in order of the actual clinical process an endoscopic evaluation focused on the invasion depth of an early colorectal cancer, which is defined as confirmed cancer cells present in the mucosa or the submucosa, regardless of lymph node metastasis.

2.1. White-light non-magnifying endoscopy

The first diagnostic step is determination of the macroscopic lesion type. Most early-stage colorectal cancer lesions are classified as Type 0 according to Borrmann classification, which is equivalent to a superficial lesion in the Paris classification. In the latter classification, superficial lesions are divided into two groups: polypoid and non-polypoid lesions; in particular, non-polypoid lesions have received considerable attention, given their clinical

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importance. Non-polypoid lesions include superficial elevated (0-IIa), completely flat (0-IIb), and depressed (0-IIc) lesions. Moreover, a superficial-type lesion of size more than 10 mm with no increase in height is called a laterally spreading tumor (LST). LSTs can be further divided into two main classes: granular type (LST-G) and non-granular type (LST-NG) (Figure 1). We know that LST-NG tumors of size more than (or equal to) 20 mm and LST-G tumors of size more than (or equal to) 30 mm harbor a significantly higher likelihood of submucosal invasion [12]; therefore, a careful evaluation of morphological features is crucial for the depth diagnosis.

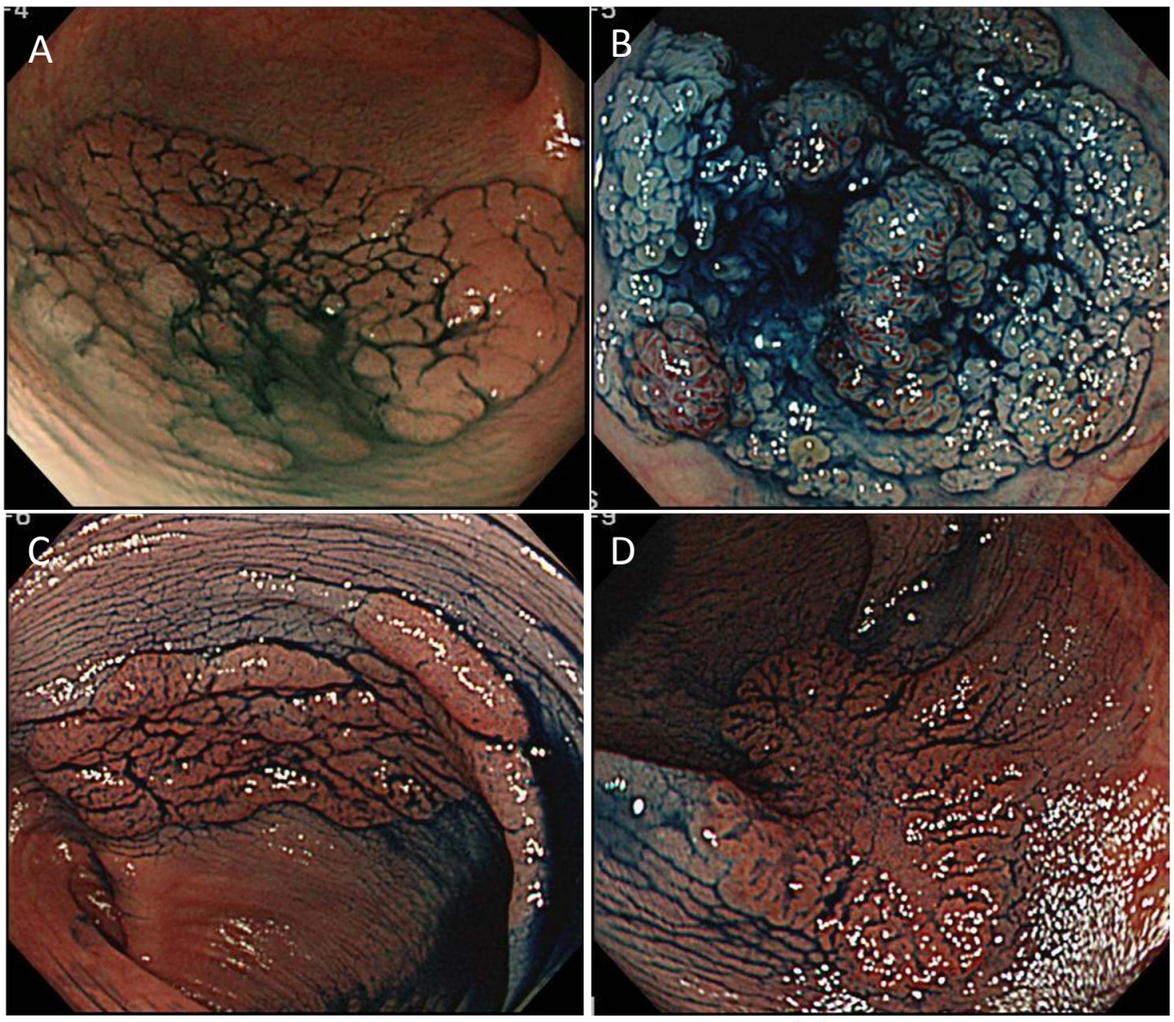

Figure 1. Subtypes of tumors with lateral spread. A: Laterally spreading tumor (LST), homogeneous granular type; B: LST, mixed granular type; C: LST, non-granular, flat elevated type; D: LST, non-granular, pseudodepressed type.

Some findings regarding the important conventional colonoscopic findings for determining the invasion depths of non-polypoid lesions have been reported in previous studies: redness, white spots (chicken-skin appearance), appearance of expansion, firm consistency, deep depression surface, irregular bottom of depression surface, and fold converging toward the tumor. Matsuda et al. verified these findings retrospectively to clarify the clinically important characteristics. White spots, redness, firm consistency, and a deep depressed area were

