

Review

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# Tips for difficult colorectal endoscopic submucosal dissection

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## Abstract

Colorectal endoscopic submucosal dissection (ESD) is now widely performed and firmly established in the treatment of early-stage colorectal cancer. In particular, there have been many studies on difficult cases of colorectal ESD. Difficult cases can be divided into two groups: difficult dissection of the lesions and difficult approach to the lesion. In most cases, a combination of strategies can solve the problem. Challenging lesions such as those in the anal canal and ileum can also be treated from an anatomical perspective. In the rectum, there are no limits to size or circumference. In addition, the indications for ESD in patients without risk of metastasis other than deep invasion are being considered. Therefore, when ESD is performed on difficult lesions, it is necessary to ensure the quality of dissection.

**Keywords:** Endoscopic submucosal dissection, difficult cases, anal canal, ileocecal, muscle retracting sign, fibrosis



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## INTRODUCTION

Thanks to the development of endoscopic techniques, a wide variety of colorectal tumors can be treated endoscopically. In particular, endoscopic submucosal dissection (ESD) techniques have made remarkable progress in the past decade. However, ESD is a time-consuming and costly procedure, and its indications must be carefully considered. Some lesions can be adequately treated with endoscopic mucosal resection (EMR), and some large lesions are acceptable for endoscopic piecemeal mucosal resection (EPMR) because they are adenomas. However, cancerous lesions need to be resected en bloc, which is sometimes difficult to perform with EMR. The indications are described in detail in the guidelines<sup>[1]</sup>. This review discusses tips for difficult cases of colorectal ESD.

## ABOUT COLORECTAL ESD

### Basics and quality control of colorectal ESD

ESD is a challenging technique, but it is possible to perform en bloc resection regardless of the size, morphology, or area occupied by the lesion. Thanks to the development of local injection agents that maintain good mucosal distension and devices suitable for colorectal ESD<sup>[2,3]</sup>, ESD can be performed even in the colon with thin walls and many flexures. The blood vessels of the gastrointestinal tract penetrate the muscularis propria to form a vascular network in the middle submucosa. Dissection between this vascular network and the muscularis propria is efficient because there are the fewest vessels to cut. Furthermore, the safest and highest quality ESD is performed with the least thermal damage to the muscle layer and lesion. A sufficiently thick resection specimen collected by this method allows for accurate depth of invasion, lymphovascular invasion, and budding grade. Any ESD device can be used, but the quality of dissection and the specimen must be ensured<sup>[4]</sup>.

### ESD results

In a multicenter study conducted in Japan, the en bloc resection rate of colorectal ESD was 94.5%<sup>[5]</sup>. Perforation is a full-thickness defect of the muscular layer, and intraoperative perforation occurred in 2.6%-4.9% of cases, 96% of which healed conservatively with clip sutures<sup>[6,7]</sup>. Endoscopic closure using over the scope clip or polyglycolic acid sheets for perforation has also been reported<sup>[8,9]</sup>. Postoperative bleeding occurred in 1.5%-4.7% of patients<sup>[6,10,11]</sup>. The long-term outcome of patients with curative resection is good<sup>[12]</sup>. The recurrence rates were 0%-2% for ESD and 12.1%-14% for EPMR<sup>[13,14]</sup>, and EPMR for early colorectal cancer has a high recurrence rate in the resection of more than five specimens<sup>[15]</sup>. There have been cases of recurrence as advanced cancer<sup>[16]</sup>, thus EPMR should be avoided as much as possible. Recently, it has been shown that local recurrence occurs due to tumor implantation. Colorectal tumors are fragile, and many tumor cells were found floating in the intestinal tract after colorectal ESD<sup>[17]</sup>. It is important to clean the intestinal lumen and ulcer bed thoroughly with water (> 1000 mL) after ESD<sup>[17]</sup>.

## DEALING WITH DIFFICULT CASES

### Difficult factors of ESD

Difficult cases can be divided into two groups: cases in which dissection of the lesion is difficult and cases in which the approach to the lesion is difficult. The former includes cases prone to bleeding, cases with fibrosis in the submucosa, and cases with abundant fat. The latter includes cases of poor scope operability due to adhesions, lesions located at the back of the folds or in the flexure, and lesions on the ileum or anal canal.

