Tips for safety in endoscopic submucosal dissection for colorectal tumors

Naohisa Yoshida[1], Yuji Naito[1], Takaaki Murakami[1], Ryohei Hirose[1], Kiyoshi Ogiso[1], Yutaka Inada[1], Rafiz Abdul Rani[2], Mitsuo Kishimoto[3], Masayoshi Nakanishi[4], Yoshito Itoh[1]

[1]Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan; [2]Gastroenterology Unit, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia; [3]Department of Surgical Pathology, [4]Department of Surgery, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

Contributions: (I) Conception and design: N Yoshida, Y Naito; (II) Administrative support: Y Itoh; (III) Provision of study materials or patients: T Murakami, R Hirose, K Ogiso, Y Inada, M Kishimoto, M Nakanishi; (IV) Collection and assembly of data: N Yoshida, K Ogiso; (V) Data analysis and interpretation: N Yoshida, R Abdul Rani; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Naohisa Yoshida, MD, PhD. Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
Email: naohisa@koto.kpu-m.ac.jp.

Abstract: In Japan, endoscopic submucosal dissection (ESD) becomes one of standard therapies for large colorectal tumors. Recently, the efficacy of ESD has been reported all over the world. However, it is still difficult even for Japanese experts in some situations. Right-sided location, large tumor size, high degree of fibrosis, difficult manipulation is related with the difficulty. However, improvements on ESD devices, suitable strategies, and increase of operators' experiences enable us to solve these problems. In this chapter, we introduce recent topics about various difficult factors of colorectal ESD and the tips such as strategy, devices, injection, and traction method [Pocket-creation method (PCM) etc.].

Keywords: Safety; tips; difficult factors; endoscopic submucosal dissection (ESD); colorectal polyp; colorectal cancer

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Introduction

In Japan, endoscopic submucosal dissection (ESD) becomes one of standard therapies for large colorectal tumors (1-6). Recently, the efficacy of ESD has been reported all over the world (7). However, it is still difficult even for Japanese experts in some situations. Colonic characteristics such as the thinness of the colonic wall and winding shape make ESD difficult. Right-sided location, large tumor size, and high degree of fibrosis and so on have been previously identified as risk factors for incomplete resection and perforation of colorectal ESD (8-10). However, improvements on ESD devices, suitable strategies, and increase of operators' experiences enable us to solve these problems (6,9). In this chapter, we introduce recent topics about various difficult factors of colorectal ESD and the tips for treating them.

Our overall ESD results and principles of ESD

Our overall therapeutic results of 1,001 ESD cases are given in *Table 1*. Mean age of the group was 68.1±10.5 years old and 564 were male (56.3%). Five-hundred five (50.5%), 203 (19.9%), and 293 (29.2%) tumors were located in the right-sided colon (cecum to transvers colon), left-sided colon (descending colon to sigmoid colon) and rectum, respectively. While the mean tumor size was 31.0±14.9 mm, 821 (83.1%) were non-polypoid tumors. The rate of en bloc resection was 91.9% (920/1,001). Procedural perforation and delayed perforation rates were 3.2% (32/1,001) and 0.1 (1/1,001). Postoperative hemorrhage rate was 1.8%

(18/1,001). Histologically, there were 393 (40.0%), 418 (42.6%), and 124 (12.6%) cases of adenomas, Tis, and T1 cancers, respectively.

Endoscopic mucosal resection (EMR) is performed as one of standard therapies for colorectal polyps in the world. However, EMR has a limitation with respect to the size of the snare (*Figure 1A*). Thus, it is difficult to achieve en bloc resection by EMR for a colorectal tumor ≥20 mm in size (11,12). On the other hand, ESD enables us to achieve en bloc resection for colorectal polyps ≥20 mm in size. However, we have to pay attention about perforation in colorectal ESD because colorectal wall thickness is only about 3 mm. Special injection solution such as hyaluronic acid is used for getting long-lasting high submucosal elevation and it makes colorectal wall thicker (1–2 cm) (*Figure 1B*) (13,14). Transparent hood is fitted on the tip of the endoscope for ESD. After injection, mucosal incision is performed, followed by submucosal dissection. According to transparent hood and appropriate dissection, we can make a mucosal flap and go below the tumor and the flap (*Figure 1C*). Below the mucosal flap, the endoscope becomes stable and submucosal dissection becomes easier by submucosal traction. Finally, the tumor is resected en bloc (*Figure 1D*).