significantly associated with an increased risk of submucosal deep invasion in a univariate analysis [13].

2.2. Narrow-band imaging with magnifying endoscopy

NBI is an innovative optical technology that uses interference filters for spectral narrowing of the bandwidth used in conventional white-light medical videoscopy. NBI allows a more detailed visualization of the mucosal architecture and capillary pattern without the need for dye spraying. Upon reviewing microvascular architecture using NBI, our institution identified four different patterns according to Sano classification [9]. By examining a lesion's microvessel pattern using NBI, invasion depth was subsequently classified as intramucosa/shallow submucosa (lack of uniformity and high vessel density; capillary pattern IIIA) or deep submucosa (nearly avascular or loose microvessel diameters; capillary pattern IIIB). Ikematsu et al. reported the diagnostic accuracy of this technique for determining the invasion depth as follows: the sensitivity, specificity, and diagnostic accuracy of capillary pattern IIIB for differentiating the intramucosa/shallow submucosa from deep submucosa were 84.8%, 88.7%, and 87.7%, respectively [9].

On the other hand, we assessed the interobserver agreement in terms of estimating the depth of invasion using NBI and pit pattern analysis and found substantial agreement with pit pattern analysis and moderate agreement for NBI with magnification [14]. Regarding the lower interobserver agreement in the interpretation of the NBI findings, we should remember that the NBI system is still a relatively new diagnostic method with an unknown learning curve; to complicate the matter, several different classifications for the evaluation of mucosal morphology in colorectal neoplasms have been proposed recently in Japan. Regarding a consensus on the microvascular architecture and classification of findings, there has not been sufficient discussion for the worldwide use of NBI to become a reality.