### Dealing with cases of difficult dissection

#### *Bleeding control*

There are individual differences in the easy bleeding and the difficult hemostasis. It is necessary to perform the technique faithfully to the basics. It is also important to decide whether to pre-coagulate with forceps based on the easy bleeding in the early stages of treatment. Pre-coagulation is also effective in forced

coagulation with a low high-frequency power setting using an Endo-Knife<sup>[18]</sup> [Figure 1].

#### *Fibrosis in the submucosa*

The degree of fibrosis in the submucosa has a significant impact on procedure time and safety<sup>[19,20]</sup>. However, it is impossible to accurately determine the degree of fibrosis before ESD. Even if there is severe fibrosis in the submucosa, high-quality ESD must be performed. The basic strategy for fibrosis is to dissect around the fibrosis at an appropriate depth between the vascular network and the muscularis propria. In the fibrotic area, the border between the myofiber bundle and the fibrotic area is carefully identified using local injection, and three techniques (sliding/scooping/tapping) are used for precise dissection<sup>[21,22]</sup> [Figure 2].

#### *Cases with abundant fat*

The fat-rich submucosa has high electrical resistance, making incision, dissection, and hemostasis inefficient. In high-voltage and high-modulation mode, such as forced coagulation, it is difficult to dissect the lesion, and, even worse, there is a lot of fat droplet scattering, which immediately clouds the field of view. Therefore, it is recommended to use low-voltage and low-modulation modes such as Swift coagulation and cut modes. On the other hand, hemostasis is reduced in these modes, so it is recommended to pre-coagulate the vessel using forceps. Because there is little fat directly above the muscularis propria, it is also important to target this layer for dissection.

### **Dealing with cases of difficult approach**

#### *Scope operability*

It is very important to stabilize the scope for colorectal ESD which takes more time than lower endoscopy and other endoscopic treatments. In colorectal ESD, CO<sub>2</sub> insufflation is essential<sup>[23]</sup>. When the operability of the scope is extremely poor, the use of a double-balloon endoscope, a single-balloon sheath, double-balloon endoluminal intervention platform, or overtube with rigidization feature may be the solution<sup>[24-26]</sup>.

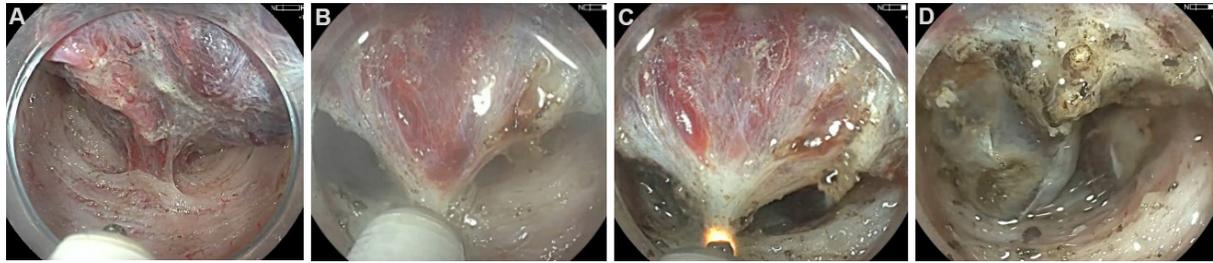
#### *Use of traction devices*

Since Oyama<sup>[27]</sup> reported the usefulness of traction devices in gastric ESD in 2002, traction devices have been evaluated as an adjunct in esophageal and gastric ESD, and various methods have been reported<sup>[28]</sup>. Because of the difficulty in attaching traction device to the colon, it has rarely been performed. In recent years, the use of traction in the deep colon has been reported<sup>[29]</sup>, and it has been shown to be effective in cases of both difficult dissection and difficult approach [Figure 3].