We introduce a standard ESD case. At first, we perform a pre-check colonoscopy before ESD for the accurate diagnosis (*Figure 2A*). Regularly, we adopt magnifying observation using narrow band imaging, blue laser imaging, and chromoendoscopy (*Figure 2B*) (15-19). We also determine the status of manipulation about endoscope. For cases with severely difficult manipulation, we give up to use regular endoscope and use double balloon endoscope

Table 1 Our overall therapeutic results of 1,001 ESD cases

Case number	1,001 tumors
Age, mean ± SD	68.1±10.5
Gender male/female, % [n]	56.3 [564]/43.7 [437]
Tumor size, mean ± SD	31.0±14.9
Tumor location (right-sided/left-sided/rectum), % [n]	50.9/19.9/29.2 (505/203/293)
Morphology (polypoid/non-polypoid), % [n]	16.9/83.1 (180/821)
Operation time (minutes), mean ± SD	81.6±52.3
En bloc resection, % [n]	91.9 [920]
Discontinuance rate, % [n]	1.9 [19]
Procedural perforation, % [n]	3.2 [32]
Delayed perforation, % [n]	0.1 [1]
Postoperative hemorrhage, % [n]	1.8 [18]
Histological diagnosis in resected 982 tumors (Ad/Tis/T1/SSA/P/others) %, [n]	40.0 [393]/42.6 [418]/12.6 [124]/1.6 [16]/3.2 [31]

ESD, endoscopic submucosal dissection; right-sided, from the cecum to the transverse colon; left-sided, from the descending colon to the sigmoid colon; Ad, adenoma; Tis, intramucosal cancer; SSA/P, sessile serrated adenoma and polyp.

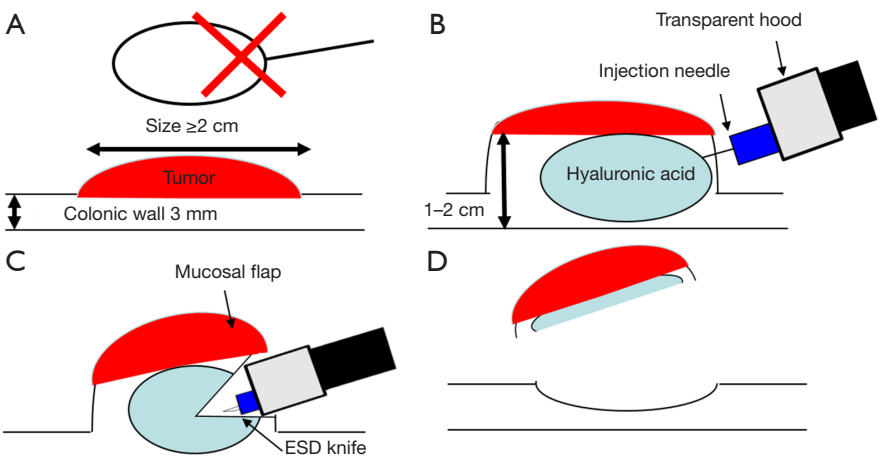

Figure 1 Theory of colorectal endoscopic submucosal dissection (ESD). (A) ESD is expected for tumor ≥2 cm in size because it is difficult to achieve en bloc resection by endoscopic mucosal resection (EMR) for large colorectal tumor; (B) special injection solution such as hyaluronic acid is used for getting long-lasting high submucosal elevation and it makes colorectal wall thicker (1–2 cm); (C) according to transparent hood and appropriate dissection, we can make a mucosal flap and go below the tumor and the flap. After that, speedy dissection is performed; (D) finally, large tumor is resected en bloc.