2.3. Pit pattern evaluation using crystal violet staining

According to the classification of colonic crypts described by Kudo and Tsuruta, type V pit patterns include areas of irregular crypts (type V_I) and apparently non-structured areas (type V_N). Type V_I pit patterns allow further subdivision into areas with mild irregularity (type V_I mild) and severe irregularity that show destroyed and severely damaged pits (type V_I severe). Type V_I severe pit patterns were defined by Tobaru et al. as areas containing pits with poor demarcation and those which contain faded or unstained stromal areas [15]. Regarding diagnostic standardization by magnifying chromoendoscopy, this classification should be directly linked to the choice of the most appropriate treatment. The depth of invasion of an early colorectal cancer is normally determined from the accumulated data of serial observations, which includes conventional imaging with no magnification. In this regard, Matsuda et al. described the clinical classification of an "invasive/non-invasive pattern" that incorporates conventional observations of lesion configuration, including depression, large nodules, and reddened areas (Figure 2) [13]. When differentiating between intramucosal/shallow submucosal lesions and deep submucosal lesions, an interpretation using this invasive pattern demonstrated a sensitivity of 85.6% and a specificity of 99.4%. In this report, the diagnostic

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accuracy was sufficient to demonstrate the efficacy of magnifying chromoendoscopy, and the clear advantage of this classification was directly reflected in the choice of treatment: endoscopic or surgical resection. Based on the pit pattern classification, the invasive pattern might include some cases classified as V_I severe and V_N pit patterns.