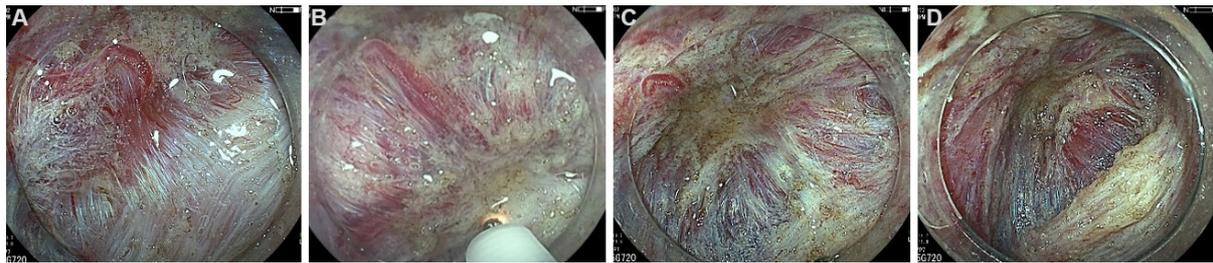
## **ESD FOR CHALLENGING COLORECTAL LESIONS**

### **Large lesion**

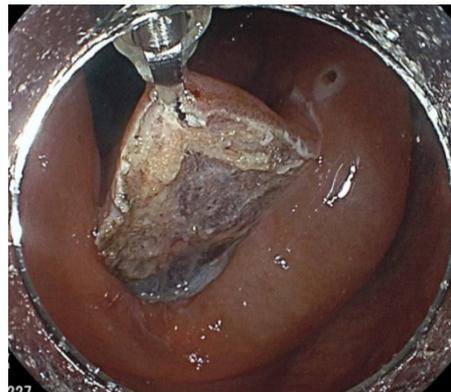
There are occasionally large intramucosal colorectal carcinomas that are indicated for endoscopic treatment. Although large lesions are often defined as difficult cases because of the longer treatment time<sup>[30]</sup>, the treatment speed per tumor area tends to be rather fast, if there are no other difficult factors<sup>[31]</sup>. While ESD of these lesions is time consuming, endoscopists often do not find it difficult. However, laparoscopic surgery for colonic lesions is less invasive and has a better functional outcome. There is no need to insist on endoscopic treatment at the risk of prolonged treatment, complications, and stricture. However, rectal surgery is highly invasive and difficult, and it affects the defecation function. Because the rectum has a large intestinal lumen and a thick muscularis propria, rectal endoscopic treatment is safer than the colon one. In addition, a large part of the rectum is extraperitoneal, which makes a perforation less dangerous. This is the area where the benefits of ESD can be best exploited.



**Figure 1.** Pre-coagulation using an Endo-Knife: (A) a penetrating vessel exposed by dissecting submucosa; (B, C) pre-coagulation by forced coagulation with a low high-frequency power setting using an Endo-Knife; and (D) after cutting the penetrating vessel.



**Figure 2.** Tapping for severe fibrosis: (A) severe fibrosis with MR sign; (B, C) the border between the transverse myofiber bundle and the longitudinal submucosal fibers was precisely dissected using the “Migaki” tapping technique; and (D) after dissecting the severe fibrotic area. MR: Muscle retracting.