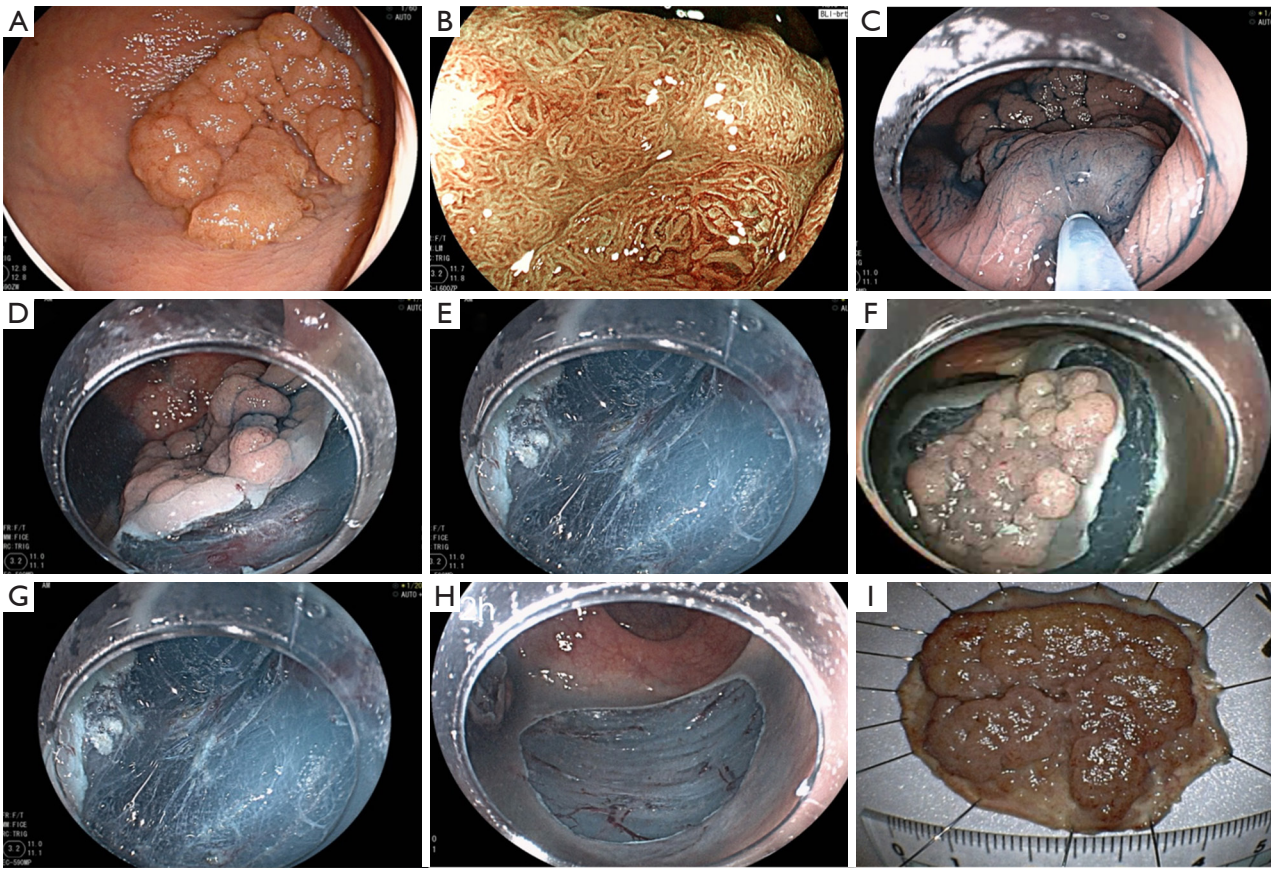

Figure 2 A case of colorectal endoscopic submucosal dissection (ESD). (A) Careful observation of a target tumor; (B) magnifying endoscope (blue laser imaging) is performed for accurate diagnosis; (C) injection is performed to the anal side of the tumor; (D) mucosal incision and submucosal dissection is performed for making a mucosal flap; (E) after making a flap, we can go below the tumor and flap; (F) a circumferential mucosal incision is performed after enough dissection; (G) following submucosal dissection is performed; (H) finally, a tumor is resected en bloc; (I) a resected tumor.

(Fujifilm Co., Tokyo, Japan) (20). A lower gastrointestinal endoscope with a single channel (EC-L600ZP, Fujifilm Medical Co., Tokyo, Japan; PCF-H290I, Olympus Co., Tokyo, Japan) is used generally. Mucosal injection is performed to the anal side of the tumor and a partial mucosal incision is performed with ESD knife (*Figure 2C,D*). Then, submucosal dissection is performed for making a mucosal flap. After making a flap, we can go below the tumor and flap (*Figure 2D,E*). Half to 2/3 of dissection is performed followed by full circumferential mucosal incision (*Figure 2F*). Next, submucosal dissection is performed from the anal side again and the tumor is resected en bloc finally (*Figure 2G-I*).

The injection solution is prepared with 0.4% hyaluronic acid solution (Mucoup, Boston Scientific Co., Tokyo, Japan and Seikagaku Co., Tokyo, Japan) including a small amount of 0.2% indigocarmine (final concentration: 0.06% indigocarmine) (*Figure 3A*) (21). Injection of hyaluronic acid is administered with a 25-gauge high flow needle (TOP Co., Tokyo, Japan) (*Figure 3B*). Hyaluronic acid is sticky and the injection pressure is higher than saline (13,14), thus, we use high flow needle. CO_2 insufflation is used for preventing severe abdominal fullness and minimizing the difficulty of manipulation (*Figure 3C*) (22). The VIO300D high-frequency generator (Erbe Elektromedizin, Tubingen, Germany) is also used for accurate incision, dissection, and hemostat (*Figure 3D*). Our routine ESD procedure is performed with a short-tipped ESD knife such as the Flush knife BT-S 2.0 mm (Fujifilm Co., Tokyo, Japan) (*Figure 3E*) (4). The Clutch cutter 3.5 or 5.0 mm (Fujifilm Co., Tokyo, Japan), a grasping scissor knife, was also used in difficult situations (23).