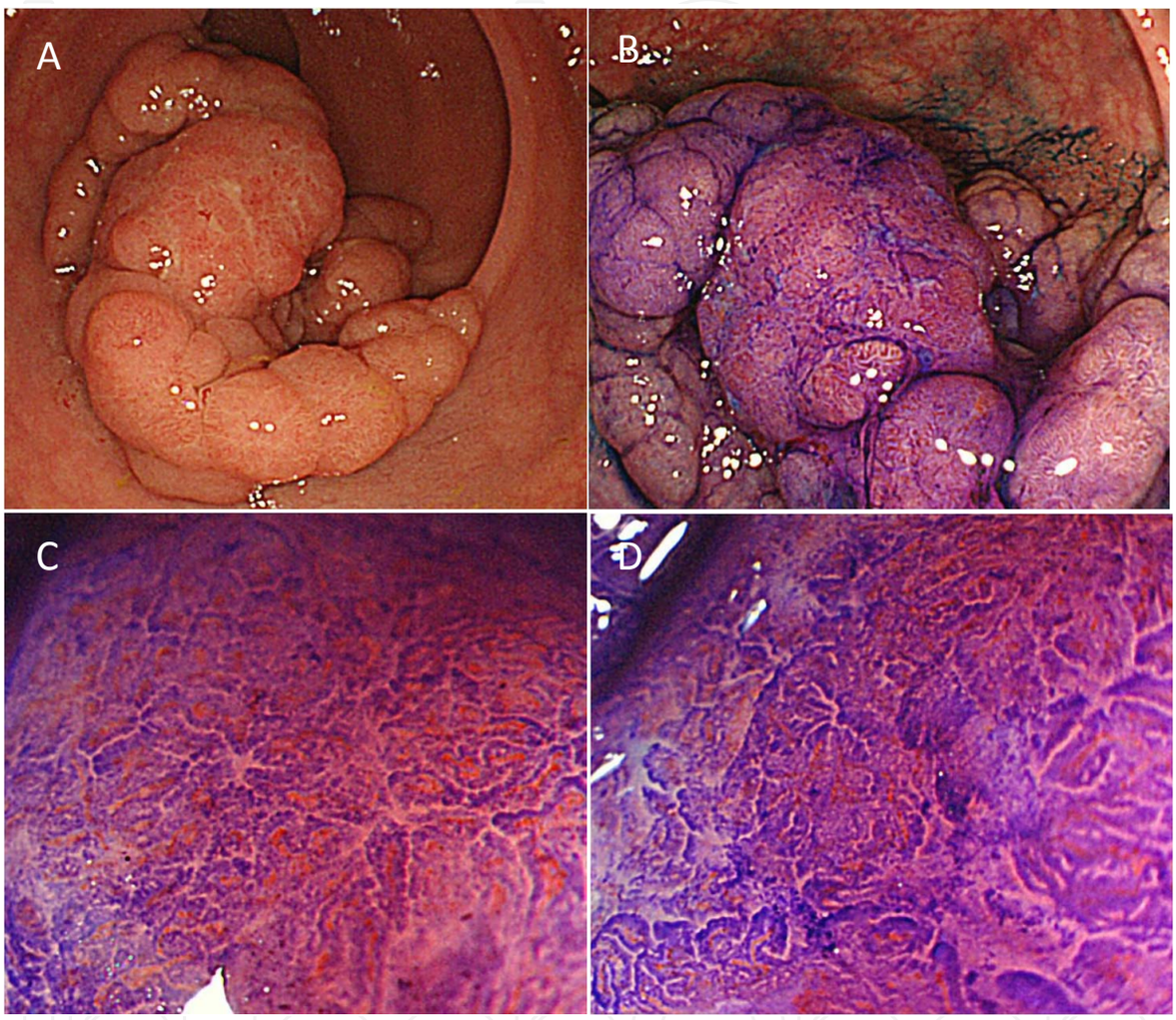

Figure 2. An invasive lesion exhibiting the "invasive pattern" visualized by magnifying chromoendoscopy with crystal violet staining. A: Large lesions with a reddish, protruding component; B: Depth diagnosis should focus on the reddish part; C, D: Reddish part displays a highly irregular type VI pit, which was demarcated as the reddish area.

2.4. Alternatives

2.4.1. Endoscopic ultrasonography

Data on the utility of high-frequency endoscopic ultrasonography (EUS) for the management of the malignant colorectal polyps is conflicting. Some previous reports have demonstrated the usefulness of EUS, in particular the advantages of high-frequency ultrasound for diagnosing the invasion depth of early colorectal cancer [16-19]. Hurlstone et al. reported that high-

frequency ultrasound was superior to magnifying chromoendoscopy for determining depth invasion (accuracy of 93% vs. 59%, respectively). Matsumoto et al. also demonstrated the diagnostic superiority of EUS (probe-EUS) in their study (negative predictive value for deep invasion of 91% vs. 54%, respectively) [19]. In contrast, Fu et al. reported that there was no significant difference between magnifying chromoendoscopy and EUS for the preoperative staging of early colorectal cancer [20].

EUS is definitely very useful for determining the invasion depth or predicting submucosal fibrosis in flat or depressed lesions; however, its limited penetration depth is a recognized disadvantage. In particular, it might be difficult to accurately evaluate the invasion depth or submucosal fibrosis in protruding lesions. Moreover, the use of EUS to observe lesions located on the oral side of folds is also considered difficult.

2.4.2. Non-lifting sign

Uno et al. first described the "non-lifting sign" in 1994 [21]. Lesion observation during and after submucosal saline injection is a simple and crucial method for not only assessing the potential for deep invasion but also predicting the technical difficulty of endoscopic resection. Lesions may not lift as a result of submucosal fibrosis, a desmoplastic reaction, or the presence of large amounts of elastic fibers in vessels [22].

Regarding the diagnostic accuracy of the non-lifting sign for predicting deep invasion, Kobayashi et al. reported a sensitivity of 62% and specificity of 98%. However, magnifying chromoendoscopy displayed a sensitivity of 85% and specificity of 98% in the same study, resulting in a significant difference in sensitivity [23]. Therefore, despite its simplicity, the non-lifting sign could not reliably predict deep invasion when compared with a magnifying observation.

3. Indication of endoscopic treatment

In Japan, colorectal ESD has been covered under health insurance since 2012. Before 2012, the performance of colorectal ESD was allowed at only a restricted number of advanced medical centers that had been approved in 2009 by the Japanese Ministry of Health, Labor, and Welfare. From this, "The Colon ESD Standardization Implementation Working Group," a sub-organization of the "Gastroenterological Endoscopy Promotion Liaison Conference," produced a draft titled "Criteria of Indications for Colorectal ESD" [24]. In essence, ESD is indicated when lesions require en bloc resection for evaluation of histological features and for lesions whose resection using conventional EMR techniques is problematic. In other words, cancerous lesions that have the potential to invade the submucosal layer require treatment using ESD. In these cases, the size and morphology of the lesion are considered as critical factors. For example, a nodular mixed type LST of size more than (or equal to) 30 mm and an LST-NG of size more than (or equal to) 20 mm are considered to contain some risk of an invasive component. In addition, lesions for which resection is technically difficult via conventional EMR are also considered an indication for ESD; these include lesions exhibiting the non-lifting sign after