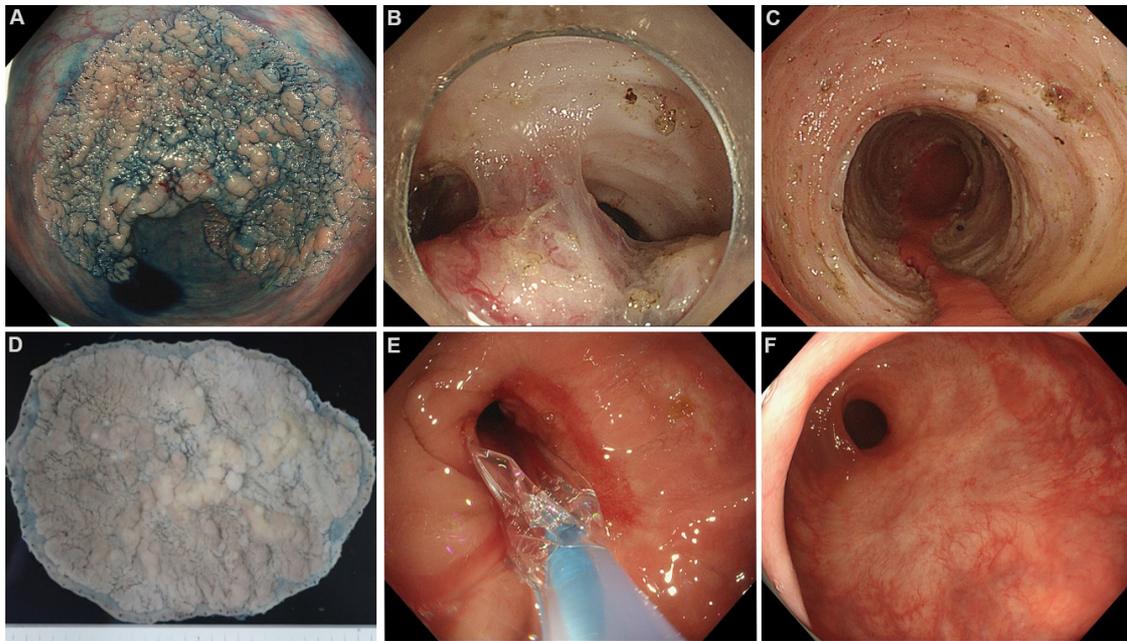
**Figure 3.** The traction device provides a good field of view.

### Large rectal lesions and stricture risk

In narrow lumen areas such as the esophagus, gastric cardia, and pyloric ring, stenosis occurs when the resection exceeds 3/4 of the circumference<sup>[32-34]</sup>. Conversely, large lesions in the rectum rarely cause stricture<sup>[35-37]</sup>. However, if more than 90% of the circumference is resected, stricture occurs<sup>[35,36]</sup>. Therefore, if the resection is more than 3/4 circumferential, the stenosis is checked every 2-3 weeks, and, if the scope does not pass, a finger bougie is performed<sup>[35]</sup>. The usefulness of local injection of steroids or steroid suppositories for this stenosis is unknown. If stenosis occurs, it is a membranous stenosis of less than 10 mm in length and can be easily dilated<sup>[35,36]</sup>. Therefore, there is no limit to the size of rectal ESD [Figure 4].

### Lesions on the anal canal

The narrow lumen of the anal canal makes it difficult to maintain a clear field of view and makes scope



**Figure 4.** Large rectal lesions and stricture risk: (A) the circumferential extension of the rectal lesion was > 75%; (B) the lesion was carefully resected with out adverse event; (C, D) the ulcer bed and specimen after ESD; (E) the stricture was treated by endoscopic balloon dilation; and (F) the lumen after three years. ESD: Endoscopic submucosal dissection.

operation unstable. There are large arteries and veins in the submucosa that can cause major bleeding. Since the anal epithelium has a sense of pain, a local anesthetic is mixed with the local injection. The incision should be made shallowly to scoop up the muscularis mucosa to avoid bleeding. However, the most difficult factor in anal canal ESD is the strong fibromuscular tissue in the submucosa formed by the conjoined longitudinal muscle and the mucosal suspensory ligament. Once this layer is properly treated, the anal canal mucosa is pulled toward the lower rectum and the submucosa is opened. Treatment of the anal canal support ligament and vascular network between the incision edge and the inner ring muscle is the most important step for anal canal ESD and is the same as the basic technique in hemorrhoid surgery. Because the strategy of ESD does not change with or without hemorrhoid, there are no differences in the results or treatment time. Postoperative pain varies widely among individuals, and non-steroidal anti-inflammatory drug suppositories and topical hemorrhoids and local anesthetics are used as appropriate. If the resection is about 90% of the circumference, we instruct the patient to perform finger bougie with local anesthetic.