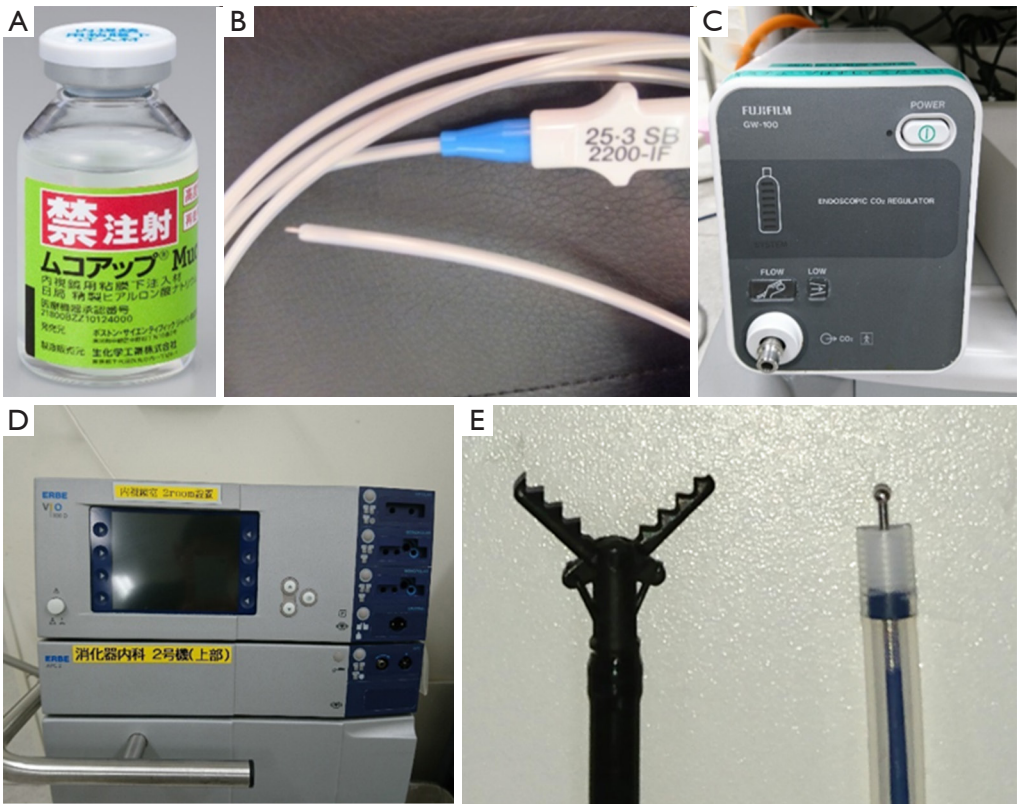

Figure 3 Improvement of devices. (A) Hyaluronic acid; (B) high-flow injection needle; (C) CO_2 insufflator; (D) electrosurgical unit; (E) Clutch cutter 5.0 mm (left) and Flush knife BT 2.0 mm (right).

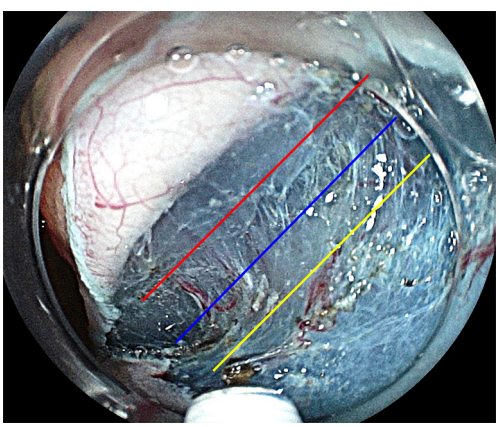

Figure 4 Tips for dissection line. Appropriate dissection depth (blue line) is important for performing accurate histological evaluation. Too shallow dissection depth makes resected specimens coagulated and damaged. Oppositely, too deep dissection depth (yellow line) occurs procedural perforation.

The goal of ESD is to achieve en bloc resection of large tumor for accurate histological diagnosis. Appropriate dissection depth (blue line) is important for that (*Figure 4*). Too shallow dissection depth makes resected specimens coagulated and damaged and it makes histological evaluation difficult. Oppositely, too deep dissection depth (yellow line) occurs procedural perforation. Especially, with respect to histological evaluation of T1 cancer, enough submucosal dissection (blue line) is needed and shallow dissection depth (yellow line) may happen vertical margin positive and incomplete resection for it (*Figure 5*).

Difficult factors of colorectal ESD

Difficulties of ESD are related with longer procedure, incomplete en bloc resection, and perforation (6-10). For preventing these problems, it is important to predict

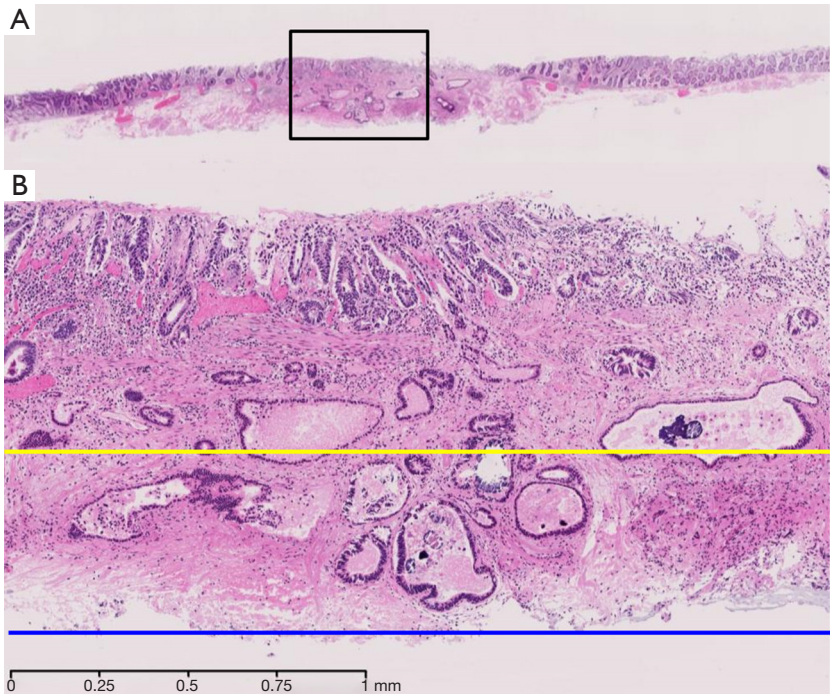

Figure 5 Ideal resected specimen by endoscopic submucosal dissection (ESD). With respect to histological evaluation of T1 cancer, enough submucosal dissection (blue line) is needed and shallow dissection depth (yellow line) may happen vertical margin positive for it.