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submucosal injection, local recurrent lesions following previous treatment, and relatively large protruding-type lesions (except pedunculated polyps). In general, the en bloc resection of large neoplastic lesions (≥20 mm in size) via conventional EMR is technically difficult, and endoscopic piecemeal mucosal resection (EPMR) is typically applied. Undoubtedly, EPMR is an important method for removing lesions that harbor minimal potential for submucosal invasion, such as intramucosal neoplasms; however, it is crucial to recognize an important disadvantage of EPMR, specifically the increased risk of local recurrence. We previously reported that the removal of more than (or equal to) 5 specimens from a single patient is an independent risk factor for local recurrence following EPMR [25]. Moreover, colonoscopy with careful surveillance is required after multiple EPMR. Given the risk and occurrence of invasive recurrence in EPMR-treated patients, it is advisable to avoid such multiple resections and explore alternative treatment strategies.

4. Endoscopic submucosal dissection

Various treatment materials have been developed and applied in the context of ESD since the introduction of this technique. Hence, we introduce our ESD strategy as an example in this chapter.

4.1. Strategy

4.1.1. Preparation

A well-cleansed colon is a key element of safe ESD in preventing such adverse events such as bacterial peritonitis following iatrogenic perforation of the colonic wall. In our institution, patients generally receive 3 to 4 L of polyethylene glycol over 4 hours in the morning before ESD. Further, they also receive 1 g of cefmetazole in a 100-mL saline solution 20 to 30 minutes prior to ESD.

4.1.2. Sedation

Intravenous administration of an anti-peristaltic agent (10 mg of scopolamine butylbromide or 0.5 mg of glucagon) is mandatory, and intravenous administration of a sedative (2–3 mg of midazolam) and analgesic (15 mg of pentazocine) is provided as required during the procedure. Maintenance of conscious sedation during the procedure is essential, as patients are occasionally required to change position to enable the dissected part of the lesion to hang down due to gravity to improve identification of the submucosal layer.

4.1.3. Treatment devices

Here, we describe the equipment that is commonly used at our institution. ESD is done using a water jet endoscope (PCF-Q260JI and GIF-Q260J, Olympus Medical System Co., Tokyo, Japan). In cases in which handling the endoscope as the operator intended during the ESD

procedure would be difficult due to the location of the lesion or paradoxical movements, a double-balloon colonoscope (EC-450BI, Fujifilm, Japan) is an available option for precise endoscope control [26].

A ball-tip bipolar needle knife with a water jet (Jet B knife, XEMEX Co., Tokyo, Japan) is used for both incision of the mucosa and dissection of the submucosa in the first step of the treatment. An important feature of this device is its use of a bipolar current system, which minimizes damage to deep tissue and decreases perforation risk [27]. Next, an insulation-tipped electrosurgical knife (IT knife nano, KD-612Q, Olympus Optical Co., Tokyo, Japan), fitted with a smaller insulation tip and short blade designed as a small disk to reduce burning of the muscular layer, is usually used to shorten the procedure time [28].

For distal attachment, we use a short-type ST hood (DH-28GR and 29CR, Fujifilm Medical Co., Tokyo, Japan) that facilitates broadening of the visual field of the operator and dissection of the submucosal layer due to its characteristic tapered configuration.

4.1.3.1. Electrosurgical current generator

The ERBE VIO 300 D (Erbe, Tubingen, Germany) is mainly used in our institution. Table 1 describes the output settings for ESD procedures.