### Ileocecal lesion

In the ileocecal location, the scope tends to be poorly maneuverable, and the lesion is often positioned in relation to the appendicular orifice and the ileocecal valve. There is strong fibrosis near the appendiceal orifice even if there is no history of appendicitis or appendectomy. In addition, the submucosal layer is thin and confronts the muscularis propria, thus extremely delicate treatment is necessary. In the submucosa of the ileocecal valve, adipose tissue is abundant. Fat has a high electrical resistance, which makes incision, dissection, and hemostasis difficult.

### Lesions in proximity to the appendiceal orifice

If there is a distance between the lesion and the appendiceal orifice, the mucosa between them should be cut first (Strategy A). Next, the incision on the anal side of the lesion, the treatment of the vascular network, and the use of a mucosal flap allow for the safe dissection of thin, fibrotic areas near the appendix orifice. If the lesion is extended or surrounding the appendix orifice, the appendiceal mucosa should be removed

together. Submucosal tissue is dissected including the area around the deep appendix and final incision of the appendiceal mucosa is made from the submucosal side (Strategy B). Although Strategy B requires significantly longer treatment time, the cases of postoperative appendicitis are rare and can be managed conservatively<sup>[38]</sup>. It is less invasive than ileocecal resection. However, the risk of incomplete resection is high if the target lesion reaches and enters the appendiceal orifice to the extent that the tumor edge cannot be seen when looking into the appendiceal lumen without appendectomy.

### **Lesions involving the ileocecal valve**

First, it is important to confirm that the endoscope can reach the oral side of the lesion. If the endoscope can reach the lesion, even lesions involving the terminal ileum can be resected. Incision of the mucosa and vascular network on the ileal side should be performed first to prevent the lesion from shifting to the ileal side. The muscularis propria in this area is bent, and the muscle fiber bundles are thin, sparse, and light in color, so it must be carefully separated from the submucosa. Compared with cecal lesions, the time and speed of the procedure are significantly inferior, but the en bloc resection rate is not different. Interestingly, there were no stenosis symptoms in all cases reported, including those with over 95% of mucosal defects of circumference<sup>[39]</sup>. It was reported that no stenosis occurred even after a full circumferential resection, and we believe that stenosis does not occur unless ESD is performed deep into the ileum [Figure 5].

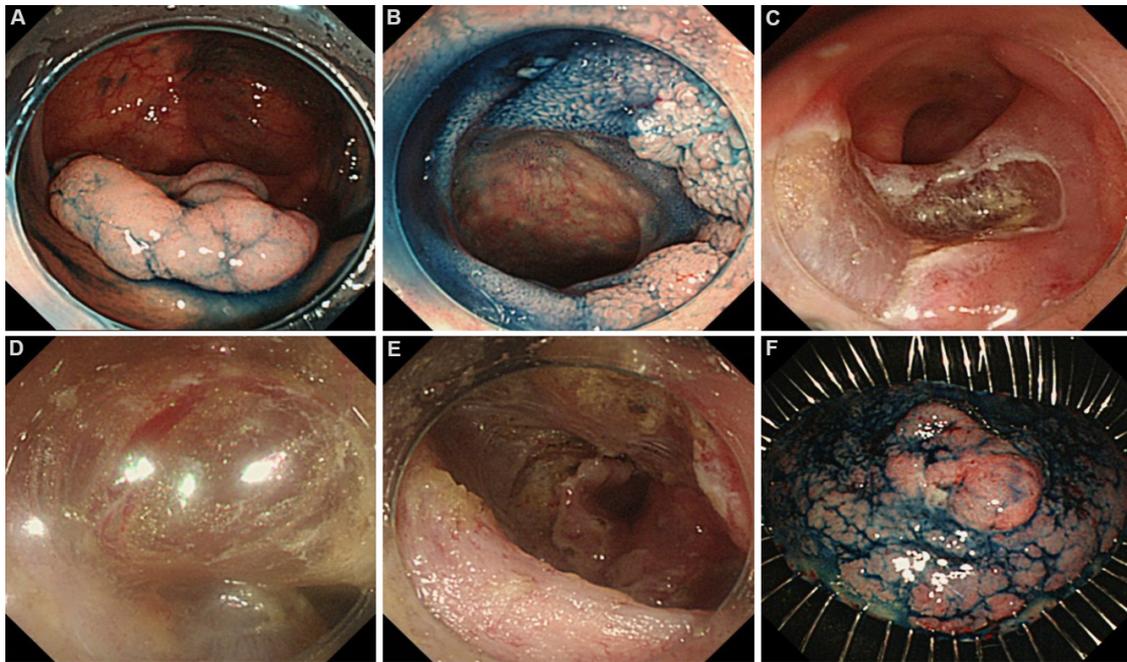
### **Large, protruded lesion and muscle retracting sign**