difficult cases. Right-sided colon tumors, fibrosis, poor endoscopic operability and deep submucosal invasion are reported to be significantly associated with incomplete en bloc resection (6,24). We previously analyzed difficult factors of colorectal ESD using 405 consecutive colorectal ESD cases performed only by an expert in our institution (25). In multivariate analyses, severe fibrosis (OR: 26.395, 95% CI: 6.587–105.764, P<0.001), difficult manipulation (OR: 4.575, 95% CI: 1.200–17.436, P=0.026), and tumor size ≥50 mm (OR: 4.452, 95% CI: 1.061–18.688), were significantly related with incomplete en bloc resection (*Table 2*). So, we have to pay attention to cases with these factors. In tumor sizes ≥50 mm, we consider two difficult points. First, large tumors need a more complicated strategy. In our institution, for tumor ≥50 mm, oral-side approach theory is adopted because anal-side approach sometimes makes oral side approach more difficult. After oral-side mucosal incision, anal-side incision and dissection are followed. Second, ESD for a large tumor has more complications such as perforation and perioperative hemorrhage than that for tumors that are <50 mm in size (5). Thus, a suitable strategy and considerable expertise should be considered when performing ESD for large tumors.

On the other hand, factors such as large tumor size, laterally spreading tumors, right-sided colon, submucosal injection without hyaluronic acid, severe fibrosis, and deeply invasive T1 cancer were reported to be associated with a higher rate of perforation in other studies (6,8,10). Poor endoscopic operability was also reported to be related with perforation (24). The rate of poor endoscopic operability was reported as 45.3%. Poor endoscopic operability is due to tumor location, breathing movement, endoscopist's experiences and so on. Thus, we analyzed it in detail using 405 colorectal ESD cases only performed by experts. It showed the rates of difficult manipulation and severe breathing movement were 23.5% and 35.8% (25). For cases with severe breathing movement and difficult manipulation cases, we use a scissor type knife (Clutch cutter) as it enables safe dissection in this situation. Difficult manipulation resulted in discontinuance of ESD significantly (25). Thus, cases with difficult manipulation should be predicted before ESD. With respect to risk factors of poor manipulation, tumor locations at the right-sided colon and on a flexure, longer insertion time, and severe breathing movement were reported to be associated with difficult manipulation (24,25).

Cases at the dental line are recently reported to be

Table 2 Univariate and multivariate analysis about difficult factors of colorectal ESD

Characteristics	Overall	Successful en bloc resection	Incomplete en bloc resection	P value	Multivariate analysis (OR)	95% CI, P value
Case number, % [n]	[405]	96.8 [392]	3.2 [13]	–	–	–
Age, mean ± SD	67.9±10.7	67.6±10.4	72.8±13.9	0.08	–	–
Gender Male/female, % [n]	51.1 [207]/48.9 [198]	57.9 [227]/42.1 [165]	76.9 [10]/23.1 [3]	0.170	–	–
Tumor size ≥50 mm, % [n]	13.6 [55]	12.7 [50]	38.4 [5]	0.020	4.452	1.061–18.688; P=0.041
Morphology (non-polypoid/polypoid), % [n]	85.6 [347]/24.4 [58]	85.7 [336]/14.3 [56]	84.6 [11]/15.4 [2]	0.910	–	–
Tumor location (right-sided/left-sided/rectum), % [n]	50.1 [203]/20.2 [82]/29.6 [120]	49.7 [195]/20.7 [81]/29.6 [116]	61.5 [8]/7.7 [1]/30.8 [4]	0.400	–	–
Severe fibrosis, % [n]	10.8 [44]	8.6 [34]	76.9 [10]	<0.001	26.395	6.587–105.764; P<0.001
Difficult manipulation, % [n]	23.5 [95]	22.1 [87]	61.5 [8]	0.003	4.575	1.200–17.436; P=0025
Severe breathing movement, % (n]	35.8 [145]	35.7 [140]	38.4 [5]	0.830	–	–
Histological diagnosis (Ad/Tis/T1), % [n]	44.7 [181]/41.0 [166]/14.3 [58]	45.4 [178]/40.8 [160]/13.8 [54]	23.1 [3]/46.2 [6]/30.7 [4]	0.110	–	–

ESD, endoscopic submucosal dissection; right-sided, from the cecum to the transverse colon; left-sided, from the descending colon to the sigmoid colon; Ad, adenoma; Tis, intramucosal cancer.