	Device	Cut mode [E: effect]	Coagulation mode [E: effect]
Mucosal incision	Jet B knife	Dry Cut, [E]3 100 W	
Submucosal dissection	Jet B knife	Dry Cut, [E]3 100 W	Forced Coag, [E]2 50 W
	IT knife nano	Dry Cut, [E]3 100 W	Swift Coag, [E]2 50 W
Hemostasis	Hemostat-Y		Bipolar, [E]5 25 W

Table 1. Output setting of VIO 300D for colorectal ESD at the National Cancer Center Hospital, Tokyo, Japan

4.1.3.2. Submucosal injection

ESD procedures are critically dependent on the maintenance of suitable submucosal elevation by injection. We therefore prefer solutions for submucosal injection which enable a longer period of submucosal elevation. Two solutions are used in our center, as follows: glyceol (10% glycerin and 5% fructose; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) mixed with small quantities of indigocarmine and epinephrine, and a 0.4% sodium hyaluronate solution (MucoUp; Seikagaku Corp, Tokyo, Japan) [29]. In practice, a small amount of Glyceol is first injected into the submucosal layer to confirm the appropriate submucosal layer elevation; MucoUp is subsequently injected into the properly elevated submucosal layer, after which an additional small amount of Glyceol is injected to flush any residual of MucoUp [30].

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4.1.4. Carbon dioxide insufflation

Carbon dioxide (CO_2) gas should be used for colonic lumen insufflation, as previously confirmed [31, 32]. CO_2 insufflation reduces the risk of pneumoperitoneum in cases of perforation, and also reduces the development of abdominal conditions pre- or post-treatment (or both).

4.1.5. ESD technique

In this section, the key points of the ESD technique performed at our institution are described (Figure 3).

The process begins in the retroflex view because endoscope handling can be better stabilized than is achievable with the forward view. After ensuring suitable submucosal elevation via injection, the initial mucosal incision is produced with the Jet B knife from the lesion's distal aspect.

In cases where a retroflex view is difficult to obtain, the tunneling method described by Yamamoto is a useful approach [33]. Briefly, incision and trimming of the mucosa are commenced from the distal aspect of the lesion until the last tissue segment is approached. Incision of the mucosa and dissection of the submucosa are then continued from the lesion's proximal aspect.

In most cases, insertion of the tip of the endoscope into the submucosal layer immediately after the initial mucosal incision is difficult. For these, trimming of the mucosa is performed. As the space for dissection is inadequate for continuation of submucosal dissection during trimming, the submucosal layer is gently and carefully cut near the mucosal layer.

Once the submucosal layer is secure in the visual field, submucosal dissection is furthered with the Jet B knife. One advantage of ESD is the clear visualization of structures in the submucosal layer, such as vessels and fibrosis. This allows the prevention of bleeding by pre-coagulation of the involved vessels. Cutting devices are used to perform pre-coagulation for thin-walled vessels; for thick-walled or pulsatile vessels, however, coagulation forceps should be used. In our center, we use Hemostat-Y forceps (H-S2518, Pentax Co., Tokyo, Japan) in bipolar mode (25 W) for the control of visible bleeding and minimization of any risk of burning of the muscle layer. In ESD, adjustment of the cutting line during submucosal dissection is also possible. In adenomatous lesions, the line of incision can be located near the mucosal layer to minimize perforation risk. In contrast, for potentially submucosal invasive cancer-type lesions, which require R0 resection, the line of incision should be located in the deeper tissues, for example near the muscularis propria, notwithstanding that the risk of perforation is increased.

Once an adequate visual field has been obtained as described, dissection is continued using the IT knife nano. The usable section of this "blade"-type knife is longer than that of other "needle"-type knives and can therefore reduce procedure time compared to those done without this knife. During the entire procedure, submucosal injection should be repeated whenever necessary to ensure suitable submucosal elevation.