In a recent analysis of factors associated with difficult colorectal ESD<sup>[40]</sup>, a large, protruded lesion is recognized as one of the difficult cases. The depth of protruded lesions larger than 3 cm cannot be accurately diagnosed even with ultrasound endoscopy, enterography, and magnifying endoscopy. Some of these lesions may be intramucosal carcinoma or adenoma, but some have muscle retracting sign (MR sign), where the muscle layer is pulled towards the lesion, and the dissection may be very difficult and dangerous<sup>[41]</sup>. Most of them are due to desmoplastic reactions associated with deep submucosal invasion, but about 30% of the lesions with MR sign are intramucosal lesions or slight submucosal carcinoma<sup>[41]</sup>. In addition, deep submucosal carcinoma has a very low rate of metastasis in the absence of risk factors other than deep invasion<sup>[42]</sup>, and expanded indications for these lesions are being discussed.

### **Pocket-creation method and per anal endoscopic myectomy**

The development of the pocket creation method (PCM) has been a major advance in ESD in recent years<sup>[43]</sup>. When conventional ESD using a mucosal flap is performed in cases with MR sign, the MR area becomes unstable, and the field of view becomes poor. PCM allows traction against the muscularis propria by diving into the submucosa through a minimal mucosal incision and suspending the submucosa with the lesion and surrounding mucosa. If opening the sides of the pocket is difficult, a traction method called retroflex traction technique can be useful. With this traction technique, the endoscope is passed through the pocket and retroflexion is performed. The lesion is lifted by the endoscope, and good counter traction makes it easy to open the sides of the pocket. In addition, we also developed per anal endoscopic myectomy (PAEM) by applying peroral endoscopic myotomy, submucosal endoscopic tumor resection, and the pocket method<sup>[44]</sup>. In PAEM, the submucosa on both sides of the severe fibrosis with MR sign is first dissected using double tunneling, and the circular muscle around the fibrosis is incised. Subsequently, the space between the circular muscle and the longitudinal muscle is dissected, and the lesion and the circular muscle is resected together. Although PAEM is limited to rectal cases, it can be applied to the treatment of anastomotic lesions and residual recurrence after transanal endoscopic microsurgery.

[Supplementary Video 1](#) demonstrated an effective retroflex traction technique procedure for opening the side of a pocket in the pocket creation method.



**Figure 5.** Lesions involving the ileocecal valve: (A, B) a lesion located on the ileocecal valve extended to the terminal ileum; (C) incision of the mucosa and vascular network on the ileal side; (D) fat-rich submucosa; and (E, F) the ulcer bed and specimen after ESD. ESD: Endoscopic submucosal dissection.

## CONCLUSION

The indications for ESD of colorectal lesions that were previously difficult to treat endoscopically, such as large lesions, difficult cases, and difficult location, have been expanding. Conversely, not all lesions must be resected by ESD, and many lesions can be treated by EMR or piecemeal resection. Laparoscopic surgery for colonic lesions is less invasive and has a better functional outcome. There is great value in endoscopic treatment for rectal lesions. It is hoped that further knowledge in this field will be accumulated and will be of benefit to patients.

## DECLARATIONS

### Author's contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Yoshizaki T, Toyonaga T, Ikezawa N, Nakano Y, Tanaka S, Ishida T, Rahni DO, Jacob H, Rahmi G, Kodama Y

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

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