difficult for ESD (26) because there are lots of vessels at the location. However, we manage thick vessels during ESD with the scissor-type knife (Clutch cutter). It can grasp vessels and dissect them and can stop hemorrhage without exchange to hemostatic forceps. Cases invading ileocecal valve is also difficult for ESD (27) because, there are lots of fatty tissues around ileocecal valve. It is difficult to determine appropriate dissection line in fatty tissue. It is yellowish and not transparent so that we can't predict the length of muscle layer from submucosal layer. Additionally, it is hardly dissected by coagulation as transparent submucosa is easily dissected. Moreover, residual liquid is supplied from ileum continuously and it makes situations worse. We think most important tips for it is strategy. Mucosal incision has to be performed at the oral ileal side first as it is applied to tumors ≥50 mm in size. Because ileum is narrow and scope control on it is poor. And ileal side is hardly approached after anal-side procedure such as injection and dissection. One more our tip for cases invading ileum is to use the scissor type knife. As we previously mentioned, it is also useful for difficult manipulation.

Tips for difficult cases

Firstly, we explain our tips about first mucosal injection using a case (*Figure 6A*). In this tumor, first mucosal injection can be performed at blue point or red point. If blue point is chosen, a tumor direction becomes periventricular to an endoscope (*Figure 6B*). It is not ideal for dissection because endoscope's direction goes to muscle layer. On the other hand, if red point is chosen, a tumor direction becomes parallel to an endoscope (*Figure 6C*). It is safe and useful for dissection, because there is not muscle layer to endoscope's direction, but high elevated submucosal layer. This theory is also useful for determining how far from the tumor the injection is performed. Too close red point (× symbol) makes tumor direction a little periventricular because part of injection goes below the tumor (*Figure 6D*). 1 cm anal side (○ symbol) from the tumor makes tumor direction parallel to an endoscope.

Secondly, some traction methods should be adopted for improving difficulties of colorectal ESD (28) because regular colonoscopy has only one channel comparing to laparoscopic surgery which has more than

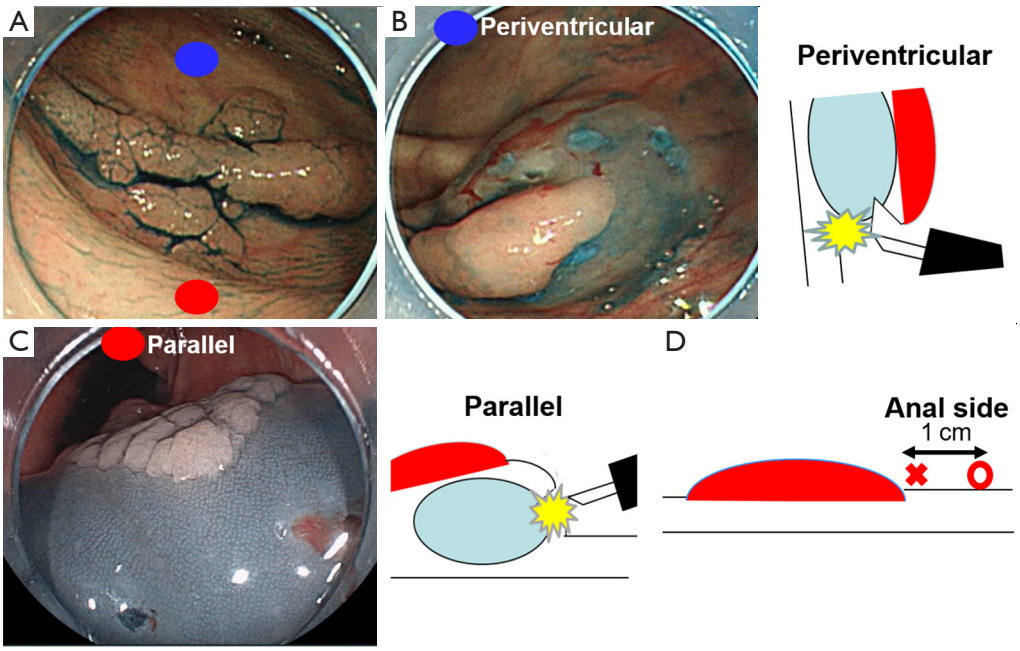

Figure 6 Tips for injection. (A) First mucosal injection can be performed at blue point or red point for this tumor; (B) if blue point is chosen, a tumor direction becomes periventricular to an endoscope; (C) if red point is chosen, a tumor direction becomes parallel to an endoscope; (D) too close red point (× symbol) makes tumor direction a little periventricular because part of injection go below the tumor. 1 cm anal side (○ symbol) from the tumor makes tumor direction parallel to an endoscope.

two ports. Tapered transparent hood is regularly used for achieving traction though it is not enough effective in some cases. Clip flap method is one of easy and useful traction methods for making mucosal flap (7).