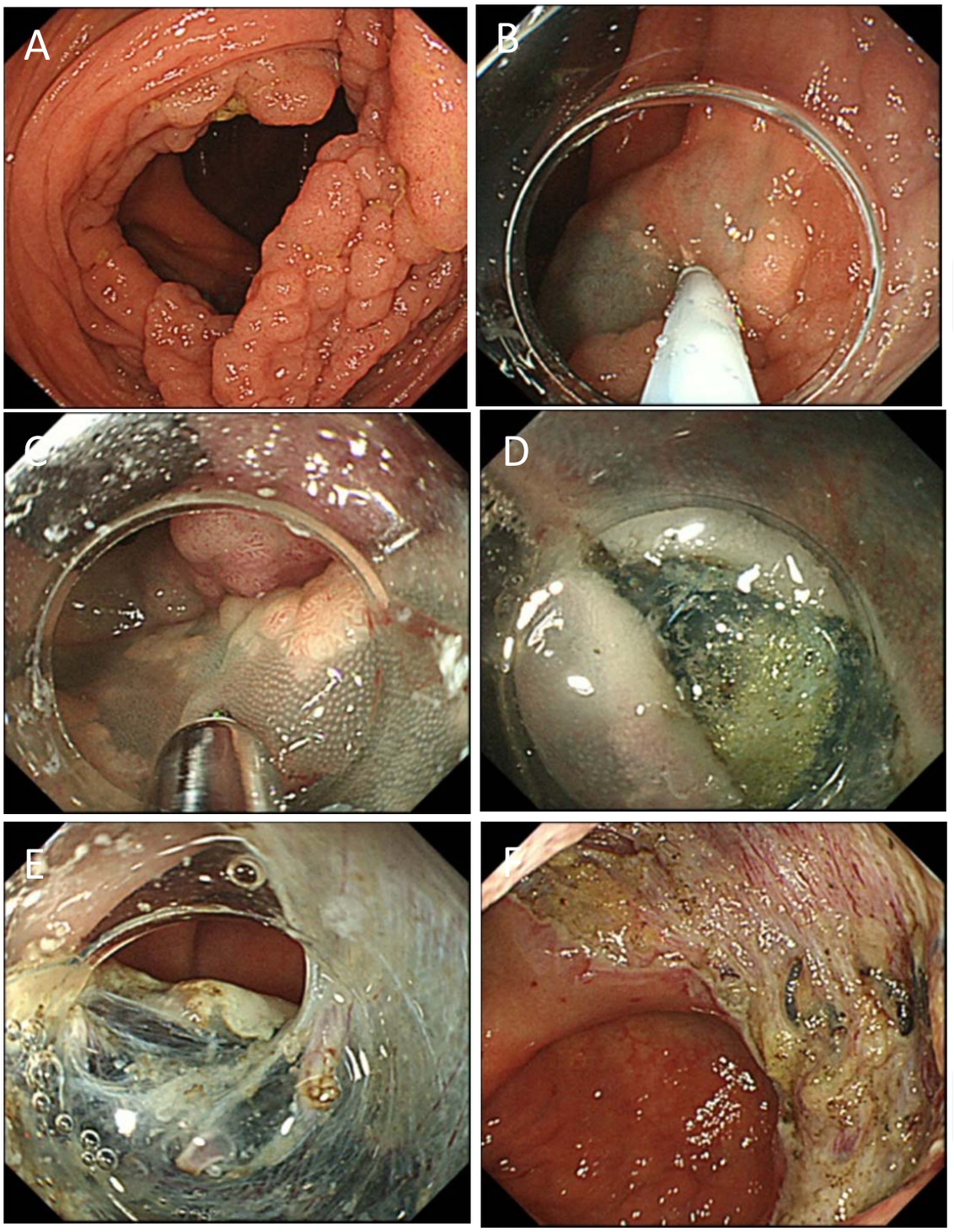

Figure 3. A case of ESD performance. A: Flat elevated lesion (85 mm) located in the ascending colon. It was impossible to maintain the retroflex view for this lesion. B, C: The submucosal injection of glyceol and first circumferential incision were initiated from the oral side of the lesion with a forward view. The first cut was made with a Jet B knife. D: After the first circumferential incision, it was difficult to slide the top of the short-type ST hood into the submucosal layer. Next, the visual field was broadened by carefully cutting the blue-colored submucosal layer near the mucosa (white dotted line). E: After step D, the top of the short-type ST hood slid easily into the submucosal layer, which became easier to cut. Here, the IT knife nano was useful and easily and quickly dissected the submucosal layer. F: En bloc resection was achieved without any adverse events during a period of 180 minutes.