Thirdly, effective lens cleaner is necessary for colorectal ESD. Water drop adhesions (WDA) and lens cloudiness impairs the clarity of endoscopic view during colorectal ESD and are particularly annoying for endoscopists. Difficult visualization requires higher mental concentration to maintain a safe procedure, inevitably increasing strain and slowing procedure speed. Recently, we developed a novel lens cleaner and the efficacy for preventing lens cloudiness during colorectal ESD had been reported (29). The novel lens cleaner is Cleash (Fujifilm Co., Tokyo, Japan, and Nagase Medicals Co., Ltd., Hyogo, Japan) created mainly of two harmless non-ionic surfactants. It can be applied on the tip of the endoscope using swab or napkin. It showed the cloudiness of the lens decreased in 14.1% of all colorectal ESD cases with this novel lens cleaner compared to a previous lens cleaner (33.0%, P=0.002). Additionally, it could clean cloudy lens inside the colon as it was injected from the endoscopic channel into an enclosed space for 30 seconds. The space was created by pressing the endoscopic hood against the mucosa. In colorectal ESD at proximal side, we don't want to remove an endoscope even if it becomes cloudy because re-insertion of endoscope is not easy in some cases during ESD. However, this novel lens cleaner doesn't need endoscopists to remove an endoscope during ESD because it can clean the lens inside the colon. It is now available in Japan and we hope it will be produced to other countries in the near future.

Pocket-creation method (PCM)

The PCM is a new method for cases with severe fibrosis and one of the traction methods (*Figure* 7) (30). The specific feature of PCM is the creation of a large submucosal pocket using a long and tapered hood (short ST hood or ST hood: Fujifilm Co., Tokyo, Japan). PCM provides good traction with the tip of the transparent hood stretching the submucosal tissue, which facilitates submucosal dissection. Additionally, endoscope becomes stable in the pocket. So,

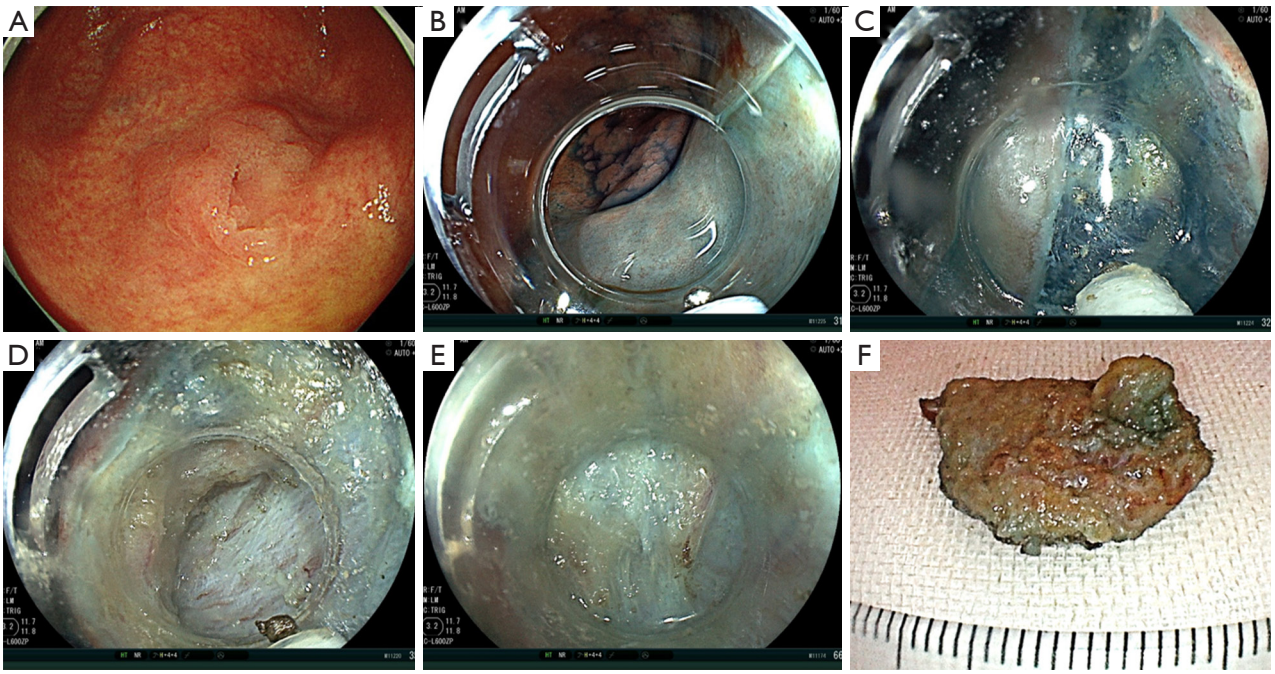

Figure 7 Pocket-creation method (PCM). (A) A non-polypoid tumor on the appendices; (B) high elevation couldn't be achieved by injection; (C) PCM was tried using short ST hood; (D) endoscope became stable in the pocket and enough traction was achieved; (E) severe fibrosis could be dissected.; (F) resected specimen (upside down view). Part of the appendices was dissected with the tumor.

our indications of PCM is giant colorectal tumors, laterally spreading tumor with depression, recurrent cases, and cases close to appendix, which may have severe fibrosis (9). And proximal sided tumors, which may happen difficult manipulation and severe breathing movement is also the indications of PCM.