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Following the completion of colorectal ESD, a routine colonoscopic review is done to identify possible perforations or exposed vessels, and minimum coagulation is conducted with hemostat-Y forceps on visible but non-bleeding vessels to minimize the risk of bleeding after the operation.

4.2. Alternative technique

Hybrid ESD, which was first reported as "endoscopic resection with local injection of hypertonic saline–epinephrine" by Hirao et al. in 1986, is considered an alternative to ESD. This procedure could enable en bloc resection or at least reduce the number of piecemeal resections for large colorectal neoplasms in a manner that is both safe and relatively rapid. The technique is simple; the first step is a circumferential incision of the mucosa, followed by placement of a snare around the mucosa via the circumferential incision, and tightening of the snare (Figure 3) [34, 35]. However, there are some limitations associated with this technique. From our limited experience, lesions of size more than (or equal to) 35 mm and LST-NG pseudo-depressed–type tumors are often difficult to treat via en bloc resection, and we consider hybrid ESD to be most suitable for lesions measuring 20 to 30 mm.

4.3. Outcomes

In Japan, The Japan Society for Cancer of the Colon and Rectum conducted a multicenter observation study of all patients treated via conventional endoscopic resection and ESD for colorectal neoplasms of size more than 20 mm from October 2007 to December 2010 [36]. A total of 816 lesions were treated via ESD, and the short-term outcomes were as follows. The mean lesion diameter was approximately 40 mm. En bloc resection was achieved in more than 90% of cases regardless of lesion size, with a perforation rate of 2.0% and delayed bleeding rate of 2.2%. No perforation cases required emergency surgery and all were treated conservatively by endoscopic closure; nothing per os, antibacterial therapy. Hence, most iatrogenic perforations are very small and can be closed by endoscopic clip placement.

4.4. Training for ESD

Given the high risk of complications that arise from the anatomical characteristics of the colon, ESD requires a high level of skill and experience in endoscopy. A better understanding of the learning curve for ESD is therefore required to standardize training, and to achieve a more global acceptance of this technique. At our institution, endoscopists who will begin using ESD must meet the following prerequisites to perform colorectal ESD: a high level of skill in the non-loop insertion colonoscopy technique (more than 10 cases of total colonoscopy completed within 5 minutes without any abdominal discomfort), skill in conventional EMR or EPMR techniques, experience with more than 20 gastric ESD cases, and assistance in more than 20 colorectal ESDs conducted by experienced endoscopists [37]. In Western countries, however, gastric cancer is less common than colorectal cancer, and the introduction of trainees to ESD using colorectal lesion resection as a first step might be difficult. When required, trainees should start clinical training in colorectal ESD with lower rectal lesions, which carry a lower risk of perforation and a similar setting to gastric lesions.

We reported the short-term outcomes of colorectal ESD performed by less-experienced endoscopists [37, 38]. In terms of the learning curve, the endoscopists could perform the technique safely and independently after preparatory training and experience of 30 or more cases. On the other hand, most LST-G tumors of size less than (or equal to) 40 mm could be treated safely within a 120-minute procedure time without any adverse events. Therefore, we recommend that an LST-G tumor of size less than 40 mm is likely suitable for introducing trainees to ESD.

5. Conclusion

Various treatment materials have been developed and applied to ESD since the introduction of this technique. Of note, ESD is reliable for the en bloc resection of large colorectal superficial neoplasms. It has a better success rate than EPMR and enables more accurate pathological evaluations. In addition, colorectal ESD reduces unwanted surgery for mucosal carcinomas and improves the overall quality of life of patients with lesions in the lower rectum. Nevertheless, the technical difficulty of ESD and the complications associated with it, including iatrogenic perforation, have held back its wider global adoption. We consider that adoption of this technique will improve in future following further development of treatment devices with improved safety and reduced technical difficulty. However, there is no exact standardized procedure for ESD, and it is important to continue efforts toward improving the safety and technical ease of the procedure.

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