Animal training model

In training of animal models for colorectal ESD, *in vivo* animal models and *ex vivo* animal models using harvested organs is used in the world (31). Porcine is mainly used as *in vivo* animal models. *In vivo* models having blood flow are ideal for training. However, *in vivo* models are expensive and inconvenient. In contrast, *ex vivo* animal models are inexpensive and convenient (*Figure 8A*). However, the weakest point of *ex vivo* animal models is the lack of blood flow. Control of perioperative hemorrhage is one of the most important techniques in clinical ESD. Special *ex vivo* animal models with blood flow has been developed in Japan and this enables ideal training for practical ESD (*Figure 8B,C*) (32). Based on various features, we recommend the porcine and bovine rectum for training of beginners in colorectal ESD. Regularly, imaginary lesion is made by coagulation of tip of ESD knifes, but it makes tissue damaged and hard. Thus, red ink is used for making imaginary lesion especially for EMR training (*Figure 8D*). In the model, ideally high submucosal elevation is achieved by injection of hyaluronic acid. The other weakness of *ex vivo* and *in vivo* animal models is the poverty of colonic fold. However, using plastic band, artificial fold is made in *ex vivo* model (*Figure 8E,F*). The shape of fold is almost similar to human one and more realistic training of ESD can be performed. These special *ex vivo* animal models are produced by Boston Scientific Japan (Tokyo, Japan), and so far they are only available in Japan. We hope it will be produced in other countries. This kind of animal model makes ESD more standardized all over the world.

Summary

We introduce recent topics about our tips about colorectal ESD in this chapter. There are some difficult aspects for it. Appropriate strategy, devices, and prediction of difficult cases are important for accomplishing en bloc resection without complications.

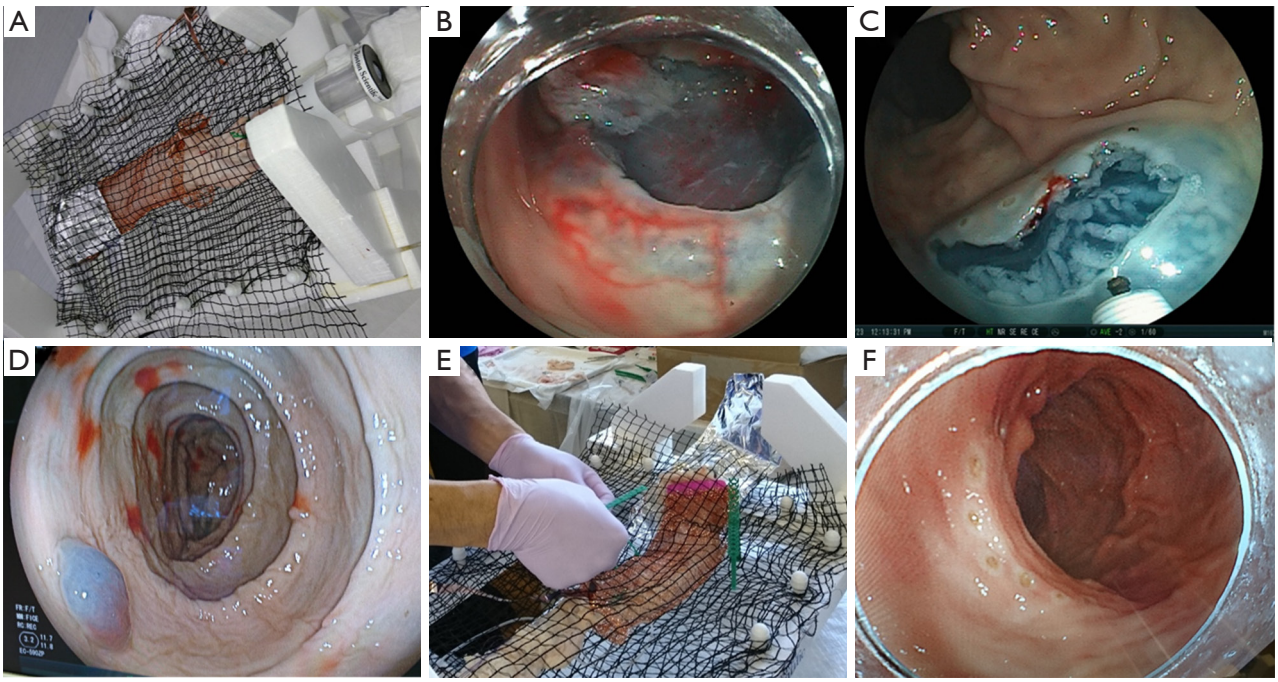

Figure 8 Animal training model for colorectal endoscopic submucosal dissection (ESD) produced by Boston Scientific Japan. (A) An *ex vivo* animal models using porcine rectum; (B) an *ex vivo* animal model with blood flow; (C) ideal submucosal dissection training can be performed; (D) red ink is used for making imaginary lesion especially for EMR training; (E,F) using plastic band to an *ex vivo* porcine and bovine model, artificial fold is made in *ex vivo* model. There is a non-polypoid lesion with marking on the fold in the animal model.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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